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ORGANIC CHEMISTRY

AS A SECOND LANGUAGE

FIFTH EDITION

SECOND SEMESTER TOPICS

DAVID KLEIN

WILEY

ORGANIC CHEMISTRY AS A SECOND LANGUAGE, 5e

Second Semester Topics

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WILEY

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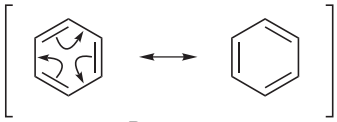
CHAPTER 1

AROMATICITY

If you are using this book, then you have likely begun the second half of your organic chemistry course. By now, you have certainly encountered aromatic rings, such as benzene. In this chapter, we will explore the criteria for aromaticity, and we will discover many compounds (other than benzene) that are also classified as aromatic.

1.1 INTRODUCTION TO AROMATIC COMPOUNDS

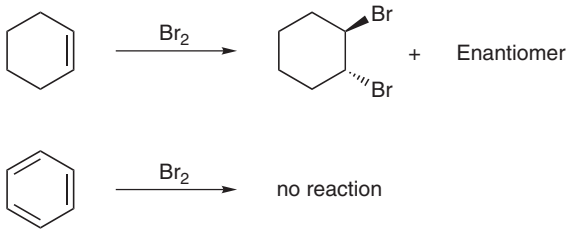
Consider the structure of benzene:



Benzene

Benzene is resonance-stabilized, as shown above, and is sometimes drawn in the following way:

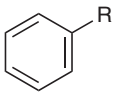
This type of drawing (a hexagon with a circle in the center) is not suitable when drawing mechanisms of reactions, because mechanisms require that we keep track of electrons meticulously. But, it is helpful to see this type of drawing, even though we won't use it again in this book, because it represents all six π electrons of the ring as a single entity, rather than as three separate π bonds. Indeed, a benzene ring should be viewed as one functional group, rather than as three separate functional groups. This is perhaps most evident when we consider the special stability associated with a benzene ring. To illustrate this stability, we can compare the reactivity of cyclohexene and benzene:



Cyclohexene is an alkene, and it will react with molecular bromine (Br_2) via an addition process, as expected for alkenes. In contrast, no reaction occurs when benzene is treated with Br_2, because the stability associated with the ring (of six π electrons) would be destroyed by an addition process. That is, the six π electrons of the ring represent a single functional group that does not react with Br_2, as alkenes do.

Understanding the source of the stability of benzene requires MO (molecular orbital) theory. You may or may not be responsible for MO theory in your course, so you should consult your textbook and/or lecture notes to see whether MO theory was covered.

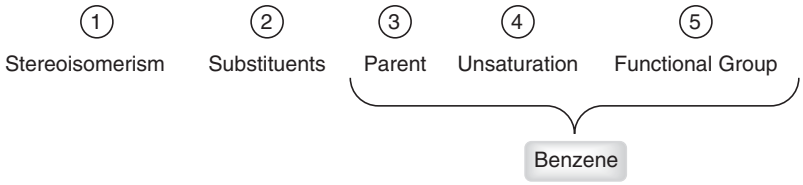
Derivatives of benzene, called substituted benzenes, also exhibit the stability associated with a ring of six π electrons:



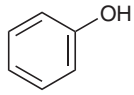
The ring can be monosubstituted, as shown above, or it can be disubstituted, or even polysubstituted (the ring can accommodate up to six different groups). Many derivatives of benzene were originally isolated from the fragrant extracts of trees and plants, so these compounds were described as being *aromatic,* in reference to their pleasant odors. Over time, it became apparent that many derivatives of benzene are, in fact, odorless. Nevertheless, the term *aromatic* is still currently used to describe derivatives of benzene, whether those compounds have odors or not.

1.2 NOMENCLATURE OF AROMATIC COMPOUNDS

As we have mentioned, an aromatic ring should be viewed as a single functional group. Compounds containing this functional group are generally referred to as *arenes*. In order to name arenes, recall that there are five parts of a systematic name, shown here (these five parts were discussed in Chapter 5 of the first volume of *Organic Chemistry as a Second Language: First Semester Topics*):

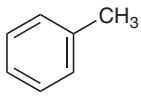


For benzene and its derivatives, the term *benzene* represents the parent, the unsaturation AND the suffix. Any other groups (connected to the ring) must be listed as substituents. For example, if a hydroxy (OH) group is connected to the ring, we do not refer to the compound as benzenol. We cannot add another suffix (-ol) to the term benzene, because that term is already a suffix itself. Therefore, the OH group is listed as a substituent, and the compound is called hydroxybenzene:

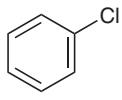


Hydroxybenzene

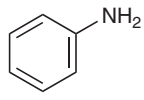
Similarly, other groups (connected to the ring) are also listed as substituents, as seen in the following examples:



Methylbenzene

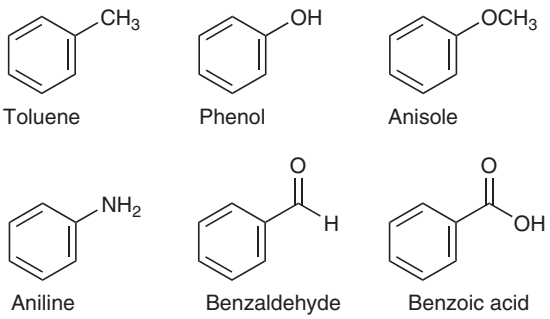


Chlorobenzene



Aminobenzene

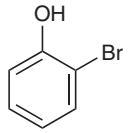
Many monosubstituted derivatives of benzene (and even some disubstituted and polysubstituted derivatives) have common names. Several common names are shown here:



Toluene Phenol Anisole

Aniline Benzaldehyde Benzoic acid

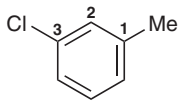
So, for example, the first compound above can either be called methylbenzene (systematic name) or toluene (common name). Similarly, the second compound above can either be called hydroxybenzene (systematic name) or phenol (common name). When more than one substituent is present, common names are often used as parents. For example, the following compound exhibits a benzene ring with two substituents. But if we use the term *phenol* as the parent (rather than benzene), then we only have to list one substituent (bromo):



2-Bromophenol

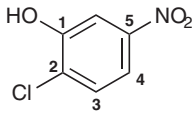
The number (2) indicates the position of Br relative to the OH group. Notice that this compound can also be called 1-bromo-2-hydroxybenzene. Both names are acceptable, although it is generally more efficient to use the common name (2-bromophenol, rather than 1-bromo-2-hydroxybenzene).

When more than one group is present, numbers must be assigned, as seen in the previous example. When assigning numbers, the #1 position is determined by the parent. For example, the following compound will be named as a substituted toluene, so the methyl group is (by definition) at the #1 position:



3-Chlorotoluene

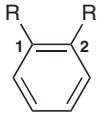
The numbers are assigned in a manner that gives the lower possible number to the next substituent (Cl). So, in this case, we assign the numbers in a counterclockwise fashion, because that gives a lower number (3-chloro, rather than 5-chloro). The same method is applied for polysubstituted rings: first we choose the parent, and then we assign numbers in the direction that gives the lower possible number to the second substituent. Consider the following example:



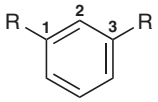
2-Chloro-5-nitrophenol

This compound can be named as a disubstituted phenol, rather than a trisubstituted benzene. So, the OH group is assigned the #1 position. Then, we continue assigning numbers in the direction that gives the lower possible number to the second substituent (2-chloro, rather than 3-nitro).

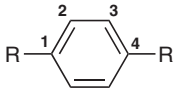
For disubstituted benzenes, there is special terminology that describes the proximity of the two groups:



ortho-disubstituted

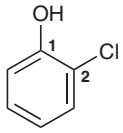


meta-disubstituted

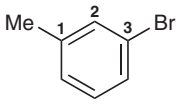


para-disubstituted

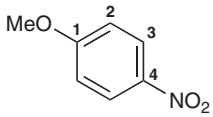
The term *ortho* is used to describe 1,2-disubstitution, the term *meta* is used to describe 1,3-disubstitution, and the term *para* is used to describe 1,4-disubstitution. These terms may be used instead of numbers, as seen in the following examples:



ortho-Chlorophenol

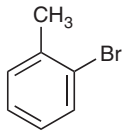


meta-Bromotoluene

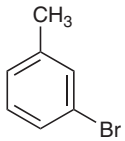


para-Nitroanisole

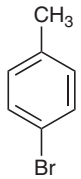
These terms (*ortho*, *meta* and *para*) will be used frequently, so it is certainly worthwhile to commit them to memory right now. Sometimes, you might see the prefixes abbreviated to just one letter (*o*, *m*, and *p*), as seen in the following examples:



o-Bromotoluene

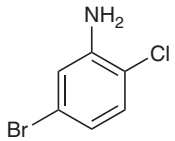


m-Bromotoluene

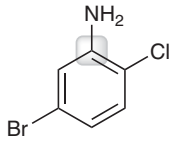


p-Bromotoluene

WORKED PROBLEM 1.1 Provide a systematic name for the following compound:

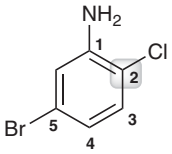


Answer This compound is a trisubstituted benzene, and it can be named as such, although it will be more efficient to name the compound as a disubstituted derivative of aniline. Since we are using a common name (aniline) as our parent, the position bearing the amino group is, by definition, position #1:

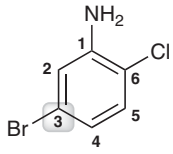


Then, we assign numbers in a clockwise fashion, rather than counterclockwise, so that the next substituent is at C2 rather than C3:

CORRECT



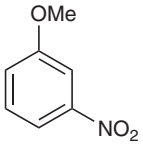
INCORRECT



Therefore, the name is 5-bromo-2-chloroaniline. Notice that the substituents appear in the name in alphabetical order, in accordance with the general rules for IUPAC nomenclature.

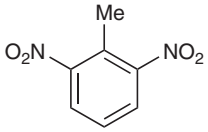
PROBLEMS Provide a systematic name for each of the following compounds:

1.2



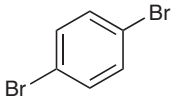
Name: _____

1.3



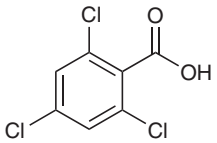
Name: _____

1.4



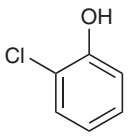
Name: _____

1.5



Name: _____

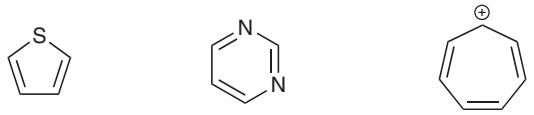
1.6



Name: _____

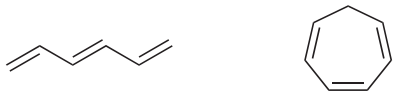
1.3 CRITERIA FOR AROMATICITY

In the previous section, we saw that benzene and its derivatives exhibit a special stability that is associated with the ring of six π electrons. We will now see that aromatic stabilization is not limited to benzene and its derivatives. Indeed, there are a large number of compounds and ions that exhibit aromatic stabilization. A few examples are shown here:



These structures are also said to be aromatic, illustrating that aromaticity is not strictly limited to six-membered rings, but indeed, even five-membered rings and seven-membered rings can be aromatic (if they meet certain criteria). In this section, we will explore the two criteria for aromaticity. Let's begin with the first criterion:

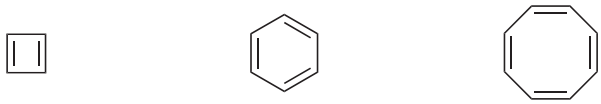
1) *There must be a ring comprised of continuously overlapping p orbitals*. The structures below do NOT satisfy this first criterion:



The first structure is not aromatic because it is not a ring, and the second structure is not aromatic because it lacks a continuous system of overlapping *p* orbitals. Six of the seven carbon atoms are sp^2 hybridized (and each of these carbon atoms does have a *p* orbital), but the seventh carbon atom (at the top of the ring) is sp^3 hybridized, thereby interrupting the overlap. The overlap of *p* orbitals must continue all the way around the ring, and it doesn't in this case because of the intervening sp^3 hybridized carbon atom.

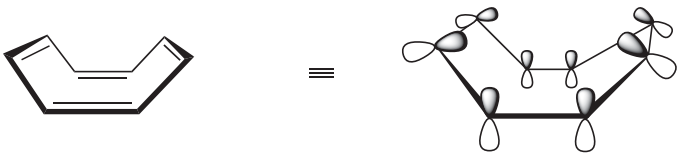
Now let's explore the second criterion for aromaticity:

2) *The ring must contain an odd number of pairs of π electrons* (one pair of electrons, three pairs of electrons, five pairs of electrons, etc.). If we compare the following compounds, we find that only the middle compound (benzene) has an odd number of pairs of π electrons (three pairs of π electrons = 6 π electrons):

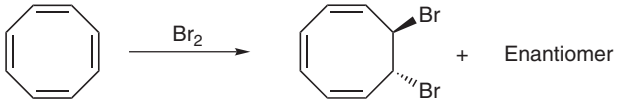


The first compound (cyclobutadiene) has two pairs of π electrons, and the last compound (cyclooctatetraene) has four pairs of π electrons. In order to understand the requirement for an odd number of pairs of π electrons, MO theory is required. Once again, consult your textbook and/or lecture notes for any coverage of MO theory. Another way of saying "an odd number of pairs of π electrons" is to say that the number of π electrons must be among the following series of numbers: 2, 6, 10, 14, 18, etc. These numbers are called Hückel numbers, and they can be summarized with the following formula: $4n + 2$, where *n* represents a series of integers (1, 2, 3, etc.). If we look closely at benzene (middle structure above), we find that there are six π electrons, which is a Hückel number. Therefore, benzene is aromatic. In contrast, each of the other two compounds above (cyclobutadiene and cyclooctatetraene) has an even number of pairs of π electrons. Cyclobutadiene has 4 π electrons, and cyclooctatetraene has 8 π electrons. These numbers (4 and 8) are NOT Hückel numbers. These numbers can be represented by the formula $4n$, where *n* represents a series of integers (1, 2, 3, etc.). These compounds are remarkably unstable (an observation that can be justified by MO theory). They are said to be *antiaromatic*. In order for a compound to be antiaromatic, it must satisfy the first criterion (it must possess a ring with a continuous system of overlapping *p* orbitals), but it must fail the second criterion (it must have $4n$, rather than $4n + 2$, π electrons).

Cyclooctatetraene can relieve much of the instability by puckering out of planarity, as shown:

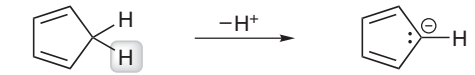


In this way, the extent of continuous overlap (of *p* orbitals) is significantly reduced, so the first criterion (a ring of continuous overlapping *p* orbitals) is not fully satisfied. The compound therefore behaves as if it were nonaromatic, rather than antiaromatic. That is, it can be isolated, unlike antiaromatic compounds, which are generally too unstable to isolate. Moreover, it is observed to undergo addition reactions, unlike aromatic compounds which do not undergo addition reactions:



Now let's explore ions (structures that have a net charge). We will identify ions that are classified as aromatic, as well as examples of antiaromatic ions. Consider the structure of the following anion, which is resonance-stabilized. Draw all of the resonance structures in the space provided:

The remarkable stability of this anion cannot be explained with resonance alone. This anion is also aromatic, because it satisfies both criteria for aromaticity. To see how this is the case, we must recognize that the lone pair occupies a *p* orbital (because any lone pair that participates in resonance must occupy a *p* orbital), so this structure does indeed exhibit a ring with a continuous system of overlapping *p* orbitals, with a Hückel number of π electrons. The delocalized lone pair represents two π electrons, and the rest of the ring has another four π electrons, for a total of six π electrons. Indeed, the aromatic nature of this anion explains why cyclopentadiene is so acidic:



Cyclopentadiene (nonaromatic) | Conjugate base (aromatic)

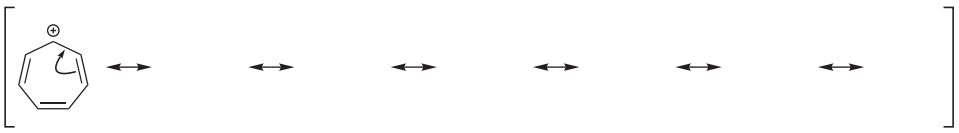
Cyclopentadiene is nonaromatic, but when it is deprotonated, the resulting conjugate base IS aromatic. Since the conjugate base is so stable, this renders cyclopentadiene fairly acidic (for a hydrocarbon). If we compare the pK_a values of cyclopentadiene and water, we find that they are similar in acidity:

pK_a = 16 | pK_a = 15.7

This is truly remarkable, because it means that the following conjugate bases are similar in stability:

You often think of hydroxide as a strong base, but remember that basicity and acidity are relative concepts. Sure, hydroxide is a strong base when compared with certain weak bases, such as the acetate ion. But hydroxide is actually a relatively weak base when compared with other very strong bases, such as the amide ion (H_2N^-) or carbanions (C^-). Above, we see an example of a carbanion that is similar in stability to a hydroxide ion. You will not find many other examples of carbanions with such remarkable stability. And as we have seen, this stability is due to its aromatic nature.

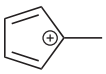
The previous example was an anion. Let's now explore an example of a cation. The cation below, called a tropylium cation, is resonance-stabilized. Draw all of the resonance structures in the space provided.



The remarkable stability of this cation is not fully explained by resonance. If we consider both criteria for aromaticity, we will find that this cation does indeed satisfy both criteria. Recall that a carbocation represents an empty *p* orbital, so we do have a ring with a continuous system of overlapping *p* orbitals, AND we have six π electrons (a Hückel number). Therefore, both criteria are satisfied, and this cation is aromatic.

Let's get some practice determining whether ions are aromatic, nonaromatic, or antiaromatic.

WORKED PROBLEM 1.7 Characterize the following ion as aromatic, nonaromatic, or antiaromatic:



Answer In order to be nonaromatic, it must fail the first criterion for aromaticity. In this case, it satisfies the first criterion, because the carbocation represents an empty *p* orbital, so we do have a ring with a continuous system of overlapping *p* orbitals. Since the first criterion is satisfied, we conclude that the structure will either be aromatic or antiaromatic, depending on whether the second criterion is met (a compound can only be nonaromatic if it fails the first criterion).

When we count the number of π electrons, we do NOT have a Hückel number in this case. With 4 π electrons, we expect this structure to be antiaromatic. That is, we expect this ion to be very unstable.

PROBLEMS Characterize each of the following structures as aromatic, nonaromatic, or antiaromatic:

1.8

Answer: _____

1.9

Answer: _____

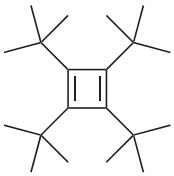
1.10

Answer: _____

1.11

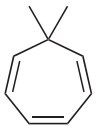
Answer: _____

1.12



Answer: _____

1.13

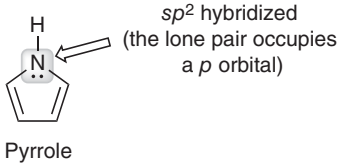


Answer: _____

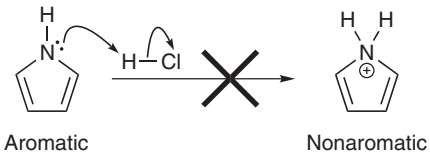
1.4 LONE PAIRS

Compare the following two structures:

We saw in the previous section that the first structure is aromatic. The second structure, called pyrrole, is also aromatic, for the same reason. The nitrogen atom adopts an sp^2 hybridized state, which places the lone pair in a *p* orbital, thereby establishing a continuous system of overlapping *p* orbitals,

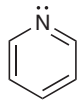


and there are six π electrons (two from the lone pair + another two from each of the π bonds = 6). Both criteria for aromaticity have been satisfied, so the compound is aromatic. Notice that the lone pair is part of the aromatic system. As such, the lone pair is less available to function as a base:

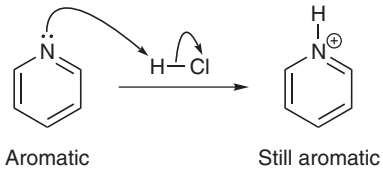


This doesn't occur, because the ring would lose aromaticity. If the nitrogen atom were to be protonated, the resulting nitrogen atom (with a positive charge) would be sp^3 hybridized. It would no longer have a *p* orbital, so the first criterion for aromaticity would not be satisfied (thus, nonaromatic). Protonation of the nitrogen atom would be extremely uphill in energy and is not observed.

In contrast, consider the nitrogen atom of pyridine:



In this case, the lone pair is NOT part of the aromatic system. This localized lone pair is not participating in resonance, and it does not occupy a *p* orbital. The nitrogen atom is sp^2 hybridized, and it does have a *p* orbital, but the *p* orbital is occupied by a π electron (as illustrated by the double bond that is drawn on the nitrogen atom). The lone pair actually occupies an sp^2 hybridized orbital, and it is therefore not contributing to the aromatic system. As such, it is available to function as a base, because protonation does not destroy aromaticity:



Indeed, pyridine is often used as a mild base, especially in reactions where HCl is a byproduct. The presence of pyridine effectively neutralizes the acid as it is produced, and for this reason, pyridine is often referred to as "an acid sponge."

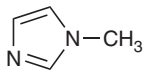
Let's explore one last example of an aromatic compound. This compound, called furan, is similar in structure to pyrrole:

Furan Pyrrole

The oxygen atom of furan is sp^2 hybridized (much like the nitrogen atom of pyrrole), which places one of the lone pairs in a *p* orbital, thereby establishing a continuous system of overlapping *p* orbitals, with a Hückel number of electrons (6 π electrons). Therefore, furan is aromatic, for the same reason that pyrrole is aromatic. Notice that the oxygen atom in furan has two lone pairs, but only one of them occupies a *p* orbital. The other lone pair occupies an sp^2 hybridized orbital. As such, we only count one of the lone pairs of the oxygen atom (not both lone pairs) when we are counting to see if we have a Hückel number.

PROBLEMS

1.14 In the following compound, identify whether each lone pair is available to function as a base, and explain your choice:



1.15 Only one of the following compounds is aromatic. Identify the aromatic compound, and justify your choice:

CHAPTER 2

IR SPECTROSCOPY

Did you ever wonder how chemists are able to determine whether or not a reaction has produced the desired products? In your textbook, you will learn about many, many reactions. And an obvious question should be: "how do chemists *know* that those are the products of the reactions?"

Until about 50 years ago, it was actually VERY difficult to determine the structures of the products of a reaction. In fact, chemists would often spend many months, or even years to elucidate the structure of a single compound. But things got a lot simpler with the advent of spectroscopy. These days, the structure of a compound can be determined in minutes. Spectroscopy is, without a doubt, one of the most important tools available for determining the structure of a compound. Many Nobel prizes have been awarded to chemists who pioneered applications of spectroscopy.

The basic idea behind all forms of spectroscopy is that electromagnetic radiation (light) can interact with matter in predictable ways. Consider the following simple analogy: imagine that you have 10 friends, and you know what kind of bakery items they each like to eat every morning. John always has a brownie, Peter always has a French roll, Mary always has a blueberry muffin, etc. Now imagine that you walk into the bakery just after it opens, and you are told that some of your friends have already visited the bakery. By looking at what is missing from the bakery, you could figure out which of your friends had just been there. If you see that there is a brownie missing, then you deduce that John was in the bakery before you.

This simple analogy breaks down when you really get into the details of spectroscopy, but the basic idea is a good starting point. When electromagnetic radiation interacts with matter, certain frequencies are absorbed while other frequencies are not. By analyzing which frequencies were absorbed (which frequencies are missing once the light passes through a solution containing the unknown compound), we can glean useful information about the structure of the compound.

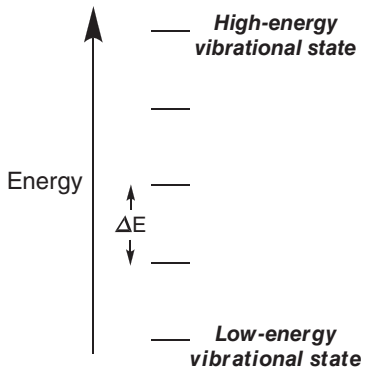
You may recall from your high school science classes that the range of all possible frequencies (of electromagnetic radiation) is known as the electromagnetic spectrum, which is divided into several regions (including X-rays, UV light, visible light, infrared radiation, microwaves, and radio waves). Different regions of the electromagnetic spectrum are used to probe different aspects of molecular structure, as seen in the table below:

Type of Spectroscopy	Region of Electromagnetic Spectrum	Information Obtained
NMR Spectroscopy	Radio Waves	The specific arrangement of all carbon and hydrogen atoms in the compound
IR Spectroscopy	Infrared (IR)	The functional groups present in the compound
UV-Vis Spectroscopy	Visible and Ultraviolet	Any conjugated π system present in the compound

We will not cover UV-Vis spectroscopy in this book. Your textbook may have a short section on that form of spectroscopy. In this chapter, we will focus on the information that can be obtained with IR spectroscopy. The next chapter will cover NMR spectroscopy.

2.1 VIBRATIONAL EXCITATION

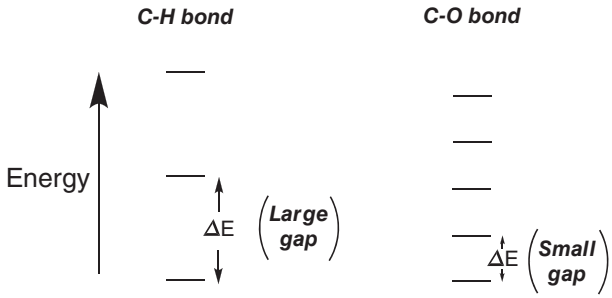
Molecules can store energy in a variety of ways. They rotate in space, their bonds vibrate like springs, their electrons can occupy a number of possible molecular orbitals, etc. According to the principles of quantum mechanics, each of these forms of energy is quantized. For example, a bond in a molecule can only vibrate at specific energy levels:



The horizontal lines in this diagram represent allowed vibrational energy levels for a particular bond. The bond is restricted to these energy levels, and cannot vibrate with an energy that is in between the allowed levels. The difference in energy (ΔE) between allowed energy levels is determined by the nature of the bond. If a photon of light possesses exactly this amount of energy, the bond (which was already vibrating) can absorb the photon to promote a *vibrational excitation*. That is, the bond will now vibrate more energetically. The energy of the photon is temporarily stored as vibrational energy, until that energy is released back into the environment, usually in the form of heat.

Bonds can store vibrational energy in a number of ways. They can *stretch*, very much the way a spring stretches, or they can *bend* in a number of ways. Your textbook will likely have images that illustrate these different kinds of vibrational excitation. In this chapter, we will devote most of our attention to stretching vibrations (as opposed to bending vibrations) because stretching vibrations generally provide the most useful information.

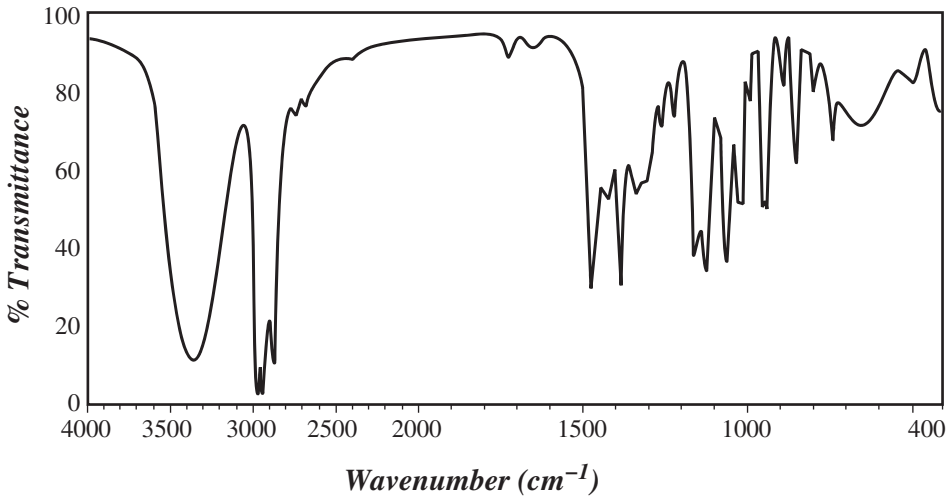
For each and every bond in a molecule, the energy gap between vibrational states is very much dependent on the nature of the bond. For example, the energy gap for a C—H bond is much larger than the energy gap for a C—O bond:



Both bonds will absorb infrared (IR) radiation, but the C—H bond will absorb a higher-energy photon. A similar analysis can be performed for other types of bonds as well, and we find that each type of bond will absorb a characteristic frequency, allowing us to determine which types of bonds are present in a compound. For example, a compound containing an O—H bond will absorb a frequency of IR radiation characteristic of O—H bonds. In this way, ***IR spectroscopy can be used to identify the presence of functional groups in a compound***. It is important to realize that IR spectroscopy does NOT reveal the entire structure of a compound. It can indicate that an unknown compound is an alcohol, but to determine the entire structure of the compound, we will need NMR spectroscopy (covered in the next chapter). For now, we are simply focusing on identifying which functional groups are present in an unknown compound. To get this information, we irradiate the compound with all frequencies of IR radiation, and then detect which frequencies were absorbed. This can be achieved with an IR spectrometer, which measures absorption as a function of frequency. The resulting plot is called an IR absorption spectrum (or IR spectrum, for short).

2.2 IR SPECTRA

An example of an IR spectrum is shown below:



Notice that all signals point down in an IR spectrum. The location of each signal on the spectrum is reported in terms of a frequency-related unit, called wavenumber ($\tilde{\nu}$). The wavenumber is simply the frequency of light (ν) divided by a constant (the speed of light, c):

$$\tilde{\nu} = \frac{\nu}{c}$$

The units of wavenumber are inverse centimeters (cm^{-1}), and the values typically range from $400\,cm^{-1}$ to $4000\,cm^{-1}$. Don't confuse the terms wavenumber and wavelength. Wavenumber is proportional to frequency, and therefore, a larger wavenumber represents higher energy. Signals that appear on the left side of the spectrum correspond with higher energy radiation, while signals on the right side of the spectrum correspond with lower energy radiation.

Every signal in an IR spectrum has the following three characteristics:

1. the *wavenumber* at which the signal appears

2. the *intensity* of the signal (strong vs. weak)

3. the *shape* of the signal (broad vs. narrow)

We will now explore each of these three characteristics, starting with wavenumber.

2.3 WAVENUMBER

For any bond, the wavenumber of absorption associated with bond stretching is dependent on two factors:

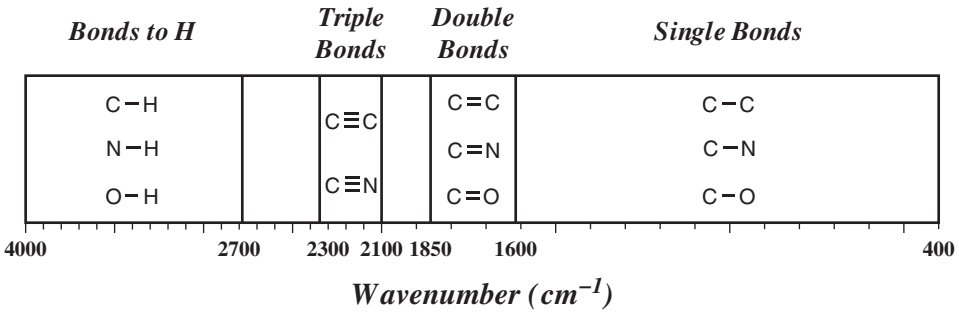
1) *Bond strength* – Stronger bonds will undergo vibrational excitation at higher frequencies, thereby corresponding to a higher wavenumber of absorption. For example, compare the bonds below. The C≡N bond is the strongest of the three bonds and therefore appears at the highest wavenumber:

C≡N	C=N	C—N
~ 2200 cm^{-1}	~ 1600 cm^{-1}	~ 1100 cm^{-1}

2) *Atomic mass* – Smaller atoms give bonds that undergo vibrational excitation at higher frequencies, thereby corresponding to a higher wavenumber of absorption. For example, compare the bonds below. The C—H bond involves the smallest atom (H) and therefore appears at the highest wavenumber.

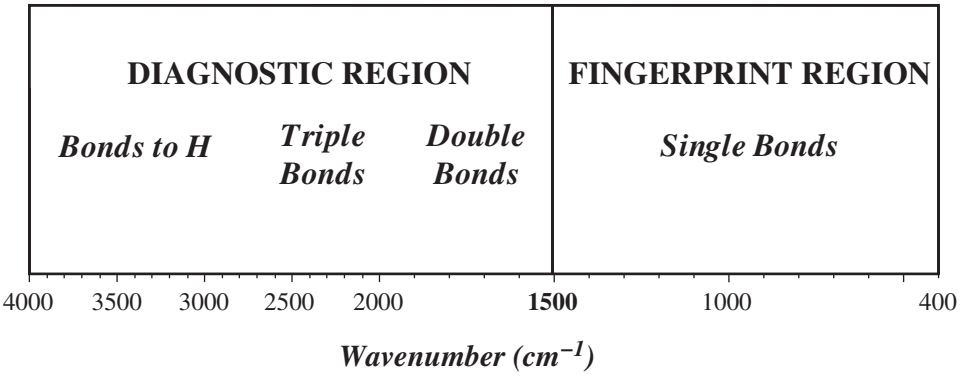
C—H	C—D	C—O	C—Cl
~ 3000 cm^{-1}	~ 2200 cm^{-1}	~ 1100 cm^{-1}	~ 700 cm^{-1}

Using the two trends shown above, we see that different types of bonds will appear in different regions of an IR spectrum:



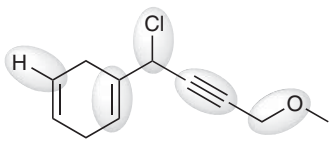
Single bonds appear on the right side of the spectrum, because single bonds are generally the weakest bonds. Double bonds appear at higher wavenumber (1600–1850 cm^{-1}) because they are stronger than single bonds, while triple bonds appear at even higher wavenumber (2100–2300 cm^{-1}) because they are even stronger than double bonds. And finally, the left side of the spectrum contains signals produced by C—H, N—H, or O—H bonds, all of which stretch at a high wavenumber because hydrogen has the smallest mass.

IR spectra can be divided into two main regions, called the diagnostic region and the fingerprint region:

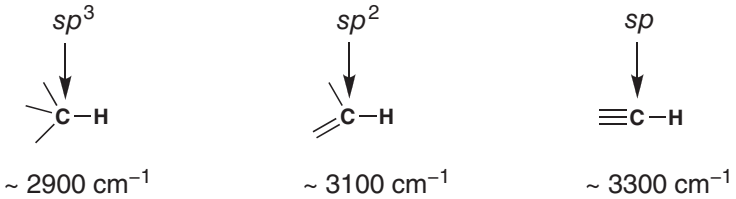


The diagnostic region generally has fewer peaks and provides the most useful information. This region contains all signals that arise from the stretching of double bonds, triple bonds, and bonds to H (C—H, N—H, or O—H). The fingerprint region contains mostly bending vibrations, as well as stretching vibrations of most single bonds. This region generally contains many signals, and is more difficult to analyze. What appears like a C—C stretch might in fact be another bond that is bending. This region is called the fingerprint region because each compound has a unique pattern of signals in this region, much the way each person has a unique fingerprint. For example, IR spectra of ethanol and propanol will look extremely similar in their diagnostic regions, but their fingerprint regions will look different. For the remainder of this chapter, we will focus exclusively on the signals that appear in the diagnostic region, and we will ignore signals in the fingerprint region. You should check your lecture notes and textbook to see if you are responsible for any characteristic signals that appear in the fingerprint region.

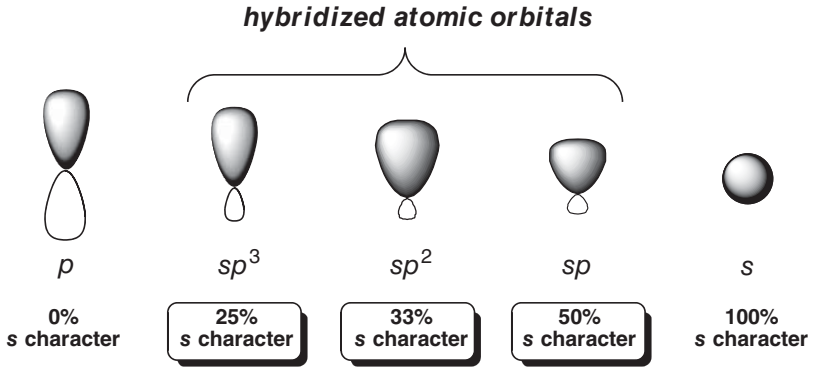
PROBLEM 2.1 For the following compound, rank the highlighted bonds in order of decreasing wavenumber.



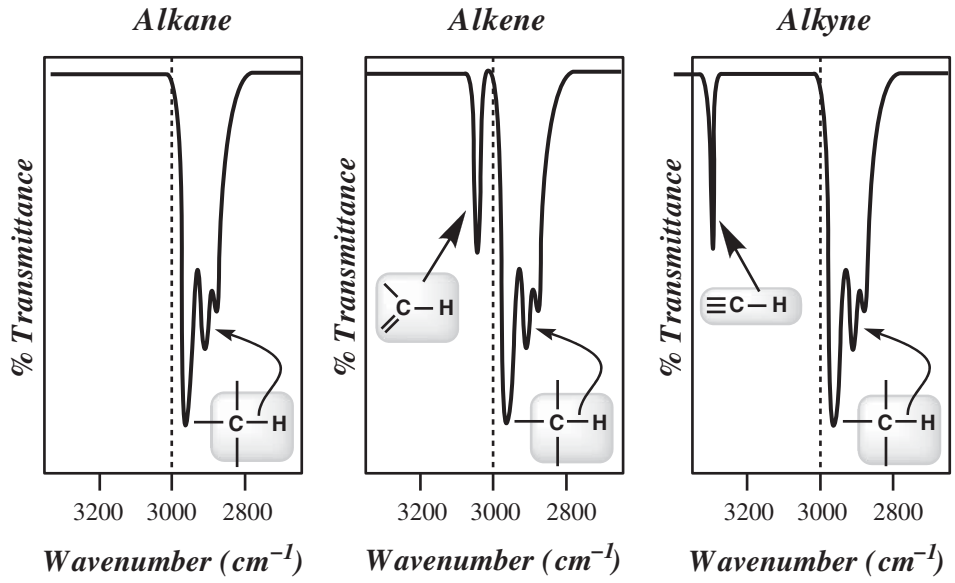
Now let's continue exploring factors that affect the strength of a bond (which therefore affects the wavenumber of absorption). We have seen that bonds to hydrogen (such as C—H bonds) appear on the left side of an IR spectrum (high wavenumber). We will now compare various kinds of C—H bonds. The wavenumber of absorption for a C—H bond is very much dependent on the hybridization state of the carbon atom. Compare the following three C—H bonds:



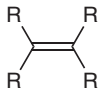
Of the three bonds shown, the C_{sp}—H bond produces the highest energy signal (~3300 cm^{-1}), while a C_{sp^3}—H bond produces the lowest energy signal (~2900 cm^{-1}). To understand this trend, we must revisit the shapes of the hybridized atomic orbitals:



As illustrated, *sp* orbitals have more *s* character than the other hybridized atomic orbitals, and therefore, *sp* orbitals more closely resemble *s* orbitals. Compare the shapes of the hybridized atomic orbitals, and note that the electron density of an *sp* orbital is closest to the nucleus (much like an *s* orbital). As a result, a C_{sp}—H bond will be shorter than other C—H bonds. Since it has the shortest bond length, it will therefore be the strongest bond. In contrast, the C_{sp^3}—H bond has the longest bond length, and is therefore the weakest bond. Compare the spectra of an alkane, an alkene, and an alkyne:

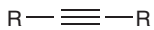


In each case, we draw a line at 3000 cm^{-1}. All three spectra have signals to the right of the line, resulting from C_{sp^3}—H bonds. The key is to look for any signals to the left of the line. An alkane does not produce a signal to the left of 3000 cm^{-1}. An alkene may produce a signal at 3100 cm^{-1}, and an alkyne may produce a signal at 3300 cm^{-1}. But be careful—the absence of a signal to the left of 3000 cm^{-1} does *not* necessarily indicate the absence of a double bond or triple bond in the compound. Tetrasubstituted double bonds do not possess any C_{sp^2}—H bonds, and internal triple bonds also do not possess any C_{sp}—H bonds.



no signal at 3100 cm^{-1}

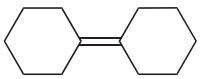
$\left(\textbf{no } C_{sp^2}-H\right)$

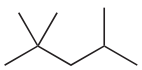


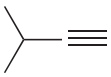
no signal at 3300 cm^{-1}

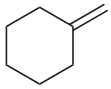
$\left(\textbf{no } C_{sp}-H\right)$

PROBLEMS For each of the following compounds, determine whether or not you would expect its IR spectrum to exhibit a signal to the left of 3000 cm^{-1}

2.2 

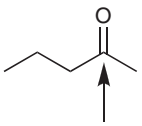
2.3 

2.4 

2.5 

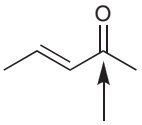
Now let's explore the effects of resonance on bond strength. As an illustration, compare the carbonyl groups (C═O bonds) in the following two compounds:

A ketone



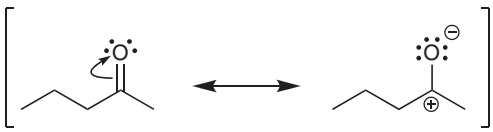
1720 cm^{-1}

A conjugated unsaturated ketone



1680 cm^{-1}

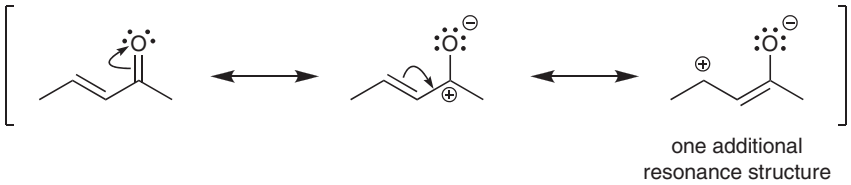
The second compound is called a conjugated, unsaturated ketone. It is *unsaturated* because of the presence of a C═C bond, and it is conjugated because the π bonds are separated from each other by exactly one sigma bond. Your textbook will explore conjugated π systems in more detail. For now, we will just analyze the effect of conjugation on the IR absorption of the carbonyl group. As shown, the carbonyl group of an unsaturated, conjugated ketone produces a signal at lower wavenumber (1680 cm^{-1}) than the carbonyl group of a saturated ketone (1720 cm^{-1}). In order to understand why, we must draw resonance structures for each compound. Let's begin with the ketone.



Ketones have two resonance structures. The carbonyl group is drawn as a double bond in the first resonance structure, and it is drawn as a single bond in the second resonance structure. This means that the carbonyl group has some double-bond character and some single-bond

character. In order to determine the nature of this bond, we must consider the contribution from each resonance structure. In other words, does the carbonyl group have more double-bond character or more single-bond character? The second resonance structure exhibits charge separation, as well as a carbon atom (C^+) that has less than an octet of electrons. Both of these reasons explain why the second resonance structure contributes only slightly to the overall character of the carbonyl group. Therefore, the carbonyl group of a ketone has mostly double-bond character.

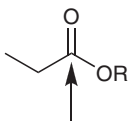
Now consider the resonance structures for a conjugated, unsaturated ketone.



Conjugated, unsaturated ketones have three resonance structures rather than two. In the third resonance structure, the carbonyl group is drawn as a single bond. Once again, this resonance structure exhibits charge separation as well as a carbon atom (C^+) with less than an octet of electrons. As a result, this resonance structure also contributes only slightly to the overall character of the compound. Nevertheless, this third resonance structure does contribute some character, giving this carbonyl group slightly more single-bond character than the carbonyl group of a saturated ketone. With more single-bond character, it is a slightly weaker bond, and therefore produces a signal at a lower wavenumber (1680 cm^{-1} rather than 1720 cm^{-1}).

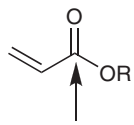
Esters exhibit a similar trend. An ester typically produces a signal at around 1740 cm^{-1}, but conjugated, unsaturated esters produce signals at a lower wavenumber, usually around 1710 cm^{-1}. Once again, the carbonyl group of a conjugated, unsaturated ester is a weaker bond, due to resonance.

An ester



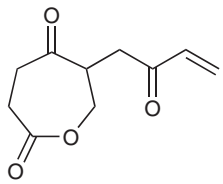
1740 cm^{-1}

A conjugated, unsaturated ester



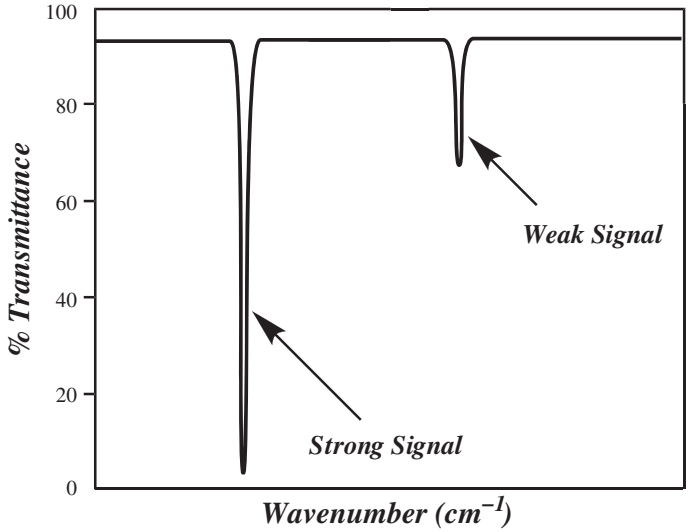
1710 cm^{-1}

PROBLEM 2.6 The following compound has three carbonyl groups. Rank them in order of decreasing wavenumber in an IR spectrum:



2.4 SIGNAL INTENSITY

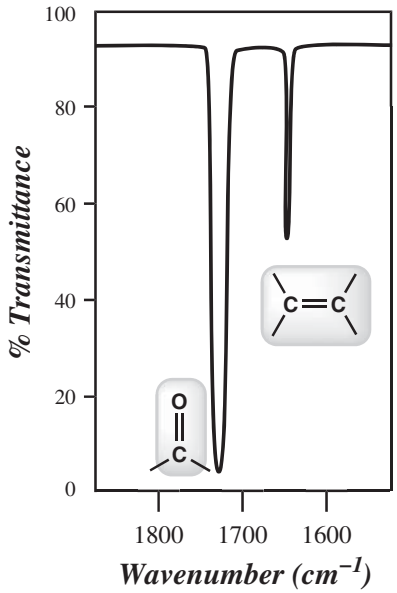
In an IR spectrum, some signals will be very strong in comparison with other signals on the same spectrum:



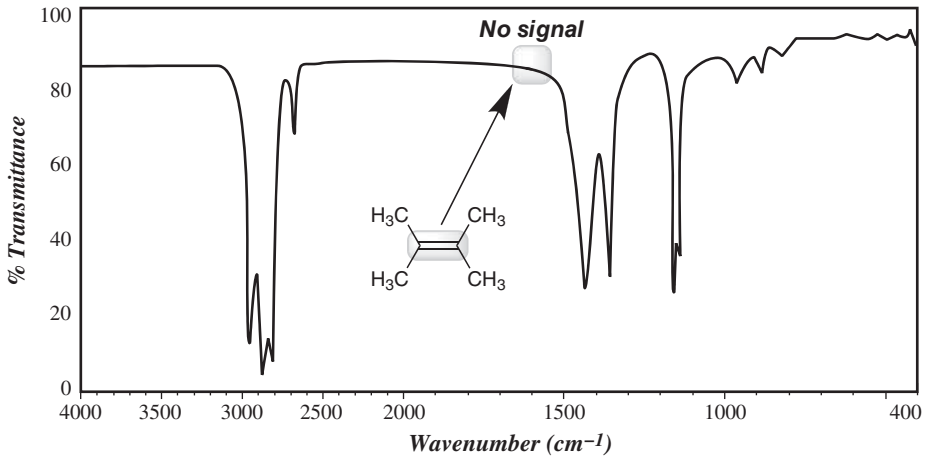
That is, some bonds absorb IR radiation very efficiently, while other bonds are less efficient at absorbing IR radiation. The efficiency of a bond at absorbing IR radiation depends on the magnitude of the dipole moment for that bond. For example, compare the following two highlighted bonds:

Each of these bonds has a measurable dipole moment, but they differ significantly in size. Let's first analyze the carbonyl group (C═O bond). Due to resonance and induction, the carbon atom bears a large partial positive charge, and the oxygen atom bears a large partial negative charge. The carbonyl group therefore has a large dipole moment. Now let's analyze the C═C bond. One vinylic position is connected to electron-donating alkyl groups, while the other vinylic position is connected to hydrogen atoms. As a result, the vinylic position bearing two alkyl groups is slightly more electron-rich than the other vinylic position, producing a small dipole moment.

Since the carbonyl group has a larger dipole moment, the carbonyl group is more efficient at absorbing IR radiation, producing a stronger signal:



Carbonyl groups often produce the strongest signals in an IR spectrum, while C═C bonds often produce fairly weak signals. In fact, some alkenes do not even produce any signal at all. For example, consider the IR spectrum of 2,3-dimethyl-2-butene:

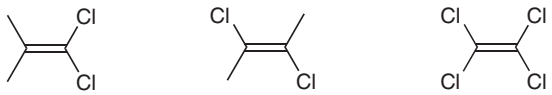


This alkene is symmetrical. That is, both vinylic positions are electronically identical, and the bond has no dipole moment at all. As such, this C═C bond is completely inefficient at absorbing IR radiation, and no signal is observed. The same is true for symmetrical C≡C bonds.

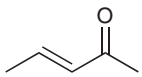
There is one other factor that can contribute significantly to the intensity of signals in an IR spectrum. Consider the group of signals appearing just below 3000 cm^{-1} in the previous spectrum. These signals are associated with the stretching of the C—H bonds in the compound. The intensity of these signals derives from the number of C—H bonds giving rise to the signals. In fact, the signals just below 3000 cm^{-1} are typically among the strongest signals in an IR spectrum.

PROBLEMS

2.7 Predict which of the following C═C bonds will produce the strongest signal in an IR spectrum:

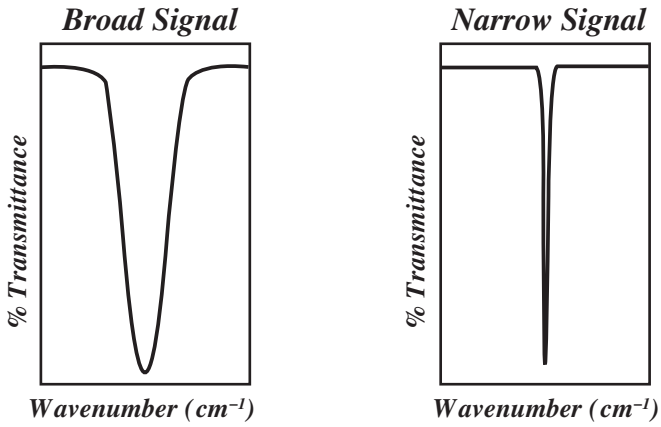


2.8 The C═C bond in the following compound produces an unusually strong signal. Explain using resonance structures:

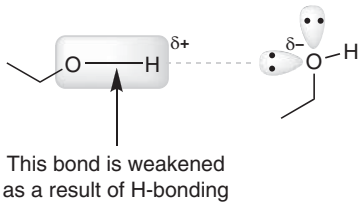


2.5 SIGNAL SHAPE

In this section, we will explore some of the factors that affect the shape of a signal. Some signals in an IR spectrum might be very broad while other signals can be very narrow:

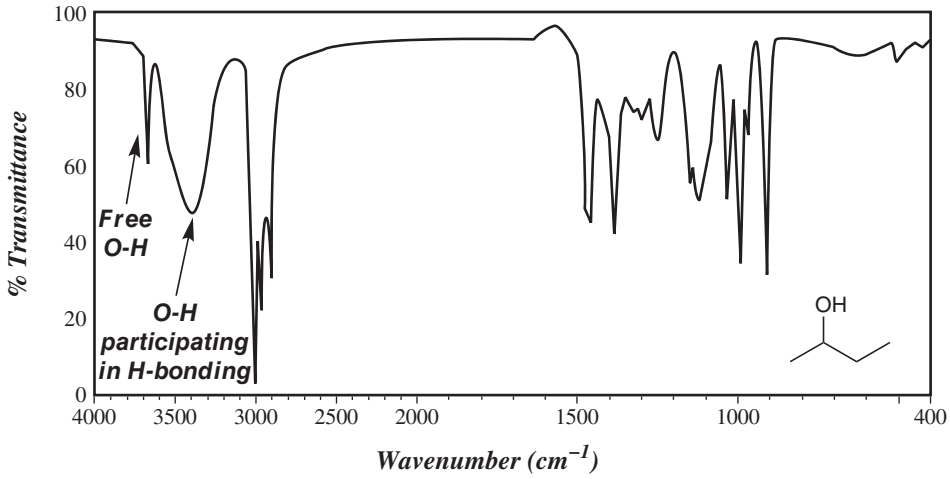


Concentrated alcohols commonly exhibit broad O—H signals, as a result of hydrogen bonding, which weakens the O—H bonds.



At any given moment in time, the O—H bond in each molecule is weakened to a different extent. As a result, all of the O—H bonds do not have a uniform bond strength, but rather, there is a *distribution* of bond strength. That is, some molecules are barely participating in H-bonding, while others are participating in H-bonding to varying degrees. The result is a broad signal.

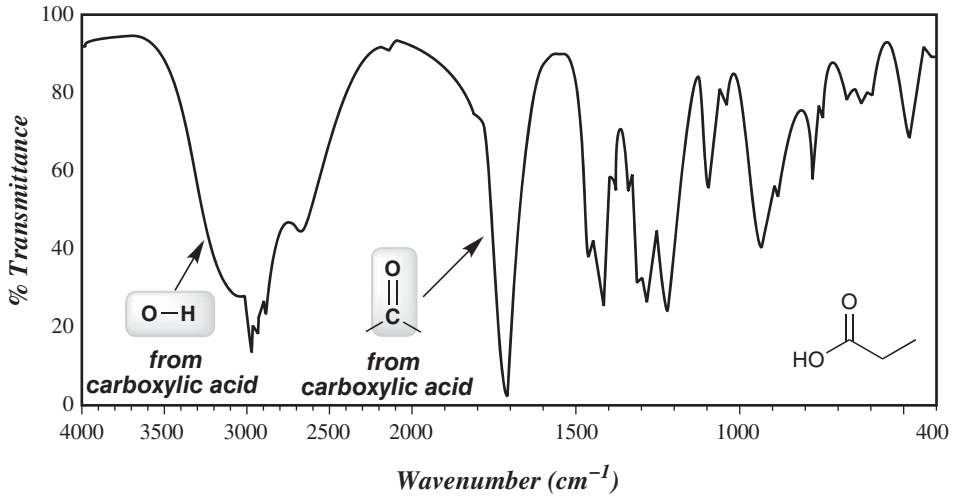
The shape of an O—H signal is different when the alcohol is diluted in a solvent that cannot form hydrogen bonds with the alcohol. In such an environment, it is likely that the O—H bonds will not participate in an H-bonding interaction. The result is a narrow O—H signal. When the solution is neither very concentrated nor very dilute, two signals may be observed. The molecules that are not participating in H-bonding will give rise to a narrow signal, while the molecules participating in H-bonding will give rise to a broad signal. As an example, consider the following spectrum of 2-butanol, in which both signals can be observed:



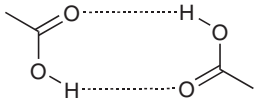
When O—H bonds do not participate in H-bonding, they generally produce a narrow signal at approximately 3600 cm^{-1}. That signal can be seen in the spectrum above. When O—H bonds participate in H bonding, they generally produce a broad signal between 3200 cm^{-1}

and 3600 cm^{-1}. That signal can also be seen in the spectrum. Depending on the conditions, an alcohol will either give a broad signal, or a narrow signal, or both. In most cases that we will encounter, O—H bonds will appear as broad signals.

Carboxylic acids exhibit similar behavior; only more pronounced. For example, consider the following spectrum of a carboxylic acid:



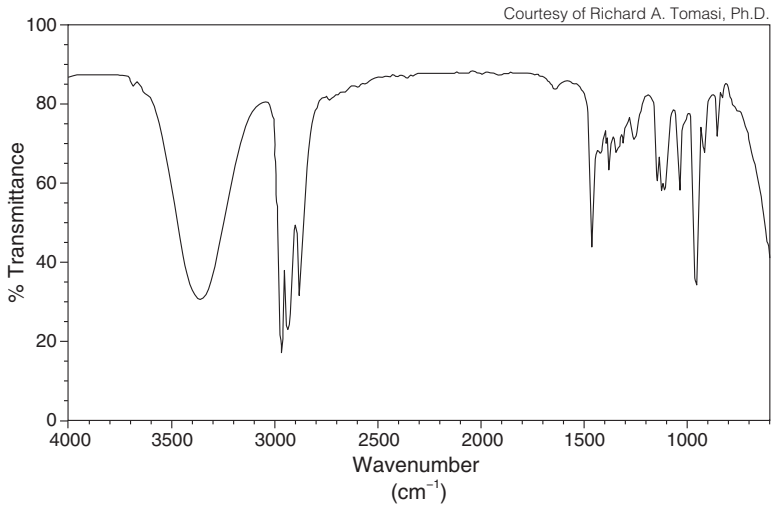
Notice the very broad signal on the left side of the spectrum, extending from 2200 cm^{-1} to 3600 cm^{-1}. This signal is so broad that it extends over the usual C—H signals that appear around 2900 cm^{-1}. This very broad signal, characteristic of carboxylic acids, is a result of H-bonding. The effect is more pronounced than alcohols, because molecules of the carboxylic acid can form two hydrogen-bonding interactions, resulting in a dimer.



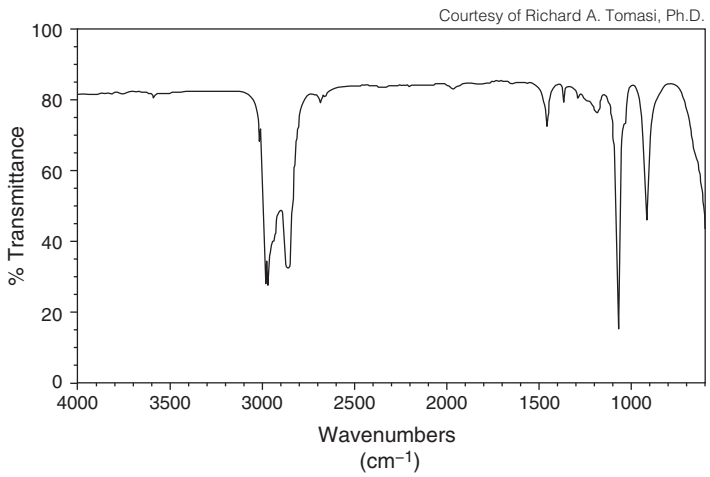
The IR spectrum of a carboxylic acid is easy to recognize, because of the characteristic broad signal that covers nearly one third of the spectrum. This broad signal is also accompanied by a strong C═O signal just above 1700 cm^{-1}.

PROBLEMS For each IR spectrum below, identify whether it is consistent with the structure of an alcohol, a carboxylic acid, or neither.

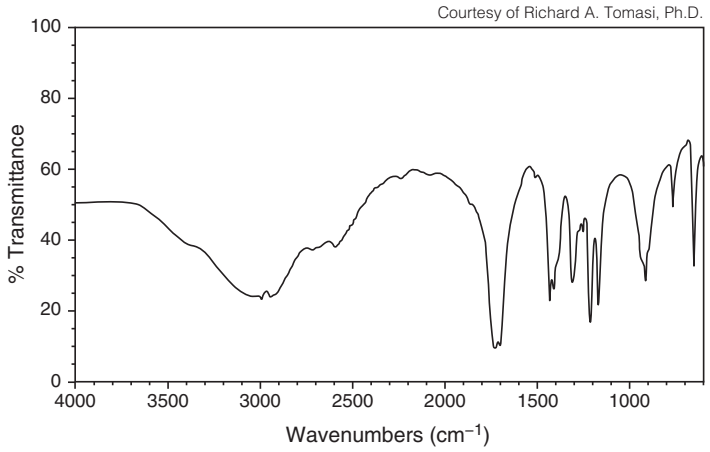
2.9



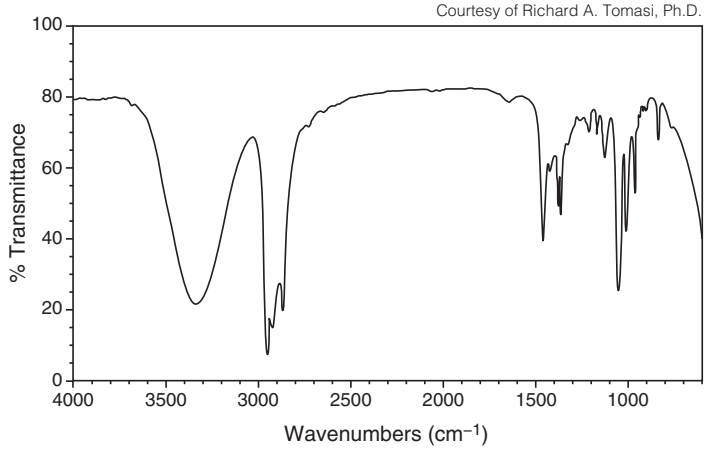
2.10


Courtesy of Richard A. Tomasi, Ph.D.
% Transmittance
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
Wavenumbers
(cm−1)

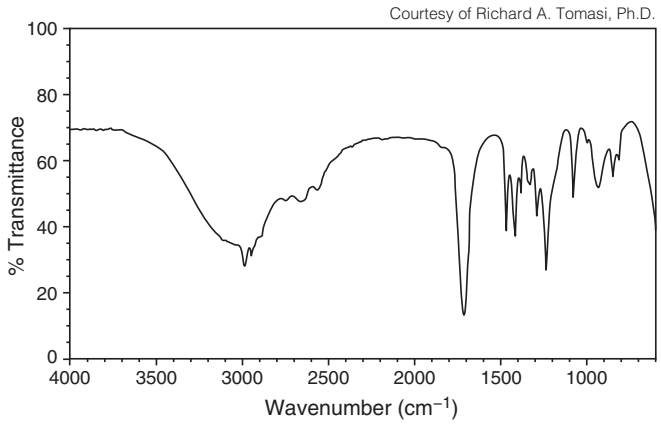
2.11


Courtesy of Richard A. Tomasi, Ph.D.
% Transmittance
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm−1)

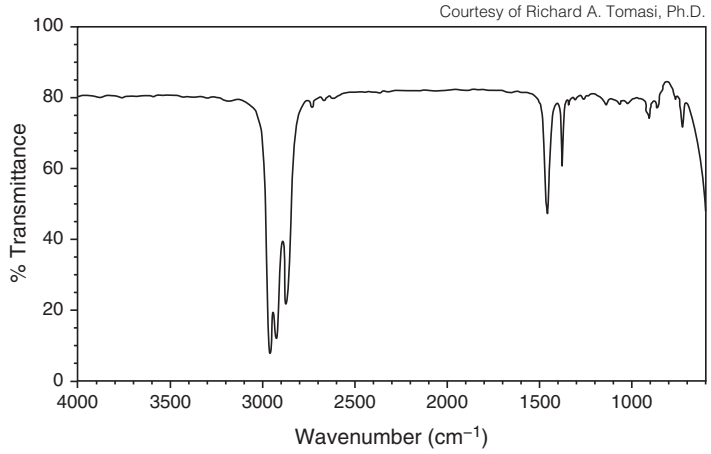
2.12


Courtesy of Richard A. Tomasi, Ph.D.
% Transmittance
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm−1)

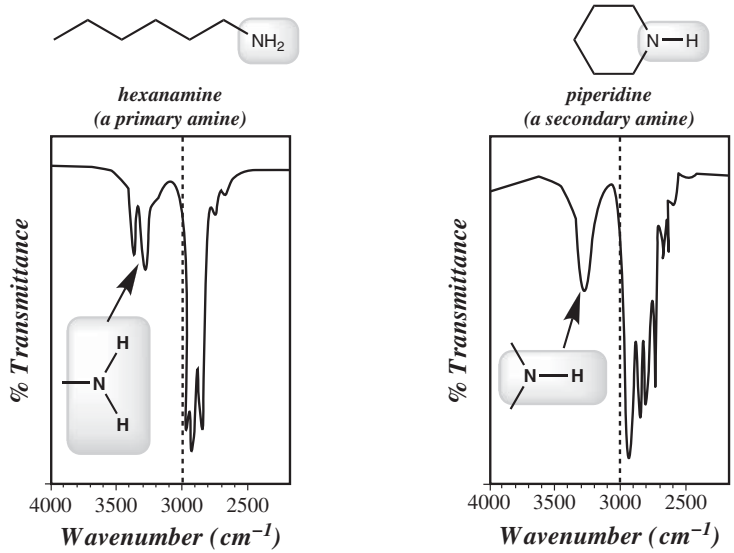
2.13



2.14

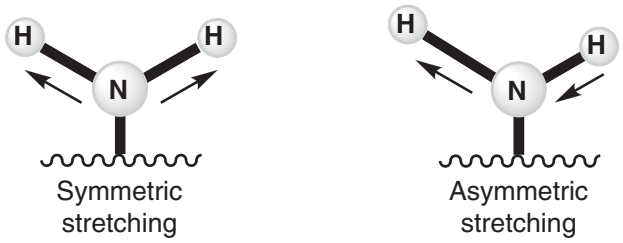


There is another important factor, in addition to H-bonding, that affects the shape of a signal. Consider the difference in shape of the N—H signals for primary and secondary amines:



The primary amine exhibits two signals: one at 3350 cm^{-1} and the other at 3450 cm^{-1}. In contrast, the secondary amine exhibits only one signal. It might be tempting to explain this by arguing that each N—H bond gives rise to a signal, and therefore a primary amine gives

two signals because it has two N—H bonds. Unfortunately, that simple explanation is not accurate. In fact, both N—H bonds of a single molecule will together produce only one signal. The reason for the appearance of two signals is more accurately explained by considering the two possible ways in which the entire NH_2 group can vibrate. The N—H bonds can be stretching in phase with each other, called *symmetric stretching*, or they can be stretching out of phase with each other, called *asymmetric stretching:*

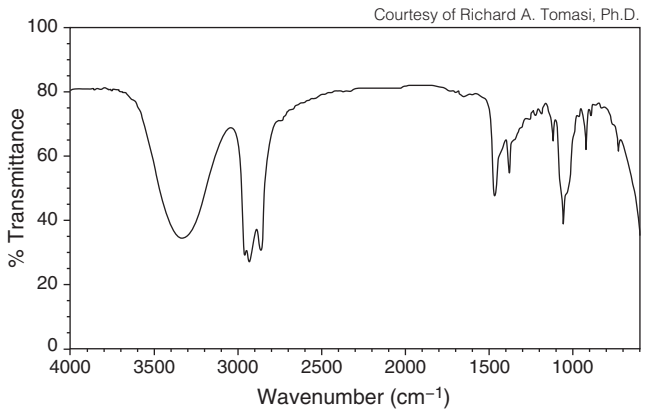


At any given moment in time, approximately half of the molecules will be vibrating symmetrically, while the other half will be vibrating asymmetrically. The molecules vibrating symmetrically will absorb a particular frequency of IR radiation to promote a vibrational excitation, while the molecules vibrating asymmetrically will absorb a different frequency. In other words, the NH_2 functional group is capable of absorbing two different frequencies. One of the signals is produced by half of the molecules, and the other signal is produced by the other half of the molecules.

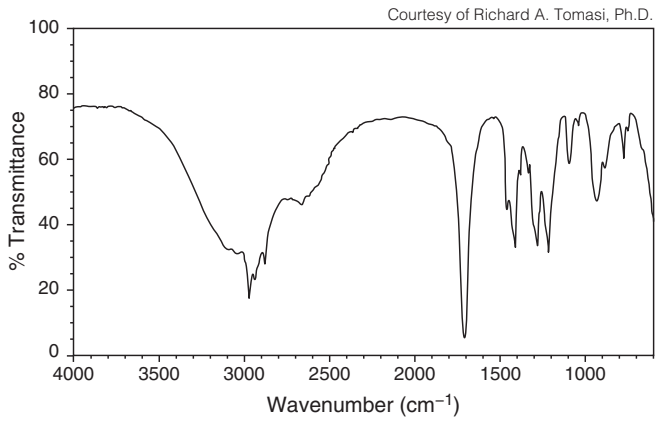
For a similar reason, the C—H bonds of a CH_3 group (appearing just below 3000 cm^{-1} in an IR spectrum) generally give rise to a series of signals, rather than just one signal. These signals arise from the various ways in which a CH_3 group can be excited both symmetrically and asymmetrically.

PROBLEMS For each IR spectrum below, determine whether it is consistent with the structure of a ketone, an alcohol, a carboxylic acid, a primary amine, or a secondary amine.

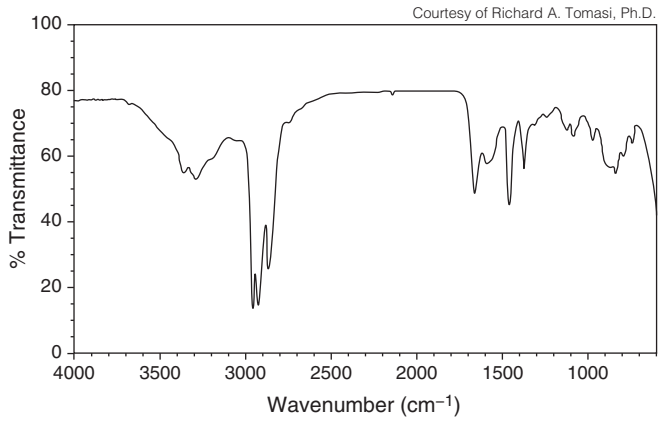
2.15



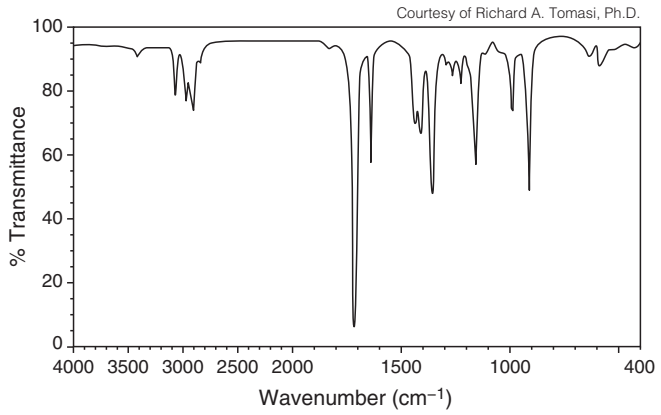
2.16



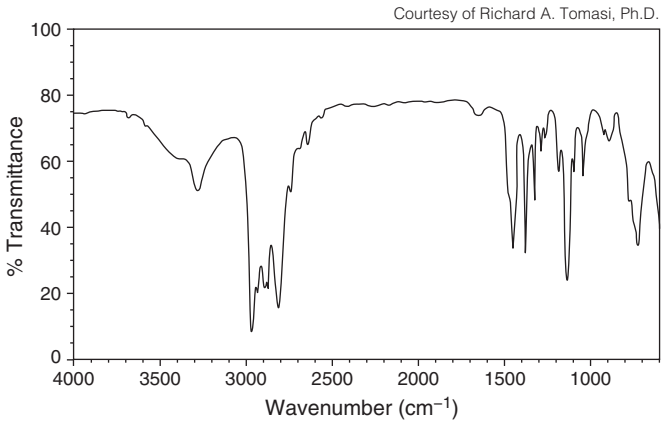
2.17


Courtesy of Richard A. Tomasi, Ph.D.
% Transmittance
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
Wavenumber (cm−1)

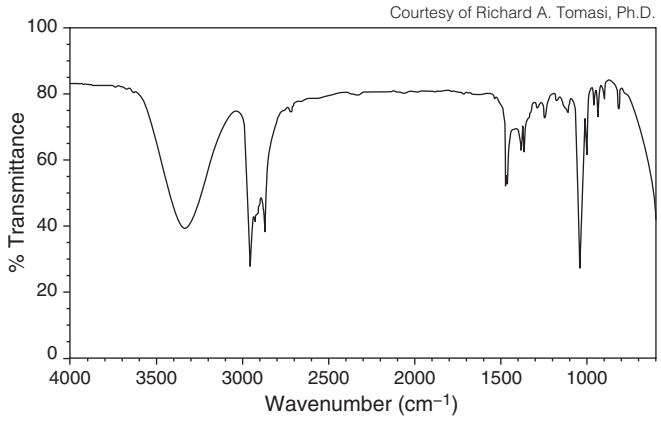
2.18


Courtesy of Richard A. Tomasi, Ph.D.
% Transmittance
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
400
Wavenumber (cm−1)

2.19


Courtesy of Richard A. Tomasi, Ph.D.
% Transmittance
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
Wavenumber (cm−1)

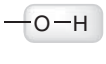
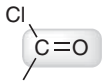
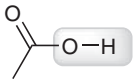
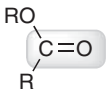
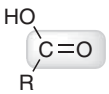
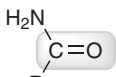
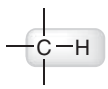
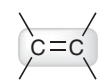
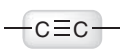
2.20



2.6 ANALYZING AN IR SPECTRUM

The following table is a summary of useful signals in the diagnostic region of an IR spectrum:

Useful Signals in the Diagnostic Region

Structural Unit	Wavenumber (cm^{-1})	Structural Unit	Wavenumber (cm^{-1})
Single Bonds (X-H)		*Double Bonds*	
	3200 - 3600		1750 - 1850
	2200 - 3600		1700 - 1750
	3350 - 3500		1700 - 1750
	~ 3300		1680 - 1750
	3000 - 3100		1650 - 1700
	2850 - 3000		1600 - 1700
	2750, 2850 (two signals)		1450 - 1600 1650 - 2000
Triple Bonds			
	2100 - 2200		
	2200 - 2300		

When analyzing an IR spectrum, the first step is to draw a line at 1500 cm^{-1}. Focus on any signals to the left of this line (the diagnostic region). In doing so, it will be extremely helpful if you can identify the following regions:

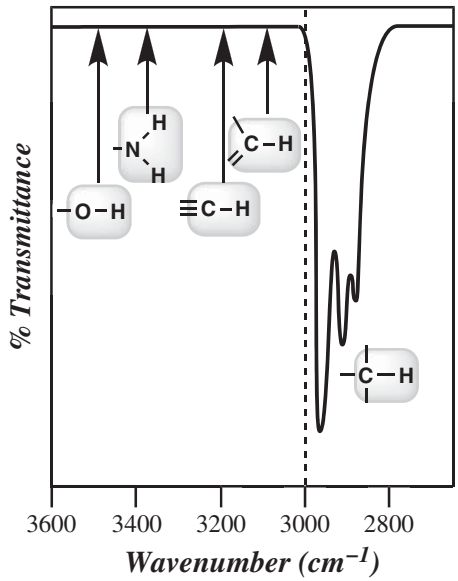
Double bonds: 1600–1850 cm^{-1}

Triple bonds: 2100–2300 cm^{-1}

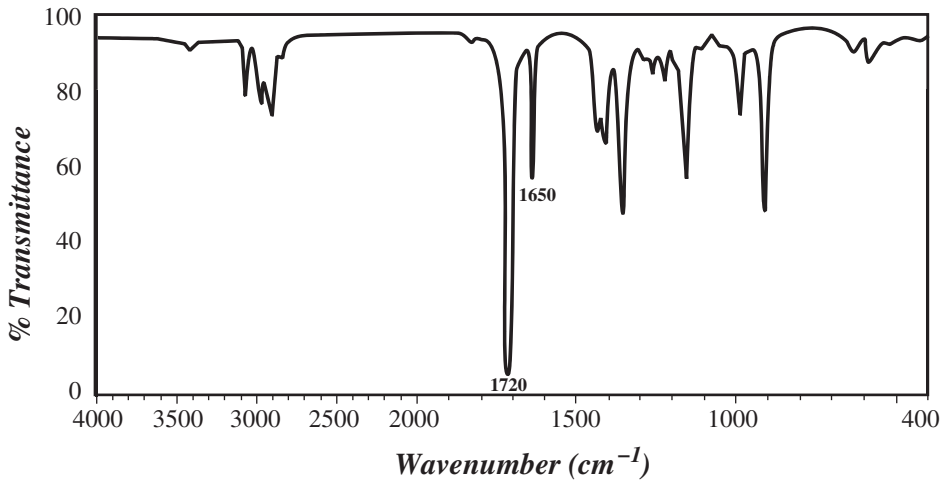
C—H, N—H, or O—H bonds: 2700–4000 cm^{-1}

Remember that each signal appearing in the diagnostic region will have three characteristics (wavenumber, intensity, and shape). Make sure to analyze all three characteristics.

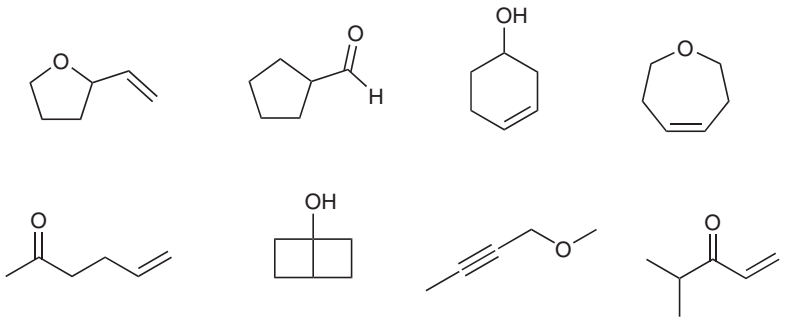
When looking for bonds to H (C—H bonds, N—H bonds, or O—H bonds), draw a line at 3000 cm^{-1} and look for signals that appear to the left of the line:



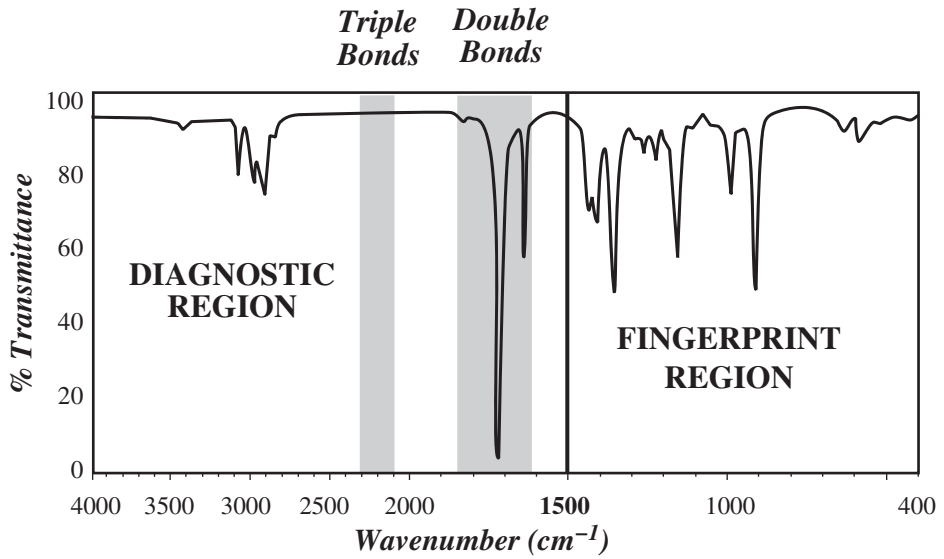
EXERCISE 2.21 A compound with the molecular formula $C_6H_{10}O$ gives the following IR spectrum:



Identify the structure below that is most consistent with the spectrum:

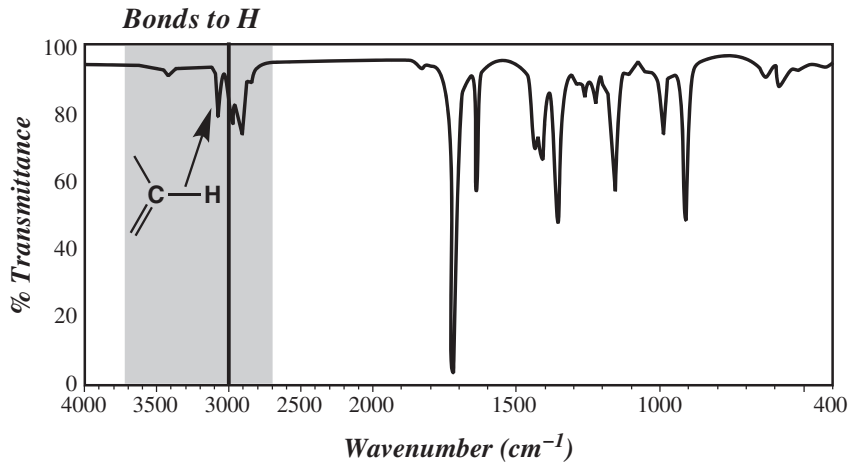


Solution Draw a line at 1500 cm^{-1}, and focus on the diagnostic region (to the left of the line). Start by looking at the double-bond region and the triple-bond region:



There are no signals in the triple-bond region, but there are two signals in the double-bond region. The signal at 1650 cm^{-1} is narrow and weak, consistent with a C═C bond. The signal at 1720 cm^{-1} is strong, consistent with a C═O bond.

Next, look for C—H bonds, N—H bonds, or O—H bonds that produce signals above 3000 cm^{-1}. Draw a line at 3000 cm^{-1}, and identify if there are any signals to the left of this line.

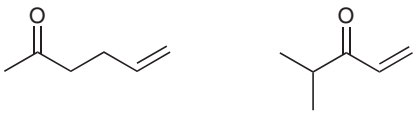


This spectrum exhibits one signal just above 3000 cm^{-1}, indicating a vinylic C—H bond.

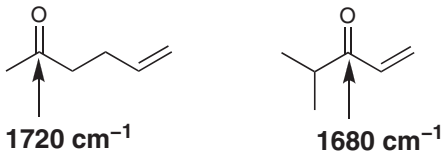
The identification of a vinylic C—H bond is consistent with the observed C═C signal present in the double-bond region (1650 cm^{-1}). There are no other signals above 3000 cm^{-1}, so the compound does not possess any OH or NH bonds.

The little bump between 3400 and 3500 cm^{-1} is not strong enough to be considered a signal. These bumps are often observed in the spectra of compounds containing a C═O bond. The bump occurs at exactly twice the wavenumber of the C═O signal, and is called an overtone of the C═O signal.

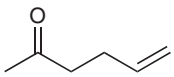
The diagnostic region provides the information necessary to solve this problem. Specifically, the compound must have the following bonds: C═C, C═O, and vinylic C—H. Among the possible choices, there are only two compounds that have these features:



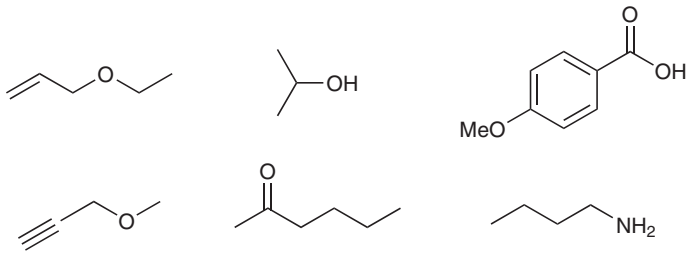
To distinguish between these two possibilities, notice that the second compound is conjugated, while the first compound is *not* conjugated (the π bonds are separated by more than one sigma bond). Recall that ketones produce signals at approximately 1720 cm^{-1}, while conjugated ketones produce signals at approximately 1680 cm^{-1}.



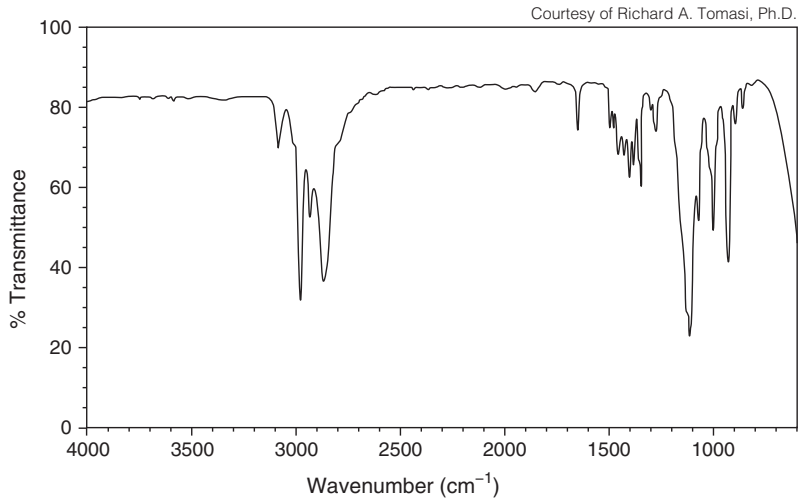
In the spectrum provided, the C═O signal appears at 1720 cm^{-1}, indicating that it is not conjugated. The spectrum is therefore consistent with the following compound:



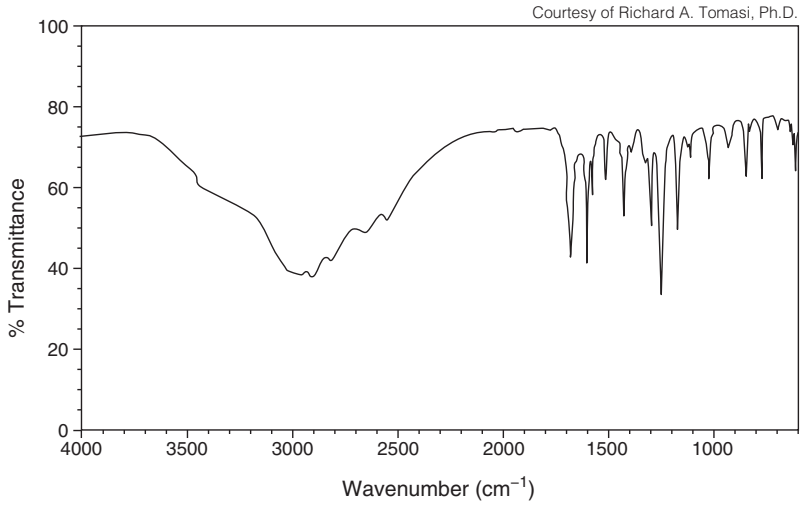
PROBLEM 2.22 Match each compound with the appropriate spectrum, and identify the signals that justify your choice.



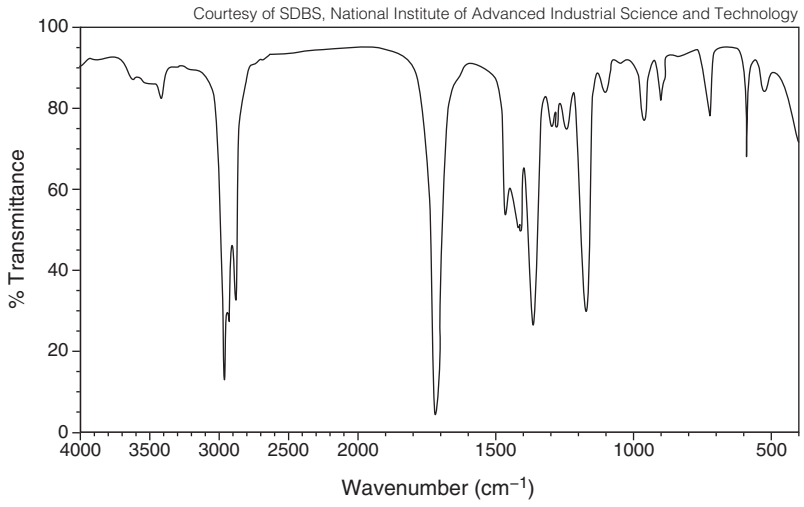
Spectrum A



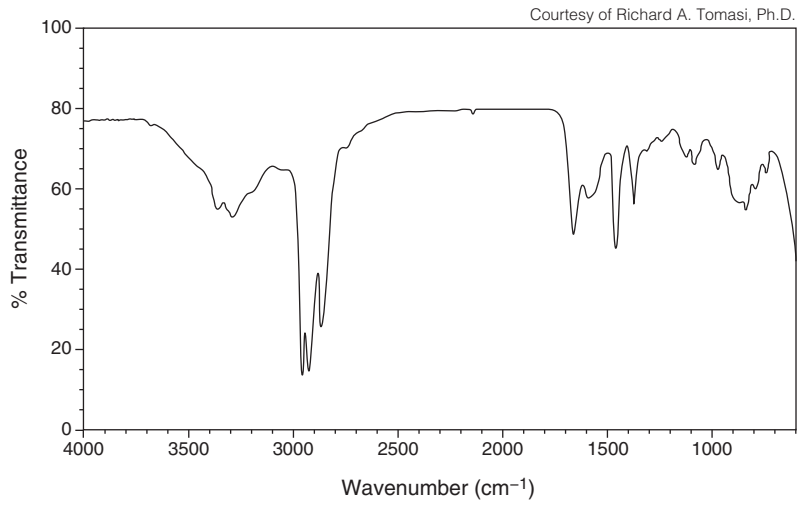
Spectrum B



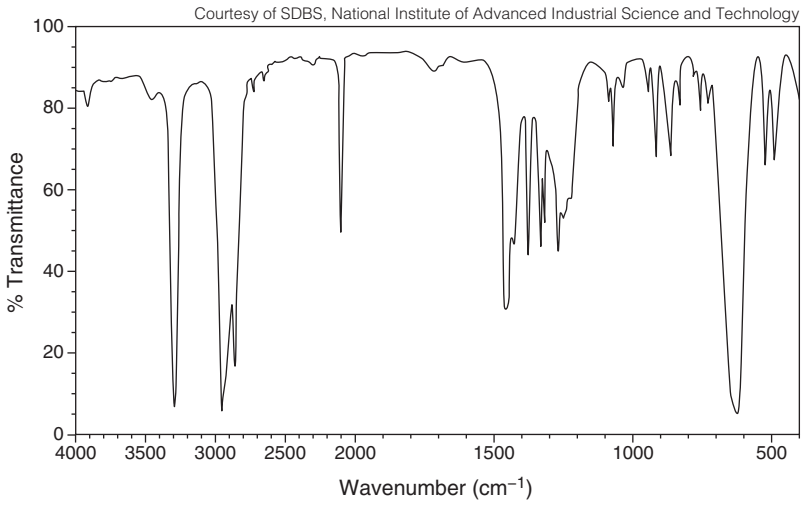
Spectrum C



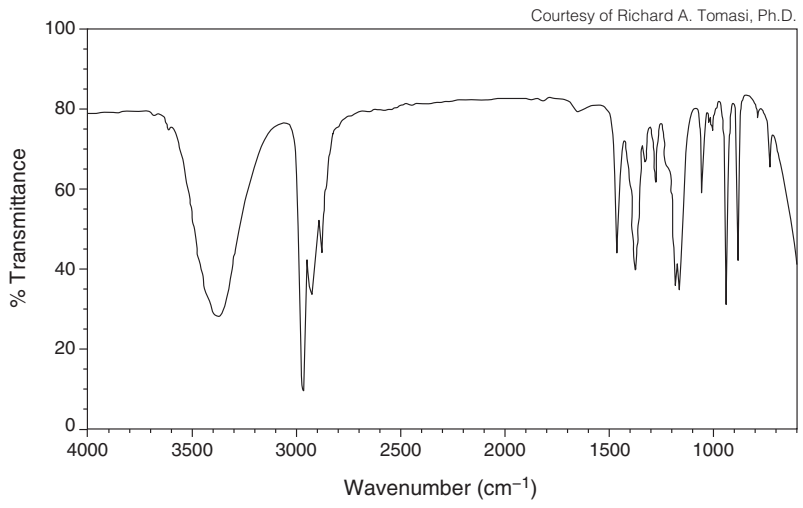
Spectrum D



Spectrum E



Spectrum F



CHAPTER 3

NMR SPECTROSCOPY

Nuclear magnetic resonance (NMR) spectroscopy is the most useful technique for structure determination that you will encounter in your textbook. Analysis of an NMR spectrum provides information about how the individual carbon and hydrogen atoms are connected to each other in a molecule. This information enables us to determine the carbon–hydrogen framework of a compound, much the way puzzle pieces can be assembled to form a picture.

Your textbook will provide an explanation of the theoretical underpinnings of NMR spectroscopy (how it works). Here is a brief summary:

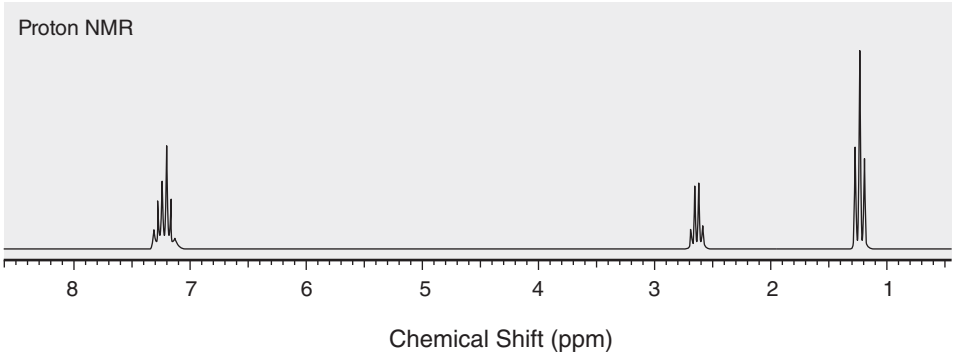
The nucleus of a hydrogen atom (which is just a proton) possesses a property called *nuclear spin*. A true understanding of this property is beyond the scope of our course, so we will think of it as a rotating sphere of charge, which generates a magnetic field, called a *magnetic moment*. When the nucleus of a hydrogen atom is subjected to an external magnetic field, the magnetic moment can align either with the field (called the α spin state) or against the field (called the β spin state). There is a difference in energy (ΔE) between these two spin states. If a proton occupying the α spin state is subjected to electromagnetic radiation, an absorption can take place IF the energy of the photon is equivalent to the energy gap between the spin states. The absorption causes the nucleus to *flip* to the β spin state, and the nucleus is said to be in *resonance*; thus the term *nuclear magnetic resonance*. NMR spectrometers employ strong magnetic fields, and the frequency of radiation typically required for nuclear resonance falls in the radio wave region of the electromagnetic spectrum (called rf radiation).

At a particular magnetic field strength, we might expect all nuclei to absorb the same frequency of rf radiation. Luckily, this is not the case, as nuclei are surrounded by electrons. In the presence of an external magnetic field, the electron density circulates, establishing a small, local magnetic field that *shields* the proton. Not all protons occupy identical electronic environments. Some protons are surrounded by more electron density and are more shielded, while other protons are surrounded by less electron density and are less shielded, or *deshielded*. As a result, protons in different electronic environments will absorb different frequencies of rf radiation. This allows us to probe the electronic environment of the hydrogen atoms in a compound.

3.1 CHEMICAL EQUIVALENCE

The spectrum produced by ^{1}H NMR spectroscopy (pronounced "proton" NMR spectroscopy) is called a proton NMR spectrum. Here is an example:

Courtesy of Richard A. Tomasi, Ph.D.



The first valuable piece of information is the number of signals (the spectrum above has three different signals). In addition, each signal has the following important characteristics:

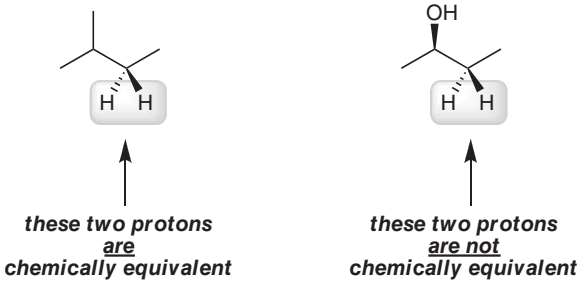
1. The *location* of each signal indicates the electronic environment of the protons giving rise to the signal.
2. The *area* under each signal indicates the number of protons giving rise to the signal.
3. The *shape* of the signal indicates the number of neighboring protons.

We will discuss these characteristics in the upcoming sections. First let's explore the information that is revealed by counting the number of signals in a spectrum.

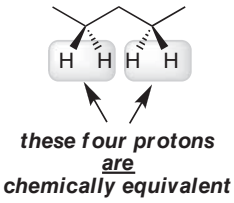
The number of signals in a proton NMR spectrum indicates the number of different kinds of protons (protons in different electronic environments). Protons that occupy identical electronic environments are called *chemically equivalent*, and they will produce only one signal.

Two protons are chemically equivalent if they can be interchanged by a symmetry operation. Your textbook will likely provide a detailed explanation, with examples. For our purposes, the following simple rules can guide you in most cases.

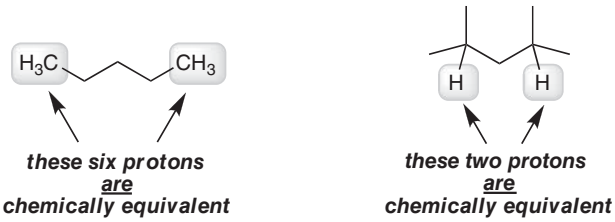
- The two protons of a CH_2 group will generally be chemically equivalent if the compound lacks chiral centers. But if the compound has a chiral center, then the protons of a CH_2 group will generally not be chemically equivalent:



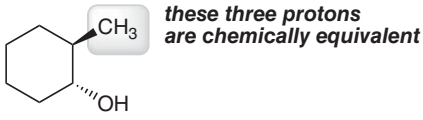
- Two CH_2 groups will be equivalent to each other (giving four equivalent protons) if the CH_2 groups can be interchanged by either rotation or reflection. Example:



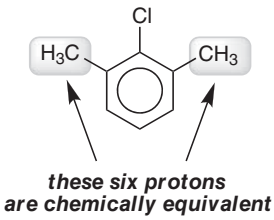
- The previous rule also applies for CH_3 groups or CH groups. Here are examples:



- The three protons of a CH_3 group are always chemically equivalent, even if there are chiral centers in the compound:

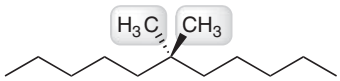


- For aromatic compounds, it will be less confusing if you draw a circle in the ring, rather than drawing alternating π bonds. For example, the following two methyl groups are equivalent, which can be easily seen when drawn in the following way:



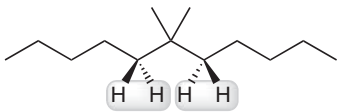
EXERCISE 3.1 Identify the number of signals expected in the ^{1}H NMR spectrum of the following compound:

Answer Let's begin with the two methyl groups at the center of this compound:



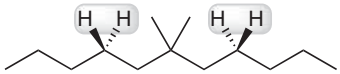
These two methyl groups are equivalent to each other, because they can be interchanged by either rotation or reflection (only one type of symmetry is necessary, but in this case we have both, reflection and rotation, so these six protons are certainly chemically equivalent). We therefore expect one signal for all six protons.

Now let's consider the following methylene (CH_2) groups:



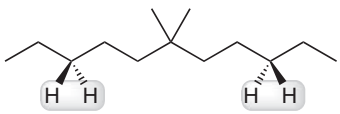
For each of these methylene groups, the two protons are chemically equivalent because there are no chiral centers. In addition, these two methylene groups will be equivalent to each other, since they can be interchanged by rotation or reflection. We therefore expect one signal for all four protons.

The same argument applies for the following two methylene groups:

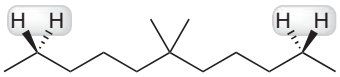


These four protons are chemically equivalent. But they are different from the other methylene groups in the compound, because they cannot be interchanged with any of the other methylene groups via rotation or reflection.

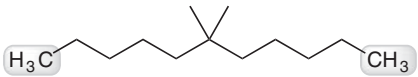
In a similar way, the following four protons are chemically equivalent:



And the following four protons are also chemically equivalent:

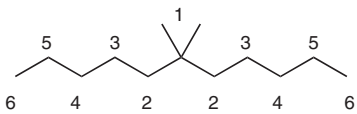


And finally, the following six protons are also chemically equivalent:



Note that these six protons are different from the six protons in the center of the compound, because the first set of six protons cannot be interchanged with the other set of six protons via either rotation or reflection.

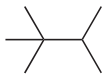
In total, there are six different types of protons:

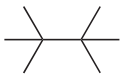


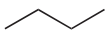
So we would expect the proton NMR spectrum of this compound to have six signals.

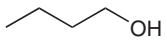
PROBLEMS Identify the number of signals expected in the proton NMR spectrum of each of the following compounds.

3.2 

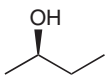
3.3 

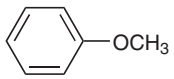
3.4 

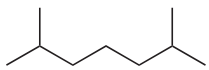
3.5 

3.6 

3.7 

3.8 

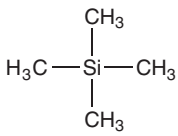
3.9 

3.10 

3.11 If you look at your answers to the previous problems, you should find that one of the structures was expected to produce an NMR spectrum with only one signal. In that structure (Problem 3.4), all six methyl groups were chemically equivalent. Using that example as guidance, propose two possible structures for a compound with the molecular formula C_9H_{18} that exhibits an NMR spectrum with only one signal.

3.2 CHEMICAL SHIFT (BENCHMARK VALUES)

We will now begin exploring the three characteristics of every signal in an NMR spectrum. The first characteristic is the location of the signal, called its *chemical shift* (δ), which is defined relative to the frequency of absorption of a reference compound, tetramethylsilane (TMS):

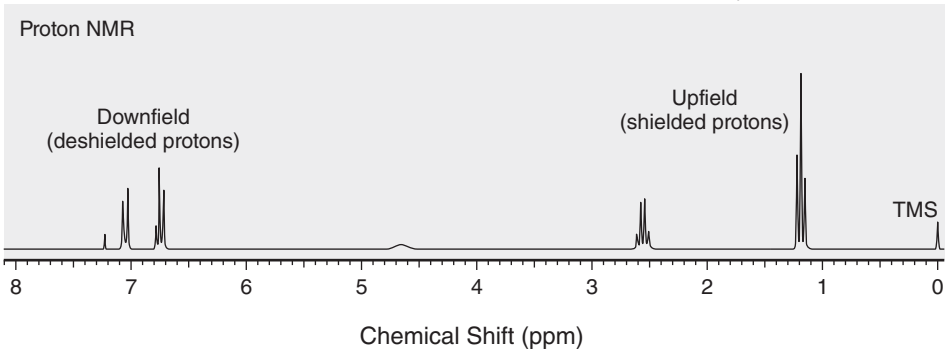


Tetramethylsilane (TMS)

Your textbook will go into greater depth in explaining chemical shift and why it is a unitless number that is reported in parts per million (ppm). For now, we will simply point out that for most organic compounds, the signals produced will fall in a range between 0 and 10 ppm. In rare cases, it is possible to observe a signal occurring at a chemical shift below 0 ppm, which results from a proton that absorbs a lower frequency than the protons in TMS. Most protons in organic compounds absorb a higher frequency than TMS, so all chemical shifts that you encounter in your textbook will be positive numbers.

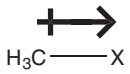
The left side of an NMR spectrum is described as *downfield*, and the right side of the spectrum is described as *upfield*:

Courtesy of Richard A. Tomasi, Ph.D.



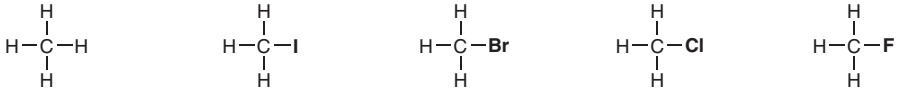
But keep in mind that these terms are used in a relative way. For example, we would say that the signal at 2.5 ppm (in the spectrum above) is downfield from the signal at 1.2 ppm. Similarly, the signal at 6.8 ppm is upfield from the signal at 7.1 ppm.

The protons of alkanes typically produce signals between 1 and 2 ppm. We will now explore some of the effects that can push a signal downfield (relative to the protons of an alkane). Recall that electronegative atoms, such as halogens, withdraw electron density from neighboring atoms:



(X = F, Cl, Br, or I)

This inductive effect causes the neighboring protons to be deshielded (surrounded by less electron density), and as a result, the signal produced by these protons is shifted downfield—that is, the signal appears at a higher chemical shift than the protons of an alkane. The strength of this effect depends on the electronegativity of the halogen. Compare the chemical shifts of the protons in the following compounds:

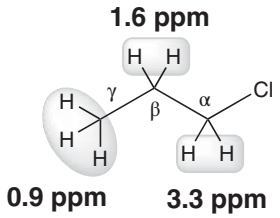


1.0 ppm **2.2 ppm** **2.7 ppm** **3.1 ppm** **4.3 ppm**

Fluorine is the most electronegative element, and therefore produces the strongest effect. When multiple halogens are present, the effect is generally additive, as can be seen when comparing the following compounds:

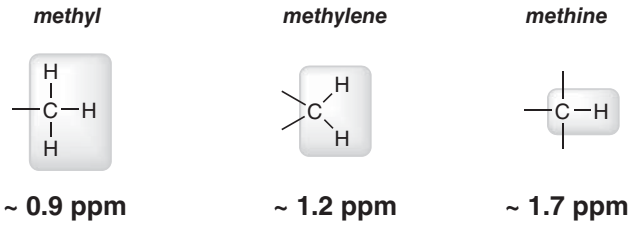
1.0 ppm **3.1 ppm** **5.5 ppm** **7.3 ppm**

Each chlorine atom adds approximately 2 ppm to the chemical shift of the signal. An important aspect of inductive effects is the fact that they taper off drastically with distance, as can be seen by comparing the chemical shifts of the protons in the following compound:

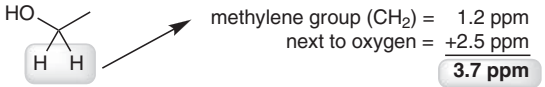
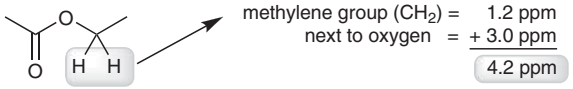
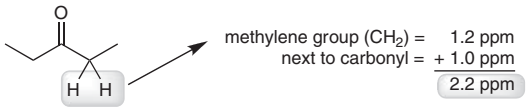


The effect is most significant for the protons at the alpha (α) position. The protons at the beta (β) position are only slightly affected, and the protons at the gamma (γ) position are virtually unaffected by the presence of the chlorine atom.

By committing a few numbers to memory, you should be able to predict the chemical shifts for the protons in a wide variety of compounds, including alcohols, ethers, ketones, esters, and carboxylic acids. The following numbers can be used as benchmark values:



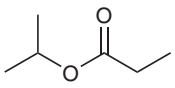
In the absence of inductive effects, a methyl group (CH_3) will generally produce a signal near 0.9 ppm, a methylene group (CH_2) will produce a signal near 1.2 ppm, and a methine group (CH) will produce a signal near 1.7 ppm. These benchmark values are then modified by the presence of neighboring functional groups, in the following way:

Functional group	Effect on α protons	Example
Oxygen of an alcohol or ether	+2.5	 methylene group (CH_2) = 1.2 ppm next to oxygen = +2.5 ppm **3.7 ppm**
Oxygen of an ester	+3	 methylene group (CH_2) = 1.2 ppm next to oxygen = + 3.0 ppm 4.2 ppm
Carbonyl group (C═O) All carbonyl groups, including ketones, aldehydes, esters, etc.	+1	 methylene group (CH_2) = 1.2 ppm next to carbonyl = + 1.0 ppm 2.2 ppm

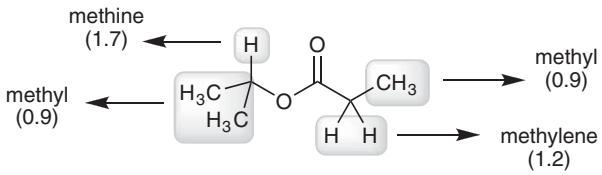
The values above represent the effect of a few functional groups on the chemical shifts of alpha protons. The effect on beta protons is generally about one-fifth of the effect on the alpha protons. For example, in an alcohol, the presence of an oxygen atom adds +2.5 ppm to the chemical shift of the alpha protons, but adds only +0.5 ppm to the beta protons. Similarly, a carbonyl group adds +1 ppm to the chemical shift of the alpha protons, but only +0.2 to the beta protons.

The values above (together with the benchmark values for methyl, methylene, and methine groups), enable us to predict the chemical shifts for the protons in a wide variety of compounds. Let's see an example.

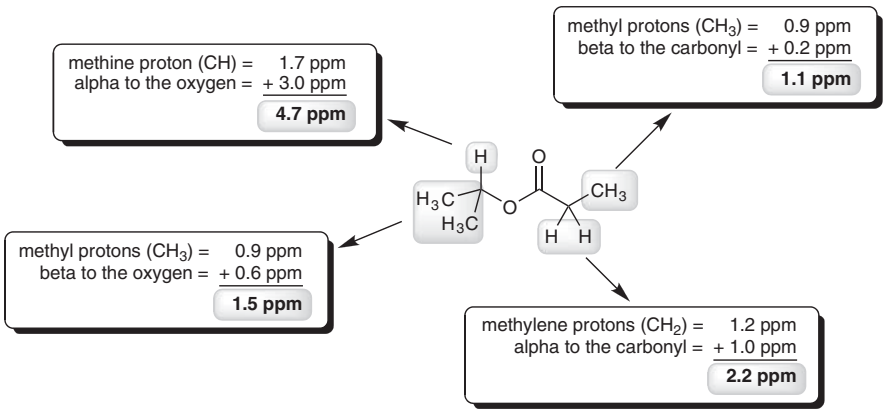
EXERCISE 3.12 Predict the chemical shifts for the signals in the proton NMR spectrum of the following compound:



Solution First determine the total number of expected signals. In this compound, there are four different kinds of protons, giving rise to four distinct signals. For each type of signal, identify whether it represents methyl (0.9 ppm), methylene (1.2 ppm), or methine (1.7 ppm) groups:

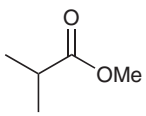


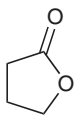
Finally, modify each of these numbers based on proximity to the oxygen and the carbonyl group:

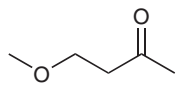


These values are only estimates, and the actual chemical shifts might differ slightly from the predicted values. Note that for the methine proton, we did not count the distant C═O bond and add +0.2, because the ester group is considered as one group, which has the effect of adding +3.0 to the chemical shift of the methine proton. Similarly, note that for the methylene protons, we did not add +0.5 for a distant oxygen. Once again, the ester group is considered as one group, which has the effect of adding +1.0 to the chemical shift of the methylene protons.

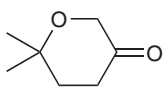
PROBLEMS Predict the chemical shifts for the signals in the proton NMR spectrum of each of the following compounds:

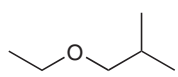
3.13 

3.14 

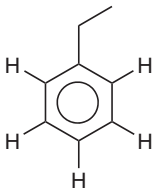
3.15 

3.16 

3.17 

3.18 

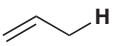
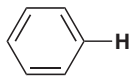
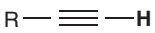
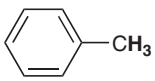
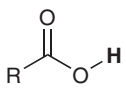
The chemical shift of a proton is also sensitive to the presence of nearby π electrons. This effect is particularly strong for aromatic protons (protons connected directly to an aromatic ring). In your textbook, you will find a diagram showing how (and why) the aromatic protons are affected. Here is a brief summary. The external magnetic field causes the π electrons to circulate, and this flow of electrons causes an induced, local magnetic field. The aromatic protons experience not only the external magnetic field, but they also experience the induced, local magnetic field. As a result, aromatic protons feel a stronger net magnetic field, which causes their signals to be shifted downfield, significantly. In fact, aromatic protons generally produce signals in the neighborhood of 7 ppm (sometimes as high as 8 ppm, sometimes as low as 6.5 ppm) in an NMR spectrum. For example, consider the structure of ethylbenzene:



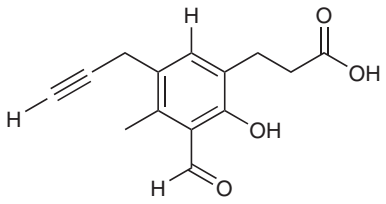
Ethylbenzene has three different kinds of aromatic protons (make sure you can identify them), producing three overlapping signals just above 7 ppm. A complex set of overlapping signals around 7 ppm is characteristic of compounds with aromatic protons.

The methylene group (CH_2) in ethylbenzene produces a signal at 2.6 ppm, rather than the expected benchmark value of 1.2 ppm. These protons have been shifted downfield because of their proximity to the aromatic ring. They are not shifted as much as the aromatic protons themselves, because the methylene protons are farther away from the ring, but there is still a noticeable effect.

All π electrons, whether they belong to an aromatic ring or not, have an effect on neighboring protons. For each type of π bond, the precise location of the nearby protons determines their chemical shift. For example, aldehydic protons produce characteristic signals at approximately 10 ppm. Below are some important chemical shifts. It would be wise to become familiar with these numbers, as they will be required in order to interpret proton NMR spectra:

Type of proton	Chemical Shift (δ)	Type of proton	Chemical Shift (δ)
methyl R—CH_3	~0.9	alkyl halide 	2–4
methylene 	~1.2	alcohol R—O—H	2–5
methine 	~1.7	vinylic 	4.5–6.5
allylic 	~2	aryl 	6.5–8
alkynyl 	~2.5	aldehyde 	~10
benzylic methyl 	~2.5	carboxylic acid 	~12

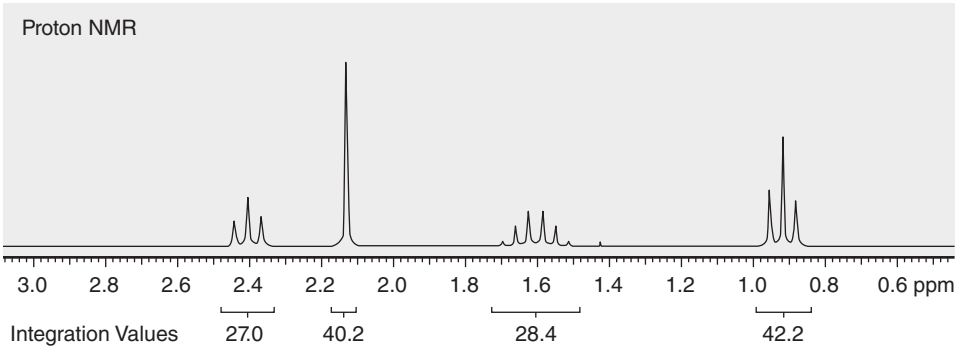
PROBLEM 3.19 Predict the expected chemical shift for each type of proton in the following compound:



3.3 INTEGRATION

In the previous section, we learned about the first characteristic of every signal, chemical shift. In this section, we will explore the second characteristic, *integration*, which is the area under each signal. This value indicates the number of protons giving rise to the signal. After acquiring a spectrum, a computer calculates the area under each signal, and then displays this area as a numerical value placed under the signal:

Courtesy of Richard A. Tomasi, Ph.D.



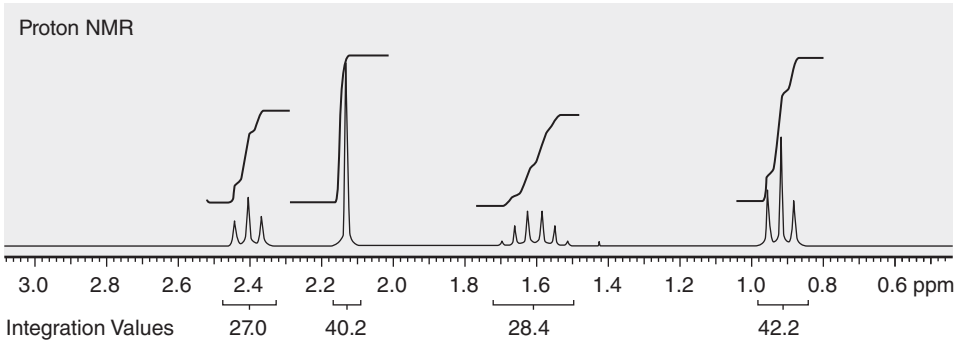
These numbers only have meaning when compared to each other. In order to convert these numbers into useful information, choose the smallest number (27.0 in this case), and then divide all integration values by this number:

$$\frac{27.0}{27.0} = 1 \qquad \frac{40.2}{27.0} = 1.49 \qquad \frac{28.4}{27.0} = 1.05 \qquad \frac{42.2}{27.0} = 1.56$$

These numbers provide the *relative number*, or ratio, of protons giving rise to each signal. This means that a signal with an integration of 1.5 involves one and a half times as many protons as a signal with an integration of 1. In order to arrive at whole numbers (there is no such thing as half a proton), multiply all the numbers above by two, giving the same ratio now expressed in whole numbers, 2 : 3 : 2 : 3. In other words, the signal at 2.4 ppm represents 2 equivalent protons, and the signal at 2.1 ppm represents 3 equivalent protons.

Integration values are often represented by *step-curves*, for example:

Courtesy of Richard A. Tomasi, Ph.D.

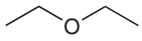


The height of each step curve represents the area under the signal. In this case, a comparison of the heights of the four step curves reveals a ratio of 2 : 3 : 2 : 3.

When interpreting integration values, don't forget that the numbers are only relative. For example, consider the structure of butane:

Butane has two kinds of protons, and will therefore produce two signals in its proton NMR spectrum. The methyl groups give rise to one signal and the methylene groups give another signal. A computer analyzes the area under each signal and provides numbers that allow us to calculate a ratio of 2 : 3. This ratio only indicates the relative number of protons giving rise to each signal, not the exact number of protons. In this case, the exact numbers are 4 (for the methylene groups) and 6 (for the methyl groups). When analyzing the NMR spectrum of an unknown compound, the molecular formula provides extremely useful information because it enables us to determine the exact number of protons giving rise to each signal. If we were analyzing the spectrum of butane, the molecular formula (C_4H_{10}) would indicate that the compound has a total of 10 protons. This information then allows us to determine that the ratio of 2 : 3 must correspond with 4 protons and 6 protons, in order to give a total of 10 protons.

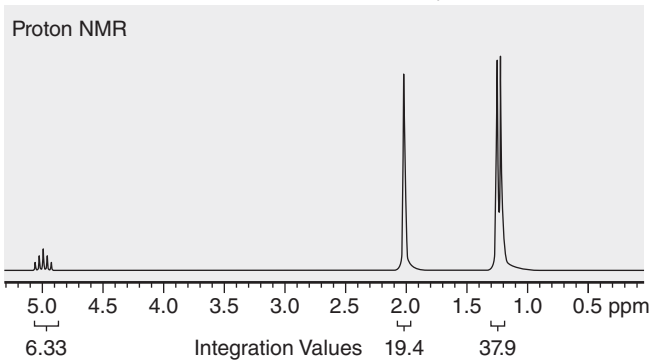
The previous example illustrated the important role that symmetry can play when considering integration values. Here is another example:



This compound has only two kinds of protons, because the two methylene groups are equivalent to each other, and the two methyl groups are equivalent to each other. The proton NMR spectrum is therefore expected to exhibit only two signals, with relative integration values of 2 : 3. But once again, the values 2 and 3 are just relative numbers. They actually represent 4 protons and 6 protons. This can be determined by inspecting the molecular formula ($C_4H_{10}O$) which indicates a total of 10 protons in the compound. Since the ratio of protons is 2 : 3, this ratio must represent 4 and 6 protons, in order for the total number of protons to be 10.

EXERCISE 3.20 A compound with the molecular formula $C_5H_{10}O_2$ has the following proton NMR spectrum. Determine the number of protons giving rise to each signal:

Courtesy of Richard A. Tomasi, Ph.D.

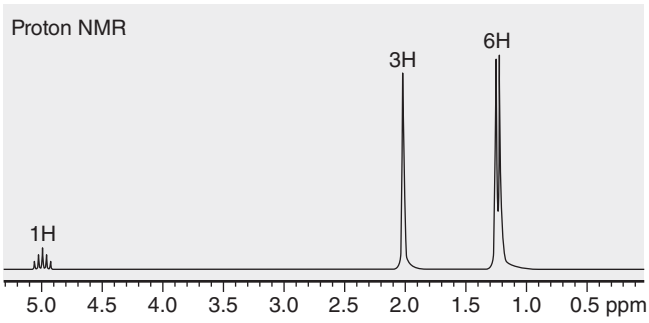


Solution The spectrum has three signals. Begin by comparing the relative integration values: 6.33, 19.4, and 37.9. Divide each of these three numbers by the smallest number (6.33):

$$\frac{6.33}{6.33} = 1 \qquad \frac{19.4}{6.33} = 3.06 \qquad \frac{37.9}{6.33} = 5.99$$

This gives a ratio of 1 : 3 : 6, but these are just relative numbers. To determine the exact number of protons giving rise to each signal, look at the molecular formula, which indicates a total of 10 protons in the compound. Therefore, the numbers 1 : 3 : 6 are not only relative values, but they are also the exact values. Exact integration values are sometimes expressed in the following way:

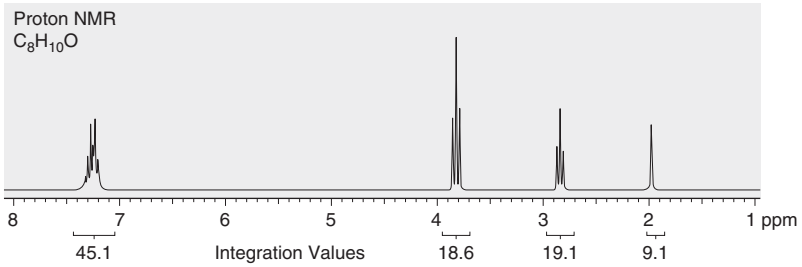
Courtesy of Richard A. Tomasi, Ph.D.



PROBLEMS

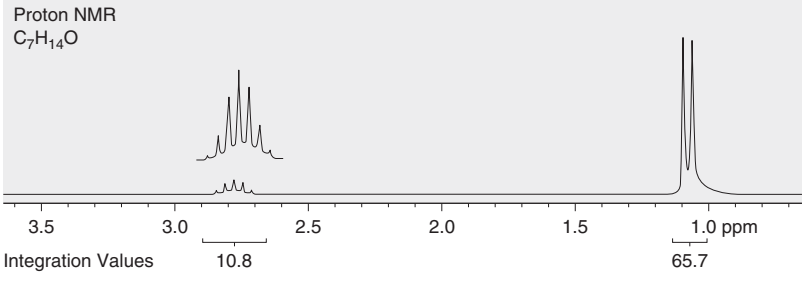
3.21 A compound with the molecular formula $C_8H_{10}O$ has the following proton NMR spectrum. Determine the number of protons giving rise to each signal.

Courtesy of Richard A. Tomasi, Ph.D.

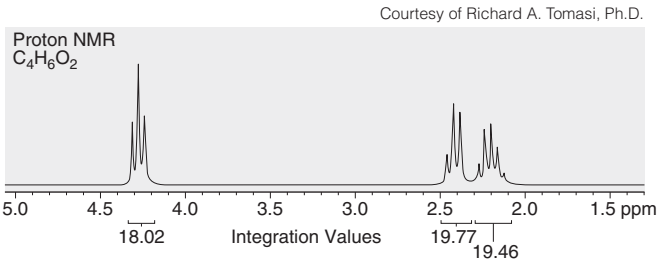


3.22 A compound with the molecular formula $C_7H_{14}O$ has the following proton NMR spectrum. Determine the number of protons giving rise to each signal.

Courtesy of Richard A. Tomasi, Ph.D.

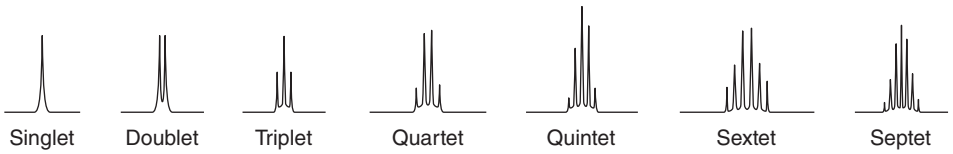


3.23 A compound with the molecular formula $C_4H_6O_2$ has the following proton NMR spectrum. Determine the number of protons giving rise to each signal.



3.4 MULTIPLICITY

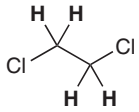
The third, and final, characteristic of each signal is its *multiplicity*, which refers to the number of peaks in the signal. A *singlet* has one peak, a *doublet* has two peaks, a *triplet* has three peaks, a *quartet* has four peaks, a *quintet* has five peaks, etc:



The multiplicity of a signal is the result of the magnetic effects of neighboring protons, and therefore indicates the number of neighboring protons. Your textbook will explain the cause for this effect in detail. The net effect can be summarized with the $n + 1$ *rule*, which states the following: if n is the number of neighboring protons, then the multiplicity will be $n + 1$. For example, a proton with three neighbors ($n = 3$) will be split into a quarter ($n + 1 = 3 + 1 = 4$ peaks).

It is important to realize that nearby protons do not always split each other. There are two major factors that determine whether or not splitting occurs:

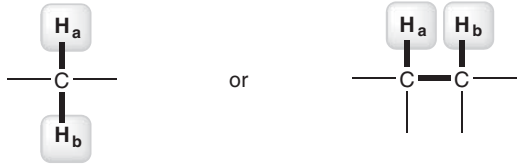
1. Equivalent protons do not split each other. Consider the two methylene groups in the following compound:



Four equivalent protons
no splitting

All four protons are chemically equivalent, and therefore, they do not split each other. Instead, they produce one signal that has no neighboring protons ($n = 0$), so the signal is a singlet ($n + 1$). In order for splitting to occur, the neighboring protons must be different than the protons producing the signal.

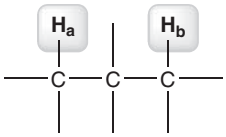
2. Splitting is most commonly observed when protons are separated by either two or three sigma bonds:



non-equivalent protons
separated by two sigma bonds

non-equivalent protons
separated by three sigma bonds

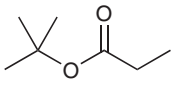
However, when two protons are separated by more than three sigma bonds, splitting is generally not observed:



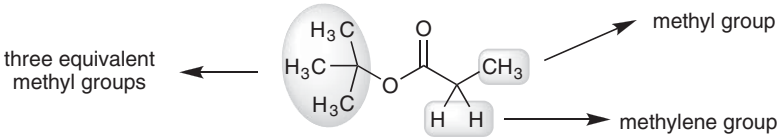
too far apart

Such long-range splitting is only observed in rigid molecules, such as bicyclic compounds, or in molecules that contain rigid structures, such as allylic systems. For purposes of this introductory treatment of NMR spectroscopy, we will avoid examples that exhibit substantial long-range splitting. Make sure to look through your lecture notes to see if any examples of long-range splitting are included.

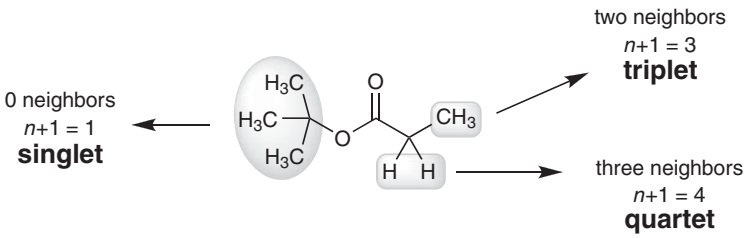
EXERCISE 3.24 Determine the multiplicity of each signal in the expected proton NMR spectrum of the following compound:



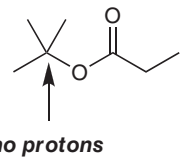
Solution Begin by identifying the different kinds of protons. That is, determine the number of expected signals.



This compound is expected to produce three signals in its proton NMR spectrum. Now let's analyze each signal, using the $n + 1$ rule:

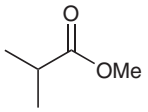


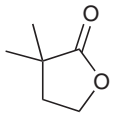
Notice that the *tert*-butyl group (on the left side of the molecule) appears as a singlet, because the following carbon atom has no protons:

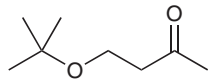


This quaternary carbon atom is directly connected to each of the three neighboring methyl groups, and as a result, each of the three methyl groups has no neighboring protons. This is characteristic of *tert*-butyl groups.

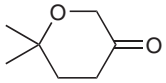
PROBLEMS Predict the multiplicity of each signal in the expected proton NMR spectrum of each of the following compounds:

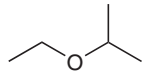
3.25 

3.26 

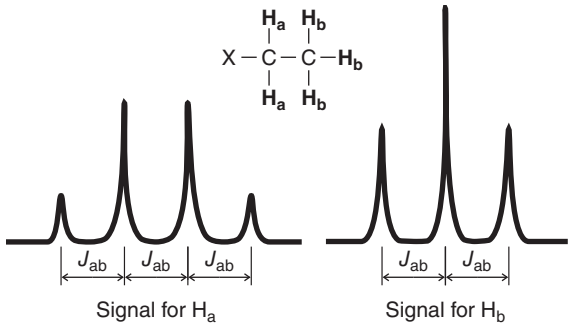
3.27 

3.28 

3.29 

3.30 

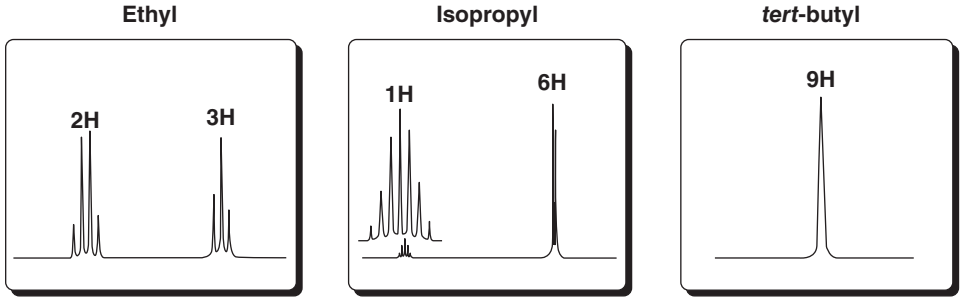
When signal splitting occurs, the distance between the individual peaks of a signal is called the *coupling constant*, or *J value*, and is measured in Hz. Neighboring protons always split each other with equal *J values*. For example, consider the two kinds of protons in an ethyl group:



The H_a signal is split into a quartet under the influence of its three neighbors, while the H_b signal is split into a triplet under the influence of its two neighbors. H_a and H_b are said to be coupled to each other. The coupling constant, J_{ab}, is the same for each proton, so the spacing between the peaks is the same in both signals.

3.5 PATTERN RECOGNITION

There are a few splitting patterns that are commonly seen in proton NMR spectra, and you will save yourself time on an exam if you can recognize these patterns:



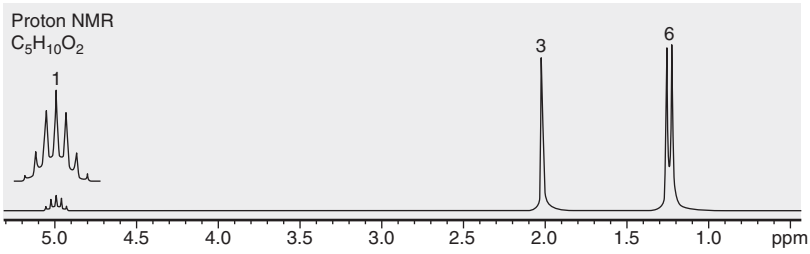
An ethyl group is characterized by a triplet with an integration of 3 and a quartet with an integration of 2. An isopropyl group is characterized by a doublet with an integration of 6 and a septet with an integration of 1. A *tert*-butyl group is characterized by a singlet with an integration of 9.

Let's get some practice recognizing these patterns.

PROBLEMS Below are proton NMR spectra of several compounds. Identify whether these compounds are likely to contain ethyl, isopropyl, and/or *tert*-butyl groups:

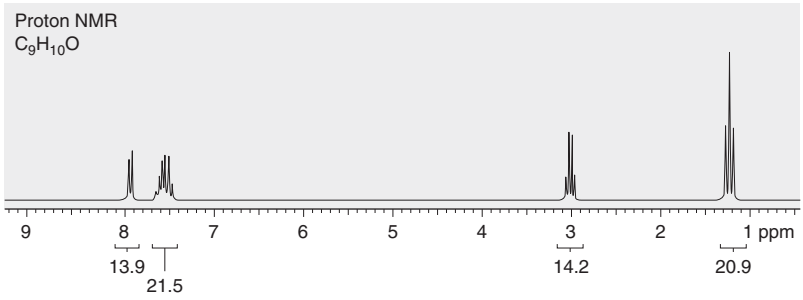
3.31

Courtesy of Richard A. Tomasi, Ph.D.



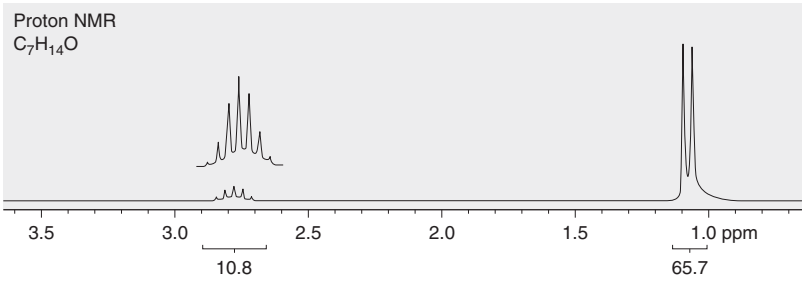
3.32

Courtesy of Richard A. Tomasi, Ph.D.



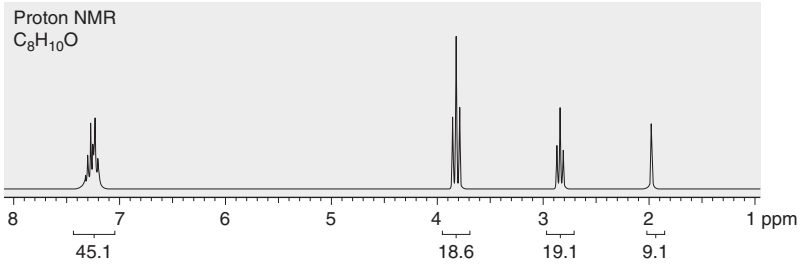
3.33

Courtesy of Richard A. Tomasi, Ph.D.



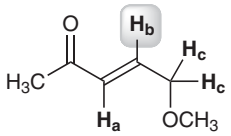
3.34

Courtesy of Richard A. Tomasi, Ph.D.

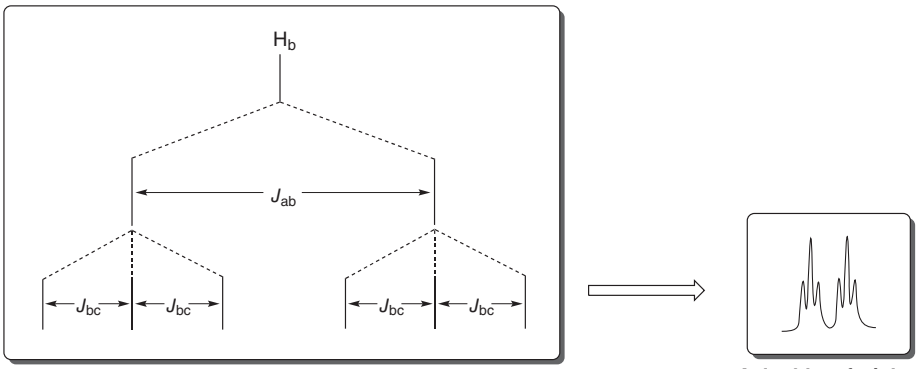


3.6 COMPLEX SPLITTING

Complex splitting occurs when a proton has two different kinds of neighboring protons. For example, consider the splitting pattern that you might expect for the highlighted proton (H_b) in the following compound

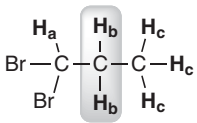


In this case, H_b has two different kinds of neighbors: there is one H_a proton to the left, and there are two H_c protons to the right. As a result, the signal for H_b is being split into a doublet because of the nearby H_a proton, and it is also being split into a triplet because of the nearby H_c protons. The signal is therefore expected to have six peaks (2×3). The shape (multiplicity) of this signal depends greatly on the J values. In this case, J_{ab} is much greater than J_{bc}, so the signal will appear as a doublet of triplets, as shown in the following splitting tree:

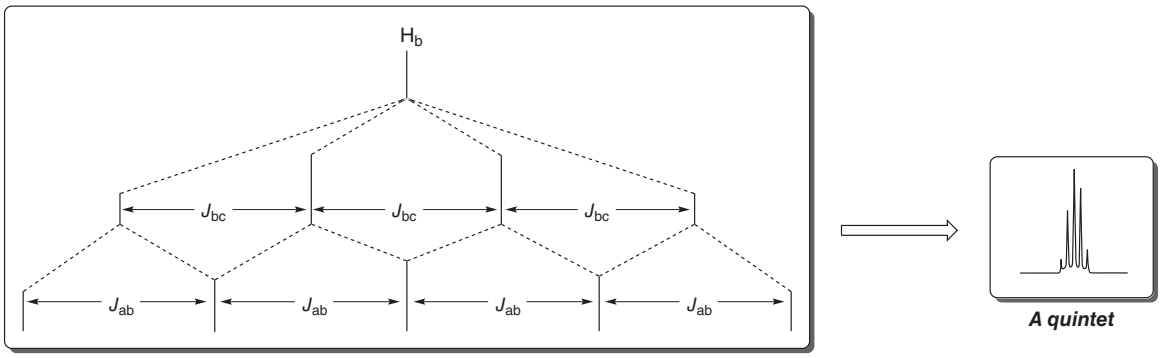


A doublet of triplets

This splitting tree shows the signal for H_b being split into a doublet by one neighboring proton (H_a), and then each peak of this doublet is further split into a triplet by the neighboring H_c protons. The result is two triplets (spaced very closely next to each other in the spectrum), and this pattern is called a doublet of triplets, as shown above. This splitting pattern is a result of the fact that the spatial arrangement between H_b and H_a is very different than the spatial arrangement between H_b and H_c, so J_{ab} is much greater than J_{bc}. Let's now consider a case in which the J values are more similar. As an example, consider the two H_b protons (highlighted) in the following compound:

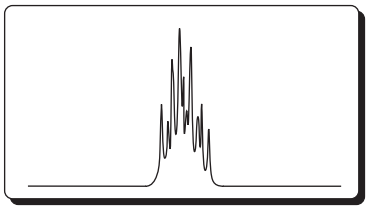


This structure lacks the rigid double bond that was in the previous example, and in such a case (where the compound has only single bonds that are all experiencing free rotation), all of the J values will generally be very similar (~7 Hz). The H_b protons have two different types of neighbors: there is one neighbor to the left (H_a), which should split the signal into a doublet; and there are three neighbors (H_c) to the right, which should split the signal into a quartet. Therefore, we might have expected either a doublet of quartets, or a quartet of doublets, if there had been a large difference between the J values, J_{ab} and J_{bc}. However, in this case, as we have pointed out, the J values are extremely similar ($J_{ab} \approx J_{ac} \approx 7$ Hz), and in such a case, we do not observe complex splitting. Rather, the H_b protons are considered to have four neighbors, and according to the $n + 1$ rule, the signal for the H_b protons will be a quintet ($n + 1 = 4 + 1 = 5 =$ quintet). This outcome can be justified with the following splitting tree:



This splitting tree shows the signal for the H_b protons first being split into a quartet by the neighboring H_c protons, and then each peak of this quartet is further split into a doublet by the neighboring H_a proton. Since $J_{ab} \approx J_{ac}$, the peaks of the signal end up overlapping perfectly to produce a signal with exactly five peaks (a quintet). Note that we get the same result (a quintet) if we draw a splitting tree where we first split the signal into a doublet, and then split each of the two peaks of the doublet into a quartet. The signal is a quintet because $J_{ab} \approx J_{ac}$.

In each of the previous examples, we have seen how the multiplicity of a signal (its shape) depends greatly on the *J* values. We saw a case where the *J* values were very different from each other, giving rise to complex splitting; and we also saw a case where the *J* values were extremely similar, in which case complex splitting was not observed. Finally, let's consider what would be the case if the *J* values are similar but not identical. In such a case, the peaks do not overlap nicely, and the result can be a signal that is difficult to analyze. This type of signal is called a multiplet. An example of a multiplet is shown below.

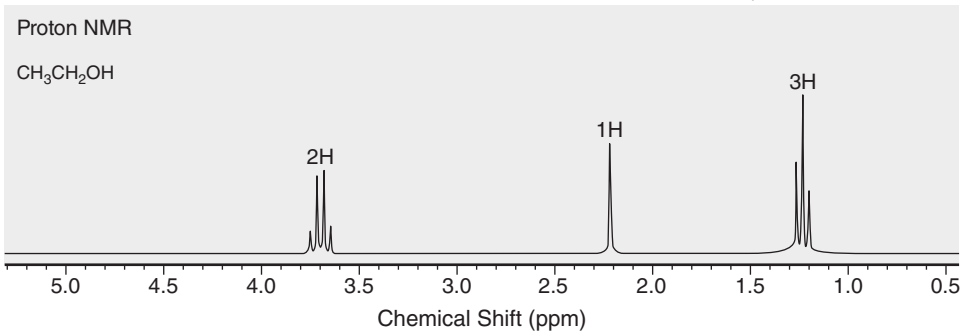


A multiplet

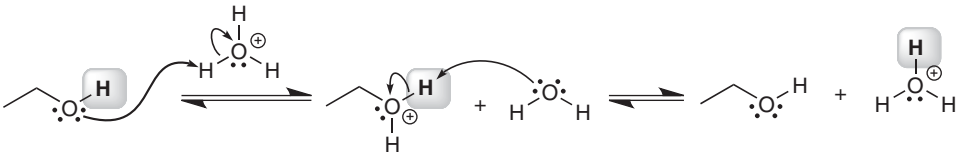
3.7 NO SPLITTING

In the previous section, we saw examples of complex splitting. Now, in this section, we will explore cases where there is no splitting at all, despite the presence of neighboring protons. Consider the proton NMR spectrum of ethanol:

Courtesy of Richard A. Tomasi, Ph.D.

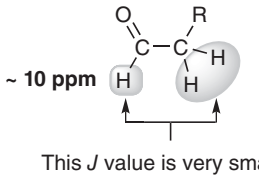


As expected, the spectrum exhibits the characteristic signals of an ethyl group (a quartet with an integration of 2 and a triplet with an integration of 3). In addition, there is another signal at 2.2 ppm, representing the hydroxyl proton (OH). Hydroxyl protons typically produce a signal between 2 and 5 ppm, and it is often difficult to predict exactly where that signal will appear. In the proton NMR spectrum above, notice that the hydroxyl proton is not split into a triplet from the neighboring methylene group. Generally, no splitting is observed across the oxygen of an alcohol, because proton exchange is a very rapid process that is catalyzed by trace amounts of acid or base:



Hydroxyl protons are said to be **labile**, because of the rapid rate at which they are exchanged. This proton transfer process occurs at a faster rate than the timescale of an NMR spectrometer, producing a blurring effect that averages out any possible splitting effect. It is possible to slow down the rate of proton transfer by scrupulously removing the trace amounts of acid and base dissolved in ethanol. Such purified ethanol does in fact exhibit splitting across the oxygen atom, so the signal at 2.2 ppm is observed to be a triplet, and the signal at 3.7 ppm is observed to be a quintet ($n = 4$).

There is one other common example of neighboring protons that often do not produce observable splitting. Aldehydic protons, which generally produce signals near 10 ppm, will often couple only weakly with their neighbors (*i.e.*, a very small J value):



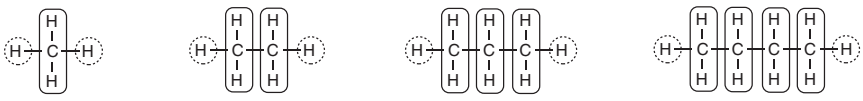
Because the J value is so small, the aldehyde signal near 10 ppm typically appears to be a singlet, despite the presence of neighboring protons.

3.8 HYDROGEN DEFICIENCY INDEX (DEGREES OF UNSATURATION)

In the previous sections of this chapter, we have learned all of the individual tools that you need for analyzing a proton NMR spectrum (considering the number of signals, analyzing chemical shifts, assessing integration values, interpreting the multiplicity of each signal, pattern recognition, etc.). Now, we are just about ready to put all of these tools together. But there is one more important tool that you will need, and we will cover that tool in this section.

Imagine that you have an unknown compound with a molecular formula of $C_6H_{12}O$. The molecular formula by itself does not provide enough information to draw the structure of the compound. There are many constitutional isomers with the molecular formula $C_6H_{12}O$. Nevertheless, a careful analysis of the molecular formula can often provide helpful clues about the structure of the compound. To see how this works, let's begin by analyzing the molecular formula of several alkanes.

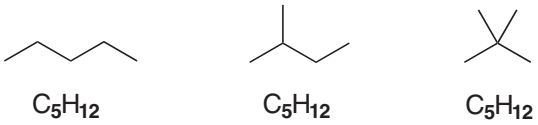
Compare the structures of the following alkanes, paying special attention to the number of hydrogen atoms attached to each carbon atom.



In each case, there are two hydrogen atoms on the ends of the structures (circled), and there are two hydrogen atoms on every carbon atom. This can be summarized like this:

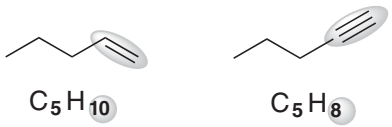
$$H—(CH_2)_n—H \tag{3.1}$$

where *n* is the number of carbon atoms in the compound. Accordingly, the number of hydrogen atoms will be $2n + 2$. In other words, all of the compounds above have a molecular formula of C_nH_{2n+2}. This is true even for compounds that are branched rather than having a straight chain.

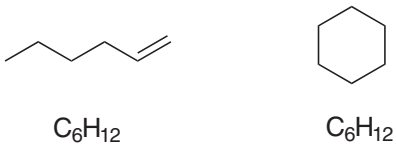


The compounds above are said to be *saturated*—that is, they possess the maximum number of hydrogen atoms possible relative to the number of carbon atoms present.

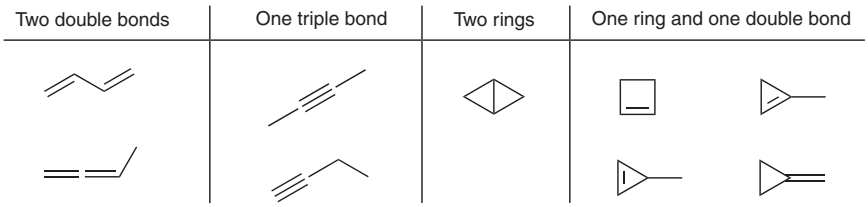
A compound with a π bond (a double or triple bond) will have fewer than the maximum number of hydrogen atoms. Such compounds are said to be *unsaturated*.



A compound containing a ring will also have fewer than the maximum number of hydrogen atoms, just like a compound with a double bond. For example, compare the structures of 1-hexene and cyclohexane:



Both compounds have the molecular formula C_6H_{12} because both are "missing" two hydrogen atoms [6 carbon atoms should be able to accommodate $(2 \times 6) + 2 = 14$ hydrogen atoms]. Each of these compounds is said to have one *degree of unsaturation*. The *hydrogen deficiency index (HDI)* is a measure of the number of degrees of unsaturation. A compound is said to have one degree of unsaturation for every two hydrogen atoms that are missing. For example, a compound with the molecular formula C_4H_6 is missing four hydrogen atoms (if saturated, it would be C_4H_{10}), so it has two degrees of unsaturation (HDI = 2). There are several ways for a compound to possess two degrees of unsaturation: two double bonds, or two rings, or one double bond and one ring, or one triple bond. Let's explore all of these possibilities for C_4H_6:

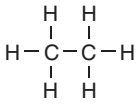


These are all of the possible constitutional isomers for C_4H_6. With this in mind, let's expand our skills set. Let's explore how to calculate the HDI when other elements are present in the molecular formula.

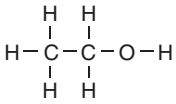
Halogens: Compare the following two compounds:

Notice that chlorine takes the place of a hydrogen atom. Therefore, for purposes of calculating the HDI, treat a halogen as if it were a hydrogen atom. For example, C_4H_9Cl should have the same HDI as C_4H_{10}.

Oxygen: Compare the following two compounds:



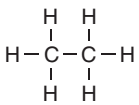
ethane



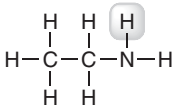
ethanol

Notice that the presence of the oxygen atom does not affect the expected number of hydrogen atoms. Therefore, whenever an oxygen atom appears in the molecular formula, it should be ignored for purposes of calculating the HDI. For example, C_4H_8O should have the same HDI as C_4H_8.

Nitrogen: Compare the following two compounds:



ethane



ethyl amine

Notice that the presence of a nitrogen atom changes the number of expected hydrogen atoms. It gives one more hydrogen atom than would be expected (highlighted above). Therefore, whenever a nitrogen atom appears in the molecular formula, one hydrogen atom must be subtracted from the molecular formula. For example, C_4H_9N should have the same HDI as C_4H_8.

In summary:

- Halogens: ***Add*** one H for each halogen
- Oxygen: ***Ignore***
- Nitrogen: ***Subtract*** one H for each N

These rules will enable you to determine the HDI for most simple compounds. Alternatively, the following formula can be used:

$$HDI = (2\times C + 2 + N - H - X)/2$$

C is the number of carbon atoms, N is the number of nitrogen atoms, H is the number of hydrogen atoms, and X is the number of halogens. This formula will work for all compounds containing C, H, N, O, and/or halogens.

Calculating the HDI is particularly helpful, because it provides clues about the structural features of the compound. For example, an HDI of zero indicates that the compound cannot have any rings or π bonds. That is extremely useful information when trying to determine the structure of a compound, and it is information that is easily obtained by simply analyzing the molecular formula. Similarly, an HDI of one indicates that the compound must have either one double bond ***or*** one ring (but not both). If the HDI is two, then there are several possibilities: two rings, or two double bonds, or one ring and one double bond, or one triple bond. Analysis of the HDI for an unknown compound can often be a useful tool, but only when the molecular formula is known with certainty.

We will use this technique in the next section. The following exercises are designed to develop the skill of calculating and interpreting the HDI of an unknown compound whose molecular formula is known.

EXERCISE 3.35 Calculate the HDI for a compound with the molecular formula $C_5H_8Br_2O_2$, and identify the structural information provided by the HDI.

Answer Use the following calculation:

# of H's:	8
Add 1 for each Br:	+2
Ignore each O:	0
Subtract 1 for each N:	0
Total =	10

This compound will have the same HDI as a compound with the molecular formula C_5H_{10}. To be fully saturated, 5 carbon atoms would require $(5 \times 2) + 2 = 12$ H atoms. According to our calculation, two hydrogen atoms are missing, and, therefore, this compound has one degree of unsaturation. HDI = 1.

Alternatively, the following formula can be used:

$$\text{HDI} = (2\times\text{C} + 2 + \text{N} - \text{H} - \text{X})/2 = (10 + 2 + 0 - 8 - 2)/2 = 2/2 = 1$$

With one degree of unsaturation, the compound must contain either one ring or one double bond, but not both. The compound cannot have a triple bond, as that would require two degrees of unsaturation.

PROBLEMS Calculate the degree of unsaturation for each of the following molecular formulas:

3.36 $C_6H_{10}O_4$ **3.37** $C_7H_{11}N$ **3.38** $C_8H_{14}O_2$

3.39 $C_5H_{12}O_2$ **3.40** $C_6H_{15}N$ **3.41** $C_8H_{10}O$

3.9 ANALYZING A PROTON NMR SPECTRUM

In this section, we will practice analyzing and interpreting NMR spectra, a process that involves four discrete steps:

1. Always begin by inspecting the molecular formula (if it is given), as it provides useful information. Specifically, calculating the hydrogen deficiency index (HDI) can provide important clues about the structure of the compound. An HDI of zero indicates that the compound does not possess any rings or π bonds. An HDI of 1 indicates that the compound has either one ring or one π bond. An HDI of four (or more) indicates the likely presence of an aromatic ring:

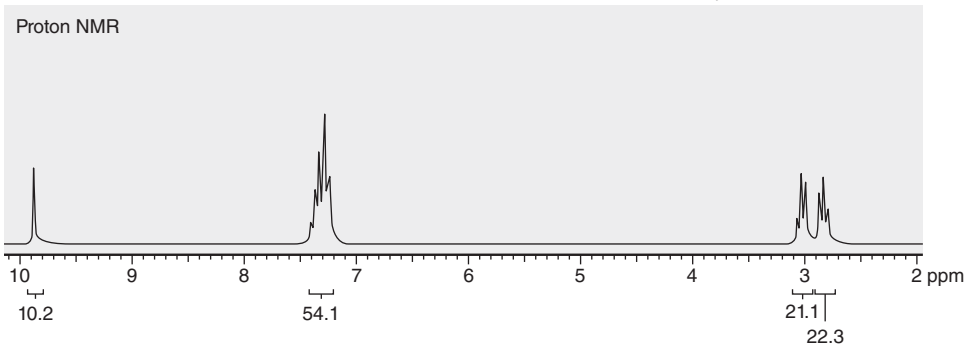
four degrees of unsaturation
(HDI = 4)

2. Consider the number of signals and integration of each signal (this gives clues about the symmetry of the compound).
3. Analyze each signal (chemical shift, integration, and multiplicity), and then draw fragments consistent with each signal. These fragments become our puzzle pieces that must be assembled to produce a molecular structure.
4. Assemble the fragments into a molecular structure.

The following exercise illustrates how this is done.

EXERCISE 3.42 Identify the structure of a compound with the molecular formula $C_9H_{10}O$ that exhibits the following proton NMR spectrum:

Courtesy of Richard A. Tomasi, Ph.D.



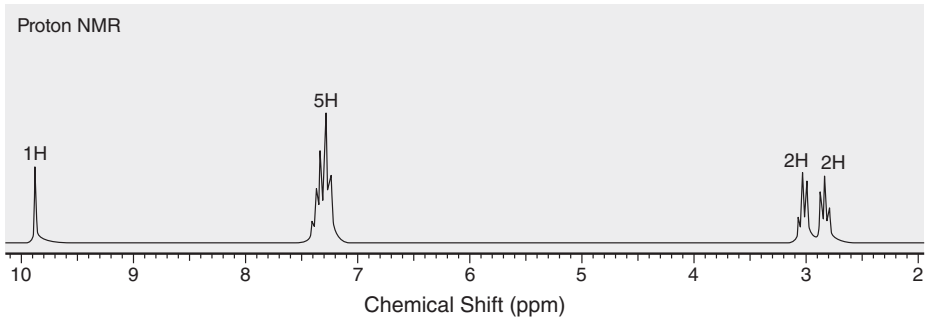
Answer The first step is to calculate the HDI. The molecular formula indicates 9 carbon atoms, which would require 20 hydrogen atoms in order to be fully saturated. There are only 10 hydrogen atoms, which means that 10 hydrogen atoms are missing, and therefore, the HDI is 5. This is a large number, and it would not be efficient to think about all the possible ways of having five degrees of unsaturation. However, anytime we encounter an HDI of 4 or more, we should be on the lookout for an aromatic ring. We must keep this in mind when analyzing the spectrum. We should expect an aromatic ring (HDI = 4) plus one other degree of unsaturation (either a ring or a double bond).

The second step is to consider the number of signals and the integration value for each signal. In this spectrum, we see four signals. In order to analyze the integration of each signal, we must first divide by the lowest number (10.2):

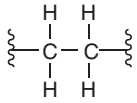
$$\frac{10.2}{10.2} = 1 \qquad \frac{54.1}{10.2} = 5.30 \qquad \frac{21.1}{10.2} = 2.07 \qquad \frac{22.3}{10.2} = 2.19$$

The ratio is 1 : 5 : 2 : 2. Now look at the molecular formula. There are 10 protons in the compound, so the relative integration values represent the actual number of protons giving rise to each signal:

Courtesy of Richard A. Tomasi, Ph.D.

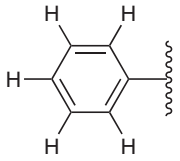


The next step is to analyze each signal. Starting upfield, there are two triplets, each with an integration of 2. This suggests that there are two adjacent methylene groups:



These signals do not appear at 1.2 where methylene groups are expected, so one or more factors is shifting these signals downfield. Our proposed structure must take that into account.

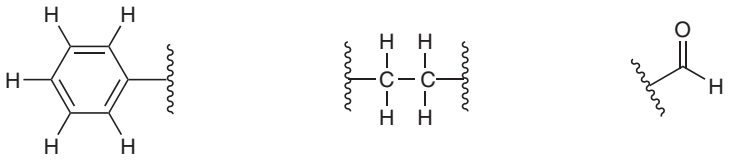
Moving downfield through the spectrum, the next signal appears just above 7 ppm, characteristic of aromatic protons (just as we suspected after analyzing the HDI). The multiplicity of aromatic protons only rarely gives useful information. More often, a messy multiplet of overlapping signals is observed. But the integration value gives important information. Specifically, there are five aromatic protons, which means that the aromatic ring is monosubstituted.



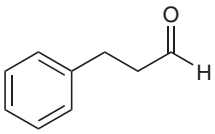
Five aromatic protons

Moving on to the last signal, we see a singlet at 10 ppm with an integration of 1. This is suggestive of an aldehydic proton.

In summary, our analysis has produced the following fragments:



The final step is to assemble these fragments. Fortunately, there is only one way to assemble these three puzzle pieces.

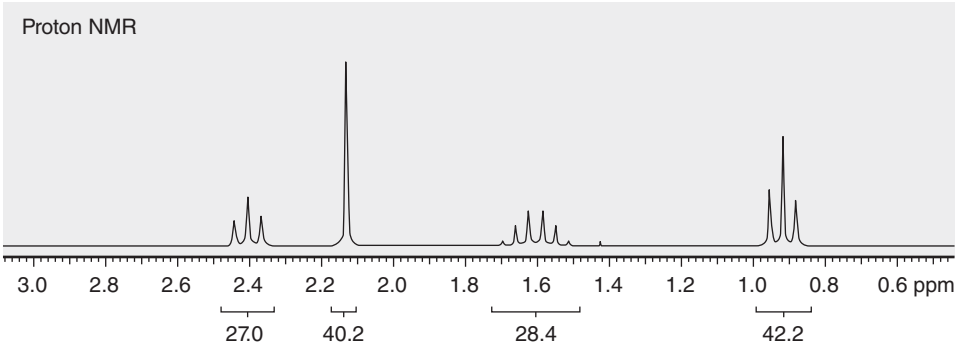


We mentioned before that each methylene group is being shifted downfield by one or more factors. Our proposed structure explains the observed chemical shifts. In particular, one methylene group is shifted significantly by the carbonyl group and slightly by the aromatic ring. The other methylene group is being shifted significantly by the aromatic ring and slightly by the carbonyl group.

PROBLEMS

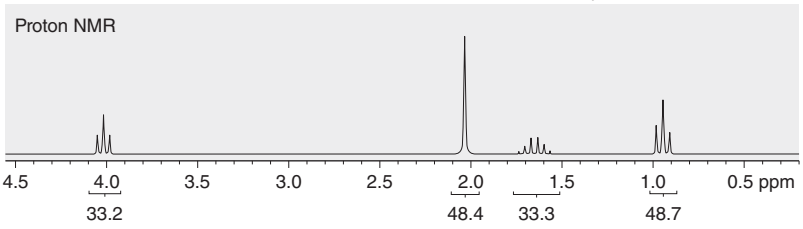
3.43 Propose a structure for a compound with the molecular formula $C_5H_{10}O$ that is consistent with the following proton NMR spectrum.

Courtesy of Richard A. Tomasi, Ph.D.



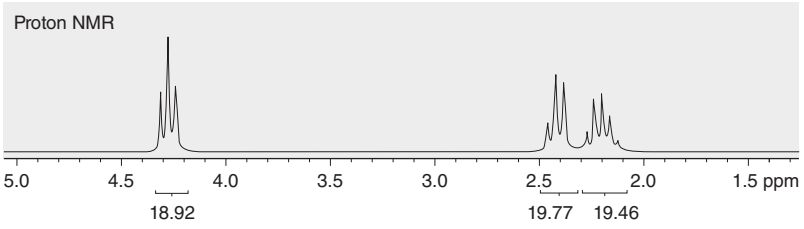
3.44 Propose a structure for a compound with the molecular formula $C_5H_{10}O_2$ that is consistent with the following proton NMR spectrum.

Courtesy of Richard A. Tomasi, Ph.D.



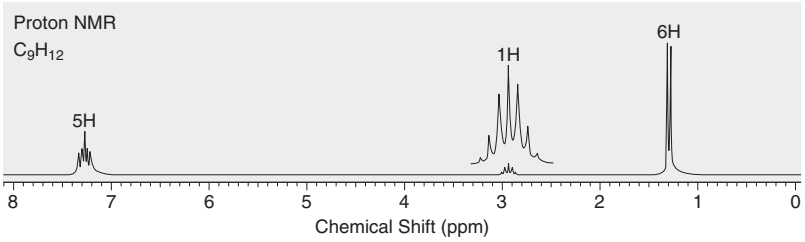
3.45 Propose a structure for a compound with the molecular formula $C_4H_6O_2$ that is consistent with the following proton NMR spectrum.

Courtesy of Richard A. Tomasi, Ph.D.



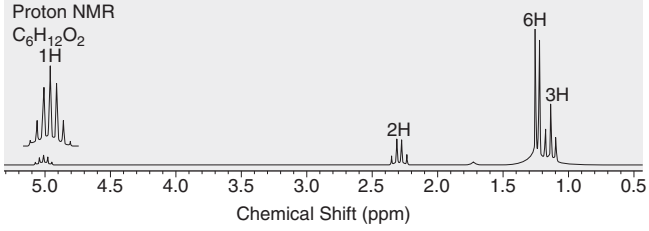
3.46 Propose a structure for a compound with the molecular formula C_9H_{12} that is consistent with the following proton NMR spectrum.

Courtesy of Richard A. Tomasi, Ph.D.



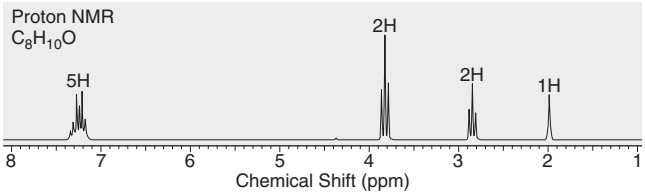
3.47 Propose a structure for a compound with the molecular formula $C_6H_{12}O_2$ that is consistent with the following proton NMR spectrum.

Courtesy of Richard A. Tomasi, Ph.D.



3.48 Propose a structure for a compound with the molecular formula $C_8H_{10}O$ that is consistent with the following proton NMR spectrum.

Courtesy of Richard A. Tomasi, Ph.D.



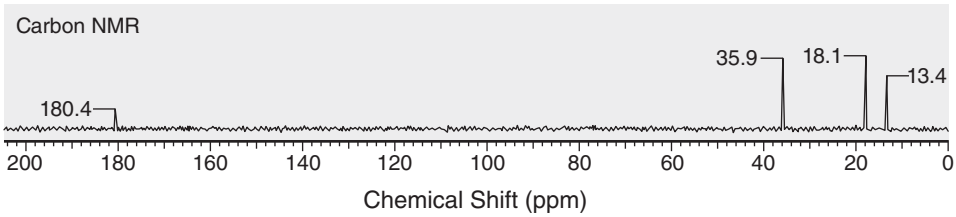
Your textbook has many more spectroscopy problems, including problems in which you are given both IR and NMR spectra. I recommend that you do ALL of those problems. The skills practiced in this chapter are meant to prepare you for those problems.

3.10 ^{13}C NMR SPECTROSCOPY

Many of the principles that apply to ^{1}H NMR spectroscopy also apply to ^{13}C NMR spectroscopy, but there are a few major differences, and we will focus on those. For example, ^{1}H is the most abundant isotope of hydrogen, but ^{13}C is only a minor isotope of carbon, representing about 1.1% of all carbon atoms found in nature. As a result, only one in every hundred carbon atoms will resonate, which demands the use of a sensitive receiver coil for ^{13}C NMR.

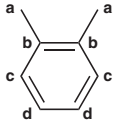
In ^{1}H NMR spectroscopy, we saw that each signal has three characteristics (chemical shift, integration, and multiplicity). In ^{13}C NMR spectroscopy, only the chemical shift is important. The integration and multiplicity of ^{13}C signals are typically not observed, which greatly simplifies the interpretation of ^{13}C NMR spectra. Integration values are not routinely calculated in ^{13}C NMR spectroscopy because the pulse technique employed by NMR spectrometers has the undesired effect of distorting the integration values, rendering them useless in most cases. Multiplicity is also not a common characteristic of typical ^{13}C NMR experiments.

Courtesy of Richard A. Tomasi, Ph.D.

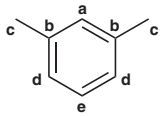


Notice that all of the signals are observed as singlets. This is a result of a special technique, called broadband decoupling, that suppresses all ^{13}C—^{1}H splitting. If we did not use this technique, then the signal of each ^{13}C atom nucleus would be split not only by the protons directly connected to it (separated by only one sigma bond), but it would also be split by the protons that are two or three sigma bonds removed. This would lead to very complex splitting patterns, and the signals would overlap to produce an unreadable spectrum. The use of broadband decoupling causes all of the ^{13}C signals to collapse to singlets, which renders the spectrum more easily interpreted.

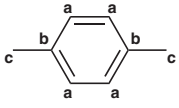
In ^{13}C NMR spectroscopy, chemical shift values typically range from 0 to 220 ppm. The number of signals in a ^{13}C NMR spectrum represents the number of carbon atoms in different electronic environments (not interchangeable by symmetry). Carbon atoms that are interchangeable by symmetry (either rotation or reflection) will only produce one signal. To illustrate this point, consider the compounds below. Each compound has eight carbon atoms, but does not produce eight signals. The equivalent carbon atoms in each compound are labeled with the same letter.



4 signals

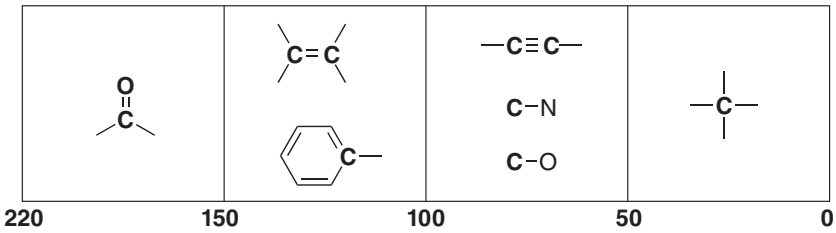


5 signals



3 signals

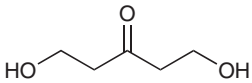
The location of each signal is dependent on shielding and deshielding effects, just as we saw in proton NMR spectroscopy. Below are chemical shifts of several important types of carbon atoms.



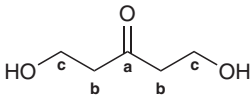
- **0–50 ppm:** This region contains signals from sp^3-hybridized carbon atoms (methyl, methylene, and methine groups).
- **50–100 ppm:** This region contains sp^3-hybridized carbon atoms that are deshielded by electronegative atoms, as well as *sp*–hybridized carbon atoms.
- **100–150 ppm:** This region contains sp^2-hybridized carbon atoms.
- **150–220 ppm:** This region contains the carbon atoms of carbonyl groups. These carbon atoms are highly deshielded.

Now let's use this information to solve the following exercise.

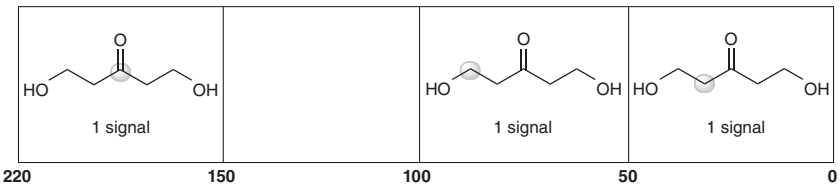
EXERCISE 3.49 Predict the number of signals and the location of each signal in the expected ^{13}C NMR spectrum of the following compound:



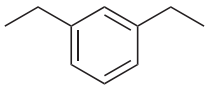
Answer Begin by determining the number of expected signals. The compound has five carbon atoms, but we must look to see if any of these carbon atoms are interchangeable by symmetry. In this case, there is symmetry, and we expect only three signals in the ^{13}C NMR spectrum.

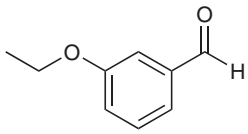


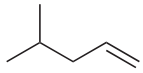
The expected chemical shifts are shown below, categorized according to the region of the spectrum in which each signal is expected to appear:

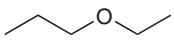


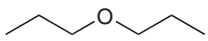
PROBLEMS For each compound below, predict the number of signals and the location of each signal in the expected ^{13}C NMR spectrum.

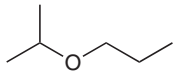
3.50 

3.51 

3.52 

3.53 

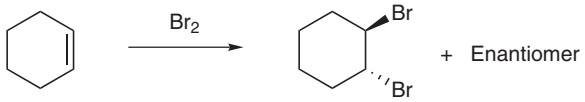
3.54 

3.55 

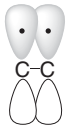
CHAPTER 4

ELECTROPHILIC AROMATIC SUBSTITUTION

We must begin this chapter with a review of a reaction from the first semester of organic chemistry. Recall the addition of bromine (Br_2) across a double bond:

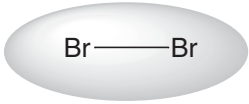


When we learned this reaction in the first semester, we saw that this reaction involves a nucleophile attacking an electrophile. The nucleophile is the double bond, and the electrophile is Br_2. To understand how a double bond can function as a nucleophile, recall that a double bond results from the overlap of two neighboring *p* orbitals, each with one electron:

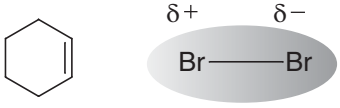


Therefore, a double bond represents a region in space of high-electron density. Even though there is no full negative charge anywhere, the double bond can function as a nucleophile and can attack an electrophile. But the obvious question is: why is Br_2 an electrophile? After all, the bond between the two bromine atoms is covalent, and therefore, we cannot say that one of the bromine atoms has any more electron density than the other. (There is no induction here because both atoms, Br and Br, have the same electronegativity.)

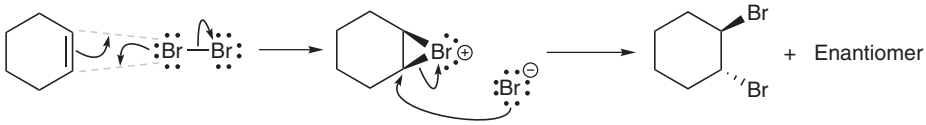
There is a simple reason why bromine can act as an electrophile here. We need to consider what happens when a molecule of Br_2 approaches an alkene. To help us see this, think of Br_2 in terms of the electron cloud surrounding it:



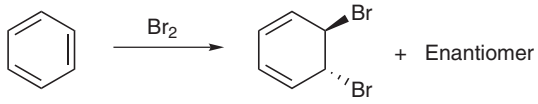
As a molecule of Br_2 gets close to the pi bond of an alkene, the electron density of the pi bond begins to repel the electron cloud around Br_2. This effect gives the Br_2 molecule an induced dipole moment (this is a temporary interaction—it only happens while the bromine molecule is near the alkene):



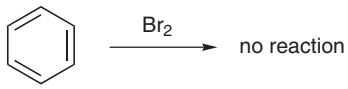
So, we have an electron-rich alkene, which can attack the nearby, electron-poor bromine atom. This gives the reaction that we saw in the first semester of organic chemistry:



Now let's consider what happens if we try to do this exact same reaction with benzene as our nucleophile. So we are trying to perform this reaction:



But when benzene is heated in the presence of Br_2, no reaction is observed.



We can understand this because benzene is an aromatic compound. It has a special stability due to its aromaticity. If we add Br_2 across benzene, aromaticity will be lost. And that is why the reaction does not take place—it would be going "uphill" in energy. But is it possible to try to "force" the reaction to happen?

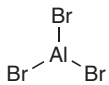
This brings us to a simple and important concept in organic chemistry. One of the driving forces for any reaction between a nucleophile and an electrophile is the difference in the electron density between the two compounds. The nucleophile is electron-rich, and the electrophile is electron-poor. Therefore, they are attracted to each other in space (opposite charges attract). So, if the reaction is not proceeding, we can try to force it along by making the attraction even stronger between the nucleophile and the electrophile. We can accomplish this in one of two ways. We can either make the nucleophile even more electron-rich (more nucleophilic), or we can make the electrophile even more electron-poor (more electrophilic).

In this chapter, we will explore both of these scenarios. For now, let us start by trying to make the electrophile a better electrophile. How do we make Br_2 a better electrophile? Let's remember why Br_2 is an electrophile in the first place. Just a few moments ago, we saw that an induced dipole moment is formed when Br_2 gets close to an alkene. This creates a partial positive charge on one of the bromine atoms. Clearly, if we had Br^+ instead of Br_2, then that would be an even better electrophile. We would not have to wait around for Br_2 to become slightly polarized.

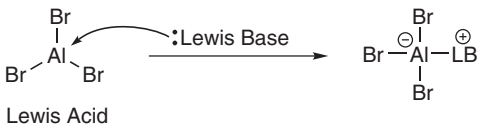
But how do we form Br^+? That is where Lewis acids come into the picture.

4.1 HALOGENATION AND THE ROLE OF LEWIS ACIDS

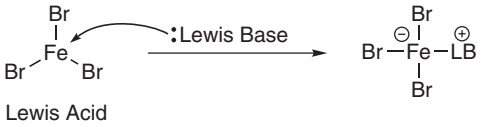
Consider the compound $AlBr_3$. The central atom in this structure is aluminum. Aluminum is in Column 3A of the periodic table, and therefore, it has three valence electrons. It uses each of these electrons to form a bond, which is why we see three bonds to the aluminum atom in $AlBr_3$:



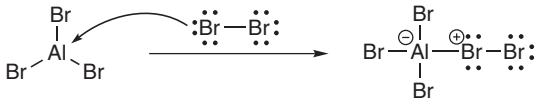
But you should notice that the aluminum atom does not have an octet. If you count the electrons around the aluminum atom, there are only six electrons. That means that aluminum has one empty orbital. That empty orbital is able to accept electrons. In fact, it will exhibit a tendency to accept electrons because that would give aluminum an octet of electrons:



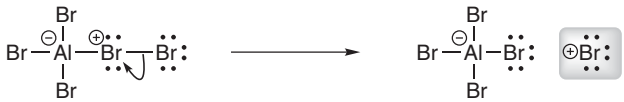
Therefore, we call $AlBr_3$ a *Lewis acid*. To put it simply, Lewis acids are just compounds that can *accept electrons*. Another common Lewis acid is $FeBr_3$:



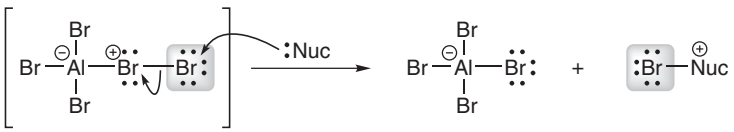
Now let's consider what happens when Br_2 is treated with a Lewis acid, such as $AlBr_3$. The Lewis acid can accept electrons from Br_2:



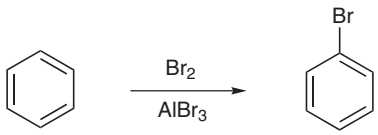
The resulting complex can then serve as a source of Br^+, like this:



It is probably not accurate to think of this as a free Br^+ that can exist in solution by itself. Rather, the complex can *transfer* Br^+ to an attacking nucleophile:

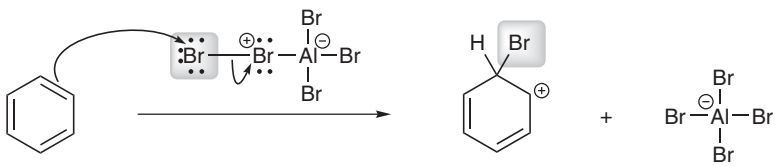


The important point is that this complex can function as a delivery agent of Br^+, and that is what we needed in order to force a reaction between benzene and bromine. So, now let's try our reaction again. When we treat benzene with bromine in the presence of a Lewis acid, such as $AlBr_3$, a reaction is indeed observed. BUT it is not the reaction that we expected. Look closely at the product:

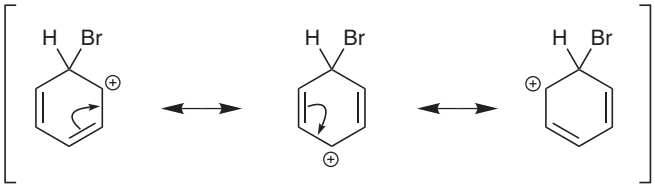


This is NOT an addition reaction. Rather, it is a *substitution* reaction. One of the aromatic protons was replaced with bromine. Since the ring is being treated with an electrophile (Br^+), we call this reaction an *electrophilic aromatic substitution*.

To see how this reaction occurs, let's take a close look at the accepted mechanism. It is absolutely critical that you fully understand this mechanism, because we will soon see that ALL electrophilic aromatic substitution reactions follow a similar mechanism. The first step shows the ring acting as a nucleophile to attack the complex, thereby transferring Br^+ to the aromatic ring:

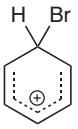


This step generates an intermediate that is not aromatic. It is true that aromaticity has been *temporarily* destroyed, but it will soon be reestablished in the second step (final step) of the mechanism. In this first step of the mechanism (shown above), the ring attacks Br^+ to form an intermediate that has three resonance structures:



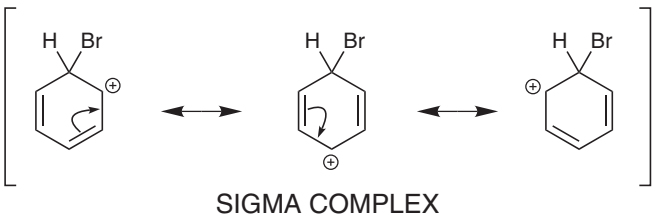
It is important to remember what resonance structures represent. Recall from the first semester that resonance is NOT a molecule flipping back and forth between different states. Rather, resonance is the way we deal with the inadequacy of our drawings. There is no one single drawing that adequately captures the essence of the intermediate, so we draw three drawings, and we meld them all together in our minds to gain a better understanding of the intermediate.

Attempts have been made to draw a single drawing for this intermediate:

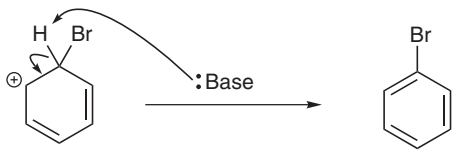


You might even see this in your textbook. I usually try to avoid using this drawing because it could easily lead you to think, erroneously, that the positive charge is spread over five atoms in the ring. This is not the case. The majority of the positive charge is actually only spread over three atoms of the ring (which we can clearly see when we look at all three resonance structures above).

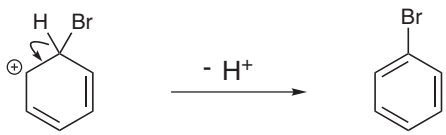
This intermediate has some special names. We often call it a sigma complex, or an Arrhenium ion. These are just two different names for the same intermediate. From now on, in this book, we will call it a sigma complex:



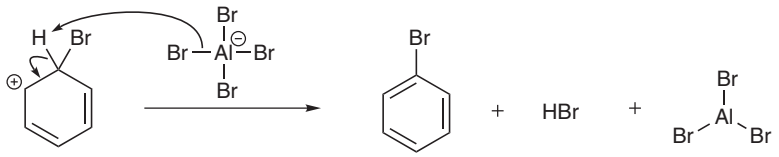
The second step (last step) of the mechanism involves deprotonation to re-form aromaticity:



Notice that the proton is removed by a base. Technically, it is not correct to just let a proton fall off into space by itself, like this:

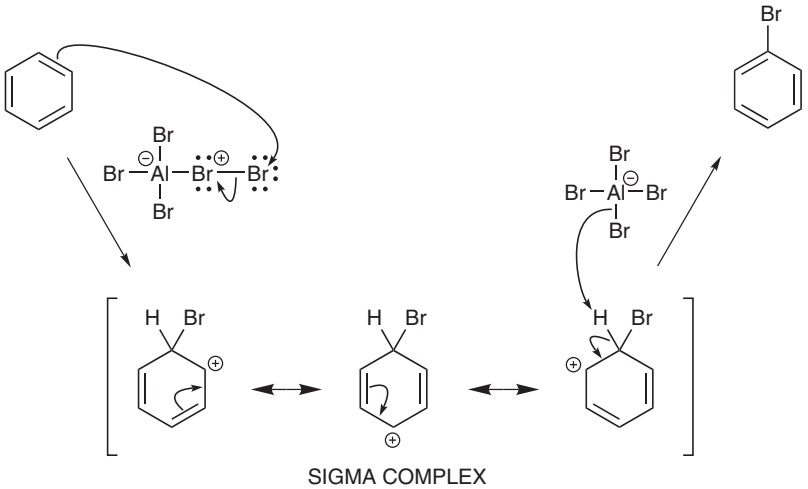


Whenever you are drawing a deprotonation step, you should show the base that is removing the proton. In this particular case, it might be tempting to use Br^- to remove the proton. But Br^- is not a good base. (In the first semester, we learned the difference between basicity and nucleophilicity, and we saw that Br^- is a very good nucleophile but a very poor base.) Instead, aluminum tetrabromide functions as the base that removes the proton. Notice that aluminum tetrabromide functions as a "delivery agent" of Br^-.



In the end, the Lewis acid ($AlBr_3$) is regenerated. So the Lewis acid is actually not being consumed by the reaction. It is only there to help the reaction along, which is why we call it a *catalyst* in this case. That is why the presence of even a small quantity of the Lewis acid will suffice.

Now that we have seen both steps of the mechanism, let's take a close look at the mechanism all at once:

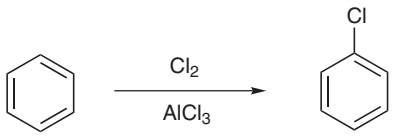


SIGMA COMPLEX

On the surface, it might seem like many steps. However, remember that resonance structures are not actually steps. Those three resonance structures (in the center of the mechanism) are necessary so that we can understand the nature of the one and only intermediate (the sigma complex). Indeed, the mechanism has only two steps. In the first step, benzene acts as a nucleophile attacking Br^+ to form the sigma complex, and in the second step, a proton is removed from the ring to reestablish aromaticity. In summary, the two steps are: attack, then deprotonate. To put it in other terms: Br^+ comes on, and then H^+ comes off. That's all there is to it.

PROBLEM 4.1 Without looking at the mechanism above, try to redraw the entire mechanism on a separate sheet of paper. Don't look above—you can figure it out. Just remember that there are two steps: E^+ on and then H^+ off. Don't forget to draw all three resonance structures of the intermediate sigma complex.

PROBLEM 4.2 Consider the following reaction, in which an aromatic ring undergoes chlorination, rather than bromination:



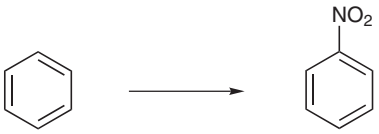
The mechanism is very similar to the mechanism for bromination. First, Cl_2 reacts with $AlCl_3$ to generate a complex that can serve as a source of Cl^+. Draw a mechanism for formation of this complex.

PROBLEM 4.3 Draw a mechanism for the electrophilic aromatic substitution reaction that occurs when benzene is treated with the complex from Problem 4.2. The mechanism is exactly the same as the mechanism for installing a Br on the ring. But PLEASE, do not look back at that mechanism to copy it. Try to do it ***without*** looking back. Then, when you are finished, compare your answer to the answer in the back of the book (and compare every arrow to make sure that all of your arrows were drawn correctly).

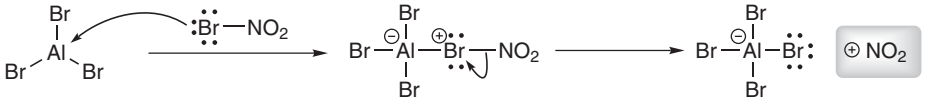
PROBLEM 4.4 Aromatic rings will also undergo iodination when treated with a suitable source of I^+. There are many ways to form I^+; you should look in your textbook and in your lecture notes to see if you are responsible for knowing how to iodinate benzene. If so, be aware that the mechanism is exactly the same as what we have seen. The only difference will be in the mechanism of how I^+ is formed. Draw a mechanism for the reaction between benzene and I^+ to form iodobenzene. In the first step of your mechanism, simply draw I^+ as the electrophile (rather than a complex which delivers I^+), and make sure to draw all resonance structures of the resulting sigma complex. Then, in the last step of your mechanism, use H_2O as the base that removes the proton to restore aromaticity (H_2O will be present for many of the methods that are used to prepare a source of I^+).

4.2 NITRATION

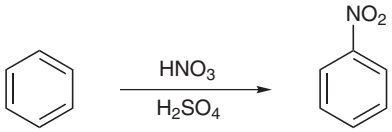
In the previous section, we saw the mechanism of an electrophilic aromatic substitution reaction. We saw that the mechanism is the same, whether you are installing Br^+, Cl^+, or I^+ on the ring. We also said that this same mechanism explains how any electrophile (E^+) can be installed on an aromatic ring. For example, let's say we wanted to convert benzene into nitrobenzene:



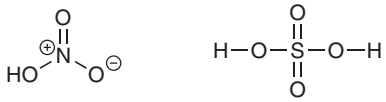
In order to form nitrobenzene, we will need NO_2^+ as our electrophile. But how do we make NO_2^+? If we look at how we made Br^+ or Cl^+ in the previous section, we might be tempted to use NO_2Br and $AlBr_3$, to get the following complex:



This complex could then serve as a source of NO_2^+. The problem is that NO_2Br is nasty stuff, and you probably would not want to work with it in a lab, especially since there is a much simpler way to make NO_2^+. We can form NO_2^+ by mixing sulfuric acid with nitric acid:

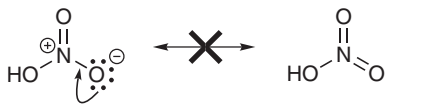


We need to take a close look at how NO_2^+ is formed under these conditions. Let's begin by drawing the structures of sulfuric acid and nitric acid:



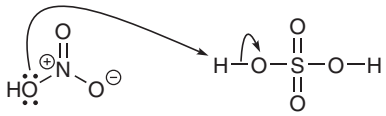
Nitric acid Sulfuric acid

Notice that nitric acid exhibits charge separation. It might be tempting to remove the charges and draw it like this:



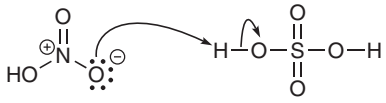
But you cannot do that because it would give five bonds to the central nitrogen atom. Nitrogen cannot EVER have five bonds because it only has four orbitals that it can use to form bonds. So nitric acid must be drawn with charge separation.

Now that we have seen the structures of both nitric acid and sulfuric acid, we must remember that the term *acidic* is a relative term. It is true that nitric acid is acidic, and it is also true that sulfuric acid is acidic. But between the two of them, sulfuric acid is a *stronger* acid. In fact, it is so much stronger as an acid that it is able to give a proton to nitric acid:



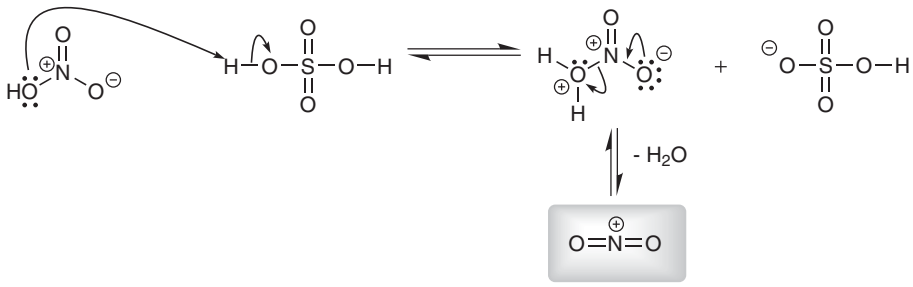
That's right—it might seem weird because nitric acid is essentially functioning *as a base* to remove a proton from sulfuric acid. And it might make us uncomfortable to use nitric acid as a base, but that is exactly what is happening. Why? Because *relative* to sulfuric acid, nitric acid is a base. It's all relative.

OK, so nitric acid removes a proton from sulfuric acid. But the obvious question is: why does the uncharged oxygen remove the proton? Wouldn't it make more sense for the negatively charged oxygen to remove the proton? Like this:



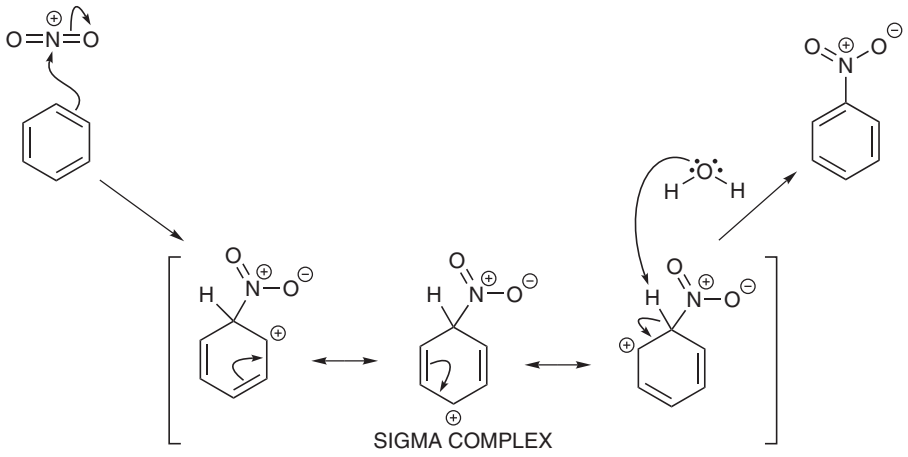
The answer is: yes, this probably would make more sense. And it probably happens like this a lot more often. The oxygen with the negative charge probably removes the proton much more readily than the uncharged oxygen atom does. However, proton transfers are reversible. Protons are being transferred back and forth all of the time. And all of this is happening very quickly. So, it is true that the negatively charged oxygen atom removes the proton more often—but when that happens, the only thing that can happen next is for the proton to be given right back to re-form nitric acid.

Every once in a while, however, the uncharged oxygen atom can remove the proton. And when that happens, something new can happen next: water can leave:



And when this happens, NO_2^+ is generated. So when we mix sulfuric acid and nitric acid, we get a little bit of NO_2^+ in the equilibrium mixture, and that NO_2^+ functions as the electrophile we need in order to install a nitro group on a benzene ring.

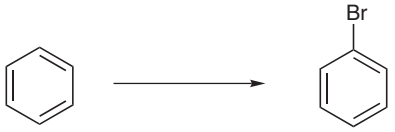
Once again, the following mechanism is essentially the same mechanism that we saw in the previous section: NO_2^+ on and then H^+ off.



In this case, we are using water to remove the proton (instead of $AlBr_4^-$), which should make sense because we don't have any $AlBr_4^-$ in this reaction. There is plenty of water, because nitric and sulfuric acids are both aqueous solutions. Notice that the mechanism is very similar to what we have already seen in the previous reactions.

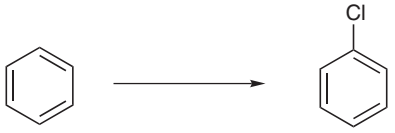
So far, we have seen how to install a halogen (Cl, Br, or I) on an aromatic ring, and we have seen how to install a nitro group. Before we move on, let's just make sure that you are familiar with the reagents necessary to perform these reactions. In each of the following cases, identify reagents that you would use in order to achieve the desired transformation.

4.5



4.6

4.7

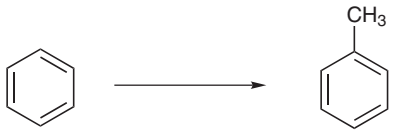


4.8 ***Without looking back*** at the previous section, try to draw the mechanism for the nitration of benzene. You will need a separate piece of paper to record your answer. Make sure to start by drawing the mechanism for formation of NO_2^+, and then show the reaction of benzene with NO_2^+. When you are finished, look back to see if you drew it correctly.

4.3 FRIEDEL–CRAFTS ALKYLATION AND ACYLATION

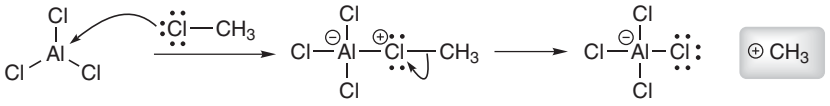
In the previous sections, we saw how to install several different groups (Br, Cl, I, or NO_2) on a benzene ring, using an electrophilic aromatic substitution. In each case, the mechanism was the same: E^+ ***on*** the ring, and then $\mathbf{H^+}$ ***off***. In this section, we will learn how to install an alkyl group.

Let's start with the simplest of all alkyl groups: a methyl group. So, the question is: what reagents would we need to achieve the following transformation:



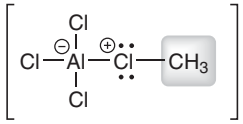
Using the logic that we have developed in this chapter, we would want to use CH_3^+ as our electrophile. But you should probably cringe when you see CH_3^+. After all, you probably remember the trend in the stability of carbocations—that tertiary carbocations are more stable than secondary carbocations, and so on. Certainly, a methyl carbocation would not be very stable at all. In fact, we deliberately avoid using methyl or primary carbocations when drawing mechanisms. But here we are, trying to make a methyl carbocation. Is it even possible? The answer is: yes. In fact, we will make it using the same method we have used in the previous sections.

If we take methyl chloride and we mix it with a pinch of $AlCl_3$, we will have a source of CH_3^+:



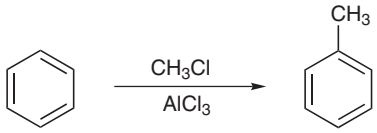
Does not really exist as free CH_3^+

The truth is that we are NOT really forming a free methyl carbocation that can float off into solution. A free CH_3^+ would be too unstable to form. So, instead, we must view this as a complex that can serve as a "source" of CH_3^+.

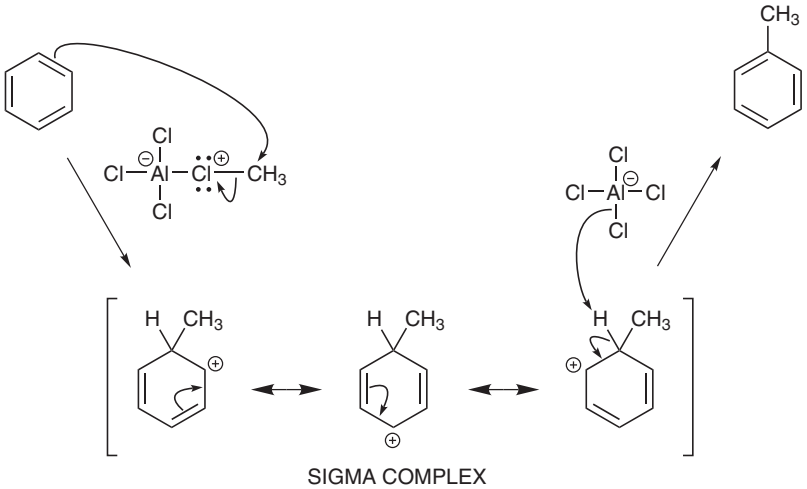


Source of CH_3^+

This provides us with a method for methylating a benzene ring:

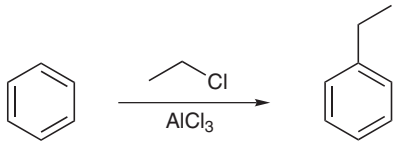


And the mechanism is, once again, the same mechanism that we have seen over and over again. It is an electrophilic aromatic substitution: CH_3^+ ***on*** the ring and then H^+ ***off***:

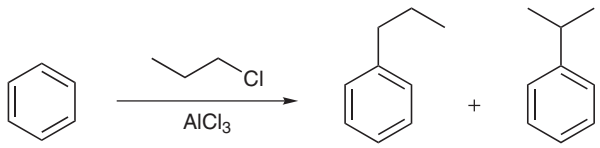


SIGMA COMPLEX

We can use the exact same process to install an ethyl group on an aromatic ring:



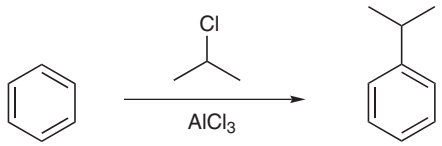
This process (installing an alkyl group onto an aromatic ring) is called a Friedel–Crafts alkylation. It works very well for installing a methyl group or an ethyl group on the ring. BUT we run into problems when we try to install a propyl group on the ring, because a mixture of products is obtained:



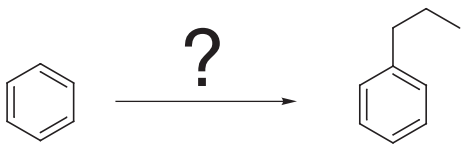
The reason for this is simple. Since we are forming a complex with carbocationic character, it is possible for a carbocation rearrangement to occur. It is not possible for a methyl carbocation to rearrange. Similarly, an ethyl carbocation cannot rearrange to become any more stable. But a propyl carbocation CAN rearrange (via a hydride shift):

And since we are forming a propyl carbocation, we can expect that sometimes it will rearrange before reacting with benzene (while other times, it will not get a chance to rearrange before it reacts with benzene). And that is why we observe a mixture of products. So you need to be careful when using a Friedel–Crafts alkylation to look out for unwanted carbocation rearrangements.

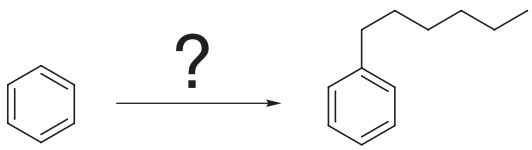
Now, if we wanted to make isopropyl benzene, we could avoid this whole issue by just using isopropyl chloride as our reagent:



But what if we want to make *n*-propyl benzene?



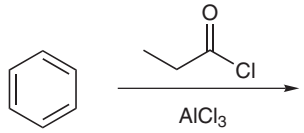
How would we do that? If we use *n*-propyl chloride, we have already seen that we will get some rearrangement, and we will not get a good yield of the desired product. In fact, we can generalize the question like this: how do we install *any* alkyl group and avoid a potential carbocation rearrangement. For example, how could we do the following transformation, ***without*** a carbocation rearrangement?



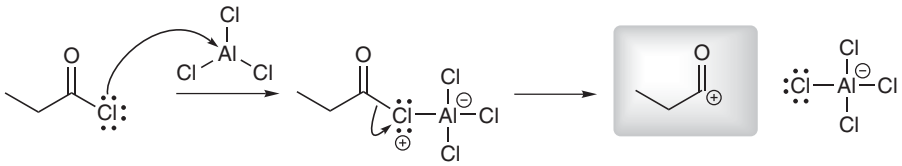
If we just use 1-chlorohexane (and $AlCl_3$), we will likely get a mixture of products.

Clearly, we need a trick. And there is a trick. To see how it works, we need to take a close look at a similar reaction that also bears the name Friedel–Crafts. But this reaction is not an ***alkyl***ation. Rather, it is called an ***acyl***ation. To see the difference, let's quickly compare an alkyl group with an acyl group.

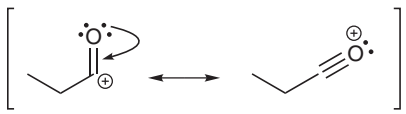
We can install an ***acyl*** group on a benzene ring in exactly the same way that we installed an alkyl group on the ring. We simply use the following reagents:



The first reagent is called an acyl chloride (or acid chloride), and we are already familiar with the role of $AlCl_3$ (the Lewis acid). The Lewis acid interacts with the Cl atom of the acyl chloride, generating a resonance-stabilized acylium ion (highlighted below):



The term ***acylium*** ion should make sense—"*acyl*" because we can see that this electrophile has an acyl group; and "*ium*" because there is a positive charge. This electrophile actually has an important resonance structure:

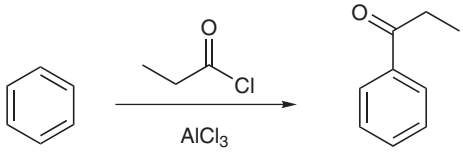


ACYLIUM ION

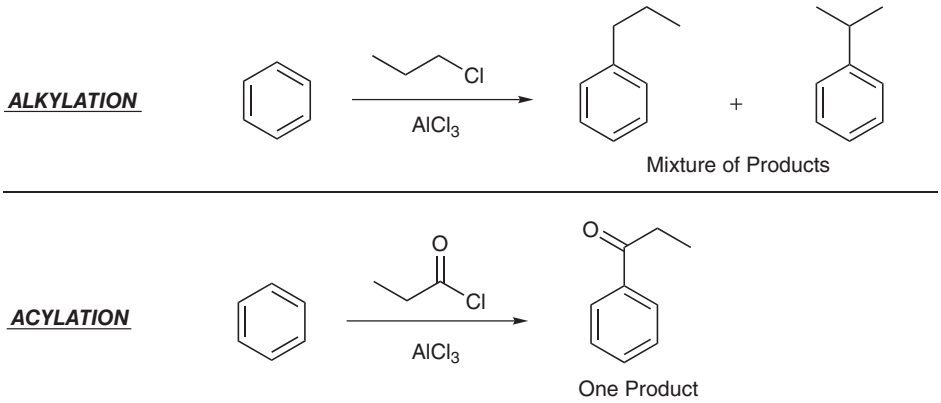
These resonance structures are important because they indicate that an acylium ion is *stabilized* by resonance, and therefore, it will NOT undergo a carbocation rearrangement. (If it did, it would lose this resonance stabilization.) Compare the following two cases:

CAN REARRANGE CANNOT REARRANGE

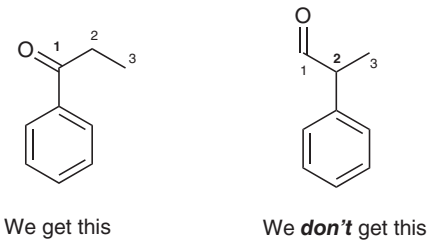
Using a Friedel–Crafts ***acyl***ation, we can cleanly install an acyl group on a benzene ring (without any rearrangements):



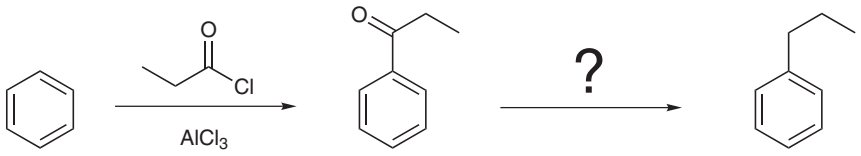
We don't observe any side products that would result from a carbocation rearrangement. Once again, compare a Friedel–Crafts ***alkyl***ation with a Friedel–Crafts ***acyl***ation:



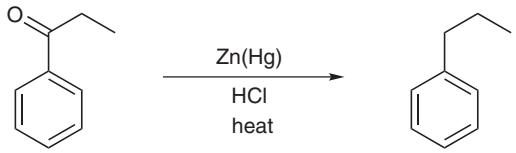
Now take a close look at the acylation above, and let's point out a very important feature. Notice that we have installed a three-carbon chain on the ring, with the chain being attached by the *first* carbon of the chain, as opposed to the middle carbon of the chain:



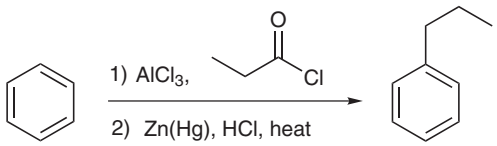
Once again, it is attached by the first carbon because a rearrangement does not occur (the acylium ion is resonance stabilized, and does not rearrange). Now, all we need is a way to reduce the ketone, and then we will have a two-step synthesis for installing an *n*-propyl group on a benzene ring:



And luckily, there is a simple way to reduce a ketone; in fact, we will see *three* common ways to reduce a ketone. We will just focus on one method right now (which uses acidic conditions), but keep in mind that we will see two other methods of doing this in the upcoming chapters (one method uses basic conditions and the other method uses neutral conditions). When we reduce a ketone under acidic conditions, we call the reaction a Clemmensen reduction:



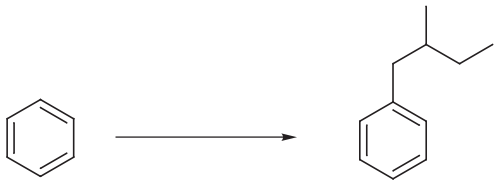
In the presence of HCl and amalgamated zinc (zinc that has been treated so that its surface is an alloy, or mixture, of zinc and mercury), the C═O bond is completely reduced and replaced with two C—H bonds. In this way, a Clemmensen reduction can be used as the second step of a two-step synthesis that installs an alkyl group on an aromatic ring *without* any rearrangement taking place:



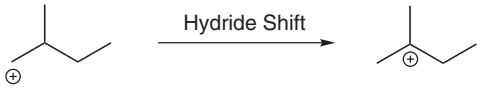
To summarize, we have seen that a Friedel–Crafts acylation can be followed up by a Clemmensen reduction, as a clever way of installing an alkyl group on an aromatic ring (without rearrangements). But there are actually times when you will want to install an acyl group on the ring, and you won't want to do a Clemmensen reduction afterward. For example:

To achieve this transformation, you would just use a Friedel–Crafts acylation, and that's it. There is no need for a Clemmensen reduction, because in this case, we don't want to reduce the C═O bond.

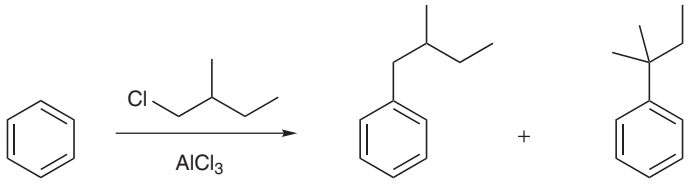
EXERCISE 4.9 Show the reagents you would use to achieve the following synthesis:



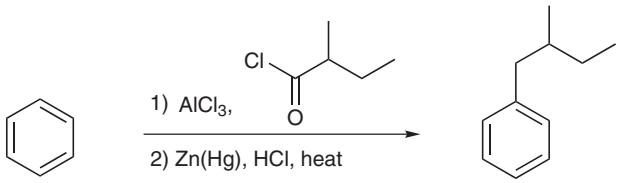
Answer In this problem, we need to install an alkyl group on a benzene ring. So, we first look to see if we could do this in just one step, using a Friedel–Crafts alkylation. In this case, we cannot do it in one step because we have to worry about a carbocation rearrangement. If we think about the electrophile that we would need to make, we will see that it could rearrange:



And this would give us a mixture of products:

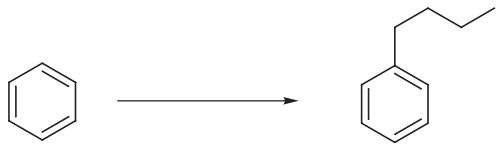


So, instead we will have to use a Friedel–Crafts acylation followed by a Clemmensen reduction:



For each of the following problems, show what reagents you would use to accomplish the transformation. In some situations, you will want to use a Friedel–Crafts alkylation, while in other situations, you will want to use a Friedel–Crafts acylation.

4.10



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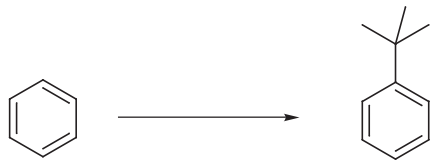

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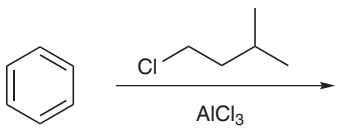
4.14

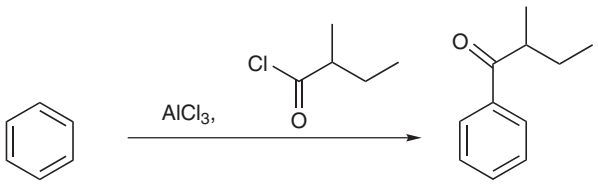
4.15 Predict the products of the following reaction.



(*Hint*: There should be a mixture of *multiple* products in this case. Be sure to consider all of the possible rearrangements that can take place. If you are rusty on carbocation rearrangements, then you should go back and review them now.)

4.16 On a separate piece of paper, draw a mechanism of formation for each one of the three products from the previous problem.

4.17 On a separate piece of paper, draw a mechanism for the following transformation. Make sure to show the mechanism of formation of the acylium ion that reacts with the ring:



Friedel–Crafts reactions have a few limitations. You should take a moment to read about them in your textbook. The two most important limitations are as follows:

1. When performing a Friedel–Crafts ***alkylation***, it is often difficult to install just one alkyl group. Each alkyl group makes the ring *more* reactive toward a subsequent attack on the same ring.
2. When performing a Friedel–Crafts ***acylation***, it is generally not possible to install more than one acyl group. The presence of one acyl group makes the ring *less* reactive toward a second acylation.

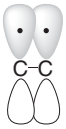
We need to understand WHY an alkyl group makes the ring more reactive, and WHY an acyl group makes the ring less reactive. We will explain this in greater detail during the upcoming sections. But first, we have one more electrophile to discuss.

4.4 SULFONATION

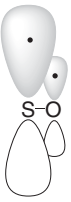
The reaction we will now explore will be used extensively in synthesis problems later in this chapter. If you do not keep this reaction in mind while you are solving synthesis problems, then you will be at a severe loss. We will explain why this reaction is so important in the upcoming sections. For now, just take my word for it, and let's just master the reaction.

The electrophile is SO_3. Let's take a close look at the structure:

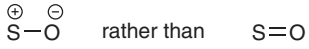
Notice that there are three S═O double bonds here. But these double bonds are not such great double bonds. Recall that a double bond is formed from the overlap of two *p* orbitals:



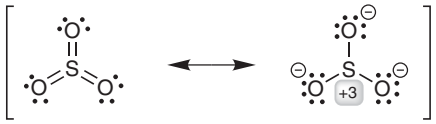
When we are talking about a carbon–carbon double bond, the overlap of the *p* orbitals is efficient because the *p* orbitals are the same size. But what happens when you try to overlap the *p* orbital of an oxygen atom with the *p* orbital of a sulfur atom? The *p* orbitals are different sizes (oxygen is in the second row of the periodic table, which means that it is using a *p* orbital from the second energy level; but sulfur is in the third row of the periodic table, so it is using a *p* orbital from the third energy level):



Therefore, the overlap is not so efficient, and it is misleading to think of S═O as being a double bond. It is probably much closer in nature to being like this:



When we do this analysis for each of the three double bonds in SO_3, we begin to see that the sulfur atom is VERY electron-poor:

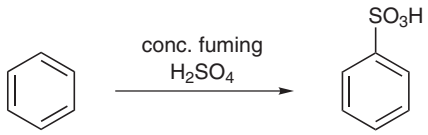


In fact, the sulfur atom is so electron-poor that it is an *excellent* electrophile, even though the compound is overall neutral (no net charge). Now we are going to see a reaction that uses SO_3 as an electrophile.

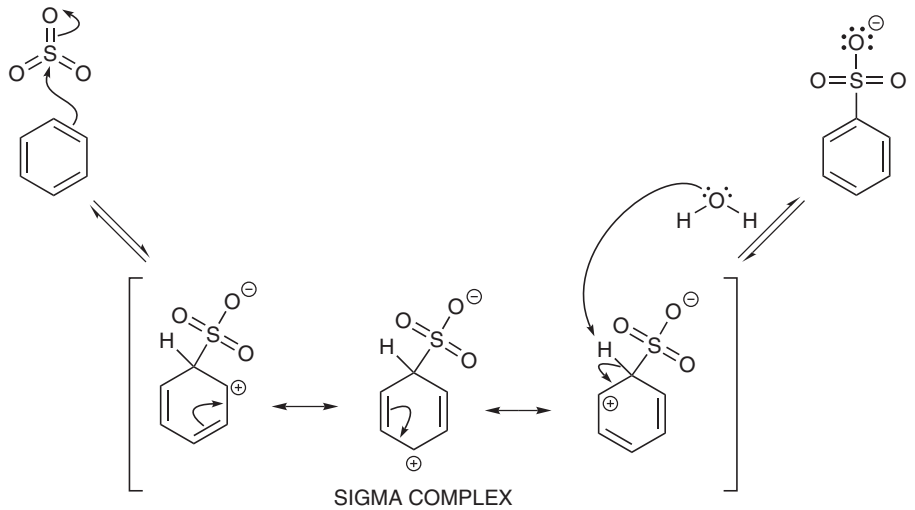
Sulfuric acid is constantly in equilibrium with SO_3 and water:

That means that any bottle of sulfuric acid will have some SO_3 in it. Fuming sulfuric acid is a mixture of sulfuric acid that has a lot of SO_3, and is called "fuming" because of the acrid fumes that it presents when exposed to moisture in the air (SO_3 reacts with moisture to produce the fumes, which are essentially an aerosol of concentrated sulfuric acid). So, from now on, whenever you see concentrated, fuming sulfuric acid, you should realize that we are talking about SO_3 as the reagent.

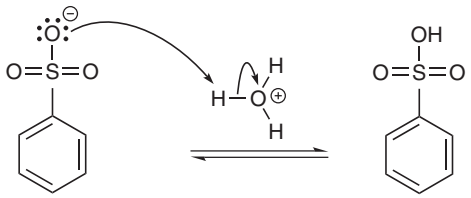
And here is the reaction:



Notice that this process, called sulfonation, installs an SO_3H group on the ring. The obvious question is: why is an H attached to the SO_3 in the end? To see why, let's take a closer look at the mechanism. Remember our two steps for any electrophilic aromatic substitution: E^+ goes on the ring, and then H^+ comes off. But wait a second .... In this case, we are not using an electrophile with a net positive charge. The electrophile in this case has no net charge. In all of the reactions we have seen so far, we put something positively charged onto the ring, and then we took something positively charged off of the ring. So in the end, our ring never gained or lost any charges. But in this case, we are putting something neutral (SO_3) onto the ring, and then we are removing something positively charged (H^+). That should leave our product with an overall negative charge, which is exactly what happens:

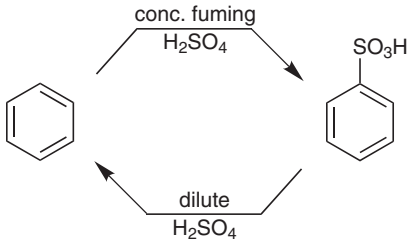


So our mechanism will have one additional step. In the presence of sulfuric acid, the negatively charged oxygen atom is protonated. The likely source of the proton is H_3O^+, rather than H_2SO_4, because aqueous sulfuric acid (even if its concentrated) is a mixture comprised mostly of H_3O^+ and HSO_4^-.



Although this reaction has this one extra step at the end of the mechanism, keep in mind that this extra step is just a proton transfer. The core reaction is still the same as we have seen in all of the previous reactions: the electrophile comes on the ring, and then H^+ comes off of the ring.

An important feature of this reaction (and this is the feature that will make this reaction so important for synthesis problems) is how easily the reaction can be reversed. The amount of product is equilibrium controlled, and it is very sensitive to the conditions. So, if you use dilute sulfuric acid instead, the equilibrium leans the other way:

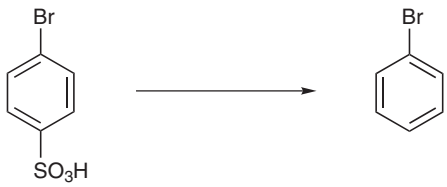


We can use this to our advantage because this provides a way to remove the SO_3H group whenever we want. We would just use dilute sulfuric acid to remove it:

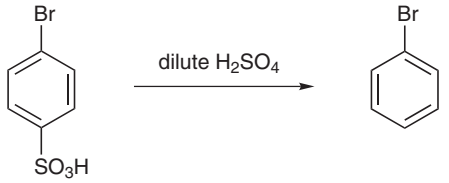
So we now have the ability to install the SO_3H group on the ring whenever we want, AND we can remove it whenever we want as well. You might wonder why you would want to install a group in order just to remove it later. On the surface, that would seem like a waste of time. But in the upcoming sections, we will see that this will become very important in synthesis problems.

For now, let's make sure that we are comfortable with the reagents.

EXERCISE 4.18 Identify the reagents that you would use to achieve the following transformation:

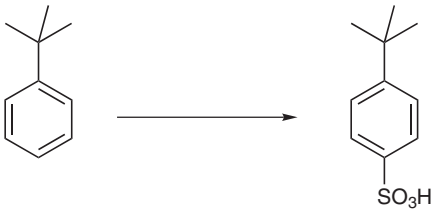


Answer We know that concentrated fuming sulfuric acid will install an SO_3H group on an aromatic ring, and dilute sulfuric acid will remove the group. In this case, we are removing the group, so we need to use dilute sulfuric acid:



Identify the reagents you would use to achieve each of the following transformations:

4.19



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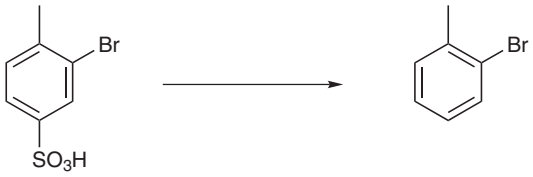

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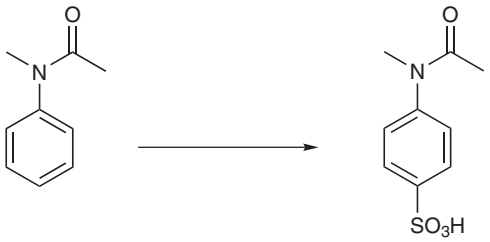

4.22

And to make sure that you are not getting rusty on the other reactions we have learned in this chapter so far, fill in the reagents you would use for the following transformations:

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4.24

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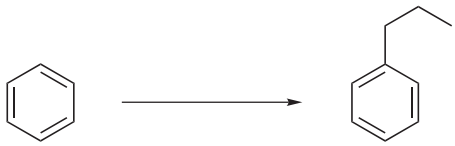
4.27

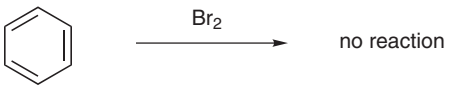


4.28 Now, let's just make sure that you can draw a mechanism for the sulfonation of benzene (on a separate piece of paper). Remember that there will be three steps: (1) electrophile comes on the ring, (2) H^+ comes off, and then (3) proton transfer. Don't forget to draw the resonance structures of the intermediate sigma complex. Try to draw the mechanism without looking back to where it is shown earlier in this section.

4.29 And now, for a challenging problem, try to draw the mechanism of a desulfonation reaction (a reaction where we take the SO_3H group off of the ring). The process will be exactly the reverse of what you just drew in the previous problem. There will be three steps: (1) remove the proton from the SO_3H group, (2) H^+ comes on the ring, and then (3) SO_3 comes off of the ring. The truth is that there are only two core steps here: H^+ comes on the ring, and then SO_3 comes off of the ring. You can actually pull the proton off of the SO_3H group at the same time that SO_3 comes off of the ring. Try to do it yourself, and if you get stuck, you can look at the answer in the back of the book. Make sure that your mechanism involves an intermediate sigma complex (with a resonance-stabilized positive charge).

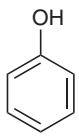
4.5 ACTIVATION AND DEACTIVATION

On the first page of this chapter, we saw that benzene is unreactive toward bromine:



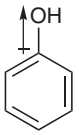
In order to force a reaction to occur, we introduced a Lewis acid into the reaction mixture, which generated a better electrophile (Br^+ is a better electrophile than Br_2). In fact, all of the reactions we have explored thus far have been examples of benzene reacting with powerful electrophiles (Cl^+, NO_2^+, $alkyl^+$, $acyl^+$, and SO_3). Now, we will turn our attention to the nucleophile—how can we modify the reactivity of the aromatic ring?

To answer this question, we will explore substituted benzene rings, and we will consider the effect that a substituent will have on the reactivity of the ring. Benzene itself (C_6H_6) has no substituents. But consider the structure of phenol:



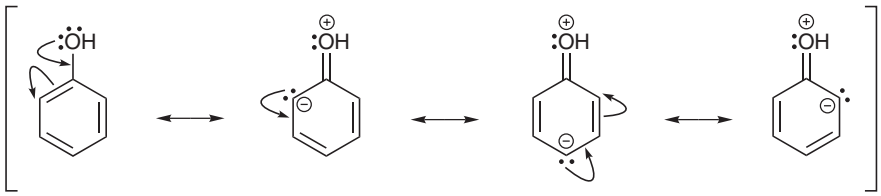
In this compound, the aromatic ring has one substituent: an OH group. What effect does this substituent have on the nucleophilicity of the aromatic ring? Is this compound a stronger nucleophile or a weaker nucleophile than benzene?

To answer this question, we must explore the effect of an OH group on the electron density of the aromatic ring. There are two factors to consider: *induction* and *resonance*. Let's begin with induction. Recall from the first semester that inductive effects can be evaluated by comparing the relative electronegativity of the atoms. In our example, we are looking specifically at the C—O bond connecting the OH group to the ring. Oxygen is more electronegative than carbon, so there is an inductive effect, shown by the following arrow:

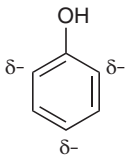


The oxygen atom is withdrawing electron density from the ring. Remember that the aromatic ring is only a nucleophile in the first place because it is electron-rich (from all of those π electrons), so withdrawing electron density from the ring (via induction) should render the ring *less* nucleophilic. But we're not done yet. We need to consider one other factor: resonance.

Below are resonance structures of phenol:



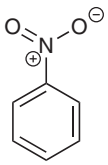
Notice that there is a negative charge spread throughout the ring. When we meld all of these resonance structures together in our minds, we obtain the following information:



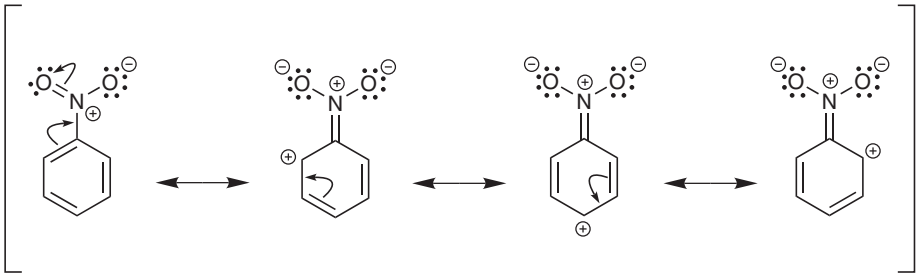
The δ− symbols indicate that there is a partial negative charge spread throughout the ring. Therefore, the effect of resonance is to *donate* electron density to the ring. So, now we have a competition. By induction, the OH group is *electron-withdrawing*, which makes the ring *less* nucleophilic. But by resonance, the OH group is *electron-donating*, which makes the ring *more* nucleophilic. Which effect is stronger? Resonance or induction? This is a common scenario in organic chemistry (where induction and resonance are in competition), and the general rule is: ***resonance is usually a stronger factor than induction***. There are some important exceptions. In fact, we will soon see one of these exceptions, but, in general, resonance wins.

Now let's apply this general rule to our case of phenol. If we say that resonance is stronger than induction, then the net effect of the OH group is to *donate* electron-density to the ring. And therefore, the net effect of the OH group is to make the ring *more nucleophilic* (as compared with benzene).

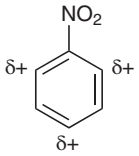
Indeed, experiments reveal that phenol is significantly more nucleophilic than benzene. The effect of the OH group on the nucleophilicity of the aromatic ring is called "activation." The OH group is said to be activating the ring (making it more nucleophilic). So, the OH group is called an *activator*. Alkyl groups (such as methyl or ethyl) are also activators (recall from the first semester that alkyl groups are electron donating because of an effect called hyperconjugation). There are some groups, though, that actually *withdraw* electron density from the ring, and we call those groups *deactivators*, because they deactivate the ring (make the ring *less* nucleophilic). An excellent example is the nitro group. Consider the structure of nitrobenzene:



Once again, the effect of the nitro group can be evaluated by exploring two factors: induction and resonance. Induction is simple. The nitrogen atom is more electronegative than the carbon atom to which it is connected (especially since the nitrogen atom bears a positive charge). So the nitro group withdraws electron density from the ring via induction, which should render the ring less nucleophilic. But we're not done yet. We still have to consider resonance. Below are resonance structures of nitrobenzene:



Notice that there is now a positive charge spread throughout the ring (rather than a negative charge, as we saw in the case of phenol). When we meld all of these resonance structures together in our minds, we obtain the following information:

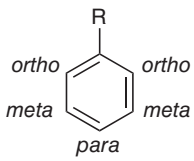


The δ+ symbols indicate that there is a partial positive charge spread throughout the ring. Therefore, the effect of resonance is to *withdraw* electron density from the ring.

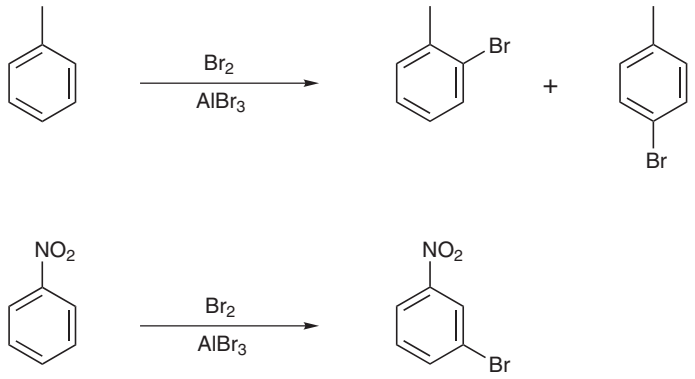
In summary, the nitro group is electron-withdrawing via resonance *and* via induction. In other words, there is no competition between resonance and induction. Both factors dictate that a nitro group should *deactivate* the ring. And that is indeed what we observe in the laboratory.

4.6 DIRECTING EFFECTS

Now let's consider electrophilic aromatic substitution reactions with substituted benzene rings. In order to explore this topic, we must first review important terminology that we will use frequently throughout the remainder of this chapter. The various positions on a monosubstituted benzene ring are referred to in the following way:



The two positions that are closest to the substituent (R) are called *ortho* positions. Then we have the *meta* positions. And finally, the farthest position from the substituent is called the *para* position. With this terminology in mind, let's consider the products obtained when toluene or nitrobenzene undergo bromination. Both reactions are shown below:

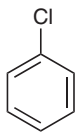


The first reaction (with toluene) is certainly faster, because the methyl group activates the ring toward electrophilic aromatic substitution, while the nitro group deactivates the aromatic ring. But consider the difference in regiochemical outcome. Specifically, notice that the methyl group directs the reaction to occur at the *ortho* and *para* positions, while the nitro group directs the reaction to occur at the *meta* position. Your textbook will give an explanation for this observation, and you should read that explanation, but here is the bottom line:

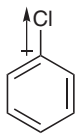
- Activators are *ortho-para* directors
- Deactivators are *meta* directors

We will not encounter any exceptions to the first rule (all activators that we encounter will be *ortho-para* directors). But there is one important exception to the second rule above. Halogens (F, Br, Cl, or I) are deactivators, so we might expect them to be *meta* directors. But instead, they are actually *ortho-para* directors. Let's try to understand why halogens are the exception.

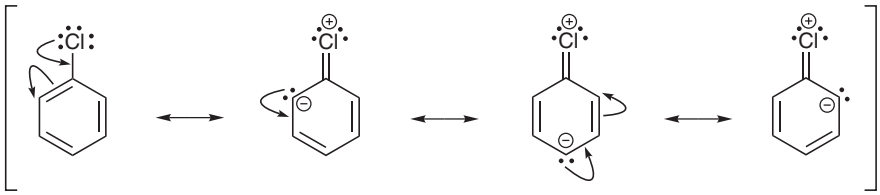
In the previous section, we analyzed the effect of an OH group on an aromatic ring, and we saw that there were two competing effects: induction and resonance. We saw that induction *withdraws* electron density from the ring, but resonance *donates* electron density to the ring. In order to know which factor dominates, we gave a general rule: ***resonance is usually a stronger factor than induction***. We also said that there was an important exception to this general rule that we would see later. Well, it is now later. Halogens are the exception. Let's take a closer look. As an example, consider the structure of chlorobenzene:



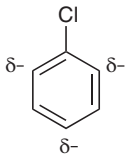
The substituent in this case (Cl) is an *ortho-para* director for the same reason that an OH group is an *ortho-para* director. But, unlike OH (which is an activator), Cl is a deactivator. To explain why, we must explore the effect of a halogen (such as Cl) on the electron density of the aromatic ring. As we have seen in the previous section, our analysis must focus on two factors: induction and resonance. Let's start with induction. Just like an OH group, a halogen is also electron-withdrawing by induction:



However, we also need to consider resonance effects. So, we draw the resonance structures:



And once again, we see that a halogen is very similar to an OH group. It is donating electron density by resonance:



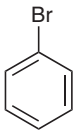
Now let's consider the net effect of a halogen. Just as we saw with the OH group, there is a competition between resonance and induction. And just as we saw with the OH group, a halogen will *withdraw* electron density by induction, and it will *donate* electron density by resonance. But, in the case of the OH group, we used the argument that resonance beats induction (we said that was a general rule that holds true most of the time). Therefore, the net effect of the OH group was to donate electron density to the ring (thus, the OH group is an activator). But with a halogen, resonance does NOT beat induction. This is one of the rare cases where induction actually beats resonance. Why is resonance not the predominant factor in this case? To answer this question, notice that the resonance structures of chlorobenzene exhibit a positive charge on Cl. Halogens do not easily bear positive charges. So, these resonance structures do not contribute very much character to the overall structure of the compound. Resonance is a weak effect in this case, so induction actually beats resonance. Therefore, the net effect of a halogen substituent is to *withdraw* electron density from the aromatic ring, rendering the ring less nucleophilic (deactivation).

Now we are ready to modify the rules we gave earlier when we said that all activators are *ortho-para* directors and all deactivators are *meta* directors. Here is our new-and-improved formula:

- All activators are *ortho-para* directors.
- All deactivators are *meta* directors, ***except for halogens (which are deactivators, but nevertheless, they are ortho-para directors)***.

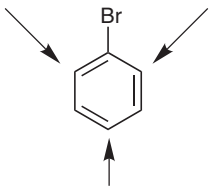
With that in mind, let's try to predict some directing effects.

EXERCISE 4.30 Look closely at the following monosubstituted benzene ring.

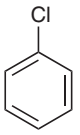


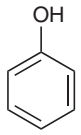
If this compound were to undergo an electrophilic aromatic substitution reaction, predict where the incoming substituent would be installed.

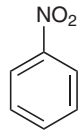
Answer Br is a halogen (remember that the halogens are F, Cl, Br, and I). We have seen that halogens are the one exception to the general rules. That is, they are deactivators but they are not *meta* directors, like most other deactivators. Rather, they are *ortho-para* directors. Therefore, if we use this compound in an electrophilic aromatic substitution, we expect substitution to take place at the *ortho* and *para* positions:

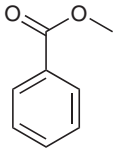


Identify the expected directing effects that would be observed if each of the following compounds were to undergo an electrophilic aromatic substitution reaction.

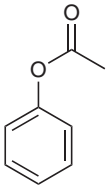
4.31 

4.32 

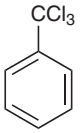
4.33 

4.34 

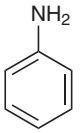
This group is a deactivator.

4.35 

This group is an activator.

4.36 

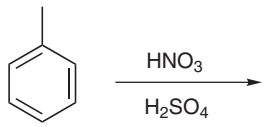
This group is a deactivator.

4.37 

This group is an activator.

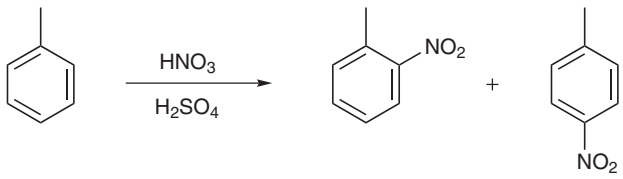
Clearly, you can only predict where the substitution will take place if you know whether the group is an activator or a deactivator. In the next section, we will learn how to predict whether a group is an activator or a deactivator. But for now, let's get some practice predicting products.

EXERCISE 4.38 Predict the major product(s) of the following reaction:

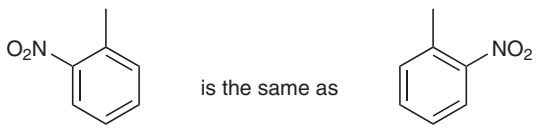


Answer We begin by looking at the reagents, so that we can determine what kind of reaction is taking place. The reagents are nitric acid and sulfuric acid. We have seen that these reagents generate NO_2^+ as an electrophile, which can react with an aromatic ring in an electrophilic aromatic substitution reaction. The end result is to install a nitro group on an aromatic ring. So, now the question is: where is the nitro group installed?

To answer this question, we must predict the directing effects of the group already present on the ring (before the reaction takes place). There is a methyl group on the ring, and we have seen that methyl groups are activators. Therefore, we predict that the reaction will take place at the *ortho* and *para* positions, relative to the methyl group:

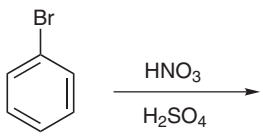


Notice that substitution at either *ortho* position gives the same product:

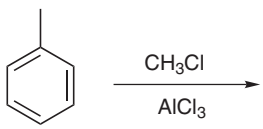


Predict the major product(s) for each of the following reactions:

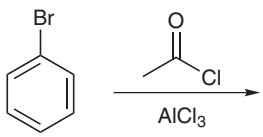
4.39



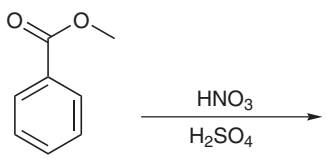
4.40



4.41

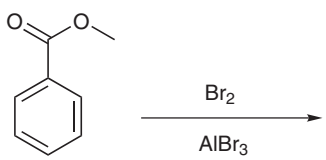


4.42



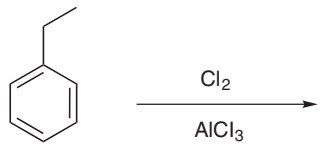
Hint: The group on the ring is a deactivator.

4.43



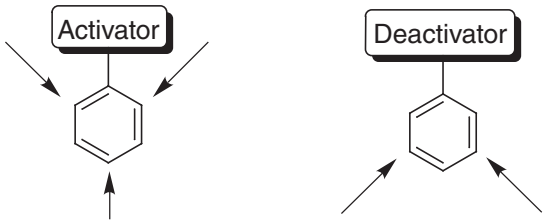
Hint: The group on the ring is a deactivator.

4.44



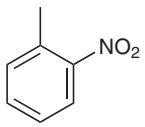
Hint: The group on the ring is an activator.

So far, we have focused on the directing effects when you have *only one group* on a ring. And we have seen that activators direct toward the *ortho* and *para* positions, whereas deactivators direct toward the *meta* positions:



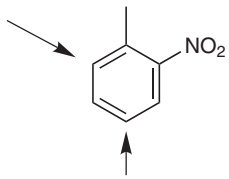
and we saw only one exception (the halogens).

But how do you predict the directing effects when you have *more than one group* on a ring? For example, consider the following compound:



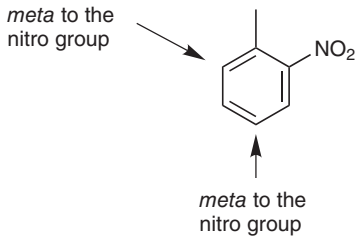
What if we used this compound in an electrophilic aromatic substitution reaction? For example, let's say we try to brominate this compound. Where will the bromine atom be installed?

Let's first consider the effect of the methyl group. We mentioned before that a methyl group is an activator, so we predict that it will direct toward the *ortho* and *para* positions:



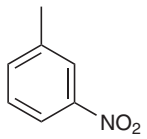
Notice that we do ***not*** point to the *ortho* position that already bears the nitro group (we only look at positions that are unoccupied—remember that in an electrophilic aromatic substitution, E^+ comes on the ring and $\underline{\boldsymbol{H}^+}$ comes off). So, the methyl group is directing toward *two* spots, as shown above.

Now let's consider the effect of the nitro group. We mentioned before that the nitro group is a powerful deactivator. Therefore, we predict that it should direct to the positions that are *meta* ***to the nitro group:***

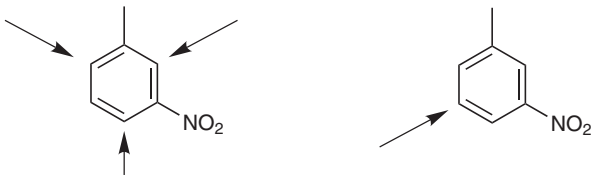


We see that the nitro group and the methyl group are directing toward the same two spots. So, in this case there is no conflict between the directing effects of the nitro group and the methyl group.

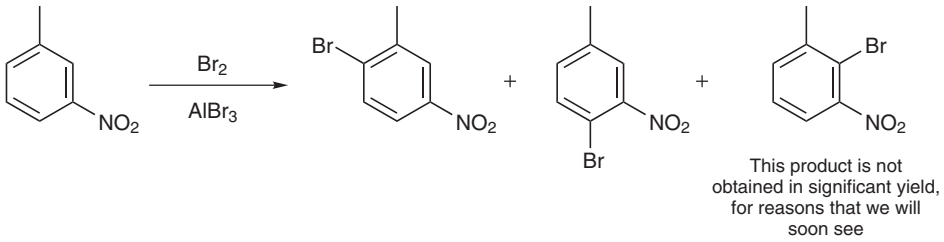
But consider this case:



The methyl group and the nitro group are now directing toward different positions:

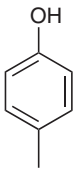


So, the big question is: which group wins? It turns out that the directing effects of the methyl group trump the directing effects of the nitro group. So, if we brominate this ring, we will get the following products (where the Br is installed *ortho* or *para* to the methyl group):

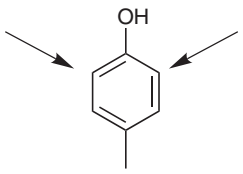


It is common to see a situation where the directing effects of two groups are competing with each other (like the methyl group and nitro group in the above example). So we clearly need rules for determining which group wins. It turns out that you need to know just two simple rules in order to determine which group will dominate the directing effects:

1. *Ortho-para directors always beat meta directors.* The example we just saw is a perfect illustration of this rule. The methyl group is an activator (an *ortho-para* director), and the nitro group is a deactivator (a *meta* director), so the methyl group wins.
2. *Strong activators always beat weak activators.* For example, consider the following case:



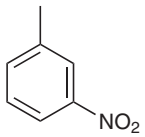
The OH group is a *strong* activator, and the methyl group is a *weak* activator. (We will learn in the next section how to predict which groups are strong and which are weak—for now, just take my word for it.) So, the OH group will win, and the directing effects are as follows:



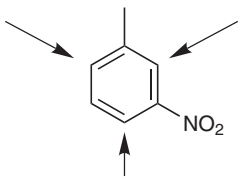
So, we have seen two rules:

- *ortho-para directors always beat meta directors*.
- ***Strong** activators always beat **weak** activators*.

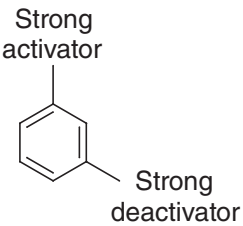
Keep in mind that the first rule always trumps the second rule. So if you have a weak activator against a strong deactivator, the weak activator wins. Even though the activator is weak, it still beats a strong deactivator because activators (*ortho-para* directors) always beat deactivators (*meta* directors). This rule was already seen in one of our previous examples:



The methyl group is a weak activator, and the nitro group is a strong deactivator. So, in this case, the methyl group wins (and the directing effects are *ortho* and *para* to the methyl group; and ***not** meta* to the nitro group):

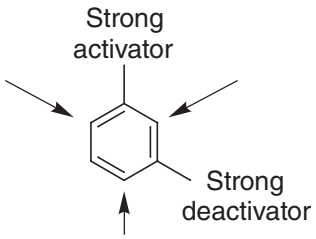


EXERCISE 4.45 Predict the directing effects for an electrophilic aromatic substitution reaction involving the following type of disubstituted aromatic ring.

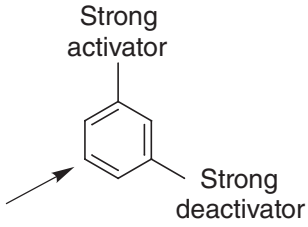


For this problem, you should assume that the deactivator is *not* a halogen.

Answer We have two groups. The activator will direct toward the positions that are *ortho* or *para* to itself, and the deactivator will direct toward the positions that are *meta* to itself:

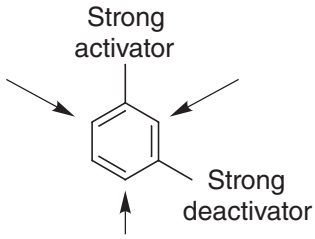


Directing effects of the activator

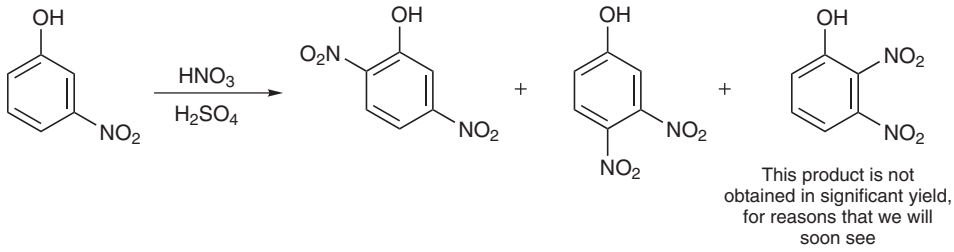


Directing effects of the deactivator

So, there is a competition in the directing effects. Between the two groups, the strong activator beats the strong deactivator because the strong activator is an *ortho-para* director. So the directing effects are:



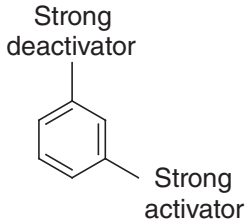
If we performed an electrophilic aromatic substitution on a compound of this type, we might expect three products (because the directing effects are toward three positions, shown above). Here is a specific example of a reaction like this.



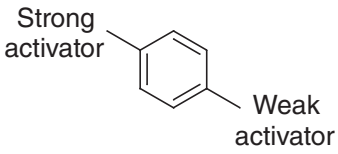
The starting aromatic ring has two substituents. The OH group is a strong activator, and the nitro group is a strong deactivator.

Predict the directing effects for an electrophilic aromatic substitution reaction involving each of the following types of disubstituted aromatic rings. Unless otherwise indicated, assume that anything labeled as a deactivator is not a halogen (unless it is specifically indicated as a halogen).

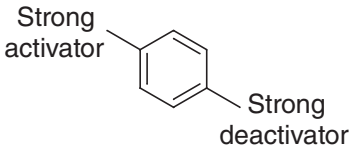
4.46



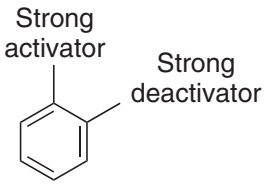
4.47



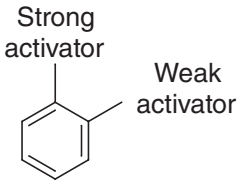
4.48



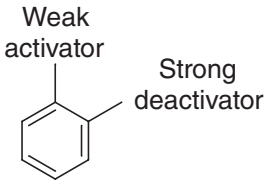
4.49



4.50



4.51

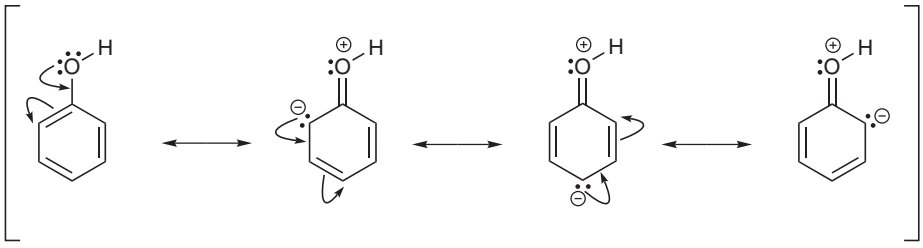


4.7 IDENTIFYING ACTIVATORS AND DEACTIVATORS

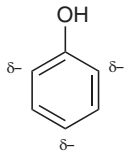
In the previous section, we learned how to predict the directing effects in a situation where you have more than one group on the ring. But in all of the cases in the previous section, I had to tell you whether each group was an activator or a deactivator and whether it was strong or weak. In this section, we will learn how to predict this, so that you won't have to memorize the characteristics of every possible group. In fact, very little memorization is actually involved here. We will see a few concepts that should make sense. And with those concepts, you should be able to identify the nature of any group, even if you have never seen it before.

We will go through this methodically, starting with strong activators.

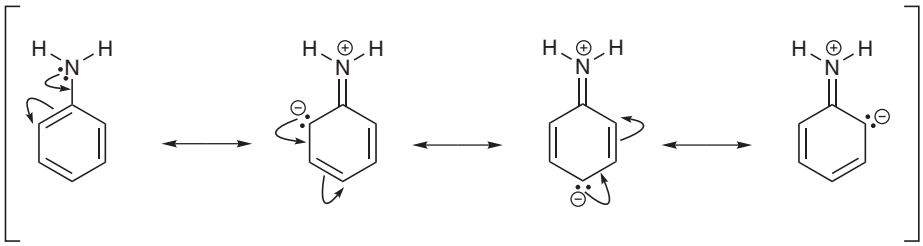
Strong activators are groups that have a lone pair next to the aromatic ring. We have already seen an example of this. When an OH group is connected to the ring, there is a lone pair next to the ring, which gives rise to the following resonance structures:



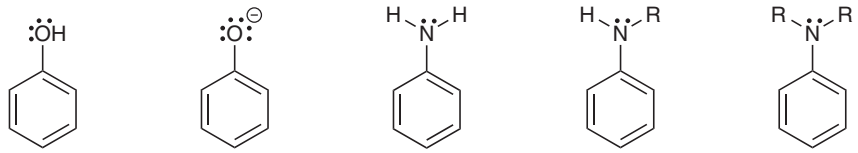
We concluded in the previous section that this resonance effect is very strong and that the OH group is therefore donating a lot of electron density to the ring:



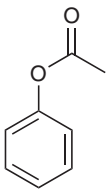
Since the ring is electron-rich, it is a stronger nucleophile than benzene and is more reactive (activated) toward reaction with an electrophile. This effect is observed not only for the OH group, but also for other groups that have a lone pair next to the ring. The same kind of resonance structures can be drawn for an amino group connected to a ring:



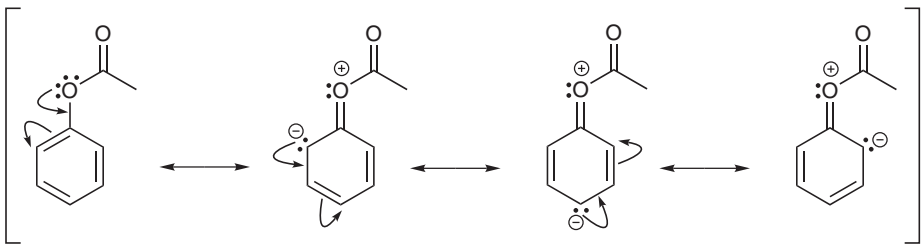
Here are several examples of strong activators. Make sure that you can easily see the common feature (the lone pair next to the ring):



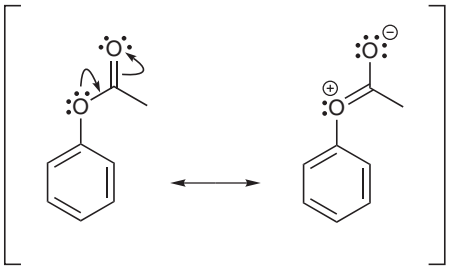
Next, we move on to the *moderate* activators. Moderate activators are groups that have a lone pair next to the ring, BUT that lone pair is already partially tied up in resonance. For example, consider the following group:



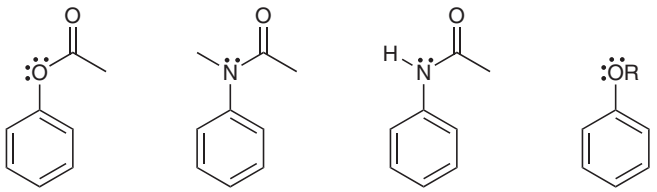
This compound has all of the resonance structures that place electron density into the ring (just like an OH group does):



BUT there is an additional resonance structure, which has the electron density *outside* of the ring:



Therefore, the electron density is more spread out (with some in the ring and some out of the ring). This group is therefore not a *strong* activator. Rather, we call it a *moderate* activator. (Some textbooks do not point out this subtle distinction between strong activators and moderate activators.) Here are several examples of moderate activators:



Look closely at the examples above. They all have a lone pair that is tied up in resonance outside of the ring. BUT WAIT A SECOND. What about the last group on this list (the OR group)? This group has a lone pair that is NOT tied up in resonance outside of the ring. We should predict that this group should belong in the first category (*strong* activators), but for some reason, it isn't in that category. It is actually just a *moderate* activator. This is one of the rare examples that departs from the logical explanations that we have given so far. I have spent quite a bit of time trying to figure out why the OR group is a moderate activator (rather than a strong activator). I have come up with several answers over the years, but I am not going to spend several pages dedicated to an esoteric topic that you will certainly not need for your exams (perhaps you might think of it as a brain teaser—something to think about …). For now, you will just have to remember that the OR group doesn't follow the trends we have seen. It is a moderate activator.

Now let's turn our attention to *weak* activators. Alkyl groups (such as methyl, ethyl, propyl, etc.) are weak activators because they donate electron density to the ring via hyperconjugation (a weak effect). We previously encountered hyperconjugation to explain why tertiary carbocations are more stable than secondary carbocations. Similarly here, alkyl groups also exhibit an electron-donating effect (albeit weak), and they are therefore weak activators.

Now we have seen all of the different categories of activators (strong, moderate, and weak). To review, this is what we saw:

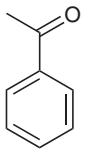
Strong Activators	Lone pair next to ring
Moderate Activators	Lone pair next to ring, but tied up in resonance outside of ring as well
Weak Activators	Alkyl groups

Now, we will turn our attention to the different categories of ***de****activators*. This time, we will begin with the *weak* deactivators and work our way toward *strong* deactivators (rather than starting with strong). There is a reason for using this order, and that reason will soon become clear.

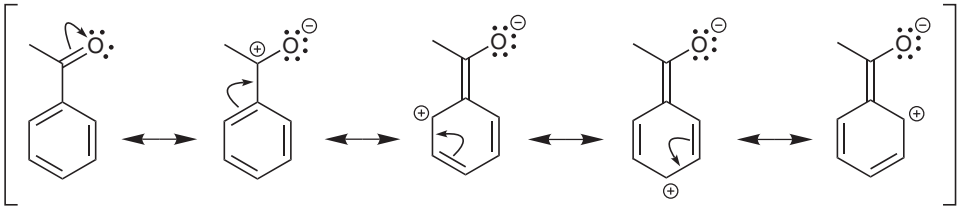
Weak deactivators are the halogens. We have already seen that halogens are the one case where induction beats resonance (and therefore, we argued that the net effect of a halogen is to *withdraw* electron density from the ring). So, we saw that halogens are deactivators. But you should know that the competition between induction and resonance (in the case of the halogens) is a close competition, so halogens are only weakly deactivating.

We will summarize all of this information in one complete chart, but for now let's move on to moderate deactivators.

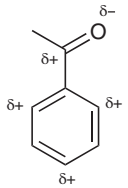
Groups that withdraw electron density from the ring via resonance are moderate deactivators. For example, consider the following group:



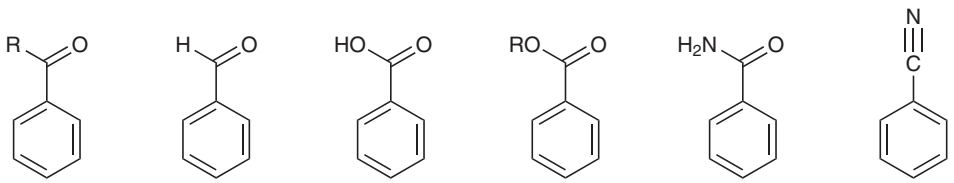
This group does *not* have a lone pair next to the ring (so it is *not* an activator). But it does have a pi bond next to the ring, giving rise to the following resonance structures:



When we look closely at these resonance structures, we can see that the substituent is *withdrawing* electron density from the ring:

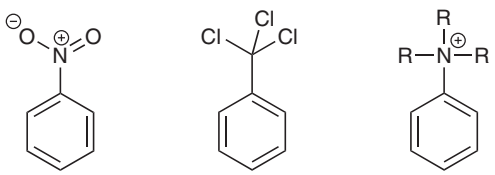


Therefore, this group is a *moderate deactivator*. Numerous other similar groups can also withdraw electron density from the ring. Here is a list of many examples:



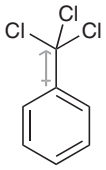
All of these substituents are withdrawing electron density from the ring via resonance. They all have one feature in common: a pi bond to an electronegative atom. Take a close look at the last example. A cyano group is a pi bond (a triple bond) to an electronegative atom (nitrogen). So we see that a triple bond can also be included in this category.

And now for the last category: *strong* deactivators. There are a few common functional groups that fall into this category:

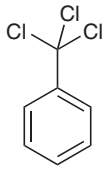


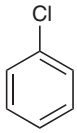
We have already explained why the nitro group is so powerfully electron-withdrawing. The nitro group is electron-withdrawing by resonance *and* induction.

To understand why the second group shown (the trichloromethyl group) is a strong deactivator, we need to focus on the collective inductive effects of all of the chlorine atoms:



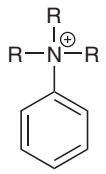
The inductive effects of each chlorine atom add together to give one very powerful deactivating group. Be careful not to confuse this group with a halogen on a ring:



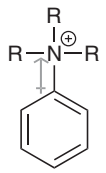


When a halogen is connected directly to the ring (above right), then there are resonance effects to consider. (We spent a lot of time talking about the competition between resonance and induction in the case of halogens.) The group we are talking about now (above left) does not have any resonance effects to consider because the lone pairs are *not* directly next to the ring. So, there is only an inductive effect to consider, and this inductive effect is very significant in this case (because there are three inductive effects adding together).

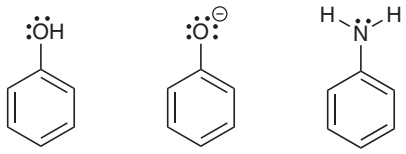
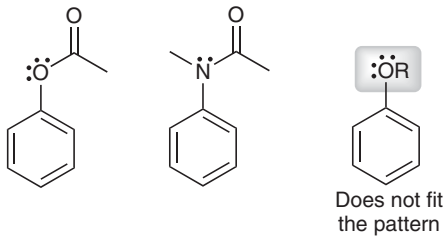
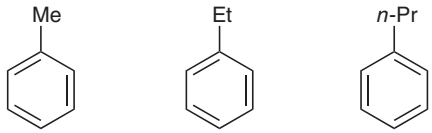
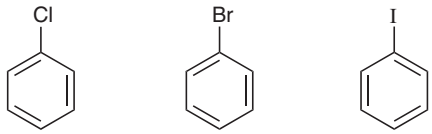
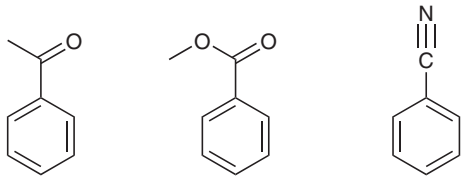
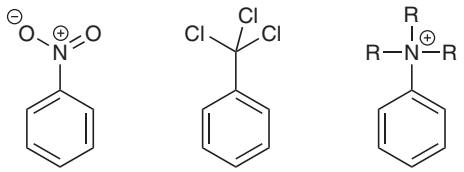
When we consider our final example of a *strong deactivator*, we see a nitrogen atom with a positive charge next to the ring:



The nitrogen atom is so poor in electron density that it is practically sucking electron density out of the ring like a vacuum cleaner:

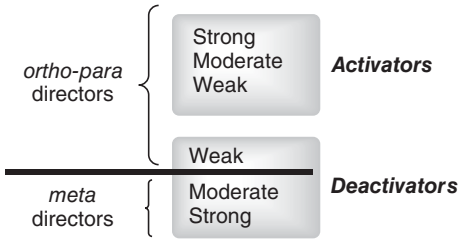


Now we are ready to summarize everything we have seen into one chart:

	Common Feature	Some Examples
ACTIVATORS		
Strong	Lone pair next to ring	
Moderate	Lone pair next to ring But tied up in resonance outside of ring as well	 Does not fit the pattern
Weak	Alkyl groups	
DEACTIVATORS		
Weak	Halogens	
Moderate	Pi bond to an electronegative atom (next to ring)	
Strong	Very powerfully electron-withdrawing	

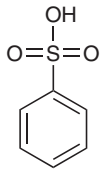
Take a close look at this chart and make sure that every category makes sense to you. As you look over the chart, you should be able to remember the arguments that we gave for each category. If you have trouble with this, you might want to review the last few pages of explanation.

And now we can understand why we looked at weak deactivators first (before strong deactivators). When we organize it like this, we can clearly organize the directing effects in our minds:



This chart shows that all activators are *ortho-para* directors and all deactivators are *meta* directors, with the exception of the weak deactivators (halogens).

EXERCISE 4.52 Look closely at the following substituent:

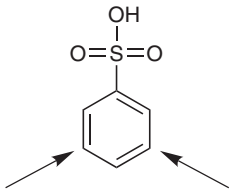


Try to predict what kind of group it is (a strong activator, a moderate activator, a weak activator, a weak deactivator, a moderate deactivator, or a strong deactivator).

Use this information to predict the directing effects if this compound were to undergo an electrophilic aromatic substitution reaction.

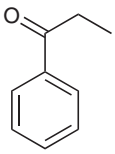
Answer This group does not have a lone pair next to the ring, and it is not an alkyl group. Therefore, it is not an activator. This group has a pi bond to an oxygen atom (next to the ring), and therefore, it is a moderate deactivator.

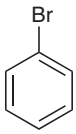
Because all deactivators are *meta* directors (except for weak deactivators—halogens), we predict the following directing effects (Note: substitution at either position leads to the same product):

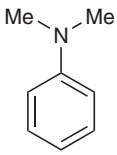


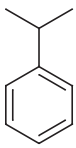
For each of the following substituents, determine what kind of group it is (a strong activator, a moderate activator, a weak activator, a weak deactivator, a moderate deactivator, or a strong deactivator). Place your answer on the space provided. Try to do this ***without*** looking at the chart that we constructed. You won't have access to this chart on an exam. Try to remember and apply the explanations that we used.

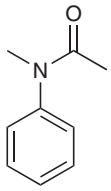
Then, use that information to predict the directing effects. Indicate the directing effects using arrows for pointing to the positions where you would expect an electrophilic aromatic substitution to occur:

4.53  Answer: _____

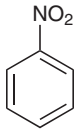
4.54  Answer: _____

4.55  Answer: _____

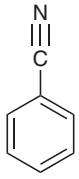
4.56  Answer: _____

4.57 

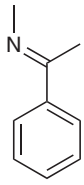
Answer: _____

4.58 

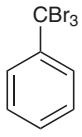
Answer: _____

4.59 

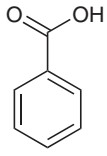
Answer: _____

4.60 

Answer: _____

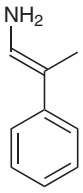
4.61 

Answer: _____

4.62 

Answer: _____

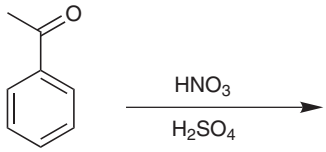
4.63 Can you explain why the following group is a strong activator:



(*Hint*: Think about what strong activators have in common.)

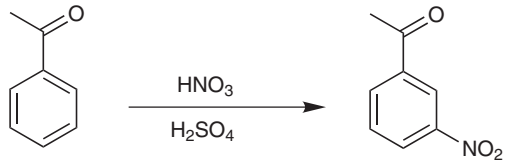
Now we can use the skills that we developed in this section to predict the products of a reaction. Let's see an example:

EXERCISE 4.64 Predict the major product(s) of the following reaction:



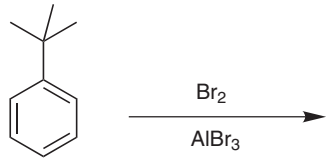
Answer We look at the reagents to see what kind of reaction we expect. The reagents are nitric acid and sulfuric acid. These reagents generate NO_2^+, which is an excellent electrophile. So, we know that the reaction will install a nitro group on the ring. But the question is: where?

To answer this question, we must predict the directing effects of the group that is currently on the ring. We recognize that this group is a moderate deactivator, which means that it must be a *meta* director. So, we predict the following product:

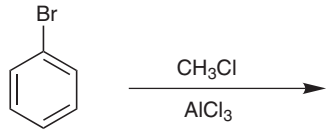


Predict the major product(s) of the following reactions:

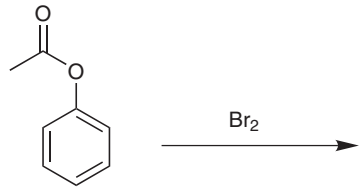
4.65



4.66



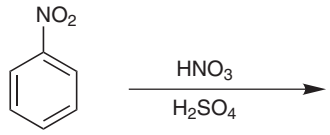
4.67



Notice that in this reaction, we do not need a Lewis acid catalyst. Can you explain why not?

4.68

4.69

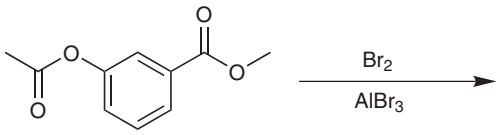


Now let's combine what we did in the previous section with the material in this section. Recall from the previous section that we learned how to predict the directing effects when you have more than one group on the ring. When the two groups are competing with each other, we saw that you can determine the directing effects by using the following two rules:

- *ortho-para directors always beat meta directors.*
- ***Strong** activators always beat **weak** activators.*

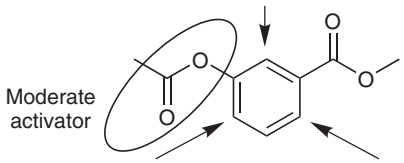
Now that we have learned how to categorize the various kinds of groups, let's get practice using our skills to predict products:

EXERCISE 4.70 Predict the major product(s) of the following reaction:

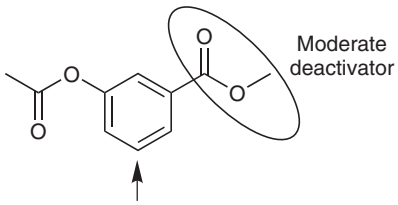


Answer We look at the reagents to see what kind of reaction we expect. The reagents are bromine and aluminum tribromide. These reagents generate Br^+, which is an excellent electrophile. So, we know that we will be installing a Br atom on the ring. But the question is: where?

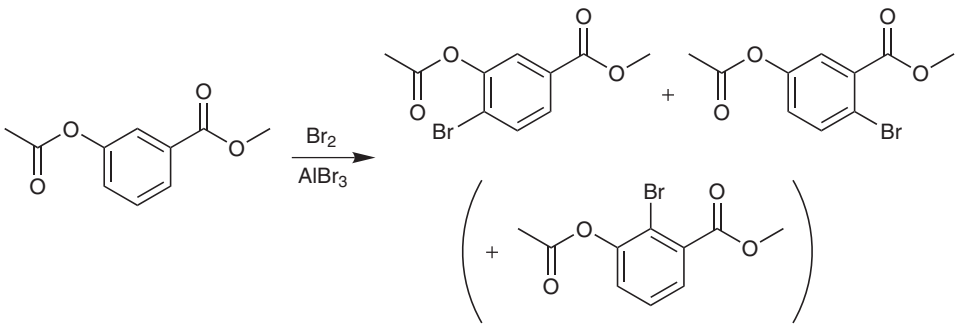
To answer this question, we must predict the directing effects of the two groups that are currently on the ring. The group on the left is a moderate activator (make sure that you know why), and therefore, it directs *ortho* and *para* to itself:



The group on the right is a moderate deactivator (make sure you know why), so it directs *meta* to itself:



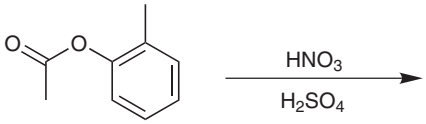
There is a competition between these two groups. Remember our first rule for determining which group wins: *ortho-para* directors beat *meta* directors. So, we expect the following products:



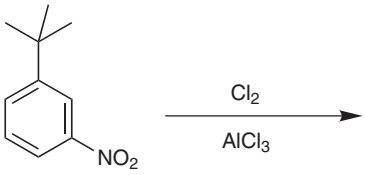
Notice that I placed the last product in parentheses. This product is actually a very minor product. We will see why in the next section. For now, we will just write that we expect three products. Then, we will fine-tune this prediction in the next section.

PROBLEMS Predict the products of the following reactions:

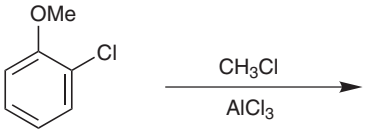
4.71



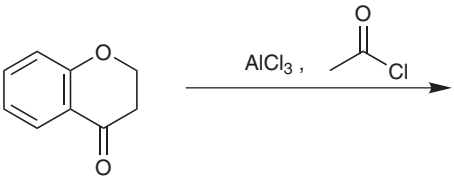
4.72



4.73



4.74

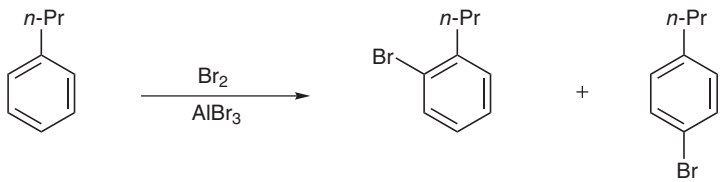


(*Hint*: Consider this aromatic ring as having two separate substituents, and analyze each separately.)

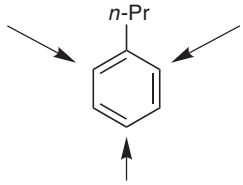
4.8 PREDICTING AND EXPLOITING STERIC EFFECTS

In the previous sections, we learned the skills that we need in order to predict the products of an electrophilic aromatic substitution. We saw many cases where there is ***more*** than one product. For example, if the ring is activated, then we expect *ortho* ***and*** *para* products. In this section, we will see that it is possible to predict which product will be the major product and which will be the minor product (*ortho* vs. *para*). It is even possible *to control* the ratio of products (*ortho* vs. *para*). This is VERY important for synthesis problems, which will be the next (and final) section of this chapter.

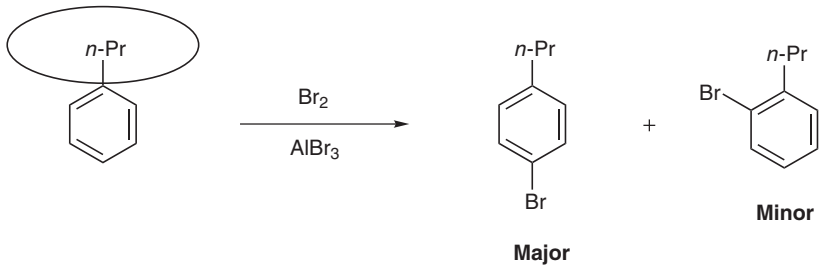
Consider an electrophilic aromatic substitution with *n*-propyl benzene. The *n*-propyl group is a weak activator, and therefore, we expect the directing effects to be *ortho-para*:



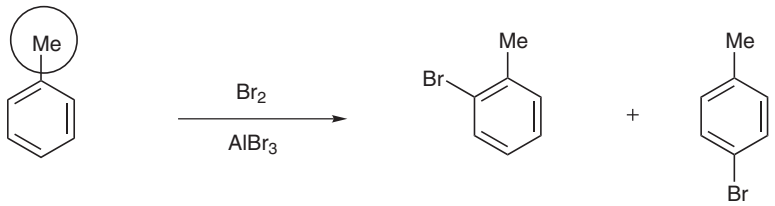
There are two products here. But let's try to figure out which one of these products is the major product? *ortho* or *para*? At first, we might be tempted to say that the *ortho* product should be major. Let's see why. The *n*-propyl group is an *ortho-para* director, so there should be a total of three positions that can get attacked (two *ortho* positions and one *para* position):



Therefore, the chances of attacking an *ortho* position should be twice as likely as the chances of attacking the *para* position. From a purely statistical point of view, we should therefore expect our product distribution to be 67% *ortho* and 33% *para*. But the product ratio is different from what we might expect, because of steric considerations. Specifically, the *n*-propyl group is fairly large, and it partially "blocks" the *ortho* positions. We do still observe *ortho* products, but much less than 67%. In fact, the *para* product is the major product in this case:

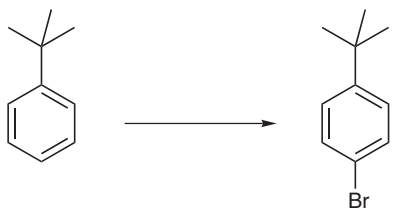


This is usually the case (that *para* is the major product). A notable exception is toluene (methylbenzene), for which the ratio of *ortho* and *para* products is sensitive to the conditions employed, such as the choice of solvent. In some cases, the *para* product is favored; in other cases, the *ortho* product is favored. Therefore, it is generally not wise to use the directing effects of a methyl group to favor a reaction at the *para* position over the *ortho* position.



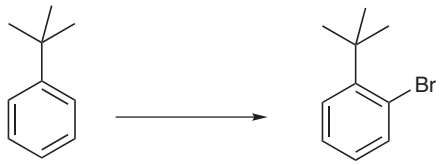
But this is only the case with a methyl group. With just about any other group, we should expect that the *para* product will be the major product. Keep that in mind because it is very important—*para* is usually the major product.

With that in mind, imagine that I asked you to propose an efficient synthesis for the following transformation:



This is simple to do. The *tert*-butyl group is so large that we expect the *para* product to be the major product. So we just use Br_2 and $AlBr_3$, and we should obtain the desired product.

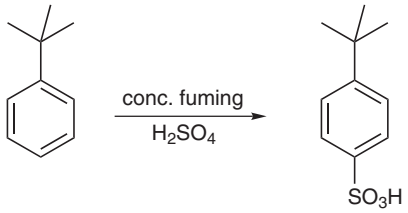
But suppose we wanted substitution to occur at the *ortho* position:



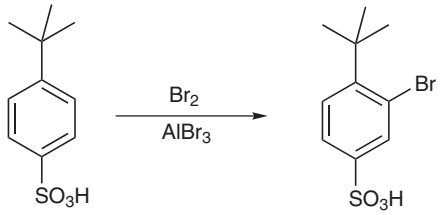
How would we do this? When confronted with this problem, students often suggest using the same reaction as before, with the understanding that the *ortho* product will be a minor product (so *some ortho* product will be formed). But you can't do that. Whenever you have a synthesis problem, you must choose reagents that give you the desired compound as the MAJOR product. If you propose a synthesis that would produce the desired product as a MINOR product, then your synthesis is not efficient. So we have a problem here. How do we run the reaction so that the *ortho* product will be the major product?

The answer is: we cannot do it in one step. There is no way to "turn off" steric effects. However, there is a way to exploit them. At the start of this chapter, we learned about sulfonation (using fuming sulfuric acid to install an SO_3H group on the ring). We saw that this group can be installed on the ring, ***and*** it can be removed from the ring very easily. We said that this feature (reversibility) would be VERY important in synthesis problems. Now we are ready to see why.

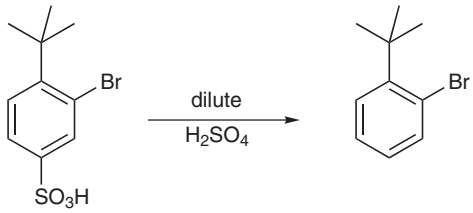
If we perform a sulfonation reaction first, we will expect the SO_3H group to go predominantly in the *para* position (the major product will be from *para* substitution):



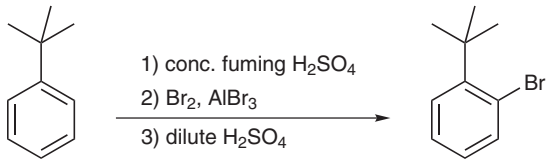
Now think about what we have done. We have "blocked" the *para* position. Now if we brominate, the incoming Br will be installed in the *ortho* position (because the *para* position is already taken). So, the reaction installs Br in the desired location:



Finally, we can perform a desulfonation to remove the SO_3H group. To do so, remember that we need to use dilute sulfuric acid:



And this is the desired product. In summary, here is our entire synthesis:

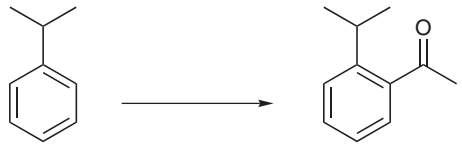


Notice that it took three steps (where the first step was used to block the *para* position and the third step was used to unblock the *para* position). Three steps might seem inefficient, BUT we did not need to rely on isolating minor products. At each step of the way, we were using the major product to move on to the next step.

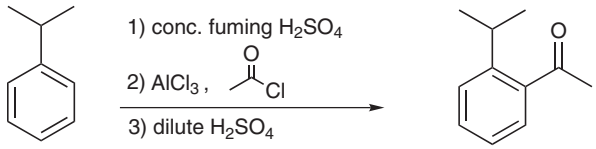
If you think about what we have done, you should realize that this trick is really very clever. We recognized that we cannot just "turn off" the steric effects. So, instead, we developed a strategy that *uses* the steric effects. Notice that the SO_3H group is not in our final product at all. It was just used temporarily, as a "blocking group." This type of concept is very important in organic chemistry. As you move through the course, you will see a few other examples of blocking groups (in reactions that have nothing to do with electrophilic aromatic substitution). The basic strategy is applicable elsewhere. By temporarily blocking the position where the reaction would primarily occur (and then unblocking after you perform the desired reaction), it is possible to form a product that would otherwise be the minor product.

Now let's get practice using this technique:

EXERCISE 4.75 Propose an efficient synthesis for the following transformation:

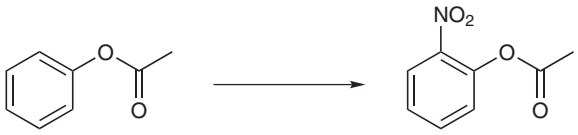


Answer We see that we need to install an acyl group in the *ortho* position. If we just perform a Friedel–Crafts acylation, we would expect the *para* product to be the major product (because of steric effects). So, we must perform a sulfonation reaction to block the *para* position. Our answer is:

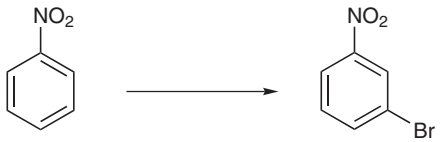


Propose an efficient synthesis for each of the following transformations. Use sulfonation only when necessary (I am purposefully giving you at least one problem that does not require sulfonation—to make sure that you understand *when* to use this blocking technique):

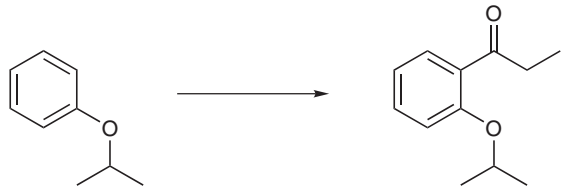
4.76



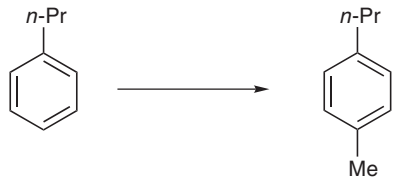
4.77



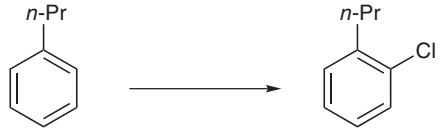
4.78



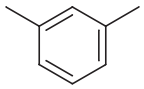
4.79



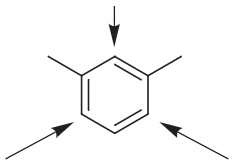
4.80



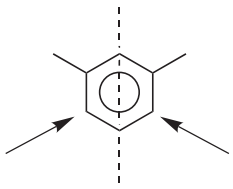
Before we move on to the final section of this chapter, you should be familiar with a few other steric effects. So far, we have seen the steric effects of ONE group on a ring. But what happens when we have two groups on a ring. For example, consider the directing effects of *meta*-xylene:



This compound has *two* methyl groups on the ring. Both methyl groups are directing to the same three positions:

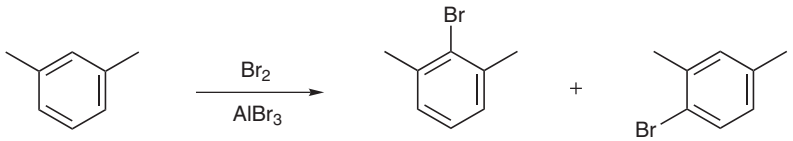


Two of these positions are equivalent because of symmetry:



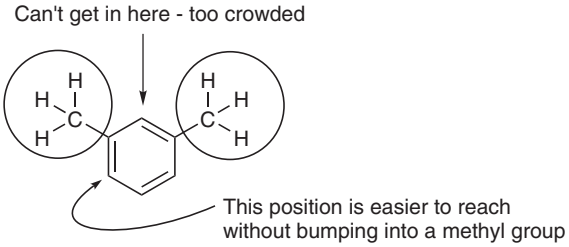
Attacking either of these two positions would yield the same product

So, if we brominate this compound, we will expect to get only two products (rather than three):

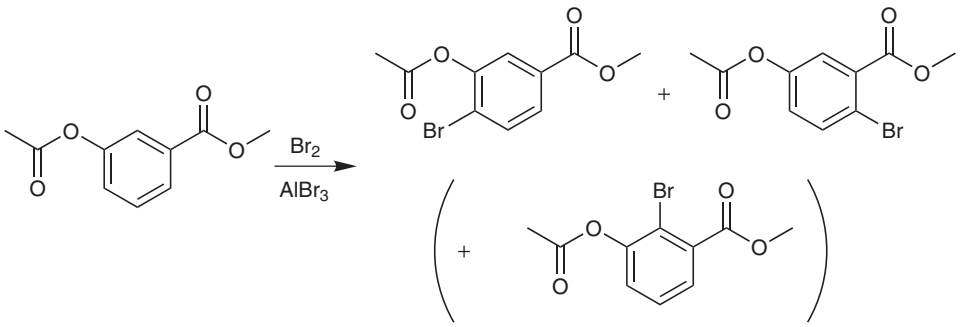


Minor **Major**

Notice that we have indicated that one of the products is major. To understand why, we must consider steric effects. The position in between the two methyl groups is more sterically hindered than the other positions. Therefore, we primarily get just one product.

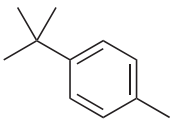


This type of argument can be used in a variety of similar situations. For example, you might remember that we saw the following reaction earlier in this chapter:

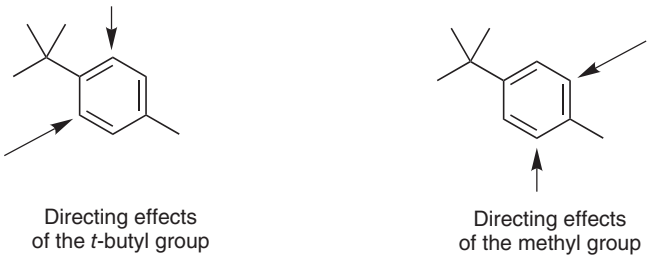


At the time, we said that one of the three products would only be a minor product (the one shown above in parentheses). Now we can understand that it is a minor product, because of steric considerations. The starting compound has two groups that are *meta* to each other, so the spot in between the two groups is sterically hindered.

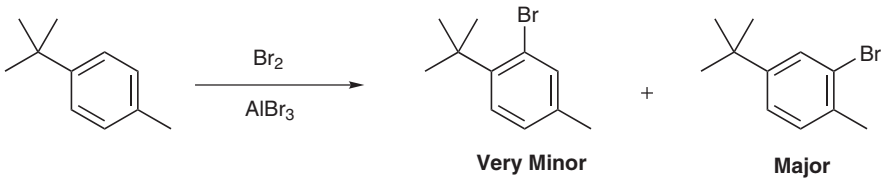
But suppose you have a disubstituted benzene ring where the two groups are *para* to each other. For example, consider the directing effects for the following compound:



In this case, we have two groups that are *para* to each other. Here is a summary of the directing effects of each group:



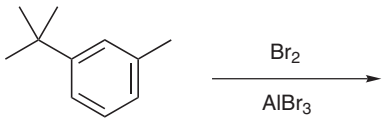
So, these two groups are directing to all four potential spots. Both groups are weak activators (alkyl groups). So, when we consider electronic factors, we don't really see any preference among the possible spots. However, when we consider steric factors, we notice that the *tert*-butyl group is very large compared to the methyl group. As a result, we observe the following products:



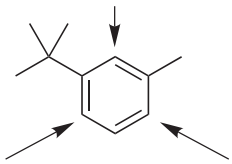
In fact, the *tert*-butyl group is so large that you will find some textbooks that do not even show the minor product above at all. It is so minor that it is almost not worth mentioning.

In this section, we have seen many examples where steric effects play a significant role in determining the product distribution. Now let's get some practice using these principles.

EXERCISE 4.81 Predict the major product of the following reaction:



Answer This example has two groups on the ring: a *tert*-butyl group and a methyl group. Both are weak activators (*ortho-para* directors), and both groups are directing to the same positions:

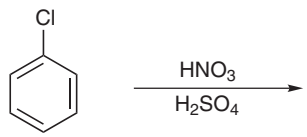


Of these three positions, the one in between the two groups is the most sterically hindered (reaction at that position would be extremely slow). Also, the position next to the *tert*-butyl group is fairly hindered, so we won't expect the reaction to take place there either. Thus, we expect the reaction to take place most often at the least hindered position, next to the methyl group:

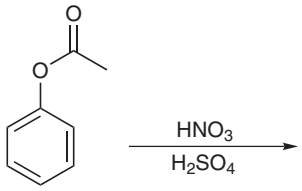
Major

Predict the MAJOR product of each of the following reactions (you do NOT need to show any minor products in these problems):

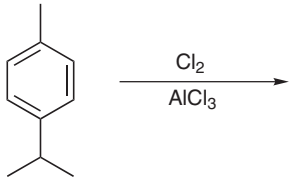
4.82



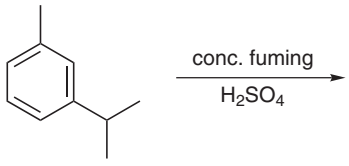
4.83



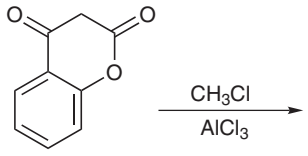
4.84



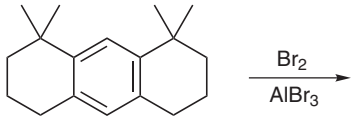
4.85



4.86

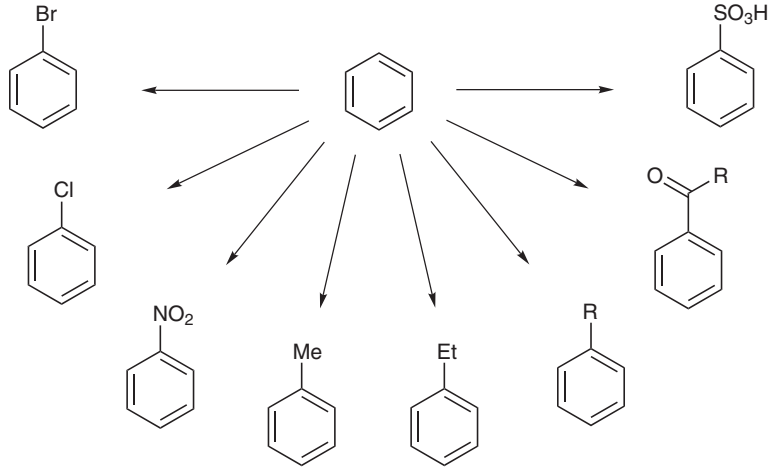


4.87



4.9 SYNTHESIS STRATEGIES

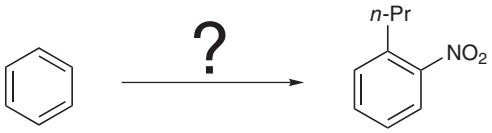
In this section, we will discuss some strategies for synthesis problems. Let's begin with a quick review of the reactions we have seen earlier in this chapter. We have seen how to install many different groups on a benzene ring:



Carefully look at the chart above and make sure that you know the reagents that you would use to achieve each of these transformations. If you are not able to recall the reagents, then you will be totally unable to do synthesis problems.

It would be nice if all synthesis problems were just one-step problems, like this one:

Usually, however, synthesis problems require a few steps, where you must install two or more groups on a ring, like this:

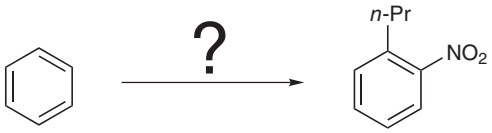


When dealing with such problems, there are many considerations to keep in mind:

- Take a close look at the groups on the ring and make sure you know how to install each group individually.
- Consider the order of events. In other words, which group do you install first? After you install the first group, the directing effects of that group will determine where the next group will be installed. This is an important consideration because it will affect the relative position of the two groups in the product. In the example above, the two groups are *ortho* to each other. So we must choose a strategy that installs the two groups *ortho* to each other.
- Take steric effects into account (and determine when you need to use sulfonation as a blocking technique).

There are certainly other considerations, but these will help you begin to master synthesis problems. The first consideration above is just a simple knowledge of the reagents necessary to install any group on a ring. The last two considerations can be summarized like this: electronics and sterics (hopefully, this will make it easy for you to remember these considerations). Whenever you are solving any problem, you must always consider electronic effects and steric effects. As you move through this course, you will find the same theme in every chapter. You will find that you must always consider electronic effects and steric effects.

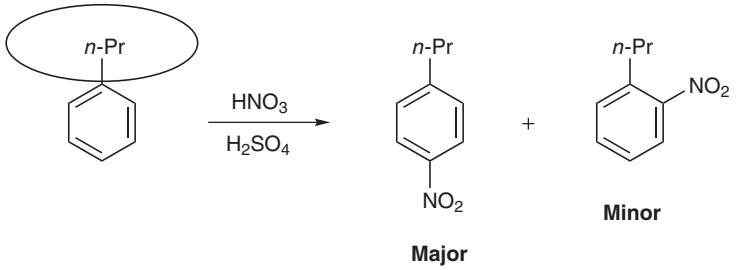
Let's try to use these considerations to solve the problem we just saw:



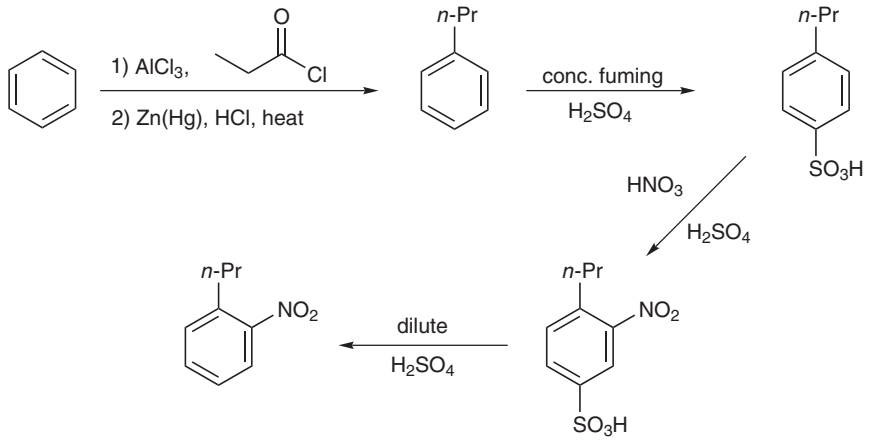
Let's begin by making sure we know how to install both of these groups individually. There are two groups that we need to install on the ring: an *n*-propyl group and a nitro group. The nitro group is easy—we just perform a nitration (using sulfuric acid and nitric acid). The *n*-propyl group is a bit trickier because we *cannot* use a Friedel–Crafts alkylation (remember carbocation rearrangements). Instead, we must use a Friedel–Crafts acylation, followed by a reduction to reduce the C═O double bond. So far, we need at least three steps: one step to install the nitro group and two steps to install the *n*-propyl group.

Now let's focus on electronic considerations. In this case, we can begin to appreciate the importance of "order of events." Imagine that we install the nitro group first. The nitro group is a *meta* director, so the next group will end up being installed *meta* to the nitro group. That doesn't work for us because we want the groups to be *ortho* to each other in the final product. So, we have decided that we cannot install the nitro group first. Instead, let's try to install the *n*-propyl group first. That should work because the *n*-propyl group is an *ortho-para* director. So the *n*-propyl group will direct the incoming nitro group into the correct position (*ortho*). BUT the *n*-propyl group will also direct to the *para* position. And this is where we must consider steric effects.

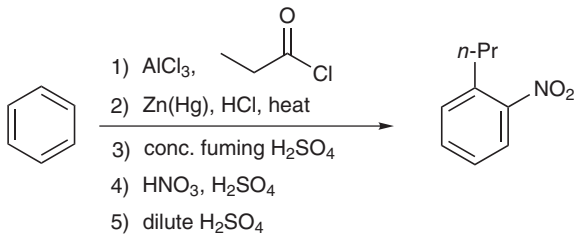
When we look at the steric effects, we encounter a difficulty. The steric effects are not in our favor here. We should expect the following results:



Notice that the compound we want to make is the *minor* product. But we need a way to obtain the *ortho* product as our major product. And we have seen exactly how to do that. We just use sulfonation to block the *para* position. So, our overall synthesis goes like this:



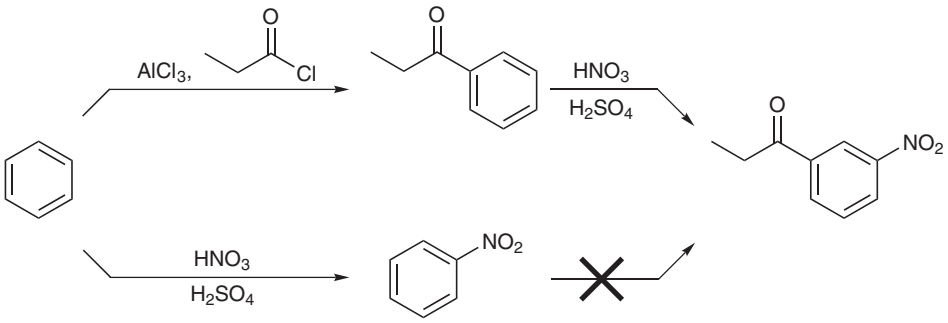
The answer that we just developed can be summarized like this:



Now let's consider another example in which the order of events is especially relevant. Consider how you might achieve the following transformation:

In this case, we must install an acyl group and a nitro group, and the two groups must be *meta* to each other. Both groups are *meta* directing, so it might seem like we can install them in either order (first acylation and then nitration, or vice versa). However, there is a

serious limitation to Friedel–Crafts reactions that we have not mentioned until now. And that limitation will dictate the order of events that we must follow in this case. It turns out that a Friedel–Crafts reaction cannot be performed on a ring that is either moderately deactivated or strongly deactivated. You *can* perform a Friedel–Crafts on a weakly deactivated ring (and certainly on an activated ring). But not on a significantly deactivated ring—the reaction just doesn't work (you can perform other reactions with deactivated rings, such as bromination, but not Friedel–Crafts reactions). With that in mind, the nitro group cannot be installed first.



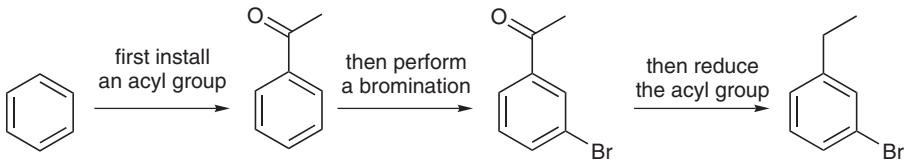
This synthesis teaches us the importance of "order of events." Whenever you are trying to solve a synthesis problem, you must always consider the order of events.

EXERCISE 4.88 Propose an efficient synthesis for the following transformation:

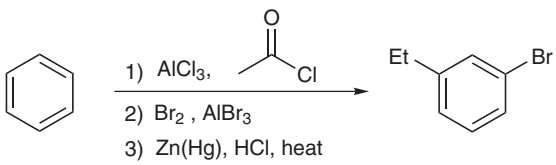
Answer We must install two groups on the ring: an ethyl group and bromine. Let's first make sure that we know what reagents we would use to install each group individually. To install bromine, we would use Br_2 and a Lewis acid. To install the ethyl group, we would use a Friedel–Crafts alkylation (or acylation, followed by a reduction). Whenever we install an ethyl group on a ring, we don't need to worry about carbocation rearrangements, so we can use a simple alkylation (rather than an acylation followed by reduction).

But we immediately see a serious issue when we consider the directing effects of each substituent. The bromine is *ortho-para* directing, so we can't install the bromine on the ring first (if we did, we would not get the groups to be *meta* to each other). And the ethyl group is also *ortho-para* directing. So, whichever group we put on first, there would seem to be no way to get these two groups to be *meta* to each other.

UNLESS we use an acylation (rather than an alkylation). If we do that, we will install an acyl group on the ring first. *And acyl groups are meta directing*. That would allow us to install the bromine in the correct spot. So our strategy would go like this:



The reagents for our proposed synthesis are as follows:



Propose an efficient synthesis for each of the following. You might want to use a separate piece of paper to help you work through each of these problems.

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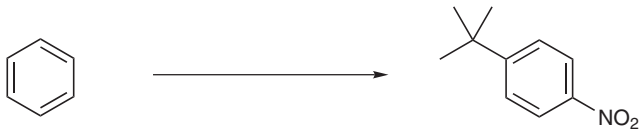

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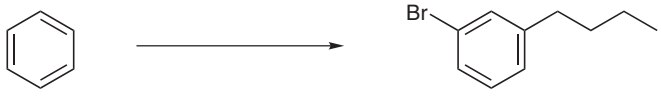

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Before we end this chapter, it is important that you realize what we have covered here and, more importantly, what we have ***not*** covered. We did not cover everything in your textbook chapter on electrophilic aromatic substitution. As you go through your lecture notes and your textbook chapter, you will find a few reactions that we did not cover here. You will need to go through your textbook and your notes carefully to make sure that you learn those reactions. You should find that we covered 80%, or even 90%, of what you read in your textbook.

The purpose of this chapter was not to cover everything but rather to serve as a foundation for your mastery of electrophilic aromatic substitution. If you went through this chapter, then you should feel comfortable with the steps involved in proposing mechanisms, predicting products, and proposing a synthesis. You should know how directing effects work and how to use them when proposing syntheses. You should also know about steric effects and how to use them when proposing syntheses.

With all of that as a foundation, you should now be ready to go through your textbook and lecture notes, and polish off the rest of the material that you must know for your exam. Through the foundation that we have developed in this chapter, you should find (hopefully) that the content in your textbook will seem easy.

Do the problems in your textbook. Do all of them. Good luck.

CHAPTER 5

NUCLEOPHILIC AROMATIC SUBSTITUTION

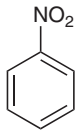
5.1 CRITERIA FOR NUCLEOPHILIC AROMATIC SUBSTITUTION

In the previous chapter, we learned all about *electrophilic* aromatic substitution reactions.

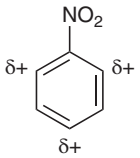
In this short chapter, we will look at the flipside: is it possible for an aromatic ring to function as an electrophile and react with a nucleophile? In other words, is it possible for the aromatic ring to be so electron-poor that it is subject to attack by a nucleophile? The answer is: yes.

But in order to observe this kind of reaction, called nucleophilic aromatic substitution, we will need to meet three very specific criteria. Let's look closely at each one of these criteria:

1. The ring must have a very powerful electron-withdrawing group. The most common example is the nitro group:

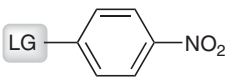


We saw in the previous chapter that the nitro group is a strong deactivator toward electrophilic aromatic substitution because the nitro group very powerfully withdraws electron density from the ring (by resonance). This causes the electron density in the ring to be very poor:

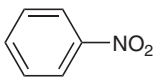


At the time, we wanted the aromatic ring to function as a nucleophile. And we saw that the effect of a nitro group is to ***de****activate* the ring. But now, in this chapter, we want the ring to act as an *electrophile*. So, the effect of the nitro group is a very good thing. In fact, it is ***necessary*** to have a powerful electron-withdrawing group if you want the ring to function as an electrophile. The presence of the electron-withdrawing group is the first criterion that must be met in order for the ring to function as an electrophile. Now, let's look at the second criterion:

2. There must be a leaving group that can leave.



reactive toward
nucleophilic aromatic substitution



NOT reactive toward
nucleophilic aromatic substitution

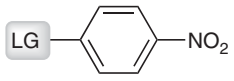
To understand this, let's think back to what happened in the previous chapter, when the ring always functioned as a nucleophile. We saw that all the reactions from the previous chapter could be summarized like this: E^+ comes on the ring, and then H^+ comes off (or, in other

words: attack, then deprotonate). But now, in this chapter, we want the ring to function as an electrophile. So we are trying to see if we can get a nucleophile (Nuc^-) to attack the ring. If we can make it happen, and a nucleophile (with a negative charge) actually does attack the ring, then something with a negative charge is going to have to come off of the ring. We can summarize it like this: Nuc^- comes on the ring, and X^- comes off.

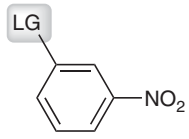
There is one main difference between the mechanism here and the one we saw in Chapter 4. The difference is in the kind of charges we are dealing with. In the previous chapter, we dealt with something positively charged coming onto the ring to form a positively charged sigma complex, and then H^+ came off the ring to restore aromaticity. In those mechanisms, everything was positively charged. But now, we are dealing with negative charges. A nucleophile with a negative charge will attack the ring to form some kind of negatively charged intermediate. That intermediate must then expel something negatively charged. And that explains the second criterion for this reaction to occur: we need the ring to have some leaving group that can leave with a negative charge.

If there is no leaving group that can leave with a negative charge, then the ring will have no way of reforming aromaticity. And we cannot just kick off H^- because H^- is a terrible leaving group. NEVER kick off H^-. Good leaving groups include halides (Cl^-, Br^-, I^-) and sulfonates (such as TsO^-). If you are a bit rusty on leaving groups, you might want to go back to first-semester material and quickly review which groups are good leaving groups.

3. The final criterion is: the leaving group must be *ortho* or *para* to the electron-withdrawing group:



reactive toward
nucleophilic aromatic substitution



NOT reactive toward
nucleophilic aromatic substitution

To understand why, we will need to take a closer look at the accepted mechanism. In the upcoming section, we will explore this mechanism so that we can understand this last criterion. For now, let's just make sure that we can identify when all three criteria have been met. Once again, the three criteria are:

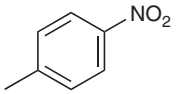
1. There must be an electron-withdrawing group on the ring.

2. There must be a leaving group on the ring.

3. The leaving group must be *ortho* or *para* to the electron-withdrawing group.

Now let's get some practice looking for all three criteria:

EXERCISE 5.1 Predict whether the following compound can function as a suitable electrophile in a nucleophilic aromatic substitution reaction.



Answer In order to have a nucleophilic aromatic substitution, all three criteria must be met.

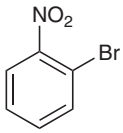
We look at the ring, and we see that it does have a nitro group. Therefore, the first criterion has been met.

We then look for a leaving group. There is NO leaving group here. A methyl group is NOT a leaving group. Why not? Because a carbon atom with a negative charge is a *terrible* leaving group. So criterion 2 has not been met.

Therefore, we conclude that this compound will not function as an electrophile in a nucleophilic aromatic substitution reaction.

Determine whether each of the following compounds can function as a suitable electrophile in a nucleophilic aromatic substitution reaction. If you determine that the three criteria have not been met, then simply write "no reaction."

5.2



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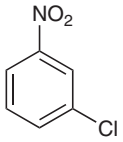

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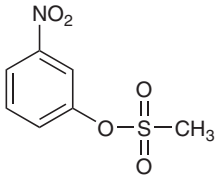

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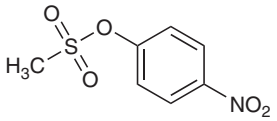

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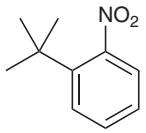

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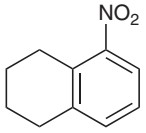
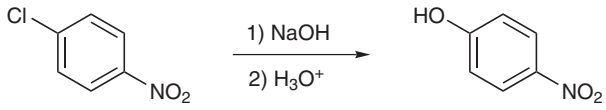
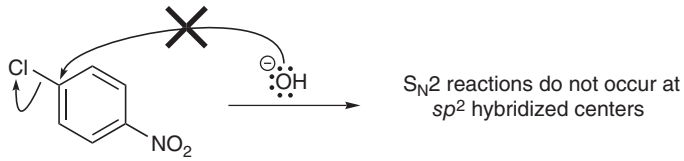


5.2 S_NAr MECHANISM

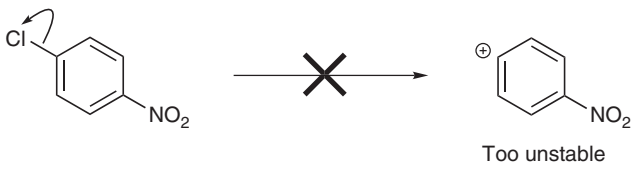
In the previous section, we saw the three criteria that are necessary in order for an aromatic ring to undergo a nucleophilic aromatic substitution reaction. The following transformation is an example:



Let's explore some possible mechanisms for this process. It cannot be an S_N2 process because S_N2 processes do not readily occur at an sp^2-hybridized center:

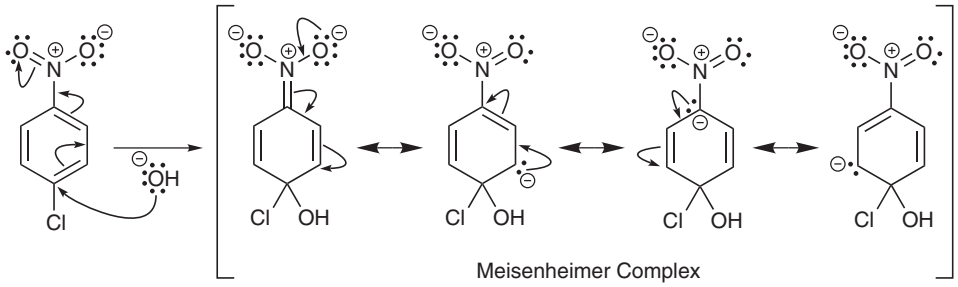


S_N2 processes are only effective with sp^3-hybridized centers. So our reaction cannot be an S_N2 mechanism. What about S_N1? That would require the loss of the leaving group *first* to form a carbocation:

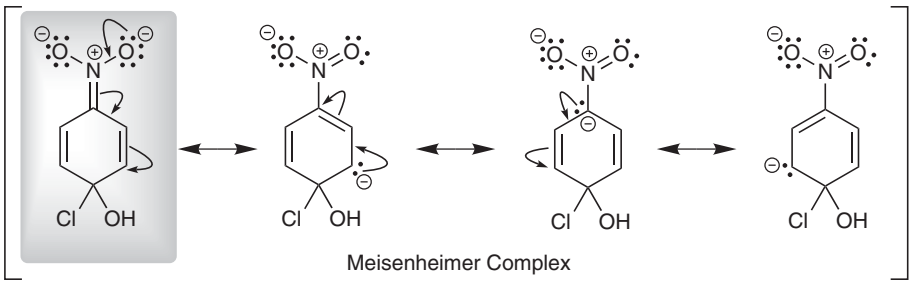


This kind of carbocation is not stabilized by resonance. It is a very high-energy intermediate, and we don't expect the leaving group to leave if it means creating an unstable intermediate. Therefore, we don't expect the mechanism to be an S_N1 mechanism either.

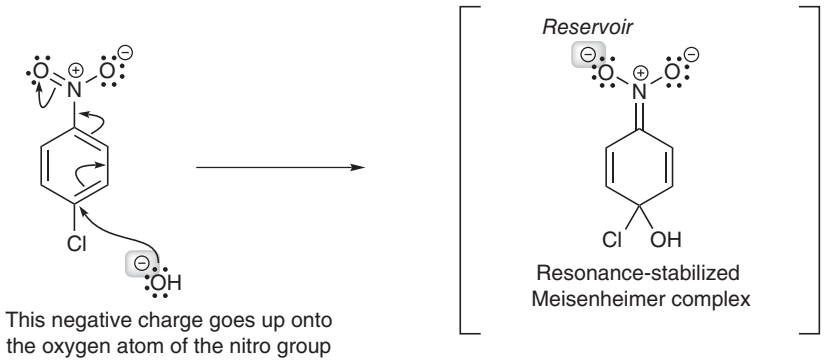
So, if it's not S_N2 and its not S_N1, then what is it? And the answer is: it's a new mechanism, called S_NAr. In many textbooks, it is called an ***addition–elimination*** mechanism. In the first step of the mechanism, the ring is attacked by a nucleophile, generating a resonance-stabilized intermediate, called a Meisenheimer complex:



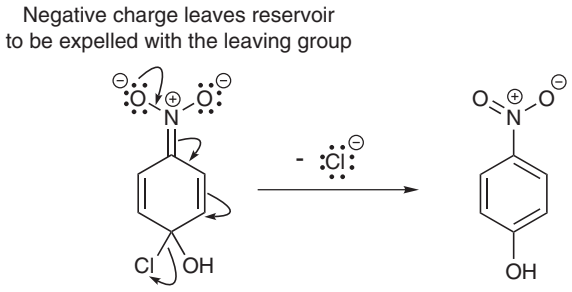
This intermediate should remind us of the intermediate in an electrophilic aromatic substitution reaction (the sigma complex), but the main difference is that a Meisenheimer complex is *negatively* charged (a sigma complex is positively charged). Let's take a close look at the Meisenheimer complex, and let's focus our attention on one particular resonance structure:



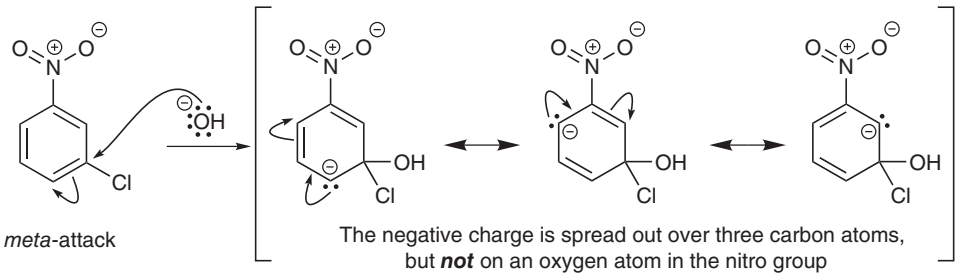
The highlighted resonance structure is special because it places the negative charge on an *oxygen* atom. Since the negative charge is spread out over three carbon atoms *and an oxygen atom*, the negative charge is fairly stabilized by resonance. You should think of the reaction like this: A nucleophile attacks the ring, kicking the negative charge up into a reservoir:



Then, in the second step of the mechanism, the reservoir releases its load by pushing the electron density back down onto a leaving group, thereby restoring aromaticity to the ring:

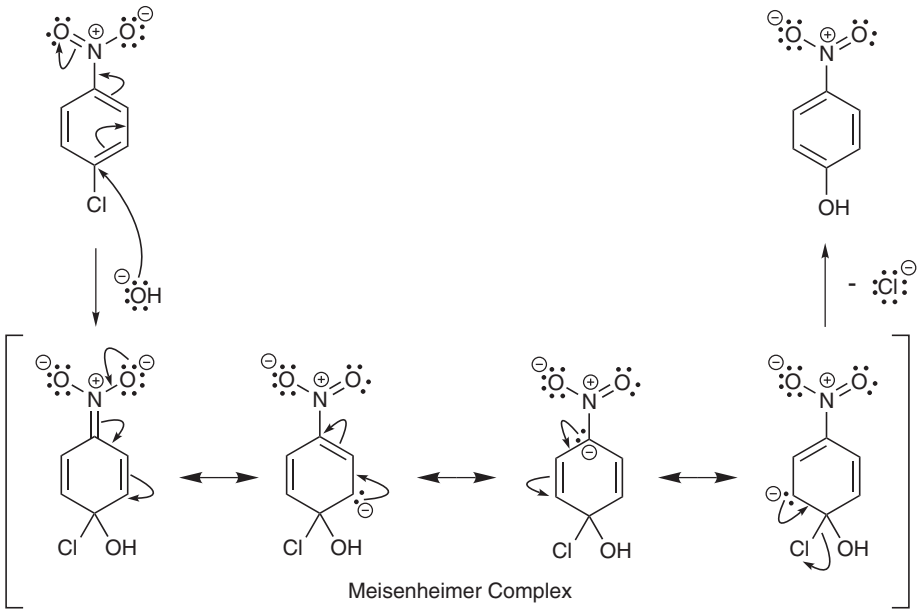


And now we are ready to understand the reason for the third criterion (that the leaving group must be *ortho* or *para* to the electron-withdrawing group). Now we can understand that the reservoir is available only if the nucleophile attacks at the *ortho* or *para* positions. If the nucleophile attacks at the *meta* position, there is no way to place the negative charge up onto the reservoir:

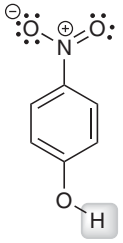


Therefore, the intermediate is not stabilized. So the reaction doesn't happen. And that is why the leaving group must be *ortho* or *para* to the electron-withdrawing group.

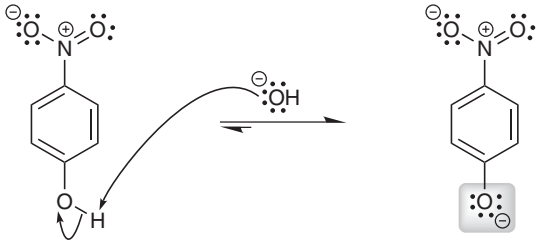
Before you get practice drawing the complete mechanism of an S_NAr process, there is one subtle point that deserves attention. Let's first summarize what we have seen so far:



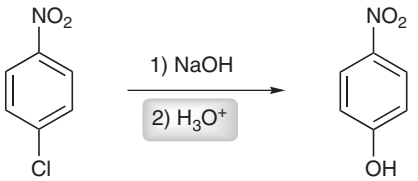
There are two steps: 1) a nucleophile attacks the ring to generate a Meisenheimer complex, followed by 2) loss of a leaving group to restore aromaticity. But inspect the product very carefully. It contains a phenolic proton, highlighted below:



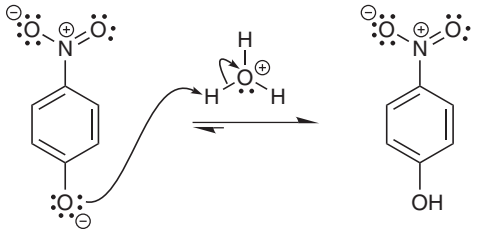
This proton is mildly acidic and cannot survive the strongly basic conditions being employed (hydroxide is a strong base, and hydroxide is present in the reaction flask). So, under these reaction conditions, the product is deprotonated (whether we like it or not), to give the following:



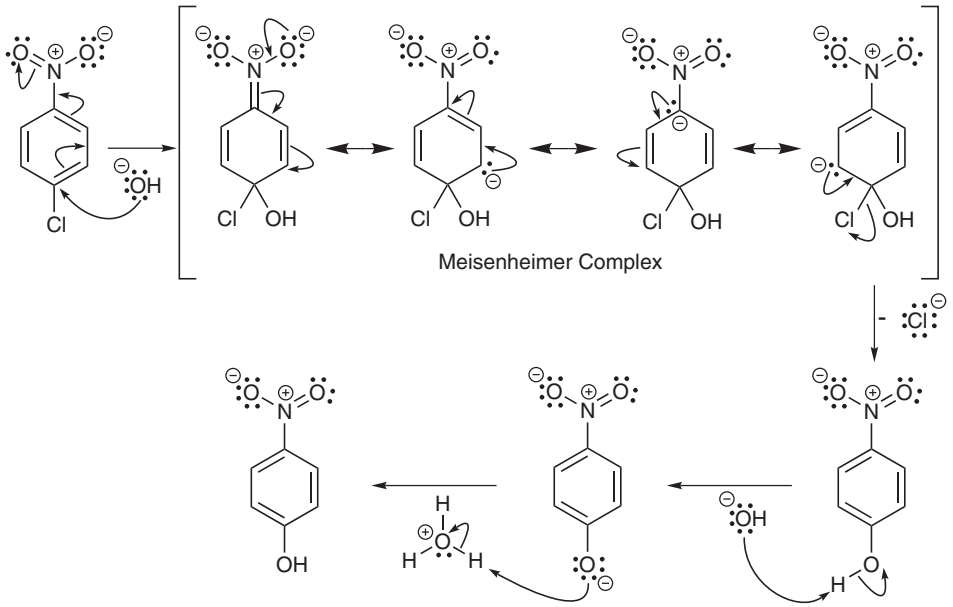
Therefore, in order to regenerate the desired product, a proton source must be introduced into the reaction flask (after the reaction is complete), which is shown like this:



The acid (H_3O^+) is used to achieve the following proton transfer:



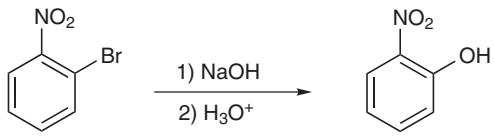
If you draw a complete mechanism for this process, it would look like this:



When you stare at this mechanism, you might be surprised by the last two steps (deprotonation, followed by protonation). Specifically, you might wonder why the mechanism needs to show these last two steps. After all, if we delete these last two steps from the mechanism, isn't the product still correct? Yes, that is true, but these last two steps are necessary. Why? Because under the reaction conditions employed (strongly basic conditions), the phenolic proton does not survive. Deprotonation occurs, whether we like it or not. The mechanism, as drawn, indicates that we understand that subtle point. By drawing the last two steps of the mechanism, you are demonstrating that you understand why a proton source (like H_3O^+) must be added to the reaction flask after the reaction is complete.

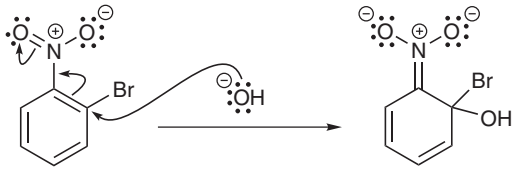
Now we are ready to get some practice drawing an S_NAr mechanism.

EXERCISE 5.8 Draw a mechanism for the following reaction.

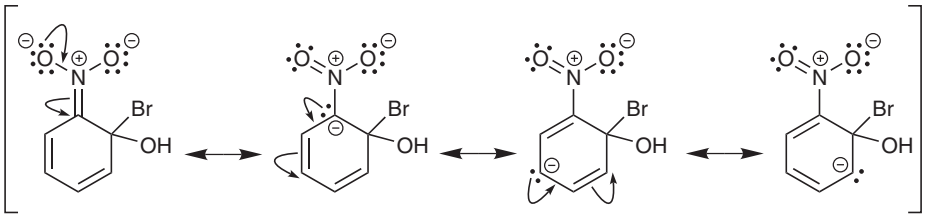


Answer The reagent is a strong nucleophile (hydroxide), and the starting compound meets all three criteria for an S_NAr mechanism: an electron withdrawing group (NO_2) and a leaving group (Br) that are *ortho* to each other.

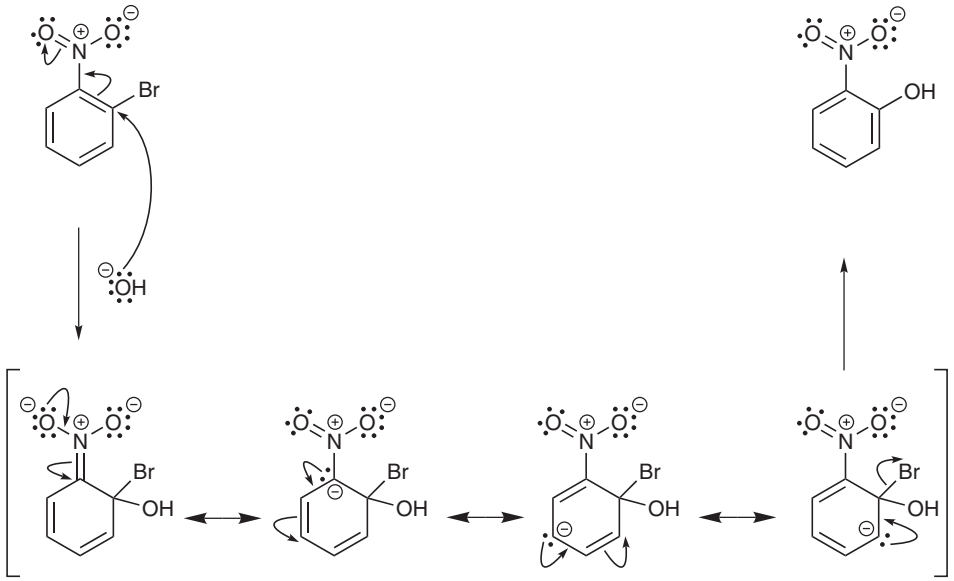
In a nucleophilic aromatic substitution reaction, the nucleophile (hydroxide) attacks at the position bearing the leaving group, and electrons are pushed up into the reservoir:



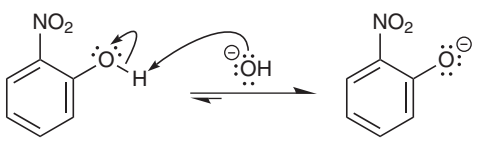
The resulting intermediate is a Meisenheimer complex, and it has the following resonance structures:



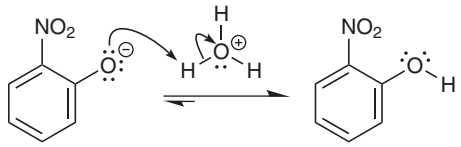
Then, in the second step of the mechanism, the leaving group is expelled to give the product. The first step and the second step of the mechanism are shown here:



This might appear to be a complete mechanism. But remember, that under basic conditions, the product is deprotonated:

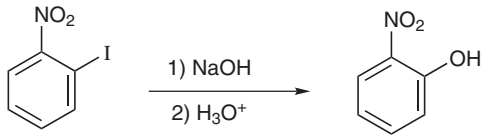


And that is why an acid source is necessary after the reaction is complete:

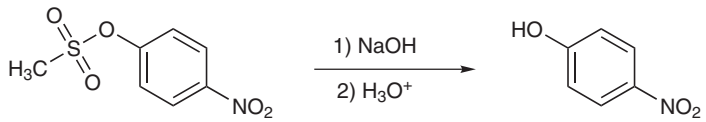


Propose a mechanism for each of the following transformations:

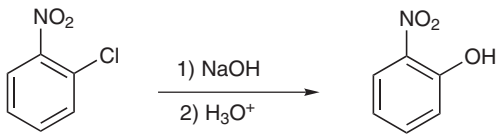
5.9



5.10



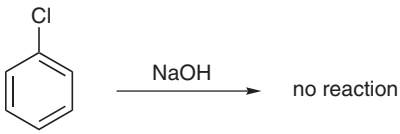
5.11



5.3 ELIMINATION–ADDITION

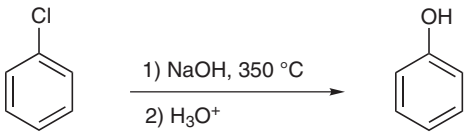
In the previous section, we discussed the three criteria that you need in order to get an S_NAr mechanism. The obvious question is: can it occur without all three criteria? For example, what if there is no electron-withdrawing group?

If we treat chlorobenzene with hydroxide, no reaction is observed:



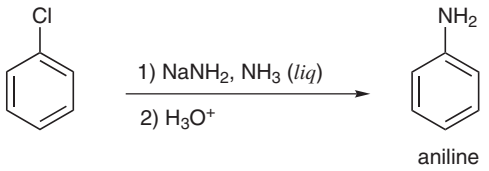
The hydroxide ion does not displace the leaving group via an S_NAr mechanism because there is no "reservoir" to hold the electron density for a moment. In fact, if we try to apply heat, there is still no reaction.

However, at much higher temperatures, such as 350 °C, a reaction is in fact observed:



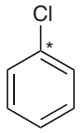
This reaction, called the Dow process, is commercially important because it is an efficient way of making phenol.

We can use this same process to make ***aniline***:



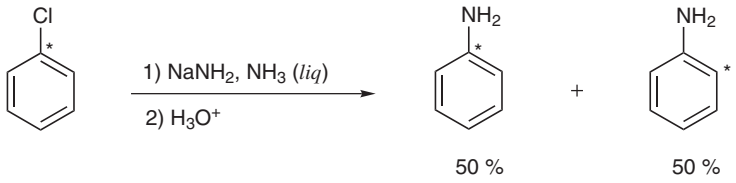
We don't even need high temperatures to make aniline. We just use H_2N^- in liquid ammonia. So we have a serious question: if there is no "reservoir" to temporarily hold the electron density to enable S_NAr, then how does this reaction work? What is the mechanism?

To understand the mechanism, chemists have used an important technique called isotopic labeling. All elements have isotopes (for example, deuterium is an isotope of hydrogen because deuterium has a neutron in the nucleus while hydrogen does not). Carbon also has some important isotopes. ^{13}C is an important isotope because we can easily determine the position of a ^{13}C atom in a compound using NMR spectroscopy. So if we enrich a specific spot with ^{13}C, then we can follow where that carbon atom goes during the reaction. For example, let's say we take chlorobenzene, and we enrich one particular site with ^{13}C:



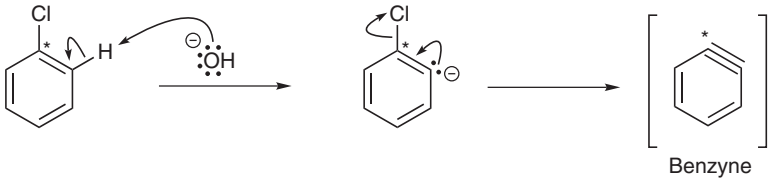
The site with the asterisk is the location where we placed the ^{13}C. When we say that we enriched that spot with ^{13}C, we mean that most of the molecules in the flask have a ^{13}C atom in that position.

Now let's see what happens to that isotopic label as the reaction proceeds. After running the reaction, here are the results that are observed:

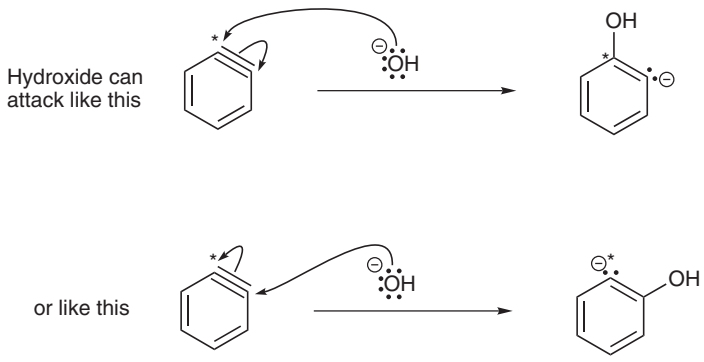


This seems quite strange: how does the isotopic label "move" its position? We will not be able to explain this with a simple nucleophilic aromatic substitution. Even if we could somehow ignore the issue of not having a reservoir for the electron density during the reaction, we would still not be able to explain the isotopic labeling results.

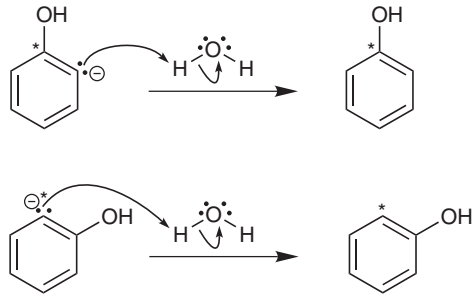
So here is a proposal that explains the isotopic labeling experiments. Imagine that in the first step, the hydroxide ion acts as a base (rather than a nucleophile), giving an elimination reaction:



This generates a very strange-looking (and very reactive) intermediate, which is called benzyne. Then, another hydroxide ion is involved, this time acting as a nucleophile to attack benzyne. But there are two places it can attack:



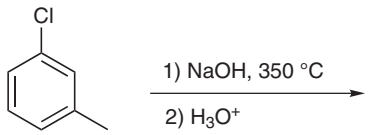
And there is no reason to prefer one site over the other, so we must assume that these two pathways occur with equal probability. That would give a 50–50 mixture of the two anions above, which would undergo proton transfers to generate phenol, with the isotopic labels in the appropriate locations:



Just as we saw in the previous section, phenol has an acidic proton and will therefore undergo deprotonation as a result of the basic reaction conditions (hydroxide). So, just as we saw in the previous section, a proton source (such as H_3O^+) must be introduced into the reaction flask after the reaction is complete.

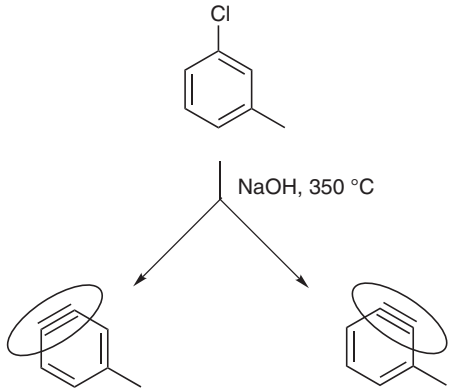
This proposed mechanism is essentially an elimination followed by an addition. So, it makes sense that we call this process an ***elimination–addition*** reaction (as compared with the S_NAr mechanism, which was called *addition–elimination*). This mechanism certainly seems a bit off the wall when you think about. Benzyne? It looks like a terrible intermediate. But chemists have been able to show (with other experiments) that benzyne is in fact the intermediate of this reaction. Your textbook or instructor will most likely provide some evidence for the short-lived existence of benzyne (we use a trapping technique involving a Diels–Alder reaction). If you are curious about the evidence, you can look in your textbook. For now, let's make sure that you can predict the products of elimination–addition reactions.

EXERCISE 5.12 Predict the products for the following reaction:

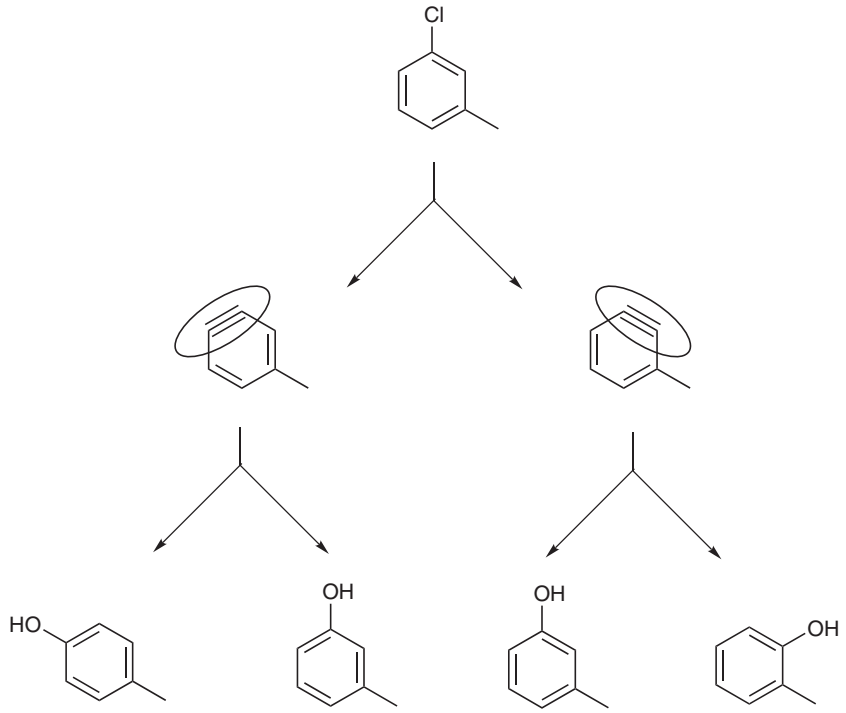


Answer The ring does *not* have an electron-withdrawing group, so we are not dealing with an S_NAr mechanism. Rather, we must be dealing with an elimination–addition mechanism.

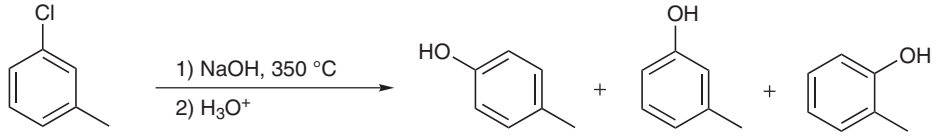
Elimination can occur on either side of the chlorine atom:



Then, we can add across either triple bond above, giving us the following products:



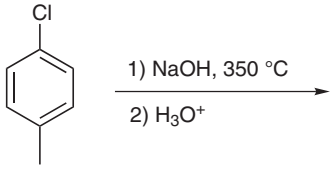
If you look closely at these products, you will see that the middle two are the same. So, we expect the following three products from this reaction:



Predict the products for each of the following reactions. Just to keep you on your toes, I will throw in some problems that go through an addition–elimination mechanism (S_NAr), rather than an elimination–addition. In each case, you will have to decide which mechanism is

responsible for the reaction (based on whether or not you have all three criteria for an S_NAr mechanism). Your products will be based on that decision.

5.13



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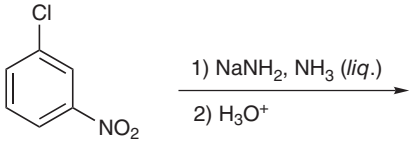

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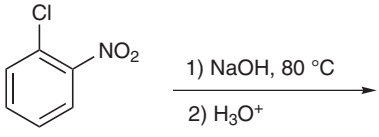

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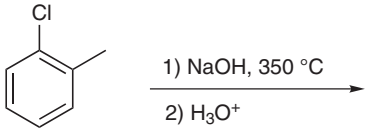
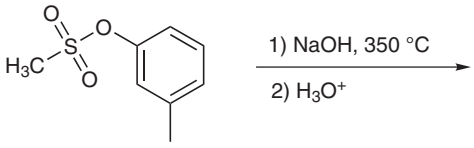
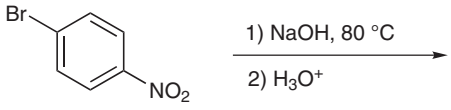


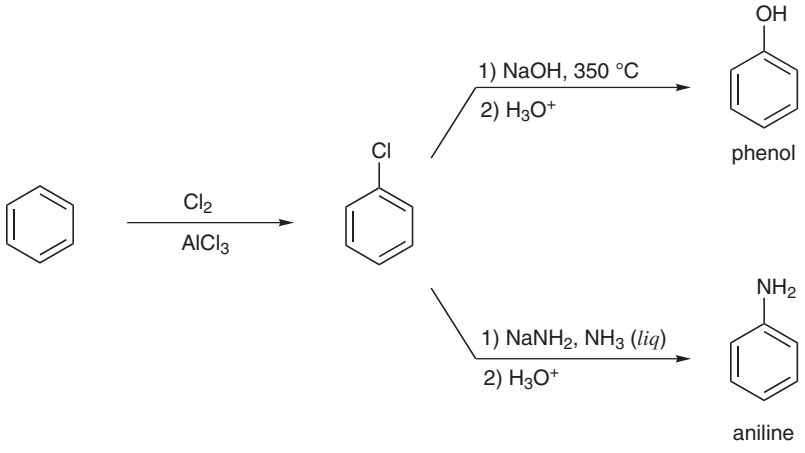
5.17



5.18



In this section, we have seen how to install an OH group or an NH_2 group on an aromatic ring. This is important because we did not see how to achieve either of these two transformations in the previous chapter. Here is a summary of how to install an OH group or NH_2 group on an aromatic ring. In each case, it is a two-step process that starts with installing a Cl on the ring:



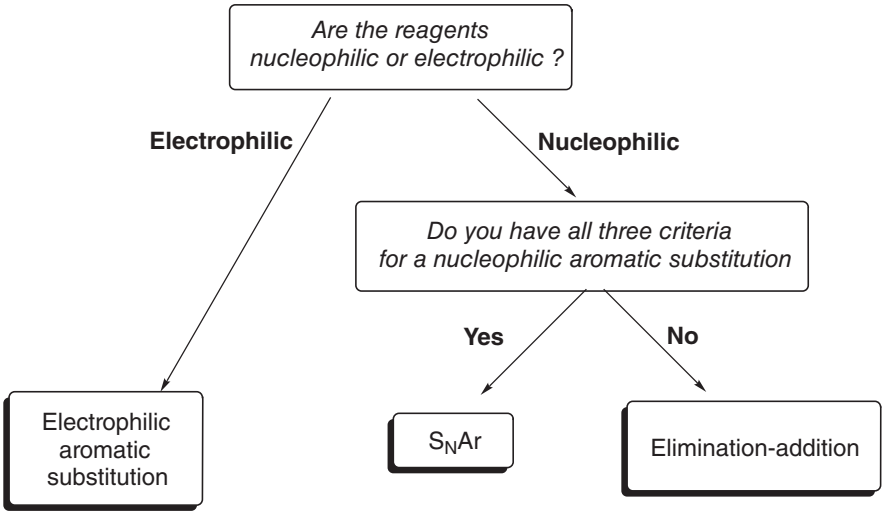
We begin with chlorination of benzene (which is just an electrophilic aromatic substitution reaction), followed by an elimination–addition reaction. When we perform the elimination–addition process, we must carefully choose the reagents. If we use NaOH followed by H_3O^+, the product will be phenol. If we use $NaNH_2$ followed by H_3O^+, the product will be aniline (shown in the scheme above).

5.4 MECHANISM STRATEGIES

So far, we have seen three different mechanisms involving aromatic rings:

1. Electrophilic aromatic substitution
2. S_NAr (also called addition–elimination)
3. Elimination–addition

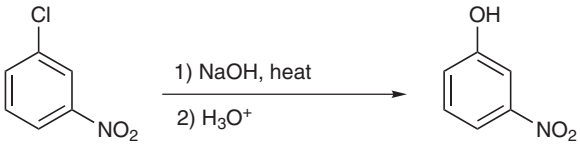
When you are given a problem, you must be able to look at all of the information and determine which of the three mechanisms is operating. This is not difficult to do. Here is a simple chart that shows the thought processes involved:



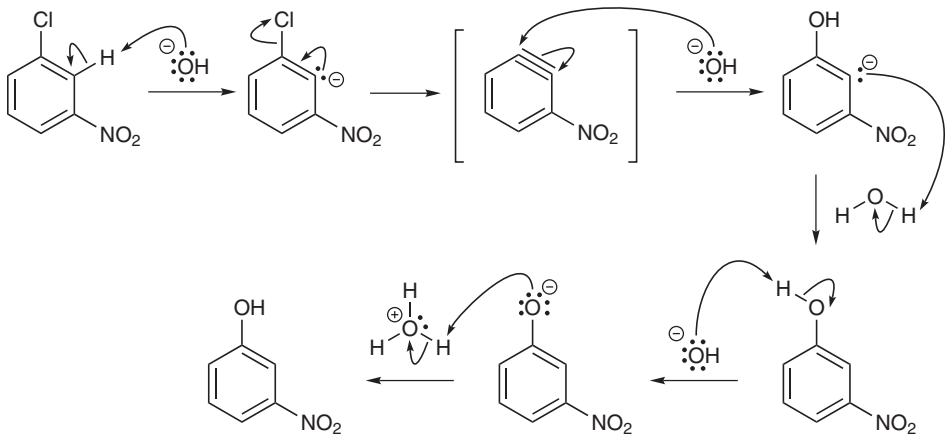
You first look at the reagents that are reacting with the aromatic ring. If the reagents are electrophilic (like all of the reagents we saw in the previous chapter), then expect an electrophilic aromatic substitution. But if the reagents are nucleophilic, then you have to decide between an S_NAr reaction and an elimination–addition reaction. To do that, look for the three criteria necessary for an S_NAr reaction.

Let's see an example:

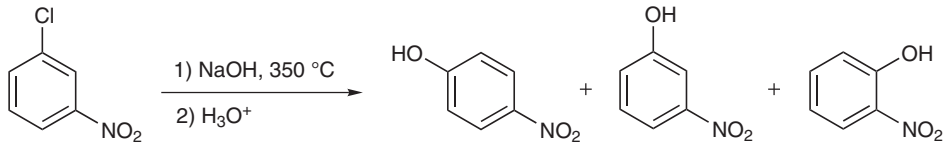
EXERCISE 5.19 Propose a mechanism for the following reaction:



Answer We begin by looking at the reagents. Hydroxide is a nucleophile, so we do NOT expect an electrophilic aromatic substitution. We must decide between an S_NAr mechanism and an elimination–addition mechanism. We look for the three criteria that we need for an S_NAr reaction. (1) We do have an electron-withdrawing group, and (2) we do have a leaving group, BUT (3) the electron-withdrawing group and the leaving group are NOT *ortho* or *para* to each other. That means that an S_NAr mechanism is unlikely to occur. (When the electron-withdrawing group and the leaving group are *meta* to each other, we don't have the "reservoir" to use.) Therefore, the mechanism must be an elimination–addition:



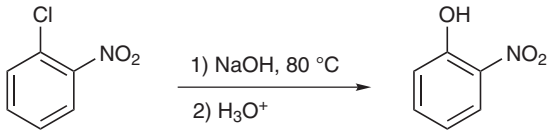
In this particular example, we would expect a total of three products from an elimination–addition mechanism:



But keep in mind that mechanism problems do not always show you all of the products. The problem will typically show you just one product, and you will need to show the mechanism for forming that product (and only that product). In some cases, it might even be a minor product. But the problem is not making any claims that the product is major or minor. A mechanism problem is simply asking you to justify "how" the product was formed, regardless of how much of it was actually obtained from the reaction.

Propose a mechanism for each of the following reactions:

5.20



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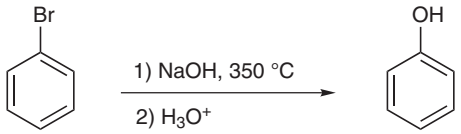

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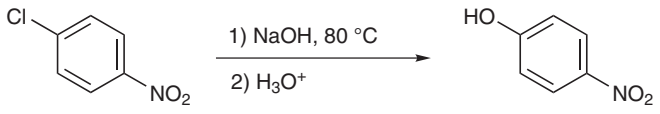

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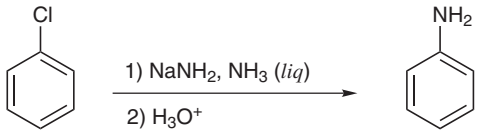


CHAPTER 6

KETONES AND ALDEHYDES

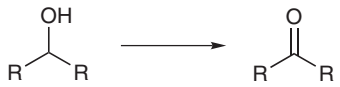
6.1 PREPARATION OF KETONES AND ALDEHYDES

Before we can explore the reactions of ketones and aldehydes, we must first make sure that we know how *to make* ketones and aldehydes. That information will be vital for solving synthesis problems.

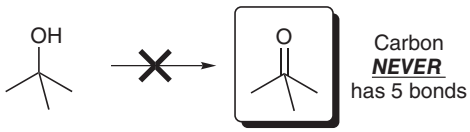
Ketones and aldehydes can be made in many ways, as you will see in your textbook. In this book, we will only see a few of these methods. These few reactions should be sufficient to help you solve many synthesis problems in which a ketone or aldehyde must be prepared.

The most useful type of transformation is forming a C═O bond from an alcohol. *Primary* alcohols can be oxidized to form aldehydes:

And *secondary* alcohols can be oxidized to form ketones:

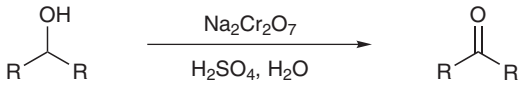


Tertiary alcohols cannot be oxidized, because carbon cannot form five bonds:

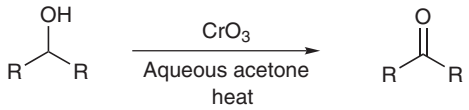


So, we need to be familiar with the reagents that will oxidize primary and secondary alcohols (to form aldehydes or ketones, respectively). Let's start with secondary alcohols.

A secondary alcohol can be converted into a ketone upon treatment with sodium dichromate and sulfuric acid:



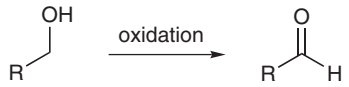
Alternatively, the Jones reagent can be used, which is formed from CrO_3 in aqueous acetone:



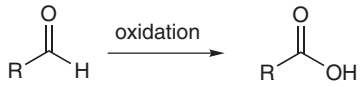
Whether you use sodium dichromate or the Jones reagent, you are essentially performing an oxidation that involves a chromic acid oxidizing agent (the alcohol is being oxidized and the chromium reagent is being reduced). You should look through your lecture notes and textbook to see if you are responsible for the mechanisms of these oxidation reactions. Whatever the case, you should definitely have

these reagents at your fingertips, because you will encounter many synthesis problems that require the conversion of an alcohol into a ketone or aldehyde.

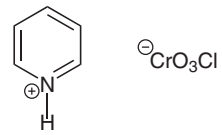
Chromic acid oxidations work well for secondary alcohols, but we run into a problem when we try it on a primary alcohol. The initial product is indeed an aldehyde:



But under these strong oxidizing conditions, the aldehyde does not survive. The aldehyde is further oxidized to give a carboxylic acid:

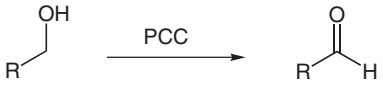


So clearly, we need a way to oxidize a primary alcohol into an aldehyde, under conditions that will ***not*** further oxidize the aldehyde. This can be accomplished with a reagent called pyridinium chlorochromate (or PCC):



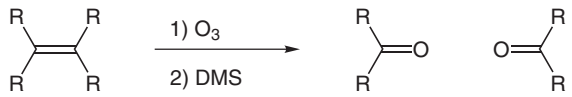
pyridinium chlorochromate
(PCC)

This reagent provides milder oxidizing conditions, and therefore, the reaction stops at the aldehyde. That is, PCC will oxidize a primary alcohol to give an aldehyde:

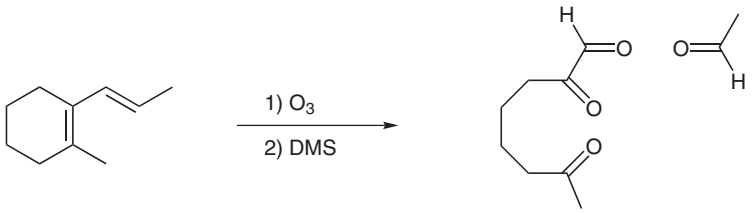


PCC can also be used to convert a secondary alcohol into a ketone.

There is another common way to form a C═O bond (other than oxidation of an alcohol). You might remember the following process from last semester:



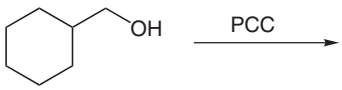
This process is called ozonolysis. It essentially takes every C═C bond in the compound, and breaks it apart into two C═O bonds:



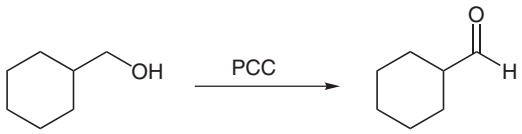
There are many reagents that can be used for the second step of this process (other than DMS). You should look in your lecture notes to see what reagents your instructor (or textbook) used for step 2 of an ozonolysis.

So far, this section has covered only a few ways to make a C═O bond. We saw that an aldehyde can be made by treating a primary alcohol with PCC, and we saw that a ketone can be made by treating a secondary alcohol with a strong oxidizing agent such as sodium dichromate, the Jones reagent, or even PCC. We also saw that ketones and aldehydes can be made via ozonolysis. Let's get some practice with these reactions.

EXERCISE 6.1 Predict the major product(s) of the following reaction:



Answer The oxidizing agent in this case is PCC, and we have seen that PCC will convert a primary alcohol into an aldehyde:



PROBLEMS Predict the major product for each of the following reactions:

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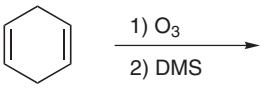

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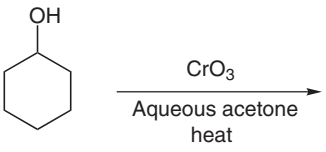

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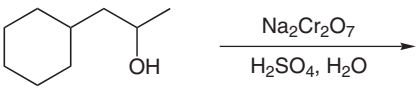

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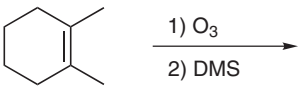

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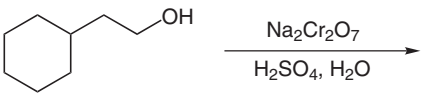

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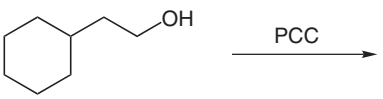
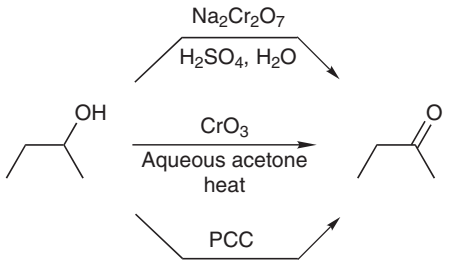


It is not enough to simply "recognize" the reagents when you see them (like we did in the previous problems). But you actually need to know the reagents well enough to write them down when they are not in front of you. Let's get some practice:

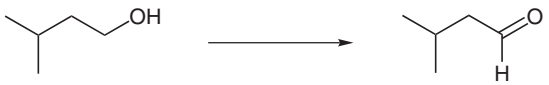
EXERCISE 6.8 Identify the reagents you would use to achieve the following transformation:

Answer In this case, a secondary alcohol must be converted into a ketone. This can be accomplished with a number of reagents, such as sodium dichromate, or the Jones reagent, or even with PCC:



PROBLEMS Identify reagents that you could use to achieve each of the following transformations. Try not to look back at the previous problems while you are working on these problems.

6.9



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6.2 STABILITY AND REACTIVITY OF C═O BONDS

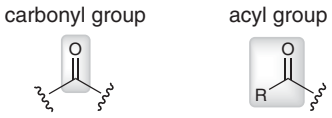
Ketones and aldehydes are very similar to each other in structure:

Therefore, they are also very similar to each other in terms of reactivity. Most of the reactions that we see in this chapter will work for both ketones and aldehydes. So, it makes sense to learn about ketones and aldehydes in the same breath.

But before we can get started, we need to know some basics about C═O bonds. Let's start with a bit of terminology that we will use throughout the entire chapter. Instead of constantly using the expression "C═O double bond," we will call it a *carbonyl group*. This term is NOT used for nomenclature. You will never see the term "carbonyl" appearing in the IUPAC name of a compound. Rather, it is just a

term that we use when we are talking about mechanisms, so that we can quickly refer to the C═O bond without having to say "C═O double bond" all of the time.

Don't confuse the term "carbonyl" with the term "acyl." The term "acyl" is used to refer to a carbonyl group *together with* one alkyl group:

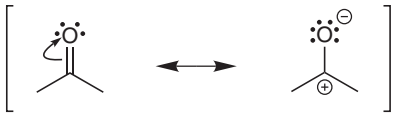


We will use the term "acyl" in the next chapter. But in this chapter, we will focus on the carbonyl group.

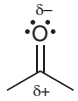
If we want to know how a carbonyl group will react, we must first consider electronic effects (the locations of δ+ and δ−). There are always two factors to explore: induction and resonance. If we start with induction, we notice that oxygen is more electronegative than carbon, and therefore, the oxygen atom will withdraw electron density:

As a result, the carbon atom of the carbonyl group is δ+ and the oxygen atom is δ−.

Next, we look at resonance:

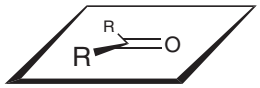


And we see, once again, that the carbon atom is δ+ and the oxygen atom is δ−, this time because of resonance. So, both induction and resonance paint the same picture:

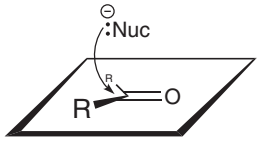


This means that the carbon atom is very electrophilic, and the oxygen atom is electron-rich. We will focus all of our attention in this chapter on the carbon atom of a carbonyl group. We will see *how* the carbon atom functions as an electrophile, *when* it functions as an electrophile, and *what happens after* it functions as an electrophile.

The geometry of a carbonyl group facilitates the carbon atom functioning as an electrophile. We saw in the first semester of organic chemistry that sp^2-hybridized carbon atoms have trigonal planar geometry:



This makes it easy for a nucleophile to attack the carbonyl group, because there is little steric hindrance that would block the incoming nucleophile:



In this chapter, we will see many different kinds of nucleophiles that can attack a carbonyl group. In fact, this entire chapter will be organized based on the kinds of nucleophiles that can attack. We will start with hydrogen nucleophiles and continue with oxygen nucleophiles, sulfur nucleophiles, nitrogen nucleophiles, and, finally, carbon nucleophiles. This approach (dividing the chapter based

on the kinds of nucleophiles) might be somewhat different than your textbook. But hopefully, the order that we use here will help you appreciate the similarity between the reactions.

There is one more feature of carbonyl groups that must be mentioned before we can get started. Carbonyl groups are thermodynamically very stable. In other words, forming a carbonyl group is generally a process that is downhill in energy. As a result, the formation of a carbonyl group is often the driving force for a reaction. We will use that argument many times in this chapter, so make sure you are prepared for it. The mechanisms in this chapter will be explained in terms of the stability of carbonyl groups.

Now let's just quickly review the important characteristics that we have seen so far. The carbon atom (of a carbonyl group) is electrophilic, and it is readily attacked by a nucleophile (and there are MANY different kinds of nucleophiles that can attack it). We have also seen that a carbonyl group is very stable. So, the formation of a carbonyl group can serve as a driving force.

These principles will guide us throughout the rest of the chapter, and they can be summarized like this:

- A carbonyl group can be attacked by a nucleophile, and
- After a carbonyl group is attacked, it will try to re-form, if possible.

6.3 H-NUCLEOPHILES

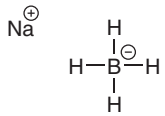
We will now explore the various nucleophiles that can attack ketones and aldehydes. We will divide all nucleophiles into categories, and in this section, we will focus on hydrogen nucleophiles. I call them "hydrogen" nucleophiles, because they are a source of a negatively charged hydrogen atom (which we call a "hydride" ion) that can attack a ketone or aldehyde. The simplest way to get a hydride ion is from sodium hydride (NaH). This compound is ionic, so it is composed of Na^+ and H^- ions (very much the way NaCl is composed of Na^+ and Cl^- ions). So, NaH is certainly a good source of hydride ions.

However, you will not see any reactions where we use NaH as a source of hydride *nucleophiles*. As it turns out, NaH is a very strong base, but it is not a strong nucleophile. This is an excellent example of how basicity and nucleophilicity do NOT completely parallel each other. The reason for this goes back to something from the first semester of organic chemistry. Try to remember back to the difference between basicity and nucleophilicity. Let's review it quickly.

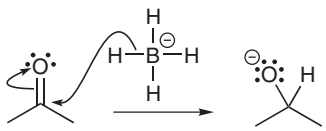
The strength of a base is determined by the *stability* of the negative charge. An unstable negative charge corresponds with a strong base, while a stabilized negative charge corresponds with a weak base. But nucleophilicity is NOT based on stability. Nucleophilicity is based on *polarizability*. Polarizability describes the ability of an atom or molecule to distribute its electron density unevenly in response to external influences. Larger atoms are more polarizable, and are therefore strong nucleophiles; while smaller atoms are less polarizable, and are therefore weak nucleophiles.

With that in mind, we can understand why H^- is a strong base, but not a strong nucleophile. It is a strong base, because hydrogen does not stabilize the charge well. But when we consider the nucleophilicity of H^-, we realize that hydrogen is the smallest atom, and therefore, the least polarizable. As a result, H^- is generally not observed to function as a nucleophile. So, how do we form a hydrogen nucleophile?

Although H^- itself cannot be used as a nucleophile, there are many reagents that can serve as a "delivery agent" of H^-. For example, consider the structure of sodium borohydride ($NaBH_4$):



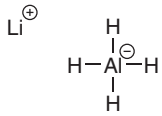
If we look at the periodic table, we see that boron is in Column 3A, and therefore, it has three valence electrons. Accordingly, it can form three bonds. But in sodium borohydride (above), the central boron atom has *four* bonds. So it must be using one extra electron, and therefore, it has a negative formal charge (for our purposes, we can ignore the sodium ion, Na^+, and treat it as if it was just a counter ion). This reagent can serve as a delivery agent of H^-, as seen in the following example:



Notice that H^- never really exists by itself in this reaction. Rather, H^- is "delivered" from one place to another. That is a good thing, because H^- by itself would not serve as a nucleophile (as we saw earlier). But sodium borohydride can serve as a source of a hydrogen

nucleophile, because the central boron atom is somewhat polarizable. The polarizability of the boron atom allows the entire compound to serve as a nucleophile, and *deliver* a hydride ion to attack the ketone. Now, it is true that boron is not so large, and therefore, it is not very polarizable. As a result, $NaBH_4$ is a somewhat tame nucleophile. In fact, we will soon see that $NaBH_4$ is selective in its reactivity. It will not react with all carbonyl groups (for example, it will not react with an ester). But it will react with ketones ***and*** with aldehydes (and that is our focus in this chapter).

There is another common reagent that is very similar to sodium borohydride, but it is much more reactive. This reagent is called lithium aluminum hydride ($LiAlH_4$):

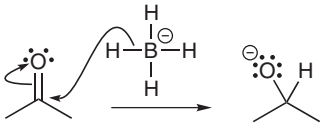


This reagent is very similar to $NaBH_4$ because aluminum is also in Column 3A of the periodic table (directly beneath boron). So, it also has three valence electrons. In the structure above, the aluminum atom has four bonds, which is why it has a negative charge. Just as we saw with $NaBH_4$, $LiAlH_4$ is also a source of nucleophilic H^-. But compare these two reagents to each other—aluminum is larger than boron. That means that it is more polarizable, and therefore, $LiAlH_4$ is a much better nucleophile than $NaBH_4$. $LiAlH_4$ will react with almost any carbonyl group (not just ketones and aldehydes).

It will soon become very important that $LiAlH_4$ is more reactive than $NaBH_4$. But for now, we are talking about nucleophilic attack of ketones and aldehydes; and both $NaBH_4$ and $LiAlH_4$ will react with ketones and aldehydes.

In addition to $NaBH_4$ and $LiAlH_4$, there are other sources of hydrogen nucleophiles as well, but these two are the most common reagents. You should look through your textbook and lecture notes to see if you are responsible for being familiar with any other hydrogen nucleophiles.

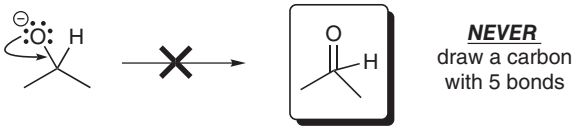
Now let's take a close look at what can happen after a hydrogen nucleophile attacks a carbonyl group. As we have seen, the reagent (either $NaBH_4$ or $LiAlH_4$) can deliver a hydride ion to the carbonyl group, like this:



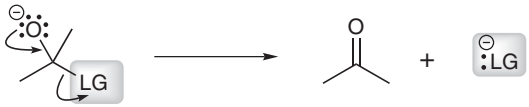
In the beginning of this chapter, we covered two important rules that govern the behavior of a carbonyl group:

- it is easily attacked by nucleophiles (as we just saw in the step above), and
- after a carbonyl group is attacked, it will try to re-form, if possible. Now we need to understand what we mean when we say: "if possible."

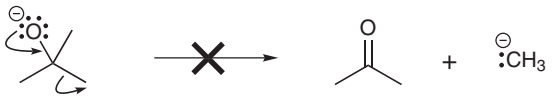
In trying to re-form the carbonyl group, we realize that the central carbon atom cannot form a fifth bond:



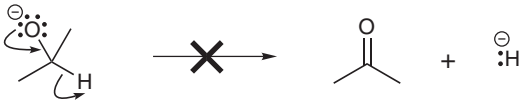
That would be impossible, because carbon only has four orbitals to use. So, in order for the carbonyl group to re-form, a leaving group must be expelled, like this:



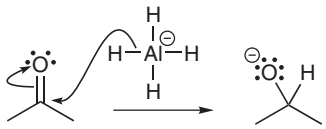
When considering which groups can function as leaving groups, avoid expelling H^- or C^- (there are a few exceptions to this rule, which we will see later, but unless you recognize that you are dealing with one of the rare exceptions, do NOT expel H^- or C^-). For example, never do this:



And never do this:



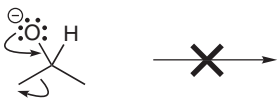
We have just learned a simple general rule. Now let's try to apply this rule to determine the outcome that is expected when a ketone or aldehyde is treated with a hydrogen nucleophile. Once again, the first step was for the hydrogen nucleophile to attack the carbonyl group:



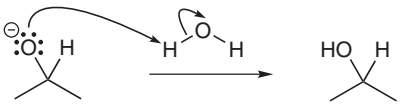
Now let's consider what can possibly happen next. In order for the carbonyl group to re-form, a leaving group must be expelled. But there are no leaving groups in this case. The carbonyl cannot re-form by expelling C^-:

And it cannot re-form by expelling H^-:

And it cannot re-form by expelling C^-:

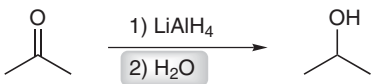


So we are stuck. Once a hydrogen nucleophile delivers H^- to the carbonyl group, then it will not be possible for the carbonyl group to re-form. So the reaction is complete, and it just waits for us to introduce a source of protons to "work-up" the reaction (to protonate the alkoxide ion). To achieve this protonation, we can introduce either water or H_3O^+ as the source of protons:

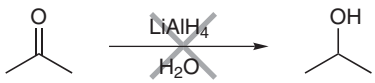


Regardless of the identity of the proton source that we add to the reaction flask after the reaction is complete, the product of this reaction will be an alcohol.

Whenever you are using this transformation in a synthesis, you must clearly show that the proton source is added AFTER the reaction has occurred:

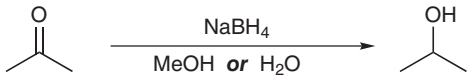


In other words, it is important to show that $LiAlH_4$ and water are ***two separate steps***. Do ***not*** show it like this:



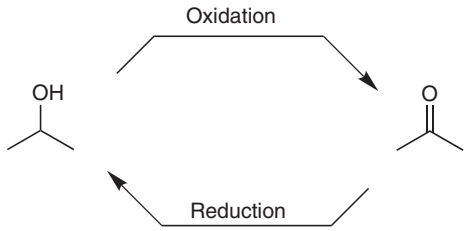
This would mean that $LiAlH_4$ and H_2O are present at the same time, and that is not possible. $LiAlH_4$ would react violently with water to form H_2 gas (because H^+ and H^- would react with each other).

As it turns out, $NaBH_4$ is a milder source of hydride, and therefore, $NaBH_4$ can actually be present at the same time as the proton source:



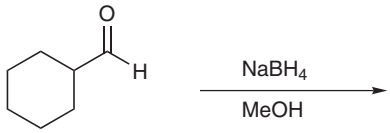
Common proton sources include MeOH and water (sometimes you might see EtOH). Notice that we didn't show it as two separate steps. When you are dealing with $LiAlH_4$, you must show two steps (one step for $LiAlH_4$ and another step for the proton source); but when you are dealing with $NaBH_4$, you should show the proton source in the same step as $NaBH_4$.

$LiAlH_4$ and $NaBH_4$ are very useful reagents. They allow us to *reduce* a ketone or aldehyde, which is important when you realize that we already learned the reverse process:

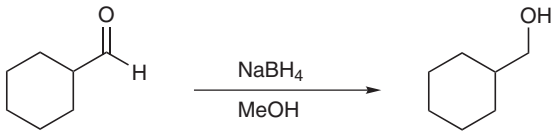


These two transformations will be *tremendously* helpful when you are trying to solve synthesis problems later on. You would be surprised just how many synthesis problems involve the conversion between alcohols and ketones. You need to have these two transformations at your fingertips.

EXERCISE 6.13 Predict the major product of the following reaction:

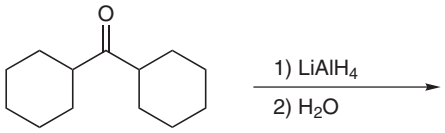


Answer The starting compound is an aldehyde, and it is being treated with sodium borohydride. This hydrogen nucleophile will *deliver* H^- to the aldehyde, and the carbonyl group will not be able to re-form, because there is no leaving group. In this case, methanol serves as the proton source, and an alcohol will be obtained:

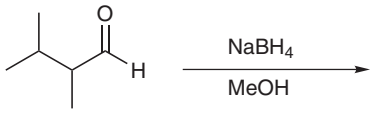


PROBLEMS Predict the major product for each of the following reactions:

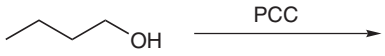
6.14



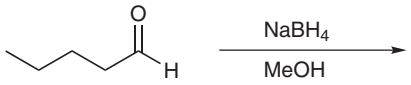
6.15



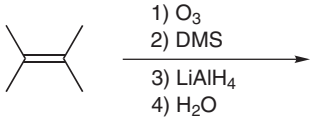
6.16



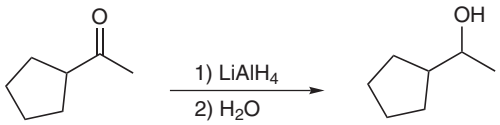
6.17



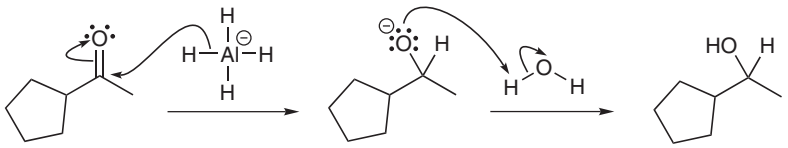
6.18



EXERCISE 6.19 Draw a mechanism for the following transformation:

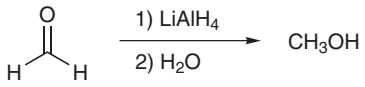


Answer First, $LiAlH_4$ delivers a hydride ion to the ketone. Then, the carbonyl group is not able to re-form, so the intermediate waits for a proton from water, during the workup step:

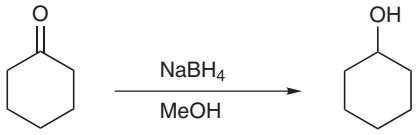


PROBLEMS Propose a mechanism for each of the following transformations. The following problems will probably seem too easy—but just do them anyway. These basic arrows need to become *routine* for you, because we will step up the complexity in the next section, and you will want to have these basic skills down cold:

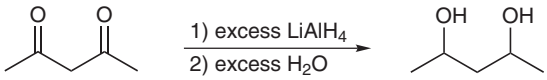
6.20



6.21



6.22

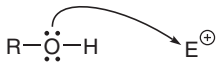


6.4 O-NUCLEOPHILES

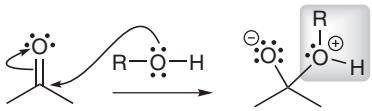
In this section, we will focus our attention on oxygen nucleophiles. Let's begin by exploring what happens when an alcohol functions as a nucleophile and attacks a ketone or aldehyde.

Be warned: the mechanism we are about to see is one of the longer mechanisms that you will encounter in this course. But it is incredibly important because it lays the foundation for so many other mechanisms. If you can master this mechanism, then you will be in really good shape to move on. And to be honest, there is no other option; you MUST master this mechanism. So, be prepared to read through the next several pages slowly, and then be prepared to practice the material on these pages as many times as necessary until you know this mechanism extremely well.

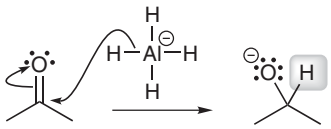
Alcohols are nucleophilic because the oxygen atom has lone pairs that can attack an electrophile:



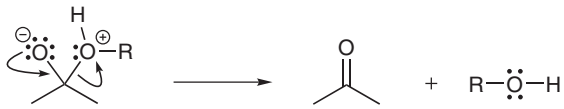
When an alcohol attacks a carbonyl group, an intermediate is generated that should remind us of the intermediate that was formed in the previous section:



Notice how similar this is to the hydride attack we explored in the previous section:



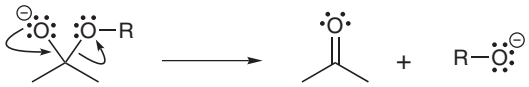
But there is one major difference here. When we saw the attack of a hydrogen nucleophile in the previous section, we argued that the carbonyl group could not re-form after the attack because there was no leaving group. But here, in this section (with an alcohol functioning as a nucleophile), there is a leaving group. So, it ***is*** possible for the carbonyl group to re-form:



The attacking nucleophile (ROH) can function as the leaving group. But, of course, that gets us right back to where we started. As soon as a molecule of alcohol attacks the carbonyl group, it just gets expelled immediately, and there is no net reaction.

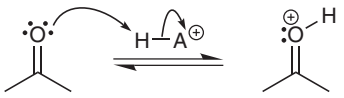
So, let's explore other possible avenues, to see if there is a reaction that can occur. First of all, we should realize that the attack of an alcohol is much slower than the attack of a hydrogen nucleophile, because alcohols do not have a negative charge and are not strong nucleophiles. So, if we want to speed up this reaction, we would want to make the nucleophile more nucleophilic (for example, using RO^- instead of ROH):

Theoretically, this would speed up the reaction, but under these conditions, we would have the same problem that we just had a moment ago. We cannot prevent the carbonyl group from re-forming. The initial intermediate will just eject the nucleophile, and we would get right back to where we started:



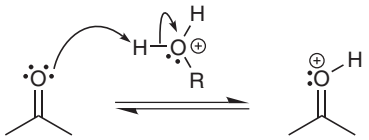
So, we will take a slightly different approach. Rather than making the nucleophile more nucleophilic, we will focus on making the electrophile more electrophilic. So, let's focus on the electrophile of our reaction:

How do we make a carbonyl group even more electrophilic? By introducing a small quantity of catalytic acid into the reaction flask:



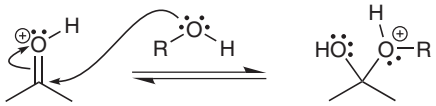
The resulting protonated ketone is significantly more electrophilic (this entity bears a full positive charge, rendering the carbonyl group more electron-poor). This is VERY IMPORTANT, because we will see this many times throughout this chapter. Many acids can be used for this purpose, including H_2SO_4. When drawing a mechanism for the protonation of a ketone in the presence of an acid catalyst, we should recognize that the identity of the acid ($H—A^+$) is most likely a protonated alcohol, which received its extra proton from H_2SO_4.

So protonation of the ketone most likely occurs in the following way:



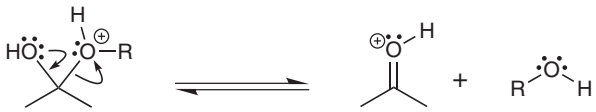
As we continue to discuss this mechanism, we will just show $H—A^+$ as the proton source, and it is expected that you will understand that the identity of $H—A^+$ is likely a protonated alcohol.

Now that the ketone has been protonated, rendering it more electrophilic, let's consider what happens if an alcohol molecule functions as a nucleophile and attacks the protonated ketone:

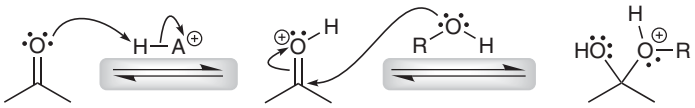


This gives an intermediate that has a tetrahedral geometry (the starting ketone was sp^2 hybridized, and therefore trigonal planar; but this intermediate is now sp^3 hybridized, and therefore tetrahedral). So, we will refer to this intermediate as a "tetrahedral intermediate."

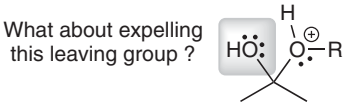
Doesn't this tetrahedral intermediate give us the same problem? Doesn't it simply expel a leaving group to re-form the protonated ketone?



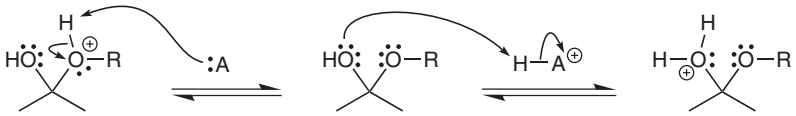
Yes, this ***can*** happen. In fact, it ***does*** happen—most of the time. That is in fact why we are using equilibrium arrows, highlighted below:



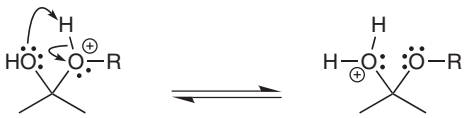
So it is true that there is an equilibrium between the forward and reverse processes. But every now and then, there is something else that can happen. There is a different way in which the carbonyl group can be re-formed:



In other words, we are exploring whether HO^- can be expelled as a leaving group, which should theoretically work because we said before that anything can be expelled except for H^- and C^-. Nonetheless, *we cannot expel HO^- in acidic conditions*. Rather, it will have to be protonated first, which converts it into a better leaving group (this is a BIG DEAL—make sure that this rule becomes part of the way you think—NEVER expel HO^- into acidic conditions—always protonate it first). So we draw the following proton transfer steps:

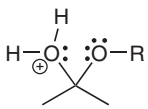


Notice that we first deprotonated to form an intermediate with no charge, and only then protonated. We specifically chose this order (first protonate, then deprotonate) to avoid having an intermediate with two positive charges. This is another important rule that you should make part of the way you think from now on. Avoid intermediates with two similar charges. Now, there are always some clever students who try to combine the two steps above into one step, by transferring a proton intramolecularly, like this:

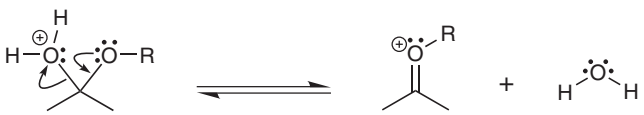


While this might make sense on paper, it actually doesn't occur that way because the oxygen atom and the proton are simply too far apart in space to interact. An intramolecular proton transfer would require a transition state that resembles a 4-membered ring, which is high in energy and unlikely to occur. So, when drawing a mechanism, you must first remove a proton, and only then, do you protonate (and it is probably not going to be the same exact proton that was removed).

The result of our two separate proton transfer steps is the following intermediate:

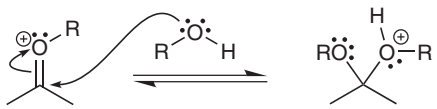


And now we are ready to expel the leaving group (which is now H_2O, rather than HO^-) to re-form a carbonyl group, like this:

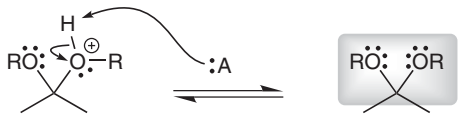


This new intermediate now ***does*** have a carbonyl group, ***but*** there is no easy way to remove the charge. You can't just lose R^+ the way you can lose a proton:

But there is another way for the charge to be removed. This intermediate can be attacked by *another* molecule of alcohol, just like the protonated ketone was attacked at the beginning of the mechanism:

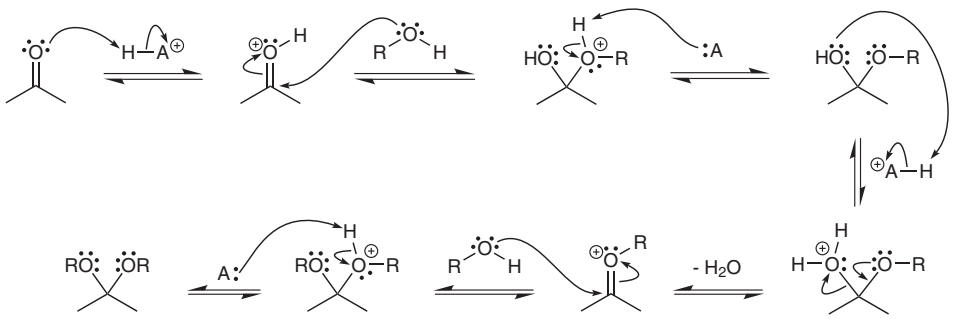


And finally, removal of a proton gives our product:

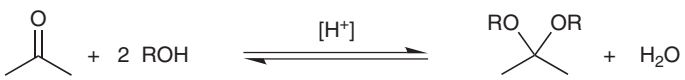


The overall transformation can be summarized as follows:

To make sure that we understand some of the key features of this mechanism, let's take a close look at the whole thing all at once. There are seven steps:



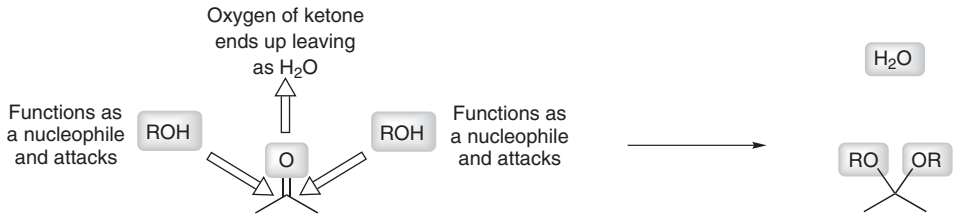
First let's focus our attention on all of the proton transfers in the entire mechanism. Four of the steps above are proton transfer steps. Two of them involve protonation and two involve deprotonation. So, in the end, the acid is not consumed by the reaction. It is a *catalyst* here. From now on, we will place brackets around the acid to indicate that its function is catalytic:



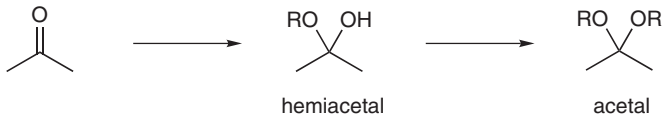
It is interesting to realize that *most* of the steps in the mechanism above are just proton transfer steps. There are only three steps other than proton transfers, and they are: nucleophilic attack (with ROH as the nucleophile), loss of a leaving group (H_2O), and another nucleophilic

attack (again, with ROH as the nucleophile). All of the proton transfers are simply used to facilitate these three steps (proton transfers make the carbonyl group more electrophilic, to produce water as a leaving group instead of hydroxide, and to avoid multiple charges). It is important that you see the reaction in this way. It will greatly simplify the whole mechanism in your mind.

The drawing below is NOT a mechanism—the arrows in this drawing are only being used to help you review all three critical steps at once:

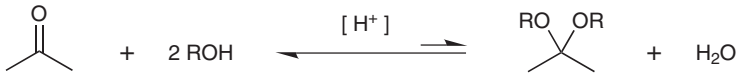


The product of this reaction is called an *acetal*. When we form an acetal from a ketone, there is one intermediate that gets a special name, because it is the only intermediate that does not have a charge. It is called a *hemiacetal*, and you can think of it as "half-way" toward making an acetal:

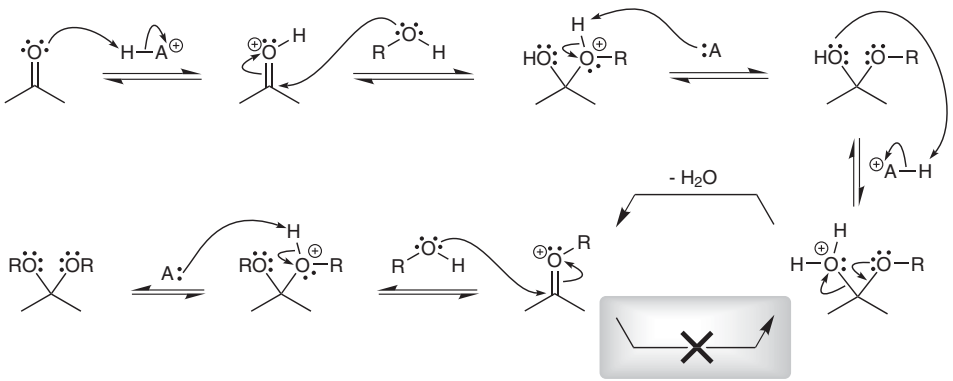


We give it a special name because it is theoretically possible to isolate it and store it in a bottle (although in most cases, this is very difficult to actually do), and because this type of intermediate will be important if/when you learn biochemistry.

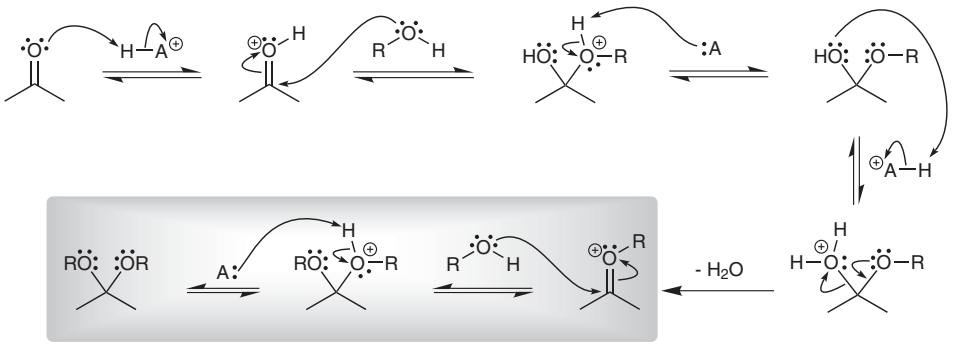
Notice that an acetal does not have a carbonyl group. This means that the equilibrium will lean toward the starting materials, rather than the products:



In other words, if we try to perform this reaction in a lab, we will obtain very little (if any) product. So, the question is: how can we force the reaction to form the acetal? There is a clever trick for doing this, and it involves removing water from the reaction as the reaction proceeds. If we remove water as it is formed, we will essentially stop the reverse path at a particular step (highlighted in the following mechanism). It is like putting up a brick wall that prevents the reverse reaction from occurring:



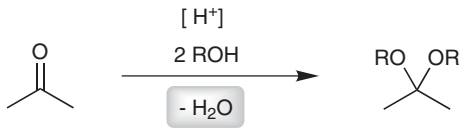
By removing water as it is being formed, we force the reaction to a certain point. Now let's focus on all of the steps (highlighted below) that come after the water-removal step:



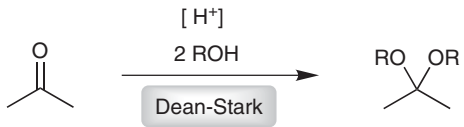
In the highlighted area, we see three structures in equilibrium with each other. Two of them are positively charged, and one of them (the product) is uncharged. This equilibrium now favors formation of the uncharged product.

In summary, formation of the acetal can be favored by removing the water as it is formed. Re-forming the carbonyl group (the reverse reaction) would require water, but there is no water present because it has been removed. This very clever trick allows us to force the equilibrium to favor the products even though they are less stable than the reactants.

In your textbook and in your lectures, you will probably explore the way that chemists remove water from the reaction as it proceeds. It is called azeotropic distillation, and there is a special piece of glassware that is used (called a Dean–Stark trap). I will not go into the details of azeotropic distillation here, but I wanted to just briefly mention it, because you should know how to indicate the removal of water. There are at least two common ways to show it:

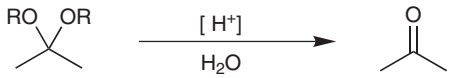


or like this:

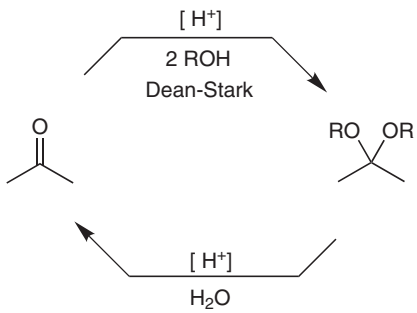


By just writing the words "Dean–Stark," you are indicating that you understand that it is necessary to remove water in order to form the acetal.

Now we can also appreciate how you would reverse this reaction. Suppose you have an acetal, and you want to convert it back into a ketone. You would just add water with a catalytic amount of acid, and the acetal would be converted back into a ketone. This reaction is called acetal hydrolysis:

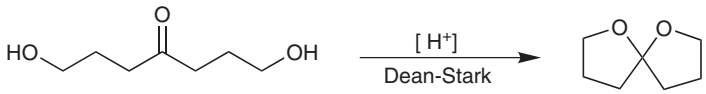


Under these conditions, the equilibrium will favor formation of the ketone. So, now we know how to convert a ketone into an acetal, and we know how to convert the acetal back into a ketone:

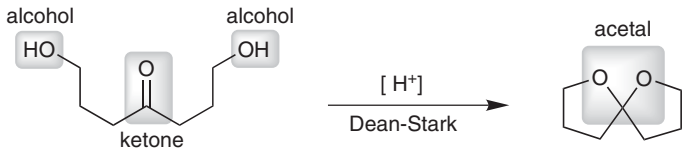


It is very important that we are able to control the conditions to push the reaction in either direction. We will soon see why this is so important. But first, let's make sure we are comfortable with the mechanism of acetal formation:

EXERCISE 6.23 Draw a mechanism for the following reaction.

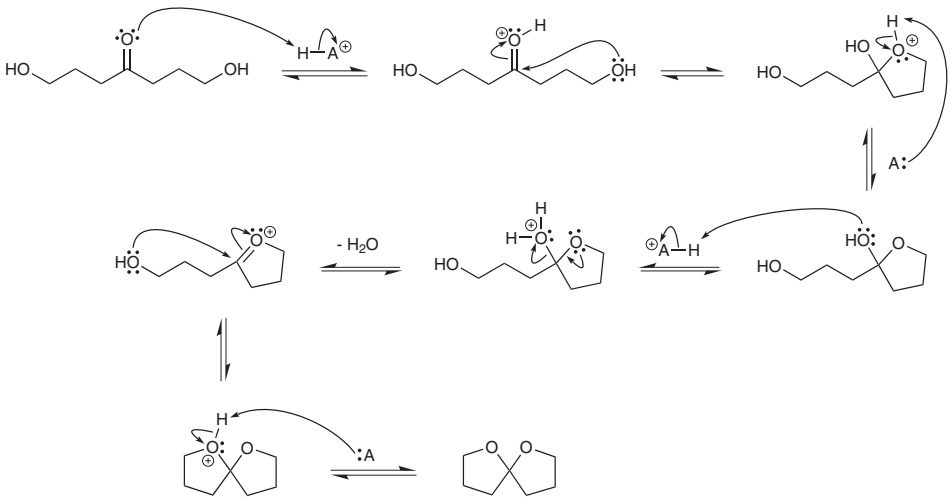


Answer Notice that we are starting with a ketone, and we are ending up with an acetal. It is a bit tricky to see, because it is all happening in an intramolecular fashion. In other words, the two alcoholic OH groups are *tethered* to the ketone:



So, the mechanism should follow the same order of steps as the mechanism we have already seen. Namely, there are three critical steps (nucleophilic attack, loss of water, and another nucleophilic attack) surrounded by many proton transfer steps. The proton transfer steps are just there to facilitate these three steps. We use a proton transfer in the very first step to render the carbonyl group more electrophilic. Then, we use proton transfers to form water (so that it can leave). And finally, we use a proton transfer to remove the charge and generate the product.

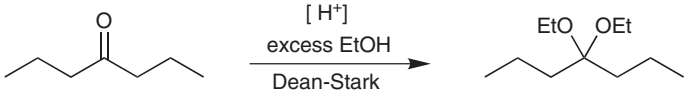
Perhaps you should try to draw the mechanism for this reaction on a separate piece of paper. Then, when you are done, you can compare your work to the following answer:



We said before that this type of mechanism is so incredibly important because there will be so many more reactions that build upon the concepts that we developed in this mechanism. To get practice, you should work through the following problems slowly and methodically.

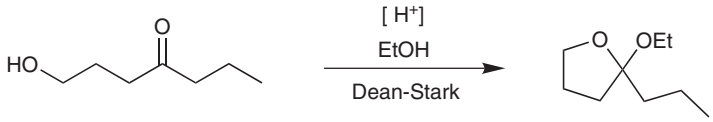
PROBLEMS Draw a mechanism for each of the following transformations. You will need a separate piece of paper for each mechanism.

6.24

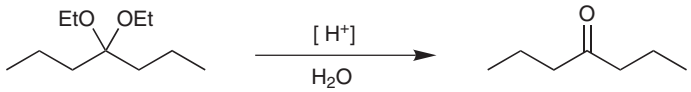


6.25

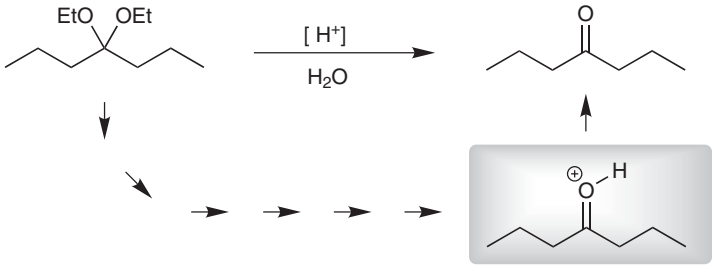
6.26



6.27 There is one sure way to know whether or not you have mastered a mechanism forward and backwards—you should try to actually draw the mechanism backwards. That's right, backwards. For example, draw a mechanism for the following reaction. Make sure to first read the advice below before attempting to draw a mechanism.

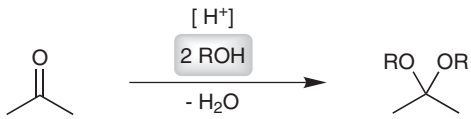


My advice for this mechanism is to start at the end of the mechanism (with the ketone), and then draw the intermediate you would get if you were converting the ketone into an acetal, like this:

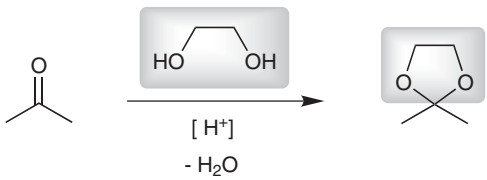


Keep drawing only the intermediates, working your way backwards, until you arrive at the acetal. But ***don't*** draw any curved arrows yet. Draw only the intermediates, working backwards from the ketone to the acetal. Then, once you have all of the intermediates drawn, then come back and try to fill in arrows, starting at the beginning, with the acetal. Use a separate sheet of paper to draw your mechanism. When you are finished, you can compare your answer to the answer in the back of the book.

In this section, we have seen acetal formation, a reaction that takes place between a ketone and ***two*** molecules of ROH, in the presence of an acid catalyst and under Dean–Stark conditions:

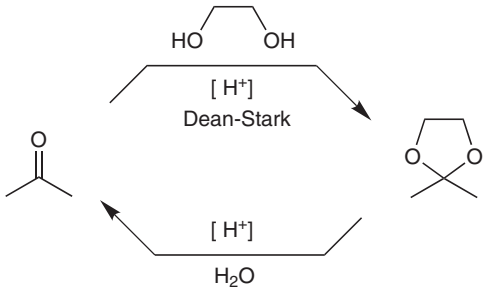


We saw a mechanism, in which the ketone is attacked twice. This same reaction can occur when both nucleophilic OH groups are in the same molecule. This produces a *cyclic* acetal:



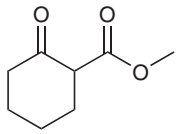
This type of reaction might appear several times throughout your lectures and textbook, so it would be wise to be familiar with this process. The diol in the reaction above is called ethylene glycol, and the transformation can be extremely useful. Let's see why.

We have seen before that we can manipulate the conditions of this reaction to control whether the ketone is favored or whether the acetal is favored. The same is true when we use ethylene glycol to form a cyclic acetal:

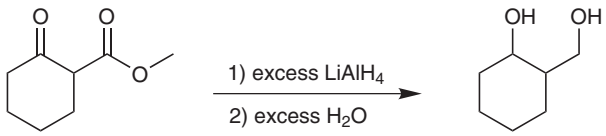


This is important because it allows us to *protect* a ketone from an undesired reaction. Let's see a specific example of this (it will take us a couple of pages to develop this concrete example, so please be patient as you read through this).

Consider the following compound:

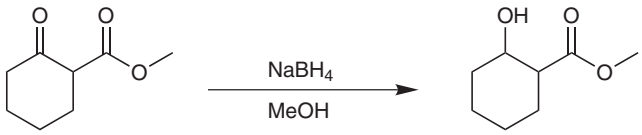


When this compound is treated with excess $LiAlH_4$, followed by water, both carbonyl groups are reduced:



$LiAlH_4$ attacks the ketone ***and*** the ester. It may be difficult to see why the ester is converted into an alcohol—we will focus on that in the next chapter. But if you are curious to test your abilities, you have actually learned everything you need in order to figure out how an ester is converted into an alcohol in the presence of excess $LiAlH_4$ (remember that you should always re-form a carbonyl group if you can, but never expel H^- or C^-).

So, we see that $LiAlH_4$ will reduce both carbonyl groups in the compound above. If instead, we treat the starting compound with excess $NaBH_4$, we observe that only the ketone is reduced:

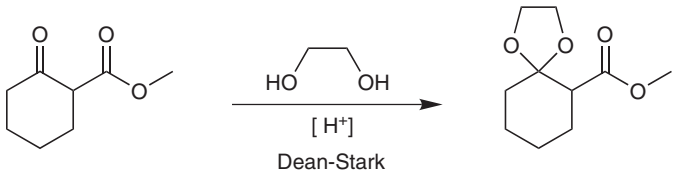


The ester is ***not*** reduced, because $NaBH_4$ is a milder source of hydride (as we have explained earlier). We will see in the next chapter that $NaBH_4$ will not react with esters (only with ketones and aldehydes) because the carbonyl group of an ester is less reactive than the carbonyl group of a ketone.

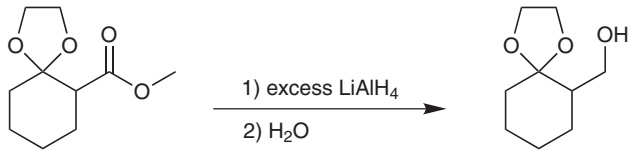
Now suppose you want to achieve the following transformation:

Essentially, you want to reduce the ester, ***but not*** the ketone. That would seem impossible, because esters are less reactive than ketones. Any reagent that reduces an ester should also reduce a ketone.

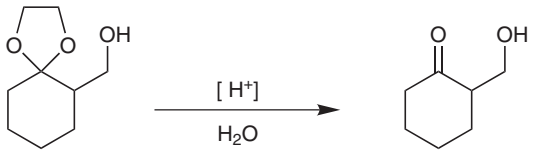
But there is a way to achieve the desired goal. Suppose we "protect" the ketone by converting it into an acetal:



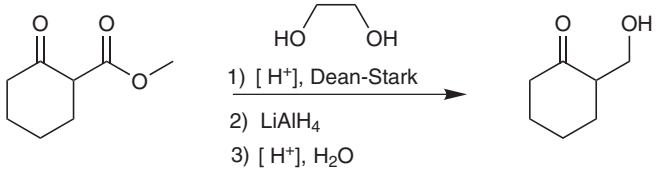
Only the ketone is converted into an acetal. The carbonyl group of the ester is ***not*** converted into an acetal because only aldehydes and ketones can be converted to acetals. Thus, we are able to selectively "protect" the ketone. Now, we can treat this compound with excess $LiAlH_4$, followed by water, and the acetal will not be affected (acetals do not react with bases or nucleophiles under basic conditions):



Notice that we use water above in the second step (as we have done every other time that we used $LiAlH_4$. In the presence of water, the acetal is removed but only if the conditions are acidic. So, to remove the acetal in this case, we would use aqueous acid, rather than H_2O, after the reduction:

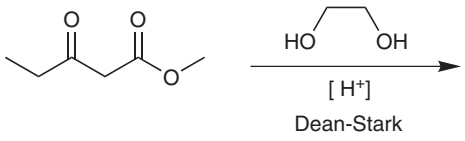


In the end, we have a 3-step process for reducing the ester group ***without affecting*** the ketone:

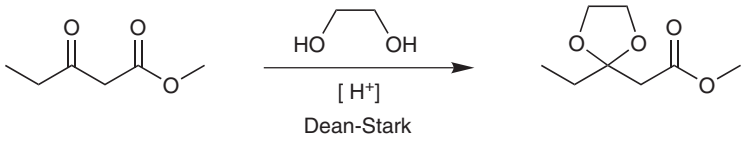


We will talk more about this strategy in the next chapter. For now, let's just focus on knowing the reactions well enough to predict products.

EXERCISE 6.28 Predict the major product of the following reaction:

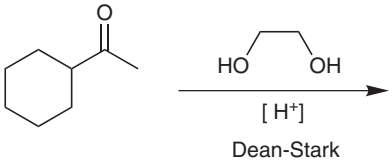


Answer This reaction utilizes ethylene glycol, so we expect a cyclic acetal. Our starting compound has two carbonyl groups. One is a ketone, and the other is an ester group. We have seen that only ketones (not esters) are converted into acetals. So, the major product should be as follows:

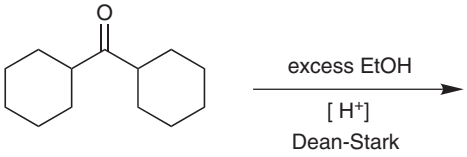


PROBLEMS Predict the major product of each of the following reactions:

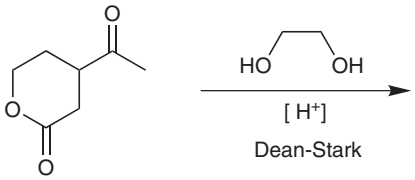
6.29



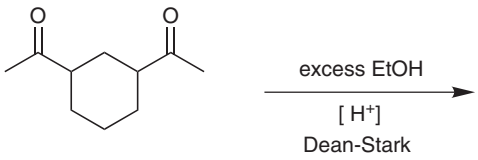
6.30



6.31

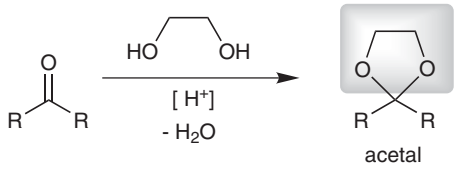


6.32

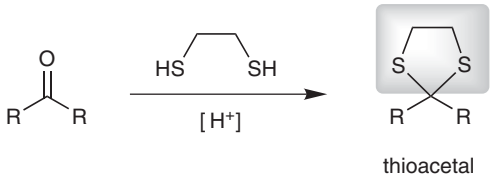


6.5 S-NUCLEOPHILES

Sulfur is directly below oxygen on the periodic table (in Column 6A). Therefore, the chemistry of sulfur-containing compounds is very similar to the chemistry of oxygen-containing compounds. In the previous section, we saw a method for converting a ketone into an acetal:

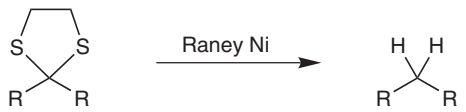


In much the same way, a ketone can also be converted into a ***thio***acetal ("thio" means sulfur instead of oxygen):

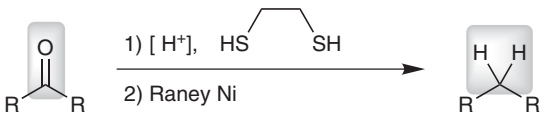


thioacetal

But thioacetals will undergo a transformation not observed for acetals. Specifically, thioacetals are reduced when treated with Raney nickel:



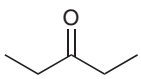
Raney nickel is finely divided nickel that has hydrogen atoms adsorbed to it. The mechanism for this reduction process is beyond the scope of this course. But, this is a useful synthetic transformation. So it is worth remembering, even if you don't know the mechanism. It provides a way to completely reduce a ketone down to an alkane:

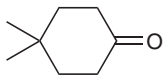


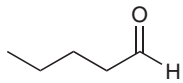
We have actually already seen one way to achieve this kind of transformation. It was called the Clemmensen reduction, which we explored in Chapter 4 (electrophilic aromatic substitution). We will also see one more way to achieve this transformation in the upcoming section.

Why do we need three different ways to do the same thing? Because each of these methods involves a different set of conditions. The Clemmensen reduction employs strongly acidic conditions. The method we learned just now (desulfurization with Raney nickel) employs catalytic acid. And the method in the upcoming section will employ ***basic*** conditions. As we move through the course, we will see times when it won't be good to subject an entire compound to acidic conditions, and we will see other times when it won't be good to subject an entire compound to basic conditions.

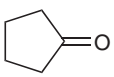
PROBLEMS Predict the major product that is expected when each of the following compounds is treated with ethylene thioglycol ($HSCH_2CH_2SH$) in the presence of catalytic acid.

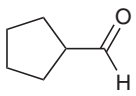
6.33 

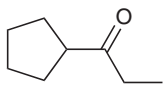
6.34 

6.35 

PROBLEMS Predict the major product that is expected when each of the following compounds is treated with ethylene thioglycol ($HSCH_2CH_2SH$) in the presence of catalytic acid, followed by Raney nickel.

6.36 

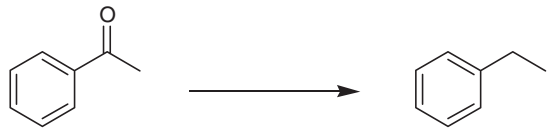
6.37 

6.38 

PROBLEMS Identify reagents that you could use to achieve each of the following transformations:

6.39 

6.40



6.41

6.42

6.43

6.44

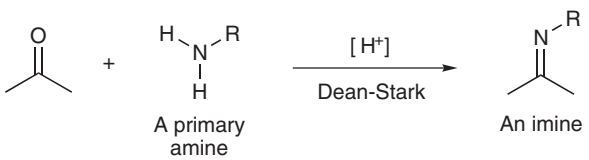
6.45

6.46

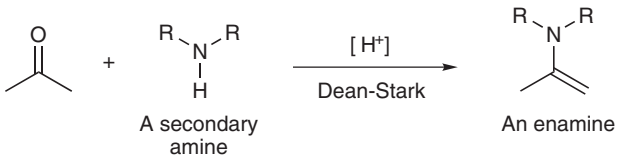
6.6 N-NUCLEOPHILES

In this section, we will focus on reactions between ketones and nitrogen nucleophiles, such as primary and secondary amines:

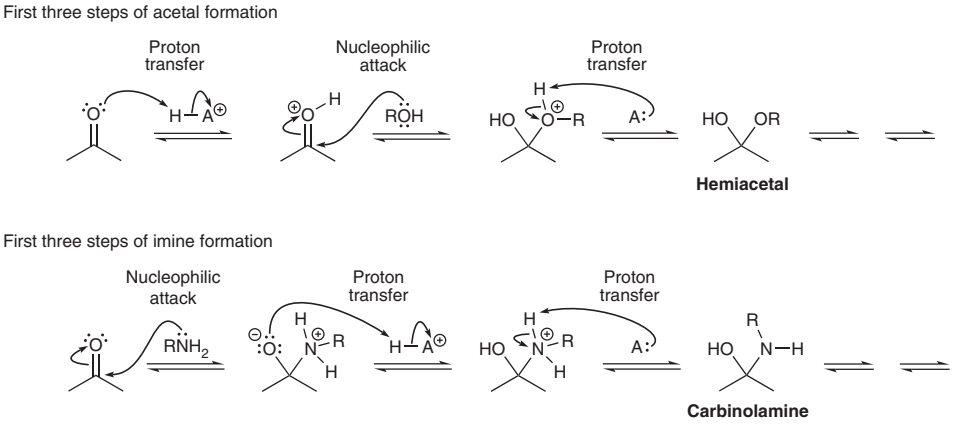
A primary amine has one alkyl group connected to the nitrogen atom, while a secondary amine has two alkyl groups. Primary and secondary amines are excellent nucleophiles, as a result of the localized lone pair on the nitrogen atom. Under the right conditions (catalytic acid, and removal of water), both primary amines and secondary amines will react with ketones or aldehydes. The reaction with a primary amine yields a product with a C═N bond, called an imine,



while the reaction with a secondary amine yields a product called an enamine:



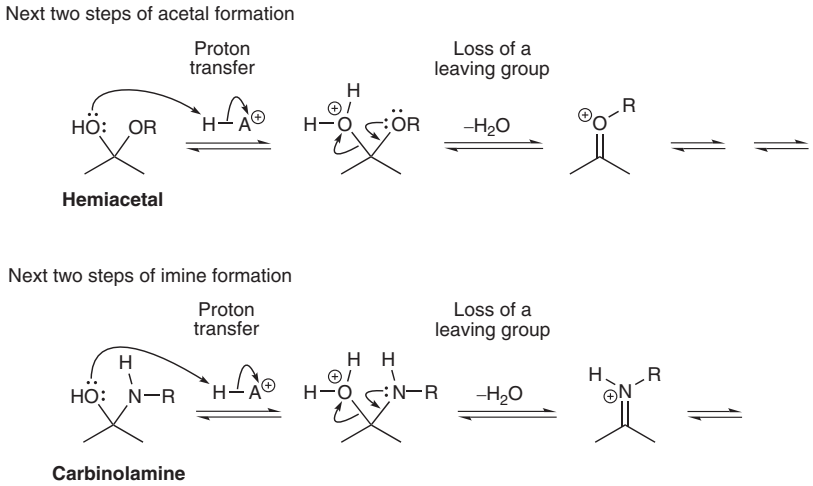
We will explore each of these reactions now, starting with the reaction of primary amines to give imines. To get started, it will be helpful if we compare imine formation with acetal formation (Section 6.4). These two mechanisms are extremely similar, with only a couple of key differences. By focusing on these differences, it will hopefully be easier to study and remember the mechanisms. Let's begin by comparing the first three steps of imine formation and first three steps of acetal formation, and let's focus our attention specifically on the third step in each case:



In each case, the third step is a proton transfer step in which the base (represented by the letter A) removes a proton to generate an uncharged intermediate. In the first case (acetal formation), the uncharged intermediate is called a hemiacetal, while in the second case (imine formation), the uncharged intermediate is called a carbinolamine. Notice that these two intermediates are similar in structure. In fact, we can say that these two processes are very much analogous, although one main difference between the two processes is the order of the first two steps. For acetal formation, the ketone is first protonated, and then the protonated ketone is attacked by a nucleophile. But for imine formation, these two steps are reversed. That is, the ketone is first attacked by the nucleophile (before being protonated), and only then it is protonated (after the nucleophilic attack). Why should there be a difference in the order of these two steps? To understand this, we must consider the identity of HA^+ in each case. For acetal formation, the identity of HA^+ is most likely a protonated alcohol (as we saw in section 6.4). But for imine formation, the identity of HA^+ is most likely a protonated amine (called an ammonium ion), which received its extra proton from the acid catalyst:

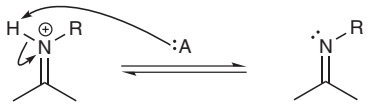
If we compare the pK_a values of an ammonium ion (~10) and a protonated ketone (~ −7), we will find that it is extremely unlikely for an ammonium ion to give a proton to a ketone to generate a protonated ketone. Such a process would be forming a much stronger acid from a much weaker one (an unlikely process). It is more likely that the ketone will first be attacked by a molecule of the amine, which is sufficiently nucleophilic to attack the ketone without prior protonation.

Now that we have seen that the first three steps of imine formation are very similar to the first three steps of acetal formation (with the exception of the order of the first two steps), we can move on to the rest of the mechanism. Once again, we will continue to compare the mechanisms for imine formation and acetal formation, because the next two steps are directly analogous in each mechanism:

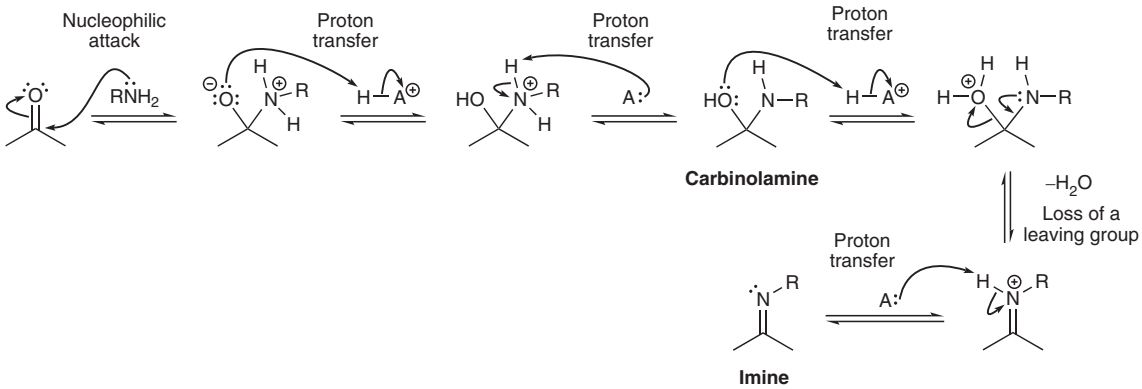


Notice that in each case, the OH group is protonated, followed by loss of a leaving group (water) to give a cationic intermediate (O^+ in the first case, and N^+ in the second case). At this point, our two mechanisms will finally diverge from each other. We can understand why the mechanisms end differently if we focus on the difference between the two intermediates that have been produced thus far (O^+ vs. N^+):

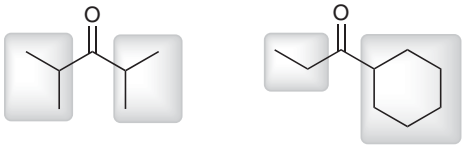
In the first case (during acetal formation), the oxygen atom does not bear a proton, so deprotonation is not an option. This intermediate is extremely electrophilic, so it is readily attacked by another nucleophile (another molecule of ROH), ultimately giving an acetal. However, during imine formation, the intermediate above (N^+) has a proton on the nitrogen atom, which the base removes to yield an imine:



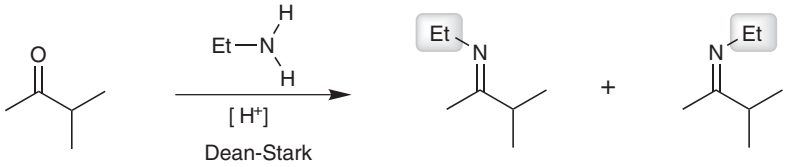
So the mechanism of imine formation is really very similar to the mechanism of acetal formation, with two key differences (the order of the first two steps are reversed, and the ending is different). The following is a summary of the entire mechanism that has been presented for imine formation:



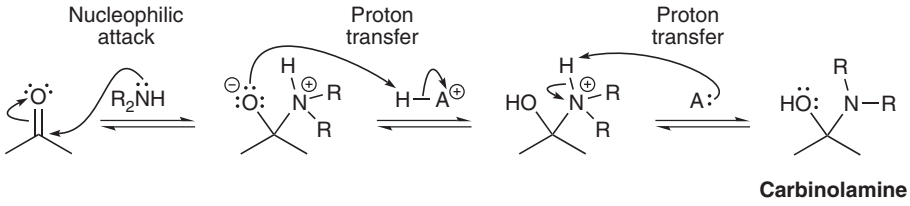
When converting a ketone into an imine, we need to take special notice of whether or not the starting ketone is symmetrical:



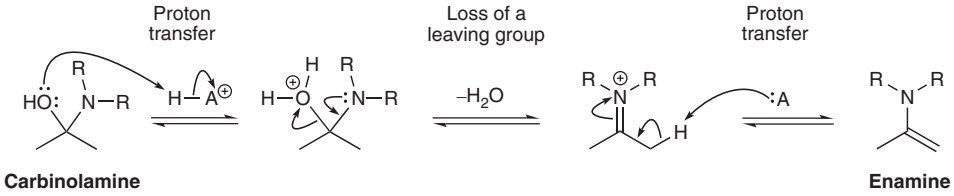
If the starting ketone is ***un***symmetrical, then we should expect two diastereomeric imines, for example:



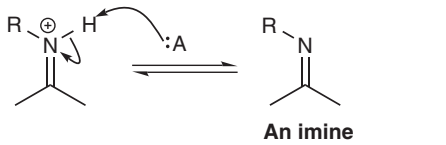
So far, we have seen that *primary* amines will react with ketones (under acid-catalyzed conditions) to give imines. Now, let's focus our attention on the reaction of *secondary* amines with ketones to give enamines. The accepted mechanism for enamine formation is extremely similar to the mechanism that we just saw for imine formation. The first three steps give a carbinolamine (exactly as we saw during imine formation):

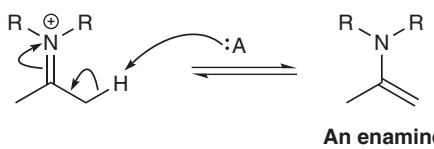


And the last three steps convert the carbinolamine into an enamime:



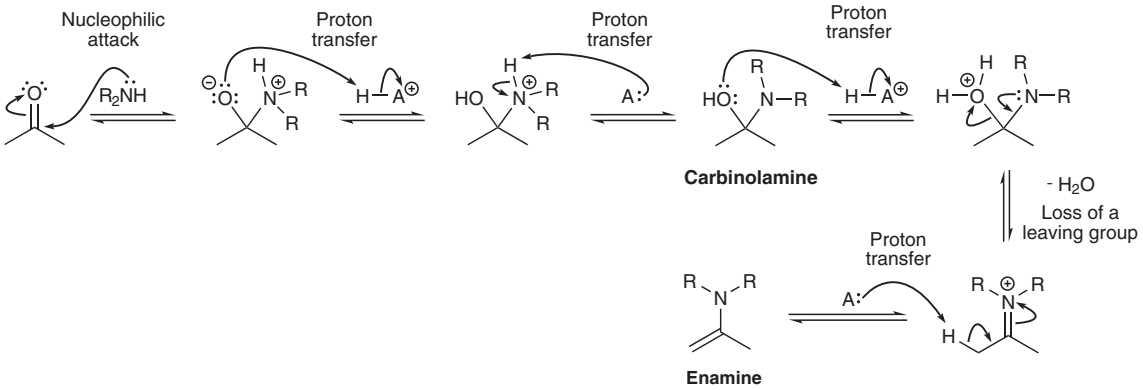
Notice that these three final steps are almost exactly the same as the three final steps of imine formation. But there is one major difference, in the very last step. Let's compare the last step of imine formation with the last step of enamine formation:



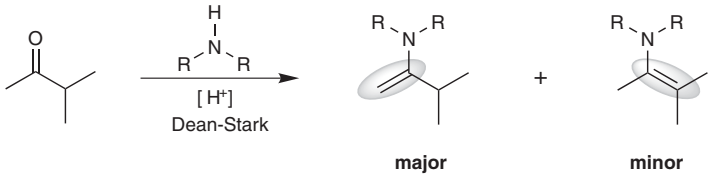


In the first case, the nitrogen atom bears a proton, which is removed by a weak base (A) to give the imine. However, in the second case, the nitrogen atom does not bear a proton that can be removed. Instead, the base removes a different proton, as shown, to give an enamine.

The following is a summary of the entire mechanism that has been presented for enamine formation:

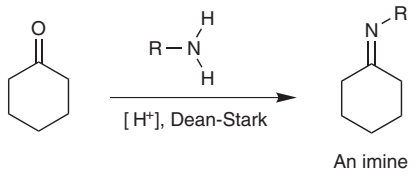


Once again, we need to be careful to check if the ketone is unsymmetrical. If it is, then there will be two ways to form the double bond in the last step of the mechanism. This will give two different enamine products. Here is an example:

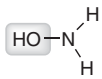


In a situation like this (where we start with an unsymmetrical ketone), the major product will generally be the enamine with the *less*-substituted double bond.

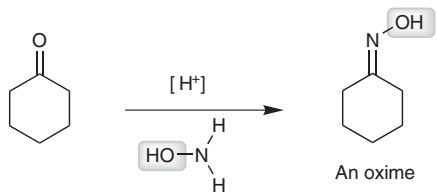
So far in this section, we have seen two new reactions (with primary amines, and with secondary amines), and we have seen the similarities in the mechanisms. Now, we will revisit the first reaction (the reaction between a ketone and a *primary* amine):



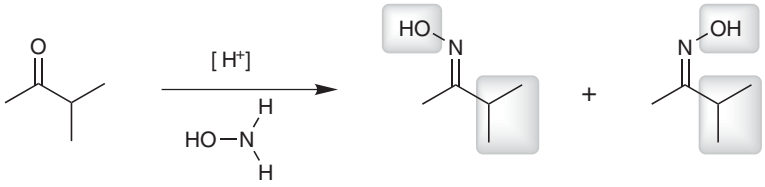
The "R" in RNH_2 refers to an alkyl group (that is usually what R means). But imagine that, in place of the R group, there was something *other than an alkyl group*. For example, imagine that R was an OH group, rather than an alkyl group. In other words, imagine that we were starting with the following amine:



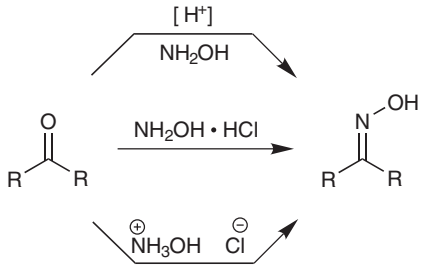
This compound is called hydroxylamine, and the product that it forms (when it reacts with a ketone) is not surprising at all:



It is the same reaction as if it were a primary amine reacting with the ketone. But, instead of obtaining an imine, the reaction gives a product called an oxime. Remember to always look if the starting ketone is unsymmetrical. If it is, expect two diastereomeric oximes:

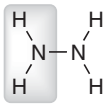


When you see this type of reaction, there are several ways that the presence of hydroxylamine can be indicated:

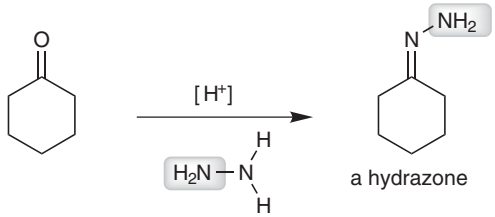


All of these representations are just different ways of showing the same reagent.

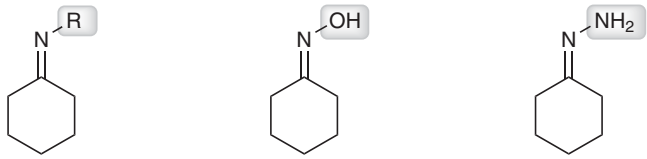
Now that we have seen a special N-nucleophile (RNH_2 where R = OH), let's take a close look at another special N-nucleophile. Let's look at a case where R = NH_2. In other words, we are using the following nucleophile:



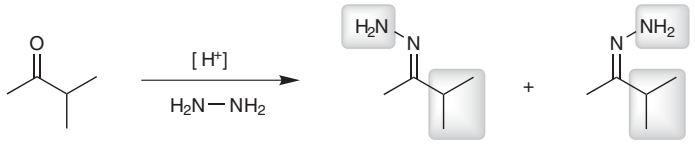
This compound is called hydrazine, and the product that it forms (when it reacts with a ketone) is not surprising at all:



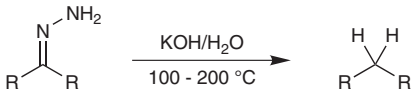
It is the same reaction as if it were a primary amine reacting with a ketone. But, instead of obtaining an imine or an oxime, we obtain a product called a hydrazone.



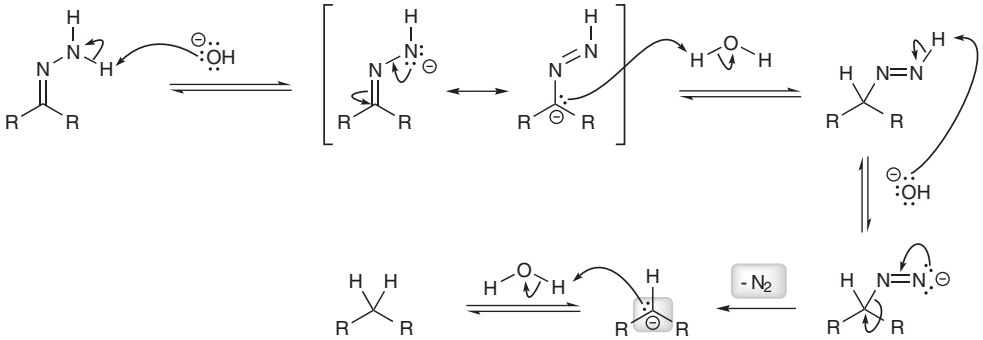
Just like with all of the other reactions we have seen in this section, we need to take special notice of whether or not the starting ketone is symmetrical. If the starting ketone is unsymmetrical, then we should expect to form two diastereomeric hydrazones:



Hydrazones are useful for many reasons. In the past, chemists formed hydrazones as a way of identifying ketones, but nowadays, with the advent of NMR techniques, no one uses hydrazones that way anymore. But the chemistry of hydrazones remains useful in some ways. For example, a hydrazone can be reduced to an alkane under basic conditions:

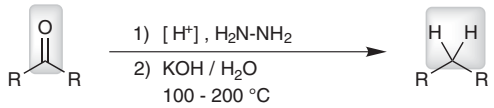


The following is a mechanism for this process:



The formation of a carbanion (highlighted in the second-to-last step) certainly creates an uphill battle (in terms of energy), so we might expect very little product to form. However, notice that the formation of the carbanion is accompanied by loss of N_2 gas (also highlighted in the mechanism above). This explains why the reaction goes to completion. The small amount of nitrogen gas (produced by the equilibrium) will bubble out of the solution and escape into the atmosphere. That forces the equilibrium to produce a little bit more nitrogen gas, which also then escapes into the atmosphere. And the process continues until the reaction reaches completion. Essentially, a reagent is being removed as it is being formed, and that is what pushes the equilibrium over the high energy barrier created by the instability of the carbanion. If you think about it, this concept is not so different from the previous sections where we removed water from a reaction as it was being formed (as a way of pushing the equilibrium towards formation of the acetal).

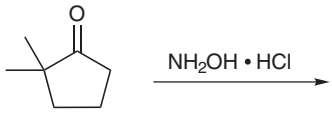
This now provides a two-step method for reducing a ketone to an alkane:



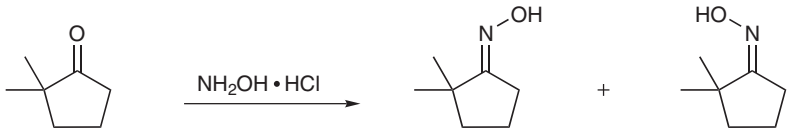
We have already seen two other ways to do this kind of transformation (the Clemmensen reduction and desulfurization with Raney Nickel). This is now our third way to reduce a ketone to an alkane, and it is called a Wolff-Kishner reduction.

In this section, we have only seen a few reactions involving nitrogen nucleophiles. Here is a short summary. We first saw how a ketone can react with a *primary amine* to form an *imine* (and we saw that the mechanism was very similar to acetal formation, except for the beginning and the end). Then, we saw how a ketone can react with a *secondary amine* to form an *enamine*. We also encountered two special N-nucleophiles (NH_2OH and NH_2NH_2), both of which gave products that we expected. The reaction with NH_2NH_2 was of special interest, because it provided a new method for reducing ketones to alkanes.

EXERCISE 6.47 Predict the major product(s) of the following reaction:



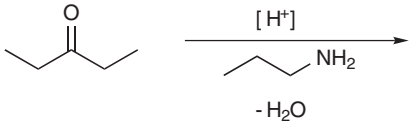
Answer The starting material is a ketone, and the reagent is hydroxyl amine. As we have seen in this section, the product of this reaction should be an oxime. Since the starting ketone is unsymmetrical, we would expect two diastereomeric oximes:



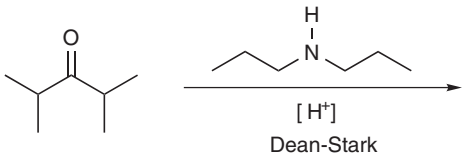
We saw several reactions in this chapter. You must be able to recognize the reagents for these reactions, so that you will be able to predict products. Let's get some practice with the following problems.

PROBLEMS Predict the major product(s) for each of the following transformations:

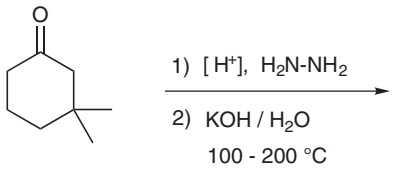
6.48



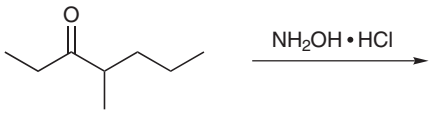
6.49



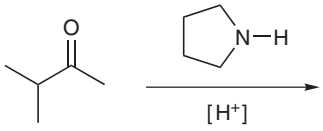
6.50



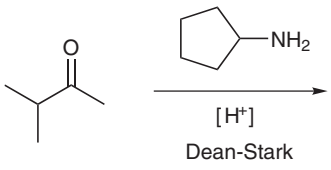
6.51



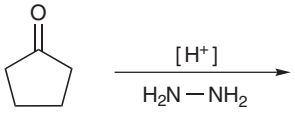
6.52



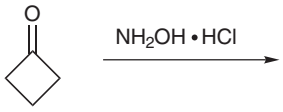
6.53



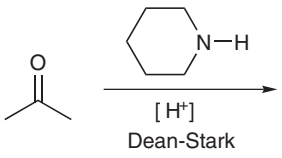
6.54



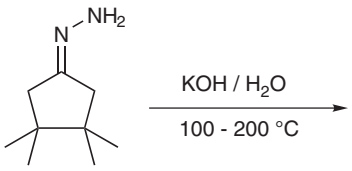
6.55



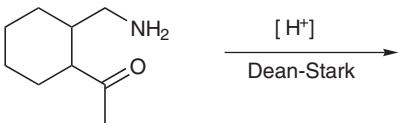
6.56



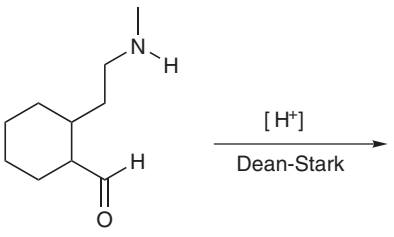
6.57



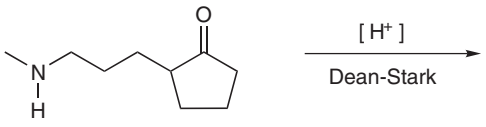
6.58



6.59



6.60

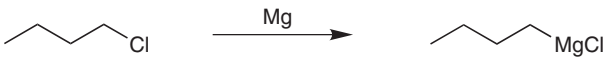


6.7 C-NUCLEOPHILES

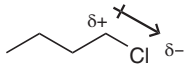
In this chapter, we have seen many different kinds of nucleophiles that can attack ketones and aldehydes. We started with hydrogen nucleophiles. Then we moved on to oxygen nucleophiles and sulfur nucleophiles. In the previous section, we covered nitrogen nucleophiles. In this section we will discuss carbon nucleophiles. We will see three types of carbon nucleophiles.

Our first carbon nucleophile is the Grignard reagent. You may have encountered this reagent in the first semester. If you didn't, here is a quick overview:

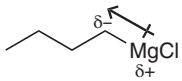
Alkyl (or aryl) halides will react with magnesium in the following way:



Essentially, an atom of magnesium inserts itself in between the C—Cl bond (this reaction works with other halides as well, such as Br or I). This magnesium atom has a significant electronic effect on the carbon atom to which it is attached. To see the effect, consider the alkyl halide (before Mg entered the picture):



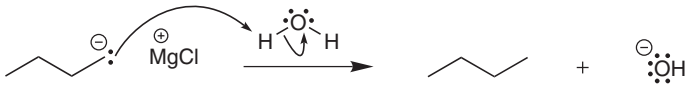
The carbon atom (connected to the halogen) is poor in electron density, or δ+, because of the inductive effects of the halogen. But after magnesium is inserted between C and Cl, the story changes very drastically:



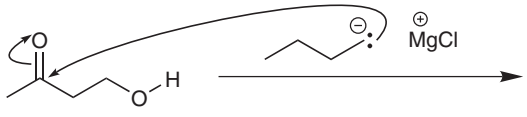
Carbon is much more electronegative than magnesium. Therefore, the inductive effect is now reversed, placing a lot of electron density on the carbon atom, making it very δ−. The C—Mg bond has significant ionic character, so for purposes of simplicity, we will just treat it like an ionic bond:

Carbon is not very good at stabilizing a negative charge, so this reagent (called a Grignard reagent) is highly reactive. It is a very strong nucleophile and a very strong base. Now, let's see what happens when a Grignard reagent attacks a ketone or aldehyde.

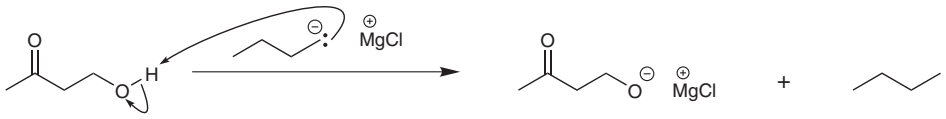
In the previous section, we always started each mechanism by protonating the ketone (turning it into a better electrophile). That does not occur here, because the Grignard reagent is such a strong nucleophile that it has no problem attacking a carbonyl group directly. In fact, we could ***not*** use acid catalysis here (even if we wanted to), because protons destroy Grignard reagents. For example, consider what happens when a Grignard reagent is exposed even to a weak acid, such as water:



The Grignard reagent acts as a base and removes a proton from water, to form a more stable hydroxide ion. The negative charge is MUCH more stable on an electronegative atom (oxygen), and as a result, the reaction is irreversible. This means that you can never use a Grignard reagent to attack a compound that has acidic protons. For example, the following reaction would not work:

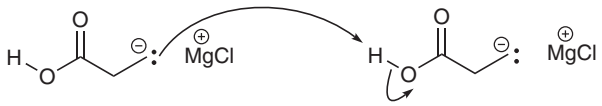


Because this would happen instead:

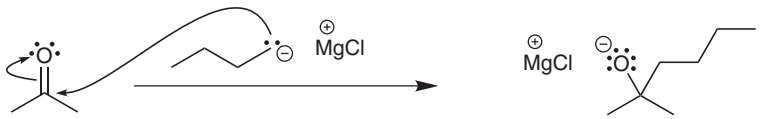


In general, proton transfers are faster than nucleophilic attack. And when the Grignard reagent removes a proton, it irreversibly destroys the Grignard reagent. Similarly, you could never prepare the following kinds of Grignard reagents:

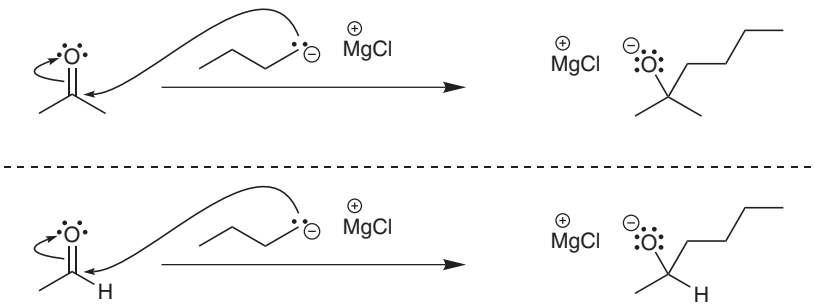
These reagents could not be formed, because each of these reagents could react with a second molecule of itself to remove the negative charge on the carbon atom, for example:



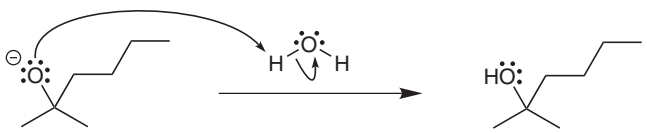
All of that was a quick review of Grignard reagents. Now let's see how Grignard reagents can attack a ketone or aldehyde. When a ketone or aldehyde is treated with a Grignard reagent, the negatively charged carbon atom of the Grignard reagent can attack the electrophilic carbon atom of the carbonyl group to give an alkoxide intermediate:



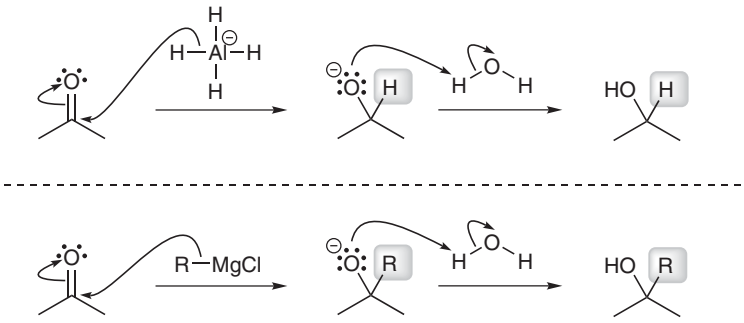
This intermediate then will attempt to re-form the carbonyl group, if it can. But let's see if it can. Remember our rules from the beginning of this chapter: re-form the carbonyl if you can, but never expel H^- or C^-. This intermediate is NOT able to re-form the carbonyl group, because there are no leaving groups to expel. This is true whether the Grignard reagent attacks a ketone or an aldehyde:



So, in either case, the reaction is complete, and we must now introduce a proton source into the reaction flask in order to protonate the alkoxide ion, giving an alcohol:

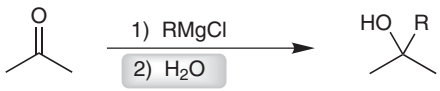


This reaction is not so different from the reactions we saw earlier in this chapter when we explored hydrogen nucleophiles ($NaBH_4$ and $LiAlH_4$). We saw a similar scenario there: the nucleophile attacked, and then the carbonyl group was NOT able to re-form because there was no leaving group. Compare one of those reactions to this reaction:



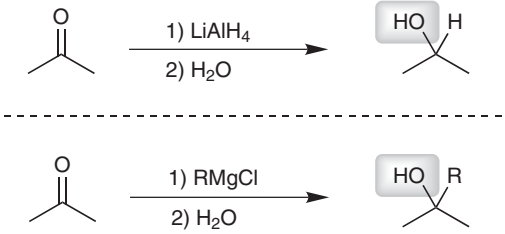
Notice that these mechanisms are similar. And it is worth a minute of time to think about why these reactions are so similar (while the other reactions in this chapter were different from these two reactions). What is special about these two reactions that makes them so similar? Remember our golden rule: never expel H^- or C^-. So, if we attack a ketone (or aldehyde) with either H^- or C^-, then the carbonyl group will be unable to re-form. And that is what these two reactions have in common.

When you write down the reagents of a Grignard reaction (in a synthesis problem), make sure you show the proton source (either H_2O or H_3O^+) ***as a separate step***, like this:

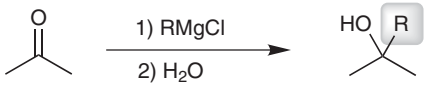


We saw this important subtlety when we learned about $LiAlH_4$, where we also had to show the proton source as a separate step. The same subtlety exists here, because (as we have very recently seen) a Grignard reagent will not survive *in the presence* of a proton source. The proton source must come AFTER the reaction is complete (after the Grignard reagent has been consumed by the reaction).

In order to add this reaction to your toolbox of synthetic transformations, let's compare it one more time to the reaction with $LiAlH_4$. But this time, let's focus on comparing the products, rather than comparing the mechanisms:

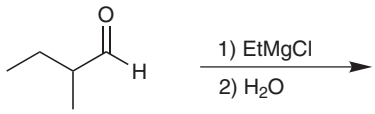


Notice that in both reactions, we are reducing the ketone to an alcohol. But in the case of a Grignard reaction, the reduction is accompanied by the installation of an alkyl group:

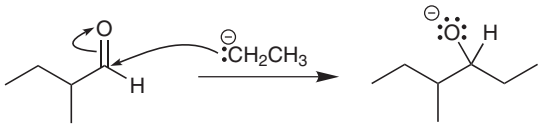


This will be helpful as we explore synthesis problems at the end of this chapter.

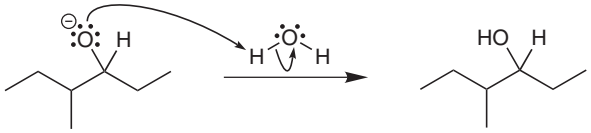
EXERCISE 6.61 Predict the major product of the following reaction:



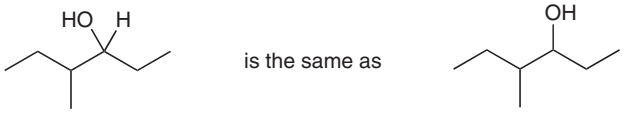
Answer The starting material is an aldehyde, and it is going to react with a Grignard reagent. First, the Grignard attacks:



The carbonyl group cannot re-form, because H^- or C^- cannot be expelled, and there is nothing else that can be expelled in this case. Our product (an alcohol) is obtained when a proton source is introduced, such as H_2O:

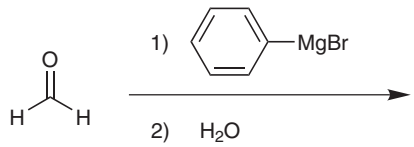


Remember that bond-line drawings don't have to show hydrogen atoms attached to carbon atoms, so we can redraw the product:

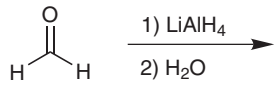


PROBLEMS Predict the major product(s) for each of the following reactions:

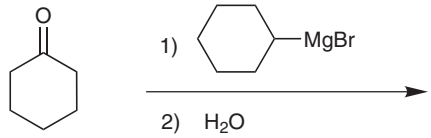
6.62



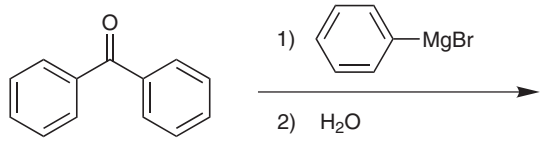
6.63



6.64

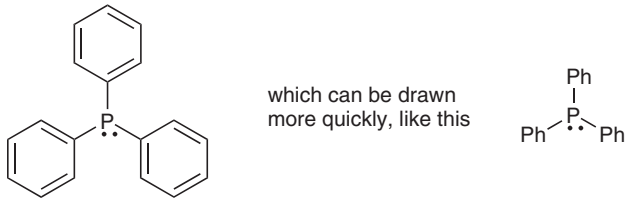


6.65

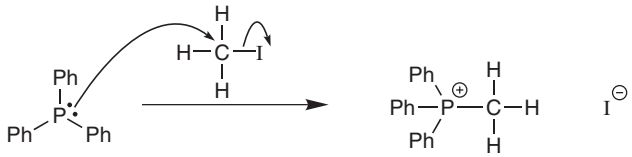


There are two more carbon nucleophiles that we must explore. Both of them are different from the Grignard reagent. Both reactions involve "ylides" (pronounced "ILL–ids"). Let's take a close look at the first ylide, by exploring how it is prepared:

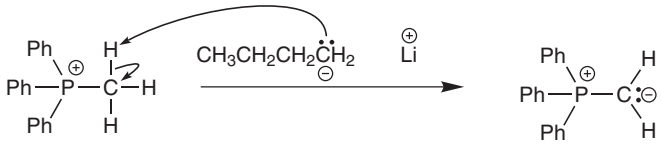
We start with a compound called triphenylphosphine:



and we treat it with an alkyl halide such as methyl iodide (resulting in an S_N2 reaction):



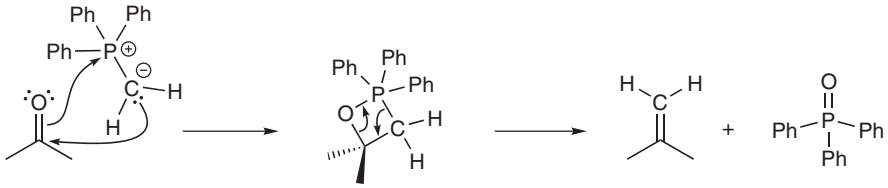
Then, we use *n*-butyllithium (*n*-BuLi), a very strong base, to remove a proton and form the ylide:



An ylide

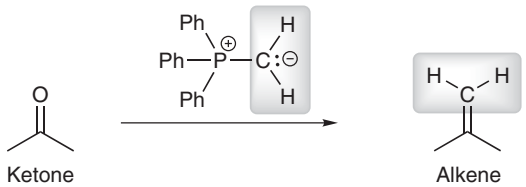
An ylide is a compound with two adjacent, oppositely charged atoms (in this case, P^+ and C^-). Notice that this ylide has a region of high electron density on a carbon atom. As a result, this ylide can function as a carbon nucleophile. In a few moments, we will see another type of ylide (one that uses sulfur instead of phosphorus). The ylide above (based on phosphorus) has a special name. It is called a Wittig reagent (pronounced "Vittig"). And when a ketone or aldehyde is treated with a Wittig reagent, the observed reaction is called a Wittig reaction. So, let's take a close look at a mechanism for the Wittig reaction.

The Wittig reaction is believed to occur via the following two-step mechanism:



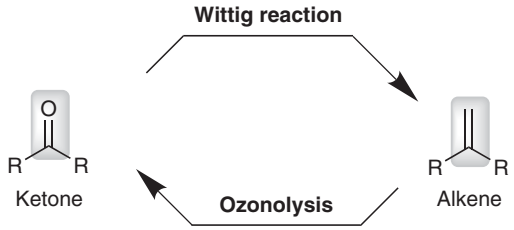
An oxaphosphetane

The first step involves a cycloaddition process, generating an oxaphosphetane (notice that the nucleophilic carbon atom of the Wittig reagent reacts with the electrophilic carbonyl group, as we might expect). Then, in the second step, the oxaphosphetane undergoes fragmentation to give an alkene as the product. This process enables us to achieve the following type of transformation:



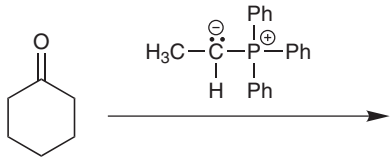
Ketone Alkene

This reaction is incredibly useful for synthesis. We already saw how to convert an *alkene* into a *ketone*, using an ozonolysis reaction. Now, with a Wittig reaction, we can go either way:

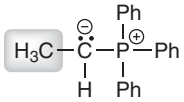


You should always take special notice whenever you learn how to interconvert two functional groups (going in either direction), like above. We have seen several cases like this so far.

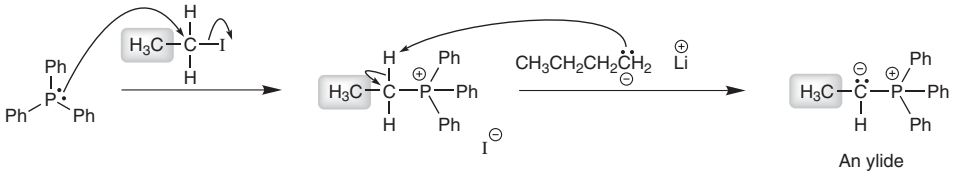
EXERCISE 6.66 Predict the product of the following reaction.



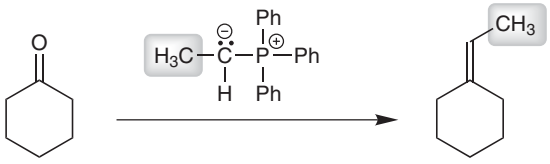
Answer We recognize the reagent to be a Wittig reagent. But this reagent is slightly different than the one we saw before. Compare this reagent to the one we saw on the previous page. This reagent has an extra methyl group:



The way to form a reagent like this is to use Et-I instead of Me-I when you are making the Wittig reagent, like this.



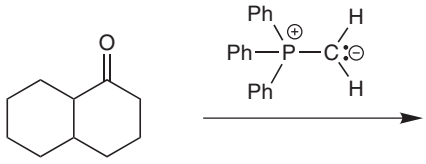
The extra methyl group (highlighted) comes along for the ride, and the final product looks like this:



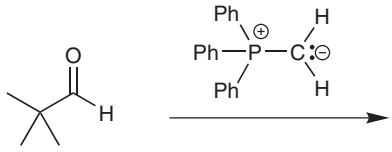
You should try to draw out a mechanism for this reaction to make sure that you can "watch" the extra carbon atom coming along for the ride.

PROBLEMS Predict the major product for each of the following Wittig reactions:

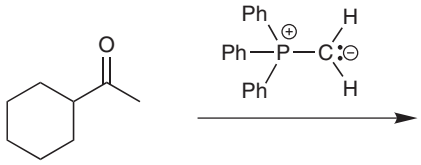
6.67



6.68

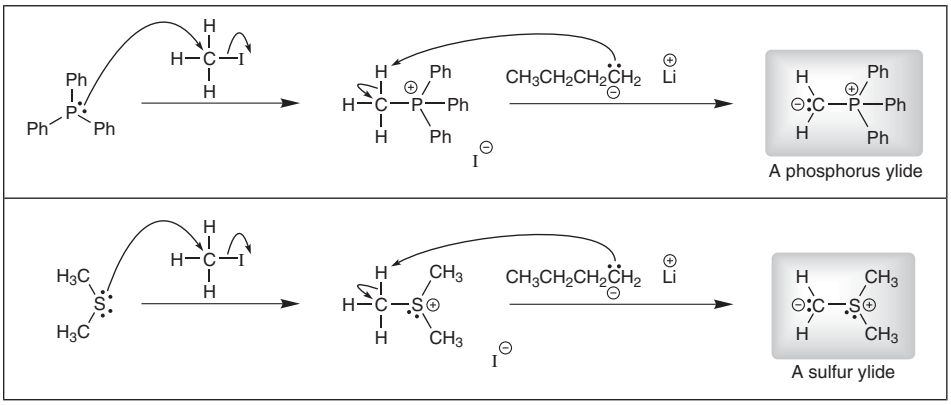


6.69



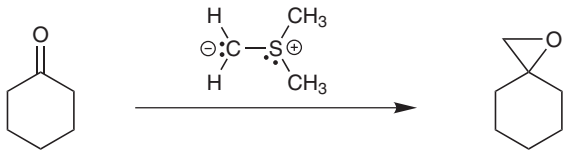
Now we will explore another kind of ylide. This time, it is a *sulfur* ylide, rather than a *phosphorus* ylide. Many instructors (and textbooks) do not cover sulfur ylides, so you might want to look through your lecture notes and textbook to find out if you are responsible for the following reaction.

The mechanism for forming a *sulfur* ylide is very similar to the mechanism for forming a *phosphorus* ylide. Let's compare them:

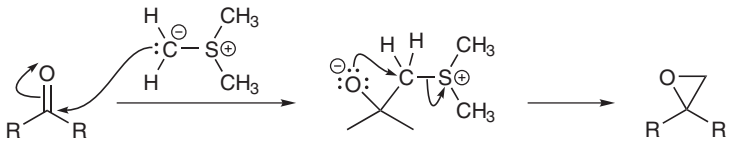


To form a sulfur ylide, we start with dimethyl sulfide (DMS). From that point on, everything is the same: the alkyl halide is attacked, followed by deprotonation with a very strong base to form a sulfur ylide.

But when a sulfur ylide attacks a ketone (or aldehyde), we observe a very different product. We ***don't*** obtain an alkene as our product (like we did in the Wittig reaction). Instead, we obtain an epoxide:

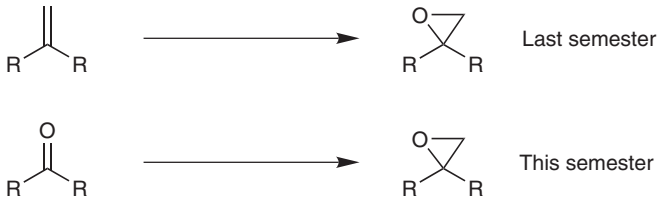


A mechanism for this process is shown here:

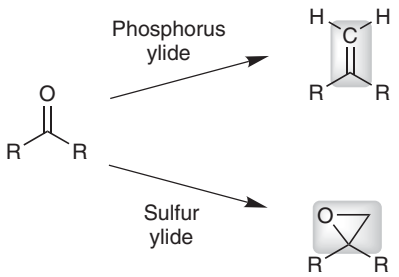


The sulfur ylide attacks the carbonyl group, giving an intermediate that undergoes an intramolecular S_N2-type process to give an epoxide.

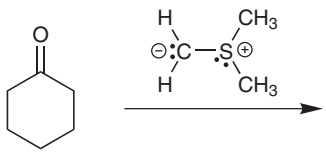
This reaction is very useful, because it provides a method for making epoxides from ketones. You should remember from the first semester that you learned how to convert an *alkene* into an epoxide. But now, we see that we can make an epoxide from a ketone as well:



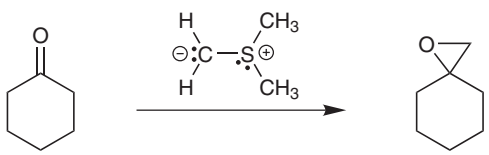
In summary, we have explored three carbon nucleophiles in this section. We started with Grignard reagents, and then we moved on to ylides (phosphorus ylides and sulfur ylides). We have seen that phosphorus ylides and sulfur ylides produce alkenes and epoxides, respectively:



EXERCISE 6.70 Predict the major product of the following reaction:

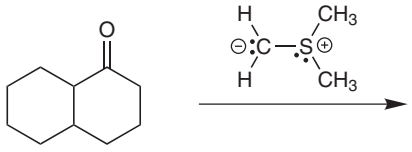


Answer This reagent is a sulfur ylide, which is used to convert ketones into epoxides. So, our product is an epoxide:

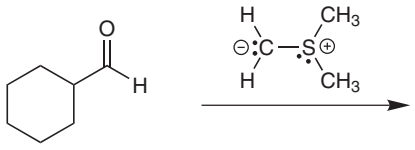


PROBLEMS Predict the major product for each of the following reactions:

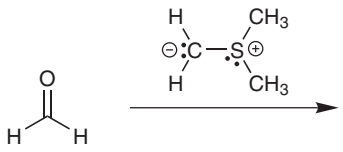
6.71



6.72



6.73



6.8 EXCEPTIONS TO THE RULE

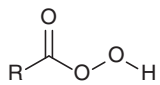
In the beginning of this chapter, we saw a golden rule that helped us understand most of the chemistry that we explored. That rule was: always re-form the carbonyl if you can, but never expel H^- or C^-.

The truth is that there are a few, rare exceptions to this rule. In this section, we will look at two of these exceptions.

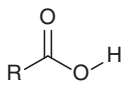
In the Cannizzaro reaction, it "seems" as though we are expelling H^- to re-form a carbonyl. I am not going to go into great detail on the Cannizzaro reaction, because this reaction has very little synthetic utility. It is unlikely that you will use this reaction more than once, if at all. So, I will just mention it in passing. Look up that reaction in your textbook and in your lecture notes. If you don't need to know that reaction, then you can ignore it. But if you are responsible for knowing that reaction, then you should look carefully at the mechanism in your textbook. If you focus on the step where H^- gets expelled, you will see that H^- is not really expelled by itself. Rather, it is transferred from one place to another. And in that sense, we can understand it a bit better. It is true that H^- is too unstable to ever leave as a leaving group. That is why we never expel H^- into solution. But in the Cannizzaro reaction, it never actually leaves as a leaving group.

We will now explore one other exception to the golden rule. There is a reaction where it seems like we are re-forming a carbonyl group to expel C^-. This reaction, called the Baeyer–Villiger reaction, is extremely useful. If you know how to use it properly, you will find that you might use it many times to solve synthesis problems in this course. So, we will spend some time covering that reaction now.

The Baeyer–Villiger reaction uses a peroxy acid (RCO_3H) as the reagent. Compare the structure of a peroxy acid with the structure of a carboxylic acid:

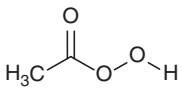


A peroxy acid
(RCO_3H)

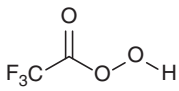


A carboxylic acid
(RCO_2H)

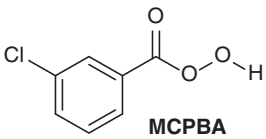
Notice that a peroxy acid (RCO_3H) has one additional oxygen atom, as compared with a carboxylic acid (RCO_2H). The R group of the peroxy acid can be a small alkyl group (such as a methyl group), or it can be a much larger group. Below are three commonly used peroxy acids:



CH_3CO_3H

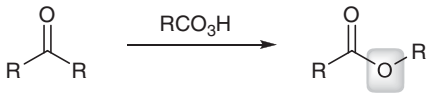


CF_3CO_3H

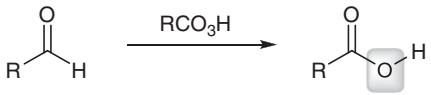


MCPBA

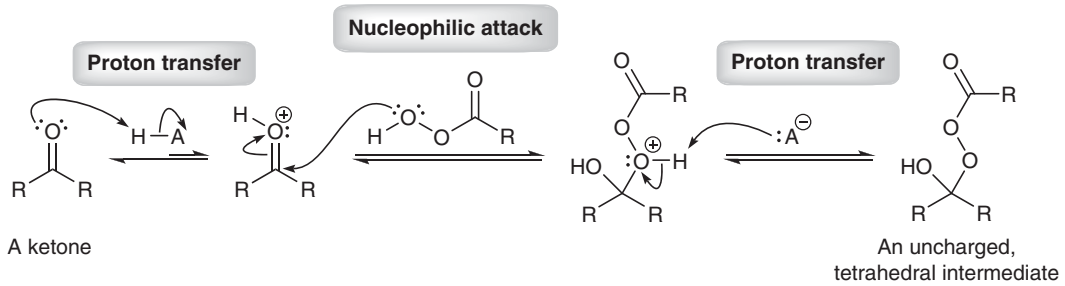
The third example is called ***meta*-chloro perbenzoic acid**, or just MCPBA for short. So when you see the letters MCPBA, you should recognize that we are talking about a peroxy acid (RCO_3H). In a Baeyer–Villiger reaction, a peroxy acid is used to insert an oxygen atom next to the carbonyl group of a ketone, producing an ester:



A similar reaction can be used to convert an aldehyde into a carboxylic acid:

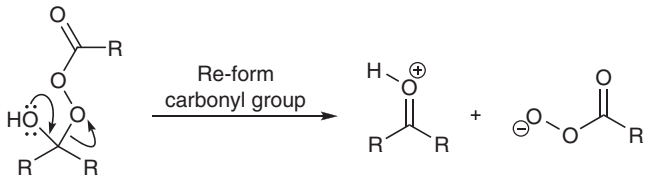


Once again, the outcome of this reaction is to "insert" an oxygen atom next to the carbonyl group. This is very useful, so let's see the accepted mechanism for this process. We will begin with the first three steps of the mechanism, shown here:

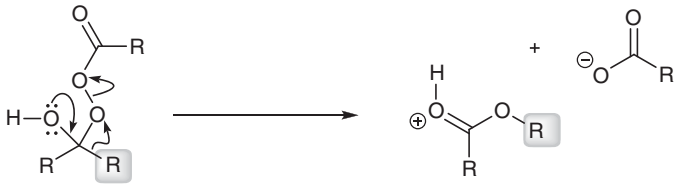


These three steps should seem very familiar, because they are analogous to the first three steps of acetal formation (as seen earlier in this chapter). Under acidic conditions, the ketone is first protonated by an acid (H–A), where H–A represents either the peroxy acid (RCO_3H) or a carboxylic acid (RCO_2H, which accumulates as a byproduct as the reaction proceeds, as we will soon see). The resulting protonated ketone is a powerful electrophile and can be attacked by the peroxy acid (which functions as a nucleophile). The resulting tetrahedral intermediate is then deprotonated by A^- (the conjugate base of H–A) to give an uncharged, tetrahedral intermediate.

If we focus on the structure of the uncharged, tetrahedral intermediate, we would conclude that the only way to re-form the carbonyl group would be to expel the group that was recently installed:

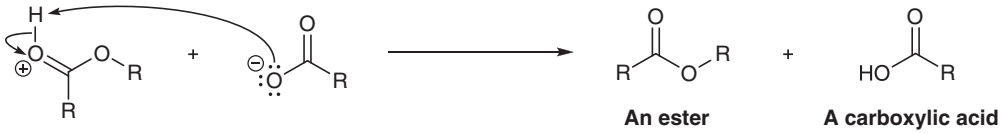


Indeed, this probably happens, but it doesn't lead to the formation of a new product. It effectively regenerates the starting materials. So, we apply our golden rule to see if we can expel any other leaving group. We cannot expel H^- or C^-, and there are no other groups to expel. BUT, this is an apparent exception to the golden rule. Something unique happens, and you will not see this in any other mechanism (so don't worry about trying to apply this next step in any other mechanism). A rearrangement occurs, in which an alkyl group is said to *migrate*:



Let's focus on the fate of the migrating alkyl group (highlighted above). Notice that the carbonyl group is re-forming to expel this R group, which migrates to the nearby oxygen atom. In other words, it looks like we are expelling C^-. But the truth is that we are not *really* expelling C^- into solution by itself. After all, C^- is too unstable. Rather, it is just ***migrating*** from one place to another (it is migrating over to attack the neighboring oxygen atom). It never really becomes C^- for any period of time, and that explains how we can have an exception here.

The final step of the mechanism is a proton transfer step to give the product (an ester), as well as a carboxylic acid by-product (RCO_2H):

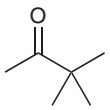


An ester
(the product)

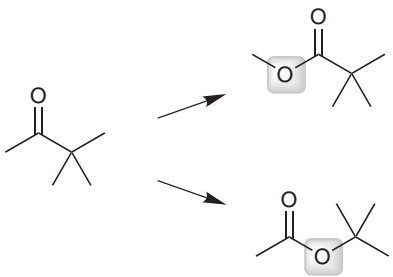
A carboxylic acid
(the by-product)

This mechanism is truly unique, and you should not worry if you feel that you would not be able to predict when this could happen in other situations. This is probably the first time you are ever seeing a rearrangement that does not involve a carbocation. So, this is truly different. You will not need to apply this mechanism to any other situations. So for now, don't focus too much on this mechanism. Instead, let's focus on how to use this reaction when you are solving synthesis problems, because it will be a very useful reaction for you to have in your back pocket.

In order to use this reaction properly, you will need to know how to predict where the oxygen atom is installed. For example, consider the following ketone:



This ketone is unsymmetrical, so we must decide where the oxygen atom will be installed during a Baeyer–Villiger reaction. Which of the following two products are expected?

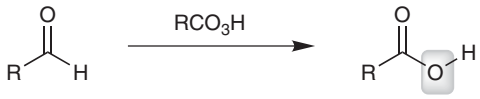


To answer this question, we need to know which alkyl group is more likely to migrate. If you look back at the mechanism above, you will see that the migrating R group is the one that ends up connected to the oxygen atom in the product. So, we just have to decide which alkyl group can migrate faster.

There is an order to how fast alkyl groups can migrate in this reaction, and we call it "migratory aptitude":

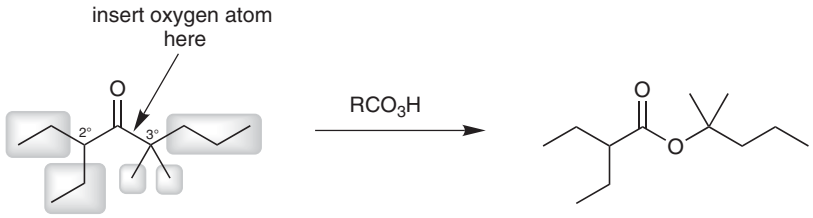
H > 3° > 2° or Ph > 1° > methyl

Notice that phenyl groups have similar migratory aptitude as secondary alkyl groups. Also notice that H migrates the fastest. This explains how we can use this reaction to convert aldehydes into carboxylic acids:



H migrates faster than any other group, so it doesn't even matter what the R group is.

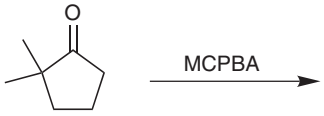
If you are starting with a ketone instead of an aldehyde, then you should look for the most substituted alkyl group. For example:



Notice that the oxygen atom is inserted on the side that is more substituted.

In order to use this reaction in synthesis, you must make sure that you can predict where the oxygen atom will be inserted. Let's do some problems to make sure you got it:

EXERCISE 6.74 Predict the major product of the following reaction:



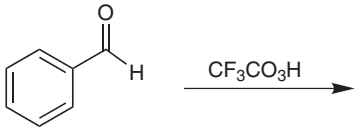
Answer A ketone is being treated with a peroxy acid, so we expect a Baeyer–Villiger reaction to occur. We look closely at our starting ketone, and we see that it is unsymmetrical. So, we must predict where the oxygen atom will be inserted. We look at both sides, and we see that the left side is more substituted. The more substituted R group will migrate faster, and that is where the oxygen atom will be inserted.

This specific case is an interesting example, because the insertion of an oxygen atom causes a ring expansion:

The product is not just an ester, but it is a *cyclic* ester. Cyclic esters are also called *lactones*.

PROBLEMS Predict the major product for each of the following reactions:

6.75



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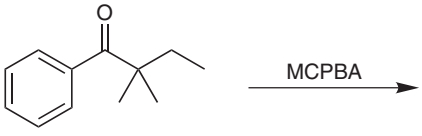

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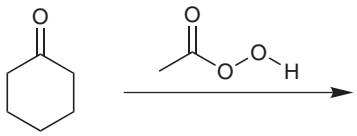

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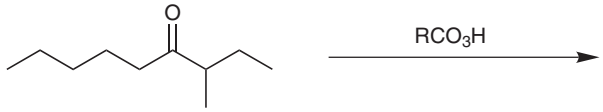

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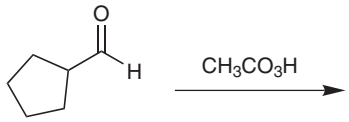


6.9 HOW TO APPROACH SYNTHESIS PROBLEMS

In this chapter, we have seen many reactions. In order to solve synthesis problems, you will need to have all of these reactions at your fingertips. In the beginning of this chapter, we saw a few ways to make aldehydes and ketones. Do you remember those reactions? If you don't, then you are in trouble. This is why organic chemistry can get tough at times. It is not sufficient to be a master of mechanisms. That is an excellent start, and it builds an excellent foundation for understanding the material. But at the end of the day, you have to be able to solve synthesis problems as well. And in order to do that, you must have all of the reactions organized in your mind.

Let's start with a short review of everything we saw:

We started with a few ways of making ketones and aldehydes (two ways to oxidize, and then an ozonolysis). Then, we explored hydrogen nucleophiles ($NaBH_4$ and $LiAlH_4$) and oxygen nucleophiles (making acetals), and we saw that acetals can be used to protect ketones. Then we explored sulfur nucleophiles (to form thioacetals), and we saw how they can be used to *reduce* ketones and aldehydes. Next, we explored nitrogen nucleophiles (primary amines and secondary amines), we examined special primary amines (hydroxylamine and hydrazine), and we saw how hydrazones could be used to reduce ketones to alkanes. Then, we moved on to three kinds of carbon nucleophiles—Grignard reagents, phosphorus ylides, and sulfur ylides. Finally, we examined the Baeyer–Villiger oxidation, focusing on its utility for synthesis. That is everything we saw in this chapter.

In this last section of the chapter, we will bring everything together to solve synthesis problems. The first step is to make sure that you know these reactions well enough to claim that you have them at your fingertips. To ensure that you achieve that goal, try to do the following. Take a separate piece of paper and try to write down all of the reactions listed in the paragraph above (without looking back in the chapter, if possible). Make sure that you can draw all of the reagents, and all of the products. If you cannot do this, then you are simply not ready to even START thinking about synthesis problems. Students often complain that they just don't know how to approach synthesis problems. But the difficulty is usually NOT due to the student's poor abilities, but rather, the difficulty arises from the student's poor study habits. You CAN do synthesis problems. You might even enjoy them, believe it or not. But, you have to walk before you can run. If you try to run before you learn how to walk, you will trip and you will get frustrated. Too many students make this mistake with synthesis problems.

So, take my advice, and focus right now on mastering the individual reactions. Try to fill out a blank sheet of paper with everything that we have done in this chapter. If you find that you have to look back into the chapter to get the exact reagents (or to see what the exact products are), then that is fine. It is part of the studying process—BUT don't trick yourself into thinking that you are ready for synthesis problems once you have filled out the sheet. You are not ready until you can fill out the entire sheet of paper, start-to-finish, without looking back even once into the chapter to get the fine details. Keep filling out a new sheet, again and again, until you can do it all without looking back. Ideally, you should get to a point where you do not even need to look at the short summary that we just gave. You should get to a point where you can reconstruct the summary in your head, and then based on that summary, you should be able to write a list of all the reactions.

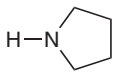
It sounds like a lot of work. And it is. It will take you a while. But when you are done, you will be in an excellent position to start tackling synthesis problems. If you get lazy, and you decide to skip this advice, then don't complain later if you are frustrated with synthesis problems. It would be your own fault for trying to run before you have mastered walking.

Once you get to the point where you have all of the reactions at your fingertips, then you can come back to here, and try to prove it, by doing some simple problems. These problems are designed to test you on your ability to list the reagents that you would need in order

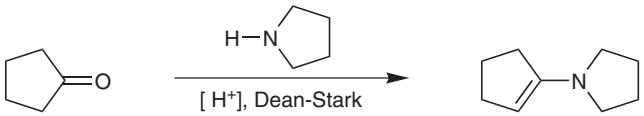
to do simple one-step transformations. Once you have all of the reactions down cold, then we will be able to move on and conquer some multistep synthesis problems.

EXERCISE 6.80 What reagents would you use to achieve the following transformation:

Answer The starting material is a ketone, and the product is an enamine, so we will need a nitrogen nucleophile. We just need to decide what kind of nitrogen nucleophile. Since our product is an enamine, we will need a secondary amine. When we look at the product, we can determine that we would need to use the following secondary amine:

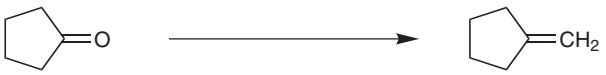


Finally, we just need to decide if there are any special conditions that should be mentioned. And we did learn that there are special conditions for the reaction between a ketone and a secondary amine. Specifically, we need to have acid-catalysis, and Dean–Stark conditions. So, our answer is:



PROBLEMS The following problems are designed to be simple, so that you can prove to yourself that you know these reactions cold. I highly recommend that you photocopy the following problems ***before*** filling them out. You might find that you get stuck on a few problems, and it might be helpful for you to come back to these problems in the near future to fill them out again. The following problems are not listed in the order in which they appear in this chapter.

6.81



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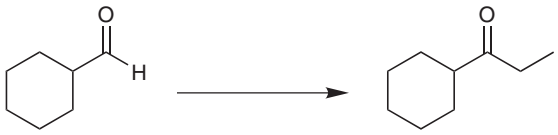
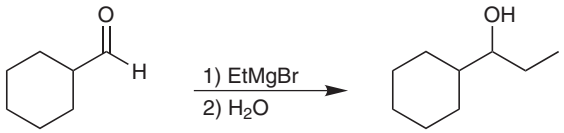
If you felt comfortable with those problems, then you should be ready to move on to solving some multistep synthesis problems. Let's see an example:

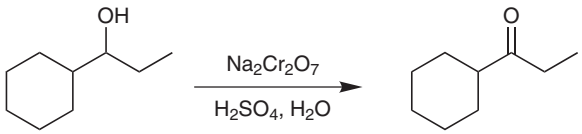
EXERCISE 6.101 Propose an efficient synthesis for the following transformation:



Answer This transformation is a bit more involved than the previous problems, because it cannot be achieved in one step. We need to install an ethyl group, while maintaining the presence of the carbonyl group. If we use a Grignard reagent, we can install the ethyl group, but we will reduce the ketone to an alcohol in the process:



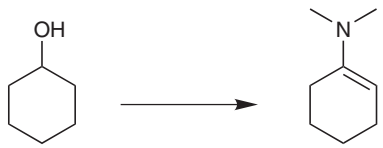
But, this issue can be easily overcome, because we can oxidize the alcohol back up to a ketone:



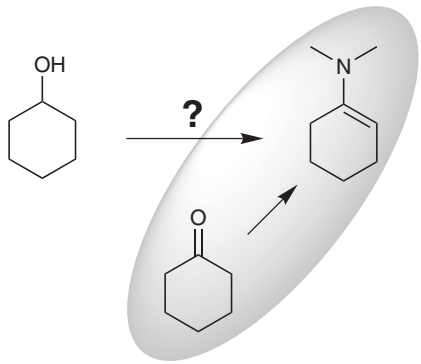
So, we have a two-step synthesis to accomplish this transformation.

Before you try to solve some problems yourself, there is one more important point to make about synthesis problems. Very often, it is helpful to work "backwards." We call this *retrosynthetic analysis*. Let's see an example:

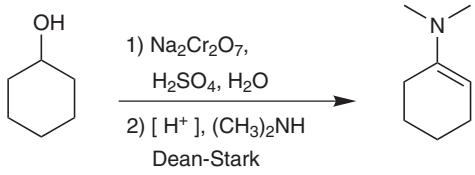
EXERCISE 6.102 Propose an efficient synthesis for the following transformation:



Answer If we focus on the product, we notice that it is an enamine. We have only seen one way to make an enamine—from the reaction between a ketone and a secondary amine. So, we can work our way backwards:



All we need to do is find a way to convert the starting compound into a ketone. And we have seen how to do that. We can convert an alcohol into a ketone using an oxidation reaction. So, our synthesis is:



Of course, this last problem was not very difficult, because it had a two-step solution. As you solve problems that require more steps, this approach (retrosynthetic analysis) will become more and more important. But don't worry. You won't have to solve any problems that require ten steps. That is way beyond the scope of this course. You will generally not have to deal with syntheses that require more than three to five steps. So, with a lot of practice, it is definitely realistic to become a master of solving synthesis problems. Once again, it all depends on how well you know all of the reactions.

As you work through the following problems, keep in mind that there is rarely only one answer to a synthesis problem. As we learn more and more reactions, you will find that there are often multiple correct ways to achieve a transformation. Don't get stuck into thinking that you have to find THE answer. You may even come across a perfectly acceptable answer that no one else in the class thought of. Those are the most exciting moments. There actually is room for you to express some creativity when you solve synthesis problems. Now let's get some practice:

PROBLEMS For each of the following problems, suggest an efficient synthesis. Remember that there might be more than one correct answer for each of these problems. If you propose an answer, and it does not match the answer in the back of the book, do not be discouraged. Carefully analyze your answer, because it might also be correct.

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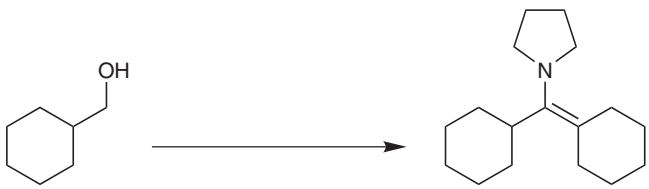


In this chapter, we did ***not*** see EVERY reaction that is in your textbook or lecture notes. We covered the core reactions (probably 90% or 95% of the reactions you need to know). The goal of this chapter was NOT to cover every reaction. Rather, our goal was to lay a foundation for you when you are reading your textbook and lecture notes. We saw the similarities between mechanisms, and we saw a simple way of categorizing all nucleophiles (hydrogen nucleophiles, oxygen nucleophiles, sulfur nucleophiles, etc.).

Now you can go back through your textbook and lecture notes, and look for the reactions that we did not cover here in this chapter. With the foundation we have built in this chapter, you should be in good shape to fill in the gaps and study more efficiently.

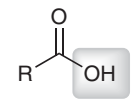
And make sure to do ALL of the problems in your textbook. You will find more synthesis problems there. The more you practice, the better you will get. Good luck.

CHAPTER 7

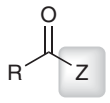
CARBOXYLIC ACID DERIVATIVES

7.1 REACTIVITY OF CARBOXYLIC ACID DERIVATIVES

Carboxylic acid derivatives are similar to carboxylic acids, but the OH group has been replaced with a different group (Z),

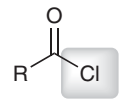


Carboxylic acid

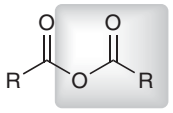


Carboxylic acid derivative

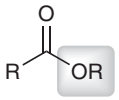
where Z is a heteroatom (an atom other than C or H, such as Cl, O, N, etc.). Several types of carboxylic acid derivatives are shown below:



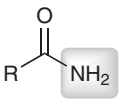
acid halide



acid anhydride

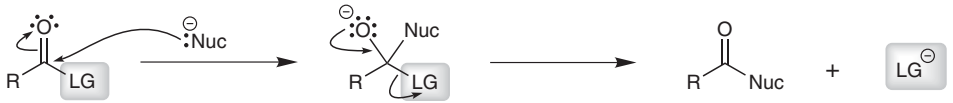


ester

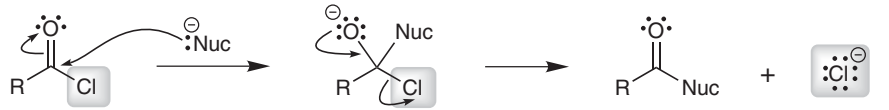


amide

The chemistry of carboxylic acid derivatives is different from the chemistry of ketones and aldehydes, because carboxylic acid derivatives possess a built-in leaving group, which allows the carbonyl group to re-form after being attacked:



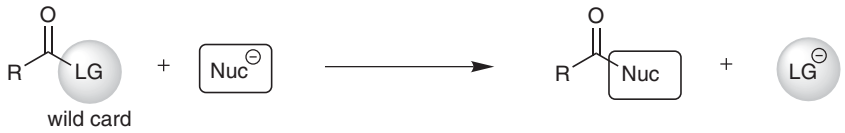
The identity of the leaving group will determine how reactive the compound is. For example, acid chlorides are extremely reactive because the built-in leaving group (chloride) is very stable:



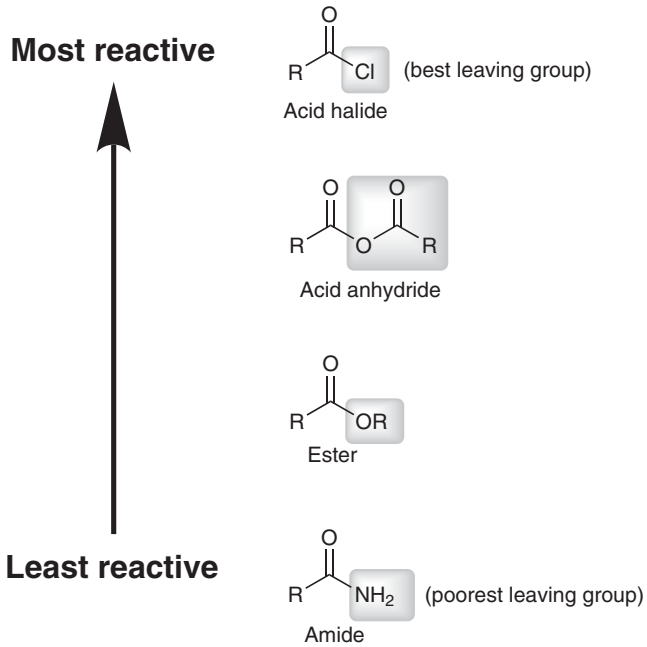
acid chloride

Chloride is a great leaving group because it is a weak base. For this reason, acid halides (also called acyl halides) are the most reactive of the carboxylic acid derivatives. This is very useful, because it means that we can use acid halides to form any of the other carboxylic acid derivatives.

Carboxylic acid derivatives can be viewed as having a "wild card" next to the carbonyl group. I am calling it a "wild card," because it can be easily exchanged for a different group:



In this chapter, we will learn how to exchange the groups so that we can convert one carboxylic acid derivative into another. In order to do this, we will have to know something about the order of reactivity of carboxylic acid derivatives:



As we learn to exchange the "wild card," we will see that there are just a few simple rules that will determine everything. We will see dozens of reactions, but all of these reactions are completely predictable and understandable if you know how to apply just a few simple rules, covered in the following section.

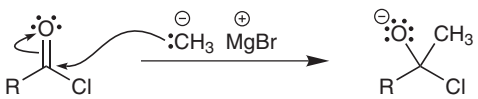
We will NOT cover every reaction in your textbook or lecture notes. Rather, we will focus on the core skills you need. When you are finished with this chapter, you must make sure to go through your textbook and lecture notes to learn any reactions that we did not cover here in this chapter. This chapter will arm you with the skills you need in order to master the material in your textbook.

7.2 GENERAL RULES

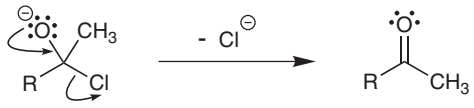
The most important rule was already covered in the previous chapter. We called it our "golden rule" and it went like this: after attacking a carbonyl group, always try to re-form the carbonyl group if you can, but never expel H^- or C^-.

With this rule, we can now appreciate that a carboxylic acid derivative will react differently with H^- or C^- than it will with any other type of nucleophile. When we use a hydrogen nucleophile or a carbon nucleophile to attack a carboxylic acid derivative, *two equivalents* of the nucleophile are consumed. Let's see why:

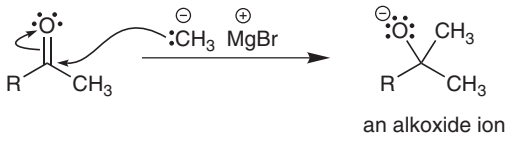
Consider, for example, the reaction that occurs when an acid halide is treated with an excess of Grignard reagent. First, the Grignard reagent attacks the carbonyl group, just as we would expect:



Then, we apply our golden rule: re-form the carbonyl group, if you can, but don't expel H^- or C^-. In this case, Cl^- can be expelled, so we expect the carbonyl group to re-form:

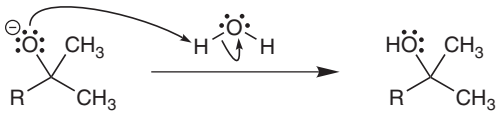


This step generates a ketone, and under these conditions, the ketone can be attacked by a second equivalent of the nucleophile, generating an alkoxide ion:



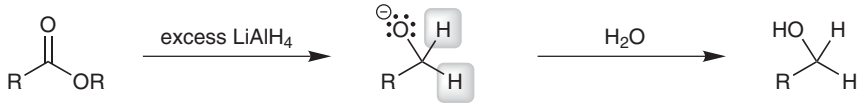
an alkoxide ion

The resulting alkoxide ion is now unable to re-form the carbonyl group, because there is no leaving group. We have already said numerous times that H^- or C^- cannot be expelled to re-form the carbonyl group. So, the reaction is complete. In order to protonate the alkoxide ion, a proton source must be introduced into the reaction flask (note that the proton source must be introduced into the reaction flask AFTER the reaction is complete):

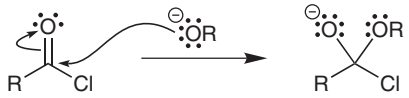


In the end, the product is an alcohol.

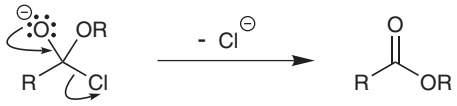
A similar result is expected when an acid halide is attacked by a hydrogen nucleophile. Once again, the acid halide can react with two equivalents of the nucleophile to generate an alcohol:



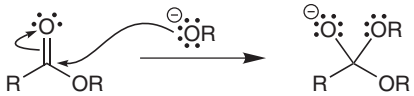
The situation is very different when we use any other nucleophile (not H^- or C^-). Suppose, for example, an acid halide is treated with RO^-:



As we might expect, the resulting tetrahedral intermediate is capable of re-forming the carbonyl group by expelling a chloride ion, generating an ester:



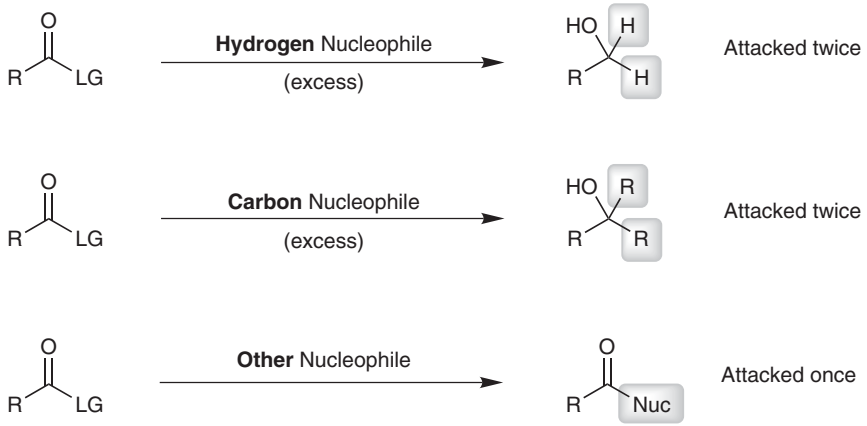
Now, it might be true that the resulting carbonyl group (of the ester) CAN be attacked by another alkoxide ion:



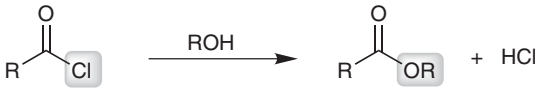
But the resulting tetrahedral intermediate will simply re-form the carbonyl group, by expelling the second RO^- that just attacked. This brings us right back to the ester:

The second attack is only irreversible when the nucleophile is H^- or C^-. And this should make sense based on our golden rule; if the second attack is by H^- or C^-, then the carbonyl group will not be able to re-form after the second attack occurs.

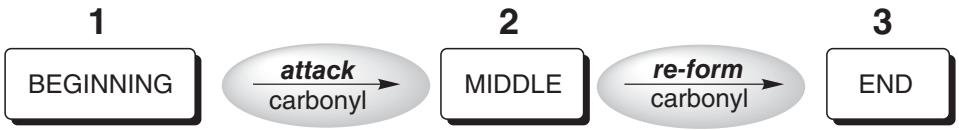
So, we have seen that there is a difference in the types of products we obtain when we use H^- or C^- vs. when we use any other nucleophile. Keep this in mind: H^- or C^- will attack twice, but all other nucleophiles will only attack once:



Now let's focus our attention on the last case above (nucleophiles other than H^- or C^-), in which the nucleophile attacks only once. In those reactions, the outcome will be to exchange one type of carboxylic acid derivative for another. For example:

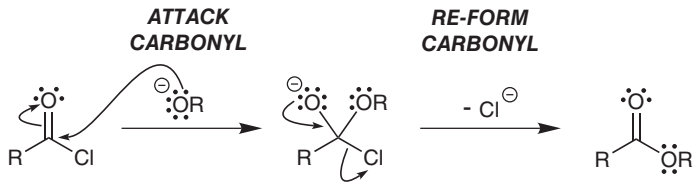


The mechanism for this process (and all others like it) involves two core steps: attack the carbonyl group, and then re-form the carbonyl group. That's it. Just two core steps. But very often, proton transfer steps are necessary when drawing a mechanism. Proton transfers can only occur at three different moments: the beginning, the middle, or the end:

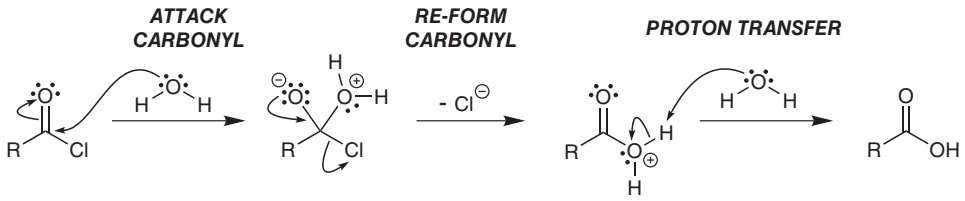


1. A proton transfer step may or may not be required at the *beginning* of the mechanism, before the nucleophile has attacked the carbonyl group.
2. Proton transfer steps may or may not be required in the *middle* of the mechanism, after the carbonyl group has been attacked, but before the carbonyl group has re-formed.
3. A proton transfer step may or may not be required at the *end* of the mechanism, after the carbonyl group has re-formed.

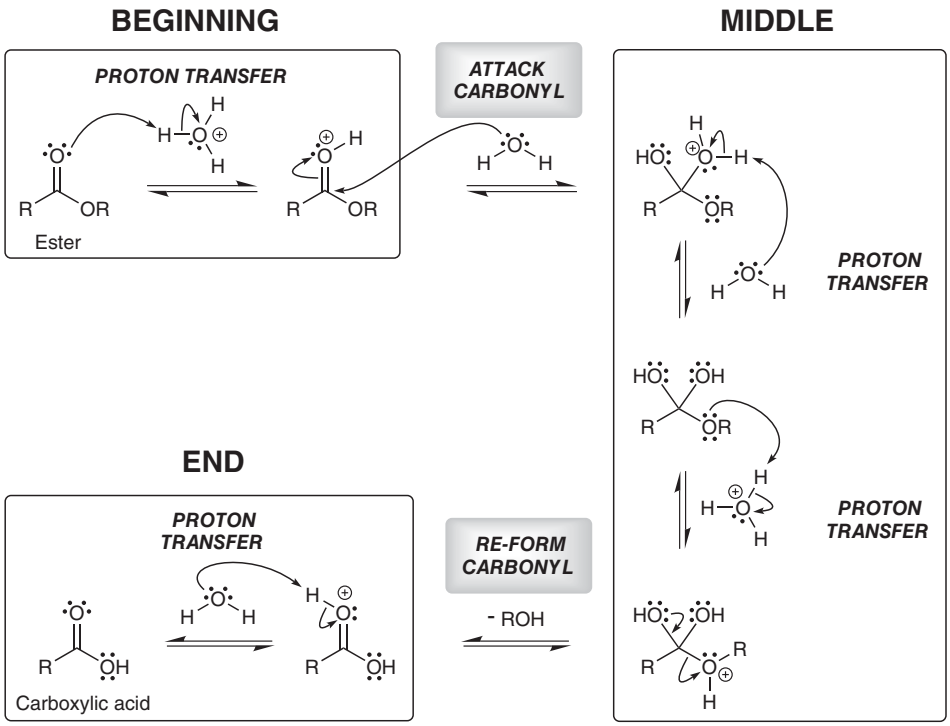
Sometimes, a mechanism won't involve any proton transfers at all. For example, when an acid halide is treated with an alkoxide ion, no proton transfers occur:



And sometimes, a mechanism will involve only one proton transfer. For example, when an acid halide is treated with water, one proton transfer occurs at the end of the mechanism:



But sometimes, proton transfers occur at all three moments in the mechanism (beginning, middle, and end). For example, consider the following mechanism for the reaction in which an ester is treated with aqueous acid, generating a carboxylic acid:

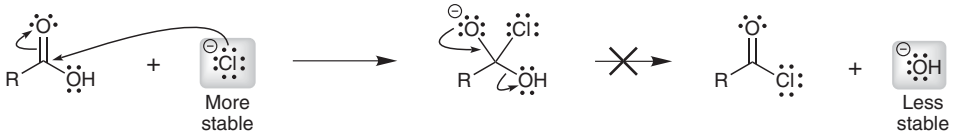


This is a long mechanism, with six steps. The two core steps (attack the carbonyl, and then re-form the carbonyl) are highlighted in gray. Notice that proton transfer steps occur at all three possible moments throughout the mechanism (beginning, middle, and end). Later in this chapter, we will study this reaction in greater detail, and we will explain the rationale behind each and every proton transfer step in this mechanism.

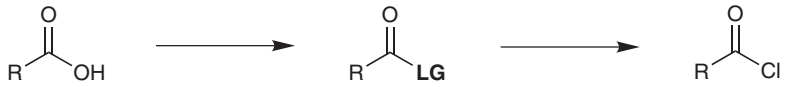
7.3 ACID HALIDES

As we have mentioned, acid halides are the most reactive of the carboxylic acid derivatives, because they produce the most stable leaving groups. Therefore, we can prepare any of the other carboxylic acid derivatives from acid halides. So, it is critical that you know how to make an acid halide. It is very common to encounter a synthesis problem where you will need to make an acid halide at some point in the synthesis.

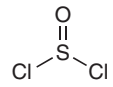
To make an acid halide, it would be nice if Cl^- would attack a carboxylic acid directly, expelling HO^- as a leaving group:



But this doesn't work, because HO^- is less stable than Cl^-, so this would be an uphill battle. Cl^- is not going to expel HO^-. So, we must first convert the OH group into a different group that CAN be expelled by Cl^-. So, here is our strategy:

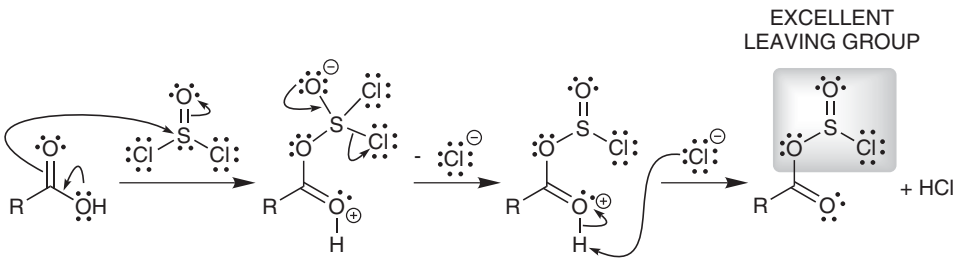


Thionyl chloride, $SOCl_2$, is a reagent that can be used to execute both steps of this strategy:



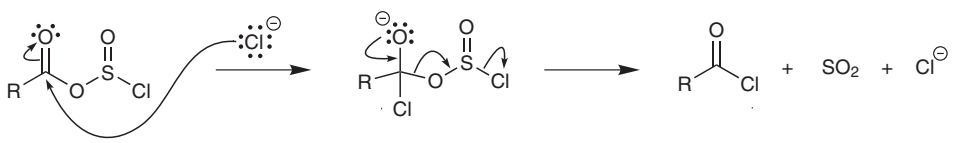
Thionyl chloride
($SOCl_2$)

An acid halide can generally be obtained in good yields by treating a carboxylic acid with thionyl chloride. This reagent achieves two objectives in one reaction flask: (1) it converts the OH group into a better leaving group and (2) it serves as a source of chloride ions that will attack the carbonyl group and expel the newly formed leaving group. The first objective (converting OH into a better leaving group) is achieved via the following mechanism:



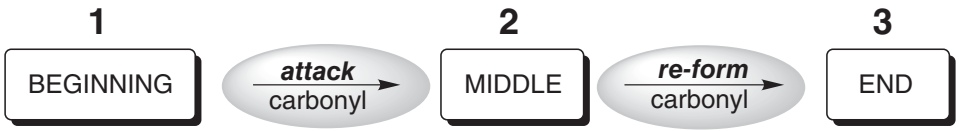
The carboxylic acid functions as a nucleophile and attacks the S═O bond. The S═O bond is then re-formed (by expelling a chloride ion), followed by a proton transfer step. The net result of these three steps is the conversion of an OH group into a better leaving group, thereby achieving the first objective.

The second objective is then achieved when the chloride ion (generated during the steps above), attacks the carbonyl group, expelling the leaving group:

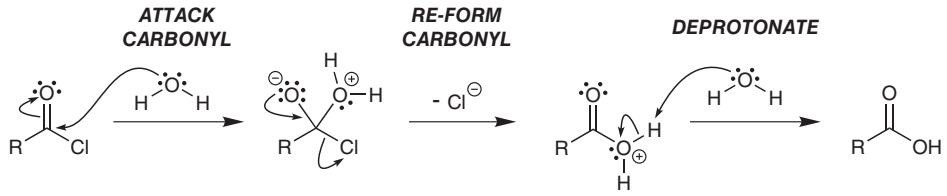


Notice that SO_2 is formed as a by-product. This is important because SO_2 is a gas, which bubbles out of solution, thereby forcing the reaction to completion.

Now that we have covered a method for preparing acid halides, we are ready to explore reactions of acid halides. We will see many reactions. BUT don't try to memorize them. Instead, try to appreciate that they all follow the same general rules. We saw in the previous section that there are two core steps (attack, and re-form the carbonyl). Then, we just need to be careful about proton transfers in the three possible moments when they might be necessary:



With acid halides, it gets much easier, because proton transfers generally only occur at the end of the mechanism (you can skip "1" and "2" on the diagram above). Consider the following example, in which an acid halide is treated with water to generate a carboxylic acid:

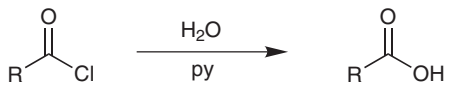


Carefully consider the three steps of this mechanism: attack, re-form, and deprotonate. Say that out loud 10 times real fast (attack, re-form, and deprotonate). You will find that this order of events keeps repeating itself in many of the reactions we are about to see.

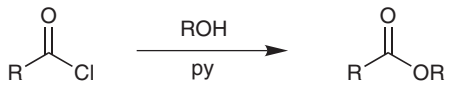
Notice that the by-products of the reaction are Cl^- and H_3O^+ which, together, represent an aqueous solution of HCl. The build-up of acid can often produce undesired reactions (depending on what other functional groups might be present in the compound), so pyridine is used to remove the acid as it is produced:

pyridine pyridinium chloride

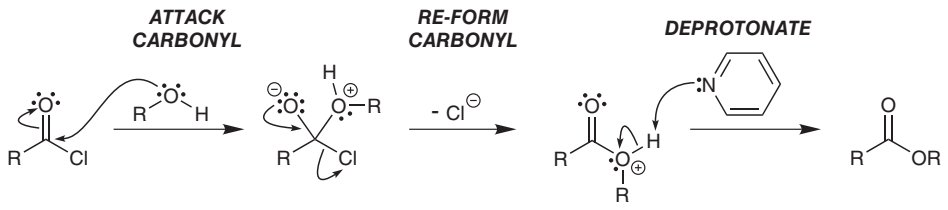
Pyridine is a base that reacts with HCl to form pyridinium chloride. This process effectively traps the HCl so that it is unavailable for any other side reactions. The use of pyridine is often represented with the letters "py," like this:



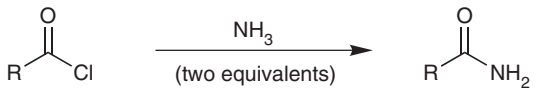
When an acid halide is treated with an alcohol, in the presence of pyridine, the product is an ester:



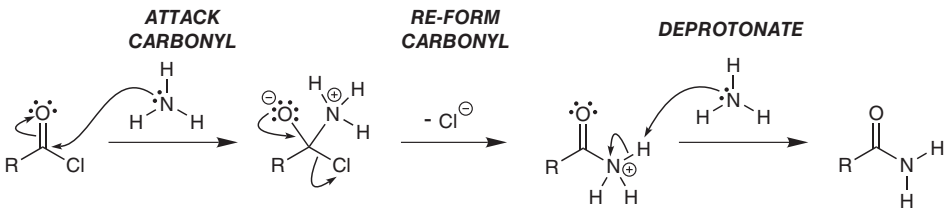
The mechanism for this process has the familiar three steps: attack, re-form, and deprotonate:



When an acid halide is treated with an amine, the product is an amide:

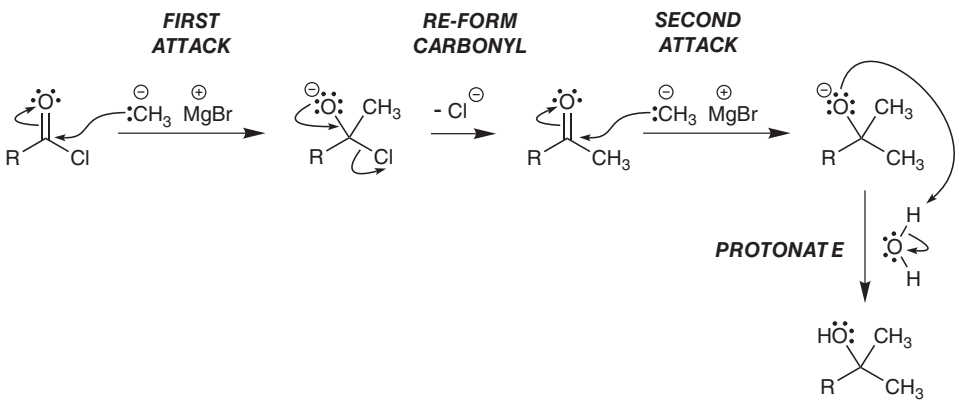


Notice that pyridine is not used in this case. Instead, we use two equivalents of ammonia (twice as much ammonia as acid chloride). One equivalent serves as a nucleophile in the first step of the mechanism, and the other equivalent serves as a base in the last step of the mechanism:

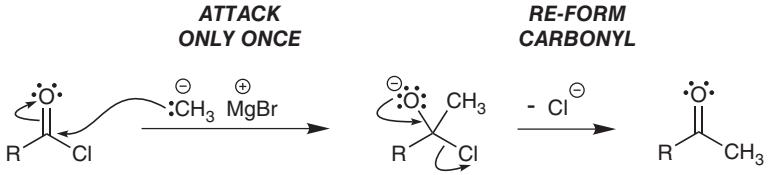


Once again, notice that this process has the familiar three steps: attack, re-form, and deprotonate.

Now let's consider what happens when an acid halide is treated with H^- or C^-. We have already seen that H^- and C^- are special, because they will attack twice:

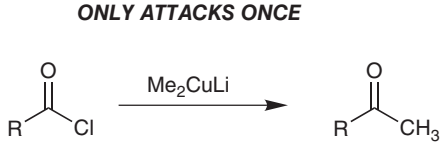


This leaves us with an obvious question. What if we wanted to attack with C^- just once? In other words, suppose we wanted the following outcome:

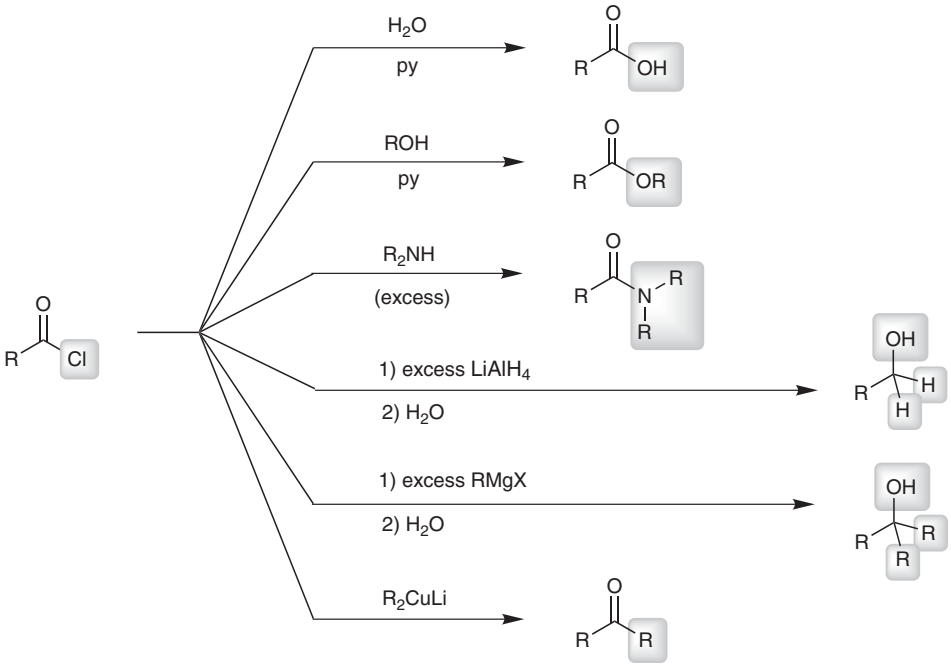


What if the ketone is the desired product? We have a problem here, because the starting acid halide will react with two equivalents of the nucleophile, giving an alcohol. If we just try to use exactly one equivalent of the Grignard reagent, we will observe a mess of products (some molecules of the acid halide will get attacked twice, and others will not get attacked at all). In order to prepare the ketone, we need a carbon nucleophile that will only react with an acid halide, but will ***not*** react with a ketone. And we are in luck, because there is a class of compounds that will do exactly that. They are called lithium dialkyl cuprates (R_2CuLi).

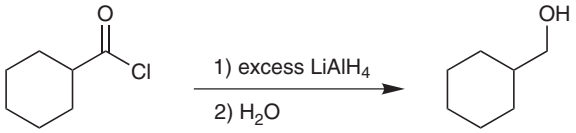
You might have been introduced to these compounds in the first semester of organic chemistry. Lithium dialkyl cuprates are carbon nucleophiles, but they are less reactive than Grignard reagents. Lithium dialkyl cuprates will react with acid halides, but not with ketones. And therefore, we can use these reagents to convert acid halides into ketones:



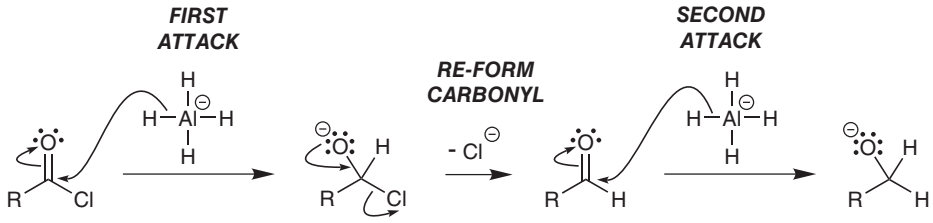
Thus far, we have seen a lot of reactions, so let's just quickly review them:



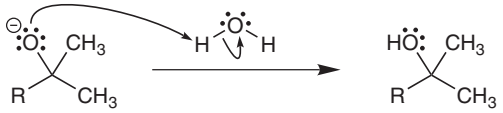
EXERCISE 7.1 Propose a mechanism for the following reaction:



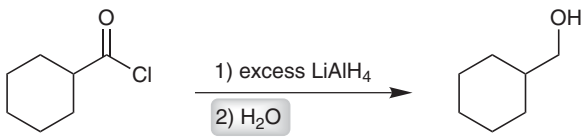
Answer The starting material is an acid chloride, so let's carefully consider the reagents. $LiAlH_4$ is a hydrogen nucleophile (source of H^-), and it is expected to attack the carbonyl group twice:



Finally, a proton transfer will be required at the end of the mechanism:

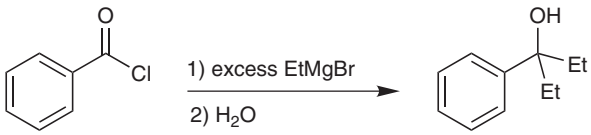


That is, in fact, the reason why H_2O is shown as a separate step:

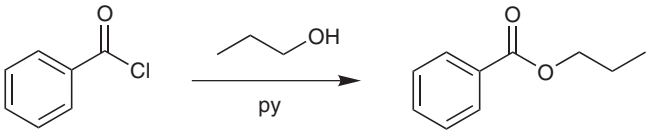


PROBLEMS Propose a plausible mechanism for each of the following reactions. Space has been provided for you to record your answer directly below each reaction:

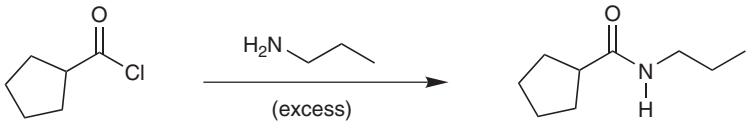
7.2



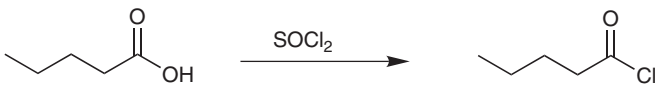
7.3



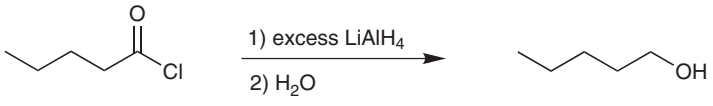
7.4



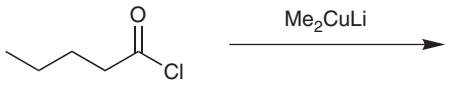
7.5



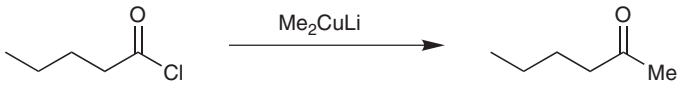
7.6



EXERCISE 7.7 Predict the major product of the following reaction:

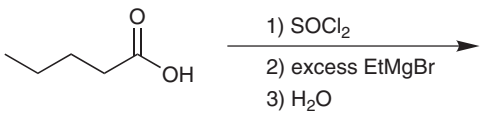


Answer We are starting with an acid halide. So, in order to predict the major product of this reaction, we will have to determine if the nucleophile attacks once or twice. The reagent is a lithium dialkyl cuprate. This reagent is a carbon nucleophile, but it is not like a Grignard reagent—it does not attack twice. Instead, it will only attack once, because it is a very *tame* carbon nucleophile, as we saw earlier in this section. And the product is expected to be a ketone:

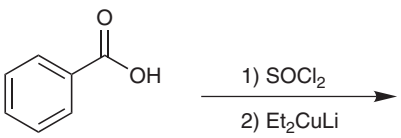


PROBLEMS Predict the major product in each of the following cases:

7.8

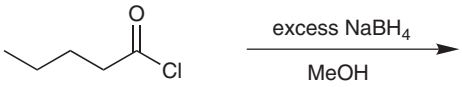


7.9

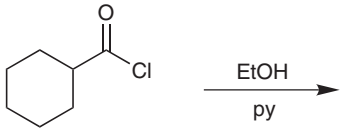


7.10

7.11



7.12

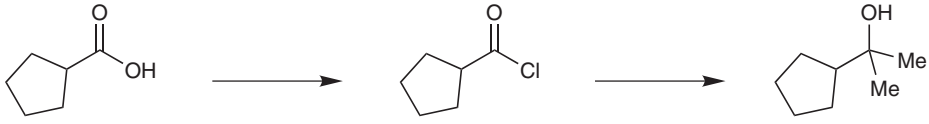


EXERCISE 7.13 Identify the reagents you would use to achieve the following transformation:

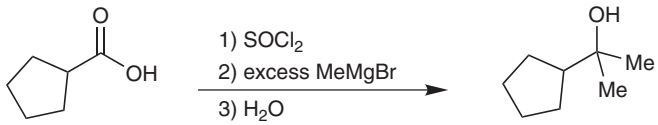
Answer We are starting with a carboxylic acid, and the final product is an alcohol. We also notice that there are two methyl groups in the product:

We therefore need to install ***two*** methyl groups, which means that we need to attack the carbonyl group ***twice***. And in the process, the carbonyl group must be reduced to an alcohol. This sounds like a Grignard reaction.

But we have to be careful. We cannot perform a Grignard reaction with a carboxylic acid. Remember that a Grignard reagent is sensitive to its conditions—if there are any acidic protons available, the Grignard reagent will be destroyed. Since our starting compound (a carboxylic acid) has an acidic proton, we must first convert the carboxylic acid into an acid halide. So our strategy goes like this:



And to achieve this, we could use the following reagents:



PROBLEMS Identify the reagents you would use to achieve each of the following transformations:

7.14

7.15

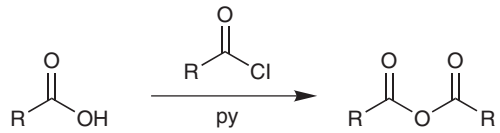
7.16

7.17

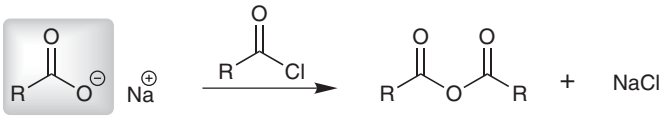
7.18

7.4 ACID ANHYDRIDES

Anhydrides can be prepared by the reaction between a carboxylic acid and an acid halide:

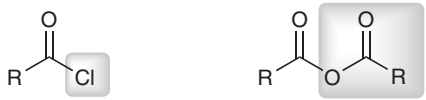


Notice that pyridine is used, once again, to remove the HCl that is formed as a by-product. We can avoid the need for pyridine by using a carboxylate ion (a deprotonated carboxylic acid) instead of a carboxylic acid:

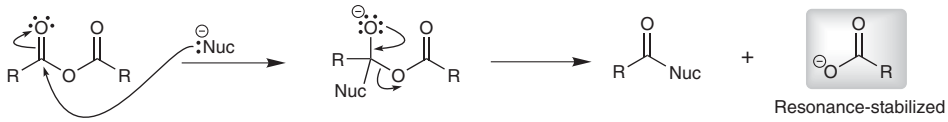


Notice that the by-product is NaCl, rather than HCl, so pyridine is no longer needed.

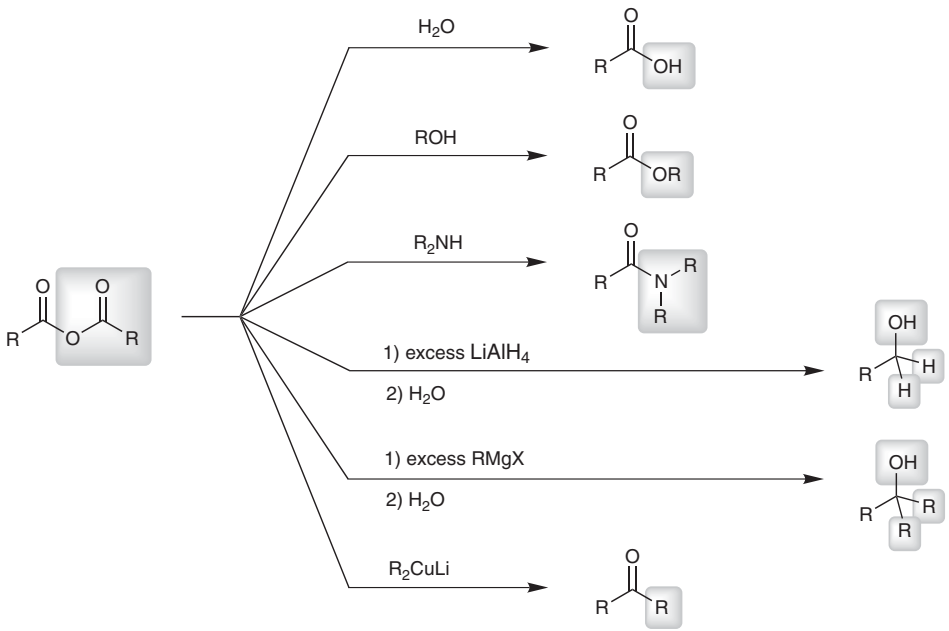
Acid anhydrides are almost as reactive as acid halides. So, the reactions of acid anhydrides are very similar to the reactions of acid halides. You just have to train your eyes to see the leaving group:



When a nucleophile attacks an acid anhydride, the carbonyl group can re-form to expel a leaving group that is resonance-stabilized:

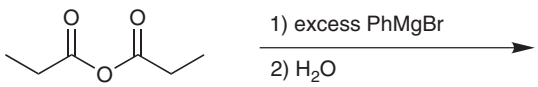


So, an acid anhydride can be treated with any of the nucleophiles that we saw in the previous section to give the same products that we saw in the previous section:

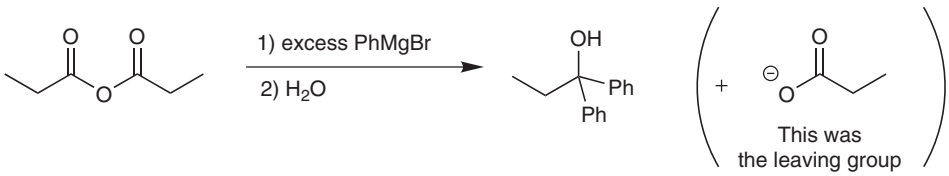


Notice that pyridine is not required in any of these reactions, because HCl is not a by-product.

EXERCISE 7.19 Predict the major product of the following reaction:

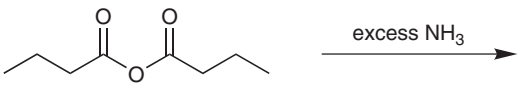


Answer In order to predict the major product of this reaction, we will have to determine if the nucleophile attacks once or twice. The reagent is a Grignard reagent, which is a strong carbon nucleophile. So we expect that the anhydride will react with two equivalents of the Grignard reagent, which will produce an alcohol:

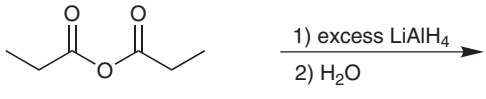


PROBLEMS Predict the major product for each of the following reactions:

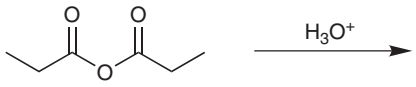
7.20



7.21

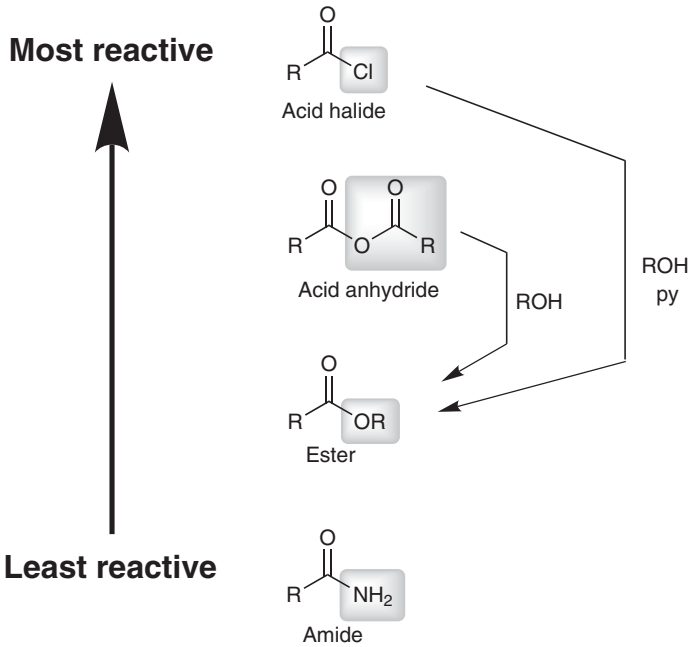


7.22

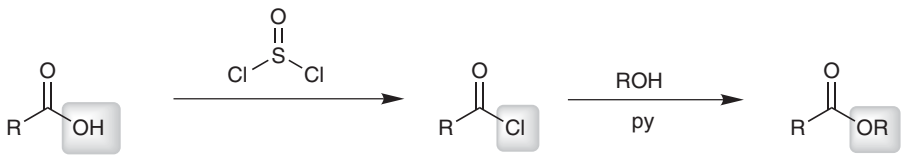


7.5 ESTERS

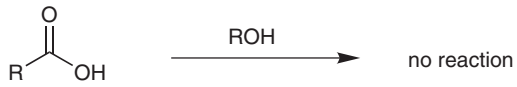
Esters can be made from carboxylic acid derivatives that are more reactive than esters. In other words, we can make an ester from an acid halide, or from an anhydride:



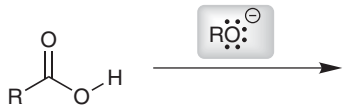
And we have already seen how to make acid halides—we can make them from carboxylic acids (using thionyl chloride). So, this provides a two-step method for making an ester from a carboxylic acid:



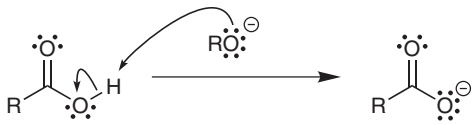
The carboxylic acid is first converted into an acid halide, which is then converted into an ester. But this begs the question: can we achieve the desired transformation *in one reaction*? That is, can we convert a carboxylic acid into an ester in just one reaction, avoiding the need to prepare an acid halide? If we simply try to mix an alcohol and a carboxylic acid, we do ***not*** observe a reaction:



So, let's see what we can do to force this reaction along. Let's consider what happens if we try to make the nucleophile more nucleophilic. In other words, suppose we try to use RO^- instead of ROH:

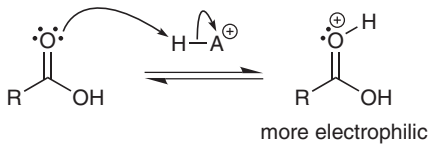


Recall that carboxylic acids have a mildly acidic proton, and alkoxide ions (RO^-) are strong bases. So, the alkoxide ion would just function as a base and deprotonate the carboxylic acid:

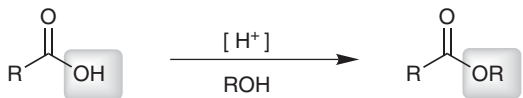


So, once again, an ester would NOT be produced.

But there is one more thing we can try. Rather than making the nucleophile more nucleophilic, we can try to make the electrophile more electrophilic. Do you remember how to do that? We saw in the previous chapter (Section 5.4) that a carbonyl group becomes more electrophilic when it is protonated:

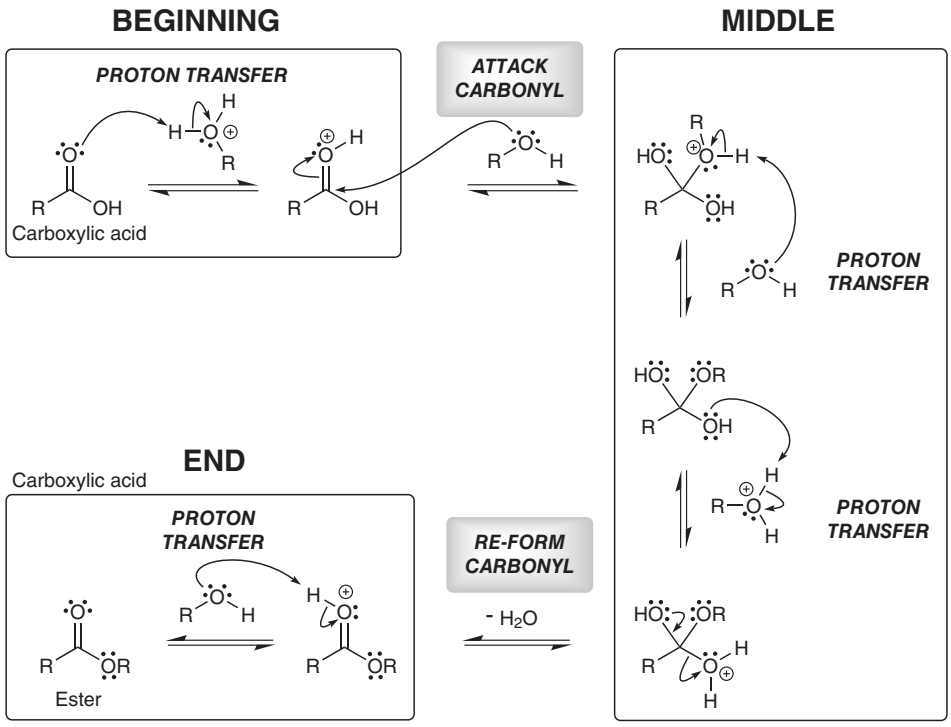


As we will soon see, the acid is not consumed during the reaction, so its function is catalytic (just as we saw in Section 5.4). And under these conditions (acidic conditions), we ***do*** observe the desired reaction (a one-step synthesis of an ester from a carboxylic acid):

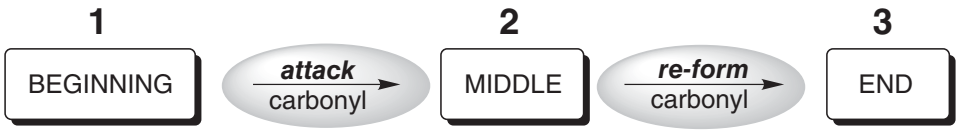


This reaction is incredibly useful and important (and it is considered to be a staple of any organic chemistry course), so let's explore the accepted mechanism, step-by-step.

The mechanism has six steps, but you should notice that there are only two core steps here: attack, and then re-form. All other steps are just proton transfers:

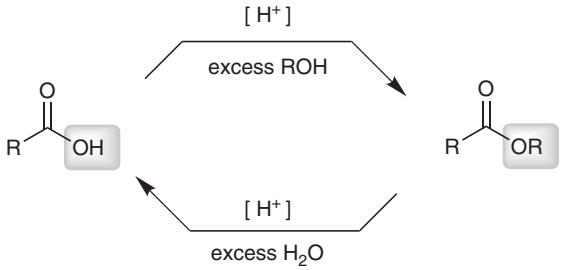


Carefully consider the mechanism above, and you will see there are three moments at which proton transfer steps occur. This exactly follows the pattern that we described in the beginning of this chapter:



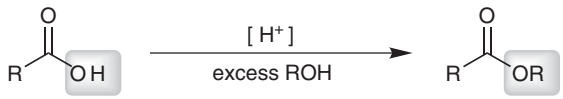
1. *In the beginning of the mechanism*, a proton transfer step is necessary in order to protonate the carbonyl group, rendering it more electrophilic.
2. *In the middle of the mechanism* (after attack of the carbonyl, but before re-forming the carbonyl), two proton transfers are required to protonate the leaving group (HO^- cannot be expelled in acidic conditions). Notice that two proton transfer steps are required. It would not be OK to simply protonate the OH group without first deprotonating the OR group, because that would give an intermediate with two positive charges. So, first we deprotonate to remove the positive charge, and then, we protonate the OH group to give a good leaving group.
3. *In the end of the mechanism*, a proton transfer is required to remove the positive charge and generate the product.

This reaction is called a Fischer esterification. The position of equilibrium is very sensitive to the concentrations of starting materials and products. Excess ROH favors formation of the ester, while excess water favors the carboxylic acid:



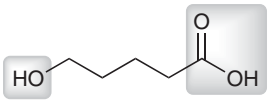
This is very helpful, because it provides a way to convert an acid into an ester, ***or*** an ester into an acid.

For now, let's focus on converting an acid into an ester:

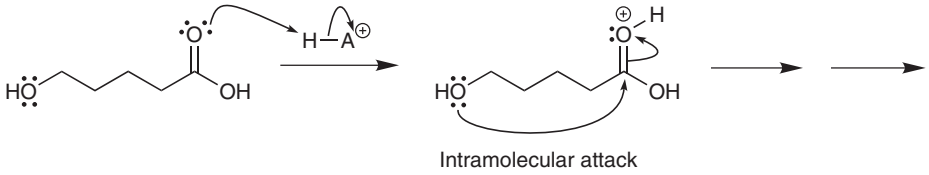


We will spend some time on the reverse process very soon.

We have seen that a Fischer esterification is the reaction between a carboxylic acid and an alcohol (with acid catalysis). If a single compound contains both functional groups (COOH and OH), it is possible to observe an intramolecular Fischer esterification. For example, consider the following compound:

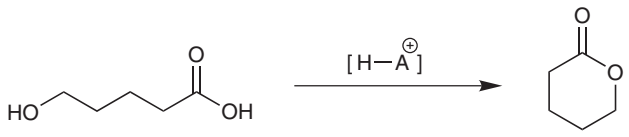


This compound has both a COOH group and an OH group. And, in this case, an intramolecular reaction is observed:

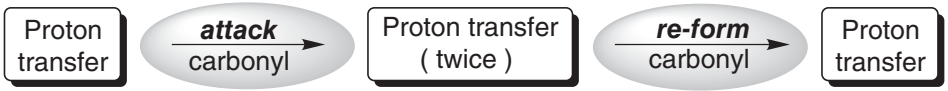


The rest of the mechanism is directly analogous to what we have already seen. The mechanism has two core steps (attack and re-form), with proton transfer steps in the beginning, middle, and end.

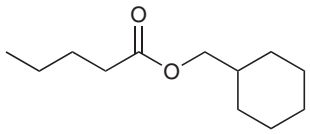
PROBLEM 7.23 In the space provided on the next page, draw a mechanism for the following transformation:



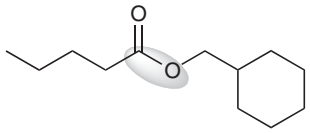
Remember that the general steps are:



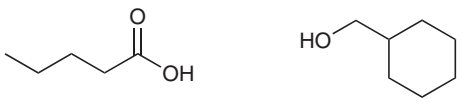
EXERCISE 7.24 Identify the reagents you would use to make the following compound via a Fischer esterification:



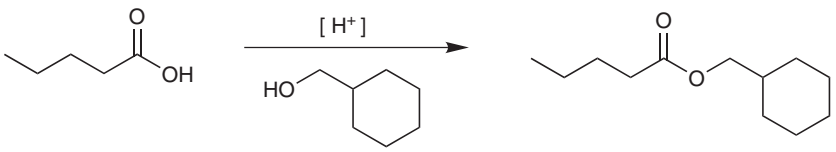
Answer To make an ester using a Fischer esterification, we need to start with a carboxylic acid and an alcohol. The question is: how do we decide which carboxylic acid and which alcohol to use? To do this, we must identify the bond that will be formed during the reaction (highlighted):



To form the highlighted bond via a Fischer esterification, we will need the following reagents:

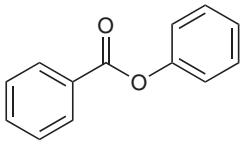


And, don't forget that we need acid catalysis. So our synthesis would look like this:

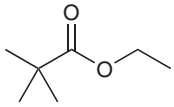


PROBLEMS Identify the reagents you would use to make each of the following esters:

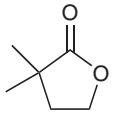
7.25



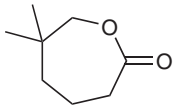
7.26



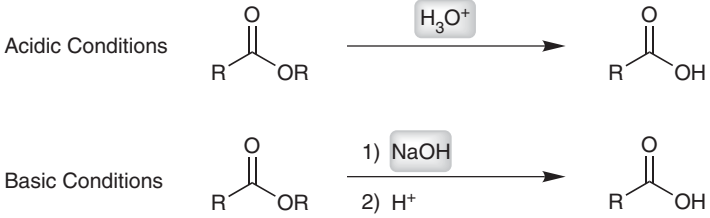
7.27



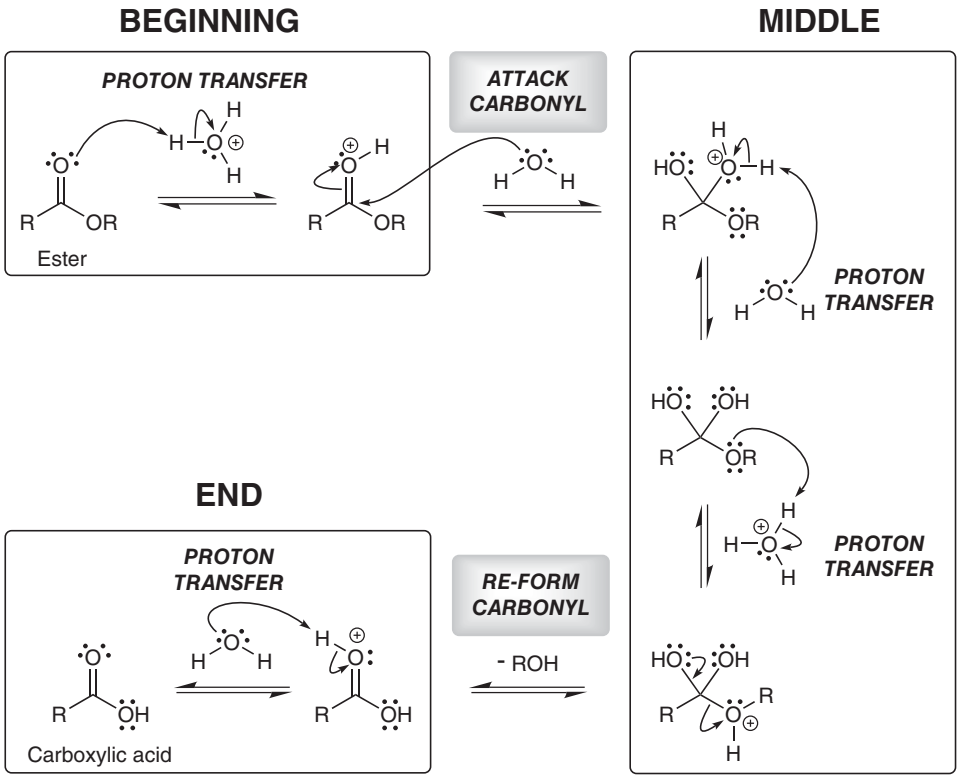
7.28



Now that we have seen how to make esters, let's focus our attention on the reactions of esters. We will center on two reactions in particular. Esters can be hydrolyzed to give carboxylic acids, under two different sets of conditions:

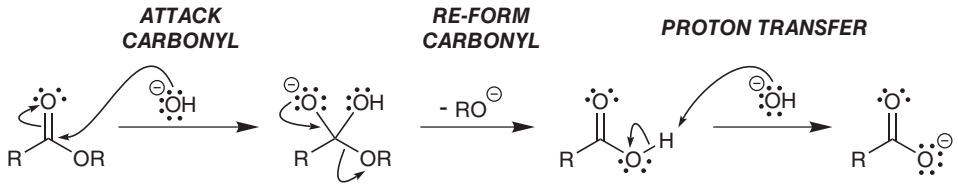


The first set of conditions above (acidic conditions) should seem very familiar to you. This reaction is simply the reverse of a Fischer esterification. Let's explore the accepted mechanism for this process:

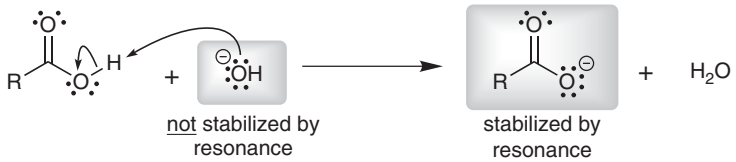


Once again, we see the same pattern again and again. Look closely at this mechanism. There are two core steps: attack, and re-form. All other steps in the mechanism are just proton transfers that facilitate the reaction. One proton transfer is required in the beginning (to protonate the carbonyl group), two proton transfers are required in the middle (so that the leaving group can leave as a neutral species, ROH), and one proton transfer is required at the end (to deprotonate).

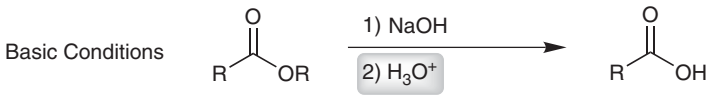
The process above occurs under acidic conditions. But it is also possible to hydrolyze an ester under basic conditions as well. The following is a mechanism for that process:



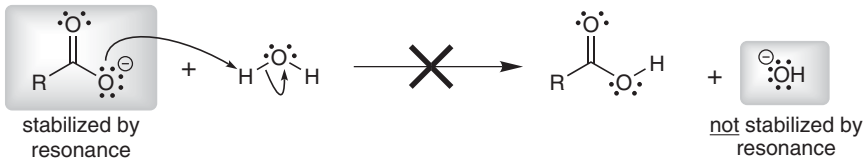
Once again, we have two core steps (attack and re-form), followed by a deprotonation. This proton transfer at the end is unavoidable under these conditions. In basic conditions, a carboxylic acid will be deprotonated. In fact, formation of a more stable anion is the driving force for this reaction:



This resonance-stabilized anion is called a carboxylate ion, and its formation serves as a driving force. In order to protonate the carboxylate ion, a proton source must be introduced into the reaction flask (note that the proton source is introduced into the reaction flask AFTER the reaction is complete, and must be indicated as a separate step):

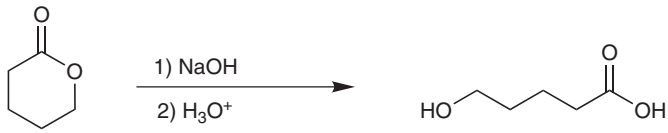


Notice that we need to use H_3O^+ rather than H_2O, because a carboxylate ion will not remove a proton from water:

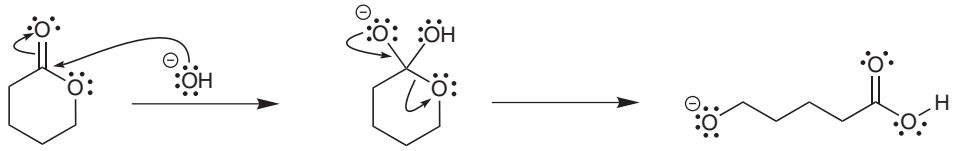


This process (hydrolysis of an ester under basic conditions) has a special name: *saponification*.

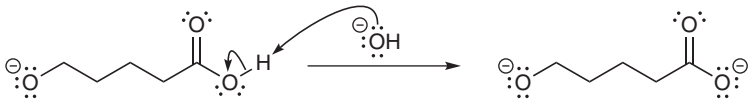
EXERCISE 7.29 Propose a mechanism for the following transformation:



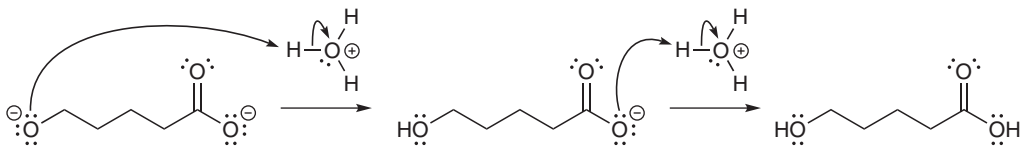
Answer This reaction utilizes basic conditions to hydrolyze an ester (a process called saponification). We begin by attacking the carbonyl group, and then re-forming it:



Notice that we just produced a carboxylic acid (a weak acid) under strongly basic conditions. Under these conditions, the carboxylic acid is deprotonated to give a carboxylate ion:

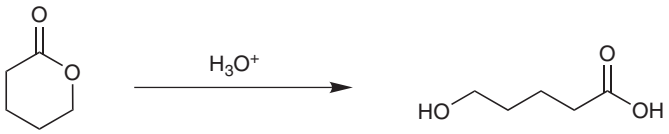


After the reaction is complete, an acid is introduced into the reaction flask to protonate the dianion (notice that the stronger base is protonated first):

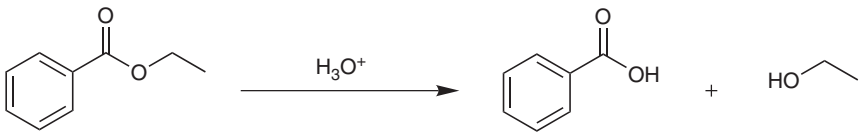


PROBLEMS In the space provided, draw a mechanism for each of the following transformations:

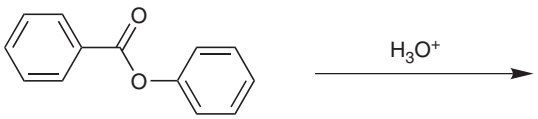
7.30



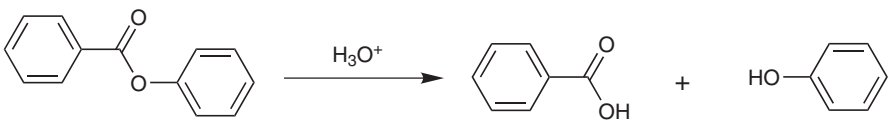
7.31



EXERCISE 7.32 Predict the products of the following reaction:

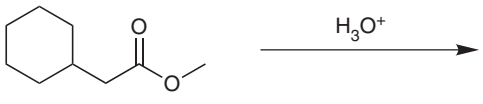


Answer We are starting with an ester, and we are subjecting it to aqueous acidic conditions. This will convert the ester into a carboxylic acid and an alcohol (the reverse of a Fischer esterfication). We expect the following products:

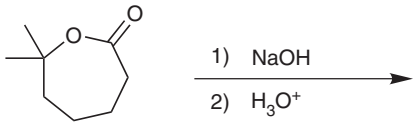


PROBLEMS Predict the products of each of the following reactions:

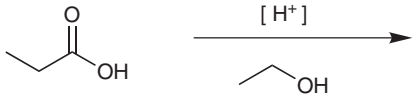
7.33



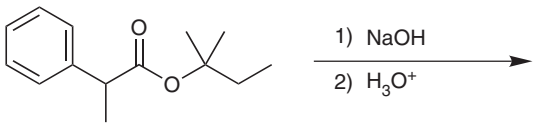
7.34



7.35

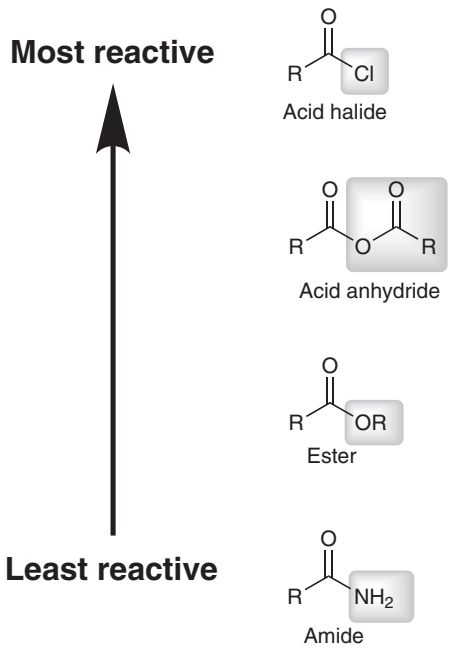


7.36



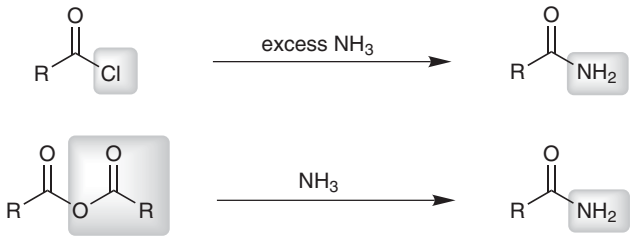
7.6 AMIDES AND NITRILES

We have said before that a carboxylic acid derivative can be prepared from any other carboxylic acid derivative that is more reactive. Let's go back to our reactivity chart to see what this means practically:

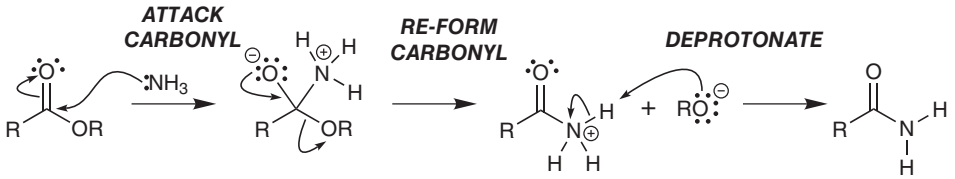


Since amides are the least reactive of the carboxylic acid derivatives (shown on the chart above), we can therefore make amides from any carboxylic acid derivatives that are higher on the chart. In other words, we can make amides from acid halides, from anhydrides, or from esters.

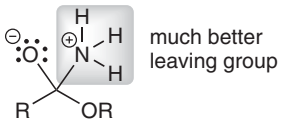
Earlier in this chapter, we saw how to make amides from acid halides or anhydrides:



But now the question is: how do we make amides from esters? Esters are less reactive than acid halides or anhydrides. So, we have to use some kind of trick to coax the reaction along. We cannot use acid or base (an acid would just protonate the attacking amine, rendering it useless; and a base would cause other side reactions that we will learn in the next chapter). Instead, we use brute force and patience. We just heat the reaction for a long time, and a reaction is observed, which can occur via the following mechanism:

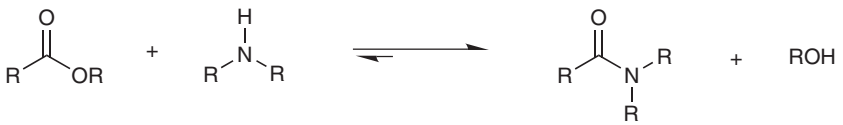


Notice that RO^- is expelled to re-form the carbonyl group. That might seem strange, because there is a much better leaving group available to leave:



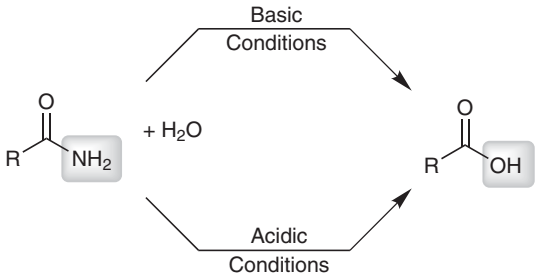
But this gets back to something we have said many times before. Of course it is possible for the amine to leave. In fact, it happens all of the time. The amine attacks, and then it gets expelled. It attacks, and is then expelled again. Every time this happens, there is no change to observe. But every once in a while, something else can happen. RO^- can be expelled, which is then immediately protonated, as shown in the mechanism above. We are allowed to expel RO^- when re-forming a carbonyl group, because the tetrahedral intermediate is so high in energy (negative charge on an oxygen atom).

The equilibrium for this process favors the products (amide + alcohol) over the reactants (ester + amine):

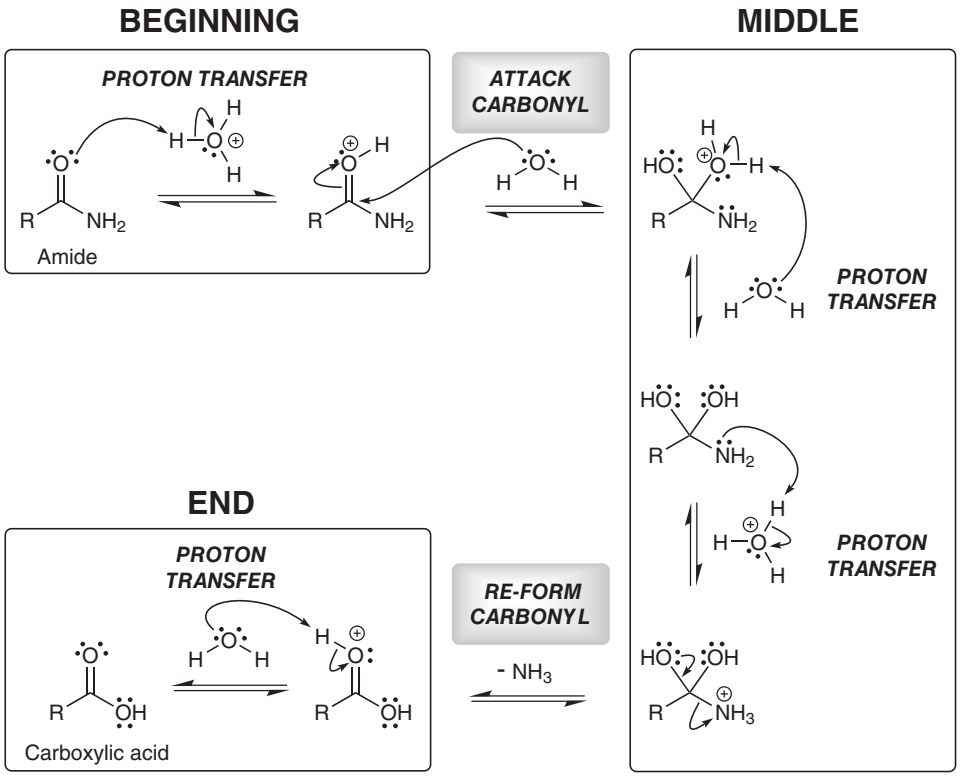


So, this is another method for making amides, however, the process is extremely slow and is not really a practical synthetic technique. Therefore, you should avoid using this reaction in a synthesis, if possible. A better method to make amides is to start with a more reactive carboxylic acid derivative.

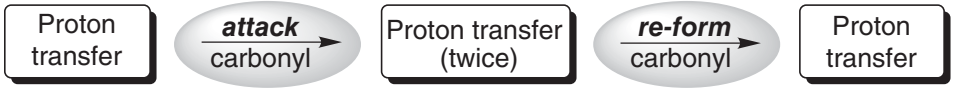
So far, in this section, we have seen that we can make amides from acid halides or from acid anhydrides. Now that we know how to make amides, let's explore some important reactions of amides. Specifically, we will explore hydrolysis of amides (first under acidic conditions, and then under basic conditions). It is worth mentioning that much of biochemistry is dependent on how, when, and why amides will undergo hydrolysis. So, if you plan on taking biochemistry, you should certainly be familiar with the hydrolysis of amides, which can occur under either basic conditions or acidic conditions:



Let's begin with acid-catalyzed conditions. This reaction is really no different than the other acid-catalyzed reactions we have seen. Take a close look at the following mechanism:

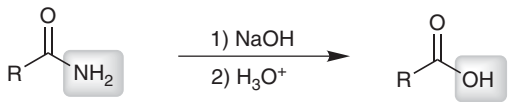


Notice that it follows the exact same pattern that we have seen again and again:

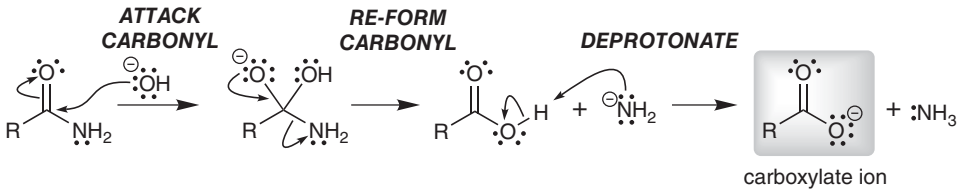


This pattern is common among the acid-catalyzed reactions that we have seen so far in this chapter.

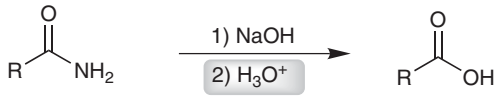
Now let's explore base-catalyzed conditions for the hydrolysis of an amide:



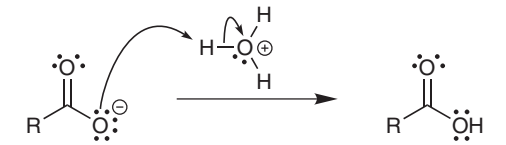
This transformation can occur via the following mechanism:



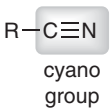
Under basic conditions, the product is a carboxylate ion (highlighted above), and that is why an acid is listed as a reagent (in a separate step):



When the reaction is complete and H_3O^+ is then added to the reaction flask, the carboxylate ion is protonated to generate the carboxylic acid:



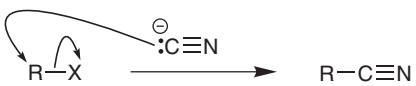
Before we do some problems, let's look at one last carboxylic acid derivative that we have not yet seen. Compounds containing a cyano group are called nitriles:



You might be wondering why nitriles are considered to be carboxylic acid derivatives. After all, a nitrile looks very different from the other carboxylic acid derivatives. To make sense of this, we need to consider oxidation states. Each of the carboxylic acid derivatives has three bonds to electronegative atoms:

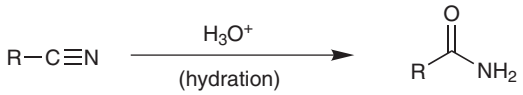
The carbon atom of the carbonyl group has two bonds with oxygen, and it also has one more bond with some heteroatom, Z (O, N, Cl, etc.). That gives a total of three bonds to heteroatoms. The carbon atom of a cyano group also has three bonds to a heteroatom. So, nitriles are at the same oxidation level as the other carboxylic acid derivatives.

Nitriles can be prepared using cyanide as a nucleophile to attack an alkyl halide:



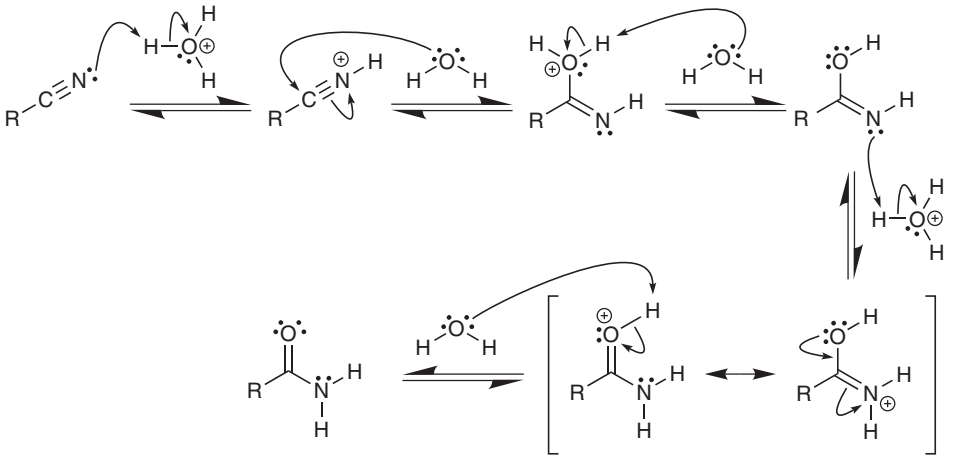
This is an S_N2 process, so you can only use this method with primary or secondary alkyl halides (primary halides are much better). Don't use this method with tertiary alkyl halides. There are other ways to make nitriles. You should look through your textbook (and your lecture notes) to see if you are responsible for knowing any other ways to make nitriles.

We can easily see that nitriles really are at the same oxidation level as other carboxylic acid derivatives, because hydration (which is ***not*** an oxidation–reduction reaction) produces an amide:



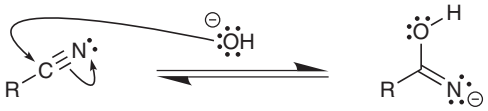
Hydration can occur either under acidic conditions or under basic conditions.

Whether we perform an acid-catalyzed hydration or a base-catalyzed hydration, the core steps are slightly different than the core steps of the mechanisms we have seen in this chapter. So far, all of our reaction mechanism have had at least ***two*** core steps (attack the carbonyl, and then expel a leaving group to re-form the carbonyl), with all other steps being proton transfers. But now, we will see a mechanism that has just ***one*** core step (attack the carbonyl). When it comes to the hydration of nitriles, no leaving group is expelled. The carbonyl group can form simply through proton transfers (after the nucleophilic attack):



This is the mechanism for the hydration of a nitrile under ***acidic*** conditions, and it is analagous to hydration of an alkyne under acidic conditions to give a ketone. Notice that the second step in the mechanism shows a nucleophile (H_2O) attacking a protonated cyano group (very much the way a protonated carbonyl group can be easily attacked). All other steps in the mechanism are just proton transfers. When you think of it this way, it greatly simplifies the mechanism. The many proton transfers are necessary to avoid the formation of a strong base, which cannot occur under acidic conditions.

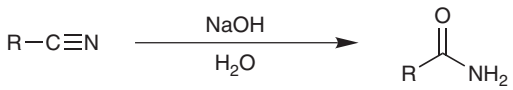
Now let's consider the hydration of nitriles under ***basic*** conditions. The mechanism is actually VERY similar to the mechanism above. There is also only ***one*** core step (attacking the cyano group), and all the other steps are just proton transfers. But in basic conditions, the cyano group is *not* first protonated. Rather, it is attacked by hydroxide first:



The rest of the mechanism is all just proton transfer steps. In order to draw the proton transfers properly, you must keep one thing in mind: stay consistent with the conditions. In acidic conditions, avoid the formation of a strong base. In basic conditions, avoid the formation of a strong acid.

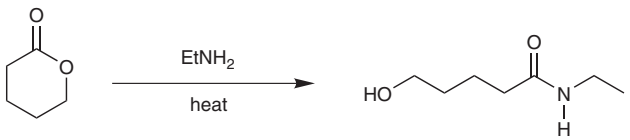
With this in mind, complete the following exercise (Problem 7.37) to see if you can draw a plausible mechanism for the hydration of a nitrile under basic conditions.

PROBLEM 7.37 Based on everything we have just seen, propose a mechanism for the hydration of a nitrile under basic conditions:

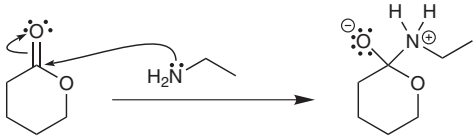


Remember, there is just one core step (attacking the cyano group with hydroxide). After that, all other steps are just proton transfers. Use the space below to record your answer. When you have finished, you can look in the back of the book (or in your textbook) to see if you got it right.

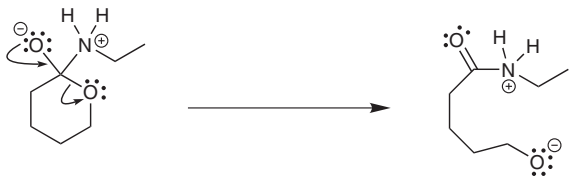
EXERCISE 7.38 Draw a plausible mechanism for the following transformation:



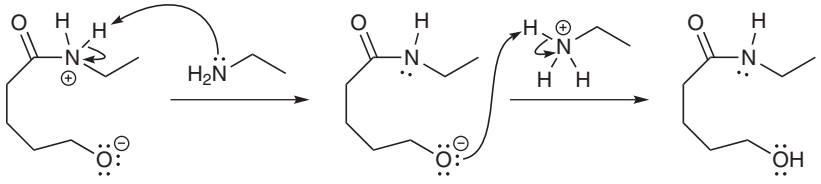
Answer In this reaction, an ester is being treated with an amine under conditions of heating. We have seen these conditions before. A source of protons (an acid) has not been indicated among the reagents, so the carbonyl group is not protonated. The first step of the mechanism will involve the amine directly attacking the carbonyl group of the ester:



Then the carbonyl group is re-formed via expulsion of an alkoxide ion (RO^-) as a leaving group:

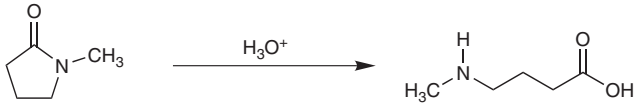


This intermediate is then converted into the product via two successive proton transfer steps:

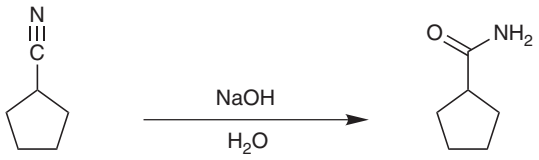


PROBLEMS Propose a plausible mechanism for each of the following transformations.

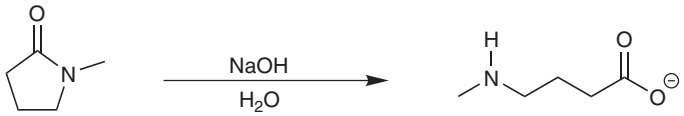
7.39



7.40

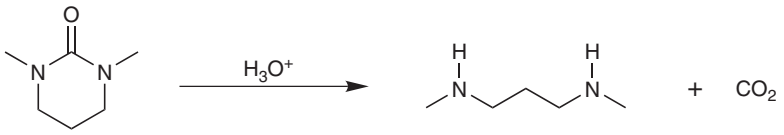


7.41

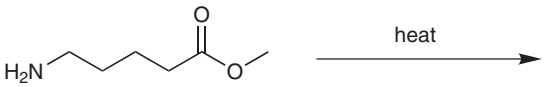


And now let's just do one more challenging mechanism. I say "challenging" not because it is difficult, but because you have not seen this exact mechanism before. Rather, you should be able to work your way through the mechanism, using all of the skills we have developed in this chapter:

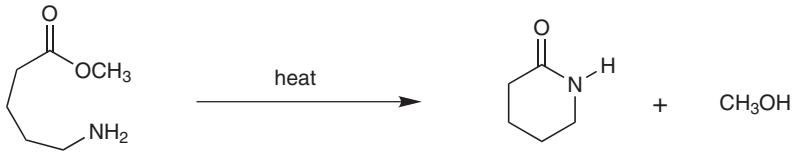
PROBLEM 7.42 Propose a mechanism for the following reaction:



EXERCISE 7.43 Predict the products of the following reaction:

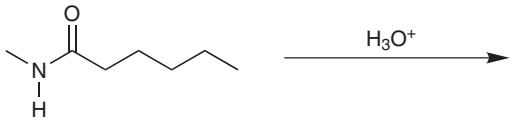


Answer We were not given any reagents here (just conditions of heat), so we look carefully at the starting material to see if we can have an intramolecular reaction. We notice that there are two functional groups in our starting compound (an ester and an amine). And we have seen that an ester can react with an amine under conditions of heating. The products should be an amide and an alcohol:

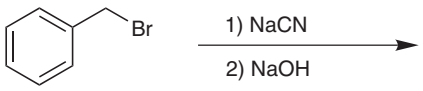


PROBLEMS Predict the products for each of the following reactions:

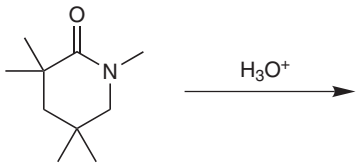
7.44



7.45

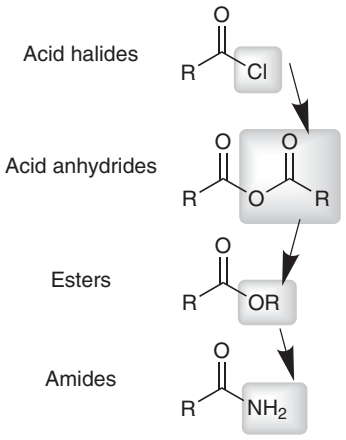


7.46

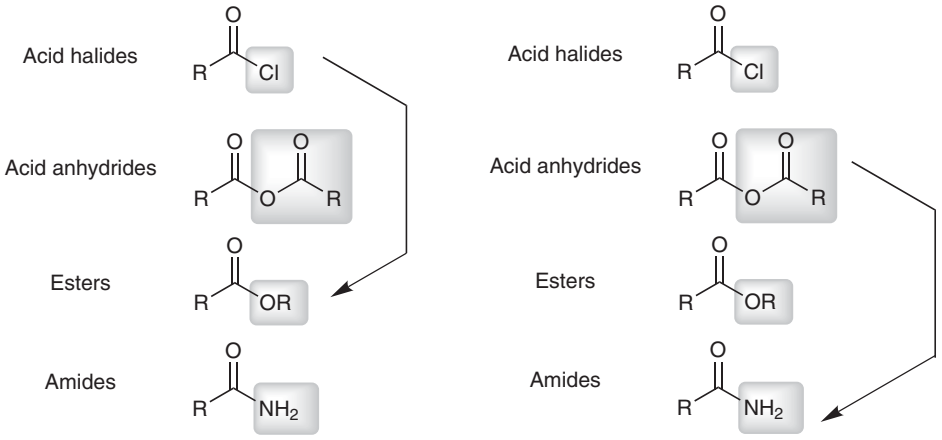


7.7 SYNTHESIS PROBLEMS

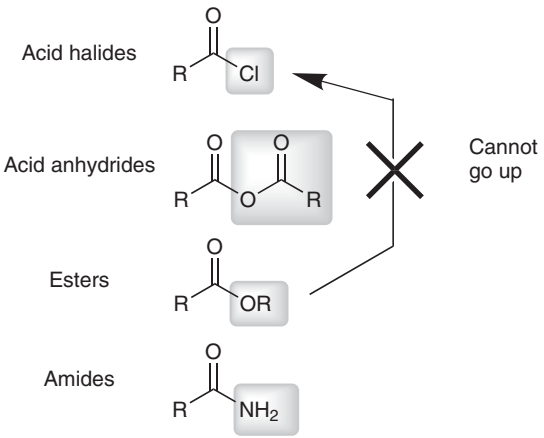
We have seen a lot of reactions in this chapter. Almost all of them involved the conversion of one carboxylic acid derivative into another. We saw that you can make a carboxylic acid derivative from any other derivative that is more reactive. In other words, you can always step your way ***down*** the following chart:



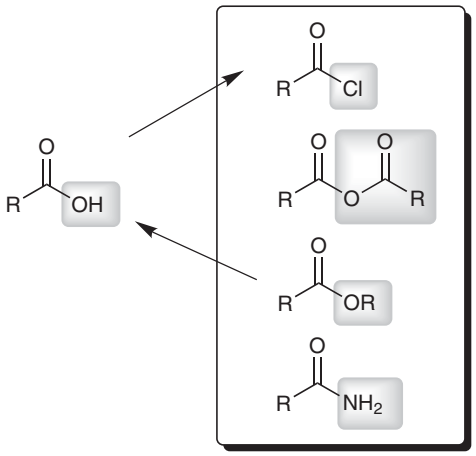
You can even jump down the chart if you want:



But travelling ***up*** the chart is more difficult:



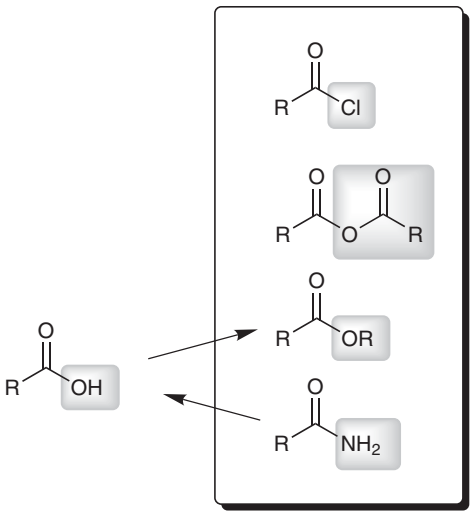
So, how do you travel ***up*** the chart, if you need to? Here is the way to do it: You can exit this chart by converting into a carboxylic acid, and then come back into the chart, like this:



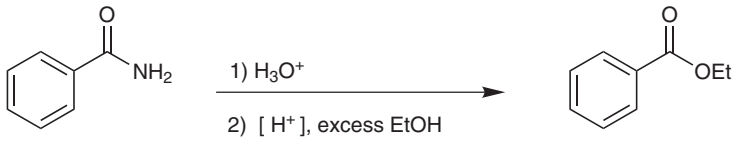
Let's get some practice with this:

EXERCISE 7.47 Propose an efficient synthesis for the following transformation:

Answer We must convert an amide into an ester, but we have not learned a way to do this directly in one step (because that would involve going ***up*** the chart). Amides are less reactive than esters, so we cannot go directly from an amide to an ester. Instead, we can first convert the amide into a carboxylic acid, and then we can convert the carboxylic acid into an ester:



To achieve this transformation, we would use the following reagents:



PROBLEMS Propose an efficient synthesis for each of the following transformations:

7.48

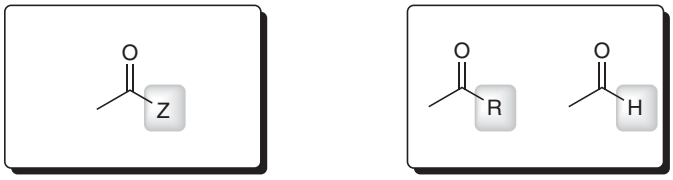
7.49

7.50

7.51

7.52

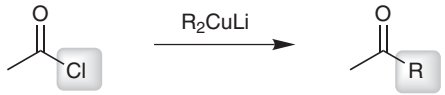
There is one other important strategy to keep in mind when you are proposing a synthesis. In this chapter, we explored the chemistry of carboxylic acid derivatives; and in the previous chapter, we explored the chemistry of ketones/aldehydes. These two chapters represent two different realms:



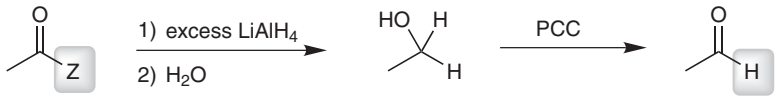
Realm of carboxylic acid derivatives

Realm of ketones and aldehydes

But these realms are not completely isolated from one another, because we have seen ways to convert from one realm into another. In this chapter, we saw how to convert an acid halide into a ketone:

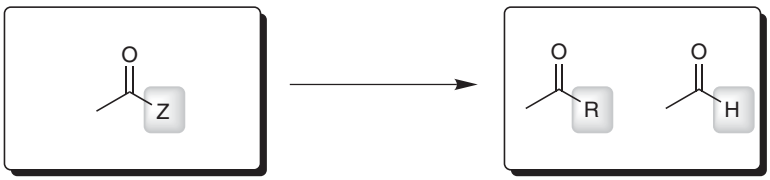


There is also another way to cross over from the realm of carboxylic acids into the realm of ketones and aldehydes. Rather than making a ketone (like above), we can make an aldehyde using the following two steps:



Some textbooks and instructors will teach you a reagent that can achieve this overall transformation in one step (converting from an acid halide into an aldehyde). There are actually many hydride reagents that are sufficiently selective to convert an acid halide into an aldehyde (very much the way lithium dialkyl cuprates are sufficiently selective to convert an acid halide into a ketone, without attacking the carbonyl group a second time). You should look through your textbook and lecture notes to see if you have covered a selective hydride nucleophile. If you haven't, you can always use the two-step method (shown above) for converting an acid halide into an aldehyde.

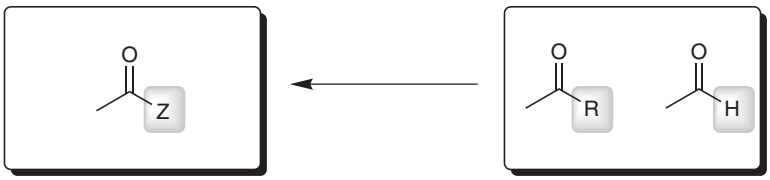
With the reactions above, we have seen how to "cross over" from the realm of carboxylic acid derivatives into the realm of ketones and aldehydes:



Realm of carboxylic acid derivatives

Realm of ketones and aldehydes

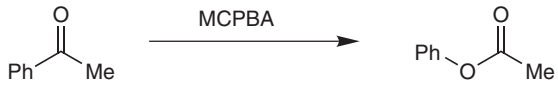
But what about the reverse direction? Do we have a way to "cross over" from the realm of ketones and aldehydes into the realm of carboxylic acid derivatives?



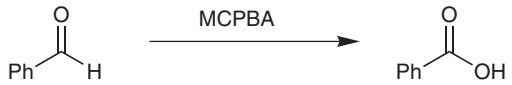
Realm of carboxylic acid derivatives

Realm of ketones and aldehydes

Yes, we have seen a way to do this also. Recall (from the previous chapter) that a Baeyer–Villiger oxidation will convert a ketone into an ester:



We can also use a Baeyer–Villiger oxidation to convert an aldehyde into a carboxylic acid (remember migratory aptitude?):

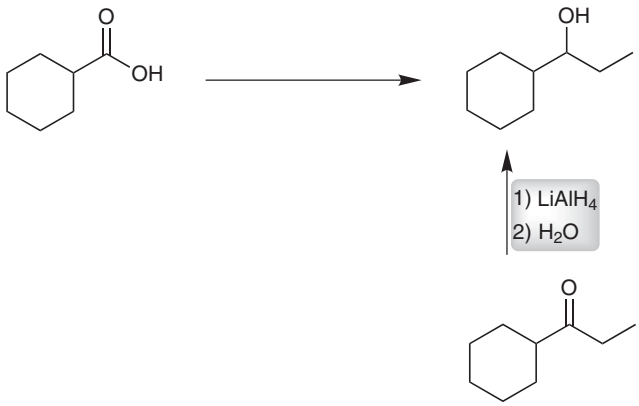


So, we now have reactions that allow us to "cross over" from one realm into the other (in either direction). Let's see an example of how to use this:

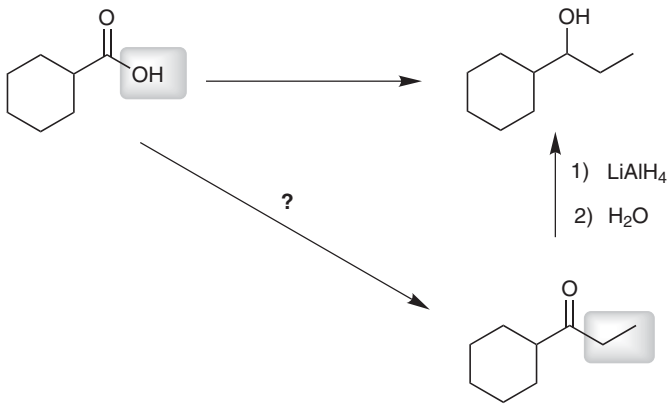
EXERCISE 7.53 Propose an efficient synthesis for the following transformation:

Answer The final product is an alcohol, and in the process of converting the carboxylic acid into an alcohol, an ethyl group must be installed. It might be hard to see, at first glance, how this transformation can be achieved. But don't get discouraged. You are not expected to know how to solve problems like this instantly. Synthesis problems require thought and strategizing. Remember that you always want to try to go backwards as much as possible (retrosynthetic analysis). So, let's work our way backwards.

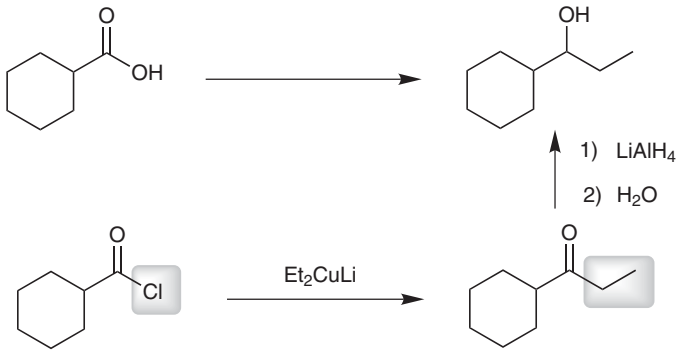
Did we learn any simple ways to make alcohols? In the previous chapter, we learned how to make an alcohol from a ketone, using $LiAlH_4$:



With this one important step, we are now in a position to realize that this problem can be thought of as a "cross-over" problem. The starting material is a carboxylic acid, and we need to turn it into a ketone:

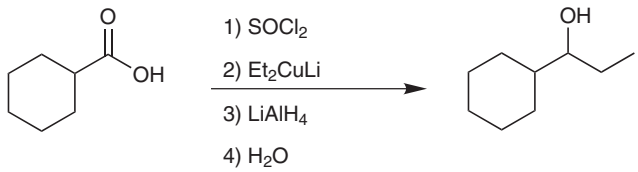


In other words, we need to cross over from the realm of carboxylic acids into the realm of ketones. And we did see one reaction that allows us to do that. We can make a ketone from an acid halide, using a lithium dialkyl cuprate. So, now we have worked backwards again:



To complete the synthesis, we just need to convert the carboxylic acid into an acid halide, and we can do that in one step with thionyl chloride.

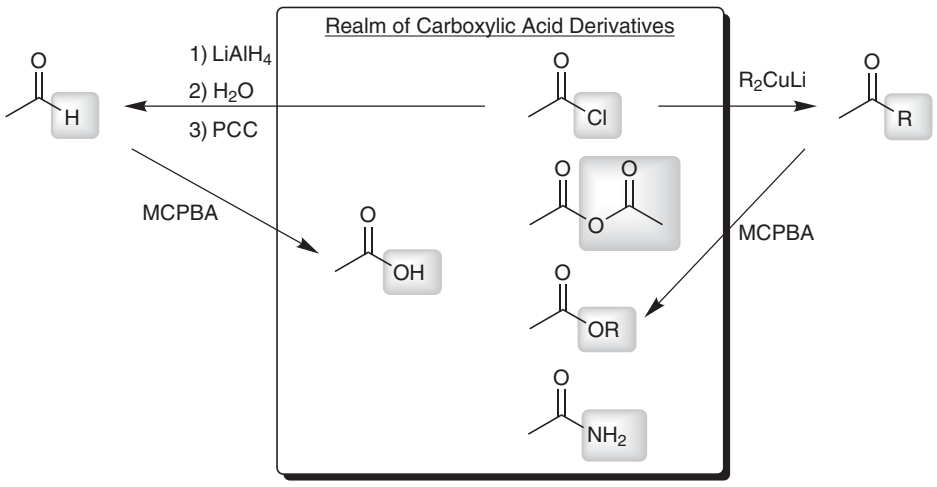
So, our answer is:



Now let's get some practice with some more "cross-over" problems. In order to do these problems, you will need to review this chapter ***and*** the previous chapter (ketones and aldehydes)—you will need to have all of the reactions from both chapters at your fingertips.

At first, you might find it difficult to identify the following problems as cross-over problems, but hopefully, you will start to see some trends as you solve these problems.

In solving these problems, make sure that you are familiar with the ways that we have seen for crossing over. We have seen four such reactions so far, all of which are summarized in the following chart:

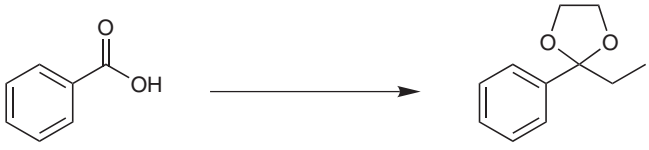


Study this chart carefully. To help you remember them, you should notice one thing that all four reactions have in common. They are all reduction–oxidation reactions. This should make sense because carboxylic acid derivatives are at a different oxidation state than ketones and aldehydes.

You will need some time to do the following problems, so don't sit down to do these problems when you only have 5 minutes to study. That would just frustrate you. Make sure that you have some time to spend when you sit down to work through these problems.

PROBLEMS Propose an efficient synthesis for each of the following transformations. In each case, remember to work backwards (retrosynthetic analysis), and try to determine which cross-over reaction to use. When you compare your answers to the answers in the back of the book, keep in mind that there is often more than one way to solve a synthesis problem. If your answer is different from the answer in the back of the book, you should not necessarily conclude that your answer is wrong.

7.54



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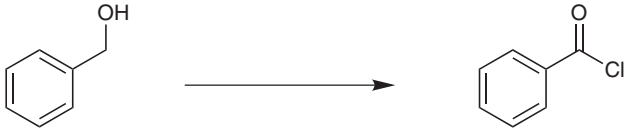

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The goal of this chapter was to lay a foundation that will enable you to study your textbook and lecture notes more efficiently. We saw a few simple rules that govern all of the mechanisms in this chapter, and we learned several synthesis strategies.

Now you can go back through your textbook and lecture notes, and look for those reactions that we did not cover here in this chapter. With the foundation we have built in this chapter, you should be in good shape to fill in the gaps and study more efficiently.

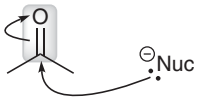
And make sure to do ALL of the problems in your textbook. You will find more synthesis problems there. The more you practice, the better you will get. Good luck.

CHAPTER 8

ENOLS AND ENOLATES

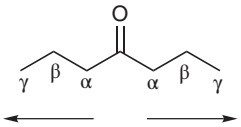
8.1 ALPHA PROTONS

In the previous two chapters, we focused on the reactions that can take place when a nucleophile attacks a carbonyl group:



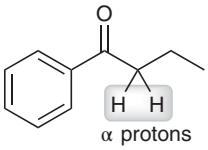
We first learned about nucleophilic attack on ketones and aldehydes (in Chapter 6). Then, in Chapter 7, we explored reactions of carboxylic acid derivatives. Now, we are ready to move away from the carbonyl group, and explore the chemistry that can take place at the alpha (α) carbon:

We call this the alpha carbon, because it is the carbon atom directly connected to the carbonyl group. We use the Greek alphabet to label carbon atoms, moving away from the carbonyl group, in either direction:

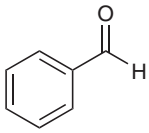


Notice that in this compound, there are two alpha positions. In this chapter, we will focus on the chemistry that can take place at the alpha positions.

Before we get started, we should discuss one more piece of terminology. Any protons connected to an alpha carbon are called alpha protons:



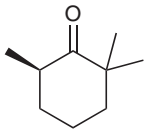
Not all alpha carbon atoms will have alpha protons. For example, consider the following compound:



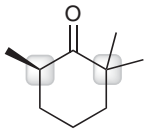
This compound has no alpha protons. If you look just to the right of the carbonyl group, you will see that there is no alpha carbon (it is just an aldehyde). That aldehydic H is NOT an alpha proton because it is not connected to an alpha carbon. And if you look just to the left of the carbonyl group, you will see that there IS an alpha carbon, but this carbon has no protons connected to it.

It is important to recognize the presence or absence of alpha protons. We will see a lot of reactions in this chapter, and most of these reactions will be based on the presence of alpha protons. It turns out that alpha protons are somewhat acidic; and the removal of an alpha proton generates an anion that is fairly reactive. We will see this in greater detail very soon. For now, let's just make sure that we can identify alpha protons when we see them.

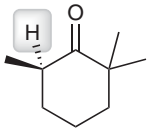
EXERCISE 8.1 Identify all alpha protons in the following compound:



Answer To see if there are any α protons, we must first identify the alpha carbon atoms:



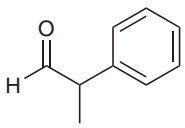
The alpha carbon on the right does ***not*** have any protons connected to it. The alpha carbon on the left ***does*** have a proton (highlighted):



So, there is just one alpha proton in this compound.

PROBLEMS For each of the compounds below, identify all alpha protons (some compounds may not have any alpha protons).

8.2



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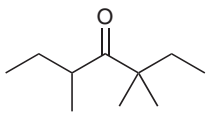
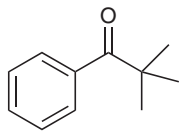


8.4



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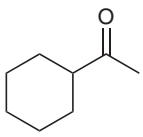

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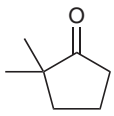
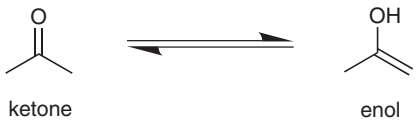


8.7

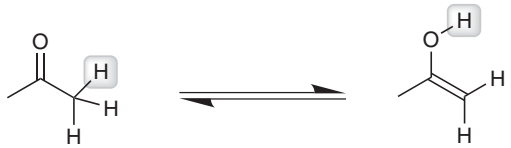
8.2 KETO-ENOL TAUTOMERISM

When a ketone has an alpha proton, there is an interesting thing that can happen. In the presence of either acid or base, the ketone exists in equilibrium with another compound:



This other compound is called an ***enol***, because it has a C═C bond ("ene") and an OH group ("ol"). The equilibrium shown above is actually very important, because you will see it in many mechanisms. So, let's take a closer look.

If we focus on the connections of atoms, we will find that the two compounds differ from each other in the placement of one proton. The ketone has the proton attached to an alpha carbon, and the enol has the proton connected to oxygen:



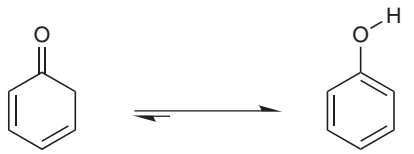
It is true that the π bond is also in a different location. But when we just focus on the atoms (which atoms are connected to which other atoms), we find that the difference is in the placement of just one proton. We have a special name to describe the relationship between compounds that differ from each other in the placement of just one proton. We call them *tautomers*. So, the enol above is said to be the *tautomer* of the ketone, and similarly, the ketone is the *tautomer* of the enol. The equilibrium shown above is called *keto-enol tautomerism*.

Keto-enol tautomerism is ***NOT*** resonance. The two compounds shown above are NOT two representations of the same compound. They are, in fact, different compounds. These two compounds are in equilibrium with each other.

In most cases, the equilibrium greatly favors the ketone:

This should make sense, because the last two chapters focused on the formation of C═O bonds as a driving force for reactions. A ketone has a C═O bond, but an enol does not. So we should not be surprised that the equilibrium favors the ketone.

There are some situations where the equilibrium can favor the enol. For example:

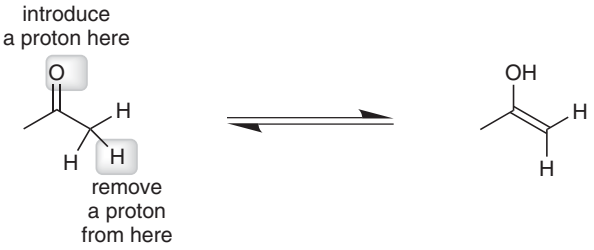


In this case, the enol is an aromatic compound, and it is much more stable than the ketone (which is not aromatic). There are many other situations where an enol can be more stable than its tautomer. You will probably find some of these examples in your textbook (such as 1,3-diketones). But in most cases (other than these few exceptional cases), the equilibrium will favor a ketone over an enol.

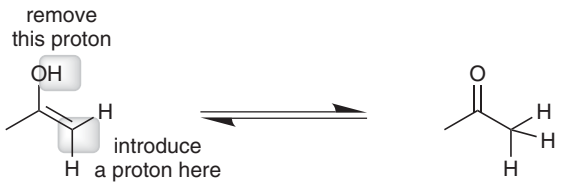
It is very hard (close to impossible) to prevent the equilibrium from being established. Imagine that you are performing a reaction that generates an enol as the product, and you take great efforts to remove all traces of acid or base. Your hope is that you can prevent the equilibrium from being established, so as to avoid the conversion of the enol into a ketone. But you will find that your efforts will likely be unsuccessful. Even trace amounts of acid or base adsorbed on the glassware (that you cannot remove) will allow the equilibrium to be established.

We will now explore a mechanism for keto-enol tautomerism. We said that compounds will tautomerize in the presence of either acid or base, so we will need to explore two mechanisms: one under *acidic* conditions, and one under *basic* conditions.

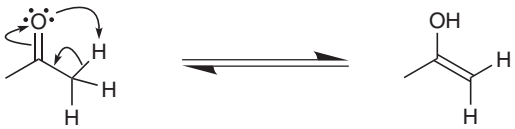
We saw that, by definition, tautomers will differ in the position of one proton. So, the conversion of a ketone into an enol requires two steps: 1) introduce a proton, and 2) remove a proton:



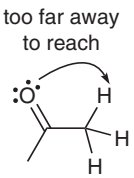
Similarly, the conversion of an enol into a ketone also requires the same two steps: 1) introduce a proton, and 2) remove a proton:



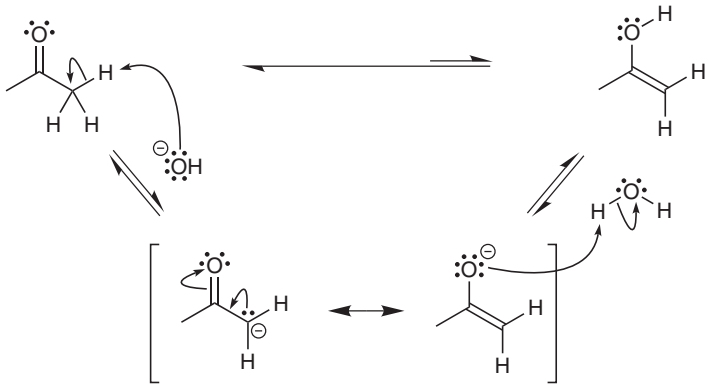
You might wonder why two separate steps are required. Why can't the proton just move over, in one step (in an intramolecular proton-transfer reaction), like this:



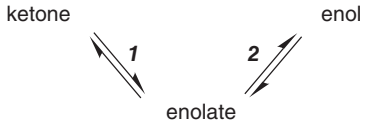
This doesn't work, because the oxygen atom is just too far away (in space) from the proton it is trying to remove:



The mechanism requires two separate proton transfer steps, but the order of these steps depends on the conditions. Under acidic conditions, the first step is protonation. But under basic conditions, the first step is deprotonation. Here is the mechanism under basic conditions:

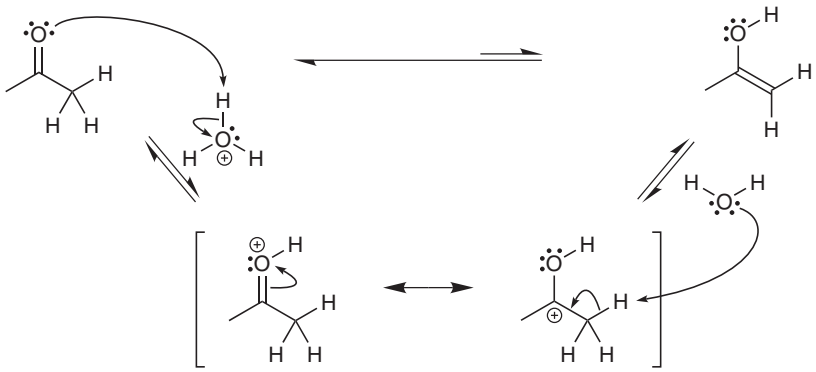


Notice that there is one intermediate (for which we must draw resonance structures), and this intermediate is negatively charged. If you look at the second resonance structure, it looks like an enol that is missing a proton. So, we call this intermediate an ***enolate***. Don't be fooled into thinking that the mechanism above has more than two steps. Resonance (of the intermediate) is NOT a step. Our mechanism only has two steps, like this:



The enolate is very important for the rest of this chapter, because it can function as a nucleophile. We will see many examples in the coming sections. For now, let's finish our discussion of keto-enol tautomerism.

In the mechanism above, the first step was deprotonation, because the conditions were basic. Under acidic conditions, the first step is protonation:

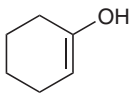


Once again, there are just two steps here. Don't be fooled by the resonance of the intermediate. Resonance is not a step. Resonance is just our way of dealing with the fact that we cannot draw the intermediate with only one drawing. We need two drawings to capture its character. And if you look at these resonance structures, you will see that this intermediate is positively charged.

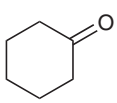
Notice the difference between these two mechanisms (acidic vs. basic conditions). The first mechanism (basic conditions) has a negatively charged intermediate, and the second mechanism (acidic conditions) has a positively charged intermediate. Other than that, the difference between these two mechanisms is pretty small. Each mechanism has only two steps. And both steps are just proton transfers. The only question is the sequence of events. Is it: deprotonate, then protonate? Or is it: protonate, then deprotonate?

When drawing the mechanism of a keto-enol tautomerization, we must look carefully at the conditions. In acidic conditions, protonation occurs first, giving a positively charged intermediate, which is consistent with acidic conditions. But in basic conditions, deprotonation occurs first, giving a negatively charged intermediate, which is consistent with basic conditions.

EXERCISE 8.8 It is not possible to isolate and purify the following compound, because upon formation, it will rapidly tautomerize to form a ketone. Draw a mechanism for the conversion of this enol into a ketone under acidic conditions.

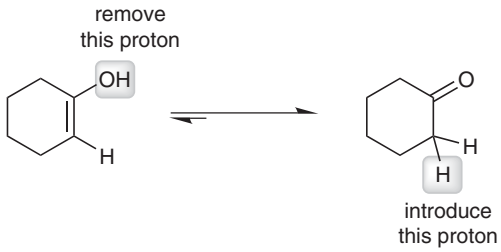


Answer This compound is an enol, and its tautomer will be the following ketone:

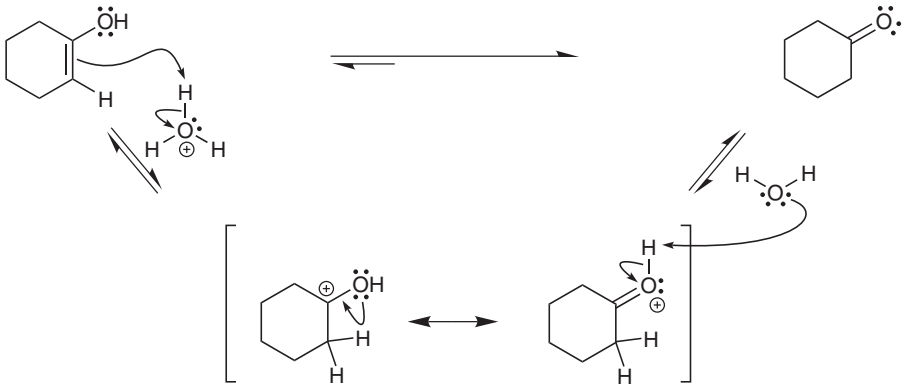


To convert the enol into a ketone, our mechanism will have two steps: protonate and deprotonate. But we must decide what order to use. Do we first protonate? Or do we first deprotonate? To answer this question, we look at the conditions. Since we are in acidic conditions, we should first protonate (forming a positively charged intermediate), and only then do we remove the other proton.

Now that we have determined the order of events, we must also decide ***where*** to protonate, and ***where*** to deprotonate. To figure this out, we look at the overall reaction:



When we analyze the reaction like this, it is easy to see ***where*** to introduce a proton and ***where*** to remove a proton. This might seem trivial, but it is extremely important because it showed us that we must protonate the double bond (rather than protonating the oxygen atom), like this:



So often, students will start this problem by protonating the OH group. Although that might make sense at first, you will find that this step will NOT lead to formation of the ketone. The first step is to protonate the double bond; ***not*** the OH group. Think about why this is the case. Protonation of the double bond leads to a resonance-stabilized intermediate, while protonation of the OH group would lead to an intermediate that is not resonance-stabilized (and therefore higher in energy).

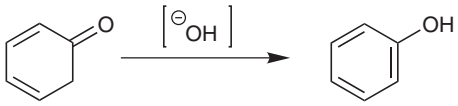
When drawing a mechanism, make sure to never use HO^- and H_3O^+ in the same mechanism. When acidic conditions are indicated, use H_3O^+ to protonate and use $\boldsymbol{H_2O}$ to deprotonate. Don't use hydroxide to remove a proton, because there are not many hydroxide ions present under acidic conditions.

Similarly, when basic conditions are indicated, use HO^- to remove the proton and use $\boldsymbol{H_2O}$ to protonate. Don't use H_3O^+ to protonate, because we are in basic conditions. Here is the take home message: always stay consistent with your conditions.

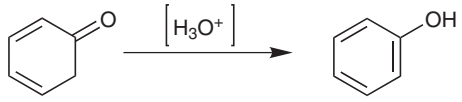
So, to recap, there are three things to consider in order to correctly draw the mechanism of a keto-enol tautomerization: 1) what ***order*** to use (first protonate or first deprotonate), 2) ***where*** to protonate and where to deprotonate, and 3) ***what reagents*** to show when drawing the proton transfer steps (stay consistent with the conditions).

PROBLEMS For each of the following transformations, propose a mechanism that is consistent with the conditions indicated (you will need a separate piece of paper to record your answers):

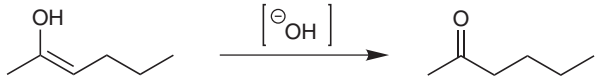
8.9



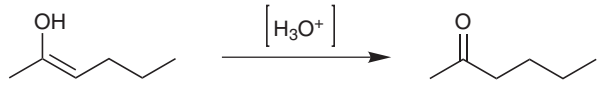
8.10



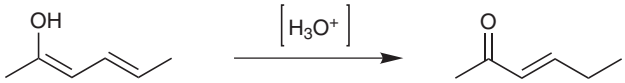
8.11



8.12



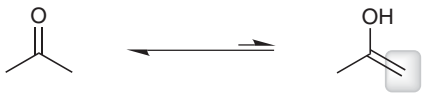
8.13 Propose a plausible mechanism for the following keto-enol tautomerization. Remember to ask three important questions: 1) what ***order*** to use (first protonate or first deprotonate), and 2) ***where*** to protonate and deprotonate, and 3) ***what reagents*** to show for each step of the mechanism. You will need a separate piece of paper to record your answer.



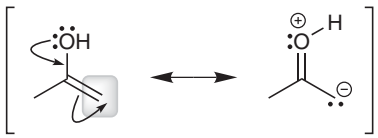
8.3 REACTIONS INVOLVING ENOLS

It is hard to see how the alpha carbon of a ketone can be nucleophilic:

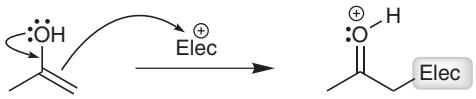
The alpha carbon does ***not*** have a lone pair or a π bond that can function as a nucleophilic center. However, when we examine the structure of the enol (that is in equilibrium with the ketone), we get a different picture:



The enol has a π bond on the alpha carbon, which renders it nucleophilic. Also, consider the resonance structure of the enol:



Notice that there is a negative charge on the alpha position, and therefore, the alpha carbon can function as a nucleophile to attack some electrophile:



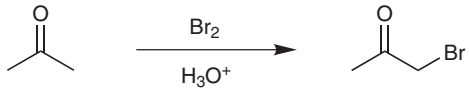
In order for the attack to occur, we are relying on the ability of a ketone to tautomerize. But, not every ketone will exist in equilibrium with an enol. A ketone that lacks alpha protons will ***not*** tautomerize to form an enol:

No proton to remove here

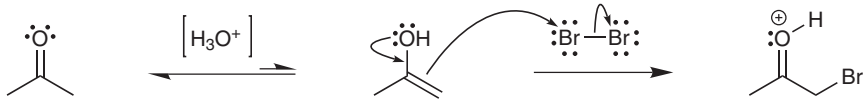
NEVER draw a carbon atom with five bonds

Most ketones do in fact have alpha protons, and therefore, a typical ketone will exist in equilibrium with an enol. In the previous section, we saw some rare cases where the equilibrium can actually favor the enol, but in general, the equilibrium favors the ketone. Therefore, you will generally only have trace amounts of the enol present in equilibrium with the ketone.

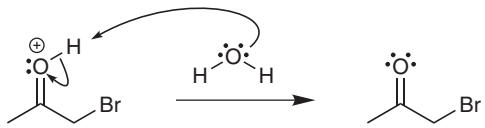
This small amount of enol is able to react as a nucleophile and attack some electrophile. After the enol attacks the electrophile, the keto-enol equilibrium is re-established by producing some more enol (to account for the enol that "disappeared" as a result of the reaction). Slowly but surely, most of the ketone molecules end up converting into enols and reacting with the electrophile. One example is alpha-halogenation, which can occur when a ketone is treated with Br_2 in aqueous acid (H_3O^+) to generate an α-halo ketone:



Let's explore how this process occurs. The ketone tautomerizes to generate a small amount of enol. Then comes the critical step: the enol functions as a nucleophile to attack Br_2 (the electrophile):

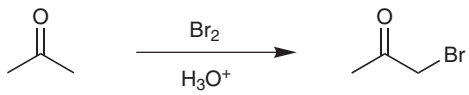


Deprotonation then generates the product:

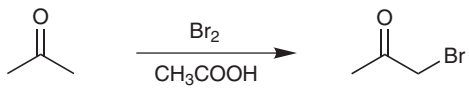


Notice that most of the steps in this mechanism are just proton transfers. Our mechanism represents the following pattern: tautomerize, attack, deprotonate. But "tautomerize" is just a new name for a special combination of two proton transfer steps. There is really only one step where an attack takes place (when the enol attacks the electrophile).

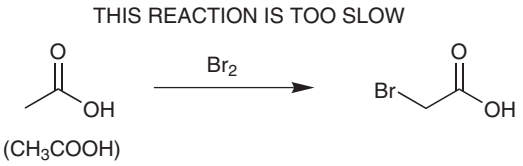
In the end, this provides a method for installing a halogen at the alpha position of a ketone:



Alternatively, we might see a different reagent other than H_3O^+, for example:

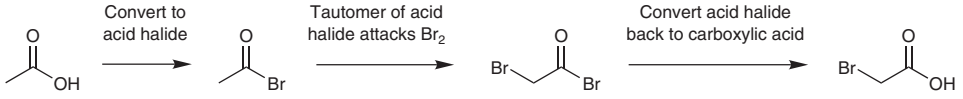


Acetic acid, CH_3COOH, can be used as a mild acid to facilitate the tautomerization. We don't have to worry about this acid undergoing halogenation itself (at its alpha position), like this:



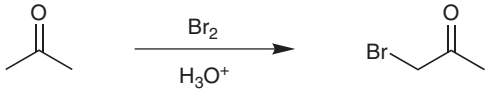
We don't have to worry about this, because carboxylic acids are much slower to react in this kind of reaction.

If we ***want*** to halogenate the alpha position *of a carboxylic acid*, it is possible, but it will require some extra steps. First, we must convert the carboxylic acid into an acid halide. We do this because the enol of an acid halide will rapidly attack a halogen. Then, in the end, we just convert the acid halide back into a carboxylic acid:

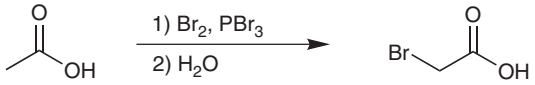


This strategy (for halogenating carboxylic acids) is called the Hell–Volhard–Zelinsky reaction.

Here is the bottom line: in this section, we have seen two reactions that exploit the nucleophilic nature of enols. These reactions can be used to install a halogen at the alpha position of a ketone,

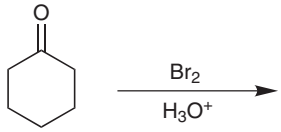


or to install a halogen at the alpha position of a carboxylic acid:

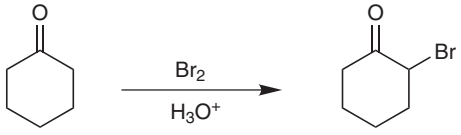


Notice the reagents that we used. For halogenation of a ketone, the reagents were Br_2 in acidic conditions. But to halogenate a carboxylic acid, we use a different set of reagents. We use Br_2 and PBr_3, followed by H_2O. The function of Br_2 and PBr_3 is to make the acid halide, form the enol, and then have the enol attack Br_2. Then, water is used in the last step to convert the acid halide back into a carboxylic acid.

EXERCISE 8.14 Predict the product of the following reaction:

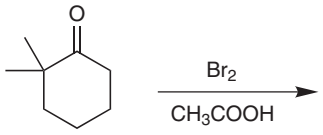


Answer We are starting with a ketone, and we are subjecting it to Br_2 in acidic conditions. The acid promotes tautomerization to the enol, which then attacks the Br_2 in an alpha halogenation. So, in the end, our product will have a Br at one of the alpha positions. Either side is the same, so we can just pick a side:

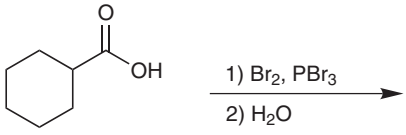


PROBLEMS Predict the products of each of the following reactions. Remember that you can only halogenate an alpha position that has protons.

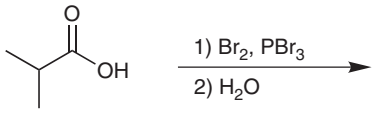
8.15



8.16



8.17



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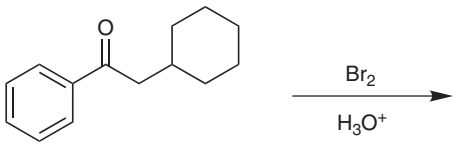
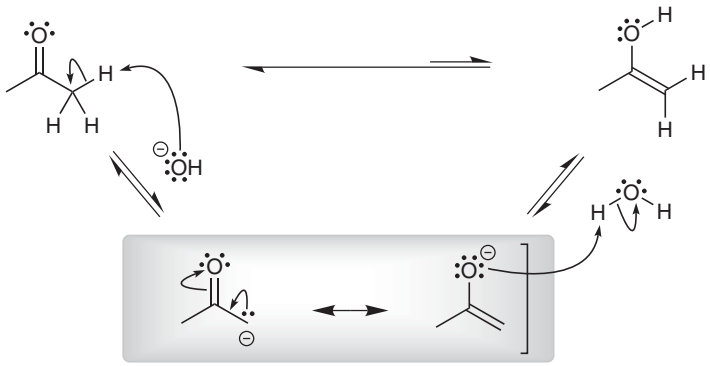
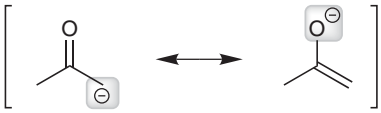


8.4 MAKING ENOLATES

In the previous section, we saw that enols can be nucleophilic. But enols are only mild nucleophiles. So, the question is: how can we make the alpha position even more nucleophilic (so that we can have a broader range of possible reactions)? There is a way to do this. We just need to give the alpha position a negative charge. To see how this can be achieved, let's quickly review the mechanism we saw for tautomerization under basic conditions, and let's focus on the intermediate (highlighted below):



The intermediate is negatively charged, and we mentioned before that it is called an enolate. In order to capture the essence of the enolate, we must draw resonance structures. Remember what resonance structures represent. We cannot draw this ***one*** intermediate with any single drawing, so we draw two drawings, and we meld these two images together in our minds in order to get a better picture of this intermediate. And that picture shows the enolate as being electron rich in two locations: the alpha carbon ***and*** the oxygen atom:



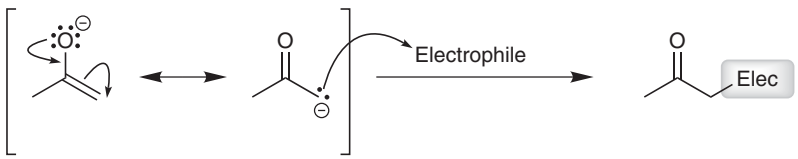
enolate

So, we expect ***both*** of these locations to be very nucleophilic. Nevertheless, we won't explore any reactions in which the oxygen atom functions as a nucleophile (called O-attack). Most textbooks and instructors do not teach the conditions for O-attack, because reactions at that site are far less common than reactions at the alpha carbon. So, from now on, we will only explore examples of C-attack (where the alpha carbon acts as the nucleophile, attacking some electrophile):

Notice that, in showing the attack, we have drawn only one resonance structure of the enolate. If we had used the other resonance structure, it would have looked like this:

This is just another way of showing the same step. Many textbooks will show it the second way (starting with the resonance form that has the negative charge on oxygen). Perhaps this is more appropriate, because this resonance form is contributing more to the overall character of the enolate. However, in this book, we will use the resonance structure where the negative charge is on carbon:

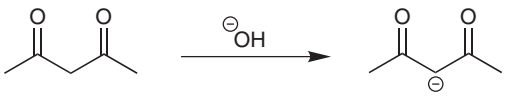
We will do it this way, because it will make the mechanisms easier to follow. To be absolutely correct, we should actually draw *both* resonance forms, like this:



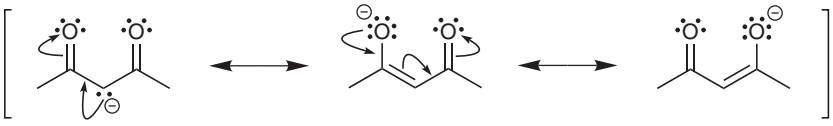
But for simplicity, we will just show one resonance structure for the enolate (in most of the mechanisms that we will see in this chapter).

Now let's think about what kind of base we would need ***to make*** an enolate. If we use bases such as HO^- or RO^- (bases with a negative charge on oxygen), we find that these bases are *not* strong enough to completely convert the ketone into an enolate. Rather, an equilibrium is established between the ketone and enolate. This equilibrium only produces very small amounts of the enolate, but that doesn't matter. Once an enolate reacts with an electrophile, the equilibrium produces more enolate to replenish the supply. Over time, all of the ketone can convert into the enolate and then react with some electrophile. This is very similar to the situation we saw with enols. Once again, we are relying on the equilibrium to continuously produce more of the enolate. The major difference here is that enolates are so much more reactive than enols. Therefore, the chemistry of enolates is more robust than the chemistry of enols.

As an example for the richness of enolate chemistry, consider this: some enolates are much more stabilized than other enolates. These "stabilized" enolates are more "tame" nucelophiles (more selective in what they react with). For example, a compound with two carbonyl groups (separated by one carbon) can be deprotonated to form an intermediate described as a "stabilized" enolate:



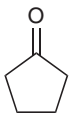
The negative charge in this intermediate is delocalized over both carbonyl groups:



And therefore it is extremely stable. In fact, it is even more stable than HO^- or RO^-. So, when we use bases such as HO^- or RO^-, the equilibrium greatly favors the enolate:

We will soon see that the position of this equilibrium will be a driving force in the Claisen condensation (later in this chapter).

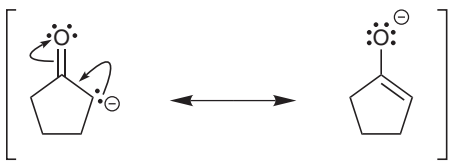
EXERCISE 8.19 Consider the following compound:



Draw the enolate that is formed when this compound is deprotonated. Make sure to draw all resonance structures.

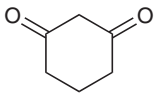
Answer We just need to identify the alpha proton, and then remove it:

And then we draw the resonance structures:

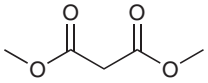


PROBLEMS Draw the enolate that would be generated when each of the following compounds is treated with hydroxide. Make sure to draw all significant resonance structures.

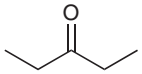
8.20



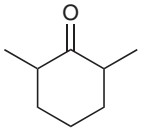
8.21



8.22



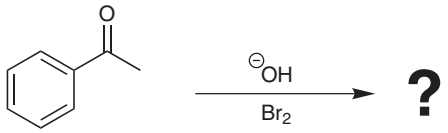
8.23



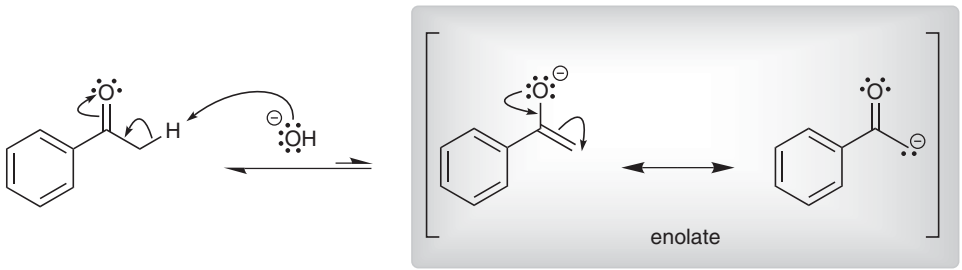
8.5 HALOFORM REACTION

In the previous section, we learned how to make enolates. Now, we will begin to see what an enolate can attack. In this section, we will explore the reaction between an enolate and a halogen (such as Br, Cl, or I). In the following sections, we will explore the reactions between an enolate and other electrophiles.

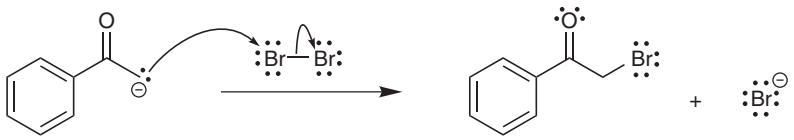
Consider what might happen under the following conditions:



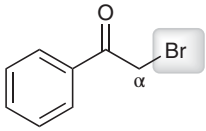
We have a ketone and hydroxide, which means that the equilibrium will involve a small amount of enolate:



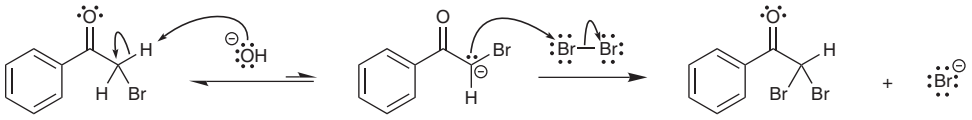
This enolate is formed in the presence of Br_2, which can function as an electrophile. The initial product is not surprising:



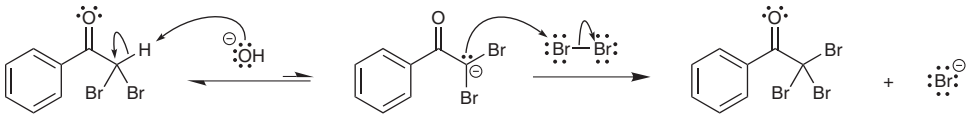
The enolate attacks Br_2 and expels Br^- as a leaving group. The result is that we have installed a bromine atom at the alpha position:



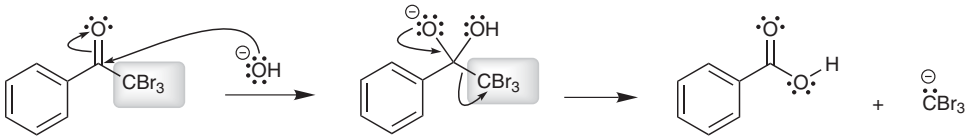
But the reaction doesn't stop there. Remember that the base (hydroxide) is still present in solution. So hydroxide can remove another alpha proton. In fact, it is even easier to remove this proton, because the inductive effect of the bromine atom serves to further stabilize the resulting enolate, which can then attack Br_2 again:



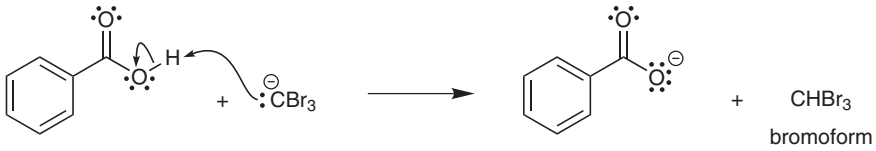
Now we have ***two*** Br atoms in our compound. And then, it happens again:



Think about what has happened so far. A methyl group (CH_3) group has been converted into a CBr_3 group. This transformation is very significant, because a CBr_3 group is able to function as a leaving group:

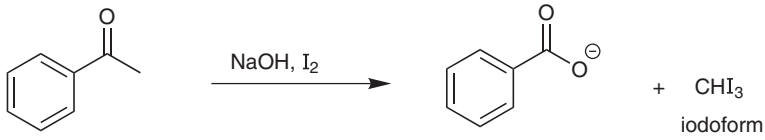


At this point, you should be feeling uncomfortable. You probably remember our golden rule from the previous chapters (don't expel H^- or C^-), and it seems as though we are breaking our golden rule. Aren't we kicking off a C^- here? Yes, we are. This is actually one of the rare exceptions to the golden rule. In general, the golden rule holds true ***most*** of the time, because C^- is generally too unstable to serve as a leaving group. But there are cases where a C^- can be stabilized enough for it to serve as a leaving group, and this is one of those rare situations. Br_3C^- is actually a pretty good leaving group, because of the combined electron-withdrawing effects of all three bromine atoms. In addition, the loss of this leaving group is driven by the formation of the stable carbonyl group. But even though it can leave, it is not the most stable anion on the planet. In fact, it is not even as stable as a carboxylate ion (the conjugate base of a carboxylic acid). So, the following proton transfer occurs:



This forms a carboxylate anion and $CHBr_3$ (called bromoform). And this is the end of our mechanism. If we want to isolate the carboxylic acid, we will have to introduce a source of protons into the reaction flask in order to protonate the carboxylate anion.

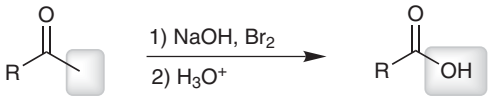
When the same reaction is performed with iodine instead of bromine, iodoform is obtained as a by-product, instead of bromoform:



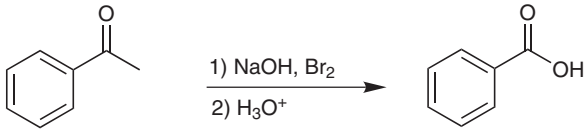
Iodoform is a yellow solid that will precipitate out of solution. Therefore, this reaction can be used to probe the identity of an unknown compound. If the unknown compound is a methyl ketone, then it will produce iodoform under these conditions (NaOH and I_2). This

iodoform test is not really used anymore (we now have spectroscopy techniques that give us this information and much, much more). So, this chemical test is really a relic of the past. But for some reason, it is still used in textbook problems. You will usually see it like this: "An unknown compound tests positive for iodoform, and ...." The beginning of this problem is telling you that you have a methyl ketone. If you see this in a problem in your textbook, you should know what it means.

But there is a much more important use for this reaction. You can use it when solving synthesis problems. This reaction provides a way to convert a methyl ketone into a carboxylic acid:

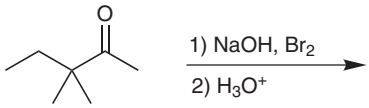


The haloform reaction is most efficient when the other side of the ketone has no α protons, for example.

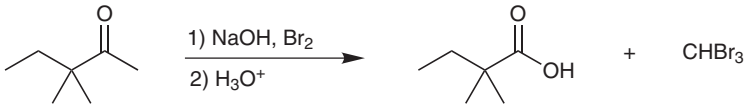


This should stick out in your mind, because it is a new example of a "cross-over" reaction. In the previous chapter, we talked about ways of converting ketones into carboxylic acid derivatives (cross-over reactions). The process that we explored in this section can be used to convert a methyl ketone into a carboxylic acid. You should add this to your synthetic toolbox.

EXERCISE 8.24 Predict the products of the following reaction:

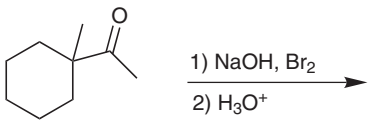


Answer The reactant is a methyl ketone and the reagents will convert a methyl ketone into a carboxylic acid (with a by-product of bromoform):

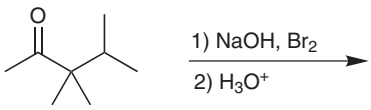


PROBLEMS Predict the products for each of the following reactions:

8.25



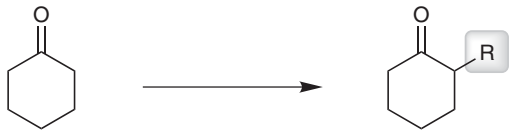
8.26



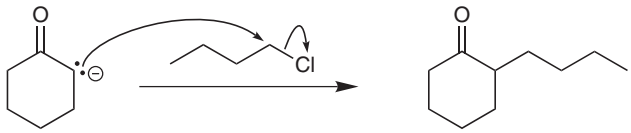
8.27 On a separate piece of paper, draw a mechanism for the transformation in the previous Problem (8.26).

8.6 ALKYLATION OF ENOLATES

In this section, we will continue to explore reactions between enolates and electrophiles. Specifically, we will learn how to install an alkyl group at an alpha position:

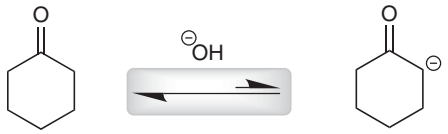


In order to alkylate the alpha position, it makes sense to use an enolate to attack an alkyl halide, for example:



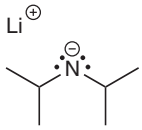
This is just an S_N2 reaction, so it should work with ***primary*** alkyl halides (if a secondary alkyl halide is used, the enolate will function as a base, and elimination will be favored over substitution).

But we run into a major obstacle when we try to make the enolate by treating a ketone with hydroxide. Remember that when we use hydroxide as the base to form our enolate, we find that the equilibrium lies very far to the side of the ketone:

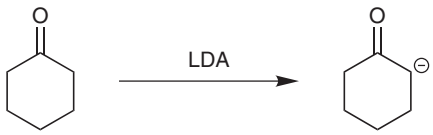


At equilibrium, there is a very small amount of enolate, but there is a lot of ketone and a lot of hydroxide present. So, if we introduce some alkyl halide into the reaction flask, we run into a major obstacle. The excess hydroxide can react with the alkyl halide (elimination or substitution), which creates competing side reactions that generate a mixture of undesired products.

In order to avoid this problem, we will need to form the enolate under conditions where most of the ketone molecules are converted into enolates. If we are able to do this, we will have very little base left over, and therefore, we won't have to worry about the base reacting with the alkyl halide. It is possible to do this, but we will need to use a base that is much stronger than the bases we have been using so far (HO^- and RO^-). We can use the following base instead:

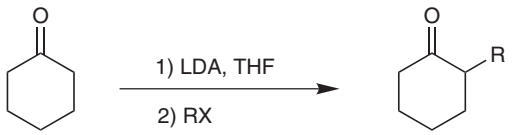


The name of this compound is lithium diisopropylamide, or LDA for short. LDA is a very strong base, because the negative charge is on a nitrogen atom (which is less stable than a negative charge on an oxygen atom). The two isopropyl groups are sterically bulky, so LDA is ***not*** a good nucleophile. LDA is primarily used as a strong, sterically hindered base, which is exactly what we need in our situation. By using LDA, we can achieve an efficient conversion of the ketone into the enolate.



So, we will have mostly enolates in our reaction flask (and very little ketone or base). Now when we introduce some alkyl halide into our reaction flask, the risk of competing side reactions is greatly reduced.

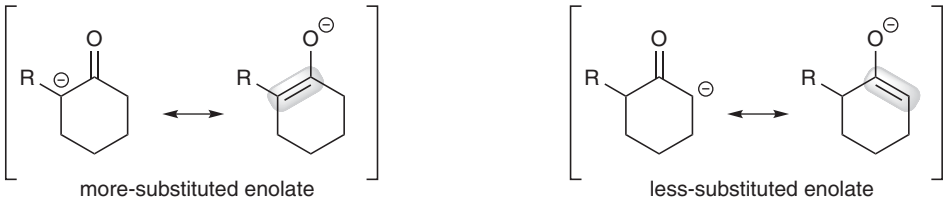
So, to alkylate a ketone, we use the following reagents:



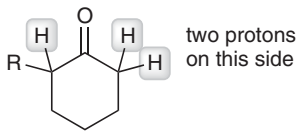
In step 1, we use LDA to deprotonate the ketone, to form an enolate. When you see THF in the reagents above, don't get confused. THF (tetrahydrofuran) is just the solvent that is typically used with LDA. In step 2 above, we use an alkyl halide (RX) to install the alkyl group, where R is some primary alkyl group, and X is a halogen (Cl, Br, or I).

In the situation above, the starting ketone was symmetrical. But what happens when we start with an unsymmetrical ketone? For example, consider the following situation:

Where will the incoming alkyl group be installed? On the left side, or on the right? In order to answer this question, we need to take a close look at the two possible enolates:



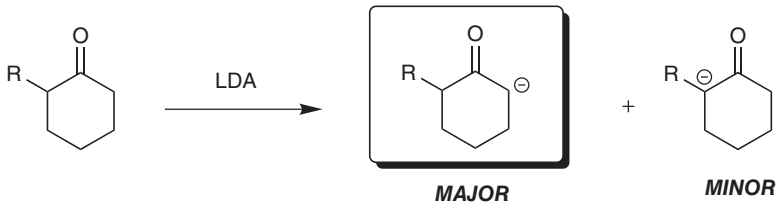
The more-substituted enolate (above left) is the more stable enolate because it has a more substituted pi bond. However, the less-substituted enolate (above right) can form faster, because there are twice as many protons available on the less-substituted side:



So from a probability point of view, we expect the less-substituted enolate to form more rapidly. Also, we expect the sterically hindered base to have a much easier time removing one of these protons. So, we have two competing arguments:

This is a classic example of thermodynamics vs. kinetics. Thermodynamics is all about stability and energy levels. So, a thermodynamic argument says that we should predominantly form the more stable enolate. However, a kinetic argument tells us to expect the other enolate,

simply because it forms faster. Which argument wins? The truth is that a mixture of products is observed. But with LDA at low temperature, there is a clear preference to form the kinetic enolate:

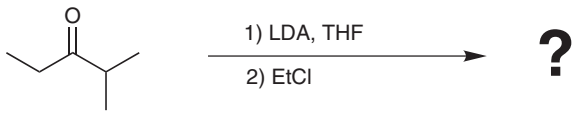


When we introduce the alkyl halide to the reaction flask, alkylation will occur primarily at the less-substituted alpha position:

That works very well if we ***want*** to install the alkyl group at the less-substituted position. But what if we want to install the alkyl group at the more-substituted position? In other words, what if we want to do this:

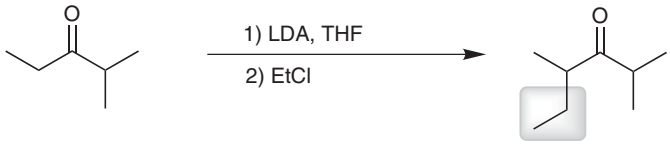
There are many different ways to achieve this transformation. Essentially, you need to form the thermodynamic enolate, rather than the kinetic enolate. Some textbooks will teach one or two ways to do this, while other textbooks will skip it altogether. You should look through your textbook and lecture notes to see if you are responsible for knowing how to alkylate the more-substituted side.

EXERCISE 8.28 Predict the major product of the following reaction:



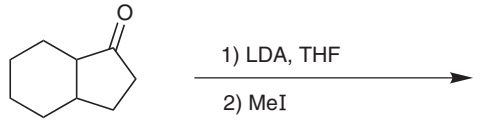
Answer This is an alkylation reaction. In step 1, we are using LDA to form an enolate. And then in step 2, we are using an alkyl halide to alkylate.

Because the alkyl halide is ethyl chloride in this case, we will be installing an ethyl group on an alpha carbon. The only question is: which alpha carbon? The more-substituted carbon or the less-substituted carbon? The use of LDA as our base predominantly gives the kinetic enolate (the less-substituted enolate). Therefore, our major product will have the ethyl group at the less-substituted alpha position:

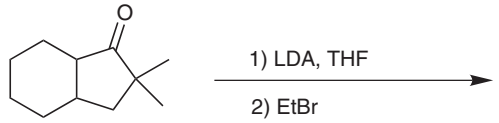


PROBLEMS Predict the major product for each of the following reactions:

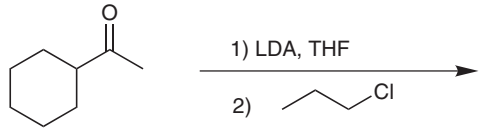
8.29



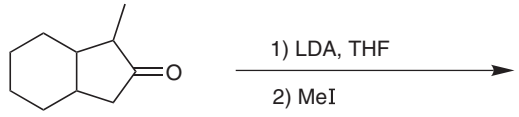
8.30



8.31

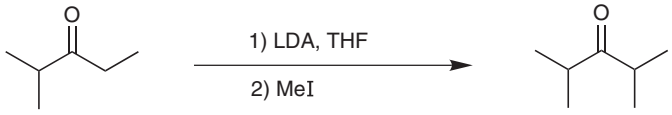


8.32



EXERCISE 8.33 What reagents would you use to achieve the following transformation:

Answer If we look at the difference between the starting material and the product, we will see that there is an extra methyl group that was introduced at an alpha position. This methyl group was installed at the less substituted position, which can be achieved by treating the ketone with LDA, followed by methyl iodide:

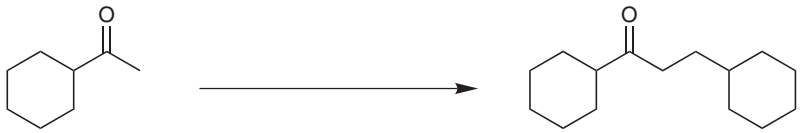


PROBLEMS Identify reagents that can be used to achieve each of the following transformations:

8.34

8.35

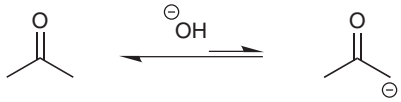
8.36



8.7 ALDOL REACTIONS

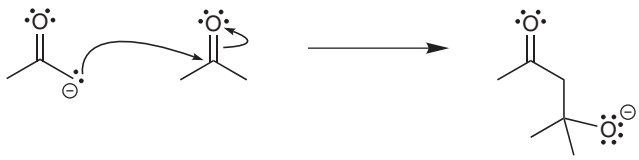
So far in this chapter, we have learned how to make enolates, and we have used them to attack various electrophiles (including halogens and alkyl halides). In this section, we will explore what happens when an enolate attacks a ketone or aldehyde.

Suppose we start with a simple ketone, and we subject it to basic conditions, using hydroxide as a base. We have already seen that an equilibrium will be established between the ketone and the enolate:

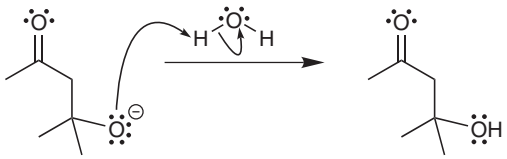


If we do this in the presence of an electrophile, the enolate can attack the electrophile. And then the equilibrium will produce more enolate to replenish the supply. But what if we do not add any other electrophiles to the reaction mixture? What if we just treat the ketone with hydroxide?

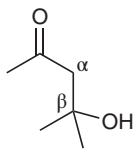
It turns out that there actually is an electrophile present. We said that the enolate is in equilibrium with the ketone (and there is a lot of ketone present). Well, ketones are electrophilic, aren't they? We devoted an entire chapter to the reactions that take place when ketones get attacked. So, what happens when an enolate attacks a ketone?



The enolate attacks the ketone, forming an alkoxide intermediate. Now, our golden rule tells us to try and re-form the carbonyl group, but don't expel H^- or C^-. In this case, we have no leaving groups that can be expelled. So, the only way to remove the charge is to protonate. In these basic conditions, the proton source is water (not H_3O^+, because the concentration of H_3O^+ is insignificant in basic conditions):

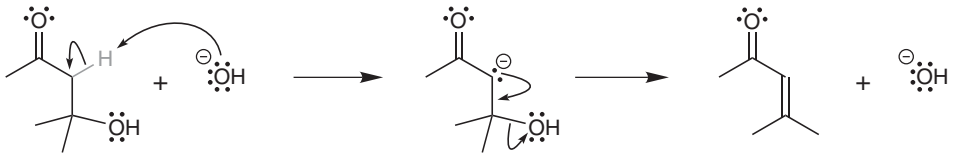


This is the initial product of this reaction. Notice that the OH group is at the β position relative to the surviving carbonyl group:



This will always be the case whenever an enolate attacks a carbonyl group, regardless of the structure of the starting ketone and the structure of the enolate. The alpha carbon of the enolate is directly attacking the carbonyl group of the ketone. That will always place the OH group in the beta position. Always. This product is called a *β-hydroxy ketone*, and the reaction is called an ***aldol*** addition.

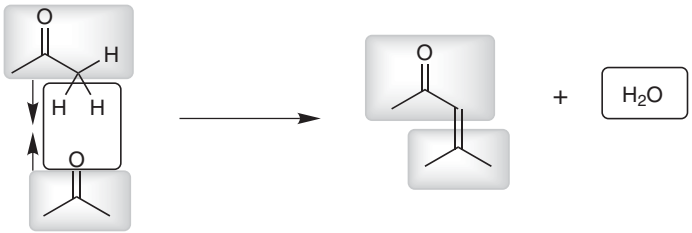
In general, the reaction doesn't stop there (at the β-hydroxy ketone). With heating, the basic conditions favor an elimination to form a double bond:



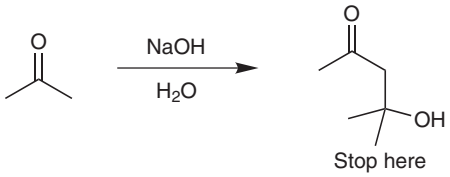
This product has a double bond in conjugation with the carbonyl group. The double bond is located between the α and β positions. So, the product is called an *α,β-unsaturated ketone*.

In the laboratory, we can often control how far the reaction goes. By carefully controlling the conditions of the reaction (temperature, concentrations, etc.), we can usually control whether the reaction stops at a *β-hydroxy ketone*, or whether it continues to form an *α,β-unsaturated ketone*.

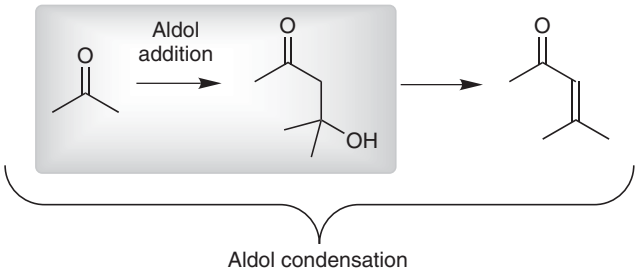
But you should be familiar with the proper terminology. When we go all the way to the *α,β-unsaturated ketone*, we call the reaction an aldol ***condensation***. By definition, a condensation is any reaction where two molecules come together, and in the process, a small molecule is liberated. The small molecule can be N_2 or CO_2 or H_2O, etc. In this case, we have two molecules of ketone coming together, and in the process, a molecule of water is liberated:



Therefore, we call this reaction an aldol ***condensation***. But what if we control the reaction conditions so that we stop at the *β-hydroxy ketone?*

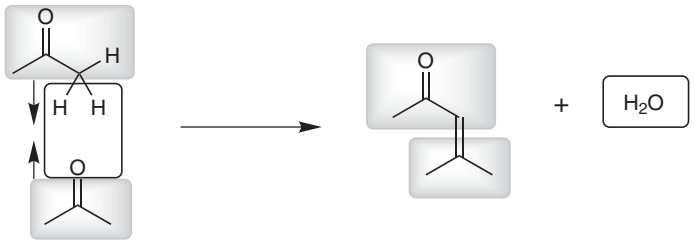


If we stop here, then we cannot call it a condensation reaction anymore, because a water molecule was not lost in the process. So, instead, we call it an aldol addition. The difference between an aldol ***condensation*** and an aldol ***addition*** is how far we go in the process:



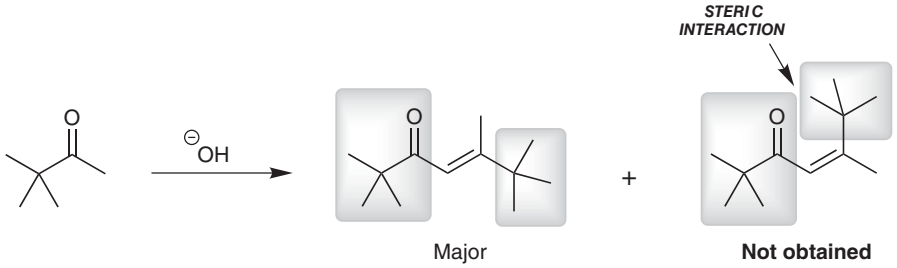
This distinction (between the aldol *addition* and the aldol *condensation*) is often absent in textbooks, and you might find the terms being used interchangeably in your textbook. I am taking the time to point out the distinction, because I believe that it will help you to remember and master the mechanism.

The mechanism of an aldol condensation is fairly straightforward. But sometimes, it can get hard to see what reagents to use when proposing a synthesis. So try to think of it the way we showed it just a few moments ago:



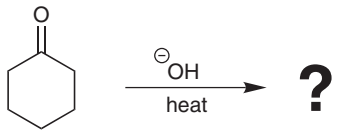
We are removing two alpha protons from one ketone, and we are removing the oxygen atom from the other ketone. Do ***not*** confuse the drawing above with a mechanism. A mechanism is when you show all of the curved arrows and intermediates. But this way of thinking about the reaction might come in handy when proposing syntheses.

In a case where two stereoisomers are expected, the major product will be the one that exhibits fewer steric interactions, for example:



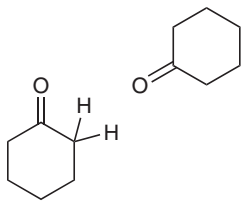
Let's get some practice:

EXERCISE 8.37 Draw the aldol condensation product that is obtained when the following compound is heated in the presence of hydroxide ions:

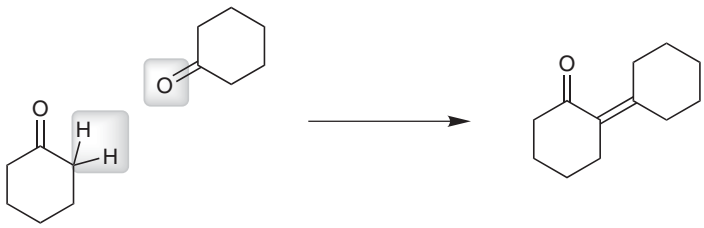


Answer We can certainly work through the mechanism to get the answer, and we will soon get practice with that. But for now, let's just make sure that we can use our simple method for drawing the expected product.

We start by drawing two molecules of the ketone, so that the oxygen of one ketone is pointing directly at the alpha protons of the other ketone:



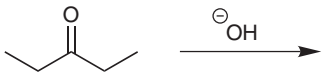
Then, we erase the two alpha protons and the oxygen atom, and we push the fragments together (connecting them with a double bond):



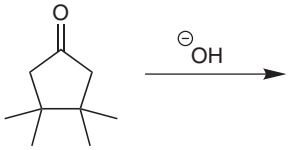
That's all there is to it. It is an efficient way of drawing the product.

PROBLEMS Predict the major product for each of the following reactions. In each case, assume that a condensation takes place, and draw the α,β-unsaturated ketone that is produced.

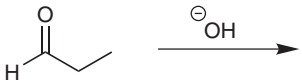
8.38



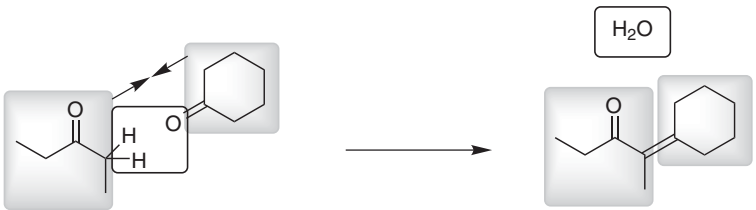
8.39



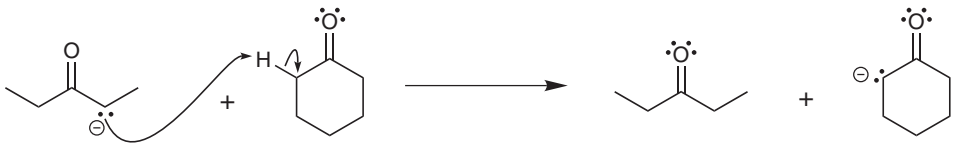
8.40



In all of the aldol condensations that we have seen so far, two molecules *of the same ketone* (or aldehyde) were reacting with each other. One molecule of ketone was deprotonated to give an enolate, which then attacked another molecule of the same ketone. But what if we had used two different ketones? For example, what if we try to do this:

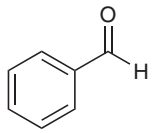


Notice that the ketones are different from each other. We call this a ***crossed***-aldol. This can work, but care must be taken to avoid generating many different products. To see why this is the case, we must realize that it is possible for enolates and ketones to exchange protons:

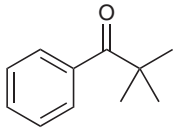


So, you can't really control which ketone will be converted into the enolate. This means that there will be more than one type of enolate and more than one type of ketone present in solution. So there are a number of possible reactions that can take place, and this will give a mixture of undesired products.

So, practically, it is important to try to avoid these types of situations. There is one very easy way to avoid this issue. If one of the ketones has no alpha protons, then it cannot form an enolate. For example, consider the following compound:

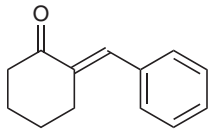


This compound, called benzaldehyde, has no alpha protons. Therefore, it cannot be converted into an enolate. It will just wait to be attacked. Here is another example of a compound with no alpha protons:

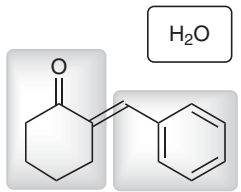


So, one way to achieve a crossed aldol is to make sure that one of the reagents has no alpha protons. That will minimize the number of potential products. Your textbook may or may not show methods for achieving a crossed aldol where both starting ketones have alpha protons. You should look through your textbook and lecture notes to see if you are responsible for such methods.

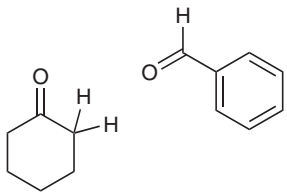
EXERCISE 8.41 Identify the starting materials that you would use to make the following compound, using an aldol condensation:



Answer We can use the same method we used earlier. We just need to do it in reverse. We break the molecule apart into two fragments in order to insert water. We break it apart at the C═C bond:

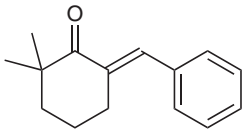


And we just have to decide which fragment gets the oxygen atom and which fragment gets the protons. The fragment on the left already has a carbonyl group, so that fragment must get the two alpha protons. The fragment on the right will get a carbonyl group in place of the C═C bond:

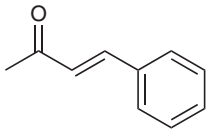


PROBLEMS Identify the starting materials that you would use to make each of the following compounds (using an aldol condensation):

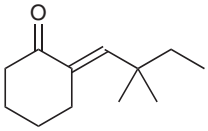
8.42



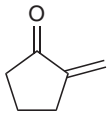
8.43



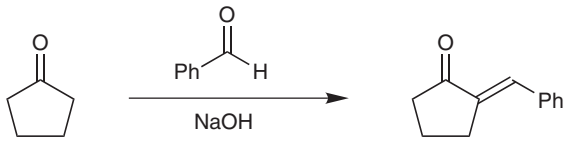
8.44



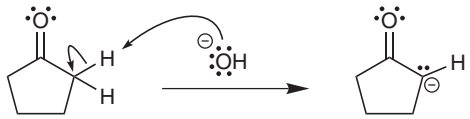
8.45



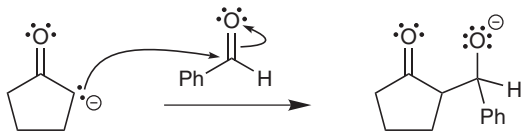
EXERCISE 8.46 Propose a plausible mechanism for the following transformation:



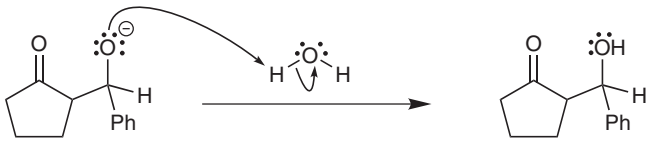
Answer In the first step, hydroxide functions as a base and removes an alpha proton to generate an enolate:



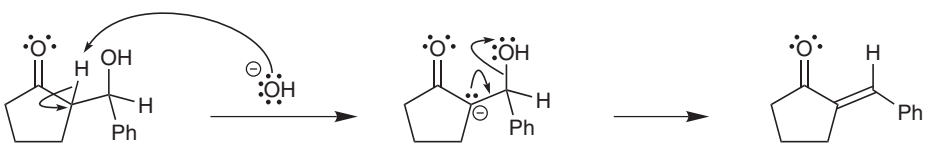
Then, this enolate can function as a nucleophile and attack benzaldehyde:



Water then functions as a proton source to generate the β-hydroxy ketone:

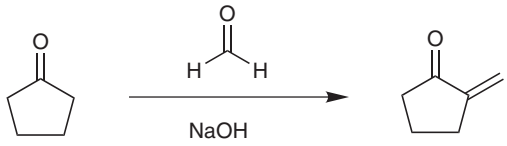


Finally, water is eliminated to generate the α,β-unsaturated ketone:

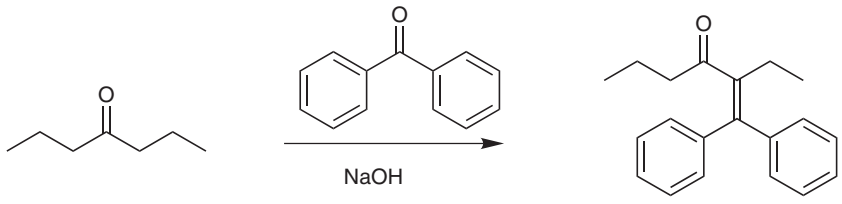


PROBLEMS Now let's get some practice drawing mechanisms for aldol condensations. Draw a mechanism for each of the following transformations. You will need a separate piece of paper to record each of your answers:

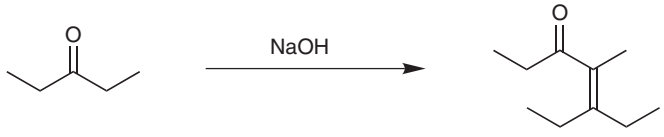
8.47



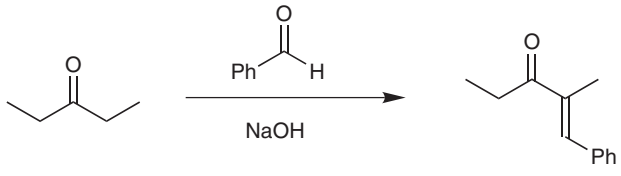
8.48



8.49



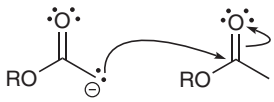
8.50



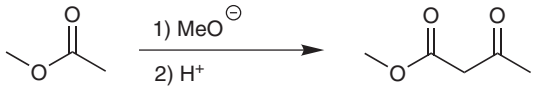
8.8 CLAISEN CONDENSATION

In the previous section, we saw that an enolate can attack a ketone:

In this section, we will explore what happens when an ***ester enolate*** attacks an ester:

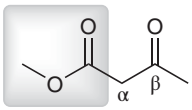


An ester enolate is similar to a regular enolate: an ester enolate is nucleophilic, and it will also attack a carbonyl group. When an ester enolate attacks an ester (shown above), the reaction that takes place is called a Claisen condensation. Here is the overall transformation:



The product is called a β-keto ester:

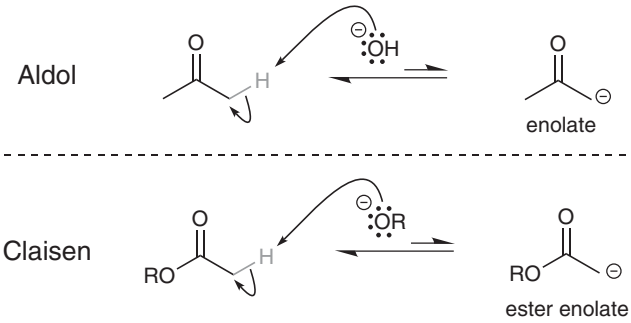
The ester gets priority over the other carbonyl, so we label the carbon atoms (α, β, γ, etc.) moving away ***from the ester***



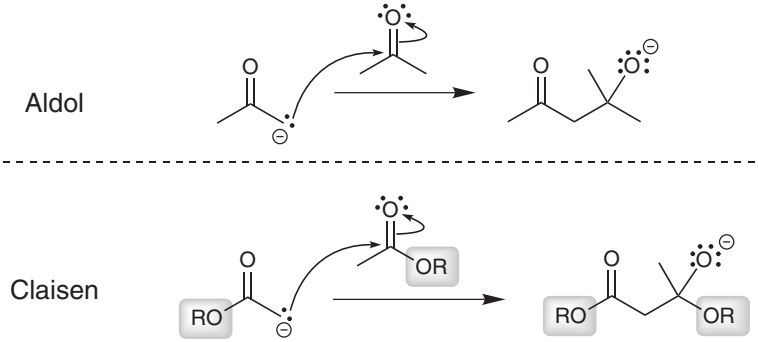
The "keto" group is located at the *beta* position

At first glance, this product seems very different from the α,β-unsaturated ketones obtained from aldol condensations. But when we explore the mechanism, we will see the parallel between the aldol and Claisen condensations.

Let's start with the first step: preparing the enolate:

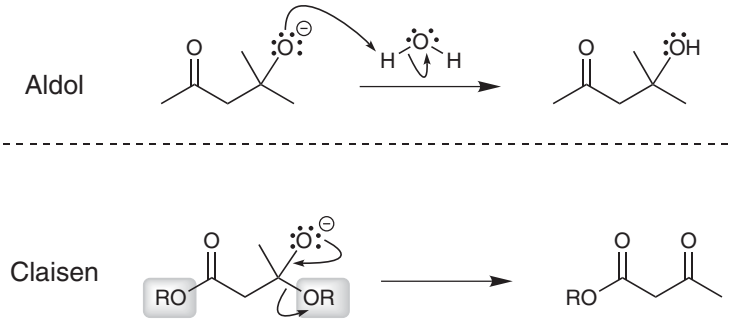


So far, both mechanisms are almost identical. The only difference is the choice of base (the aldol condensation uses hydroxide, and the Claisen condensation uses an alkoxide), and we will discuss the reason for this shortly. For now, let's continue comparing the mechanisms. In the next step, the enolate attacks:

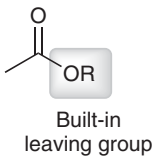


Once again, we see that both mechanisms are essentially identical. In the Claisen condensation, the alkoxy groups seem to just come along for the ride.

But now the two reactions take different routes. And we can use our golden rule to understand why. In the aldol reaction, the carbonyl group cannot re-form, so the oxygen atom must be protonated with a suitable proton source. But in a Claisen condensation, the carbonyl group CAN re-form, because there is a group that can leave:



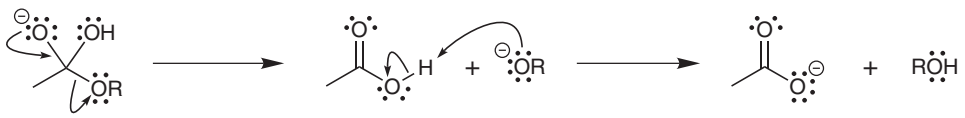
And this is why the product of a Claisen condensation looks very different from the product of an aldol condensation. But when you understand the mechanisms, you can appreciate that these reactions are very similar. The difference between these two reactions stems from the fact that Claisen condensations involve esters; and esters have a "built-in" leaving group:



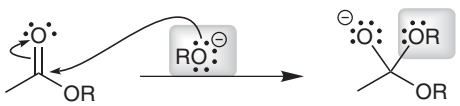
Now let's go back and explore the mechanism in more detail. In the first step, we made an ester enolate. To do this, we used a strong base. But we pointed out at the time that we did NOT use hydroxide. Instead, we used an alkoxide ion. Let's try to understand why.

If we had used hydroxide, then we might have observed a competing reaction. Instead of hydroxide acting as a base to remove a proton, it is possible for hydroxide to function as a nucleophile, attacking the carbonyl group of the ester:

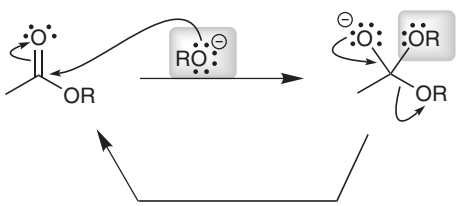
After the initial attack, the carbonyl group could re-form by expelling an alkoxide ion. This unwanted side reaction would hydrolyze the ester and produce a carboxylate ion (we saw this saponification reaction in the previous chapter):



In order to avoid this, we use an alkoxide as our base. It is true that alkoxides can *also* function as nucleophiles, but think about what happens if the alkoxide ion functions as a nucleophile and attacks:

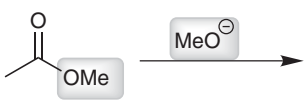


When the carbonyl group re-forms, it doesn't matter which alkoxy group gets expelled. Either way, the original ester will be regenerated:

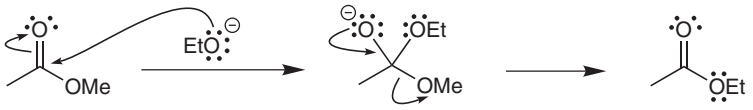


Although the alkoxide ***can*** attack the carbonyl group, we don't have to worry about it, because it does not actually lead to new products. So, we can avoid unwanted side reactions by using an alkoxide ion as the base for a Claisen condensation.

Be careful, though. We cannot just use *any* alkoxide ion. We must choose the alkoxide ion carefully. If we are dealing with a methyl ester, then we would use methoxide:

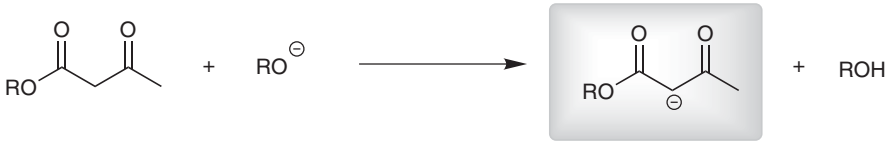


The reason for this is simple. Suppose we used ethoxide in this case. This would actually change some of our ester:

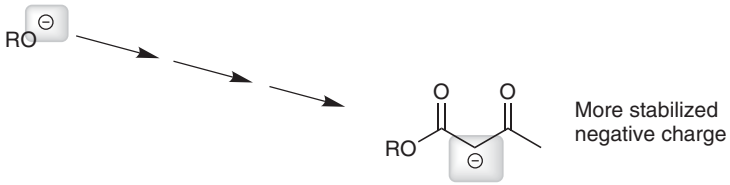


This is called *transesterification*, and we can avoid this by choosing our base to match the alkoxy group of the ester. That way, we avoid unwanted side reactions. If we are dealing with an ethyl ester, then we just use ethoxide as our base:

Now that we know what base to choose for a Claisen condensation, let's talk about another special role that the base plays in a Claisen condensation. We said that the final product is a β-keto ester. But remember that this reaction is performed under basic conditions (in the presence of alkoxide ions). Under these conditions, the β-keto ester will be deprotonated to form an enolate that is especially stabilized:

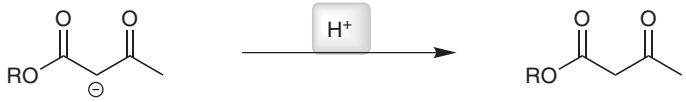


In the beginning of this chapter, we talked about this kind of "stabilized" enolate. This enolate is much more stable than an alkoxide ion. That is an important point, because it means that the reaction will favor formation of the product. Why? Because the reaction is converting alkoxide ions into enolate ions (which are more stable):



The formation of this stabilized enolate is a strong driving force pushing this reaction toward the formation of products.

So, when the reaction is finished, a proton source must be introduced into the reaction flask in order to protonate the enolate and obtain the product:



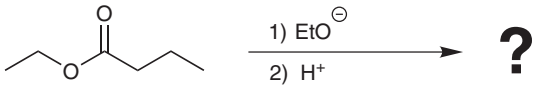
The Claisen condensation is important because it gives us a way to make β-keto esters. And we will soon see that there is a clever synthetic trick that you can perform with β-keto esters. So, let's make sure that we have mastered the Claisen condensation.

Overall, here is what is happening:

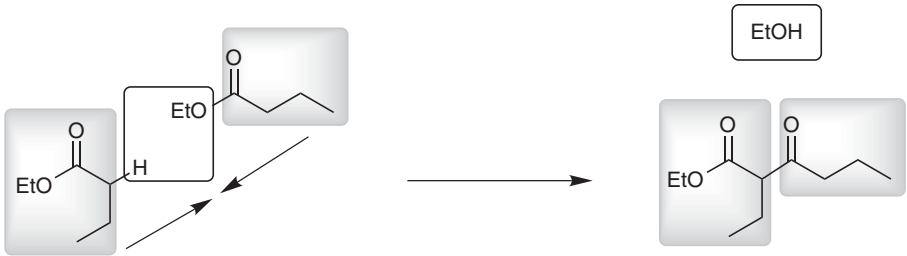
We are removing an alpha proton from one ester, and we are removing an alkoxy group from the other ester. The remaining fragments are then joined together. Notice that a small molecule is liberated in the process (ROH). That is why we call this reaction a Claisen ***condensation***.

Now let's practice predicting products. We will soon come back and master the mechanism. But for now, let's make sure that you train your eyes to see the products of a Claisen condensation in an instant. You will need that skill for proposing syntheses.

EXERCISE 8.51 Draw the product of the following Claisen condensation:

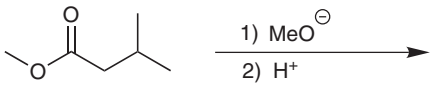


Answer The following two fragments are adjoined, while EtOH is expelled, like this:

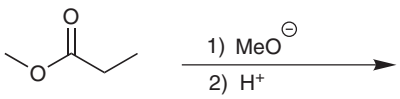


PROBLEMS Draw the product for each of the following Claisen condensations:

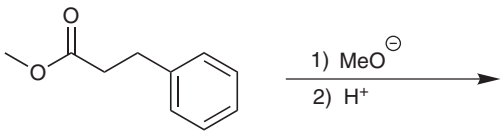
8.52



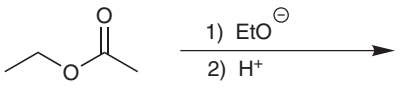
8.53



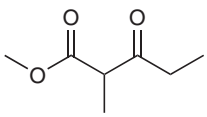
8.54



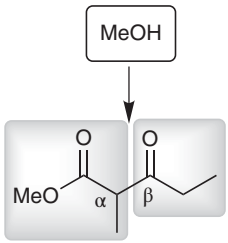
8.55



EXERCISE 8.56 Identify the starting materials and reagents you would use to prepare the following compound using a Claisen condensation:

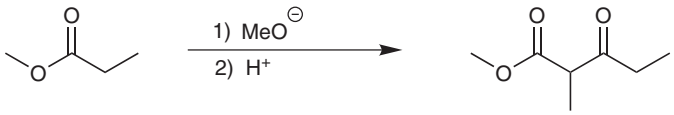


Answer We break the molecule apart into two fragments in order to insert MeOH. We break it apart between the α and β positions:



And we just have to decide which fragment gets the methoxy group and which fragment gets the proton. The fragment on the left already has its alkoxy group, so that must be the fragment that gets the proton. The fragment on the right will get the alkoxy group:

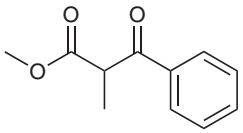
These two esters are identical, which is good. That means that we just need one kind of ester. We choose our base to match the alkoxy group (methoxide in this group), so our synthesis would look like this:



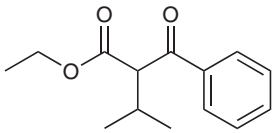
It is possible to achieve crossed Claisen condensations (just like we can achieve crossed aldol condensations), but we would have the same concerns as before. We would have to worry about potential side reactions. A crossed Claisen condensation will be more efficient when one of the esters has no alpha protons. You will see that some of the problems below are the products of crossed Claisen condensations. Keep an eye out for them.

PROBLEMS Identify the starting materials and reagents you would use to prepare each of the following compounds using a Claisen condensation:

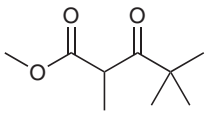
8.57



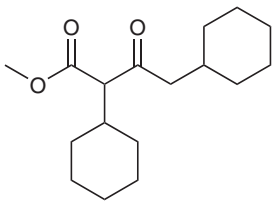
8.58



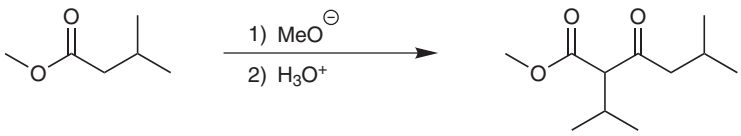
8.59



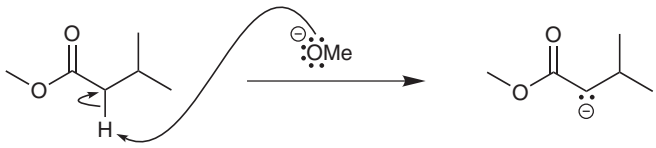
8.60



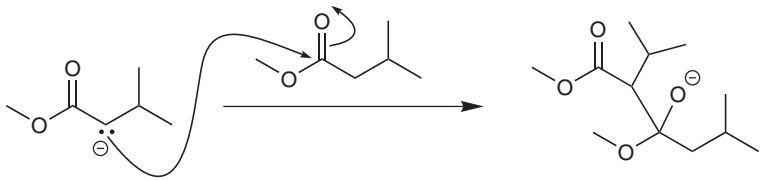
EXERCISE 8.61 Propose a mechanism for the following transformation:



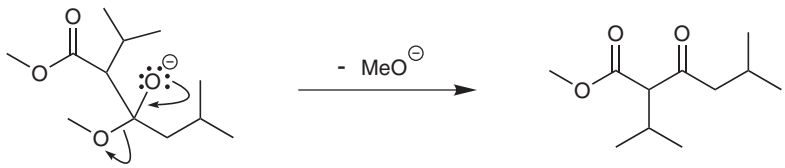
Answer First, methoxide functions as a base and deprotonates the ester:



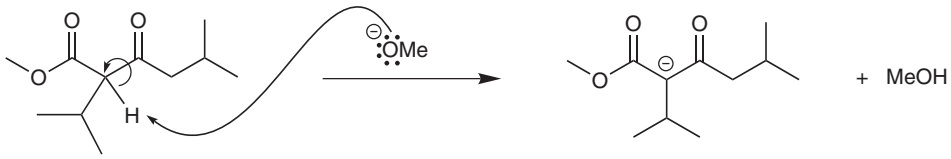
This ester enolate then attacks an ester to give the following intermediate:



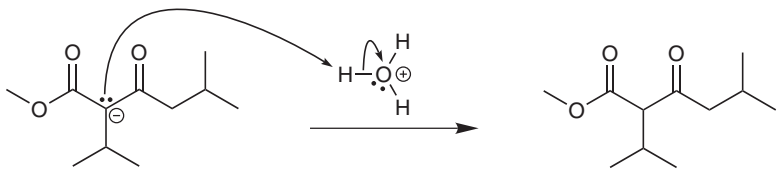
This intermediate then can re-form the carbonyl group by expelling methoxide:



Under these basic conditions (methoxide), the β-keto ester is deprotonated:

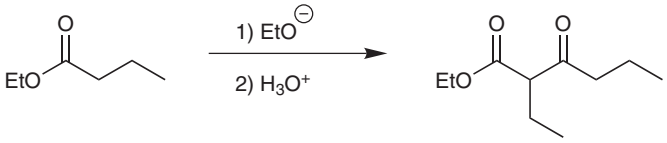


This deprotonation step is important, because the formation of this stabilized anion is the driving force for the reaction. That is why we must show this step. Notice that the reagents indicate that acid is added to the flask at the end of the reaction, because a source of protons is required to regenerate the final product:

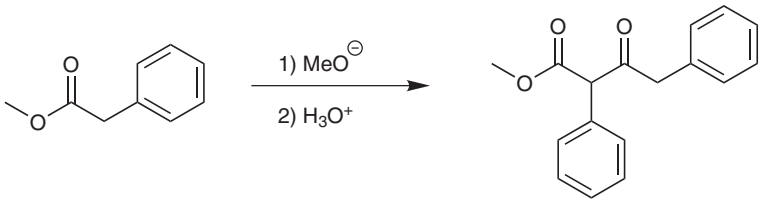


PROBLEMS Propose a mechanism for each of the following reactions. You will need a separate piece of paper to record your answers:

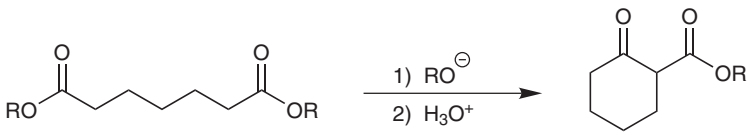
8.62



8.63



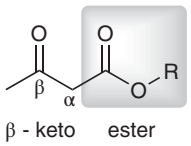
8.64 When a diester is used as a starting material, it is possible to achieve an ***intramolecular*** Claisen condensation:



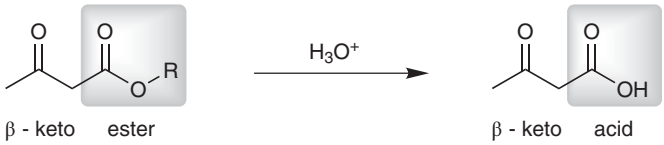
Notice once again that the product is just a β-keto ester. This reaction has its own name (the Dieckmann condensation). But it is really just an intramolecular Claisen condensation. Therefore, the steps of this mechanism are identical to the steps of a regular Claisen condensation. Propose a mechanism for the Dieckmann condensation. Try to do it without looking back at your previous work. You will need a separate piece of paper to record your answer.

8.9 DECARBOXYLATION

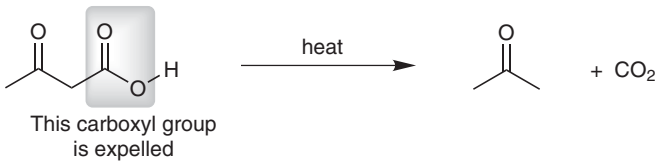
In the previous section, we learned how to use a Claisen condensation to prepare a β-keto ester:



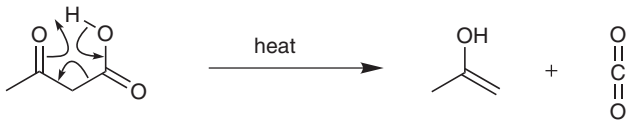
Now let's see what we can do with β-keto esters. There are some very useful synthetic techniques that start with β-keto esters. In order to see how they work, we will need to remind ourselves of one reaction that we saw in the previous chapter. When we explored the chemistry of carboxylic acid derivatives, we saw that esters can be hydrolyzed to give carboxylic acids. We can use the exact same process to hydrolyze a β-keto ester, like this:



And the product is a β-keto acid, which will undergo a unique reaction when heated. Specifically, the carboxyl group is completely expelled:



We call this process a *decarboxylation*. This reaction is the basis for the synthetic techniques we will learn in this section, so let's make sure we understand how a decarboxylation occurs. The process begins with a pericyclic reaction that liberates CO_2 as a gas:

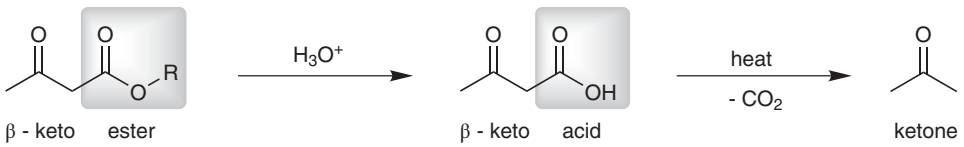


Pericyclic reactions are characterized by a ring of electrons moving around in a circle. There are many kinds of pericyclic reactions (for example, the Diels–Alder reaction is an important pericyclic reaction that we will cover in Chapter 10). Pericyclic reactions truly deserve their own chapter, and unfortunately, many textbooks do not devote an entire chapter to pericyclic reactions (they are just scattered throughout the various chapters). Perhaps your instructor will spend some time on pericyclic reactions. We will not cover them right now, as we must continue with the topic at hand.

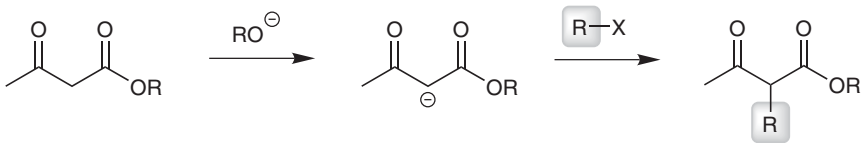
In the reaction above, CO_2 gas is liberated (that's how the carboxyl group is expelled), generating an enol. And we know that enols will quickly tautomerize to give ketones:

So, when a β-keto acid is heated, the carboxyl group is expelled, and we end up with a ketone.

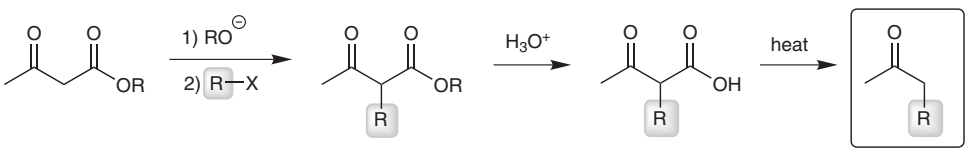
Now consider what we have just done. We took a β-keto ester (which is the product of a Claisen condensation), and we hydrolyzed it to produce a β-keto ***acid***. Then, we heated this compound, and we expelled the carboxyl group:



In the end, the product is a ketone. To see why this is so useful, we need to add just one more step at the very beginning of the overall process. Imagine that we first alkylate the β-keto ester:



We have already seen this kind of reaction before (Section 8.6). It is just an alkylation. We used an alkoxide ion to produce a stabilized enolate, which then attacks the alkyl halide in an S_N2 reaction. If we then continue with the rest of the strategy (hydrolysis, followed by decarboxylation), the following product is obtained:



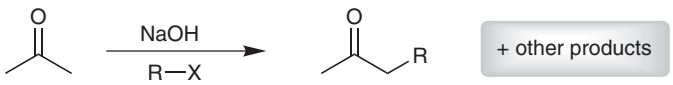
Take a close look at the product. This compound is a substituted derivative of acetone:

acetone

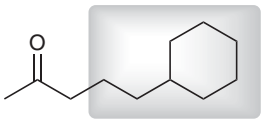
a substituted derivative of acetone

This provides a method to make a wide variety of substituted derivatives of acetone.

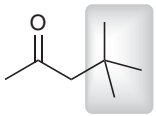
This is useful, because we would encounter an obstacle if we tried to alkylate acetone directly:



The desired product would be produced together with many other undesired products (from polyalkylation and from elimination reactions). So the strategy we have learned provides a clean way to make substituted derivatives of acetone. But be careful—remember that the alkylation step is an S_N2 process, so primary alkyl halides will be more efficient. In other words, you ***could*** use this strategy to prepare the following compound:

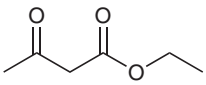


But you could ***not*** use this synthetic strategy to make this compound:



because that would have required an alkylation step involving a tertiary alkyl halide, which cannot function as a substrate in an S_N2 process.

In order to use this synthetic strategy, we will always start with the following compound:

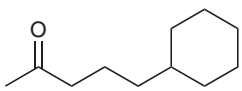


This compound is called ethyl acetoacetate. This compound belongs to a class of compounds called acetoacetic esters. Therefore, we call our strategy the ***acetoacetic ester synthesis***.

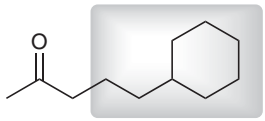
To summarize what we have seen, the acetoacetic ester synthesis has three main steps: alkylate, hydrolyze, and then decarboxylate.

Now let's get some practice using this synthetic strategy:

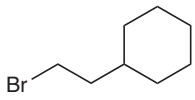
EXERCISE 8.65 Starting with ethyl acetoacetate, show how you would prepare the following compound:



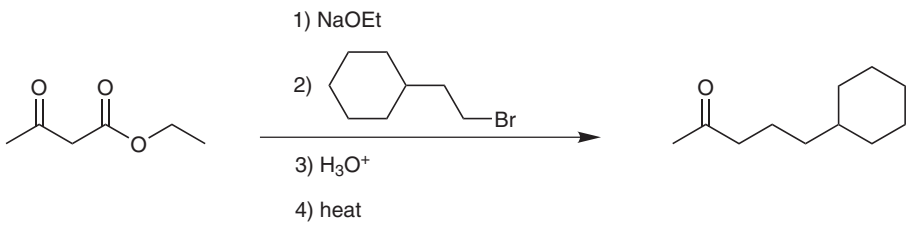
Answer Remember that the acetoacetic ester synthesis has the following steps: alkylate, hydrolyze, and then decarboxylate. So, in order to solve this problem, we must identify the alkyl group that should be installed:



So, we will need the following alkyl halide:

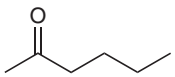


Now that we have determined what alkyl halide to use, we are ready to propose our synthesis:

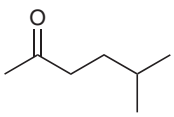


PROBLEMS Show how you would prepare each of the following compounds from ethyl acetoacetate:

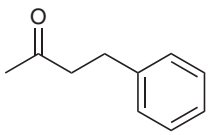
8.66



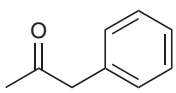
8.67



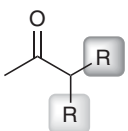
8.68



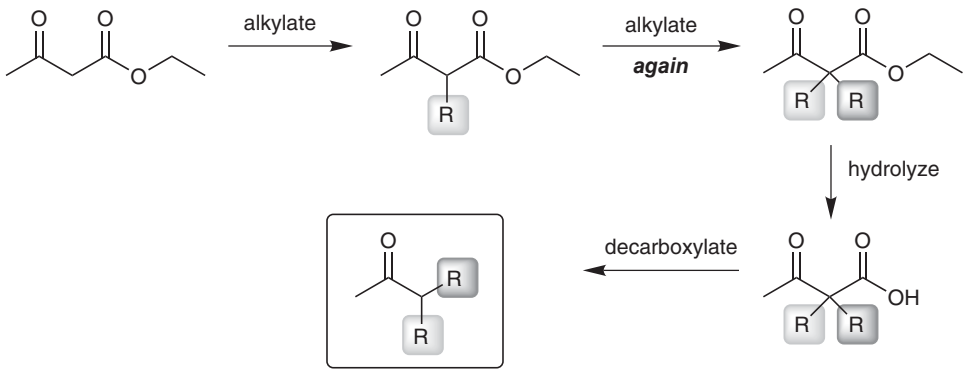
8.69 Explain why the following compound ***cannot*** be made with an acetoacetic ester synthesis.



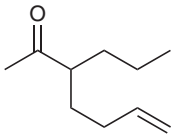
In all of the problems we have done so far, we have focused on alkylating ***once***. But it is also possible to alkylate twice, which would give a product with two alkyl groups:



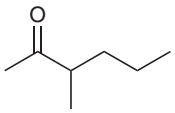
And the R groups don't even have to be the same. In the following sequence, the alkyl groups may be different.



8.70 Show how you would prepare the following compound from ethyl acetoacetate:

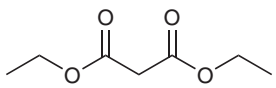


8.71 Show how you would prepare the following compound from ethyl acetoacetate:

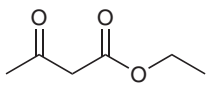


8.72 Propose a synthesis for the following transformation. (*Hint:* This reaction is similar to an acetoacetic ester synthesis, but we are just starting with a different β-keto ester):

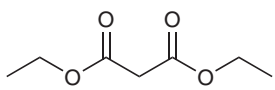
There is another common synthetic strategy that utilizes the same concepts as the acetoacetic ester synthesis. So, let's now focus on this other strategy. It is called the *malonic ester synthesis*, because the starting material is a malonic ester (called diethyl malonate):



We follow the same three steps that we followed in our previous strategy: alkylate, hydrolyze, and then decarboxylate. The only difference is that we start with a slightly different starting material (malonic ester, instead of acetoacetic ester), and therefore, our product will be slightly different. Compare the structures of ethyl acetoacetate and diethyl malonate:



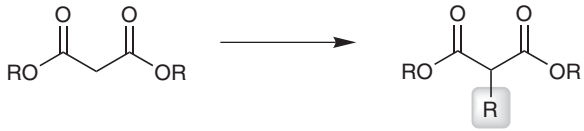
ethyl acetoacetate



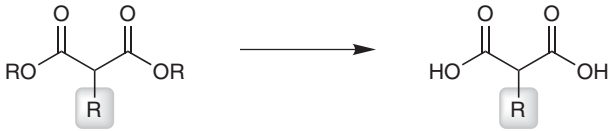
diethyl malonate

Notice that diethyl malonate has ***two*** carboxyl groups (as opposed to ethyl acetoacetate, which has one carboxyl group and one carbonyl group). To see how this extra carboxyl group affects the structure of our end product, let's go through the three steps: alkylate, hydrolyze, and then decarboxylate.

We start with an alkylation:



Then, we hydrolyze:

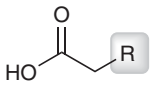


Notice that ***both*** sides get hydrolyzed.

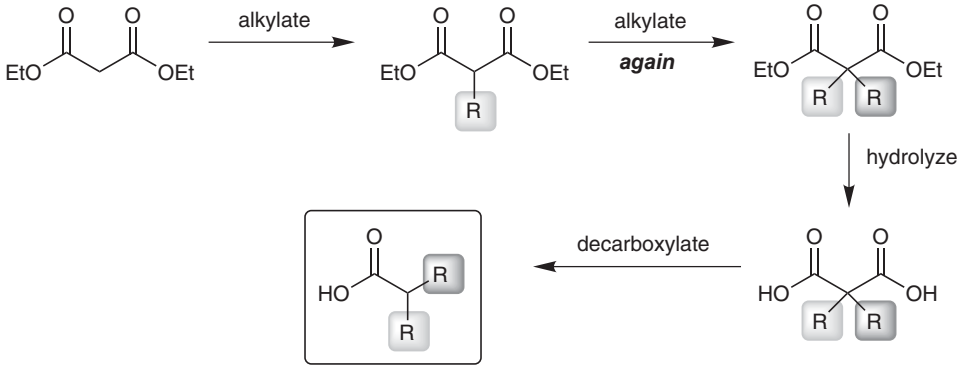
Then, finally, we decarboxylate:

Only one side undergoes decarboxylation. Why? Remember how a decarboxylation works. It is a pericyclic reaction that can occur when a C═O bond is α,β to a carboxylic acid group. After the first carboxyl group is expelled, there is no longer a C═O bond that is β to the remaining carboxylic acid group. Try to draw a mechanism for the second carboxyl group leaving, and you should find that you can't do it.

Notice that the product is now a substituted carboxylic acid. This is the power of the malonic ester synthesis. It provides a method for making a wide variety of substituted carboxylic acids:

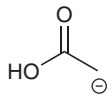


This synthesis can also be used to install ***two*** alkyl groups (just like we did with the acetoacetic ester synthesis). We would just alkylate twice at the beginning of our procedure:



Once again, the process is most efficient for primary R groups, because alkylation is an S_N2 process.

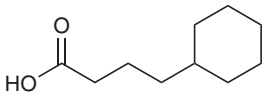
This strategy is very useful, because it would be very difficult to alkylate a carboxylic acid directly. If we try to alkylate a carboxylic acid directly, we immediately run into an obstacle, because we cannot form an enolate of a carboxylic acid:



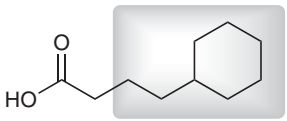
Cannot form this enolate

You cannot form an enolate in the presence of an acidic proton. So, the malonic ester synthesis gives us a way around this obstacle. It provides a method for making substituted carboxylic acids. Let's get some practice with this:

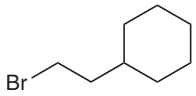
EXERCISE 8.73 Starting with diethyl malonate, show how you would prepare the following compound:



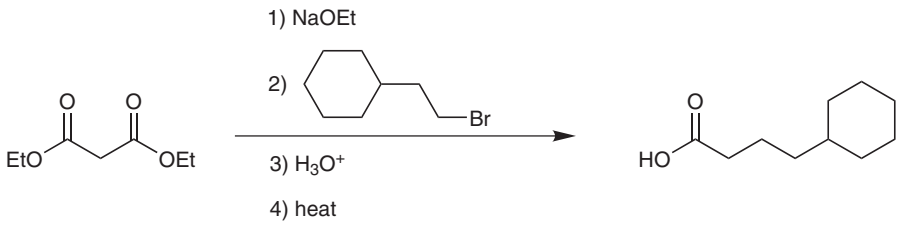
Answer Remember that the malonic ester synthesis has the following steps: alkylate, hydrolyze, and then decarboxylate. So, in order to solve this problem, we must identify the alkyl group that should be installed.



So, we will need the following alkyl halide:



Now that we have determined what alkyl halide to use, we are ready to propose our synthesis:



PROBLEMS Identify what reagents you would use to achieve each of the following transformations:

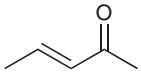
8.74

8.75

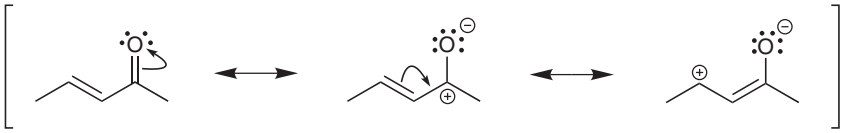
8.76

8.10 MICHAEL REACTIONS

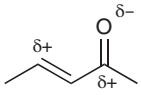
In this chapter, we have seen that enolates can attack a wide variety of electrophiles. We started the chapter with the reaction between enolates and halogens. Then we looked at the reaction between enolates and alkyl halides. We also saw that enolates can attack ketones or esters. In this section, we will conclude our discussion of enolates by looking at a special kind of electrophile that can be attacked by an enolate. Consider the following compound:



This compound is an α,β-unsaturated ketone, and we have seen that compounds of this type can be made with an aldol condensation. This compound is a special kind of electrophile. To understand why it is special, let's take a close look at the resonance structures:

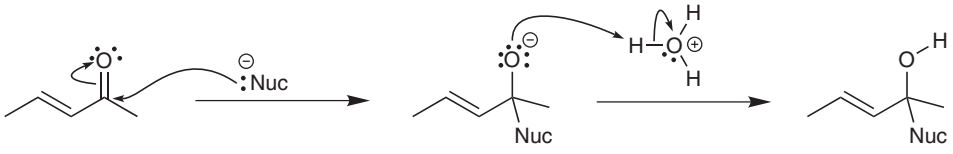


These resonance structures paint the following picture:

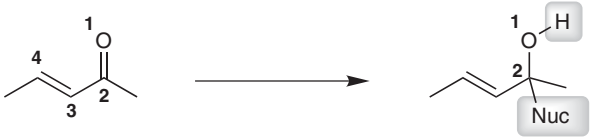


We see that there are ***two*** electrophilic centers. We already knew that the carbonyl group itself is electrophilic. But now, we can appreciate that the β position is also electrophilic. So, an attacking nucleophile has two choices. It can attack at the carbonyl group (as we have seen many times already), ***or*** it can attack at the β position. Let's look at both possibilities, and we will compare the products.

Consider what happens if the nucleophile attacks the carbonyl group, and the resulting intermediate is then protonated:



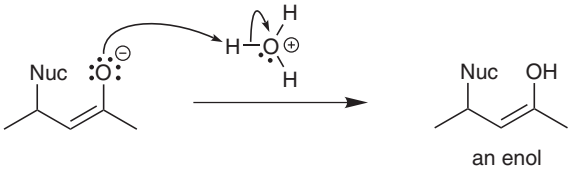
Notice that we had a π system that spanned 4 atoms, and we installed the nucleophile and the H in positions 1 and 2:



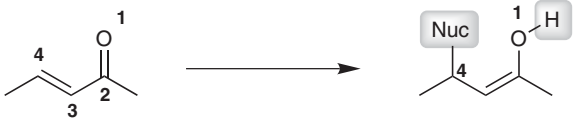
Therefore, we call this a ***1,2-addition***.

Now consider what happens if the nucleophile attacks the β position, rather than the carbonyl group. The initial intermediate is an enolate:

Then, when this enolate is protonated, an enol is formed:

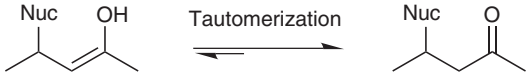


Once again, we have added the nucleophile and H across the π system. But this time, we have added them across the *ends* of this system:

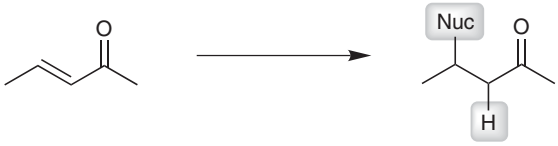


So, we call this a ***1,4-addition***. Chemists have given this reaction other names as well. A 1,4-addition is often called a ***conjugate addition***, or a ***Michael addition***.

We know that the product of a 1,4-addition is not going to stay in the form of an enol, because an enol will tautomerize to form a ketone:



When you look at this ketone, it is hard to see why we call it a 1,4-addition. After all, it looks like the nucleophile and the H have added across the C═C bond:

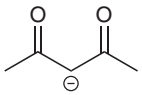


You need to draw the entire mechanism in order to see why we call it a 1,4-addition.

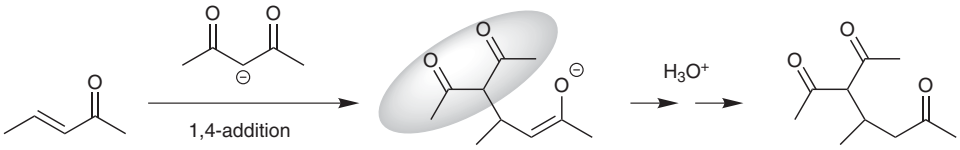
Now that we know the difference between a 1,2-addition and a 1,4-addition, let's take a look at what happens when our attacking nucleophile is an enolate.

If an α,β-unsaturated ketone is treated with an enolate, a mixture of products is obtained. Not only do we observe both possibilities (the enolate attacking the carbonyl group, or the enolate attacking the β position), but it gets even more complicated. The product of the 1,4-addition is a ketone, which can be attacked again by an enolate. You can get crossed aldol condensations, and all sorts of unwanted products. So, we can't use an enolate to attack an α,β-unsaturated ketone. The enolate is simply too reactive, and we observe a mixture of undesired products.

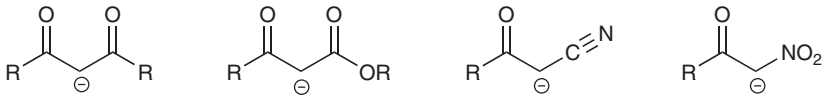
The way around this problem is to create an enolate that is more stabilized. A more stable enolate will be less reactive, and therefore, it will be more selective in what it reacts with. But how do we make a more stabilized enolate? We have actually already seen such an example in this chapter. Consider the following enolate:



We argued that this enolate is more stable than a regular enolate, because the negative charge is delocalized over ***two*** carbonyl groups. If we use this enolate to attack an α,β-unsaturated ketone, we find that the predominant reaction is a 1,4-addition:

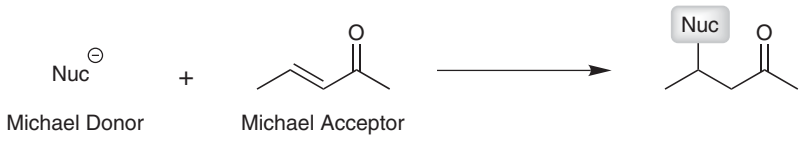


We said earlier that a 1,4-addition is also called a Michael addition. In order to get a Michael addition, you need to have a stabilized nucleophile, like the stabilized enolate shown in the reaction above. This stabilized enolate is called a Michael donor. There are many other examples of ***Michael donors***. Look at them carefully, because you will need to recognize them as being Michael donors when you see them:

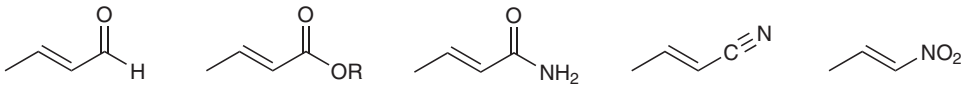


All of these nucleophiles are sufficiently stabilized to function as Michael donors. Organocuprates, R_2CuLi, are also stabilized nucleophiles and will also attack an α,β-unsaturated ketone to give a 1,4-addition reaction.

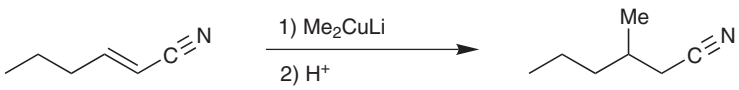
In any Michael reaction, there is always a Michael donor ***and*** a Michael acceptor:



In the reaction above, the Michael acceptor is an α,β-unsaturated ketone. But there are other compounds that can also function as Michael acceptors:

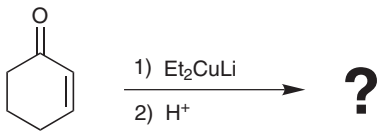


You can use any Michael donor to attack any Michael acceptor. The following reaction would also be considered a conjugate addition reaction:

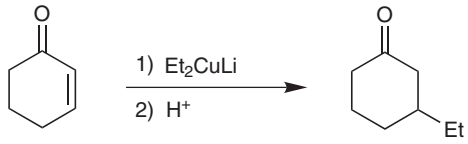


In order to do this next set of problems, you will need to review the lists of Michael donors and Michael acceptors.

EXERCISE 8.77 Draw the expected product of the following conjugate addition reaction:



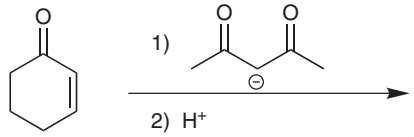
Answer First identify the nucleophile and the electrophile. The α,β-unsaturated ketone is the electrophile, and the lithium dialkyl cuprate is the nucleophile, and we expect a conjugate addition reaction.



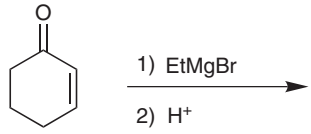
Stare at this transformation for a few moments. It might be helpful to you on an exam.

PROBLEMS For each of the reactions below, determine whether you expect an efficient conjugate addition reaction. If so, then draw the product you expect.

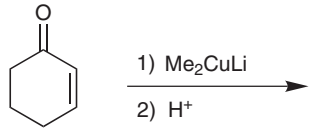
8.78



8.79

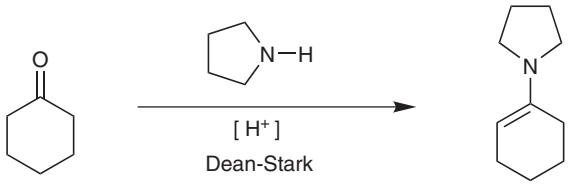


8.80

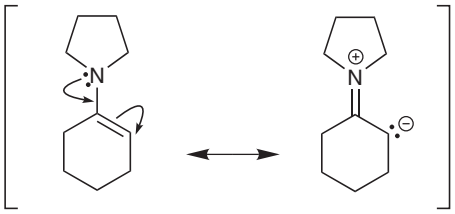


There is one more Michael donor that requires special mention. Enamines are very special Michael donors, because they provide us with a useful synthetic strategy.

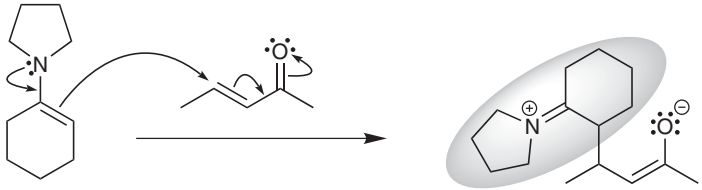
When we learned about ketones and aldehydes (Chapter 6), we saw that you can prepare an enamine by treating a ketone with a secondary amine, under the following conditions:



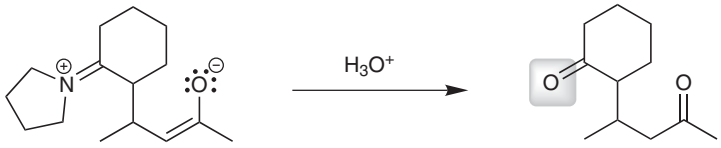
This was our way of converting a ketone into an enamine. To understand how an enamine can function as a Michael donor, let's take a close look at the resonance structures of an enamine:



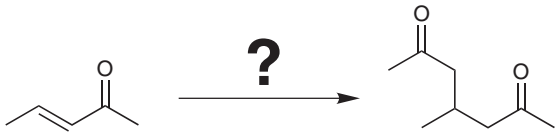
When we meld these two images together in our minds, we see that the carbon atom is nucleophilic (it has some partial negative character). But, it is a fairly weak nucleophile, because the compound does not have a *full* negative charge. Rather, the carbon atom only has *partial* negative character. Therefore, this compound is a *stabilized* nucleophile (in other words, it will be selective in its reactivity). This means we must add it to our list of Michael donors. If we use an enamine as a nucleophile to attack a Michael acceptor, a Michael reaction will occur:



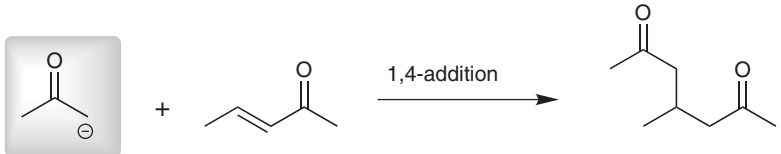
And then, the resulting iminium group can be removed by adding water under acidic conditions (and under these conditions, the enolate is protonated to form an enol, which tautomerizes to form a ketone):



But why is this so important? Why am I singling out this one Michael donor, and why are we learning about enamines again? To understand the usefulness of enamines here, let's imagine that we wanted to achieve the following transformation:



You decide that it should be simple. Your plan is to use a nucleophile that can attack an α,β-unsaturated ketone in a 1,4-addition:

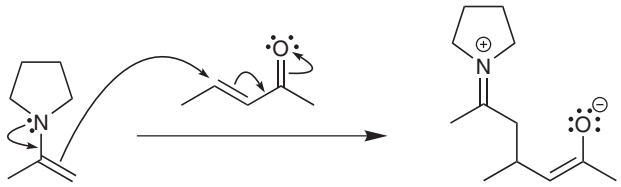


This is the nucelophile that you would need

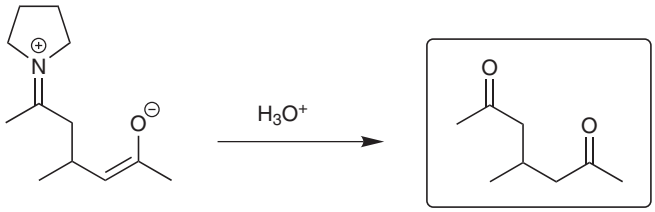
But, when you try to perform this reaction, you obtain a mixture of undesired products. Why? Because this enolate is ***not*** a Michael donor, and therefore, it will not efficiently attack in a 1,4-addition. So, how do you get around this problem? This is where our enamine comes in handy.

Instead of using an enolate as the nucleophile, suppose we convert the ketone into an enamine:

This enamine ***is*** a Michael donor, and it ***will*** attack cleanly in a 1,4-addition:



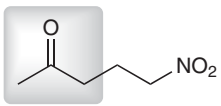
Finally, we use H_3O^+ to remove the iminium group and protonate the enolate (which then turns into a ketone):



In the end, we prepared the desired product. This synthetic strategy is called the ***Stork enamine synthesis***, and it can come in handy when you are proposing syntheses. Whenever you are trying to propose a synthesis, and you decide that you need an enolate to attack as a nucleophile in a 1,4-addition, you will have a problem. Regular enolates are not stable enough to be Michael donors. But, you can convert it into an enamine, which ***is*** stable enough to be a Michael donor. Then, you can remove the enamine in the end. The enamine serves as a way of temporarily modifying the reactivity of the enolate so that we can achieve the desired result. It is very clever when you really think about it.

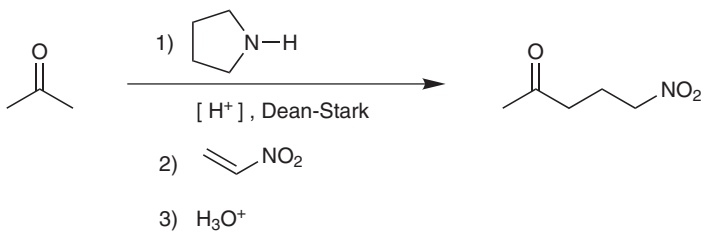
EXERCISE 8.81 Propose a plausible synthesis for the following transformation:

Answer When we inspect this transformation, we see that we need to install the following fragment:



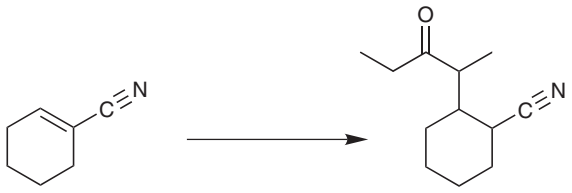
and at the same time, we need to remove the double bond that was in the starting material. We can accomplish both of these at the same time by performing a 1,4-addition with the appropriate nucleophile. When we look carefully to see what nucleophile we would need, we realize that we will need to use the following enolate:

This enolate is ***not*** stable enough to function as a Michael donor, so we need to use a Stork enamine synthesis:

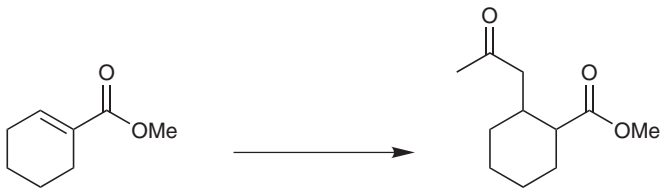


PROBLEMS Propose a synthesis for each of the following transformations. In some cases, you will need to use a Stork enamine synthesis, but in other cases, it will not be necessary. Analyze each problem carefully to see if a Stork enamine synthesis is necessary.

8.82

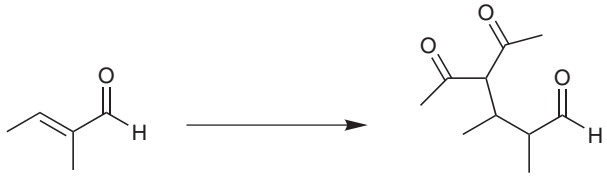


8.83



8.84

8.85

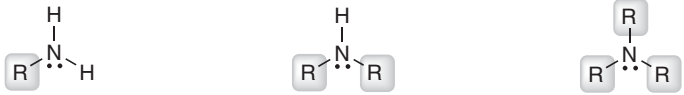


CHAPTER 9

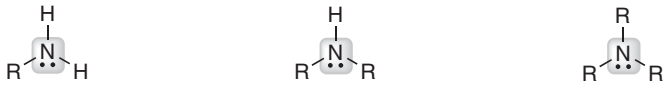
AMINES

9.1 NUCLEOPHILICITY AND BASICITY OF AMINES

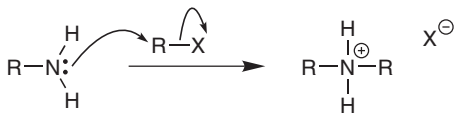
Amines are classified based on the number of alkyl groups attached to the nitrogen atom:



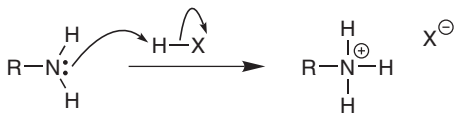
The reactivity of all amines derives from the presence of a lone pair on the nitrogen atom. All amines have this lone pair:



This lone pair can function as a nucleophile (attacking an electrophile):



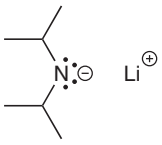
or it can function as a base (receiving a proton):



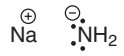
By focusing on this lone pair, we can understand why amines are good nucleophiles ***and*** good bases. When an amine participates in a reaction, the first step will always be one of these two possibilities: either the lone pair will receive a proton or the lone pair will attack an electrophile.

Of course, if we had a negative charge on the nitrogen atom, it would be an even stronger base. To get a negative charge on the nitrogen atom, we must deprotonate the amine. Tertiary amines don't have a proton that can be removed, but primary and secondary amines can be deprotonated to give the following anions:

These anions are stronger bases than uncharged amines. We call these structures ***amides***. Here are two examples of amides that we have seen so far in this course:

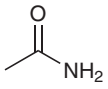


Lithium diisopropyl ***amide***
(LDA)



Sodium ***amide***

The term ***amide*** is actually a terrible name, because we have already used this term to describe a type of carboxylic acid derivative:



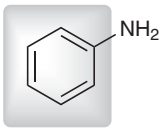
an ***amide***

amide ion

Perhaps chemists could have assigned different names to these structures (so that it would be less confusing to students). But historically, chemists have used the term ***amide*** to refer to both of these types of structures. And old habits die hard. Since we are probably not going to convince chemists around the world to change their terminology, we will just have to get used to the terminology that is in use. Don't let this confuse you.

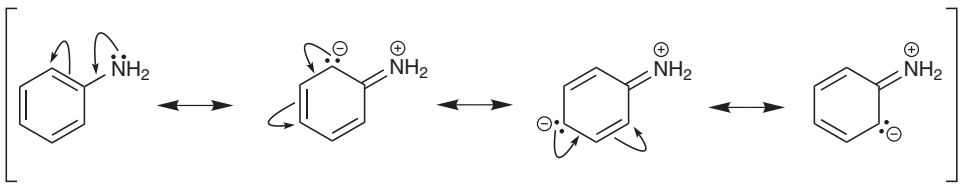
Now let's get back to uncharged amines. Some amines are actually less nucleophilic and less basic than regular amines. For example, compare the following two amines:

An alkyl amine



An aryl amine

The first amine is called an ***alkyl*** amine, because the nitrogen atom is connected to an alkyl group. The second compound is called an ***aryl*** amine, because the nitrogen atom is connected to an aromatic ring. Aryl amines are less nucleophilic and less basic, because the lone pair is delocalized into the aromatic ring. We can see this when we draw the resonance structures:

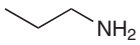


Since the lone pair is delocalized, it will be less available to function as a nucleophile or as a base. That does not mean that an aryl amine can't attack something. In fact, we will soon see a reaction where an aryl amine ***is*** used as a nucleophile. It ***can*** function as a nucleophile—but it is just ***less*** nucleophilic than an alkyl amine.

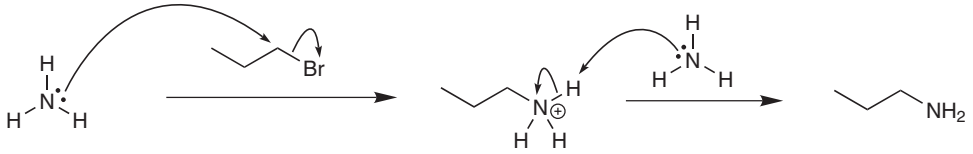
Now that we have had an introduction to amines, let's focus on a few ways to make amines.

9.2 PREPARATION OF AMINES THROUGH S_N2 REACTIONS

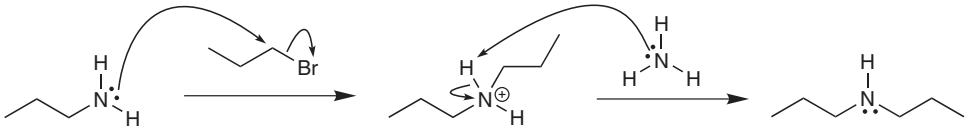
Suppose you wanted to make the following primary amine:



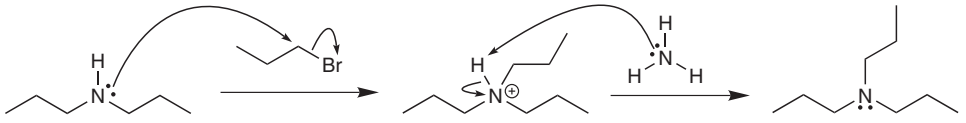
It might be tempting to suggest the following synthesis:



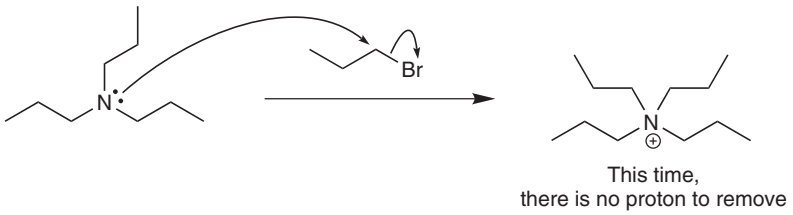
This is just an S_N2 reaction, followed by a deprotonation. This approach does work, BUT it is difficult to get the reaction to stop after monoalkylation. The product is also a nucleophile and it competes with NH_3 for the alkyl halide. In fact, the product is an even better nucleophile than NH_3, because the alkyl group is electron donating. Therefore, it will attack again:



And then it attacks again:

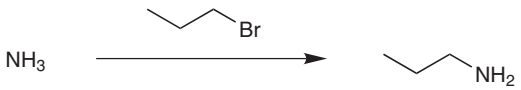


And then one last time:



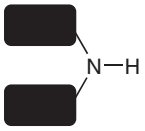
The final product has four alkyl groups (which is referred to as ***quaternary***), and the nitrogen has a positive charge (called an ***ammonium* ion**). So, we call this a ***quaternary ammonium ion***. This structure does not have a lone pair, so it is neither nucleophilic nor basic.

If our intention is to make a quaternary ammonium salt, then the synthesis above is a good approach. But what if we want to make a primary amine? We cannot simply alkylate ammonia:

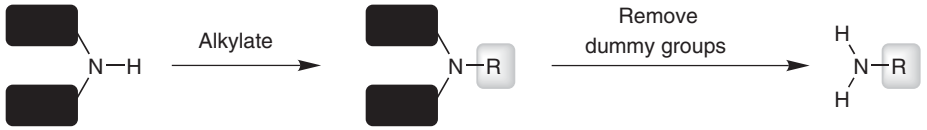


because it is too difficult to stop the reaction at this stage. The alkyl halide will react again with the primary amine. Even if we try to use only one mole of alkyl halide and one mole of ammonia, we will still get a mixture of undesired products. We will get some polyalkylated products, and we will get some ammonia that could not find any alkyl halide to attack. So what do we do?

To get around this problem, we use a clever trick. We use a starting amine that already has two dummy groups on it:

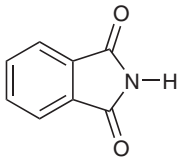


And we choose our dummy groups so that they are easily removable after we alkylate. So, first alkylate, and then we remove the dummy groups:

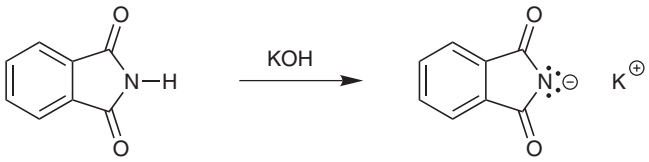


This strategy is called the Gabriel synthesis. It is a very good way of making primary amines from primary alkyl halides, so let's explore this strategy in more detail.

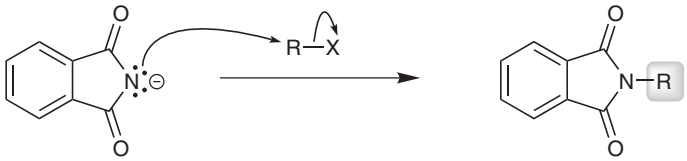
We start with the following compound, called phthalimide:



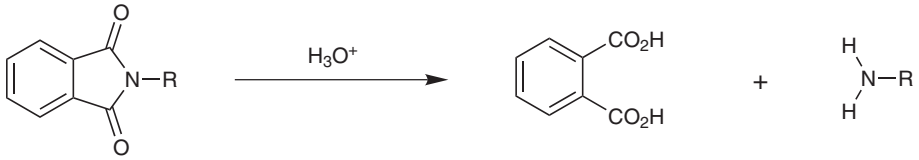
We use a base (KOH) to remove the proton, which gives the following anion:



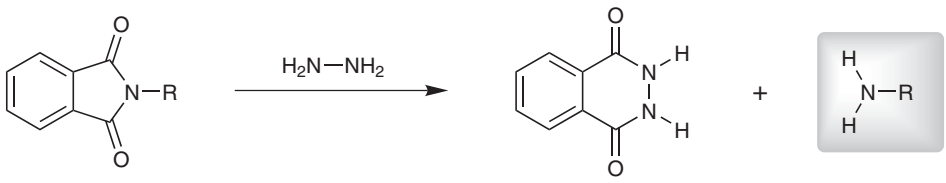
Notice that this negative charge is very stabilized (delocalized) by resonance. This is similar to the Michael donors that we saw in the end of the previous chapter. It is a stabilized nucleophile. We use this nucleophile to attack an alkyl halide:



This reaction proceeds via an S_N2 process, so tertiary alkyl halides cannot be used. Acid-catalyzed or base-catalyzed hydrolysis is then performed to release the amine. Acidic conditions are more common than basic conditions.



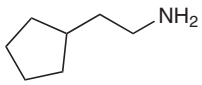
The mechanism of hydrolysis is directly analogous to the hydrolysis of amides, as seen in Section 6.6. The hydrolysis step is slow, and many alternative approaches have been developed. One such alternative employs hydrazine to release the amine:



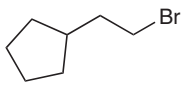
In this step, the dummy groups are removed, generating the desired product.

The Gabriel synthesis is very useful for making primary amines from primary alkyl halides:

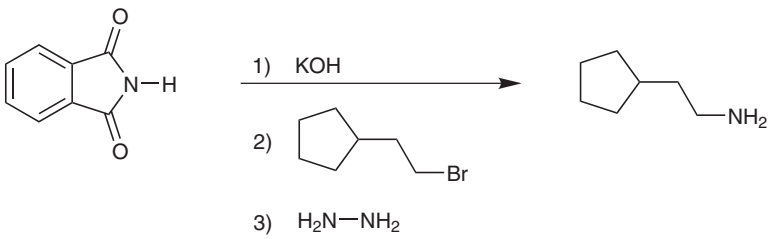
EXERCISE 9.1 Identify how we would use a Gabriel synthesis to prepare the following amine:



Answer In order to perform a Gabriel synthesis, we must identify the alkyl halide that is necessary. To do this, we just draw a halogen instead of NH_2, like this:

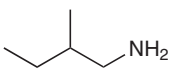


Now that we know what alkyl halide to use, we are ready to propose our synthesis:

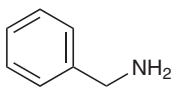


PROBLEMS Identify how you would use a Gabriel synthesis to prepare each of the following compounds.

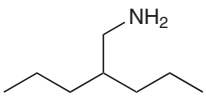
9.2



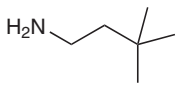
9.3



9.4

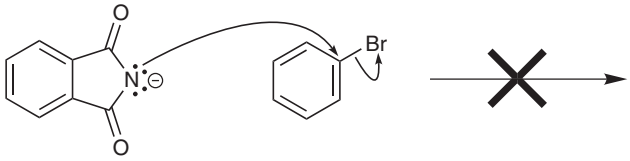


9.5

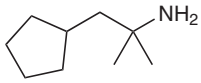


The Gabriel synthesis has its limitations, though. Since it relies on an S_N2 reaction, it will work well with ***primary*** alkyl halides. But it is not so great for secondary alkyl halides, and it will not work at all for tertiary alkyl halides.

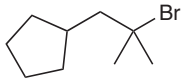
In addition, it will not work for aryl halides, because you cannot perform an S_N2 process on an aryl halide:



EXERCISE 9.6 Is it possible to prepare the following compound with a Gabriel synthesis?



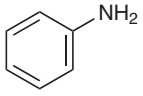
Answer We draw the alkyl halide that would be necessary,



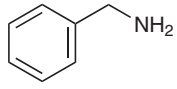
and we see that it is a tertiary alkyl halide, so we ***cannot*** use a Gabriel synthesis to make the desired product in this case.

PROBLEMS Identify whether each of the following compounds could be made with a Gabriel synthesis, and provide a Gabriel synthesis for those that are possible.

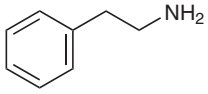
9.7



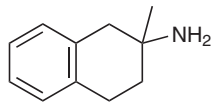
9.8



9.9

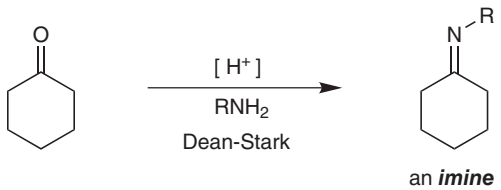


9.10



9.3 PREPARATION OF AMINES THROUGH REDUCTIVE AMINATION

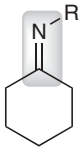
In the previous section, we learned how to make amines via an S_N2 process. That method works very well for making primary amines. In this section, we will learn a way to make secondary amines, using a two-step synthesis (where the first step is a reaction that we have already seen). When we learned about ketones and aldehydes, we saw how to make ***imines***:



an ***imine***

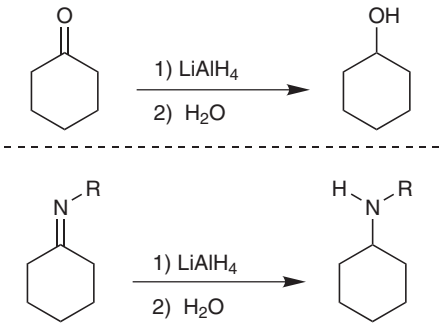
We saw that a ketone can be converted into an imine. Now, we will use this reaction to make amines.

When we form an imine, we are forming the essential C—N connection that you need in order to have an amine:

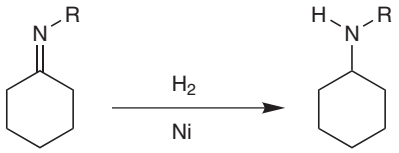


But, the oxidation state is not correct. In order to get an amine, we need to do the following conversion:

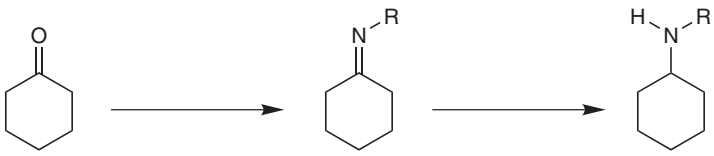
In order to convert an ***i***mine into an ***a***mine, we will need to perform a reduction. One way to do so is to reduce the imine in much the same way that a ketone is reduced, using $LiAlH_4$:



Alternatively, the C═N bond can undergo hydrogenation (in the presence of a catalyst):



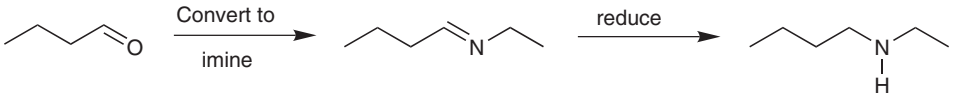
There are many other ways to reduce an imine as well. But the bottom line is that we now have a two-step synthesis for preparing amines:



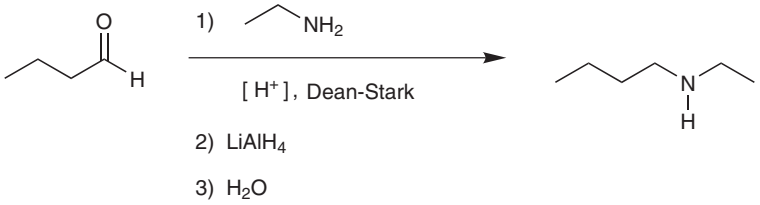
This process is called ***reductive amination***, because we are forming an amine (a process called *amination*) via a *reduction*.

EXERCISE 9.11 Suggest an efficient synthesis for the following transformation:

Answer This problem involves the conversion of an aldehyde into a secondary amine. This should alert us to the possibility of a reductive amination. If we used a reductive amination, our strategy would go like this:



So, our synthesis will look like this:



PROBLEMS Suggest an efficient synthesis for each of the following transformations.

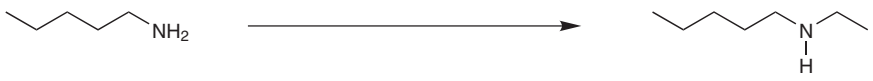
9.12

9.13

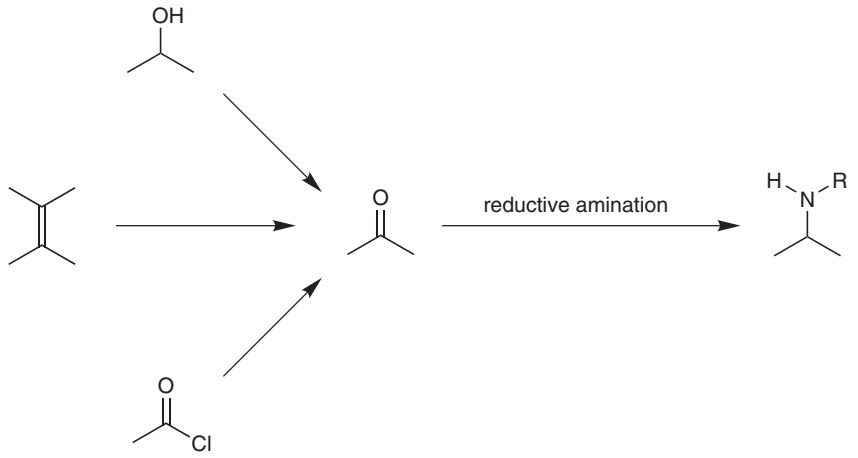
9.14

9.15

9.16

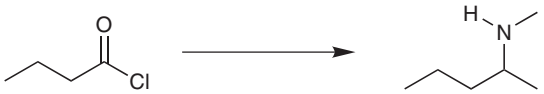


Reductive amination is a useful technique, because the starting material is a ketone or aldehyde. And we have seen many ways to make ketones or aldehydes. This gives us a way to make amines from a variety of compounds:



Students often have difficulty combining reactions from different chapters to propose a synthesis, so let's get some practice:

EXERCISE 9.17 Suggest an efficient synthesis for the following transformation:



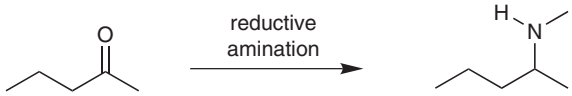
Answer Our product is a secondary amine, so we will explore if we can achieve this synthesis using a reductive amination. Let's work backwards.

If we did use a reductive amination, our last step would need to be the reduction of the following imine:

imine

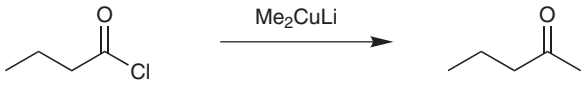
So, we would need to make the imine above, and we could have done that starting with the following ketone:

So, our goal is to make this ketone. If we can make this ketone, then we can use a reductive amination to form our product:

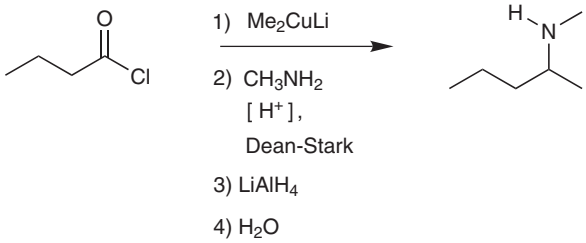


But how do we make this ketone from the starting material?

This would involve converting a carboxylic acid derivative into a ketone. In this case, we need a cross-over reaction (think back to our discussion of cross-over reactions in Chapter 8):



Therefore, our overall synthesis goes like this:



PROBLEMS Suggest an efficient synthesis for each of the following transformations. In each case, you should work backwards. Start by asking what ketone or aldehyde you would need in order to make the desired product via a reductive amination. Then, ask yourself how you could make that ketone from the starting material.

9.18

9.19

9.20

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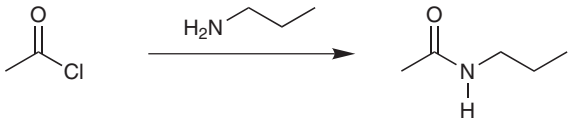
9.22

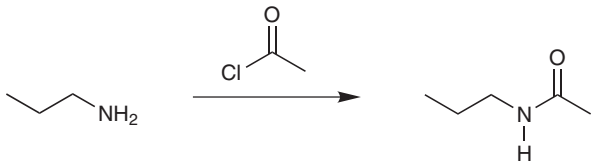
9.4 ACYLATION OF AMINES

So far in this chapter, we have focused on ways of ***making*** amines. For the rest of the chapter, we will shift our focus. We will now explore reactions of amines.

We will begin our survey with a reaction that we have actually already seen in a previous chapter. When we learned about carboxylic acid derivatives (Chapter 7), we saw that you can convert an acid halide into an amide. For example:

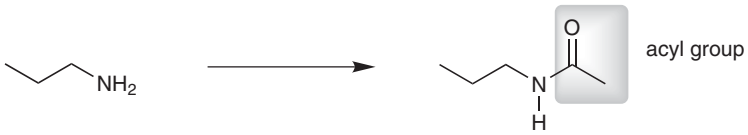


When we draw it this way (with the amine over the reaction arrow), the focus is on what happens to the acid halide (it is converted into an amide). But what if we choose to focus on the amine instead? In other words, let's rewrite the same reaction a bit differently. Let's put the acid halide on top of the reaction arrow, like this:



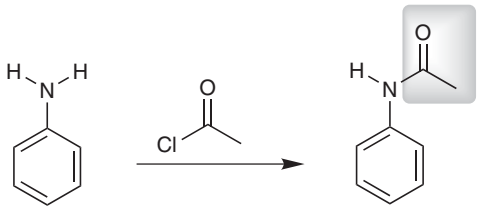
We have not changed the reaction at all. It is still the same reaction (an amine reacting with an acid halide). But when we draw it like this, our attention focuses on converting the ***amine*** into an ***amide***. The acid halide is just the reagent that we use to accomplish this conversion.

Overall, we have introduced an ***acyl*** group onto the amine:

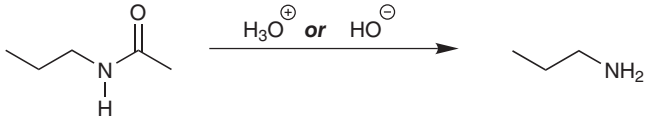


Therefore, we call this an ***acylation*** reaction.

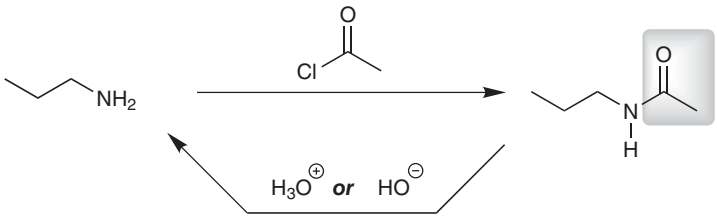
Most primary and secondary amines can be acylated. Here is another example:



Now that we have seen how to acylate an amine, let's take a look at how to remove the acyl group. This reaction was also covered in the chapter on carboxylic acid derivatives. It is just the hydrolysis of an amide:

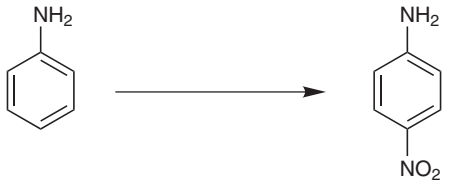


Notice that we have removed the acyl group to regenerate the amine. So, now we know how to install an acyl group, and we know how to remove it:

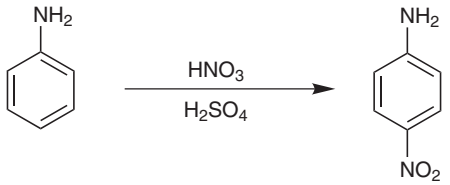


But the obvious question is: why would we want to do that? Why would we ever install a group, just to remove it later? The answer to this question is very important, because it illustrates a common strategy that organic chemists use. Let's try to answer this question through a specific example.

Imagine that we want to achieve the following transformation:

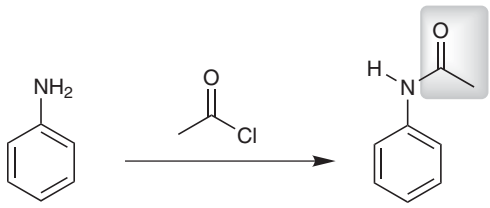


This seems easy to do. Do you remember how to install a nitro group on an aromatic ring (Chapter 4)? We just used a mixture of nitric acid and sulfuric acid. The amino group is an activator, so it will direct to the *ortho* and *para* positions, with a preference for *para* substitution (for steric reasons). So, we propose the following:

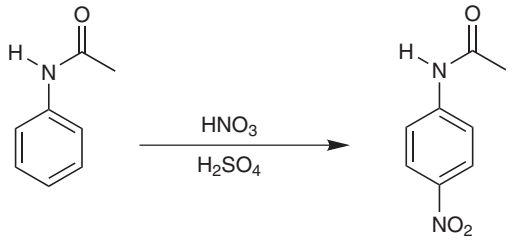


But when we try to perform this reaction, we find that it does not work. It is true that an amino group is a strong activator, but under the strongly acidic reaction conditions, the amino group is protonated to give an ammonium ion, which is a strong deactivator (and a *meta*-director). Under those conditions, any reaction that occurs will be undesired. So, how can we generate the desired product?

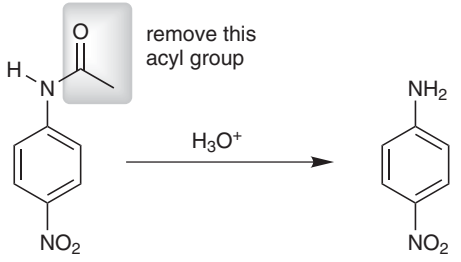
The way to do it is actually very clever. We first acylate the amino group:



This converts the amino group into an amide group, which is a weaker base, because the lone pair is further delocalized into the carbonyl group of the amide. As such, the nitrogen atom of the amide group is not protonated under acidic conditions. And since the amide group is an activator, the ring will undergo nitration in the desired location:

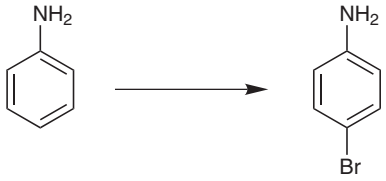


Then, we remove the acyl group to obtain the desired product:



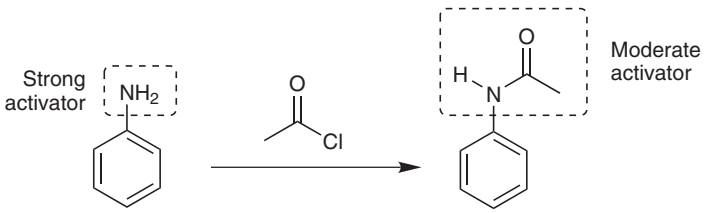
Think about what we just did. We used an acylation process as a way of ***temporarily modifying*** the electronics of the amino group, so that it would not interfere with the desired reaction. This strategy is used all of the time by organic chemists. This idea of temporarily modifying a functional group (and then converting it back later) is an idea that is used in many other situations as well (not just for acylation of amines).

EXERCISE 9.23 Suppose we want to achieve the following transformation:

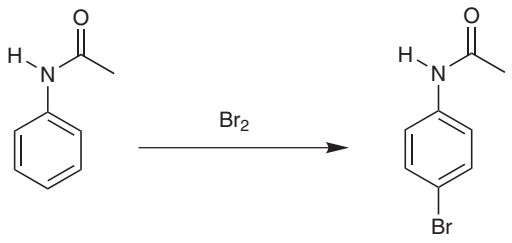


We try to perform this transformation using Br_2, but we find that aniline is too reactive, and we get a mixture of mono-, di-, and tribrominated products. What can we do to obtain the desired product and avoid polybromination?

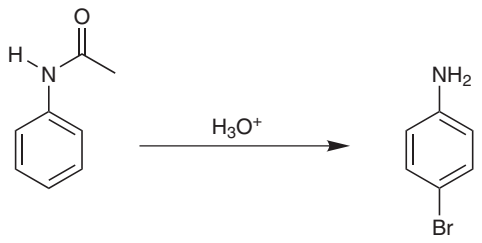
Answer The problem is the amino group. It is too strongly activating. To circumvent this obstacle, we use the strategy we have developed in this section. We acylate the amino group, and that makes the ring less activated (temporarily):



Now we are able to brominate:



and that installs one bromine atom in the *para* position. Finally, we remove the acyl group to obtain the desired product:



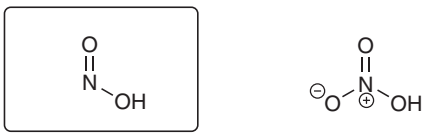
PROBLEMS Propose an efficient synthesis for each of the following transformations:

9.24

9.25

9.5 REACTIONS OF AMINES WITH NITROUS ACID

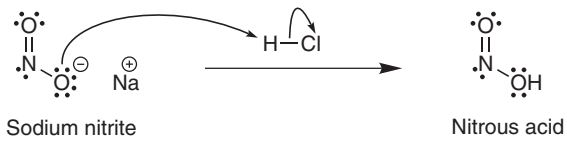
In this section, we will begin to explore the reactions that take place between amines and nitrous acid. Compare the structures of nitr***ous*** acid and nitr***ic*** acid:



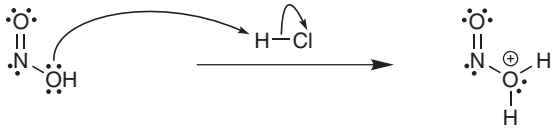
Nitrous acid Nitric acid

When nitrous acid reacts with amines, the products are very useful. We will soon see that these products can be used in a large number of synthetic transformations. So, let's make sure that you are comfortable with the reactions between amines and nitrous acid.

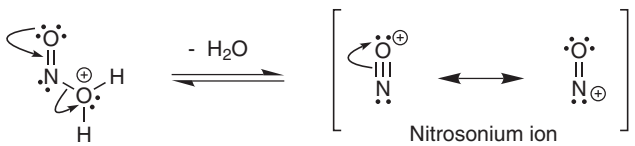
Let's start by looking at the source of nitrous acid. It turns out that nitrous acid is fairly unstable and, therefore, we cannot just store it in a bottle. Rather, we have to make nitrous acid in the reaction flask. To do this, we use sodium nitrite ($NaNO_2$) and HCl:



Under these (acidic) conditions, nitrous acid is protonated again, to produce a positively charged intermediate:



This intermediate can then lose water to give a highly reactive intermediate, called a nitrosonium ion:

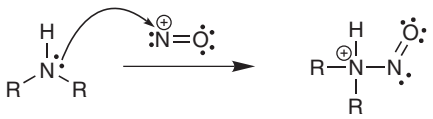


This intermediate (the nitrosonium ion) is the intermediate we must focus on. Whenever we talk about an amine reacting with nitrous acid, we really mean to say that the amine is reacting with a nitrosonium ion (NO^+). You might notice the similarity between this intermediate and the NO_2^+ intermediate (that we used in nitration reactions). Do not confuse these two intermediates. NO^+ and NO_2^+ are different intermediates. In this section, we are only talking about the reactions of amines with the nitrosonium ion (NO^+).

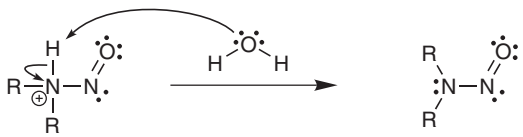
As we said a few moments ago, nitrosonium ions cannot be stored in a bottle. Instead, we must make them ***in the presence of an amine***. That way, as soon as the nitrosonium ion is formed, it will immediately react with the amine before it has a chance to do anything else. This is called an ***in situ*** preparation.

So, now the question is: what happens when an amine reacts with a nitrosonium ion? Let's begin by exploring secondary amines (and then we will explore primary amines).

A secondary amine can attack a nitrosonium ion like this:

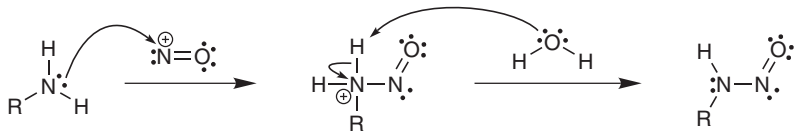


Deprotonation then generates the product:

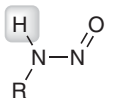


This product is called an ***N-nitroso amine***. For short, chemists often call it a ***nitrosamine***.

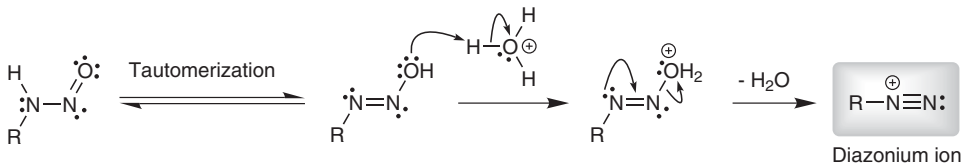
This reaction is not very useful. But when a ***primary*** amine attacks a nitrosonium ion, the resulting reaction is extremely important. The amine attacks, to initially form a nitrosamine:



Since we started with a primary amine, we notice that we have a proton in our nitrosamine:

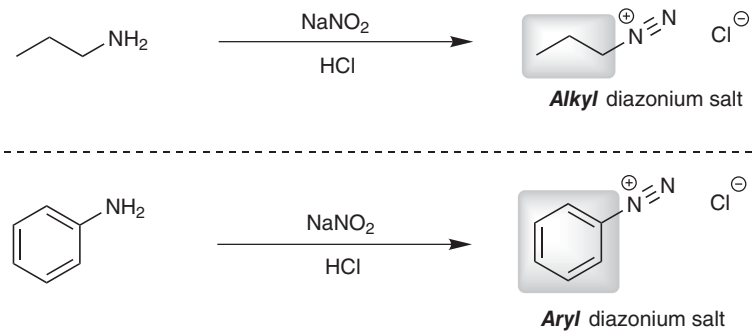


Because of this proton, the nitrosamine continues to react in the following way:



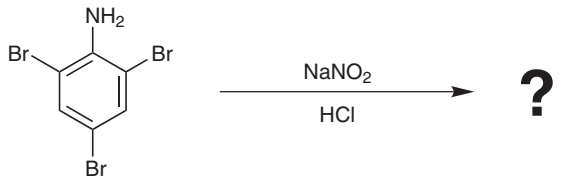
This cation is called a ***diazonium*** ion. The term ***azo*** means nitrogen, so ***diazo*** means two nitrogen atoms. And, of course, ***onium*** means a positive charge. That is what we have here: two nitrogen atoms connected to each other, and a positive charge; thus, the name ***diazonium***.

Primary ***alkyl*** amines will give ***alkyl*** diazonium salts, and primary ***aryl*** amines will give ***aryl*** diazonium salts:

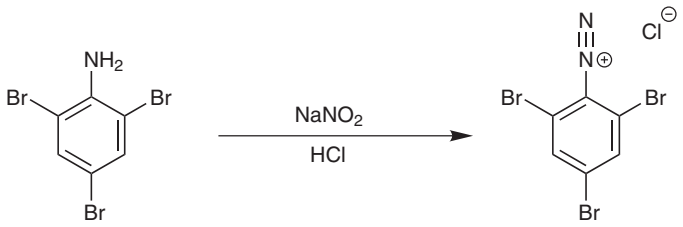


Alkyl diazonium salts are not terribly useful. They are very explosive, and as a result, they are very dangerous to prepare. But ***aryl*** diazonium salts are much more stable, and they are incredibly useful, as we will see in the upcoming section. For now, let's just make sure that we know how to make diazonium salts:

EXERCISE 9.26 Predict the product of the following reaction:

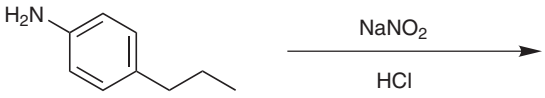


Answer Our starting material is a primary amine. These reagents (sodium nitrite and HCl) are used to form nitrous acid, which then forms a nitrosonium ion. Primary amines react with a nitrosonium ion to give a diazonium salt. So, the product of this reaction is:

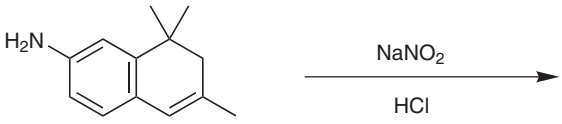


PROBLEMS Predict the major product for each of the following reactions:

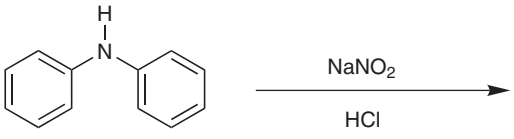
9.27



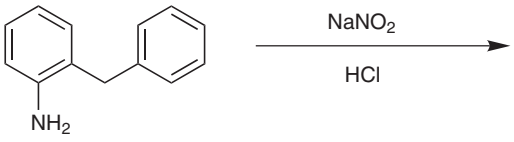
9.28



9.29

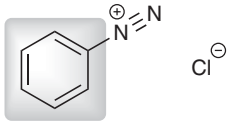


9.30



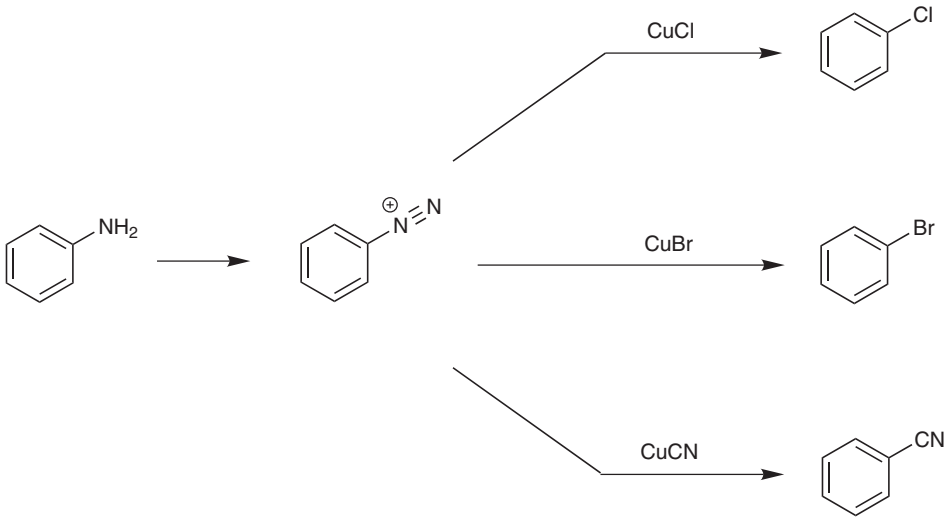
9.6 AROMATIC DIAZONIUM SALTS

In the previous section, we learned how to make aryl diazonium salts:



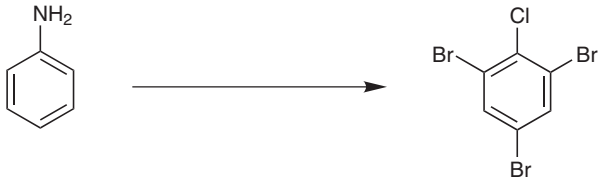
An ***aryl*** diazonium salt

Now we will learn what we can do with aryl diazonium salts. Here are a just few reactions:

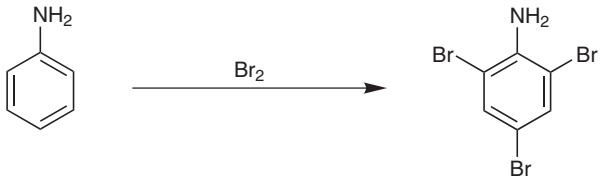


In all of these reactions, we are using copper salts as the reagents. These reactions are called ***Sandmeyer reactions***. They are useful, because they allow us to achieve transformations that we could not otherwise achieve with the chemistry that we learned in Chapters 4 and 5 (electrophilic and nucleophilic aromatic substitution). As a case in point, we did not see how to install a cyano group on an aromatic ring. This is our first way to do this.

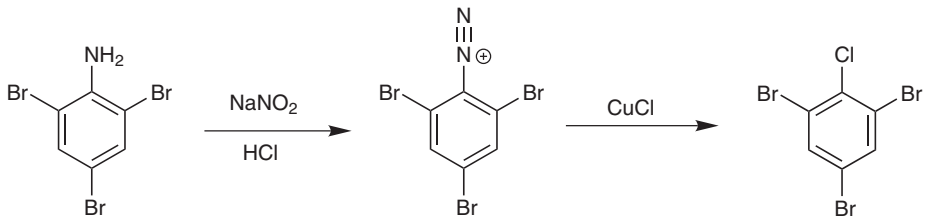
EXERCISE 9.31 What reagents would you use to achieve the following transformation:



Answer If we brominate aniline, we will find that the amino group is so activated that we will obtain a tribrominated product:



Then, we can convert the amino group into a chloro group. To do this, we make a diazonium salt, followed by a Sandmeyer reaction:



PROBLEMS What reagents would you use to achieve each of the following transformations:

9.32

9.33

9.34

9.35

9.36

So far, we have seen a few reactions that you can perform with aryl diazonium salts. Many instructors will cover additional reactions of aryl diazonium salts. You should look through your lecture notes to see what you are responsible for. Your textbook will certainly show you several more reactions that can be performed with aryl diazonium salts.

These reactions are very useful in synthesis problems. You will find that some problems will combine these reactions with electrophilic aromatic substitution reactions. These problems can range in difficulty, and they can get really tough at times. You will find many such problems in your textbook. As you go through some of the challenging problems in your textbook, I will leave you with a bit of last-minute advice:

There are two important activities that you must do in order to master these types of problems.

1. You must review the reactions and principles from the entire course. Go through your textbook and your lecture notes again and again and again. Make sure that you get to a point where you know all of the reactions cold (you should have a strong command over all of the reactions).
2. You must do as many problems as possible. If you don't get practice, you will find that even a very strong grasp of the reactions will be insufficient. In order to truly master the art of problem solving, you must ***practice, practice, practice***. I recommend that you do as many problems as possible. You might even find that they can be fun, believe it or not.

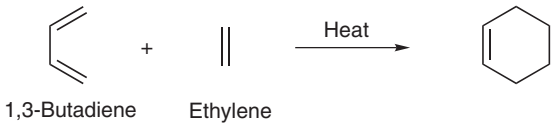
CHAPTER 10

DIELS–ALDER REACTIONS

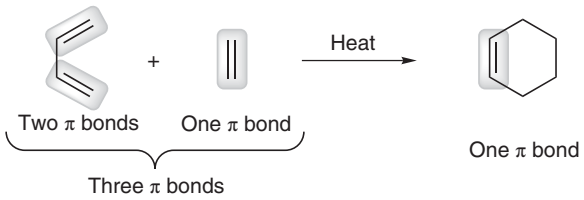
10.1 INTRODUCTION AND MECHANISM

During your organic chemistry course, you will encounter hundreds of reactions. Most (~95%) of these reactions can be characterized as *ionic reactions*, because they involve the participation of ions as reactants, intermediates, or products. However, you will encounter some reactions that do not involve ions. These reactions can generally be classified into one of two categories: *radical reactions* or *pericyclic reactions*. In this chapter, we will discuss one type of pericyclic reaction, called a *Diels–Alder* reaction. Other pericyclic reactions will be briefly introduced in the last section of this chapter.

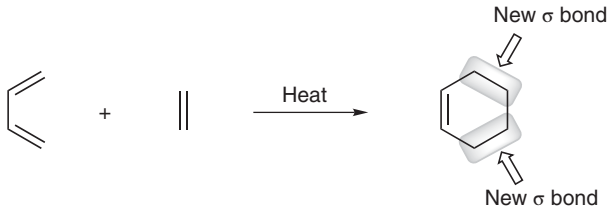
The following reaction, between 1,3-butadiene and ethylene, is a Diels–Alder reaction:



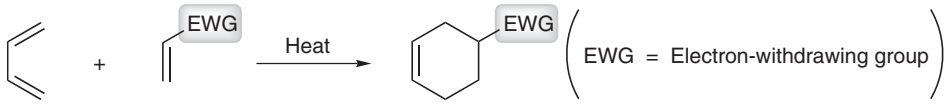
Notice that there are two reactants, but only one product, because the two reactants join together to form a six-membered ring. Also notice that the reactants have a total of three π bonds, while the product has only one π bond:



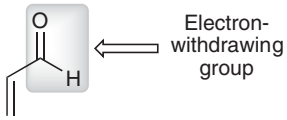
The disappearance of two π bonds is accompanied by the appearance of two new σ bonds, which form the six-membered ring:



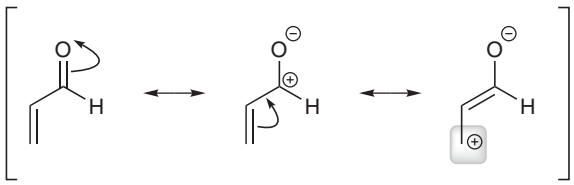
The yield of this reaction is actually quite poor (~20%). However, the yield is dramatically increased (making the reaction useful as a synthetic technique) if we use a substituted ethylene, in which the substituent is an electron-withdrawing group (EWG):



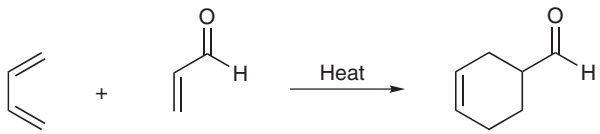
The following highlighted group is an example of an electron-withdrawing group:



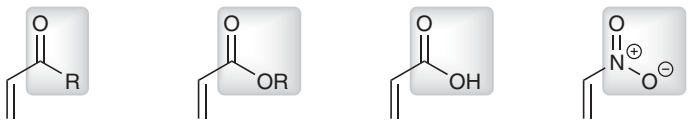
To rationalize why this group is electron withdrawing, we draw the resonance structures, and we focus specifically on the third resonance structure shown below:



Notice the position of the positive charge (highlighted) in the third resonance structure. The location of this charge indicates that the substituent withdraws electron density from the electron-rich π bond. When this compound reacts with 1,3-butadiene in a Diels–Alder reaction, the yield is observed to be very high (~100%):

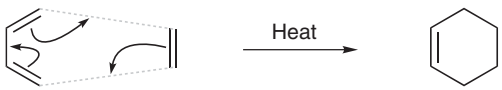


Other examples of electron-withdrawing groups are shown below (highlighted). Each of these compounds will react with 1,3-butadiene in a Diels–Alder reaction to give a high yield of product:



To rationalize why each of these groups is electron withdrawing, resonance structures can be drawn (just as we did for the aldehyde group a moment ago).

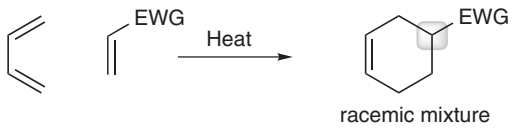
Diels–Alder reactions proceed via a mechanism that does NOT involve ions. Rather, these reactions occur via a single, concerted step, in which the π electrons move in a ring, as shown by the following curved arrows:



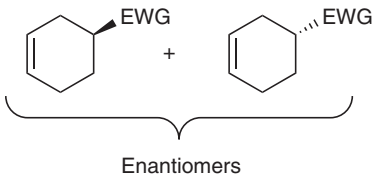
This process does not involve intermediates, because everything happens in one, concerted step. The electrons can be shown moving in a clockwise fashion, as shown above, or in a counterclockwise fashion, as shown here:

Depending on what textbook you are using, you may also see the curved arrows drawn like this (without dotted lines):

When a monosubstituted ethylene is used in a Diels–Alder reaction, the product will contain a chiral center (highlighted below):

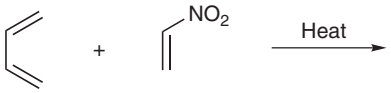


Since the reactants are achiral, the product is a racemic mixture. In other words, the product is a pair of enantiomers:

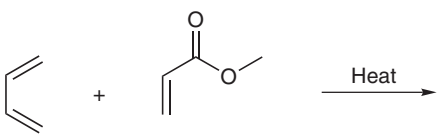


PROBLEMS Predict the major product(s) for each of the following reactions:

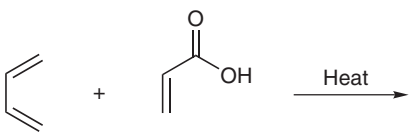
10.1



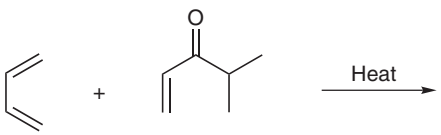
10.2



10.3



10.4

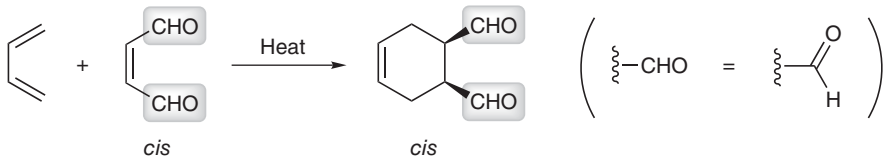


10.2 THE DIENOPHILE

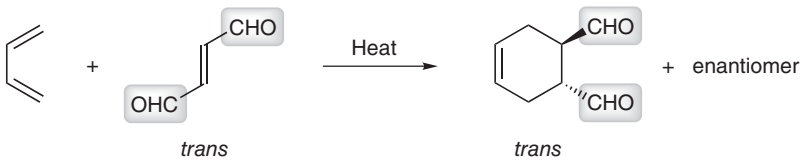
In a Diels–Alder reaction, we refer to the reactants as the *diene* and the *dienophile*:

The former is called a diene because it has two π bonds, and the latter is called a dienophile because it reacts with the diene. In this section, we will explore a variety of dienophiles in Diels–Alder reactions. The next section will focus on dienes.

When a 1,2-disubstituted ethylene is used as the dienophile in a Diels–Alder reaction, the configuration of the dienophile is preserved in the product. For example, a *cis*-disubstituted dienophile will react with 1,3-butadiene to give a *cis*-disubstituted product:

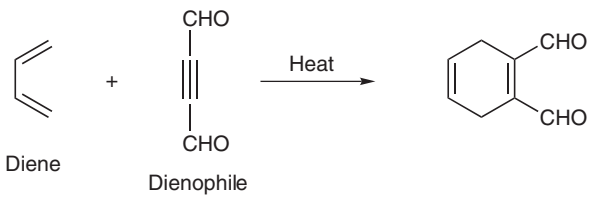


Similarly, a *trans*-disubstituted dienophile gives a *trans*-disubstituted product:

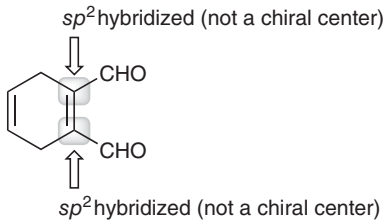


In each of the previous examples, the configuration of the dienophile was retained in the product.

Thus far, we have only seen alkenes (substituted ethylenes) functioning as dienophiles. There are, however, other functional groups that can function as dienophiles. The following example shows an alkyne functioning as a dienophile:



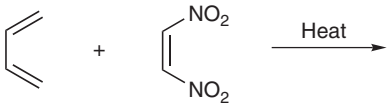
In this case, the dienophile has an extra π bond (compared with an alkene). This extra π bond "comes along for the ride," so to speak, which explains the extra π bond in the product (in between the two electron-withdrawing groups). Notice also that the product has no chiral centers:



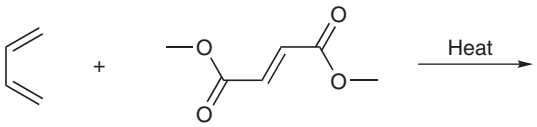
Therefore, we do not draw any wedges or dashes in this case.

PROBLEMS Predict the major product for each of the following reactions:

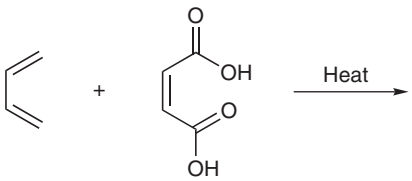
10.5



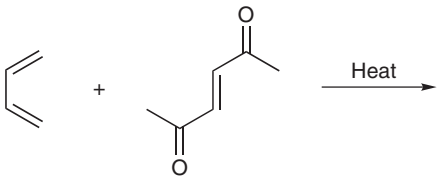
10.6



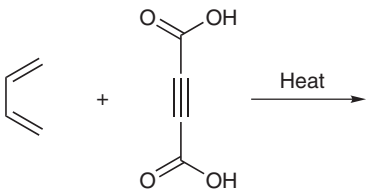
10.7



10.8

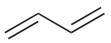


10.9



10.3 THE DIENE

In the previous section, we focused on dienophiles for Diels–Alder reactions. Now let's focus our attention on the other reactant in Diels–Alder reactions: the diene. As its name indicates, a diene has two π bonds. There are several conditions that must be met in order for a diene to react with a dienophile in a Diels–Alder reaction. First and foremost, the two π bonds of the diene must be *conjugated*:



A conjugated diene

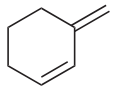
In a conjugated diene, the two π bonds are separated by exactly one sigma bond, highlighted here:

A Diels–Alder reaction will NOT occur if the two π bonds of the diene are too close to each other (as in cumulated dienes) or too far apart from each other (as in isolated dienes):

Now let's explore another important condition that must be met in order for a diene to react in a Diels–Alder reaction. Not only does it have to be conjugated, but it must also be capable of adopting an *s-cis* conformation. To illustrate what this means, consider the following two conformations of 1,3-butadiene:

In each of these conformations, all four *p* orbitals are aligned so that they can overlap to form a single, extended π system. An equilibrium is established between these two conformations, although the *s-trans* conformation is favored because it is more stable. At any moment in time, only 2% of the molecules are in an *s-cis* conformation. The Diels–Alder reaction only occurs when the diene is in an *s-cis* conformation. When the compound adopts an *s-trans* conformation, the ends of the diene are too far apart to react with the dienophile.

Some dienes cannot adopt an *s-cis* conformation, and as a result, they cannot react with dienophiles in a Diels–Alder reaction. As an example, consider the following compound:



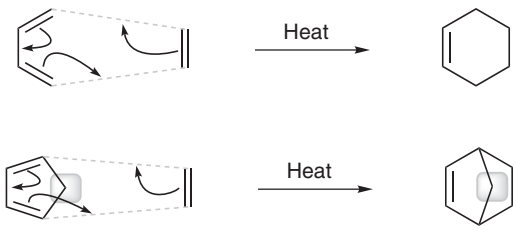
The geometry of the six-membered ring effectively locks this diene (permanently) in an *s-trans* conformation, so this compound will not react with a dienophile in a Diels–Alder reaction.

In contrast, a Diels–Alder reaction will be extremely rapid if the diene is permanently locked in an *s-cis* conformation, as in the following example, called cyclopentadiene:

Cyclopentadiene

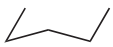
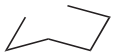
When cyclopentadiene is used as the diene in a Diels–Alder reaction, the reaction occurs very rapidly, because all of the molecules of the diene spend 100% of the time (rather than just 2% of the time) in the conformation necessary for a Diels–Alder reaction.

Now let's try to draw the product that we expect when cyclopentadiene is used as the diene in a Diels–Alder reaction. We expect the extra carbon atom (highlighted below) to "come along for the ride," so to speak. We expect the following:

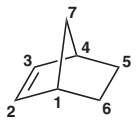


When cyclopentadiene is used as the diene, the product is bicyclic, and is more appropriately drawn in the following way:

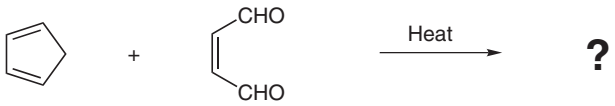
This type of 3D drawing is very useful, and you should practice drawing it, using the following steps:

STEP ONE	STEP TWO	STEP THREE	STEP FOUR	STEP FIVE	STEP SIX
Draw two lines in the shape of a shallow roof.	Starting at each end of the roof, draw a line going up and to the right. These two new lines must be parallel to each other.	Draw another roof that connects the tops of the two lines that you just drew. But only draw the right side of this new roof. We will connect the other side last.	Draw two new lines that will form the bridge of our structure, as shown.	Complete the bicyclic structure with a broken line, to indicate it is behind the vertical line.	Dont forget the pi bond.
					

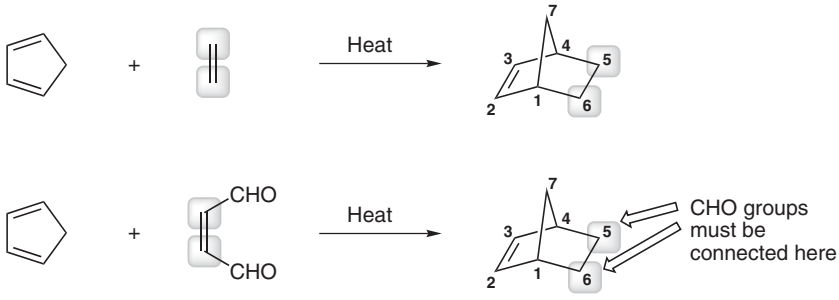
Practice these steps on a blank piece of paper, and repeat them until you feel comfortable drawing the skeleton without instructions. This skeleton will be formed whenever cyclopentadiene is used as the diene in a Diels–Alder reaction. If substituents are present, then we must place them in the correct locations, using the following numbering system:



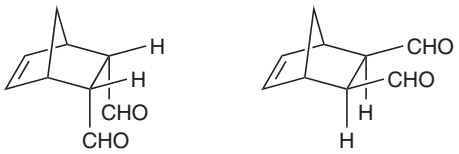
For example, consider the following reaction:



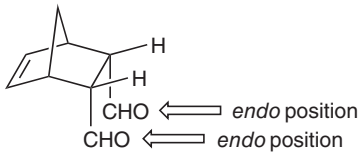
This is a Diels–Alder reaction involving cyclopentadiene, so we expect a bicyclic structure. To draw this bicyclic product, we must consider where the two aldehyde groups will be connected in the product:



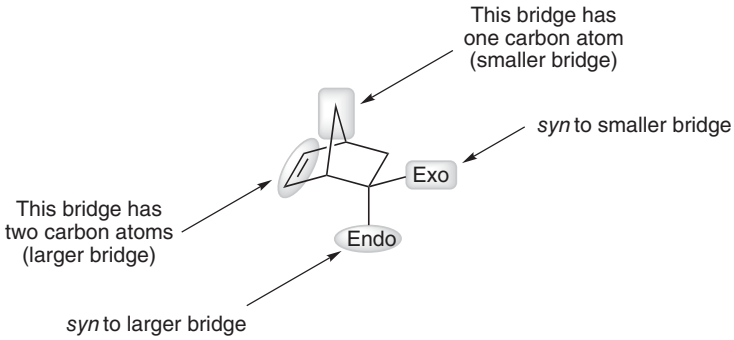
When we draw the product, we must place the aldehyde groups at positions C5 and C6, as shown above. When drawing these substituents in the product, remember that the configuration of the dienophile must be preserved in the product. In this case, the dienophile has a *cis* configuration, so the two aldehyde groups must be *cis* to each other in the product, as shown in each of the following two structures:



These are the two structures that we expect, however, the reaction does not actually produce both of them. In fact, one of these products is highly favored—the structure in which both aldehyde groups occupy *endo* positions:

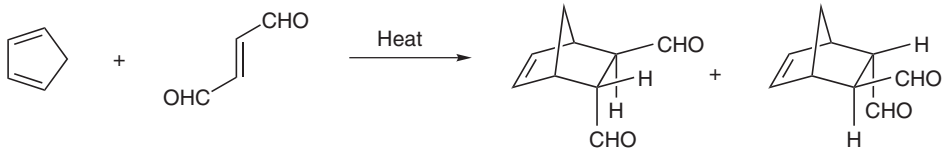


The *endo* position is defined as the position that is *syn* to the larger bridge, as illustrated here:

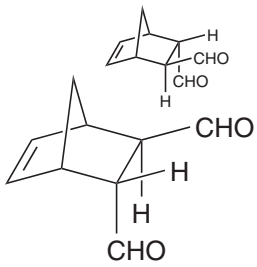


We observe a clear preference for the substituents (connected to the dienophile) to be located in *endo* positions in the bicyclic product, rather than in *exo* positions. What is the source of this preference? During formation of the *endo* product, there is a stabilizing interaction that occurs between the electron-withdrawing substituents (on the dienophile) and the developing π bond (on the diene). This stabilizing effect is absent during formation of the *exo* product. As such, formation of the *endo* product has a lower-energy transition state (and therefore a lower energy of activation) and so it occurs more rapidly than formation of the *exo* product.

If the dienophile is *trans*-disubstituted, then both substituents cannot occupy *endo* positions in the bicyclic product, because the *trans* configuration of the dienophile must be preserved. Two products are obtained:

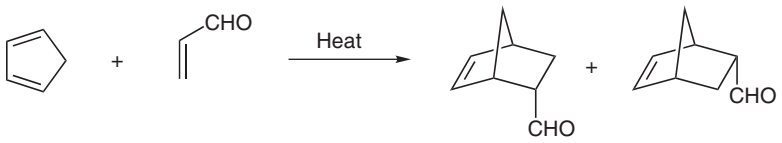


In each product, one aldehyde group occupies an *endo* position and the other aldehyde group occupies an *exo* position. These two products represent a pair of enantiomers. In order to see that they are enantiomers, imagine placing one in front of the other:

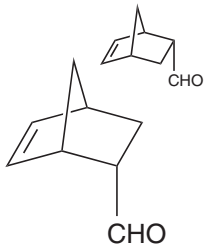


This more clearly shows that they are mirror images (the plane of the mirror is in between the two compounds).

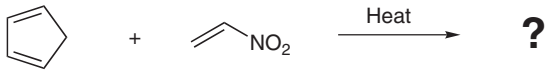
If the dienophile is a monosubstituted ethylene, as in the following case, then the following products are obtained:



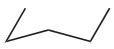
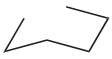
Notice that the aldehyde group occupies an *endo* position in each product. And once again, we can see that these products represent a pair of enantiomers (mirror images that are nonsuperimposable) if we place one compound in front of the other:



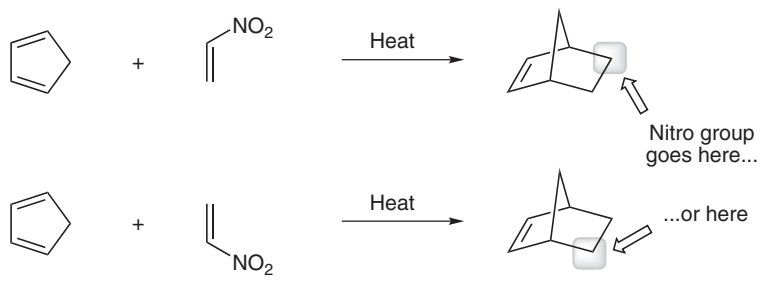
WORKED PROBLEM 10.10 Predict the products that are expected when cyclopentadiene is treated with nitroethylene:



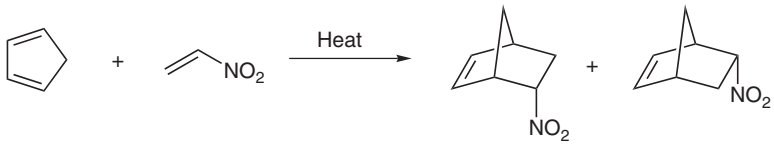
Answer The reactants are a diene and a dienophile, so we expect a Diels–Alder reaction. The diene is cyclopentadiene, so we expect a bicyclic skeleton, which we can draw using the following steps

STEP ONE	STEP TWO	STEP THREE	STEP FOUR	STEP FIVE	STEP SIX
Draw two lines in the shape of a shallow roof.	Starting at each end of the roof, draw a line going up and to the right. These two new lines must be parallel to each other.	Draw another roof that connects the tops of the two lines that you just drew. But only draw the right side of this new roof. We will connect the other side last.	Draw two new lines that will form the bridge of our structure, as shown.	Complete the bicyclic structure with a broken line, to indicate it is behind the vertical line.	Dont forget the pi bond.
					

The dienophile bears one substituent (a nitro group), which will end up in one of the following two locations:



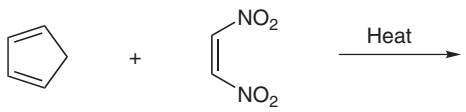
At each of these locations, we expect the nitro group to occupy an *endo* position, rather than an *exo* position, giving the following two products:



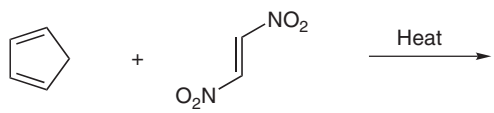
These products represent a pair of enantiomers.

PROBLEMS Predict the major product(s) for each of the following reactions:

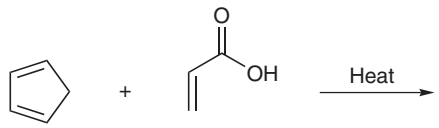
10.11



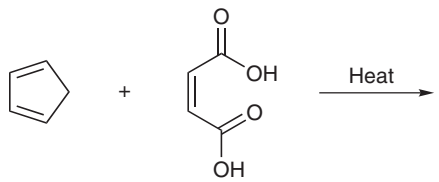
10.12

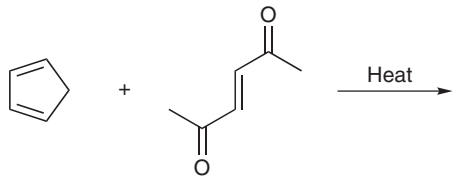


10.13

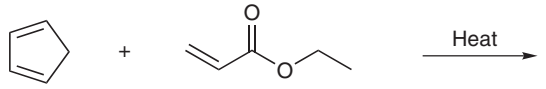


10.14





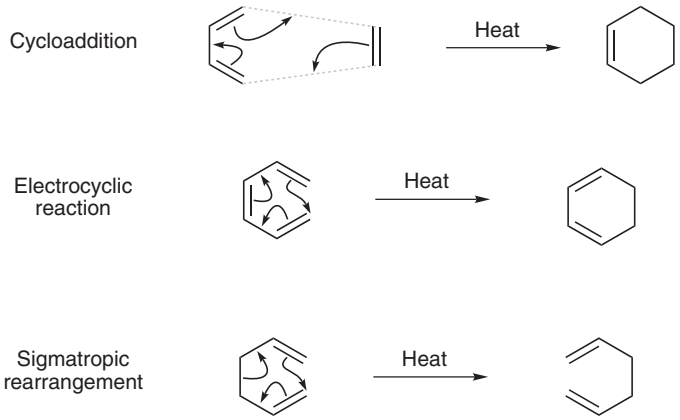
10.15



10.16

10.4 OTHER PERICYCLIC REACTIONS

Diels–Alder reactions belong to one category of pericyclic reactions, called cycloaddition reactions. However, there are two other major categories of pericyclic reactions, called electrocyclic reactions and sigmatropic rearrangements. The three major categories of pericyclic reactions are shown here:



The first category (cycloaddition) was introduced in this chapter. If we compare the other two categories to cycloaddition, we find some similarities. In each case, the curved arrows are moving around in a ring, and the entire process occurs in one concerted step. Indeed, these are some of the features that place these reactions under the larger umbrella of pericyclic reactions. But if we inspect the reactions above more carefully, we will begin to see some important differences. For example, cycloaddition reactions require two reactants (an *inter*molecular process), while electrocyclic and sigmatropic reactions have only one reactant (*intra*molecular processes). Also, if we count the number of bonds being broken and formed in each category, we will see a key difference between the categories. In a cycloaddition process, two π bonds are replaced with two new σ bonds. In an electrocyclic reaction, one π bond is replaced with one new σ bond. In sigmatropic rearrangements, the number of π bonds and σ bonds does not change (only their locations change).

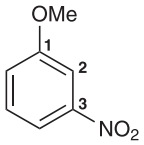
You should consult your textbook and/or lecture notes to see if you are responsible for any examples of electrocyclic reactions or sigmatropic rearrangements (such as the Cope rearrangement or the Claisen rearrangement).

DETAILED SOLUTIONS

CHAPTER 1

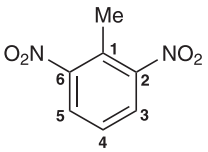
1.2 This compound is a disubstituted benzene, and it can be named 1-methoxy-3-nitrobenzene. The methoxy group is assigned the lower number because it comes first alphabetically.

We can also name the compound as a monosubstituted derivative of anisole. Since we are using a common name (anisole) as the parent, we must assign numbers starting with the carbon atom connected to the methoxy group. This means that the methoxy group is connected to C1, by definition. In this case, we assign numbers in a clockwise fashion, so that the nitro group is at C3 rather than C5. Therefore, this compound can be named 3-nitroanisole or *meta*-nitroanisole.

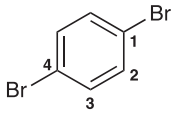


1.3 This compound is a trisubstituted benzene, and it can be named 2-methyl-1,3-dinitrobenzene. When naming in this way, the numbers are assigned to give the lowest possible numbers to all three substitutents (C1, C2, and C3). In the name, the methyl group appears first because "m" precedes "n" alphabetically.

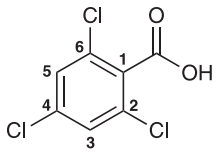
We can also name the compound as a disubstituted derivative of toluene. Since we are using a common name (toluene) as the parent, we must assign numbers starting with the carbon atom connected to the methyl group. This means that the methyl group is connected to C1, by definition. In this case, the numbers can be assigned either clockwise or counterclockwise; either way, there will be a nitro group at C2 and another nitro group at C6. Therefore, this compound can be named 2,6-dinitrotoluene.



1.4 This compound is a disubstituted benzene, in which the two substituents are *para* to each other. This compound can be called 1,4-dibromobenzene or *para*-dibromobenzene.

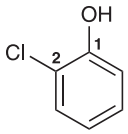


1.5 This compound can be named as a trisubstituted derivative of benzoic acid. Since we are using a common name (benzoic acid) as the parent, we must assign numbers starting with the carbon atom connected to the carboxylic acid group. This means that the carboxylic acid group is connected to C1, by definition. In this case, the numbers can be assigned either clockwise or counterclockwise; either way, there will be three chloro substituents, at C2, C4, and C6. Therefore, this compound can be named 2,4,6-trichlorobenzoic acid.



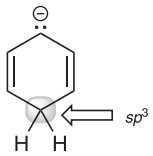
1.6 This compound is a disubstituted benzene, and it can be named 1-chloro-2-hydroxybenzene. The chlorine substituent is assigned the lower number because it comes first alphabetically.

Alternatively, we can name the compound as a monosubstituted derivative of phenol. Since we are using a common name (phenol) as the parent, we must assign numbers starting with the carbon atom connected to the hydroxy group. This means that the hydroxy group is connected to C1, by definition. In this case, we assign numbers in a counterclockwise fashion, so that the chloro substituent is at C2 rather than C6. Therefore, this compound can be named 2-chlorophenol or *ortho*-chlorophenol.



1.8 The first criterion for aromaticity is not satisfied, because the ring contains an sp^3 hybridized carbon atom (highlighted).

Since the ring lacks a continuous system of overlapping *p* orbitals, this anion is nonaromatic.



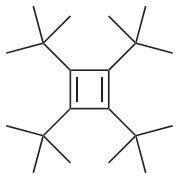
1.9 Recall that a carbocation represents an empty *p* orbital. Accordingly, the first criterion for aromaticity is satisfied (a ring with a continuous system of overlapping *p* orbitals), and the second criterion is also satisfied (there are 2 π electrons). Therefore, this cation is aromatic.

1.10 Recall that a carbocation represents an empty *p* orbital. Accordingly, the first criterion for aromaticity is satisfied (a ring with a continuous system of overlapping *p* orbitals), and the second criterion is also satisfied (there are 6 π electrons). Therefore, this cation is aromatic.

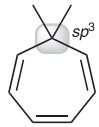
1.11 The first criterion for aromaticity is satisfied (a ring with a continuous system of overlapping *p* orbitals), but the second criterion is not satisfied (there are 8 π electrons in this case). As such, this structure is antiaromatic and is therefore very unstable.

Perhaps some of the instability could be reduced if the lone pair occupies an sp^3 hybridized orbital rather than a *p* orbital (thereby disrupting the continuous system of overlapping *p* orbitals), although this would render the lone pair localized (not stabilized by resonance) because a lone pair only participates in resonance when it occupies a *p* orbital. So, there is no way for this anion to be stable. Indeed, this anion is very unstable and is classified as antiaromatic.

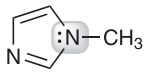
1.12 The first criterion for aromaticity is satisfied (a ring with a continuous system of overlapping *p* orbitals), but the second criterion is not satisfied (there are 4 π electrons in this case). As such, this structure is antiaromatic.



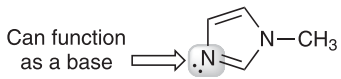
1.13 The first criterion for aromaticity is not satisfied, because the ring contains an sp^3 hybridized carbon atom (highlighted below). Since the ring lacks a continuous system of overlapping *p* orbitals, this structure is nonaromatic.



1.14 The lone pair highlighted here occupies a *p* orbital and is part of the aromatic system. So this lone pair is not available to function as a base:



In contrast, the other lone pair (highlighted below) occupies an sp^2 hybridized orbital and is not part of the aromatic system, so it is available to function as a base:

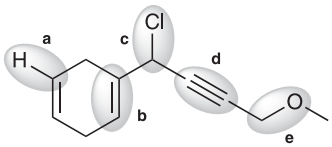


1.15 In the structure below, the sulfur atom has two lone pairs. One of these lone pairs occupies a *p* orbital, giving a continuous system of overlapping *p* orbitals with 6 π electrons. Therefore, this structure (called thiophene) is aromatic:

In the other structure (with two sulfur atoms), if each sulfur atom were to adopt sp^2 hybridization (and each were to place one lone pair in a *p* orbital), then there would be eight π electrons, which would be antiaromatic.

CHAPTER 2

2.1 Among the highlighted bonds, the C—H bond will produce the signal with the highest wavenumber, because hydrogen has the smallest mass. The other single bonds that are highlighted (C—O and C—Cl) will produce signals with low wavenumbers because they are single bonds. When comparing these two bonds to each other, oxygen has a smaller mass than chlorine, so a C—O bond will produce a signal with a higher wavenumber than a C—Cl bond. Therefore, the C—Cl bond will produce the signal with the lowest wavenumber, and the C—O bond will produce the signal with the second-lowest wavenumber. Among the remaining two bonds that are highlighted, the triple bond is stronger than the double bond and will therefore produce a signal with a higher wavenumber. In summary, the highlighted bonds are ranked below in order of decreasing wavenumber.

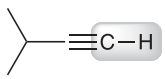


a > d > b > e > c

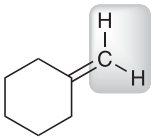
2.2 This compound has a double bond, but it is tetrasubstituted, so there are no C_{sp^2}—H bonds. Since the compound lacks C_{sp^2}—H and C_{sp}—H bonds, we do not expect there to be a signal above 3000 cm^{-1}.

2.3 This compound has no double or triple bonds. In fact, it does not have any functional groups and is classified as an alkane. Since the compound lacks C_{sp^2}—H and C_{sp}—H bonds, we do not expect there to be a signal above 3000 cm^{-1}.

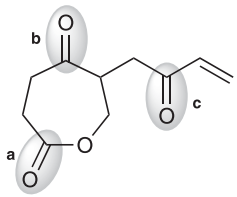
2.4 This compound is a terminal alkyne. Since it has a C_{sp}—H bond (highlighted below), we expect there to be a signal above 3000 cm^{-1}, likely near 3300 cm^{-1}.



2.5 This compound is a disubstituted alkene. Since it has a C_{sp^2}—H bonds (highlighted below), we expect there to be a signal above 3000 cm^{-1}, likely near 3100 cm^{-1}.

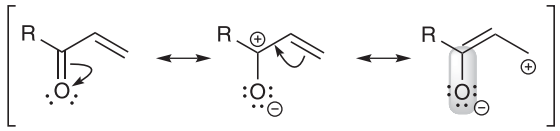


2.6 The carbonyl group "a" below is part of an ester, which generally produces a signal at 1740 cm^{-1}. The carbonyl group "b" below is part of a ketone, which generally produces a signal at 1720 cm^{-1}. The remaining carbonyl group is part of a conjugated unsaturated ketone, which is expected to produce a signal at a lower wavenumber than a saturated ketone (1680 cm^{-1}, rather than 1720 cm^{-1}).

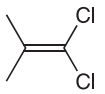


a > b > c

The conjugated unsaturated ketone ("c") produces a signal at a lower wavenumber than the saturated ketone ("b"), because of an additional resonance structure (shown below) that gives additional single-bond character to the C═O bond (see the highlighted bond below). This decreases the strength of the C═O bond, thereby resulting in a signal at a lower wavenumber.



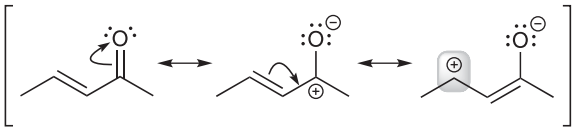
2.7 The strongest signal will be produced by the C═C bond with the greatest dipole moment. Among the three structures shown in the problem statement, the structure below has the C═C bond with the greatest dipole moment, because the two vinylic positions (the two carbon atoms of the C═C bond) are in different electronic environments.



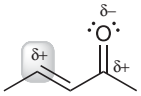
One vinylic position (left) is electron-rich as a result of the electron-donating methyl groups, while the other vinylic position (right) is electron-poor as a result of the electron-withdrawing chlorine atoms. This results in the C═C bond having a relatively strong dipole moment for a C═C bond, giving rise to a relatively strong signal in an IR spectrum.

In contrast, each of the other two compounds has a C═C bond with no dipole moment, because in each case, both vinylic positions occupy identical electronic environments.

2.8 We begin by drawing all resonance structures and considering the location of the partial positive charge in the last resonance structure (highlighted).



The last resonance structure contributes some of its character to the overall resonance hybrid. As a result, the highlighted carbon atom has partial positive character in the resonance hybrid, as shown here:



Since the two vinylic carbon atoms (the two carbon atoms of the C═C bond) occupy very different electronic environments, this C═C bond will have a relatively strong dipole moment, and as a result, this C═C bond will produce a relatively strong signal in an IR spectrum (compared with the relatively weak signals that are generally associated with C═C bonds).

2.9 This IR spectrum exhibits a broad signal between 3200 cm^{-1} and 3600 cm^{-1}. The presence of this signal in the IR spectrum is consistent with the structure of an alcohol.

2.10 This IR spectrum does not have any signals above 3000 cm^{-1}, so it is not consistent with the structure of an alcohol or a carboxylic acid.

2.11 This IR spectrum exhibits an extremely broad signal between 2200 cm^{-1} and 3600 cm^{-1}, as well as a strong signal just above 1700 cm^{-1}. The presence of these signals in the IR spectrum is consistent with the structure of a carboxylic acid.

2.12 This IR spectrum exhibits a broad signal between 3200 cm^{-1} and 3600 cm^{-1}. The presence of this signal in the IR spectrum is consistent with the structure of an alcohol.

2.13 This IR spectrum exhibits an extremely broad signal between 2200 cm^{-1} and 3600 cm^{-1}, as well as a strong signal just above 1700 cm^{-1}. The presence of these signals in the IR spectrum is consistent with the structure of a carboxylic acid.

2.14 This IR spectrum does not have any signals above 3000 cm^{-1}, so it is not consistent with the structure of an alcohol or a carboxylic acid.

2.15 This IR spectrum exhibits a broad signal between 3200 cm^{-1} and 3600 cm^{-1}. The presence of this signal in the IR spectrum is consistent with the structure of an alcohol.

2.16 This IR spectrum exhibits an extremely broad signal between 2200 cm^{-1} and 3600 cm^{-1}, as well as a strong signal just above 1700 cm^{-1}. The presence of these signals in the IR spectrum is consistent with the structure of a carboxylic acid.

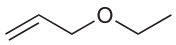
2.17 This IR spectrum exhibits a pair of signals at 3350 cm^{-1} and 3450 cm^{-1}. The presence of these signals in the IR spectrum is consistent with the structure of a primary amine.

2.18 This IR spectrum exhibits a strong signal just above 1700 cm^{-1}. The presence of this signal in the IR spectrum is consistent with the structure of a ketone (the little bump at 3400 cm^{-1} can be ignored, as will be explained in the solution to Problem 2.21).

2.19 This IR spectrum exhibits a broad, weak signal at approximately 3400 cm^{-1}. The presence of this signal in the IR spectrum is consistent with the structure of a secondary amine.

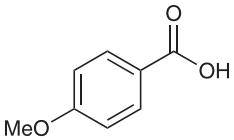
2.20 This IR spectrum exhibits a broad signal between 3200 cm^{-1} and 3600 cm^{-1}. The presence of this signal in the IR spectrum is consistent with the structure of an alcohol.

2.22 Spectrum A exhibits a weak signal at around 1650 cm^{-1}, suggesting the presence of a C═C bond that is unsymmetrical. There is also a signal just above 3000 cm^{-1}, suggesting the presence of a C_{sp^2}—H bond. Both of these features are consistent with the following structure, which has an unsymmetrical C═C bond with at least one attached hydrogen atom:



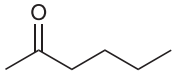
A

Spectrum B exhibits an extremely broad signal between 2200 cm^{-1} and 3600 cm^{-1}, as well as a somewhat strong signal just above 1700 cm^{-1}. The presence of these signals in the IR spectrum is consistent with the structure of a carboxylic acid. There is also a signal at 1600 cm^{-1} suggesting the presence of C═C bonds. These features are consistent with the following structure:



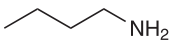
B

Spectrum C exhibits a strong signal just above 1700 cm^{-1}. The presence of this signal in the IR spectrum is consistent with the structure of a ketone (the C═O overtone signal at 3400 cm^{-1} can be ignored, as was explained in the solution to Problem 2.21).



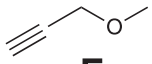
C

Spectrum D exhibits a pair of signals at 3350 cm^{-1} and 3450 cm^{-1}. The presence of these signals in the IR spectrum is consistent with the structure of a primary amine.



D

Spectrum E exhibits a signal just above 2100 cm^{-1}, suggesting the presence of a C≡C bond that is unsymmetrical. There is also a narrow signal at 3300 cm^{-1}, suggesting the presence of a C_{sp}—H bond. Both of these features are consistent with the following structure, which is a terminal alkyne:



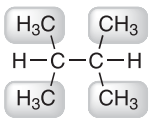
E

Finally, spectrum F exhibits a broad signal between 3200 cm^{-1} and 3600 cm^{-1}. The presence of this signal in the IR spectrum is consistent with the structure of an alcohol.

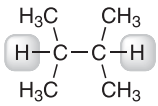
F

CHAPTER 3

3.2 In this structure, all four methyl groups are interchangeable via symmetry, so the protons of these methyl groups (highlighted) are chemically equivalent:

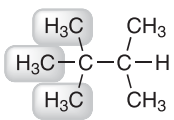


The remaining two protons are interchangeable via symmetry and are therefore chemically equivalent:

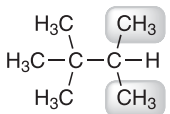


so this compound will have a proton NMR spectrum with exactly two signals.

3.3 In this structure, the three methyl groups highlighted below are all chemically equivalent (in much the same way that the three protons of a single methyl group are equivalent to each other):

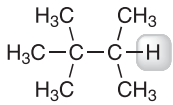


Furthermore, the remaining two methyl groups are interchangeable via symmetry, so they are chemically equivalent to each other:



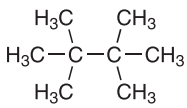
Note that there are a total of five methyl groups, and they are NOT all equivalent to each other. Rather, the three methyl groups on the left represent one type of proton, and the two methyl groups on the right represent a different type of proton.

Finally, there is one more proton, highlighted here:



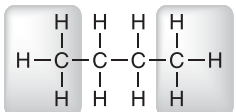
so this compound will have a proton NMR spectrum with exactly three signals.

3.4 In this structure, the three methyl groups on the left side of the structure are chemically equivalent (as we saw in the previous problem), and the three methyl groups on the right side of the structure are also equivalent to each other (for the same reason).

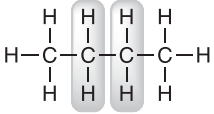


In this case, there is additional symmetry that was absent in the previous problem. Here, the methyl groups on the left side ARE identical to the methyl groups on the right side, because they are interchangeable via symmetry. Therefore, all six methyl groups are chemically equivalent, so this compound will have a proton NMR spectrum with only one signal.

3.5 In this structure, the two methyl groups (highlighted) are interchangeable via symmetry, so the protons of these methyl groups are chemically equivalent:

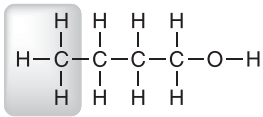


The remaining two methylene (CH_2) groups are interchangeable via symmetry, so all four of these protons (highlighted) are chemically equivalent:

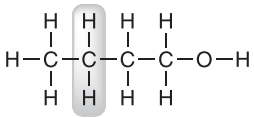


In summary, this compound will have a proton NMR spectrum with exactly two signals.

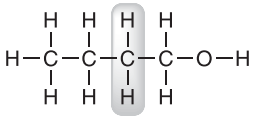
3.6 The three protons of the methyl group are all equivalent to each other:



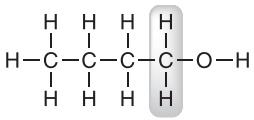
Furthermore, since this compound lacks a chiral center, the two protons of this methylene (CH_2) group are chemically equivalent to each other:



For a similar reason, the following two protons are also equivalent to each other:

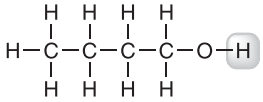


and these two protons are also equivalent to each other:



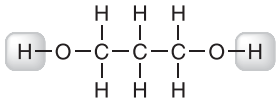
Note that the three CH_2 groups are NOT all equivalent to each other (they represent three different types of protons), because they do NOT occupy identical electronic environments (they are not interchangeable by symmetry). They differ from each other in their proximity to the oxygen atom.

Finally, there is one more signal from the proton connected to the oxygen atom:

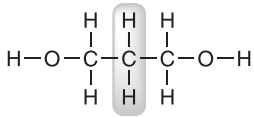


In summary, the proton NMR spectrum of this compound will have exactly five signals.

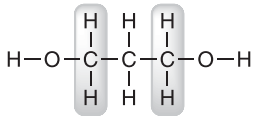
3.7 The protons connected to the oxygen atoms are interchangeable via symmetry and are therefore chemically equivalent:



Furthermore, since this compound lacks a chiral center, the two protons of the central methylene (CH_2) group are chemically equivalent to each other:



Similarly, the following four protons are also chemically equivalent to each other:



Note that the three CH_2 groups are NOT all equivalent to each other (they represent two different types of protons, not one type of proton), because they do NOT all occupy identical electronic environments. Each of the outer two CH_2 groups is connected directly to one of the oxygen atoms, while the central CH_2 group is NOT connected directly to an oxygen atom.

In summary, the proton NMR spectrum of this compound will have exactly three signals.

3.8 Each of the methyl groups produces its own signal:

These two methyl groups are not chemically equivalent to each other, because they occupy different electronic environments. The methyl group on the left is closer to the oxygen atom, while the methyl group on the right is more distant from the oxygen atom.

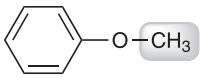
There is also a proton connected directly to the oxygen atom, and there is a CH proton (shown below), each of which produces its own signal:

So far, we have counted four signals (CH_3, CH_3, OH, and CH). Finally, we consider the methylene (CH_2) group. In this case, the structure contains a chiral center, and therefore, we expect the two protons of the methylene group to be different (not chemically equivalent):

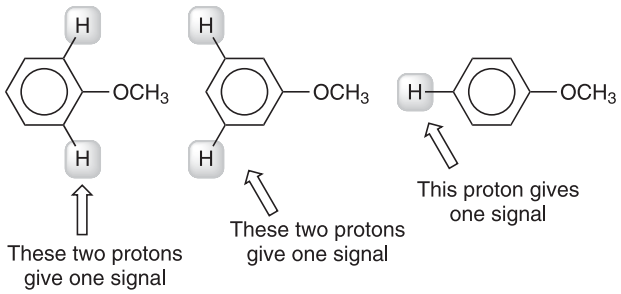
In summary, the proton NMR spectrum of this compound will have six signals.

In practice, depending on the type of NMR spectrometer that is used, the two signals corresponding to the CH_2 protons could possibly appear as one signal (rather than two), especially if the spectrum is acquired with an NMR spectrometer that uses a relatively weak magnetic field. With an NMR spectrometer that uses a strong magnetic field, the two signals corresponding to the CH_2 protons can be easily distinguished.

3.9 The three protons of the methyl group produce one signal:

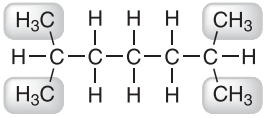


The five aromatic protons give rise to three distinct signals, corresponding to the highlighted protons shown here:

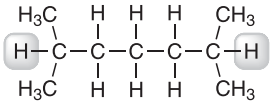


In summary, the proton NMR spectrum of this compound will have four signals.

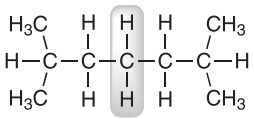
3.10 In this structure, all four methyl groups are interchangeable via symmetry, so the protons of these methyl groups (highlighted) are chemically equivalent:



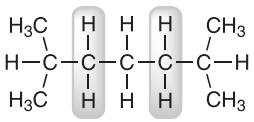
Similarly, the CH protons (highlighted below) are chemically equivalent to each other:



Furthermore, since this compound lacks a chiral center, the two protons of the central methylene (CH_2) group are chemically equivalent to each other:



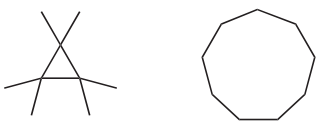
Similarly, the following four protons are also chemically equivalent:



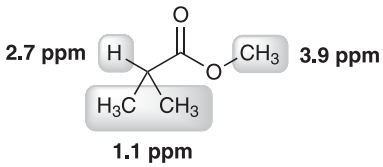
Note that the three CH_2 groups are NOT all equivalent to each other (they represent two different types of protons, not just one type of proton), because they do NOT all occupy identical electronic environments.

In summary, the proton NMR spectrum of this compound will have exactly four signals.

3.11 Both of the structures below have the molecular formula C_9H_{18}, and in each case, all 18 protons are chemically equivalent. In the first structure, all six methyl groups are chemically equivalent (giving rise to just one signal); in the second structure, all nine CH_2 groups are chemically equivalent (once again, giving rise to just one signal).



3.13 The proton NMR spectrum of this compound will have three signals, corresponding to the groups of protons highlighted below.

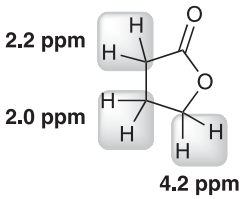


The methyl protons on the right side of the structure (benchmark value = 0.9 ppm) are alpha to the oxygen atom of an ester, which adds +3, so the predicted chemical shift = 0.9 + 3 = 3.9 ppm.

The methyl protons on the left side of the structure (benchmark value = 0.9 ppm) are beta to a carbonyl group, which adds +0.2, so the predicted chemical shift = 0.9 + 0.2 = 1.1 ppm.

And finally, the methine proton (benchmark value = 1.7 ppm) is alpha to a carbonyl group, which adds +1.0, so the predicted chemical shift = 1.7 + 1 = 2.7 ppm.

3.14 The proton NMR spectrum of this compound will have three signals, corresponding to the groups of protons highlighted below.

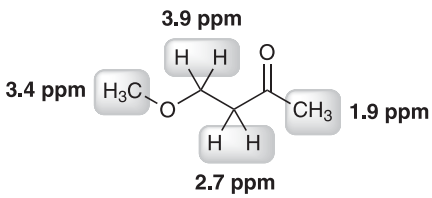


Starting at the top of the ring, and going counterclockwise around the ring, the first methylene group should give a signal near 2.3 ppm because a methylene group has a benchmark value of 1.2 ppm, and this methylene group is alpha to a carbonyl group (+1). Thus, 1.2 + 1 = 2.2 ppm.

The next methylene group should give a signal near 2.0 ppm because a methylene group has a benchmark value of 1.2 ppm, and this methylene group is beta to a carbonyl group (+0.2) and beta to the oxygen of an ester (+0.6). Thus, 1.2 + 0.2 + 0.6 = 2.0 ppm.

And finally, the last methylene group should give a signal near 4.2 ppm because a methylene group has a benchmark value of 1.2 ppm, and this methylene group is alpha to the oxygen of an ester (+3). Thus, 1.2 + 3 = 4.2 ppm.

3.15 The proton NMR spectrum of this compound will have four signals, corresponding to the groups of protons highlighted below.



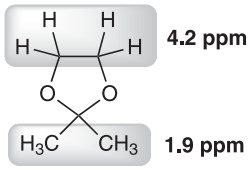
The methyl protons on the left side of the structure (benchmark value = 0.9 ppm) are alpha to the oxygen atom of an ether, which adds +2.5, so the predicted chemical shift = 0.9 + 2.5 = 3.4 ppm.

The methyl protons on the right side of the structure (benchmark value = 0.9 ppm) are alpha to a carbonyl group, which adds +1, so the predicted chemical shift = 0.9 + 1 = 1.9 ppm.

There are two other signals, both corresponding to methylene groups. Let's begin with the methylene group on the left. The benchmark value for a methylene group is 1.2 ppm, but this methylene group is alpha to the oxygen atom of an ether (+2.5) and beta to a carbonyl group (+0.2), so the predicted chemical shift = 1.2 + 2.5 + 0.2 = 3.9 ppm.

For the remaining methylene group, the benchmark value is 1.2 ppm, but this methylene group is alpha to a carbonyl group (+1) and beta to the oxygen atom of an ether (+0.5), so the predicted chemical shift = 1.2 + 1 + 0.5 = 2.7 ppm.

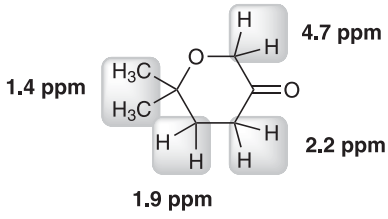
3.16 The proton NMR spectrum of this compound will have two signals, corresponding to the groups of protons highlighted below.



The methyl groups are chemically equivalent to each other, and they collectively produce one signal. The benchmark value for a methyl group is 0.9 ppm, and each of these methyl groups is beta to two ether groups (+0.5 + 0.5), which should give a signal near 0.9 + 0.5 + 0.5 = 1.9 ppm.

The methylene groups are chemically equivalent to each other, and they collectively produce one signal. The benchmark value for a methylene group is 1.2 ppm, and each of these methylene groups is alpha to one ether group (+2.5) and beta to another ether group (+0.5), which should give a signal near 1.2 + 2.5 + 0.5 = 4.2 ppm.

3.17 The proton NMR spectrum of this compound will have four signals, corresponding to the groups of protons highlighted below.



Going counterclockwise around the ring, we first encounter two equivalent methyl groups that collectively produce one signal. The benchmark value for a methyl group is 0.9 ppm, and each of these

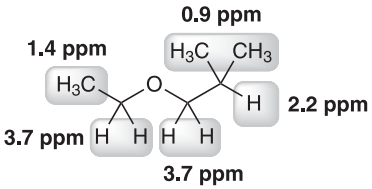
methyl groups is beta to an ether group (+0.5), which should give a signal near 0.9 + 0.5 = 1.4 ppm.

Moving counterclockwise through the structure, we next encounter a methylene group, which should give a signal near 1.9 ppm because a methylene group has a benchmark value of 1.2 ppm, and this methylene group is beta to a carbonyl group (+0.2) and beta to the oxygen of an ether (+0.5). Thus, 1.2 + 0.2 + 0.5 = 1.9 ppm.

Moving counterclockwise through the structure, we next encounter a methylene group, which should give a signal near 2.2 ppm because a methylene group has a benchmark value of 1.2 ppm, and this methylene group is alpha to a carbonyl group (+1). Thus, 1.2 + 1 = 2.2 ppm.

And finally, the last methylene group should give a signal near 4.7 ppm because a methylene group has a benchmark value of 1.2 ppm, and this methylene group is alpha to the oxygen of an ether (+2.5) and alpha to a carbonyl group (+1). Thus, 1.2 + 2.5 + 1 = 4.7 ppm.

3.18 The proton NMR spectrum of this compound will have five signals, corresponding to the groups of protons highlighted below.



Moving from left to right through structure, we first encounter a methyl group (benchmark value = 0.9 ppm) that is beta to the oxygen atom of an ether, which adds +0.5, so the predicted chemical shift = 0.9 + 0.5 = 1.4 ppm.

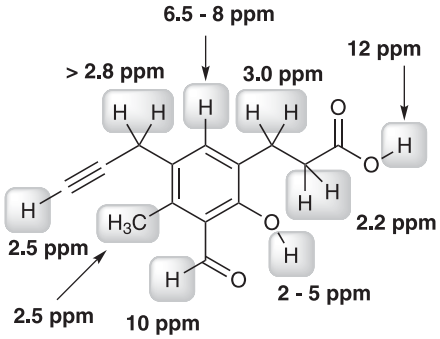
Next, we encounter a methylene group (benchmark value = 1.2 ppm) that is alpha to the oxygen atom of an ether, which adds +2.5, so the predicted chemical shift = 1.2 + 2.5 = 3.7 ppm.

Next, we encounter another methylene group (benchmark value = 1.2 ppm) that is also alpha to the oxygen atom of an ether, which adds +2.5, so the predicted chemical shift = 1.2 + 2.5 = 3.7 ppm. Notice that we predict that two of the signals should be very close to each other, if not overlapping.

Next we encounter a methine proton (benchmark value = 1.7 ppm) that is beta to the oxygen atom of an ether, which adds +0.5, so the predicted chemical shift = 1.7 + 0.5 = 2.2 ppm.

Finally, there are two equivalent methyl groups that should appear at 0.9 ppm (all inductive effects are distant and practically negligible).

3.19 The proton NMR spectrum of this compound will have nine signals, corresponding to the groups of protons highlighted below. The values for these signals can be found in the table that immediately precedes the problem statement.

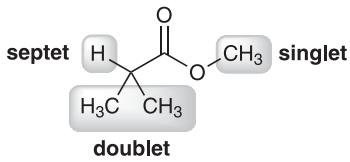


3.21 We identify the smallest integration value (in this case, 9.1) and we then divide all of the integration values by that number, giving the ratio 5:2:2:1. The molecular formula indicates that there are a total of 10 protons, so the numbers 5:2:2:1 represent not only relative values, but they also represent exact values (5 protons, 2 protons, 2 protons, and 1 proton).

3.22 We identify the smallest integration value (in this case, 10.8), and we then divide all of the integration values by that number, giving the ratio 1:6. The molecular formula indicates that there are a total of 14 protons, so the values 1 and 6 are just relative numbers. They actually represent 2 protons and 12 protons, in order for the total number of protons to be 14.

3.23 We identify the smallest integration value (in this case, 18.02), and we then divide all of the integration values by that number, giving the approximate ratio 1:1:1. The molecular formula indicates that there are a total of 6 protons, so the values 1, 1, and 1 are just relative numbers. They actually represent 2 protons, 2 protons, and 2 protons, in order for the total number of protons to be 6.

3.25 The proton NMR spectrum of this compound will have three signals, corresponding to the groups of protons highlighted below. In each case, the multiplicity is determined by the number of neighboring protons, using the $n + 1$ rule.



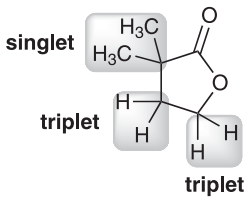
The methyl group on the right side of the structure has no neighbors ($n = 0$), so it will give a singlet ($n + 1 = 1$).

The methine proton has six neighbors ($n = 6$), so it will give a septet ($n + 1 = 7$).

And the two equivalent methyl groups have one neighbor ($n = 1$), so they will give a doublet ($n + 1 = 2$).

3.26 The proton NMR spectrum of this compound will have three signals, corresponding to the groups of protons highlighted below.

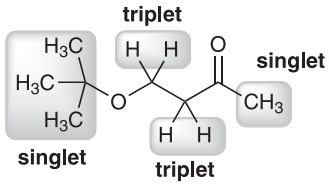
In each case, the multiplicity is determined by the number of neighboring protons, using the $n + 1$ rule.



Moving counterclockwise around the structure, we first encounter two equivalent methyl groups, both of which are connected to a carbon atom that has no protons ($n = 0$). Therefore, these methyl groups collectively give rise to a singlet ($n + 1 = 1$).

The methylene groups are nonequivalent (because of their proximity to the oxygen atom), and they are neighboring each other, so each methylene group has two neighbors ($n = 2$). Therefore, each of these methylene groups will give rise to a triplet ($n + 1 = 3$).

3.27 The proton NMR spectrum of this compound will have four signals, corresponding to the groups of protons highlighted below. In each case, the multiplicity is determined by the number of neighboring protons, using the $n + 1$ rule.

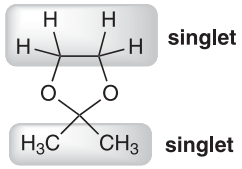


Moving from left to right, we first encounter a *tert*-butyl group, which has three equivalent methyl groups, all connected to a carbon atom that has no protons ($n = 0$). Therefore, these three methyl groups collectively give rise to a singlet ($n + 1 = 1$). This is characteristic of a *tert*-butyl group.

The nonequivalent methylene groups are neighboring each other, so each methylene group has two neighbors ($n = 2$). Therefore, each of these methylene groups will give rise to a triplet ($n + 1 = 3$).

Finally, the methyl group on the right has no neighbors ($n = 0$), giving rise to a singlet ($n + 1 = 1$).

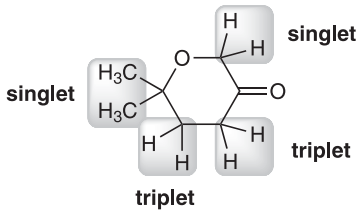
3.28 The proton NMR spectrum of this compound will have two signals, corresponding to the groups of protons highlighted below. In each case, the multiplicity is determined by the number of neighboring protons, using the $n + 1$ rule.



At the bottom of the structure, there are two equivalent methyl groups, each of which is connected to a carbon atom that has no protons ($n = 0$). Therefore, these two methyl groups collectively give rise to a singlet ($n + 1 = 1$).

The methylene groups are neighboring each other, but they don't split each other, because they are chemically equivalent protons. Instead, they collectively give rise to a singlet (chemically equivalent protons do NOT split each other).

3.29 The proton NMR spectrum of this compound will have four signals, corresponding to the groups of protons highlighted below. In each case, the multiplicity is determined by the number of neighboring protons, using the $n + 1$ rule.

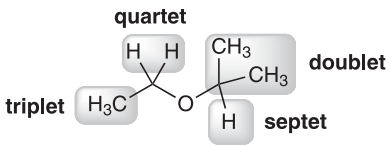


Moving counterclockwise around the structure, we first encounter two equivalent methyl groups, each of which is connected to a carbon atom that has no protons ($n = 0$). Therefore, these two methyl groups collectively give rise to a singlet ($n + 1 = 1$).

Next we encounter two nonequivalent methylene groups that are neighboring each other, so each methylene group has two neighbors ($n = 2$). Therefore, each of these methylene groups will give rise to a triplet ($n + 1 = 3$).

Finally, the remaining methylene group has no neighbors ($n = 0$), giving rise to a singlet ($n + 1 = 1$).

3.30 The proton NMR spectrum of this compound will have four signals, corresponding to the groups of protons highlighted below. In each case, the multiplicity is determined by the number of neighboring protons, using the $n + 1$ rule.



Moving from left to right, we first encounter a methyl group that has two neighbors ($n = 2$), giving rise to a triplet ($n + 1 = 3$).

Next we encounter a methylene group with three neighbors ($n = 3$), giving rise to a quartet ($n + 1 = 4$).

There is also a methine proton with six neighbors ($n = 6$), giving rise to a septet ($n + 1 = 7$).

Finally, there are two equivalent methyl groups, which are both connected to a carbon atom bearing only one proton ($n = 1$), so these methyl groups will collectively give rise to a doublet ($n + 1 = 2$).

3.31 This spectrum exhibits a septet with an integration of 1 and a doublet with an integration of 6. These two signals are characteristic of an isopropyl group.

3.32 We begin by identifying the smallest integration value (in this case, 13.9), and we then divide all of the integration values by that number, giving the ratio 1 : 1.5 : 1 : 1.5. There is no such thing as half of a proton, so we multiply these numbers by 2, to give the ratio 2 : 3 : 2 : 3. The molecular formula indicates that there are a total of 10 protons, so these values represent the actual number of protons giving rise to each signal (2 protons, 3 protons, 2 protons, and 3 protons = 10 protons).

Now that we know the integration values, we can see that this spectrum exhibits a quartet with an integration of 2, and a triplet with an integration of 3. These two signals are characteristic of an ethyl group.

3.33 We begin by identifying the smallest integration value (in this case, 10.8), and we then divide all of the integration values by that number, giving the ratio 1:6. Now that we know the integration values, we can see that this spectrum exhibits a septet with an integration of 1 and a doublet with an integration of 6. These two signals are characteristic of an isopropyl group.

The molecular formula indicates that there are a total of 14 protons, so the values 1 and 6 are just relative numbers. They actually represent 2 protons and 12 protons, in order for the total number of protons to be 14 (there are two equivalent isopropyl groups).

3.34 We begin by identifying the smallest integration value (in this case, 9.1), and we then divide all of the integration values by that number, giving the ratio 5:2:2:1. The molecular formula indicates that there are a total of 10 protons, so the numbers 5:2:2:1 represent not only relative values, but they also represent exact values (5 protons, 2 protons, 2 protons, and 1 proton).

Now that we know the integration values, we can see that this spectrum does not contain the characteristic signals for an isopropyl group, or an ethyl group, or a *tert*-butyl group. This structure does not have any of these three groups.

3.36 For purposes of calculating degrees of unsaturation, we inspect the molecular formula, and we can ignore the presence of oxygen atoms. So a compound with the molecular formula $C_6H_{10}O_4$ has the same HDI as a compound with the molecular formula C_6H_{10}. To be fully saturated, a compound with 6 carbon atoms would need to have 14 hydrogen atoms. This compound has only 10 hydrogen atoms, so it is missing 4 hydrogen atoms. Therefore, this compound has 2 degrees of unsaturation.

3.37 For purposes of calculating degrees of unsaturation, we inspect the molecular formula, and we can subtract one hydrogen atom for each nitrogen atom that is present. So a compound with the molecular formula $C_7H_{11}N$ has the same HDI as a compound with the molecular formula C_7H_{10}. To be fully saturated, a compound with 7 carbon atoms would need to have 16 hydrogen atoms. But the molecular formula C_7H_{10} has 10 hydrogen atoms, so 6 hydrogen atoms are missing. Therefore, this compound has 3 degrees of unsaturation.

3.38 For purposes of calculating degrees of unsaturation, we inspect the molecular formula, and we can ignore the presence of oxygen atoms. So a compound with the molecular formula $C_8H_{14}O_2$ has the same HDI as a compound with the molecular formula C_8H_{14}. To be fully saturated, a compound with 8 carbon atoms would need to have 18 hydrogen atoms. This compound has only 14 hydrogen atoms, so it is missing 4 hydrogen atoms. Therefore, this compound has 2 degrees of unsaturation.

3.39 For purposes of calculating degrees of unsaturation, we inspect the molecular formula, and we can ignore the presence of oxygen atoms. So a compound with the molecular formula $C_5H_{12}O_2$ has the same HDI as a compound with the molecular formula C_5H_{12}. To be fully saturated, a compound with 5 carbon atoms would need to have 12 hydrogen atoms. This compound does have 12 hydrogen atoms, so it is not missing any hydrogen atoms. Therefore, this compound is saturated and has 0 degrees of unsaturation.

3.40 For purposes of calculating degrees of unsaturation, we inspect the molecular formula, and we can subtract one hydrogen atom for each nitrogen atom that is present. So a compound with the molecular formula $C_6H_{15}N$ has the same HDI as a compound with the molecular formula C_6H_{14}, which is fully saturated. Therefore, this compound has 0 degrees of unsaturation.

3.41 For purposes of calculating degrees of unsaturation, we inspect the molecular formula, and we can ignore the presence of oxygen atoms. So a compound with the molecular formula $C_8H_{10}O$ has the same HDI as a compound with the molecular formula C_8H_{10}. To be fully saturated, a compound with 8 carbon atoms would need to have 18 hydrogen atoms. This compound has only 10 hydrogen atoms, so it is missing 8 hydrogen atoms. Therefore, this compound has 4 degrees of unsaturation.

3.43 The first step is to calculate the HDI. With a molecular formula of $C_5H_{10}O$, this compound has 1 degree of unsaturation. Therefore, the structure must contain either a ring or a double bond (but not both).

The next step is to consider the number of signals and the integration value of each signal. This spectrum has four signals, and we can determine the relative integration of each signal by dividing all of the given integration values by the smallest integration value (27.0). This process gives the following ratio:

1 : 1.5 : 1 : 1.5

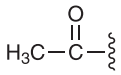
There is no such thing as half of a proton, so we multiply these numbers by two, giving the same ratio in whole numbers:

2 : 3 : 2 : 3

The total of these integration values is 10, and the molecular formula indicates the presence of 10 protons in the structure. So these values are not only relative, but they also represent the *actual* number of protons associated with each signal (2H, 3H, 2H, and 3H).

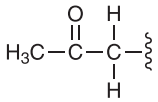
The next step is to analyze each signal. Perhaps the easiest signal to analyze is the singlet just above 2 ppm. This signal has an

integration of 3, which means that it is a methyl group, and the singlet indicates that there are no neighboring protons. A methyl group has a benchmark value of 0.9 ppm, but this signal has been shifted downfield by a little more than 1 ppm. This suggests that this methyl group is next to a carbonyl group:

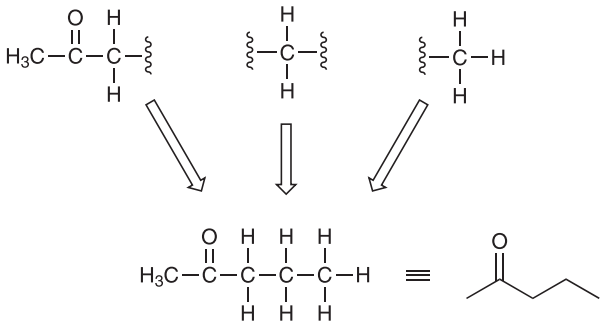


Note that the double bond accounts for the 1 degree of unsaturation.

The signal at 2.4 ppm has an integration of 2, indicating that it is a CH_2 group, and its chemical shift is shifted downfield by a little more than 1 ppm (relative to the benchmark value of 1.2 ppm for a CH_2 group) indicating that this CH_2 group is likely adjacent to the carbonyl group. So we introduce a CH_2 group next to the carbonyl group:



Now let's analyze the last two signals. One signal (at 0.9 ppm) has an integration of 3, so this signal represents a methyl group. The other signal has an integration of 2, representing a CH_2 group. If we connect these pieces, we get the following structure:



Notice the multiplicity of the signal associated with the CH_2 group that has neighbors on either side of it (the signal at 1.6 ppm). This CH_2 group has three neighbors on the right and two neighbors on the left, for a total of five neighbors. Since the *J* values are expected to be similar, the multiplicity will appear as if this CH_2 group has five equivalent neighboring protons, and according to the $n + 1$ rule, this gives a sextet, which is exactly what we see.

3.44 The first step is to calculate the HDI. With a molecular formula of $C_5H_{10}O_2$, this compound has 1 degree of unsaturation. Therefore, the structure must contain either a ring or a double bond (but not both).

The next step is to consider the number of signals and the integration value of each signal. This spectrum has four signals, and we can determine the relative integration of each signal by dividing all of the given integration values by the smallest integration value (33.2). This process gives the following ratio:

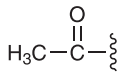
$$1 : 1.5 : 1 : 1.5$$

There is no such thing as half of a proton, so we multiply these numbers by 2, giving the same ratio in whole numbers:

$$2 : 3 : 2 : 3$$

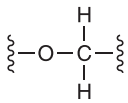
The total of these integration values is 10, and the molecular formula indicates the presence of 10 protons in the structure. So these values are not only relative, but they also represent the *actual* number of protons associated with each signal (2H, 3H, 2H, and 3H).

The next step is to analyze each signal. Perhaps the easiest signal to analyze is the singlet just above 2 ppm. This signal has an integration of 3, which means that it is a methyl group, and the singlet indicates that there are no neighboring protons. A methyl group has a benchmark value of 0.9 ppm, but this signal has been shifted downfield by a little more than 1 ppm. This suggests that this methyl group is next to a carbonyl group:

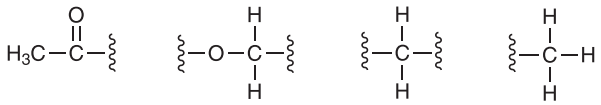


Note that the double bond accounts for the 1 degree of unsaturation.

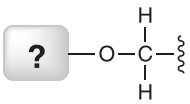
The signal at 4.0 ppm has an integration of 2, indicating that it is a CH_2 group, and its chemical shift is shifted downfield by approximately 3 ppm (relative to the benchmark value of 1.2 ppm for a CH_2 group) indicating that this CH_2 group is likely adjacent to an oxygen atom:



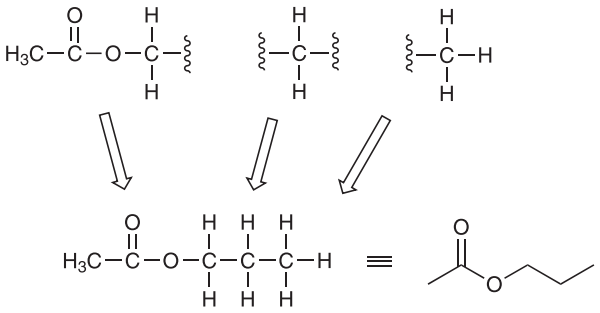
Now let's analyze the last two signals. One signal (at 0.9 ppm) has an integration of 3, so this signal represents a methyl group. The other signal has an integration of 2, representing a CH_2 group. In summary, we have the following pieces:



There is more than one way to connect these fragments. To help guide us, let's consider which fragment to connect to the oxygen atom:



We cannot connect either the CH_2 fragment or the CH_3 fragment directly to this oxygen atom, because then we would expect another signal around 4 ppm, and there is only one such signal. Therefore, this oxygen atom must be connected to the carbonyl group. This now gives only three fragments, which can only be connected in one way:



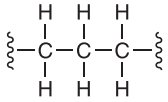
Notice the multiplicity of the signal associated with the CH_2 group that has neighbors on either side of it (the signal at 1.6 ppm). This CH_2 group has three neighbors on the right and two neighbors on the left, for a total of five neighbors. Since the *J* values are similar, which is usually the case, the multiplicity will appear as if this CH_2 group has five equivalent neighboring protons, and according to the n+1 rule, this gives a sextet, which is exactly what we see.

3.45 The first step is to calculate the HDI. With a molecular formula of $C_4H_6O_2$, this compound must have 2 degrees of unsaturation.

The next step is to consider the number of signals and the integration value of each signal. This spectrum has three signals, and we can determine the relative integration of each signal by dividing all of the given integration values by the smallest integration value (18.92). This process gives the following ratio:

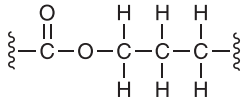
1 : 1 : 1

The total of these relative integration values is 3, but the molecular formula indicates the presence of 6 protons in the structure. So we multiply all of the integration values by 2, to give the *actual* number of protons associated with each signal (2H, 2H, and 2H). So we conclude that each of the three signals is associated with a CH_2 group. Note the multiplicities of these three signals (triplet, triplet, and quintet). This indicates that all three CH_2 groups are connected as follows:

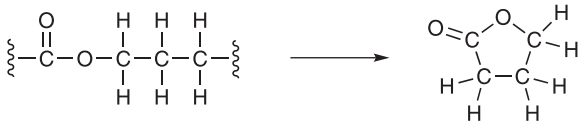


The central CH_2 group has four neighbors, so the signal for this CH_2 group is a quintet ($n + 1$ rule). And each of the other two remaining CH_2 groups is a triplet, because each has two neighbors.

Notice that one of the signals (4.3 ppm) appears shifted downfield by approximately +3 ppm (relative to the benchmark value of 1.2 ppm for a CH_2 group). This CH_2 groups must be next to an oxygen atom, likely of an ester group:



This accounts for one of the 2 degrees of unsaturation, but we still need one more degree of unsaturation, and we have already accounted for all atoms in the molecular formula ($C_4H_6O_2$). So the remaining degree of unsaturation must be associated with a ring, so we join the ends of the fragment above as follows:

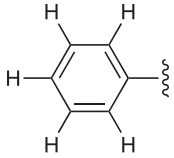


If we consider the chemical shifts of the signals associated with all CH_2 groups, they are all consistent with expected predictions. The CH_2 group next to the carbonyl group is shifted a bit more than +1 ppm from its benchmark value of 1.2 ppm. And the central CH_2 group is beta to the carbonyl group (which adds +0.2 ppm) and also beta to the oxygen atom (which adds +0.6 ppm), so its signal is shifted downfield by almost +1 ppm.

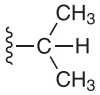
3.46 The first step is to calculate the HDI. With a molecular formula of C_9H_{12}, this compound has 4 degrees of unsaturation, which is strongly suggestive of an aromatic ring.

The next step is to consider the number of signals and the integration value of each signal. This spectrum has three signals, and the integration values are 5H, 1H, and 6H, respectively.

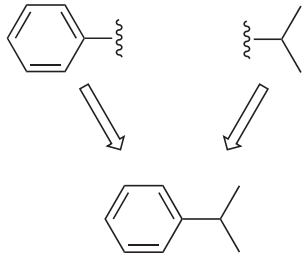
The signal just above 7 ppm is characteristic of an aromatic ring, and the integration (5H) indicates that the ring is monosubstituted.



If we consider the other two signals, we will notice that these two signals are the characteristic pattern of an isopropyl group:



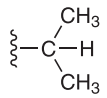
These two fragments account for all of the atoms in the molecular formula, and there is only one way to connect these fragments:



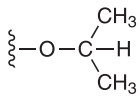
3.47 The first step is to calculate the HDI. With a molecular formula of $C_6H_{12}O_2$, this compound has 1 degree of unsaturation. Therefore, the structure must contain either a ring or a double bond (but not both).

The next step is to consider the number of signals and the integration value of each signal. This spectrum has four signals, and the integration values are 1H, 2H, 6H, and 3H, respectively.

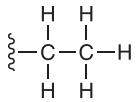
Now we are ready to analyze each signal, one at a time, but in this case, it might be more efficient to look for patterns of signals. For example, the signal very far downfield (5 ppm) is a septet with an integration of 1H, and there is also a doublet with an integration of 6H. These two signals together suggest the presence of an isopropyl group:



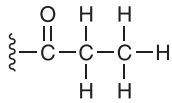
Notice that the CH signal appears at 5 ppm, which is significantly downfield from the benchmark value for a CH group (1.7 ppm). Indeed the shift is more than +3 ppm, so we conclude that the CH group is connected directly to an oxygen atom (likely of an ester):



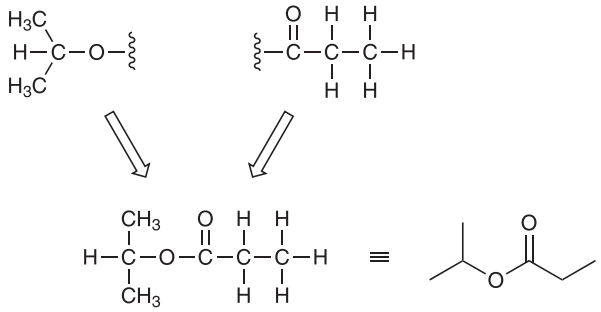
Now let's consider the remaining two signals. We have a quartet with an integration of 2H and a triplet with an integration of 3H. These two signals together suggest the presence of an ethyl group:



Notice that the CH_2 group produces a signal at 2.3 ppm, which is shifted approximately +1 ppm from the benchmark value for a CH_2 group (1.2 ppm). This suggests that the CH_2 group is connected to a carbonyl group:



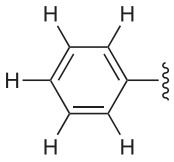
So far, we have two fragments, and these two fragments account for all of the atoms in the molecular formula. There is only one way to connect these fragments, as shown:



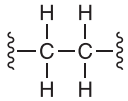
3.48 The first step is to calculate the HDI. With a molecular formula of $C_8H_{10}O$, this compound has 4 degrees of unsaturation, which is strongly suggestive of an aromatic ring.

The next step is to consider the number of signals and the integration value of each signal. This spectrum has four signals, and the integration values are 5H, 2H, 2H, and 1H, respectively.

The signal just above 7 ppm is characteristic of an aromatic ring, and the integration (5H) indicates that the ring is monosubstituted.

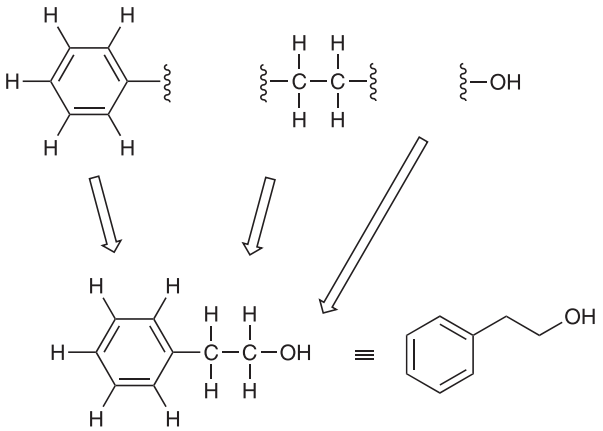


There are also two triplets, each of which has an integration of 2H, indicating that there are two CH_2 groups connected to each other (each being split into a triplet by the other):

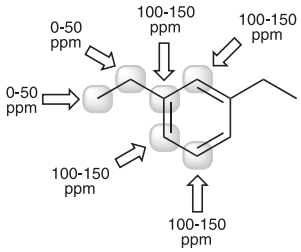


These two fragments account for almost all of the atoms in the molecular formula, with the exception of one oxygen atom and one hydrogen atom. If we attached this hydrogen atom to either CH_2 group, it would turn the CH_2 group into a CH_3 group, which is not consistent with the spectrum. So the last proton must be connected directly to the oxygen atom, which is consistent with the broad 1H

singlet around 2 ppm. This gives us three fragments, and there is only one way to connect these fragments:

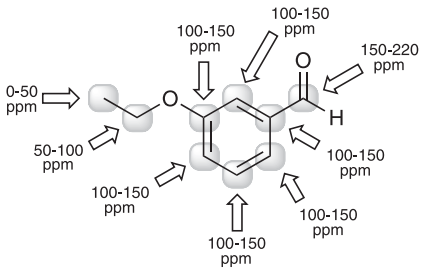


3.50 This compound has 10 carbon atoms, but it also has symmetry, so we expect fewer than 10 signals. Indeed, there are six different types of carbon atoms in this compound (highlighted below), so we expect a total of six signals in the ^{13}C NMR spectrum. Any carbon atom that is NOT highlighted is chemically equivalent to one of the highlighted carbon atoms. The expected location of each signal is indicated below.



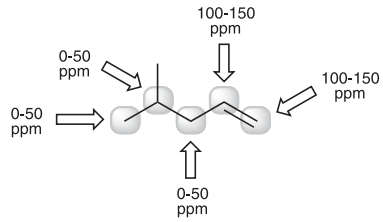
Notice that sp^2 hybridized carbon atoms are expected to produce signals between 100 and 150 ppm, while sp^3 hybridized carbon atoms are expected to produce signals in the range 0–50 ppm. The signal corresponding to the benzylic position is expected to be shifted downfield by its proximity to the aromatic ring, so perhaps it will appear closer to 50 ppm.

3.51 This compound lacks symmetry, and we expect one signal for each carbon atom, for a total of nine signals. The expected location of each signal is indicated below:



Notice that sp^2 hybridized carbon atoms are expected to produce signals between 100 and 150 ppm, while the carbonyl group is expected to produce a signal between 150 and 220 ppm. This structure has two sp^3 hybridized carbon atoms on the left side of the structure. One of them is connected to an oxygen atom and is expected to appear between 50 and 100 ppm. The other sp^3 hybridized carbon atom is expected to produce a signal in the range 0–50 ppm.

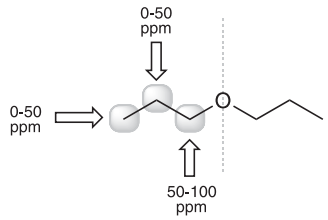
3.52 This compound has six carbon atoms, but two of them (the two methyl groups) are chemically equivalent (they occupy identical electronic environments), so we expect only five signals. The expected location of each signal is indicated below:



Notice that sp^2 hybridized carbon atoms are expected to produce signals between 100 and 150 ppm, while sp^3 hybridized carbon atoms are expected to produce signals in the range 0–50 ppm.

3.53 This compound has five carbon atoms, and there is no symmetry here, so we expect five signals. All five carbon atoms are sp^3 hybridized, although two of them are connected directly to the oxygen atom. These two carbon atoms will each produce a signal between 50 and 100 ppm (as a result of the electron-withdrawing effect from the oxygen atom), while the other three carbon atoms will produce signals between 0 and 50 ppm.

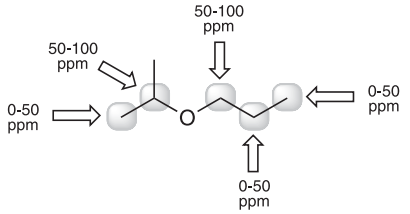
3.54 This compound has six carbon atoms, but there is symmetry here (the right half reflects the left half of the molecule), so we expect only three signals. The expected location of each signal is indicated below:



Notice that all three highlighted carbon atoms above are sp^3 hybridized, but one of them is connected directly to the oxygen atom. This carbon atom will produce a signal between 50 and 100 ppm (as a result of the electron-withdrawing effect from the oxygen atom), while the other two carbon atoms will produce signals between 0 and 50 ppm.

3.55 This compound has six carbon atoms, but two of the carbon atoms (the two methyl groups on the left side of the structure) are chemically equivalent because they occupy identical

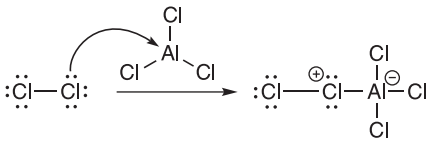
electronic environments. Accordingly, we expect only five signals. The expected location of each signal is indicated below:



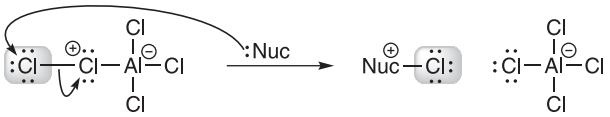
Notice that all highlighted carbon atoms above are sp^3 hybridized, but two of them are connected directly to the oxygen atom. These two carbon atoms will each produce a signal between 50 and 100 ppm (as a result of the electron-withdrawing effect from the oxygen atom), while the other three carbon atoms will produce signals between 0 and 50 ppm.

CHAPTER 4

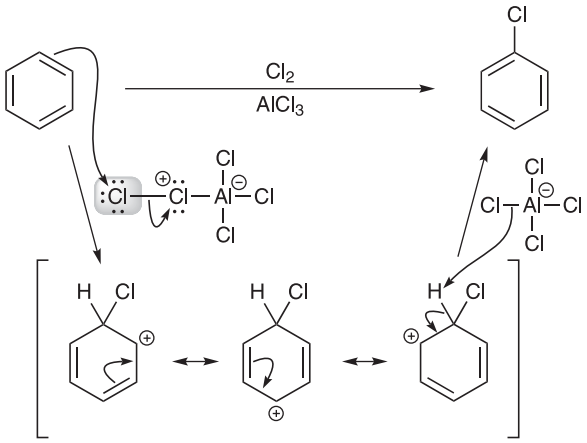
4.2 Cl_2 reacts with $AlCl_3$ to generate a Lewis acid–Lewis base complex:



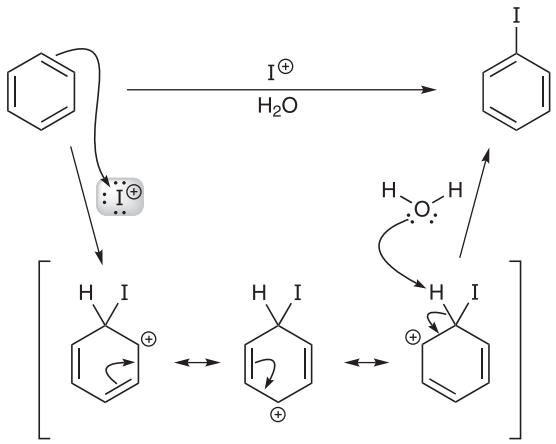
This complex can then serve as a delivery agent of Cl^+ (highlighted below):



4.3 This mechanism has only two steps. In the first step, the ring functions as a nucleophile and attacks the Lewis acid–Lewis base complex (see the solution to the previous problem), thereby transferring Cl^+ to the aromatic ring, and generating a resonance-stabilized intermediate, called a sigma complex. In the second (and final) step of the mechanism, $AlCl_4^-$ removes a proton from the sigma complex to restore aromaticity, as shown.

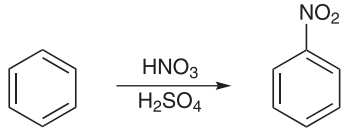


4.4 This mechanism has only two steps. In the first step, the ring functions as a nucleophile and attacks I^+, thereby generating a resonance-stabilized intermediate, called a sigma complex. In the second (and final) step of the mechanism, water functions as a base and removes a proton from the sigma complex to restore aromaticity.

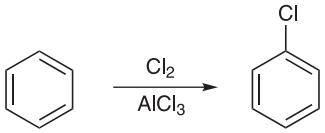


4.5 A bromine atom can be installed on the ring by treating benzene with Br_2 in the presence of a Lewis acid, such as $AlBr_3$:

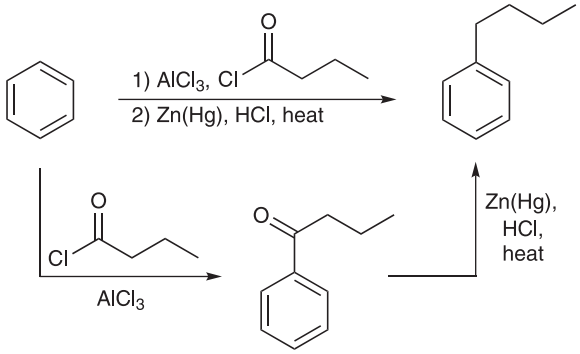
4.6 A nitro group can be installed on the ring by treating benzene with a mixture of sulfuric acid and nitric acid:



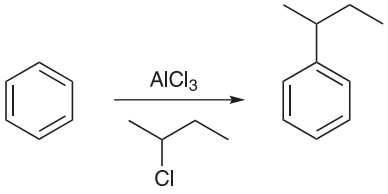
4.7 A chlorine atom can be installed on the ring by treating benzene with Cl_2 in the presence of a Lewis acid, such as $AlCl_3$:



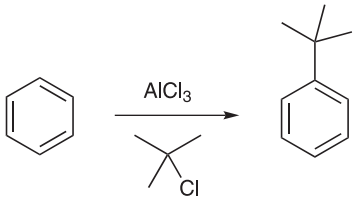
4.10 This transformation requires the installation of a butyl group, without any rearrangements. This cannot be accomplished directly via a Friedel–Crafts alkylation, because that would produce a mixture of products (as the result of rearrangement). The desired transformation can be achieved via a Friedel–Crafts acylation, followed by a Clemmensen reduction, as shown here:



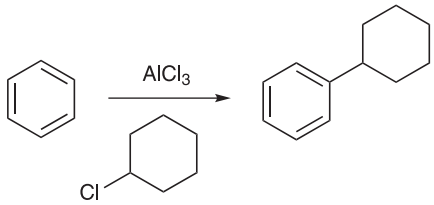
4.11 This alkylation can be achieved directly via a Friedel–Crafts alkylation process, without the concern of rearrangements (in this case, a secondary carbocation is involved, and there is no way for it to rearrange to become tertiary).



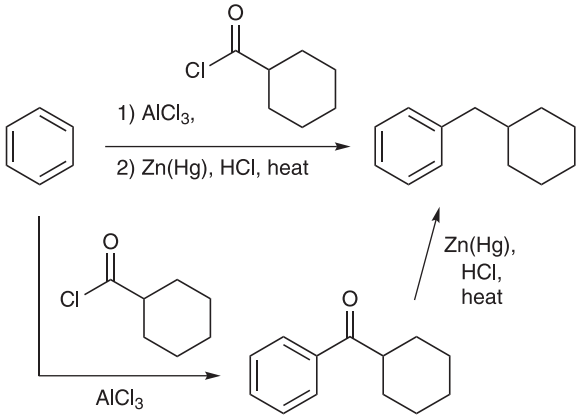
4.12 This alkylation can be achieved directly via a Friedel–Crafts alkylation process, without the concern of rearrangements (in this case, a tertiary carbocation is involved, and it cannot rearrange to become more stable).



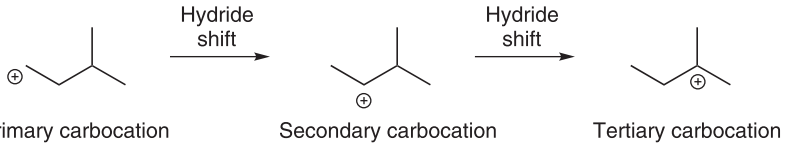
4.13 This alkylation can be achieved directly via a Friedel–Crafts alkylation process, without the concern of rearrangements (in this case, a secondary carbocation is involved, and there is no way for it to rearrange to become tertiary).



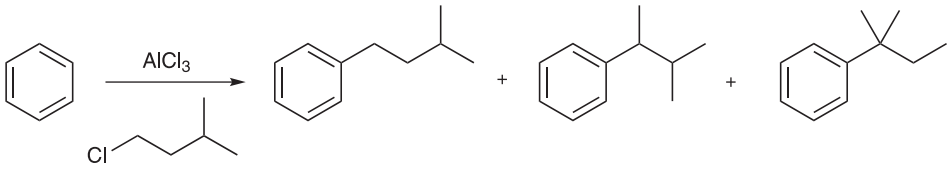
4.14 This transformation requires the installation of a primary alkyl group, without any rearrangements. This cannot be accomplished directly via a Friedel–Crafts alkylation, because that would produce a mixture of products (as the result of rearrangement). The desired transformation can be achieved via a Friedel–Crafts acylation, followed by a Clemmensen reduction, as shown here:



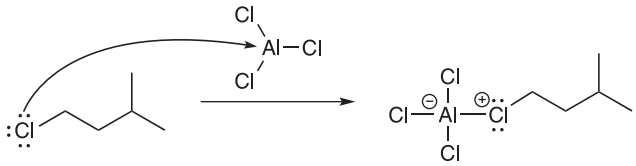
4.15 This is a Friedel–Crafts alkylation process in which a primary alkyl chloride is used. The mechanism involves a primary carbocation that can rearrange to a secondary carbocation, which can further rearrange to give a tertiary carbocation, as shown here:



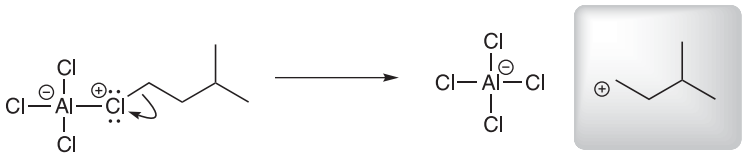
The aromatic ring can attack any one of the carbocations shown above, leading to a mixture of products:



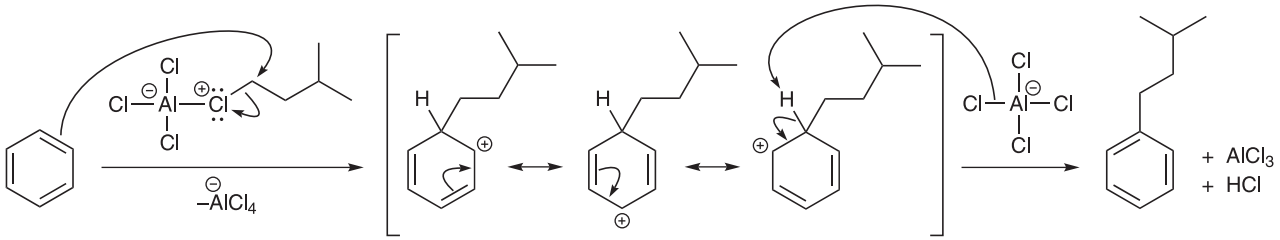
4.16 The first step is formation of a Lewis acid–Lewis base complex:



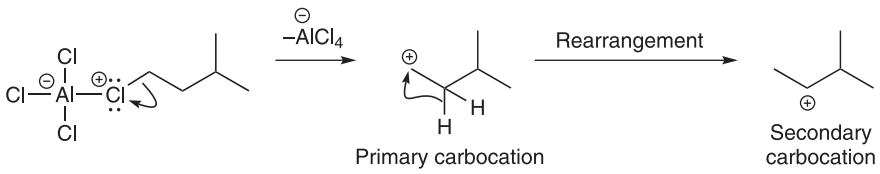
This complex can then function "as if" it were a primary carbocation:



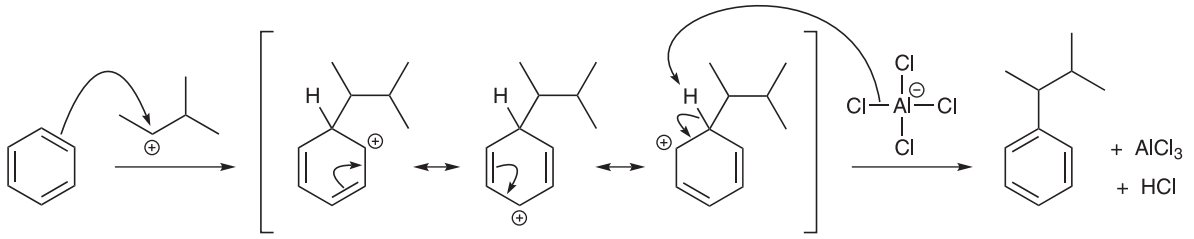
The primary carbocation is very unstable, and it is unlikely that it is actually formed. Rather, the complex has the character of a primary carbocation (it can be attacked by a nucleophile or it can undergo rearrangement). If it is attacked by a nucleophile, without first rearranging, then a primary alkyl group is installed on the ring, as shown:



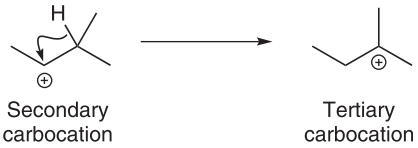
Now let's consider what happens if rearrangement occurs prior to nucleophilic attack, giving a secondary carbocation:



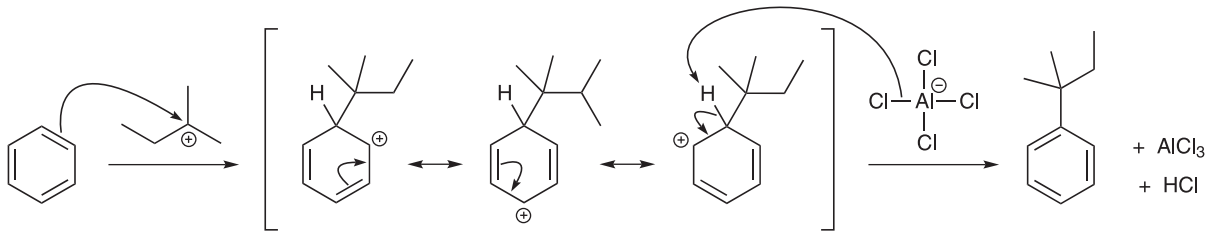
This secondary carbocation can rearrange further, but if instead, it is first attacked by the aromatic ring, then a secondary alkyl group is installed on the ring, as shown:



Now let's consider what happens if the secondary carbocation rearranges to give a tertiary carbocation prior to nucleophilic attack:

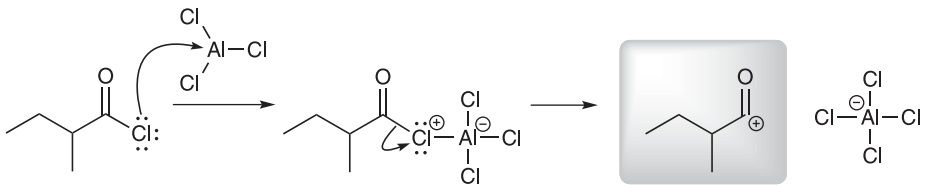


If this tertiary carbocation is attacked by the ring, then a tertiary alkyl group is installed on the ring, as shown:

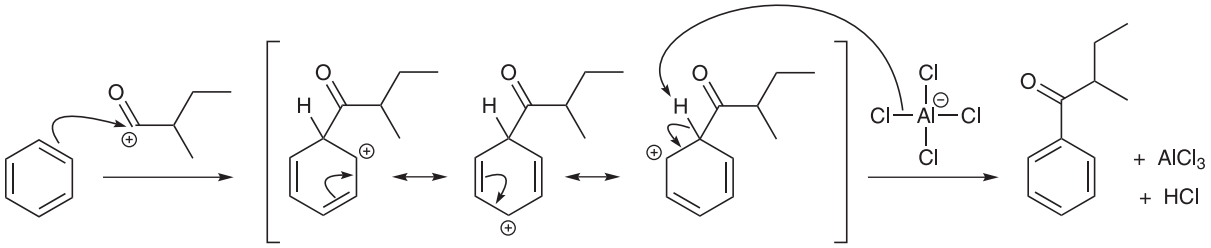


This product is likely the major product, although the exact product mixture is difficult to predict.

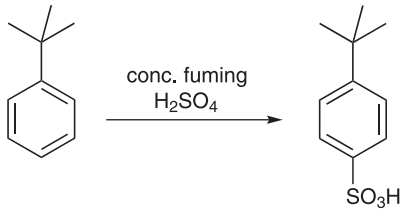
4.17 The first step is formation of the acylium ion, highlighted below:



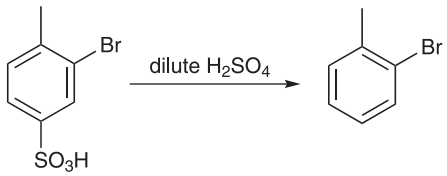
This acylium ion can function as an electrophile in an electrophilic aromatic substitution reaction, which has two steps. In the first step, the aromatic ring functions as a nucleophile and attacks the acylium ion to give a resonance-stabilized sigma complex. Then, in the second (and final) step, a proton is removed from the ring to restore aromaticity:



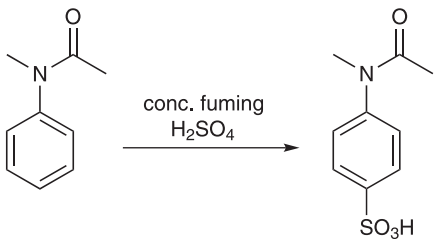
4.19 The desired transformation involves the installation of a sulfonate group on the aromatic ring, which can be achieved with concentrated fuming sulfuric acid.



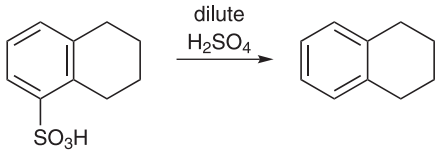
4.20 The desired transformation involves removing a sulfonate group from the aromatic ring, which can be achieved with dilute sulfuric acid.



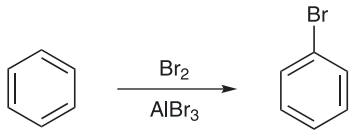
4.21 The desired transformation involves the installation of a sulfonate group on the aromatic ring, which can be achieved with concentrated fuming sulfuric acid.



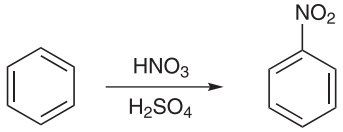
4.22 The desired transformation involves removing a sulfonate group from the aromatic ring, which can be achieved with dilute sulfuric acid.



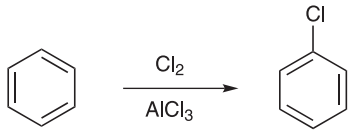
4.23 The desired transformation involves the installation of a bromine atom on the aromatic ring, which can be achieved with Br_2 and a Lewis acid, such as $AlBr_3$.



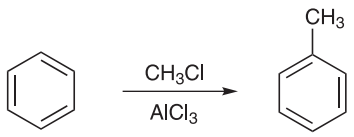
4.24 The desired transformation involves the installation of a nitro group on the aromatic ring, which can be achieved with a mixture of nitric acid and sulfuric acid.



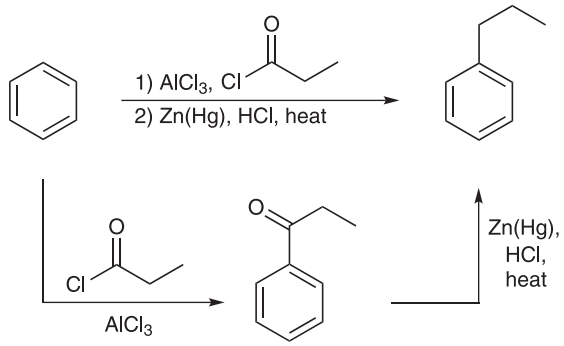
4.25 The desired transformation involves the installation of a chlorine atom on the aromatic ring, which can be achieved with Cl_2 and a Lewis acid, such as $AlCl_3$.



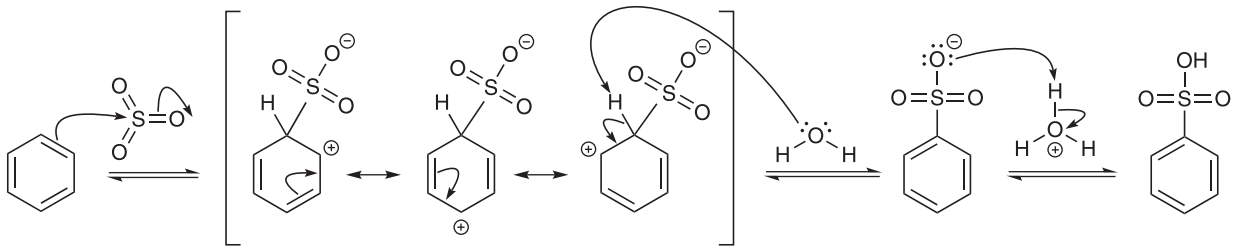
4.26 The desired transformation involves the installation of a methyl group on the aromatic ring, which can be achieved with a Friedel–Crafts alkylation.



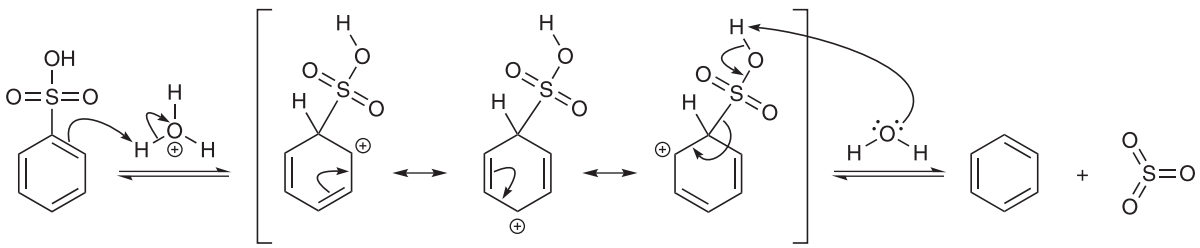
4.27 The desired transformation involves the installation of a primary alkyl group on the aromatic ring. This cannot be achieved efficiently with a Friedel–Crafts alkylation, because the possibility for carbocation rearrangement would generate a mixture of products. Instead, we can perform a Friedel–Crafts acylation (without carbocation rearrangements), and then reduce the resulting ketone with a Clemmensen reduction to give the desired product.



4.28 As indicated in the problem statement, this mechanism has three steps. In the first step of the mechanism, the aromatic ring functions as a nucleophile and attacks SO_3 (an electrophile) to give a resonance-stabilized intermediate, called a sigma complex. This sigma complex is then deprotonated (by water) to give a sulfonate anion, which is then protonated (under these acidic conditions) to give the product.



4.29 As indicated in the problem statement, this mechanism can be drawn in two steps, as shown below. In the first step, the aromatic ring is protonated to give a resonance-stabilized intermediate, called a sigma complex. This sigma complex is then deprotonated (by water) to give the product, as shown.



4.31 This ring bears a halogen substituent (Cl). Halogens are deactivators, but they are *ortho–para* directors.

4.32 This ring bears a hydroxyl group (OH), which is an activator and an *ortho–para* director.

4.33 This ring bears a nitro group (NO_2), which is a deactivator and a *meta* director.

4.34 The problem statement indicates that the substituent in this case is a deactivator. We have seen that all deactivators are *meta* directors, with the exception of the halogens. This substituent is not a halogen, so it is not an exception. If it is a deactivator, then it must be a *meta* director.

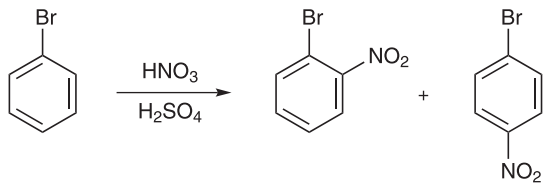
4.35 The problem statement indicates that the substituent in this case is an activator. We have seen that all activators are *ortho–para*

directors. Therefore, this substituent must be an *ortho–para* director.

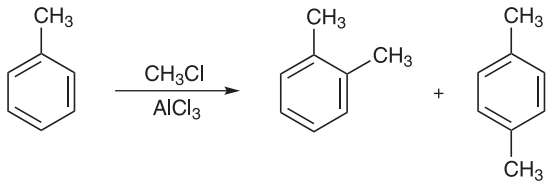
4.36 The problem statement indicates that the substituent in this case is a deactivator. We have seen that all deactivators are *meta* directors, with the exception of the halogens. This substituent is not a halogen, so it is not an exception. To be clear, this substituent does indeed contain halogens (three chlorine atoms), but none of those chlorine atoms are connected directly to the aromatic ring, so there are no resonance effects here. There are only inductive effects here, from each of the three chlorine atoms, which add together to give a powerful electron-withdrawing effect. Since this substituent (CCl_3) is a deactivator, it must be a *meta* director.

4.37 The problem statement indicates that the substituent in this case is an activator. We have seen that all activators are *ortho–para* directors. Therefore, this substituent must be an *ortho–para* director.

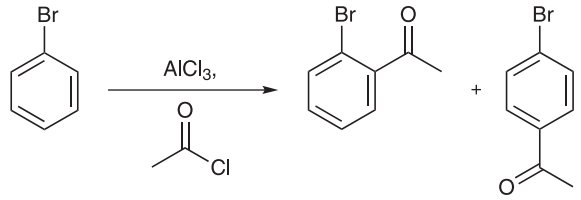
4.39 The reagents (nitric acid and sulfuric acid) indicate a nitration reaction, which means that a nitro group is installed on the aromatic ring. In order to draw the product(s), we must consider where the nitro group will be installed. That is, we must consider the existing substituent and its directing effects. In this case, the existing substituent is Br, which is an *ortho–para* director. Therefore, we expect the nitration reaction to occur at either the *ortho* position or the *para* position, giving two products, as shown:



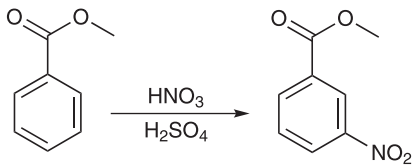
4.40 The reagents indicate a Friedel–Crafts alkylation reaction, so a methyl group is installed on the aromatic ring. In order to draw the product(s), we must consider where the methyl group will be installed. That is, we must consider the existing substituent and its directing effects. In this case, the existing substituent is a methyl group, which is an *ortho–para* director. Therefore, we expect the methylation reaction to occur at either the *ortho* position or the *para* position, giving two products, as shown:



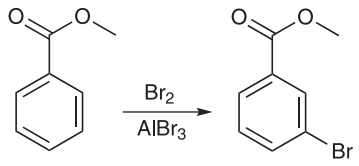
4.41 The reagents indicate a Friedel–Crafts acylation reaction, which means that an acyl group is installed on the aromatic ring. In order to draw the product(s), we must consider where the acyl group will be installed. That is, we must consider the existing substituent and its directing effects. In this case, the existing substituent is Br, which is an *ortho–para* director. Therefore, we expect the acylation reaction to occur at either the *ortho* position or the *para* position, giving two products, as shown:



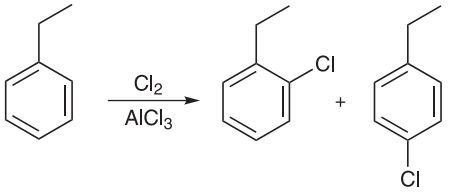
4.42 The reagents (nitric acid and sulfuric acid) indicate a nitration reaction, which means that a nitro group is installed on the aromatic ring. In order to draw the product(s), we must consider where the nitro group will be installed. That is, we must consider the existing substituent and its directing effects. The problem statement indicates that the existing substituent is a deactivator. Therefore, we expect that a nitro group will be installed at the *meta* position:



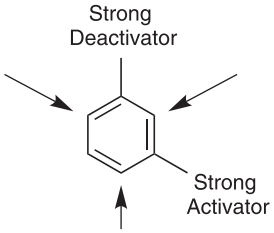
4.43 The reagents (Br_2 and $AlBr_3$) indicate a bromination reaction, which means that a bromine atom will be installed on the aromatic ring. In order to draw the product(s), we must consider where the bromine atom will be installed. That is, we must consider the existing substituent and its directing effects. The problem statement indicates that the existing substituent is a deactivator. Therefore, we expect that a bromine atom will be installed at the *meta* position:



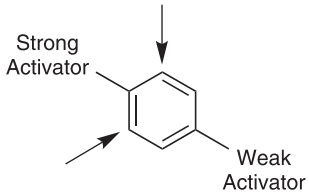
4.44 The reagents (Cl_2 and $AlCl_3$) indicate a chlorination reaction, which means that a chlorine atom will be installed on the aromatic ring. In order to draw the product(s), we must consider where the chlorine atom will be installed. That is, we must consider the existing substituent and its directing effects. The problem statement indicates that the existing substituent is an activator. Therefore, we expect that a chlorine atom will be installed either at the *ortho* position or at the *para* position:



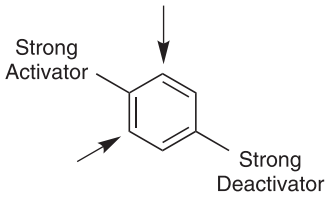
4.46 This aromatic ring has two groups: a strong deactivator and a strong activator. The deactivator is a *meta* director, while the activator is an *ortho-para* director. When a deactivator competes with an activator, the activator will control the directing effects. Therefore, we expect the following directing effects (*ortho* and *para* to the strong activator):



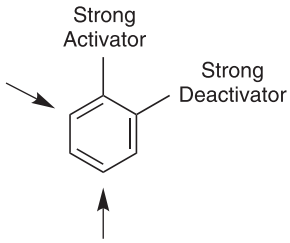
4.47 This aromatic ring has two groups: a strong activator and a weak activator. For electrophilic aromatic substitution reactions, the directing effects are controlled by the strongest activator. Therefore, we expect the directing effects to be *ortho* and *para* to the strong activator. In this case, the *para* position (relative to the strong activator) is already occupied, so we expect the following two locations to be the most reactive toward electrophilic aromatic substitution: (Note that substitution at either position gives the same product.)



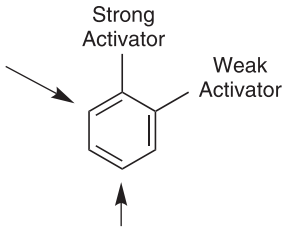
4.48 This aromatic ring has two groups: a strong activator and a strong deactivator. The activator is an *ortho–para* director, while the deactivator is a *meta* director. When an activator competes with a deactivator, the activator will control the directing effects (although there is no competition in this case, since they both direct to the same locations). Therefore, we expect the locations that are *ortho* to the strong activator to be the most reactive toward electrophilic aromatic substitution (the position that is *para* to the strong activator is already occupied). Note that substitution at either position gives the same product.



4.49 This aromatic ring has two groups: a strong activator and a strong deactivator. The activator is an *ortho–para* director, while the deactivator is a *meta* director. When an activator competes with a deactivator, the activator will control the directing effects (although in this case, they are not competing with each other because they both direct to the same locations). Therefore, we expect the locations that are *ortho* and *para* to the strong activator to be the most reactive toward electrophilic aromatic substitution (one of the positions that is *ortho* to the strong activator is already occupied):

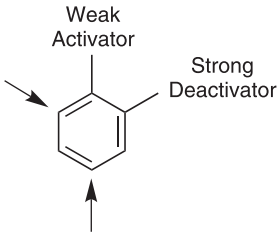


4.50 This aromatic ring has two groups: a strong activator and a weak activator. For electrophilic aromatic substitution reactions, the directing effects are controlled by the strongest activator. Therefore, we expect the directing effects to be *ortho* and *para* to the strong activator. In this case, one of the *ortho* positions (relative to the strong activator) is already occupied, so we expect the following two locations to be the most reactive toward electrophilic aromatic substitution:

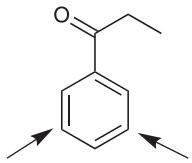


4.51 This aromatic ring has two groups: a weak activator and a strong deactivator. The activator is an *ortho–para* director, while the deactivator is a *meta* director. When an activator competes with a deactivator, the activator will control the directing effects (although there is no competition in this case, since they both direct to the same locations). Therefore, we expect the locations that are *ortho* and *para* to the activator to be the most reactive toward electrophilic

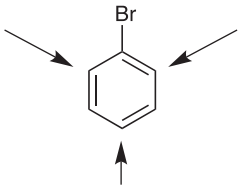
aromatic substitution (one of the positions that is *ortho* to the activator is already occupied):



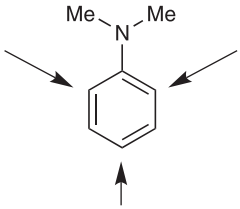
4.53 In this case, the substituent has a C═O bond connected directly to the aromatic ring, so this substituent is a moderate deactivator. Moderate deactivators are *meta* directors, so we expect the *meta* positions (indicated below) to be the most reactive toward electrophilic aromatic substitution.



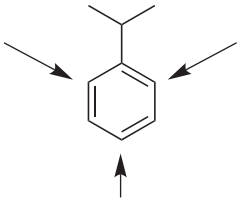
4.54 In this case, there is a halogen connected directly to the aromatic ring. We have seen that halogens are weak deactivators, but nevertheless, they are *ortho–para* directors. Therefore, we expect the *ortho* and *para* positions (indicated below) to be the most reactive toward electrophilic aromatic substitution.



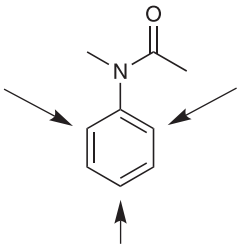
4.55 In this case, the substituent has a lone pair connected directly to the aromatic ring. This substituent is a strong activator and an *ortho–para* director. Therefore, we expect the *ortho* and *para* positions (indicated below) to be the most reactive toward electrophilic aromatic substitution.



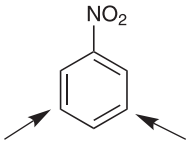
4.56 In this case, there is an alkyl group connected directly to the aromatic ring. Alkyl groups are weak activators and *ortho–para* directors. Therefore, we expect the *ortho* and *para* positions (indicated below) to be the most reactive toward electrophilic aromatic substitution.



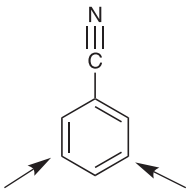
4.57 In this case, the substituent has a lone pair connected directly to the aromatic ring, but this lone pair is also participating in resonance outside of the ring. Therefore, this substituent is a moderate activator and an *ortho–para* director. As a result, we expect the *ortho* and *para* positions (indicated below) to be the most reactive toward electrophilic aromatic substitution.



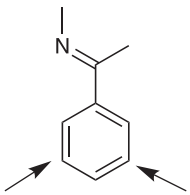
4.58 In this case, there is a nitro group connected directly to the aromatic ring, and nitro groups are strong deactivators. Strong deactivators are *meta* directors, so we expect the *meta* positions (indicated below) to be the most reactive toward electrophilic aromatic substitution.



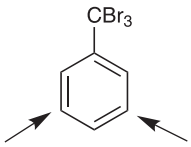
4.59 In this case, there is a C≡N bond connected directly to the aromatic ring, so this substituent is a moderate deactivator. Moderate deactivators are *meta* directors, so we expect the *meta* positions (indicated below) to be the most reactive toward electrophilic aromatic substitution.



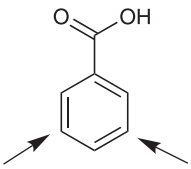
4.60 In this case, there is a C═N bond connected directly to the aromatic ring, so this substituent is a moderate deactivator. Moderate deactivators are *meta* directors, so we expect the *meta* positions (indicated below) to be the most reactive toward electrophilic aromatic substitution.



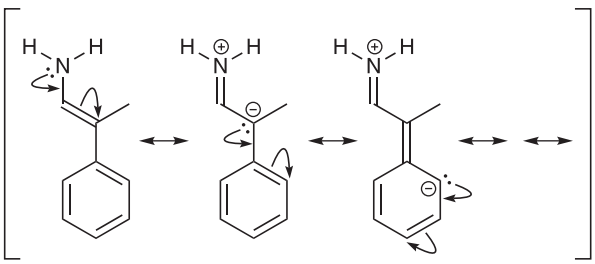
4.61 In this case, there is a CBr_3 group connected directly to the aromatic ring, and this group is a strong deactivator. Strong deactivators are *meta* directors, so we expect the *meta* positions (indicated below) to be the most reactive toward electrophilic aromatic substitution.



4.62 In this case, there is a C═O bond connected directly to the aromatic ring, so this substituent is a moderate deactivator. Moderate deactivators are *meta* directors, so we expect the *meta* positions (indicated below) to be the most reactive toward electrophilic aromatic substitution.

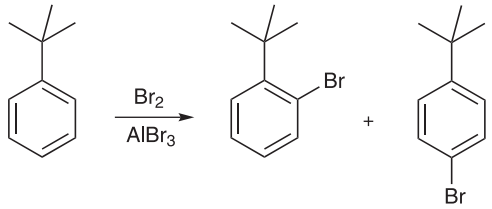


4.63 We begin by drawing the resonance structures for this compound:

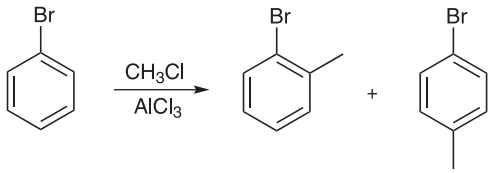


The resonance structures show that the lone pair on the nitrogen atom is delocalized, and the electron density is donated throughout the ring, which makes the ring electron-rich. The effect is similar to the effect observed when the lone pair is connected directly to the ring, so this substituent is a strong activator.

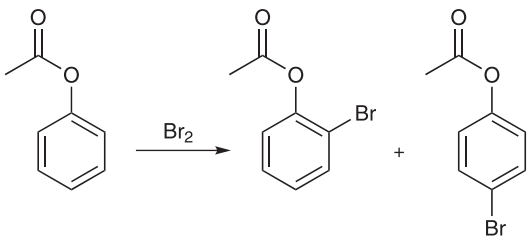
4.65 The reagents indicate a bromination reaction, so a bromine atom will be installed on the ring. The starting aromatic ring is monosubstituted, and the substituent is an alkyl group, which is a weak activator. Activators are *ortho–para* directors, so we expect that the bromine atom will be installed either at the *ortho* position or at the *para* position, giving the following products:



4.66 The reagents indicate a Friedel–Crafts alkylation reaction, so a methyl group will be installed on the ring. The starting aromatic ring is monosubstituted, and the substituent is a halogen, which is an *ortho–para* director. Therefore, we expect that the methyl group will be installed either at the *ortho* position or at the *para* position, giving the following products:

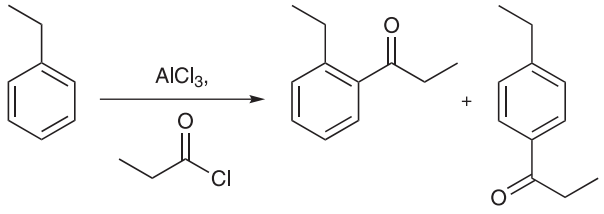


4.67 The reagents indicate a bromination reaction (a Lewis acid is not necessary here because the aromatic ring is moderately activated toward bromination), so a bromine atom will be installed on the ring. The starting aromatic ring is monosubstituted, and the substituent is an *ortho–para* director, so we expect that the bromine atom will be installed either at the *ortho* position or at the *para* position, giving the following products:

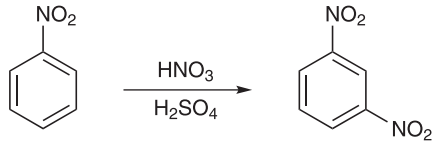


4.68 The reagents indicate a Friedel–Crafts acylation reaction, so an acyl group will be installed on the ring. The starting aromatic ring is monosubstituted, and the substituent is an ethyl group, which is

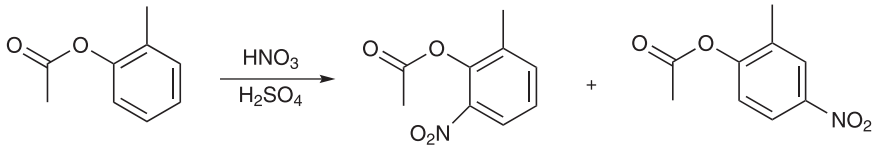
an *ortho–para* director. Therefore, we expect that the acyl group will be installed either at the *ortho* position or at the *para* position, giving the following products:



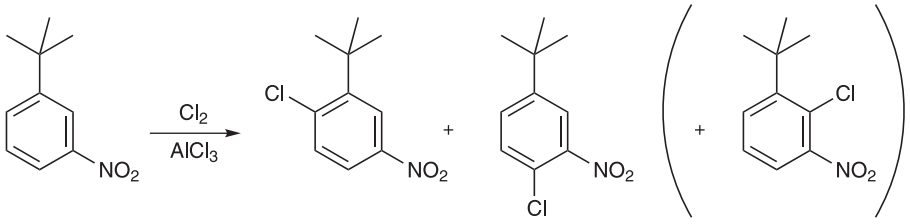
4.69 The reagents indicate a nitration reaction, so a nitro group will be installed on the ring. The starting aromatic ring is monosubstituted, and the substituent is a nitro group, which is a *meta* director. Therefore, we expect that the nitro group will be installed at the *meta* position, giving just one product:



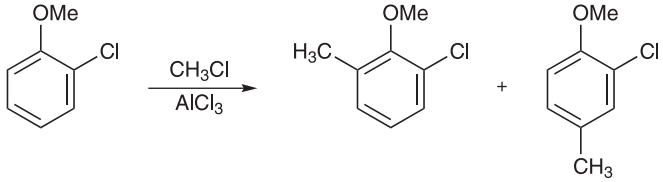
4.71 This aromatic ring has two substituents. The ester group is a moderate activator and an *ortho–para* director, while the methyl group is a weak activator and an *ortho–para* director. When a moderate activator competes with a weak activator during an electrophilic aromatic substitution, the more powerful activator (in this case, the moderate activator) controls the directing effects. The reagents indicate a nitration reaction, so we expect that a nitro group will be installed either at the position that is *ortho* to the ester or at the position that is *para* to the ester.



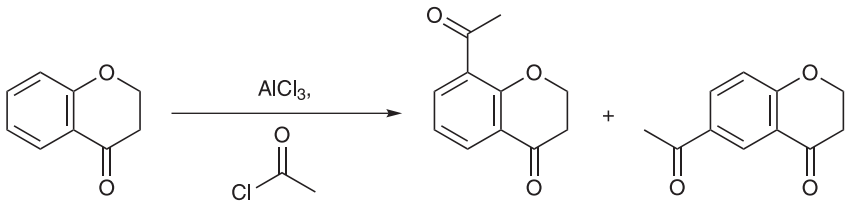
4.72 This aromatic ring has two substituents. The *tert*-butyl group is a weak activator and an *ortho–para* director, while the nitro group is a strong deactivator and a *meta* director. When an *ortho–para* director competes with a *meta* director during an electrophilic aromatic substitution, the *ortho–para* director controls the directing effects. The reagents indicate a chlorination reaction, so we expect that a chlorine atom will be installed either at a position that is *ortho* to the *tert*-butyl group (and there are two such positions) or at the position that is *para* to the *tert*-butyl group. This should give three products shown below, although we will see in the next section that one of these products (shown parenthetically) is actually a very minor product:



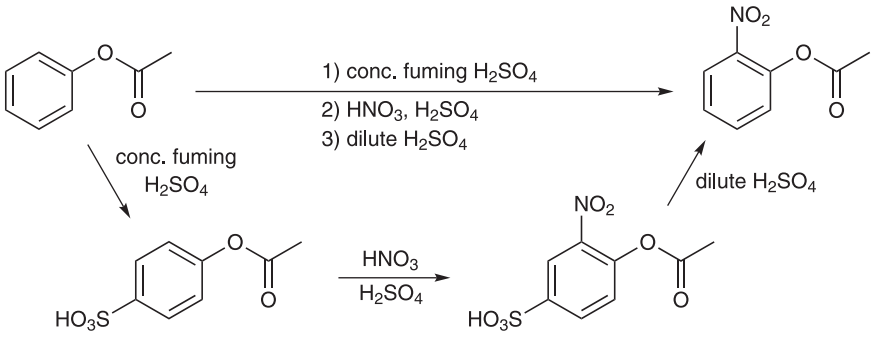
4.73 This aromatic ring has two substituents. The methoxy group is a moderate activator and an *ortho–para* director, while the chlorine atom is a weak deactivator and an *ortho–para* director. Since they are both *ortho–para* directors, the directing effects will be controlled by the more powerful activator (in this case, the methoxy group). The reagents indicate a Friedel–Crafts alkylation reaction, so we expect that a methyl group will be installed either at the position that is *ortho* to the methoxy group or at the position that is *para* to the methoxy group, giving the following two products:



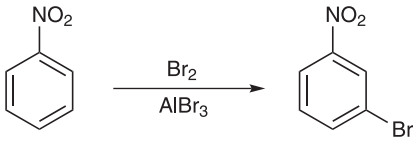
4.74 This aromatic ring has two substituents. One group is an alkoxy group (OR), which is a moderate activator and an *ortho–para* director. The other group is a carbonyl (C═O) group, which is a moderate deactivator and a *meta* director. The directing effects will be controlled by the *ortho–para* director (although in this case, there is not really a competition, because both substituents direct to the same two positions). The reagents indicate a Friedel–Crafts acylation reaction, so we expect that an acyl group will be installed either at the position that is *ortho* to the alkoxy group or at the position that is *para* to the alkoxy group:



4.76 The starting material is a monosubstituted aromatic ring, and the substituent is a moderate activator and an *ortho–para* director. So, if we perform an electrophilic aromatic substitution reaction, we would expect the reaction to occur primarily at the *para* position. The desired transformation involves installing a group at the *ortho* position, so a blocking group will be necessary. First, we perform sulfonation to "block" the *para* position. Next, we perform the desired reaction (in this case, a nitration reaction), and finally, we remove the blocking group with dilute sulfuric acid to give the desired product.

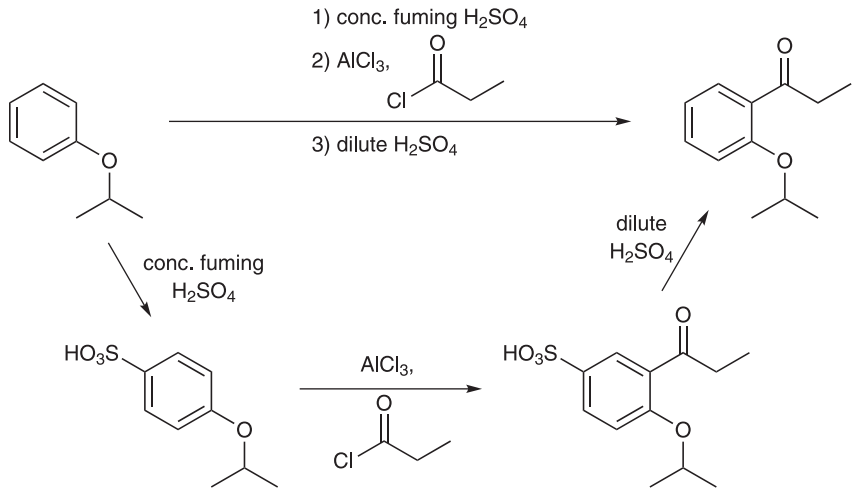


4.77 The starting material is a monosubstituted aromatic ring, and the substituent (a nitro group) is a strong deactivator and a *meta* director. So, if we perform an electrophilic aromatic substitution reaction, we would expect the reaction to occur primarily at the *meta* position. The desired transformation involves installing a group at the *meta* position, so a blocking group is not useful here. The bromine atom can be directly installed in the correct location by treating nitrobenzene with bromine and aluminum tribromide:

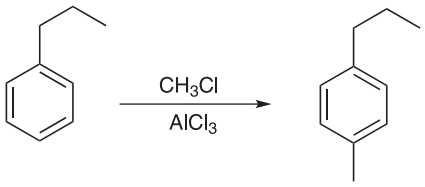


4.78 The starting material is a monosubstituted aromatic ring, and the substituent (an alkoxy group) is a moderate activator and an *ortho–para* director. So, if we perform an electrophilic aromatic substitution reaction, we would expect the reaction to occur primarily at the *para* position. The desired transformation involves installing a group at the *ortho* position, so a blocking group will be necessary.

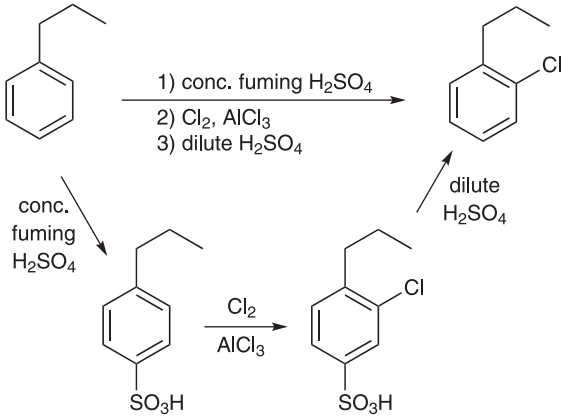
First, we perform sulfonation to "block" the *para* position. Next, we perform the desired reaction (in this case, a Friedel–Crafts acylation reaction), and finally, we remove the blocking group with dilute sulfuric acid to give the desired product.



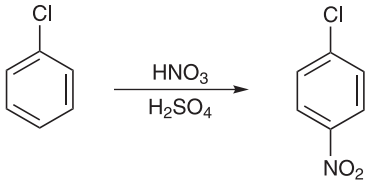
4.79 The starting material is a monosubstituted aromatic ring, and the substituent (an *n*-propyl group) is a weak activator and an *ortho–para* director. So, if we perform an electrophilic aromatic substitution reaction, we would expect the reaction to occur primarily at the *para* position. The desired transformation involves installing a group at the *para* position, so a blocking group is not needed here. A methyl group can be installed directly in the correct location via a Friedel–Crafts alkylation:



4.80 The starting material is a monosubstituted aromatic ring, and the substituent (an *n*-propyl group) is a weak activator and an *ortho–para* director. So, if we perform an electrophilic aromatic substitution reaction, we would expect the reaction to occur primarily at the *para* position. The desired transformation involves installing a group at the *ortho* position, so a blocking group will be necessary. First, we perform sulfonation to "block" the *para* position. Next, we perform the desired reaction (in this case, chlorination to install a chlorine atom at the *ortho* position), and finally, we remove the blocking group with dilute sulfuric acid to give the desired product.

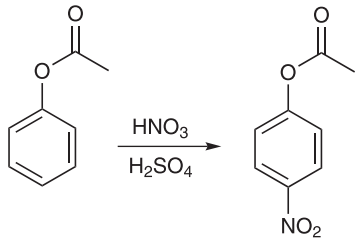


4.82 The reagents (nitric acid and sulfuric acid) indicate that this is a nitration reaction. The aromatic ring has one substituent (Cl), which is an *ortho–para* director. So we expect nitration to occur at either the *ortho* position or the *para* position, to give two products. Because of steric factors, the *para* product is the major product.



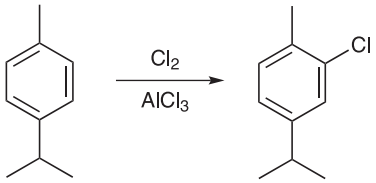
Major product

4.83 The reagents (nitric acid and sulfuric acid) indicate that this is a nitration reaction. The aromatic ring has one substituent, which is an *ortho–para* director. So we expect nitration to occur at either the *ortho* position or the *para* position, to give two products. Because of steric factors, the *para* product is the major product.



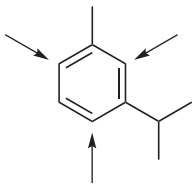
Major product

4.84 The reagents (Cl_2 and $AlCl_3$) indicate that a chlorine atom will be installed. The aromatic ring has two substituents, both of which are weak activators and *ortho–para* directors. So chlorination is favored at all positions (either *ortho* to the methyl group or *ortho* to the isopropyl group). Both products are expected, but because of steric factors, the major product results from chlorination at the position that is *ortho* to the methyl group. That position is more accessible than the position that is *ortho* to the larger isopropyl group.

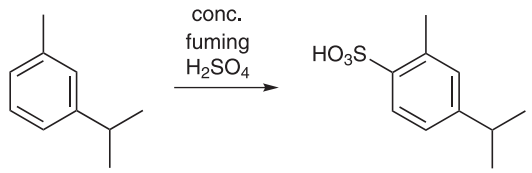


Major product

4.85 The reagent (concentrated fuming sulfuric acid) indicates a sulfonation reaction. The aromatic ring has two substituents, both of which are weak activators and *ortho–para* directors. Both groups direct to the same three locations.

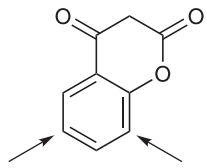


When we compare these locations, the location directly between the alkyl groups is sterically less accessible, so the reaction does not occur there rapidly. The reaction can occur at either of the other two locations, giving rise to two products. Because of steric factors, the major product results from sulfonation at the position that is *ortho* to the methyl group (as shown below). That position is more accessible than the position that is *ortho* to the larger isopropyl group.

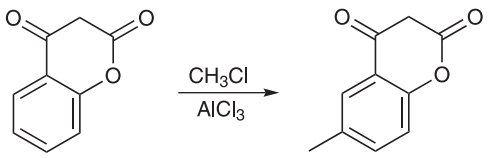


Major product

4.86 The reagents indicate a Friedel–Crafts alkylation reaction, so we expect that a methyl group will be installed. The aromatic ring has two substituents. One group is a carbonyl (C═O) group, which is a moderate deactivator and a *meta* director. The other group is an ester group, which is a moderate activator and an *ortho–para* director. The directing effects will be controlled by the *ortho–para* director, although in this case, there is not really a competition, because both substituents direct to the same two positions:

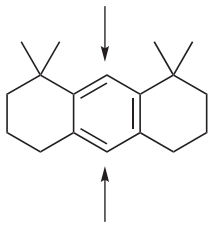


The reaction will occur more rapidly at the position on the left because it is sterically more accessible than the position on the right. Therefore, we expect the following major product:

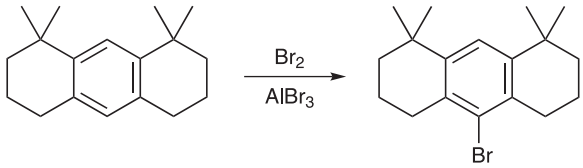


Major product

4.87 The reagents (Br_2 and $AlBr_3$) indicate that a bromine atom will be installed on the ring. This aromatic ring has four substituents, all of which are weak activators and *ortho–para* directors. These groups direct to the two available positions on the ring:



The upper position is sterically hindered (because of the methyl groups), while the lower position is more accessible. The major product results from bromination at the more sterically accessible position:

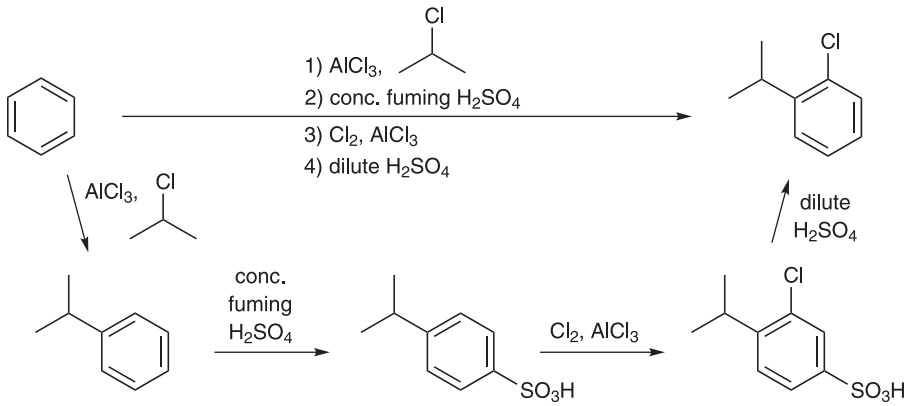


Major product

4.89 We must install an isopropyl group and a chlorine atom on the aromatic ring. The isopropyl group can be installed via a Friedel–Crafts alkylation, and the chlorine atom can be installed by treating the aromatic ring with Cl_2 in the presence of catalytic $AlCl_3$.

Now that we know how to install each substituent individually, we must consider the order of events. Both substituents are *ortho–para* directors, so theoretically, either one can be installed first. But consider the fact that an isopropyl group is an activator, while chlorine is a deactivator. To maximize the efficiency of our synthesis, it makes more sense to install the isopropyl group first, so that we can then take advantage of the enhanced reactivity of isopropyl benzene (relative to benzene) to install Cl.

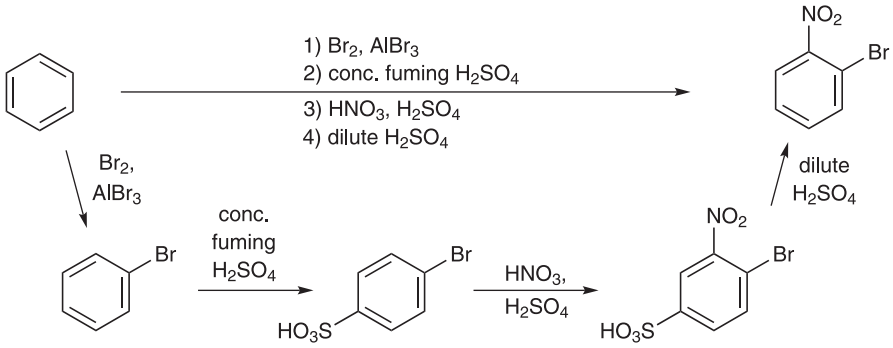
If we use the strategy described above (install the isopropyl group first and then try to install the chlorine atom next), we would expect to obtain both *ortho* and *para* products, although the reaction will occur primarily at the *para* position because of steric effects. The desired transformation involves installing a group at an *ortho* position, so a blocking group will be necessary here. After installing the isopropyl group, we perform sulfonation to "block" the *para* position. Next, we perform the desired reaction (installing Cl in the position that is *ortho* to the isopropyl group), and finally, we remove the blocking group with dilute sulfuric acid to give the desired product:



4.90 We must install a nitro group and a bromine atom on the aromatic ring. The nitro group can be installed with nitric acid and sulfuric acid, while the bromine atom can be installed with Br_2 in the presence of catalytic $AlBr_3$.

Now that we know how to install each substituent individually, we must consider the order of events. Nitro groups are *meta* directors, while Br is an *ortho–para* director. Since the two substituents must be installed so that they are *ortho* to each other, we conclude that we must install Br first, followed by the nitro group.

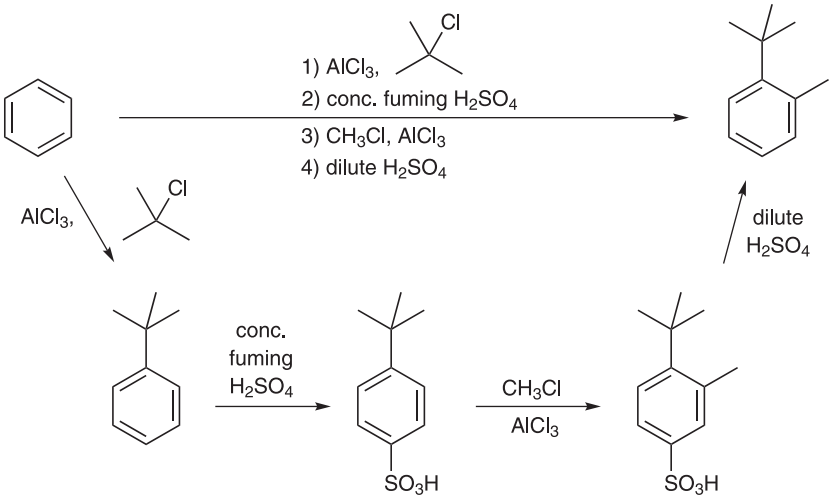
If we use the strategy described above (install Br first and then try to install the nitro group next), we would expect to obtain both *ortho* and *para* products, although the reaction will occur primarily at the *para* position because of steric effects. The desired transformation involves installing a group at an *ortho* position, so a blocking group will be necessary here. After installing the bromine atom, we perform sulfonation to "block" the *para* position. Next, we perform the desired reaction (installing a nitro group in the position that is *ortho* to Br), and finally, we remove the blocking group with dilute sulfuric acid to give the desired product:



4.91 We must install a *tert*-butyl group and a methyl group on the aromatic ring. Each of these groups can be installed via a Friedel–Crafts alkylation.

Now that we know how to install each substituent individually, we must consider the order of events. Both substituents are *ortho–para* directors, so theoretically, either one can be installed first. But consider steric effects. If we install the methyl group first, any reaction we performed next will produce a mixture of products. The methyl group is not large enough to clearly favor one position over the other (*ortho* vs. *para*), and a mixture of products is undesirable. However, if we install the *tert*-butyl group first, there is a clear preference for the next reaction to occur at the *para* position, and we will exploit that preference to obtain the desired regiochemical outcome.

We first install the *tert*-butyl group, and we then use its steric bulk to perform sulfonation at the *para* position, thereby blocking that position. Next, we install Cl in the position that is *ortho* to the *tert*-butyl group, and finally, we remove the blocking group with dilute sulfuric acid to give the desired product:

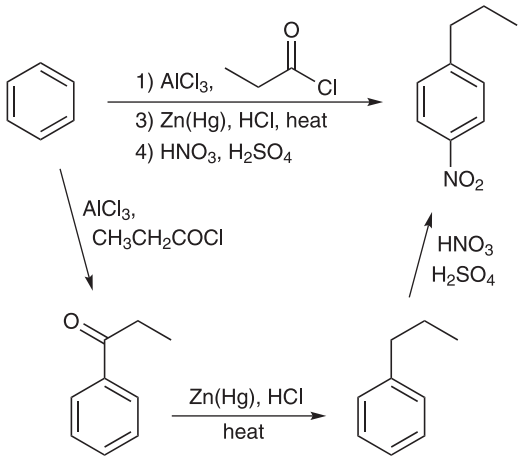


4.92 We must install an *n*-propyl group and a nitro group on the aromatic ring. A nitro group can be installed with nitric acid and sulfuric acid. The *n*-propyl group requires more than one step because it cannot be installed directly via a Friedel–Crafts alkylation, as that would produce a mixture of products (because of rearrangement). To install an *n*-propyl group, we must first perform a Friedel–Crafts acylation, and then reduce the resulting ketone with a Clemmensen reduction.

Now that we know how to install each substituent individually, we must consider the order of events. The nitro group is a *meta* director, while the *n*-propyl group is an *ortho–para* director, so we must install the *n*-propyl group first. If we try to install the nitro group first, it would direct the next reaction to the *meta* position, which is not the correct location.

If we use the strategy described above (install the *n*-propyl group first and then install the nitro group next), we would expect to obtain

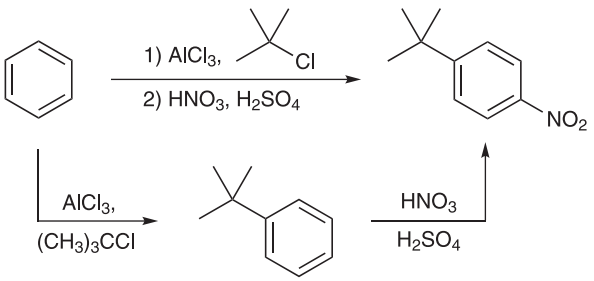
both *ortho* and *para* products, although the reaction will occur primarily at the *para* position because of steric effects. This is the desired product, so a blocking group is not needed here. The synthesis is summarized below. We perform a Friedel–Crafts acylation, followed by a Clemmensen reduction, followed by nitration:



4.93 We must install a *tert*-butyl group and a nitro group on the aromatic ring. The *tert*-butyl group can be installed via a Friedel–Crafts alkylation, while the nitro group can be installed with nitric acid and sulfuric acid.

Now that we know how to install each substituent individually, we must consider the order of events. The *tert*-butyl group is an *ortho–para* director, while the nitro group is a *meta* director, so we must install the *tert*-butyl group first. If we try to install the nitro group first, it would direct the next reaction to the *meta* position, which is not the correct location.

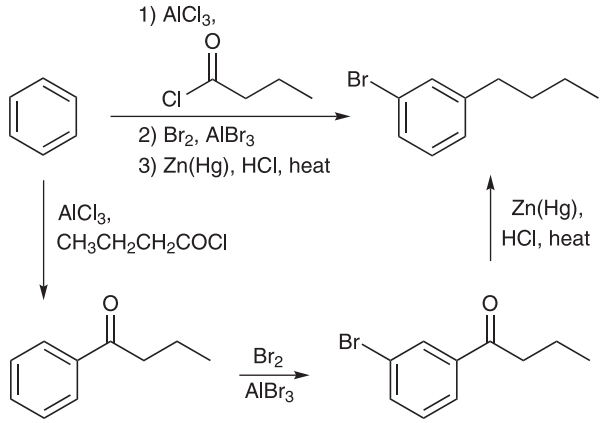
If we use the strategy described above (install the *tert*-butyl group first and then install the nitro group next), we would expect to obtain primarily the *para* product because of steric effects. This is the desired product, so a blocking group is not needed here. The synthesis is summarized below. We perform a Friedel–Crafts alkylation, followed by nitration:



4.94 We must install an *n*-butyl group and a bromine atom on the aromatic ring. The bromine atom can be installed in one step by treating an aromatic ring with Br_2 and $AlBr_3$. But the *n*-butyl group cannot be installed directly via a Friedel–Crafts alkylation, as that would produce a mixture of products (because of rearrangement). To install an *n*-butyl group, we must first perform a Friedel–Crafts acylation, and then reduce the resulting ketone with a Clemmensen reduction.

Now that we know how to install each substituent individually, we must consider the order of events. An *n*-butyl group is an *ortho–para* director, and a bromine atom is also an *ortho–para* director. This is an issue, because we need to install the substituents so that they are ultimately *meta* to each other. How do we accomplish this?

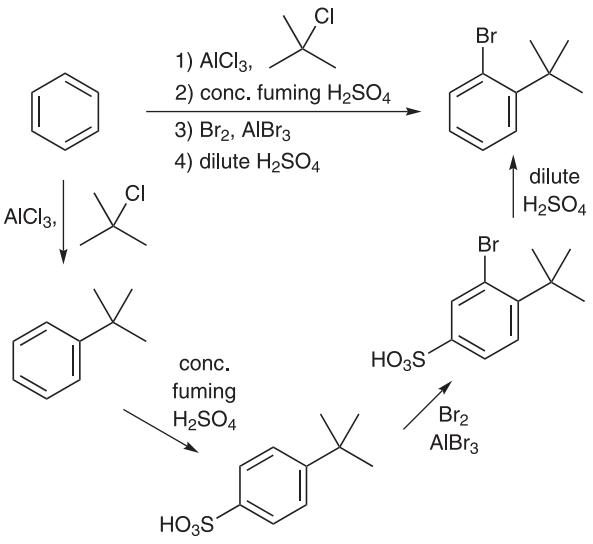
Notice that the *n*-butyl group is installed in two steps, and if we pause after the first step (after acylation), we can capitalize on the *meta*-directing effects of the carbonyl group before we reduce it. This allows us to install the bromine atom at the *meta* position. This strategy gives the desired product, as shown below:



4.95 We must install a *tert*-butyl group and a bromine atom on the aromatic ring. A *tert*-butyl group can be installed via a Friedel–Crafts alkylation, and a bromine atom can be installed with Br_2 and $AlBr_3$.

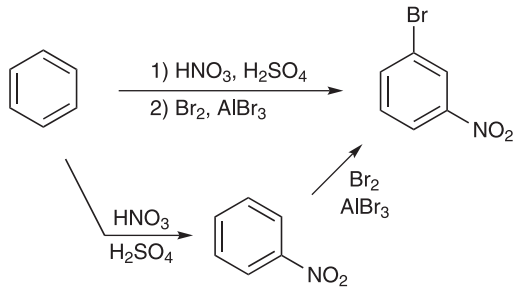
Now that we know how to install each substituent individually, we must consider the order of events. Both substituents are *ortho–para* directors, so theoretically, either one can be installed first. But consider the fact that a *tert*-butyl group is an activator, while bromine is a deactivator. To maximize the efficiency of our synthesis, it makes more sense to install the a *tert*-butyl group first, so that we can then take advantage of the enhanced reactivity of *tert*-butylbenzene (relative to benzene) to install Br. Furthermore, the bulky *tert*-butyl group creates a large distinction between the *ortho* and *para* positions, which will now be exploited.

We first install the *tert*-butyl group, and we then use its steric bulk to perform sulfonation at the *para* position, thereby blocking that position. Next, we install Br in the position that is *ortho* to the *tert*-butyl group, and finally, we remove the blocking group with dilute sulfuric acid to give the desired product:



4.96 We must install a nitro group and a bromine atom on the aromatic ring. The nitro group can be installed with nitric acid and sulfuric acid, while the bromine atom can be installed with Br_2 in the presence of catalytic $AlBr_3$.

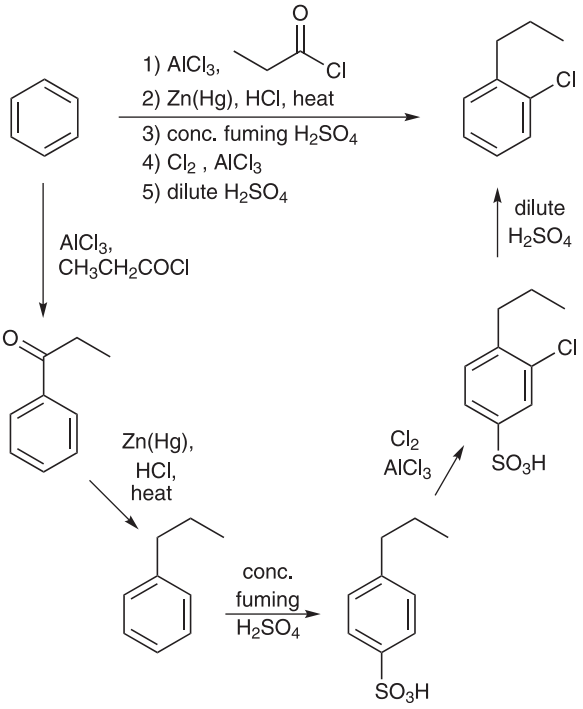
Now that we know how to install each substituent individually, we must consider the order of events. Nitro groups are *meta* directors, while Br is an *ortho–para* director. Since the two substituents must be installed so that they are *meta* to each other, we conclude that we must install the nitro group first, followed by Br:



4.97 We must install an *n*-propyl group and a chlorine atom on the aromatic ring. A chlorine atom can be installed with Cl_2 and $AlCl_3$. The *n*-propyl group requires more than one step because it cannot be installed directly via a Friedel–Crafts alkylation, as that would produce a mixture of products (because of rearrangement). To install an *n*-propyl group, we must first perform a Friedel–Crafts acylation, and then reduce the resulting ketone with a Clemmensen reduction.

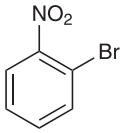
Now that we know how to install each substituent individually, we must consider the order of events. Both substituents are *ortho–para* directors, so theoretically, either one can be installed first. But consider the fact that an *n*-propyl group is an activator, while chlorine is a deactivator. To maximize the efficiency of our synthesis, it makes more sense to install the *n*-propyl group first, so that we can then take advantage of the enhanced reactivity of *n*-propylbenzene (relative to benzene) to install Cl.

If we use the strategy described above (install the *n*-propyl group first and then install the chlorine atom next), we would expect to obtain both *ortho* and *para* products, although the reaction will occur primarily at the *para* position because of steric effects. The desired transformation involves installing a group at an *ortho* position, so a blocking group will be necessary here. After installing the *n*-propyl group via Friedel–Crafts acylation followed by a Clemmensen reduction, we perform sulfonation to "block" the *para* position. Next, we perform the desired reaction (installing a chlorine atom in the position that is *ortho* to the *n*-propyl group), and finally, we remove the blocking group with dilute sulfuric acid to give the desired product:

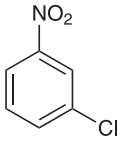


CHAPTER 5

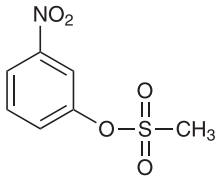
5.2 This compound meets all three criteria for a nucleophilic aromatic substitution reaction: 1) it has an electron-withdrawing group (a nitro group), 2) it has a leaving group (bromide), and 3) the leaving group is *ortho* to the electron-withdrawing group. Therefore, this compound can serve as an electrophile in a nucleophilic aromatic substitution reaction.



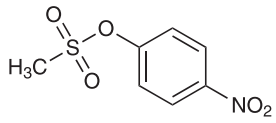
5.3 This compound has an electron-withdrawing group (a nitro group) and a leaving group (chloride), but the leaving group is *meta* to the electron-withdrawing group. Therefore, this compound will NOT serve as a suitable electrophile in a nucleophilic aromatic substitution reaction.



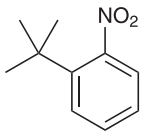
5.4 This compound has an electron-withdrawing group (a nitro group) and a leaving group (a sulfonate group), but the leaving group is *meta* to the electron-withdrawing group. Therefore, this compound will NOT serve as a suitable electrophile in a nucleophilic aromatic substitution reaction.



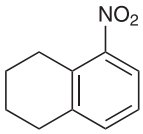
5.5 This compound meets all three criteria for a nucleophilic aromatic substitution reaction: 1) it has an electron-withdrawing group (a nitro group), 2) it has a leaving group (a sulfonate group), and 3) the leaving group is *para* to the electron-withdrawing group. Therefore, this compound can serve as an electrophile in a nucleophilic aromatic substitution reaction.



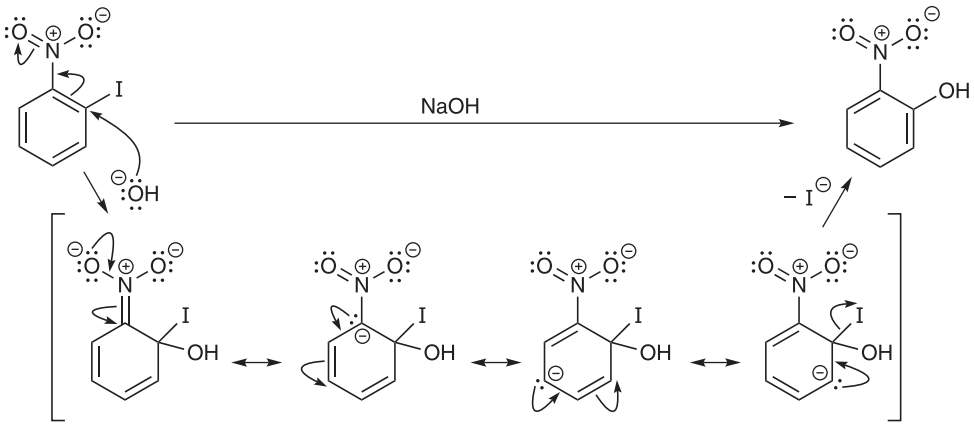
5.6 This compound has an electron-withdrawing group (a nitro group) but does NOT have a leaving group. The *tert*-butyl group cannot function as a leaving group, because a negative charge on a carbon atom is very unstable. Therefore, this compound will NOT serve as a suitable electrophile in a nucleophilic aromatic substitution reaction.



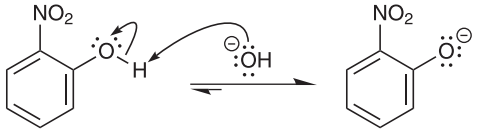
5.7 This compound has an electron-withdrawing group (a nitro group) but does NOT have a leaving group. Alkyl groups cannot function as leaving groups, because a negative charge on a carbon atom is very unstable. Therefore, this compound will NOT serve as a suitable electrophile in a nucleophilic aromatic substitution reaction.



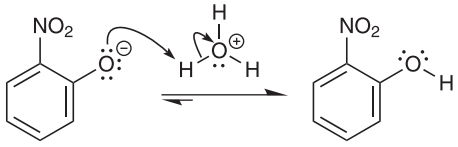
5.9 The reagent in the first step is a strong nucleophile (hydroxide), and the starting compound meets all three criteria for an S_NAr mechanism: an electron-withdrawing group (NO_2) and a leaving group (iodide) that are *ortho* to each other. In a nucleophilic aromatic substitution reaction, the nucleophile (hydroxide) attacks at the position bearing the leaving group, and electrons are pushed up into the reservoir. The resulting intermediate is a Meisenheimer complex, and it has resonance structures that should be drawn. Then, in the second step of the mechanism, the leaving group is expelled to give the product:



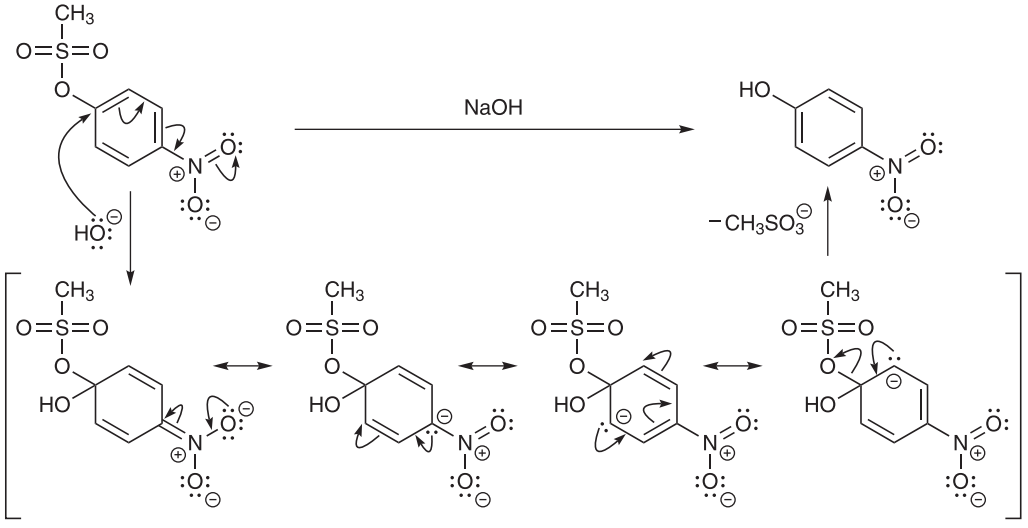
This might appear to be a complete mechanism. But remember that under basic conditions, the product is deprotonated.



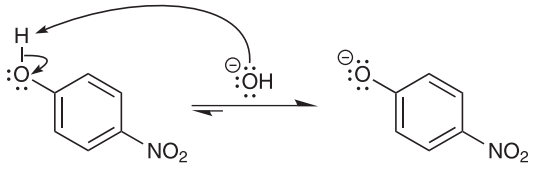
And that is why an acid source is necessary after the reaction is complete:



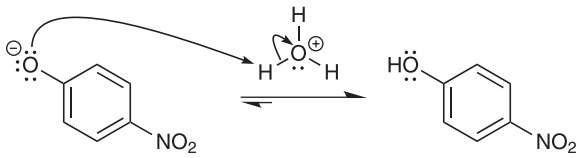
5.10 The reagent in the first step is a strong nucleophile (hydroxide), and the starting compound meets all three criteria for an S_NAr mechanism: an electron-withdrawing group (NO_2) and a leaving group (a sulfonate) that are *para* to each other. In a nucleophilic aromatic substitution reaction, the nucleophile (hydroxide) attacks at the position bearing the leaving group, and electrons are pushed up into the reservoir. The resulting intermediate is a Meisenheimer complex, and it has resonance structures that should be drawn. Then, in the second step of the mechanism, the leaving group is expelled to give the product:



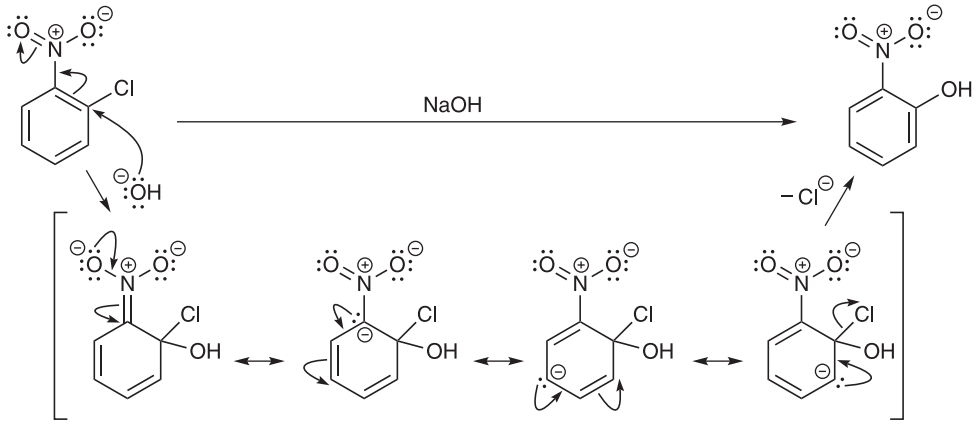
This might appear to be a complete mechanism. But remember that under basic conditions, the product is deprotonated.



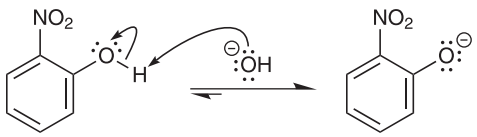
And that is why an acid source is necessary after the reaction is complete:



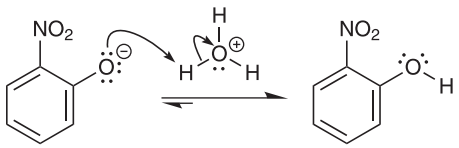
5.11 The reagent in the first step is a strong nucleophile (hydroxide), and the starting compound meets all three criteria for an S_NAr mechanism: an electron-withdrawing group (NO_2) and a leaving group (chloride) that are *ortho* to each other. In a nucleophilic aromatic substitution reaction, the nucleophile (hydroxide) attacks at the position bearing the leaving group, and electrons are pushed up into the reservoir. The resulting intermediate is a Meisenheimer complex, and it has resonance structures that should be drawn. Then, in the second step of the mechanism, the leaving group is expelled to give the product:



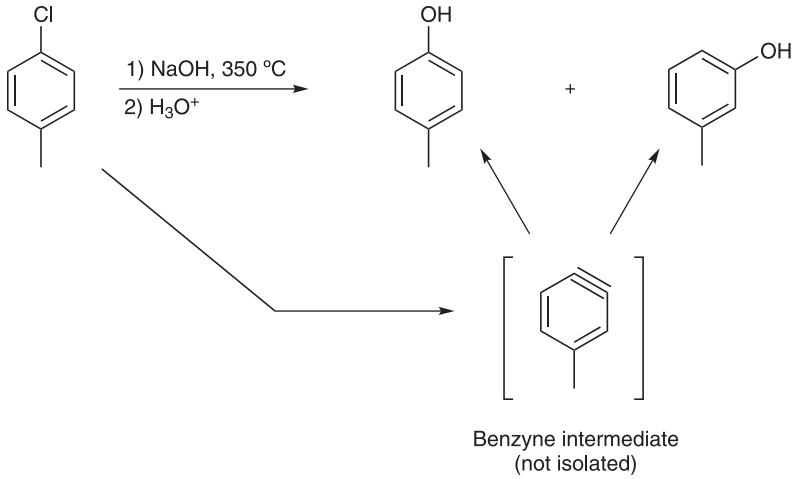
This might appear to be a complete mechanism. But remember that under basic conditions, the product is deprotonated.



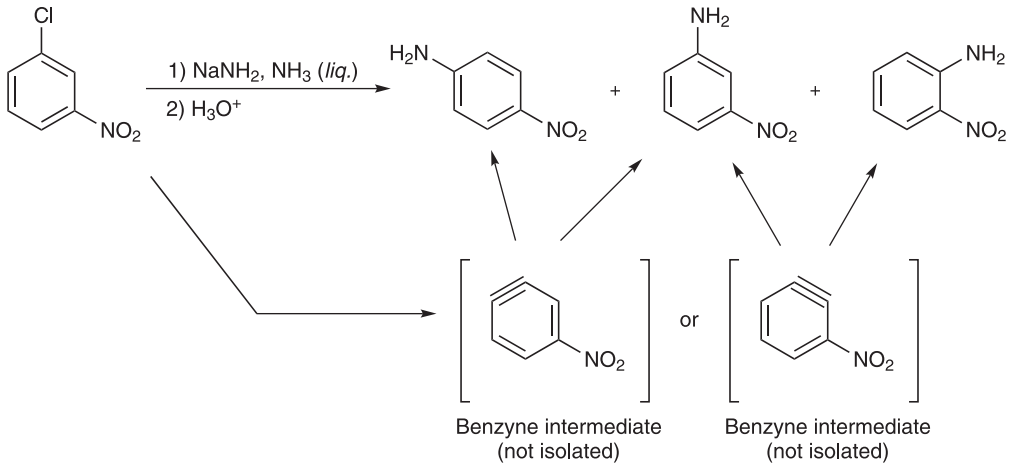
And that is why an acid source is necessary after the reaction is complete:



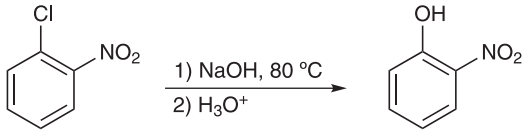
5.13 This compound has a leaving group, but it lacks a powerful electron-withdrawing group (such as a nitro group), so the reaction does NOT proceed via an S_NAr mechanism. Rather, the reaction must proceed via an elimination–addition process, as indicated by the high temperature. The reaction is expected to involve a benzyne intermediate (shown below), which can be attacked by hydroxide in either of two locations, leading to the two products shown.



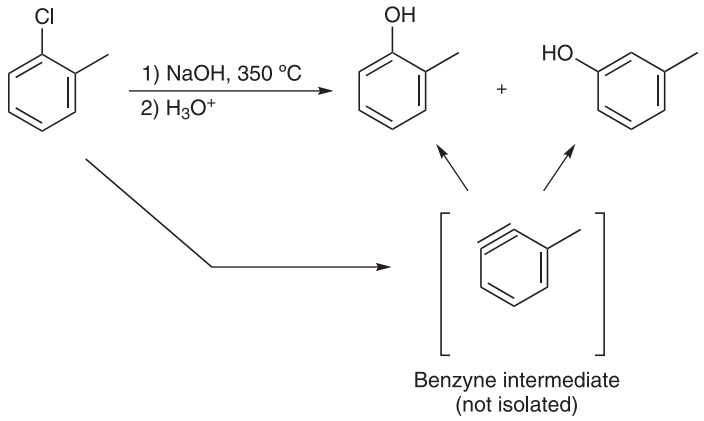
5.14 This compound has a powerful electron-withdrawing group (a nitro group) and a leaving group (chloride), BUT they are not *ortho* or *para* to each other. They are *meta* to each other, so the reaction does NOT proceed via an S_NAr mechanism. Rather, the reaction must proceed via an elimination–addition process. The reaction is expected to involve one of two possible benzyne intermediates (shown below), which can be attacked by H_2N^- to give one of the three products shown.



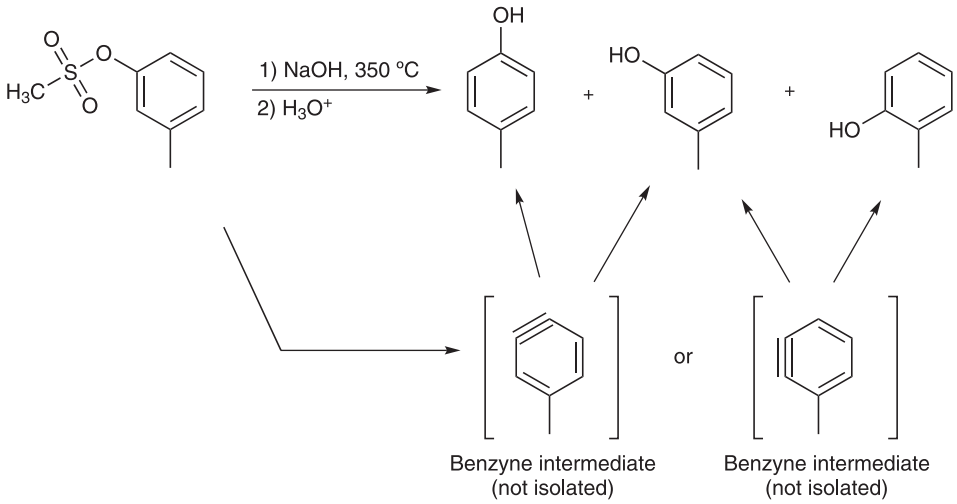
5.15 The reagent in the first step is a strong nucleophile (hydroxide), and the starting compound meets all three criteria for an S_NAr mechanism: an electron-withdrawing group (NO_2) and a leaving group (chloride) that are *ortho* to each other. We therefore expect an S_NAr reaction, in which the leaving group is replaced with a hydroxyl group:



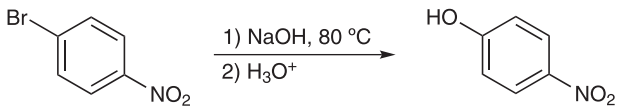
5.16 This compound has a leaving group, but it lacks a powerful electron-withdrawing group (such as a nitro group), so the reaction does NOT proceed via an S_NAr mechanism. Rather, the reaction must proceed via an elimination–addition process, as indicated by the high temperature. The reaction is expected to involve a benzyne intermediate (shown below). In this case, there is only one possible benzyne intermediate (there is only one hydrogen atom that is *ortho* to the leaving group). This benzyne intermediate is then attacked by hydroxide in either of two locations, leading to the two products shown.



5.17 This compound has a leaving group but lacks a powerful electron-withdrawing group (such as a nitro group). Therefore, the reaction does NOT proceed via an S_NAr mechanism. Rather, the reaction must proceed via an elimination–addition process, as indicated by the high temperature. The reaction is expected to involve one of two possible benzyne intermediates (shown below), which can be attacked by hydroxide to give one of the three products shown.

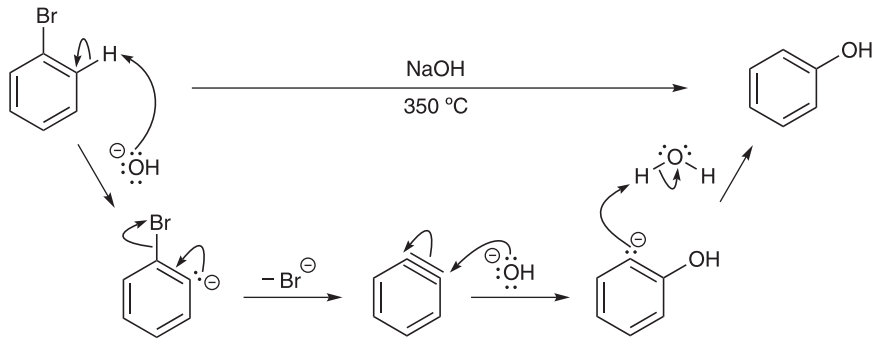


5.18 The reagent in the first step is a strong nucleophile (hydroxide), and the starting compound meets all three criteria for an S_NAr mechanism: an electron-withdrawing group (NO_2) and a leaving group (bromide) that are *para* to each other. We therefore expect an S_NAr reaction, in which the leaving group is replaced with a hydroxyl group:

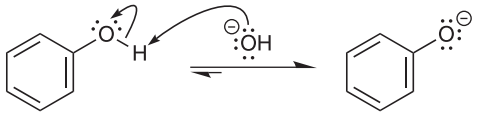


5.20 In this reaction, all three criteria for S_NAr have been met. For the mechanism, see the solution to Problem 5.11.

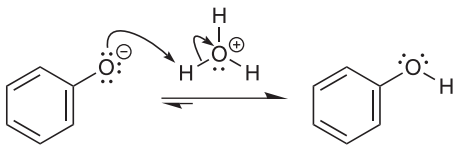
5.21 The reagent is a strong nucleophile (hydroxide), so we can rule out an electrophilic aromatic substitution reaction. The starting compound does NOT have all three criteria for an S_NAr mechanism. This compound has a leaving group (bromide), but it lacks a powerful electron-withdrawing group (such as a nitro group), so the reaction is NOT an S_NAr mechanism. Rather, the reaction must be an elimination–addition process (via a benzyne intermediate), as indicated by the high temperature.



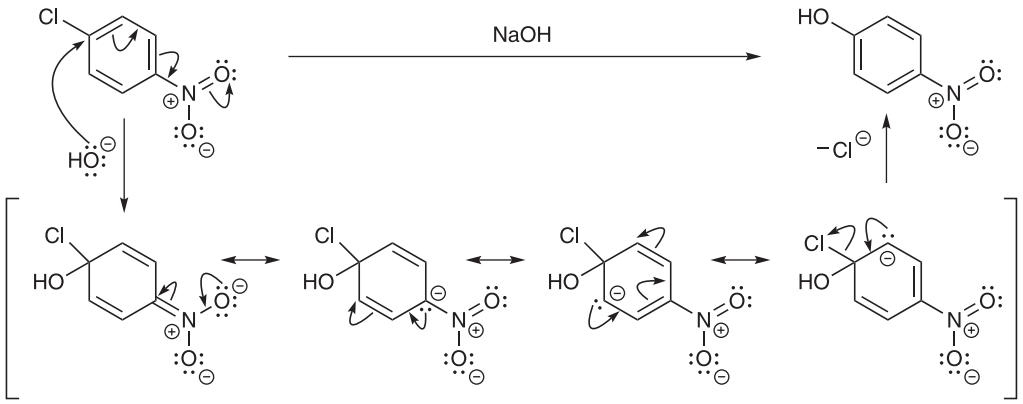
This might appear to be a complete mechanism. But remember that under basic conditions, the product is deprotonated.



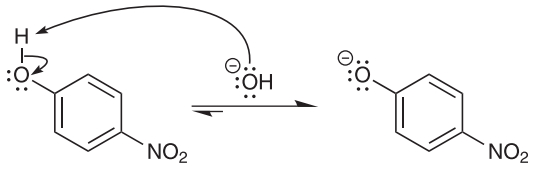
And that is why an acid source is necessary after the reaction is complete:



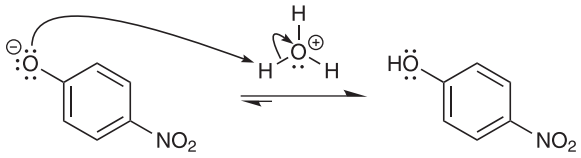
5.22 The reagent in the first step is a strong nucleophile (hydroxide), and the starting compound meets all three criteria for an S_NAr mechanism: an electron-withdrawing group (NO_2) and a leaving group (a sulfonate) that are para to each other. In a nucleophilic aromatic substitution reaction, the nucleophile (hydroxide) attacks at the position bearing the leaving group, and electrons are pushed up into the reservoir. The resulting intermediate is a Meisenheimer complex, and it has resonance structures that should be drawn. Then, in the second step of the mechanism, the leaving group is expelled to give the product:



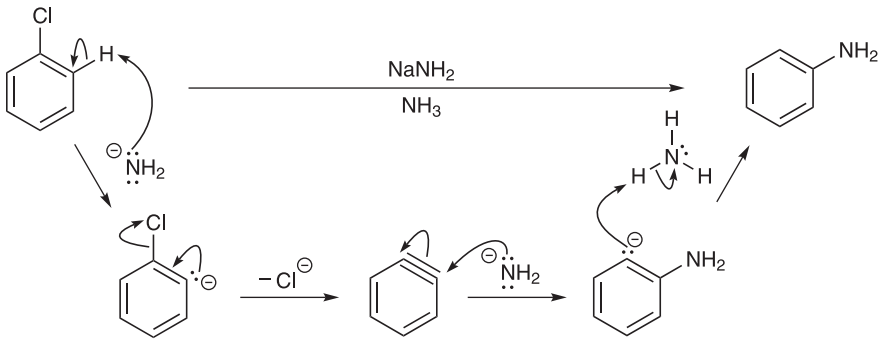
This might appear to be a complete mechanism. But remember that under basic conditions, the product is deprotonated.



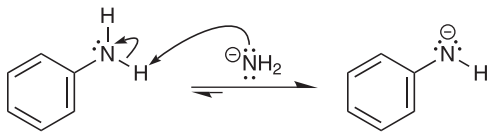
And that is why an acid source is necessary after the reaction is complete:



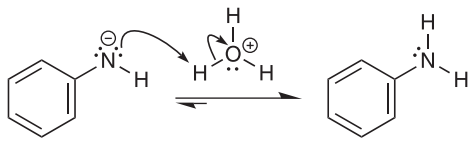
5.23 The reagent is a strong nucleophile (H_2N^-), so we can rule out an electrophilic aromatic substitution reaction. This compound has a leaving group (chloride), but it lacks a powerful electron-withdrawing group (such as a nitro group), so the reaction is NOT an S_NAr mechanism. Rather, the reaction must be an elimination–addition process (via a benzyne intermediate).



This might appear to be a complete mechanism. But, as we saw with phenol, aniline is deprotonated under these basic conditions:

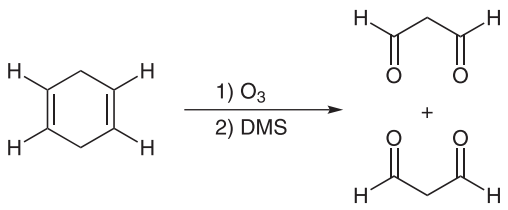


And that is why an acid source is necessary after the reaction is complete:

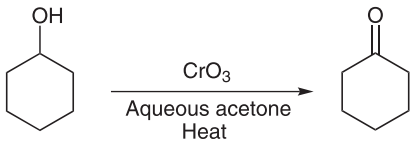


CHAPTER 6

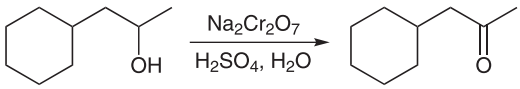
6.2 When an alkene undergoes ozonolysis, the C═C bond is cleaved and is replaced by two C═O bonds. This compound has two C═C bonds, and both are cleaved, as shown.



6.3 A secondary alcohol is converted into a ketone upon treatment with the Jones reagent:

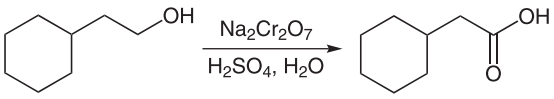


6.4 A secondary alcohol is converted into a ketone upon treatment with sodium dichromate and sulfuric acid:

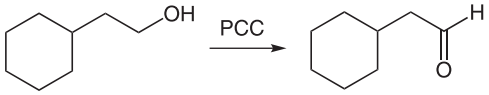


6.5 When an alkene undergoes ozonolysis, the C═C bond is cleaved and is replaced by two C═O bonds.

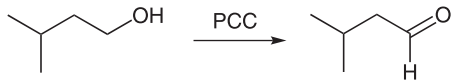
6.6 A primary alcohol is converted into a carboxylic acid upon treatment with sodium dichromate and sulfuric acid:



6.7 A primary alcohol is converted into an aldehyde upon treatment with PCC:

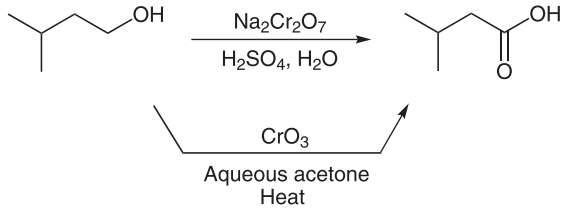


6.9 A primary alcohol can be converted into an aldehyde upon treatment with the mild oxidizing agent PCC.

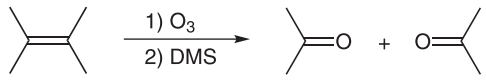


Treating this alcohol with a stronger oxidizing reagent would produce a carboxylic acid, not an aldehyde.

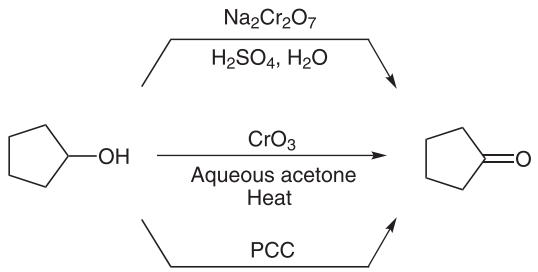
6.10 A primary alcohol can be converted into a carboxylic acid via a chromic acid oxidation, using either sodium dichromate and sulfuric acid, or the Jones reagent.



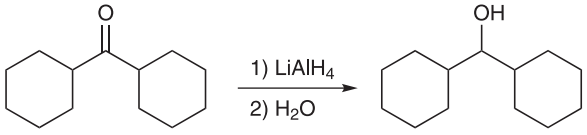
6.11 An alkene can be cleaved to give ketones via ozonolysis:



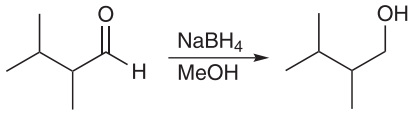
6.12 A secondary alcohol can be converted into a ketone with an oxidizing agent, such as sodium dichromate and sulfuric acid, or the Jones reagent, or even with PCC.



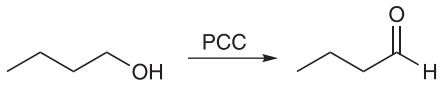
6.14 $LiAlH_4$ is a hydride reducing agent that will reduce a ketone to give a secondary alcohol:



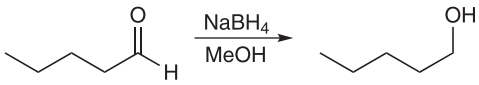
6.15 $NaBH_4$ is a hydride reducing agent that will reduce an aldehyde to give a primary alcohol:



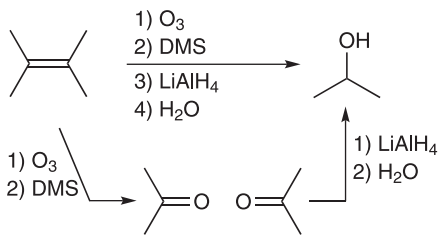
6.16 PCC is a mild oxidizing agent that will oxidize a primary alcohol to give an aldehyde, without further oxidizing the aldehyde to a carboxylic acid:



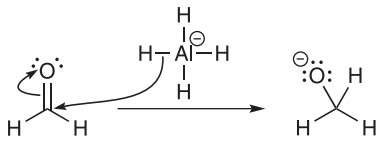
6.17 $NaBH_4$ is a hydride reducing agent that will reduce an aldehyde to give a primary alcohol:



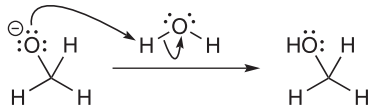
6.18 Ozonolysis of the alkene gives two equivalents of a ketone. This ketone is then reduced upon treatment with $LiAlH_4$ to give a secondary alcohol:



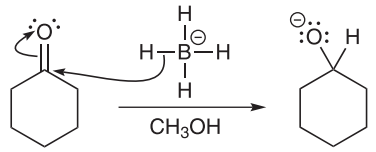
6.20 $LiAlH_4$ attacks the carbonyl group and functions as a "delivery agent" of a hydride ion, resulting in an alkoxide ion:



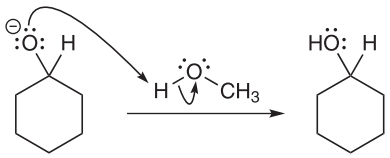
This alkoxide ion is then protonated upon treatment with a proton source, such as H_2O:



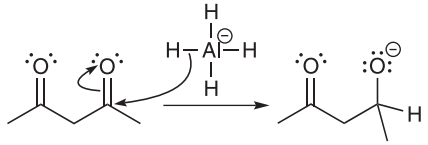
6.21 $NaBH_4$ attacks the carbonyl group and functions as a "delivery agent" of a hydride ion, resulting in an alkoxide ion:



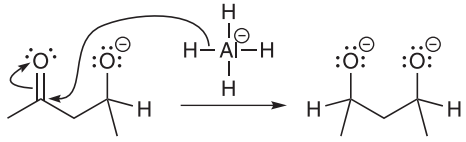
This alkoxide ion is then protonated by the proton source that is present in the reaction flask (in this case, CH_3OH):



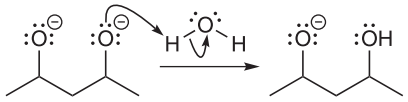
6.22 $LiAlH_4$ attacks one of the carbonyl groups and functions as a "delivery agent" of a hydride ion, resulting in an alkoxide ion:



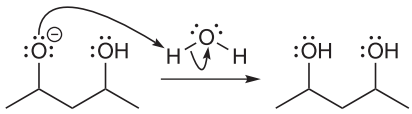
and then another equivalent of $LiAlH_4$ attacks the other carbonyl group:



When the reaction is complete, the dianion above must be treated with a proton source, such as water. When water is introduced into the reaction flask, each of the oxygen atoms is protonated. Make sure to draw each protonation step separately, and it doesn't matter which one is shown first. Here are the curved arrows for protonation of one of the oxygen atoms:

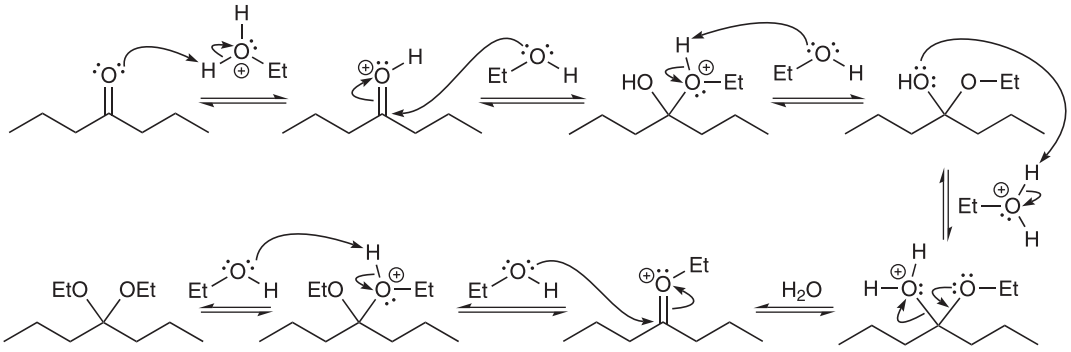


And here are the curved arrows for protonation of the other oxygen atom:



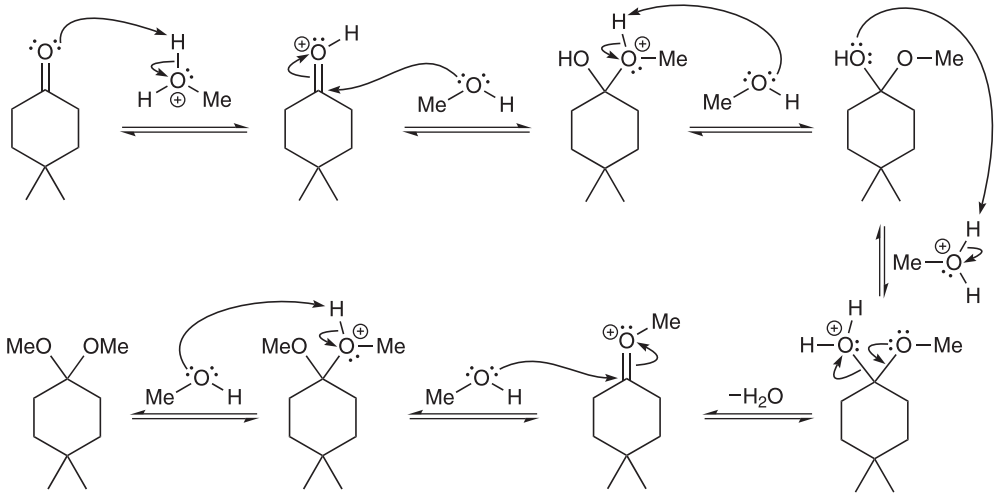
6.24 This mechanism has seven steps, described and shown below. Notice that the first three steps produce a hemiacetal, while the last four steps convert the hemiacetal into an acetal.

1. The ketone is protonated, thereby rendering the carbonyl group even more electrophilic.
2. The protonated carbonyl is then attacked by ethanol, giving a tetrahedral intermediate.
3. This intermediate is then deprotonated (by ethanol) to give a hemiacetal.
4. The hemiacetal is then protonated to generate an excellent leaving group (H_2O).
5. The leaving group (H_2O) is then expelled to regenerate the carbonyl group.
6. The carbonyl group is then attacked by ethanol to give an oxonium ion.
7. The oxonium ion is deprotonated (by ethanol) to give the product (an acetal):



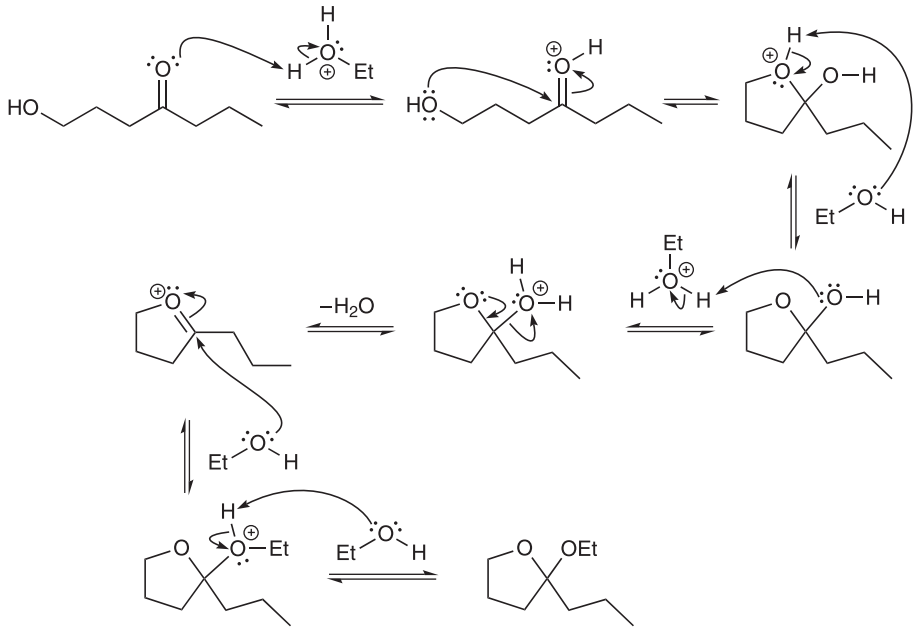
6.25 This mechanism has seven steps, described and shown below. Notice that the first three steps produce a hemiacetal, while the last four steps convert the hemiacetal into an acetal.

1. The ketone is protonated, thereby rendering the carbonyl group even more electrophilic.
2. The protonated carbonyl is then attacked by methanol, giving a tetrahedral intermediate.
3. This intermediate is then deprotonated (by methanol) to give a hemiacetal.
4. The hemiacetal is then protonated to generate an excellent leaving group (H_2O).
5. The leaving group (H_2O) is then expelled to regenerate the carbonyl group.
6. The carbonyl group is then attacked by methanol to give an oxonium ion.
7. The oxonium ion is deprotonated (by methanol) to give the product (an acetal):



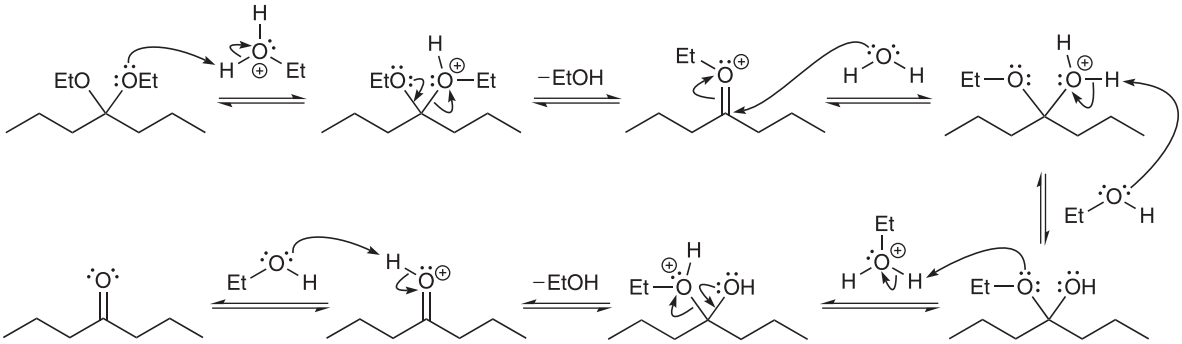
6.26 This mechanism has seven steps, described and then shown below. Notice that the first three steps produce a hemiacetal, while the last four steps convert the hemiacetal into an acetal.

1. The ketone is protonated, thereby rendering the carbonyl group even more electrophilic.
2. The protonated carbonyl is then attacked by the OH group (in an intramolecular fashion), giving a tetrahedral intermediate.
3. This intermediate is then deprotonated (by ethanol) to give a hemiacetal.
4. The hemiacetal is then protonated to generate an excellent leaving group (H_2O).
5. The leaving group (H_2O) is then expelled to regenerate the carbonyl group.
6. The carbonyl group is then attacked by ethanol to give an oxonium ion.
7. The oxonium ion is deprotonated (by ethanol) to give the product (an acetal):

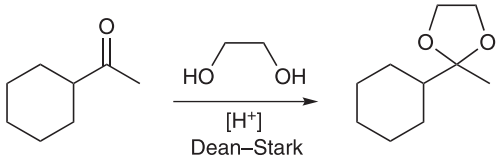


6.27 This process has seven steps, described and shown below. Notice that the order of the intermediates is the exact opposite order that we would expect for the reverse process (acetal formation).

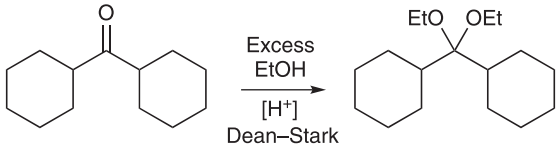
1. The acetal is protonated, thereby converting the OEt group into a better leaving group (EtOH) that is consistent with acidic conditions (we cannot expel EtO^- in acidic conditions).
2. The leaving group (EtOH) is then expelled to generate a C═O bond.
3. The C═O bond is then attacked by water to give an oxonium ion.
4. The oxonium ion is deprotonated (by ethanol) to give a hemiacetal.
5. The hemiacetal is then protonated to convert the OEt group into a better leaving group (EtOH).
6. The leaving group is expelled to give a protonated ketone.
7. The protonated ketone is deprotonated (by ethanol) to give the product (a ketone):



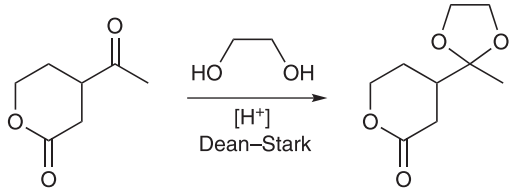
6.29 A cyclic acetal is obtained when a ketone is treated with ethylene glycol under acidic conditions and with removal of water via a Dean–Stark trap:



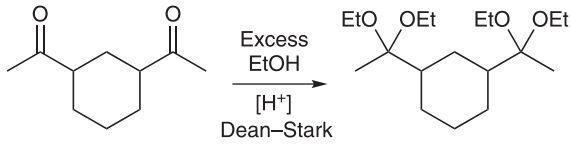
6.30 An acetal is obtained when a ketone is treated with excess alcohol under acidic conditions and with removal of water via a Dean–Stark trap:



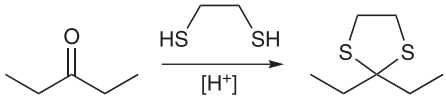
6.31 A ketone is converted into a cyclic acetal when treated with ethylene glycol under acidic conditions and with removal of water via a Dean–Stark trap. Note that the C═O bond of the ester is not reactive under these conditions.



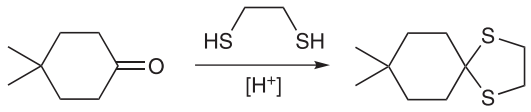
6.32 Each carbonyl group is converted into an acetal when treated with excess alcohol under acidic conditions and with removal of water via a Dean–Stark trap:



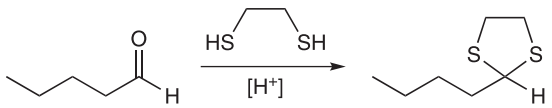
6.33 A ketone is converted into a cyclic thioacetal when treated with ethylene thioglycol under acidic conditions:



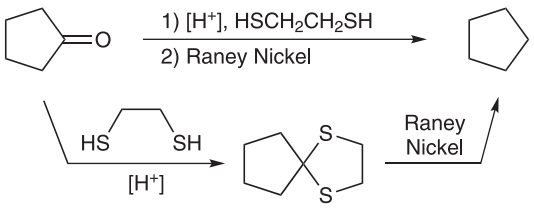
6.34 A ketone is converted into a cyclic thioacetal when treated with ethylene thioglycol under acidic conditions:



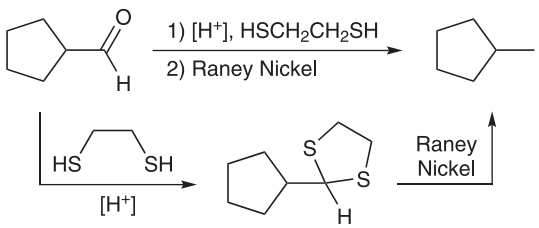
6.35 An aldehyde is converted into a cyclic thioacetal when treated with ethylene thioglycol under acidic conditions:



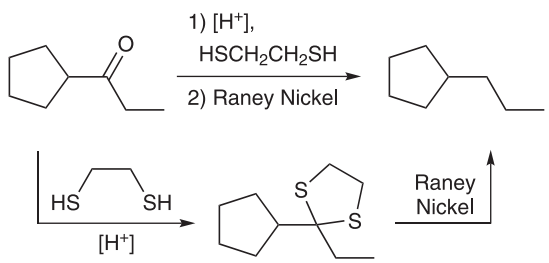
6.36 When a ketone is treated with ethylene thioglycol under acidic conditions, followed by Raney nickel, the carbonal group is reduced to give a methylene (CH_2) group.



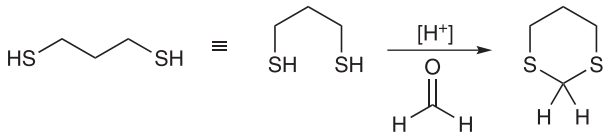
6.37 When an aldehyde is treated with ethylene thioglycol under acidic conditions, followed by Raney nickel, the carbonyl group is reduced to give a methyl group, as shown:



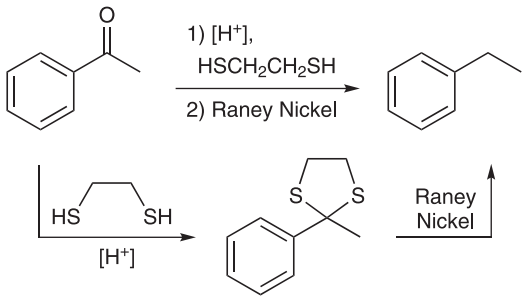
6.38 When a ketone is treated with ethylene thioglycol under acidic conditions, followed by Raney nickel, the carbonyl group is reduced to give a methylene (CH_2) group.



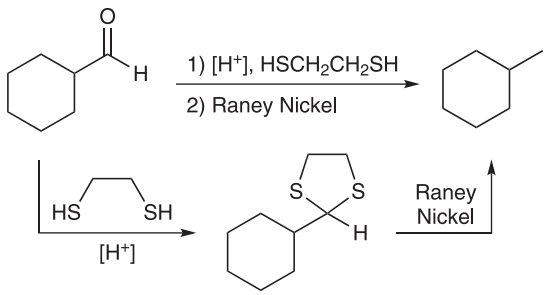
6.39 The starting material is propylene thioglycol ($HSCH_2CH_2CH_2SH$). This compound can be converted into the desired cyclic thioacetal upon treatment with formaldehyde under acidic conditions, as shown:



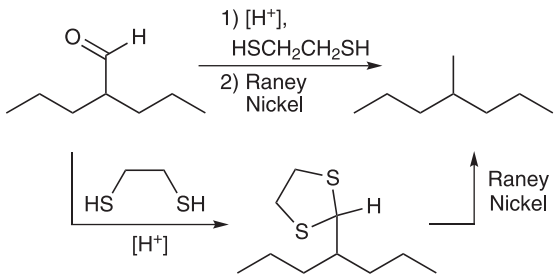
6.40 The desired transformation involves the reduction of the carbonyl group of a ketone to give a methylene (CH_2) group. This can be accomplished by converting the ketone into a cyclic thioacetal, and then reducing the cyclic thioacetal with Raney nickel, as shown below. Alternatively, the same transformation can be achieved with a Clemmensen reduction.



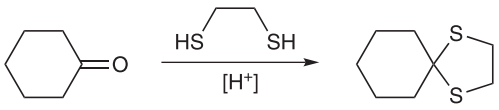
6.41 The desired transformation involves the complete reduction of the carbonyl group of an aldehyde to give a methyl group. This can be accomplished by converting the aldehyde into a cyclic thioacetal, and then reducing the cyclic thioacetal with Raney nickel, as shown below. Alternatively, the same transformation can be achieved with a Clemmensen reduction.



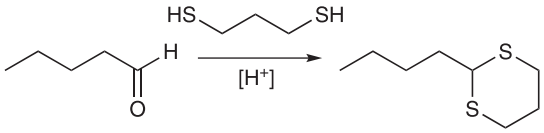
6.42 The desired transformation involves the complete reduction of the carbonyl group of an aldehyde to give an alkane. This can be accomplished by converting the aldehyde into a cyclic thioacetal, and then reducing the cyclic thioacetal with Raney nickel, as shown below. Alternatively, the same transformation can be achieved with a Clemmensen reduction.



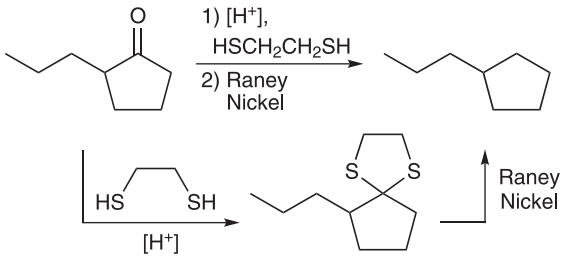
6.43 A ketone can be converted into a cyclic thioacetal upon treatment with ethylene thioglycol under acidic conditions, as shown here:



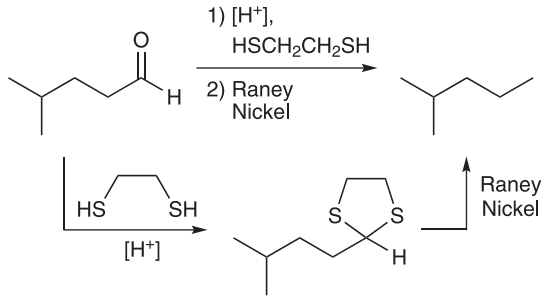
6.44 An aldehyde can be converted into a cyclic thioacetal upon treatment with propylene thioglycol under acidic conditions, as shown here:



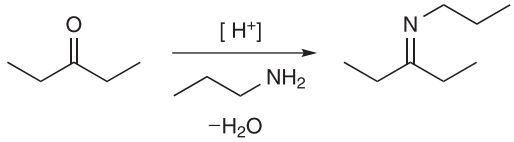
6.45 The desired transformation involves the reduction of the carbonyl group of a ketone to give a methylene (CH_2) group. This can be accomplished by converting the ketone into a cyclic thioacetal, and then reducing the cyclic thioacetal with Raney nickel, as shown below. Alternatively, the same transformation can be achieved with a Clemmensen reduction.



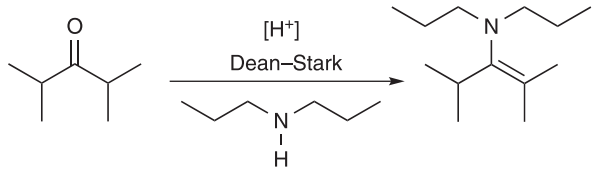
6.46 The desired transformation involves the complete reduction of the carbonyl group of an aldehyde to give an alkane. This can be accomplished by converting the aldehyde into a cyclic thioacetal, and then reducing the cyclic thioacetal with Raney nickel, as shown below. Alternatively, the same transformation can be achieved with a Clemmensen reduction.



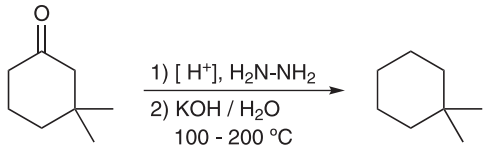
6.48 When a symmetrical ketone is treated with a primary amine under acidic conditions (and with removal of water), the ketone is converted into an imine:



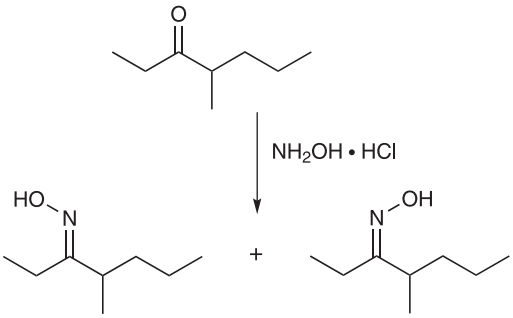
6.49 When a symmetrical ketone is treated with a secondary amine under acidic conditions (and with removal of water), the ketone is converted into an enamine:



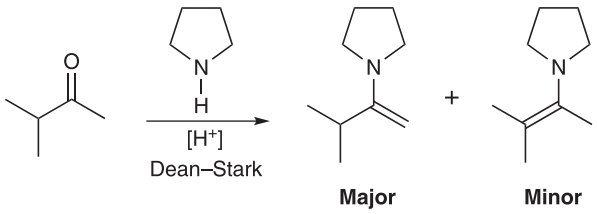
6.50 The starting material is a ketone, and the reagents indicate a Wolff–Kishner reduction. The net result of this process is to reduce the carbonyl group to give a methylene (CH_2) group:



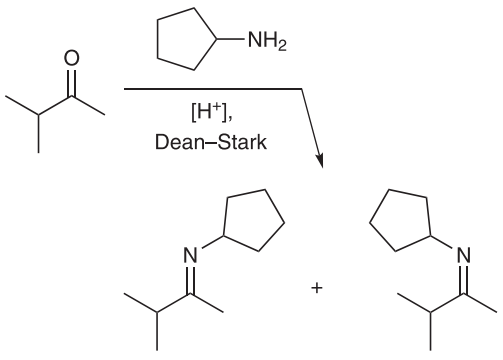
6.51 The reagent is hydroxylamine, and the starting material is an unsymmetrical ketone. Under these conditions, an unsymmetrical ketone is converted into a mixture of diastereomeric oximes:



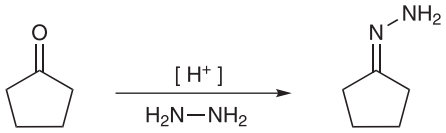
6.52 The starting material is a ketone, and the reagent is a secondary amine. A ketone is converted into an enamine upon treatment with a secondary amine under acidic conditions (and with removal of water). In this case, the ketone is unsymmetrical, so we expect a mixture of enamines, with the less-substituted enamine being favored:



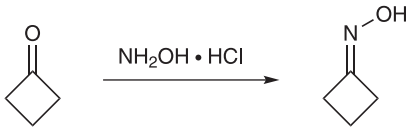
6.53 The starting material is a ketone, and the reagent is a primary amine. A ketone is converted into an imine upon treatment with a primary amine under acidic conditions (and with removal of water). In this case, the ketone is unsymmetrical, so we expect a mixture of diastereomeric imines:



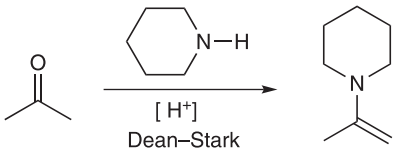
6.54 The starting material is a symmetrical ketone, and the reagent is hydrazine ($H_2N–NH_2$). A ketone is converted into a hydrazone upon treatment with hydrazine under acidic conditions.



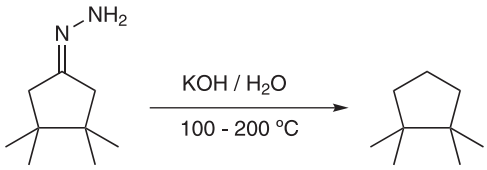
6.55 The starting material is a symmetrical ketone, and the reagent is hydroxylamine (NH_2OH). A ketone is converted into an oxime upon treatment with hydroxylamine under acidic conditions.



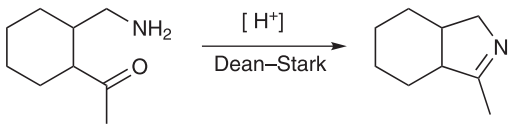
6.56 The starting material is a symmetrical ketone, and the reagent is a secondary amine. When a symmetrical ketone is treated with a secondary amine under acidic conditions (and with removal of water), the ketone is converted into an enamine:



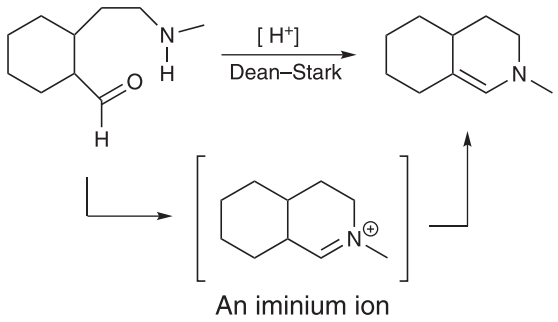
6.57 The starting material is a hydrazone, and the reagents indicate a Wolff–Kishner reduction, which gives an alkane (or in this case, a cycloalkane):



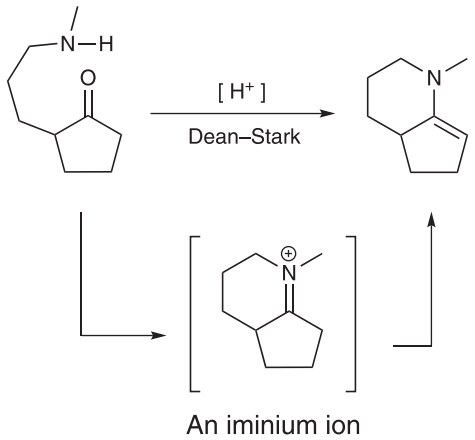
6.58 The starting material has both a primary amine and a ketone tethered together in the same molecule, allowing for an intramolecular reaction. Under acidic conditions (and with removal of water), a primary amine will react with a ketone to give an imine, as shown:



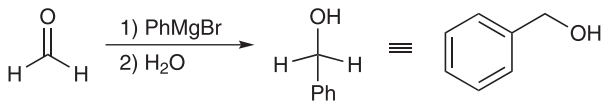
6.59 The starting material has both a secondary amine and an aldehyde tethered together in the same molecule, allowing for an intramolecular reaction. Under acidic conditions (and with removal of water), a secondary amine will react with an aldehyde to give an enamine (via the iminium ion intermediate shown):



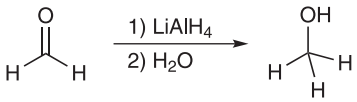
6.60 The starting material has both a secondary amine and a ketone tethered together in the same molecule, allowing for an intramolecular reaction. Under acidic conditions (and with removal of water), a secondary amine will react with a ketone to give the less-substituted enamine (via the iminium ion intermediate shown):



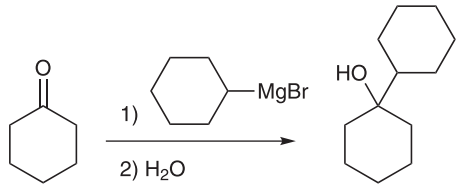
6.62 When an aldehyde is treated with a Grignard reagent, followed by water, the aldehyde is reduced to an alcohol, accompanied by the installation of an R group from the Grignard reagent. In this case, the Grignard reagent is PhMgBr, so a phenyl group (Ph) is installed, as follows:



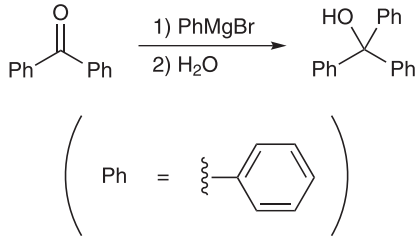
6.63 $LiAlH_4$ is a reducing agent. When an aldehyde is treated with $LiAlH_4$, followed by aqueous work-up (H_2O), the aldehyde is reduced to give an alcohol:



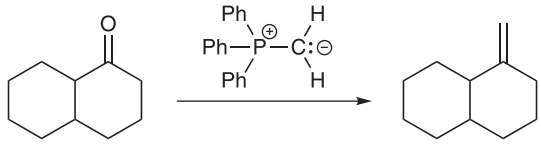
6.64 When a ketone is treated with a Grignard reagent, followed by water, the ketone is reduced to an alcohol, accompanied by the installation of an R group from the Grignard reagent. In this case, the Grignard reagent is cyclohexyl magnesium bromide, so a cyclohexyl group is installed, as follows:



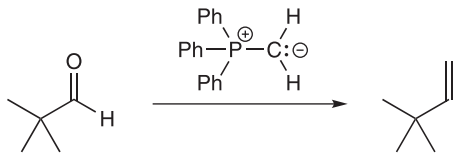
6.65 When a ketone is treated with a Grignard reagent, followed by water, the ketone is reduced to an alcohol, accompanied by the installation of an R group from the Grignard reagent. In this case, the Grignard reagent is PhMgBr, so a phenyl group (Ph) is installed, as follows:



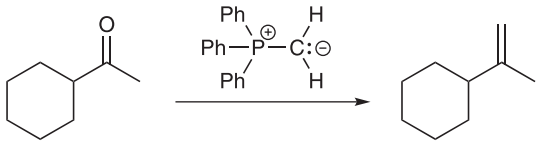
6.67 A ketone will react with a Wittig reagent to give an alkene. In this case, the Wittig reagent does not have any R groups (the carbon atom bearing the negative charge is connected to two hydrogen atoms and no R groups), so a methylene (CH_2) group is installed in place of the oxygen atom.



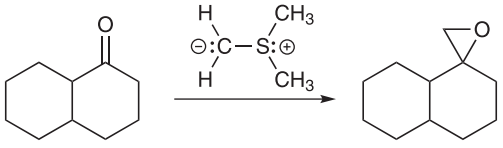
6.68 An aldehyde will react with a Wittig reagent to give an alkene. In this case, the Wittig reagent does not have any R groups (the carbon atom bearing the negative charge is connected to two hydrogen atoms and no R groups), so a methylene (CH_2) group is installed in place of the oxygen atom.



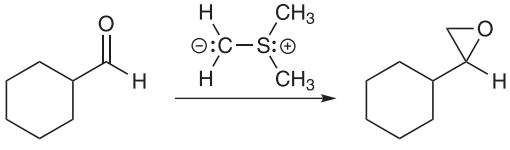
6.69 A ketone will react with a Wittig reagent to give an alkene. In this case, the Wittig reagent does not have any R groups (the carbon atom bearing the negative charge is connected to two hydrogen atoms and no R groups), so a methylene (CH_2) group is installed in place of the oxygen atom.



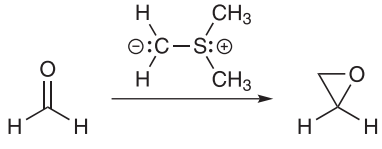
6.71 The starting material is a ketone, and the reagent is a sulfur ylide, which will convert the ketone into an epoxide, as shown:



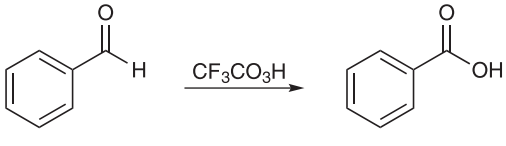
6.72 The starting material is an aldehyde, and the reagent is a sulfur ylide, which will convert the aldehyde into an epoxide, as shown:



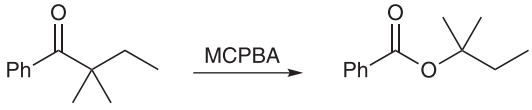
6.73 The starting material is formaldehyde, and the reagent is a sulfur ylide, which will convert formaldehyde into an epoxide, as shown:



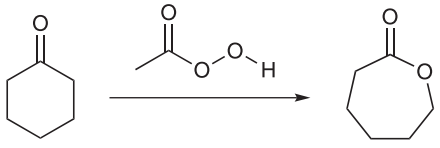
6.75 An aldehyde is being treated with a peroxy acid, so we expect a Baeyer–Villiger reaction to occur. Under these conditions, the aldehyde is oxidized to give a carboxylic acid:



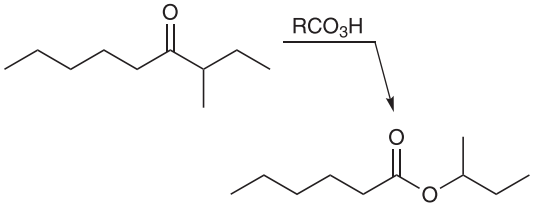
6.76 A ketone is being treated with a peroxy acid, so we expect a Baeyer–Villiger reaction to occur. We look closely at the starting ketone, and we see that it is unsymmetrical. So, we must predict where the oxygen atom will be inserted. We look at both sides, and we see that the left side is a phenyl group and the right side is tertiary (the carbon atom to the right of the carbonyl group is connected to three alkyl groups). Tertiary groups migrate faster than phenyl groups, so the oxygen atom will be inserted on the right side of the carbonyl group:



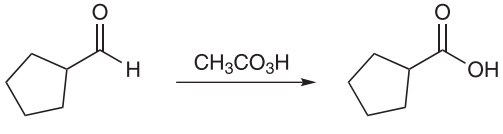
6.77 A ketone is being treated with a peroxy acid, so we expect a Baeyer–Villiger reaction to occur. The starting ketone is symmetrical, so we don't need to decide where the oxygen atom inserts itself (the left side generates the same product as the right side). The product is a cyclic ester:



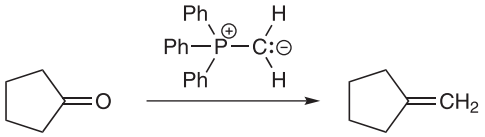
6.78 A ketone is being treated with a peroxy acid (RCO_3H), so we expect a Baeyer–Villiger reaction to occur. We look closely at the starting ketone, and we see that it is unsymmetrical. So, we must predict where the oxygen atom will be inserted. We look at both sides of the carbonyl group. The carbon atom to the left of the carbonyl group is connected to one alkyl group, while the carbon atom to the right of the carbonyl group is connected to two alkyl groups. The more-substituted group migrates faster, so the oxygen atom will be inserted on the right side of the carbonyl group:



6.79 An aldehyde is being treated with a peroxy acid (RCO_3H), so we expect a Baeyer–Villiger reaction to occur. Under these conditions, the aldehyde is oxidized to give a carboxylic acid:

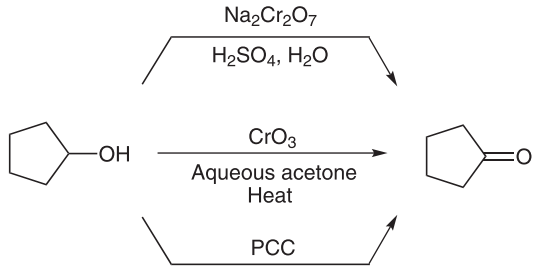


6.81 A ketone can be converted into an alkene (with the installation of a CH_2 group) via a Wittig reaction. This is achieved by treating the ketone with a phosphorus ylide (a Wittig reagent), shown here:

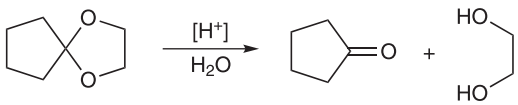


6.82 A symmetrical ketone can be converted into an ester (in this case, a cyclic ester) via a Baeyer–Villiger oxidation. This is achieved by treating the ketone with a peroxy acid, such as MCPBA:

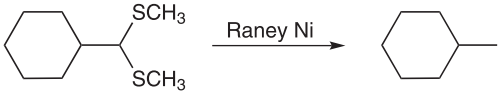
6.83 A secondary alcohol is oxidized to give a ketone upon treatment with a variety of oxidizing agents, including sodium dichromate, the Jones reagent, or even PCC:



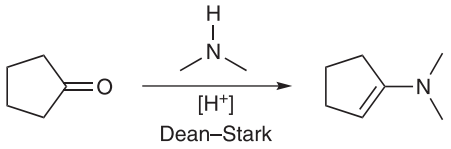
6.84 An acetal can be hydrolyzed to give a ketone upon treatment with water in the presence of an acid catalyst.



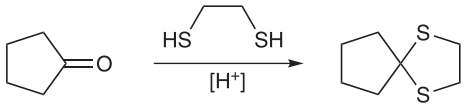
6.85 The starting material is a thioacetal (there is a carbon atom connected to two SR groups). This thioacetal can be reduced with Raney nickel to give the desired product:



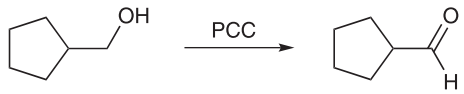
6.86 A ketone can be converted into an enamine upon treatment with a secondary amine and an acid catalyst (and with removal of water):



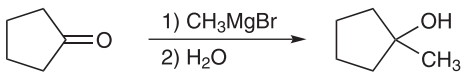
6.87 A ketone can be converted into a cyclic thioacetal upon treatment with ethylene thioglycol and an acid catalyst:



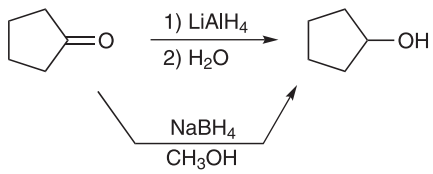
6.88 A primary alcohol is oxidized to give an aldehyde upon treatment with PCC:



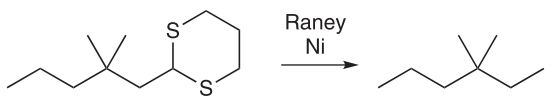
6.89 The starting material is a ketone and the product is an alcohol. That is, the carbonyl group is reduced, but together with the installation of a methyl group. This can be achieved by treating the ketone with a Grignard reagent (methyl magnesium bromide) followed by water:



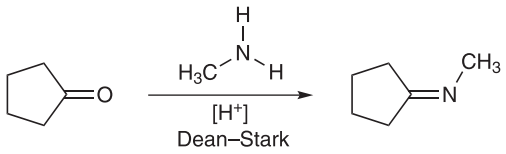
6.90 A ketone can be reduced to give a secondary alcohol upon treatment with lithium aluminum hydride, followed by water. Alternatively, sodium borohydride can be used (note that sodium borohydride is shown together with the proton source, not as a separate step):



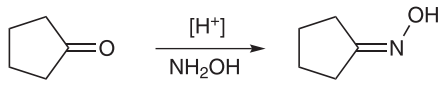
6.91 The starting material is a cyclic thioacetal, which can be reduced with Raney nickel to give the desired product:



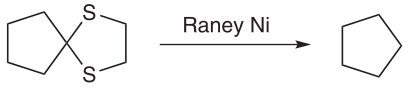
6.92 A symmetrical ketone can be converted into an imine upon treatment with a primary amine and an acid catalyst (and with removal of water):



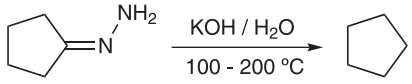
6.93 A symmetrical ketone can be converted into an oxime upon treatment with hydroxyl amine and an acid catalyst:



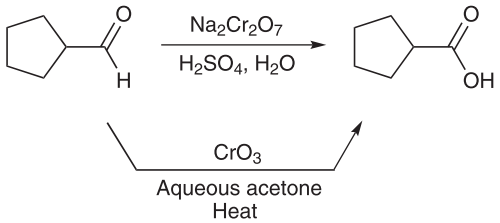
6.94 The starting material is a cyclic thioacetal, which can be reduced with Raney nickel to give the desired product:



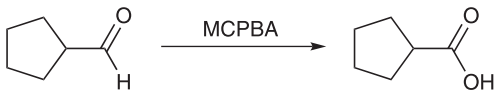
6.95 The starting material is a hydrazone, which can undergo a Wolff–Kishner reduction to give the desired product:



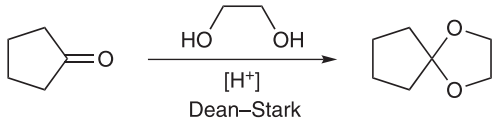
6.96 An aldehyde can be oxidized to give a carboxylic acid upon treatment with a strong oxidizing agent, such as sodium dichromate or the Jones reagent:



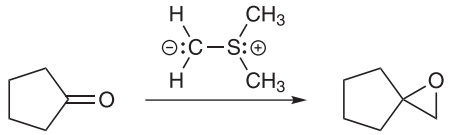
Alternatively, an aldehyde can be oxidized to give a carboxylic acid upon treatment with a peroxy acid (such as MCPBA), via a Baeyer–Villiger oxidation:



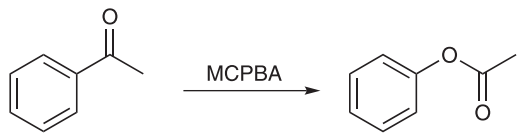
6.97 A ketone can be converted into a cyclic acetal upon treatment with ethylene glycol and an acid catalyst (and with removal of water):



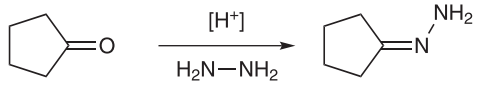
6.98 A ketone can be converted into an epoxide upon treatment with a sulfur ylide:



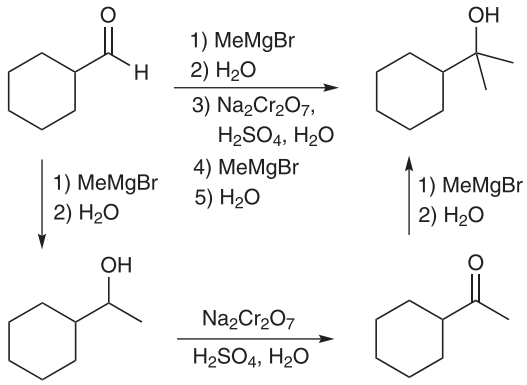
6.99 The starting material is an unsymmetrical ketone, and the product is an ester. The difference between the starting material and the product is an oxygen atom, which needs to be inserted between the aromatic ring and the carbonyl group. This can be accomplished via a Baeyer–Villiger oxidation reaction. Treating the starting ketone with a peroxy acid, such as MCPBA, will give the desired product.



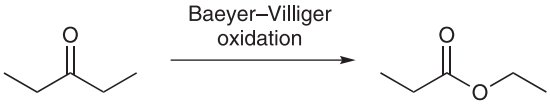
6.100 A symmetrical ketone can be converted into a hydrazone upon treatment with hydrazine and an acid catalyst:



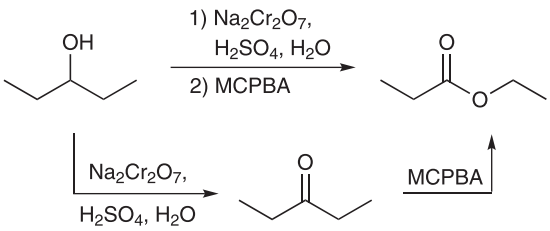
6.103 The starting material is an aldehyde, and the desired product is an alcohol. Notice also that we must install two methyl groups. We can use a Grignard reaction (with MeMgBr) to convert the aldehyde into an alcohol and simultaneously install one methyl group. The resulting alcohol is similar in structure to the desired product, but we are missing a methyl group. In order to install another methyl group, we need to oxidize the alcohol to a ketone, and then we can treat the ketone with another Grignard reagent, thereby installing another methyl group, as shown in the following synthesis:



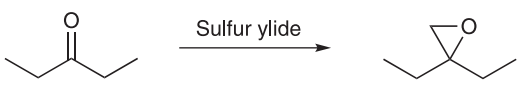
6.104 The starting material is an alcohol, and the desired product is an ester. We have not yet seen many ways to make esters, but we have seen that an ester can be made from a ketone via a Baeyer–Villiger oxidation process. So the last step of our synthesis might be a Baeyer–Villiger oxidation process, in which the product is made from the following ketone:



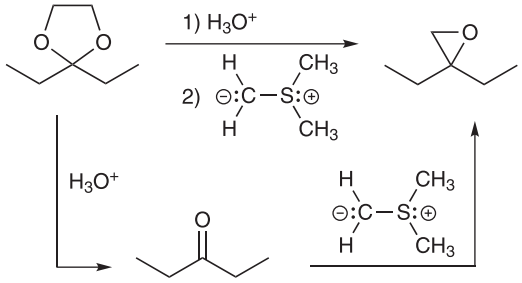
This ketone can be made directly from the starting material via oxidation. In summary, we have developed a two-step synthesis for the desired product. In the first step, the alcohol is treated with an oxidizing agent to give a ketone, and then the ketone is treated with a peroxy acid (such as MCPBA) to give the desired ester:



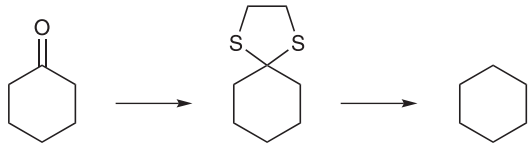
6.105 The starting material is an acetal, and the desired product is an epoxide. We have not yet seen many ways to make epoxides. But in this chapter, we have seen that an epoxide can be made by treating a ketone with a sulfur ylide. So the last step of our synthesis might be the conversion of the following ketone into the desired epoxide:



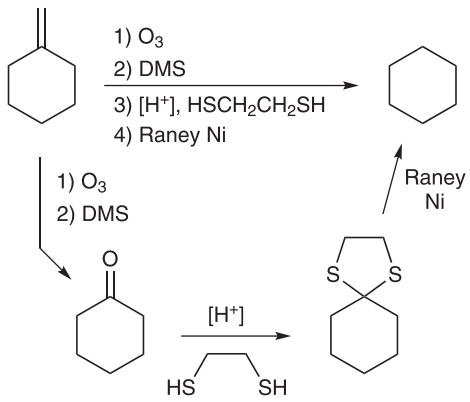
This ketone can be made directly from the starting acetal upon treatment with aqueous acid. In summary, we have developed a two-step synthesis for the desired product. In the first step, the acetal is treated with water and an acid catalyst to give a ketone, and then the ketone is treated with a sulfur ylide to give the desired epoxide:



6.106 The starting material is an alkene, and the desired product is an alkane (actually, a cycloalkane). We have not seen any direct ways to remove a methylene (CH_2) group. But in this chapter, we have seen more than one way to convert a ketone into an alkane. For example, the following transformation can be achieved by converting the ketone below into a thioacetal, followed by desulfurization with Raney nickel:



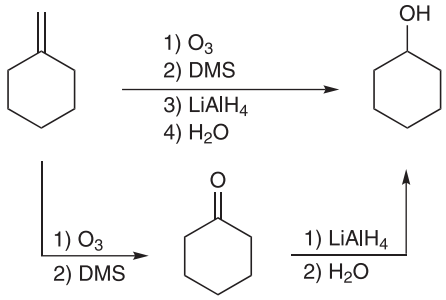
This ketone can be made directly from the starting alkene via ozonolysis. In summary, we have developed the following synthesis for the desired product. First, the alkene undergoes ozonolysis, and the resulting ketone is converted to a cyclic thioacetal, followed by desulfurization with Raney nickel, to give the desired product:



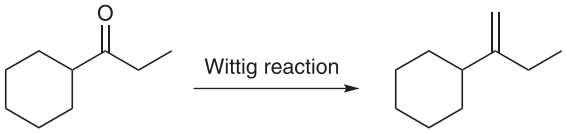
Alternatively, the ketone can be reduced to a CH_2 group via a Clemmensen reduction or via a Wolff–Kishner reduction.

6.107 The starting material is an alkene, and the desired product is an alcohol. We have not seen any direct ways to achieve this transformation. But in this chapter, we have seen that the desired alcohol can be made via reduction of the corresponding ketone:

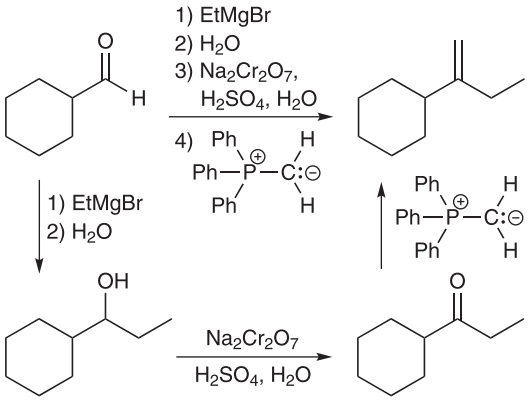
This ketone can be made directly from the starting alkene via ozonolysis. In summary, we have developed the following synthesis for the desired product. First, ozonolysis is performed to convert the alkene into a ketone, and this ketone is then reduced to give the desired product. The reduction step can be achieved either with lithium aluminum hydride (as shown) or with $NaBH_4$:



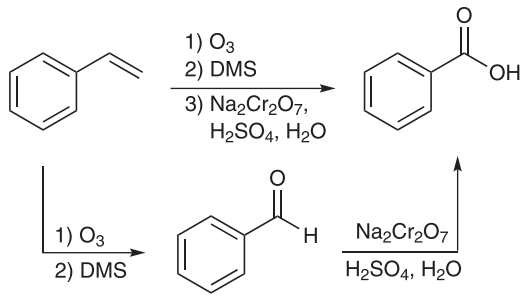
6.108 The starting material is an aldehyde, and the desired product is an alkene. We have not seen any direct ways to achieve this transformation. But in this chapter, we have seen that the desired alkene can be made via from a ketone via a Wittig reaction:



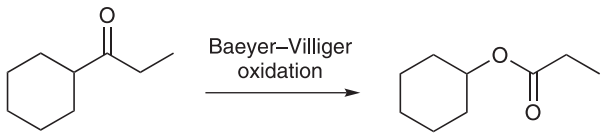
This ketone can be made from the starting aldehyde via a two-step process: 1) a Grignard reaction, followed by 2) oxidation. In summary, we have developed the following synthesis for the desired product. The starting aldehyde is treated with ethyl magnesium bromide, followed by water, to give an alcohol, which is then oxidized to give a ketone. And finally, the ketone is treated with a Wittig reagent to give the desired product:



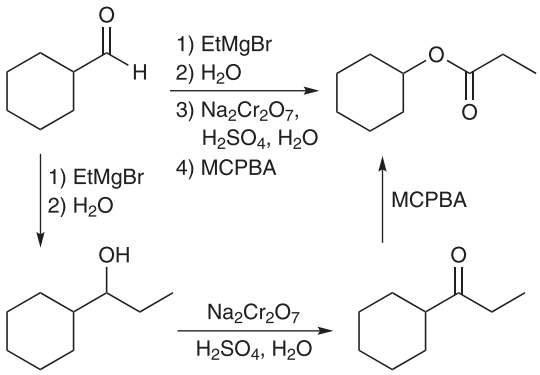
6.109 The starting material is an alkene, and the product is a carboxylic acid. Notice also that the product has one less carbon atom than the starting material. Removing a carbon atom requires breaking a bond between carbon atoms, and that can be accomplished via ozonolysis. The resulting aldehyde can then be oxidized to give the desired carboxylic acid:



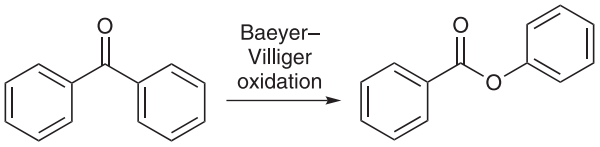
6.110 The starting material is an aldehyde, and the desired product is an ester. We have not yet seen many ways to make esters, but we have seen that an ester can be made from a ketone via a Baeyer–Villiger oxidation process. So the last step of our synthesis might be a Baeyer–Villiger oxidation process, in which the product is made from the following ketone:



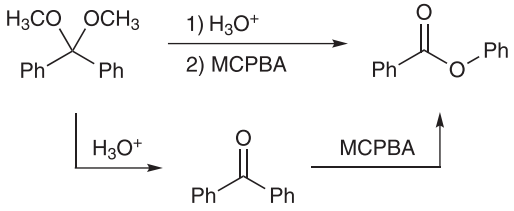
This ketone can be made from the starting aldehyde via a two-step process: 1) a Grignard reaction, followed by 2) oxidation. In summary, we have developed the following synthesis for the desired product. The starting aldehyde is treated with ethyl magnesium bromide, followed by water, to give an alcohol, which is then oxidized to give a ketone. And finally, the ketone is treated with a peroxy acid (such as MCPBA) to give the desired ester:



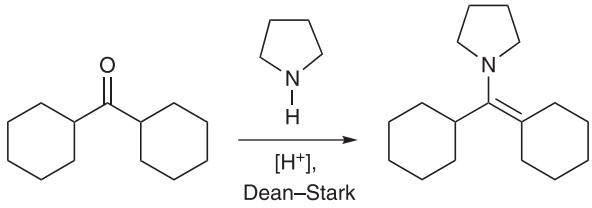
6.111 The starting material is a acetal, and the desired product is an ester. We have not yet seen many ways to make esters, but we have seen that an ester can be made from a ketone via a Baeyer–Villiger oxidation process. So the last step of our synthesis might be a Baeyer–Villiger oxidation process, in which the product is made from the following ketone:



This ketone can be made directly from the starting acetal upon treatment with aqueous acid. In summary, we have developed a two-step synthesis for the desired product. In the first step, the acetal is treated with water and an acid catalyst to give a ketone, and the ketone is then treated with a peroxy acid (such as MCPBA) to give the desired ester:

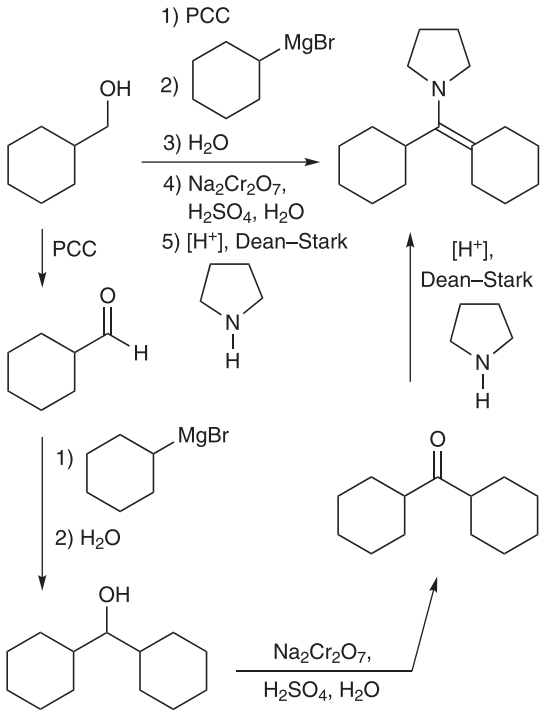


6.112 The desired product is an enamine, and we have only seen one way to make an enamine (from the reaction between a ketone and a secondary amine), so the last step of our synthesis must be the following:



Now let's work our way forward, beginning with the starting material, which is a primary alcohol. We need to introduce a cyclohexyl group into the compound, which means that we need to make a C–C bond. This can be accomplished by the reaction between a Grignard reagent and a carbonyl group, so we first oxidize the alcohol with PCC to give an aldehyde, and then treat that aldehyde with cyclohexyl magnesium bromide, followed by water. The resulting alcohol can then be oxidized to give the ketone above, which can be converted into the desired product as shown above.

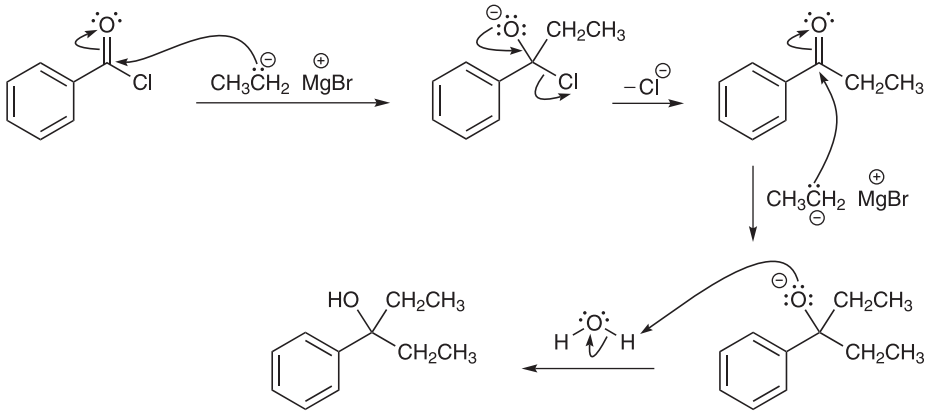
The entire synthesis is summarized here:



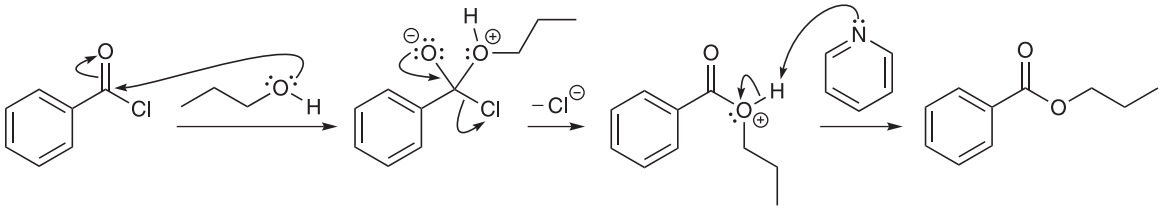
CHAPTER 7

7.2 An acid halide is being treated with an excess of Grignard reagent. First, a Grignard reagent attacks the carbonyl group of the acid halide, giving a tetrahedral intermediate, which then re-forms the carbonyl group by expelling chloride as a leaving group. The resulting ketone is then attacked by another equivalent of the Grignard reagent to give an alkoxide ion. This alkoxide ion cannot re-form the carbonyl

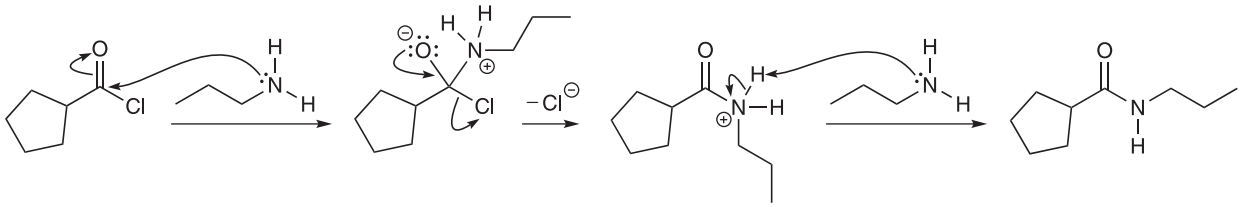
group because it has no leaving groups, so this is the end of the reaction. After the reaction is complete, water is added to the reaction flask, thereby protonating the alkoxide ion to give an alcohol:



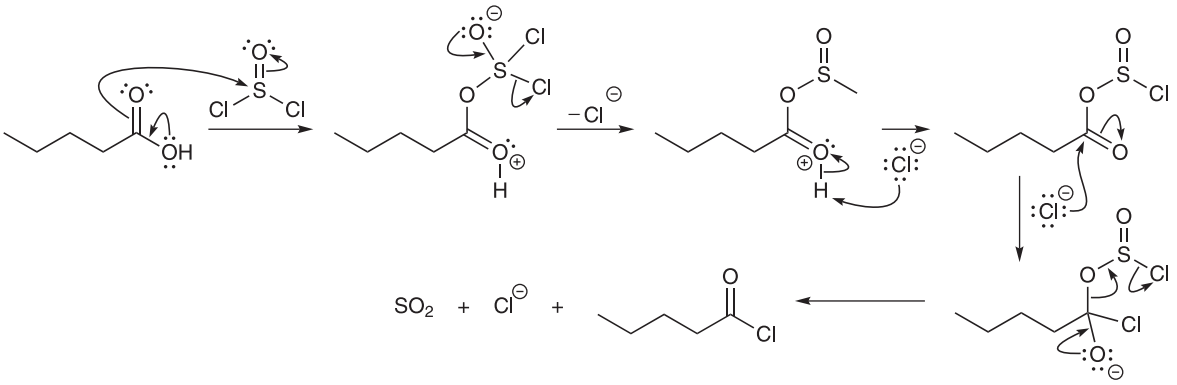
7.3 An acid halide is being treated with an alcohol in the presence of pyridine. First, the alcohol attacks the carbonyl group of the acid halide, giving a tetrahedral intermediate. This intermediate then re-forms the carbonyl group by expelling chloride as a leaving group. And finally, the resulting cation is then deprotonated by pyridine to give an ester:



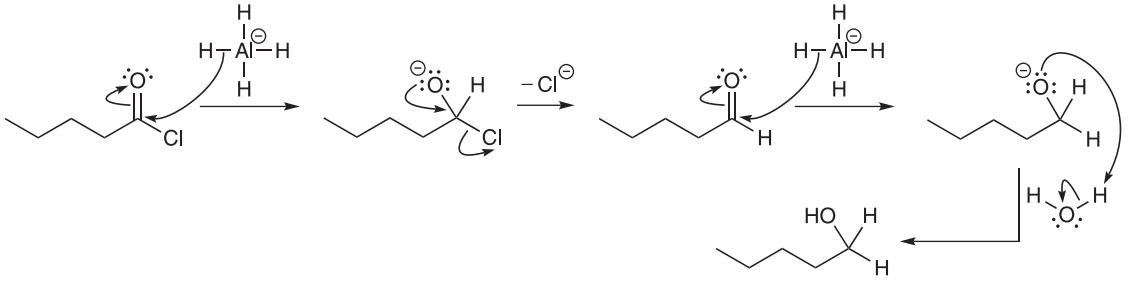
7.4 An acid halide is being treated with excess amine. First, the amine attacks the carbonyl group of the acid halide, giving a tetrahedral intermediate. This intermediate then re-forms the carbonyl group by expelling chloride as a leaving group. And finally, the resulting cation is then deprotonated by a second equivalent of the amine to give an amide:



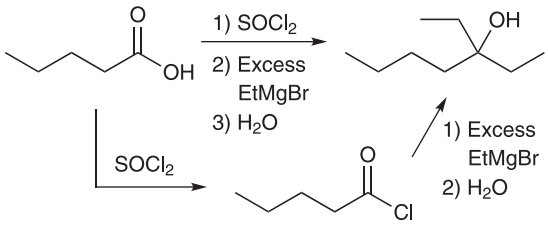
7.5 An acid halide is converted into a carboxylic acid upon treatment with thionyl chloride. First, the carboxylic acid functions as a nucleophile and attacks the S═O bond. The S═O bond is then re-formed (by expelling a chloride ion), followed by a proton transfer step. The net result of these first three steps is the conversion of an OH group into a better leaving group. A chloride ion (formed in the second step) then attacks the carbonyl group, giving a tetrahedral intermediate, which can then re-form the carbonyl group by expelling SO_2 gas and a chloride ion. The product is an acid halide:



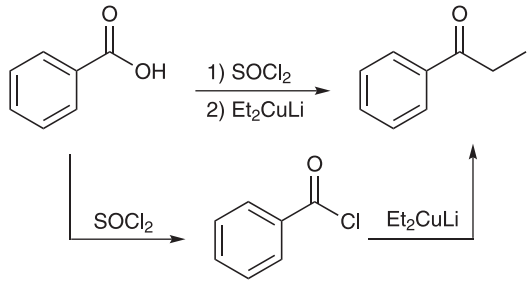
7.6 An acid halide is being treated with an excess of $LiAlH_4$, which is a hydride reducing agent. First, $LiAlH_4$ functions as a delivery agent of hydride (H^-) and attacks the carbonyl group of the acid halide, giving a tetrahedral intermediate, which then re-forms the carbonyl group by expelling chloride as a leaving group. The resulting aldehyde is then attacked by another equivalent of $LiAlH_4$ to give an alkoxide ion. This alkoxide ion cannot re-form the carbonyl group because it has no leaving groups, so this is the end of the reaction. After the reaction is complete, water is added to the reaction flask, thereby protonating the alkoxide ion to give an alcohol:



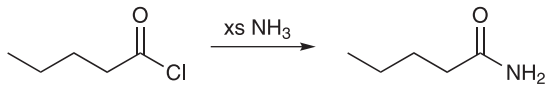
7.8 Upon treatment with thionyl chloride ($SOCl_2$), a carboxylic acid is converted into an acid halide. When this acid halide is treated with an excess of ethyl magnesium bromide (a Grignard reagent), followed by water, the acid halide reacts with two equivalents of the Grignard reagent to give an alcohol. Notice that two ethyl groups are installed.



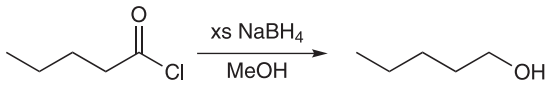
7.9 Upon treatment with thionyl chloride ($SOCl_2$), a carboxylic acid is converted into an acid halide. When this acid halide is treated with lithium diethyl cuprate (a tame carbon nucleophile), the acid halide reacts with only one equivalent of the nucleophile to give a ketone.



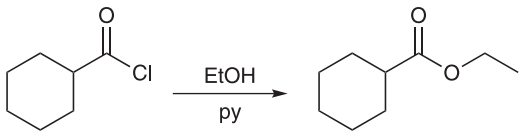
7.10 Upon treatment with excess ammonia (NH_3), a carboxylic acid is converted into an amide.



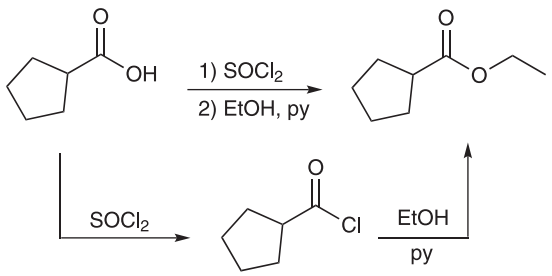
7.11 When an acid halide is treated with an excess of a hydride reducing agent, such as $NaBH_4$ or $LiAlH_4$, the acid halide will react with two equivalents of the reducing agent to give an alcohol.



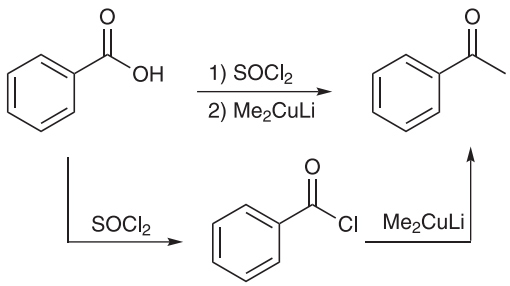
7.12 An acid halide is converted into an ester upon treatment with an alcohol in the presence of pyridine.



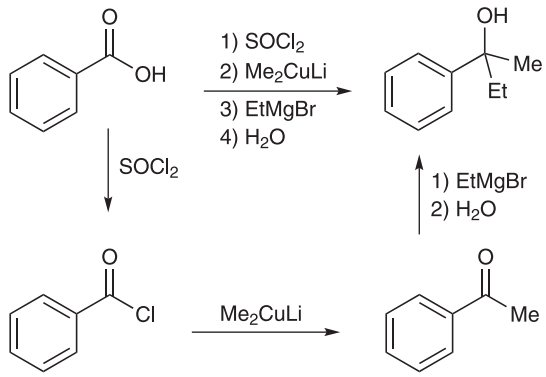
7.14 The desired ester can be made from an acid halide, which can be made from the starting carboxylic acid. This gives the following two-step synthesis:



7.15 The desired ketone can be made by treating an acid halide with lithium dimethyl cuprate. The acid halide can be made from the starting carboxylic acid. This gives the following two-step synthesis:

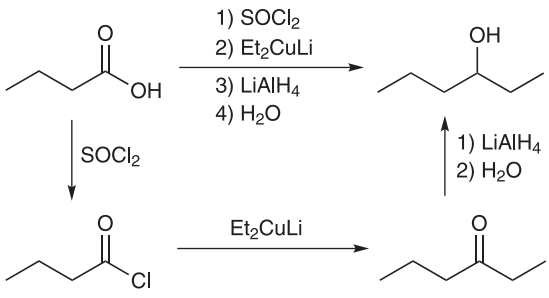


7.16 The starting material is a carboxylic acid, and the product is an alcohol. In making the alcohol, we must install one ethyl and one methyl group. This cannot be achieved by treating an acid halide with an excess of a Grignard reagent, because we need to install two different alkyl groups. Rather, the desired transformation can be achieved by converting the carboxylic acid into an acid halide, and then treating the acid halide with a lithium dialkyl cuprate. This results in the installation of only one alkyl group to give a ketone. And this ketone can then be treated with a Grignard reagent.

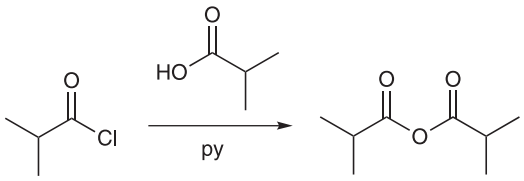


In the synthesis shown, we used Me_2CuLi followed by EtMgBr. Alternatively, we could have used Et_2CuLi, followed by MeMgBr, which would have accomplished the same goal.

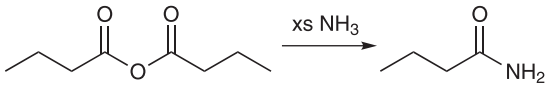
7.17 The starting material is a carboxylic acid, and the product is an alcohol. In making the alcohol, we must install one ethyl. This can be achieved by converting the carboxylic acid into an acid halide, and then treating the acid halide with lithium diethyl cuprate. This results in the installation of only one alkyl group to give a ketone. And this ketone can then be treated with a reducing agent to give the desired alcohol.



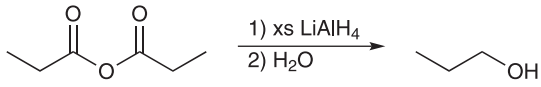
7.18 An acid halide can be converted directly into an acid anhydride upon treatment with a carboxylic acid in the presence of pyridine. The carboxylic acid functions as a nucleophile that attacks the carbonyl group of the acid halide, and pyridine functions as a base to remove the acidic protons generated during this process.



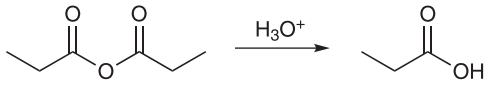
7.20 An anhydride is converted into an amide upon treatment with excess ammonia:



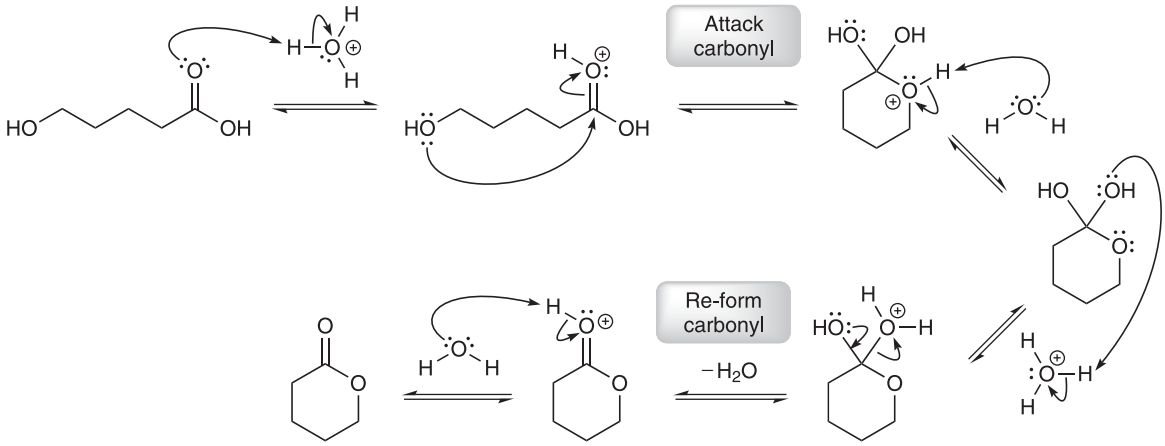
7.21 An anhydride is converted into an alcohol when treated with excess reducing agent:



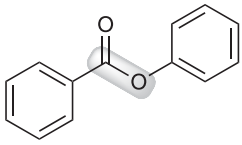
7.22 An anhydride is converted into a carboxylic acid when treated with aqueous acid:



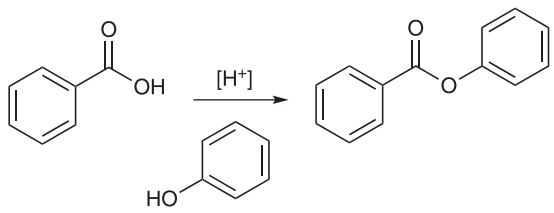
7.23 This is an intramolecular Fischer esterification process, and the mechanism should have six steps, like any Fischer esterification. There are two core steps (attack the carbonyl group, and re-form the carbonyl group), both highlighted below, and the remaining four steps are proton transfer steps that occur in order to facilitate the two core steps. In the first step of the mechanism, the carbonyl group is protonated, rendering it more electrophilic and subject to attack by a weak nucleophile. In this case, the nucleophile is an alcohol that is tethered to the carbonyl group (in the same molecule), allowing for an intramolecular attack. The resulting cyclic oxonium ion is then deprotonated by water and protonated by a hydronium ion, to give an intermediate that can re-form the carbonyl group via expulsion of a leaving group (H_2O). The resulting intermediate is then deprotonated by water to give the product:



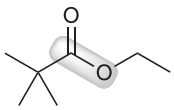
7.25 The desired ester can be made via a Fischer esterification process, which enables us to make the following bond:



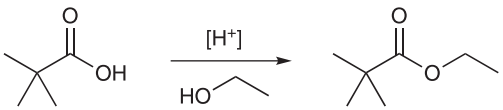
The required starting materials (a carboxylic acid and an alcohol) are shown:



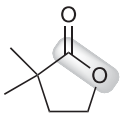
7.26 The desired ester can be made via a Fischer esterification process, which enables us to make the following bond:



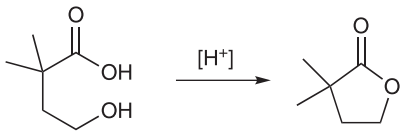
The required starting materials (a carboxylic acid and an alcohol) are shown below:



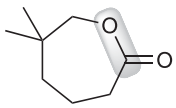
7.27 The desired ester can be made via an intramolecular Fischer esterification process, which enables us to make the following bond:



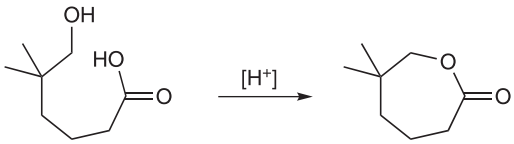
The required starting material (which is both a carboxylic acid and an alcohol) is shown:



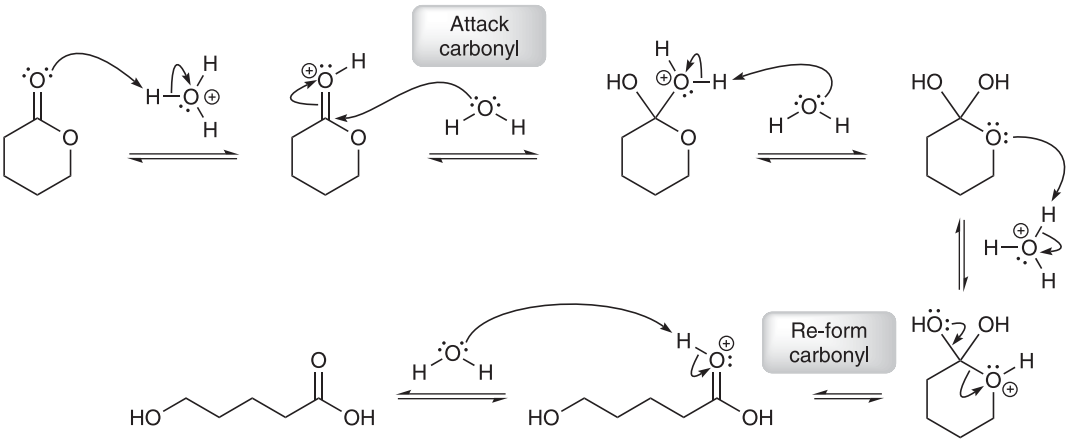
7.28 The desired ester can be made via an intramolecular Fischer esterification process, which enables us to make the following bond:



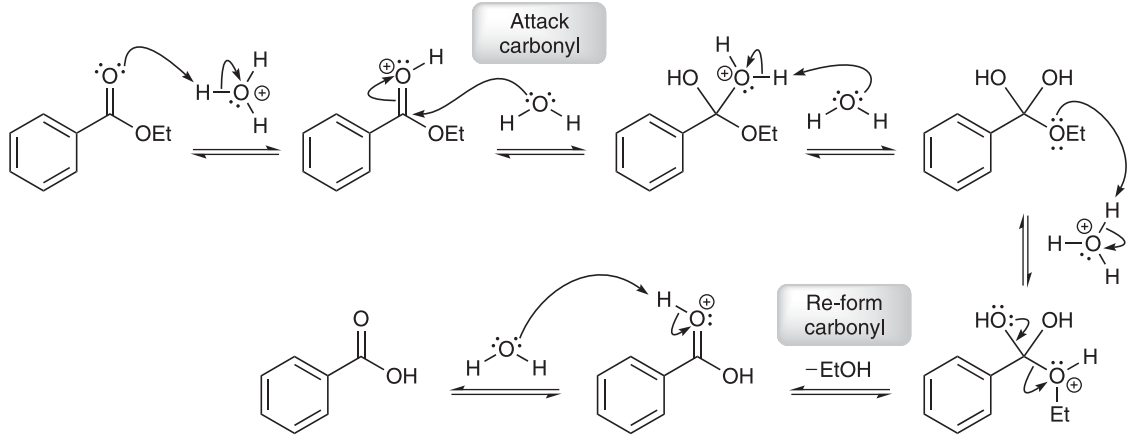
The required starting material (which is both a carboxylic acid and an alcohol) is shown below:



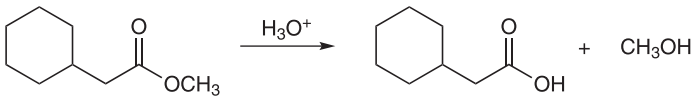
7.30 Under aqueous acidic conditions, an ester can be hydrolyzed to give a carboxylic acid and an alcohol. This process is the reverse of a Fischer esterification process, and the mechanism should have six steps. There are two core steps (attack the carbonyl group, and re-form the carbonyl group), both highlighted below, and the remaining four steps are proton transfer steps that occur in order to facilitate the two core steps. In the first step of the mechanism, the carbonyl group is protonated, rendering it more electrophilic and subject to attack by a weak nucleophile (H_2O). Water attacks the carbonyl group to give a tetrahedral intermediate. This intermediate is then deprotonated by water and then protonated by a hydronium ion, to give an intermediate that can re-form the carbonyl group via expulsion of a leaving group (ROH). Notice that after the leaving group leaves, the alcohol and the carboxylic acid are tethered to each other in one molecule (because the starting ester was cyclic). The resulting intermediate is then deprotonated by water to give the product:



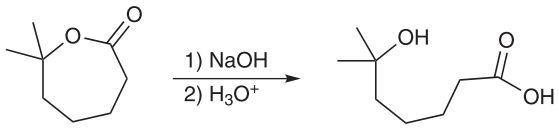
7.31 Under aqueous acidic conditions, an ester can be hydrolyzed to give a carboxylic acid and an alcohol. This process is the reverse of a Fischer esterification process, and the mechanism should have six steps. There are two core steps (attack the carbonyl group, and re-form the carbonyl group), both highlighted below, and the remaining four steps are proton transfer steps that occur in order to facilitate the two core steps. In the first step of the mechanism, the carbonyl group is protonated, rendering it more electrophilic and subject to attack by a weak nucleophile (H_2O). Water attacks the carbonyl group to give a tetrahedral intermediate. This intermediate is then deprotonated by water and then protonated by a hydronium ion, to give an intermediate that can re-form the carbonyl group via expulsion of a leaving group (EtOH). The resulting intermediate is then deprotonated by water to give a carboxylic acid:



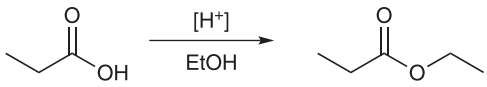
7.33 Upon treatment with aqueous acid (H_3O^+), an ester is hydrolyzed to give a carboxylic acid and an alcohol. This is the reverse of a Fischer esterification:



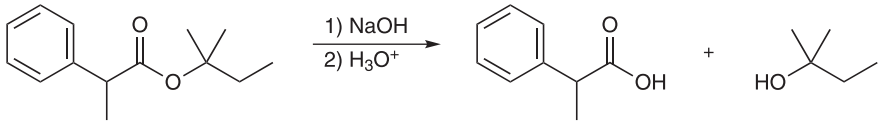
7.34 Upon treatment with hydroxide, followed by a proton source, an ester is hydrolyzed to give a carboxylic acid and an alcohol. This process is called saponification:



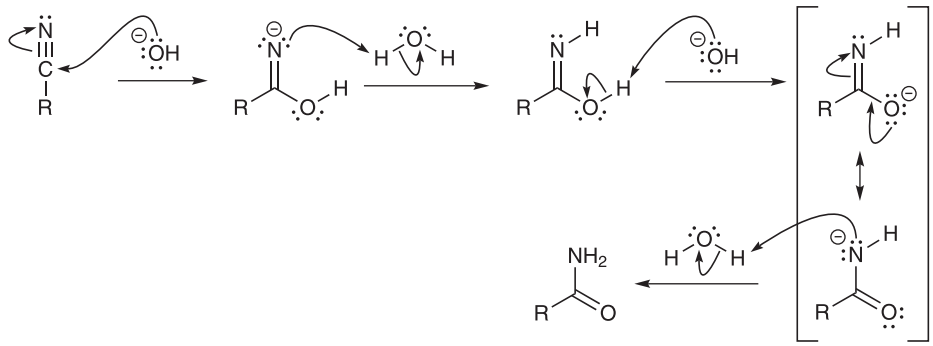
7.35 Upon treatment with an alcohol in the presence of catalytic acid, a carboxylic acid is converted to an ester. This process is called Fischer esterification:



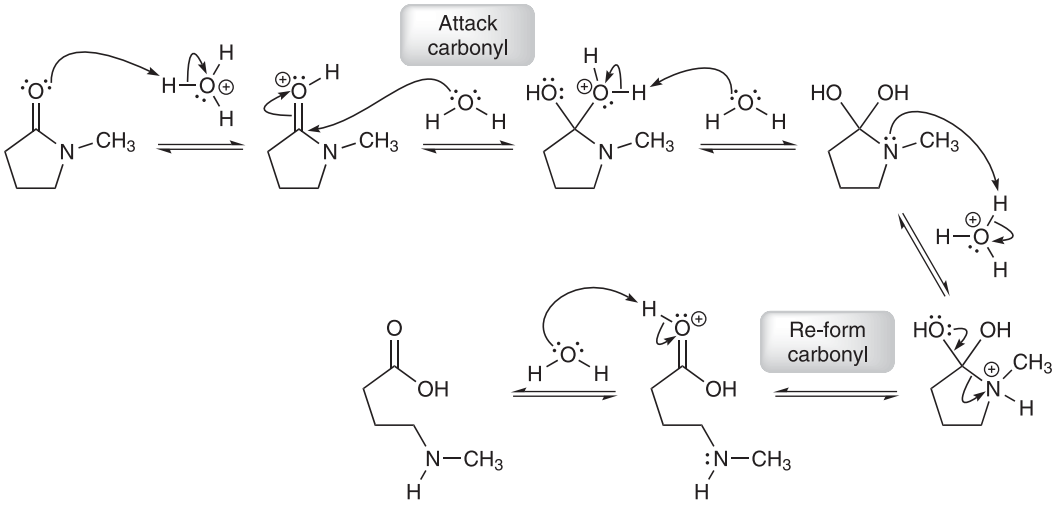
7.36 Upon treatment with hydroxide, followed by a proton source, an ester is hydrolyzed to give a carboxylic acid and an alcohol. This process is called saponification:



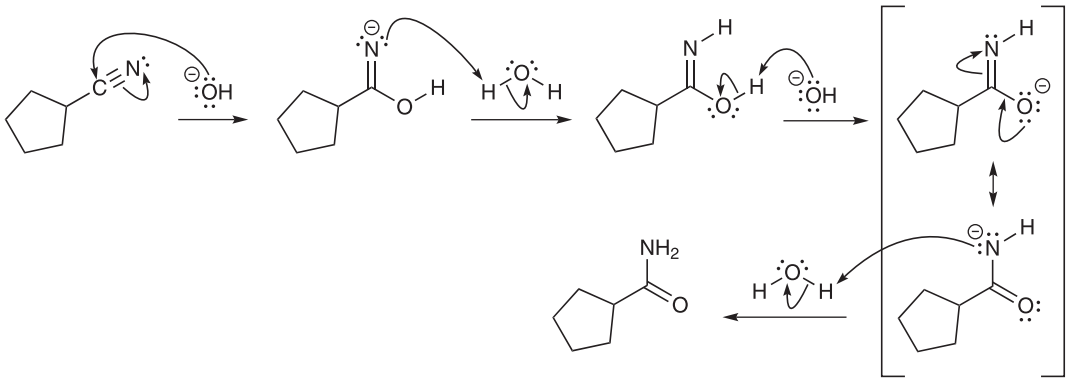
7.37 In the first step of the mechanism, hydroxide functions as a nucleophile and attacks the cyano group. The resulting anion is then protonated by water, followed by a deprotonation step to give a resonance-stabilized anion. This anion can receive a proton (from water, because there are no stronger acids present) to give the product:



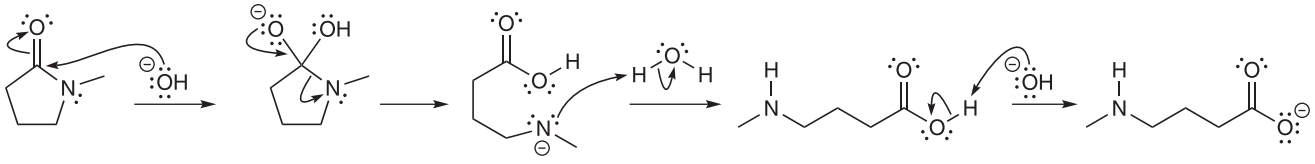
7.39 An amide is hydrolyzed under aqueous acidic conditions. This process is similar to the acid-catalyzed hydrolysis of an ester, and the mechanism should have six steps. There are two core steps (attack the carbonyl group, and re-form the carbonyl group), both highlighted below, and the remaining four steps are proton transfer steps that occur in order to facilitate the two core steps. In the first step of the mechanism, the carbonyl group is protonated, rendering it more electrophilic and subject to attack by a weak nucleophile (H_2O). Water attacks the carbonyl group to give a tetrahedral intermediate. This intermediate is then deprotonated by water and then protonated by a hydronium ion, to give an intermediate that can re-form the carbonyl group via expulsion of a leaving group (R_2NH). Notice that after the leaving group leaves, the amine and the carboxylic acid are tethered to each other in one molecule (because the starting amide was cyclic). The resulting intermediate is then deprotonated by water to give the product:



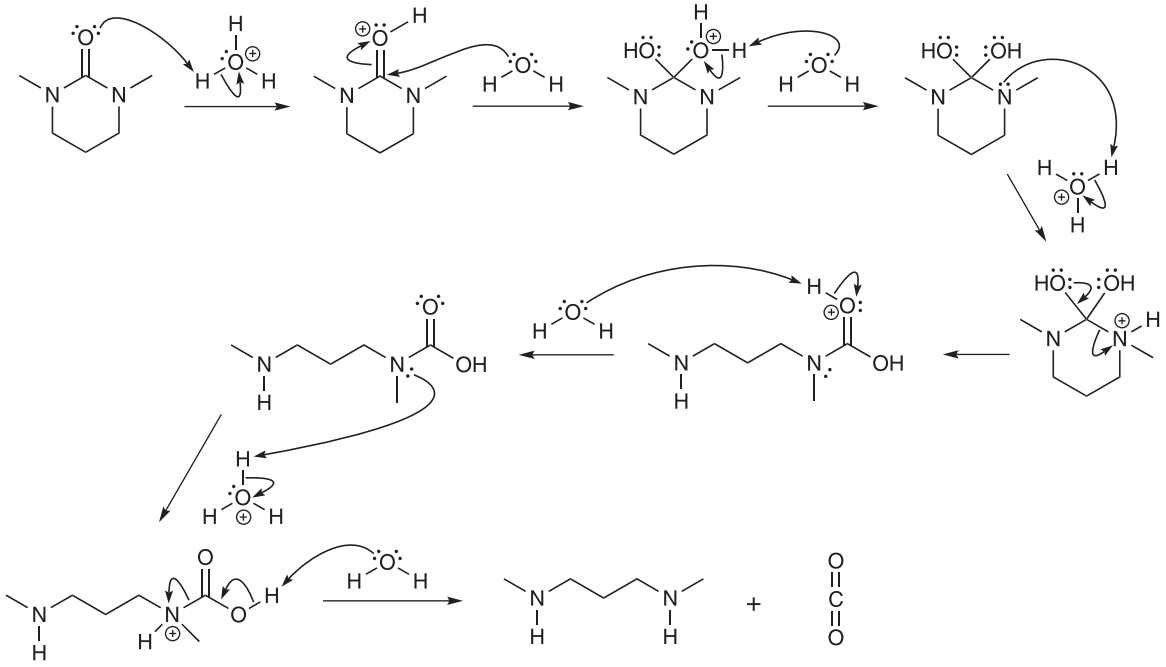
7.40 In the first step of the mechanism, hydroxide functions as a nucleophile and attacks the cyano group. The resulting anion is then protonated by water, followed by a deprotonation step to give a resonance-stabilized anion. This anion can receive a proton (from water, because there are no stronger acids present) to give the product:



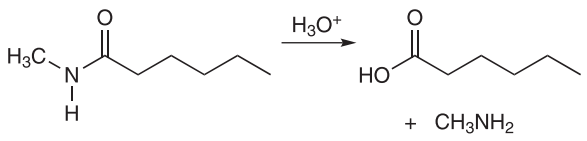
7.41 Hydroxide will attack the carbonyl group of an amide to give a tetrahedral intermediate, which can then re-form the carbonyl group. Under these basic conditions, the resulting anion then undergoes two proton transfer steps, giving a carboxylate ion:



7.42 Under acidic conditions, the carbonyl group is first protonated, which renders it more electrophilic. Water then attacks the carbonyl group, giving a tetrahedral intermediate. In order to re-form the carbonyl group and break a C–N bond, we must first protonate a nitrogen atom (so that it is a better leaving group), and we can only do this after first removing a proton (we must avoid drawing an intermediate with two positive charges). So, the intermediate undergoes two successive proton transfer steps. Then, the carbonyl group is re-formed by breaking a C–N bond, and the resulting cation is then deprotonated. In order to break the other C–N bond, the nitrogen atom must first be protonated, rendering it a better leaving group. Finally, deprotonation (and loss of carbon dioxide) gives the products. Note that this final step can be alternatively drawn as two separate steps: 1) deprotonation to make the carboxylate ion, followed by 2) expulsion of the amine and carbon dioxide.

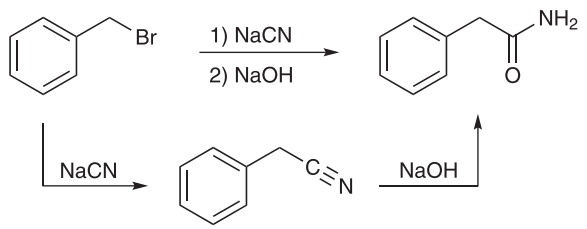


7.44 The starting material is an amide, and the reagent is aqueous acid. We expect the amide to undergo acid-catalyzed hydrolysis to give a carboxylic acid and an amine:

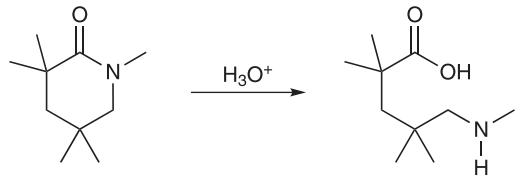


Actually, under these acidic conditions, the amine is protonated to give an ammonium ion, $CH_3NH_3^+$, (the reason will be explored in Chapter 9).

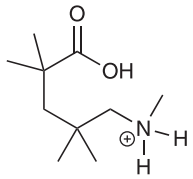
7.45 The starting material is a primary (benzylic) halide, and the cyanide is a good nucleophile that can replace bromide in an S_N2 reaction. The resulting nitrile will then react with hydroxide to give an amide, as shown:



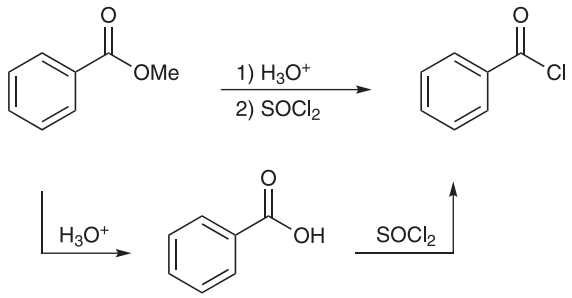
7.46 The starting material is a cyclic amide, and the reagent is aqueous acid. We expect the amide to undergo acid-catalyzed hydrolysis to give a carboxylic acid and an amine:



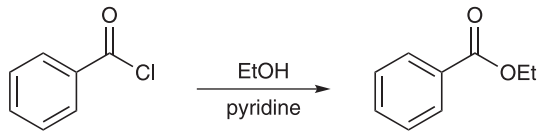
Actually, under these acidic conditions, the amine is protonated to give an ammonium ion (the reason will be explored in Chapter 9):



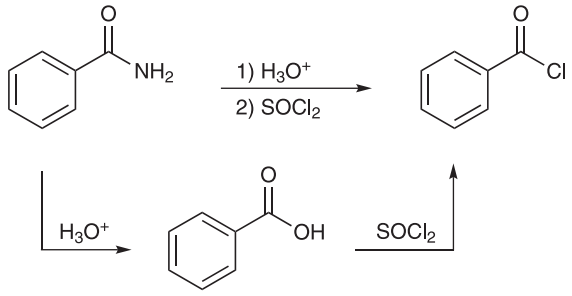
7.48 We must convert an ester into an acid halide, but we have not learned a way to do this directly in one step (esters are less reactive than acid halides). Instead, we can first convert the ester into a carboxylic acid, and then we can convert the carboxylic acid into the desired acid halide. To achieve this transformation, we can use the following reagents:



7.49 An acid chloride is more reactive than an ester, so an acid halide can be converted directly into an ester. This transformation can be achieved with an alcohol and pyridine. In this case, the desired product is an ethyl ester, so we use ethanol as the alcohol:

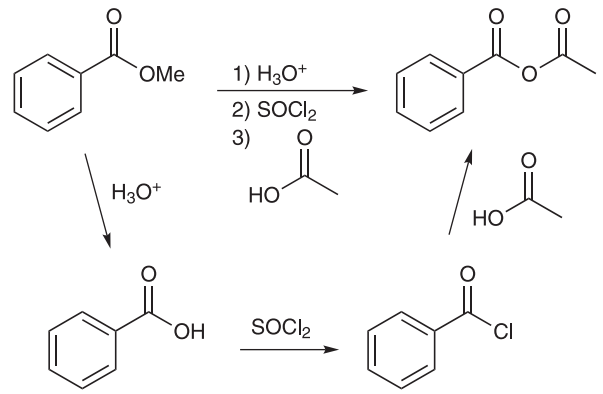


7.50 We must convert an amide into an acid halide, but we have not learned a way to do this directly in one step (amides are less reactive than acid halides). Instead, we can first convert the amide into a carboxylic acid, and then we can convert the carboxylic acid into the desired acid halide. To achieve this transformation, we can use the following reagents:

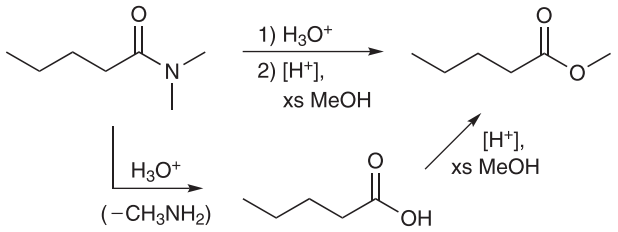


7.51 We must convert an ester into an acid anhydride, but we have not learned a way to do this directly in one step (esters are

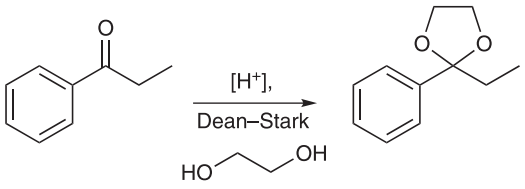
less reactive than acid anhydrides). Instead, we can first convert the ester into a carboxylic acid, and then convert the carboxylic acid into an acid halide. Finally, the acid halide can be converted into the desired acid anhydride. To achieve this transformation, we can use the following reagents:



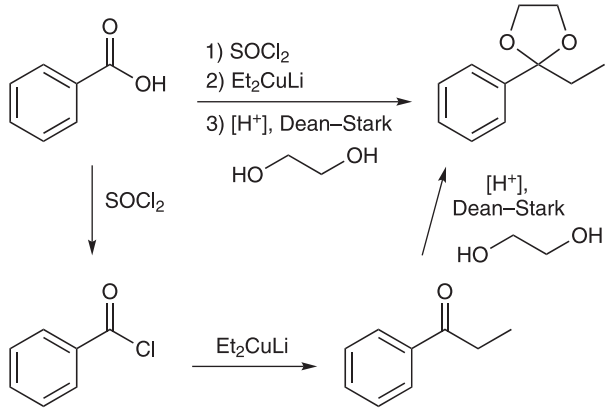
7.52 We must convert an amide into an ester, but we have not learned a way to do this directly in one step (amides are less reactive than esters). Instead, we can first convert the amide into a carboxylic acid, and then we can convert the carboxylic acid into the desired methyl ester. To achieve this transformation, we can use the following reagents:



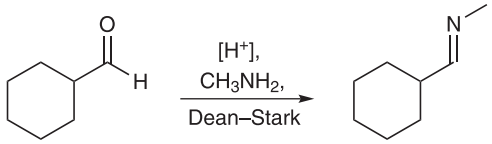
7.54 The product is an acetal, which can be made from the corresponding ketone, as shown here:



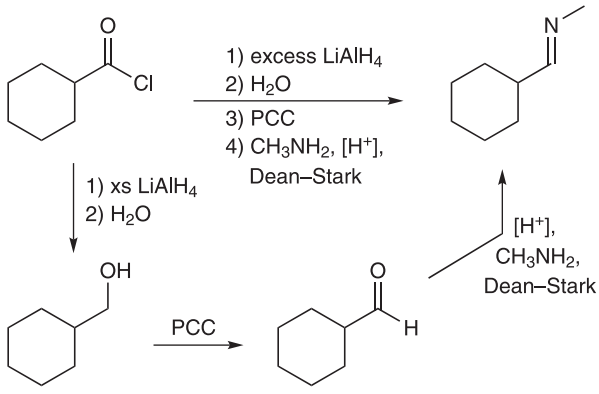
This can be the last step of our synthesis, if we can convert the starting material (a carboxylic acid) into the ketone above. Indeed, this ketone can be made in two steps from the starting carboxylic acid. The carboxylic acid is first converted into an acid halide upon treatment with thionyl chloride ($SOCl_2$), and this acid halide is then converted into the ketone upon treatment with lithium diethyl cuprate. Finally, the ketone is converted into the desired acetal upon treatment with ethylene glycol in the presence of an acid catalyst (with removal of water):



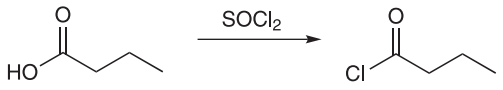
7.55 The product is an imine, which can be made from the corresponding aldehyde, as shown here:



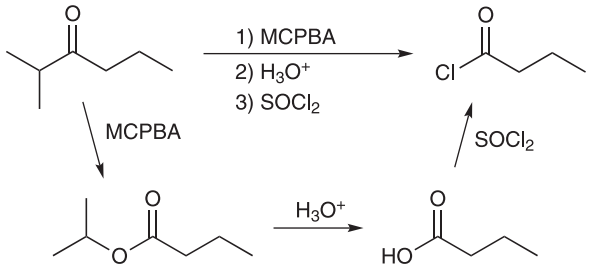
This can be the last step of our synthesis, if we can convert the starting material (an acid halide) into the aldehyde above. Indeed, this aldehyde can be made in two steps from the starting acid halide. The acid halide is first reduced to an alcohol upon treatment with excess reducing agent (such as $LiAlH_4$ or $NaBH_4$), and this alcohol is then oxidized to give the aldehyde upon treatment with PCC. Finally, the aldehyde is converted into the desired imine upon treatment with methyl amine in the presence of an acid catalyst (with removal of water):



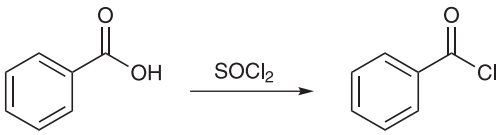
7.56 The product is an acid halide, which can be made from the corresponding carboxylic acid, as shown here:



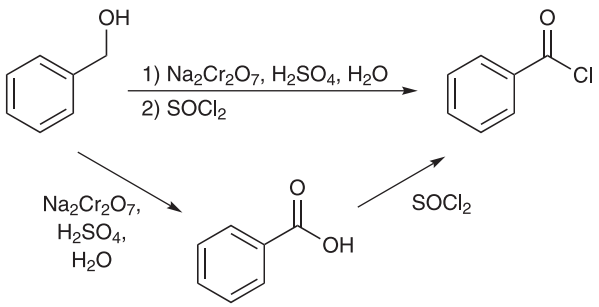
This can be the last step of our synthesis, if we can convert the starting material (a ketone) into the carboxylic acid above. Indeed, this carboxylic acid can be made in two steps from the starting ketone, as shown below. The ketone is converted into an ester upon treatment with a peroxy acid, such as MCPBA, and this ester is then hydrolyzed with aqueous acid to give the carboxylic acid. Finally, the carboxylic acid is converted into the desired acid halide upon treatment with thionyl chloride ($SOCl_2$):



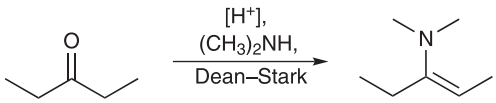
7.57 The product is an acid halide, which can be made from the corresponding carboxylic acid, as shown here:



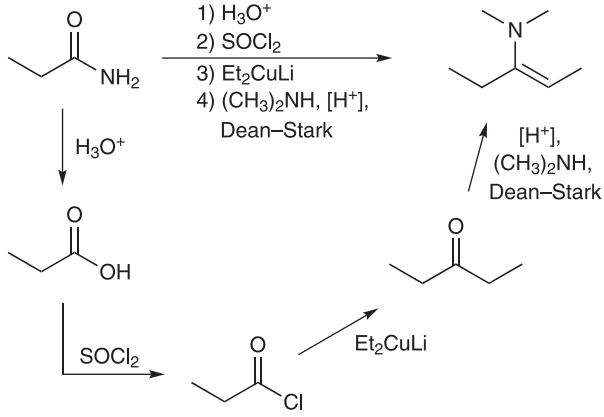
This can be the last step of our synthesis, if we can convert the starting material (an alcohol) into the carboxylic acid above. Indeed, this carboxylic acid can be made directly from the starting alcohol upon treatment with a strong oxidizing agent, giving the following synthesis:



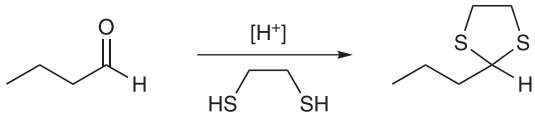
7.58 The product is an enamine, which can be made from the corresponding ketone, as shown here:



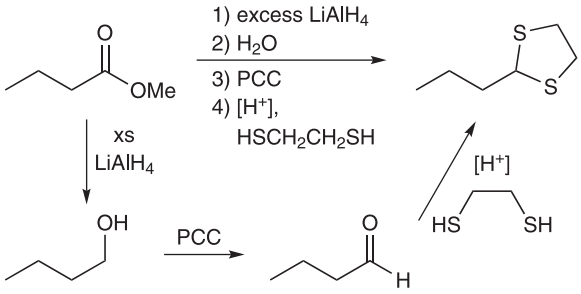
This can be the last step of our synthesis, if we can convert the starting material (an amide) into the ketone above. Indeed, this ketone can be made in a few steps from the starting amide. The amide is first hydrolyzed to a carboxylic acid upon treatment with aqueous acid. This acid is then converted into an acid halide, which is then converted into ketone above upon treatment with lithium diethyl cuprate. Finally, the ketone is converted into the desired enamine upon treatment with dimethyl amine in the presence of an acid catalyst (with removal of water):



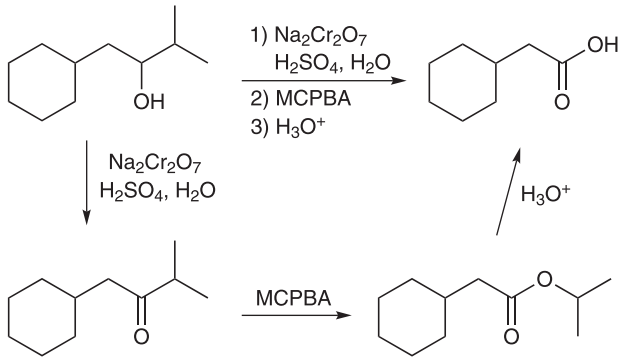
7.59 The product is a cyclic thioacetal, which can be made from the corresponding aldehyde, as shown here:



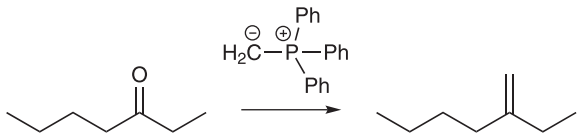
This can be the last step of our synthesis, if we can convert the starting material (an ester) into the aldehyde above. Indeed, this aldehyde can be made in two steps from the starting ester. The ester is first reduced to an alcohol upon treatment with excess $LiAlH_4$, and this alcohol is then oxidized to an aldehyde upon treatment with PCC. Finally, the aldehyde is converted into the desired thioacetal upon treatment with ethylene thioglycol ($HSCH_2CH_2SH$) in the presence of an acid catalyst:



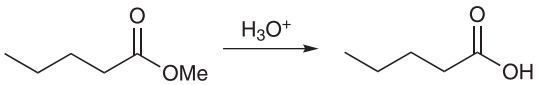
7.60 The starting material is an alcohol, and it can be oxidized upon treatment with an oxidizing agent. The resulting ketone can then be converted into the desired carboxylic acid in just two steps. The ketone is first oxidized via a Baeyer–Villiger oxidation to give an ester, and the ester is then hydrolyzed with aqueous acid to give the desired product:



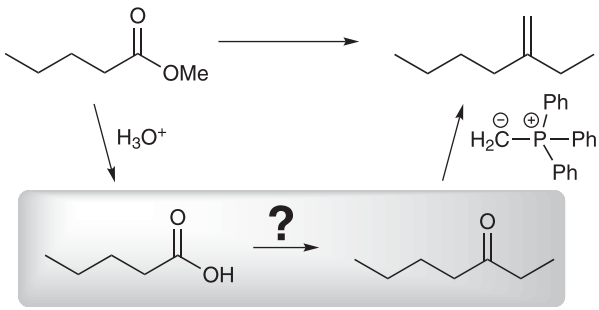
7.61 The product is an alkene, which can be made from a ketone via a Wittig reaction. This can be the last step of our synthesis:



The starting material is an ester, so the first step of our synthesis could be hydrolysis of the ester to give a carboxylic acid:

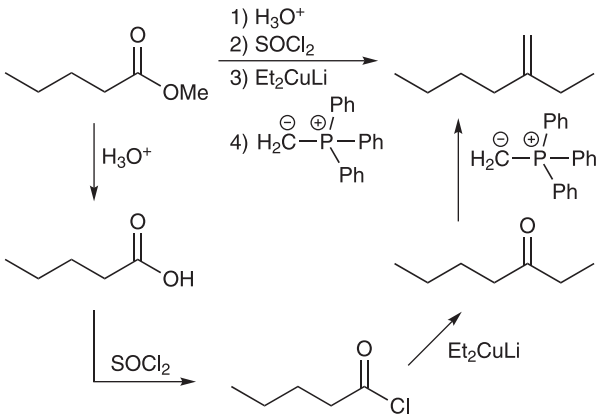


The synthesis can be completed if we can convert the carboxylic acid into the ketone:

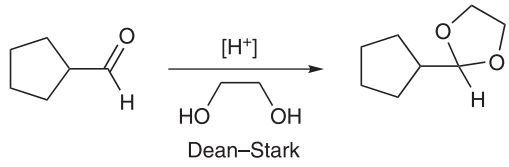


This can be accomplished in just two steps. The carboxylic acid is first converted into an acid halide, which is then converted into the ketone upon treatment with lithium diethyl cuprate.

The entire synthesis is shown here:

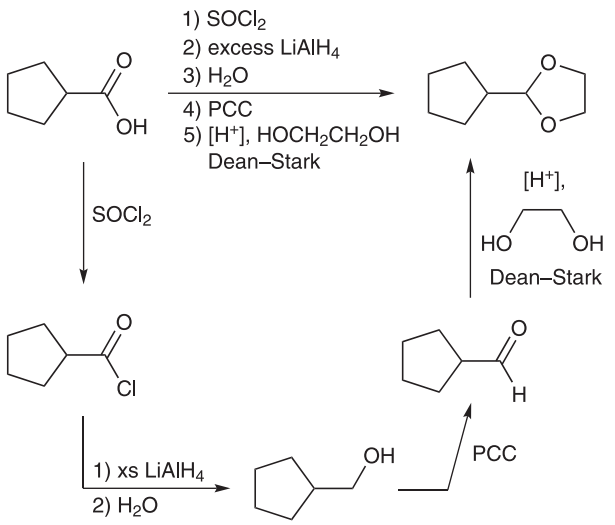


7.62 The product is a cyclic acetal, which can be made from the corresponding aldehyde, as shown here:

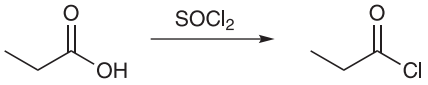


This can be the last step of our synthesis, if we can convert the starting material (a carboxylic acid) into the aldehyde above. Indeed, this aldehyde can be made in just a few steps from the starting carboxylic acid. The carboxylic acid is first converted into an acid halide, which is then reduced to an alcohol upon treatment with excess $LiAlH_4$. This alcohol is then oxidized to an aldehyde upon treatment with PCC. Finally, the aldehyde is

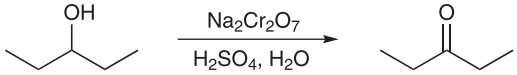
converted into the desired acetal upon treatment with ethylene glycol ($HOCH_2CH_2OH$) in the presence of an acid catalyst (with removal of water):



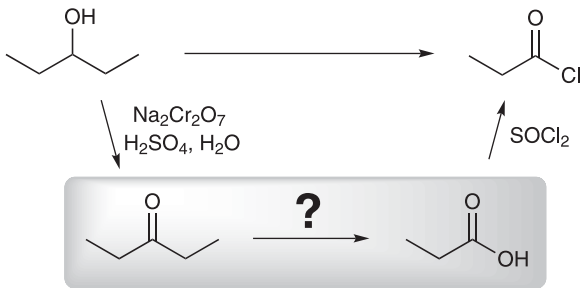
7.63 The product is an acid halide, which can be made from the corresponding carboxylic acid, so this can be the last step of our synthesis:



And the starting material is an alcohol, so the first step of our synthesis might be oxidation to give a ketone:

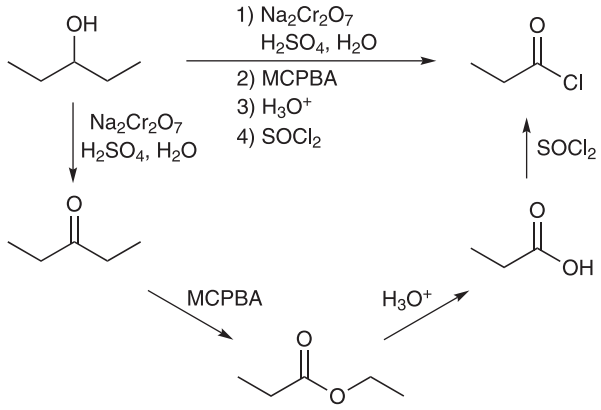


We can complete the synthesis if we can find a way to convert the ketone into a carboxylic acid:

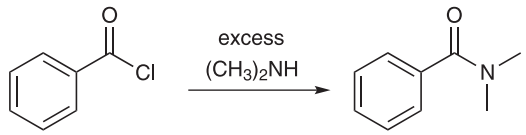


Conversion of the ketone into the carboxylic acid above can be accomplished in two steps. First the ketone is treated with a peroxy acid to give an ester (via a Baeyer–Villiger oxidation), and this ester is then hydrolyzed with aqueous acid to give the carboxylic acid.

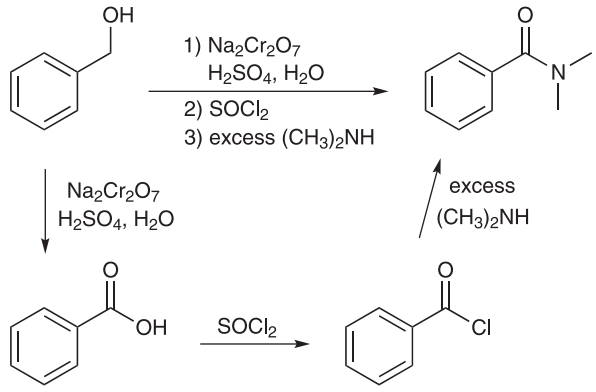
The entire synthesis is shown here:



7.64 The product is an amide, which can be made from the corresponding acid halide, as shown here:

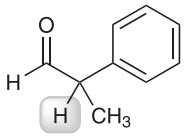


This can be the last step of our synthesis, if we can convert the starting material (an alcohol) into the acid halide above. Indeed, this acid halide can be made from the starting alcohol in just two steps. First the alcohol is oxidized to give a carboxylic acid, which is then converted into an acid halide upon treatment with thionyl chloride ($SOCl_2$). Finally, the acid halide is converted into the desired amide upon treatment with excess dimethyl amine:

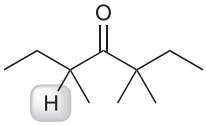


CHAPTER 8

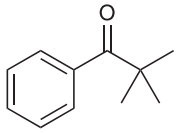
8.2 This compound has only one alpha carbon atom (to the right of the carbonyl group), and that carbon atom is connected to one alpha proton (highlighted below). Note that the proton to the left of the carbonyl group is not an alpha proton, because it is not connected to an alpha carbon (it is connected directly to the carbonyl group):



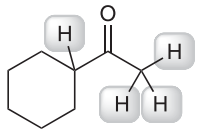
8.3 This compound has two alpha carbon atoms. The alpha carbon atom to the right of the carbonyl group is not connected directly to any protons. The alpha carbon atom to the left of the carbonyl group is connected to one alpha proton (highlighted below).



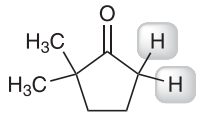
8.4 This compound has two alpha carbon atoms, but neither of them is connected to any protons, so this compound has no alpha protons.



8.5 This compound has two alpha carbon atoms. The alpha carbon atom to the right of the carbonyl group is connected to three alpha protons (highlighted), and the alpha carbon atom to the left of the carbonyl group is connected to one alpha proton (highlighted).

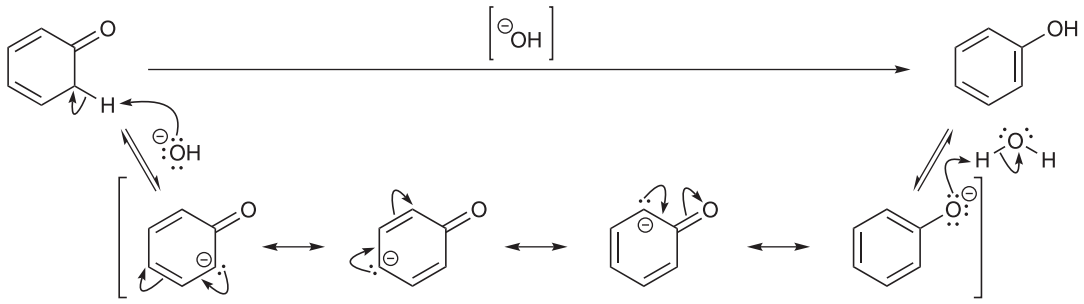


8.6 This compound has two alpha carbon atoms. The alpha carbon atom to the right of the carbonyl group is connected to two alpha protons (highlighted), while the alpha carbon atom to the left of the carbonyl group is not connected to any alpha protons.

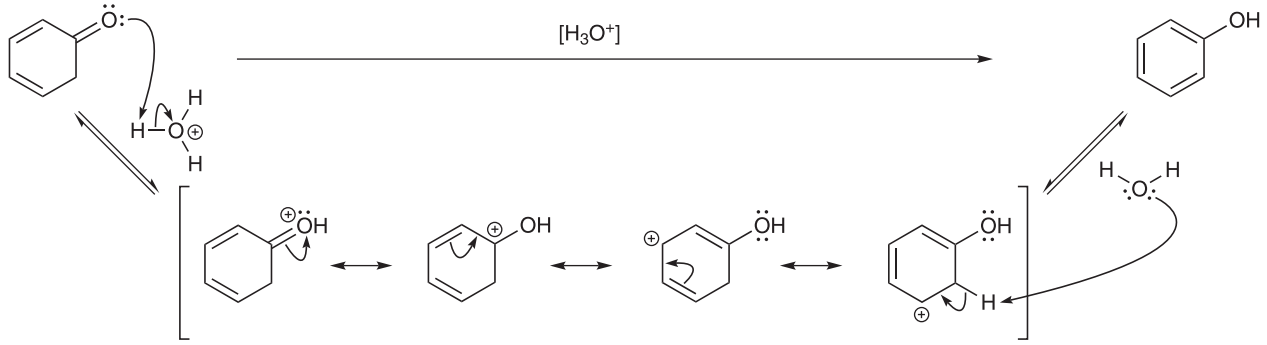


8.7 This compound does not have any alpha carbon atoms, because the carbonyl group is not connected to any carbon atoms. Therefore, this compound (called formaldehyde) does not have any alpha protons.

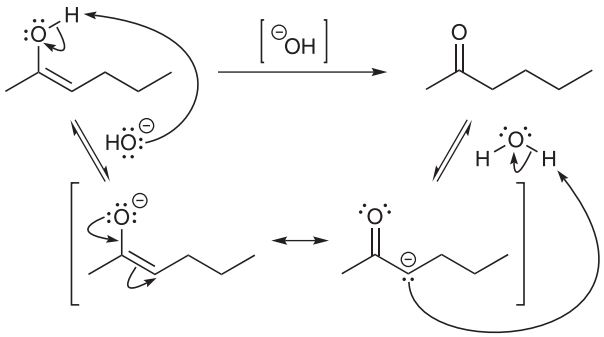
8.9 In this case, a ketone is converted into an enol, so this is a keto-enol tautomerization, which has two steps (both of which are proton transfer steps). Under basic conditions (hydroxide), we first show deprotonation to give a resonance-stabilized anion, and then we show protonation to give the product. Notice that hydroxide (rather than H_2O) functions as the base during the deprotonation step, and water (rather than H_3O^+) must be shown as the proton source during the protonation step, in order to stay consistent with basic conditions:



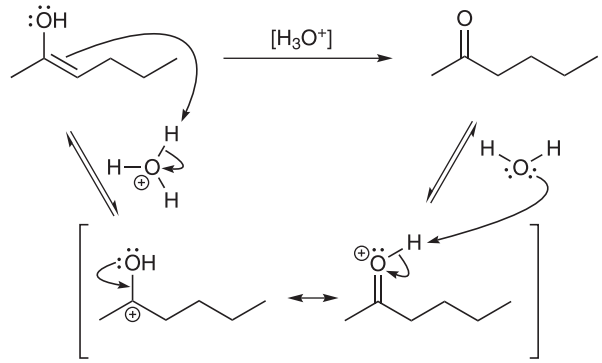
8.10 In this case, a ketone is converted into an enol, so this is a keto-enol tautomerization, which has two steps (both of which are proton transfer steps). Under acidic conditions (H_3O^+), we first show protonation to give a resonance-stabilized cation, and then we show deprotonation to give the product. Notice that H_3O^+ functions as the acid during the protonation step, and water (rather than hydroxide) must be shown as the base during the deprotonation step, in order to stay consistent with acidic conditions:



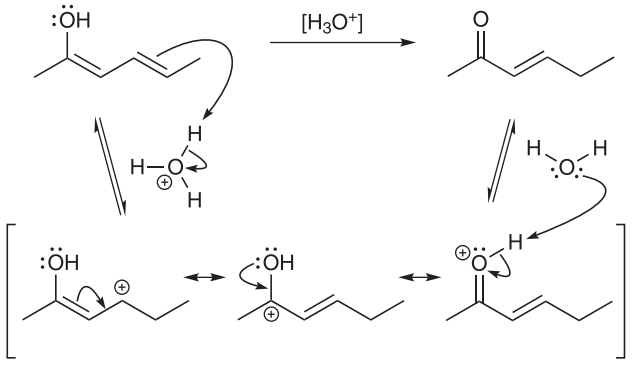
8.11 In this case, an enol is converted into a ketone, so this is a keto-enol tautomerization, which has two steps (both of which are proton transfer steps). Under basic conditions (hydroxide), we first show deprotonation to give a resonance-stabilized enolate anion, and then we show protonation to give the product. Notice that hydroxide (rather than H_2O) functions as the base during the deprotonation step, and water (rather than H_3O^+) must be shown as the proton source during the protonation step, in order to stay consistent with basic conditions:



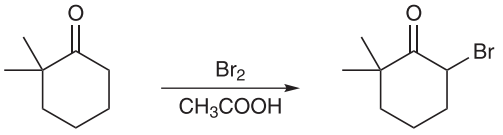
8.12 In this case, an enol is converted into a ketone, so this is a keto-enol tautomerization, which has two steps (both of which are proton transfer steps). Under acidic conditions (H_3O^+), we first show protonation to give a resonance-stabilized cation, and then we show deprotonation to give the product. Notice that H_3O^+ functions as the acid during the protonation step, and water (rather than hydroxide) must be shown as the base during the deprotonation step, in order to stay consistent with acidic conditions:



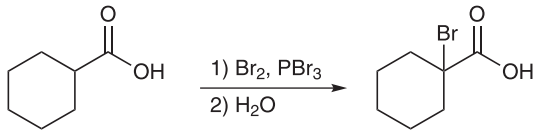
8.13 In this case, an enol is converted into a ketone, so this is a keto-enol tautomerization, which has two steps (both of which are proton transfer steps). Under acidic conditions (H_3O^+), we first show protonation to give a resonance-stabilized cation (notice that this intermediate has three resonance structures), and then we show deprotonation to give the product. Notice that H_3O^+ functions as the acid during the protonation step, and water (rather than hydroxide) must be shown as the base during the deprotonation step, in order to stay consistent with acidic conditions:



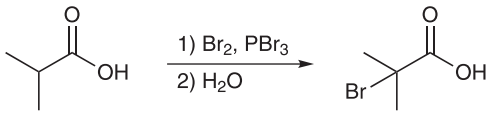
8.15 The starting material is a ketone, and the reagents are Br_2 and a mild acid. Under these conditions, a ketone will undergo alpha halogenation. This ketone has two alpha positions, but only one of these positions has protons, so the reaction occurs at this location. One of the alpha protons is replaced with Br:



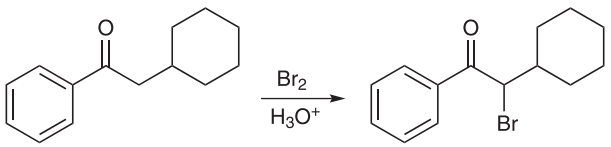
8.16 The starting material is a carboxylic acid, and the reagents indicate a Hell–Volhard–Zelinsky reaction. The result of this reaction is to install Br at the alpha position:



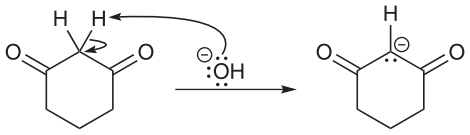
8.17 The starting material is a carboxylic acid, and the reagents indicate a Hell–Volhard–Zelinsky reaction. The result of this reaction is to install Br at the alpha position:



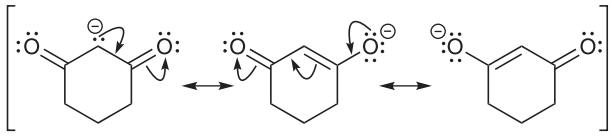
8.18 The starting material is a ketone, and the reagents are Br_2 and H_3O^+. Under these conditions, a ketone will undergo alpha halogenation. This ketone has two alpha positions, but only one of these positions has protons, so the reaction occurs at this location. One of the alpha protons is replaced with Br:



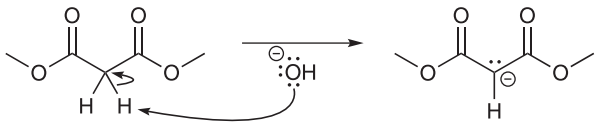
8.20 Hydroxide is a strong base, and it will remove a proton from the position in between the two carbonyl groups (this is where the most acidic proton is), to give an enolate:



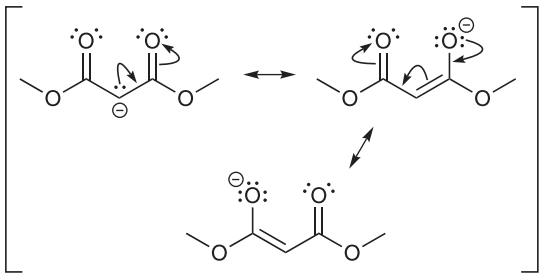
This enolate is highly stabilized by resonance. The negative charge is delocalized over two oxygen atoms:



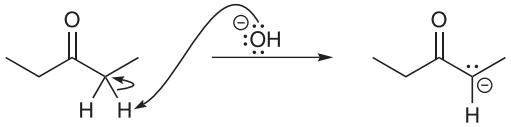
8.21 Hydroxide is a strong base, and it will remove a proton from the position in between the two carbonyl groups (this is where the most acidic proton is), to give an enolate:



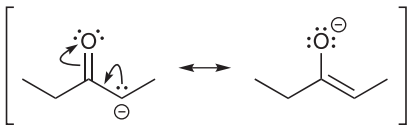
This enolate is highly stabilized by resonance. The negative charge is delocalized over two oxygen atoms:



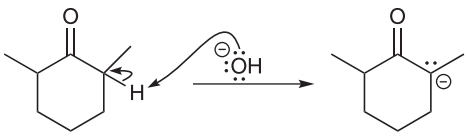
8.22 Hydroxide is a strong base, and it will remove a proton from an alpha position, resulting in an enolate ion. In this case, the starting ketone is symmetrical, so the two alpha positions are the same (deprotonation at either location leads to the same enolate):



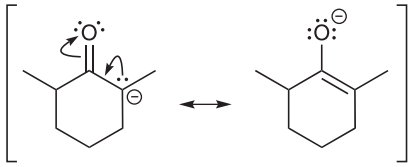
Enolate ions are stabilized by resonance:



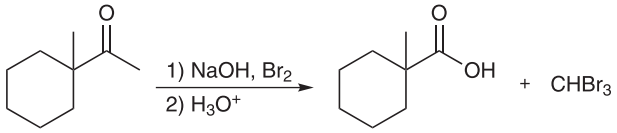
8.23 Hydroxide is a strong base, and it will remove a proton from an alpha position, resulting in an enolate ion. In this case, the starting ketone is symmetrical, so the two alpha positions are the same (deprotonation at either location leads to the same enolate):



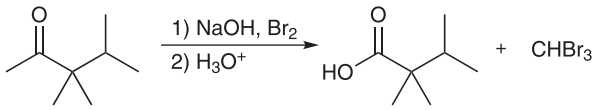
Enolate ions are stabilized by resonance:



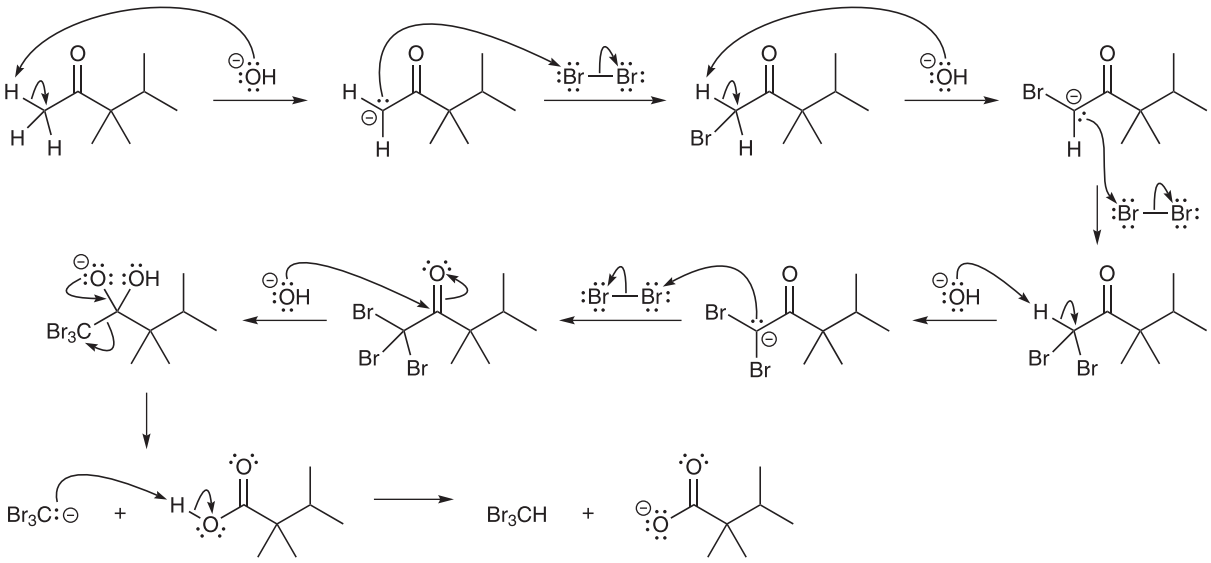
8.25 The starting material is a methyl ketone, and the reagents indicate a haloform reaction. Under these conditions, the methyl ketone is converted into a carboxylic acid, and bromoform is produced as a by-product:



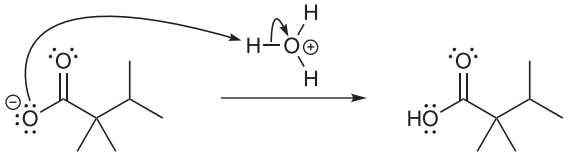
8.26 The starting material is a methyl ketone, and the reagents indicate a haloform reaction. Under these conditions, the methyl ketone is converted into a carboxylic acid, and bromoform is produced as a by-product:



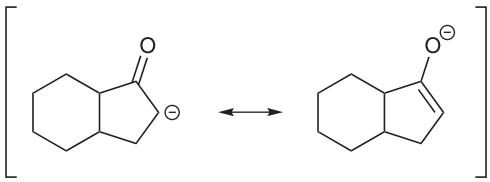
8.27 Hydroxide is a strong base, and it will deprotonate the alpha position to give an enolate ion. This enolate ion then functions as a nucleophile and attacks Br_2, thereby installing a bromine atom at the alpha position. These two steps (deprotonation, followed by nucleophilic attack) are repeated two more times, thereby installing three bromine atoms at the alpha position. Thus far, the methyl (CH_3) group has been converted into a tribromomethyl (CBr_3) group. Hydroxide now functions as a nucleophile and attacks the carbonyl group, giving a tetrahedral intermediate, which expels Br_3C^- as a leaving group to give a carboxylic acid. Under these conditions, the carboxylic acid is deprotonated to give a carboxylate ion.



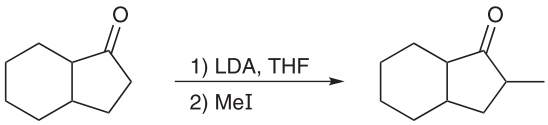
After the reaction above is complete, an acid is introduced into the reaction flask to protonate the carboxylate ion, and the carboxylic acid is obtained:



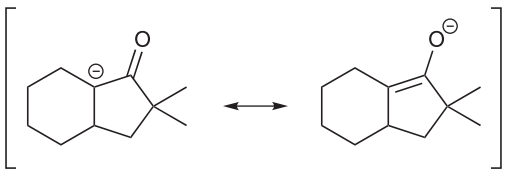
8.29 The starting material is an unsymmetrical ketone, and when treated with LDA, this ketone is deprotonated at the less-substituted position to give the kinetic enolate, shown here:



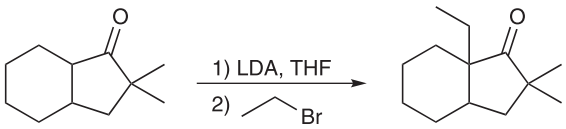
This enolate will react with methyl iodide in an S_N2 reaction, thereby installing a methyl group at the less-substituted alpha carbon, to give the product shown:



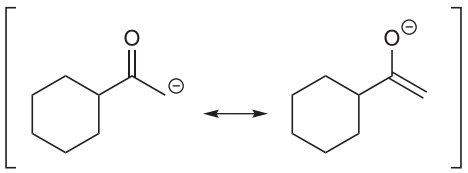
8.30 The starting material has only one alpha proton. Upon treatment with LDA, the starting material is deprotonated to give an enolate, shown here:



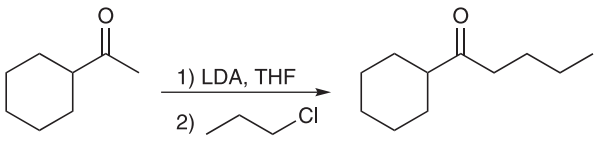
This enolate will react with ethyl bromide in an S_N2 reaction, thereby installing an ethyl group, to give the product shown:



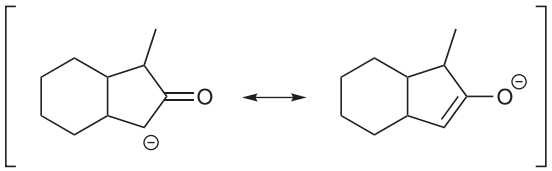
8.31 The starting material is an unsymmetrical ketone, and when treated with LDA, this ketone is deprotonated at the less-substituted position to give the kinetic enolate, shown here:



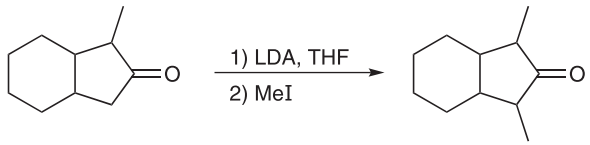
This enolate will react with *n*-propyl chloride in an S_N2 reaction, thereby installing a propyl group at the less-substituted alpha carbon, to give the product shown:



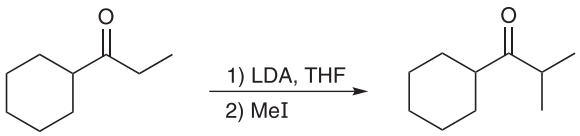
8.32 The starting material is an unsymmetrical ketone, and when treated with LDA, this ketone is deprotonated at the less-substituted position to give the kinetic enolate, shown here:



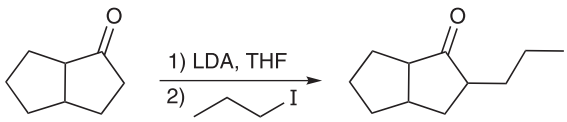
This enolate will react with methyl iodide in an S_N2 reaction, thereby installing a methyl group at the less-substituted alpha carbon, to give the product shown:



8.34 If we look at the difference between the starting material and the product, we see that there is an extra methyl group that was introduced at an alpha position. This methyl group was installed at the less-substituted alpha position, which can be achieved by treating the ketone with LDA followed by methyl iodide:

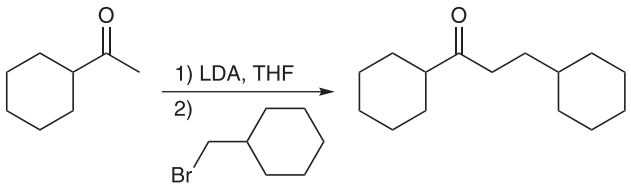


8.35 If we look at the difference between the starting material and the product, we see that there is an extra *n*-propyl group that was introduced at an alpha position. This *n*-propyl group was installed at the less-substituted alpha position, which can be achieved by treating the ketone with LDA followed by *n*-propyl iodide:

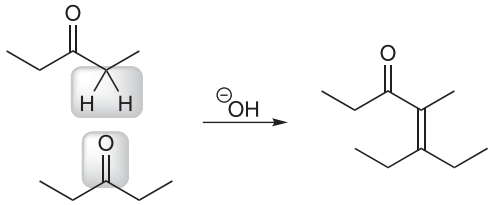


8.36 If we look at the difference between the starting material and the product, we see that there is an extra alkyl group that was introduced at an alpha position. This alkyl group was installed at the less-substituted alpha position, which can be achieved by

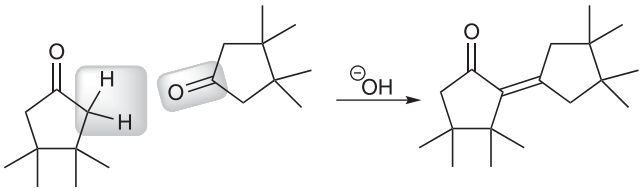
treating the ketone with LDA followed by an alkyl halide, shown below:



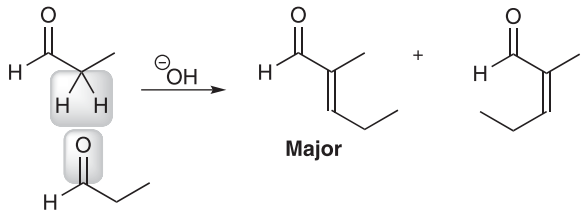
8.38 We start by drawing two molecules of the ketone, so that the oxygen atom of one ketone is pointing directly at the alpha protons of the other ketone. Then, we erase the two alpha protons and the oxygen atom (highlighted), and we push the fragments together, connecting them with a double bond. This is NOT a mechanism, but it is a useful method for drawing the product of an aldol condensation.



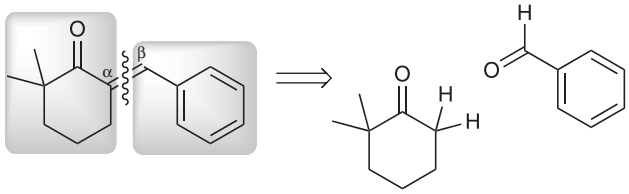
8.39 We start by drawing two molecules of the ketone, so that the oxygen atom of one ketone is pointing directly at the alpha protons of the other ketone. Then, we erase the two alpha protons and the oxygen atom (highlighted), and we push the fragments together, connecting them with a double bond. This is NOT a mechanism, but it is a useful method for drawing the product of an aldol condensation.



8.40 We start by drawing two molecules of the aldehyde, so that the oxygen atom of one aldehyde is pointing directly at the alpha protons of the other aldehyde. Then, we erase the two alpha protons and the oxygen atom (highlighted), and we push the fragments together, connecting them with a double bond. In this case, two stereoisomeric products are obtained, and the first one shown is likely the major product (the aldehydic group has lone pairs and is likely larger than a methyl group, so that aldehydic group will be *trans* to the ethyl group).

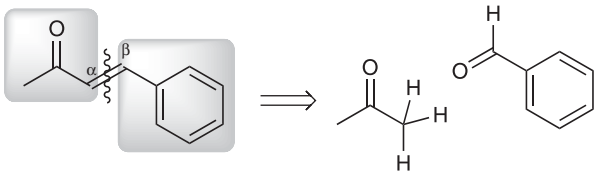


8.42 Below is a retrosynthetic analysis for the desired product, showing the C═C bond that is made during an aldol condensation. To draw the starting materials for this aldol condensation, consider the C═C bond in the product (the alpha and beta positions). The alpha position must have originally been the location of two alpha protons, and the beta position must have originally been the location of a carbonyl group, as shown here:



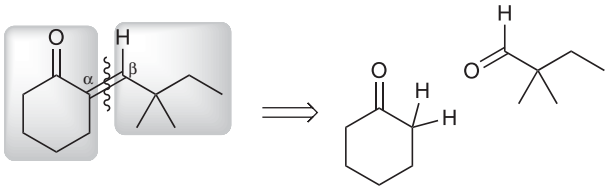
Upon treatment with NaOH, these starting materials will react with each other via an Aldol condensation to give the desired product.

8.43 Below is a retrosynthetic analysis for the desired product, showing the C═C bond that is made during an aldol condensation. To draw the starting materials for this aldol condensation, consider the C═C bond in the product (the alpha and beta positions). The alpha position must have originally been the location of two additional alpha protons, and the beta position must have originally been the location of a carbonyl group, as shown here:



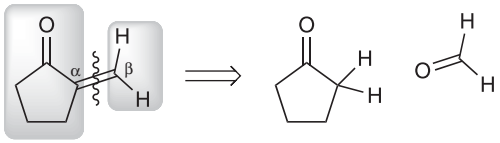
Upon treatment with NaOH, these starting materials will react with each other via an Aldol condensation to give the desired product.

8.44 Below is a retrosynthetic analysis for the desired product, showing the C═C bond that is made during an aldol condensation. To draw the starting materials for this aldol condensation, consider the C═C bond in the product (the alpha and beta positions). The alpha position must have originally been the location of two alpha protons, and the beta position must have originally been the location of a carbonyl group, as shown here:



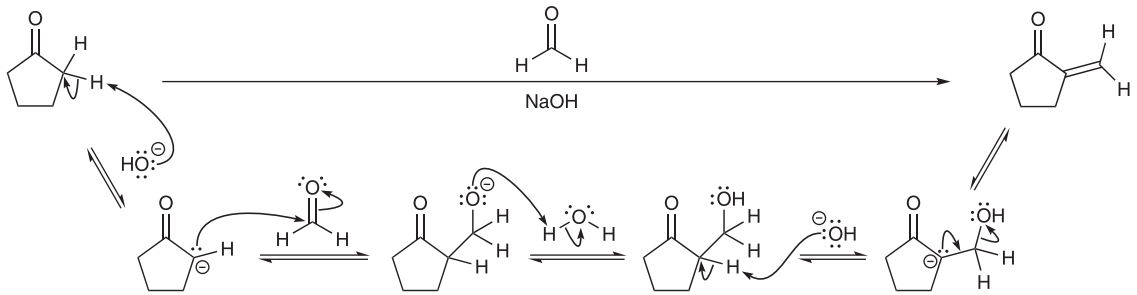
Upon treatment with NaOH, these starting materials will react with each other via an Aldol condensation to give the desired product.

8.45 Below is a retrosynthetic analysis for the desired product, showing the C═C bond that is made during an aldol condensation. To draw the starting materials for this aldol condensation, consider the C═C bond in the product (the alpha and beta positions). The alpha position must have originally been the location of two alpha protons, and the beta position must have originally been the location of a carbonyl group, as shown here:

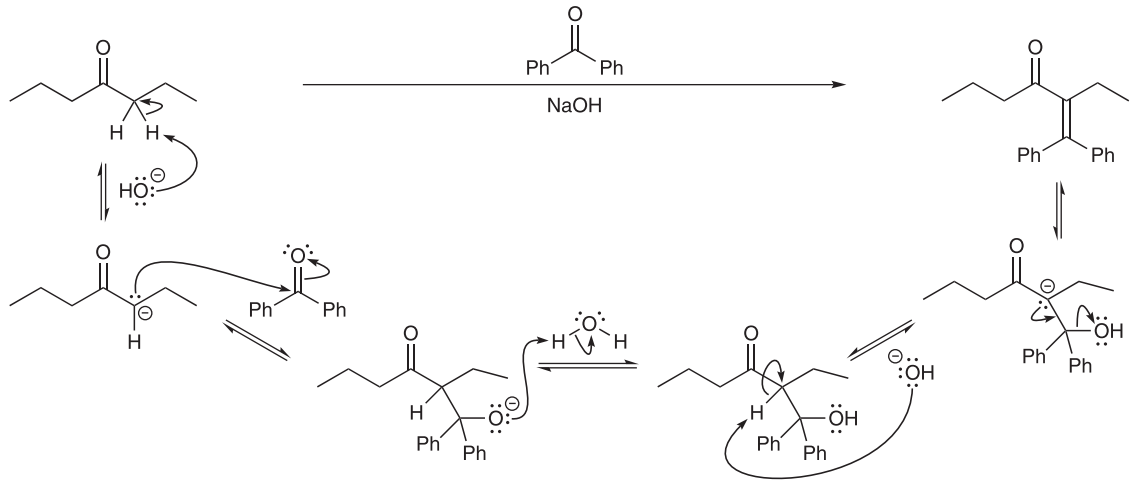


Upon treatment with NaOH, these starting materials will react with each other via an Aldol condensation to give the desired product.

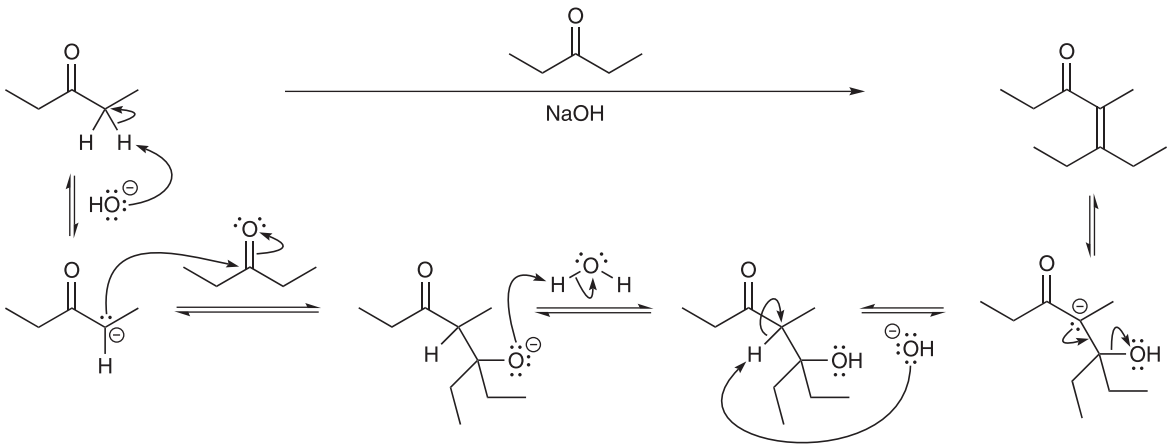
8.47 In the first step, hydroxide functions as a base and removes an alpha proton from the ketone. The resulting enolate ion then functions as a nucleophile and attacks the carbonyl group of formaldehyde. The resulting alkoxide ion is then protonated by H_2O (this is the proton source that is present under these conditions) to give a β-hydroxy ketone. Under these conditions, the β-hydroxy ketone can undergo elimination to give an α,β-unsaturated ketone. This elimination process occurs via two steps. First, hydroxide functions as a base and removes an alpha proton, and then hydroxide is expelled as a leaving group to give the product:



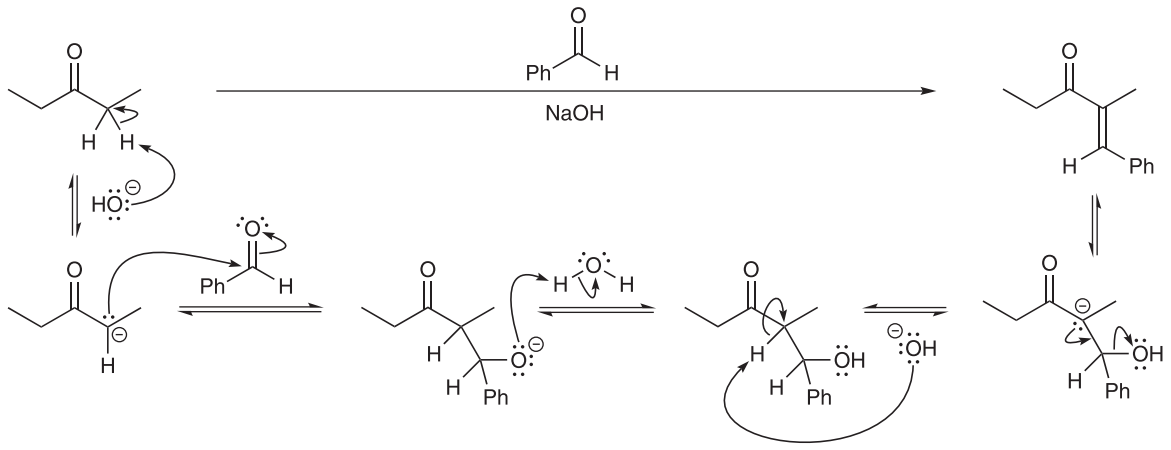
8.48 In the first step, hydroxide functions as a base and removes an alpha proton from the ketone bearing alpha protons. The resulting enolate ion then functions as a nucleophile and attacks the carbonyl group of the other ketone. The resulting alkoxide ion is then protonated by H_2O (this is the proton source that is present under these conditions) to give a β-hydroxy ketone. Under these conditions, the β-hydroxy ketone can undergo elimination to give an α,β-unsaturated ketone. This elimination process occurs via two steps. First, hydroxide functions as a base and removes an alpha proton, and then hydroxide is expelled as a leaving group to give the product:



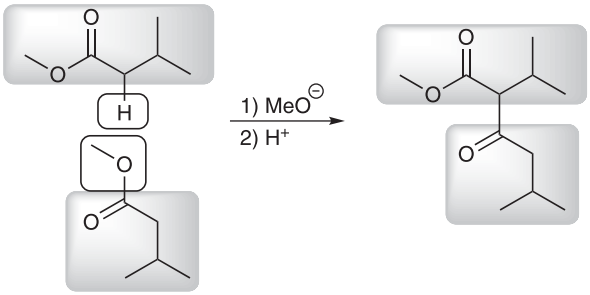
8.49 In the first step, hydroxide functions as a base and removes an alpha proton from the ketone. The resulting enolate ion then functions as a nucleophile and attacks the carbonyl group of another molecule of the same ketone. The resulting alkoxide ion is then protonated by H_2O (this is the proton source that is present under these conditions) to give a β-hydroxy ketone. Under these conditions, the β-hydroxy ketone can undergo elimination to give an α,β-unsaturated ketone. This elimination process occurs via two steps. First, hydroxide functions as a base and removes an alpha proton, and then hydroxide is expelled as a leaving group to give the product:



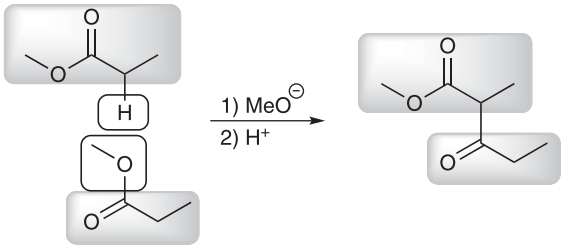
8.50 In the first step, hydroxide functions as a base and removes an alpha proton from the ketone bearing alpha protons. The resulting enolate ion then functions as a nucleophile and attacks the carbonyl group of the aldehyde. The resulting alkoxide ion is then protonated by H_2O (this is the proton source that is present under these conditions) to give a β-hydroxy ketone. Under these conditions, the β-hydroxy ketone can undergo elimination to give an α,β-unsaturated ketone. This elimination process occurs via two steps. First, hydroxide functions as a base and removes an alpha proton, and then hydroxide is expelled as a leaving group to give the product:



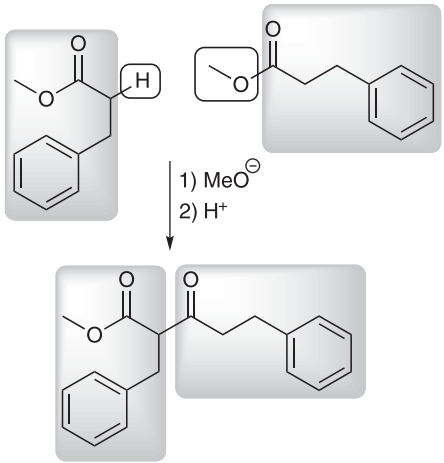
8.52 To draw the product of this Claisen condensation, we start by drawing two molecules of the ester, so that the alkoxy of one ester is pointing directly at the alpha protons of the other ester. Then, we erase the alkoxy group and one of the alpha protons, and we push the fragments together, as follows:



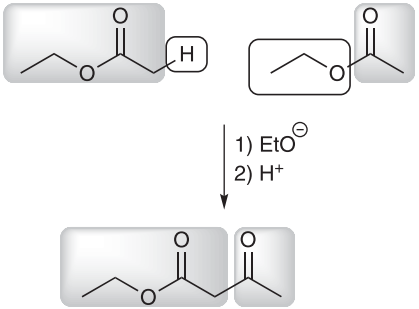
8.53 To draw the product of this Claisen condensation, we start by drawing two molecules of the ester, so that the alkoxy of one ester is pointing directly at an alpha proton of the other ester. Then, we erase the alkoxy group and the alpha proton, and we push the fragments together, as follows:



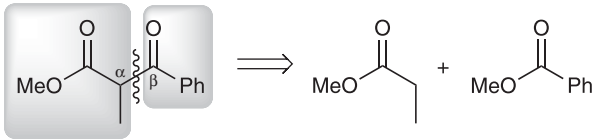
8.54 To draw the product of this Claisen condensation, we start by drawing two molecules of the ester, so that the alkoxy of one ester is pointing directly at the alpha protons of the other ester. Then, we erase the alkoxy group and one of the alpha protons, and we push the fragments together, as follows:



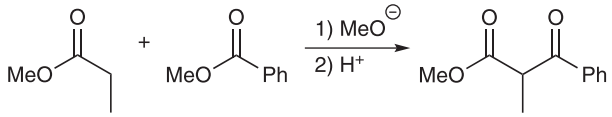
8.55 To draw the product of this Claisen condensation, we start by drawing two molecules of the ester, so that the alkoxy of one ester is pointing directly at the alpha protons of the other ester. Then, we erase the alkoxy group and one of the alpha protons, and we push the fragments together, as follows:



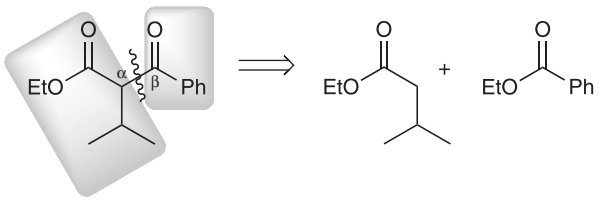
8.57 Below is a retrosynthetic analysis for the desired product, showing the C–C bond that is made during a Claisen condensation. To draw the starting materials for this Claisen condensation, consider the C–C bond in the product (between the alpha and beta positions). The alpha position must have originally been the location of an additional alpha proton, and the beta position must have originally been connected to an alkoxy group (specifically, a methoxy group, so that both esters have the same alkoxy group), as shown here:



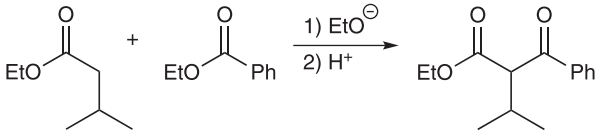
The two esters above can be used to make the desired product via a Claisen condensation reaction, as shown below. Notice that we use methoxide as our base (to avoid transesterification):



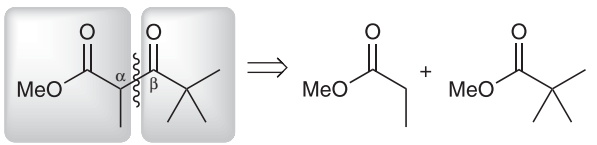
8.58 Below is a retrosynthetic analysis for the desired product, showing the C–C bond that is made during a Claisen condensation. To draw the starting materials for this Claisen condensation, consider the C–C bond in the product (between the alpha and beta positions). The alpha position must have originally been the location of an additional alpha proton, and the beta position must have originally been connected to an alkoxy group (specifically, an ethoxy group, so that both esters have the same alkoxy group), as shown here:



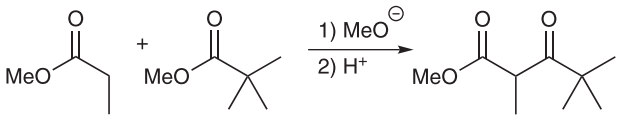
The two esters above can be used to make the desired product via a Claisen condensation reaction, as shown below. Notice that we use ethoxide as our base (to avoid transesterification):



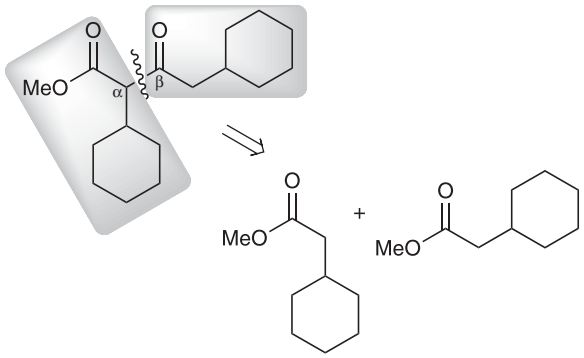
8.59 Below is a retrosynthetic analysis for the desired product, showing the C–C bond that is made during a Claisen condensation. To draw the starting materials for this Claisen condensation, consider the C–C bond in the product (between the alpha and beta positions). The alpha position must have originally been the location of an additional alpha proton, and the beta position must have originally been connected to an alkoxy group (specifically, a methoxy group, so that both esters have the same alkoxy group), as shown here:



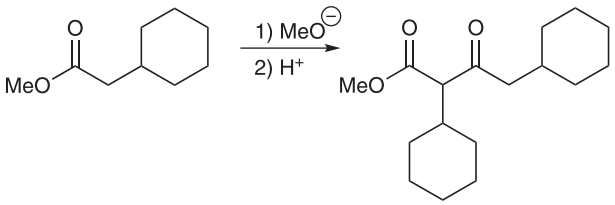
The two esters above can be used to make the desired product via a Claisen condensation reaction, as shown below. Notice that we use methoxide as our base (to avoid transesterification):



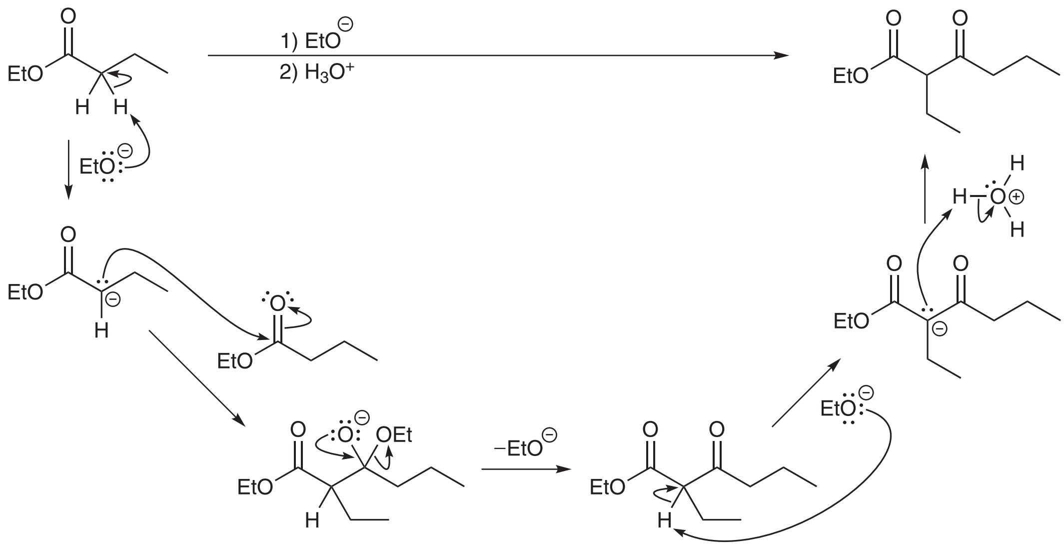
8.60 Below is a retrosynthetic analysis for the desired product, showing the C–C bond that is made during a Claisen condensation. To draw the starting materials for this Claisen condensation, consider the C–C bond in the product (between the alpha and beta positions). The alpha position must have originally been the location of an additional alpha proton, and the beta position must have originally been connected to an alkoxy group (specifically, a methoxy group, so that both esters have the same alkoxy group), as shown here:



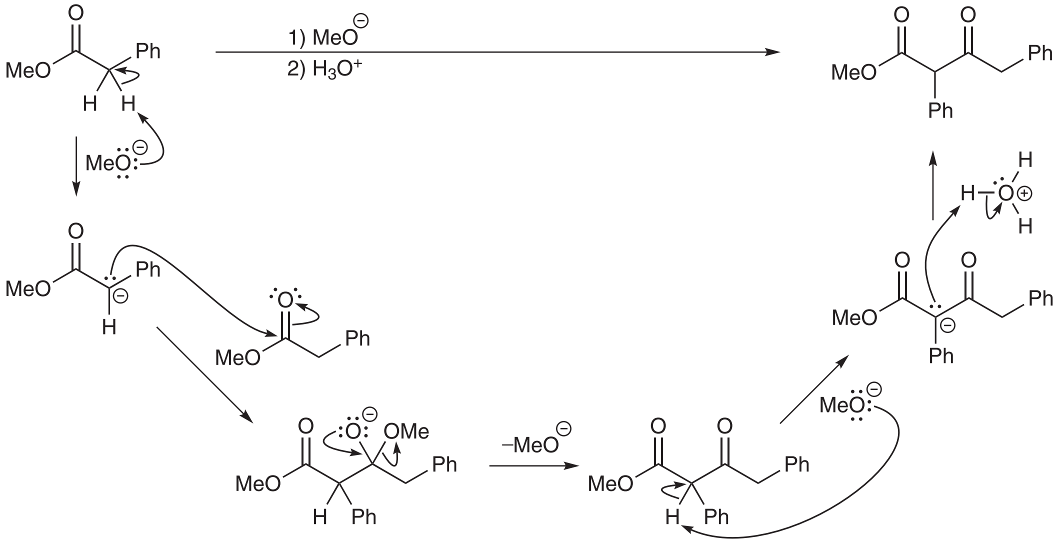
Notice that, in this case, the two esters are identical. This ester can be used to make the desired product via a Claisen condensation reaction, as shown below. Notice that we use methoxide as our base (to avoid transesterification):



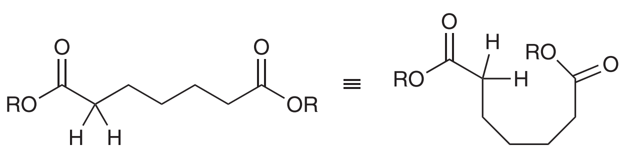
8.62 Ethoxide functions as a base and removes a proton from the alpha position of the starting ester, giving an enolate ion. This enolate ion then functions as a nucleophile and attacks another molecule of the ester (that has not been deprotonated) to give a tetrahedral intermediate. This intermediate then re-forms the carbonyl group by expelling an ethoxide ion. The resulting product (which is our desired product) is deprotonated under these basic conditions to give a stabilized enolate ion. The formation of this particularly stable anion is a driving force for the reaction. When the reaction is complete, we must then introduce a source of protons (H_3O^+) into the reaction flask to protonate the anion and regenerate the desired product.



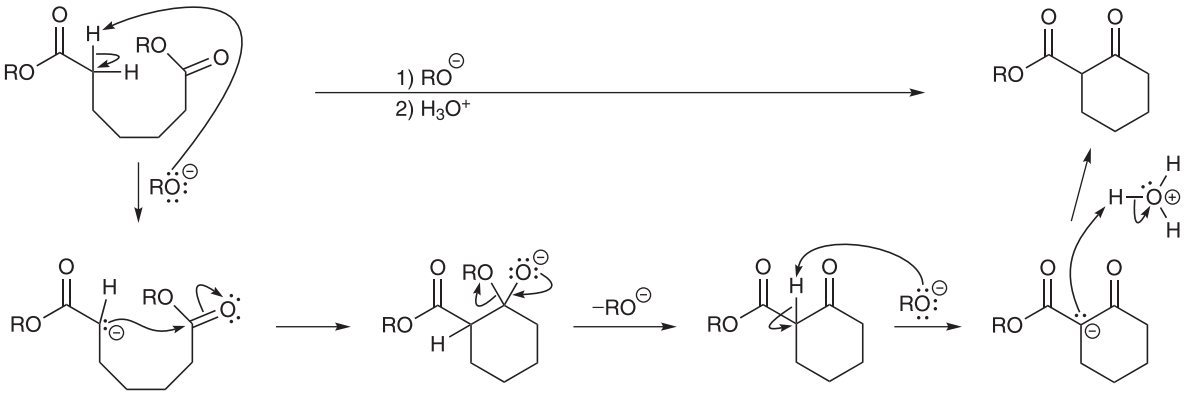
8.63 Methoxide functions as a base and removes a proton from the alpha position of the starting ester, giving an enolate ion. This enolate ion then functions as a nucleophile and attacks another molecule of the ester (that has not been deprotonated) to give a tetrahedral intermediate. This intermediate then re-forms the carbonyl group by expelling a methoxide ion. The resulting product (which is our desired product) is deprotonated under these basic conditions to give a stabilized enolate ion. The formation of this particularly stable anion is a driving force for the reaction. When the reaction is complete, we must then introduce a source of protons (H_3O^+) into the reaction flask to protonate the anion and regenerate the desired product.



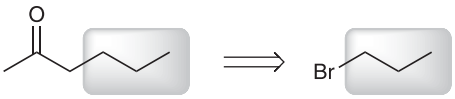
8.64 Let's begin by redrawing the starting diester:



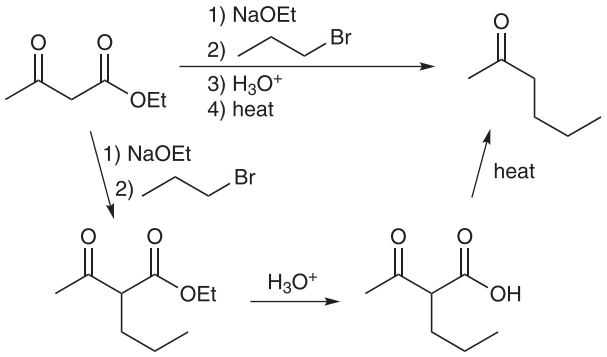
In the first step of the mechanism, an alkoxide ion functions as a base and removes a proton from one of the alpha positions of the starting diester, giving an enolate ion. This enolate ion then functions as a nucleophile and attacks the other carbonyl group (in an intramolecular fashion) to give a tetrahedral intermediate. This intermediate then re-forms the carbonyl group by expelling an alkoxide ion. The resulting product (which is our desired product) is deprotonated under these basic conditions to give a stabilized enolate ion. The formation of this particularly stable anion is a driving force for the reaction. When the reaction is complete, we must then introduce a source of protons (H_3O^+) into the reaction flask to protonate the anion and regenerate the desired product.



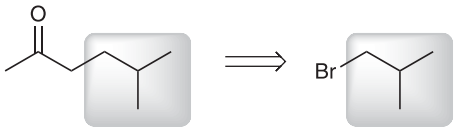
8.66 We begin by identifying an alkyl halide that can be used to make the desired product via an acetoacetic ester synthesis:



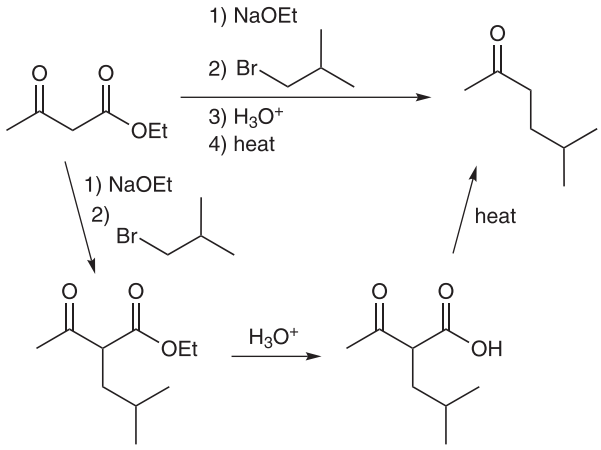
Now we can draw the forward process. In the first step, ethyl acetoacetate is treated with sodium ethoxide followed by *n*-propyl bromide, thereby installing an *n*-propyl group at the alpha position. The ester group is then hydrolyzed, and the resulting β-ketoacid is then heated to give a decarboxylation reaction, affording the desired product.



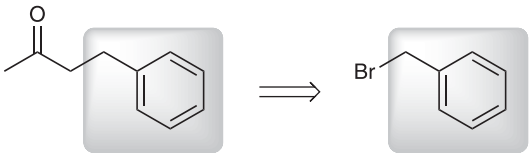
8.67 We begin by identifying an alkyl halide that can be used to make the desired product via an acetoacetic ester synthesis:



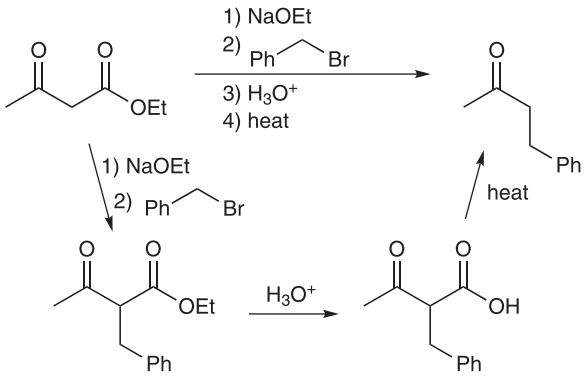
Now we can draw the forward process. In the first step, ethyl acetoacetate is treated with sodium ethoxide followed by isobutyl bromide, thereby installing an isobutyl group at the alpha position. The ester group is then hydrolyzed, and the resulting β-ketoacid is then heated to give a decarboxylation reaction, affording the desired product.



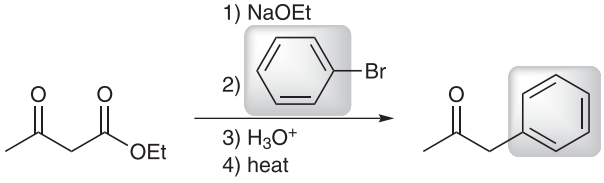
8.68 We begin by identifying an alkyl halide that can be used to make the desired product via an acetoacetic ester synthesis:



Now we can draw the forward process. In the first step, ethyl acetoacetate is treated with sodium ethoxide followed by benzyl bromide, thereby installing a benzyl group at the alpha position. The ester group is then hydrolyzed, and the resulting β-ketoacid is then heated to give a decarboxylation reaction, affording the desired product.

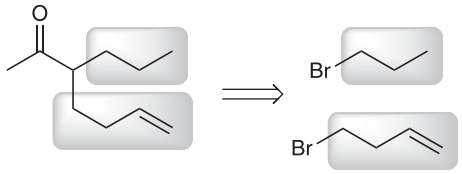


8.69 Consider the following proposed acetoacetic ester synthesis:

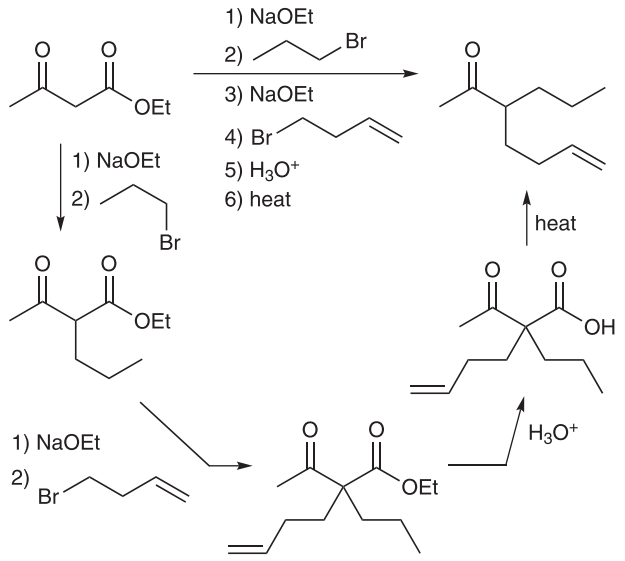


This process will not work because it would require performing an S_N2 reaction with phenyl bromide as the substrate. This will not work because S_N2 reactions cannot be performed with a substrate in which the leaving group is connected to an sp^2 hybridized carbon atom.

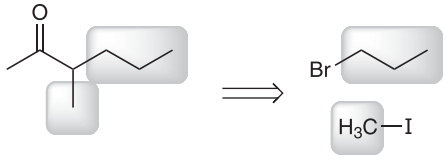
8.70 The desired product is a derivative of acetone containing two R groups, highlighted below, and can be made via an acetoacetic ester synthesis, starting with the two alkyl halides shown below:



The forward process is shown here. In the first step, ethyl acetoacetate is treated with sodium ethoxide followed by propyl bromide, thereby installing an *n*-propyl group at the alpha position. This compound is then treated again with sodium ethoxide, followed by the other alkyl halide, installing the second alkyl group (note that the two alkyl groups can be installed in either order). The ester group is then hydrolyzed, and the resulting β-ketoacid is then heated to give a decarboxylation reaction, affording the desired product.



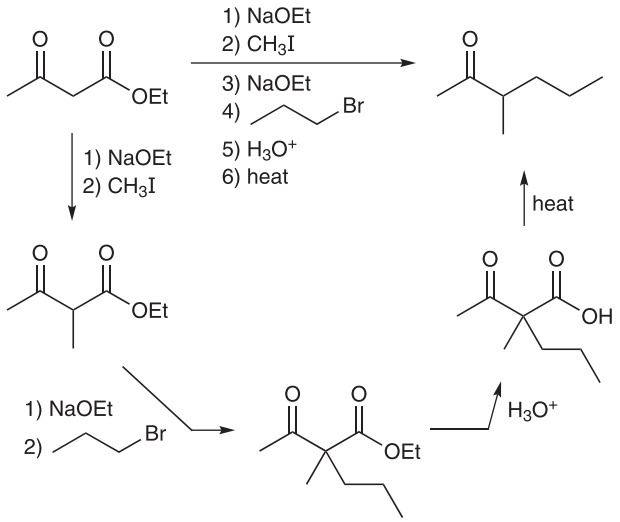
8.71 The desired product is a derivative of acetone containing two R groups, highlighted below, and can be made via an acetoacetic ester synthesis, starting with the two alkyl halides shown below:



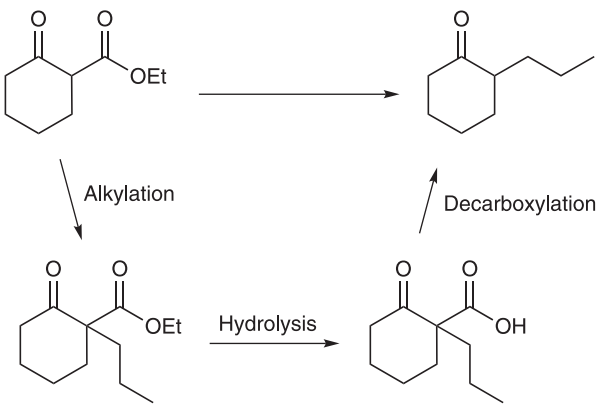
You might wonder why one alkyl halide is a bromide and the other is an iodide. In general, alkyl bromides are less expensive than alkyl iodides (even though iodides are more reactive), and they get

the job done, so bromides are often used. However, methyl bromide is not easy to use because it is a gas at room temperature. When using a methyl halide, it is best to use methyl iodide, which is a liquid at room temperature, rather than methyl bromide.

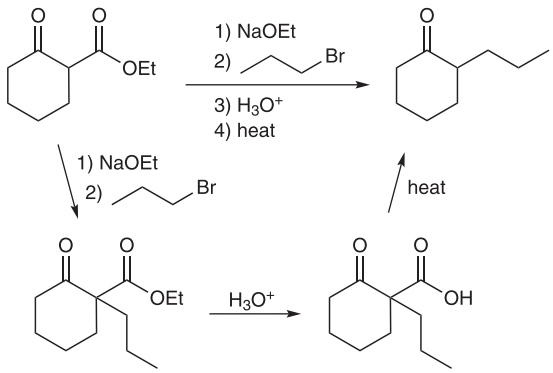
The forward process is shown here. In the first step, ethyl acetoacetate is treated with sodium ethoxide followed by methyl iodide, thereby installing a methyl group at the alpha position. This compound is then treated again with sodium ethoxide, followed by *n*-propyl bromide, thereby installing the *n*-propyl group (note that the two alkyl groups can be installed in either order). The ester group is then hydrolyzed, and the resulting β-ketoacid is then heated to give a decarboxylation reaction, affording the desired product.



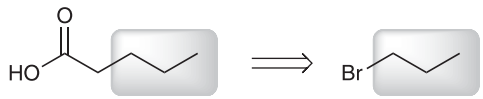
8.72 The desired transformation can be achieved using the same strategy employed in an acetoacetic acid synthesis. Three steps are involved: 1) alkylation, 2) hydrolysis, and 3) decarboxylation:



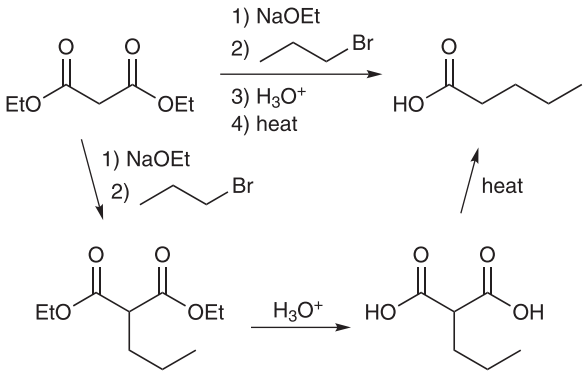
The reagents for this process are shown here:



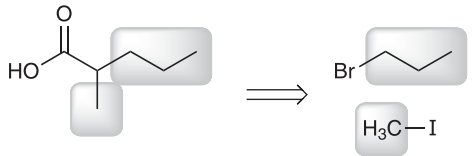
8.74 We begin by identifying an alkyl halide that can be used to make the desired product via a malonic ester synthesis:



Now we can draw the forward process. In the first step, diethyl malonate is treated with sodium ethoxide followed by *n*-propyl bromide, thereby installing an *n*-propyl group at the alpha position. The ester groups are then both hydrolyzed, and the resulting diacid is then heated to give a decarboxylation reaction, affording the desired product.

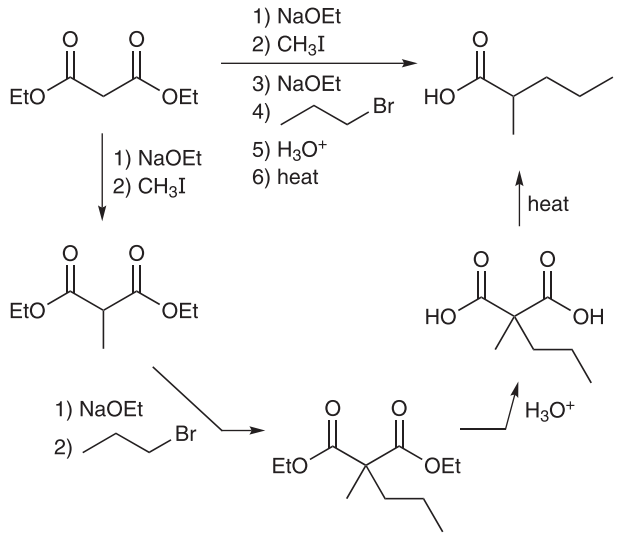


8.75 The desired product is a derivative of acetic acid containing two R groups, highlighted below. This product can be made via an acetoacetic ester synthesis, starting with the two alkyl halides shown below:

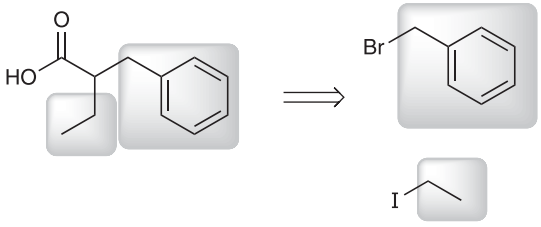


You might wonder why one alkyl halide is a bromide and the other is an iodide. You will find the explanation in the solution to Problem 8.71.

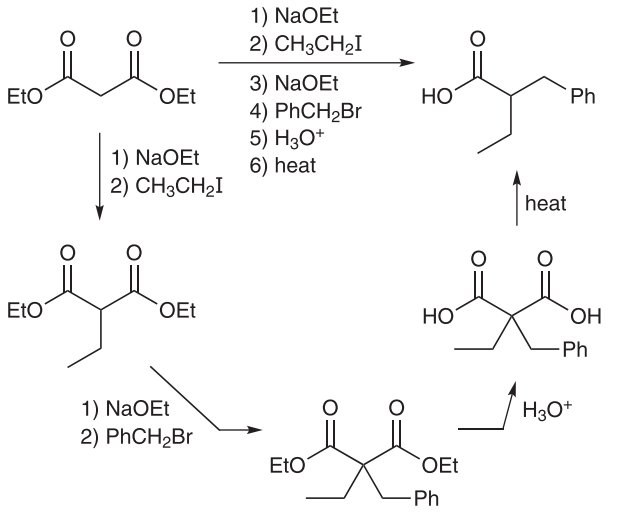
The forward process is shown here. In the first step, diethyl malonate is treated with sodium ethoxide followed by methyl iodide, thereby installing a methyl group at the alpha position. This compound is then treated again with sodium ethoxide, followed by *n*-propyl bromide, thereby installing the *n*-propyl group (note that the two alkyl groups can be installed in either order). The ester groups are then hydrolyzed, and the resulting diacid is then heated to give a decarboxylation reaction, affording the desired product.



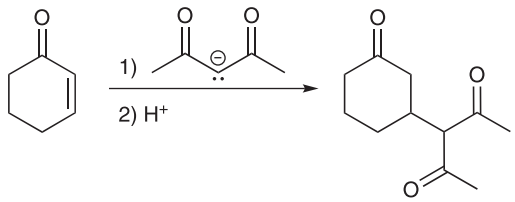
8.76 The desired product is a derivative of acetic acid containing two R groups, highlighted below. This product can be made via an acetoacetic ester synthesis, starting with the two halides shown below:



The forward process is shown here. In the first step, diethyl malonate is treated with sodium ethoxide followed by ethyl iodide, thereby installing an ethyl group at the alpha position. This compound is then treated again with sodium ethoxide, followed by benzyl bromide, thereby installing the benzyl group (note that the two R groups can be installed in either order). The ester groups are then hydrolyzed, and the resulting diacid is then heated to give a decarboxylation reaction, affording the desired product.

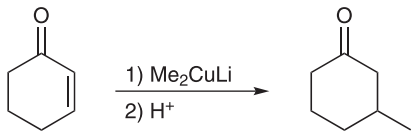


8.78 The starting material is an α,β-unsaturated ketone, which can function as a Michael acceptor. The reagent is a stabilized nucleophile, which can function as a Michael donor. So in this case, we do expect a Michael reaction in which the nucleophile is installed at the beta position:

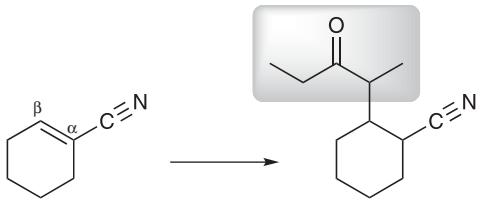


8.79 In this case, we do not expect a clean Michael reaction, because a Grignard reagent is not a good Michael donor. It is too reactive. In this case, a 1,2-addition is expected.

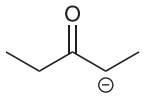
8.80 The starting material is an α,β-unsaturated ketone, which can function as a Michael acceptor. The reagent is lithium dimethyl cuprate (Me_2CuLi), which is a stabilized nucleophile that will attack the β position of the α,β-unsaturated ketone in a 1,4-addition reaction. In this case, a methyl group is installed at the beta position:



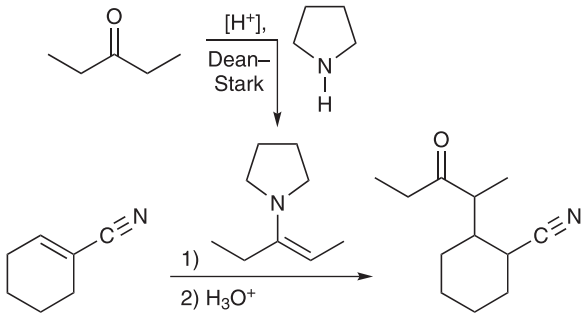
8.82 The starting material is an α,β-unsaturated nitrile, which can function as a Michael acceptor. When we compare the starting material and the desired product, we see that we must install a group at the beta position (highlighted below):



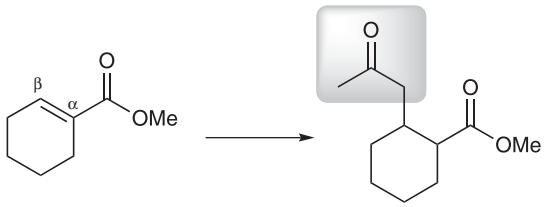
Now let's consider the nucleophile that we would need to install this group:



This is an enolate, which is not sufficiently stable to function as a Michael donor. Therefore, we will need to use a Stork enamine synthesis, in which a ketone is first converted into an enamine (rather than an enolate), because an enamine can function as a Michael donor. The enamine group is then removed (converted back to a ketone) with aqueous acid at the end of the synthesis:

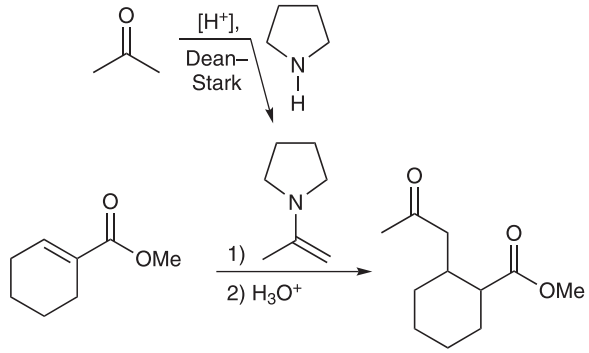


8.83 The starting material is an α,β-unsaturated ester, which can function as a Michael acceptor. When we compare the starting material and the desired product, we see that we must install a group at the beta position (highlighted below):

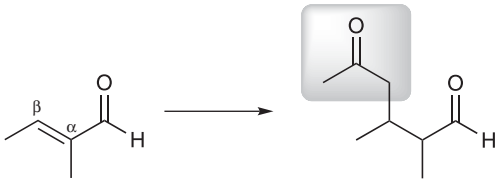


Now let's consider the nucleophile that we would need to install this group:

This is an enolate, which is not sufficiently stable to function as a Michael donor. Therefore, we will need to use a Stork enamine synthesis, in which a ketone is first converted into an enamine (rather than an enolate), because an enamine can function as a Michael donor. The enamine group is then removed (converted back to a ketone) with aqueous acid at the end of the synthesis:

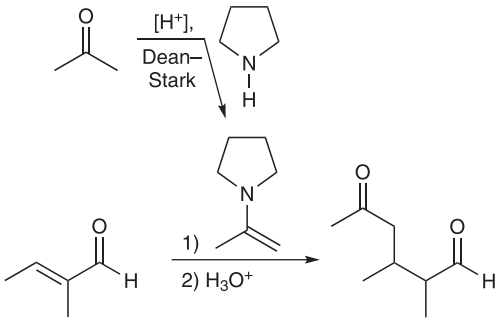


8.84 The starting material is an α,β-unsaturated aldehyde, which can function as a Michael acceptor. When we compare the starting material and the desired product, we see that we must install a group at the beta position (highlighted below):

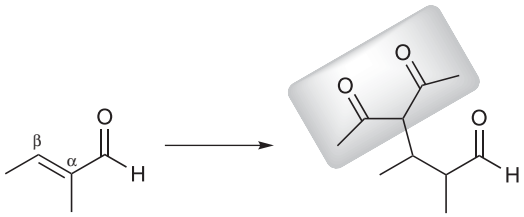


Now let's consider the nucleophile that we would need to install this group:

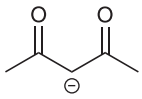
This is an enolate, which is not sufficiently stable to function as a Michael donor. Therefore, we will need to use a Stork enamine synthesis, in which a ketone is first converted into an enamine (rather than an enolate), because an enamine can function as a Michael donor. The enamine group is then removed (converted back to a ketone) with aqueous acid at the end of the synthesis:



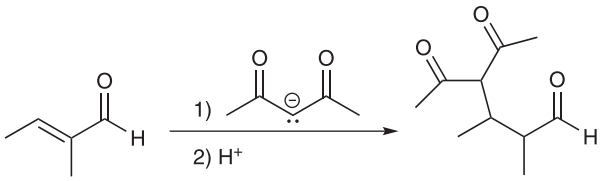
8.85 The starting material is an α,β-unsaturated aldehyde, which can function as a Michael acceptor. When we compare the starting material and the desired product, we see that we must install a group at the beta position (highlighted below):



Now let's consider the nucleophile that we would need to install this group:

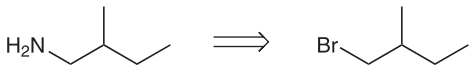


This is a stabilized enolate, which IS sufficiently stable to function as a Michael donor. Therefore, we will NOT need to use a Stork enamine synthesis in this case. Instead, we can directly perform a Michael reaction to obtain the desired product:

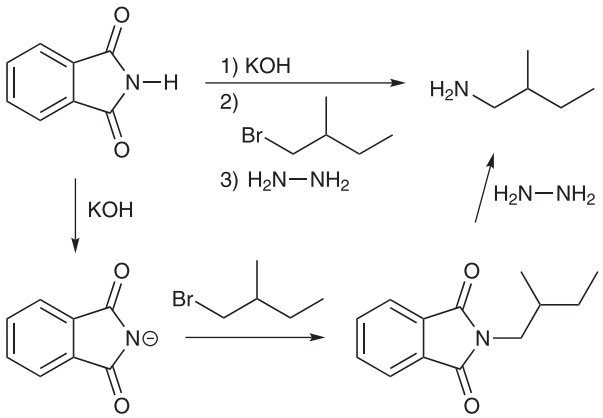


CHAPTER 9

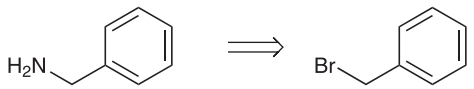
9.2 In order to perform a Gabriel synthesis, we must identify the alkyl halide that should be used. This is the only choice that we need to make when planning a Gabriel synthesis. To do this, we just draw a halogen in place of the NH_2 group, as follows:



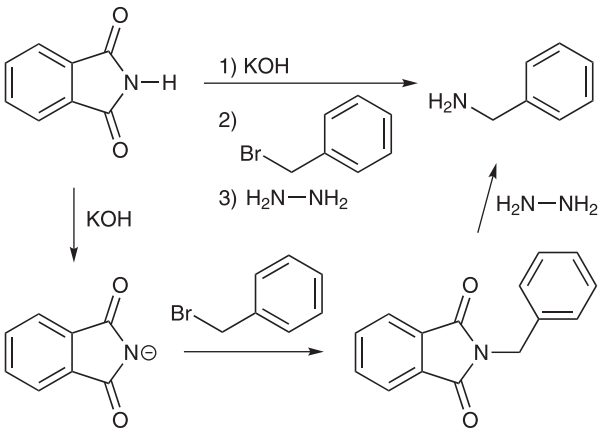
Below is the complete Gabriel synthesis in which this primary alkyl bromide is used to make the desired primary amine:



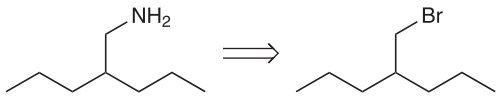
9.3 In order to perform a Gabriel synthesis, we must identify the alkyl halide that should be used. This is the only choice that we need to make when planning a Gabriel synthesis. To do this, we just draw a halogen in place of the NH_2 group, as follows:



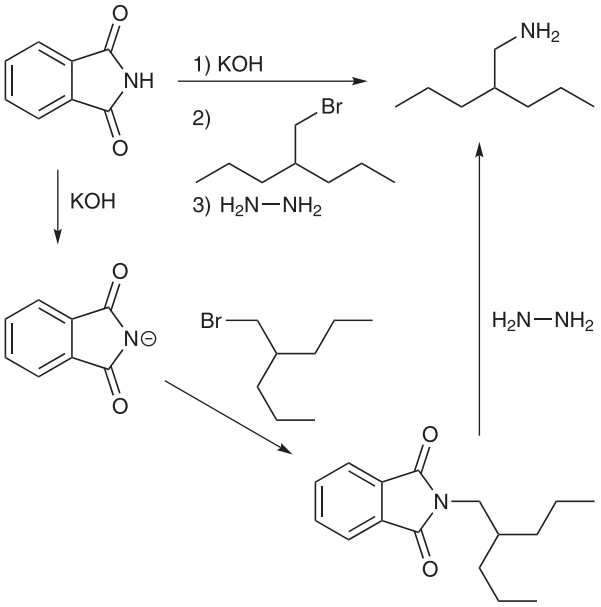
This alkyl bromide is called benzyl bromide. Below is the complete Gabriel synthesis in which benzyl bromide is used to make the desired amine (benzyl amine):



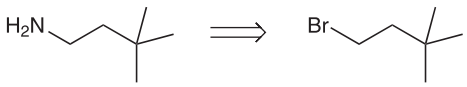
9.4 In order to perform a Gabriel synthesis, we must identify the alkyl halide that should be used. This is the only choice that we need to make when planning a Gabriel synthesis. To do this, we just draw a halogen in place of the NH_2 group, as follows:



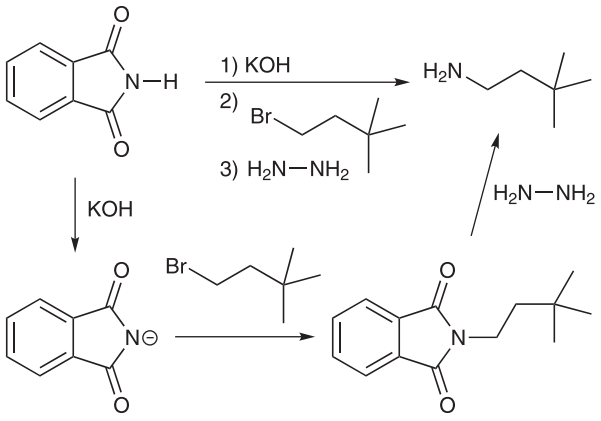
Below is the complete Gabriel synthesis in which this primary alkyl bromide is used to make the desired primary amine:



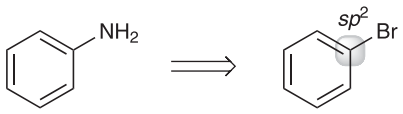
9.5 In order to perform a Gabriel synthesis, we must identify the alkyl halide that should be used. This is the only choice that we need to make when planning a Gabriel synthesis. To do this, we just draw a halogen in place of the NH_2 group, as follows:



Below is the complete Gabriel synthesis in which this primary alkyl bromide is used to make the desired primary amine:

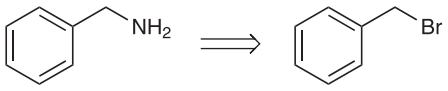


9.7 We begin by drawing the alkyl bromide that would be required to make the desired amine via a Gabriel synthesis:

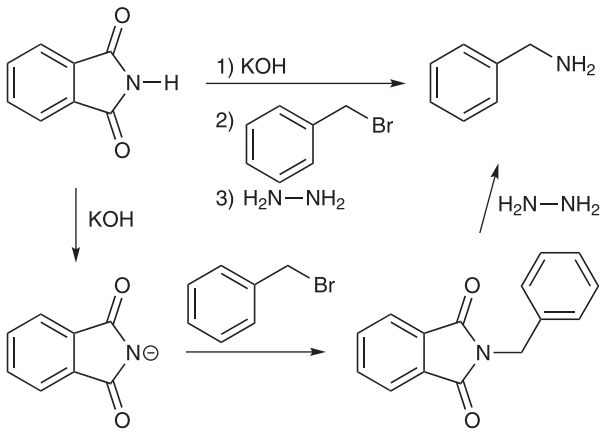


This compound has the leaving group connected to an sp^2 hybridized carbon atom, and S_N2 reactions are not observed at sp^2 hybridized centers. Therefore, the desired amine cannot be made via a Gabriel synthesis.

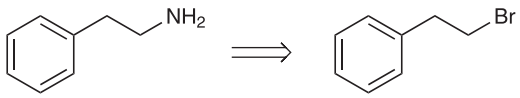
9.8 We begin by drawing the alkyl bromide that would be required to make the desired amine via a Gabriel synthesis:



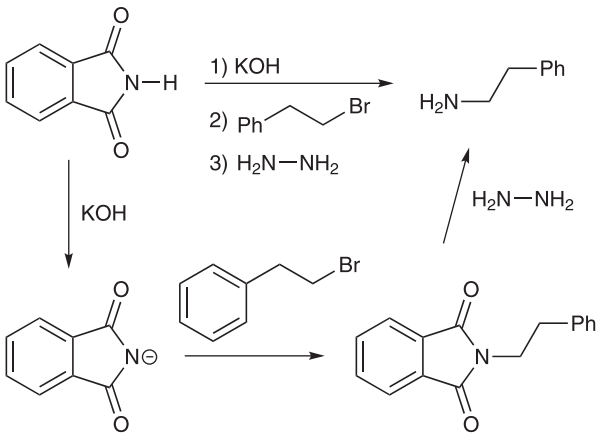
This alkyl bromide is both primary and benzylic and can serve as an excellent substrate in an S_N2 reaction. Therefore, the desired amine can be made via a Gabriel synthesis, shown below:



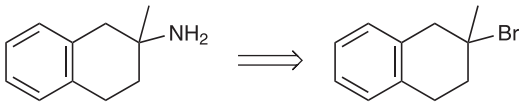
9.9 We begin by drawing the alkyl bromide that would be required to make the desired amine via a Gabriel synthesis:



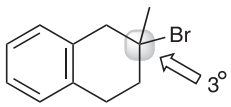
This alkyl bromide is primary and can serve as a substrate in an S_N2 reaction. Therefore, the desired amine can be made via a Gabriel synthesis, shown below:



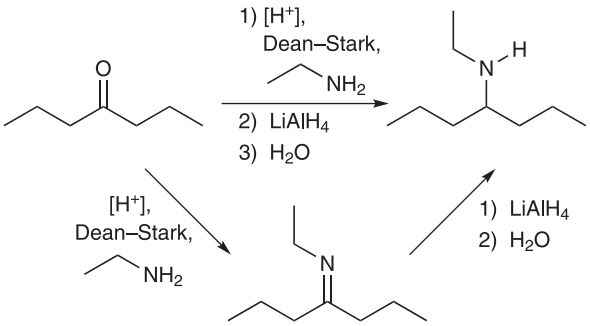
9.10 We begin by drawing the alkyl bromide that would be required to make the desired amine via a Gabriel synthesis:



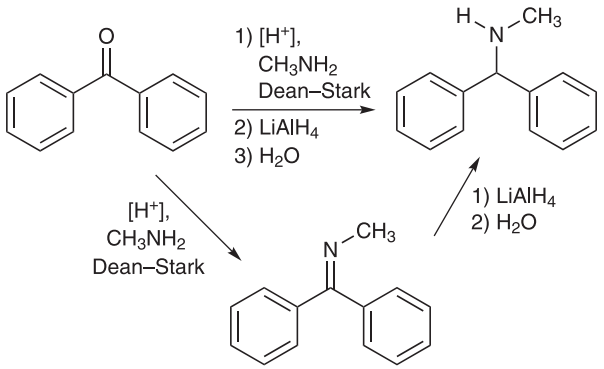
This alkyl bromide is tertiary, and S_N2 reactions do not occur with tertiary substrates (because of steric effects). Therefore, the desired amine cannot be made via a Gabriel synthesis.



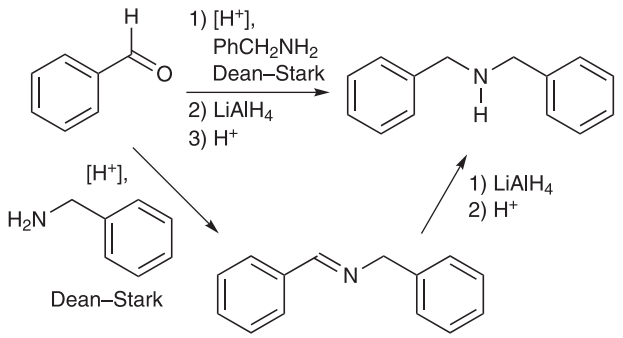
9.12 This problem involves the conversion of a ketone into a secondary amine, which should alert us to the possibility of a reductive amination. The ketone is first converted into an imine, which is then reduced to give the desired secondary amine:



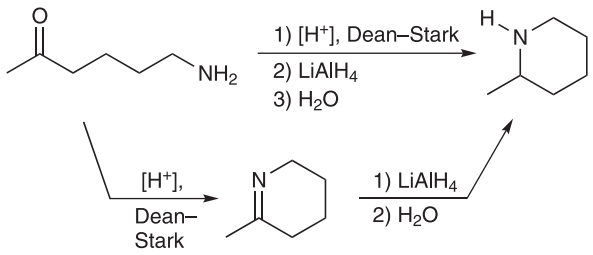
9.13 This problem involves the conversion of a ketone into a secondary amine, which should alert us to the possibility of a reductive amination. The ketone is first converted into an imine, which is then reduced to give the desired secondary amine:



9.14 This problem involves the conversion of an aldehyde into a secondary amine, which should alert us to the possibility of a reductive amination. The ketone is first converted into an imine, which is then reduced to give the desired secondary amine:

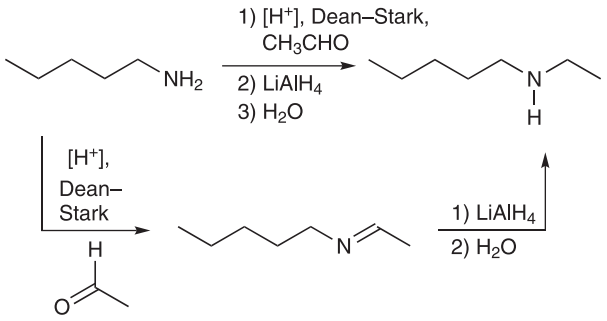


9.15 This problem involves the conversion of a ketone into a secondary amine, which should alert us to the possibility of a reductive amination. The ketone is first converted into an imine in an intramolecular fashion (giving a cyclic imine), which is then reduced to give the desired secondary amine:

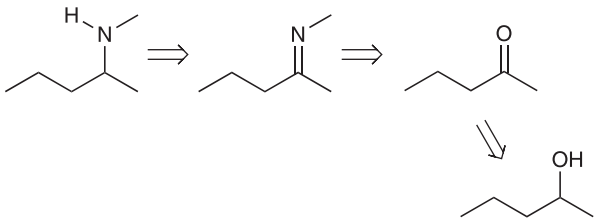


9.16 This problem involves the conversion of a primary amine into a secondary amine, which should alert us to the possibility of

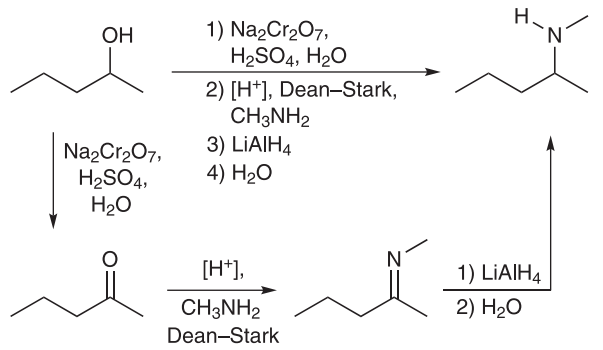
a reductive amination. The primary amine is first converted into an imine, which is then reduced to give the desired secondary amine:



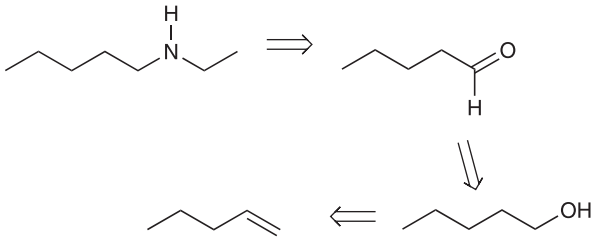
9.18 The following is a retrosynthetic strategy for making the desired amine from the starting alcohol:



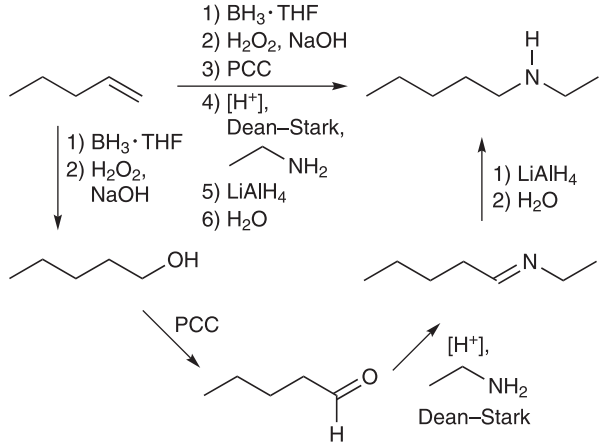
The forward synthesis is shown here. First the alcohol is oxidized to give a ketone, which is then converted into an imine. Finally, the imine is reduced to give the desired product:



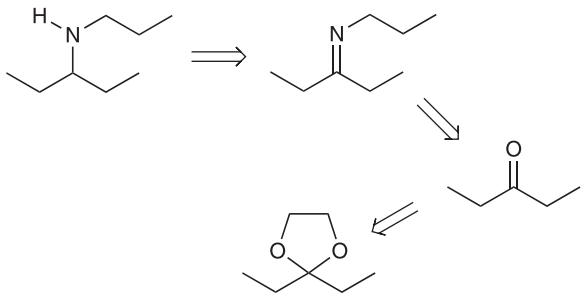
9.19 The following is a retrosynthetic strategy for making the desired amine from the starting alkene:



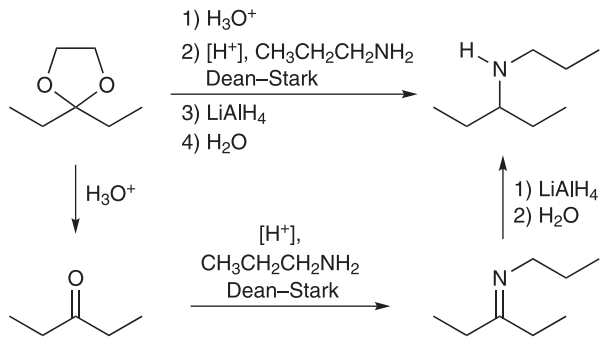
The forward synthesis is shown here. First the alkene is converted into a primary alcohol via hydroboration–oxidation to give anti-Markovnikov addition of H_2O. Then, the alcohol is oxidized with PCC to give an aldehyde. This aldehyde is then converted into an imine, which is reduced to give the desired product:



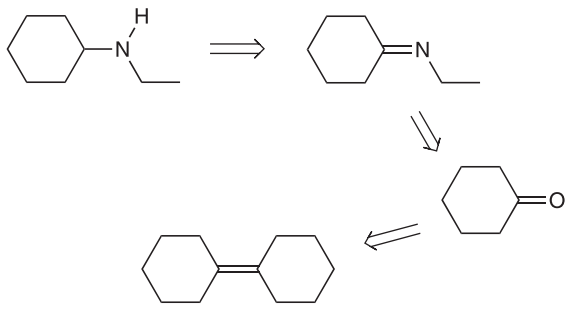
9.20 The following is a retrosynthetic strategy for making the desired amine from the starting acetal:



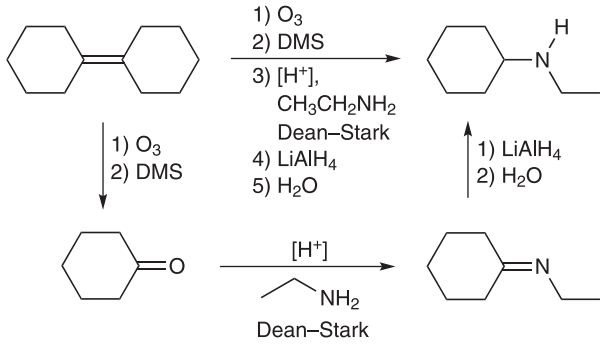
The forward synthesis is shown here. First the acetal is treated with aqueous acid to give a ketone, which is then converted into an imine. Finally, the imine is reduced to give the desired product:



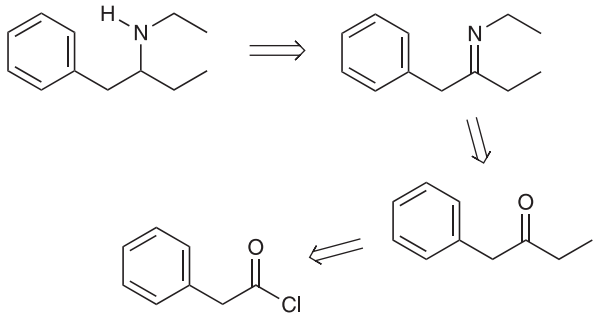
9.21 The following is a retrosynthetic strategy for making the desired amine from the starting alkene:



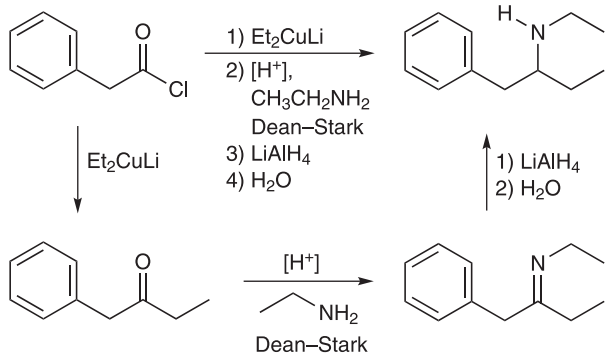
The forward synthesis is shown here. First the alkene undergoes ozonolysis to give two equivalents of a ketone. The ketone is then converted into an imine, and finally, the imine is reduced to give the desired product:



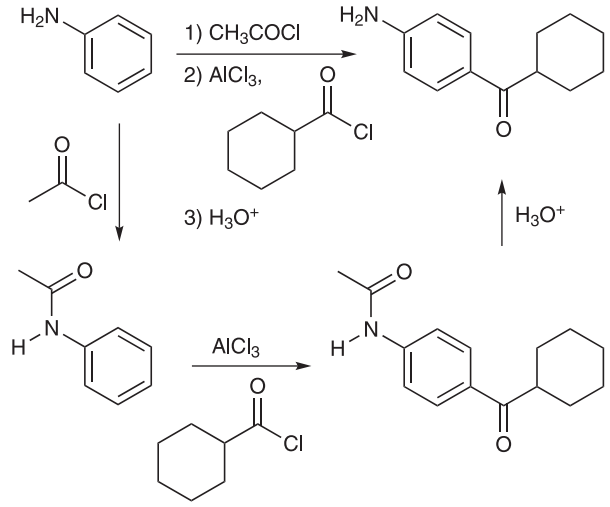
9.22 The following is a retrosynthetic strategy for making the desired amine from the starting acid halide:



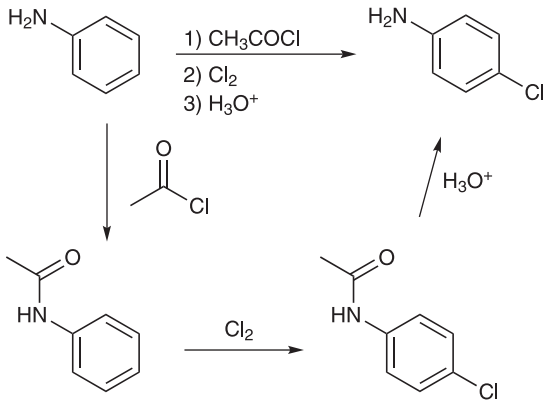
The forward synthesis is shown here. First the acid chloride is converted into a ketone upon treatment with a lithium dialkyl cuprate. This ketone is then converted into an imine, and finally, the imine is reduced to give the desired product:



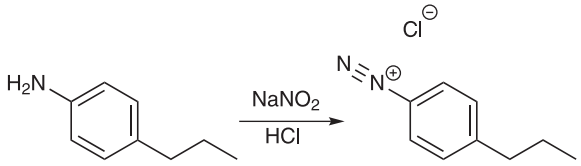
9.24 The desired transformation is a Friedel–Crafts acylation reaction at the *para* position, relative to an *ortho–para* director. Unfortunately, an acid halide (the reagent for a Friedel–Crafts acylation) will react with the amino group. We can circumvent this problem by first converting the amino group into an amide group. Then, we can perform the desired Friedel–Crafts acylation, followed by converting the amide group back into an amino group:



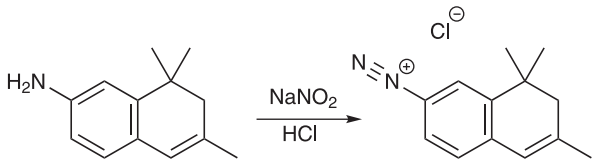
9.25 If we try direct chlorination of the starting material, we will obtain a trichlorinated product, because the *ortho* positions and *para* position are all activated, and the ring is very reactive. To achieve monochlorination rather than polychlorination, we can first convert the amino group into an amide group, thereby making the ring less activated. Chlorination of this compound will install a chlorine atom in the *para* position, and finally, the amide group can be hydrolyzed to convert it back into an amino group:



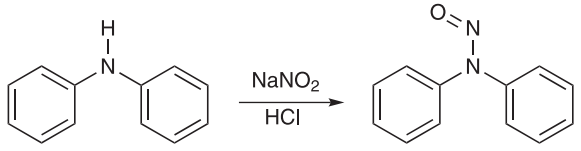
9.27 The starting material is a primary amine, and the reagents indicate an *in situ* preparation of nitrous acid (HONO). Under these conditions, a primary amine is converted into a diazonium salt:



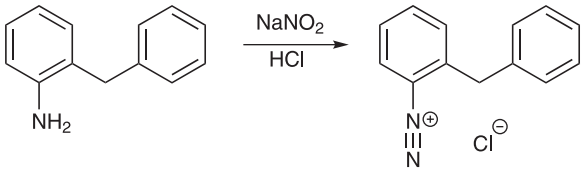
9.28 The starting material is a primary amine, and the reagents indicate an *in situ* preparation of nitrous acid (HONO). Under these conditions, a primary amine is converted into a diazonium salt:



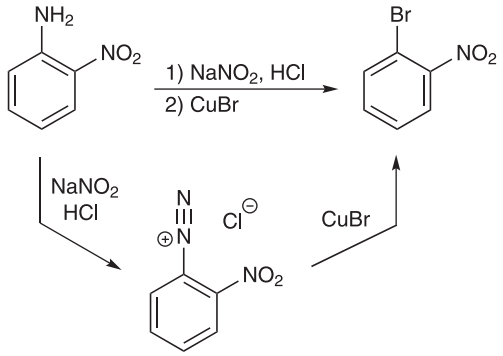
9.29 The starting material is a secondary amine, and the reagents indicate an *in situ* preparation of nitrous acid (HONO). Under these conditions, a secondary amine is converted into a nitrosamine:



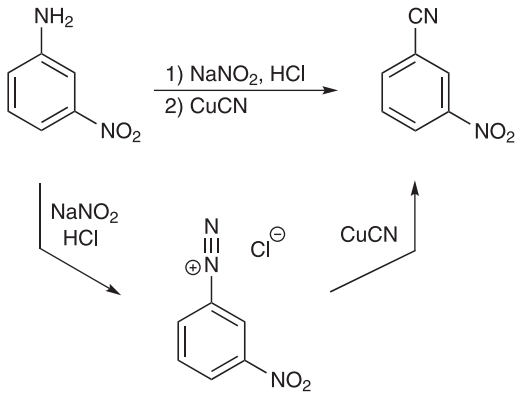
9.30 The starting material is a primary amine, and the reagents indicate an *in situ* preparation of nitrous acid (HONO). Under these conditions, a primary amine is converted into a diazonium salt:



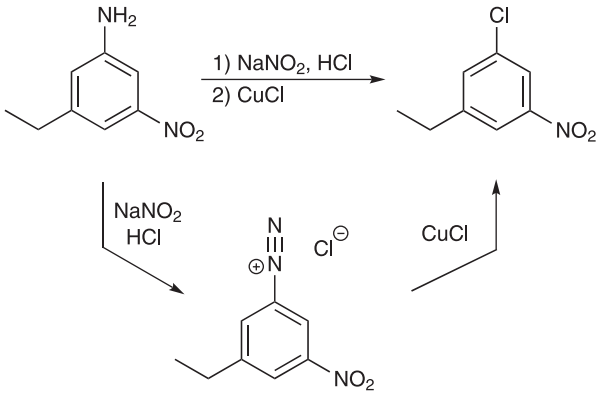
9.32 The starting material is a disubstituted aromatic ring where one of the substituents is an amino group. This amino group must be replaced with a bromine atom. This transformation can be achieved by first converting the starting material into a diazonium salt, and then using a Sandmeyer reaction to convert the diazonium salt into the desired product.



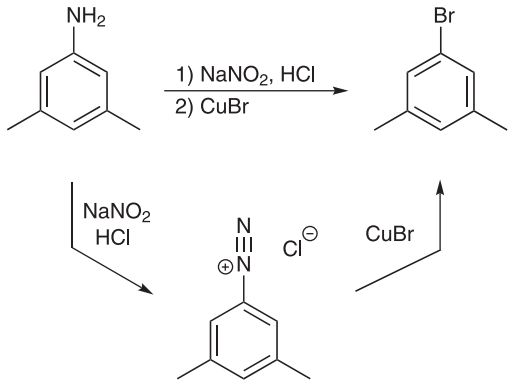
9.33 The starting material is a disubstituted aromatic ring where one of the substituents is an amino group. This amino group must be replaced with a cyano group. This transformation can be achieved by first converting the starting material into a diazonium salt, and then using a Sandmeyer reaction to convert the diazonium salt into the desired product.



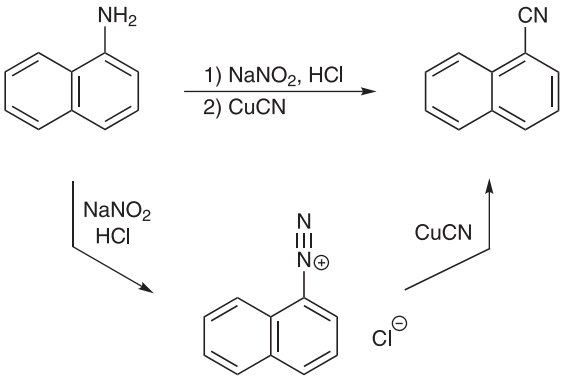
9.34 The starting material is a trisubstituted aromatic ring where one of the substituents is an amino group. This amino group must be replaced with a chlorine atom. This transformation can be achieved by first converting the starting material into a diazonium salt, and then using a Sandmeyer reaction to convert the diazonium salt into the desired product.



9.35 The starting material is a trisubstituted aromatic ring where one of the substituents is an amino group. This amino group must be replaced with a bromine atom. This transformation can be achieved by first converting the starting material into a diazonium salt, and then using a Sandmeyer reaction to convert the diazonium salt into the desired product.

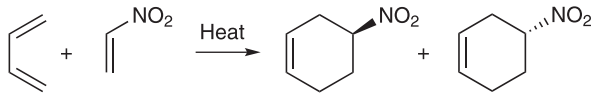


9.36 The starting material is an aromatic compound where one of the substituents is an amino group. This amino group must be replaced with a cyano group. This transformation can be achieved by first converting the starting material into a diazonium salt, and then using a Sandmeyer reaction to convert the diazonium salt into the desired product.

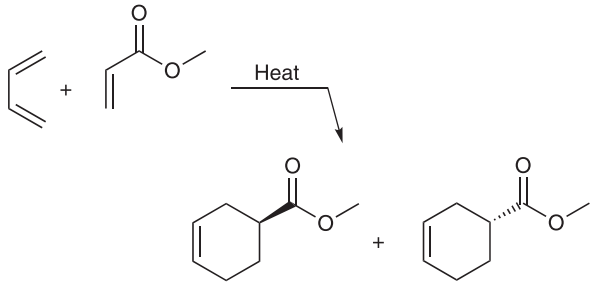


CHAPTER 10

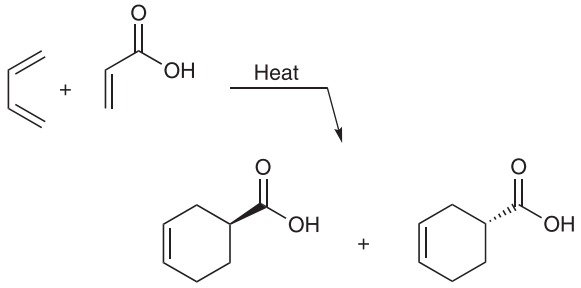
10.1 This is a Diels–Alder reaction between 1,3-butadiene and a monosubstituted ethylene, so the product will have one chiral center. Since the starting materials are achiral, the product is a racemic mixture:



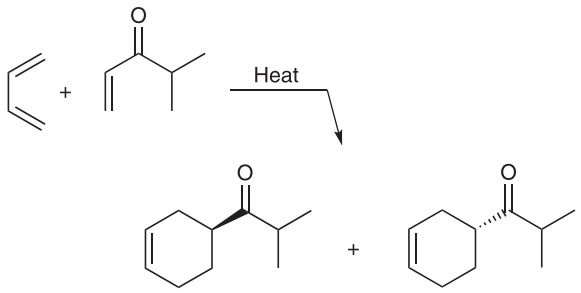
10.2 This is a Diels–Alder reaction between 1,3-butadiene and a monosubstituted ethylene, so the product will have one chiral center. Since the starting materials are achiral, the product is a racemic mixture:



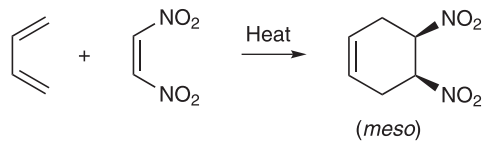
10.3 This is a Diels–Alder reaction between 1,3-butadiene and a monosubstituted ethylene, so the product will have one chiral center. Since the starting materials are achiral, the product is a racemic mixture:



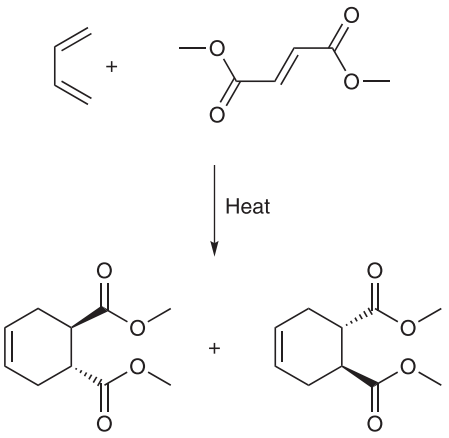
10.4 This is a Diels–Alder reaction between 1,3-butadiene and a monosubstituted ethylene, so the product will have one chiral center. Since the starting materials are achiral, the product is a racemic mixture:



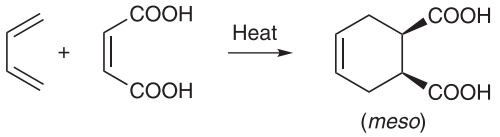
10.5 This is a Diels–Alder reaction between 1,3-butadiene and a *cis*-disubstituted ethylene. Notice that the configuration of the dienophile is preserved in the product, so the product is *cis*-disubstituted. Since the product has a plane of symmetry, it is a *meso* compound and has no enantiomers:



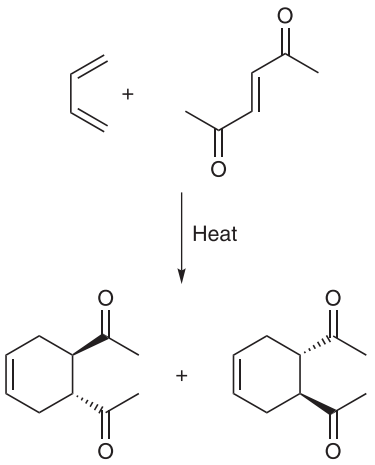
10.6 This is a Diels–Alder reaction between 1,3-butadiene and a *trans*-disubstituted ethylene. Notice that the configuration of the dienophile is preserved in the product, so the product is *trans*-disubstituted. A racemic mixture of enantiomers is expected, as shown:



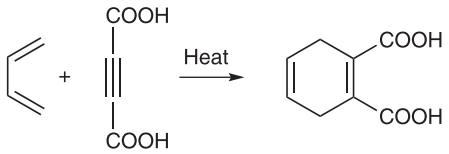
10.7 This is a Diels–Alder reaction between 1,3-butadiene and a *cis*-disubstituted ethylene. Notice that the configuration of the dienophile is preserved in the product, so the product is *cis*-disubstituted. Since the product has a plane of symmetry, it is a *meso* compound and has no enantiomers:



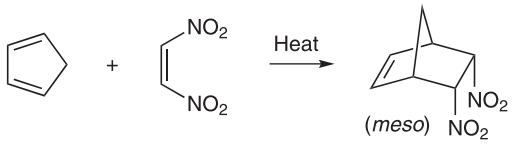
10.8 This is a Diels–Alder reaction between 1,3-butadiene and a *trans*-disubstituted ethylene. Notice that the configuration of the dienophile is preserved in the product, so the product is *trans*-disubstituted. A racemic mixture of enantiomers is expected, as shown:



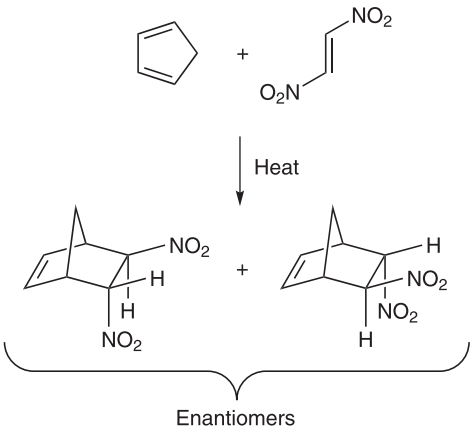
10.9 This is a Diels–Alder reaction between 1,3-butadiene and a disubstituted alkyne. Notice that the product has no chiral centers, and only one product is obtained:



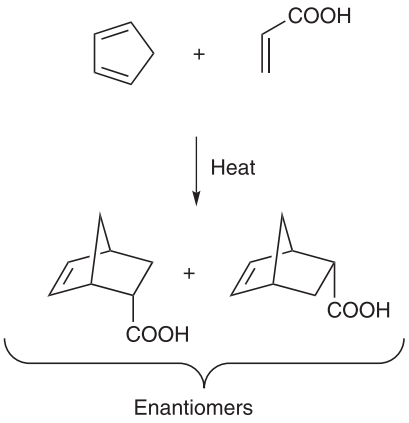
10.11 This is a Diels–Alder reaction involving cyclopentadiene, so we expect the product to have a bicyclic skeleton. The dienophile is *cis*-disubstituted, so the product must be *cis*-disubstituted. Notice that both substituents occupy *endo* positions. Since the product has a plane of symmetry, it is a *meso* compound and has no enantiomers:



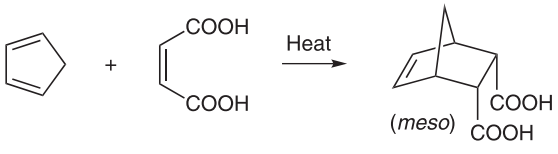
10.12 This is a Diels–Alder reaction involving cyclopentadiene, so we expect the product to have a bicyclic skeleton. The dienophile is *trans*-disubstituted, so the product must be *trans*-disubstituted. A mixture of enantiomers is obtained:



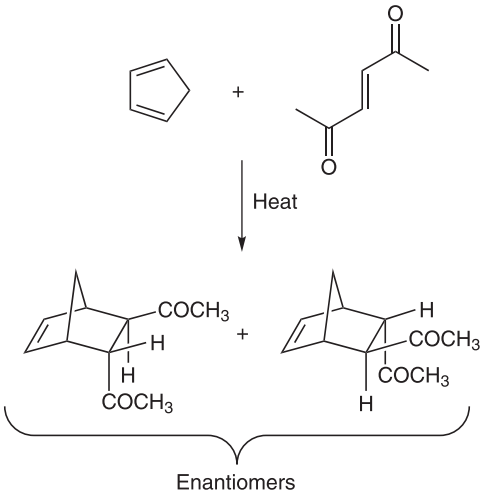
10.13 This is a Diels–Alder reaction involving cyclopentadiene, so we expect the product to have a bicyclic skeleton. The dienophile is a monosubstituted ethylene, so we expect the following pair of enantiomers. Notice that the substituent occupies an *endo* position in each enantiomer.



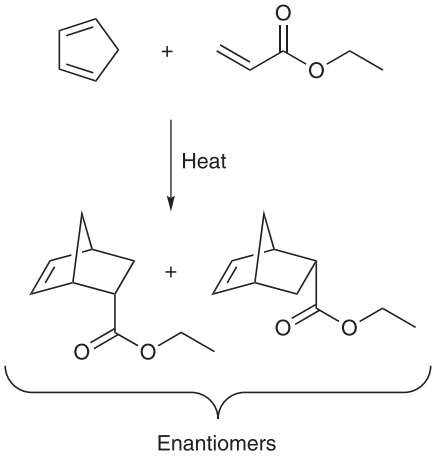
10.14 This is a Diels–Alder reaction involving cyclopentadiene, so we expect the product to have a bicyclic skeleton. The dienophile is *cis*-disubstituted, so the product must be *cis*-disubstituted. Notice that both substituents occupy *endo* positions. Since the product has a plane of symmetry, it is a *meso* compound and has no enantiomers:



10.15 This is a Diels–Alder reaction involving cyclopentadiene, so we expect the product to have a bicyclic skeleton. The dienophile is *trans*-disubstituted, so the product must be *trans*-disubstituted. A mixture of enantiomers is obtained:



10.16 This is a Diels–Alder reaction involving cyclopentadiene, so we expect the product to have a bicyclic skeleton. The dienophile is a monosubstituted ethylene, so we expect the following pair of enantiomers. Notice that the substituent occupies an *endo* position in each enantiomer.



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