Ketones and Aldehydes

Carbonyl Compounds

$(C=O)$

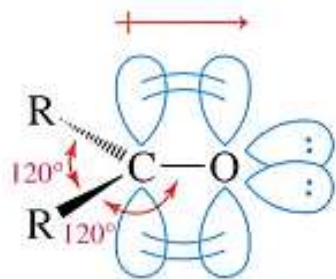|		
ketone	aldehyde	carbonyl group
RCOR′	RCHO	
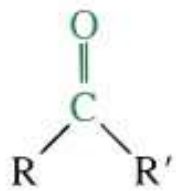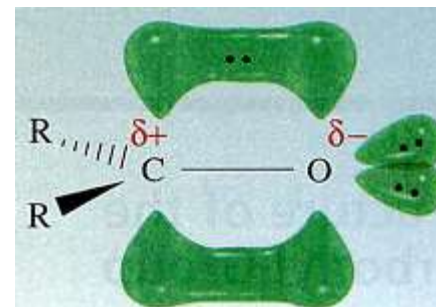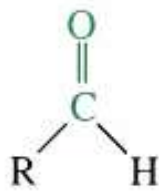
condensed structures:

Ketone: Two alkyl groups bonded to a carbonyl group.

Aldehyde: One alkyl group and one hydrogen bonded to a carbonyl group.
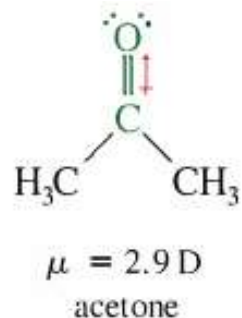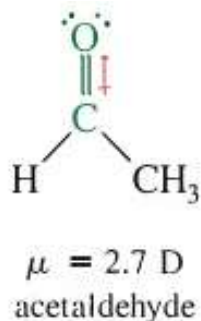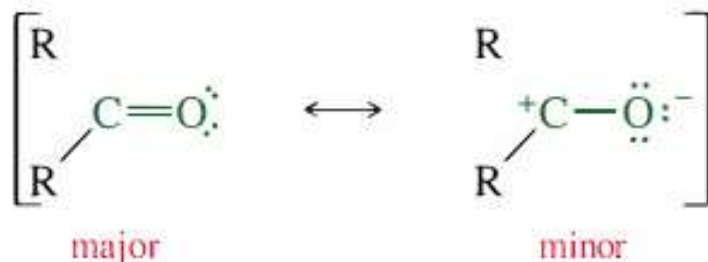
TABLE 18-1   Some Common Classes of Carbonyl Compounds

Class	General Formula	Class	General Formula
ketones	$R-\overset{\overset{\text{O}}{\|\|}}{C}-R'$	aldehydes	$R-\overset{\overset{\text{O}}{\|\|}}{C}-H$
carboxylic acids	$R-\overset{\overset{\text{O}}{\|\|}}{C}-OH$	acid chlorides	$R-\overset{\overset{\text{O}}{\|\|}}{C}-Cl$
esters	$R-\overset{\overset{\text{O}}{\|\|}}{C}-O-R'$	amides	$R-\overset{\overset{\text{O}}{\|\|}}{C}-NH_2$

Structure of the Carbonyl Group

	length	energy
ketone C=O bond	1.23 Å	745 kJ/mol (178 kcal/mol)
alkene C=C bond	1.34 Å	611 kJ/mol (146 kcal/mol)

$$\left[\begin{array}{c} R \\ \diagdown \\ R \end{array} C=\ddot{O}\!\!: \longleftrightarrow \begin{array}{c} R \\ \diagdown \\ R \end{array} {}^{+}C-\ddot{\ddot{O}}\!:^{-} \right]$$

major   minor

Compare with:

μ = 2.7 D
acetaldehyde

μ = 2.9 D
acetone

μ = 1.9 D
chloromethane

μ = 1.30 D
dimethyl ether
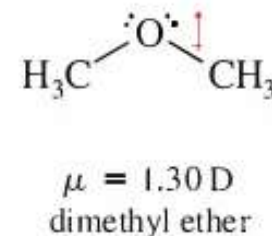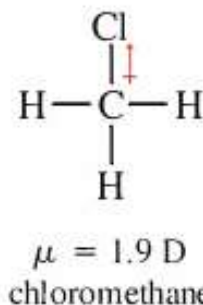
Nomenclature of Ketones and Aldehydes

**IUPAC Names** Systematic names of ketones are derived by replacing the final -*e* in the alkane name with -*one*. The "alkane" name becomes "alkanone." In open-chain ketones, we number the longest chain that includes the carbonyl carbon from the end closest to the carbonyl group, and we indicate the position of the carbonyl group by a number. In cyclic ketones, the carbonyl carbon atom is assigned the number 1.
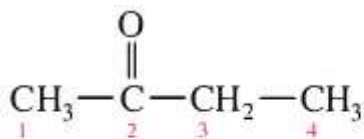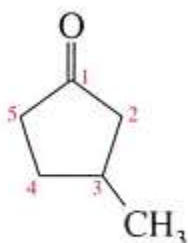
2-butanone
butan-2-one
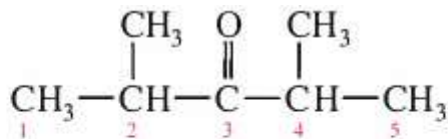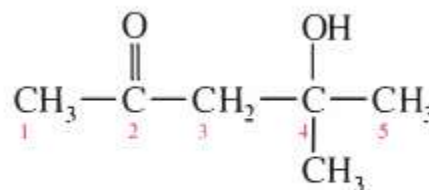
2,4-dimethyl-3-pentanone
2,4-dimethylpentan-3-one
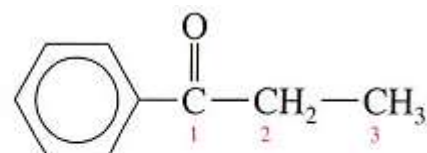
1-phenyl-1-propanone
1-phenylpropan-1-one

3-methylcyclopentanone

2-cyclohexenone
cyclohex-2-en-1-one

4-hydroxy-4-methyl-2-pentanone
4-hydroxy-4-methylpentan-2-one

Systematic names for aldehydes are derived by replacing the final -e of the alkane name with -al. An aldehyde carbon is at the end of a chain, so it is number 1. If the aldehyde group is attached to a large unit (usually a ring), the suffix *carbaldehyde* is used.
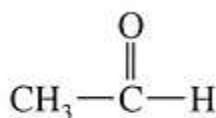
ethanal
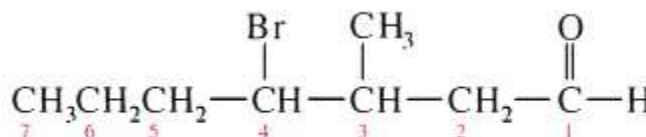
4-bromo-3-methylheptanal
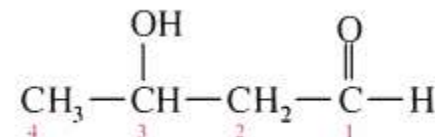
3-hydroxybutanal
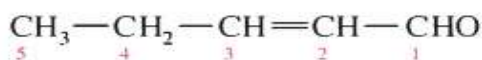
2-pentenal
pent-2-enal
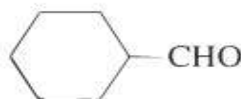
cyclohexanecarbaldehyde

2-hydroxycyclopentane-1-carbaldehyde

A ketone or aldehyde group can also be named as a substituent on a molecule with another functional group as its root. The ketone carbonyl is designated by the prefix *oxo-*, and the —CHO group is named as a *formyl* group. Carboxylic acids frequently contain ketone or aldehyde groups named as substituents.
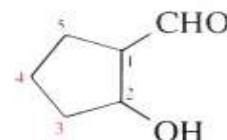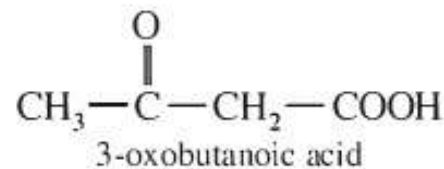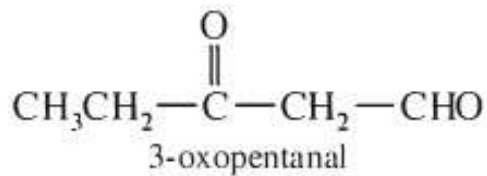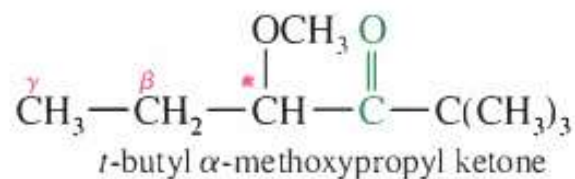
$$CH_3CH_2-\underset{\underset{O}{\|}}{C}-CH_2-CHO$$
3-oxopentanal

2-formylbenzoic acid

$$CH_3-\underset{\underset{O}{\|}}{C}-CH_2-COOH$$
3-oxobutanoic acid

Common Names   As with other classes of compounds, ketones and aldehydes are often called by common names instead of their systematic IUPAC names. Ketone common names are formed by naming the two alkyl groups bonded to the carbonyl group. Substituent locations are given using Greek letters, beginning with the carbon *next to* the carbonyl group.

$$CH_3CH_2-\underset{\underset{O}{\|}}{C}-CH_3$$
methyl ethyl ketone

$$CH_3CH_2-\underset{\underset{CH_3}{|}}{CH}-\underset{\underset{O}{\|}}{C}-\underset{\underset{CH_3}{|}}{CH}-CH_2CH_3$$
di-*sec*-butyl ketone

$$Br-\underset{\beta}{CH_2}-\underset{\alpha}{CH_2}-\underset{\underset{O}{\|}}{C}-\underset{\underset{CH_3}{|}}{CH}-CH_3$$
β-bromoethyl isopropyl ketone

$$\underset{\gamma}{CH_3}-\underset{\beta}{CH_2}-\underset{\underset{OCH_3}{|}}{CH}-\underset{\underset{O}{\|}}{C}-C(CH_3)_3$$
t-butyl α-methoxypropyl ketone

4
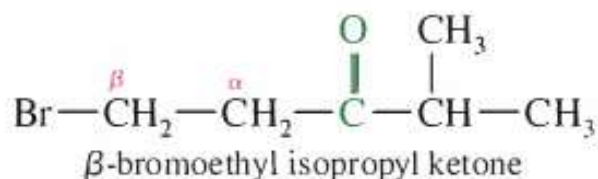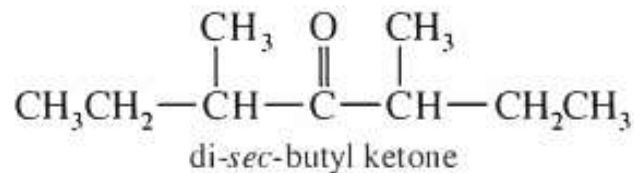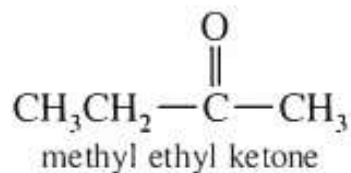
Some ketones have historical common names. Dimethyl ketone is always called *acetone*, and alkyl phenyl ketones are usually named as the acyl group followed by the suffix -*phenone*.

acetone   acetophenone   propiophenone   benzophenone
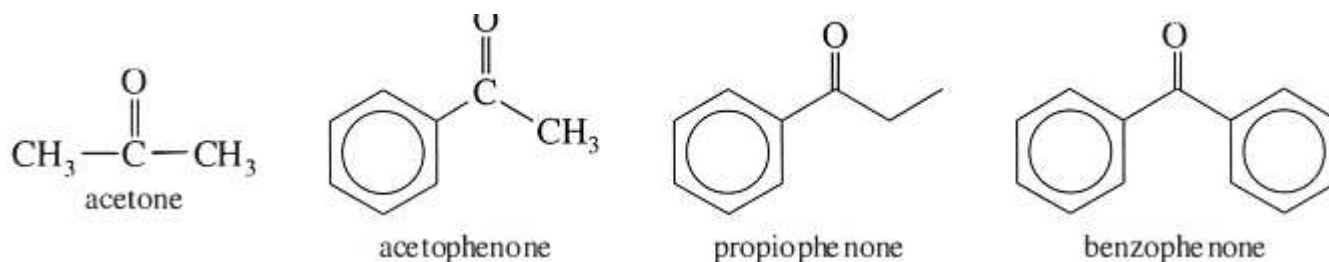
Common names of aldehydes are derived from the common names of carboxylic acids (Table 18-2). These names often reflect the Latin or Greek term for the original source of the acid or the aldehyde. Greek letters are used with common names of aldehydes to give the locations of substituents. The first letter (α) is given to the carbon atom *next to* the carbonyl group.
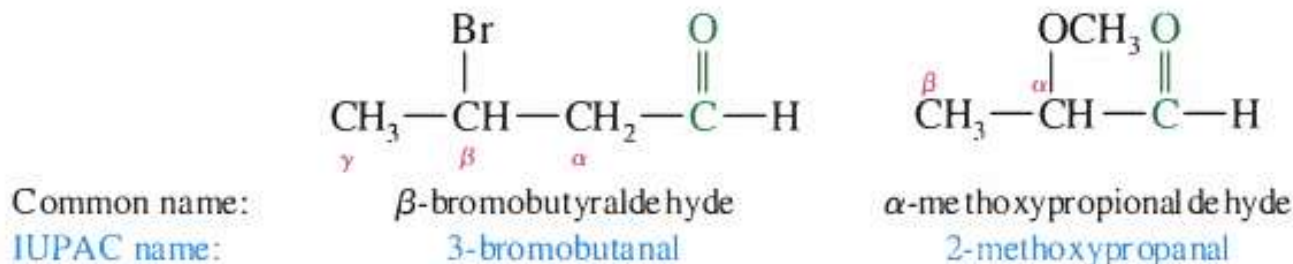

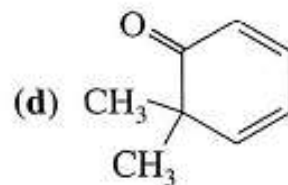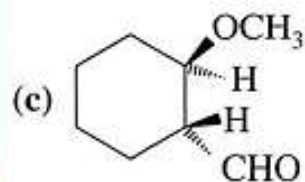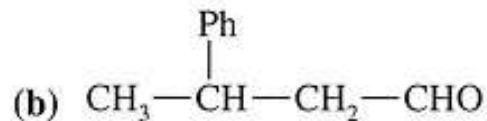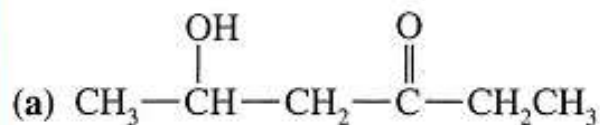|		
Common name:	β-bromobutyraldehyde	α-methoxypropionaldehyde
IUPAC name:	3-bromobutanal	2-methoxypropanal

TABLE 18-2 Common Names of Aldehydes

Carboxylic Acid	Derivation	Aldehyde
$$H-\overset{\overset{\displaystyle O}{\|\|}}{C}-OH$$ formic acid	*formica*, "ants"	$$H-\overset{\overset{\displaystyle O}{\|\|}}{C}-H$$ formaldehyde (methanal)
$$CH_3-\overset{\overset{\displaystyle O}{\|\|}}{C}-OH$$ acetic acid	*acetum*, "sour"	$$CH_3-\overset{\overset{\displaystyle O}{\|\|}}{C}-H$$ acetaldehyde (ethanal)
$$CH_3-CH_2-\overset{\overset{\displaystyle O}{\|\|}}{C}-OH$$ propionic acid	*protos pion*, "first fat"	$$CH_3-CH_2-\overset{\overset{\displaystyle O}{\|\|}}{C}-H$$ propionaldehyde (propanal)
$$CH_3-CH_2-CH_2-\overset{\overset{\displaystyle O}{\|\|}}{C}-OH$$ butyric acid	*butyrum*, "butter"	$$CH_3-CH_2-CH_2-\overset{\overset{\displaystyle O}{\|\|}}{C}-H$$ butyraldehyde (butanal)
benzoic acid	*gum benzoin*, "blending"	benzaldehyde

PROBLEM 18-1

Give the IUPAC name and (if possible) a common name for each compound.

(a) $CH_3-\overset{\underset{\displaystyle |}{OH}}{CH}-CH_2-\overset{\underset{\displaystyle }{\overset{\displaystyle O}{\parallel}}}{C}-CH_2CH_3$

(b) $CH_3-\overset{\underset{\displaystyle |}{Ph}}{CH}-CH_2-CHO$

(c)

(d)

Physical Properties of Ketones and Aldehydes

$CH_3CH_2CH_2CH_3$
butane
bp 0°C

$CH_3-O-CH_2CH_3$
methoxyethane
bp 8°C

$CH_3CH_2-\overset{\overset{\displaystyle O}{\parallel}}{C}-H$
propanal
bp 49°C

$CH_3-\overset{\overset{\displaystyle O}{\parallel}}{C}-CH_3$
acetone
bp 56°C

$CH_3CH_2CH_2-OH$
1-propanol
bp 97°C
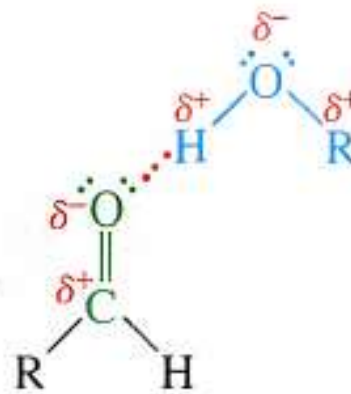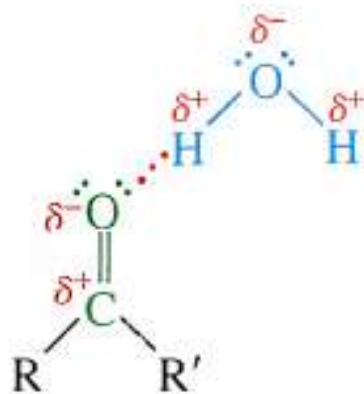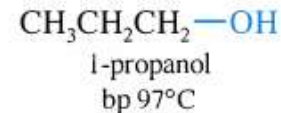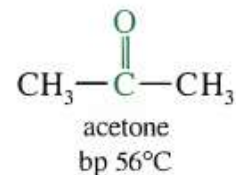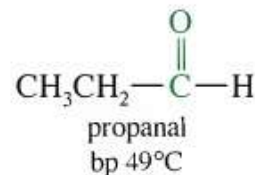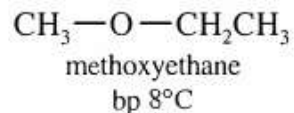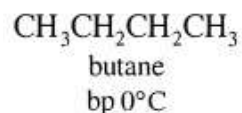
Industrial Importance of Ketones and Aldehydes

TABLE 18-4   Ketones and Aldehydes Used in Household Products

butyraldehyde

vanillin

acetophenone

trans-cinnamaldehyde
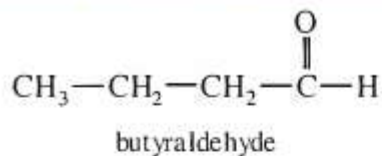
Odor:	buttery	vanilla	pistachio	cinnamon
Uses:	margarine, foods	foods, perfumes	ice cream	candy, foods, drugs

camphor

pyrethrin

carvone

muscone
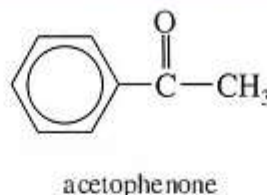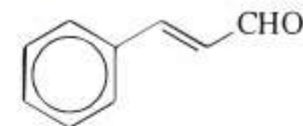
Odor:	"camphoraceous"	floral	(−) enantiomer: spearmint (+) enantiomer: caraway seed	musky aroma
Uses:	liniments, inhalants	plant insecticide	candy, toothpaste, etc.	perfumes
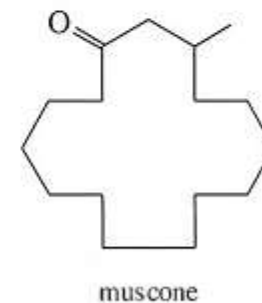
Review of Syntheses of Ketones and Aldehydes

Ketones and Aldehydes from Oxidation of Alcohols

$$R-MgX + R'-\overset{\displaystyle O}{\overset{\|}{C}}-H \xrightarrow[\text{ether}]{} \xrightarrow{H_3O^+} R-\overset{\displaystyle OH}{\overset{|}{C}H}-R' \xrightarrow[\text{H}_2\text{SO}_4]{Na_2Cr_2O_7} R-\overset{\displaystyle O}{\overset{\|}{C}}-R'$$

Grignard   aldehyde   secondary alcohol   ketone

borneol $\xrightarrow[\text{H}_2\text{SO}_4]{Na_2Cr_2O_7}$ camphor (88%)
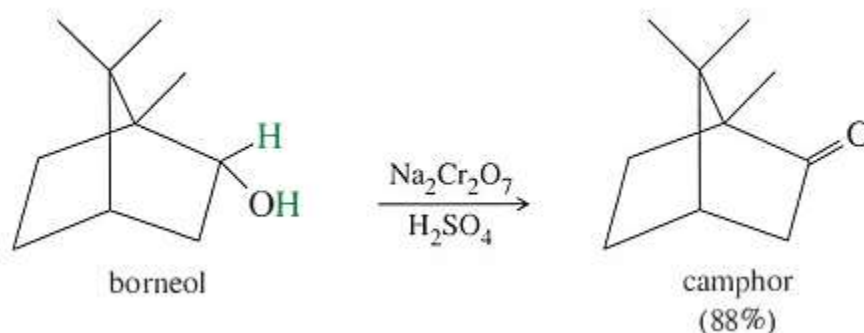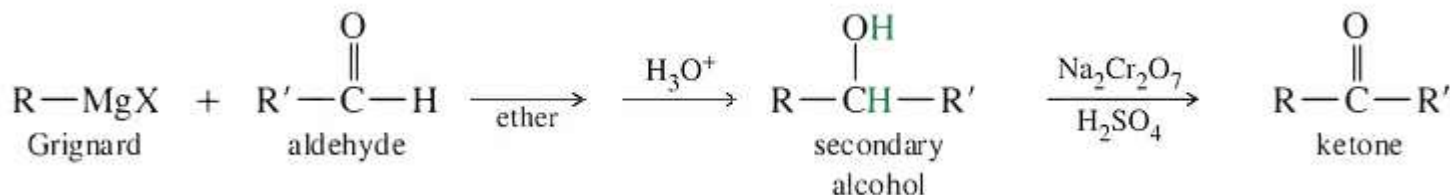
Primary alcohols → aldehydes

$$R-\overset{\displaystyle OH}{\overset{|}{C}H_2} \xrightarrow[-2\,H]{\text{[oxidizing agent]}} R-\overset{\displaystyle O}{\overset{\|}{C}}-H \xrightarrow[\text{[O]}]{\text{[overoxidation]}} R-\overset{\displaystyle O}{\overset{\|}{C}}-OH$$

primary alcohol   aldehyde   carboxylic acid
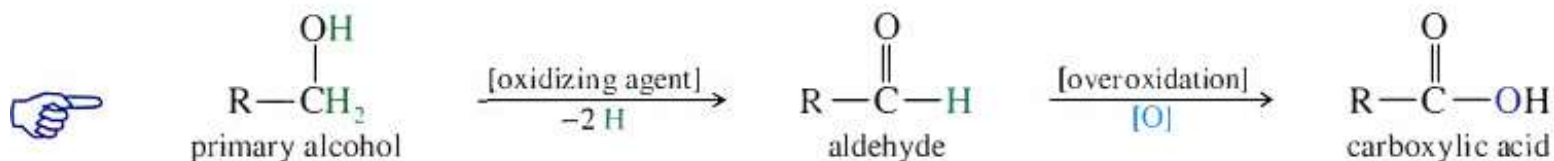
Oxidation of a primary alcohol to an aldehyde requires careful selection of an oxidizing agent to avoid over-oxidation to the carboxylic acid. *Pyridinium chlorochromate* (PCC), a complex of chromium trioxide with pyridine and HCl, provides good yields of aldehydes without over-oxidation.

cyclohexylmethanol → (PCC) → cyclohexanecarbaldehyde (90%)
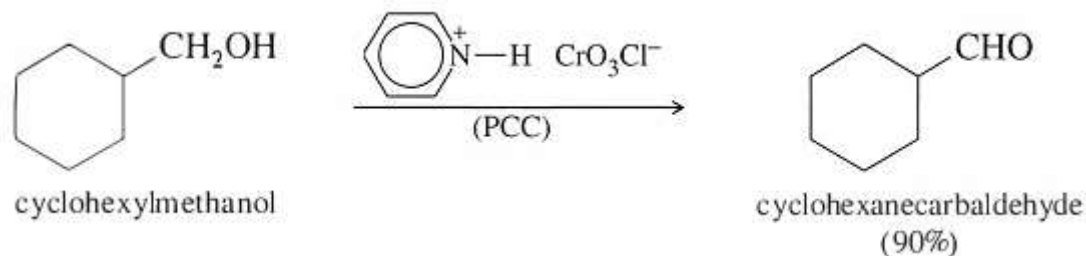
Ketones and Aldehydes from Ozonolysis of Alkenes

(1) O_3
(2) $(CH_3)_2S$

1-methylcyclohexene → (1) O_3 (2) $(CH_3)_2S$ → 6-oxoheptanal (65%)
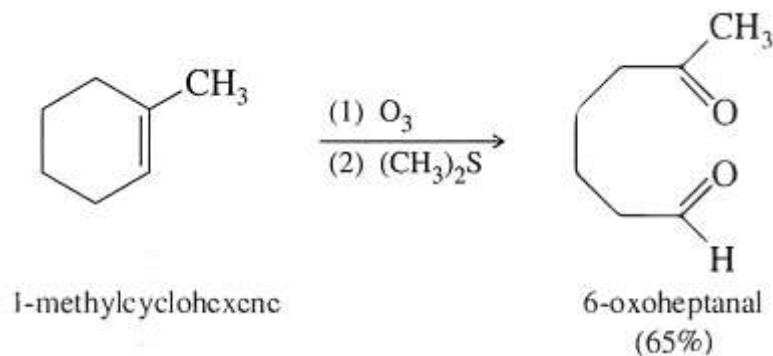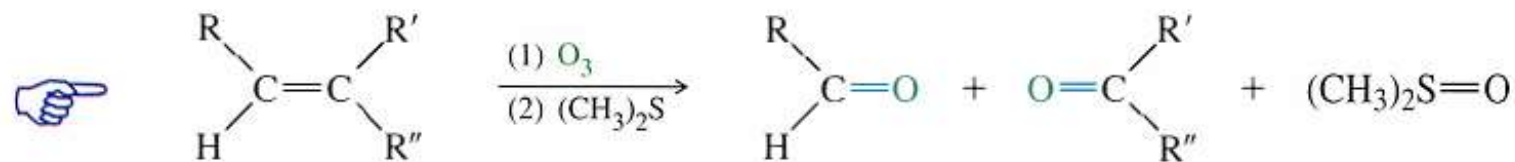
Phenyl Ketones and Aldehydes: Friedel–Crafts Acylation

(1) $AlCl_3$
(2) H_2O

R is alkyl or aryl; G is hydrogen, an activating group, or a halogen.

p-nitrobenzoyl chloride
p-nitrobenzophenone (90%)
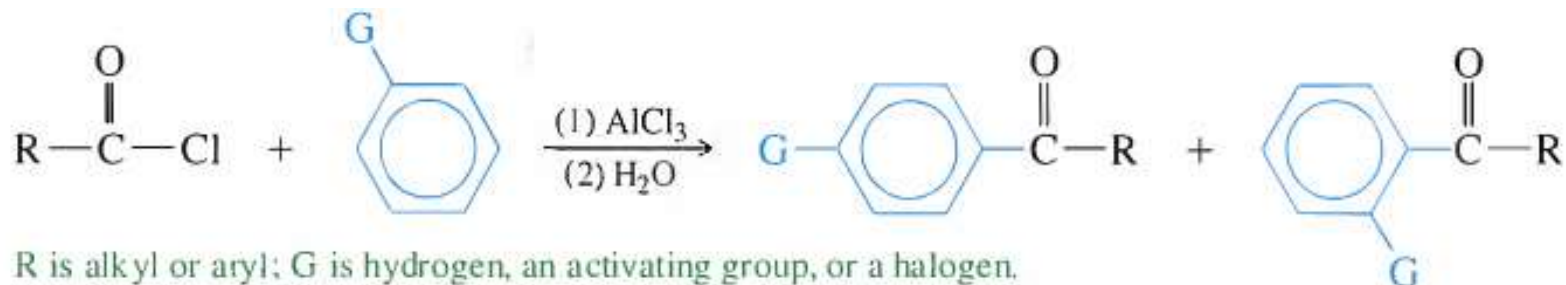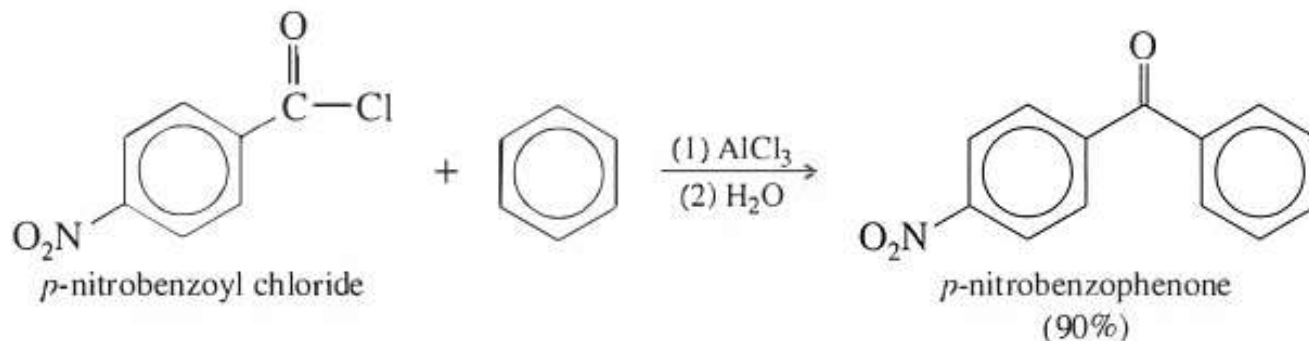
The Gatterman–Koch synthesis is a variant of the Friedel–Crafts acylation in which carbon monoxide and HCl generate an intermediate that reacts like formyl chloride. Like Friedel–Crafts reactions, the Gatterman–Koch formylation succeeds only with benzene and activated benzene derivatives.

toluene
p-methylbenzaldehyde (major) (50%)
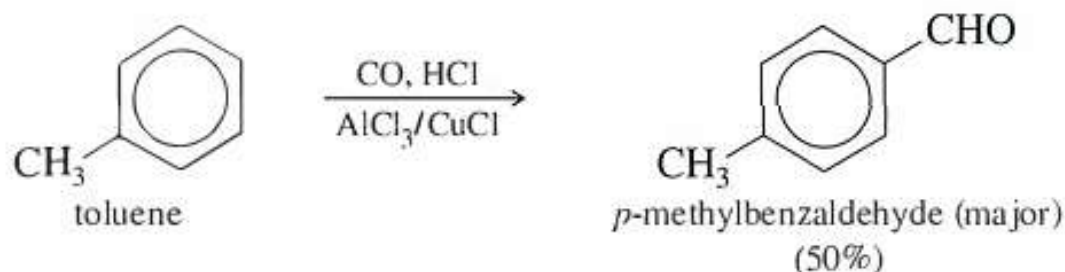
'D   Ketones and Aldehydes from Hydration of Alkynes

Catalyzed by Acid and Mercuric Salts

alkyne
enol (not isolated)
methyl ketone

Example

ethynylcyclohexane   enol   cyclohexyl methyl ketone
(90%)
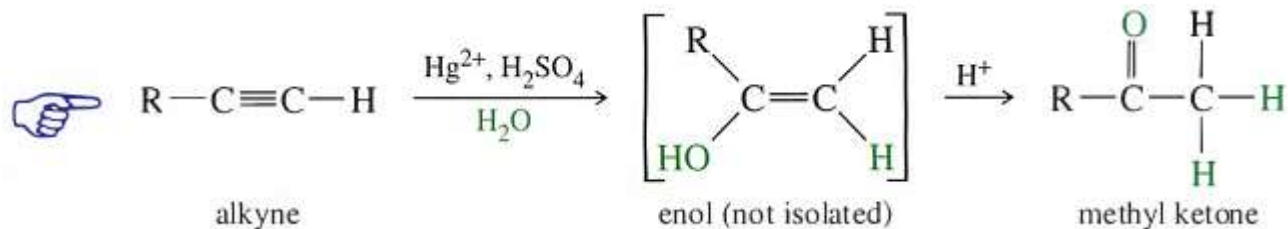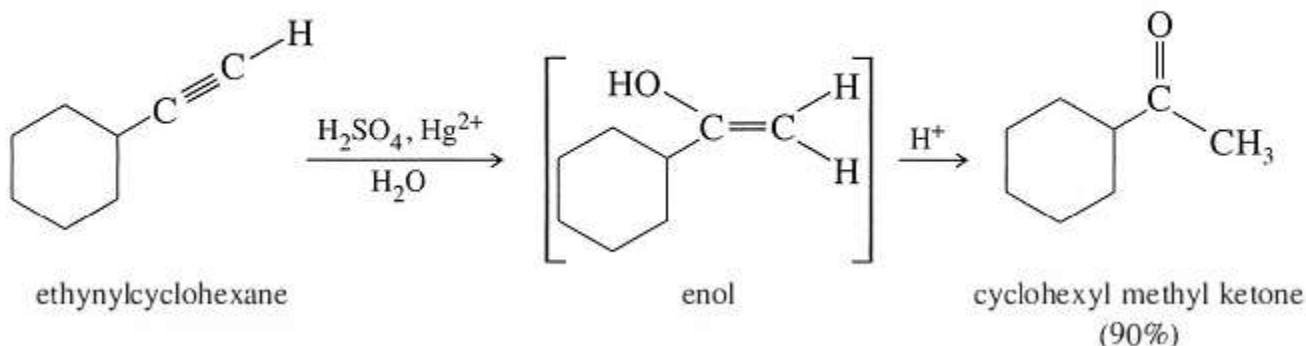
Hydroboration–Oxidation of Alkynes   Hydroboration–oxidation of an alkyne gives anti-Markovnikov addition of water across the triple bond. Di(secondary isoamyl)borane, called *disiamylborane*, is used, since this bulky borane cannot add twice across the triple bond. On oxidation of the borane, the unstable enol quickly tautomerizes to an aldehyde.

alkyne   enol (not isolated)   aldehyde

Example

ethynylcyclohexane   cyclohexylethanal
(65%)

12
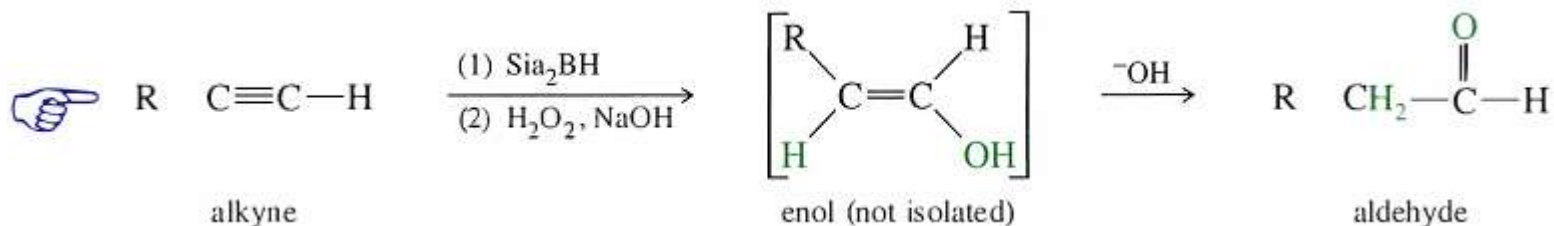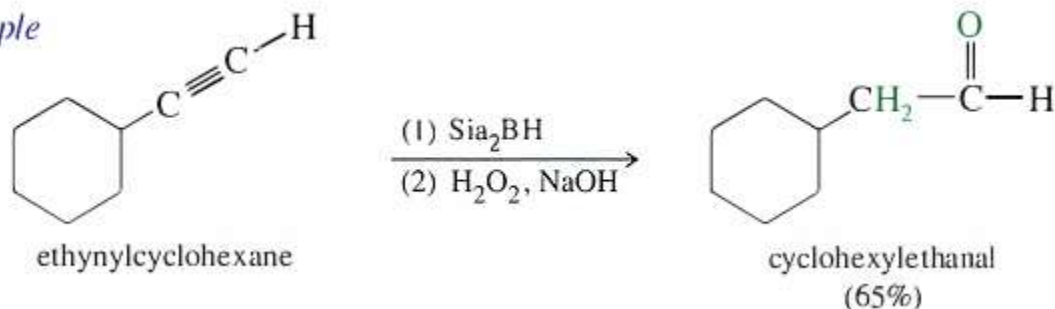
SOLVED PROBLEM 18-1

Show how you would synthesize each compound from starting materials containing no more than six carbon atoms.

(a)

(b)
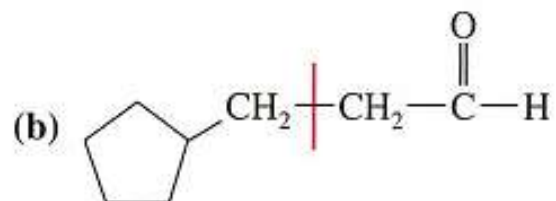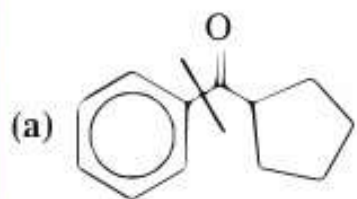
SOLUTION

(a) This compound is a ketone with 12 carbon atoms. The carbon skeleton might be assembled from two six-carbon fragments using a Grignard reaction, which gives an alcohol that is easily oxidized to the target compound.
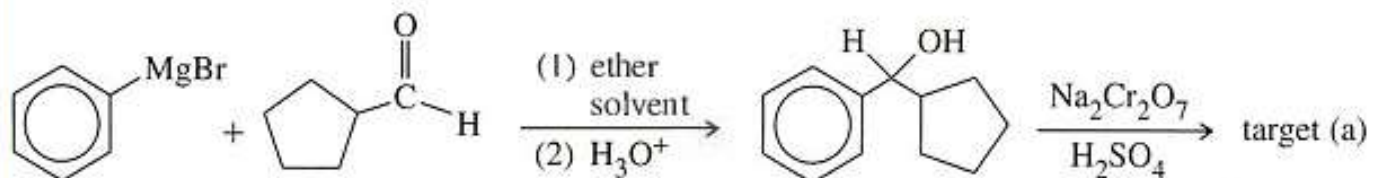
An alternative route to the target compound involves Friedel–Crafts acylation.
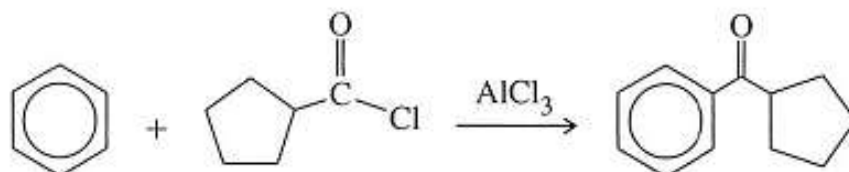
(b) This compound is an aldehyde with eight carbon atoms. An aldehyde might come from oxidation of an alcohol (possibly a Grignard product) or hydroboration of an alkyne. If we use a Grignard, the restriction to six-carbon starting materials means we need to add two carbons to a methylcyclopentyl fragment, ending in a primary alcohol. Grignard addition to an epoxide does this.

Alternatively, we could construct the carbon skeleton using acetylene as the two-carbon fragment. The resulting terminal alkyne undergoes hydroboration to the correct aldehyde.
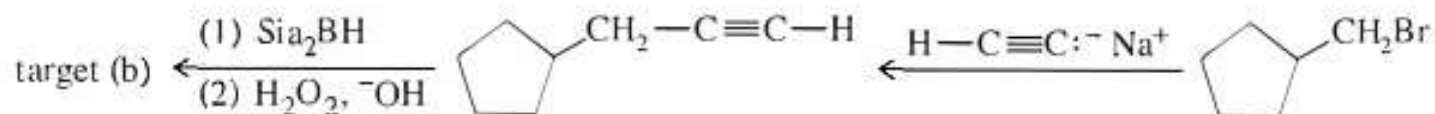

## PROBLEM 18-6

Show how you would synthesize each compound from starting materials containing no more than six carbon atoms.

(a)　　　　　　　　　(b)　　　　　　　　　(c)
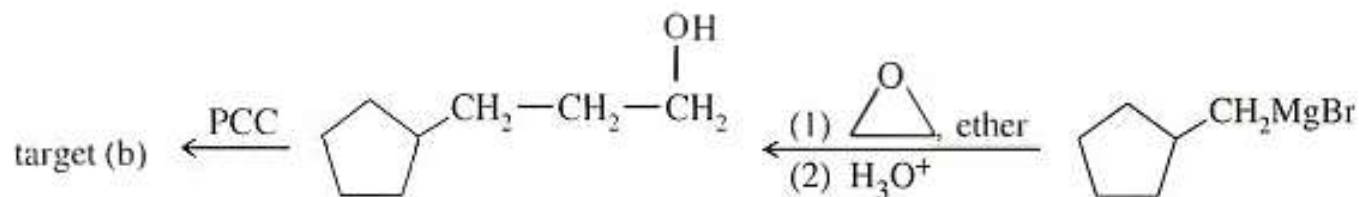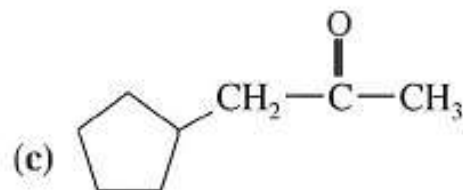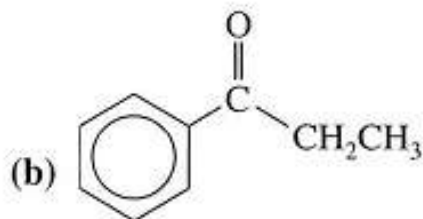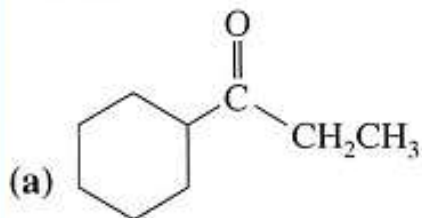
Synthesis of Ketones from Carboxylic Acids

carboxylic acid → lithium carboxylate → dianion → hydrate → ketone

cyclohexane carboxylic acid → (phenyllithium) → dianion → hydrate → cyclohexyl phenyl ketone
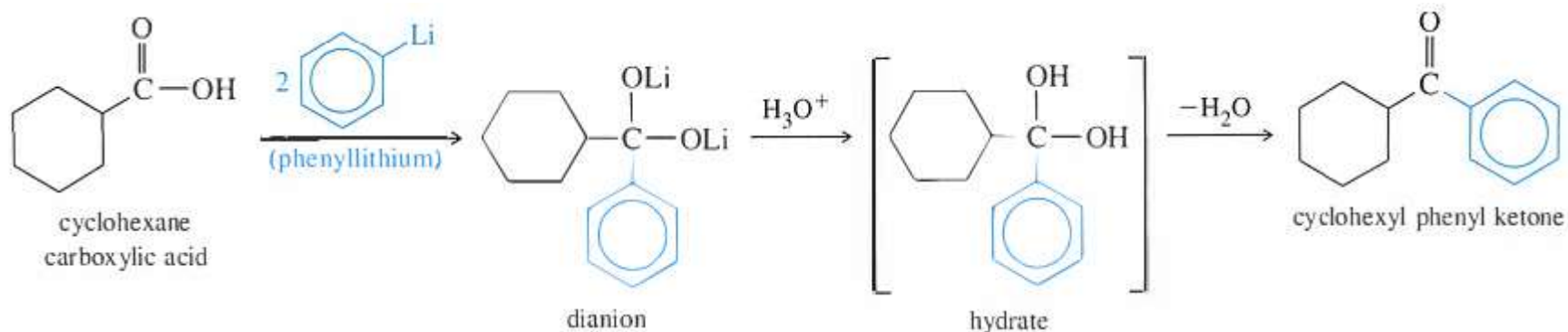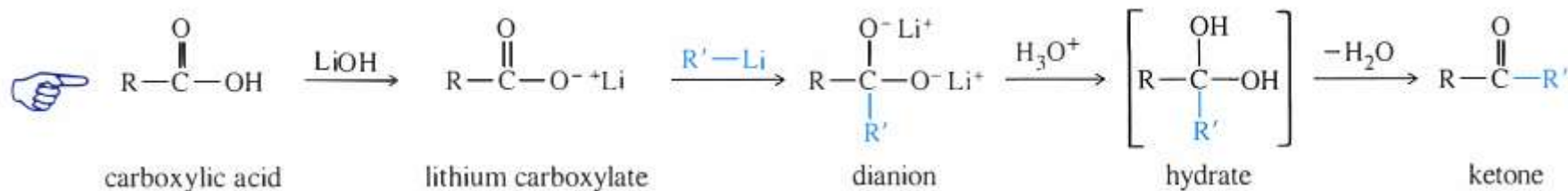
PROBLEM 18-8

Predict the products of the following reactions.

(a)

$\xrightarrow{\text{(1) excess } CH_3Li}{\text{(2) } H_3O^+}$

(b) CH_3COOH $\xrightarrow{\text{(1) 2 (cyclohexyl-Li)}}{\text{(2) } H_3O^+}$

(c) $CH_3(CH_2)_3COOH$ $\xrightarrow{\text{(1) excess } CH_3CH_2Li}{\text{(2) } H_3O^+}$
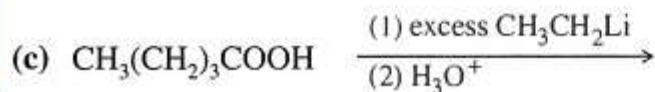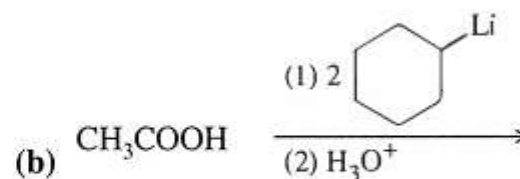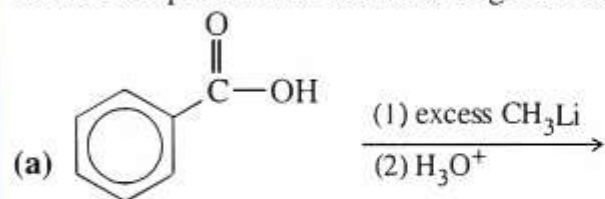
Synthesis of Ketones from Nitriles

nucleophilic attack   Mg salt of imine   imine   ketone

Example

benzonitrile   phenylmagnesium bromide   benzophenone imine (magnesium salt)   benzophenone (80%)
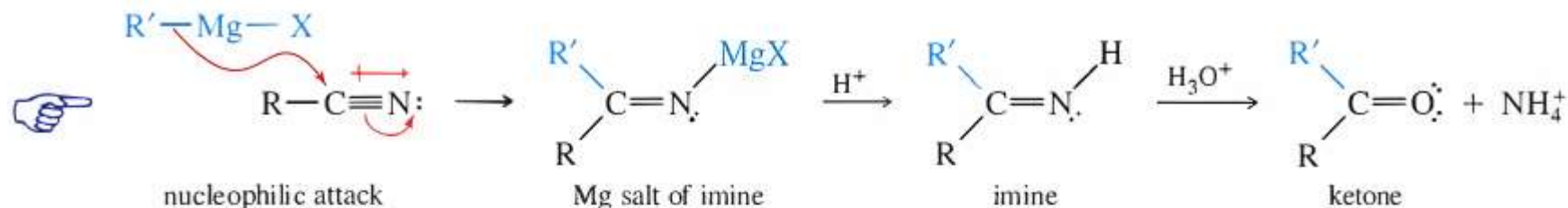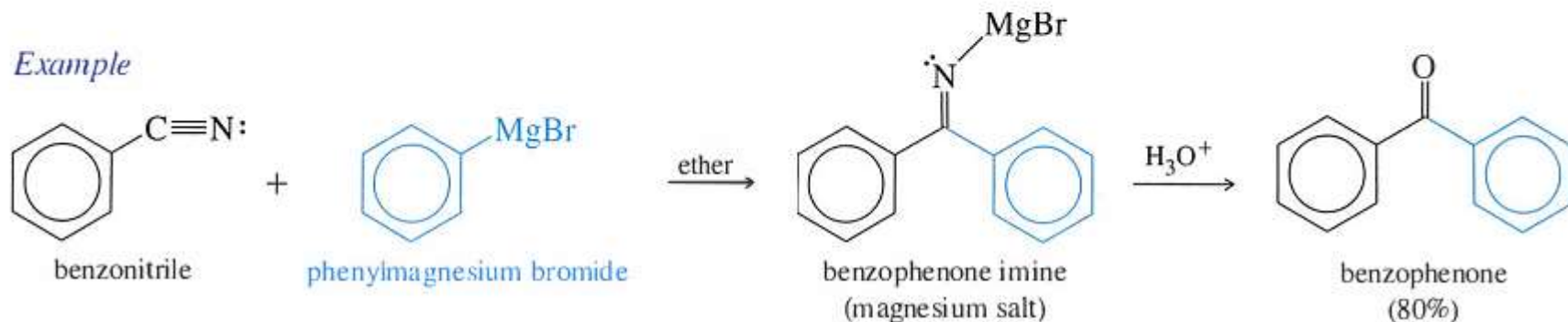
PROBLEM 18-9

Predict the products of the following reactions.
(a) $CH_3CH_2CH_2CH_2-C\equiv N + CH_3CH_2-MgBr$, then H_3O^+
(b) benzyl bromide + sodium cyanide
(c) product of (b) + cyclopentylmagnesium bromide, then acidic hydrolysis

PROBLEM 18-10

Show how the following transformations may be accomplished in good yield. You may use any additional reagents that are needed.
(a) bromobenzene → propiophenone   (b) CH_3CH_2CN → 3-heptanone
(c) pentanoic acid → 3-heptanone   (d) toluene → benzyl cyclopentyl ketone

Synthesis of Aldehydes and Ketones from Acid Chlorides

$$R-\overset{\overset{\displaystyle O}{\|}}{C}-OH \xrightarrow[\text{(slow)}]{\text{LiAlH}_4} \left[R-\overset{\overset{\displaystyle O}{\|}}{C}-H \right] \xrightarrow[\text{(fast)}]{\text{LiAlH}_4} R-CH_2-O^-$$

acid   aldehyde (not isolable)   alkoxide

☞ $R-\overset{\overset{\displaystyle O}{\|}}{C}-OH \;+\; Cl-\overset{\overset{\displaystyle O}{\|}}{S}-Cl \longrightarrow R-\overset{\overset{\displaystyle O}{\|}}{C}-Cl \;+\; HCl \;+\; SO_2\uparrow$

acid   thionyl chloride   acid chloride

☞ $R-\overset{\overset{\displaystyle O}{\|}}{C}-Cl \xrightarrow[\text{lithium aluminum tri(}t\text{-butoxy)hydride}]{\text{Li}^+ \ ^-\text{AlH(O-}t\text{-Bu)}_3} R-\overset{\overset{\displaystyle O}{\|}}{C}-H$

acid chloride   aldehyde

Example

$$CH_3\overset{\overset{\displaystyle CH_3}{|}}{C}HCH_2-\overset{\overset{\displaystyle O}{\|}}{C}-OH \xrightarrow{\text{SOCl}_2} CH_3\overset{\overset{\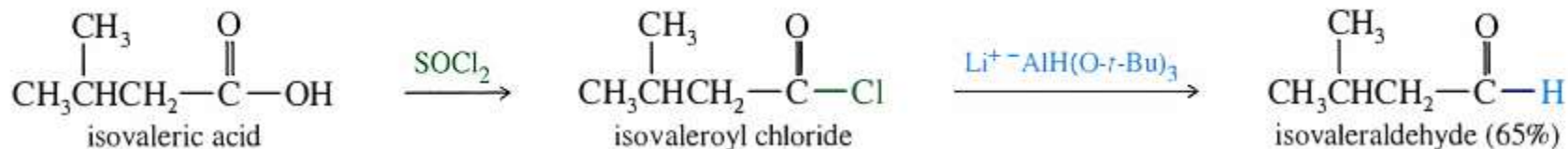displaystyle CH_3}{|}}{C}HCH_2-\overset{\overset{\displaystyle O}{\|}}{C}-Cl \xrightarrow{\text{Li}^+ \ ^-\text{AlH(O-}t\text{-Bu)}_3} CH_3\overset{\overset{\displaystyle CH_3}{|}}{C}HCH_2-\overset{\overset{\displaystyle O}{\|}}{C}-H$$

isovaleric acid   isovaleroyl chloride   isovaleraldehyde (65%)

Synthesis of Ketones

$$R'-\overset{\overset{\displaystyle O}{\|}}{C}-Cl \xrightarrow[\text{(fast)}]{\text{RMgX}} \left[R'-\overset{\overset{\displaystyle O}{\|}}{C}-R \right] \xrightarrow[\text{(fast)}]{\text{RMgX}} R'-\overset{\overset{\displaystyle O^- \ ^+MgX}{|}}{\underset{\underset{\displaystyle R}{|}}{C}}-R$$

acid chloride   ketone   alkoxide
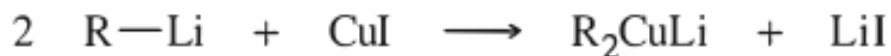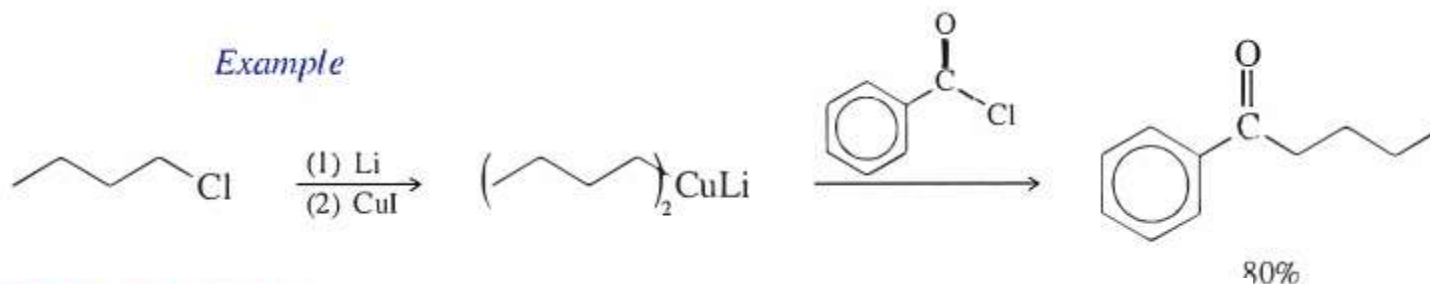
To stop at the ketone stage, a weaker organometallic reagent is needed: one that reacts faster with acid chlorides than with ketones. A **lithium dialkylcuprate (Gilman reagent)** is such a reagent.
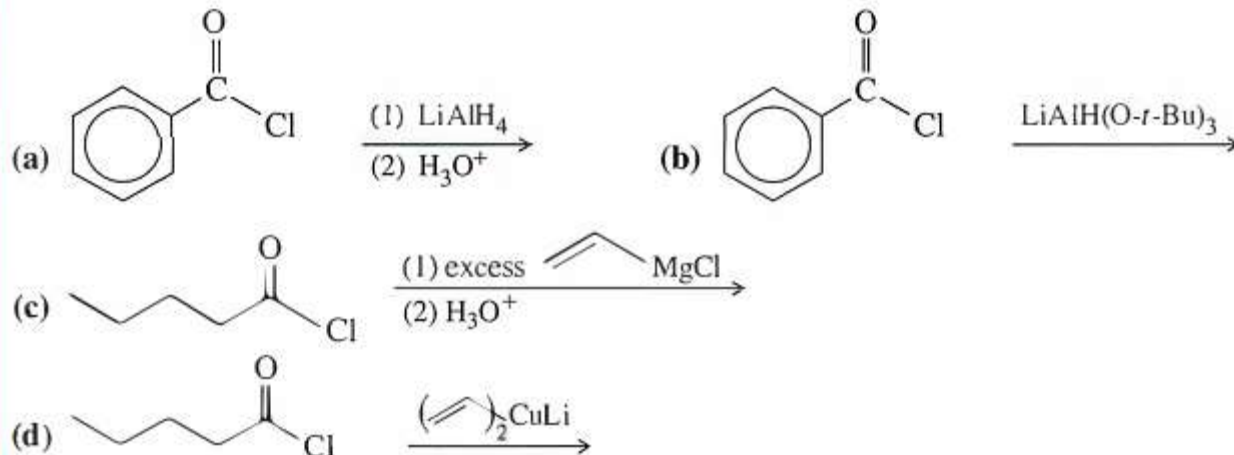
$$R_2CuLi \quad + \quad R'-\overset{\overset{O}{\|}}{C}-Cl \quad \longrightarrow \quad R'-\overset{\overset{O}{\|}}{C}-R \quad + \quad R-Cu \quad + \quad LiCl$$

a lithium dialkylcuprate

$$2 \quad R-Li \quad + \quad CuI \quad \longrightarrow \quad R_2CuLi \quad + \quad LiI$$

Example

80%

PROBLEM 18-11

Predict the products of the following reactions:

(a) $\xrightarrow[\text{(2) } H_3O^+]{\text{(1) LiAlH}_4}$

(b) $\xrightarrow{\text{LiAlH(O-}t\text{-Bu)}_3}$

(c) $\xrightarrow[\text{(2) } H_3O^+]{\text{(1) excess } \diagup\!\!\diagdown \text{MgCl}}$

(d) $\xrightarrow{(\diagup\!\!\diagdown)_2 CuLi}$

Reactions of Ketones and Aldehydes: Nucleophilic Addition

nucleophilic attack — alkoxide — product
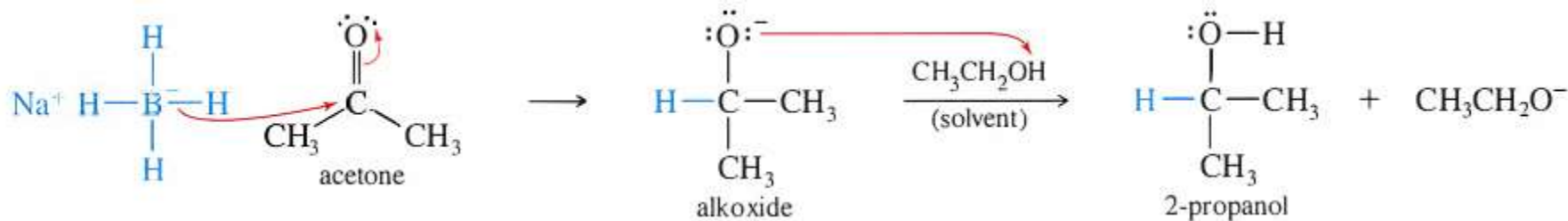

ethylmagnesium bromide + acetone → alkoxide → 2-methyl-2-butanol

acetone → alkoxide → 2-propanol

activated carbonyl

acetone

protonated, activated acetone

attack by water

loss of H$^+$

acetone hydrate
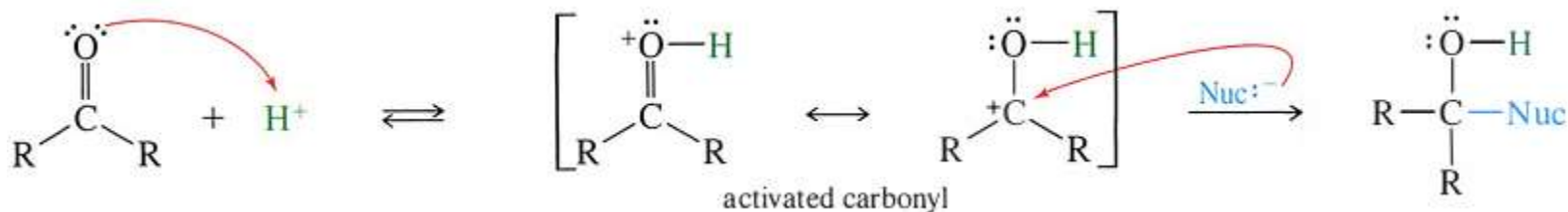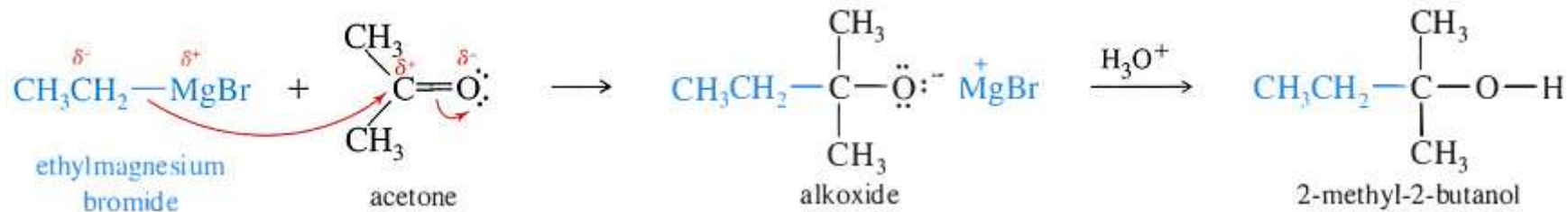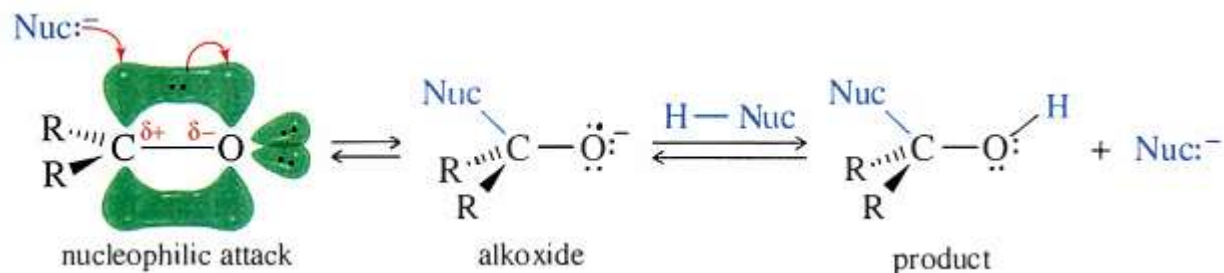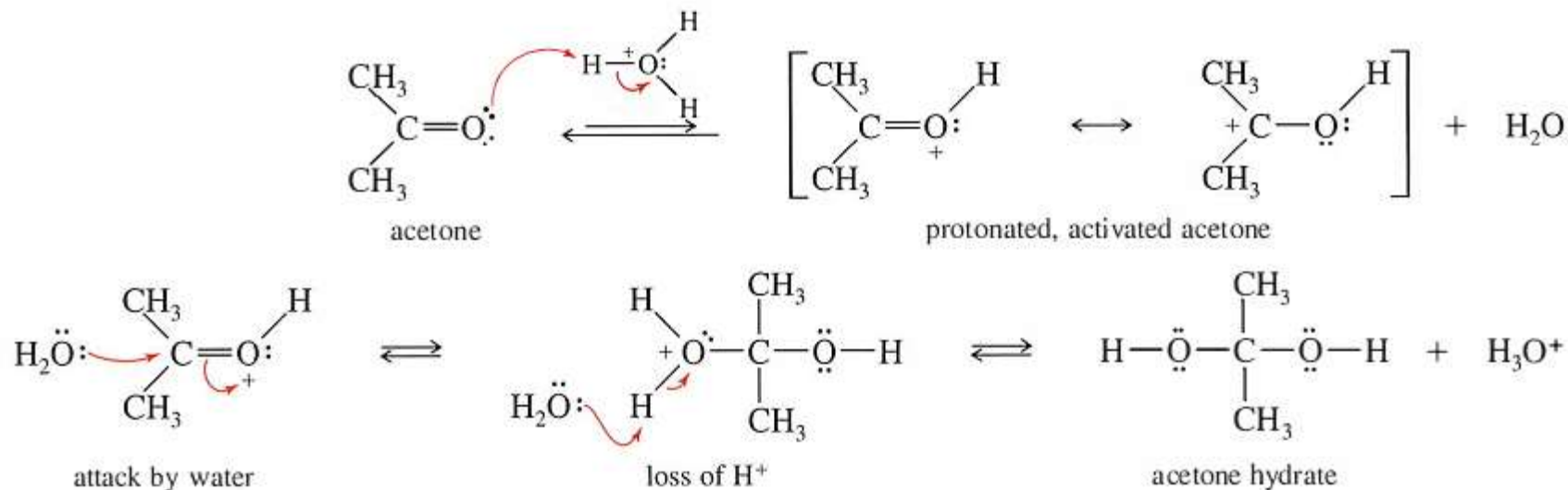
In most cases, aldehydes are more reactive than ketones toward nucleophilic additions. They usually react more quickly than ketones, and the position of the equilibrium usually lies more toward the products than with ketones.
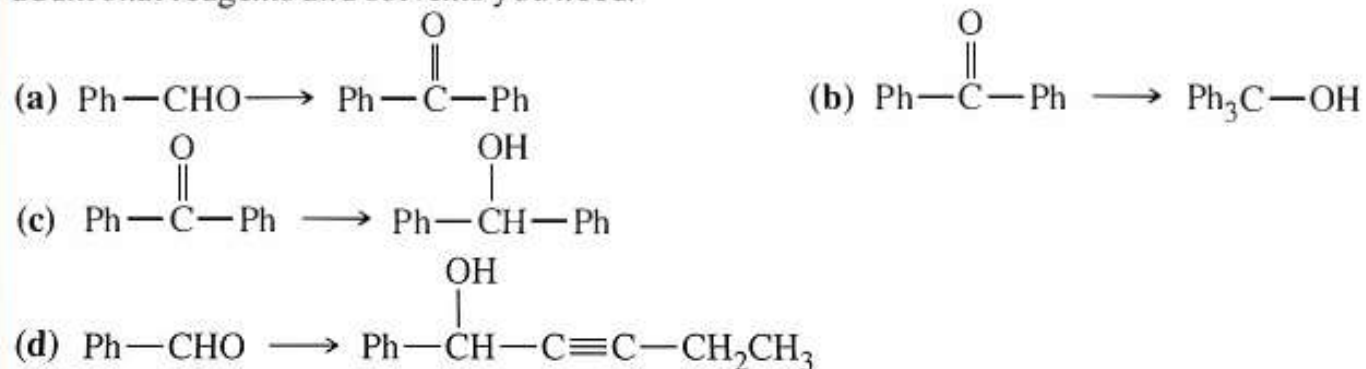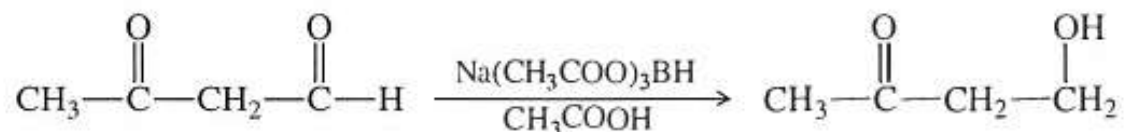

ketone
less electrophilic

alkoxide
more crowded

product
more crowded

aldehyde
more electrophilic

alkoxide
less crowded

product
less crowded
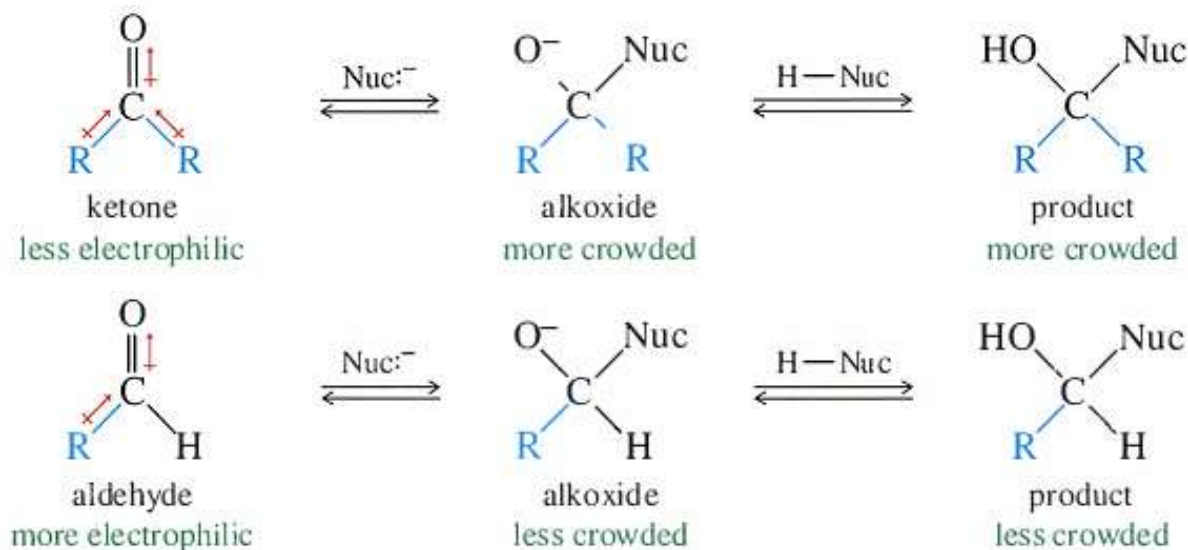
PROBLEM 18-12

Show how you would accomplish the following synthetic conversions. You may use any additional reagents and solvents you need.

(a) $Ph-CHO \longrightarrow Ph-\overset{\overset{\displaystyle O}{\|}}{C}-Ph$

(b) $Ph-\overset{\overset{\displaystyle O}{\|}}{C}-Ph \longrightarrow Ph_3C-OH$

(c) $Ph-\overset{\overset{\displaystyle O}{\|}}{C}-Ph \longrightarrow Ph-\overset{\overset{\displaystyle OH}{|}}{CH}-Ph$

(d) $Ph-CHO \longrightarrow Ph-\overset{\overset{\displaystyle OH}{|}}{CH}-C\equiv C-CH_2CH_3$

PROBLEM 18-13

Sodium triacetoxyborohydride, $Na(CH_3COO)_3BH$, is a mild reducing agent that reduces aldehydes much more quickly than ketones. It can be used to reduce aldehydes in the presence of ketones, such as in the following reaction:

$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-CH_2-\overset{\overset{\displaystyle O}{\|}}{C}-H \xrightarrow[\text{CH}_3\text{COOH}]{\text{Na(CH}_3\text{COO)}_3\text{BH}} CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-CH_2-\overset{\overset{\displaystyle OH}{|}}{CH_2}$$

(a) Draw a complete Lewis structure for sodium triacetoxyborohydride.
(b) Propose a mechanism for the reduction of an aldehyde by sodium triacetoxyborohydride.

Basic Conditions (strong nucleophile)

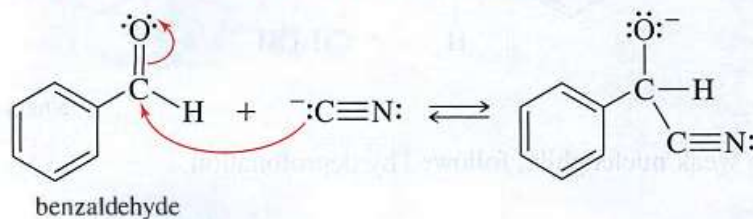***Step 1:*** A strong nucleophile adds to the carbonyl group to form an alkoxide.
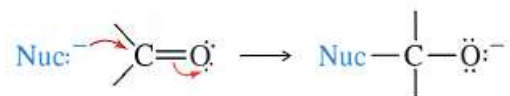
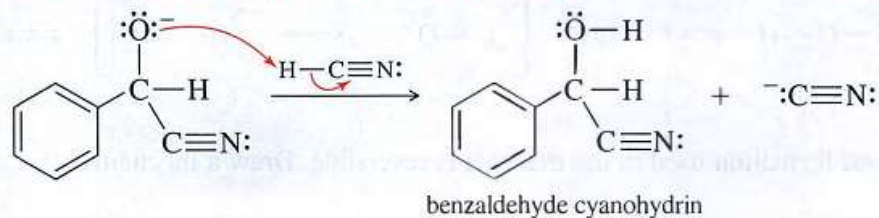***Step 2:*** A weak acid protonates the alkoxide to give the addition product.
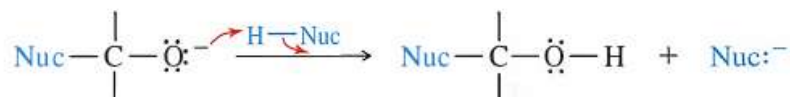
EXAMPLE: Formation of a Cyanohydrin (covered in Section 18-15)

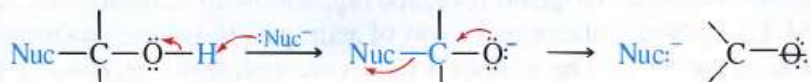***Step 1:*** A strong nucleophile adds to the carbonyl group to form an alkoxide.

benzaldehyde

Step 2: A weak acid protonates the alkoxide to give the addition product.

benzaldehyde cyanohydrin

Reverse reaction: Deprotonation, followed by loss of the nucleophile.
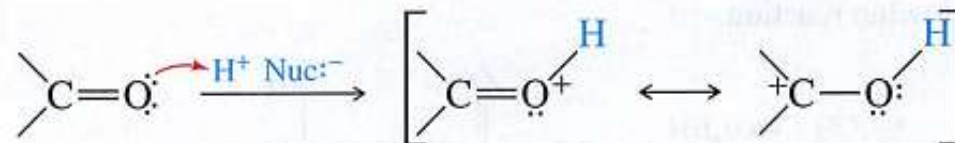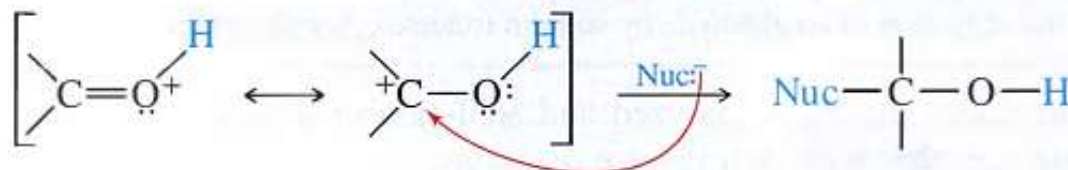
Reverse reaction:

PROBLEM: The cyanohydrin formation used in the example is reversible. Draw a mechanism for the reverse reaction.

Acidic Conditions (weak nucleophile, activated carbonyl)

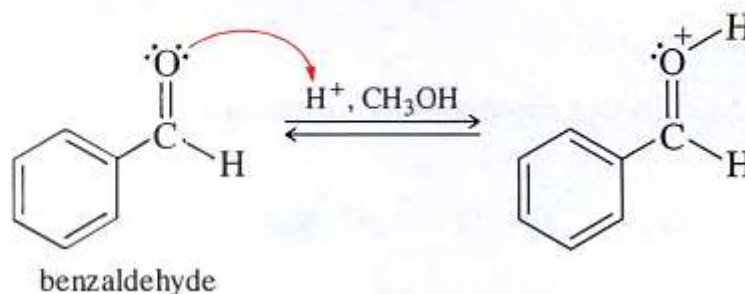**Step 1:** Protonation activates the carbonyl group toward nucleophilic attack.

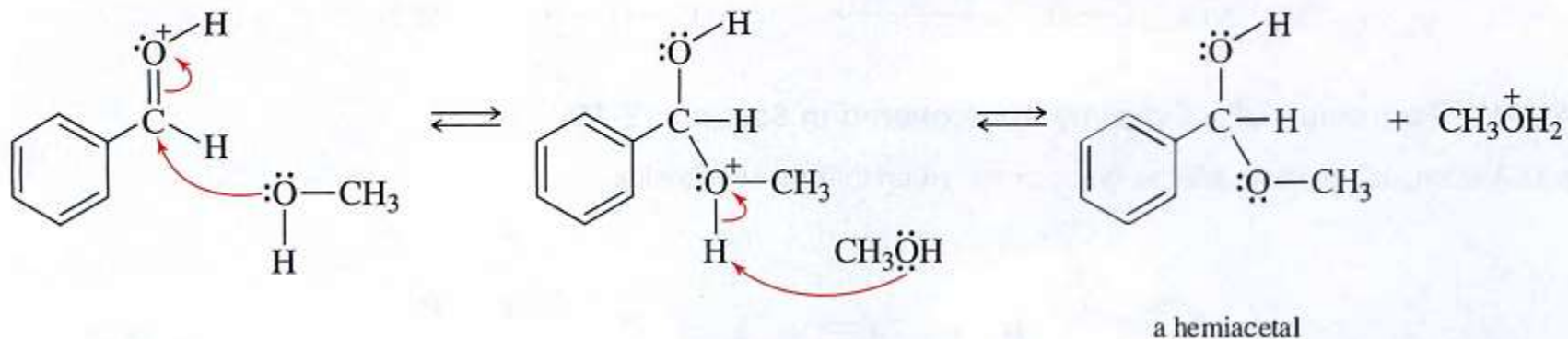**Step 2:** A weak nucleophile adds to the activated (protonated) carbonyl group.

EXAMPLE: Formation of a Hemiacetal (covered in Section 18-18)

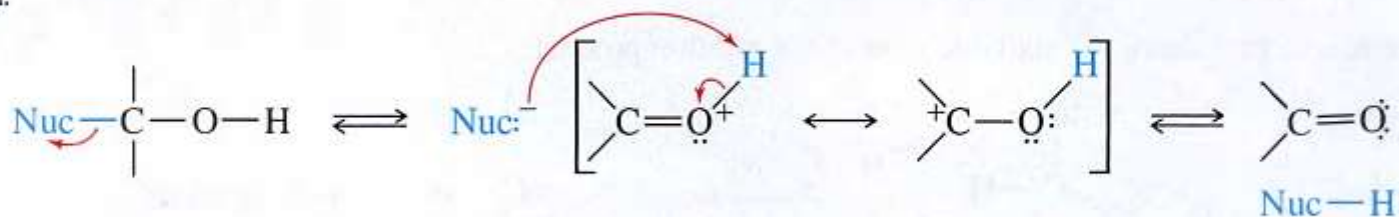**Step 1:** Protonation activates the carbonyl group toward nucleophilic attack.

benzaldehyde

Step 2: A weak nucleophile adds to the activated (protonated) carbonyl group. Deprotonation of the product gives the hemiacetal.

a hemiacetal

Reverse reaction: Loss of the weak nucleophile, followed by deprotonation.
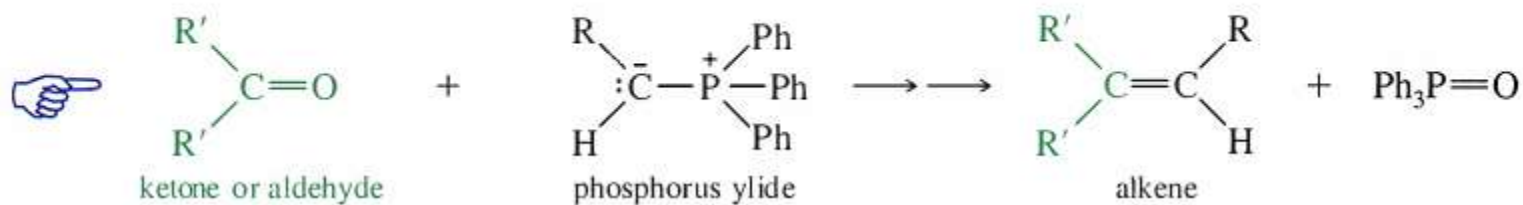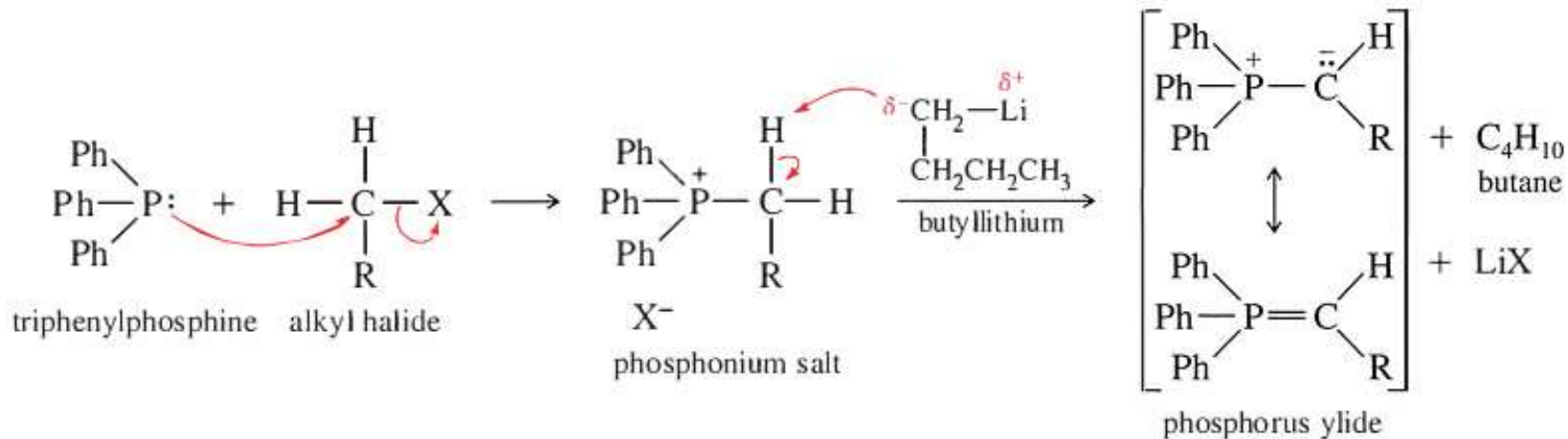
Reverse reaction:

PROBLEM: The hemiacetal formation used in the example is reversible. Draw a mechanism for the reverse reaction.
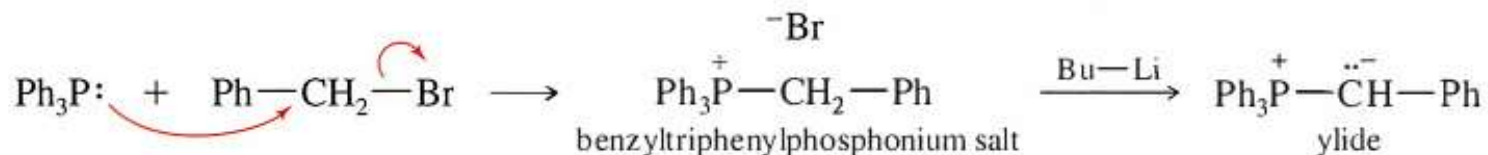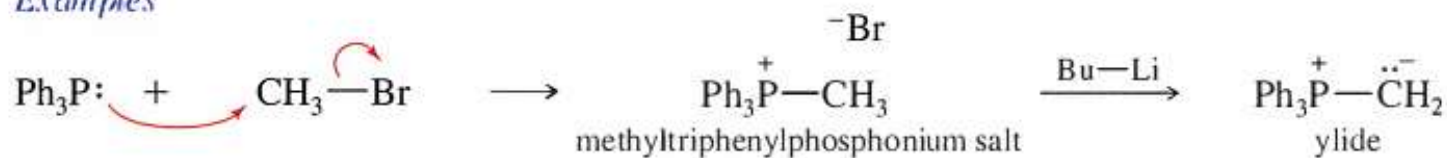
The Wittig Reaction

The Wittig reaction

ketone or aldehyde   phosphorus ylide   alkene

Ph—P: + H—C—X ⟶ Ph—P⁺—C—H $\xrightarrow[\text{butyllithium}]{\delta^- CH_2—Li \quad \delta^+ \atop CH_2CH_2CH_3}$

triphenylphosphine alkyl halide   X⁻
phosphonium salt

phosphorus ylide   + C_4H_{10} butane   + LiX

Examples

$Ph_3P: + CH_3—Br \longrightarrow Ph_3\overset{+}{P}—CH_3 \xrightarrow{Bu—Li} Ph_3\overset{+}{P}—\overset{..-}{C}H_2$

⁻Br
methyltriphenylphosphonium salt   ylide

$Ph_3P: + Ph—CH_2—Br \longrightarrow Ph_3\overset{+}{P}—CH_2—Ph \xrightarrow{Bu—Li} Ph_3\overset{+}{P}—\overset{..-}{C}H—Ph$
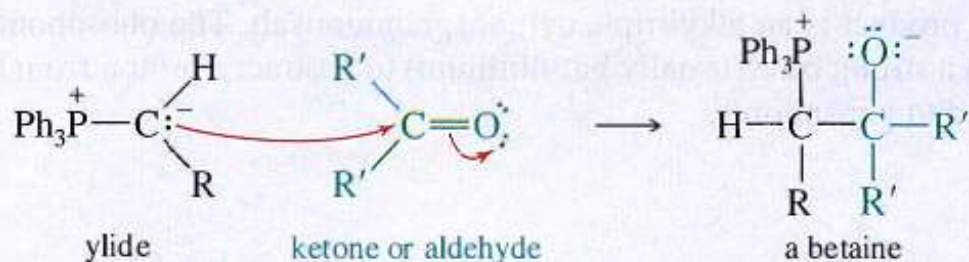
⁻Br
benzyltriphenylphosphonium salt   ylide

PROBLEM 18-14

Trimethylphosphine is much less expensive than triphenylphosphine. Why is trimethylphosphine unsuitable for making most phosphorus ylides?
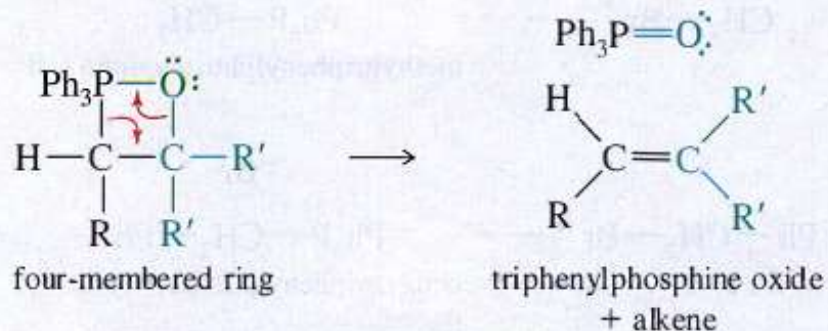
**Step 1:** The ylide attacks the carbonyl to form a betaine.

$$Ph_3P-C \quad \quad C=O \quad \longrightarrow \quad H-C-C-R'$$

ylide   ketone or aldehyde   a betaine

Step 2: The betaine closes to a four-membered ring oxaphosphetane (first P—O bond formed).

a betaine   oxaphosphetane
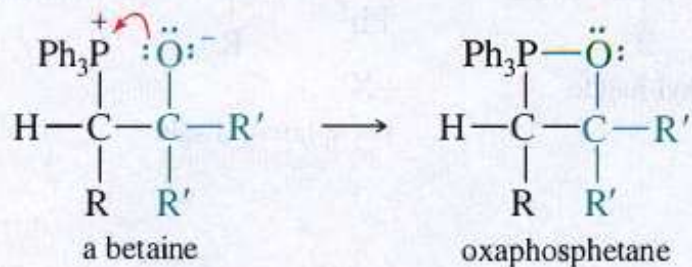
Step 3: The ring collapses to the products (second P—O bond formed).

four-membered ring   triphenylphosphine oxide + alkene

The following examples show the formation of carbon–carbon double bonds using the Wittig reaction. Mixtures of cis and trans isomers often result when geometric isomerism is possible.


85%
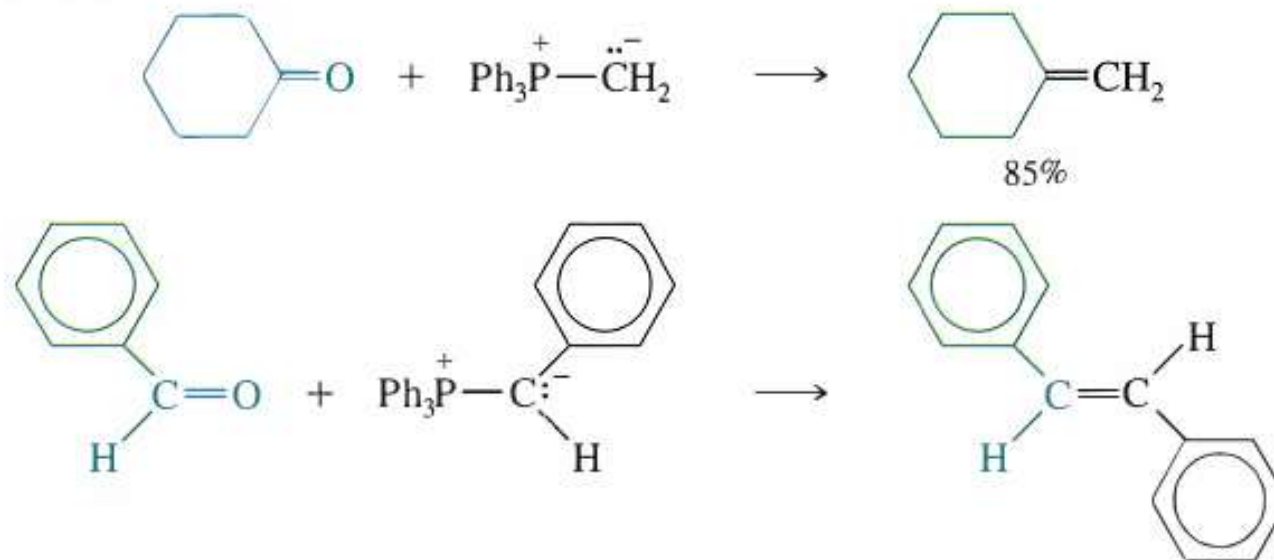
PROBLEM 18-15

Like other strong nucleophiles, triphenylphosphine attacks and opens epoxides. The initial product (a betaine) quickly cyclizes to an oxaphosphetane that collapses to an alkene and triphenylphosphine oxide.
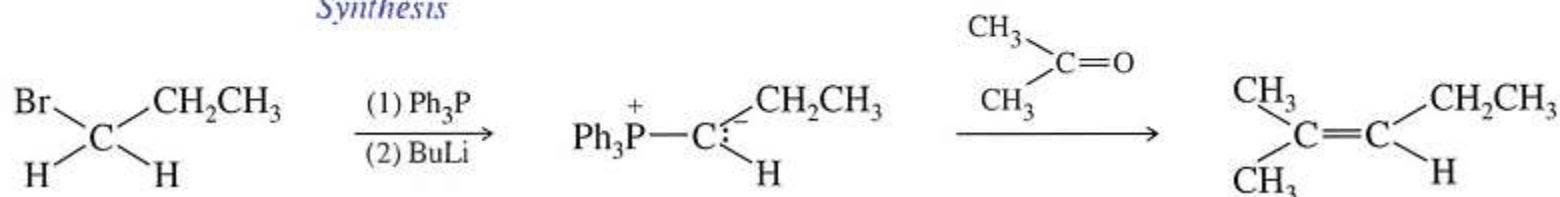
(a) Show each step in the reaction of *trans*-2,3-epoxybutane with triphenylphosphine to give 2-butene. What is the stereochemistry of the double bond in the product?

(b) Show how this reaction might be used to convert *cis*-cyclooctene to *trans*-cyclooctene.

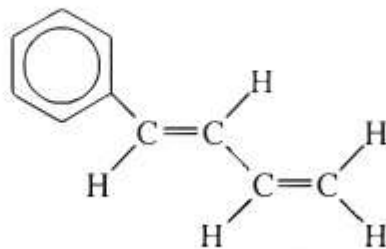## Planning a Wittig Synthesis

Analysis
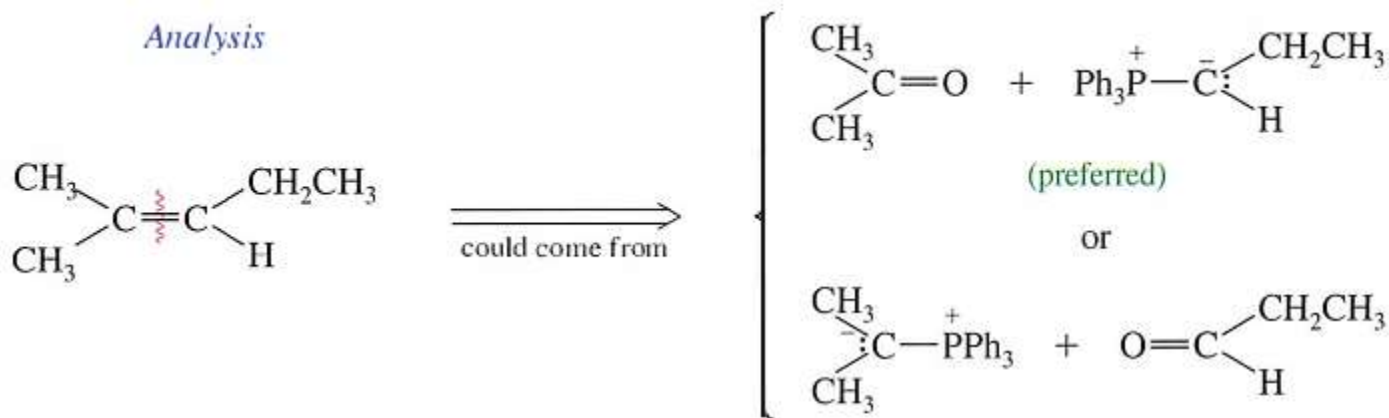
Synthesis

SOLVED PROBLEM 18-2

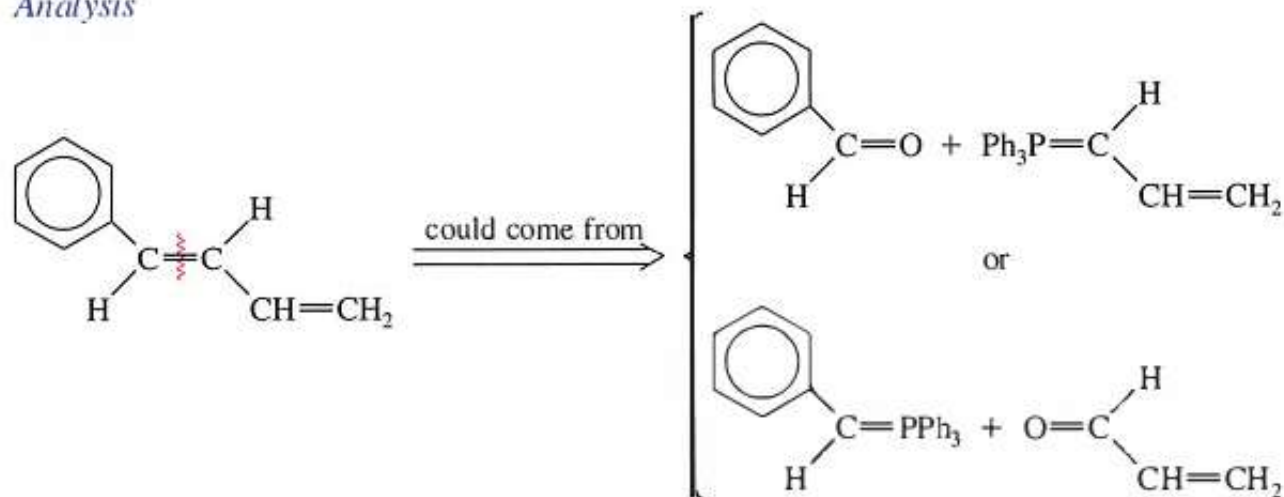Show how you would use a Wittig reaction to synthesize 1-phenyl-1,3-butadiene.

1-phenyl-1,3-butadiene

SOLUTION

This molecule has two double bonds that might be formed by Wittig reactions. The central double bond could be formed in either of two ways. Both of these syntheses will probably work, and both will produce a mixture of cis and trans isomers.
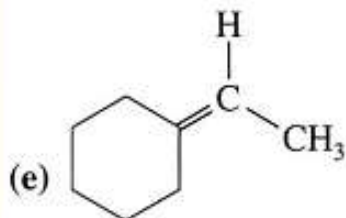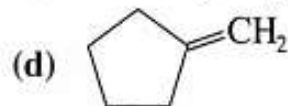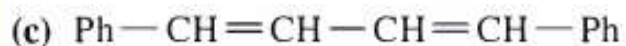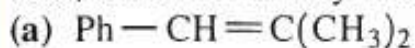
Analysis

You should complete this solution by drawing out the syntheses indicated by this analysis (Problem 18-16).
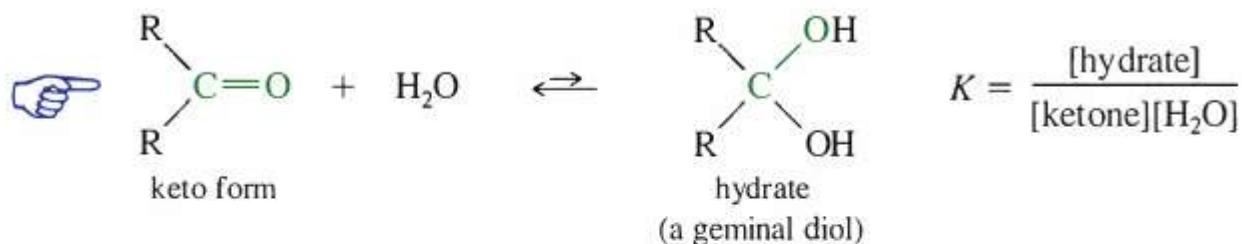
PROBLEM 18-16

(a) Outline the syntheses indicated in Solved Problem 18-2, beginning with aldehydes and alkyl halides.
(b) Both of these syntheses of 1-phenyl-1,3-butadiene form the central double bond. Show how you would synthesize this target molecule by forming the terminal double bond.
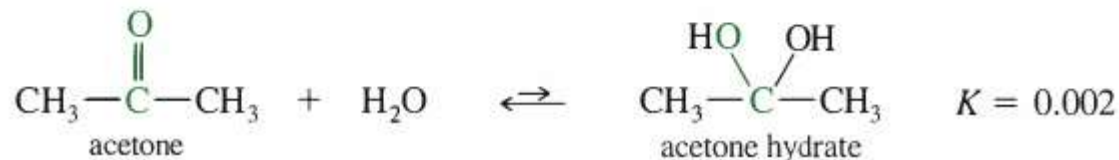
PROBLEM 18-17

Show how Wittig reactions might be used to synthesize the following compounds. In each case, start with an alkyl halide and a ketone or an aldehyde.

(a) $Ph-CH=C(CH_3)_2$

(b) $Ph-C(CH_3)=CH_2$

(c) $Ph-CH=CH-CH=CH-Ph$

(d)

(e)

Hydration of Ketones and Aldehydes

$$K = \frac{[\text{hydrate}]}{[\text{ketone}][H_2O]}$$

keto form   hydrate (a geminal diol)

Example

$$CH_3-\overset{\overset{O}{\|}}{C}-CH_3 + H_2O \rightleftarrows CH_3-\overset{\overset{HO}{|}}{\underset{\underset{OH}{|}}{C}}-CH_3 \qquad K = 0.002$$
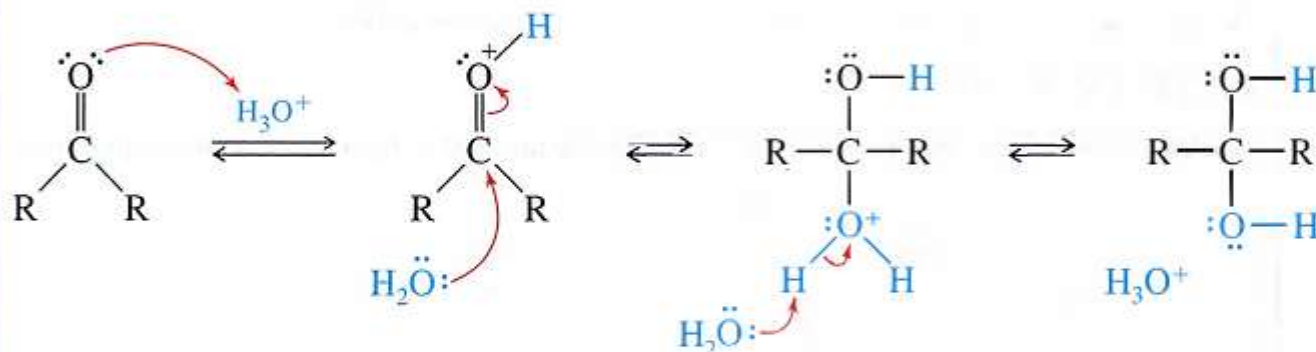
acetone   acetone hydrate

In acid

The acid-catalyzed hydration is a typical acid-catalyzed addition to the carbonyl group. Protonation, followed by addition of water, gives a protonated product. Deprotonation gives the hydrate.

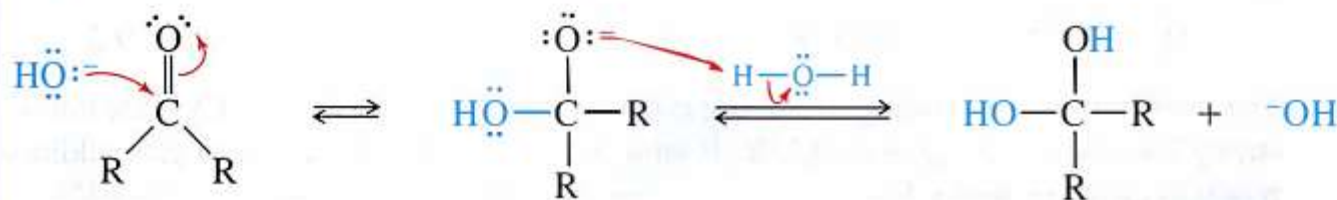**Step 1:** Protonation.   **Step 2:** Water adds.   **Step 3:** Deprotonation.
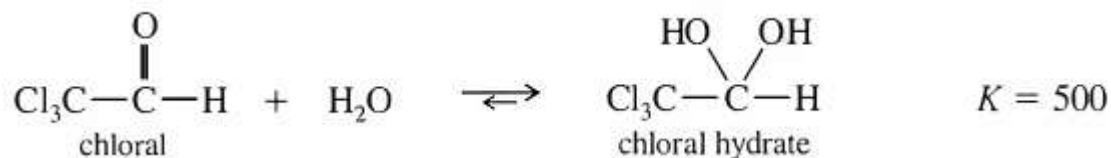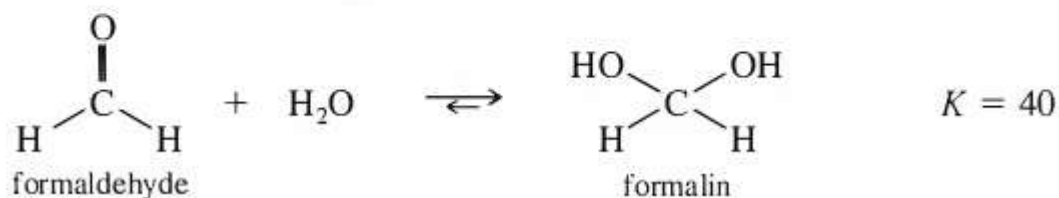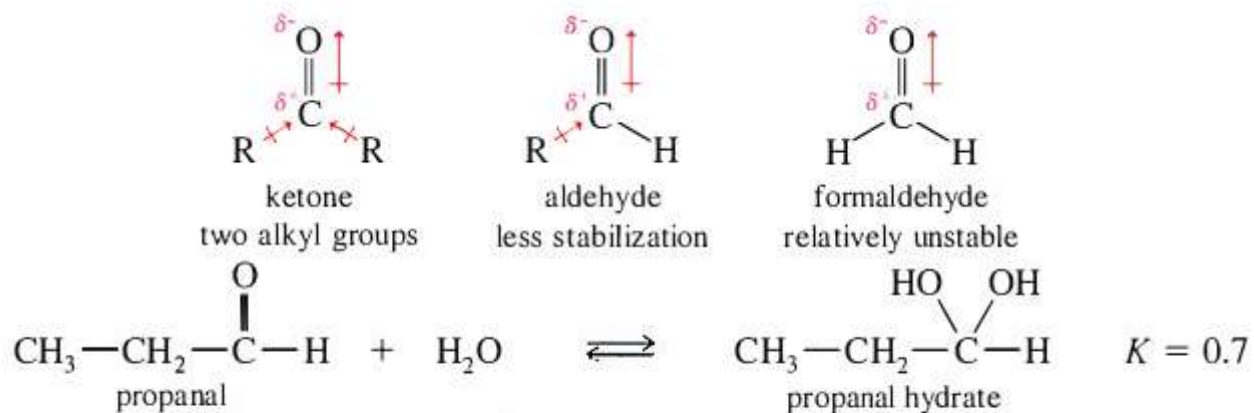

In base

The base-catalyzed hydration is a perfect example of base-catalyzed addition to a carbonyl group. The strong nucleophile adds, then protonation gives the hydrate.

Step 1: Hydroxide adds.   **Step 2:** Protonation.

31

ketone
two alkyl groups

aldehyde
less stabilization

formaldehyde
relatively unstable

$$CH_3—CH_2—\overset{O}{\overset{||}{C}}—H \;+\; H_2O \;\rightleftharpoons\; CH_3—CH_2—\overset{HO\;\;\;OH}{\underset{|}{C}}—H \qquad K = 0.7$$

propanal

propanal hydrate

$$\underset{H}{\overset{O}{\underset{}{\overset{||}{C}}}}\underset{}{\overset{}{}}H \;+\; H_2O \;\rightleftharpoons\; \overset{HO\;\;\;OH}{\underset{H\quad\;\;H}{C}} \qquad K = 40$$

formaldehyde

formalin

The body rapidly reduces chloral (trichloroacetaldehye) to trichloro-ethanol, which is responsible for the drug's sleep-inducing effect.

$$Cl_3C—\overset{O}{\overset{||}{C}}—H \;+\; H_2O \;\rightleftharpoons\; Cl_3C—\overset{HO\;\;\;OH}{\underset{|}{C}}—H \qquad K = 500$$
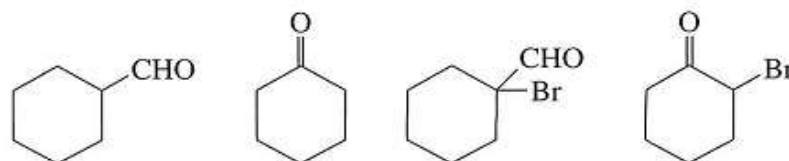
chloral

chloral hydrate

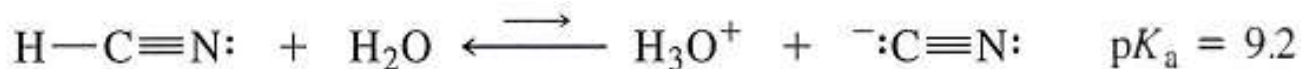**PROBLEM 18-18**

Propose mechanisms for
(a) The acid-catalyzed hydration of chloral to form chloral hydrate.
(b) The base-catalyzed hydration of acetone to form acetone hydrate.

PROBLEM 18-19

Rank the following compounds in order of increasing amount of hydrate present at equilibrium.

Formation of Cyanohydrins

$$H-C\equiv N: \quad + \quad H_2O \quad \rightleftharpoons \quad H_3O^+ \quad + \quad ^-:C\equiv N: \qquad pK_a = 9.2$$
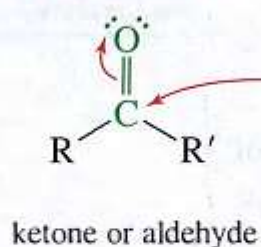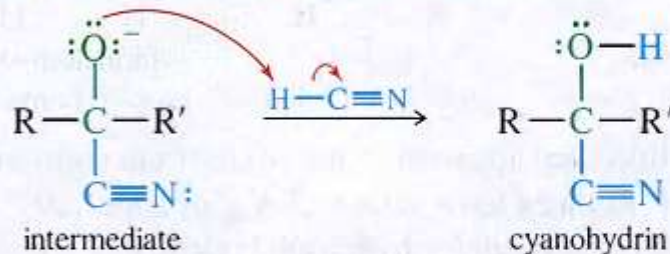
MECHANISM 18-4   Formation of Cyanohydrins

Cyanohydrin formation is a perfect example of base-catalyzed addition to a carbonyl group. The strong nucleophile adds in the first step to give an alkoxide. Protonation gives the cyanohydrin.
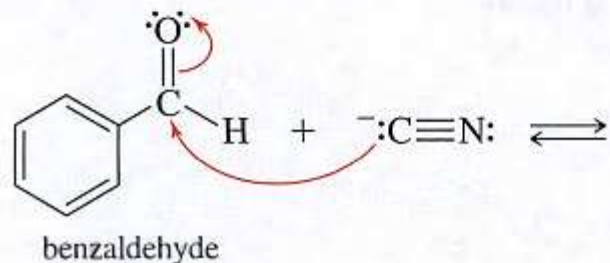
Step 1: Cyanide adds to the carbonyl.

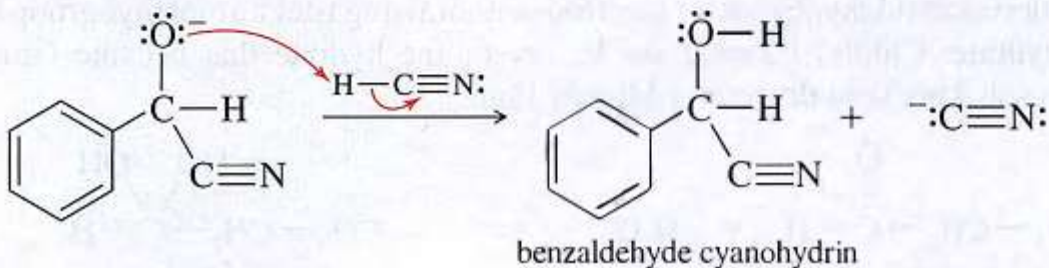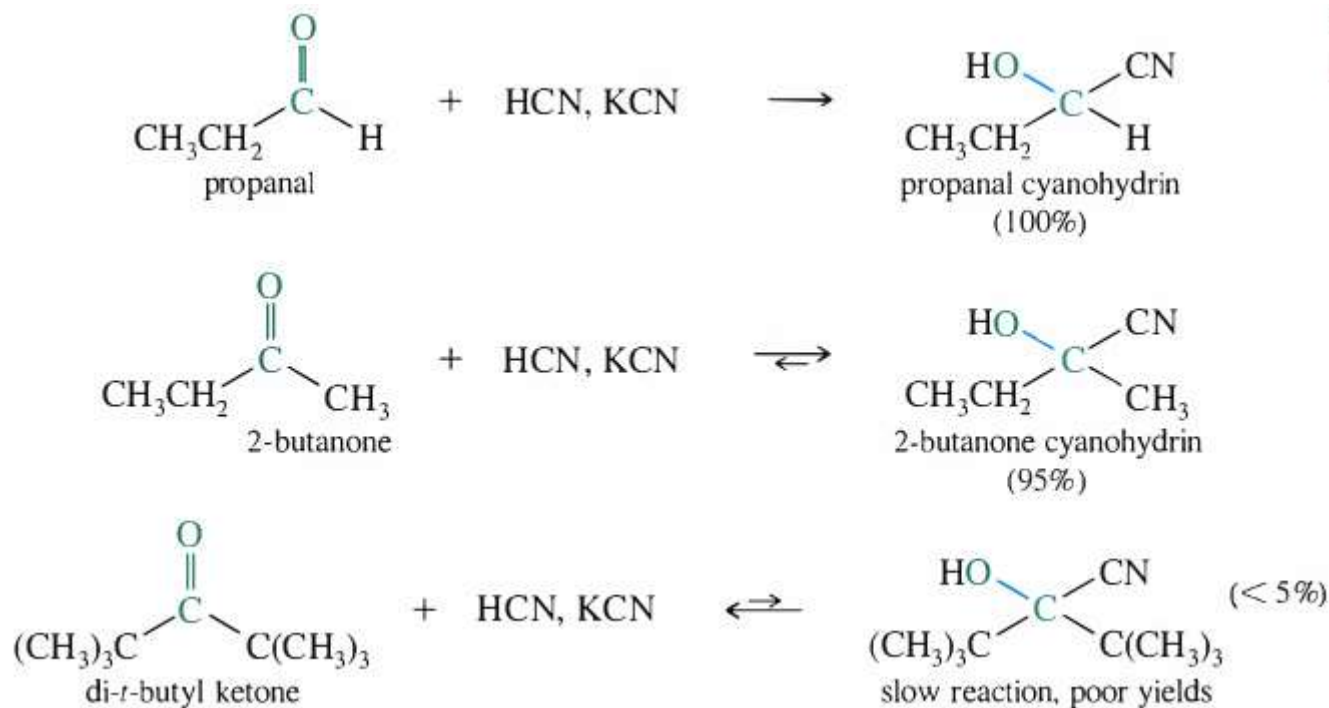**Step 2:** Protonation gives the cyanohydrin.

ketone or aldehyde   intermediate   cyanohydrin

EXAMPLE: Formation of benzaldehyde cyanohydrin.

Step 1: Cyanide adds to the carbonyl.

Step 2: Protonation gives the cyanohydrin.

benzaldehyde   benzaldehyde cyanohydrin

CH₃CH₂—C(=O)—H propanal + HCN, KCN → propanal cyanohydrin (HO, CN on central C) (100%)

CH₃CH₂—C(=O)—CH₃ 2-butanone + HCN, KCN ⇌ 2-butanone cyanohydrin (95%)

(CH₃)₃C—C(=O)—C(CH₃)₃ di-t-butyl ketone + HCN, KCN ⇌ (HO, CN) (<5%) slow reaction, poor yields

PROBLEM 18-20

Propose a mechanism for each cyanohydrin synthesis just shown.

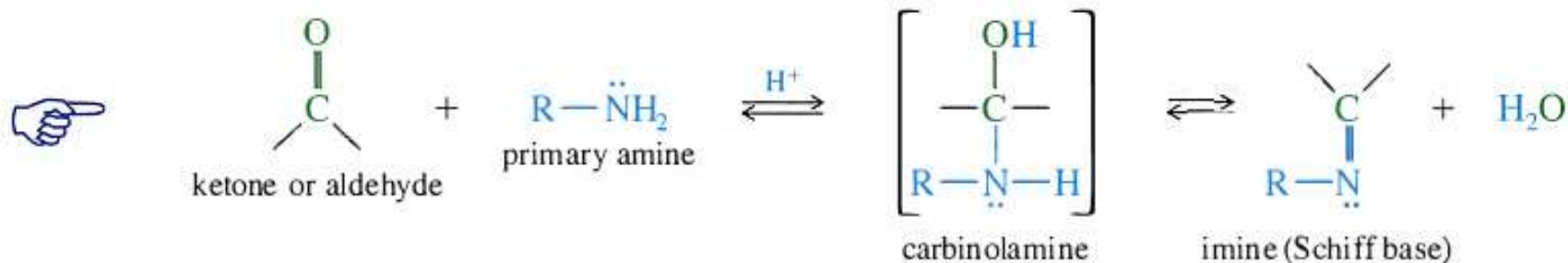R—C(=O)—H aldehyde + HCN ⟶(⁻:CN) R—C(OH)(CN)—H cyanohydrin ⟶(H₃O⁺) R—C(OH)(H)—C(=O)—OH α-hydroxy acid

34

PROBLEM 18-21

Show how you would accomplish the following syntheses.
(a) acetophenone → acetophenone cyanohydrin
(b) 1-hexanol → hexanal cyanohydrin

(c)

Formation of Imines

ketone or aldehyde + primary amine ⇌ carbinolamine ⇌ imine (Schiff base) + H_2O
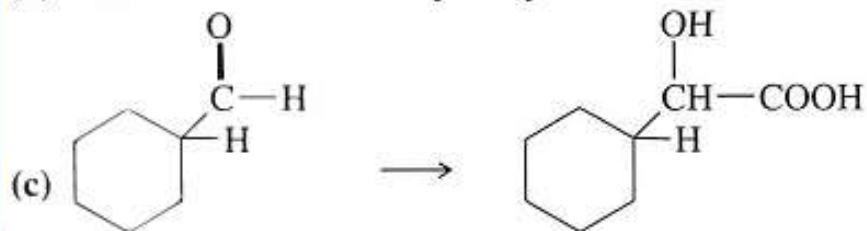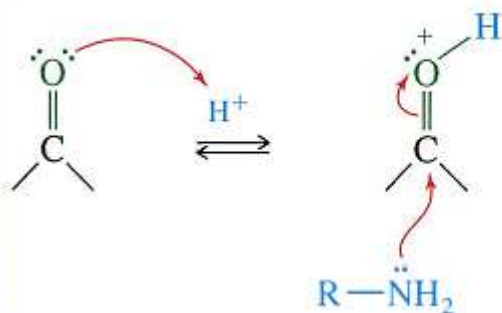
KEY MECHANISM 18-5   Formation of Imines

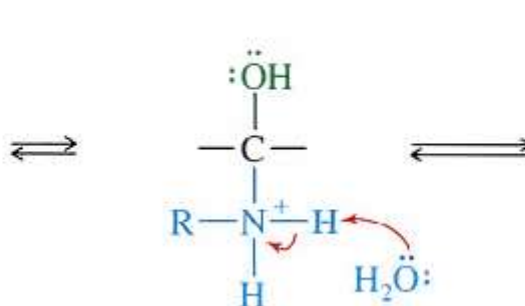This mechanism is more easily remembered by dividing it into two parts:[1]

1. Acid-catalyzed addition of the amine to the carbonyl group.
2. Acid-catalyzed dehydration.

First part: Acid-catalyzed addition of the amine to the carbonyl group.
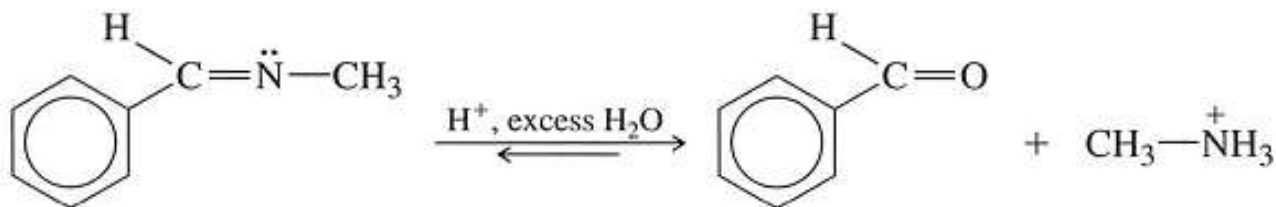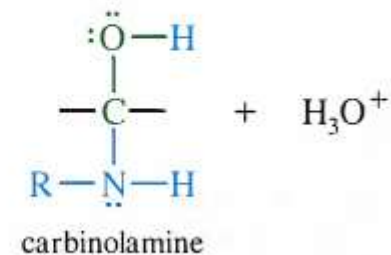
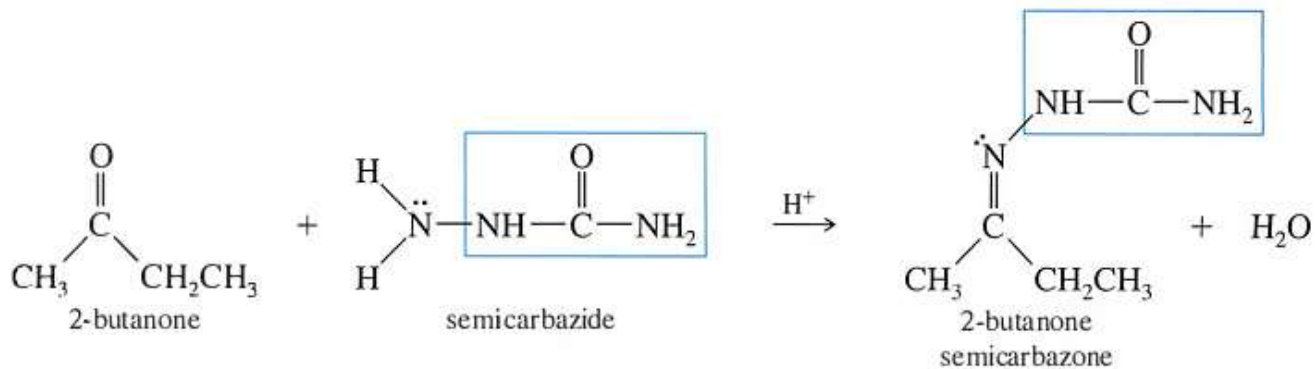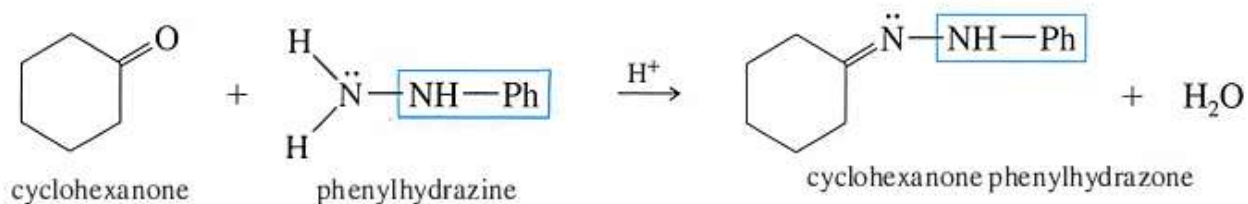**Step 1:** Protonation of the carbonyl. **Step 2:** Addition of the amine. **Step 3:** Deprotonation

H^+

$R-\overset{..}{N}H_2$

:ÖH

$R-\overset{+}{N}-H$
|
H

$H_2\overset{..}{O}:$

:Ö—H

$R-\overset{..}{N}-H$

carbinolamine

$+$ H_3O^+

$\underset{C=\overset{..}{N}-CH_3}{H}$ (benzaldehyde methyl imine)

$\xrightarrow{H^+,\ \text{excess } H_2O}$

$\underset{C=O}{H}$

$+$ $CH_3-\overset{+}{N}H_3$
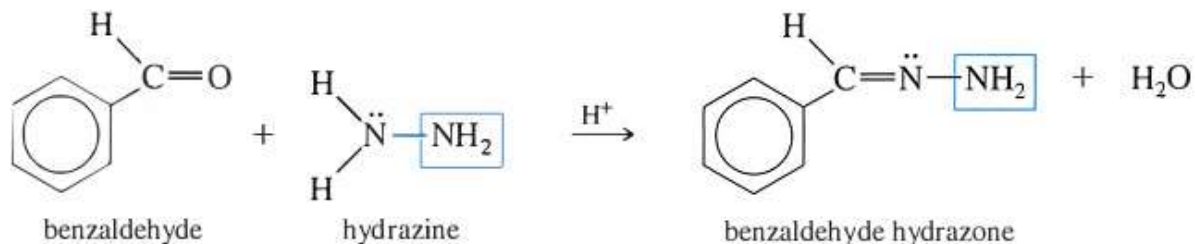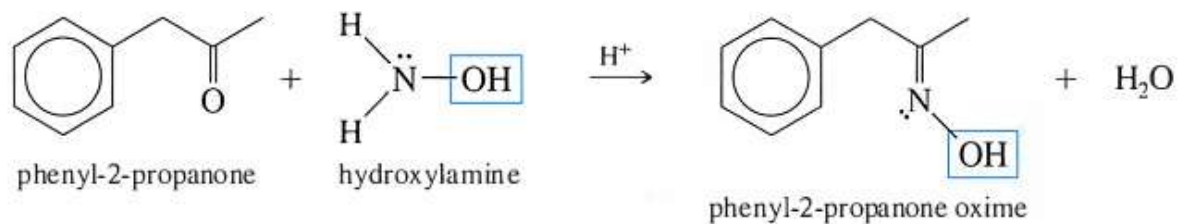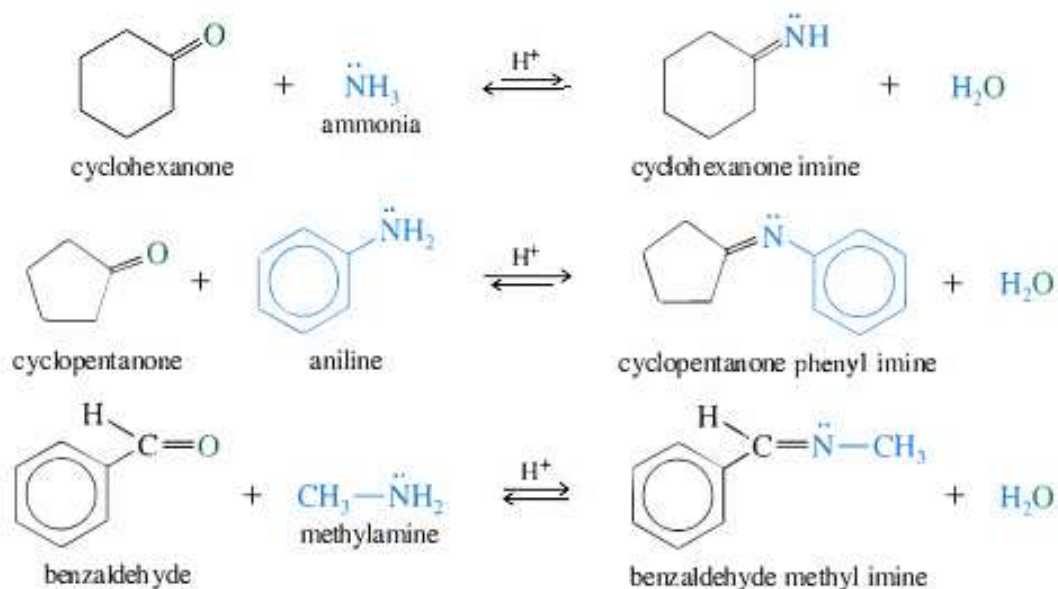
PROBLEM 18-25

Propose a mechanism for the hydrolysis of benzaldehyde methyl imine just shown.

Condensations with Hydroxylamine and Hydrazines

phenyl-2-propanone + hydroxylamine $\xrightarrow{H^+}$ phenyl-2-propanone oxime + H_2O

benzaldehyde + hydrazine $\xrightarrow{H^+}$ benzaldehyde hydrazone + H_2O

cyclohexanone + phenylhydrazine $\xrightarrow{H^+}$ cyclohexanone phenylhydrazone + H_2O

2-butanone + semicarbazide $\xrightarrow{H^+}$ 2-butanone semicarbazone + H_2O

The following equations show some typical imine-forming reactions. In each case, notice that the C=O group of the ketone or aldehyde is replaced by the C=N—R group of the imine.

cyclohexanone   + $\ddot{N}H_3$ ⇌ (H⁺)   cyclohexanone imine   + H_2O
                       ammonia

cyclopentanone   +   aniline   ⇌ (H⁺)   cyclopentanone phenyl imine   + H_2O

benzaldehyde   + CH_3—$\ddot{N}H_2$ ⇌ (H⁺)   benzaldehyde methyl imine   + H_2O
   methylamine

PROBLEM 18-22

Propose mechanisms for the three imine-forming reactions just shown.

PROBLEM 18-23

Depending on the reaction conditions, two different imines of formula C_8H_9N might be formed by the reaction of benzaldehyde with methylamine. Explain, and give the structures of the two imines.

PROBLEM 18-24

Give the structures of the carbonyl compound and the amine used to form the following imines.
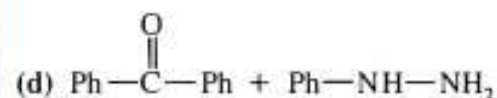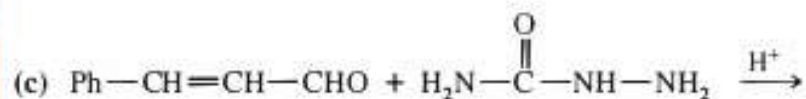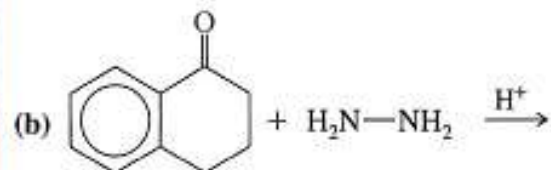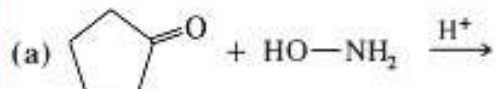
(a)

(b)

(c)

(d)
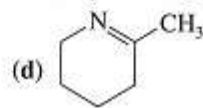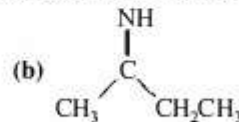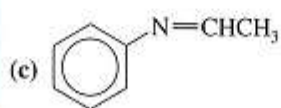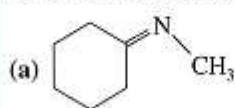
2,4-Dinitrophenylhydrazine is frequently used for making derivatives of ketones and aldehydes because the products (2,4-dinitrophenylhydrazones, called **2,4-DNP derivatives**) are even more likely than the phenylhydrazones to be solids with sharp melting points. Propose a mechanism for the reaction of acetone with 2,4-dinitrophenylhydrazine in a mildly acidic solution.

PROBLEM-SOLVING *Hint*

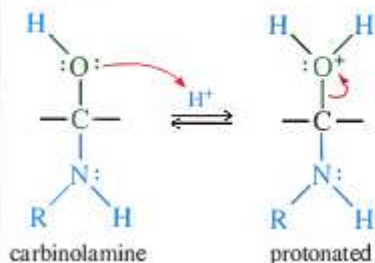Please learn these common derivatives. You will see many examples, especially in the laboratory.

PROBLEM 18-27

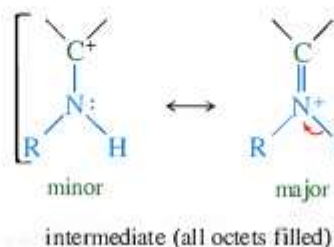Predict the products of the following reactions.

(a) + HO—NH$_2$ $\xrightarrow{H^+}$

(b) + H$_2$N—NH$_2$ $\xrightarrow{H^+}$

(c) Ph—CH=CH—CHO + H$_2$N—$\overset{\displaystyle O}{\overset{\|}{C}}$—NH—NH$_2$ $\xrightarrow{H^+}$

(d) Ph—$\overset{\displaystyle O}{\overset{\|}{C}}$—Ph + Ph—NH—NH$_2$

Second part: Acid-catalyzed dehydration.

Step 4: Protonation of the —OH group.   **Step 5:** Loss of H$_2$ **Step 6:** Deprotonation.

carbinolamine   protonated   intermediate (all octets filled)   imine
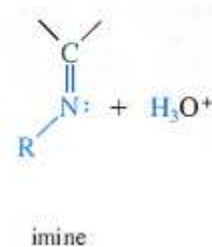
EXAMPLE: Formation of benzaldehyde methyl imine

First part: Acid-catalyzed addition of the amine to the carbonyl group.

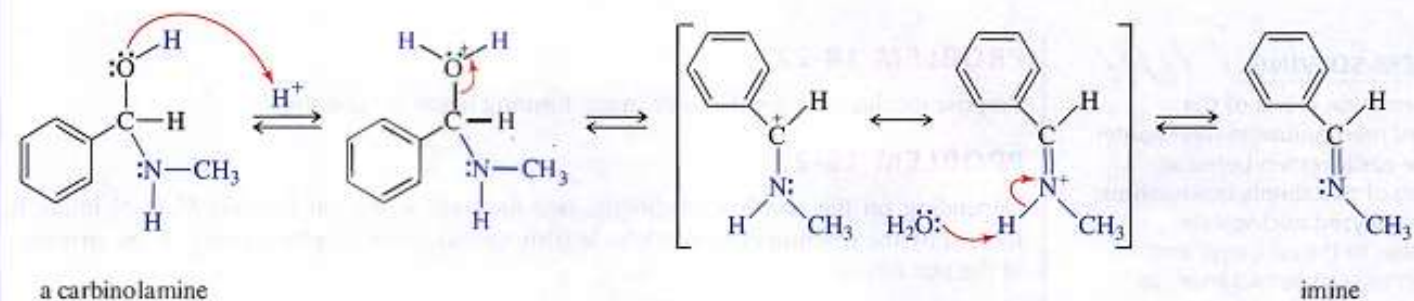*Step 1:* Protonation of the carbonyl. *Step 2:* Addition of the amine. *Step 3:* Deprotonation.

benzaldehyde   methylamine   a carbinolamine

Second part: Acid-catalyzed dehydration.

Step 4: Protonation of the —OH group. *Step 5:* Loss of H_2 *Step 6:* Deprotonation.

a carbinolamine   imine
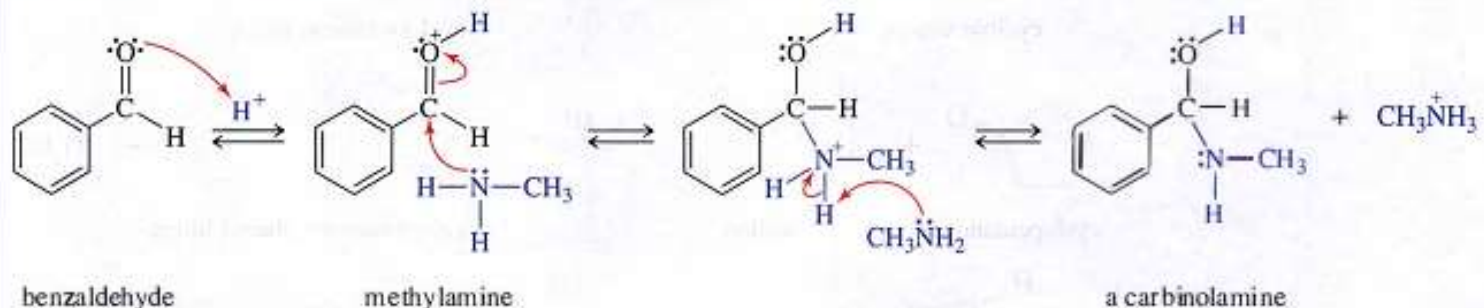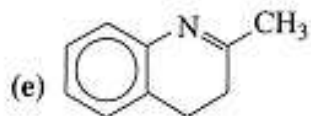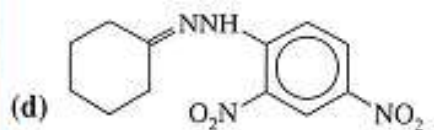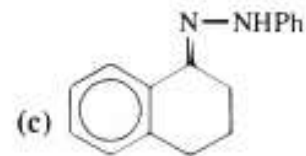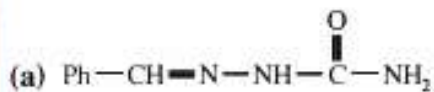
PROBLEM

(a) What would happen if the reaction were made too acidic by the addition of too much acid?
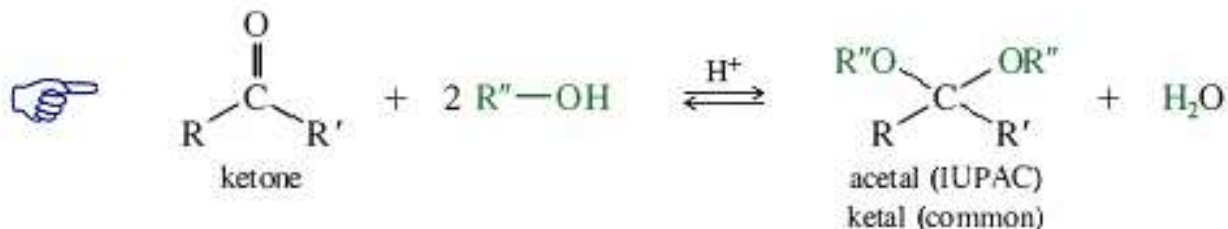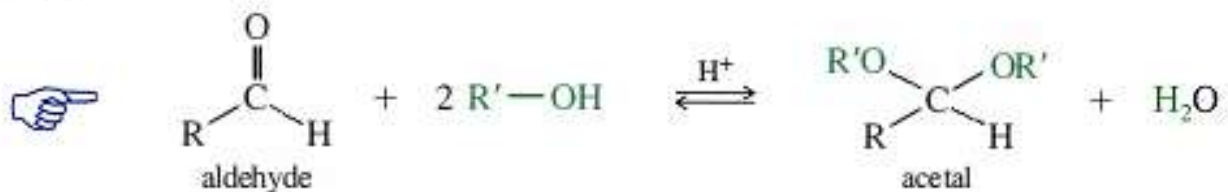(b) What would happen if it were too basic?

PROBLEM 18-28

Show what amines and carbonyl compounds combine to give the following derivatives.

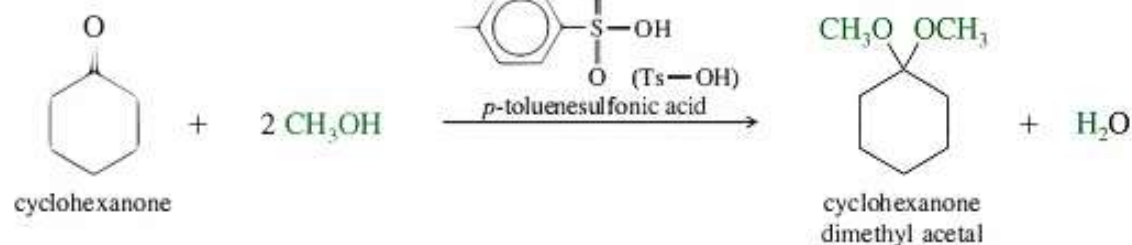(a) $Ph-CH\!=\!N-NH-\overset{\displaystyle O}{\overset{\|}{C}}-NH_2$

(b)

(c)

(d)

(e)

Formation of Acetals

In the formation of an acetal, two molecules of alcohol add to the carbonyl group, and one molecule of water is eliminated.
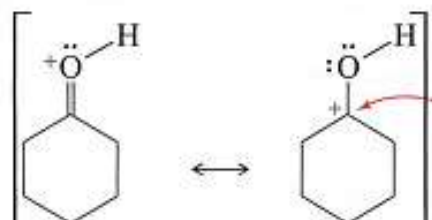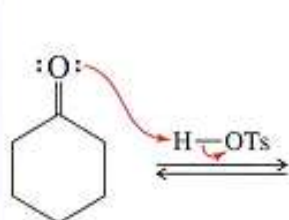
☞
$$\underset{\text{aldehyde}}{\overset{\displaystyle O}{\overset{\|}{\underset{R\quad\quad H}{C}}}} \;+\; 2\,R'\!-\!OH \quad\overset{H^+}{\rightleftharpoons}\quad \underset{\text{acetal}}{\overset{R'O\quad\quad OR'}{\underset{R\quad\quad H}{C}}} \;+\; H_2O$$

☞
$$\underset{\text{ketone}}{\overset{\displaystyle O}{\overset{\|}{\underset{R\quad\quad R'}{C}}}} \;+\; 2\,R''\!-\!OH \quad\overset{H^+}{\rightleftharpoons}\quad \underset{\substack{\text{acetal (IUPAC)}\\\text{ketal (common)}}}{\overset{R''O\quad\quad OR''}{\underset{R\quad\quad R'}{C}}} \;+\; H_2O$$

Overall reaction

cyclohexanone + 2 CH₃OH →[(Ts—OH) p-toluenesulfonic acid]→ cyclohexanone dimethyl acetal + H₂O

First part: Acid-catalyzed addition of the alcohol to the carbonyl group.
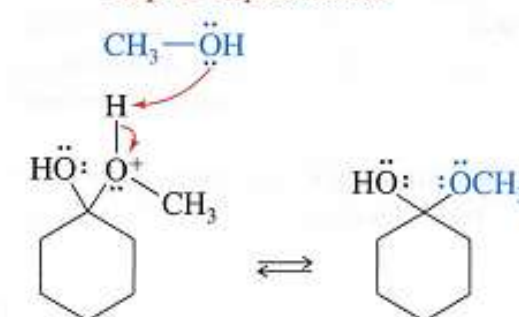
Step 1: Protonation.   **Step 2:** Alcohol adds.   **Step 3:** Deprotonation.

ketone   protonated (activated) ketone   hemiacetal
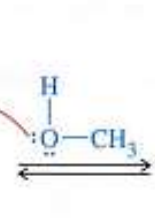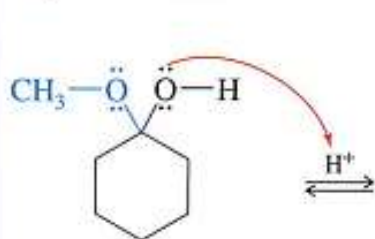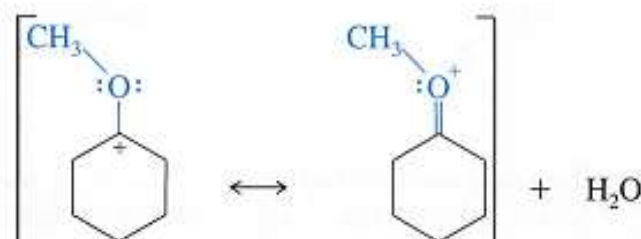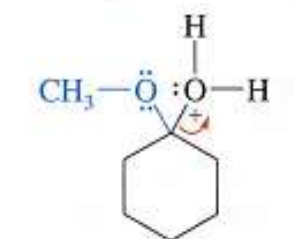
The second half begins like an acid-catalyzed dehydration

Step 4: Protonation.   **Step 5:** Loss of water.

hemiacetal   protonation, loss of water   resonance-stabilized carbocation   + H₂O

42   Monday, January 7, 2019
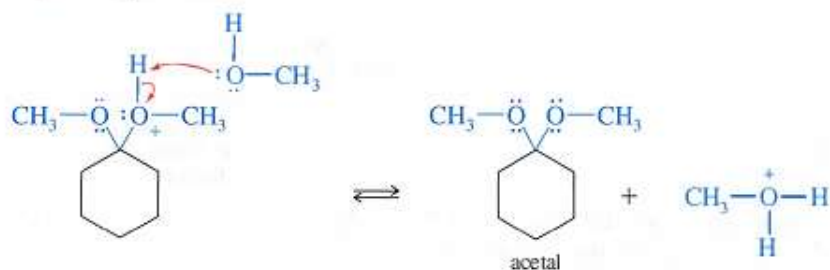
Step 6: Second alcohol adds.   **Step 7:** Deprotonation.

attack by methanol   acetal
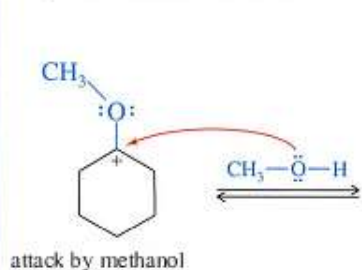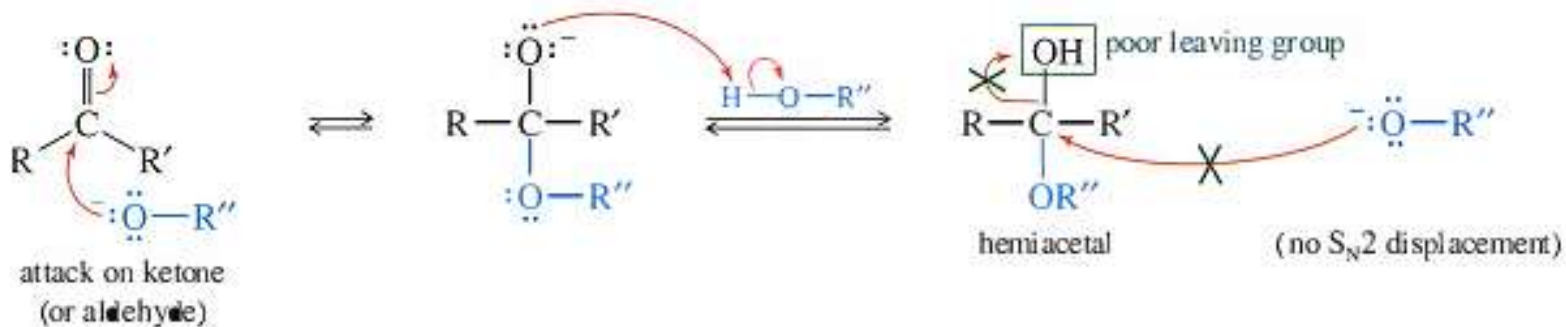
PROBLEM 18-29

Propose a mechanism for the acid-catalyzed reaction of benzaldehyde with methanol to give benzaldehyde dimethyl acetal.

Attempted base-catalyzed acetal formation

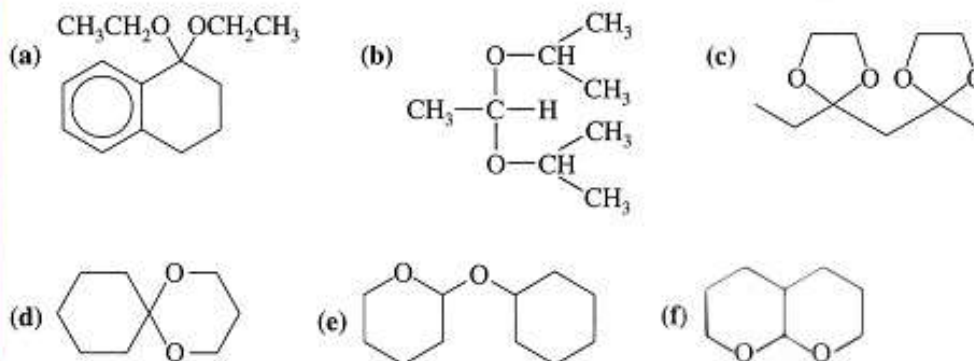attack on ketone
(or aldehyde)

hemiacetal   (no S_N2 displacement)

$$H^+, \text{excess } H_2O$$

$+$ $2\,CH_3OH$

PROBLEM 18-30

Propose a mechanism for the acid-catalyzed hydrolysis of cyclohexanone dimethyl acetal.
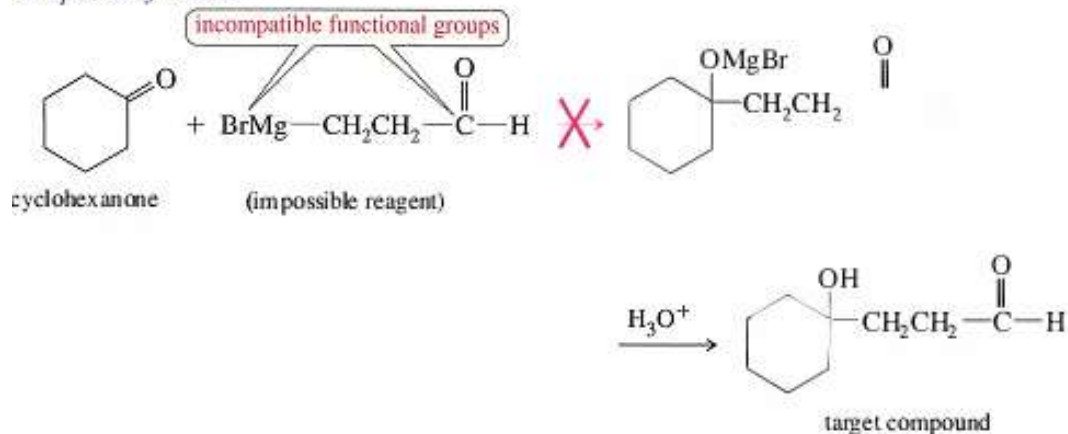
PROBLEM 18-31

Show what alcohols and carbonyl compounds give the following derivatives.

Use of Acetals as Protecting Groups
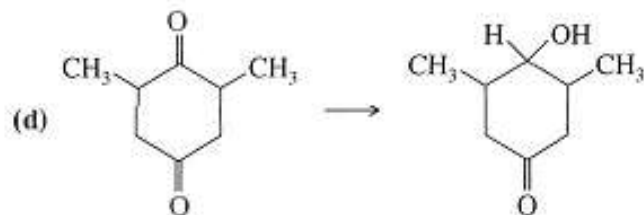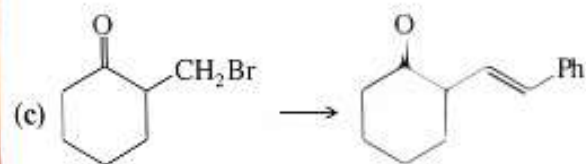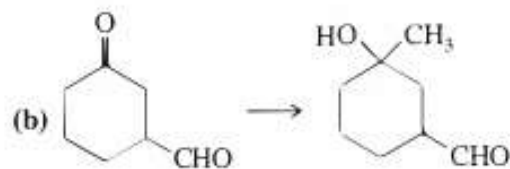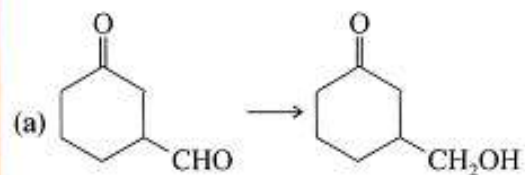
Proposed synthesis

PROBLEM 18-34

Show how you would accomplish the following syntheses. You may use whatever additional reagents you need.

(a)

(b)

(c)

(d)

(e)

(f) $BrCH_2CH_2CCH_3$ ⟶ $HC≡CCH_2CH_2CCH_3$

Oxidation of Aldehydes

☞ $R-\overset{O}{\overset{||}{C}}-H$ $\xrightarrow[\text{(oxidizing agent)}]{[O]}$ $R-\overset{O}{\overset{||}{C}}-OH$

Examples

$CH_3-\underset{\underset{CH_3}{|}}{CH}-\overset{O}{\overset{||}{C}}-H$ $\xrightarrow[\text{dil } H_2SO_4]{Na_2Cr_2O_7}$ $CH_3-\underset{\underset{CH_3}{|}}{CH}-\overset{O}{\overset{||}{C}}-OH$

isobutyraldehyde   isobutyric acid (90%)

$\xrightarrow[\text{THF/H}_2O]{Ag_2O}$

(97%)

$$R-\overset{\displaystyle O}{\overset{\|}{C}}-H \;+\; 2\,\overset{+}{A}g(NH_3)_2 \;+\; 3\,{}^-OH \;\xrightarrow{\;H_2O\;}\; 2\,Ag\downarrow \;+\; R-\overset{\displaystyle O}{\overset{\|}{C}}-O^- \;+\; 4\,NH_3 \;+\; 2\,H_2O$$

aldehyde   Tollens reagent   silver   carboxylate
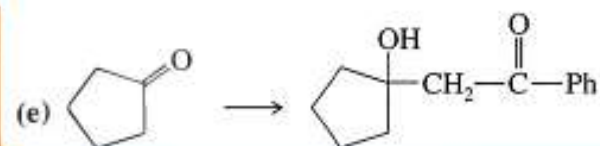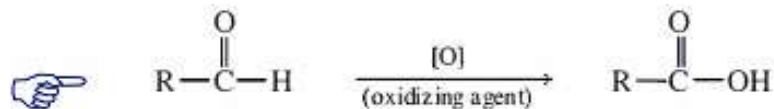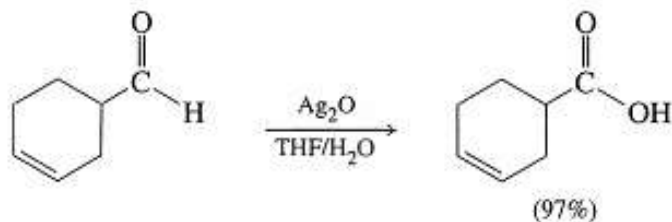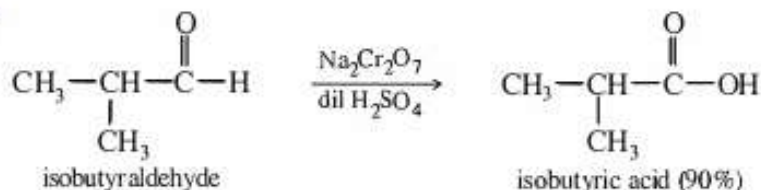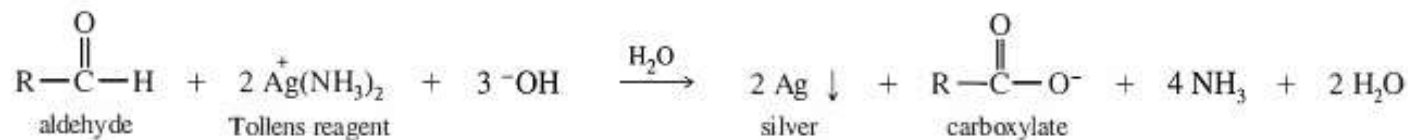
PROBLEM 18-35

Predict the major products of the following reactions.

(a) + Ag_2O (b) + $K_2Cr_2O_7/H_2SO_4$ (c) + $\overset{+}{A}g(NH_3)_2\ {}^-OH$

(d) + $KMnO_4$ (cold, dilute)
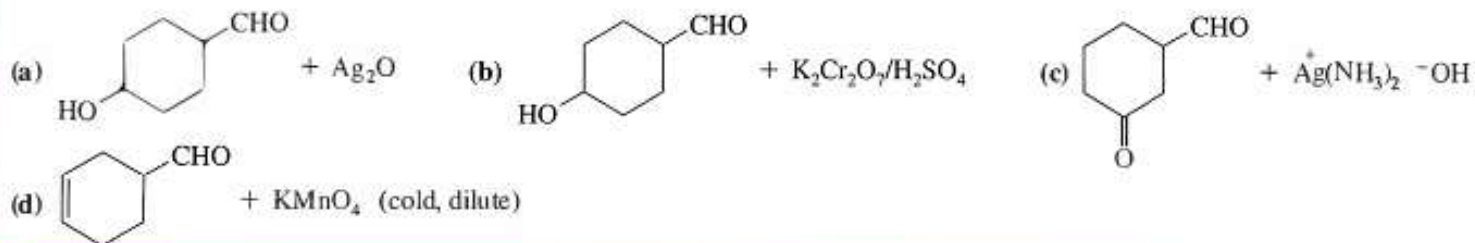
Reductions of Ketones and Aldehydes

Hydride Reductions (Review)

cyclohexane carbaldehyde $\xrightarrow{\;NaBH_4,\ CH_3CH_2OH\;}$ cyclohexyl methanol (95%)

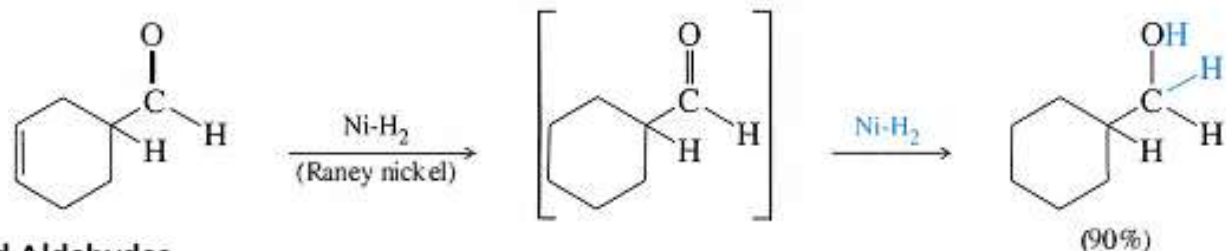$$CH_3-\overset{\displaystyle O}{\overset{\|}{C}}-CH_2CH_3 \;\xrightarrow{\;NaBH_4,\ CH_3OH\;}\; CH_3-\overset{\displaystyle OH}{\overset{|}{C}H}-CH_2CH_3$$

2-butanone   (±) 2-butanol (100%)
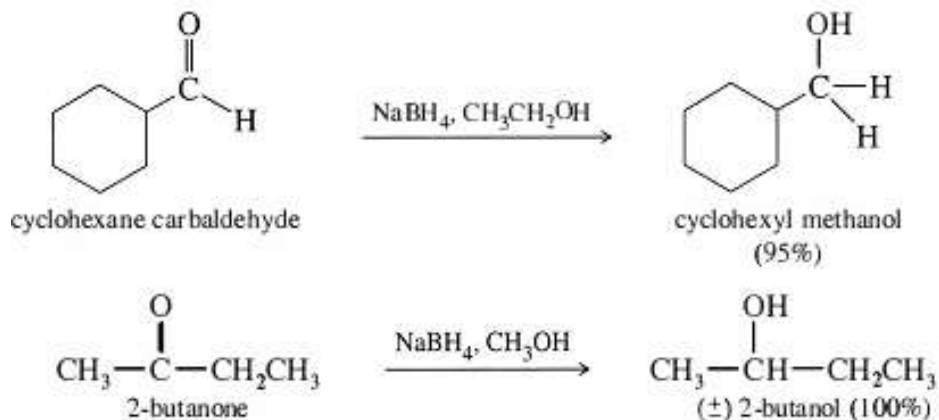
Catalytic Hydrogenation

(90%)

Deoxygenation of Ketones and Aldehydes

deoxygenation

Zn(Hg), HCl or H_2NNH_2, KOH

R—C—R'   ketone
$\xrightarrow[\text{or LiAlH}_4]{\text{NaBH}_4}$
R—C—R'   alcohol
$\xrightarrow[\text{(2) LiAlH}_4]{\text{(1) TsCl}}$
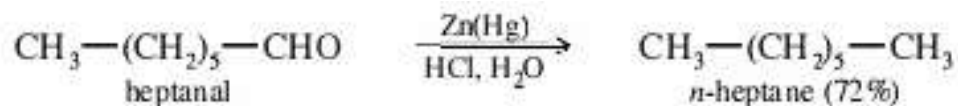R—C—R'   methylene group
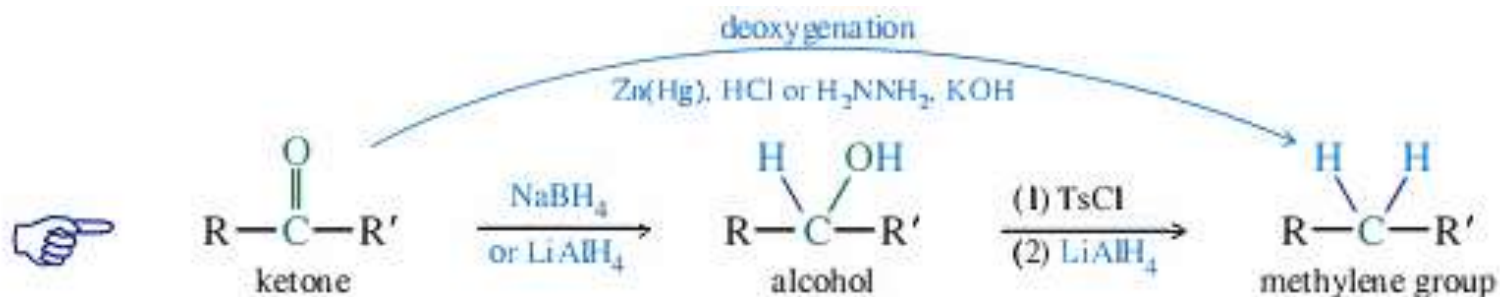
Clemmensen Reduction (Review)   The Clemmensen reduction

$CH_3—(CH_2)_5—CHO$
heptanal
$\xrightarrow[\text{HCl, H}_2\text{O}]{\text{Zn(Hg)}}$
$CH_3—(CH_2)_5—CH_3$
n-heptane (72%)

cyclohexanone
$\xrightarrow[\text{HCl, H}_2\text{O}]{\text{Zn(Hg)}}$

cyclohexane (75%)
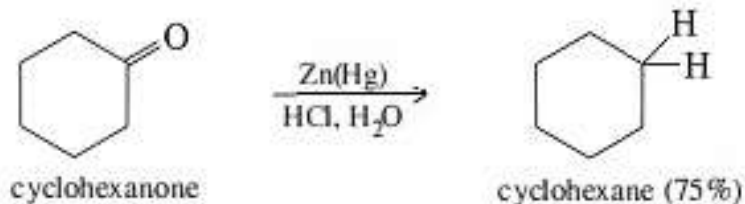
Wolff–Kishner Reduction