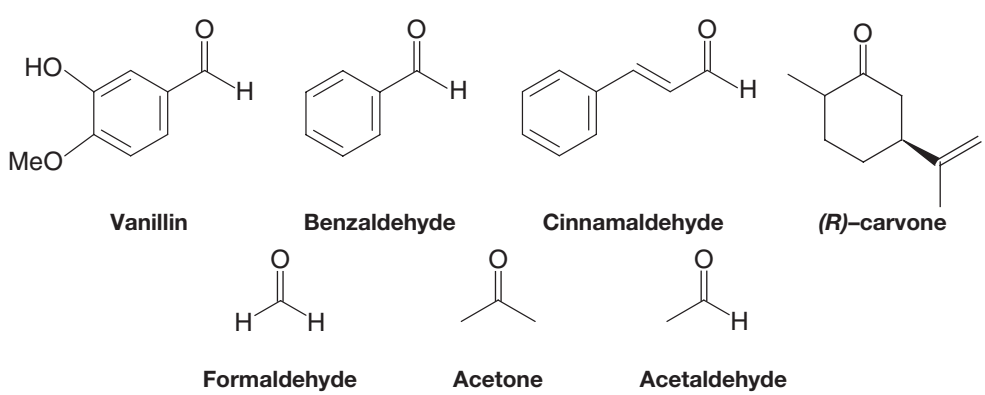
CHAPTER

16

Aldehydes and Ketones

NUCLEOPHILIC ADDITION TO THE CARBONYL GROUP

You may not know it, but you already have experience with aldehydes and ketones based on things you have likely smelled and tasted. Vanillin is responsible for the smell of vanilla, while almond flavor results from benzaldehyde, cinnamon from cinnamaldehyde, and spearmint from (*R*)-carvone. Other odors and sensations that are far less pleasant can also be caused by aldehydes and ketones—for example, the pungent odor of formaldehyde or acetone, or the hangover caused by acetaldehyde that results from drinking too many alcoholic beverages.



Vanillin **Benzaldehyde** **Cinnamaldehyde** ***(R)*–carvone**

Formaldehyde **Acetone** **Acetaldehyde**

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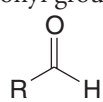
IN THIS CHAPTER WE WILL CONSIDER:

- the structure and reactivity of aldehydes and ketones
- methods for their synthesis from other functional groups
- unique functional groups that can arise from aldehydes and ketones that have special reactivity of their own

[WHY DO THESE TOPICS MATTER?] At the end of the chapter, we will show how some of the functional groups that can be obtained from aldehydes and ketones provide a triggering device that sea sponges use in molecules meant to kill or injure predators. Amazingly, these same molecules and functional groups provide a potential treatment for various forms of human cancer.

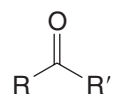
16.1 INTRODUCTION

- Aldehydes have a **carbonyl group** bonded to a carbon atom on one side and a hydrogen atom on the other side. (Formaldehyde is an exception because it has hydrogen atoms on both sides.)
- Ketones have a carbonyl group bonded to carbon atoms on both sides.



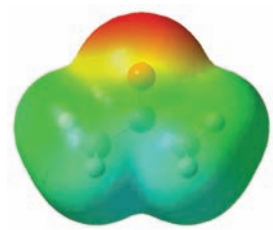
RCHO

General formulas for aldehydes



RCOR′

General formulas for ketones



Acetone

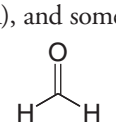
Although earlier chapters have given us some insight into the chemistry of carbonyl compounds, we shall now consider their chemistry in detail. The reason: the chemistry of the carbonyl group is central to the chemistry of most of the chapters that follow.

In this chapter we focus our attention on the preparation of aldehydes and ketones, their physical properties, and especially *nucleophilic addition reactions at their carbonyl groups*.

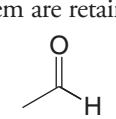
16.2 NOMENCLATURE OF ALDEHYDES AND KETONES

- Aliphatic aldehydes are named substitutively in the IUPAC system by replacing the final **-e** of the name of the corresponding alkane with **-al**.

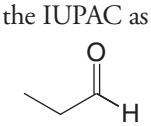
Since the aldehyde group must be at an end of the carbon chain, there is no need to indicate its position. When other substituents are present the carbonyl group carbon is assigned position 1. Many aldehydes also have common names; these are given below in parentheses. These common names are derived from the common names for the corresponding carboxylic acids (Section 17.2A), and some of them are retained by the IUPAC as acceptable names.



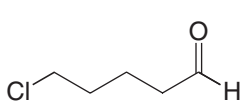
Methanal (formaldehyde)



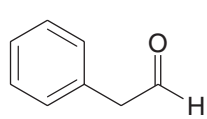
Ethanal (acetaldehyde)



Propanal (propionaldehyde)

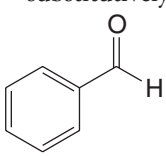


5-Chloropentanal

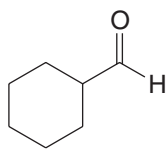


Phenylethanal (phenylacetaldehyde)

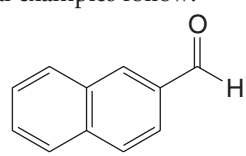
- Aldehydes in which the —CHO group is attached to a ring system are named substitutively by adding the suffix **carbaldehyde**. Several examples follow:



Benzenecarbaldehyde (benzaldehyde)



Cyclohexanecarbaldehyde

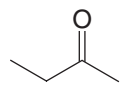


2-Naphthalenecarbaldehyde

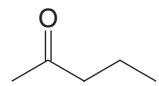
The common name *benzaldehyde* is far more frequently used than benzenecarbaldehyde for C_6H_5CHO, and it is the name we shall use in this text.

- Aliphatic ketones are named substitutively by replacing the final **-e** of the name of the corresponding alkane with **-one**.

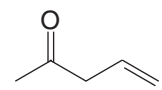
The chain is then numbered in the way that gives the carbonyl carbon atom the lower possible number, and this number is used to designate its position.



Butanone
(ethyl methyl ketone)



2-Pentanone
(methyl propyl ketone)

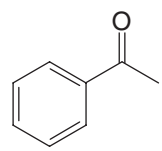


Pent-4-en-2-one
(not 1-penten-4-one)
(allyl methyl ketone)

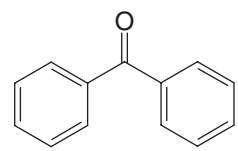
Common functional group names for ketones (in parentheses above) are obtained simply by separately naming the two groups attached to the carbonyl group and adding the word **ketone** as a separate word.

Some ketones have common names that are retained in the IUPAC system:

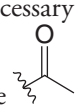
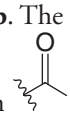
Acetone
(propanone)

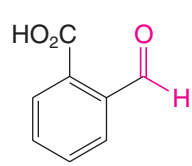


Acetophenone
(1-phenylethanone
or methyl phenyl ketone)



Benzophenone
(diphenylmethanone
or diphenyl ketone)

When it is necessary to name the  group as a prefix, it is the **methanoyl** or **formyl group**. The  group is called the **ethanoyl** or **acetyl group** (often abbreviated as Ac). When  groups are named as substituents, they are called **alkanoyl** or **acyl groups**.



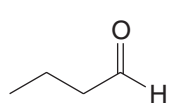
2-Methanoylbenzoic acid
(*o*-formylbenzoic acid)

4-Ethanoylbenzenesulfonic acid
(*p*-acetylbenzenesulfonic acid)

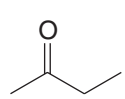
SOLVED PROBLEM 16.1

Write bond-line formulas for three isomeric compounds that contain a carbonyl group and have the molecular formula C_4H_8O. Then give their IUPAC names.

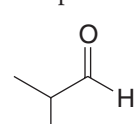
STRATEGY AND ANSWER: Write the formulas and then name the compounds.



Butanal



Butanone



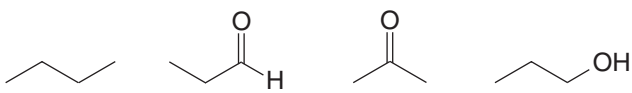
2-Methylpropanal

PRACTICE PROBLEM 16.1

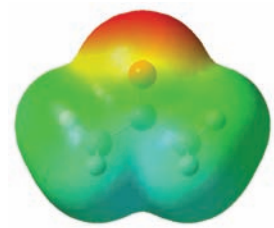
(a) Give IUPAC substitutive names for the seven isomeric aldehydes and ketones with the formula $C_5H_{10}O$. **(b)** Give structures and names (common or IUPAC substitutive names) for all the aldehydes and ketones that contain a benzene ring and have the formula C_8H_8O.

16.3 PHYSICAL PROPERTIES

The carbonyl group is a polar group; therefore, aldehydes and ketones have higher boiling points than hydrocarbons of the same molecular weight. However, since aldehydes and ketones cannot have strong hydrogen bonds *between their molecules*, they have lower boiling points than the corresponding alcohols. The following compounds that have similar molecular weights exemplify this trend:



Butane	Propanal	Acetone	1-Propanol
bp −0.5 °C	bp 49 °C	bp 56.1 °C	bp 97.2 °C
(MW = 58)	(MW = 58)	(MW = 58)	(MW = 60)



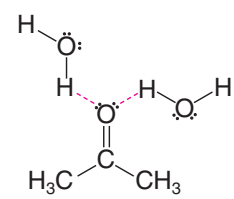
A map of electrostatic potential for acetone shows the polarity of the carbonyl C═O bond.

PRACTICE PROBLEM 16.2

Which compound in each of the following pairs has the higher boiling point? (Answer this problem without consulting tables.)

(a) Pentanal or 1-pentanol
(b) 2-Pentanone or 2-pentanol
(c) Pentane or pentanal
(d) Acetophenone or 2-phenylethanol
(e) Benzaldehyde or benzyl alcohol

The carbonyl oxygen atom allows molecules of aldehydes and ketones to form strong hydrogen bonds to molecules of water. As a result, low-molecular-weight aldehydes and ketones show appreciable solubilities in water. Acetone and acetaldehyde are soluble in water in all proportions.

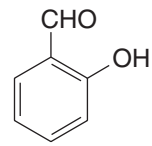


Hydrogen bonding (shown in red) between water molecules and acetone

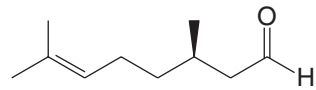
TABLE 16.1 PHYSICAL PROPERTIES OF ALDEHYDES AND KETONES

Formula	Name	mp (°C)	bp (°C)	Solubility in Water
HCHO	Formaldehyde	−92	−21	Very soluble
CH_3CHO	Acetaldehyde	−125	21	∞
CH_3CH_2CHO	Propanal	−81	49	Very soluble
$CH_3(CH_2)_2CHO$	Butanal	−99	76	Soluble
$CH_3(CH_2)_3CHO$	Pentanal	−92	102	Slightly soluble
$CH_3(CH_2)_4CHO$	Hexanal	−51	131	Slightly soluble
C_6H_5CHO	Benzaldehyde	−26	178	Slightly soluble
$C_6H_5CH_2CHO$	Phenylacetaldehyde	33	193	Slightly soluble
CH_3COCH_3	Acetone	−95	56.1	∞
$CH_3COCH_2CH_3$	Butanone	−86	80	Very soluble
$CH_3COCH_2CH_2CH_3$	2-Pentanone	−78	102	Soluble
$CH_3CH_2COCH_2CH_3$	3-Pentanone	−39	102	Soluble
$C_6H_5COCH_3$	Acetophenone	21	202	Insoluble
$C_6H_5COC_6H_5$	Benzophenone	48	306	Insoluble

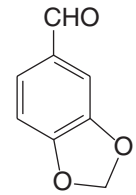
Table 16.1 lists the physical properties of a number of common aldehydes and ketones. Some aldehydes obtained from natural sources have very pleasant fragrances. The following are some in addition to those we mentioned at the beginning of this chapter.



Salicylaldehyde (from meadowsweet)



Citronellal (the scent of lemon in certain plants)



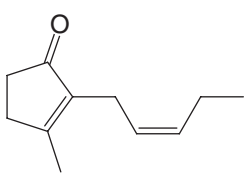
Piperonal (made from safrole; odor of heliotrope)

THE CHEMISTRY OF... Aldehydes and Ketones in Perfumes

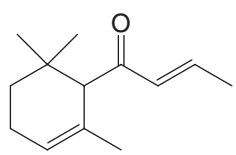
Many aldehydes and ketones have pleasant fragrances and, because of this, they have found use in perfumes. Originally, the ingredients for perfumes came from natural sources such as essential oils (Section 23.3), but with the development of synthetic organic chemistry in the nineteenth century, many ingredients now used in perfumes result from the creativity of laboratory chemists.

Practitioners of the perfumer's art, those who blend perfumes, talk of their ingredients in a language derived from music. The cabinet that holds the bottles containing the compounds that the perfumer blends is called an "organ." The ingredients themselves are described as having certain "notes." For example, highly volatile substances are said to display "head notes," those less volatile and usually associated with flowers are said to have "heart notes," and the least volatile ingredients, usually with woody, balsamic, or musklike aromas, are described as "base notes."*

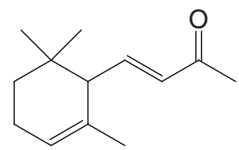
(*Z*)-Jasmone (with the odor of jasmine) and α-damascone (odor of roses) have "heart notes," as do the ionones (with the odor of violets). All of these ketones can be obtained from natural sources.



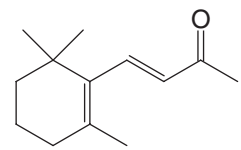
***Z*-Jasmone**



α-Damascone

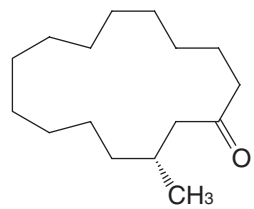


α-Ionone

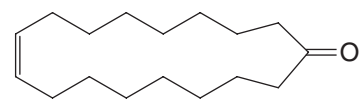


β-Ionone

Two ketones from exotic natural sources are muscone (from the Himalayan musk deer) and civetone (from the African civet cat).



Muscone



Civetone

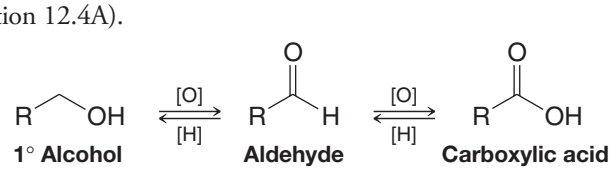
Stereochemistry has a marked influence on odors. For example, the (*R*)-enantiomer of muscone (depicted above) is described as having a "rich and powerful musk," whereas the (*S*)-enantiomer is described as being "poor and less strong." The (*R*)-enantiomer of α-damascone has a rose petal odor with more apple and fruitier notes than the (*S*)-enantiomer.

*For an in-depth discussion of the perfume industry, see Fortineau, A.-D. "Chemistry Perfumes Your Daily Life," *J. Chem. Educ.*, **2004**, *81*, 45–50.

16.4 SYNTHESIS OF ALDEHYDES

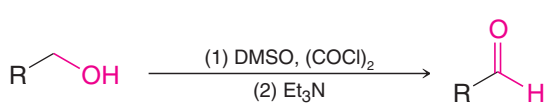
16.4A Aldehydes by Oxidation of 1° Alcohols

- The oxidation state of an aldehyde lies between that of a 1° alcohol and a carboxylic acid (Section 12.4A).

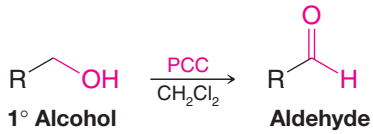


1° Alcohol **Aldehyde** **Carboxylic acid**

Aldehydes can be prepared from 1° alcohols by the Swern oxidation (Section 12.4B) and oxidation with pyridinium chlorochromate ($C_5H_5\overset{+}{N}HCrO_3Cl^-$, or PCC, Section 12.4D):



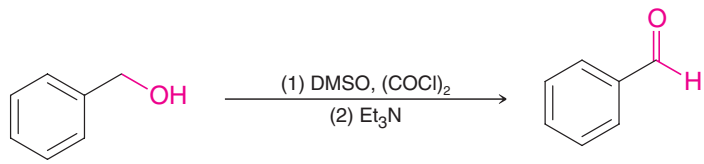
Swern oxidation of a 1° alcohol to an aldehyde.



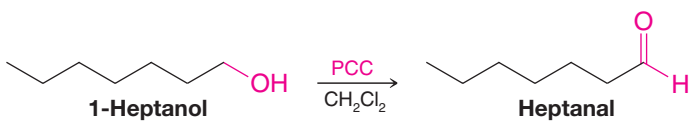
1° Alcohol — Aldehyde

PCC oxidation of a 1° alcohol to an aldehyde

The following are examples of the use of the Swern oxidation and PCC in the synthesis of aldehydes.



Benzyl alcohol — **Benzaldehyde**

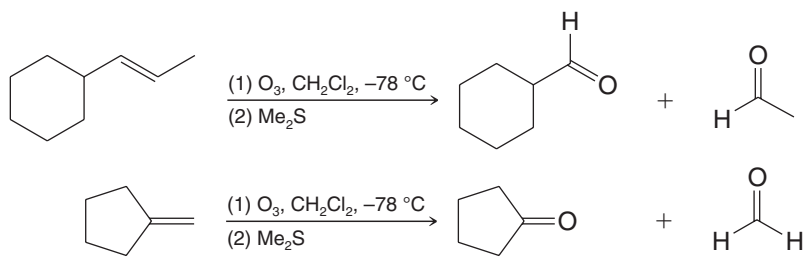


1-Heptanol — **Heptanal**

16.4B Aldehydes by Ozonolysis of Alkenes

- Alkenes can be cleaved by ozonolysis of their double bond (Section 8.17B). The products are aldehydes and ketones.

In Chapter 8 we also saw how this procedure has utility in structure determination. The following examples illustrate the synthesis of aldehydes by ozonolysis of alkenes.

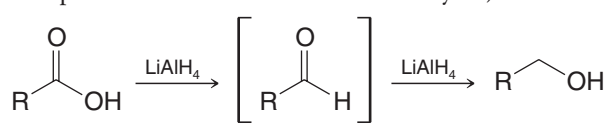


16.4C Aldehydes by Reduction of Acyl Chlorides, Esters, and Nitriles

Theoretically, it ought to be possible to prepare aldehydes by reduction of carboxylic acids. In practice, this is not possible with the reagent normally used to reduce a carboxylic acid, lithium aluminum hydride ($LiAlH_4$ or LAH).

- When any carboxylic acid is treated with LAH, it is reduced all the way to the 1° alcohol.
- This happens because LAH is a very powerful reducing agent and aldehydes are very easily reduced.

Any aldehyde that might be formed in the reaction mixture is immediately reduced by LAH to the 1° alcohol. (It does not help to use a stoichiometric amount of LAH, because as soon as the first few molecules of aldehyde are formed in the mixture, there will still be much unreacted LAH present and it will reduce the aldehyde.)



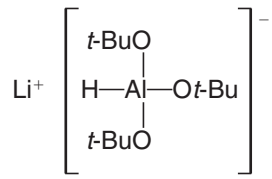
Carboxylic acid — **Aldehyde** — **1° Alcohol**

The secret to success here is not to use a carboxylic acid itself, but to use a derivative of a carboxylic acid that is more easily reduced, and an aluminum hydride derivative that is less reactive than LAH.

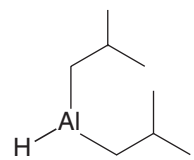
- Acyl chlorides (RCOCl), esters (RCO_2R'), and nitriles (RCN) are all easily prepared from carboxylic acids (Chapter 17), and they all are more easily reduced.

(Acyl chlorides, esters, and nitriles all also have the same oxidation state as carboxylic acids. Convince yourself of this by applying the principles that you learned in Section 12.2A).

- Two derivatives of aluminum hydride that are less reactive than LAH, in part because they are much more sterically hindered, are **lithium tri-*tert*-butoxyaluminum hydride** and **diisobutylaluminum hydride (DIBAL-H)**:

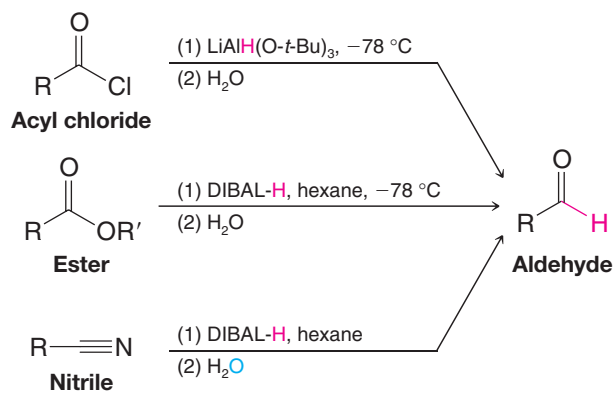


Lithium tri-*tert*-butoxyaluminum hydride



Diisobutylaluminum hydride (abbreviated *i*-Bu_2AlH or DIBAL-H)

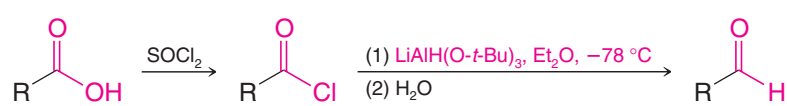
- The following scheme summarizes how lithium tri-*tert*-butoxyaluminum hydride and DIBAL-H can be used to synthesize aldehydes from acid derivatives:



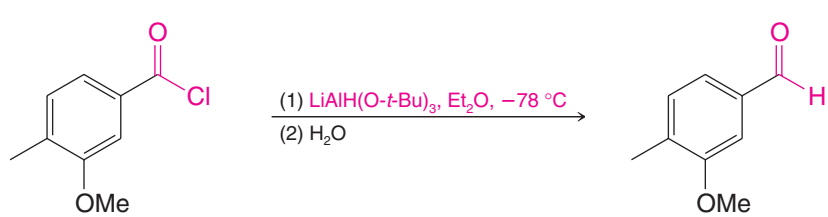
We now examine each of these aldehyde syntheses in more detail.

Aldehydes from Acyl Chlorides: RCOCl → RCHO

- Acyl chlorides can be reduced to aldehydes by treating them with $LiAlH[OC(CH_3)_3]_3$, lithium tri-*tert*-butoxyaluminum hydride, at −78 °C.
- Carboxylic acids can be converted to acyl chlorides by using $SOCl_2$ (see Section 15.7).



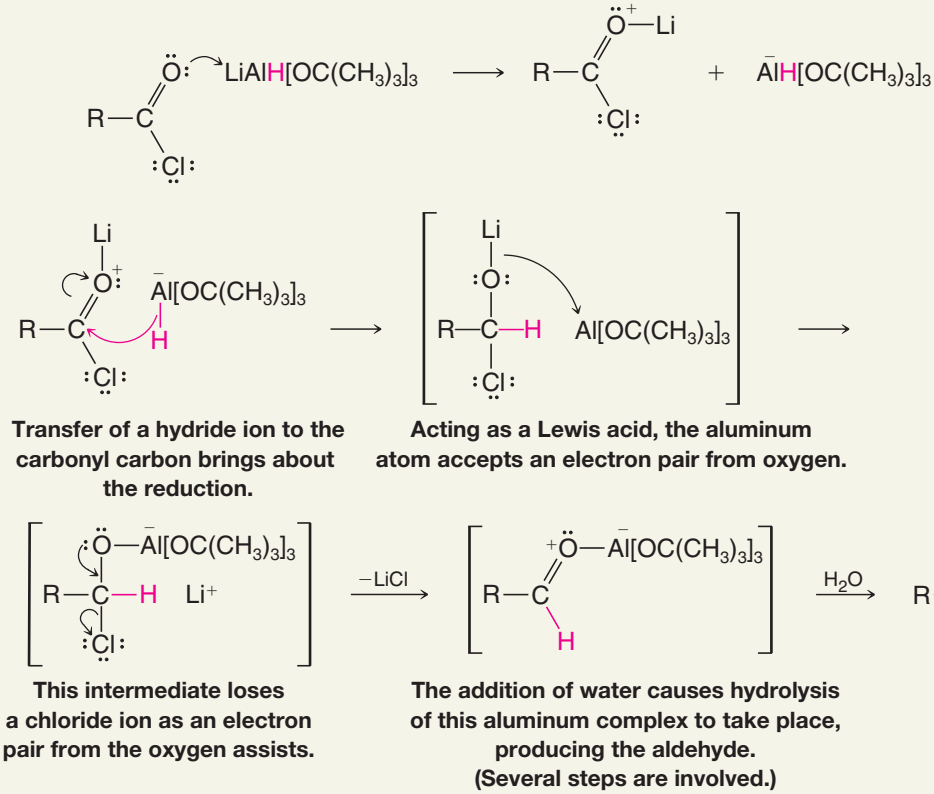
The following is a specific example:



3-Methoxy-4-methylbenzoyl chloride **3-Methoxy-4-methylbenzaldehyde**

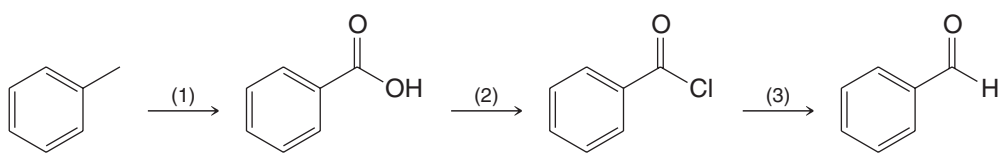
Mechanistically, the reduction is brought about by the transfer of a hydride ion from the aluminum atom to the carbonyl carbon of the acyl chloride (see Section 12.3). Subsequent hydrolysis frees the aldehyde.

A MECHANISM FOR THE REACTION — Reduction of an Acyl Chloride to an Aldehyde



SOLVED PROBLEM 16.2

Provide the reagents for transformations (1), (2), and (3).



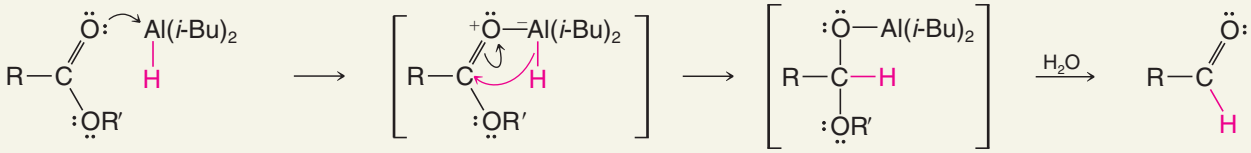
STRATEGY AND ANSWER: In (1), we must oxidize methylbenzene to benzoic acid. To do this we use hot potassium permanganate in a basic solution followed by an acidic workup (see Section 15.13C). For (2), we must convert a carboxylic acid to an acid chloride. For this transformation we use thionyl chloride or phosphorus pentachloride (see Section 15.7). For (3), we must reduce an acid chloride to an aldehyde. For this we use lithium tri-*tert*-butoxyaluminum hydride (see above).

Aldehydes from Esters and Nitriles: $RCO_2R' \rightarrow RCHO$ and $RC{\equiv}N \rightarrow RCHO$

- Both esters and nitriles can be reduced to aldehydes by DIBAL-H.

Carefully controlled amounts of DIBAL-H must be used to avoid overreduction, and the ester reduction must be carried out at low temperatures. Both reductions result in the formation of a relatively stable intermediate by the addition of a hydride ion to the carbonyl carbon of the ester or to the carbon of the $-C{\equiv}N$ group of the nitrile. Hydrolysis of the intermediate liberates the aldehyde. Schematically, the reactions can be viewed in the following way:

A MECHANISM FOR THE REACTION — Reduction of an Ester to an Aldehyde

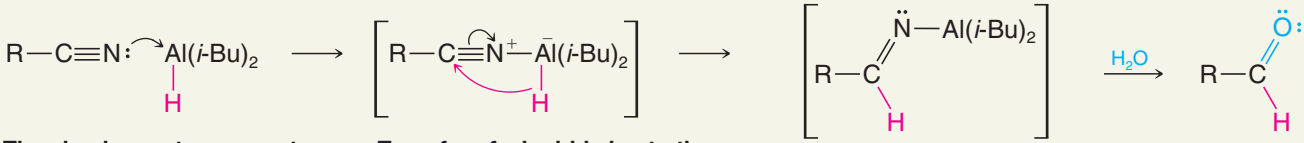


The aluminum atom accepts an electron pair from the carbonyl oxygen atom in a Lewis acid-base reaction.

Transfer of a hydride ion to the carbonyl carbon brings about its reduction.

Addition of water at the end of the reaction hydrolyzes the aluminum complex and produces the aldehyde.

A MECHANISM FOR THE REACTION — Reduction of a Nitrile to an Aldehyde

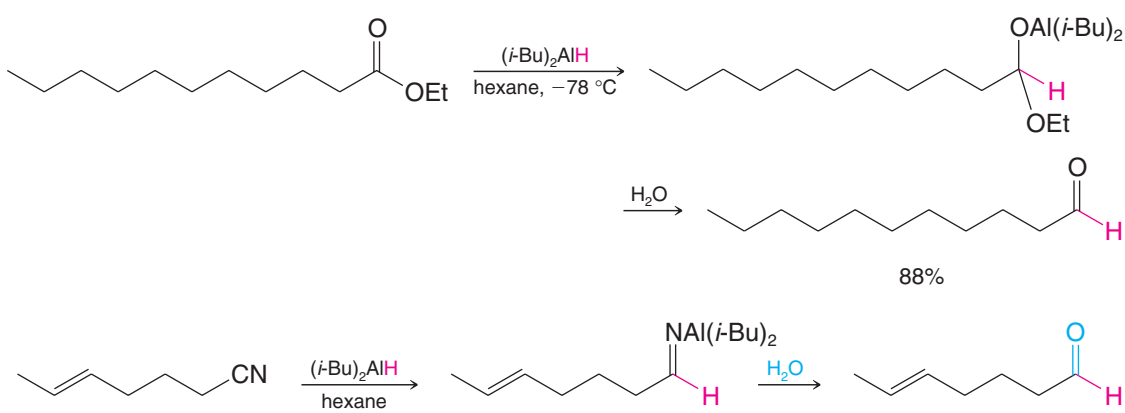


The aluminum atom accepts an electron pair from the nitrile in a Lewis acid–base reaction.

Transfer of a hydride ion to the nitrile carbon brings about its reduction.

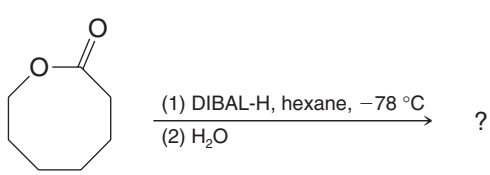
Addition of water at the end of the reaction hydrolyzes the aluminum complex and produces the aldehyde. (Several steps are involved. See Section 16.8 relating to imines.)

The following specific examples illustrate these syntheses:

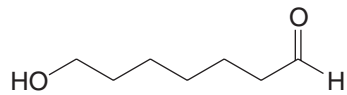


SOLVED PROBLEM 16.3

What is the product of the following reaction?

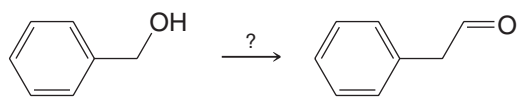


STRATEGY AND ANSWER: The starting compound is a cyclic ester, so the product would be an aldehyde that also contains an alcohol hydroxyl group.

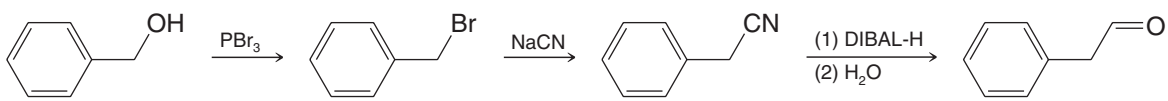


SOLVED PROBLEM 16.4

Starting with benzyl alcohol, outline a synthesis of phenylethanal.



STRATEGY AND ANSWER: Convert the benzyl alcohol to benzyl bromide with PBr_3, then replace the bromine by cyanide in an S_N2 reaction. Lastly, reduce the nitrile to phenylethanal.



PRACTICE PROBLEM 16.3

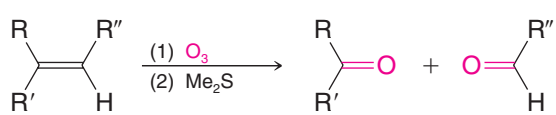
Show how you would synthesize propanal from each of the following: **(a)** 1-propanol and **(b)** propanoic acid ($CH_3CH_2CO_2H$).

16.5 SYNTHESIS OF KETONES

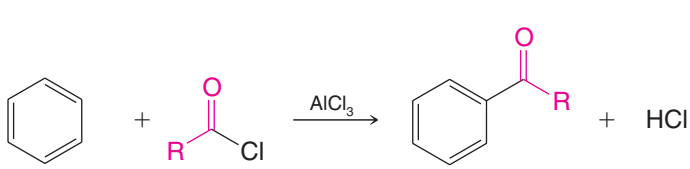
16.5A Ketones from Alkenes, Arenes, and 2° Alcohols

We have seen three laboratory methods for the preparation of ketones in earlier chapters:

1. Ketones (and aldehydes) by ozonolysis of alkenes (discussed in Section 8.17B).



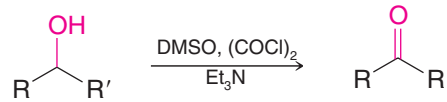
2. Ketones from arenes by Friedel–Crafts acylations (discussed in Section 15.7). For example:



Alternatively,

A diaryl ketone

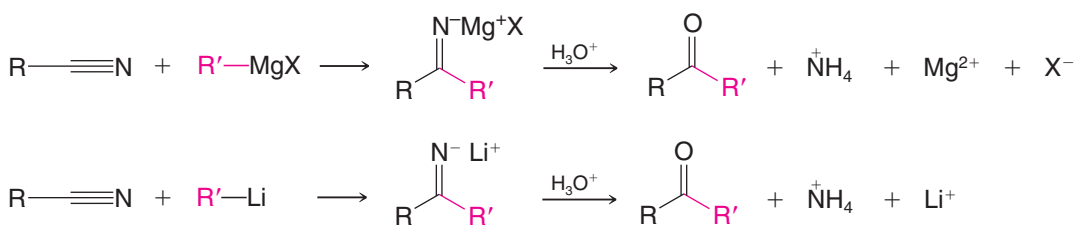
3. Ketones from secondary alcohols by Swern oxidation and other methods (discussed in Section 12.4):



16.5B Ketones from Nitriles

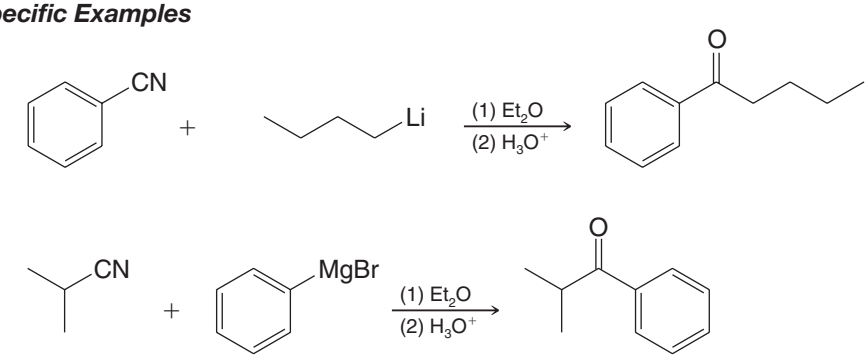
Treating a nitrile (R—C≡N) with either a Grignard reagent or an organolithium reagent followed by hydrolysis yields a ketone.

General Reactions



The mechanism for the acidic hydrolysis step is the reverse of one that we shall study for imine formation in Section 16.8A.

Specific Examples



2-Cyanopropane

2-Methyl-1-phenylpropanone (isopropyl phenyl ketone)

Even though a nitrile has a triple bond, addition of the Grignard or lithium reagent takes place only once. The reason: if addition took place twice, this would place a double negative charge on the nitrogen.

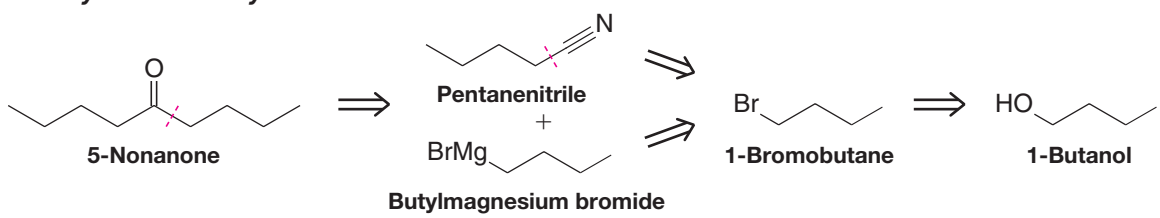
(The dianion does not form.)

SOLVED PROBLEM 16.5

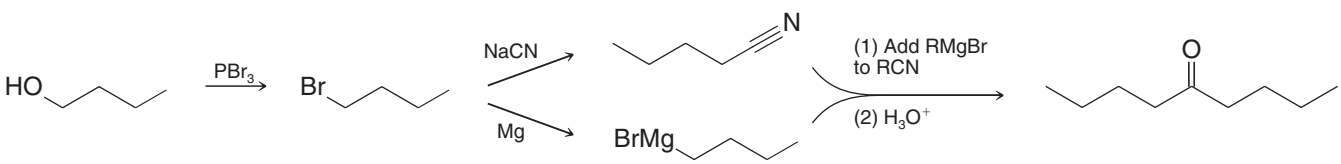
ILLUSTRATING A MULTISTEP SYNTHESIS: With 1-butanol as your only organic starting compound, devise a synthesis of 5-nonanone. Begin by writing a retrosynthetic analysis.

ANSWER: Retrosynthetic disconnection of 5-nonanone suggests butylmagnesium bromide and pentanenitrile as immediate precursors. Butylmagnesium bromide can, in turn, be synthesized from 1-bromobutane. Pentanenitrile can also be synthesized from 1-bromobutane, via S_N2 reaction of 1-bromobutane with cyanide. To begin the synthesis, 1-bromobutane can be prepared from 1-butanol by reaction with phosphorus tribromide.

Retrosynthetic Analysis



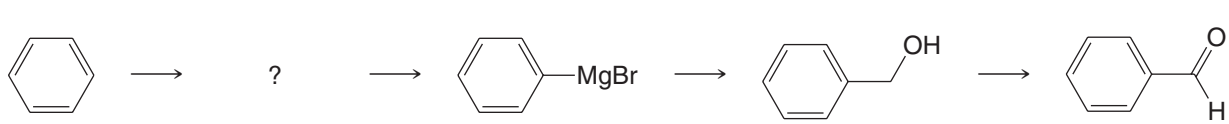
Synthesis



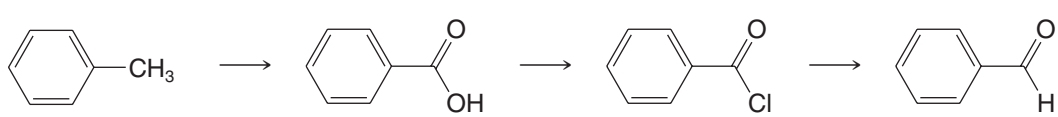
PRACTICE PROBLEM 16.4

Provide the reagents and indicated intermediates in each of the following syntheses.

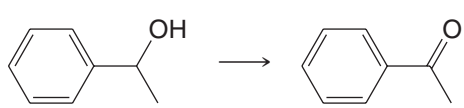
(a)



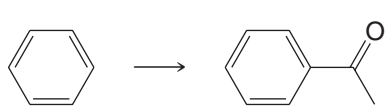
(b)



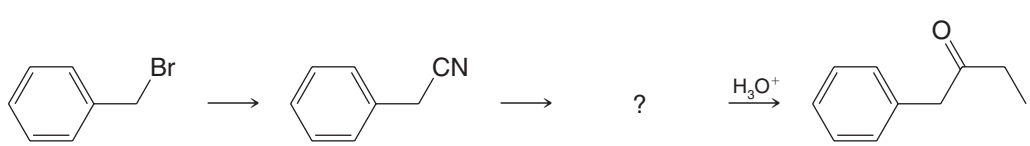
(c)



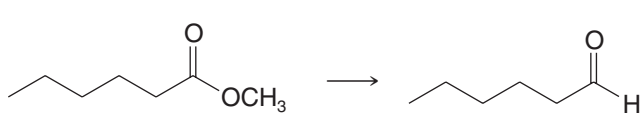
(d)



(e)



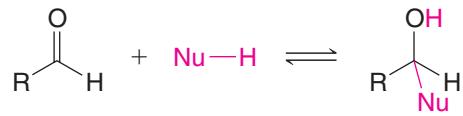
(f)



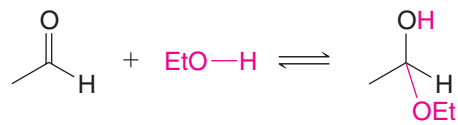
16.6 NUCLEOPHILIC ADDITION TO THE CARBON–OXYGEN DOUBLE BOND

- The most characteristic reaction of aldehydes and ketones is *nucleophilic addition* to the carbon–oxygen double bond.

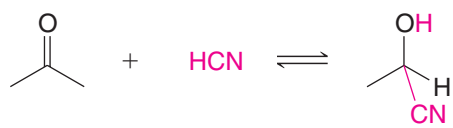
General Reaction



Specific Examples

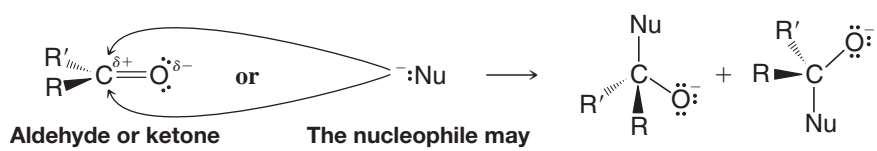


A hemiacetal (see Section 16.7)



A cyanohydrin (see Section 16.9)

Aldehydes and ketones are especially susceptible to nucleophilic addition because of the structural features that we discussed in Section 12.1 and that are shown below.



Aldehyde or ketone (R or R′ may be H) **The nucleophile may attack from above or below.**

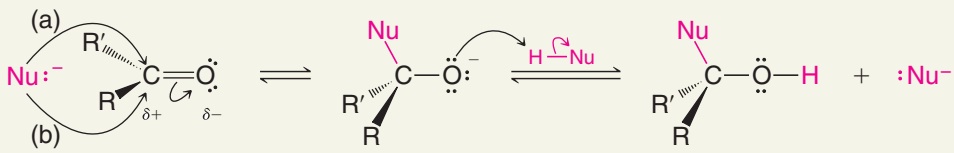
- The trigonal planar arrangement of groups around the carbonyl carbon atom means that the carbonyl carbon atom is relatively open to attack from above or below the plane of the carbonyl group (see above).
- The positive charge on the carbonyl carbon atom means that it is especially susceptible to attack by a nucleophile.
- The negative charge on the carbonyl oxygen atom means that nucleophilic addition is susceptible to acid catalysis.

Nucleophilic addition to the carbon–oxygen double bond occurs, therefore, in either of two general ways.

1. **When the reagent is a strong nucleophile** (Nu:$^-$), addition usually takes place in the following way (see the mechanism box on the following page), converting the trigonal planar aldehyde or ketone into a tetrahedral product.

   In this type of addition the nucleophile uses its electron pair to form a bond to the carbonyl carbon atom. As this happens the electron pair of the carbon–oxygen π bond shifts out to the electronegative carbonyl oxygen atom and the hybridization state of both the carbon and the oxygen changes from sp^2 to sp^3. ***The important aspect of this step is the ability of the carbonyl oxygen atom to accommodate the electron pair of the carbon–oxygen double bond.***

A MECHANISM FOR THE REACTION — Addition of a Strong Nucleophile to an Aldehyde or Ketone



In this step the nucleophile forms a bond to the carbon by donating an electron pair to the top or bottom face of the carbonyl group [path (a) or (b)]. An electron pair shifts out to the oxygen.

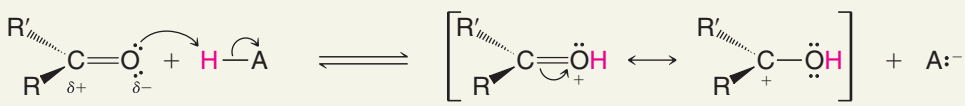
In the second step the alkoxide oxygen, because it is strongly basic, removes a proton from H—Nu or some other acid.

In the second step the oxygen atom accepts a proton. This happens because the oxygen atom is now much more basic; it carries a full negative charge as an alkoxide anion.

2. **When an acid catalyst is present and the nucleophile is weak**, reaction of the carbonyl oxygen with the acid enhances electrophilicity of the carbonyl group.

A MECHANISM FOR THE REACTION — Acid-Catalyzed Nucleophilic Addition to an Aldehyde or Ketone

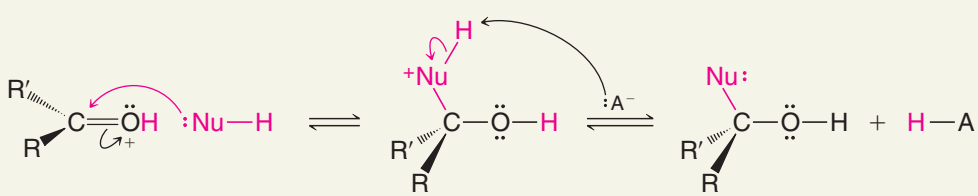
Step 1



(or a Lewis acid)

In this step an electron pair of the carbonyl oxygen accepts a proton from the acid (or associates with a Lewis acid), producing an oxonium cation. The carbon of the oxonium cation is more susceptible to nucleophilic attack than the carbonyl of the starting ketone.

Step 2



In the first of these two steps, the oxonium cation accepts the electron pair of the nucleophile. In the second step, a base removes a proton from the positively charged atom, regenerating the acid.

This mechanism operates when carbonyl compounds are treated with *strong acids* in the presence of *weak nucleophiles*. In the first step the acid donates a proton to an electron pair of the carbonyl oxygen atom. The resulting protonated carbonyl compound, an **oxonium cation**, is highly reactive toward nucleophilic attack at the carbonyl carbon atom because the carbonyl carbon atom carries more positive charge than it does in the unprotonated compound.

Helpful Hint

Any compound containing a positively charged oxygen atom that forms three covalent bonds is an *oxonium cation*.

16.6A Reversibility of Nucleophilic Additions to the Carbon–Oxygen Double Bond

- Many nucleophilic additions to carbon–oxygen double bonds are reversible; the overall results of these reactions depend, therefore, on the position of an equilibrium.

This contrasts markedly with most electrophilic additions to carbon–carbon double bonds and with nucleophilic substitutions at saturated carbon atoms. The latter reactions are essentially irreversible, and overall results are a function of relative reaction rates.

16.6B Relative Reactivity: Aldehydes versus Ketones

- In general, aldehydes are more reactive in nucleophilic additions than are ketones. Both steric and electronic factors favor aldehydes.

Steric Factors In aldehydes, where one group is a hydrogen atom, the central carbon of the tetrahedral product formed from the aldehyde is less crowded and the product is more stable. Formation of the product, therefore, is favored at equilibrium. With ketones, the two alkyl substituents at the carbonyl carbon cause greater steric crowding in the tetrahedral product and make it less stable. Therefore, a smaller concentration of the product is present at equilibrium.

Electronic Factors Because alkyl groups are electron releasing, aldehydes are more reactive on electronic grounds as well. Aldehydes have only one electron-releasing group to partially neutralize, and thereby stabilize, the positive charge at their carbonyl carbon atom. Ketones have two electron-releasing groups and are stabilized more. Greater stabilization of the ketone (the reactant) relative to its product means that the equilibrium constant for the formation of the tetrahedral product from a ketone is smaller and the reaction is less favorable:

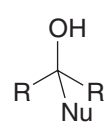
Aldehyde **Ketone**

The ketone carbonyl carbon is less positive because it has two electron-releasing alkyl groups.

On the other hand, electron-withdrawing substituents (e.g., $-CF_3$ or $-CCl_3$ groups) cause the carbonyl carbon to be more positive (and the starting compound to become less stable), causing the **addition reaction** to be more favorable.

16.6C Addition Products Can Undergo Further Reactions

Nucleophilic addition to a carbonyl group may lead to a product that is stable under the reaction conditions that we employ. If this is the case we are then able to isolate products with the following general structure:



In other reactions the product formed initially may be unstable and may spontaneously undergo subsequent reactions. One common subsequent reaction is an *elimination reaction*, especially *dehydration*. Even if the initial addition product is stable, we may deliberately bring about a subsequent reaction by our choice of reaction conditions.

PRACTICE PROBLEM 16.5

The reaction of an aldehyde or ketone with a Grignard reagent (Section 12.8) is a nucleophilic addition to the carbon–oxygen double bond. **(a)** What is the nucleophile? **(b)** The magnesium portion of the Grignard reagent plays an important part in this reaction. What is its function? **(c)** What product is formed initially? **(d)** What product forms when water is added?

PRACTICE PROBLEM 16.6

The reactions of aldehydes and ketones with $LiAlH_4$ and $NaBH_4$ (Section 12.3) are nucleophilic additions to the carbonyl group. What is the nucleophile in these reactions?

16.7 THE ADDITION OF ALCOHOLS: HEMIACETALS AND ACETALS

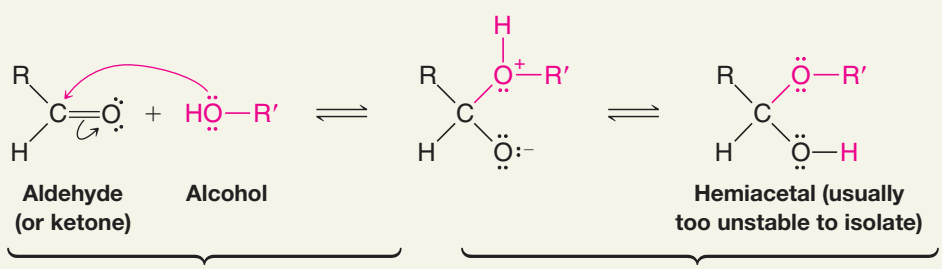
- Aldehydes and ketones react with alcohols to form **hemiacetals** and **acetals** by an equilibrium reaction.

16.7A Hemiacetals

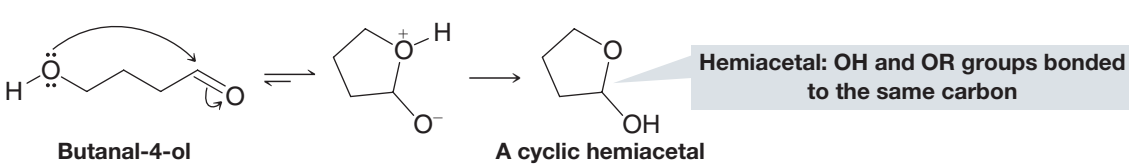
- The essential structural features of a **hemiacetal** are an —OH and an —OR group attached to the same carbon atom.

The hemiacetal results by nucleophilic addition of an alcohol oxygen to the carbonyl carbon of an aldehyde or ketone.

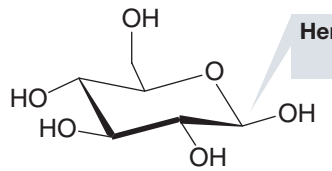
A MECHANISM FOR THE REACTION — Hemiacetal Formation



- Most open-chain hemiacetals are not sufficiently stable to allow their isolation. Cyclic hemiacetals with five- or six-membered rings, however, are usually much more stable.



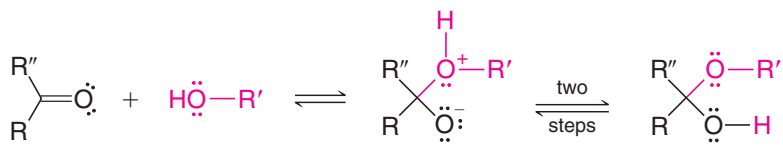
Most simple sugars (Chapter 22) exist primarily in a cyclic hemiacetal form. Glucose is an example:



Hemiacetal: OH and OR groups bonded to the same carbon

(+)-Glucose (a cyclic hemiacetal)

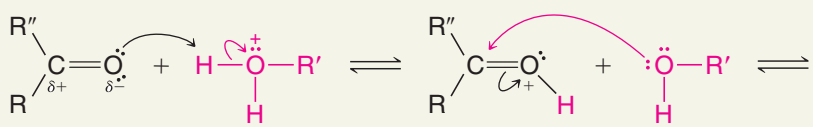
Whether the carbonyl reactant is an aldehyde or a ketone, the product with an —OH and an —OR group is called a **hemiacetal**.



Ketone **Hemiacetal**

- The formation of hemiacetals is catalyzed by acids and bases.

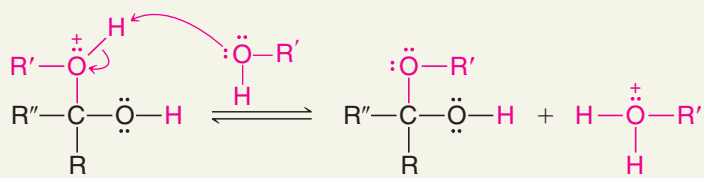
A MECHANISM FOR THE REACTION — Acid-Catalyzed Hemiacetal Formation



(R″ may be H)

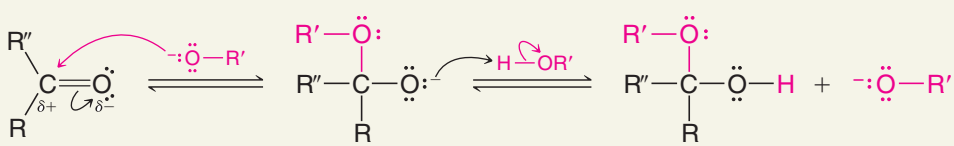
Protonation of the aldehyde or ketone oxygen atom makes the carbonyl carbon more susceptible to nucleophilic attack. [The protonated alcohol results from reaction of the alcohol (present in excess) with the acid catalyst, e.g., gaseous (anhydrous) HCl.]

An alcohol molecule adds to the carbon of the oxonium cation.



The transfer of a proton from the positive oxygen to another molecule of the alcohol leads to the hemiacetal.

A MECHANISM FOR THE REACTION — Base-Catalyzed Hemiacetal Formation

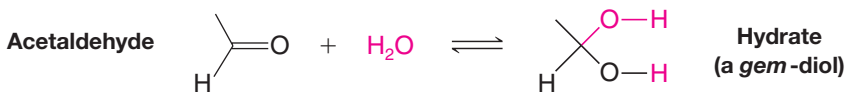


(R″ may be H)

An alkoxide anion acting as a nucleophile attacks the carbonyl carbon atom. An electron pair shifts onto the oxygen atom, producing a new alkoxide anion.

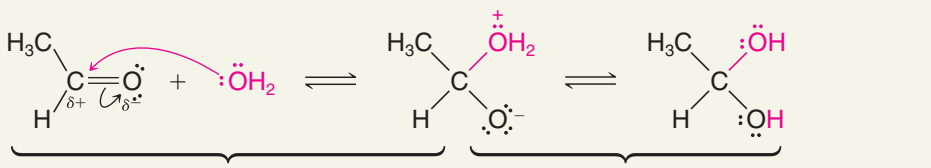
The alkoxide anion abstracts a proton from an alcohol molecule to produce the hemiacetal and regenerates an alkoxide anion.

Aldehyde Hydrates: *gem*-Diols Dissolving an aldehyde such as acetaldehyde in water causes the establishment of an equilibrium between the aldehyde and its **hydrate**. This hydrate is in actuality a 1,1-diol, called a geminal diol (or simply a *gem*-diol).



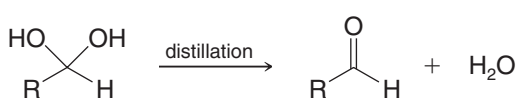
The *gem*-diol results from a nucleophilic addition of water to the carbonyl group of the aldehyde.

A MECHANISM FOR THE REACTION — Hydrate Formation

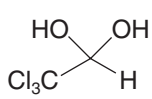


The equilibrium for the addition of water to most ketones is unfavorable, whereas some aldehydes (e.g., formaldehyde) exist primarily as the *gem*-diol in aqueous solution.

It is not possible to isolate most *gem*-diols from the aqueous solutions in which they are formed. Evaporation of the water, for example, simply displaces the overall equilibrium to the right and the *gem*-diol (or hydrate) reverts to the carbonyl compound:



Compounds with strong electron-withdrawing groups attached to the carbonyl group can form stable *gem*-diols. An example is the compound called chloral hydrate:



Chloral hydrate

PRACTICE PROBLEM 16.7

Dissolving formaldehyde in water leads to a solution containing primarily the *gem*-diol $CH_2(OH)_2$. Show the steps in its formation from formaldehyde.

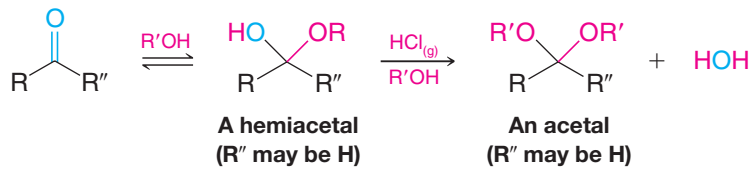
PRACTICE PROBLEM 16.8

When acetone is dissolved in water containing ^{18}O instead of ordinary ^{16}O (i.e., $H_2{}^{18}O$ instead of $H_2{}^{16}O$), the acetone soon begins to acquire ^{18}O and becomes $CH_3\overset{\overset{^{18}O}{\|}}{C}CH_3$. The formation of this oxygen-labeled acetone is catalyzed by traces of strong acids and by strong bases (e.g., HO^-). Show the steps that explain both the acid-catalyzed reaction and the base-catalyzed reaction.

16.7B Acetals

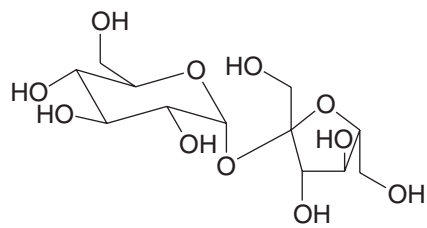
- An **acetal** has two —OR groups attached to the same carbon atom.

If we take an alcohol solution of an aldehyde (or ketone) and pass into it a small amount of gaseous HCl, a hemiacetal forms, and then the hemiacetal reacts with a second molar equivalent of the alcohol to produce an **acetal**.



A hemiacetal (R″ may be H) **An acetal (R″ may be H)**

PRACTICE PROBLEM 16.9 Shown below is the structural formula for sucrose (table sugar). Sucrose has two acetal groupings. Identify these.

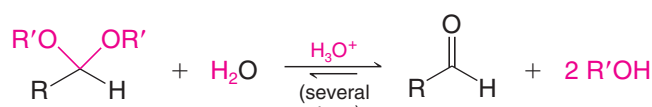


- The mechanism for acetal formation involves acid-catalyzed formation of the hemiacetal, then an acid-catalyzed elimination of water, followed by a second *addition* of the alcohol and loss of a proton.
- All steps in the formation of an acetal from an aldehyde are reversible.

Helpful Hint
Equilibrium conditions govern the formation and hydrolysis of hemiacetals and acetals.

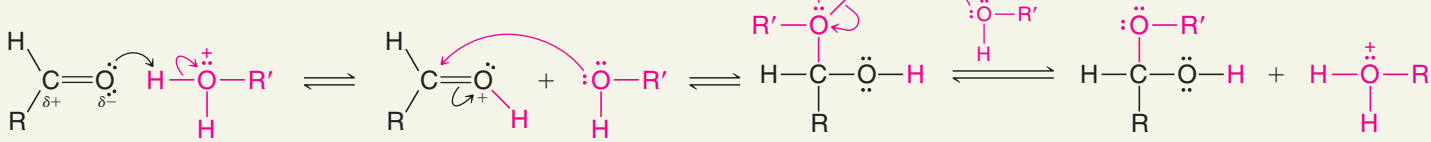
If we dissolve an aldehyde in a large excess of an anhydrous alcohol and add a small amount of an anhydrous acid (e.g., gaseous HCl or concentrated H_2SO_4), the equilibrium will strongly favor the formation of an acetal. After the equilibrium is established, we can isolate the acetal by neutralizing the acid and evaporating the excess alcohol.

If we then place the acetal in water and add a catalytic amount of acid, all of the steps reverse. Under these conditions (an excess of water), the equilibrium favors the formation of the aldehyde. The acetal undergoes ***hydrolysis***:

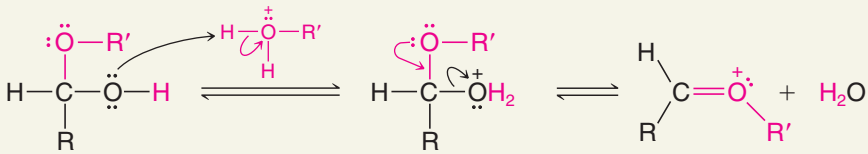


Acetal **Aldehyde**

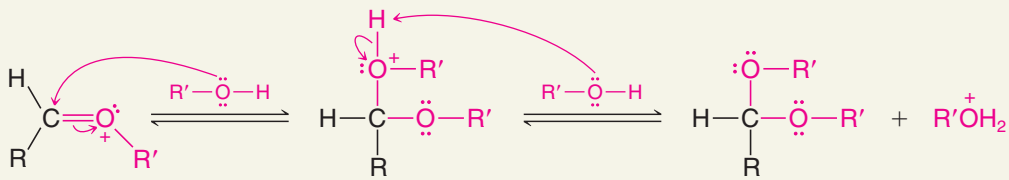
A MECHANISM FOR THE REACTION — Acid-Catalyzed Acetal Formation



Proton transfer to the carbonyl oxygen **Nucleophilic addition of the first alcohol molecule** **Proton removal from the positive oxygen results in formation of a hemiacetal.**



Protonation of the hydroxyl group leads to elimination of water and formation of a highly reactive oxonium cation.



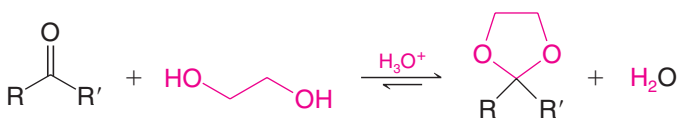
Attack on the carbon of the oxonium ion by a second molecule of the alcohol, followed by removal of a proton, leads to the acetal.

PRACTICE PROBLEM 16.10

Write a detailed mechanism for the formation of an acetal from benzaldehyde and methanol in the presence of an acid catalyst.

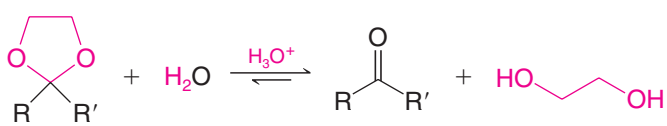
Cyclic Acetals

- Cyclic acetal formation is favored when a ketone or an aldehyde is treated with an excess of a 1,2-diol and a trace of acid:



Ketone **(excess)** **Cyclic acetal**

This reaction, too, can be reversed by treating the acetal with aqueous acid:



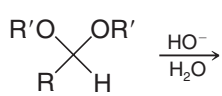
Acetal formation is not favored when ketones are treated with simple alcohols and gaseous HCl.

PRACTICE PROBLEM 16.11

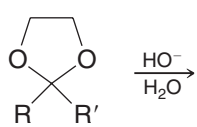
Outline all steps in the mechanism for the formation of a cyclic acetal from acetone and ethylene glycol (1,2-ethanediol) in the presence of gaseous HCl.

16.7C Acetals Are Used as Protecting Groups

- Although acetals are hydrolyzed to aldehydes and ketones in aqueous acid, ***acetals are stable in basic solutions***:



No reaction



No reaction

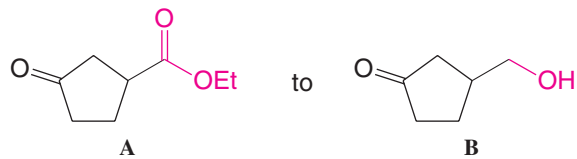
- Acetals are used to protect aldehydes and ketones from undesired reactions in basic solutions.

Helpful Hint

Protecting groups are strategic tools for synthesis. See Sections 11.11D, 11.11E, and 12.9 also.

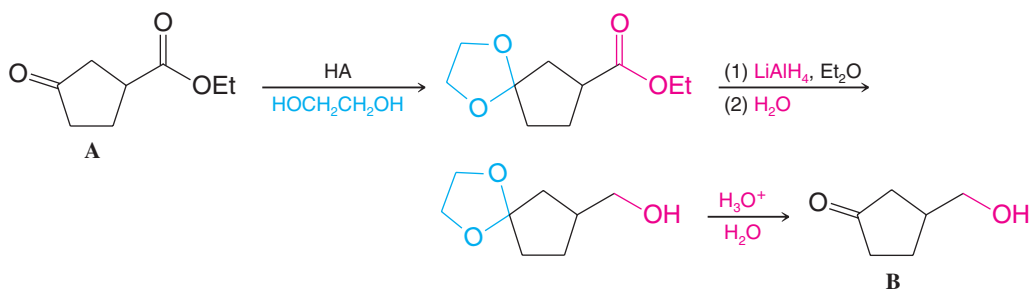
We can convert an aldehyde or ketone to an acetal, carry out a reaction on some other part of the molecule, and then hydrolyze the acetal with aqueous acid.

As an example, let us consider the problem of converting



A **B**

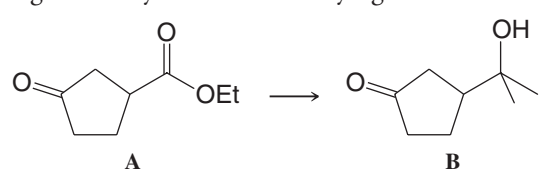
Keto groups are more easily reduced than ester groups. Any reducing agent (e.g., $LiAlH_4$ or H_2/Ni) that can reduce the ester group of **A** reduces the keto group as well. But if we "protect" the keto group by converting it to a cyclic acetal (the ester group does not react), we can reduce the ester group in basic solution without affecting the cyclic acetal. After we finish the ester reduction, we can hydrolyze the cyclic acetal and obtain our desired product, **B**:



A **B**

PRACTICE PROBLEM 16.12 What product would be obtained if **A** were treated with lithium aluminum hydride without first converting it to a cyclic acetal?

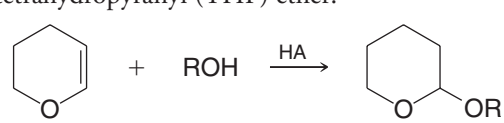
PRACTICE PROBLEM 16.13 **(a)** Show how you might use a cyclic acetal in carrying out the following transformation:



A **B**

(b) Why would a direct addition of methylmagnesium bromide to **A** fail to give **B**?

PRACTICE PROBLEM 16.14 Dihydropyran reacts readily with an alcohol in the presence of a trace of anhydrous HCl or H_2SO_4 to form a tetrahydropyranyl (THP) ether:

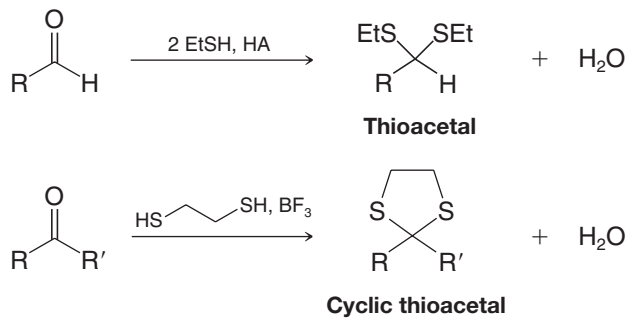


Dihydropyran **Tetrahydropyranyl ether**

(a) Write a plausible mechanism for this reaction. **(b)** Tetrahydropyranyl ethers are stable in aqueous base but hydrolyze rapidly in aqueous acid to yield the original alcohol and another compound. Explain. (What is the other compound?) **(c)** The tetrahydropyranyl group can be used as a protecting group for alcohols and phenols. Show how you might use it in a synthesis of 5-methyl-1,5-hexanediol starting with 4-chloro-1-butanol.

16.7D Thioacetals

- Aldehydes and ketones react with thiols to form *thioacetals*:

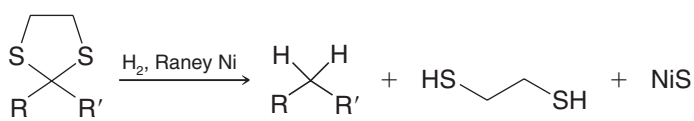


Thioacetals are important in organic synthesis because they react with hydrogen and Raney nickel to yield hydrocarbons. Raney nickel is a special nickel catalyst that contains adsorbed hydrogen.

- Thioacetal formation with subsequent "desulfurization" with hydrogen and Raney nickel gives us an additional method for converting carbonyl groups of aldehydes and ketones to —CH_2— groups:

Helpful Hint

A method for reducing the carbonyl group of aldehydes and ketones to —CH_2— groups.



The other methods we have studied are the **Clemmensen reduction** (Section 15.9A) and the **Wolff–Kishner reduction** (Section 16.9B). In Section 16.8C we will discuss the mechanism of the Wolff–Kishner reduction.

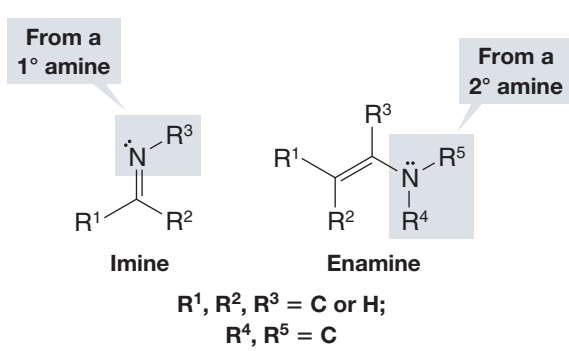
PRACTICE PROBLEM 16.15

Show how you might use thioacetal formation and Raney nickel desulfurization to convert: **(a)** cyclohexanone to cyclohexane and **(b)** benzaldehyde to toluene.

16.8 THE ADDITION OF PRIMARY AND SECONDARY AMINES

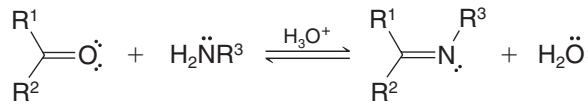
- Aldehydes and ketones react with primary amines to form **imines** and with secondary amines to form **enamines**.

Imines have a carbon–nitrogen double bond. Enamines have an amino group joined to a carbon–carbon double bond (they are alk*eneamines*).



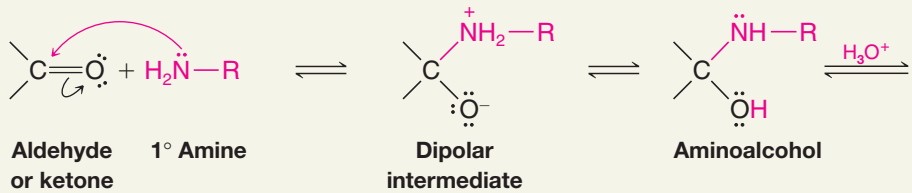
16.8A Imines

A general equation for the formation of an imine from a primary amine and an aldehyde or ketone is shown here. Imine formation is acid catalyzed, and the product can form as a mixture of (*E*) and (*Z*) isomers:



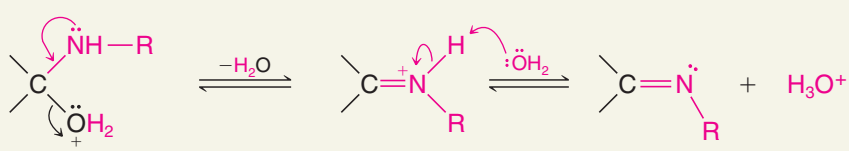
Imine formation generally takes place fastest between pH 4 and 5 and is slow at very low or very high pH. We can understand why an acid catalyst is necessary if we consider the mechanism that has been proposed for imine formation. The important step is the step in which the protonated aminoalcohol loses a molecule of water to become an iminium ion. By protonating the alcohol group, the acid converts a poor leaving group (an —OH group) into a good one (an —$^{+}$OH$_2$ group).

A MECHANISM FOR THE REACTION — Imine Formation



The amine adds to the carbonyl group to form a dipolar tetrahedral intermediate.

Intermolecular proton transfer from nitrogen to oxygen produces an aminoalcohol.



Protonation of the oxygen produces a good leaving group. Loss of a molecule of water yields an iminium ion.

Transfer of a proton to water produces the imine and regenerates the catalytic hydronium ion.

The reaction proceeds more slowly if the hydronium ion concentration is too high, because protonation of the amine itself takes place to a considerable extent; this has the effect of decreasing the concentration of the nucleophile needed in the first step. If the concentration of the hydronium ion is too low, the reaction becomes slower because the concentration of the protonated aminoalcohol becomes lower. A pH between 4 and 5 is an effective compromise.

Imine formation occurs in many biochemical reactions because enzymes often use an —NH_2 group to react with an aldehyde or ketone. An imine linkage is important in the biochemistry of pyridoxal phosphate (which is related to vitamin B_6; see "The Chemistry of ..." box on page 744).

Imines are also formed as intermediates in a useful laboratory synthesis of amines that we shall study in Section 20.4.

Helpful Hint

See "The Chemistry of ... A Very Versatile Vitamin, Pyridoxine (Vitamin B_6)" on page 744, and "The Chemistry of... Pyridoxal Phosphate" in *WileyPLUS*.

16.8B Oximes and Hydrazones

- Compounds such as hydroxylamine (NH_2OH), hydrazine (NH_2NH_2), and substituted hydrazines such as phenylhydrazine ($C_6H_5NHNH_2$) and 2,4-dinitrophenylhydrazine form C═N derivatives of aldehydes and ketones.

These derivatives are called oximes, hydrazones, phenylhydrazones, and 2,4-dinitrophenylhydrazones, respectively. The mechanisms by which these C═N derivatives form are similar to the mechanism for imine formation from a primary amine. As with imines, the formation of (*E*) and (*Z*) isomers is possible.

Oximes and the various **hydrazone** derivatives of aldehydes and ketones are sometimes used to identify unknown aldehydes and ketones. These derivatives are usually relatively insoluble solids that have sharp, characteristic melting points. The melting point of the derivative of an unknown compound can be compared with the melting point for the same derivative of a known compound or with data found in a reference table, and on this basis one can propose an identity for the unknown compound. Most laboratory textbooks for organic chemistry include extensive tables of derivative melting points. The method of comparing melting points is only useful, however, for compounds that have derivative melting points previously reported in the literature. Spectroscopic methods (especially IR, NMR, and mass spectrometry) are more generally applicable to identification of unknown compounds (Section 16.13).

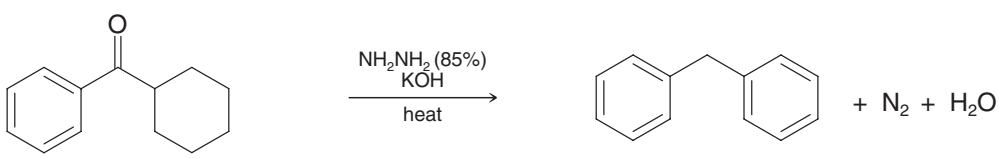
Another important use of hydrazones is the Wolff–Kishner reduction, first mentioned in Section 15.9B, and whose mechanism we shall present below now that we have discussed hydrazones.

16.8C The Wolff–Kishner Reduction

A ketone can be reduced to a methylene group using the Wolff–Kishner reduction, which involves heating the ketone with hydrazine and base. The mechanism for the Wolff–Kishner reduction involves initial formation of a hydrazone followed by a tautomerization and elimination of nitrogen. The Wolff–Kishner reduction is complementary to the Clemmensen reduction (Section 15.9A), which involves acid, and to the reduction of dithioacetals (Section 16.7D), which involves catalytic hydrogenation.

Benzophenone can be reduced to diphenylmethane by the Wolff–Kishner reduction, for example.

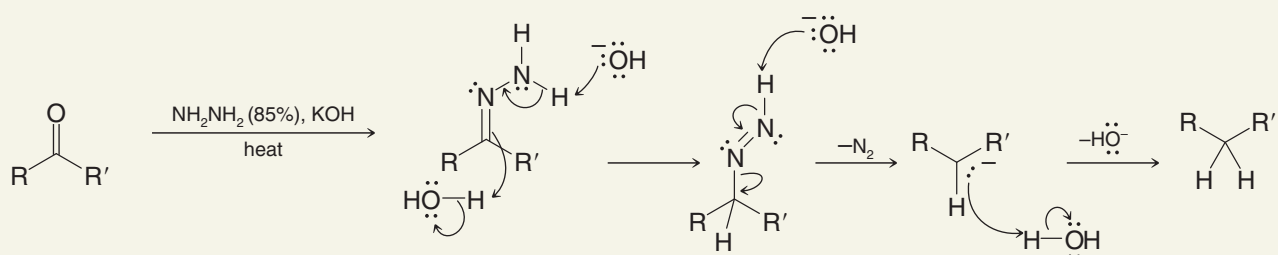
A Wolff–Kishner reduction



Benzophenone → **Diphenylmethane (83%)**

The mechanism for the Wolff–Kishner reaction is as follows:

A MECHANISM FOR THE REACTION — The Wolff–Kishner Reduction



Hydrazine hydrate reacts with the carbonyl compound to form a hydrazone.

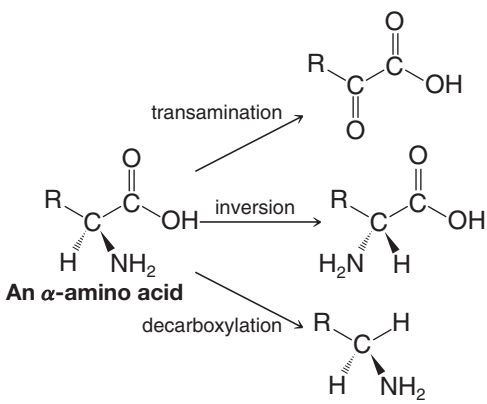
Base promoted tautomerization transfers a proton from nitrogen to carbon.

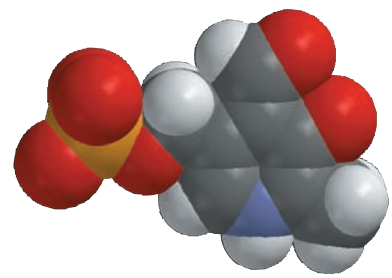
Elimination of N_2 leads to a carbanion, which is then protonated.

THE CHEMISTRY OF... A Very Versatile Vitamin, Pyridoxine (Vitamin B_6)

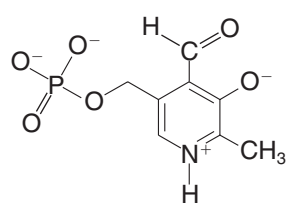
Pyridoxal phosphate (PLP) is at the heart of chemistry conducted by a number of enzymes. Many of us know the coenzyme pyridoxal phosphate by the closely related vitamin from which it is derived in our diet—pyridoxine, or vitamin B_6. Wheat is a good dietary source of vitamin B_6. Although pyridoxal phosphate (see below and the model) is a member of the aldehyde family, when it is involved in biological chemistry, it often contains the closely related functional group with a carbon–nitrogen double bond, the imine group.

Some enzymatic reactions that involve PLP include *transaminations*, which convert amino acids to ketones for use in the citric acid cycle and other pathways; *decarboxylation* of amino acids for biosynthesis of neurotransmitters such as histamine, dopamine, and serotonin; and *inversion* of amino acid chirality centers, such as required for the biosynthesis of cell walls in bacteria.

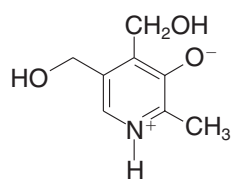




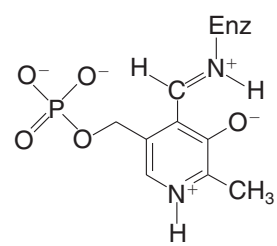
Pyridoxal phosphate (vitamin B_6)



Pyridoxal phosphate (PLP)



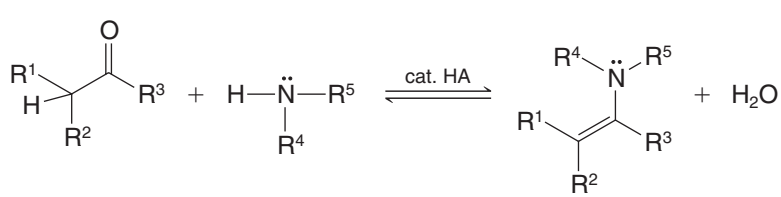
Pyridoxine



PLP with an imine group

16.8D Enamines

Aldehydes and ketones react with secondary amines to form enamines. The following is a general equation for enamine formation:



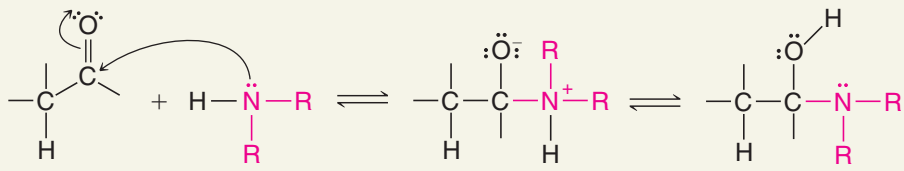
Secondary amine Enamine

A mechanism for the reaction is given in the following box. Note the difference between the previously described mechanism for imine formation and this mechanism for enamine formation. In enamine formation, which involves a secondary amine, there is no proton for removal from the nitrogen in the iminium cation intermediate. Hence, a neutral imine cannot be formed. A proton is removed from a carbon adjacent to the former carbonyl group instead, resulting in an enamine. We shall see in Chapter 18 that enamines are very useful for carbon–carbon bond formation (Section 18.9).

Tertiary amines do not form stable addition products with aldehydes and ketones because, on forming the tetrahedral intermediate, the resulting formal positive charge cannot be neutralized by loss of a proton.

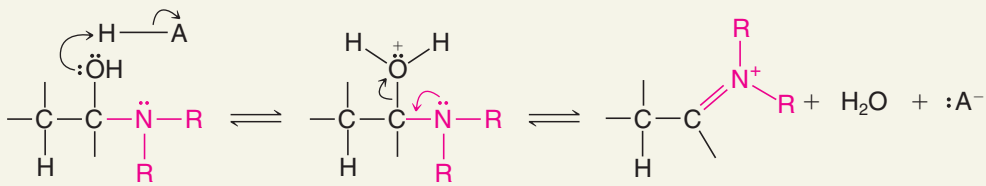
A MECHANISM FOR THE REACTION — Enamine Formation

Step 1



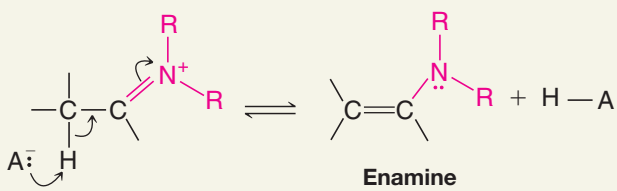
The amine adds to the ketone or aldehyde carbonyl to form a tetrahedral adduct. Intermolecular proton transfer leads to the aminoalcohol intermediate.

Step 2



The aminoalcohol intermediate is protonated by the catalytic acid. Contribution of an unshared electron pair from the nitrogen atom and departure of a water molecule lead to an iminium cation intermediate.

Step 3

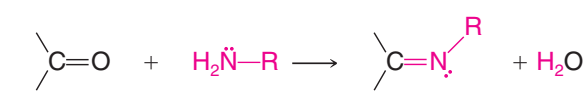


A proton is removed from the carbon adjacent to the iminium group. Proton removal occurs from the carbon because there is no proton to remove from the nitrogen of the iminium cation (as there would have been if a primary amine had been used). This step forms the enamine, neutralizes the formal charge, and regenerates the catalytic acid. (If there had been a proton to remove from the nitrogen of the iminium cation, the final product would have been an imine.)

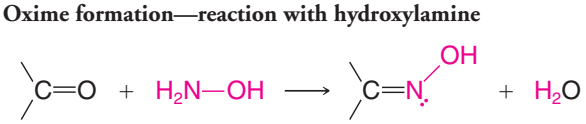
Table 16.2 summarizes the reactions of aldehydes and ketones with derivatives of ammonia.

TABLE 16.2 REACTIONS OF ALDEHYDES AND KETONES WITH DERIVATIVES OF AMMONIA

1. Imine formation—reaction with a primary amine

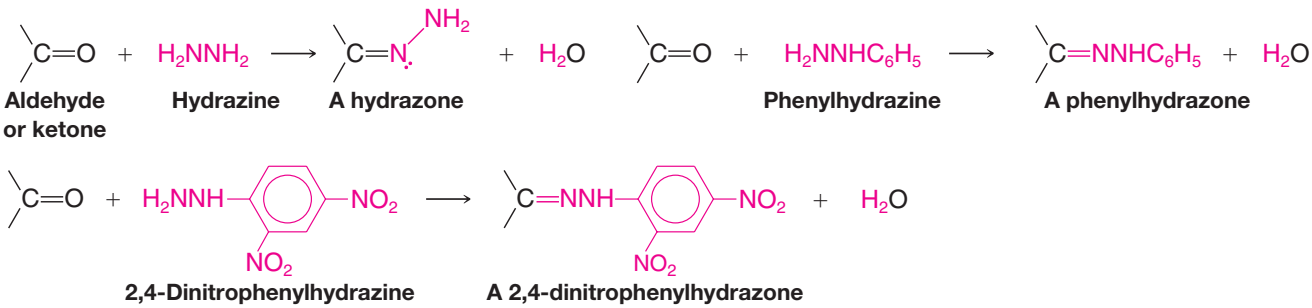


2. Oxime formation—reaction with hydroxylamine

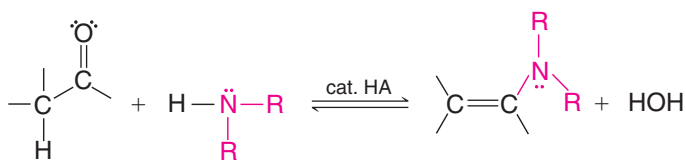


(Table continues on next page)

3. Hydrazone and substituted hydrazone formation—reactions with hydrazine, phenylhydrazine, and 2,4-dinitrophenylhydrazine [each derivative can form as an (*E*) or (*Z*) isomer]

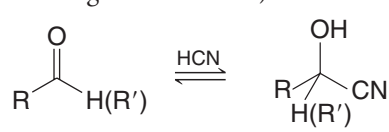


4. Enamine formation—reaction with a secondary amine



16.9 THE ADDITION OF HYDROGEN CYANIDE: CYANOHYDRINS

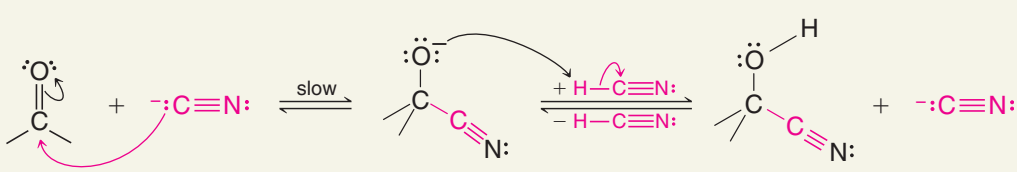
- Hydrogen cyanide adds to the carbonyl groups of aldehydes and most ketones to form compounds called **cyanohydrins**. (Ketones in which the carbonyl group is highly hindered do not undergo this reaction.)



A cyanohydrin

Cyanohydrins form fastest under conditions where cyanide anions are present to act as the nucleophile. Use of potassium cyanide, or any base that can generate cyanide anions from HCN, increases the reaction rate as compared to the use of HCN alone. The addition of hydrogen cyanide itself to a carbonyl group is slow because the weak acidity of HCN ($pK_a \sim 9$) provides only a small concentration of the nucleophilic cyanide anion. The following is a mechanism for formation of a cyanohydrin.

A MECHANISM FOR THE REACTION — Cyanohydrin Formation

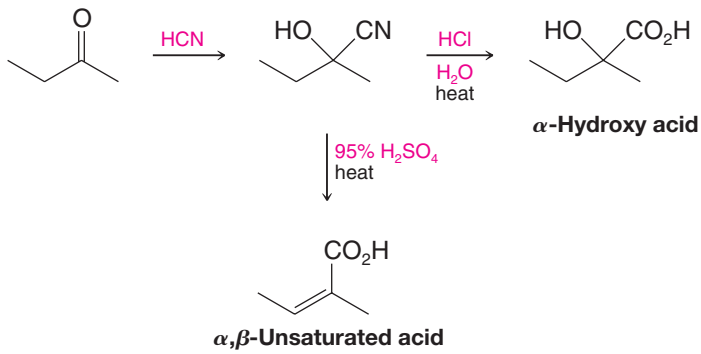


Great care must be taken when working with hydrogen cyanide due to its high toxicity and volatility. Reactions involving HCN must be conducted in an efficient fume hood.

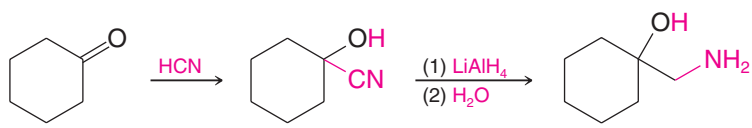
Cyanohydrins are useful intermediates in organic synthesis because they can be converted to several other functional groups.

- Acidic hydrolysis converts cyanohydrins to α-hydroxy acids or to α,β-unsaturated acids.

The mechanism for this hydrolysis is discussed in Section 17.8H. The preparation of α-hydroxy acids from cyanohydrins is part of the Kiliani–Fischer synthesis of simple sugars (Section 22.9A):

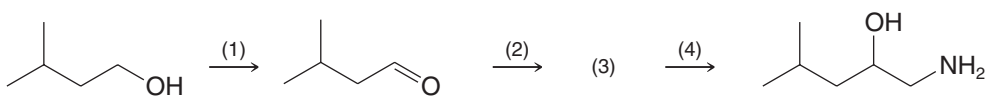


- Reduction of a cyanohydrin with lithium aluminum hydride gives a β-aminoalcohol:

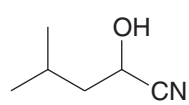


SOLVED PROBLEM 16.6

Provide the missing reagents and intermediate in the following synthesis.

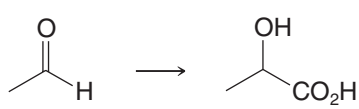


STRATEGY AND ANSWER: Step (1) requires oxidation of a primary alcohol to an aldehyde; use PCC (Section 12.4). To reach the final product from the aldehyde we need to add a carbon atom to the chain and introduce a primary amine. This combination suggests use of a nitrile, which we know can be reduced to a primary amine. Thus, adding HCN to the aldehyde in step (2) forms the cyanohydrin (3), shown below. This step also affords the alcohol group present in the final product. In step (4) we reduce the nitrile to a primary amine using $LiAlH_4$.



PRACTICE PROBLEM 16.16

(a) Show how you might prepare lactic acid from acetaldehyde through a cyanohydrin intermediate. **(b)** What stereoisomeric form of lactic acid would you expect to obtain?

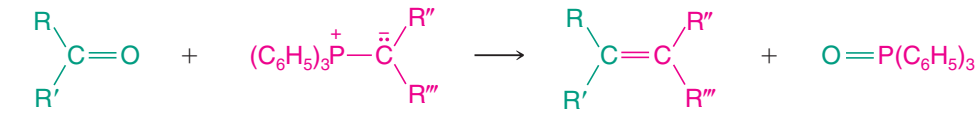


16.10 THE ADDITION OF YLIDES: THE WITTIG REACTION

- Aldehydes and ketones react with phosphorus ylides to yield alkenes and triphenylphosphine oxide (a by-product). This reaction is known as the **Wittig reaction**.

The Wittig reaction has proved to be a valuable method for synthesizing alkenes. The **ylide** required for the reaction is a molecule with no net charge but which has a

negative carbon atom adjacent to a positive heteroatom, which in the Wittig reaction is a phosphorus atom. Phosphorus ylides are also called phosphoranes.

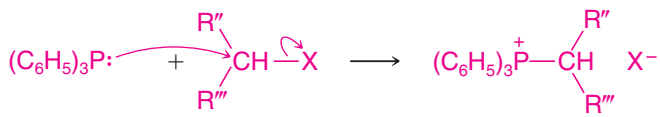


The Wittig reaction is applicable to a wide variety of compounds, and although a mixture of (*E*) and (*Z*) isomers may result, the Wittig reaction offers a great advantage over most other alkene syntheses in that *no ambiguity exists as to the location of the double bond in the product*. (This is in contrast to E1 eliminations, which may yield multiple alkene products by rearrangement to more stable carbocation intermediates, and both E1 and E2 elimination reactions, which may produce multiple products when different β hydrogens are available for removal.)

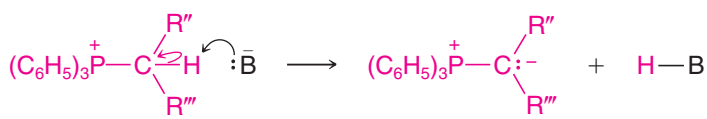
Phosphorus ylides are easily prepared from triphenylphosphine and primary or secondary alkyl halides. Their preparation involves two reactions:

General Reaction

Reaction 1

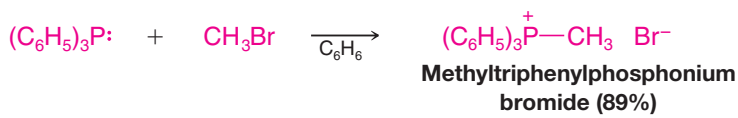


Reaction 2

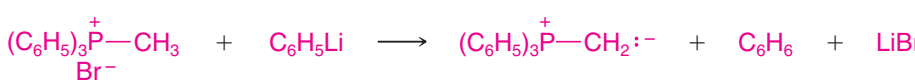


Specific Example

Reaction 1

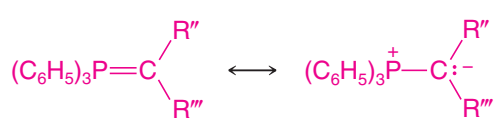


Reaction 2



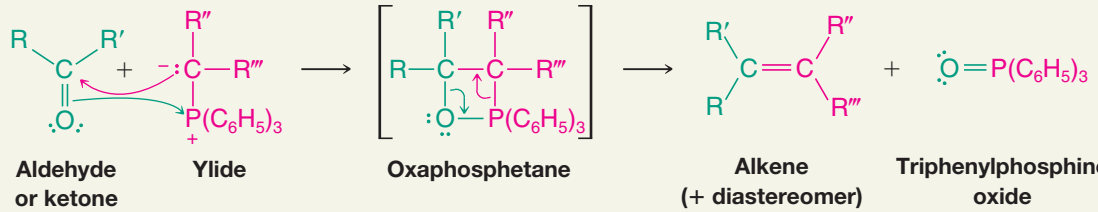
The first reaction is a nucleophilic substitution reaction. Triphenylphosphine is an excellent nucleophile and a weak base. It reacts readily with 1° and 2° alkyl halides by an S_N2 mechanism to displace a halide ion from the alkyl halide to give an alkyltriphenylphosphonium salt. **The second reaction is an acid–base reaction**. A strong base (usually an alkyllithium or phenyllithium) removes a proton from the carbon that is attached to phosphorus to give the ylide.

Phosphorus ylides can be represented as a hybrid of the two resonance structures shown here. Quantum mechanical calculations indicate that the contribution made by the first structure is relatively unimportant.

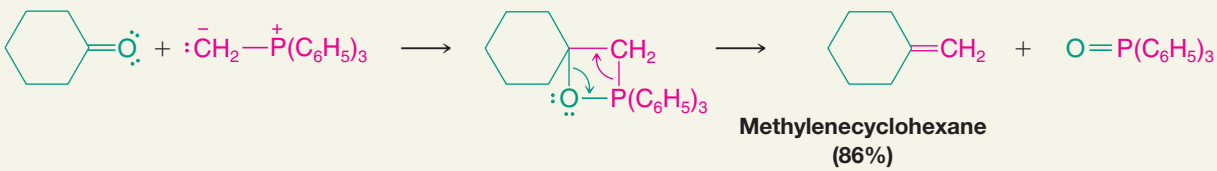


Studies by E. Vedejs (University of Michigan) indicate that the Wittig reaction takes place in two steps. In the first step (below), the aldehyde or ketone combines with the ylide in a cycloaddition reaction to form the four-membered ring of an oxaphosphetane. Then in a second step, the oxaphosphetane decomposes to form the alkene and triphenylphosphine oxide. The driving force for the reaction is the formation of the very strong ($DH° = 540$ kJ mol^{-1}) phosphorus–oxygen bond in triphenylphosphine oxide.

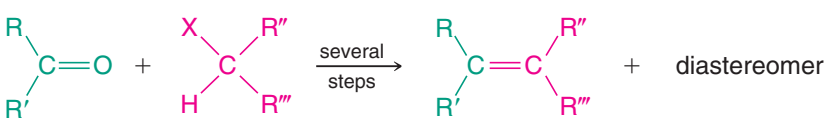
A MECHANISM FOR THE REACTION — The Wittig Reaction



Specific Example



While Wittig syntheses may appear to be complicated, in practice they are easy to carry out. Most of the steps can be carried out in the same reaction vessel, and the entire synthesis can be accomplished in a matter of hours. The overall result of a Wittig synthesis is:



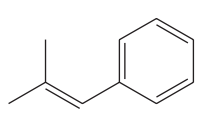
16.10A HOW TO Plan a Wittig Synthesis

Planning a Wittig synthesis begins with recognizing in the desired alkene what can be the aldehyde or ketone component and what can be the halide component. Any or all of the R groups may be hydrogen, although yields are generally better when at least one group is hydrogen. The halide component must be a primary, secondary, or methyl halide.

SOLVED PROBLEM 16.7

Synthesize 2-methyl-1-phenylprop-1-ene using a Wittig reaction. Begin by writing a retrosynthetic analysis.

STRATEGY AND ANSWER: We examine the structure of the compound, paying attention to the groups on each side of the double bond:

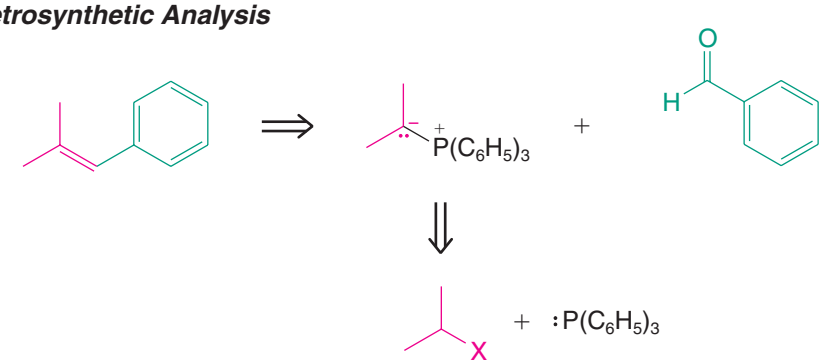


2–Methyl–1–phenylprop–1–ene

We see that two retrosynthetic analyses are possible.

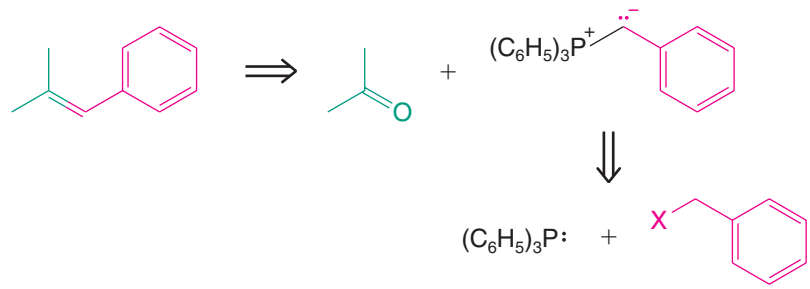
Retrosynthetic Analysis

(a)



(continues on next page)

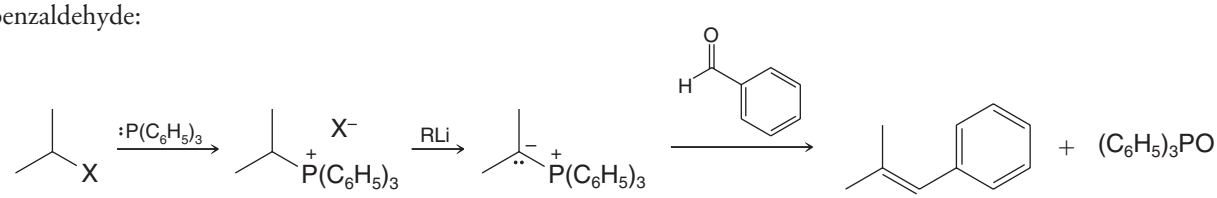
(b)



Synthesis

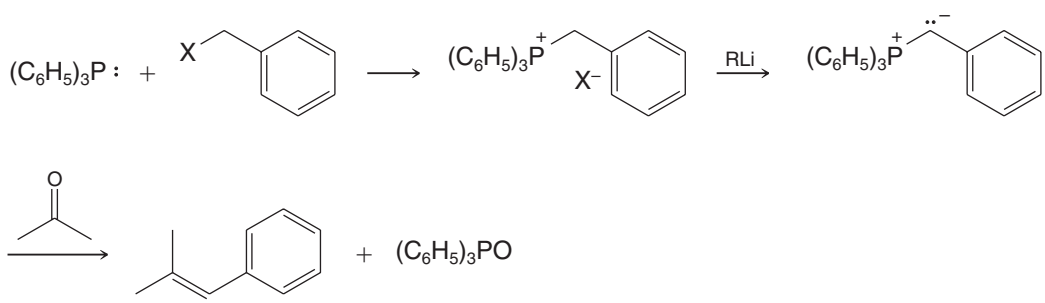
Following retrosynthetic analysis (a), we begin by making the ylide from a 2-halopropane and then allow the ylide to react with benzaldehyde:

(a)



Following retrosynthetic analysis (b), we make the ylide from a benzyl halide and allow it to react with acetone:

(b)



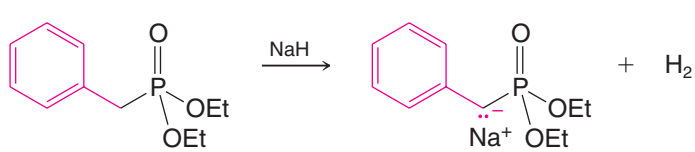
16.10B The Horner–Wadsworth–Emmons Reaction: A Modification of the Wittig Reaction

A widely used variation of the Wittig reaction is the **Horner–Wadsworth–Emmons** modification.

- The Horner–Wadsworth–Emmons reaction involves use of a phosphonate ester instead of a triphenylphosphonium salt. The major product is usually the (*E*)-alkene isomer.

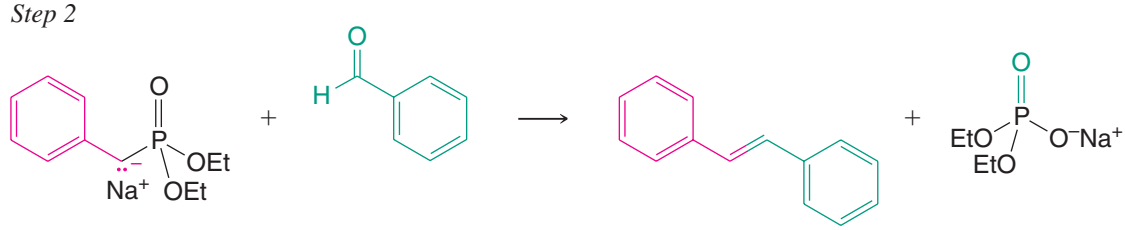
Some bases that are typically used to form the phosphonate ester carbanion include sodium hydride, potassium *tert*-butoxide, and butyllithium. The following reaction sequence is an example:

Step 1



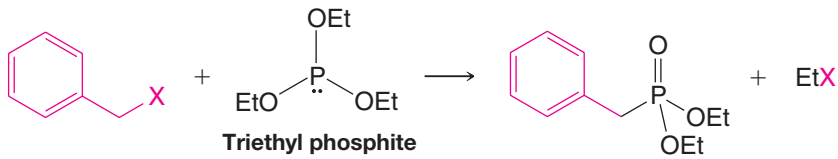
A phosphonate ester

Step 2



84%

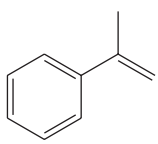
The phosphonate ester is prepared by reaction of a trialkyl phosphite [$(RO)_3P$] with an appropriate halide (a process called the Arbuzov reaction). The following is an example:



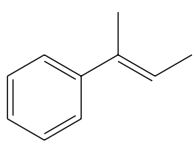
PRACTICE PROBLEM 16.17

In addition to triphenylphosphine, assume that you have available as starting materials any necessary aldehydes, ketones, and organic halides. Show how you might synthesize each of the following alkenes using the Wittig reaction:

(a)

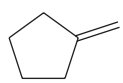


(b)

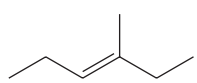


(c)

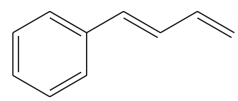
(d)



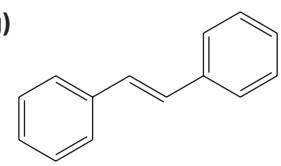
(e)



(f)

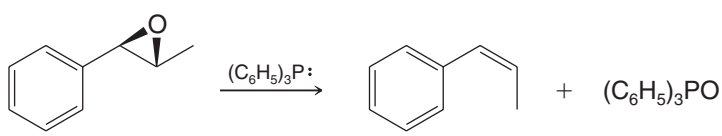


(g)



PRACTICE PROBLEM 16.18

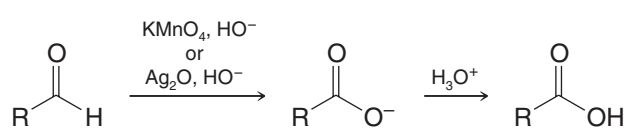
Triphenylphosphine can be used to convert epoxides to alkenes—for example,



Propose a likely mechanism for this reaction.

16.11 OXIDATION OF ALDEHYDES

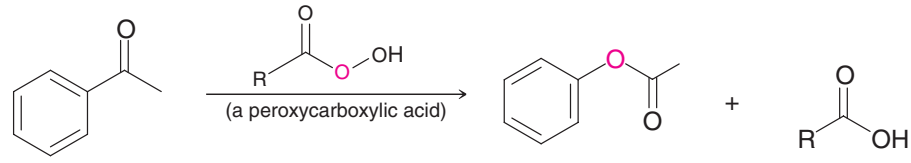
Aldehydes are much more easily oxidized than ketones. Aldehydes are readily oxidized by strong oxidizing agents such as potassium permanganate, and they are also oxidized by such mild oxidizing agents as silver oxide:



Notice that in these oxidations aldehydes lose the hydrogen that is attached to the carbonyl carbon atom. Because ketones lack this hydrogen, they are more resistant to oxidation. Aldehydes undergo slow oxidation by oxygen in the air, and thus stored samples of aldehydes often contain the corresponding carboxylic acid as an impurity.

16.12 THE BAEYER–VILLIGER OXIDATION

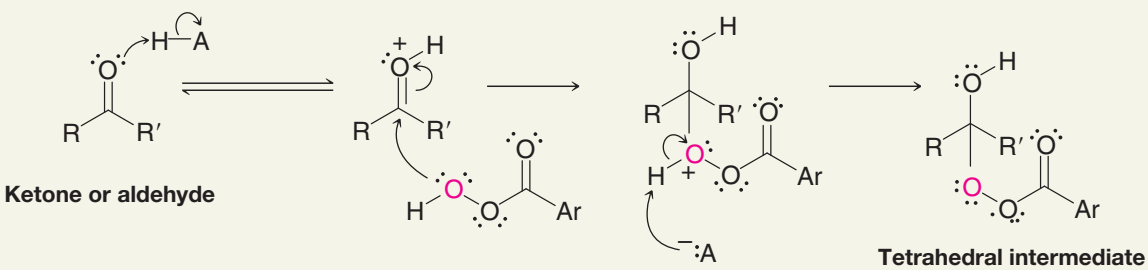
The Baeyer-Villiger oxidation is a useful method for conversion of aldehydes or ketones to esters by the insertion of an oxygen atom from a peroxycarboxylic acid (RCO_3H). For example, treating acetophenone with a peroxycarboxylic acid converts it to the ester, phenyl acetate.



Acetophenone **Phenyl acetate**

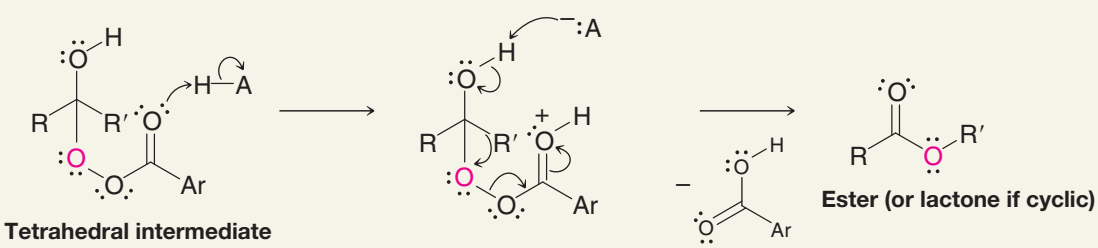
The Baeyer–Villiger oxidation is also widely used for synthesizing lactones (cyclic esters) from cyclic ketones. A common reagent used to carry out the Baeyer–Villiger oxidation is *meta*-chloroperoxybenzoic acid (*m*CPBA). Certain other peroxycarboxylic acids can be used as well. The following is a mechanism for Baeyer–Villiger oxidation.

A MECHANISM FOR THE REACTION — The Baeyer–Villiger Oxidation



Ketone or aldehyde **Tetrahedral intermediate**

The peroxycarboxylic acid (e.g., *m*CPBA, where Ar is a 3-chlorophenyl group) attacks the carbonyl group of the protonated ketone or aldehyde, leading to a tetrahedral intermediate.



Tetrahedral intermediate **Ester (or lactone if cyclic)**

A group bonded to the initial ketone or aldehyde carbon migrates to oxygen, producing the ester (or lactone) as the peroxycarboxylic acid is released as a carboxylic acid.

The group that migrates from the original ketone or aldehyde carbon to the oxygen of the peroxycarboxylic acid is a function of "migratory aptitude." Studies have shown the migratory aptitude of groups is H > phenyl > 3° alkyl > 2° alkyl > 1° alkyl > methyl.

PRACTICE PROBLEM 16.19

When benzaldehyde reacts with a peroxy acid, the product is benzoic acid. The mechanism for this reaction is analogous to the one just given for the oxidation of acetophenone, and the outcome illustrates the greater migratory aptitude of a hydrogen atom compared to phenyl. Outline all the steps involved.

PRACTICE PROBLEM 16.20

Give the structure of the product that would result from a Baeyer–Villiger oxidation of cyclopentanone.

PRACTICE PROBLEM 16.21

What would be the major product formed in the Baeyer-Villiger oxidation of 3-methyl-2-butanone?

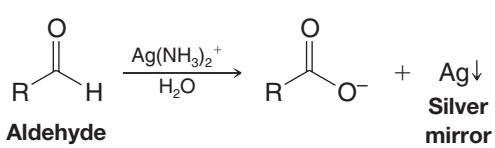
16.13 CHEMICAL ANALYSES FOR ALDEHYDES AND KETONES

16.13A Derivatives of Aldehydes and Ketones

Aldehydes and ketones can be differentiated from noncarbonyl compounds through their reactions with derivatives of ammonia (Section 16.8B). 2,4-Dinitrophenylhydrazine and hydroxylamine react with aldehydes and ketones to form precipitates. Oximes are usually colorless, whereas 2,4-dinitrophenylhydrazones are usually orange. The melting points of these derivatives can also be used in identifying specific aldehydes and ketones.

16.13B Tollens' Test (Silver Mirror Test)

The ease with which aldehydes undergo oxidation differentiates them from most ketones. Mixing aqueous silver nitrate with aqueous ammonia produces a solution known as Tollens' reagent. The reagent contains the diaminosilver(I) ion, $Ag(NH_3)_2^+$. Although this ion is a very weak oxidizing agent, it oxidizes aldehydes to carboxylate anions. As it does this, silver is reduced from the +1 oxidation state [of $Ag(NH_3)_2^+$] to metallic silver. If the rate of reaction is slow and the walls of the vessel are clean, metallic silver deposits on the walls of the test tube as a mirror; if not, it deposits as a gray-to-black precipitate. Tollens' reagent gives a negative result with all ketones except α-hydroxy ketones:



Aldehyde

16.14 SPECTROSCOPIC PROPERTIES OF ALDEHYDES AND KETONES

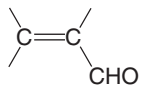
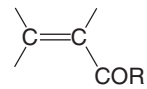
16.14A IR Spectra of Aldehydes and Ketones

- Carbonyl groups of aldehydes and ketones give rise to very strong C=O stretching absorption bands in the 1665–1780-cm^{-1} region.

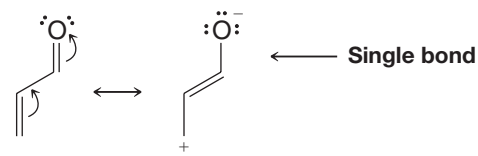
The exact location of the carbonyl IR absorption (Table 16.3) depends on the structure of the aldehyde or ketone and is one of the most useful and characteristic absorptions in the IR spectrum.

- Saturated acyclic aldehydes typically absorb near 1730 cm^{-1}; similar ketones absorb near 1715 cm^{-1}.
- Conjugation of the carbonyl group with a double bond or a benzene ring shifts the C=O absorption to lower frequencies by about 40 cm^{-1}.

TABLE 16.3 IR CARBONYL STRETCHING BANDS OF ALDEHYDES AND KETONES

C=O Stretching Frequencies			
Compound	Range (cm^{-1})	Compound	Range (cm^{-1})
R—CHO	1720–1740	RCOR	1705–1720
Ar—CHO	1695–1715	ArCOR	1680–1700
	1680–1690		1665–1680
		Cyclohexanone	1715
		Cyclopentanone	1751
		Cyclobutanone	1785

This shift to lower frequencies occurs because the carbonyl double bond of a conjugated compound has more single-bond character (see the resonance structures below), and single bonds are easier to stretch than double bonds.



The location of the carbonyl absorption of cyclic ketones depends on the size of the ring (compare the cyclic compounds in Table 16.3). *As the ring grows smaller, the* C=O *stretching peak is shifted to higher frequencies.*

Vibrations of the C—H bond of the CHO group of aldehydes also give two weak bands in the 2700–2775-cm^{-1} and 2820–2900-cm^{-1} regions that are easily identified.

Figure 16.1 shows the IR spectrum of phenylethanal.

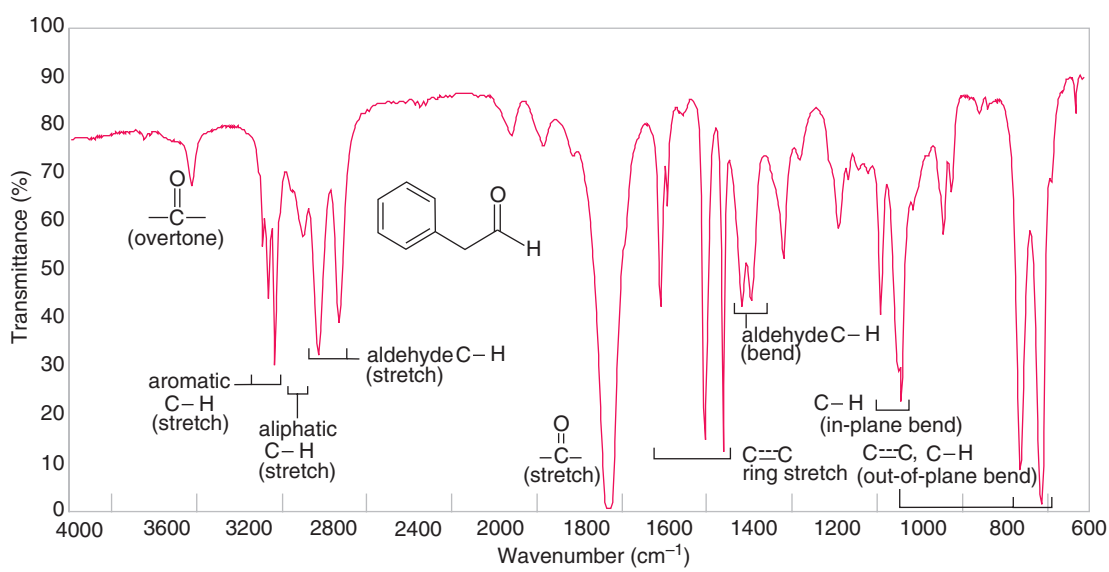


FIGURE 16.1
The infrared spectrum of phenylethanal.

16.14B NMR Spectra of Aldehydes and Ketones

^{13}C NMR Spectra

- The carbonyl carbon of an aldehyde or ketone gives characteristic NMR signals in the δ 180–220 region of ^{13}C spectra.

Since almost no other signals occur in this region, *the presence of a signal in this region (near δ 200) strongly suggests the presence of a carbonyl group.*

^{1}H NMR Spectra

- An aldehyde proton gives a distinct ^{1}H NMR signal downfield in the δ 9–12 region where almost no other protons absorb; therefore, it is easily identified.

The aldehyde proton of an aliphatic aldehyde shows spin–spin coupling with protons on the adjacent α carbon, and the splitting pattern reveals the degree of substitution of the α carbon. For example, in acetaldehyde (CH_3CHO) the aldehyde proton signal is split into a quartet by the three methyl protons, and the methyl proton signal is split into a doublet by the aldehyde proton. The coupling constant is small, however (about 3 Hz, as compared with typical vicinal splitting of about 7 Hz).

- Protons on the α carbon are deshielded by the carbonyl group, and their signals generally appear in the δ 2.0–2.3 region.
- Methyl ketones show a characteristic (3H) singlet near δ 2.1.

Figures 16.2 and 16.3 show annotated ^{1}H and ^{13}C spectra of phenylethanal.

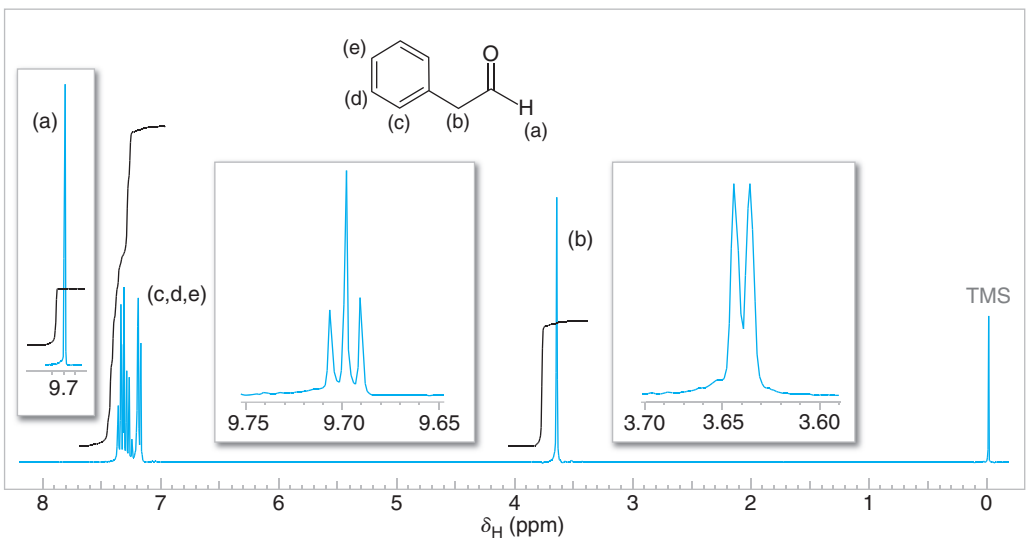


FIGURE 16.2 The 300-MHz ^{1}H NMR spectrum of phenylethanal. The small coupling between the aldehyde and methylene protons (2.6 Hz) is shown in the expanded offset plots.

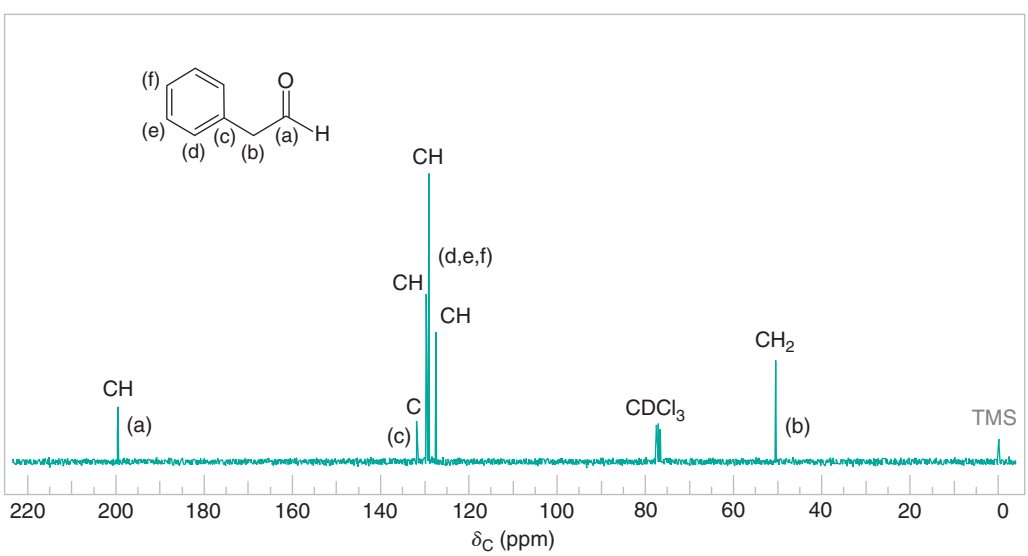


FIGURE 16.3 The broadband proton-decoupled ^{13}C NMR spectrum of phenylethanal. DEPT ^{13}C NMR information and carbon assignments are shown near each peak.

16.14C Mass Spectra of Aldehydes and Ketones

The mass spectra of ketones usually show a peak corresponding to the molecular ion. Aldehydes typically produce a prominent $M^{+}-1$ peak in their mass spectra from cleavage of the aldehyde hydrogen. Ketones usually undergo cleavage on either side of the carbonyl group to produce acylium ions, $RC{\equiv}O:^{+}$, where R can be the alkyl group from either side of the ketone carbonyl. Cleavage via the McLafferty rearrangement (Section 9.16D) is also possible in many aldehydes and ketones.

16.14D UV Spectra

The carbonyl groups of saturated aldehydes and ketones give a weak absorption band in the UV region between 270 and 300 nm. This band is shifted to longer wavelengths (300–350 nm) when the carbonyl group is conjugated with a double bond.

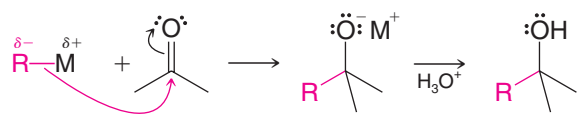
16.15 SUMMARY OF ALDEHYDE AND KETONE ADDITION REACTIONS

The nucleophilic addition reactions of aldehydes and ketones occurring at the carbonyl carbon atom that we have studied so far are summarized below. In Chapters 18 and 19 we shall see other examples.

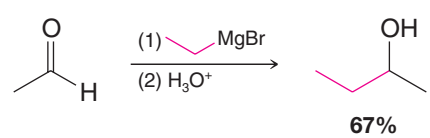
NUCLEOPHILIC ADDITION REACTIONS OF ALDEHYDES AND KETONES

1. ***Addition of Organometallic Compounds*** **(Section 12.7C)**

General Reaction



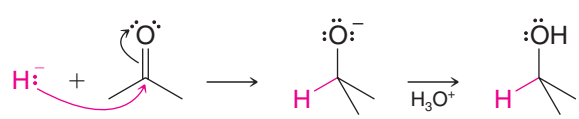
Specific Example Using a Grignard Reagent **(Section 12.7C)**



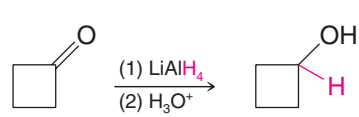
67%

2. ***Addition of Hydride Ion*** **(Section 12.3)**

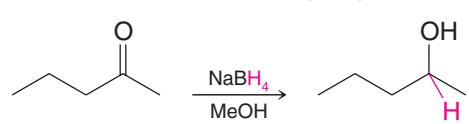
General Reaction



Specific Examples Using Metal Hydrides **(Section 12.3)**



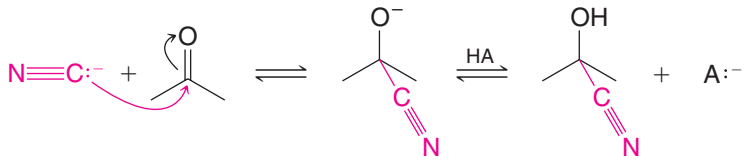
(90%)



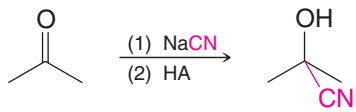
(100%)

3. ***Addition of Hydrogen Cyanide*** **(Section 16.9)**

General Reaction



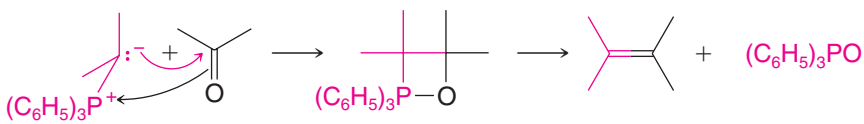
Specific Example



Acetone cyanohydrin (78%)

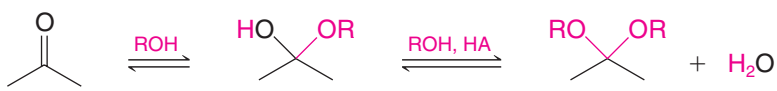
4. ***Addition of Ylides*** **(Section 16.10)**

The Wittig Reaction



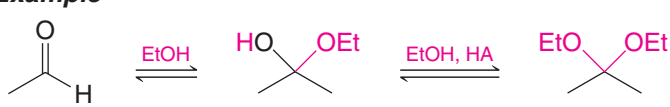
5. ***Addition of Alcohols*** **(Section 16.7)**

General Reaction



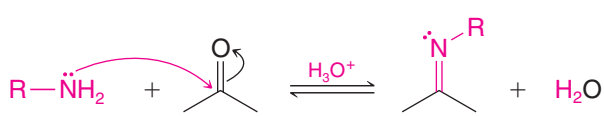
Hemiacetal **Acetal**

Specific Example



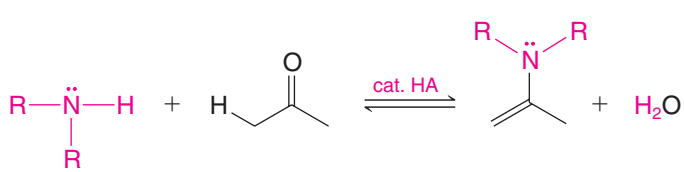
6. ***Addition of Derivatives of Ammonia*** **(Section 16.8)**

Imines



1° Amine **Aldehyde or ketone** **Imine [(*E*) and (*Z*) isomers]**

Enamines



2° Amine **Enamine**

[WHY Do These Topics Matter?

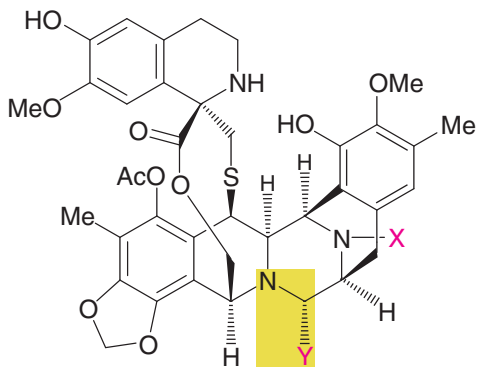
TRIGGERS FOR BIOCHEMICAL REACTIVITY

One of the things that makes sea sponges and other organisms that comprise coral reefs so beautiful is their bright and varied colors. However, this same feature, coupled with their inability to move, renders them easy targets for predators. Yet they survive because they have a chemical defense system that uses small, highly toxic molecules to ward off, injure, or even kill sea-based organism that might consume them. What is perhaps even more amazing is that many of these compounds have a far different

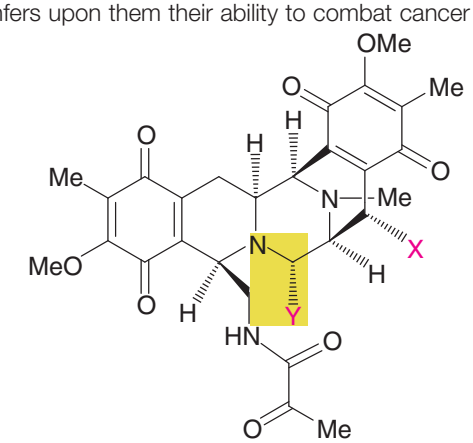
(continues on next page)

effect in humans: the ability to treat cancer by attacking cells that are replicating aberrantly. Moreover, the way in which this happens sometimes takes advantage of functional groups that you have seen in this chapter!

The ecteinascidins and the saframycins are two such groups of compounds. There are several variants of these compounds based on the identity of the atoms at the positions marked with X and Y. The key element for their biological activity is the highlighted configuration of atoms that includes Y. The groups at position Y are most commonly CN or OH, options that generate either the nitrogen functional group analog of a cyanohydrin or a hemiacetal (known as a hemiaminal). As we have seen, such functional groups can participate in a number of reactions, and this reactivity confers upon them their ability to combat cancer cells.

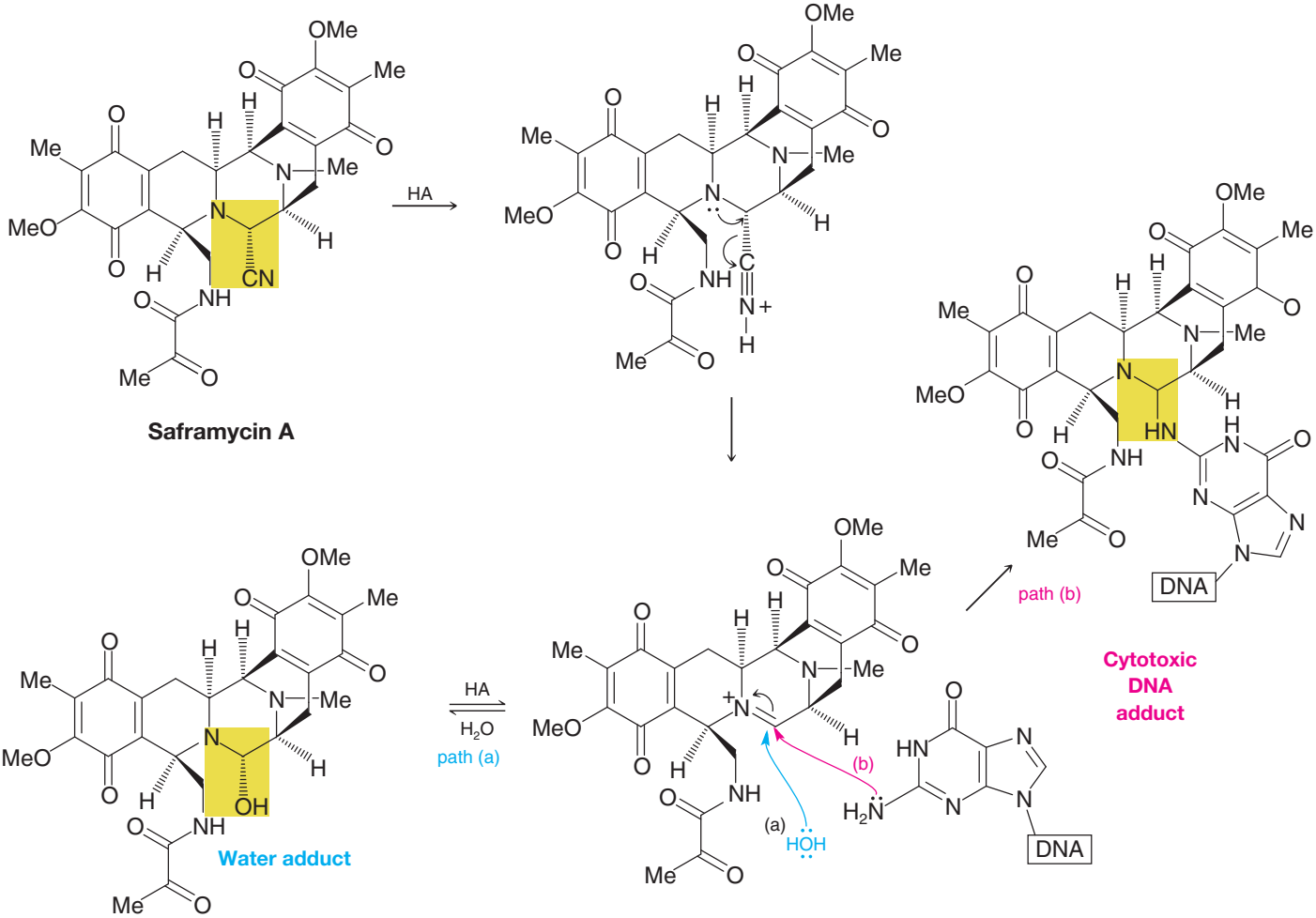


Ecteinascidins



Saframycins

In saframycin A, shown below, proton activation of the nitrile functional group creates a better leaving group, one that can lead to the formation of an iminium ion through the participation of the neighboring nitrogen atom. This reactive iminium species can then either be trapped reversibly by water (path a) to generate a hemiaminal, or if formed in the nucleus of a cell, it can be attacked by the nucleophilic free amine of a guanine residue from DNA (path b). If the latter happens, the other aromatic rings within saframycin A can then convert molecular oxygen into new reactive radical species that can damage the DNA and lead to cell death (we will learn this chemistry in Chapter 21).



What can be appreciated for now is a beautifully engineered triggering system for activity based entirely on some of the functional groups that can arise from carbonyl groups. To put the power of that design into some perspective, these compounds are among the most potent antitumor agents that have ever been identified from marine sources. In fact, some studies have estimated that a 5-mg dose of some compounds would be more than sufficient to eradicate several forms of human cancer. Clinical trials are currently evaluating that potential.

To learn more about these topics, see:

1. Lown, J. W.; Joshua, A. V.; Lee, J. S. "Molecular mechanisms of binding and single-strand scission of deoxyribonucleic acid by the antitumor antibiotics saframycins A and C" in *Biochemistry* **1982**, *21*, 419–428.
2. Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II*. Wiley-VCH: Weinheim, **2003**, pp. 109–136 and references therein.

SUMMARY AND REVIEW TOOLS

The study aids for this chapter include key terms and concepts (which are hyperlinked to the Glossary from the bold, blue terms in the *WileyPLUS* version of the book at wileyplus.com), Mechanism Summaries regarding reactions of aldehydes and ketones with amines as well as with other nucleophiles, and a Synthetic Connections scheme regarding transformations of aldehydes and ketones.

PROBLEMS

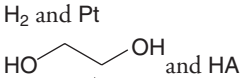
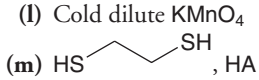
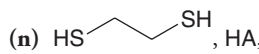
Note to Instructors: Many of the homework problems are available for assignment via *WileyPLUS*, an online teaching and learning solution.

REACTIONS AND NOMENCLATURE

16.22 Give a structural formula and another acceptable name for each of the following compounds:

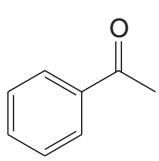
(a) Formaldehyde
(b) Acetaldehyde
(c) Phenylacetaldehyde
(d) Acetone
(e) Ethyl methyl ketone
(f) Acetophenone
(g) Benzophenone
(h) Salicylaldehyde
(i) Vanillin
(j) Diethyl ketone
(k) Ethyl isopropyl ketone
(l) Diisopropyl ketone
(m) Dibutyl ketone
(n) Dipropyl ketone
(o) Cinnamaldehyde

16.23 Write structural formulas for the products formed when propanal reacts with each of the following reagents:

(a) $NaBH_4$ in aqueous NaOH
(b) C_6H_5MgBr, then H_3O^+
(c) $LiAlH_4$, then H_2O
(d) Ag_2O, HO^-
(e) $(C_6H_5)_3\overset{+}{P}-\ddot{\overset{-}{C}}H_2$
(f) H_2 and Pt
(g)  and HA
(h) $CH_3\ddot{\overset{-}{C}}-\overset{+}{P}(C_6H_5)_3$
(i) $Ag(NH_3)_2^+$
(j) Hydroxylamine
(k) Phenylhydrazine
(l) Cold dilute $KMnO_4$
(m)  , HA
(n)  , HA, then Raney nickel
(o) *m*CPBA

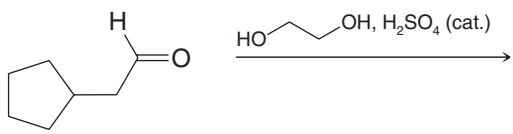
16.24 Give structural formulas for the products formed (if any) from the reaction of acetone with each reagent in Exercise 16.23.

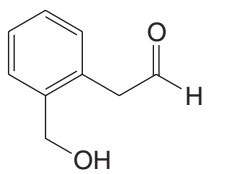
16.25 What products would be obtained when acetophenone reacts under each of the following conditions?

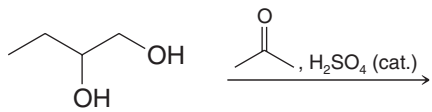

Acetophenone

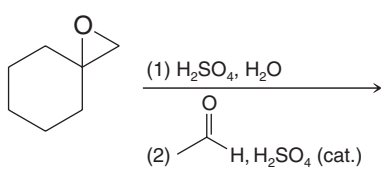
(a) $\xrightarrow[H_2SO_4]{HNO_3}$
(b) $\xrightarrow{C_6H_5NHNH_2,\ HA}$
(c) $\xrightarrow{H_2\ddot{\overset{-}{C}}-\overset{+}{P}(C_6H_5)_3}$
(d) $\xrightarrow[CH_3OH]{NaBH_4}$
(e) $\xrightarrow[(2)\ NH_4Cl]{(1)\ C_6H_5MgBr}$
(f) $\xrightarrow[\Delta]{NH_2NH_2,\ HO^-}$
(g) $\xrightarrow{m\text{CPBA}}$

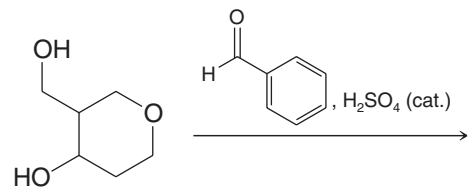
16.26 Predict the major organic product from each of the following reactions.

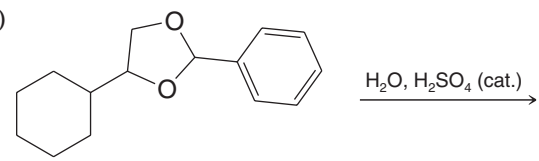
(a) 

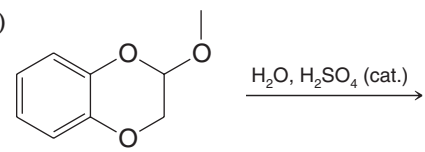
(b) 

(c) 

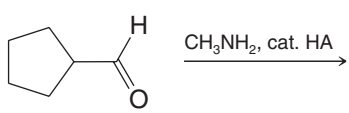
(d) 

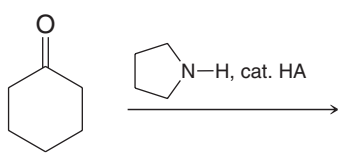
(e) 

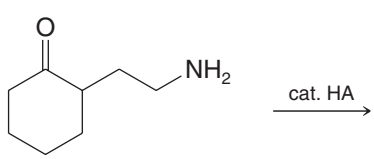
(f) 

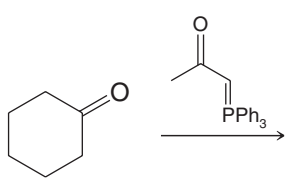
(g) 

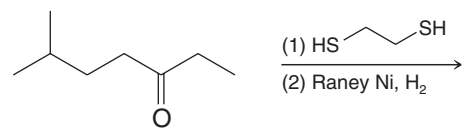
16.27 Predict the major product from each of the following reactions.

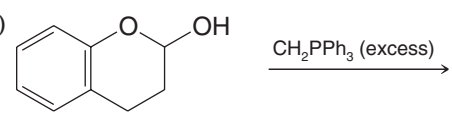
(a) 

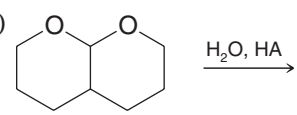
(b) 

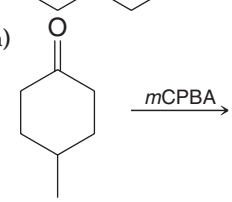
(c) 

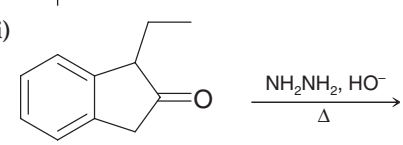
(d) 

(e) 

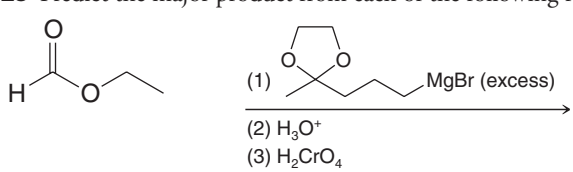
(f) 

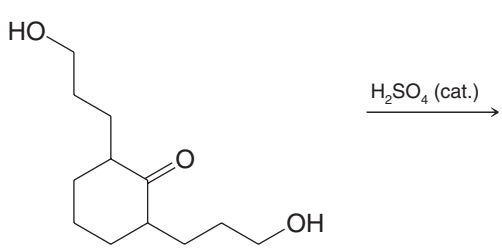
(g) 

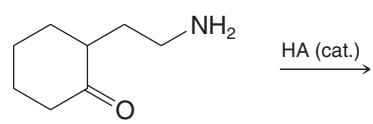
(h) 

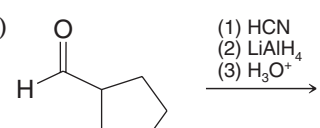
(i) 

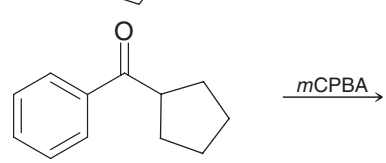
16.28 Predict the major product from each of the following reactions.

(a) 

(b) 

(c) 

(d) 

(e) 

16.29 Provide the reagents needed to accomplish each of the following transformations.

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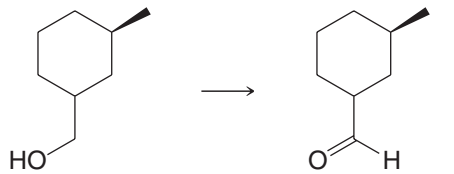

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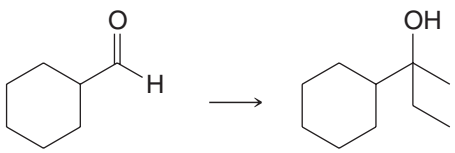

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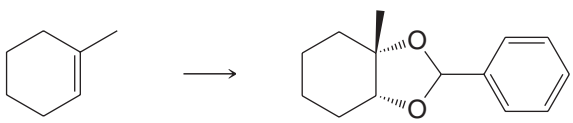

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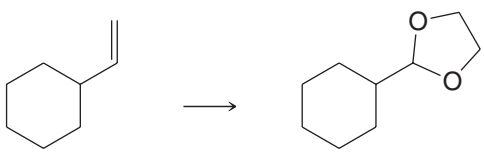

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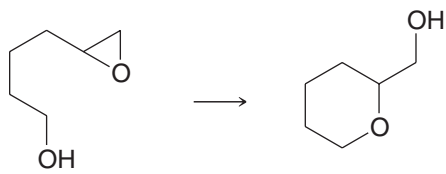

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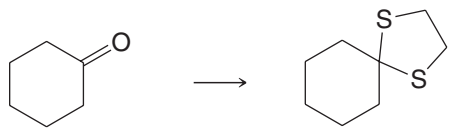

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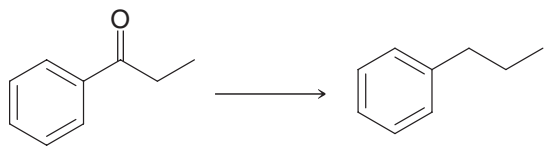

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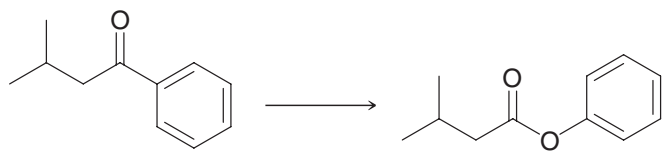
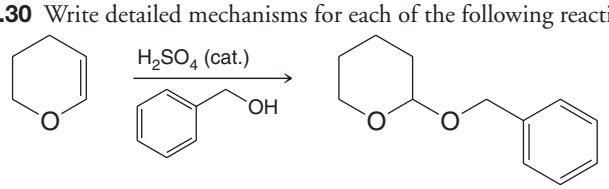


16.30 Write detailed mechanisms for each of the following reactions.

(a)



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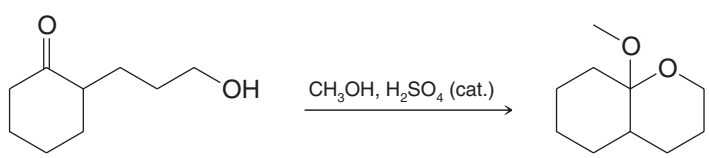

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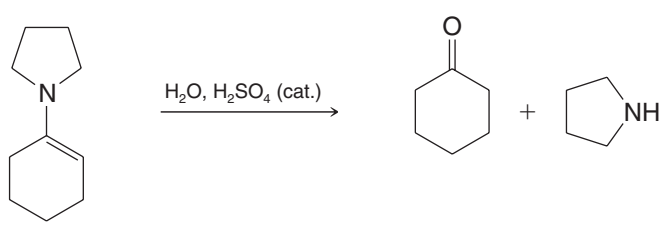
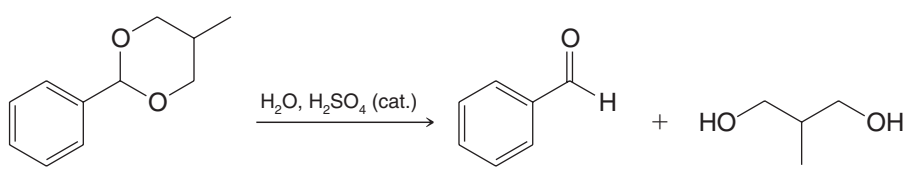
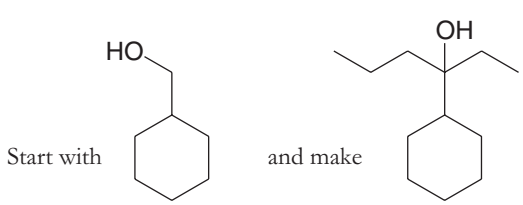


(d)



16.31 Provide the reagents necessary for the following synthesis.



SYNTHESIS

16.32

(a) Synthesize phenyl propyl ketone from benzene and any other needed reagents.

(b) Give two methods for transforming phenyl propyl ketone into butylbenzene.

16.33 Show how you would convert benzaldehyde into each of the following. You may use any other needed reagents, and more than one step may be required.

(a) Benzyl alcohol
(b) Benzoic acid
(c) Benzoyl chloride
(d) Benzophenone
(e) 1-Phenylethanol
(f) 3-Methyl-1-phenyl-1-butanol
(g) Benzyl bromide
(h) Toluene
(i) $C_6H_5CH(OCH_3)_2$
(j) $C_6H_5CH^{18}O$
(k) C_6H_5CHDOH
(l) $C_6H_5CH(OH)CN$
(m) $C_6H_5CH{=}NOH$
(n) $C_6H_5CH{=}NNHC_6H_5$
(o) $C_6H_5CH{=}CHCH{=}CH_2$

16.34 Show how ethyl phenyl ketone ($C_6H_5COCH_2CH_3$) could be synthesized from each of the following:

(a) Benzene
(b) Benzonitrile, C_6H_5CN
(c) Benzaldehyde

16.35 Show how benzaldehyde could be synthesized from each of the following:

(a) Benzyl alcohol
(b) Benzoic acid
(c) Phenylethyne
(d) Phenylethene (styrene)
(e) $C_6H_5CO_2CH_3$
(f) $C_6H_5C{\equiv}N$

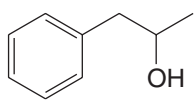
16.36 Give structures for compounds **A–E**.

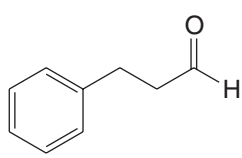
$$\text{Cyclohexanol} \xrightarrow[\text{acetone}]{H_2CrO_4} \mathbf{A}\ (C_6H_{10}O) \xrightarrow[(2)\ H_3O^+]{(1)\ CH_3MgI} \mathbf{B}\ (C_7H_{14}O) \xrightarrow[\text{heat}]{\text{HA}}$$

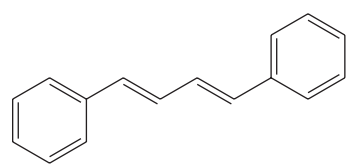
$$\mathbf{C}\ (C_7H_{12}) \xrightarrow[(2)\ Me_2S]{(1)\ O_3} \mathbf{D}\ (C_7H_{12}O_2) \xrightarrow[(2)\ H_3O^+]{(1)\ Ag_2O,\ HO^-} \mathbf{E}\ (C_7H_{12}O_3)$$

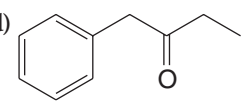
16.37 Warming piperonal (Section 16.3) with dilute aqueous HCl converts it to a compound with the formula $C_7H_6O_3$. What is this compound, and what type of reaction is involved?

16.38 Starting with benzyl bromide, show how you would synthesize each of the following:

(a) 

(b) 

(c) 

(d) 

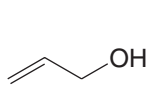
16.39 Compounds **A** and **D** do not give positive Tollens' tests; however, compound **C** does. Give structures for **A–D**.

$$\text{4-Bromobutanal} \xrightarrow{HOCH_2CH_2OH,\ HA} \mathbf{A}\ (C_6H_{11}O_2Br) \xrightarrow{Mg,\ Et_2O}$$

$$[\mathbf{B}\ (C_6H_{11}MgO_2Br)] \xrightarrow[(2)\ H_3O^+,\ H_2O]{(1)\ CH_3CHO} \mathbf{C}\ (C_6H_{12}O_2) \xrightarrow[HA]{CH_3OH} \mathbf{D}\ (C_7H_{14}O_2)$$

16.40 Dianeackerone is a volatile natural product isolated from secretory glands of the adult African dwarf crocodile. The compound is believed to be a pheromone associated with nesting and mating. Dianeackerone is named after Diane Ackerman, an author in the field of natural history and champion of the importance of preserving biodiversity. The IUPAC name of dianeackerone is 3,7-diethyl-9-phenylnonan-2-one, and it is found as both the (3*S*,7*S*) and (3*S*,7*R*) stereoisomers. Draw structures for both stereoisomers of dianeackerone.

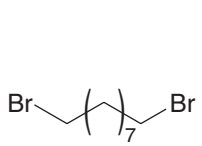
16.41 Outlined here is a synthesis of glyceraldehyde (Section 5.15A). What are the intermediates **A–C** and what stereoisomeric form of glyceraldehyde would you expect to obtain?



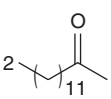
$$\xrightarrow[CH_2Cl_2]{PCC} \mathbf{A}\ (C_3H_4O) \xrightarrow{CH_3OH,\ HA} \mathbf{B}\ (C_5H_{10}O_2) \xrightarrow[\text{cold, dilute}]{KMnO_4,\ HO^-} \mathbf{C}\ (C_5H_{12}O_4) \xrightarrow[H_2O]{H_3O^+} \text{glyceraldehyde}$$

16.42 Consider the reduction of (*R*)-3-phenyl-2-pentanone by sodium borohydride. After the reduction is complete, the mixture is separated by chromatography into two fractions. These fractions contain isomeric compounds, and each isomer is optically active. What are these two isomers and what is the stereoisomeric relationship between them?

16.43 The structure of the sex pheromone (attractant) of the female tsetse fly has been confirmed by the following synthesis. Compound **C** appears to be identical to the natural pheromone in all respects (including the response of the male tsetse fly). Provide structures for **A, B,** and **C.**



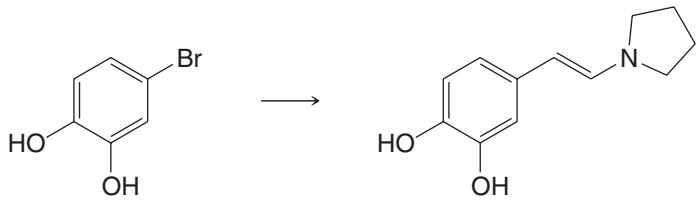
$$\xrightarrow[(2)\ 2\ RLi]{(1)\ 2\ (C_6H_5)_3P} \mathbf{A}\ (C_{45}H_{46}P_2)$$



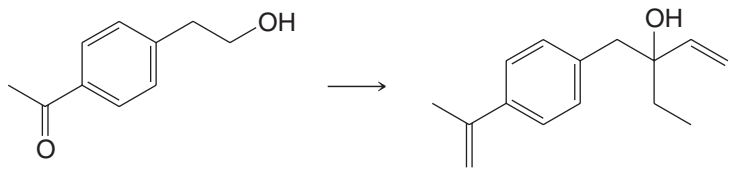
$$\xrightarrow{H_2,\ Pt} \mathbf{B}\ (C_{37}H_{72}) \xrightarrow{} \mathbf{C}\ (C_{37}H_{76})$$

16.44 Provide reagents that would accomplish each of the following syntheses. Begin by writing a retrosynthetic analysis.

(a)

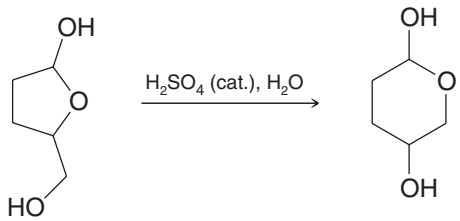


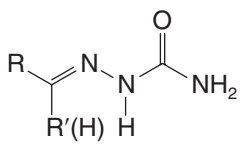
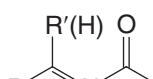
(b)



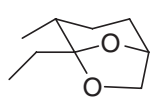
MECHANISMS AND STRUCTURE ELUCIDATION

16.45 Write a detailed mechanism for the following reaction.



16.46 When  (semicarbazide) reacts with a ketone (or an aldehyde) to form a derivative known as a semicarbazone, only one nitrogen atom of semicarbazide acts as a nucleophile and attacks the carbonyl carbon atom of the ketone. The product of the reaction, consequently, is  rather than  . What factor accounts for the fact that two nitrogen atoms of semicarbazide are relatively non-nucleophilic?

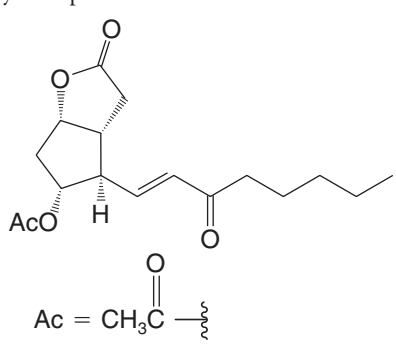
16.47 Dutch elm disease is caused by a fungus transmitted to elm trees by the elm bark beetle. The female beetle, when she has located an attractive elm tree, releases several pheromones, including multistriatin, below. These pheromones attract male beetles, which bring with them the deadly fungus.



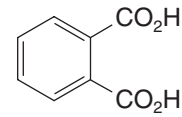
Multistriatin

Treating multistriatin with dilute aqueous acid at room temperature leads to the formation of a product, $C_{10}H_{20}O_3$, which shows a strong infrared peak near 1715 cm^{-1}. Propose a structure for this product.

16.48 The following structure is an intermediate in a synthesis of prostaglandins $F_{2\alpha}$ and E_2 by E. J. Corey (Harvard University). A Horner–Wadsworth–Emmons reaction was used to form the (*E*)-alkene. Write structures for the phosphonate ester and carbonyl reactant that were used in this process. (*Note*: The carbonyl component of the reaction included the cyclopentyl group.)



16.49 Compounds **W** and **X** are isomers; they have the molecular formula C_9H_8O. The IR spectrum of each compound shows a strong absorption band near 1715 cm^{-1}. Oxidation of either compound with hot, basic potassium permanganate followed by acidification yields phthalic acid. The ^1H NMR spectrum of **W** shows a multiplet at δ 7.3 and a singlet at δ 3.4. The ^1H NMR spectrum of **X** shows a multiplet at δ 7.5, a triplet at δ 3.1, and a triplet at δ 2.5. Propose structures for **W** and **X**.



Phthalic acid

16.50 Compounds **Y** and **Z** are isomers with the molecular formula $C_{10}H_{12}O$. The IR spectrum of each compound shows a strong absorption band near 1710 cm^{-1}. The ^1H NMR spectra of **Y** and **Z** are given in Figs. 16.4 and 16.5. Propose structures for **Y** and **Z**.

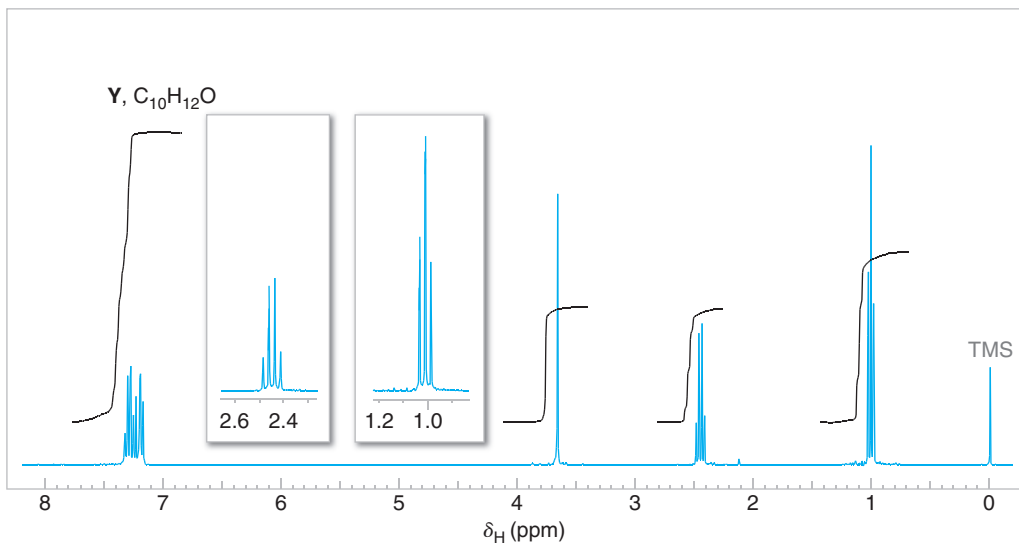


FIGURE 16.4 The 300-MHz ^1H NMR spectrum of compound **Y**, Problem 16.50. Expansions of the signals are shown in the offset plots.

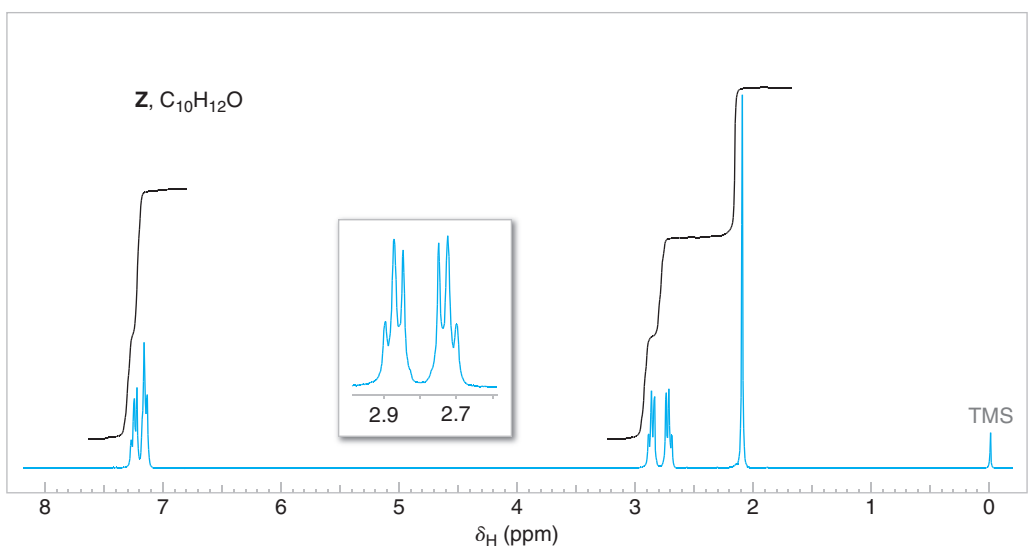


FIGURE 16.5 The 300-MHz ^1H NMR spectrum of compound **Z**, Problem 16.50. Expansions of the signals are shown in the offset plots.

16.51 Compound **A** ($C_9H_{18}O$) forms a phenylhydrazone, but it gives a negative Tollens' test. The IR spectrum of **A** has a strong band near 1710 cm^{-1}. The broadband proton-decoupled ^{13}C NMR spectrum of **A** is given in Fig. 16.6. Propose a structure for **A**.

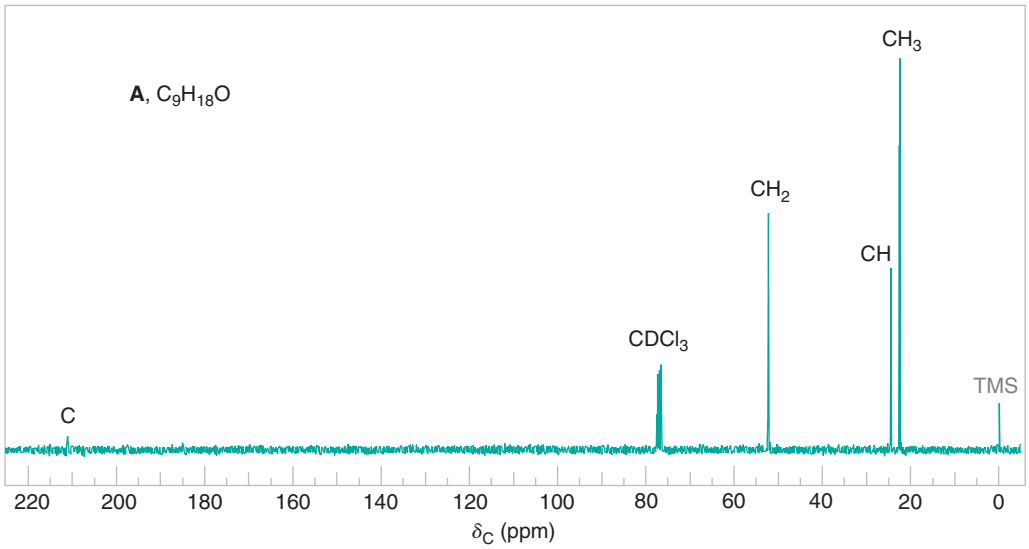


FIGURE 16.6 The broadband proton-decoupled ^{13}C NMR spectrum of compound **A**, Problem 16.51. Information from the DEPT ^{13}C NMR spectra is given above the peaks.

16.52 Compound **B** ($C_8H_{12}O_2$) shows a strong carbonyl absorption in its IR spectrum. The broadband proton-decoupled ^{13}C NMR spectrum of **B** has only three signals, at δ 19 (CH_3), 71 (C), and 216 (C). Propose a structure for **B**.

CHALLENGE PROBLEMS

16.53 **(a)** What would be the frequencies of the two absorption bands expected to be most prominent in the infrared spectrum of 4-hydroxycycloheptanone **(C)**?

(b) In reality, the lower frequency band of these two is very weak. Draw the structure of an isomer that would exist in equilibrium with **C** and that explains this observation.

16.54 One of the important reactions of benzylic alcohols, ethers, and esters is the ease of cleavage of the benzyl–oxygen bond during hydrogenation. This is another example of "hydrogenolysis," the cleavage of a bond by hydrogen. It is facilitated by the presence of acid. Hydrogenolysis can also occur with strained-ring compounds.

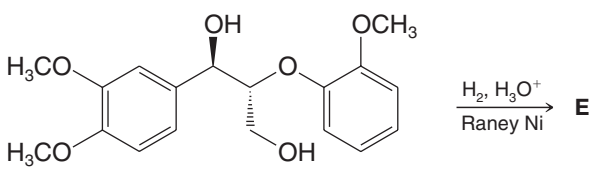
On hydrogenation of compound **D** (see below) using Raney nickel catalyst in a dilute solution of hydrogen chloride in dioxane and water, most products have a 3,4-dimethoxyphenyl group attached to a side chain. Among these, an interesting product is **E**, whose formation illustrates not only hydrogenolysis but also the migratory aptitude of phenyl groups. For product **E**, these are key spectral data:

MS (*m/z*): 196.1084 ($M^{+\cdot}$, at high resolution), 178

IR (cm^{-1}): 3400 (broad), 3050, 2850 (CH_3—O stretch)

^1H **NMR** (δ, in $CDCl_3$): 1.21 (d, 3H, $J = 7$ Hz), 2.25 (s, 1H), 2.83 (m, 1H), 3.58 (d, 2H, $J = 7$ Hz), 3.82 (s, 6H), 6.70 (s, 3H).

What is the structure of compound **E**?



D

LEARNING GROUP PROBLEMS

A synthesis of ascorbic acid (vitamin C, **1**) starting from D-(+)-galactose (**2**) is shown below (Haworth, W. N., et al., *J. Chem. Soc.*, **1933**, 1419–1423). Consider the following questions about the design and reactions used in this synthesis:

(a) Why did Haworth and co-workers introduce the acetal functional groups in **3**?

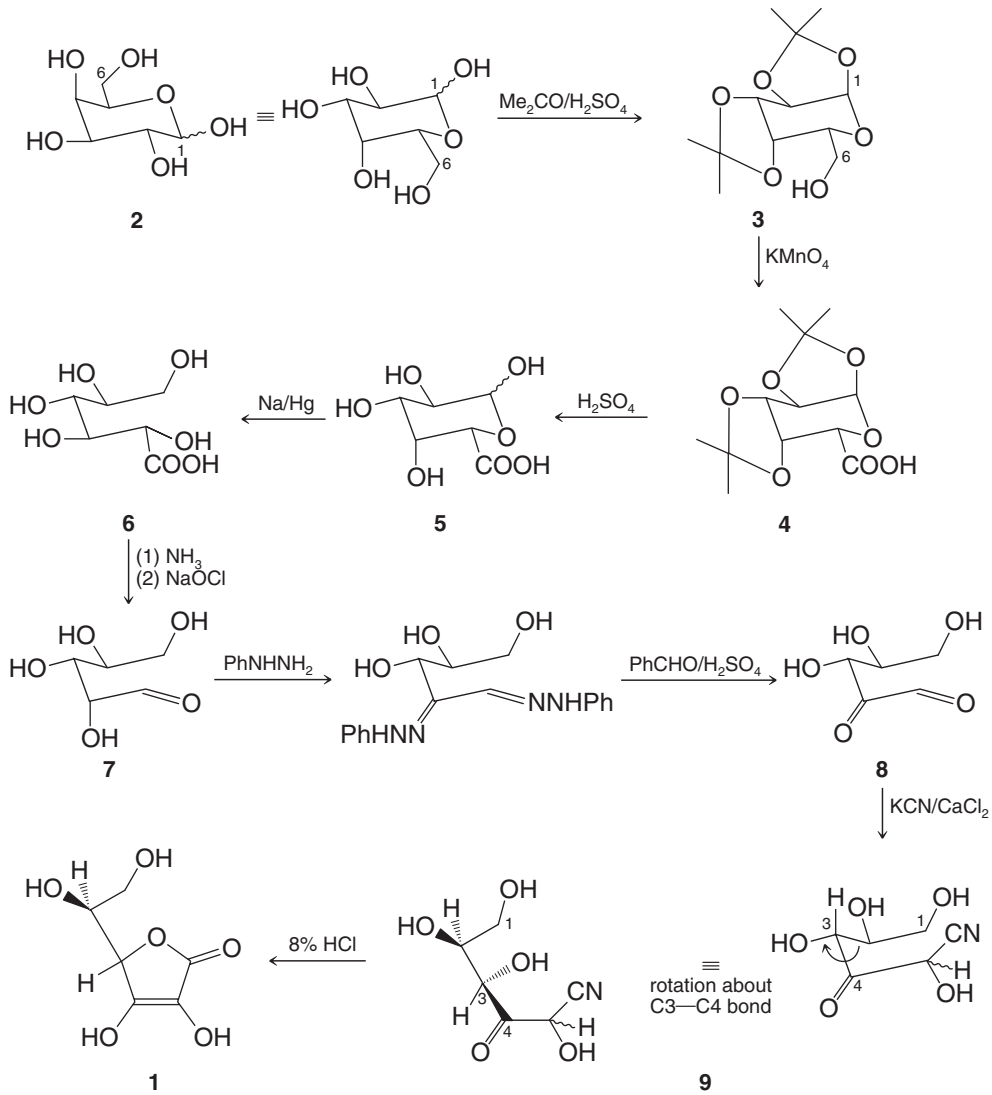
(b) Write a mechanism for the formation of one of the acetals.

(c) Write a mechanism for the hydrolysis of one of the acetals (**4** to **5**). Assume that water was present in the reaction mixture.

(d) In the reaction from **5** to **6** you can assume that there was acid (e.g., HCl) present with the sodium amalgam. What reaction occurred here and from what functional group did that reaction actually proceed?

(e) Write a mechanism for the formation of a phenylhydrazone from the aldehyde carbonyl of **7**. [Do not be concerned about the phenylhydrazone group at C2. We shall study the formation of bishydrazones of this type (called an osazone) in Chapter 22.]

(f) What reaction was used to add the carbon atom that ultimately became the lactone carbonyl carbon in ascorbic acid (**1**)?

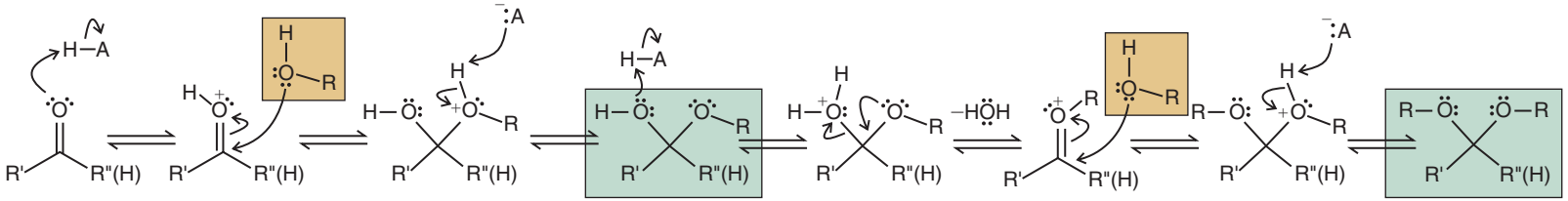


SUMMARY OF MECHANISMS

Acetals, Imines, and Enamines: Common Mechanistic Themes in Their Acid-catalyzed Formation from Aldehydes and Ketones

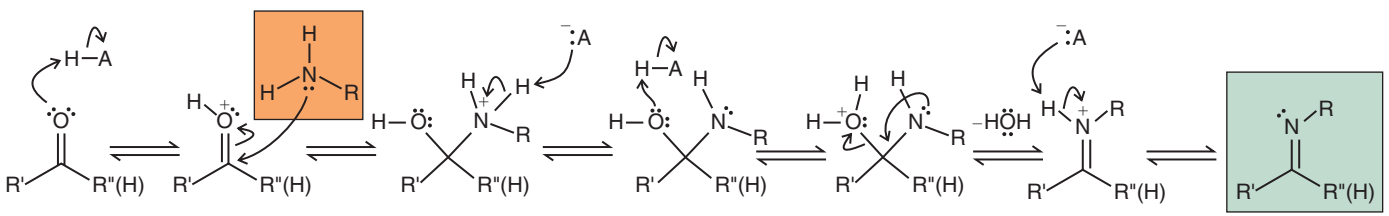
Many steps are nearly the same in acid-catalyzed reactions of aldehydes and ketones with alcohols and amines. Compare the mechanisms vertically to see the similarities and differences. Note differences in completion of the mechanism for each type of product.

I. Hemiacetal and acetal formation: reaction with alcohols



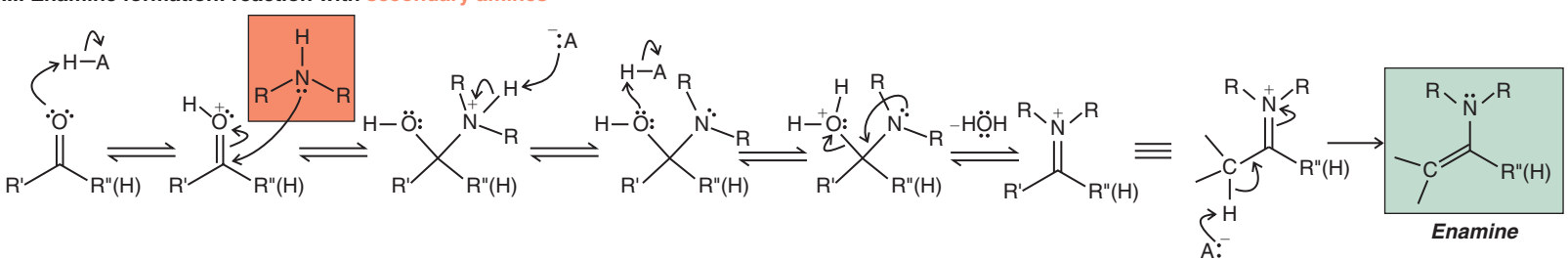
*In **acetal** formation, the oxonium ion is attacked by a second alcohol molecule.*

II. Imine formation: reaction with primary amines



*In **imine** formation, the proton on the initial iminium ion is removed, leading to the stable imine product.*

III. Enamine formation: reaction with secondary amines

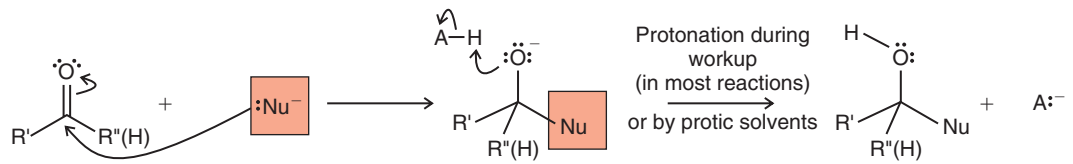


*In **enamine** formation, a proton is removed from a carbon adjacent to the iminium carbon (because no proton is available for removal from the nitrogen).*

SUMMARY OF MECHANISMS

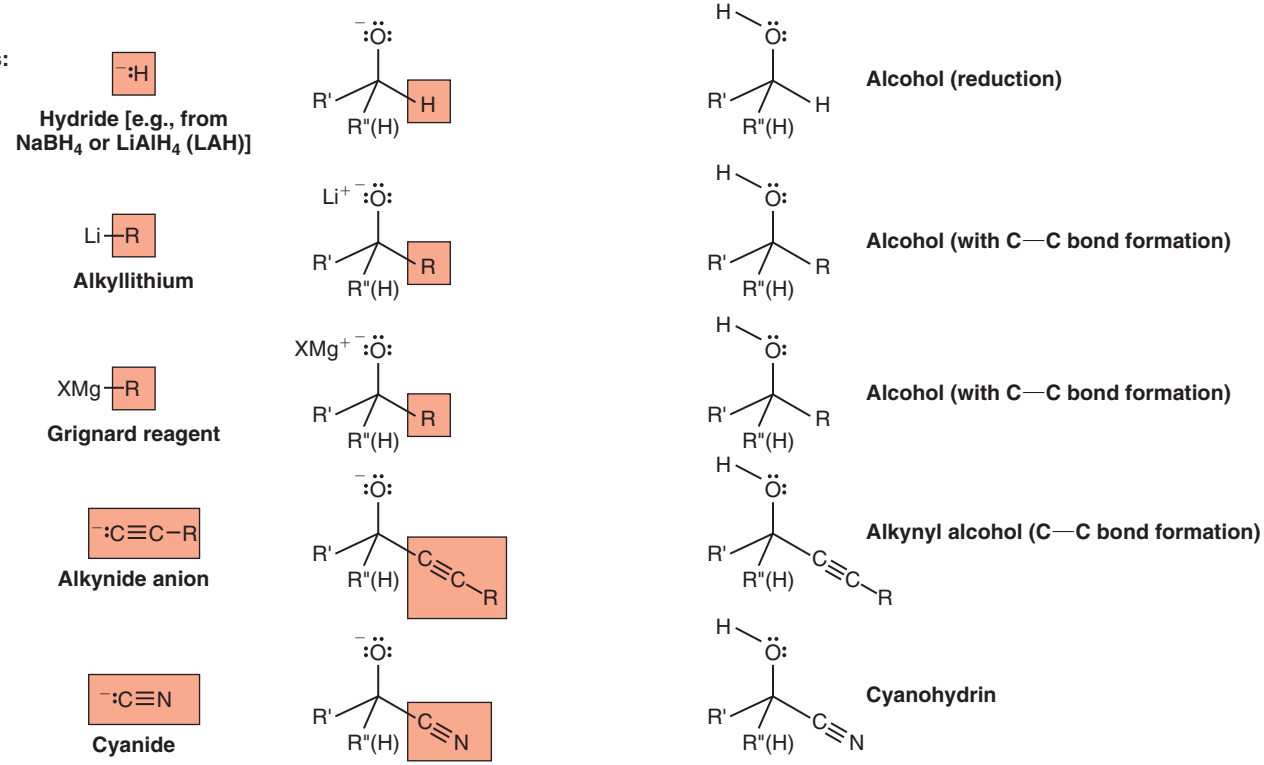
Nucleophilic Addition to Aldehydes and Ketones Under Basic Conditions

Generalized nucleophilic addition to an aldehyde or ketone:



Aldehyde or ketone | Nucleophile | Tetrahedral intermediate | Product

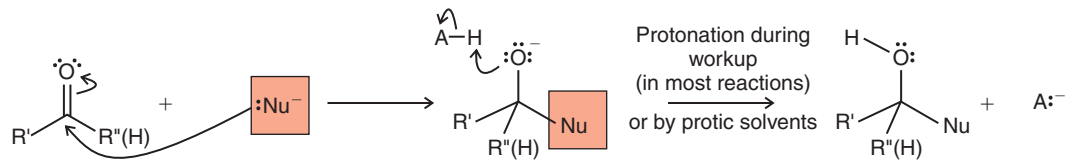
Examples:



SUMMARY OF MECHANISMS

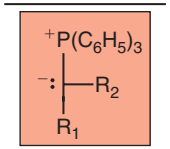
Nucleophilic Addition to Aldehydes and Ketones Under Basic Conditions

Generalized nucleophilic addition to an aldehyde or ketone:

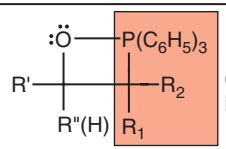


Aldehyde or ketone | **Nucleophile** | **Tetrahedral Intermediate** | **Product**

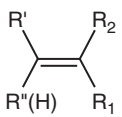
Examples (continued):



Phosphorus ylide

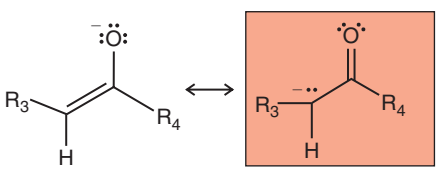


Oxaphosphetane intermediate

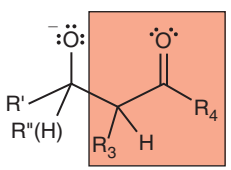


(plus diastereomer)

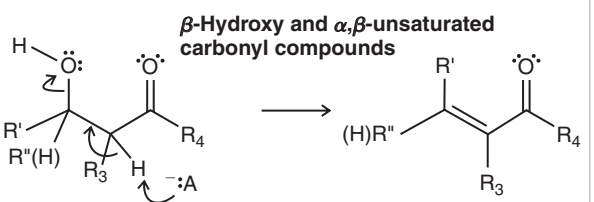
Wittig preparation of alkenes (with loss of triphenylphosphine oxide [$(C_6H_5)_3PO$])



Enolate (see Chapter 18)



β-Hydroxy and α,β-unsaturated carbonyl compounds



SYNTHETIC CONNECTIONS

Some Synthetic Connections of Aldehydes, Ketones, and Other Functional Groups

Clockwise from center, bottom:

I. Preparation of aldehydes and ketones:

- Nitrile, ester, acyl halide reduction
- Alcohol oxidation
- Ozonolysis
- Friedel–Crafts acylation
- Grignard with nitrile
- Acetal and hemiacetal hydrolysis

II. Reactions of aldehydes and ketones:

- Hemiacetal and acetal formation
- Thioacetal formation and reduction
- Wolff– Kishner reduction
- Alkynide anion addition
- Nitrile addition (cyanohydrin formation)
- Wittig synthesis of alkenes
- Enamine synthesis
- Baeyer–Villiger oxidation
- Imine synthesis
- Reduction to alcohols (left, center)