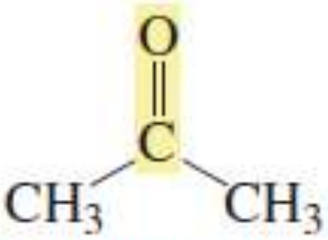
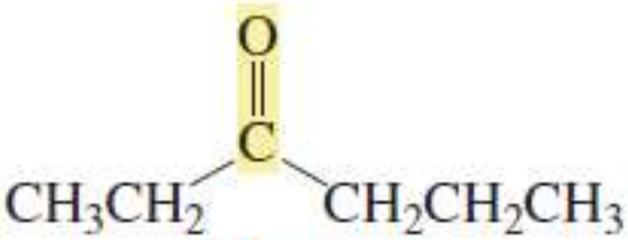
Nomenclature

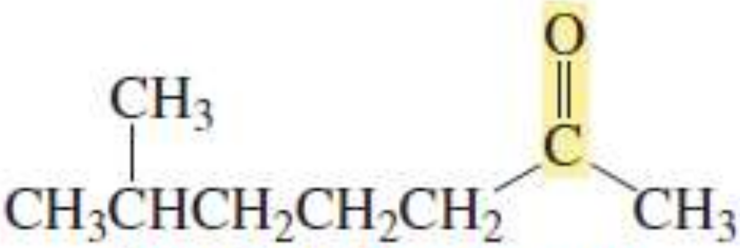


$CH_3\overset{\displaystyle O}{\overset{\|}{C}}CH_3$



$CH_3CH_2\overset{\displaystyle O}{\overset{\|}{C}}CH_2CH_2CH_3$

systematic name:	propanone	3-hexanone
common name:	acetone	
derived name:	dimethyl ketone	ethyl propyl ketone

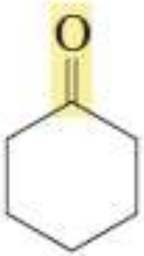


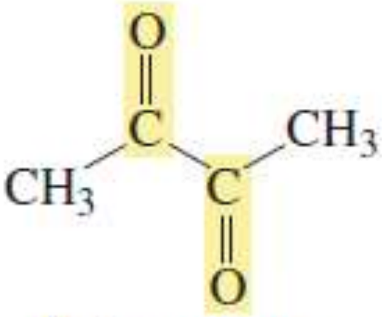
$CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2CH_2CH_2\overset{\displaystyle O}{\overset{\|}{C}}CH_3$

6-methyl-2-heptanone

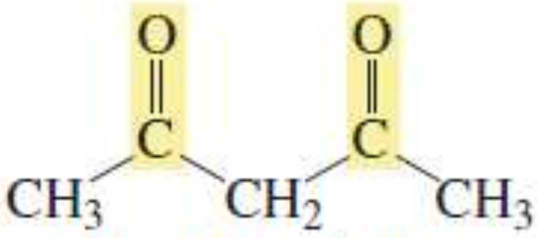
isohexyl methyl ketone

Nomenclature

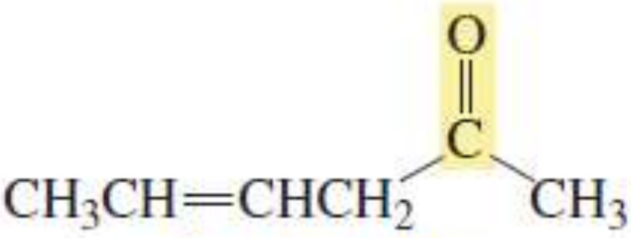




systematic name: cyclohexanone butanedione
common name:

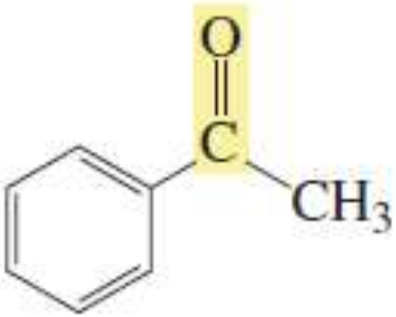


2,4-pentanedione
acetylacetone

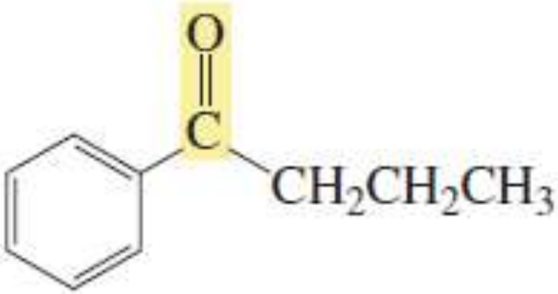


4-hexen-2-one

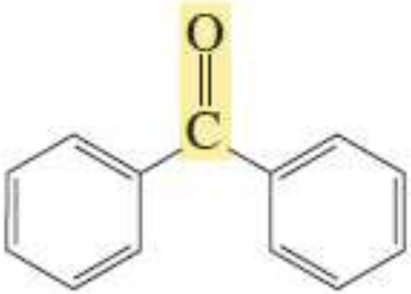
Nomenclature



common name: acetophenone
derived name: methyl phenyl ketone



butyrophenone
phenyl propyl ketone



benzophenone
diphenyl ketone

Preparation of Aldehydes

PREPARATION OF ALDEHYDES

1. **Oxidation of primary alcohols.** Discussed in Secs. 16.8 and 19.5.

P. 529

$$\underset{\text{1° Alcohol}}{RCH_2OH} \xrightarrow{K_2Cr_2O_7} \underset{\text{Aldehyde}}{R{-}\overset{\overset{\large H}{|}}{C}{=}O}$$

1° Alcohol

Aldehyde

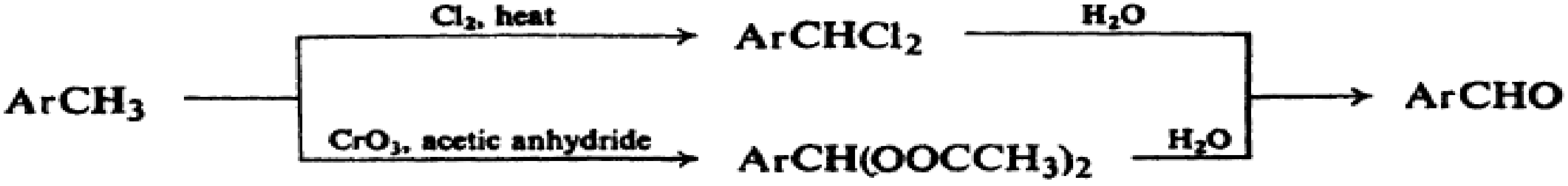
Example:

$$CH_3CH_2CH_2CH_2OH \xrightarrow{K_2Cr_2O_7,\ H_2SO_4,\ \text{warm}} CH_3CH_2CH_2CHO$$

n-Butyl alcohol
(1-Butanol)
B.p. 118°

n-Butyraldehyde
(Butanal)
B.p. 76°

2. **Oxidation of methylbenzenes.** Discussed in Sec. 19.5.



Examples:

p-Bromotoluene

p-Bromobenzaldehyde

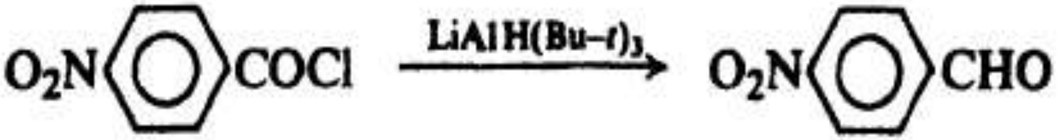
p-Nitrotoluene

p-Nitrobenzaldehyde

3. Reduction of acid chlorides. Discussed in Sec. 19.4.

$$\underset{\text{Acid chloride}}{\text{RCOCl} \quad \text{or} \quad \text{ArCOCl}} \xrightarrow{\text{LiAlH(Bu-}t)_3} \underset{\text{Aldehyde}}{\text{RCHO} \quad \text{or} \quad \text{ArCHO}}$$

Examples:



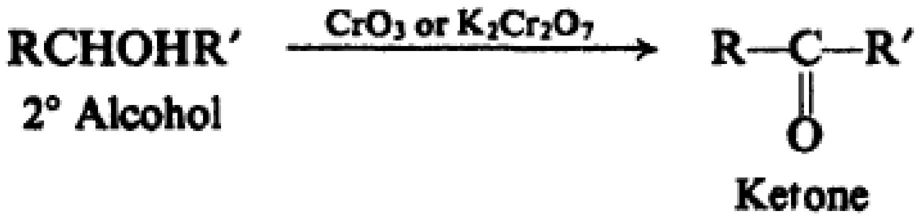
p-Nitrobenzoyl chloride

p-Nitrobenzaldehyde

Preparation Ketones

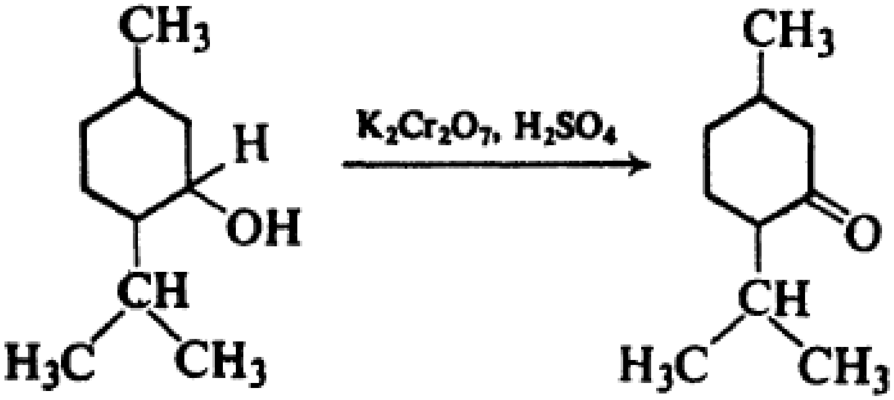
PREPARATION OF KETONES

1. Oxidation of secondary alcohols. Discussed in Sec. 16.8.



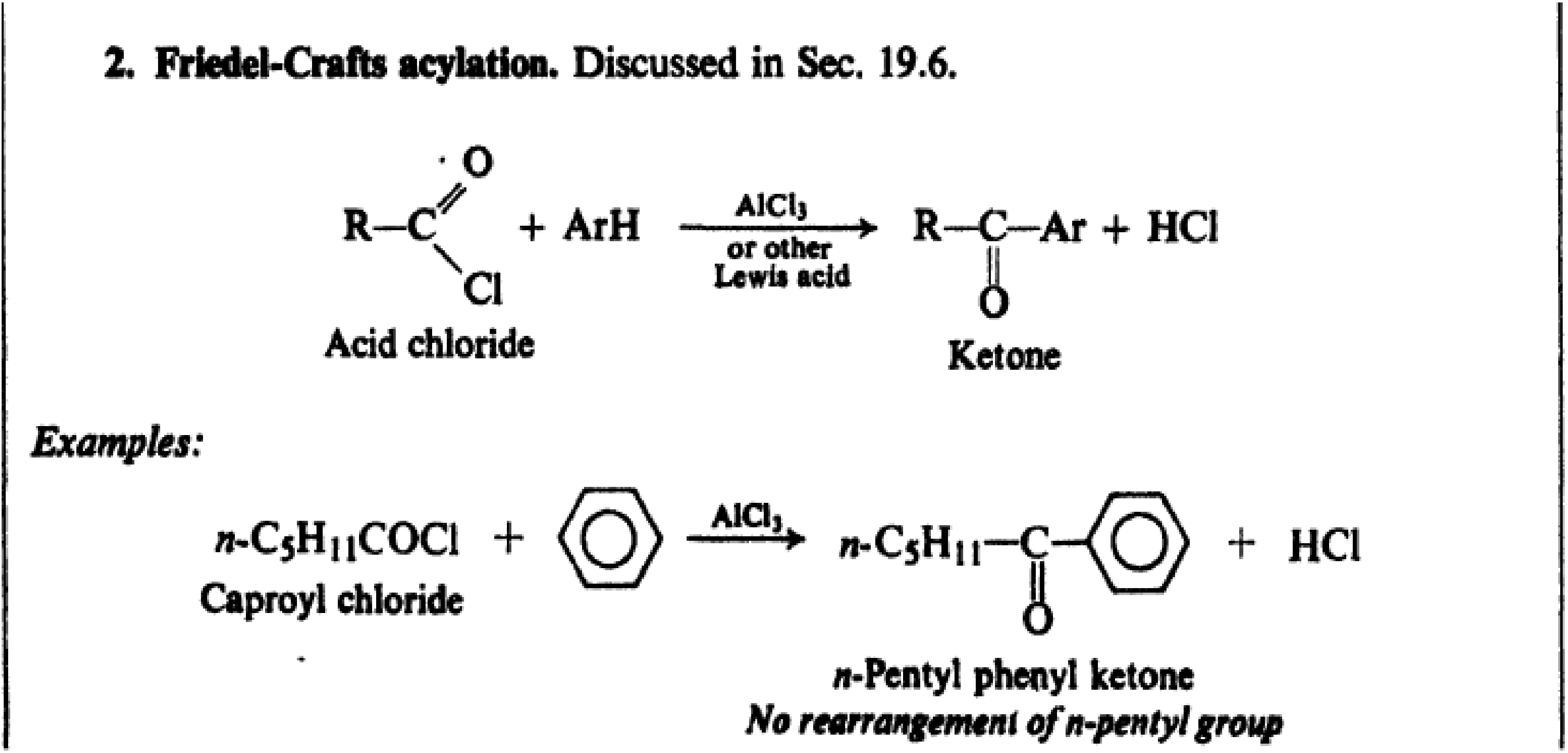
$$\underset{\text{2° Alcohol}}{RCHOHR'} \xrightarrow{CrO_3 \text{ or } K_2Cr_2O_7} \underset{\text{Ketone}}{R-\overset{\displaystyle O}{\overset{\|}{C}}-R'}$$

Example:



(−)-Menthol

(−)-Menthone



2. Friedel-Crafts acylation. Discussed in Sec. 19.6.

$$R-\overset{\overset{O}{\|}}{C}-Cl + ArH \xrightarrow[\text{or other Lewis acid}]{AlCl_3} R-\underset{\underset{O}{\|}}{C}-Ar + HCl$$

Acid chloride

Ketone

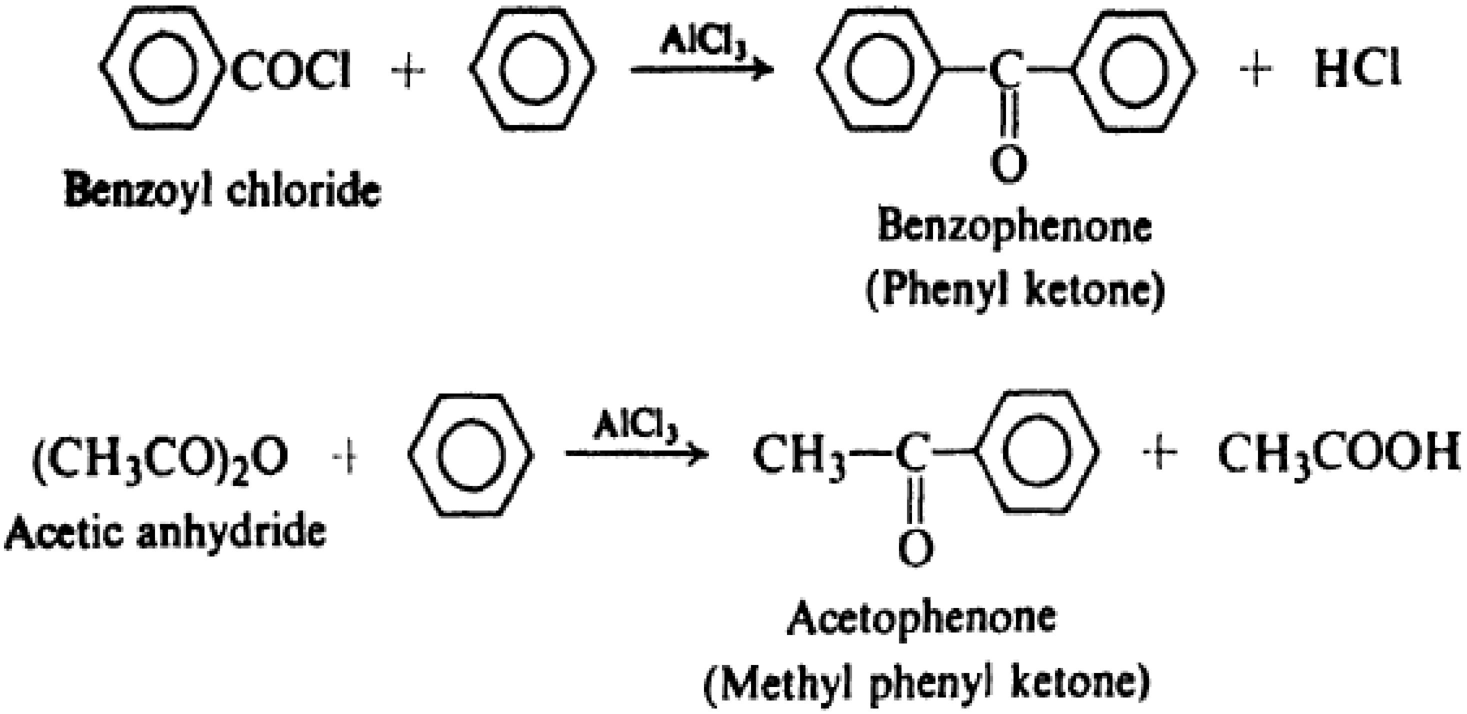
Examples:

$$n\text{-}C_5H_{11}COCl \; + \xrightarrow{AlCl_3} n\text{-}C_5H_{11}-\underset{\underset{O}{\|}}{C}- \; + \; HCl$$

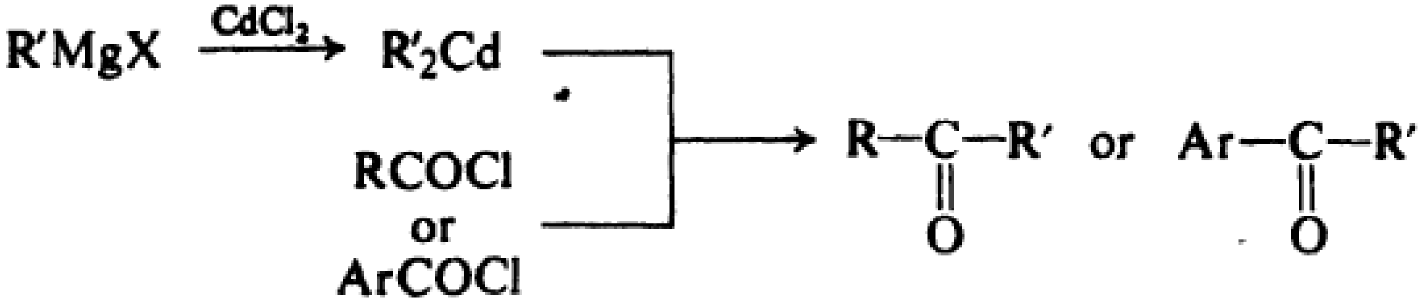
Caproyl chloride

n-Pentyl phenyl ketone

No rearrangement of n-pentyl group


COCl
Benzoyl chloride
AlCl₃
C
O
Benzophenone
(Phenyl ketone)
HCl
(CH₃CO)₂O
Acetic anhydride
AlCl₃
CH₃—C
O
Acetophenone
(Methyl phenyl ketone)
CH₃COOH

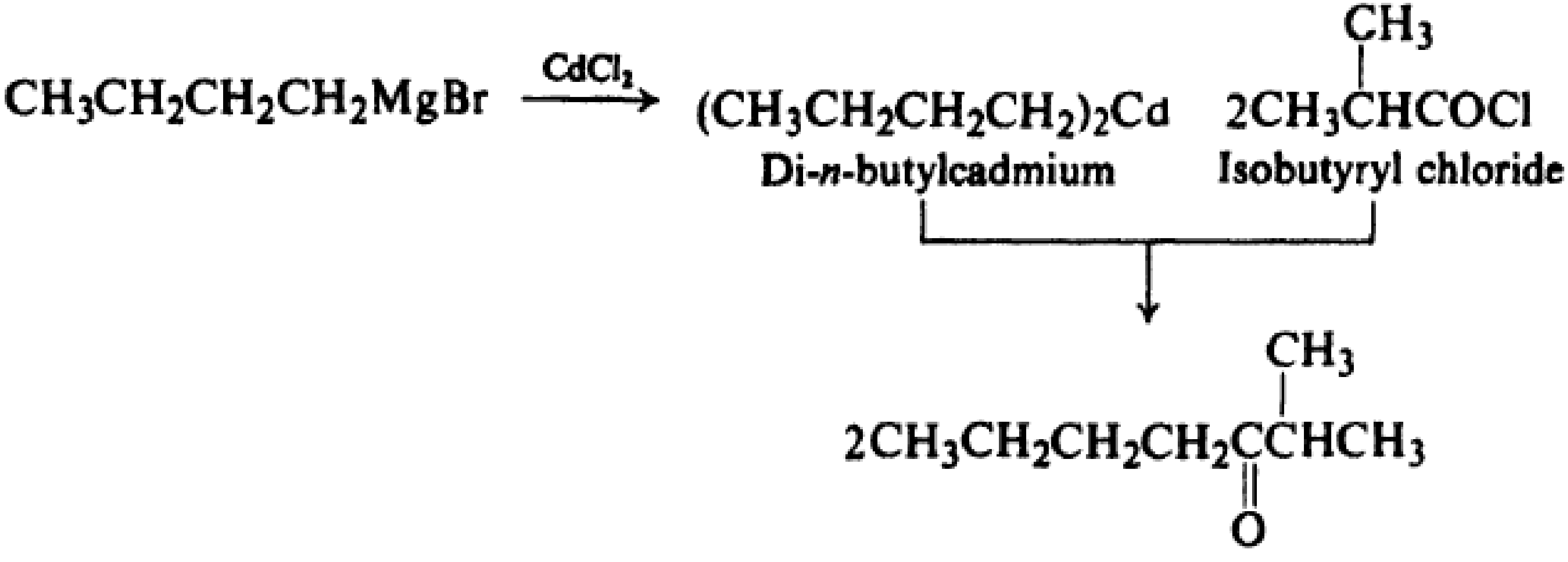
3. Reaction of acid chlorides with organocadmium compounds. Discussed in Sec. 19.7.



$$\mathrm{R'MgX} \xrightarrow{\mathrm{CdCl_2}} \mathrm{R'_2Cd} \;+\; \mathrm{RCOCl}\ \text{or}\ \mathrm{ArCOCl} \longrightarrow \mathrm{R{-}\overset{}{\underset{\underset{O}{\|}}{C}}{-}R'}\ \text{or}\ \mathrm{Ar{-}\underset{\underset{O}{\|}}{C}{-}R'}$$

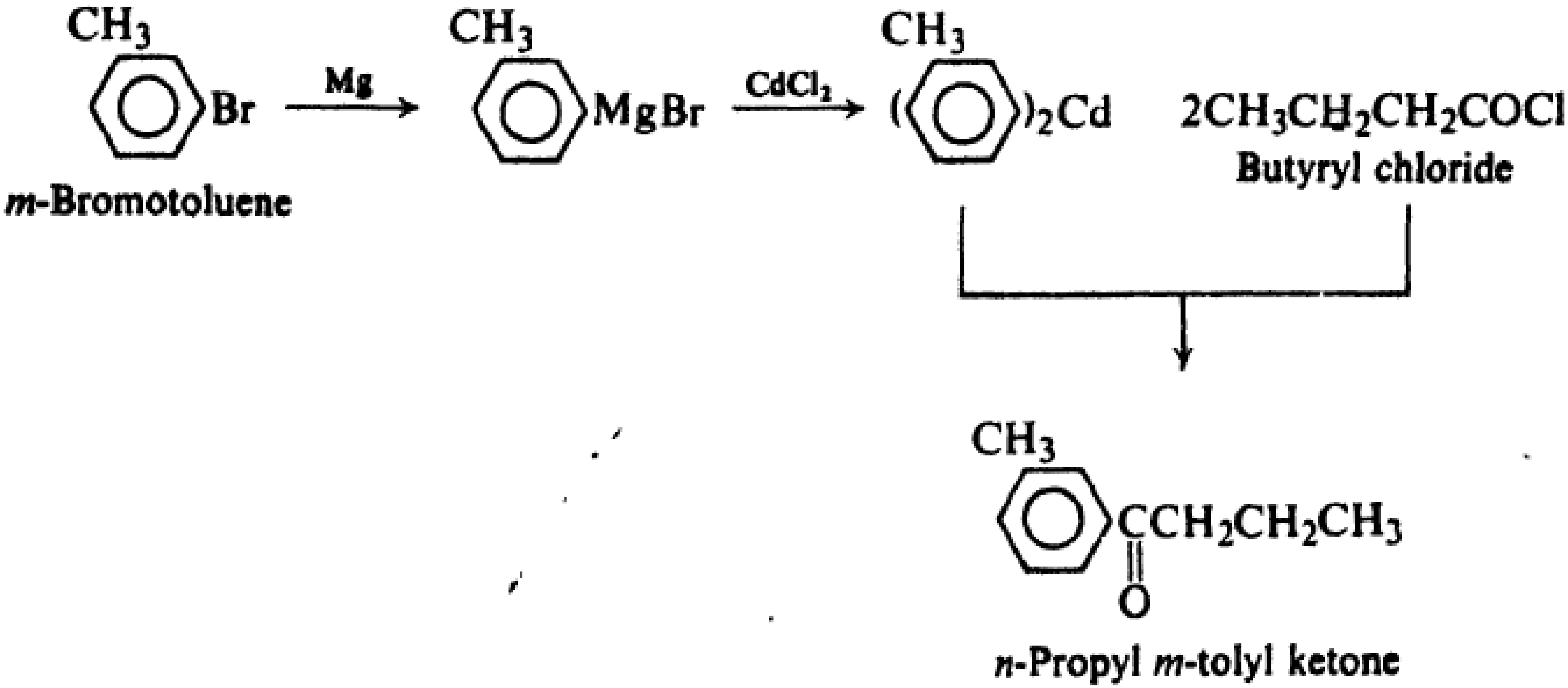
R′ must be aryl or primary alkyl

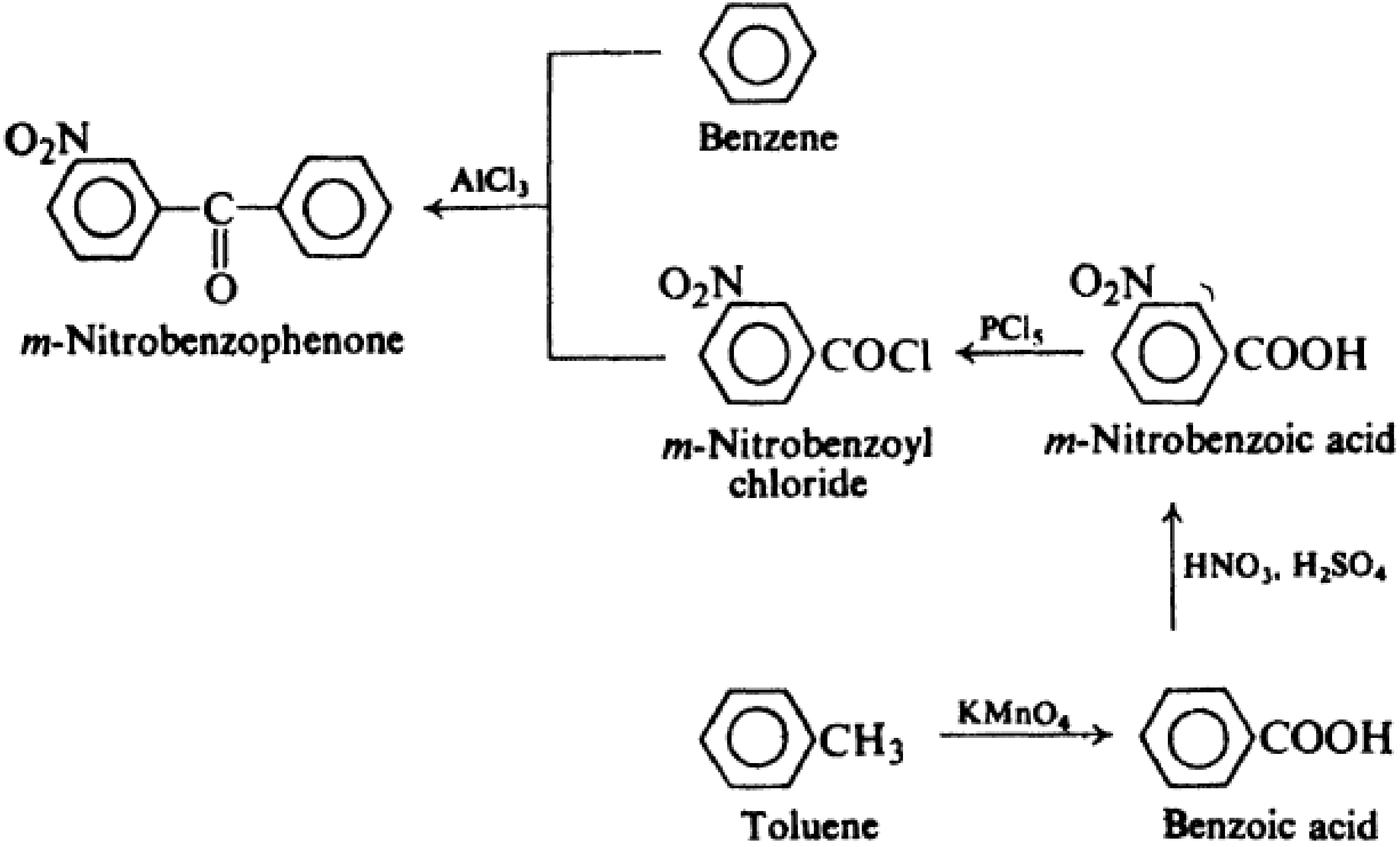
Examples:

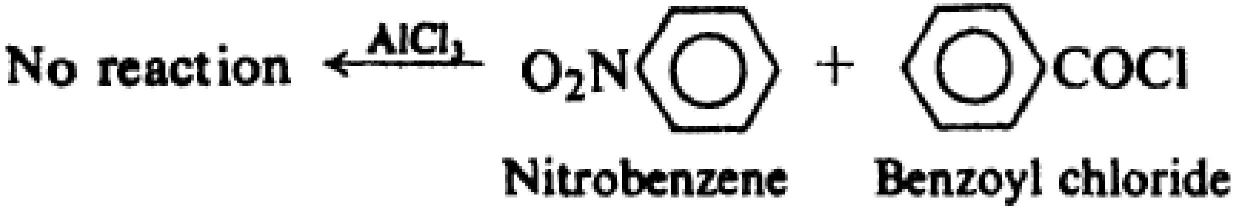


$$\mathrm{CH_3CH_2CH_2CH_2MgBr} \xrightarrow{\mathrm{CdCl_2}} \mathrm{(CH_3CH_2CH_2CH_2)_2Cd} \;+\; \mathrm{2CH_3\overset{\overset{CH_3}{|}}{C}HCOCl} \longrightarrow \mathrm{2CH_3CH_2CH_2CH_2\underset{\underset{O}{\|}}{C}\overset{\overset{CH_3}{|}}{C}HCH_3}$$

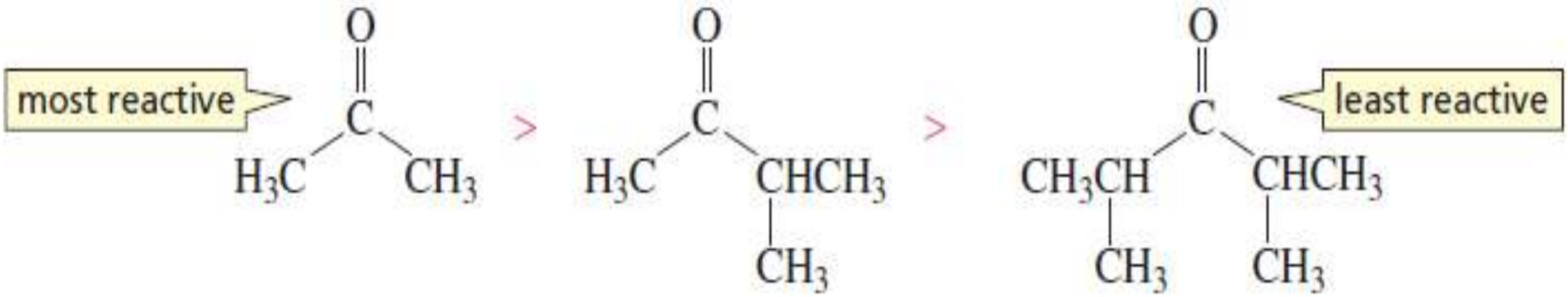
n-Butyl isopropyl ketone
(2-Methyl-3-heptanone)


CH3
Br
m-Bromotoluene
Mg
CH3
MgBr
CdCl2
CH3
( )2Cd
2CH3CH2CH2COCl
Butyryl chloride
CH3
CCH2CH2CH3
O
n-Propyl m-tolyl ketone


Benzene
AlCl₃
m-Nitrobenzophenone
PCl₅
m-Nitrobenzoyl chloride
m-Nitrobenzoic acid
HNO₃, H₂SO₄
KMnO₄
Toluene
Benzoic acid

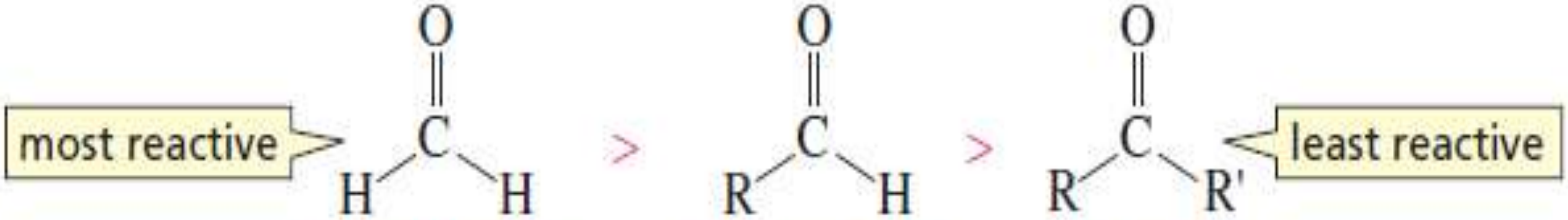

No reaction
AlCl₃
Nitrobenzene
Benzoyl chloride

relative reactivities



most reactive > > least reactive

relative reactivities



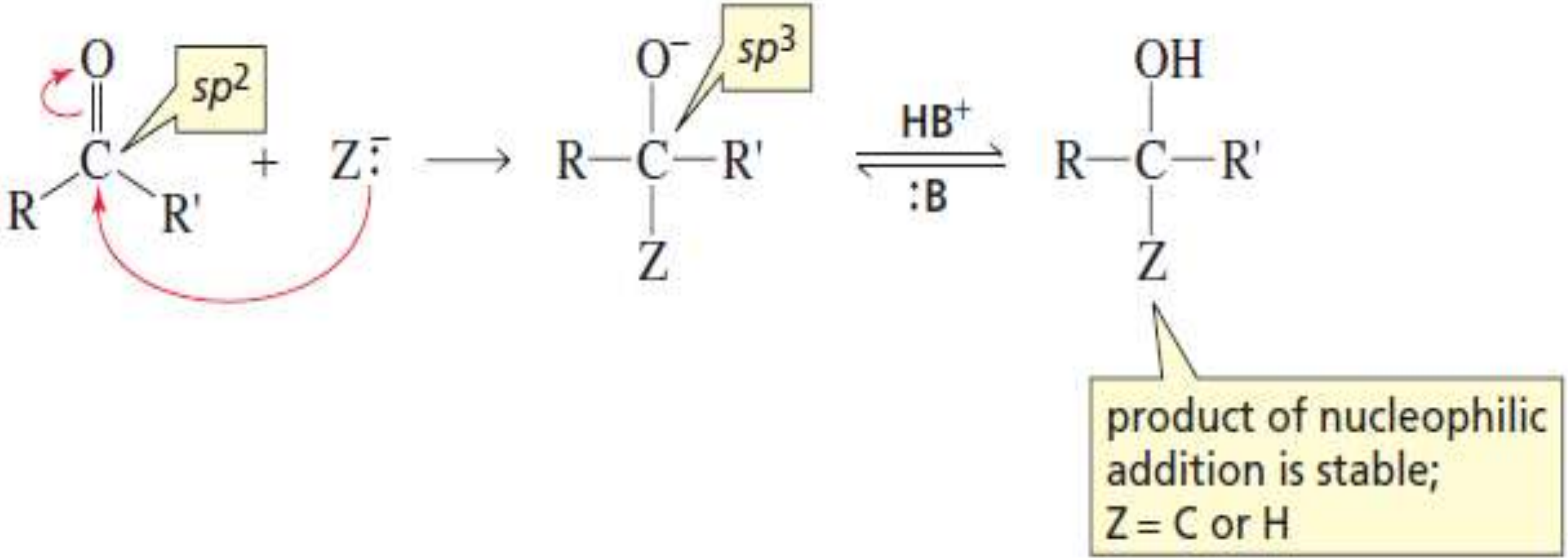
most reactive

least reactive

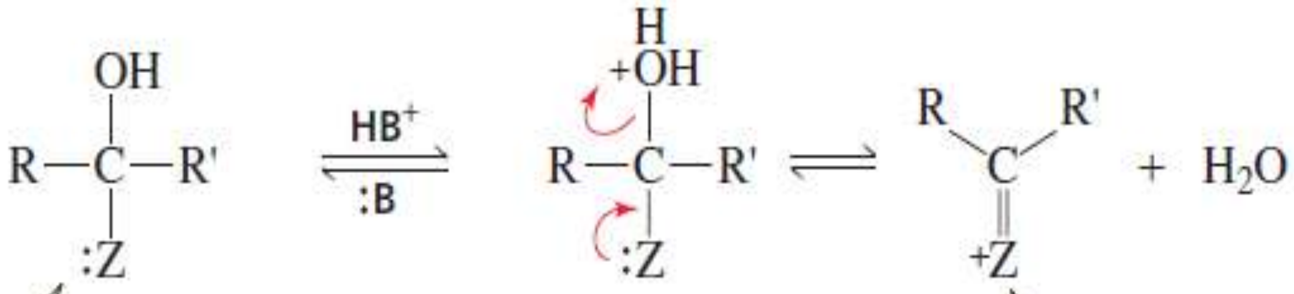
formaldehyde

an aldehyde

a ketone



product of nucleophilic addition is stable;
Z = C or H

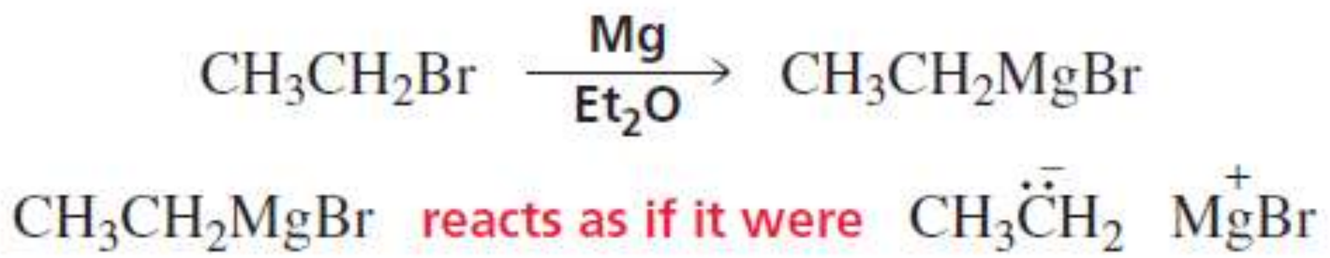


product of nucleophilic addition is not stable; Z = O or N

product of nucleophilic addition–elimination

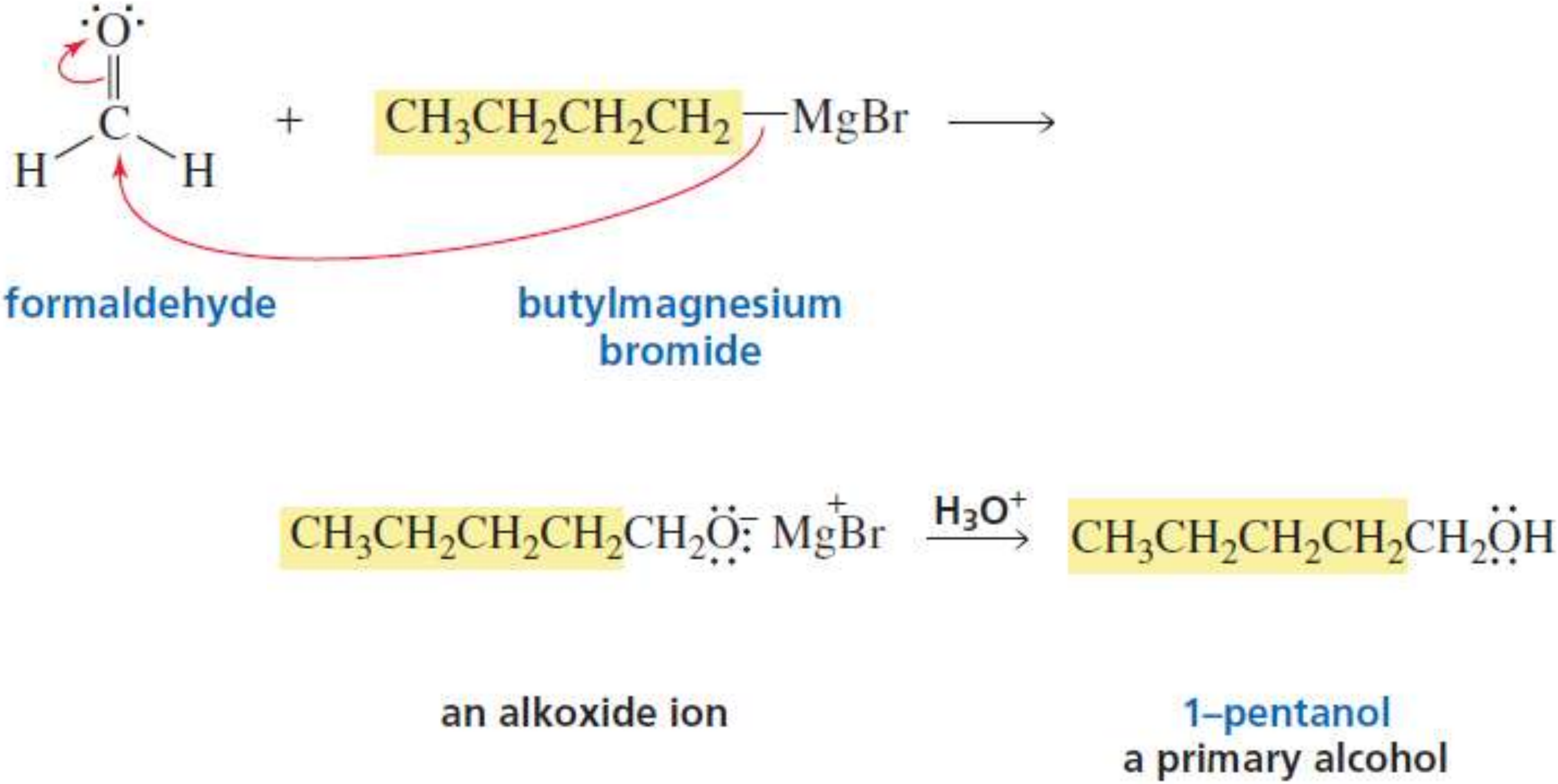
Reactions of Carbonyl Compounds with Carbon Nucleophiles

- Reaction with Grignard Reagents

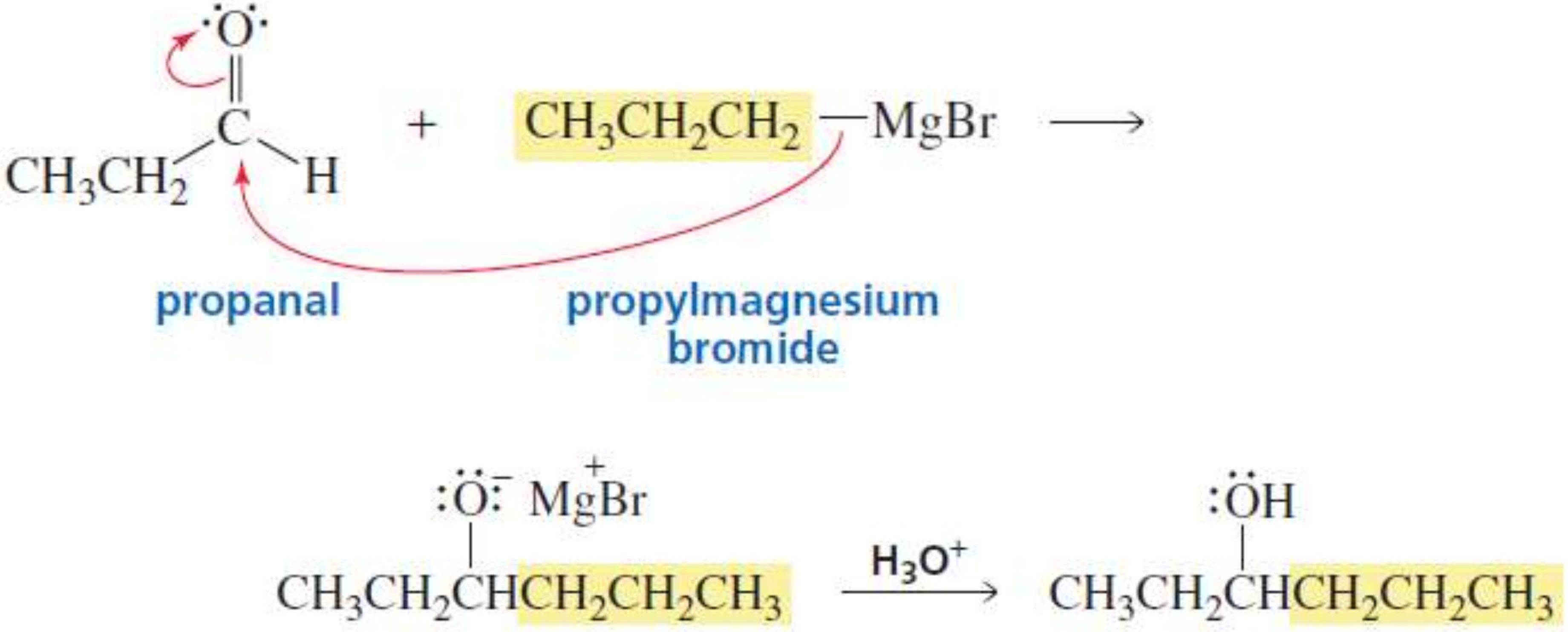


$$CH_3CH_2Br \xrightarrow[Et_2O]{Mg} CH_3CH_2MgBr$$

CH_3CH_2MgBr reacts as if it were $CH_3\overset{-}{\ddot{C}}H_2 \quad \overset{+}{Mg}Br$



$$CH_3CH_2CH_2CH_2CH_2\ddot{\underset{..}{O}}{:}^{-}\ \overset{+}{Mg}Br \xrightarrow{H_3O^+} CH_3CH_2CH_2CH_2CH_2\ddot{\underset{..}{O}}H$$



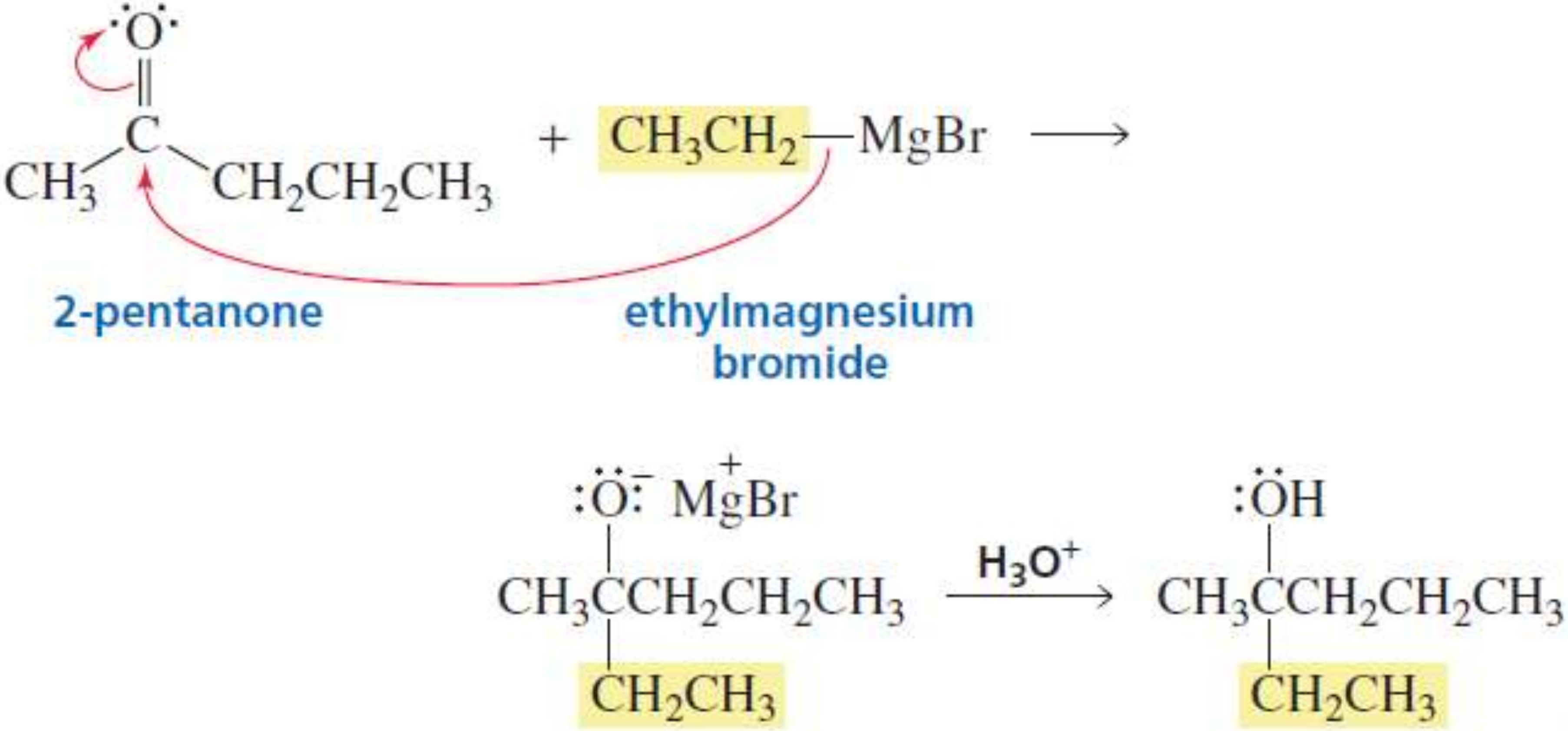
$$CH_3CH_2CHO + CH_3CH_2CH_2{-}MgBr \longrightarrow CH_3CH_2CH(O^{-}\,\overset{+}{Mg}Br)CH_2CH_2CH_3 \xrightarrow{H_3O^+} CH_3CH_2CH(OH)CH_2CH_2CH_3$$

propanal

propylmagnesium bromide

3-hexanol

a secondary alcohol



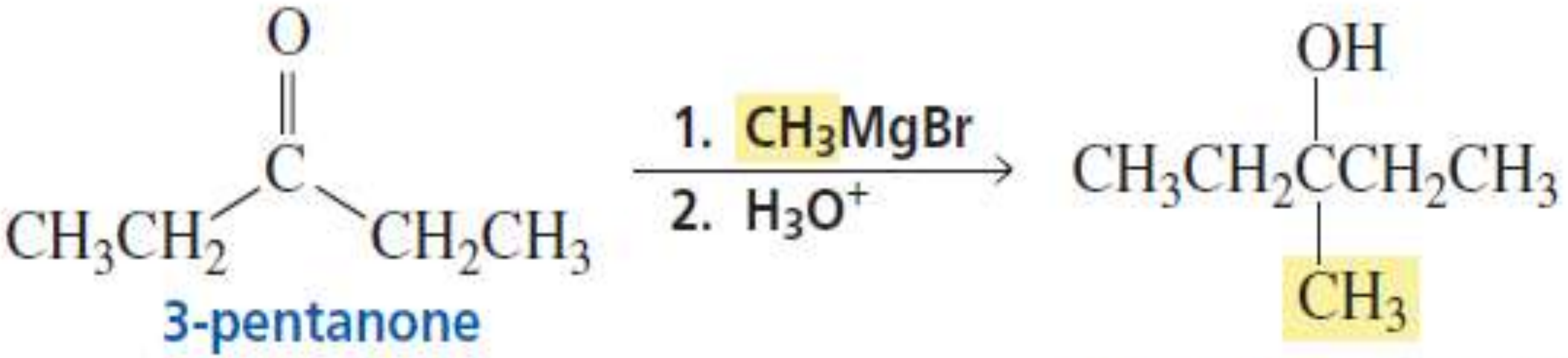
2-pentanone

ethylmagnesium bromide

$$CH_3\underset{CH_2CH_3}{\overset{:\ddot{O}:^-\ \overset{+}{Mg}Br}{C}}CH_2CH_2CH_3 \xrightarrow{H_3O^+} CH_3\underset{CH_2CH_3}{\overset{:\ddot{O}H}{C}}CH_2CH_2CH_3$$

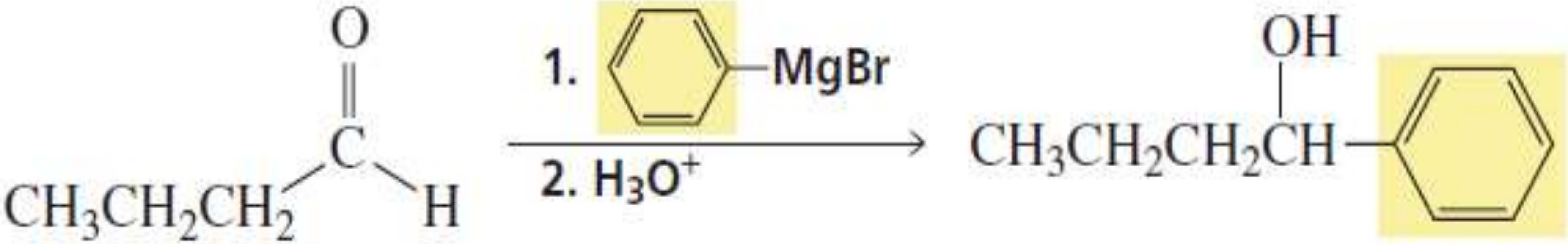
3-methyl-3-hexanol

a tertiary alcohol



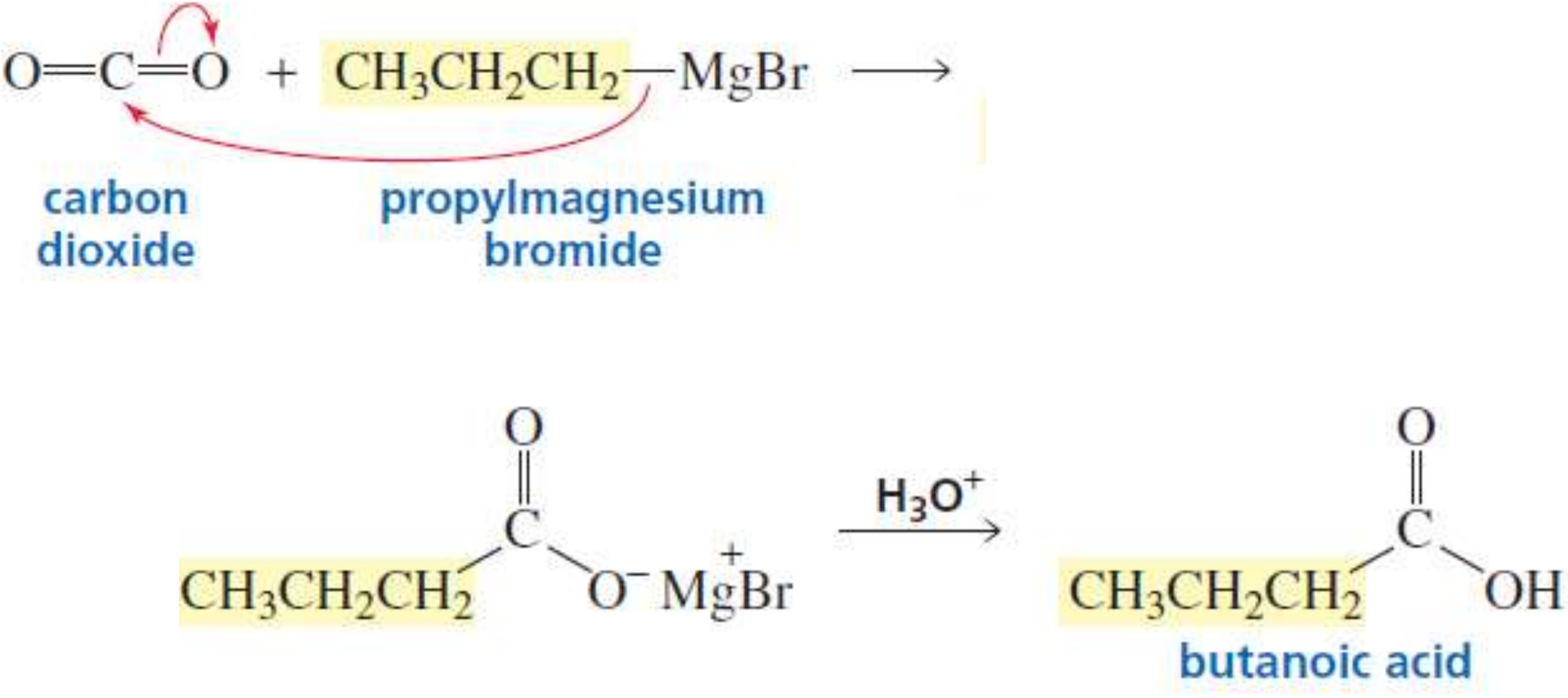
3-pentanone

3-methyl-3-pentanol



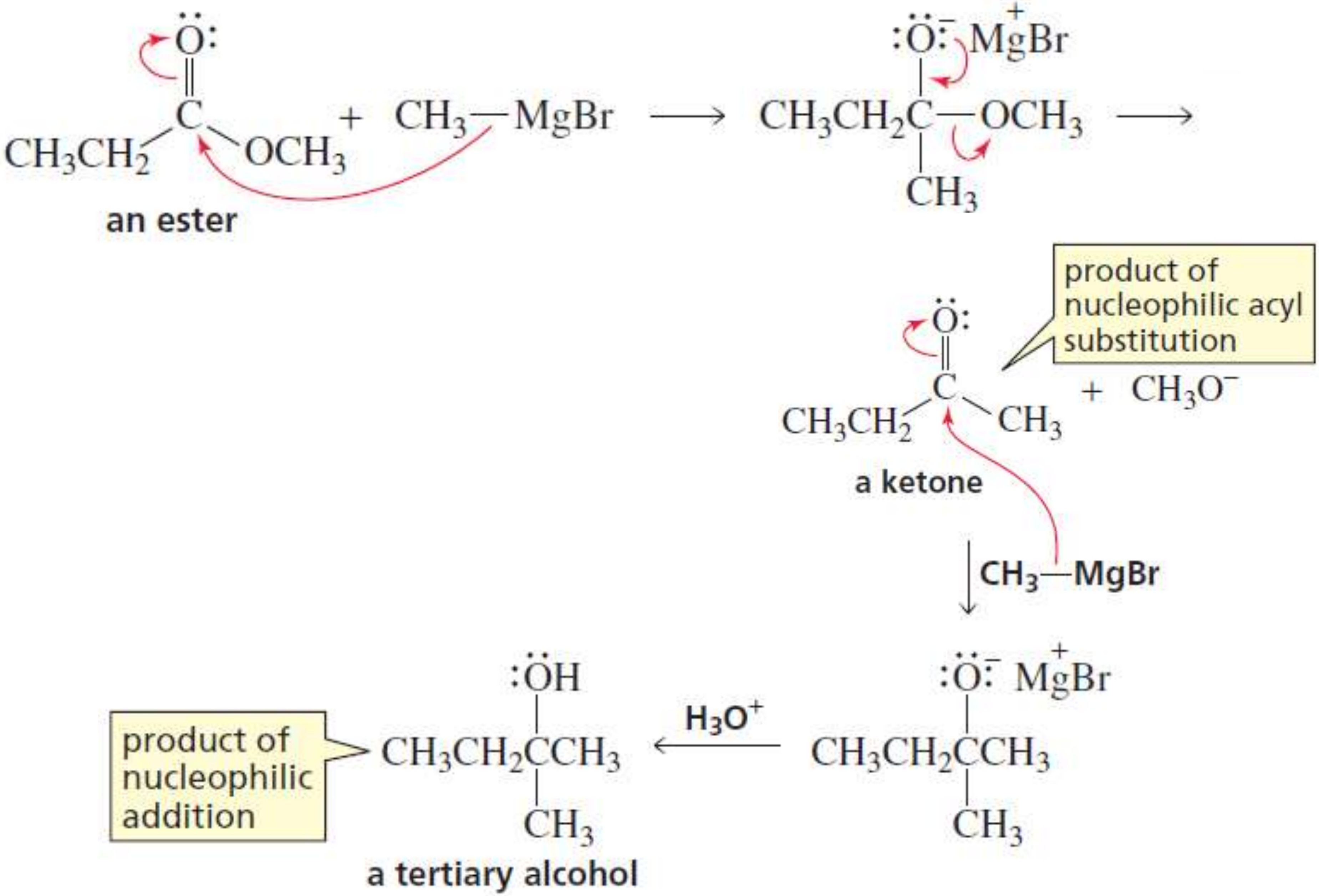
butanal

1-phenyl-1-butanol



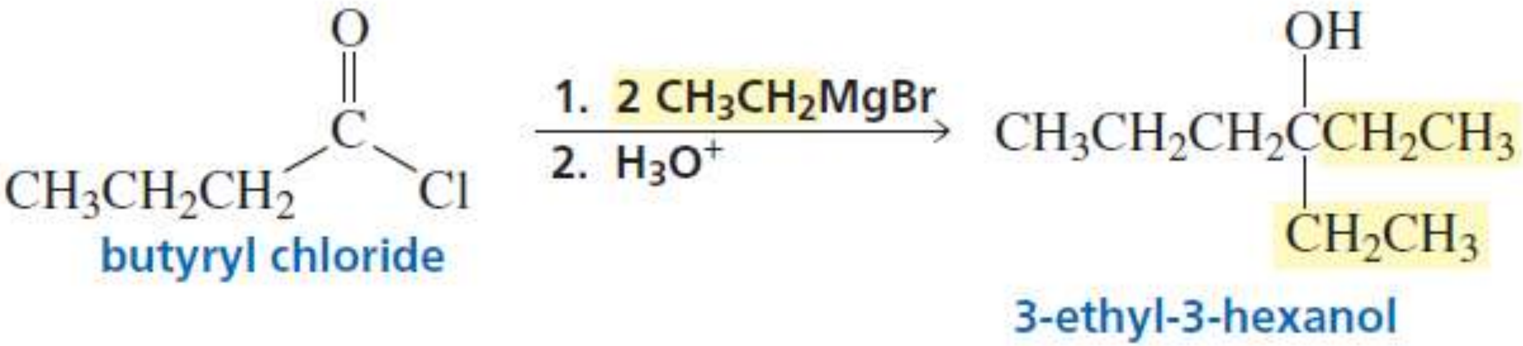
$$O{=}C{=}O + CH_3CH_2CH_2{-}MgBr \longrightarrow CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}O^{-}\,\overset{+}{Mg}Br \xrightarrow{H_3O^+} CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}OH$$

mechanism for the reaction of an ester with a Grignard reagent



product of nucleophilic acyl substitution

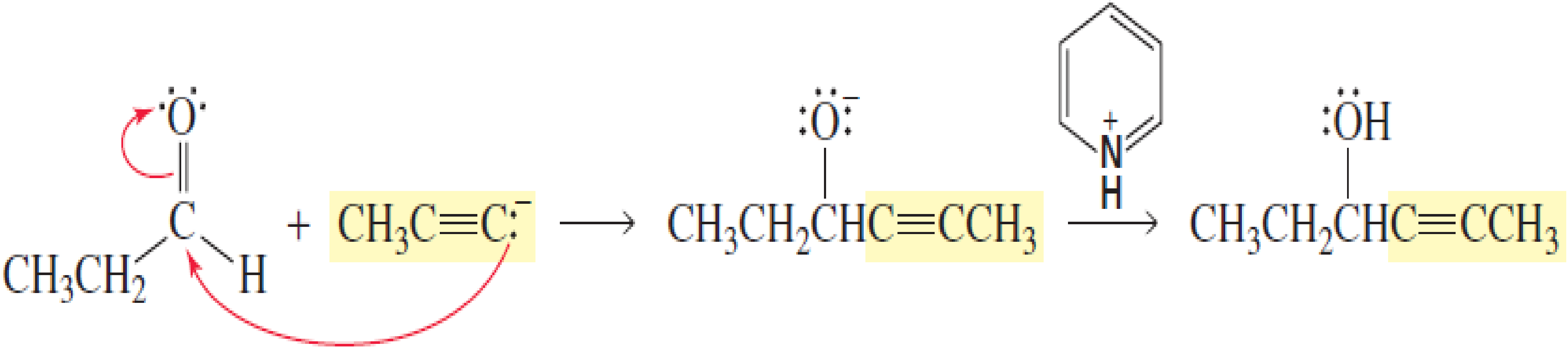
product of nucleophilic addition



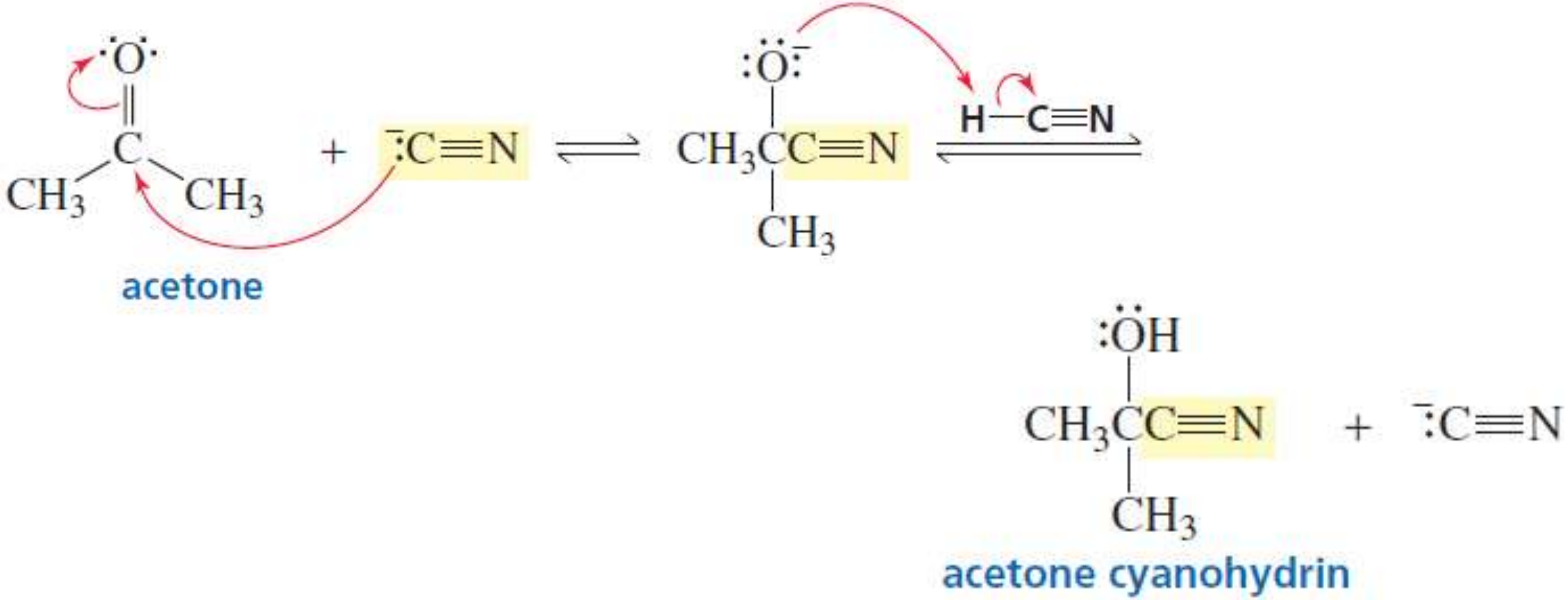
$$CH_3CH_2CH_2C(=O)Cl \xrightarrow[\text{2. } H_3O^+]{\text{1. } 2\ CH_3CH_2MgBr} CH_3CH_2CH_2C(OH)(CH_2CH_3)CH_2CH_3$$

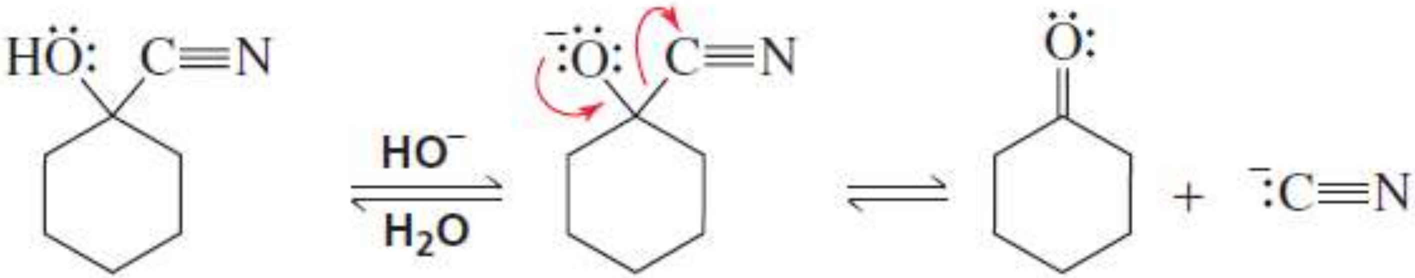
Reaction with Acetylide Ions

$$CH_3C{\equiv}CH \xrightarrow[NH_3]{NaNH_2} CH_3C{\equiv}C{:}^-$$

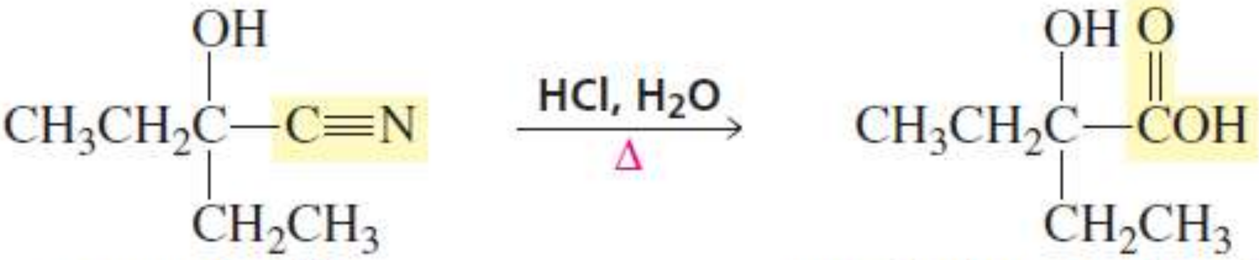


Reaction with Hydrogen Cyanide





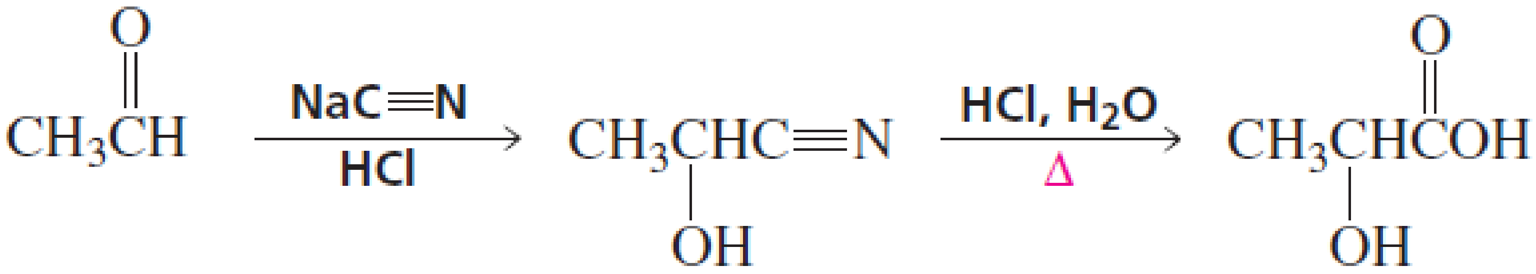
cyclohexanone cyanohydrin



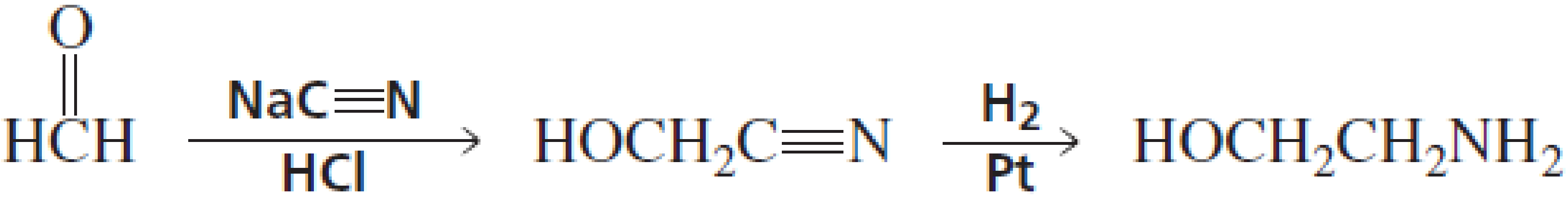
$$CH_3CH_2\overset{OH}{\underset{CH_2CH_3}{C}}-C\equiv N \xrightarrow[\Delta]{HCl,\ H_2O} CH_3CH_2\overset{OH}{\underset{CH_2CH_3}{C}}-\overset{O}{\overset{\|}{C}}OH$$

a cyanohydrin

an α-hydroxy carboxylic acid



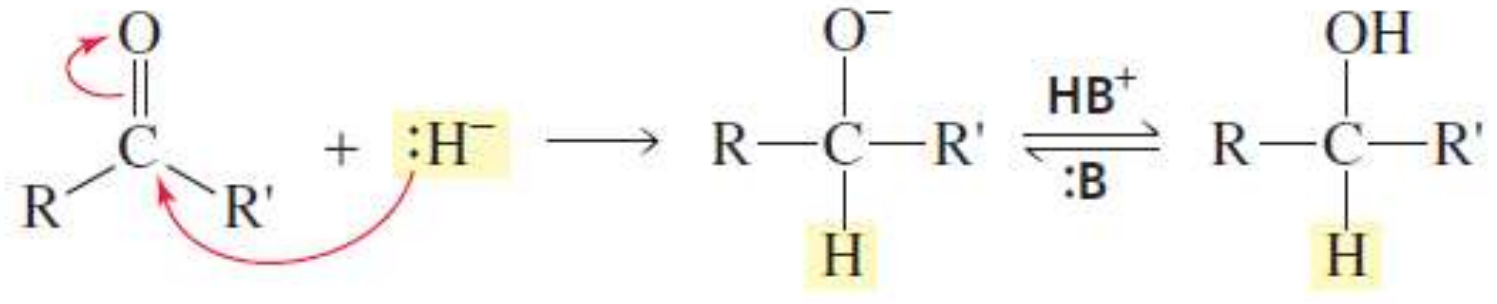
$$\mathrm{CH_3\overset{\overset{O}{\|}}{C}H \xrightarrow[HCl]{NaC\equiv N} CH_3\underset{\underset{OH}{|}}{C}HC\equiv N \xrightarrow[\Delta]{HCl,\ H_2O} CH_3\underset{\underset{OH}{|}}{C}H\overset{\overset{O}{\|}}{C}OH}$$

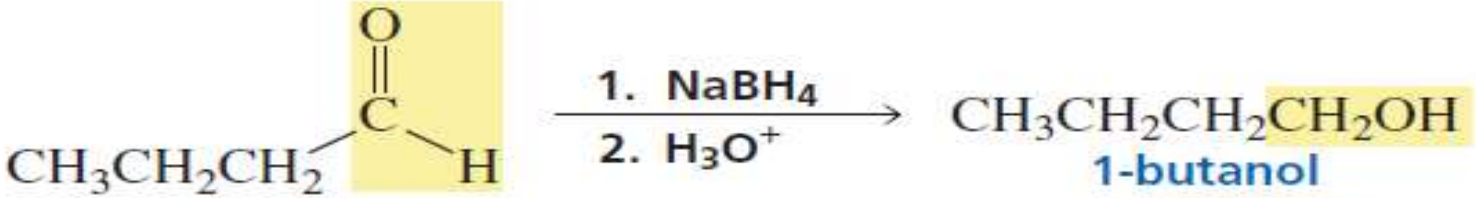


$$\mathrm{H\overset{\overset{O}{\|}}{C}H \xrightarrow[HCl]{NaC\equiv N} HOCH_2C\equiv N \xrightarrow[Pt]{H_2} HOCH_2CH_2NH_2}$$

Reactions of Carbonyl Compounds with Hydride Ion

Addition of hydride ion to an aldehyde or ketone forms an alkoxide ion. Subsequent protonation by an acid produces an alcohol. The overall reaction adds to the carbonyl group. Recall that the addition of hydrogen to an organic compound is a **reduction reaction**

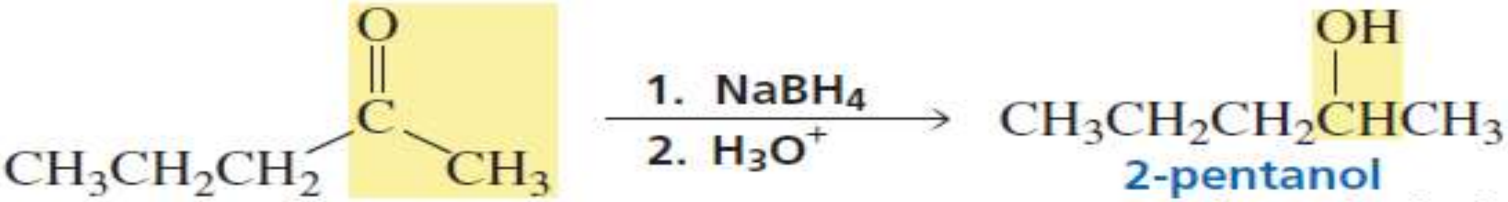




$$CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}H \xrightarrow[2.\ H_3O^+]{1.\ NaBH_4} CH_3CH_2CH_2CH_2OH$$

butanal
an aldehyde

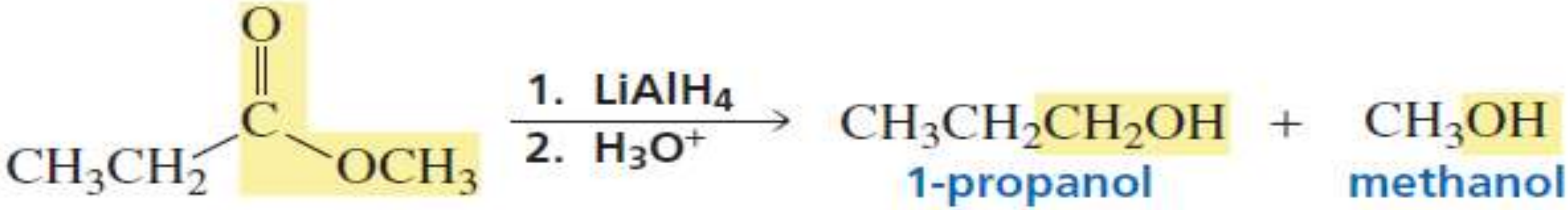
1-butanol
a primary alcohol



$$CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}CH_3 \xrightarrow[2.\ H_3O^+]{1.\ NaBH_4} CH_3CH_2CH_2\overset{\overset{OH}{|}}{C}HCH_3$$

2-pentanone
a ketone

2-pentanol
a secondary alcohol



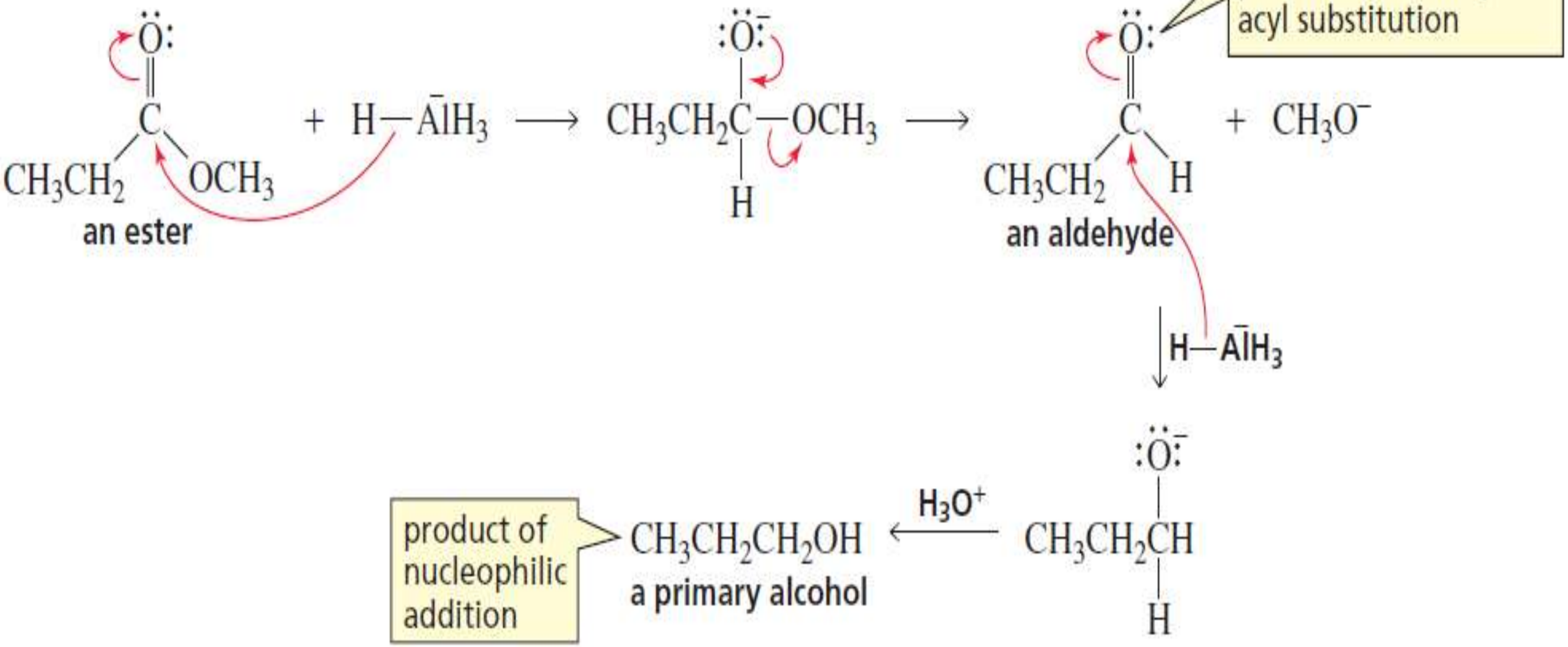
$$CH_3CH_2\overset{\overset{O}{\|}}{C}OCH_3 \xrightarrow[2.\ H_3O^+]{1.\ LiAlH_4} CH_3CH_2CH_2OH + CH_3OH$$

methyl propanoate
an ester

1-propanol

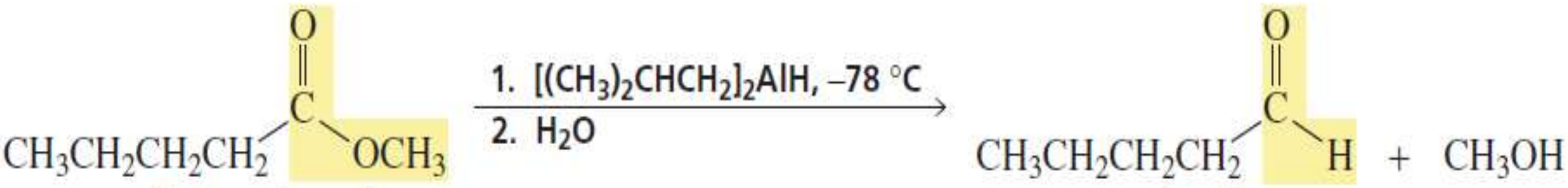
methanol

mechanism for the reaction of an ester with hydride ion



product of nucleophilic acyl substitution

product of nucleophilic addition



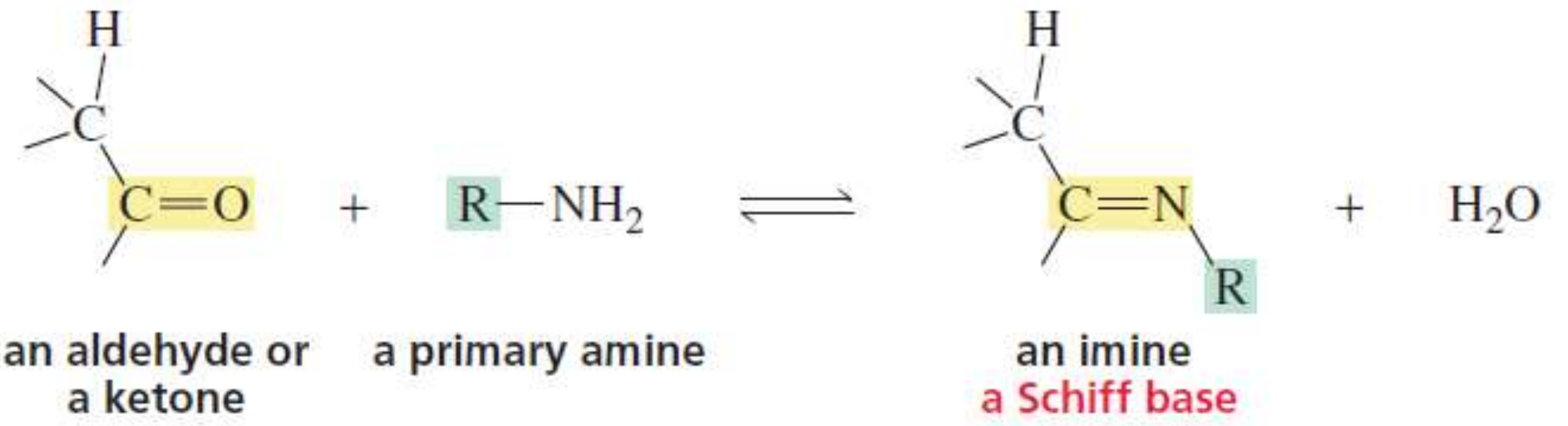
$$\mathrm{CH_3CH_2CH_2CH_2}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{OCH_3} \xrightarrow[\text{2. } \mathrm{H_2O}]{\text{1. } \mathrm{[(CH_3)_2CHCH_2]_2AlH},\ -78\ ^\circ\mathrm{C}} \mathrm{CH_3CH_2CH_2CH_2}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{H} + \mathrm{CH_3OH}$$

methyl pentanoate

pentanal

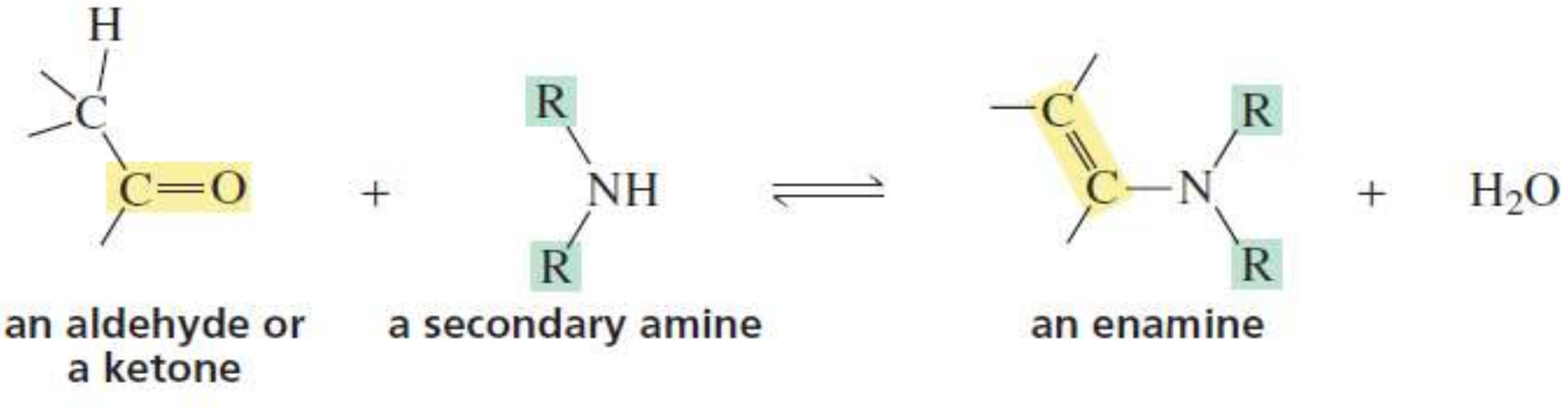
Reactions of Aldehydes and Ketones with Nitrogen Nucleophiles

Aldehydes and ketones react with a *primary amine to form an imine. An **imine*** is a compound with a carbon–nitrogen double bond. The imine obtained from the reaction of a carbonyl compound and a primary amine is often called a **Schiff base.**



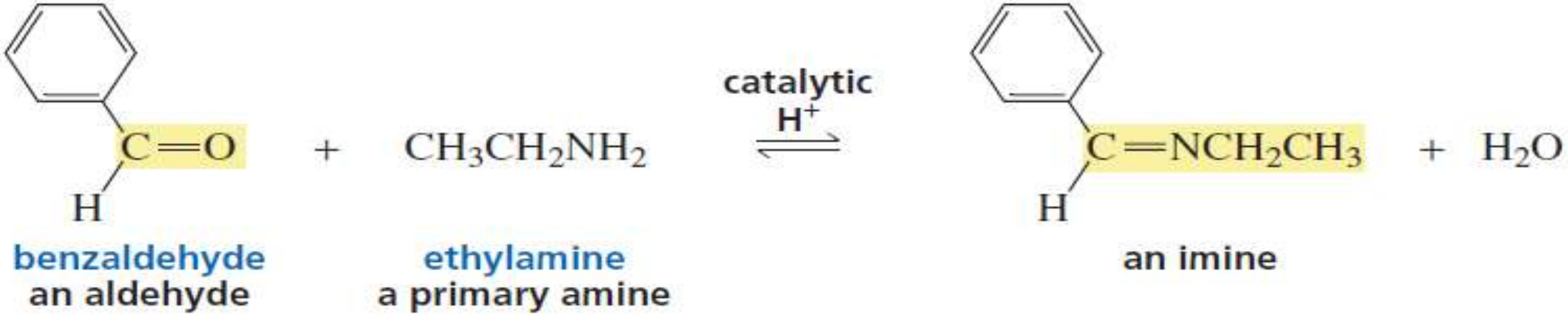
Reactions of Aldehydes and Ketones with Nitrogen Nucleophiles

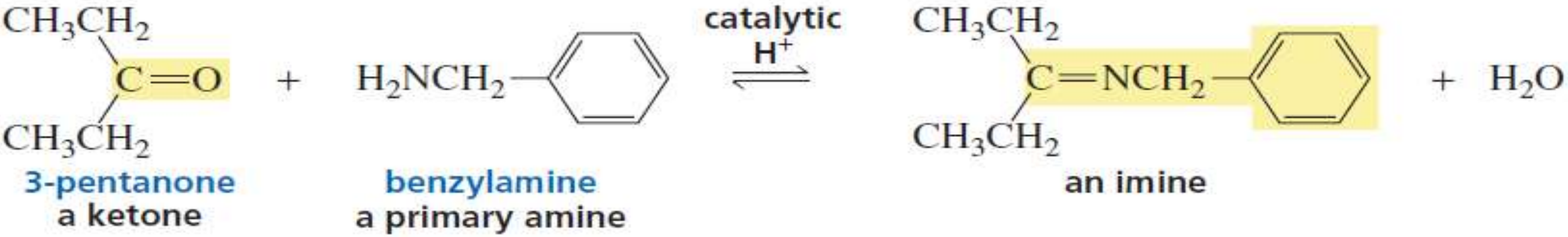
Aldehydes and ketones react with a *secondary amine to form an enamine (pronounced* “ENE-amine”). An **enamine is an α,β-unsaturated tertiary amine—a tertiary** amine with a double bond in the α,β-position relative to the nitrogen atom. Notice that the double bond is in the part of the molecule that comes from the aldehyde or ketone. The name “enamine” comes from “ene” + “amine,” with the “e” omitted in order to avoid two successive vowels.



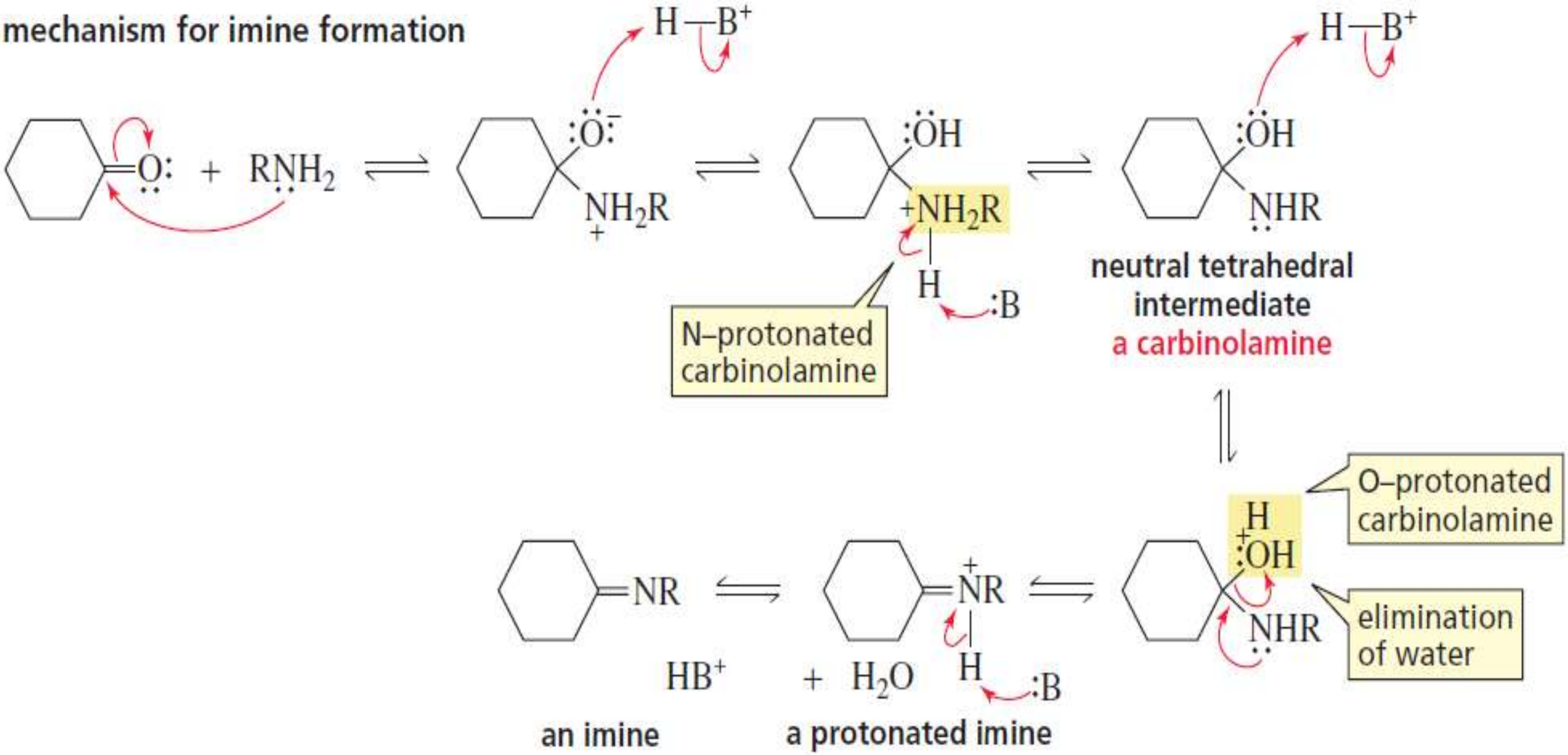
Addition of Primary Amines

- Aldehydes and ketones react with primary amines to form imines. The reaction requires a catalytic (small) amount of acid—we will see that the pH of the reaction mixture must be carefully controlled.





mechanism for imine formation



N–protonated carbinolamine

neutral tetrahedral intermediate
a carbinolamine

O–protonated carbinolamine

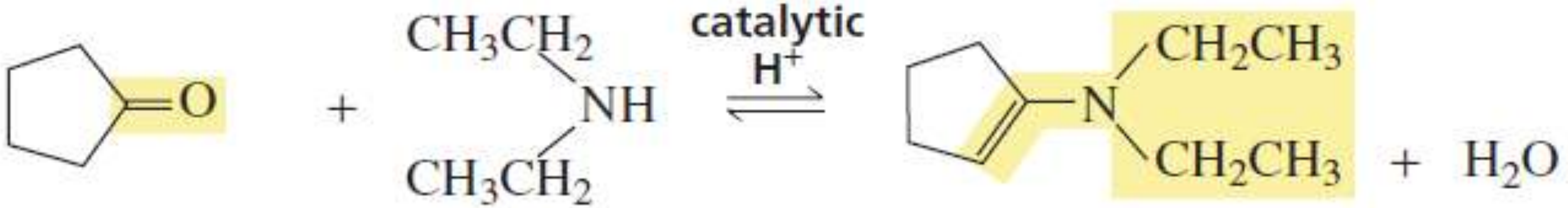
elimination of water

an imine

a protonated imine

Addition of Secondary Amines

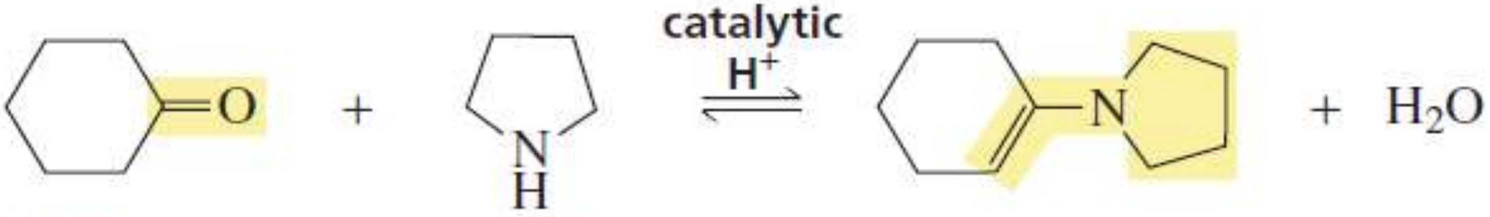
- **Aldehydes and ketones react with secondary amines to form enamines. Like imine formation, the reaction requires a trace amount of an acid catalyst.**



cyclopentanone

diethylamine
a secondary amine

an enamine

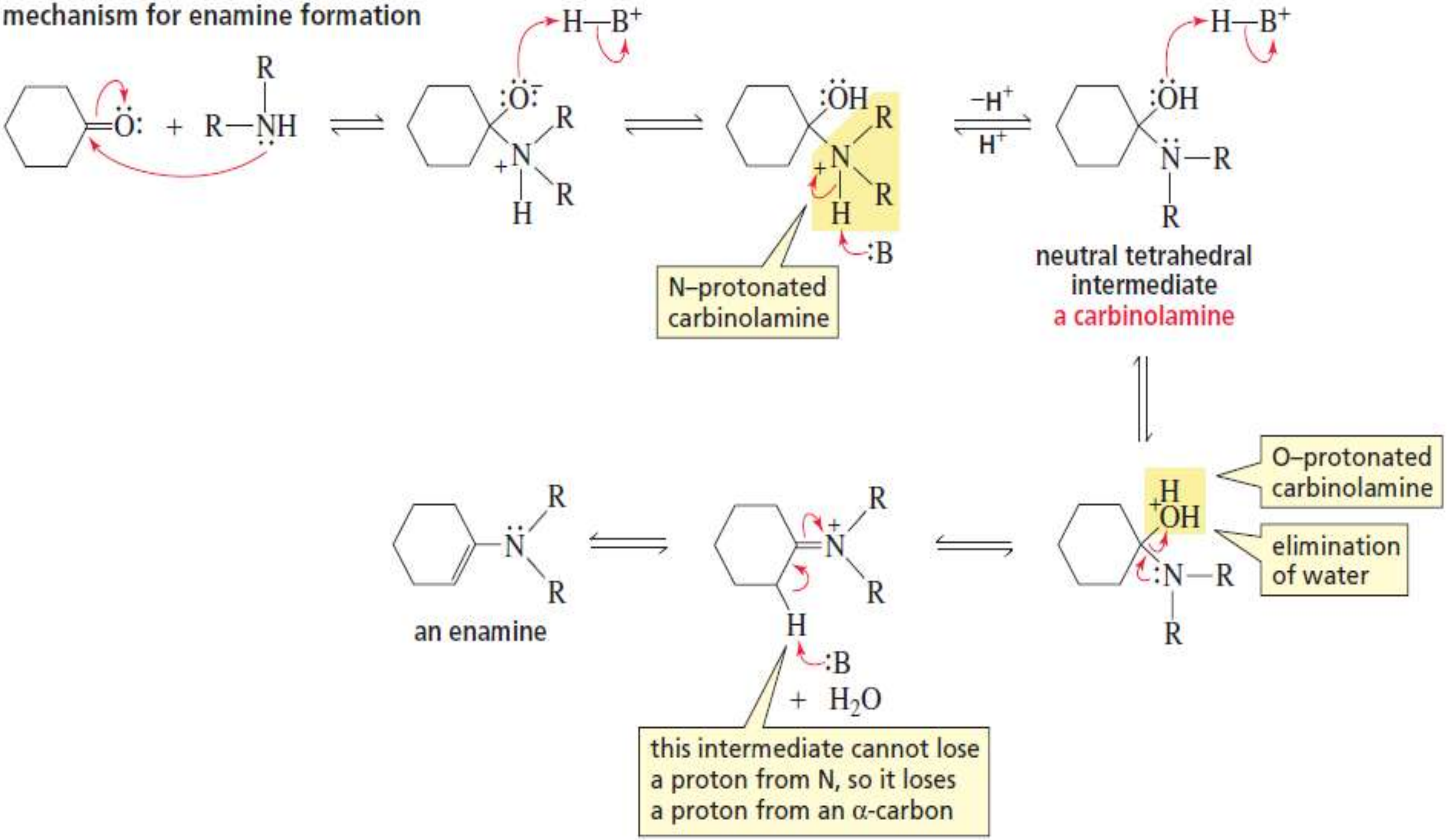


cyclohexanone

pyrrolidine
a secondary amine

an enamine

mechanism for enamine formation



N–protonated carbinolamine

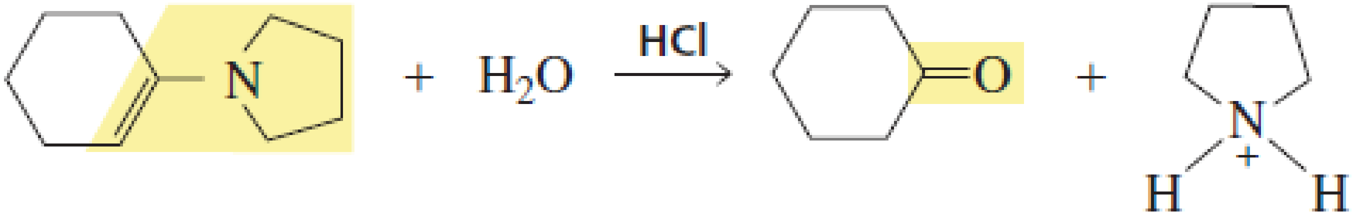
neutral tetrahedral intermediate
a carbinolamine

O–protonated carbinolamine

elimination of water

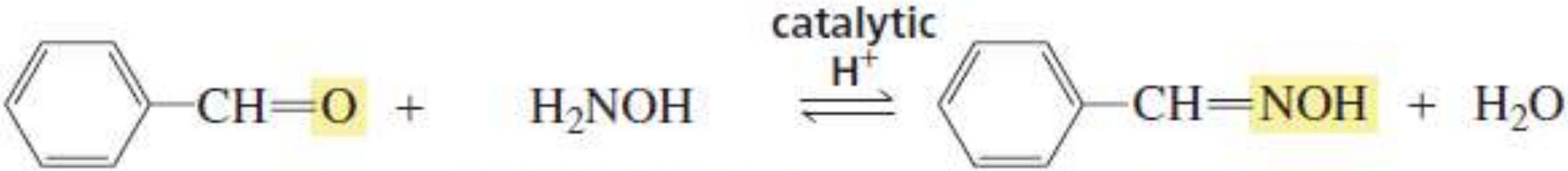
an enamine

this intermediate cannot lose a proton from N, so it loses a proton from an α-carbon


N
+
H₂O
HCl
O
+
N
+
H
H

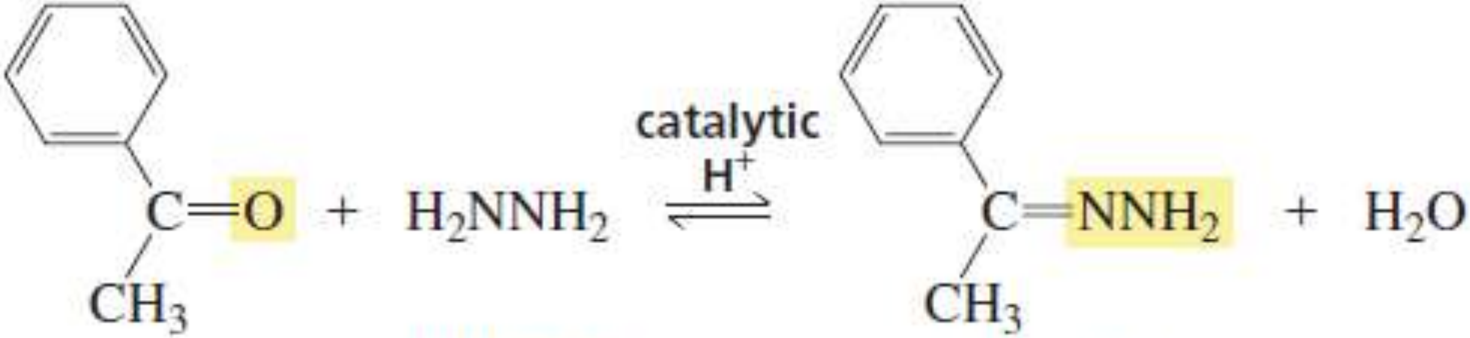
Formation of Imine Derivatives

- Compounds such as hydroxylamineNH2OH), hydrazine (NH2NH2), and semicarbazide (NH2NHCONH2) are similar to primary amines in that they all have an NH2 group. Thus, like primary amines, they react with aldehydes and ketones to form imines—often called *imine derivatives because the substituent attached to the imine* nitrogen is not an R group. The imine obtained from the reaction with hydroxylamine is called an oxime, the imine obtained from the reaction with hydrazine is called a hydrazone, and the imine obtained from the reaction with semicarbazide is called a semicarbazone.



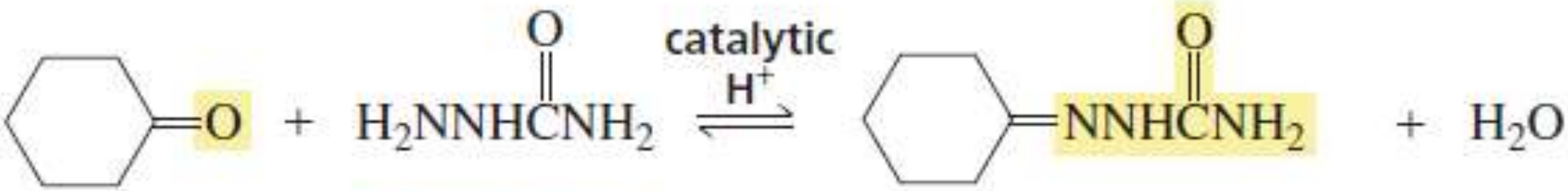
hydroxylamine

an oxime



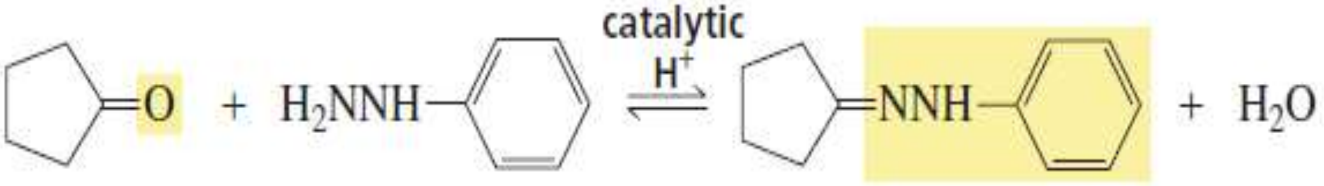
hydrazine

a hydrazone



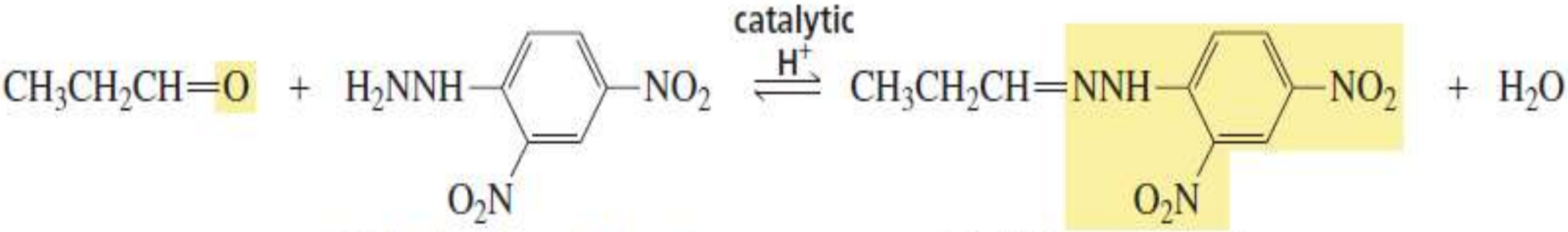
semicarbazide

a semicarbazone



phenylhydrazine

a phenylhydrazone

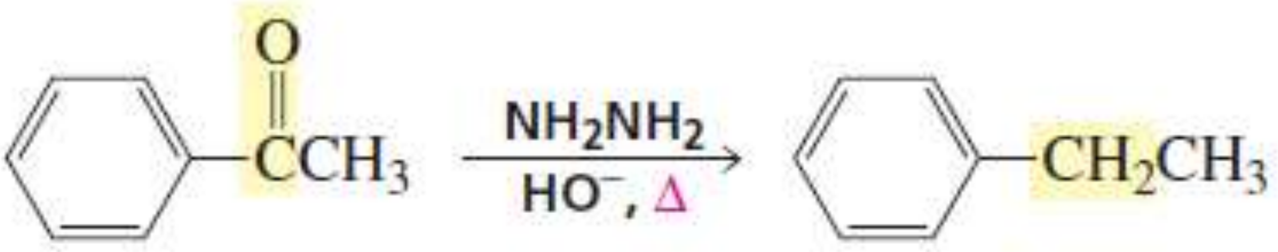


2,4-dinitrophenylhydrazine

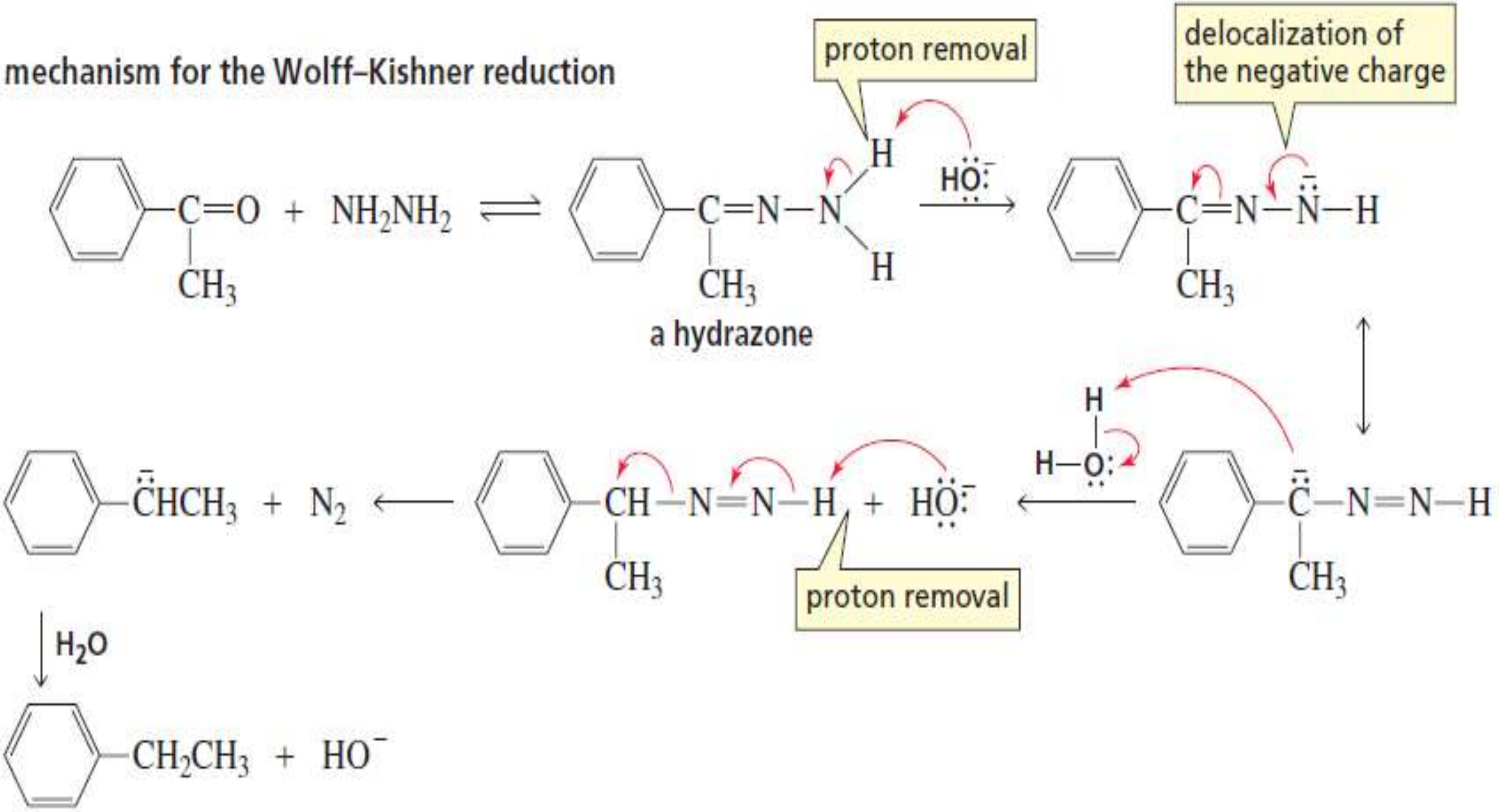
a 2,4-dinitrophenylhydrazone

The Wolff–Kishner Reduction

- When a ketone or an aldehyde is heated in a basic solution of hydrazine, the carbonyl group is converted into a methylene group. This process is called deoxygenation because an oxygen is removed from the reactant. **The reaction is known as the *Wolff–Kishner reduction.***



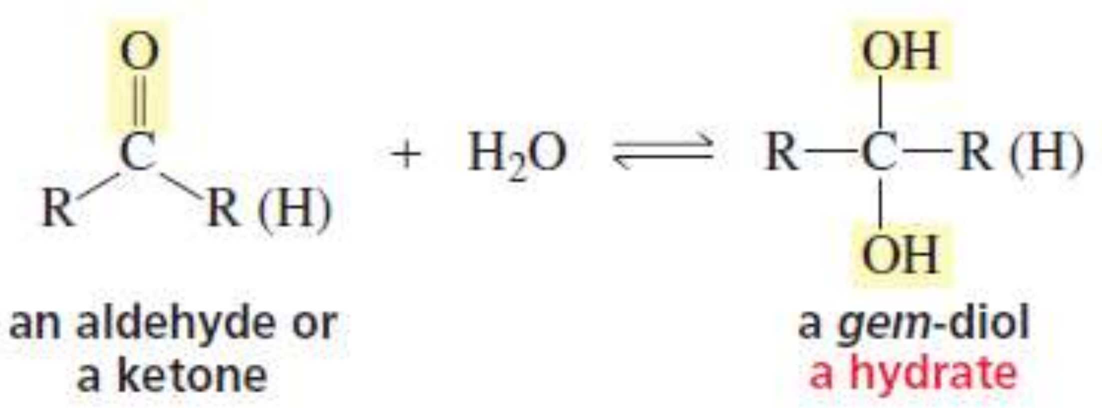
mechanism for the Wolff–Kishner reduction



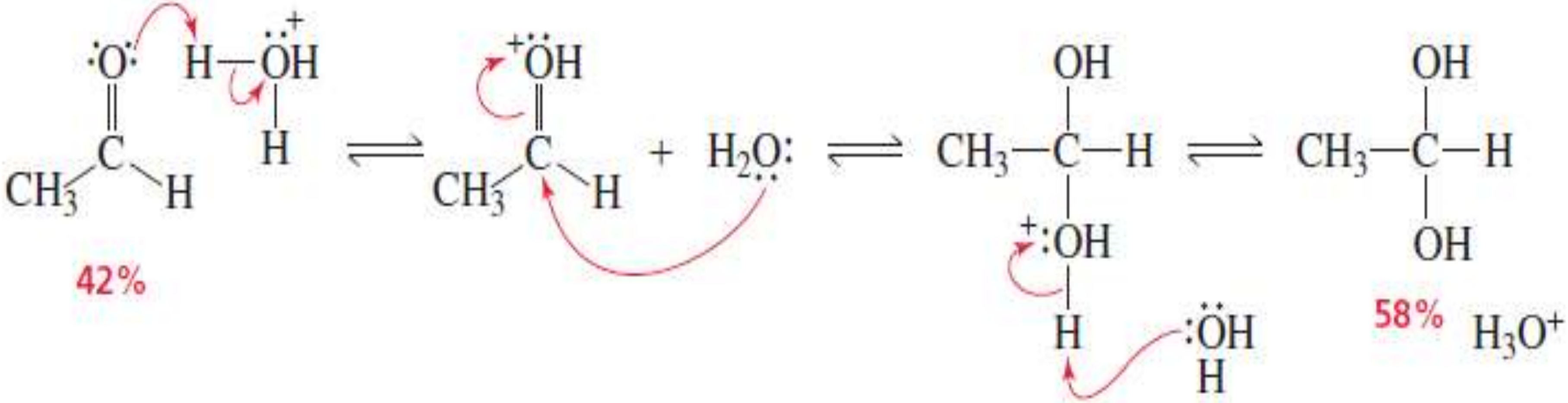
Reactions of Aldehydes and Ketones with Oxygen Nucleophiles

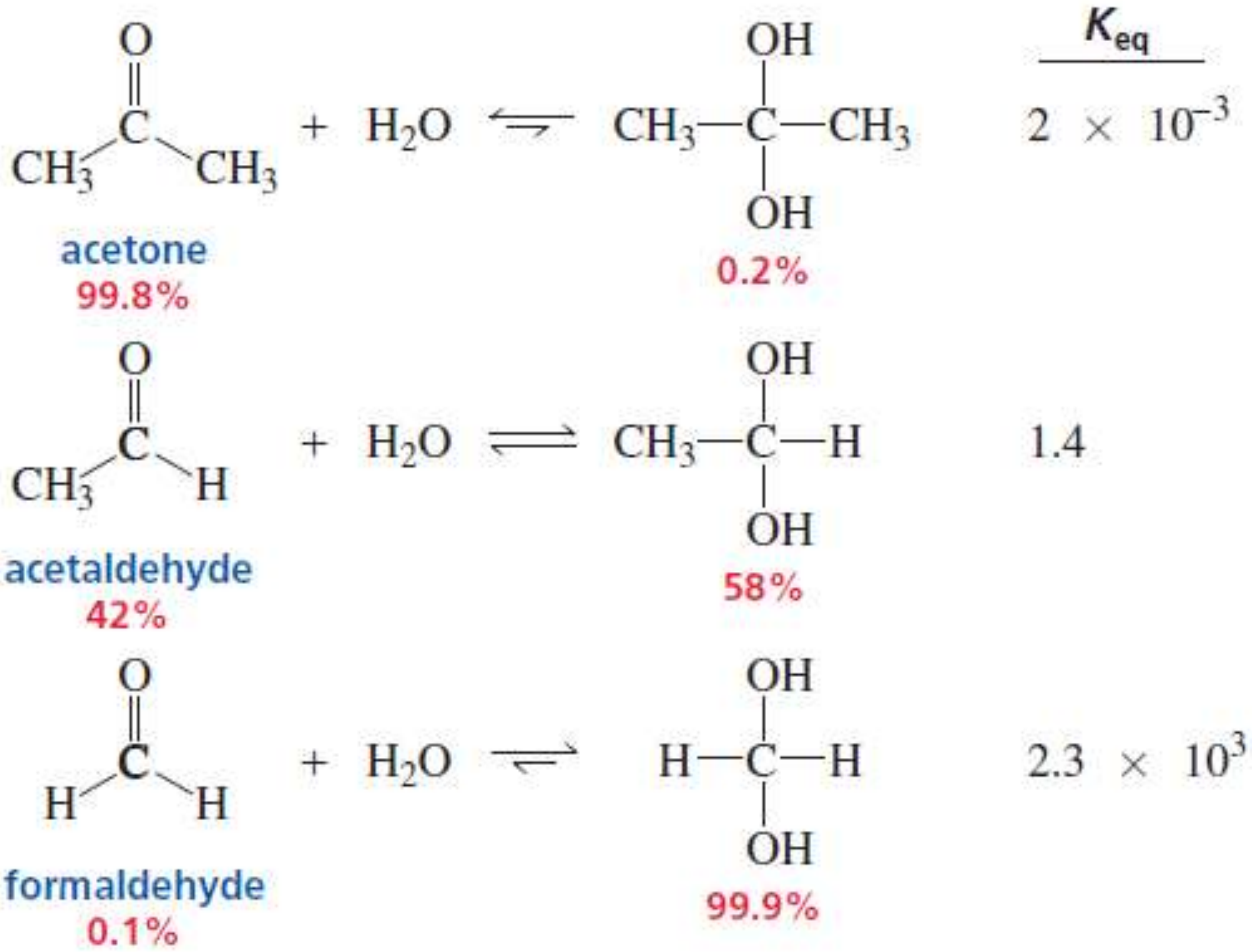
Addition of Water

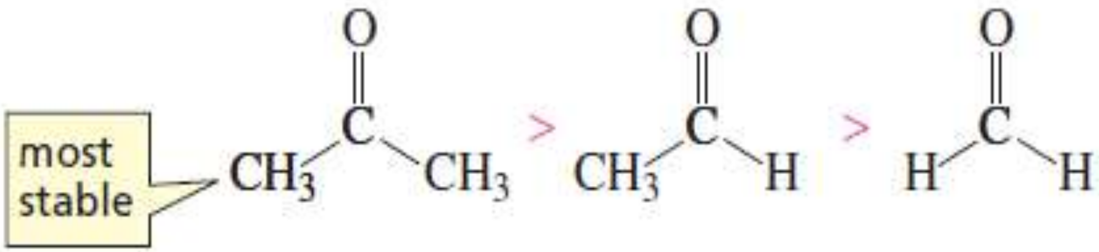
Water adds to an aldehyde or a ketone to form a *hydrate. A* ***hydrate is a molecule*** with two OH groups on the same carbon. Hydrates are also called ***gem-diols (gem*** comes from *geminus, Latin for "twin"). Hydrates of aldehydes or ketones are generally* too unstable to be isolated because the tetrahedral carbon is



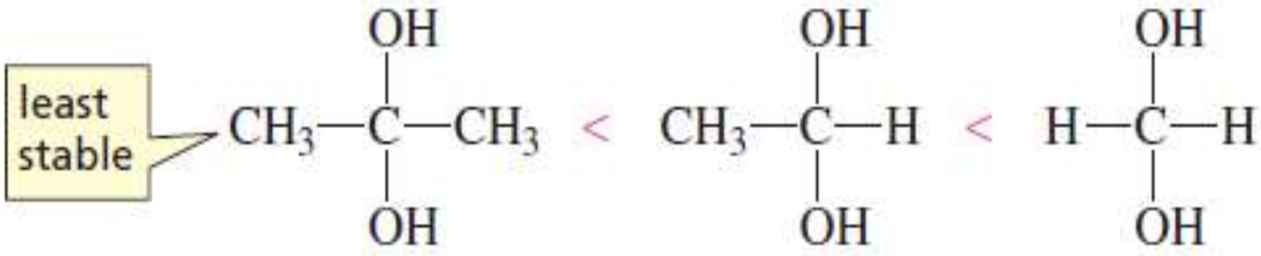
mechanism for acid-catalyzed hydrate formation



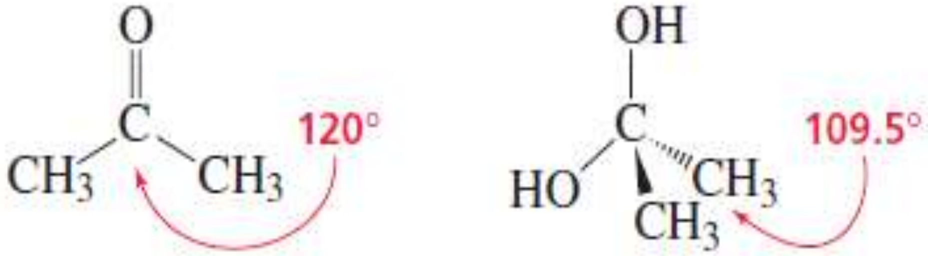

K_{eq}
$CH_3COCH_3 + H_2O \rightleftharpoons (CH_3)_2C(OH)_2$
2×10^{-3}
acetone
99.8%
0.2%
$CH_3CHO + H_2O \rightleftharpoons CH_3CH(OH)_2$
1.4
acetaldehyde
42%
58%
$HCHO + H_2O \rightleftharpoons H_2C(OH)_2$
2.3×10^{3}
formaldehyde
0.1%
99.9%

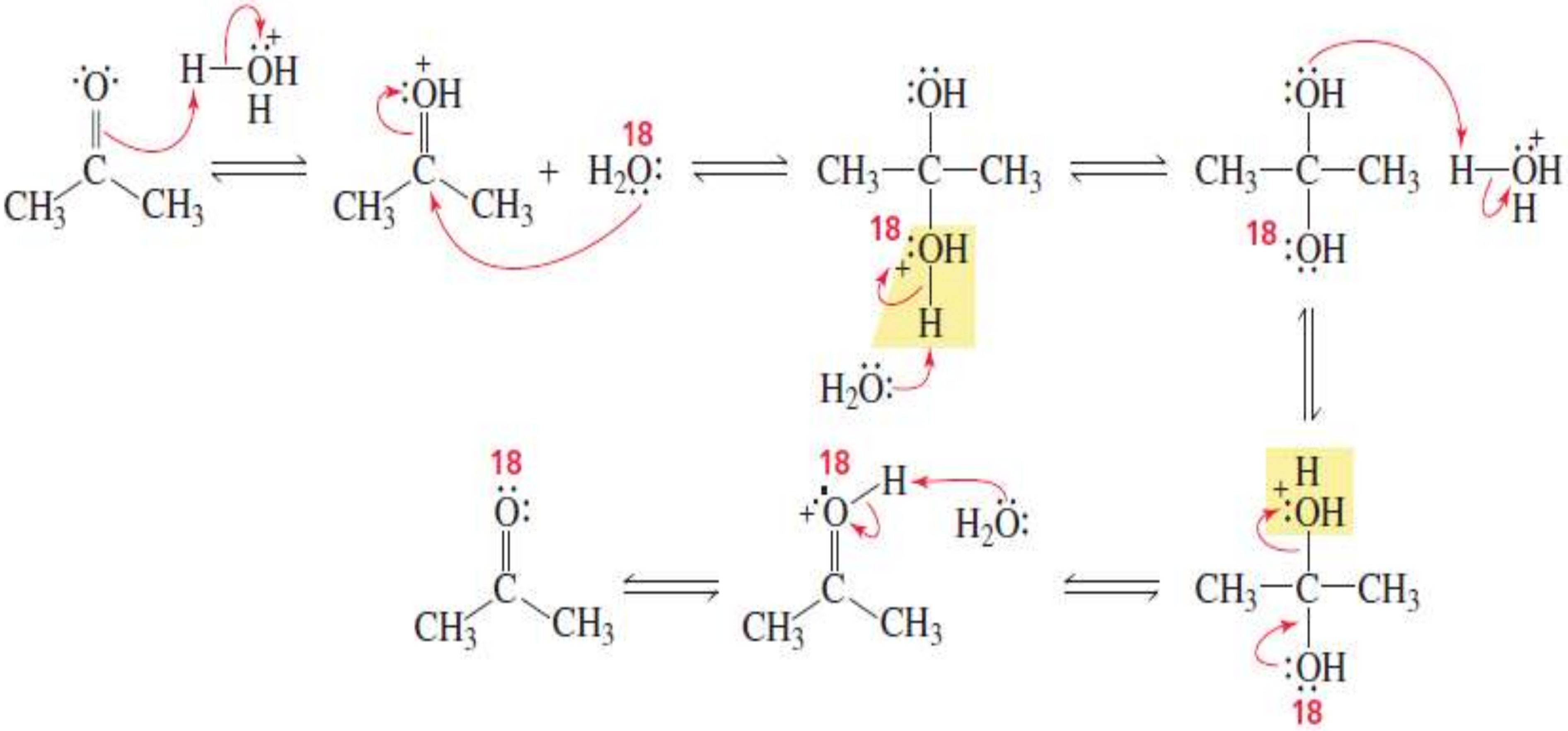


In contrast, alkyl groups make the hydrate *less stable* because of steric interactions between the alkyl groups.



The electron clouds of the alkyl substituents do not interfere with each other in the carbonyl compound because the bond angles are 120°. However, the bond angles in the tetrahedral hydrate are 109.5°, so the alkyl groups are closer to one another.

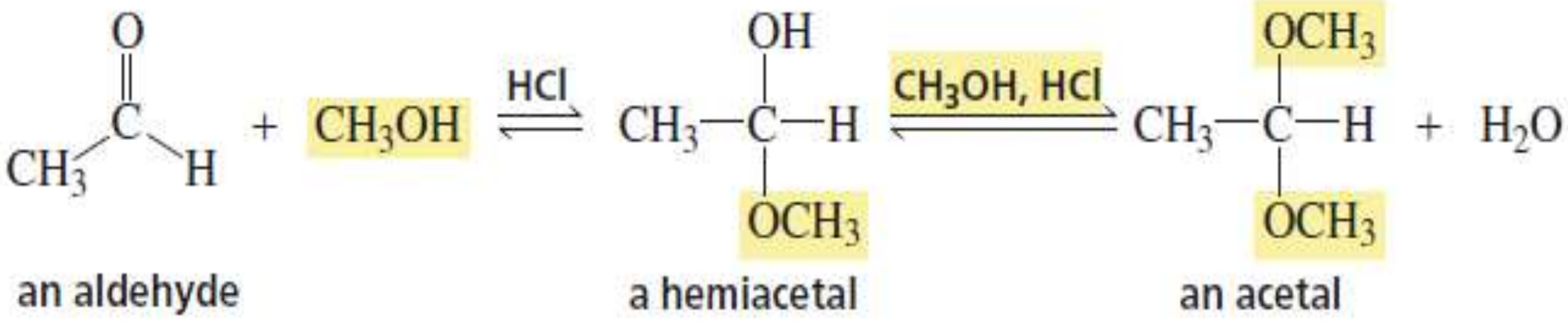




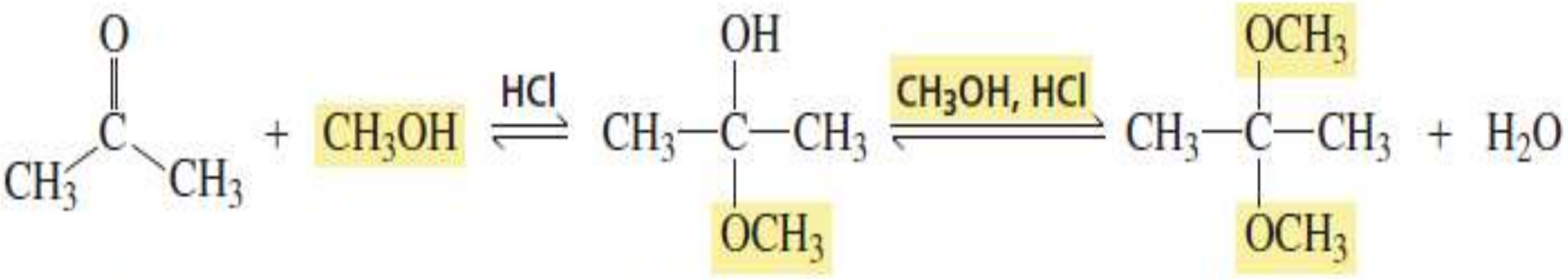
CH3
C
O
H
OH
H2O
18
+

Addition of Alcohol

- The product formed when one equivalent of an alcohol adds to an aldehyde is called a hemiacetal. The product formed when a second equivalent of alcohol is added is called an acetal. Like water, an alcohol is a poor nucleophile, so an acid catalyst is required for the reaction to take place at a reasonable rate.



- When the carbonyl compound is a ketone instead of an aldehyde, the addition products are called a hemiketal and a ketal, respectively.

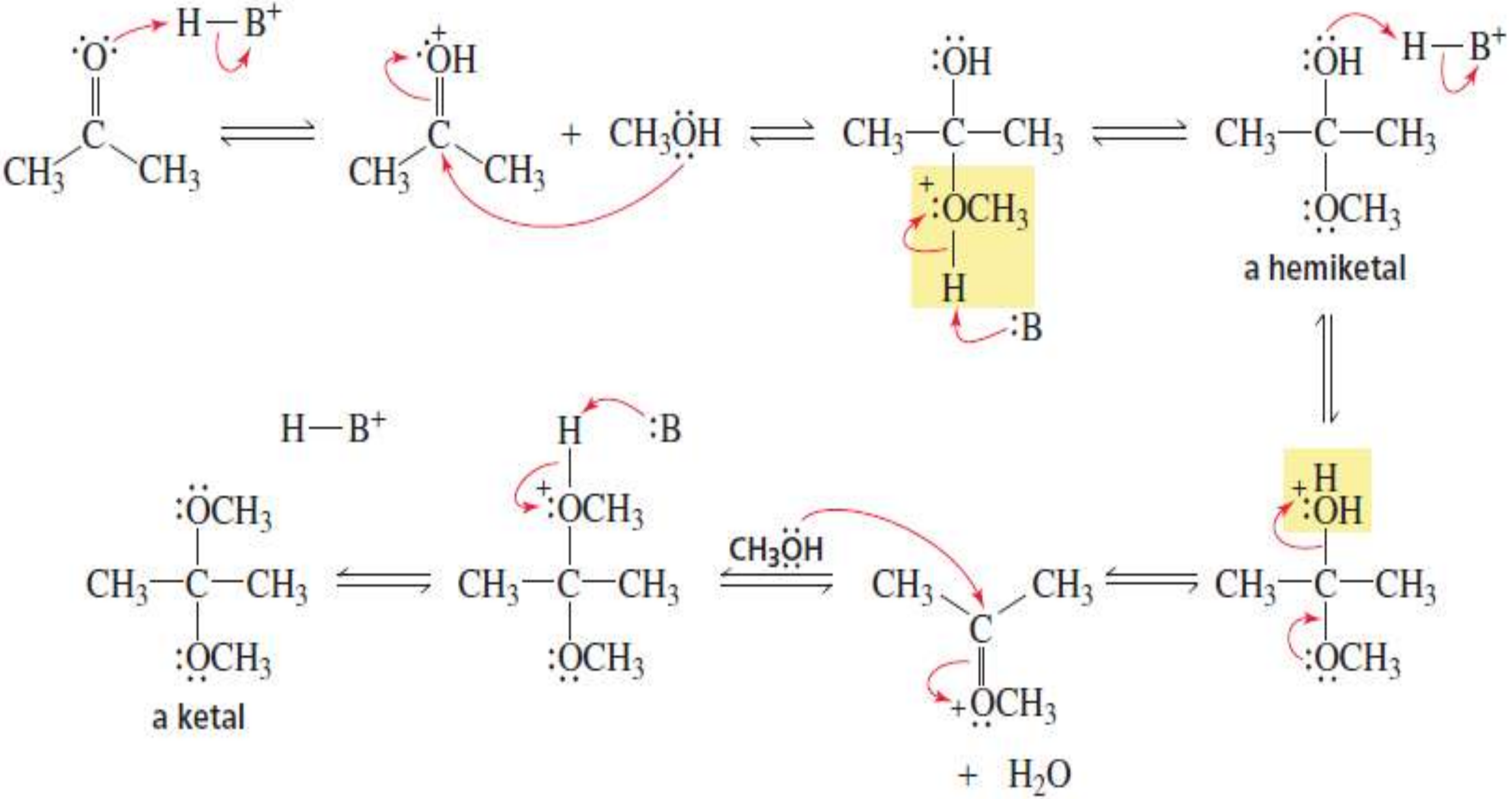


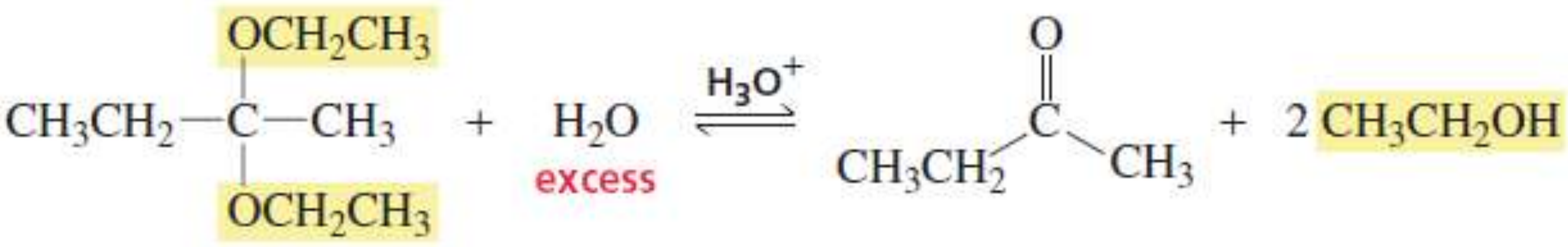
a ketone

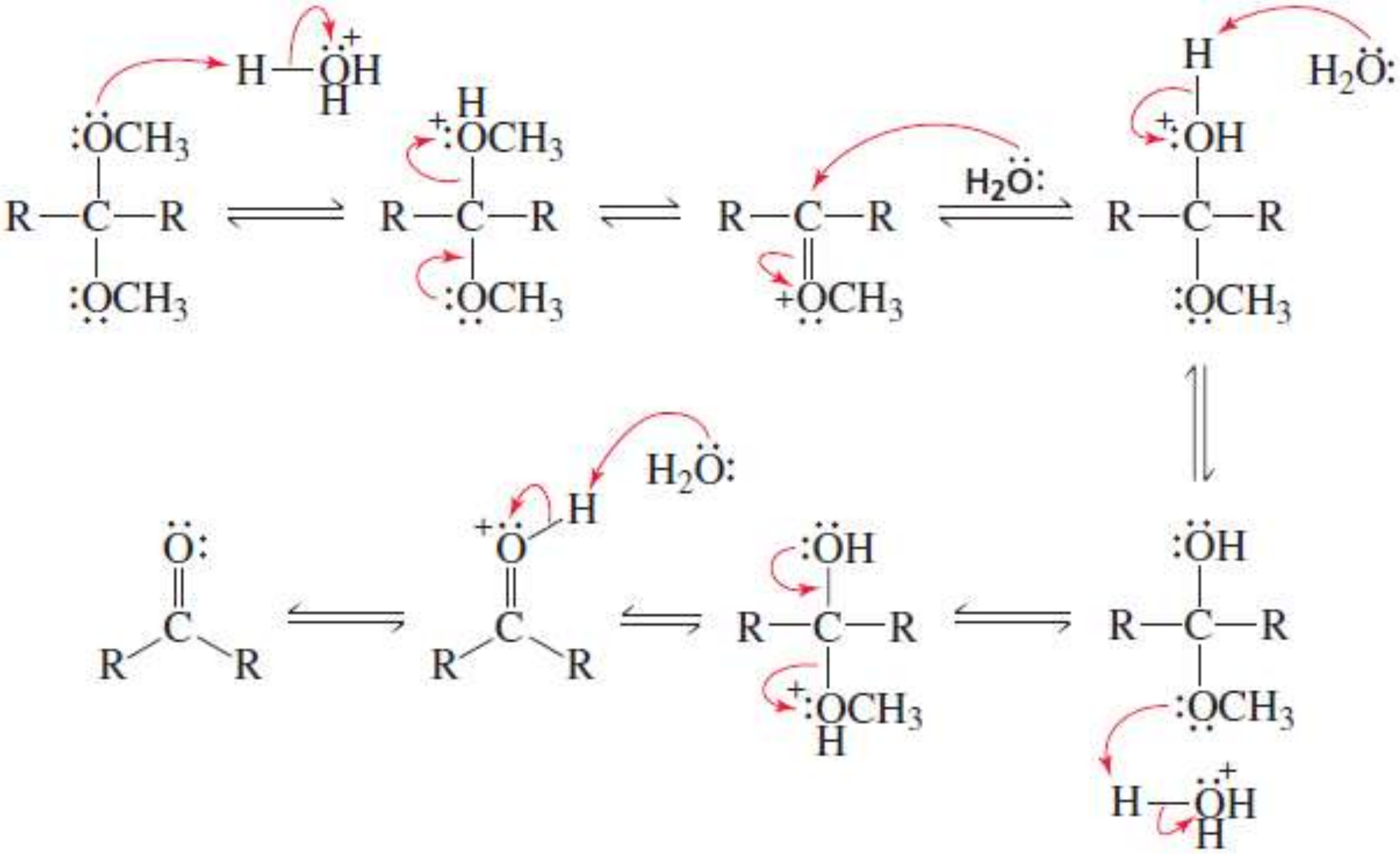
a hemiketal

a ketal

mechanism for acid-catalyzed acetal or ketal formation

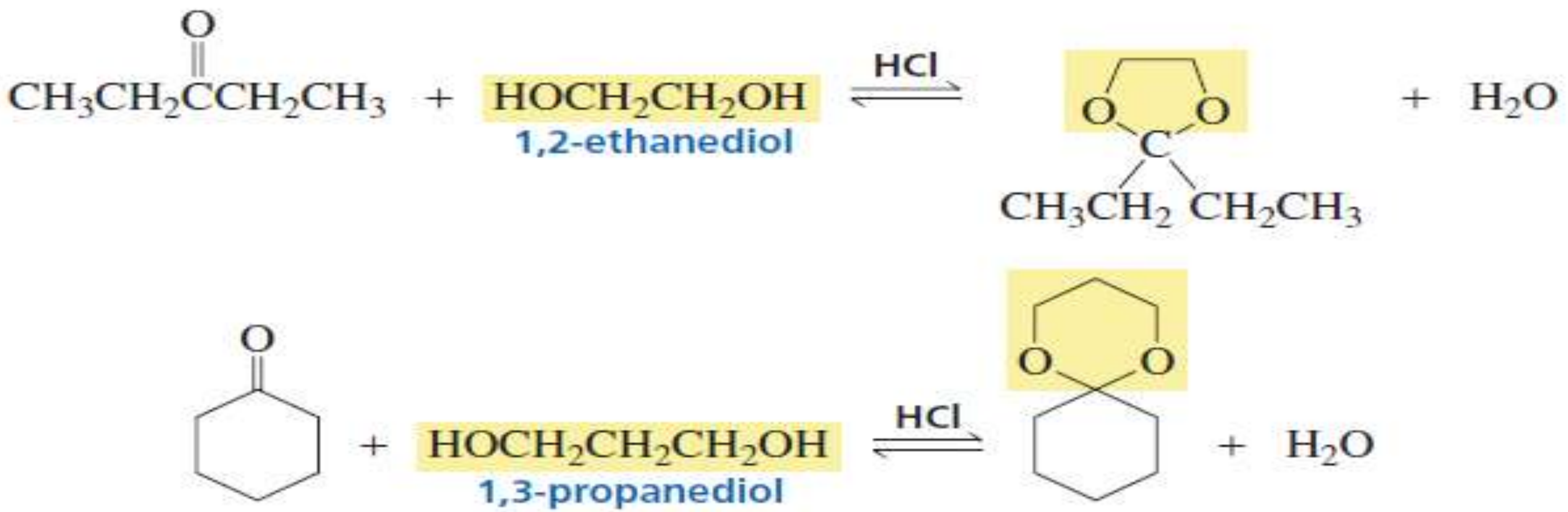



OCH2CH3
CH3CH2—C—CH3
OCH2CH3
+
H2O
excess
H3O+
O
C
CH3CH2
CH3
+
2 CH3CH2OH

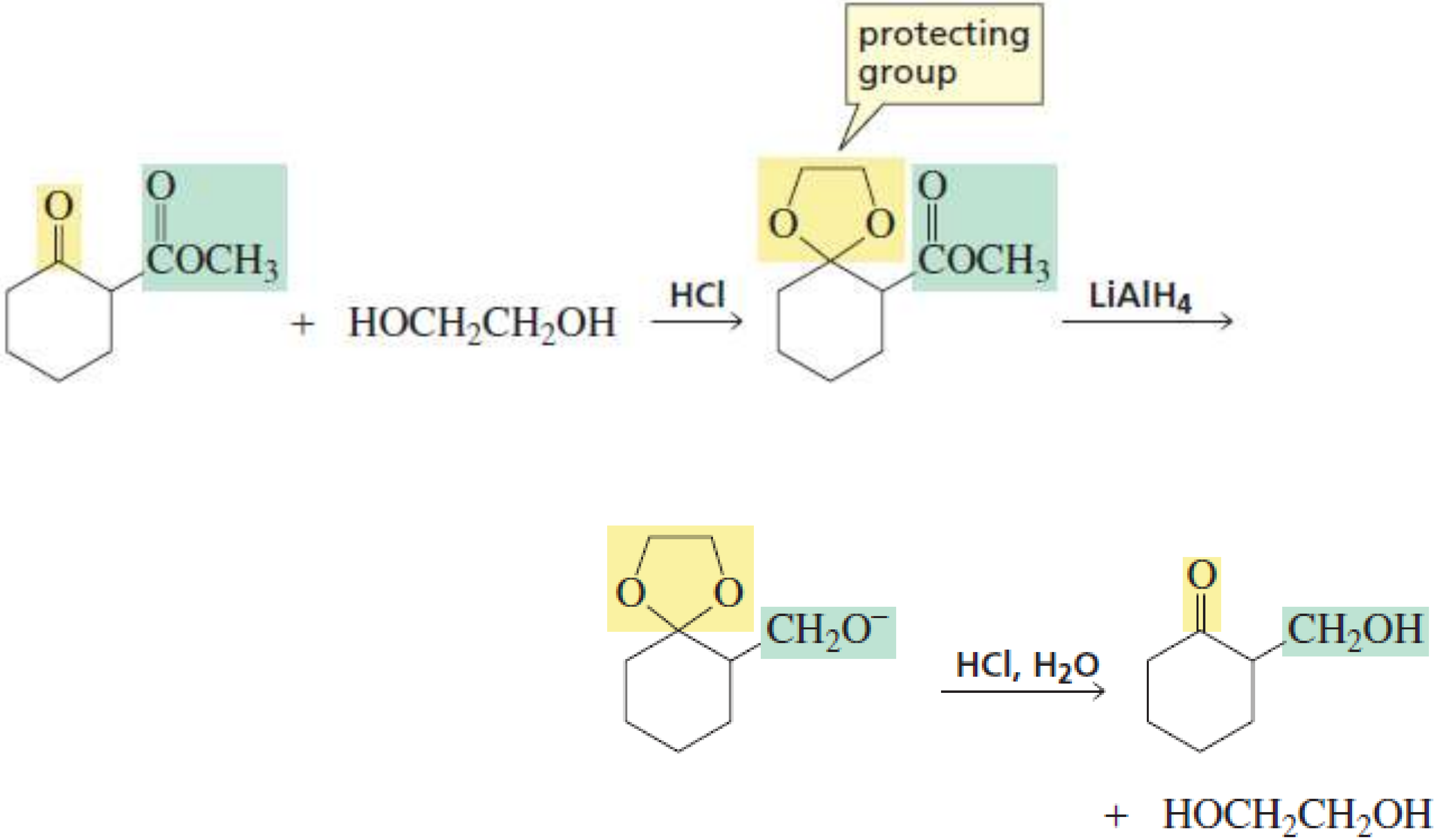

H—ÖH⁺
H
:ÖCH₃
R—C—R
:ÖCH₃
H₂Ö:
H₂Ö:
H₂Ö:
H—ÖH⁺
H

Protecting Groups

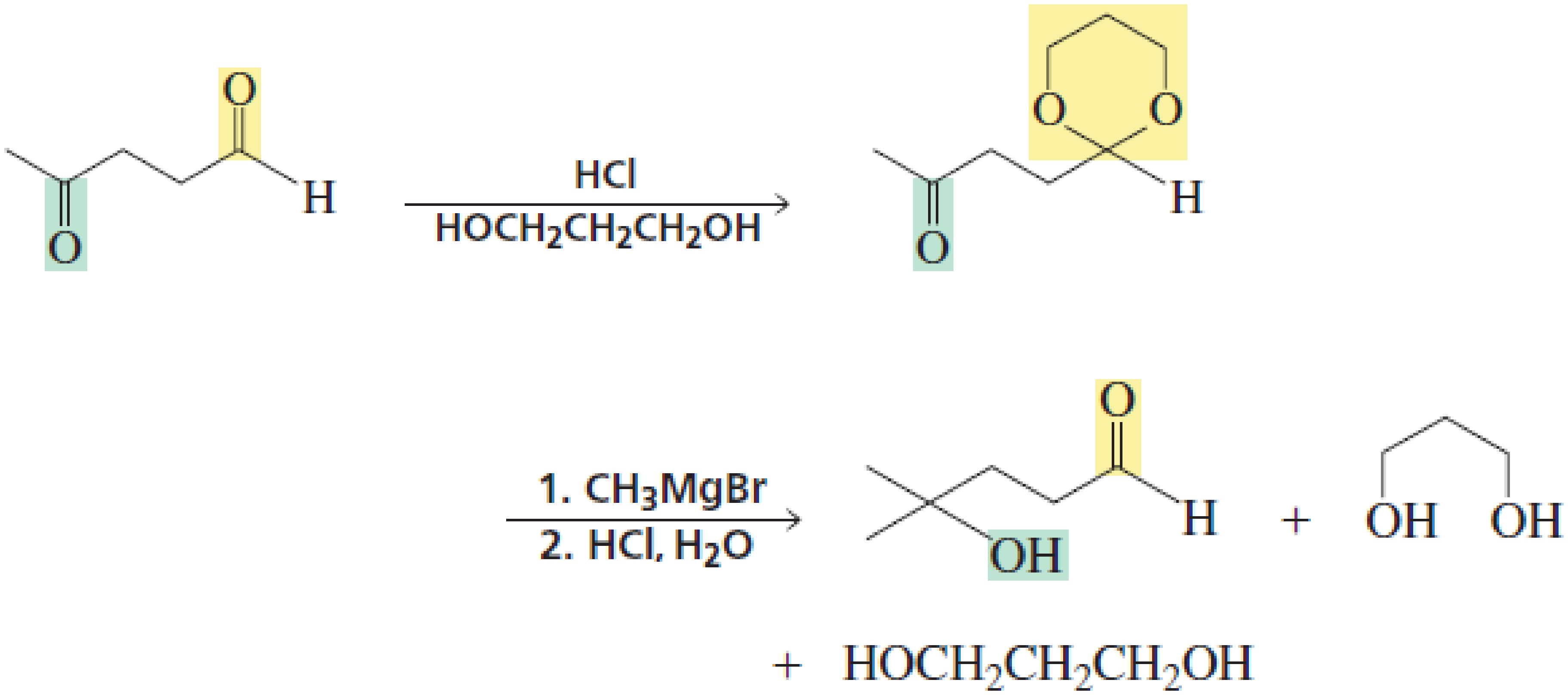
- Ketones (or aldehydes) react with 1,2-diols to form five-membered ring ketals (or acetals) and with 1,3-diols to form six-membered ring ketals (or acetals). Recall that fiveand six-membered rings are formed relatively easily



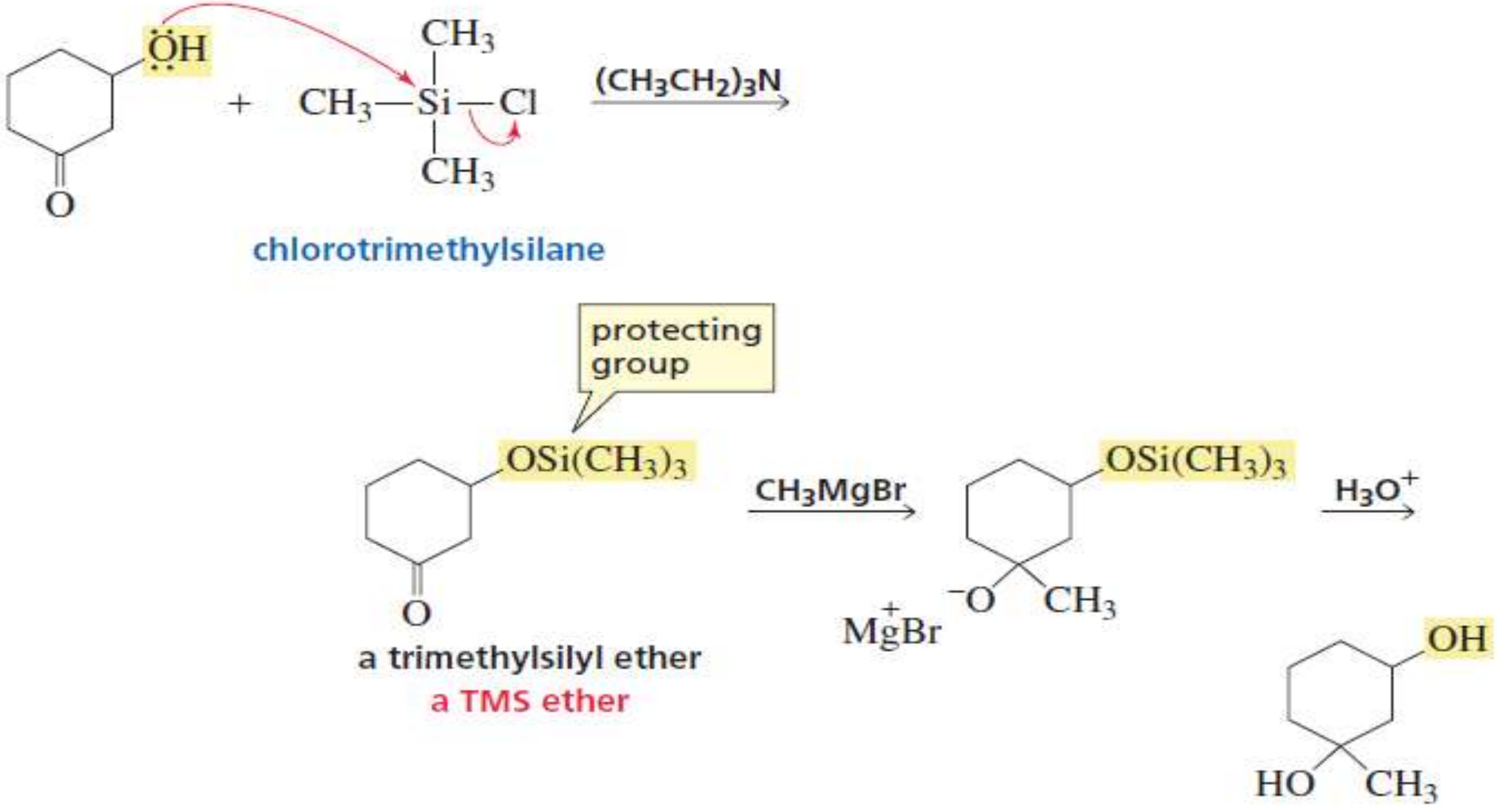
Protecting Groups



Protecting Groups



Protecting Groups



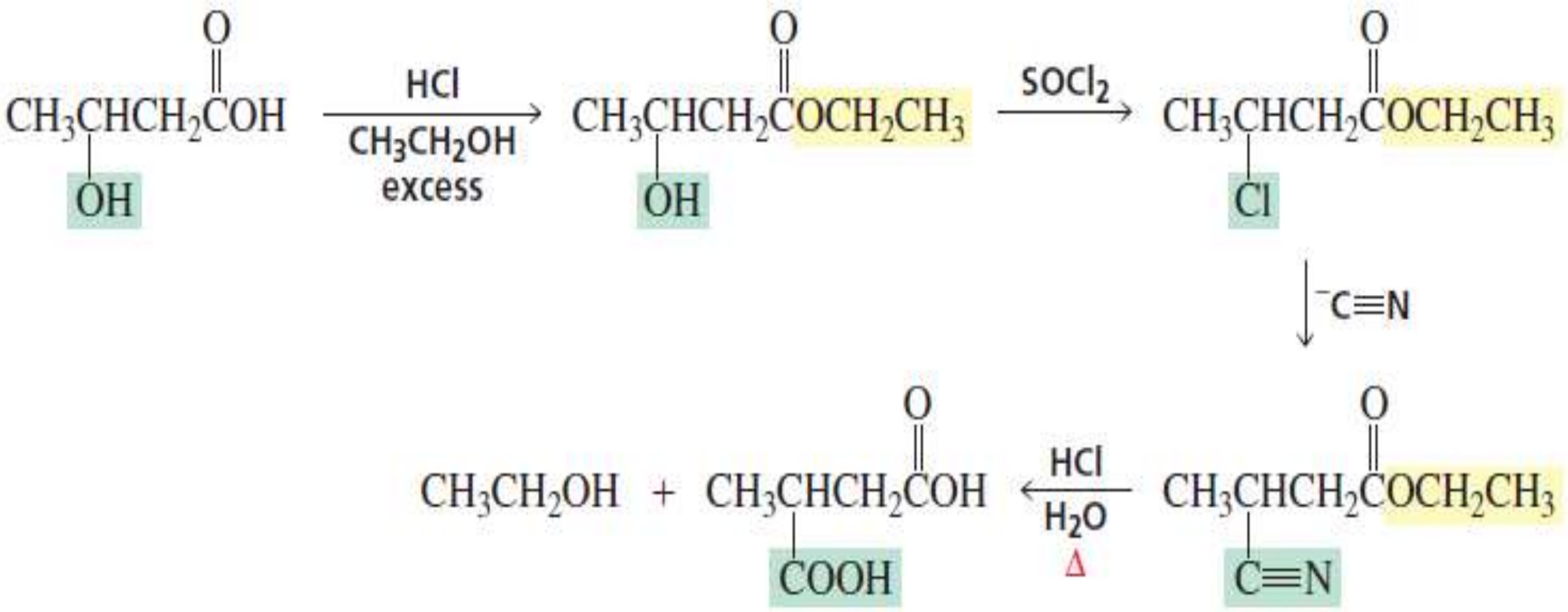
chlorotrimethylsilane

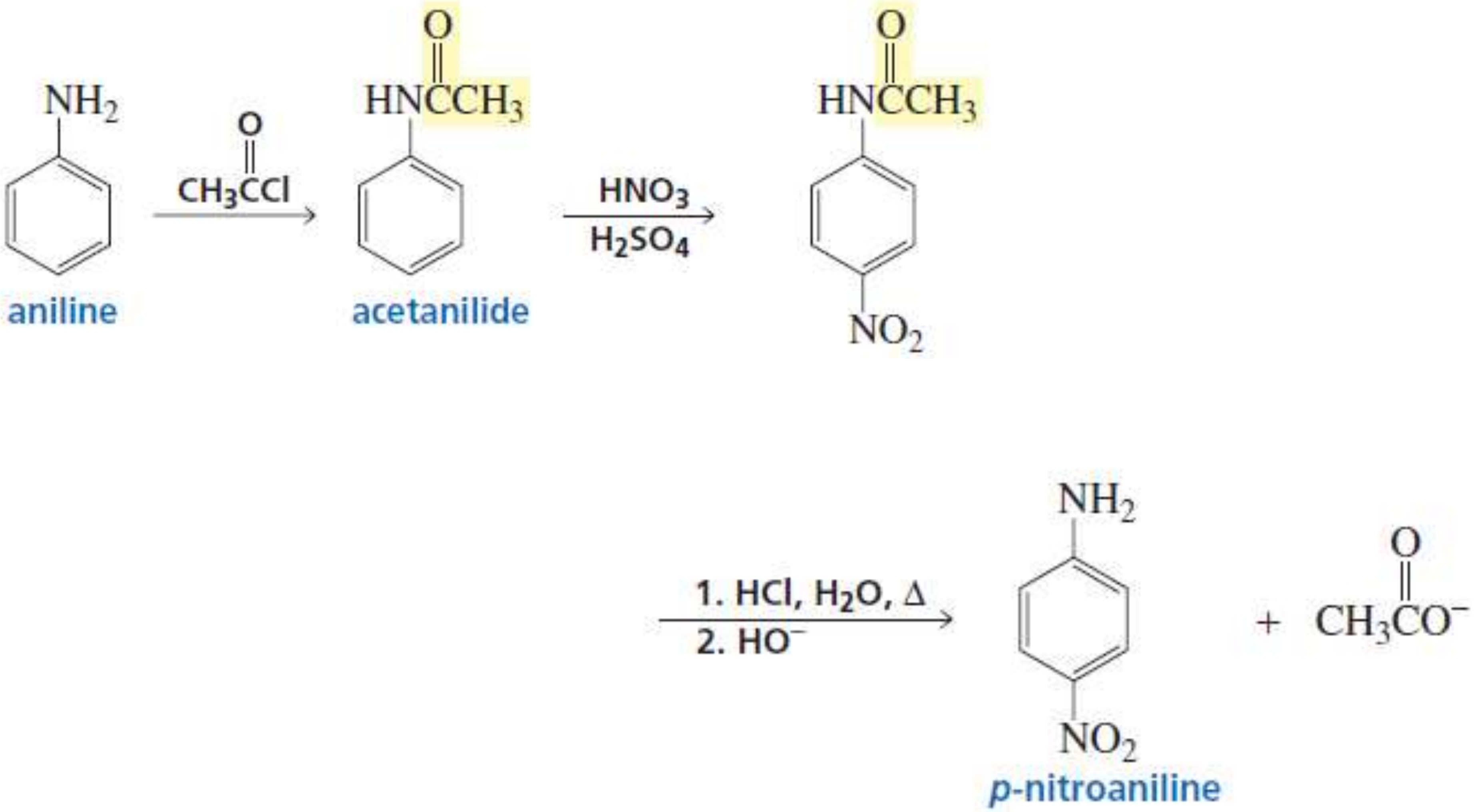
protecting group

a trimethylsilyl ether

a TMS ether

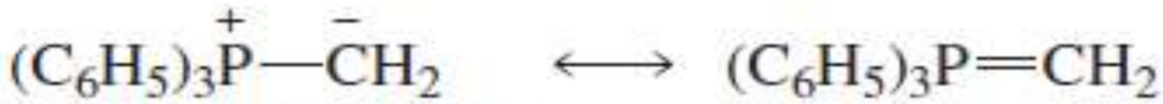
Protecting Groups




aniline
CH_3CCl (C=O)
acetanilide
HNO_3
H_2SO_4
1. HCl, H_2O, Δ
2. HO^-
p-nitroaniline
+ CH_3CO^- (C=O)

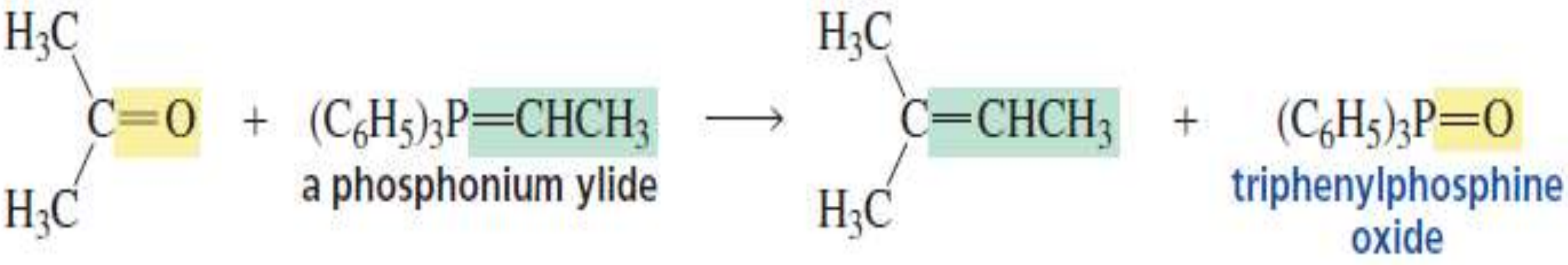
The Wittig Reaction

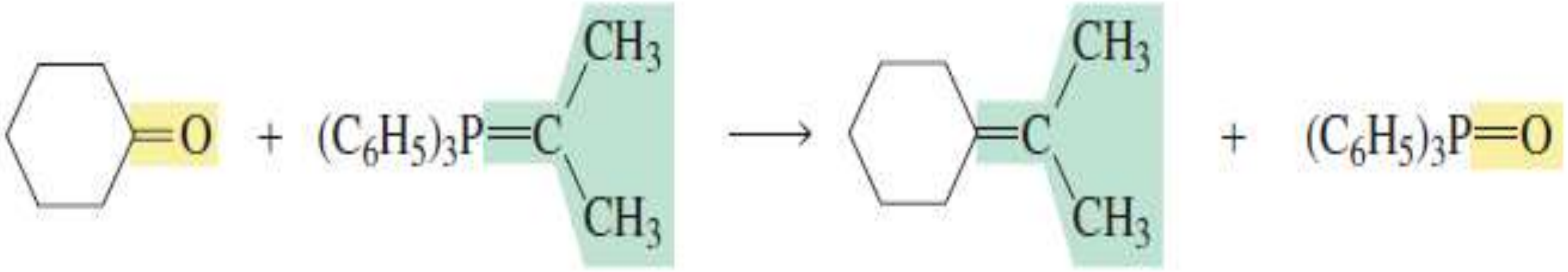
- An aldehyde or a ketone reacts with a phosphonium ylide (pronounced “ILL-id”) to form an alkene. An ylide is a compound that has opposite charges on adjacent covalently bonded atoms with complete octets. The ylide can also be written in the doublebonded form because phosphorus can have more than eight valence electrons. The reaction of an aldehyde or a ketone with a phosphonium ylide to form an alkene is called a Wittig reaction. The overall reaction amounts to interchanging the double-bonded oxygen of the carbonyl compound and the double-bonded carbon group of the phosphonium ylide.

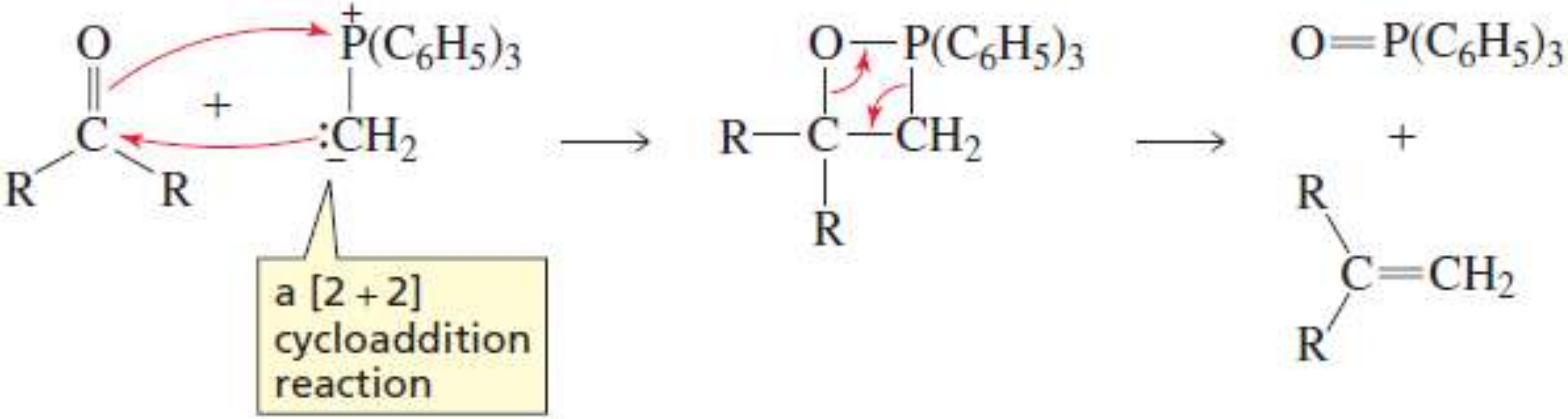


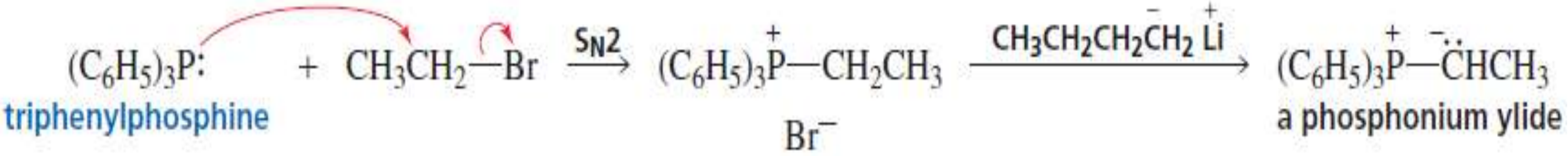
$$(C_6H_5)_3\overset{+}{P}-\overset{-}{C}H_2 \longleftrightarrow (C_6H_5)_3P{=}CH_2$$

a phosphonium ylide

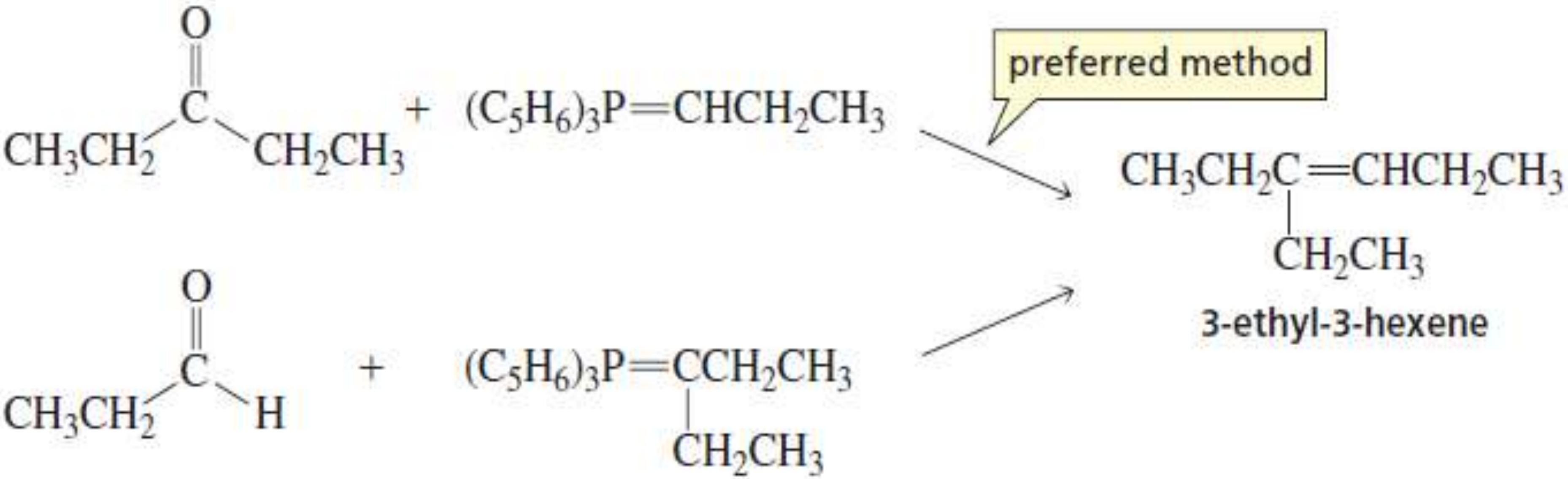

H3C
C=O
H3C
+
(C6H5)3P=CHCH3
a phosphonium ylide
H3C
C=CHCH3
H3C
+
(C6H5)3P=O
triphenylphosphine oxide


=O
+
(C6H5)3P=C
CH3
CH3
=C
CH3
CH3
+
(C6H5)3P=O


a [2 + 2] cycloaddition reaction



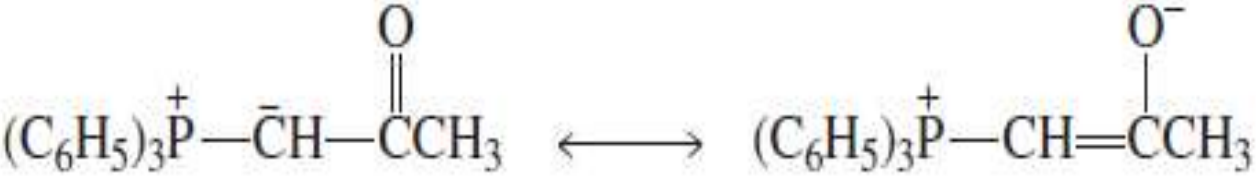
$$(C_6H_5)_3P{:} + CH_3CH_2{-}Br \xrightarrow{S_N2} (C_6H_5)_3\overset{+}{P}{-}CH_2CH_3 \;\; Br^- \xrightarrow{CH_3CH_2CH_2\overset{-}{C}H_2\,\overset{+}{Li}} (C_6H_5)_3\overset{+}{P}{-}\overset{-}{\ddot{C}}HCH_3$$



preferred method

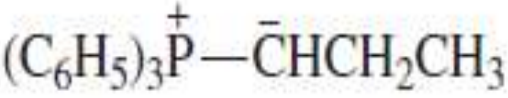
3-ethyl-3-hexene

methylenecyclohexane



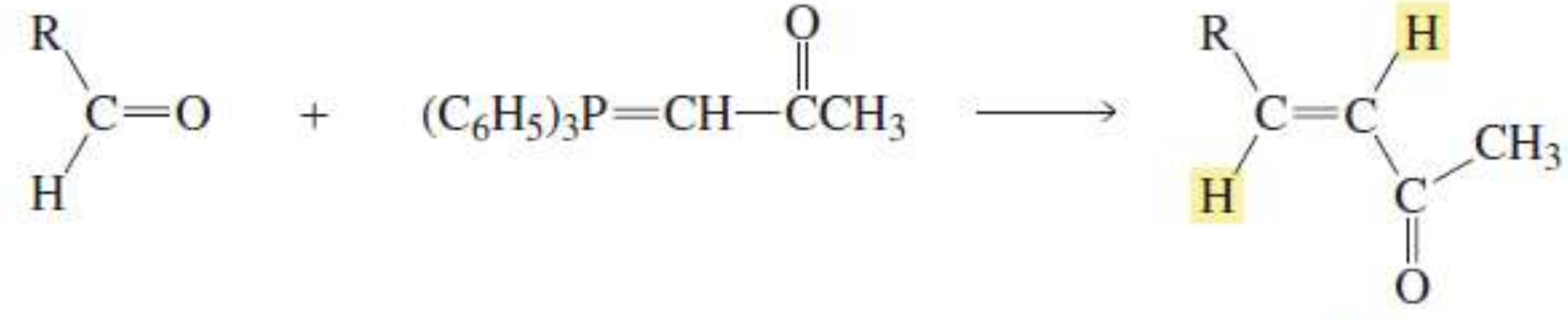
$$(C_6H_5)_3\overset{+}{P}-\overset{-}{C}H-\overset{\overset{O}{\|}}{C}CH_3 \longleftrightarrow (C_6H_5)_3\overset{+}{P}-CH=\overset{\overset{O^-}{|}}{C}CH_3$$

a stabilized ylide

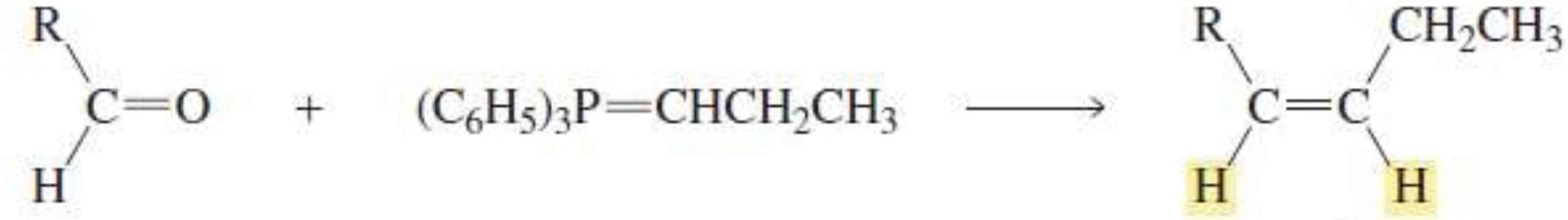


$$(C_6H_5)_3\overset{+}{P}-\overset{-}{C}HCH_2CH_3$$

an unstabilized ylide



E alkene



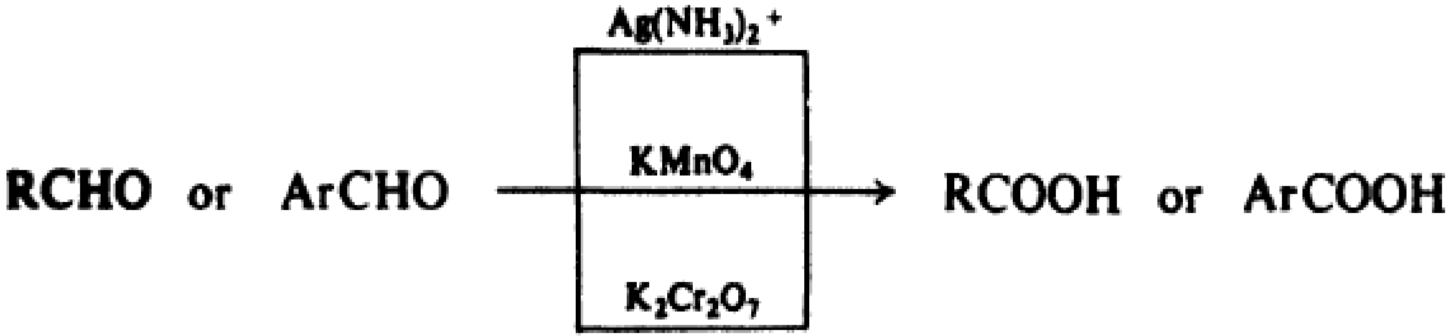
Z alkene

Reactions of Aldehydes and Ketones

REACTIONS OF ALDEHYDES AND KETONES

1. Oxidation. Discussed in Sec. 19.9.

(a) Aldehydes



$$RCHO \text{ or } ArCHO \xrightarrow[K_2Cr_2O_7]{Ag(NH_3)_2^+ \;\; KMnO_4} RCOOH \text{ or } ArCOOH$$

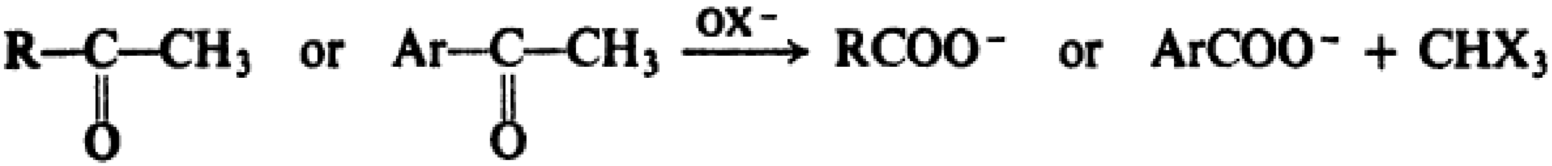
Used chiefly for detection of aldehydes

Examples:

$$CH_3CHO + \underset{\text{Colorless solution}}{2Ag(NH_3)_2^+} + 3OH^- \longrightarrow \underset{\text{Silver mirror}}{2Ag} + CH_3COO^- + 4NH_3 + 2H_2O$$

Tollens' test

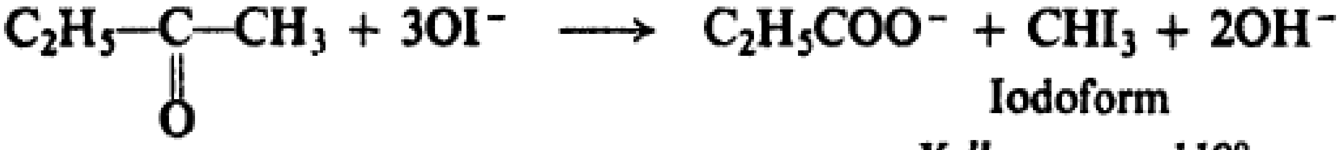
(b) Methyl ketones



$$R\!-\!\underset{\underset{O}{\|}}{C}\!-\!CH_3 \text{ or } Ar\!-\!\underset{\underset{O}{\|}}{C}\!-\!CH_3 \xrightarrow{OX^-} RCOO^- \text{ or } ArCOO^- + CHX_3$$

Haloform reaction

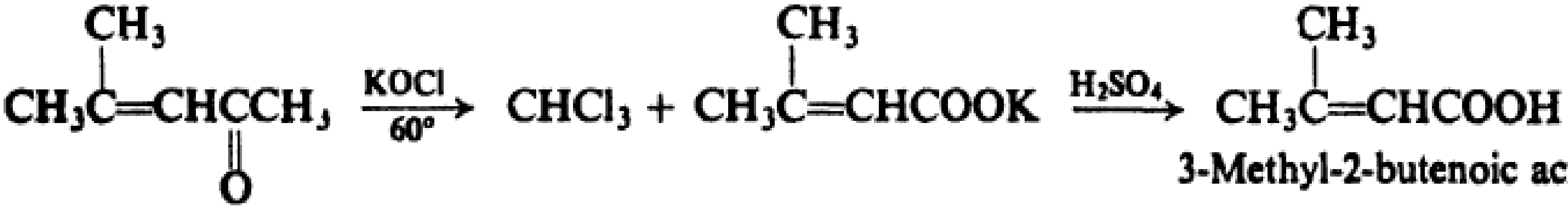
Examples:



$$C_2H_5\!-\!\underset{\underset{O}{\|}}{C}\!-\!CH_3 + 3OI^- \longrightarrow C_2H_5COO^- + CHI_3 + 2OH^-$$

Iodoform

Yellow; m.p. 119°



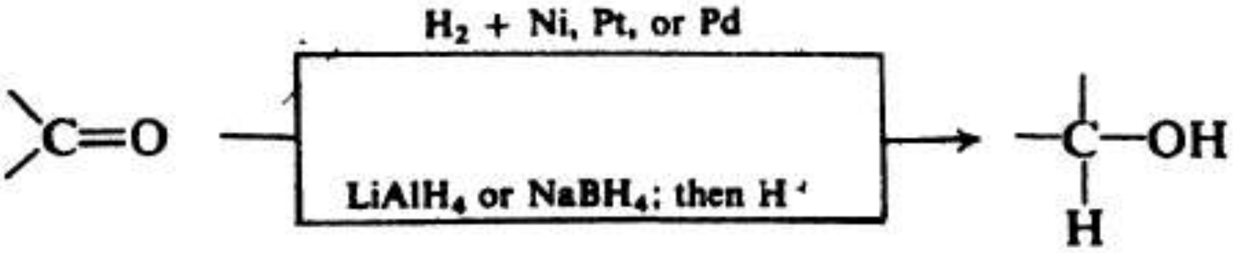
$$CH_3\overset{\overset{CH_3}{|}}{C}\!=\!CH\underset{\underset{O}{\|}}{C}CH_3 \xrightarrow[60^\circ]{KOCl} CHCl_3 + CH_3\overset{\overset{CH_3}{|}}{C}\!=\!CHCOOK \xrightarrow{H_2SO_4} CH_3\overset{\overset{CH_3}{|}}{C}\!=\!CHCOOH$$

Mesityl oxide
(4-Methyl-3-penten-2-one)

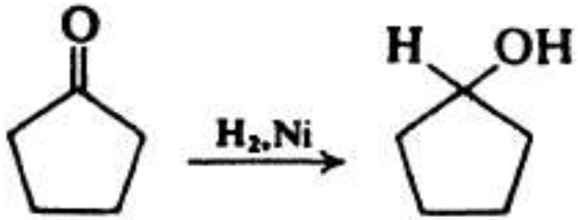
3-Methyl-2-butenoic acid

2. Reduction

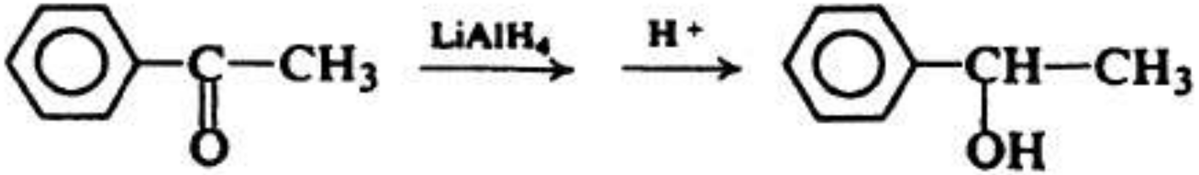
(a) Reduction to alcohols. Discussed in Sec. 19.10.



Examples:

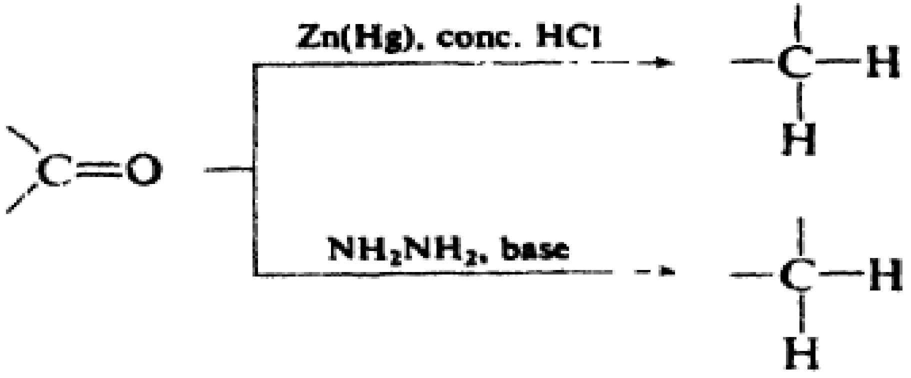


Cyclopentanone Cyclopentanol



Acetophenone α-Phenylethyl alcohol

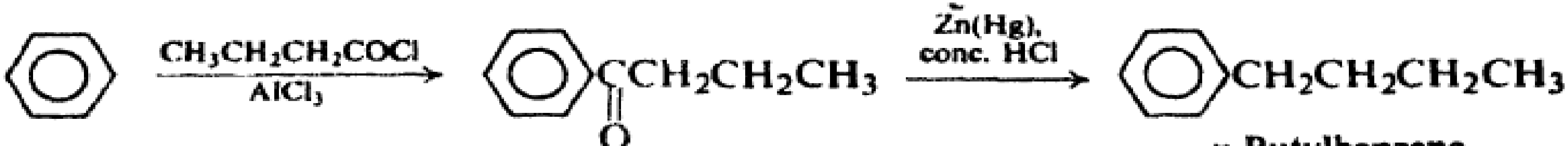
(b) Reduction to hydrocarbons. Discussed in Sec. 19.10.



Clemmensen reduction
for compounds sensitive to base

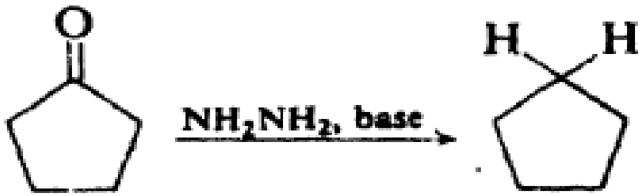
Wolff-Kishner reduction
for compounds sensitive to acid

Examples:



n-Butyrophenone
(Phenyl *n*-propyl ketone)

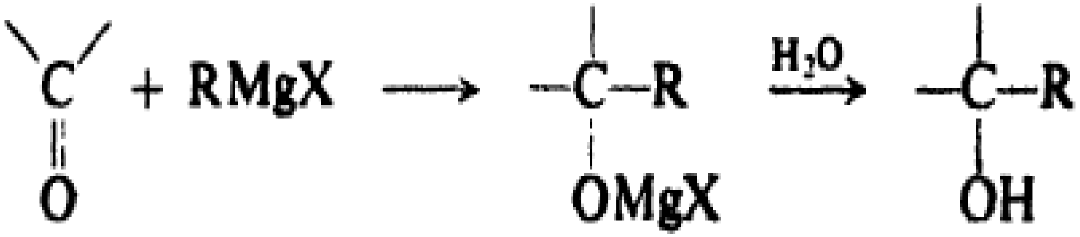
n-Butylbenzene



Cyclopentanone

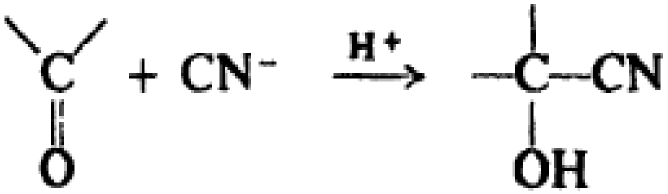
Cyclopentane

3. Addition of Grignard reagents. Discussed in Secs. 15.12–15.15 and 19.11.



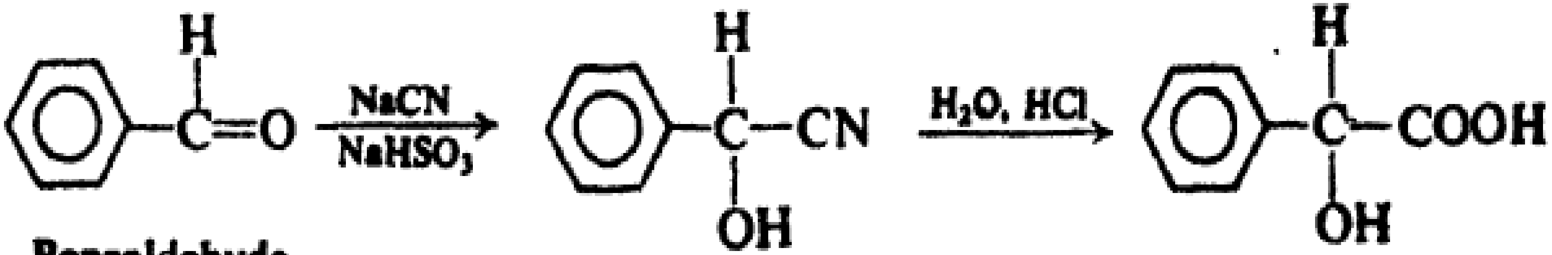
$$\overset{\diagdown\;\diagup}{\underset{\underset{O}{\|}}{C}} + RMgX \longrightarrow -\overset{|}{\underset{\underset{OMgX}{|}}{C}}-R \xrightarrow{H_2O} -\overset{|}{\underset{\underset{OH}{|}}{C}}-R$$

4. Addition of cyanide. Cyanohydrin formation. Discussed in Sec. 19.12.



Cyanohydrin

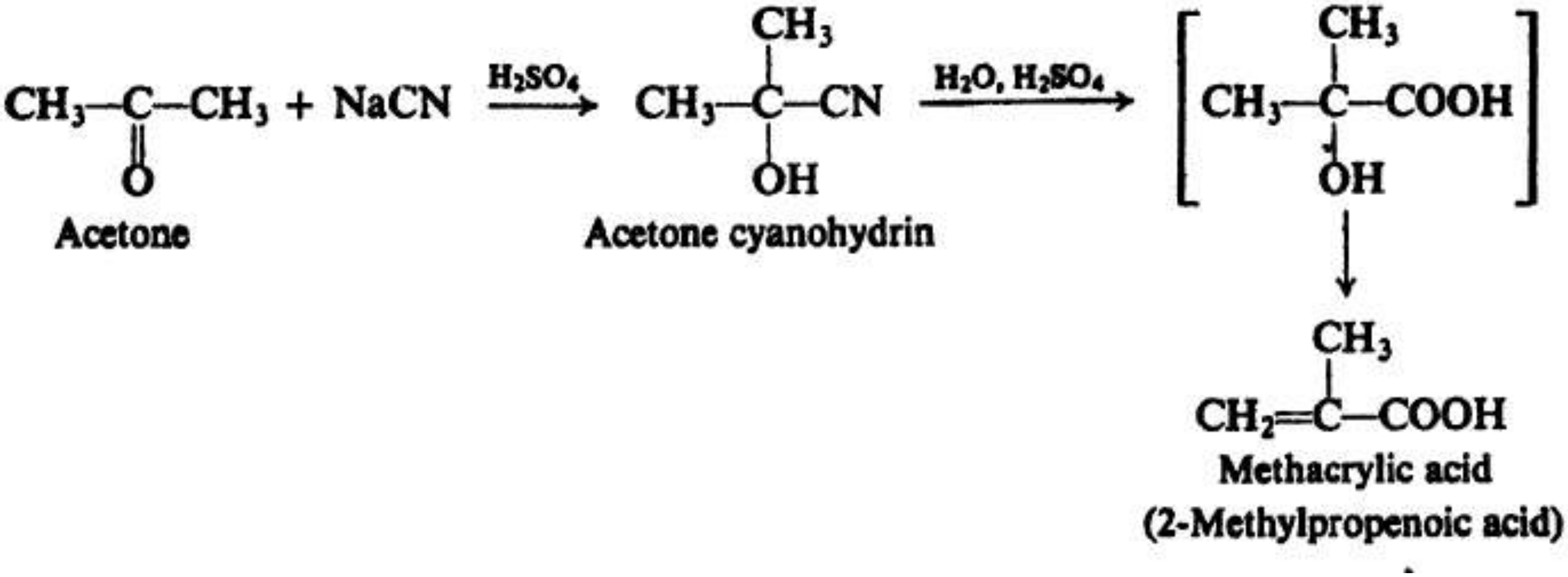
Examples:



Benzaldehyde

Mandelonitrile

Mandelic acid



$$CH_3-\underset{\underset{O}{\|}}{C}-CH_3 + NaCN \xrightarrow{H_2SO_4} CH_3-\overset{\overset{CH_3}{|}}{\underset{\underset{OH}{|}}{C}}-CN \xrightarrow{H_2O,\ H_2SO_4} \left[CH_3-\overset{\overset{CH_3}{|}}{\underset{\underset{OH}{|}}{C}}-COOH \right] \longrightarrow CH_2=\overset{\overset{CH_3}{|}}{C}-COOH$$

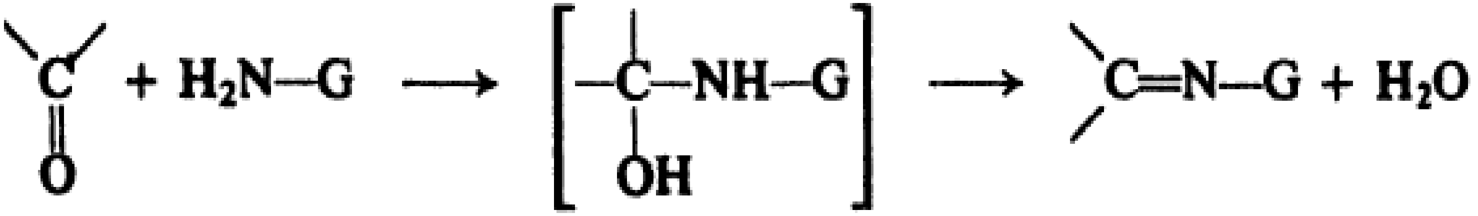
Acetone

Acetone cyanohydrin

Methacrylic acid

(2-Methylpropenoic acid)

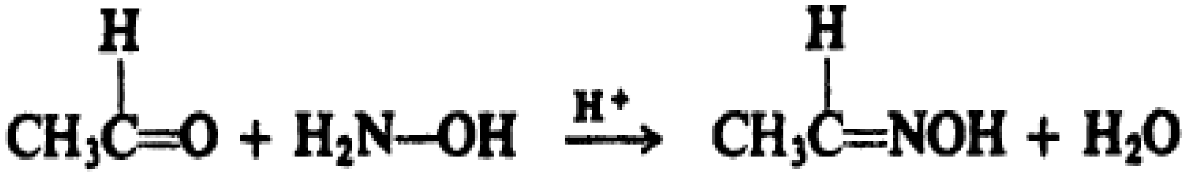
6. Addition of derivatives of ammonia. Discussed in Sec. 19.14.



Used for identification

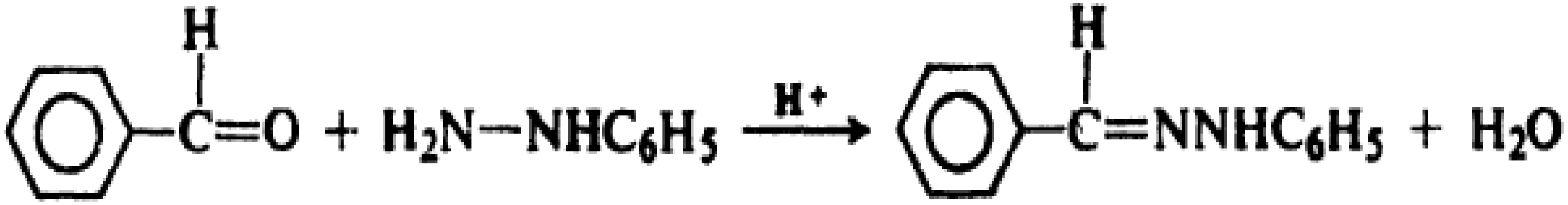
$H_2N{-}G$		**Product**	
$H_2N{-}OH$	Hydroxylamine	$>C{=}NOH$	Oxime
$H_2N{-}NH_2$	Hydrazine	$>C{=}NNH_2$	Hydrazone
$H_2N{-}NHC_6H_5$	Phenylhydrazine	$>C{=}NNHC_6H_5$	Phenylhydrazone
$H_2N{-}NHCONH_2$	Semicarbazide	$>C{=}NNHCONH_2$	Semicarbazone

Examples:



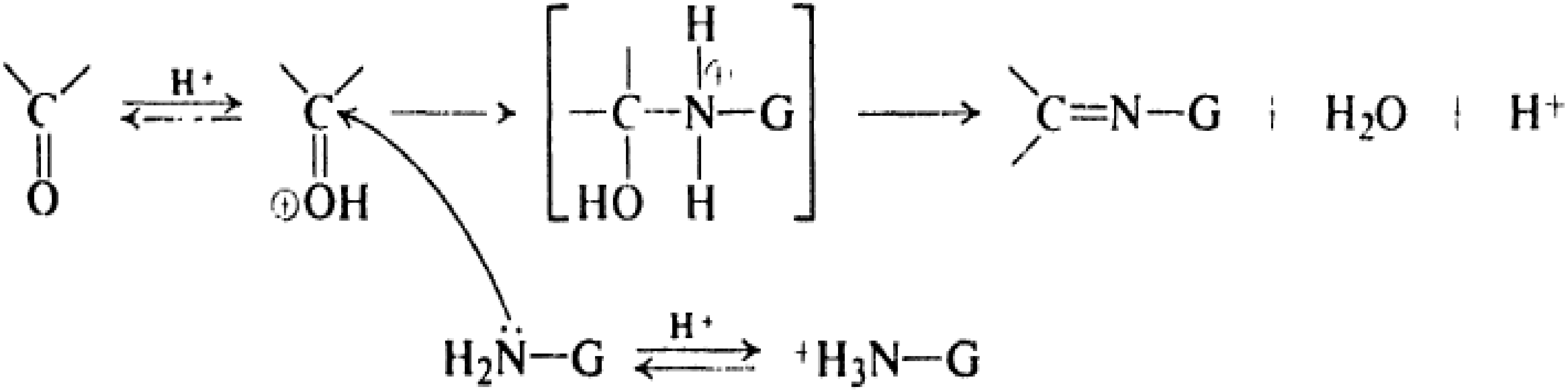
$$CH_3\overset{H}{\overset{|}{C}}{=}O + H_2N{-}OH \xrightarrow{H^+} CH_3\overset{H}{\overset{|}{C}}{=}NOH + H_2O$$

Acetaldehyde Hydroxylamine Acetaldoxime



$$C_6H_5\overset{H}{\overset{|}{C}}{=}O + H_2N{-}NHC_6H_5 \xrightarrow{H^+} C_6H_5\overset{H}{\overset{|}{C}}{=}NNHC_6H_5 + H_2O$$

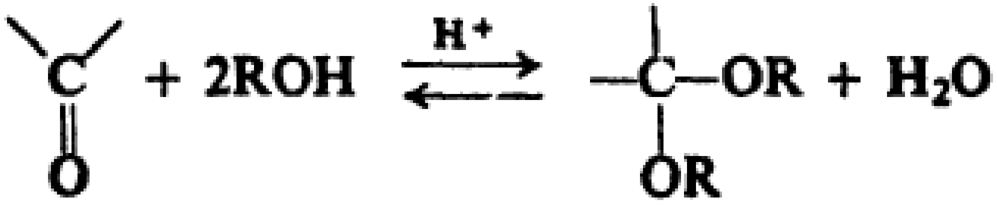
Benzaldehyde Phenylhydrazine Benzaldehyde phenylhydrazone



Free base:
nucleophilic

Salt:
not nucleophilic

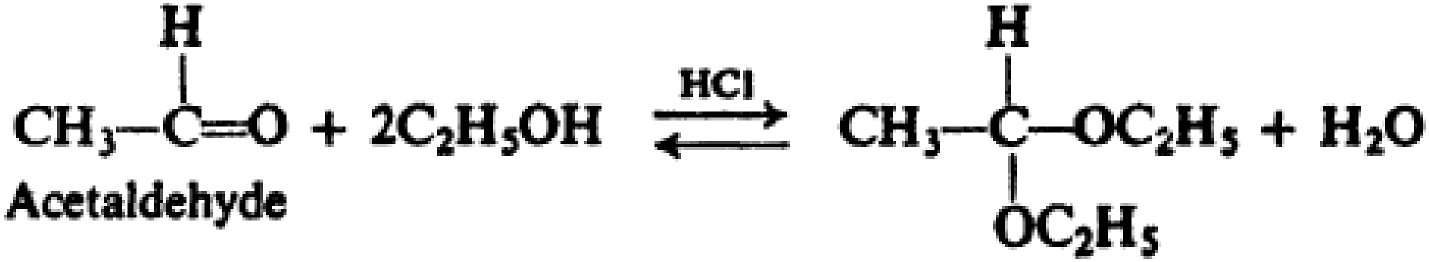
7. Addition of alcohols. Acetal formation. Discussed in Sec. 19.15.



$$\underset{\displaystyle O}{\overset{\displaystyle \diagdown\ \diagup}{\underset{\|}{C}}} + 2ROH \underset{}{\overset{H^+}{\rightleftharpoons}} -\underset{\displaystyle OR}{\underset{|}{\overset{|}{C}}}-OR + H_2O$$

An acetal

Example:

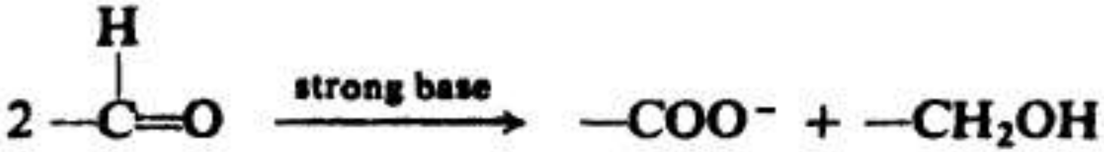


$$CH_3-\overset{\displaystyle H}{\overset{|}{C}}=O + 2C_2H_5OH \overset{HCl}{\rightleftharpoons} CH_3-\underset{\displaystyle OC_2H_5}{\underset{|}{\overset{\displaystyle H}{\overset{|}{C}}}}-OC_2H_5 + H_2O$$

Acetaldehyde

Acetal
(Acetaldehyde
diethyl acetal)

8. **Cannizzaro reaction.** Discussed in Sec. 19.16.



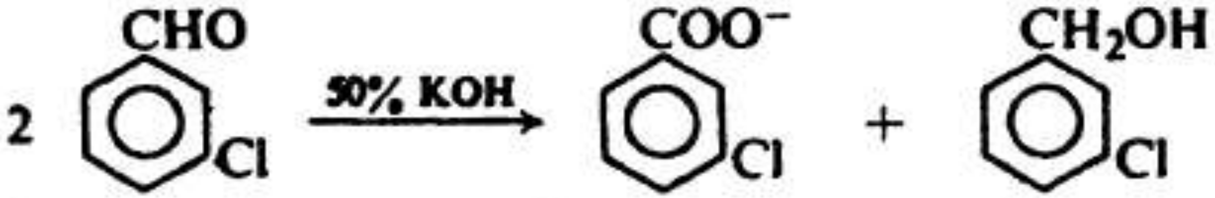
$$2\,-\overset{\overset{\displaystyle H}{|}}{C}=O \xrightarrow{\text{strong base}} -COO^- + -CH_2OH$$

An aldehyde with no α-hydrogens — Acid salt — Alcohol

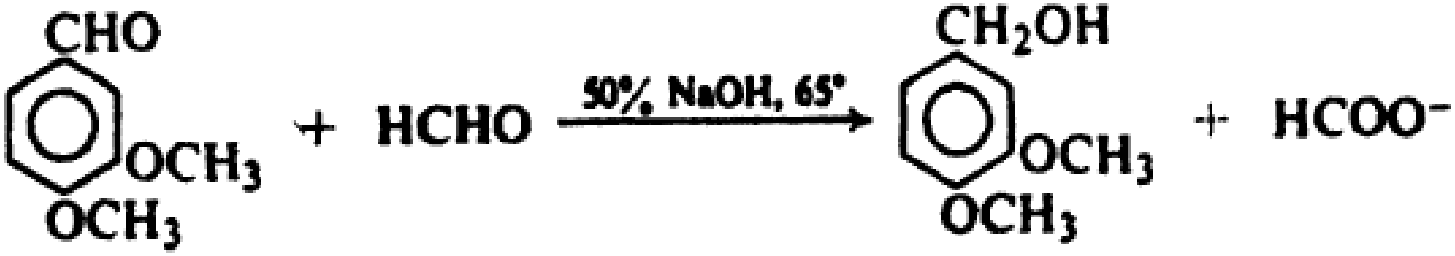
Examples:

$$2\,HCHO \xrightarrow{\text{50\% NaOH, room temperature}} HCOO^- + CH_3OH$$

Formaldehyde — Formate ion — Methanol



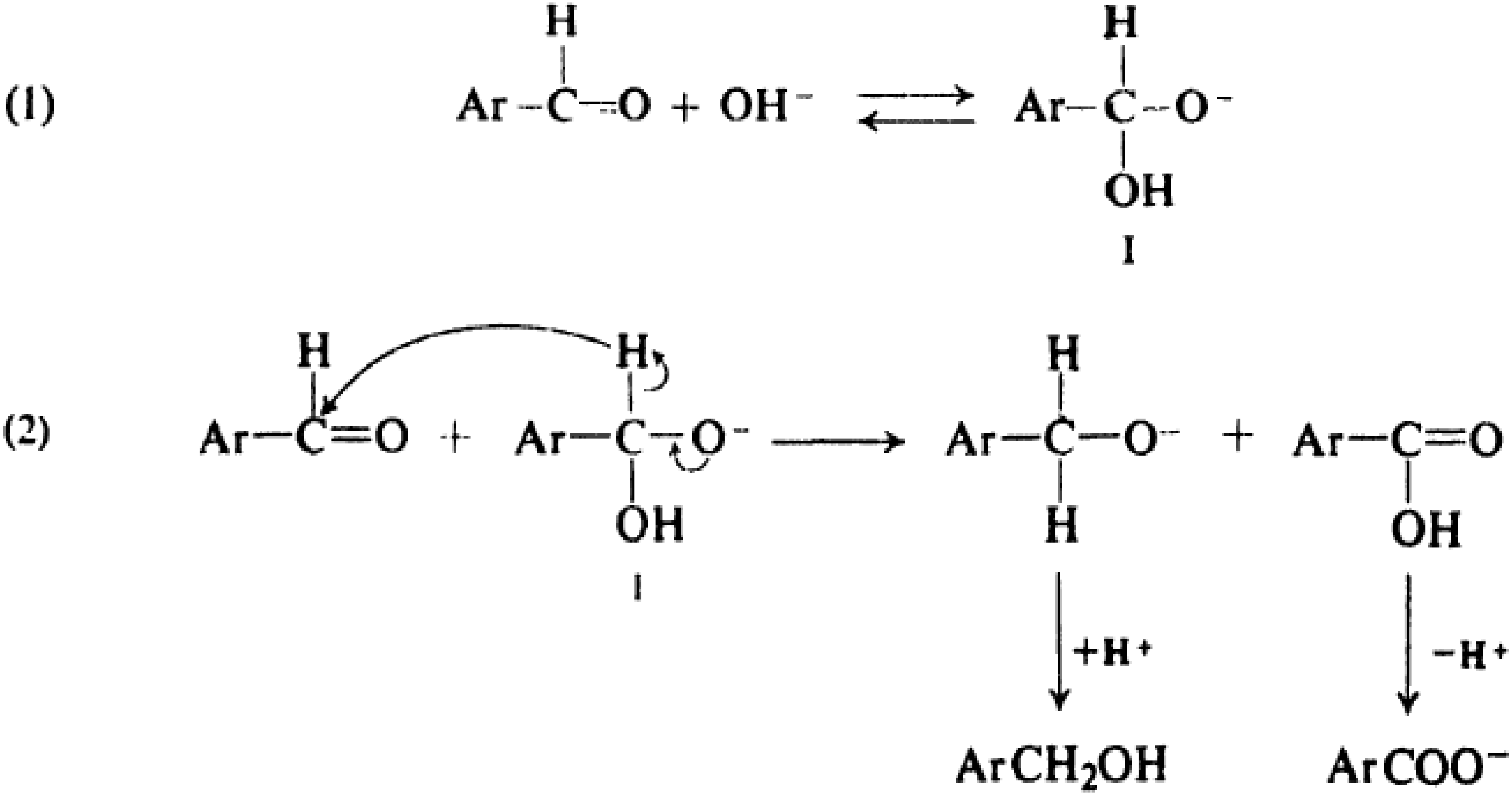
m-Chlorobenzaldehyde — *m*-Chlorobenzoate ion — *m*-Chlorobenzyl alcohol



Veratraldehyde
3,4-Dimethoxybenzaldehyde

3,4-Dimethoxybenzyl alcohol

Crossed Cannizzaro reaction



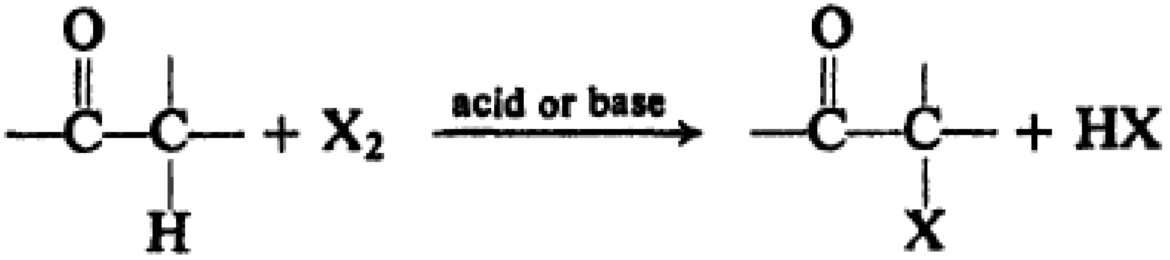
(1) $\mathrm{Ar{-}\overset{H}{C}{=}O + OH^- \rightleftharpoons Ar{-}\underset{OH}{\overset{H}{C}}{-}O^-}$ I

(2) $\mathrm{Ar{-}\overset{H}{C}{=}O + Ar{-}\underset{OH}{\overset{H}{C}}{-}O^- \longrightarrow Ar{-}\underset{H}{\overset{H}{C}}{-}O^- + Ar{-}\underset{OH}{C}{=}O}$ I

$\mathrm{Ar{-}CH_2{-}O^- \xrightarrow{+H^+} ArCH_2OH}$

$\mathrm{Ar{-}C(OH){=}O \xrightarrow{-H^+} ArCOO^-}$

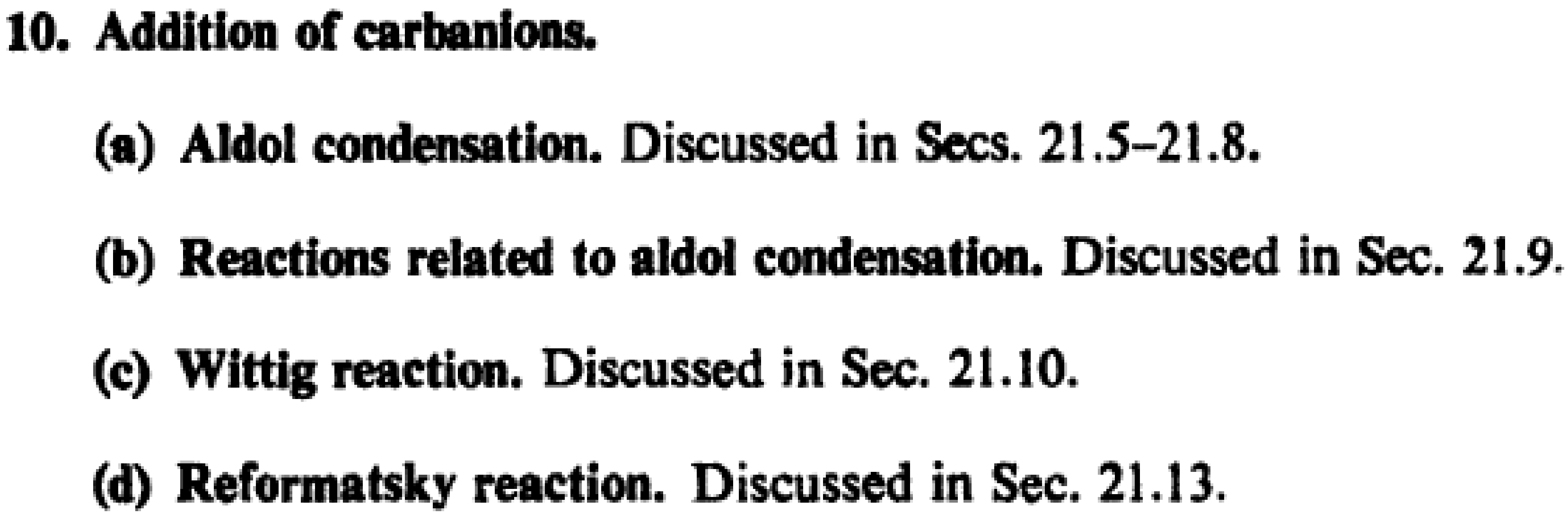
9. Halogenation of ketones. Discussed in Secs. 21.3–21.4.



$$-\overset{\overset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle H}{|}}{\overset{|}{C}}- + X_2 \xrightarrow{\text{acid or base}} -\overset{\overset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle X}{|}}{\overset{|}{C}}- + HX$$

α-Halogenation

$X_2 = Cl_2, Br_2, I_2$



10. Addition of carbanions.

(a) **Aldol condensation.** Discussed in Secs. 21.5–21.8.

(b) **Reactions related to aldol condensation.** Discussed in Sec. 21.9.

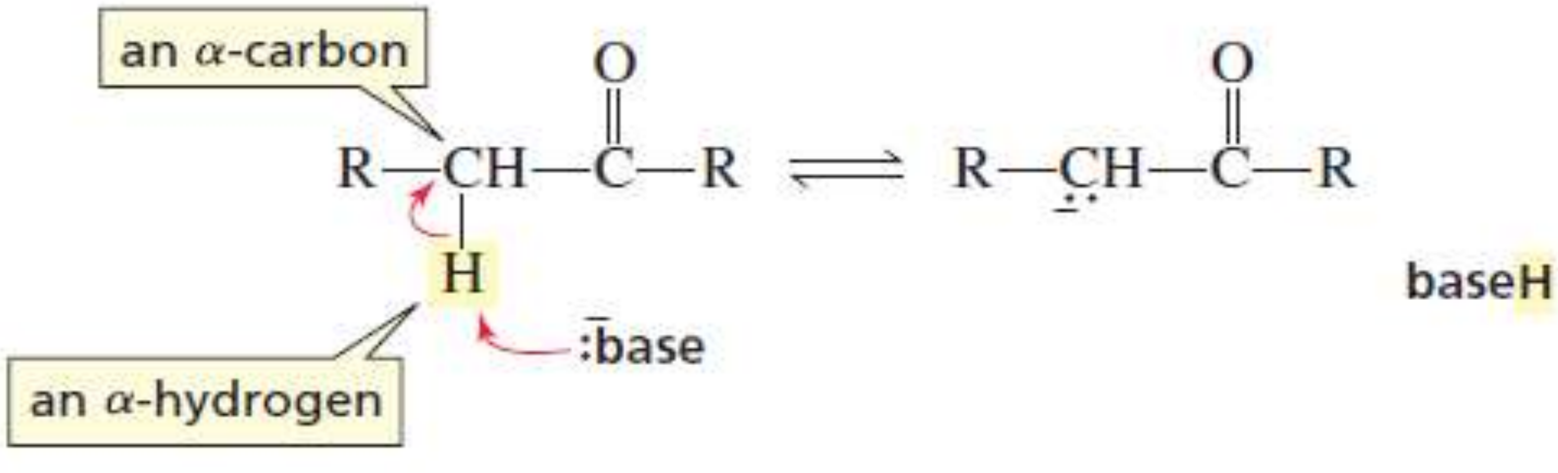
(c) **Wittig reaction.** Discussed in Sec. 21.10.

(d) **Reformatsky reaction.** Discussed in Sec. 21.13.

Carbonyl Compounds

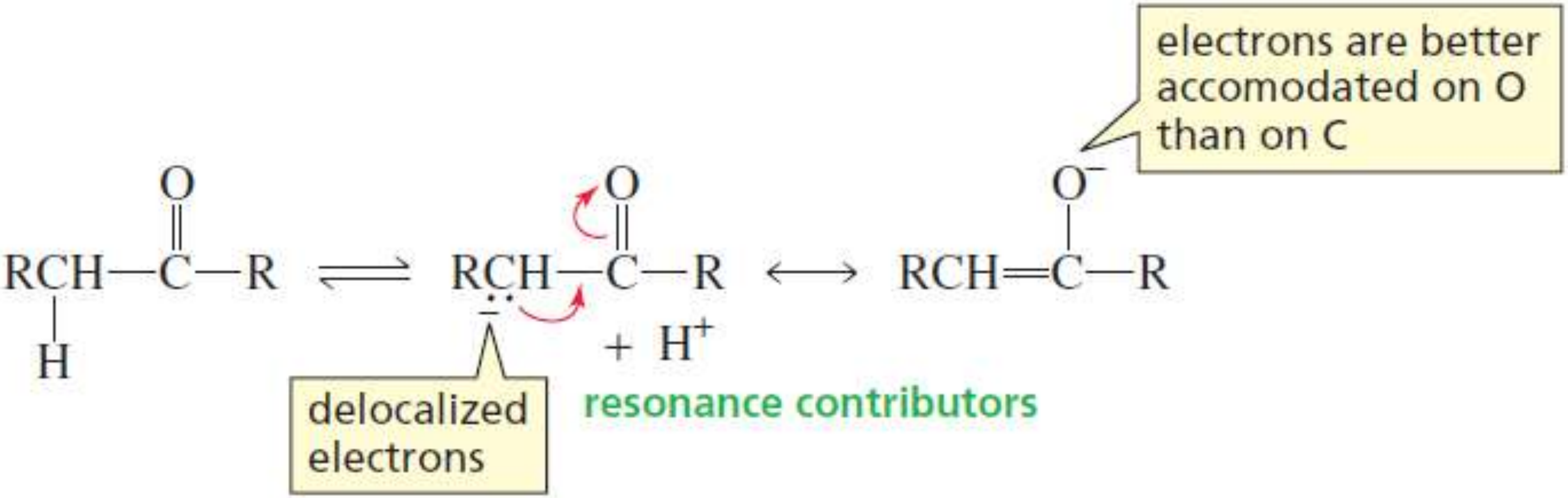
- **Reactions at the α-Carbon**

Aldehydes, ketones, esters, and *N,N-disubstituted amides have a second site of* reactivity. A hydrogen bonded to *a carbon adjacent to a carbonyl carbon is sufficiently* acidic to be removed by a strong base. The carbon adjacent to a carbonyl carbon is called an **α-carbon**. A hydrogen bonded to an α-carbon is called **α-Hydrogen**



Acidity of α-Hydrogen

Why is a hydrogen bonded to an sp^3 hybridized carbon that is adjacent to a carbonyl carbon so much more acidic than hydrogens bonded to other sp^3 hybridized carbons? An *α*-hydrogen is more acidic because the base formed when the proton is removed from the *α*-carbon is more stable than the base formed when a proton is removed from other sp^3 hybridized carbons, and acid strength is determined by the stability of the conjugate base that is formed when the acid gives up a proton (Section 1.17).



electrons are better accomodated on O than on C

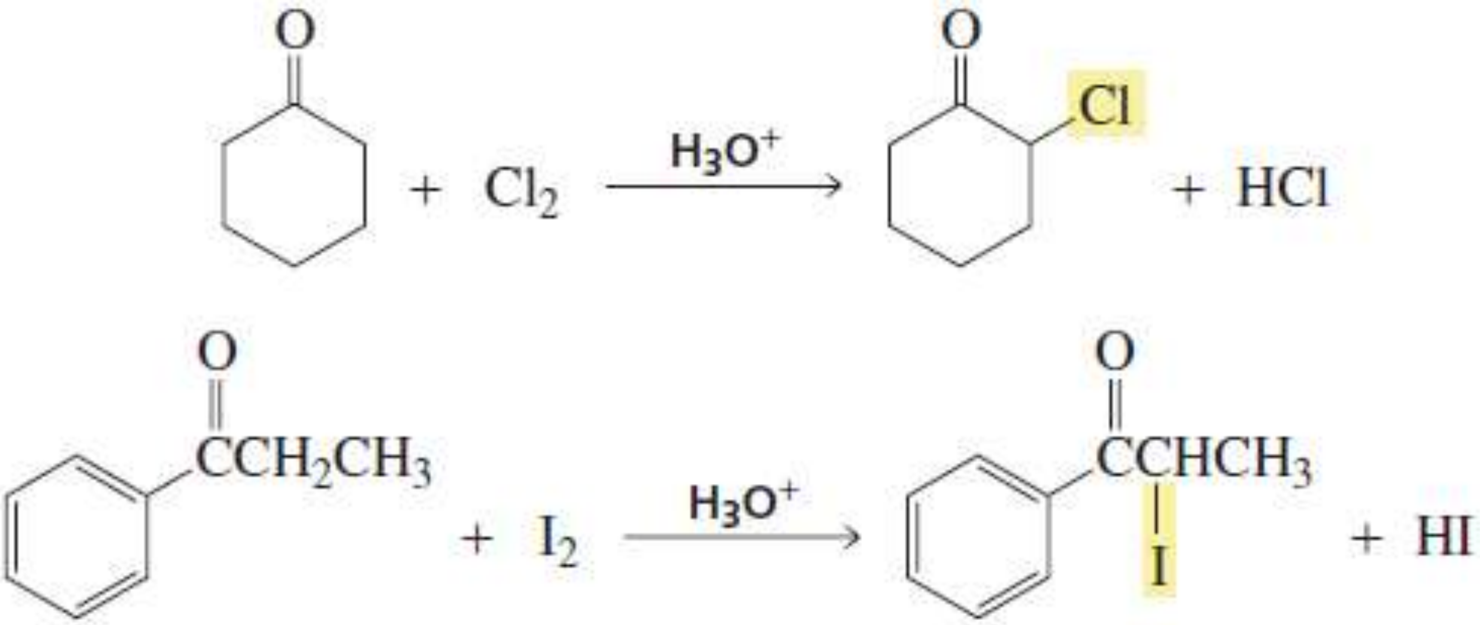
delocalized electrons

resonance contributors

Halogenation of the -Carbon of Aldehydes and Ketones

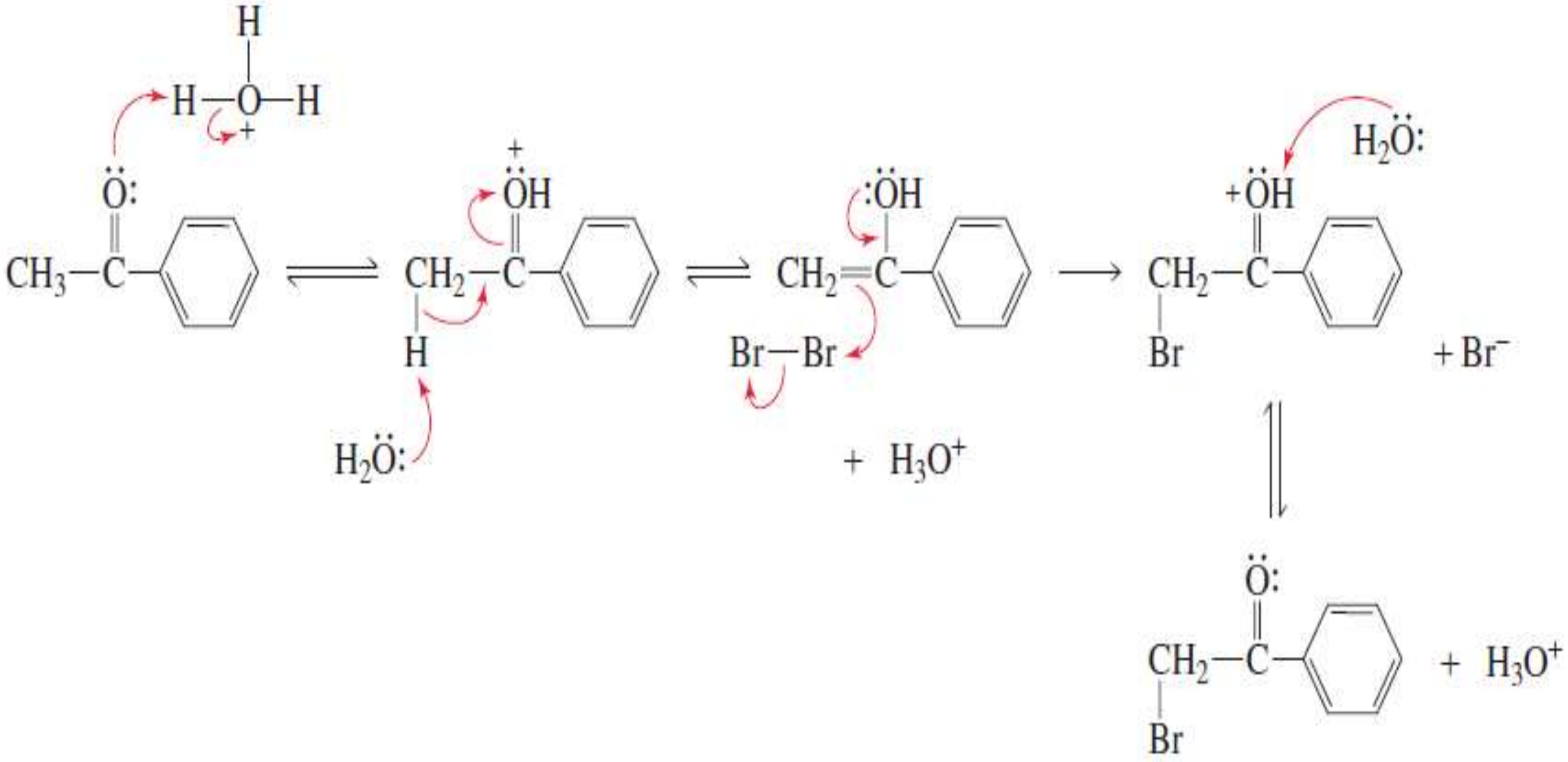
- **Acid-Catalyzed Halogenation**

When Br_2,Cl_2 or I_2 is added to an *acidic solution of an aldehyde or a ketone, a halogen* replaces *one of the* α-hydrogens *of the carbonyl compound*



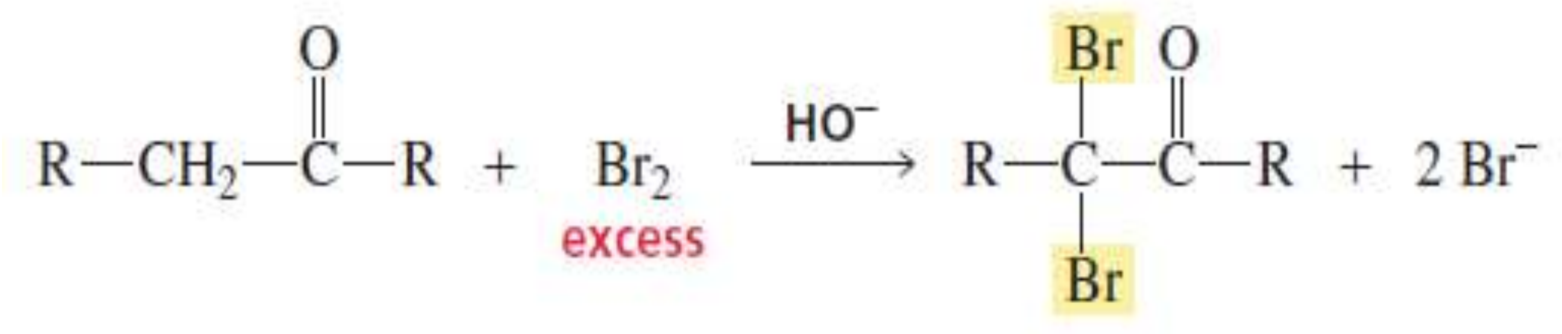
Halogenation of the -Carbon of Aldehydes and Ketones

acid-catalyzed halogenation



Halogenation of the -Carbon of Aldehydes and Ketones

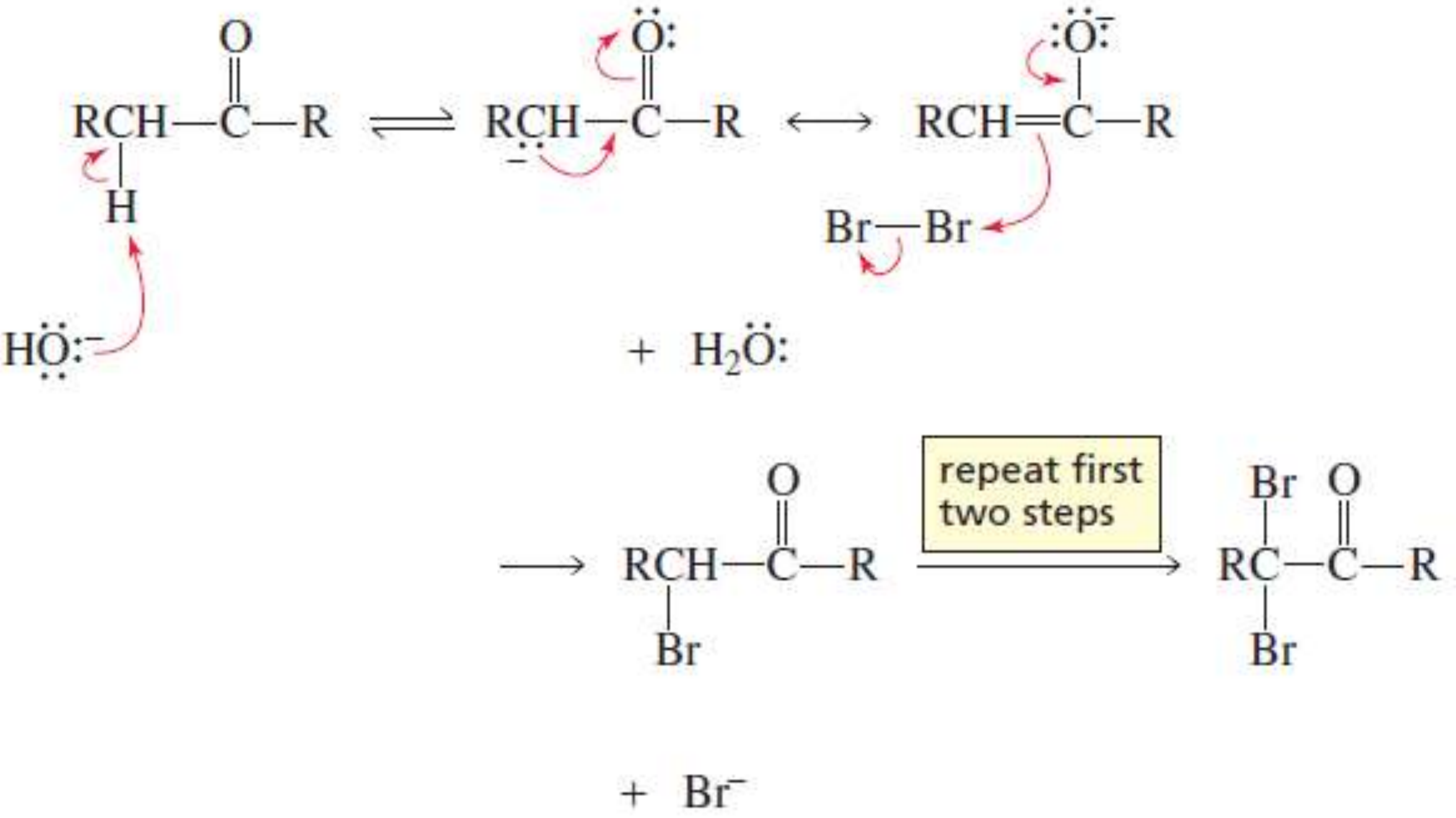
- **Base-Promoted Halogenation**
  When excess Br_2,Cl_2 or I_2 is added to a basic *solution of an aldehyde or a ketone, the halogen* replaces all *the* α-hydrogens *of the carbonyl compound*



$$R-CH_2-\overset{O}{\overset{\|}{C}}-R + \underset{\text{excess}}{Br_2} \xrightarrow{HO^-} R-\overset{Br}{\underset{Br}{C}}-\overset{O}{\overset{\|}{C}}-R + 2\,Br^-$$

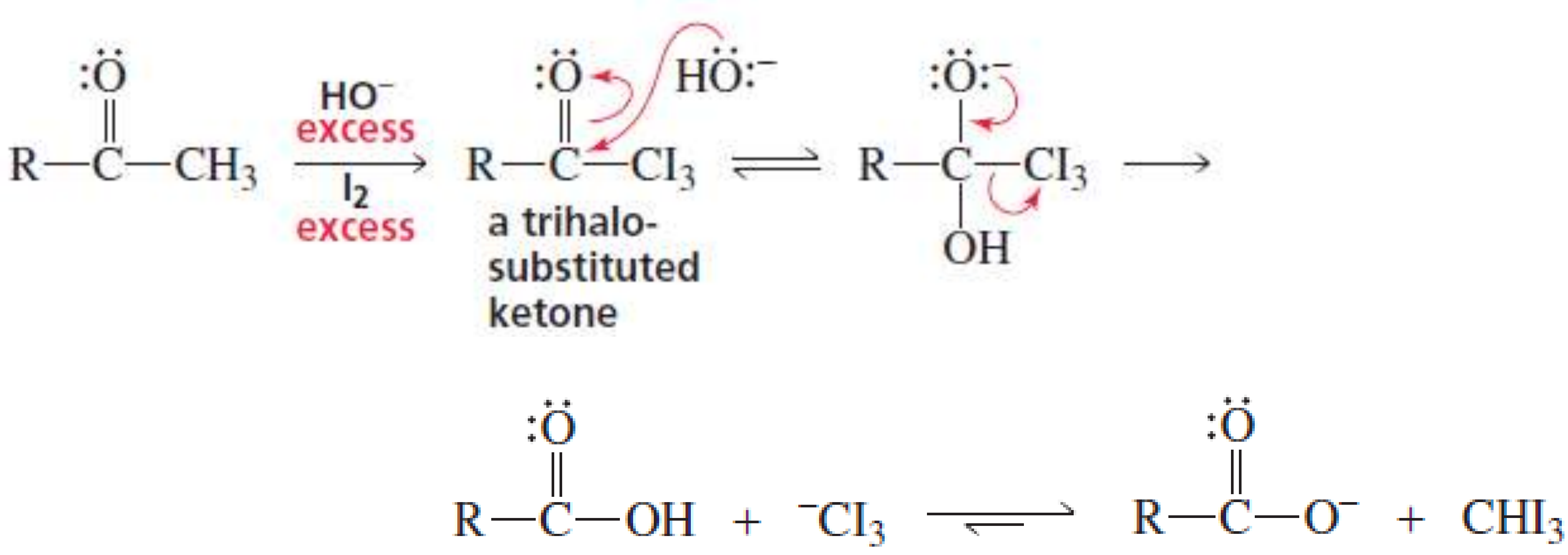
Halogenation of the -Carbon of Aldehydes and Ketones

base-promoted halogenation



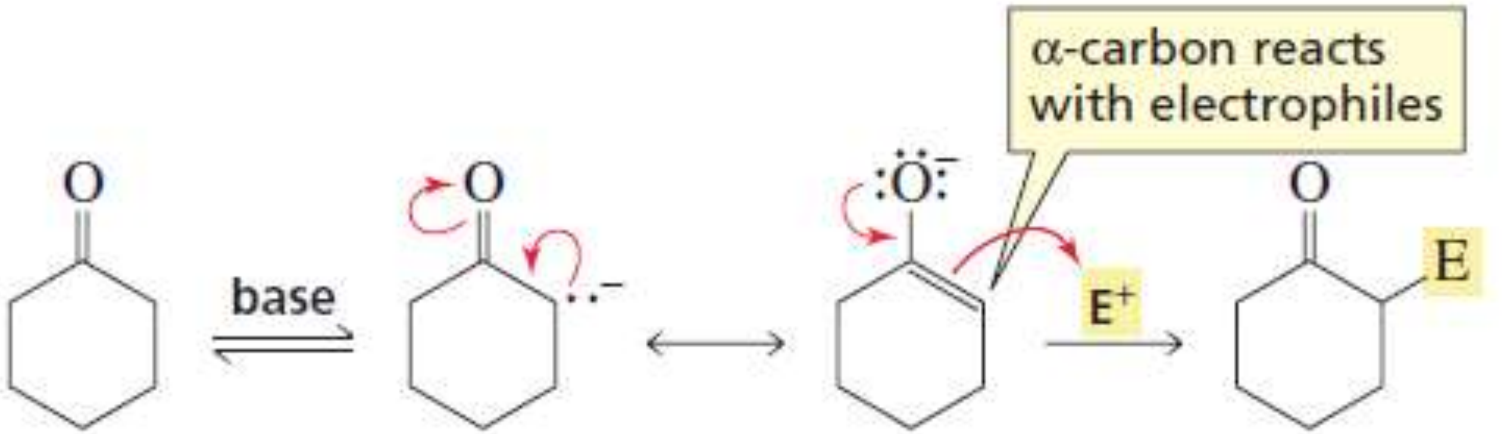
Halogenation of the -Carbon of Aldehydes and Ketones

The Haloform Reaction



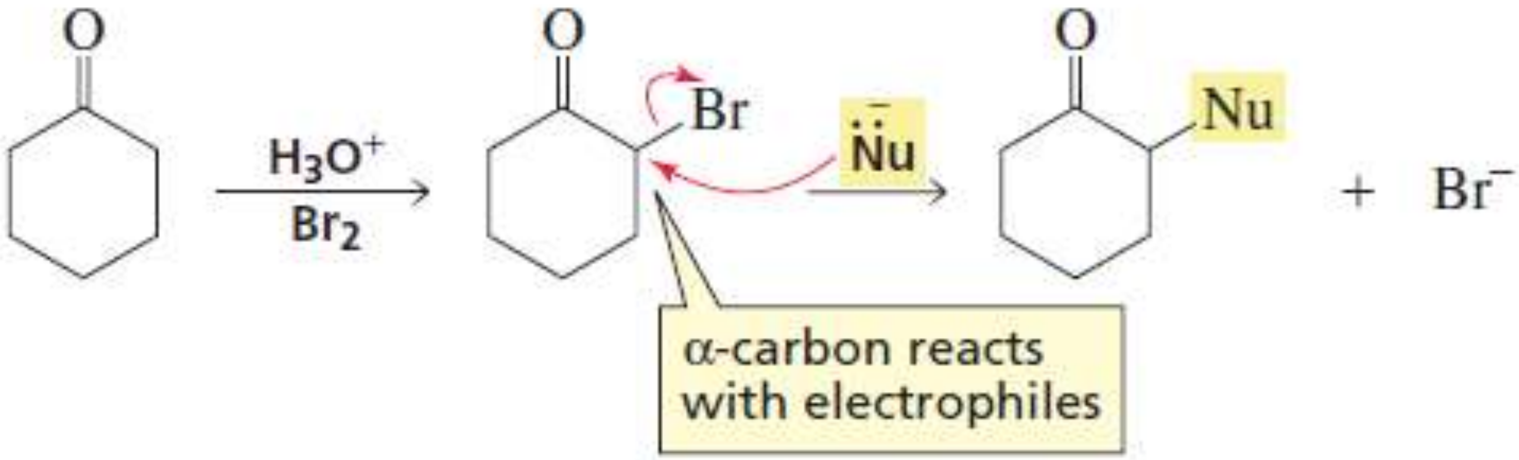
α-Halogenated Carbonyl Compounds in Synthesis

- You have seen that when a base removes a proton from an α-carbon of an aldehyde or a ketone in the previous section, the α-carbon becomes *nucleophilic—it reacts with* electrophiles.

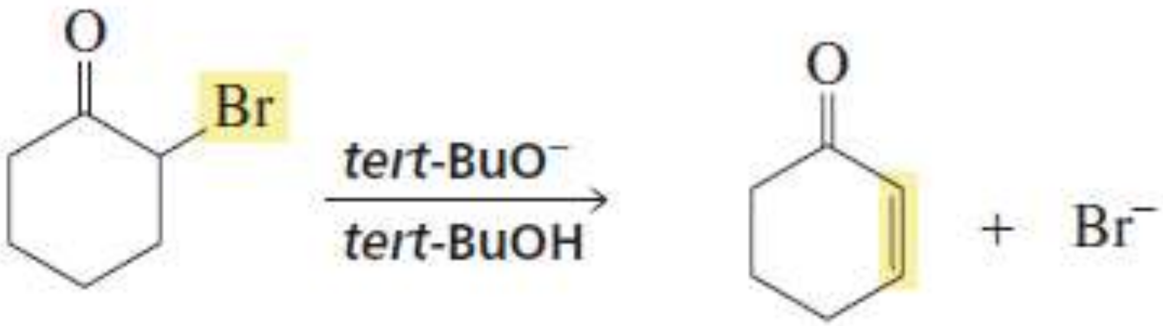


α-Halogenated Carbonyl Compounds in Synthesis

- However, when the α-position is halogenated, the α-carbon becomes *electrophilic—it* reacts with nucleophiles. Therefore, both electrophiles and nucleophiles can be placed on α-carbons.



α-Halogenated Carbonyl Compounds in Synthesis

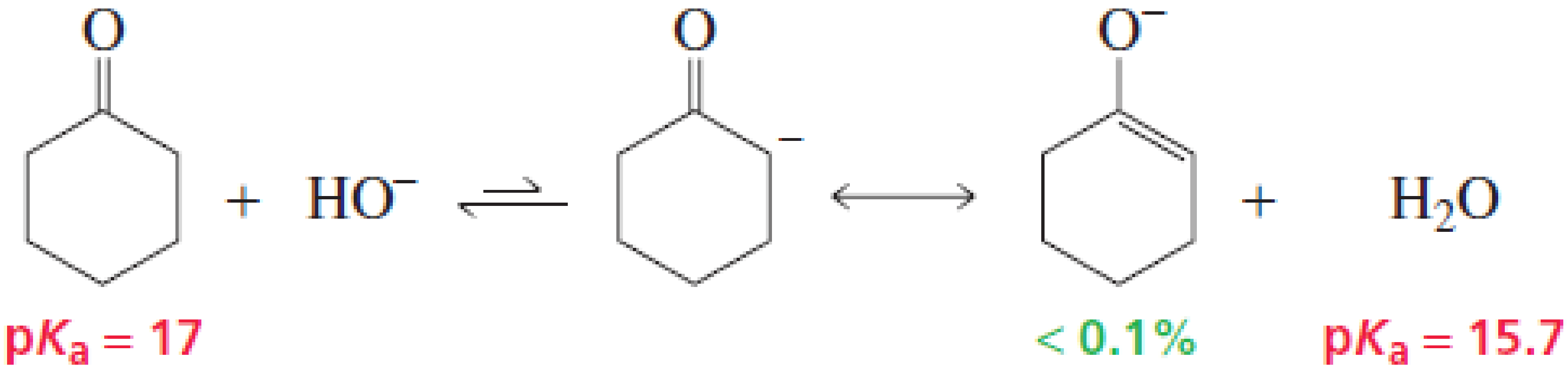


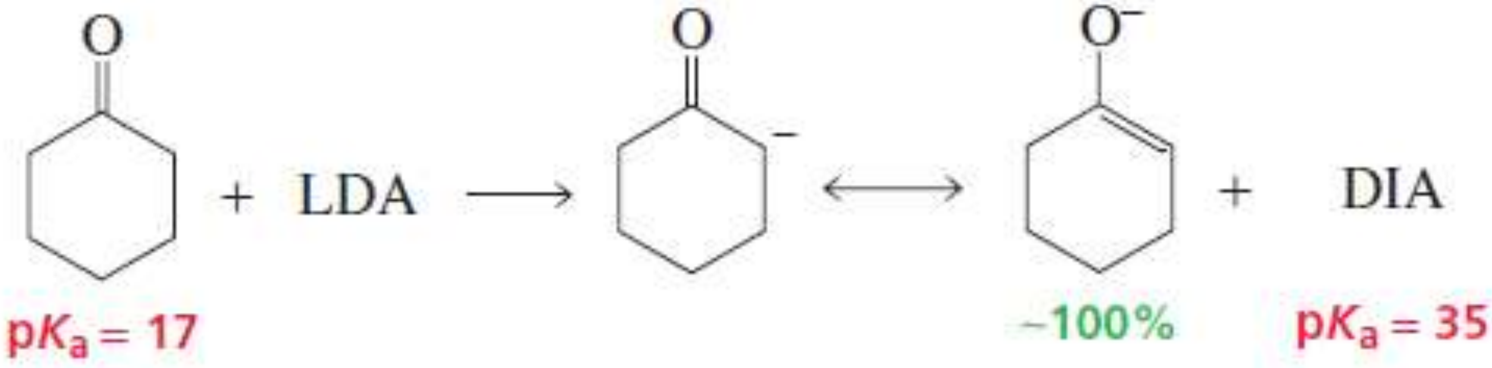
an α,β-unsaturated carbonyl compound

Using LDA to Form an Enolate

Using a nitrogen base to form an enolate can be a problem because a nitrogen base can also react as a nucleophile and attack the carbonyl carbon. However, the two bulky alkyl substituents bonded to the nitrogen of LDA make it difficult for the nitrogen to get close enough to the carbonyl carbon to react with it. Consequently, LDA is a strong base but a poor nucleophile, so it removes an α-hydrogen much faster than it attacks a carbonyl carbon. LDA is easily prepared by adding butyllithium to diisopropylamine (DIA) in THF at -78 C.

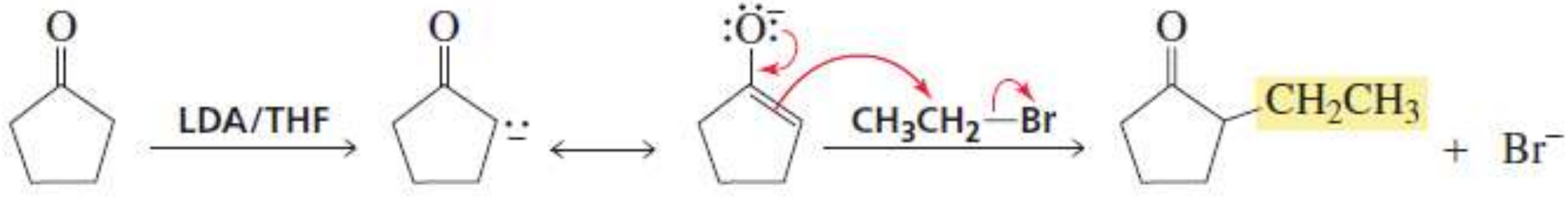
$$CH_3\overset{CH_3}{\overset{|}{C}}HNH\overset{CH_3}{\overset{|}{C}}HCH_3 + CH_3CH_2CH_2\bar{C}H_2\overset{+}{Li} \xrightarrow[-78\ ^\circ C]{THF} CH_3\overset{CH_3}{\overset{|}{C}}H\underset{Li^+}{\overset{-}{N}}\overset{CH_3}{\overset{|}{C}}HCH_3 + CH_3CH_2CH_2CH_3$$

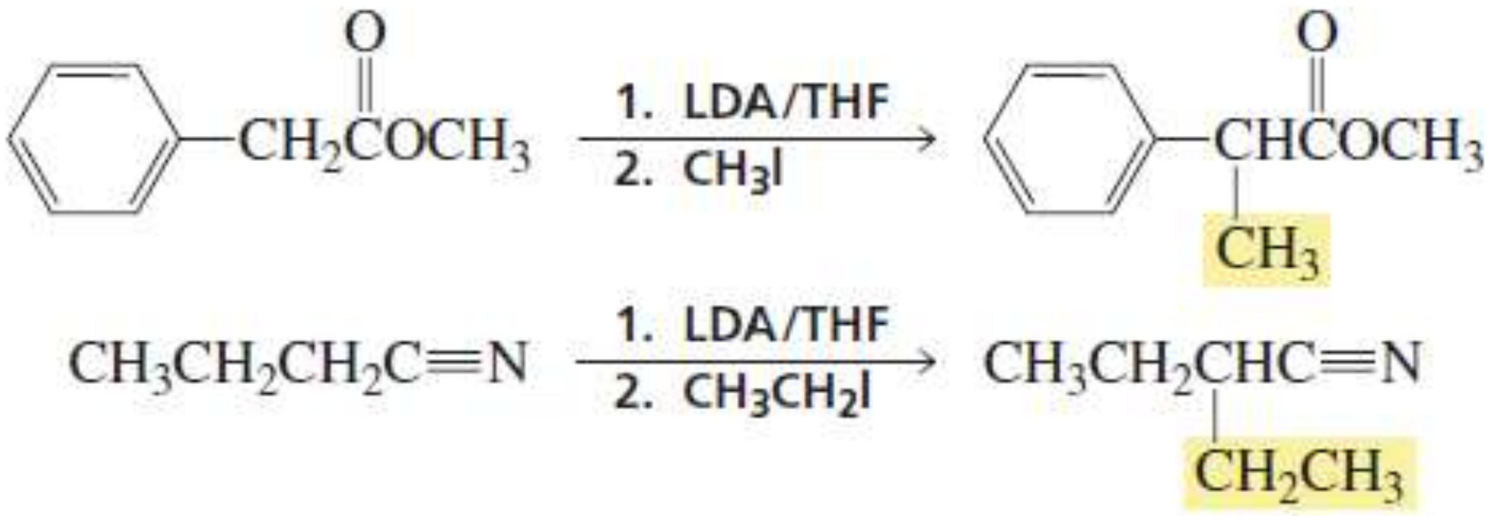

O
O
O⁻
+ HO⁻
+ H₂O
pKa = 17
< 0.1%
pKa = 15.7


O
O
O⁻
+ LDA
+ DIA
pKa = 17
~100%
pKa = 35

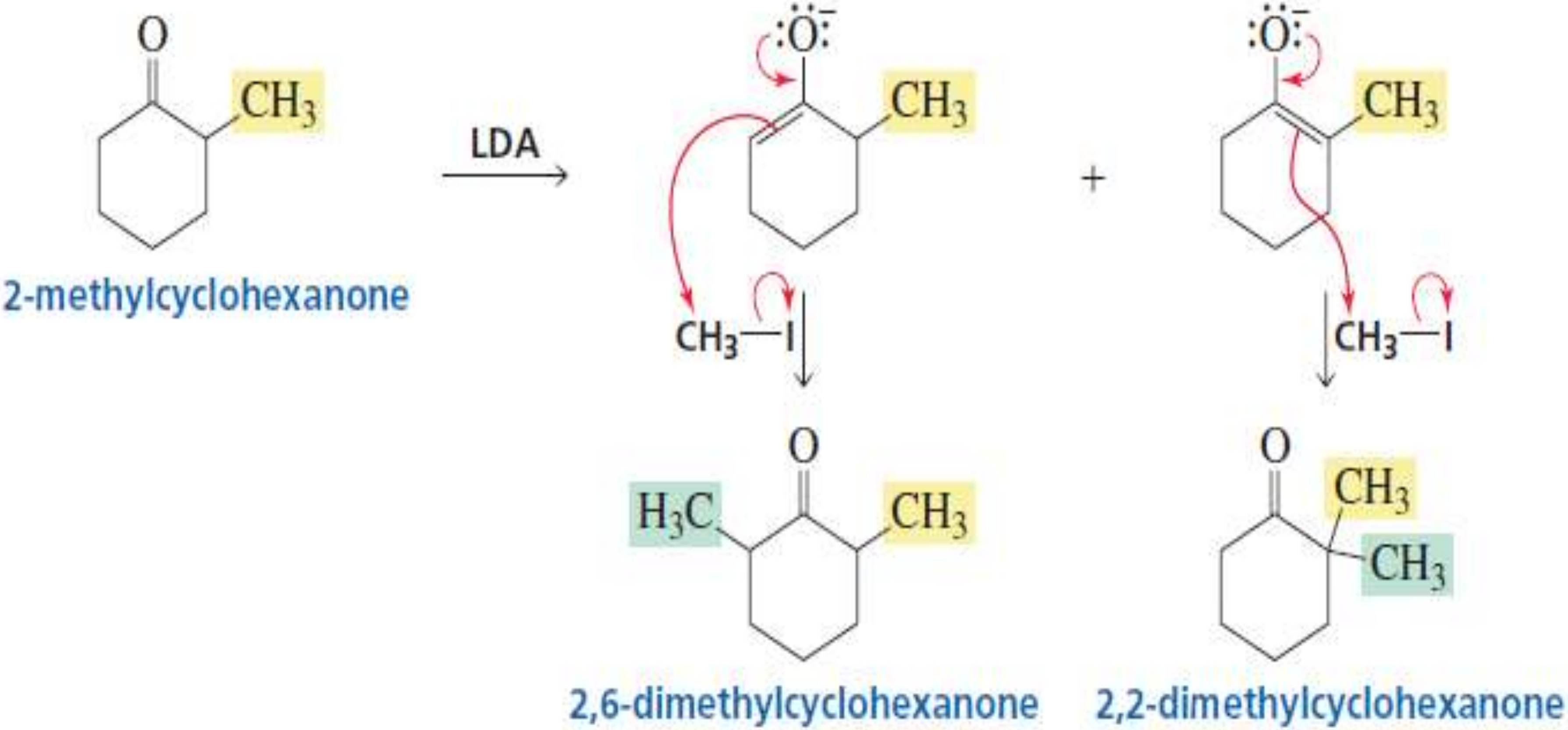
Alkylation of the α-Carbon of Carbonyl Compounds

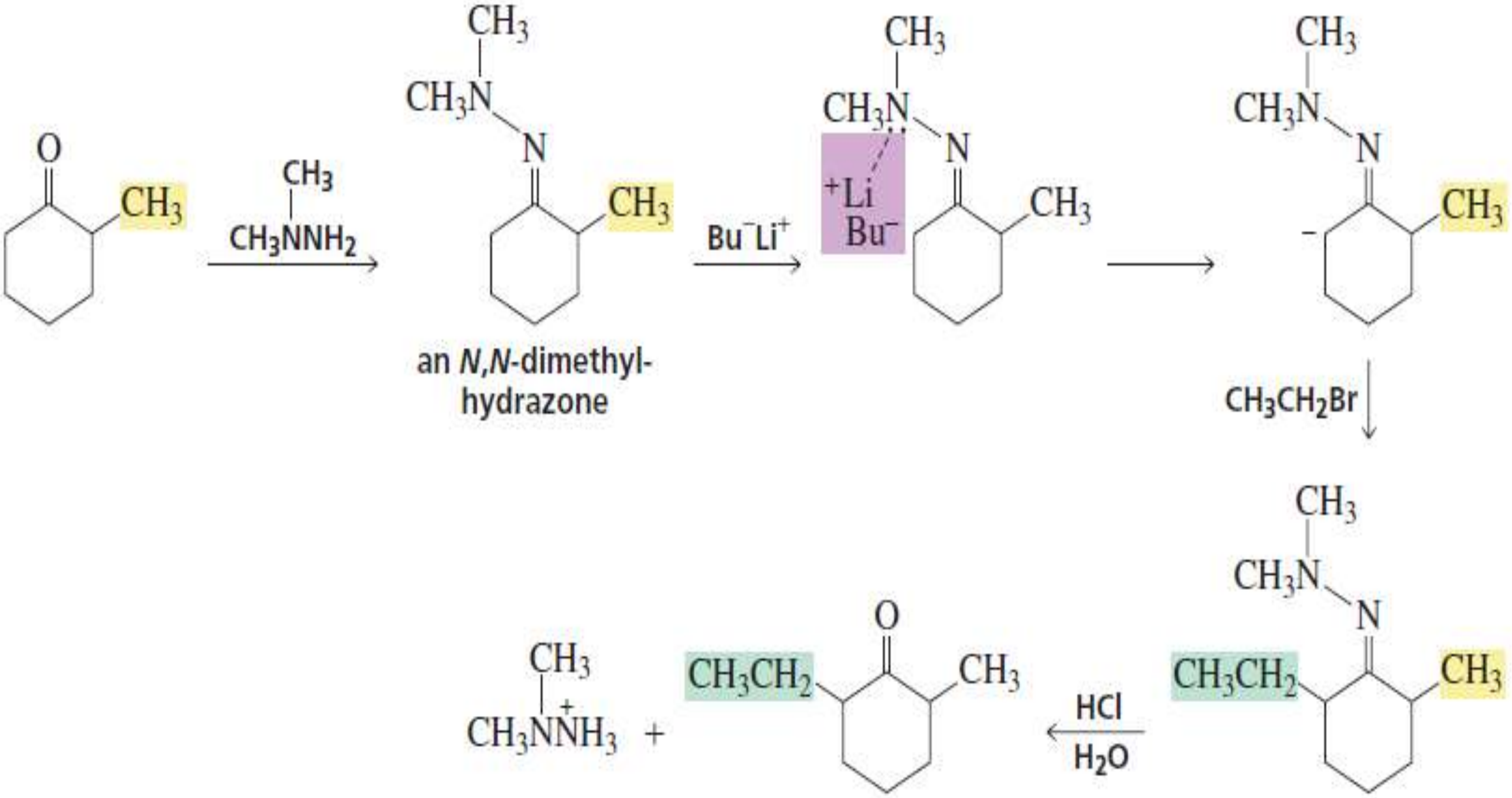
Alkylation of the α-carbon of a carbonyl compound is an important reaction because it gives us another way to form a carbon–carbon bond. Alkylation is carried out by first removing a proton from the α-carbon with a strong base such as LDA and then adding the appropriate alkyl halide. Because the alkylation is an SN2 reaction, it works best with methyl halides and primary alkyl halides

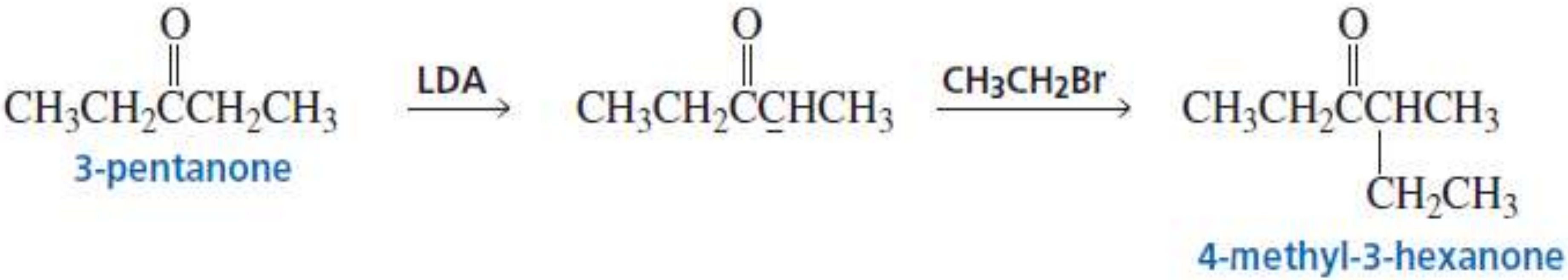




O
CH2COCH3
1. LDA/THF
2. CH3I
O
CHCOCH3
CH3
CH3CH2CH2C≡N
1. LDA/THF
2. CH3CH2I
CH3CH2CHC≡N
CH2CH3


2-methylcyclohexanone
LDA
CH3—I
CH3—I
2,6-dimethylcyclohexanone
2,2-dimethylcyclohexanone

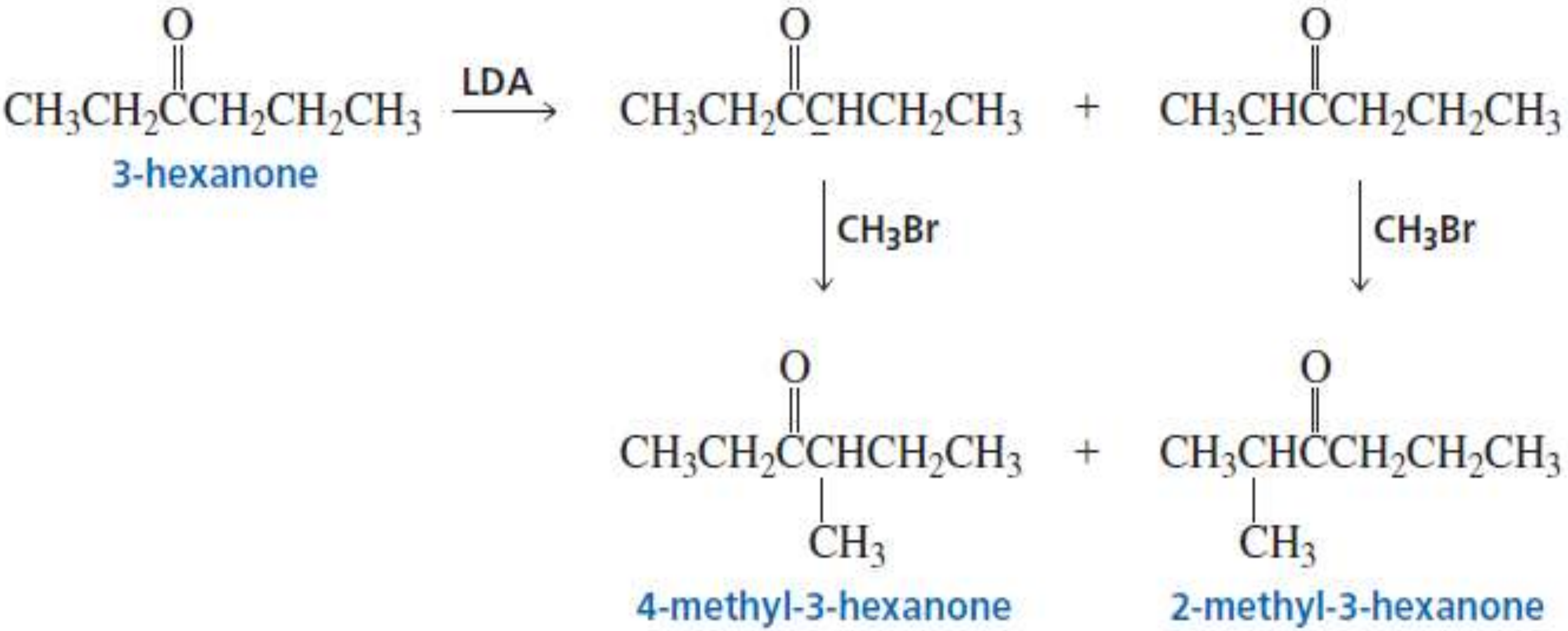

CH3
CH3NNH2
an N,N-dimethyl-hydrazone
Bu⁻Li⁺
⁺Li
Bu⁻
CH3CH2Br
HCl
H2O
CH3
CH3NNH3 +



$$CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2CH_3 \xrightarrow{LDA} CH_3CH_2\overset{O}{\overset{\|}{C}}\underline{C}HCH_3 \xrightarrow{CH_3CH_2Br} CH_3CH_2\overset{O}{\overset{\|}{C}}\underset{CH_2CH_3}{\underset{|}{C}H}CH_3$$

3-pentanone

4-methyl-3-hexanone



$$CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2CH_2CH_3 \xrightarrow{LDA} CH_3CH_2\overset{O}{\overset{\|}{C}}\underline{C}HCH_2CH_3 + CH_3\underline{C}H\overset{O}{\overset{\|}{C}}CH_2CH_2CH_3$$

$$\downarrow CH_3Br \qquad \downarrow CH_3Br$$

$$CH_3CH_2\overset{O}{\overset{\|}{C}}\underset{CH_3}{\underset{|}{C}H}CH_2CH_3 + CH_3\underset{CH_3}{\underset{|}{C}H}\overset{O}{\overset{\|}{C}}CH_2CH_2CH_3$$

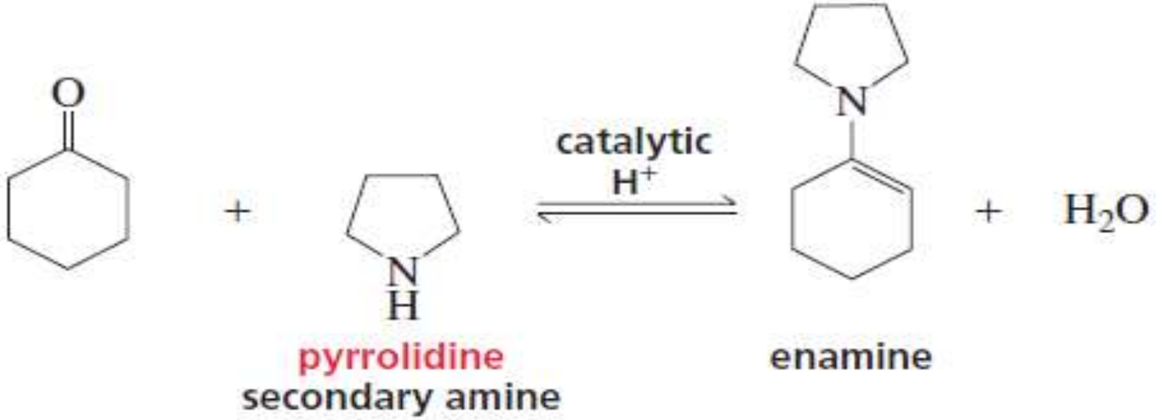
3-hexanone

4-methyl-3-hexanone

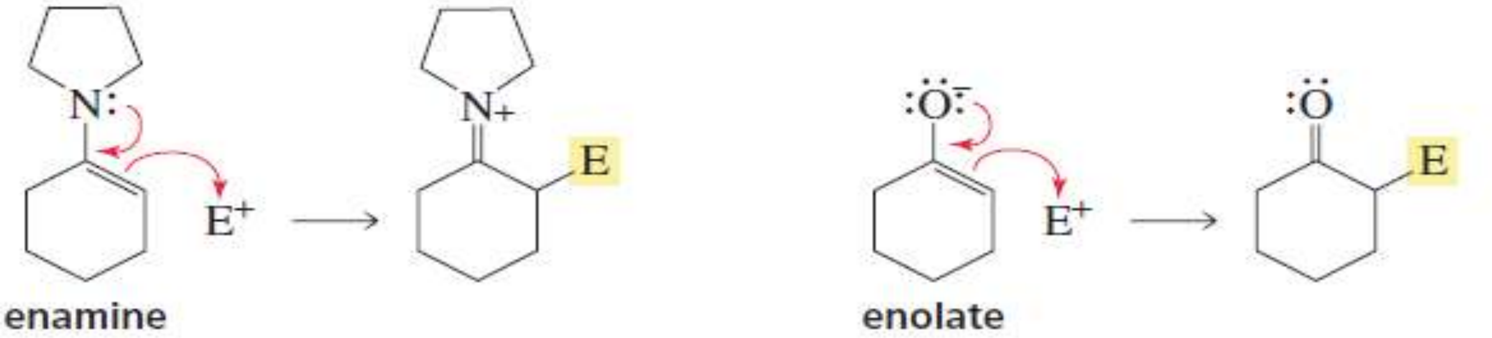
2-methyl-3-hexanone

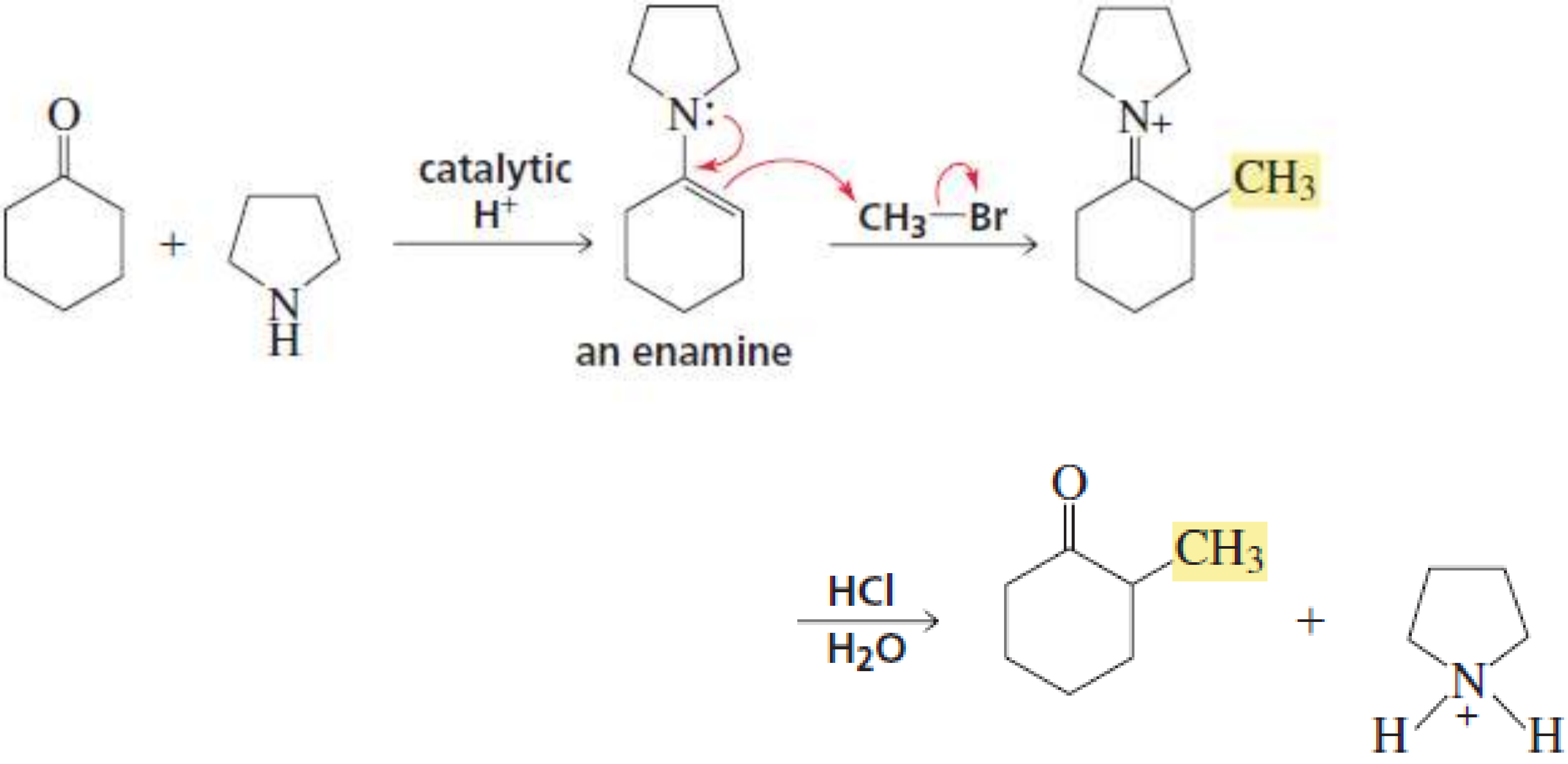
Alkylation and Acylation of the α-Carbon via an Enamine Intermediate

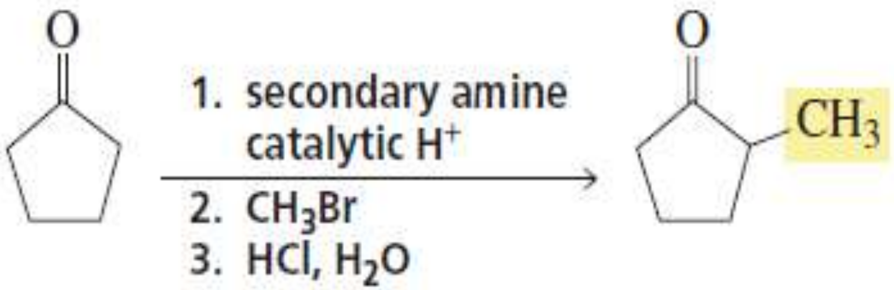
We have seen that an enamine is formed when an aldehyde or a ketone reacts with a secondary amine (Section 18.6).



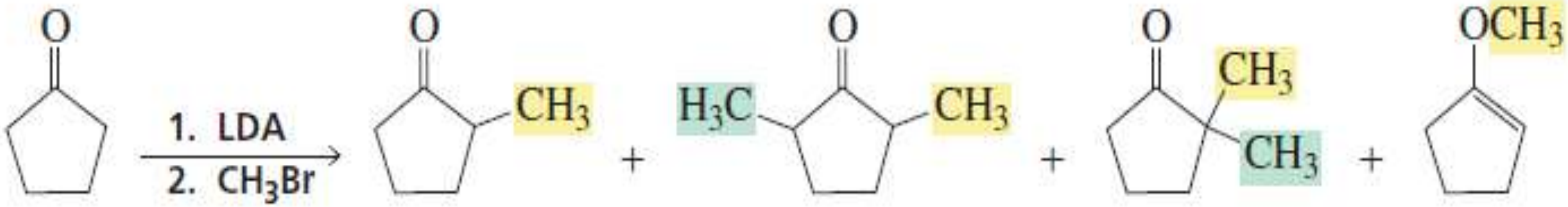
Enamines react with electrophiles in the same way that enolates do.



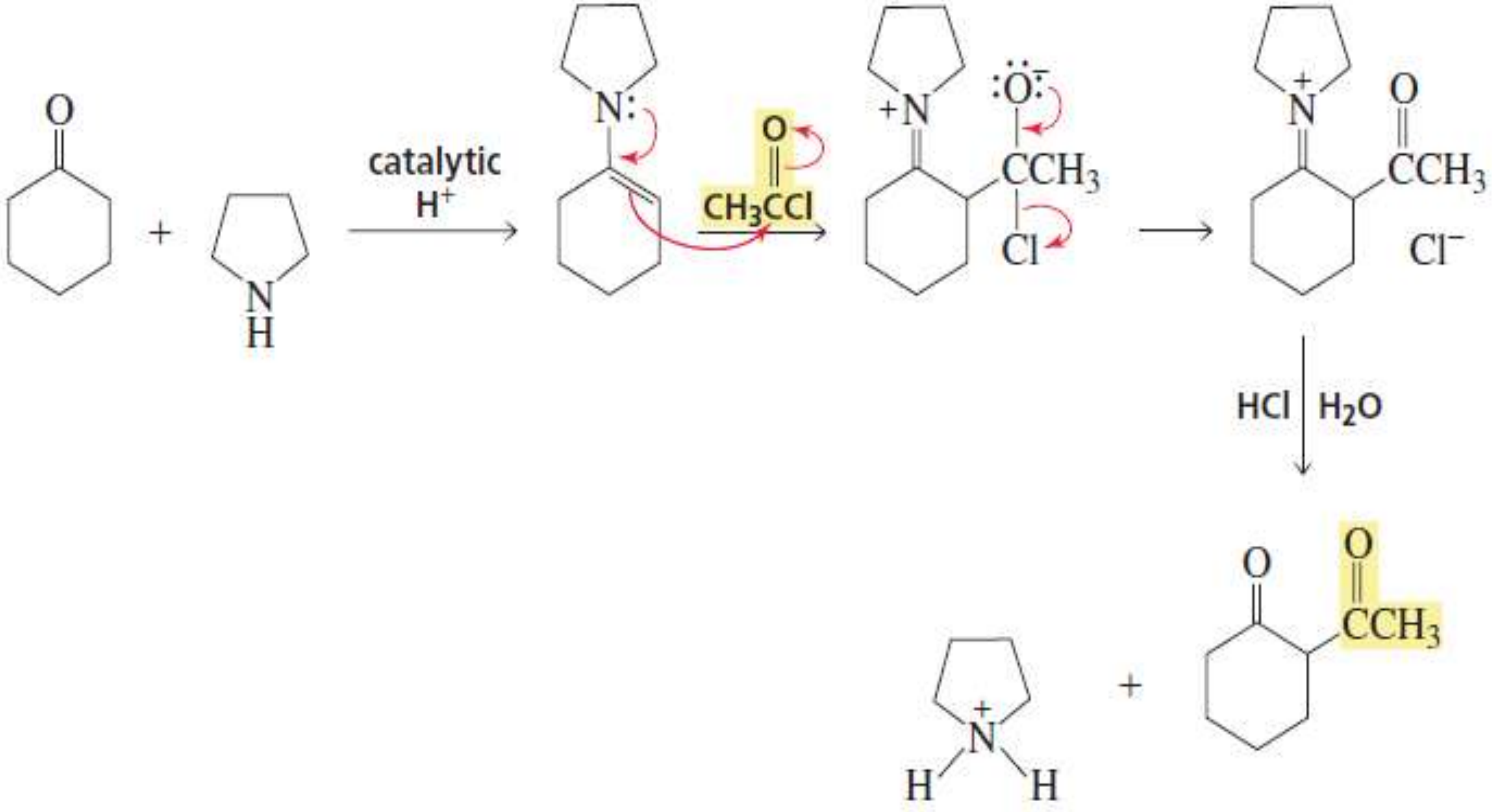

O
+
N
H
catalytic
H+
N:
an enamine
CH3—Br
N+
CH3
HCl
H2O
O
CH3
+
N
+
H
H



In contrast, when a carbonyl compound is alkylated directly, dialkylated and O-alkylated products can also be formed.



In addition to being able to be alkylated, aldehydes and ketones can also be acylated via an enamine intermediate.



The Aldol Addition

we saw that aldehydes and ketones are electrophiles and therefore react with nucleophiles. In the preceding sections of this chapter, we have seen that when a proton is removed from the α-carbon of an aldehyde or a ketone, the resulting anion is a nucleophile and therefore reacts with electrophiles. An **aldol addition is a reaction in** which *both of these activities are observed: One molecule of a carbonyl compound*—after a proton is removed from an α-carbon—reacts as a *nucleophile and attacks the electrophilic carbonyl carbon of a second molecule of the carbonyl compound.*

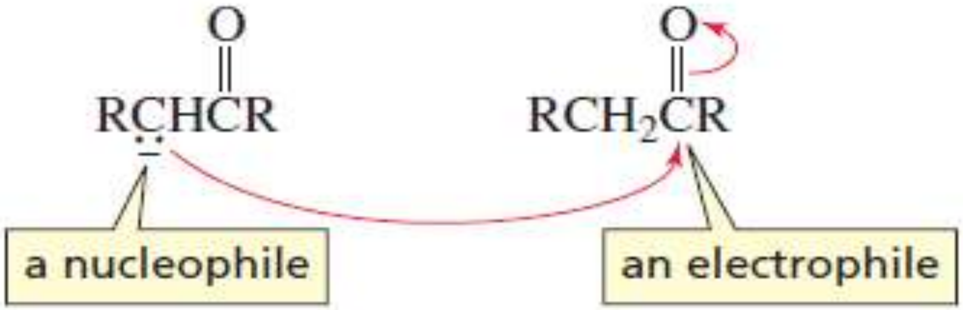


Table 18.1 Summary of Functional Group Nomenclature

Class	Suffix Name	Prefix Name
Carboxylic acid	-oic acid	Carboxy
Ester	-oate	Alkoxycarbonyl
Amide	-amide	Amido
Nitrile	-nitrile	Cyano
Aldehyde	-al	Oxo $(=O)$
Aldehyde	-al	Formyl $(-CH=O)$
Ketone	-one	Oxo $(=O)$
Alcohol	-ol	Hydroxy
Amine	-amine	Amino
Alkene	-ene	Alkenyl
Alkyne	-yne	Alkynyl
Alkane	-ane	Alkyl
Ether	—	Alkoxy
Alkyl halide	—	Halo

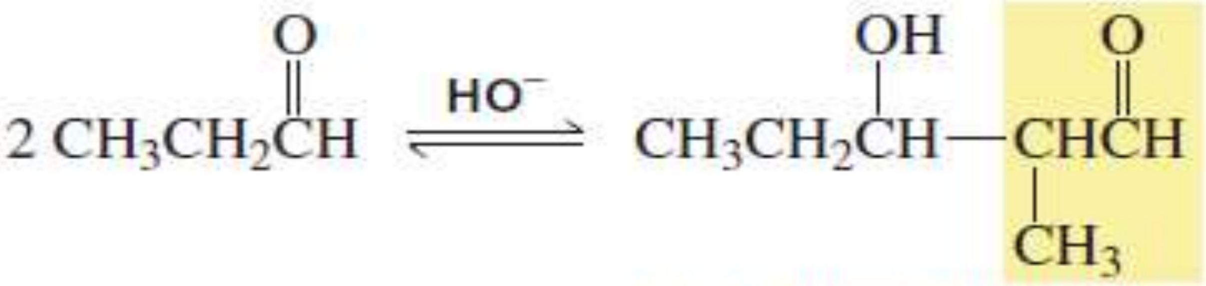
↑ increasing priority

The Aldol Addition

- An aldol addition is a reaction between two molecules of an *aldehyde or two molecules* of a *ketone. When the reactant is an aldehyde, the addition product is a* β-hydroxyaldehyde, which is why the reaction is called an aldol addition (“ald” for aldehyde, “ol” for alcohol). When the reactant is a ketone, the addition product is a β-hydroxyaldehyde. Because the addition reaction is reversible, good yields of the addition product are obtained only if it is removed from the solution as it is formed.

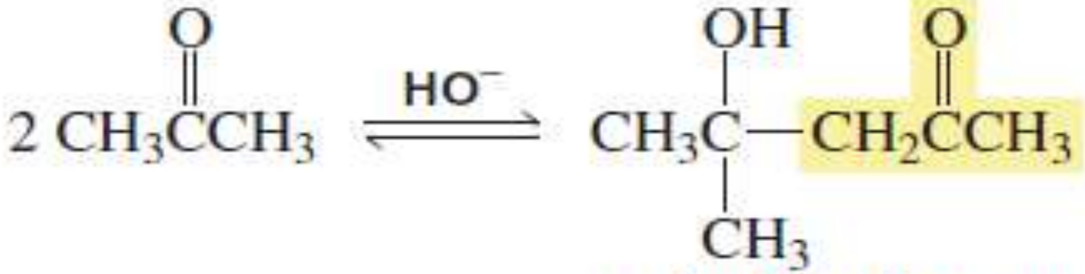
The Aldol Addition

aldol additions



$$2\,CH_3CH_2\overset{O}{\overset{\|}{C}}H \overset{HO^-}{\rightleftharpoons} CH_3CH_2\overset{OH}{\overset{|}{C}}H-\underset{\underset{CH_3}{|}}{C}H\overset{O}{\overset{\|}{C}}H$$

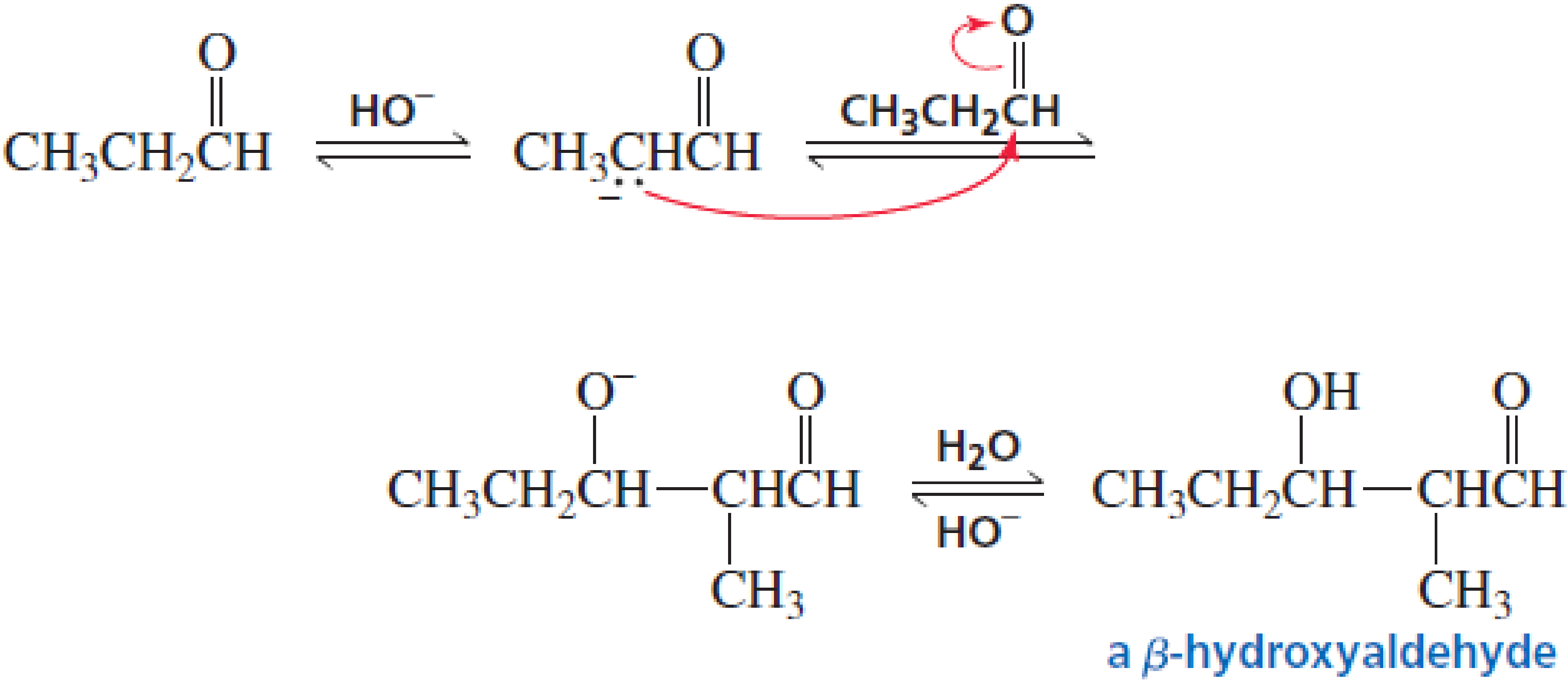
a β-hydroxyaldehyde

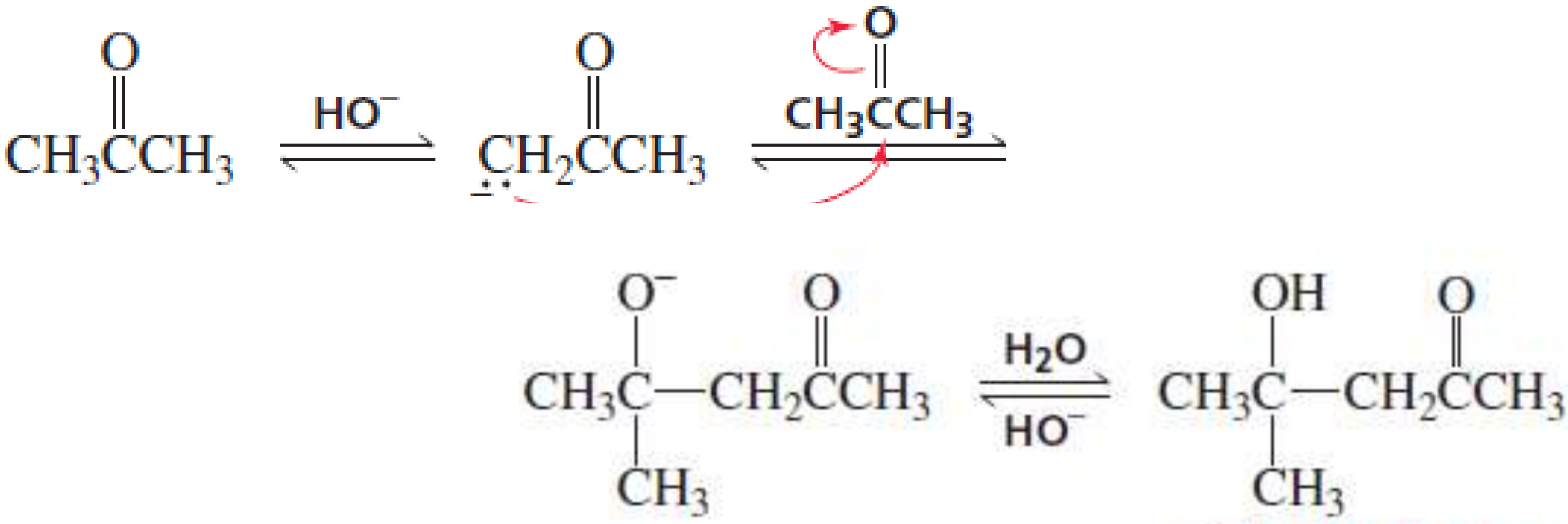


$$2\,CH_3\overset{O}{\overset{\|}{C}}CH_3 \overset{HO^-}{\rightleftharpoons} CH_3\underset{\underset{CH_3}{|}}{\overset{OH}{\overset{|}{C}}}-CH_2\overset{O}{\overset{\|}{C}}CH_3$$

a β-hydroxyketone

Mechanism for the aldol addition



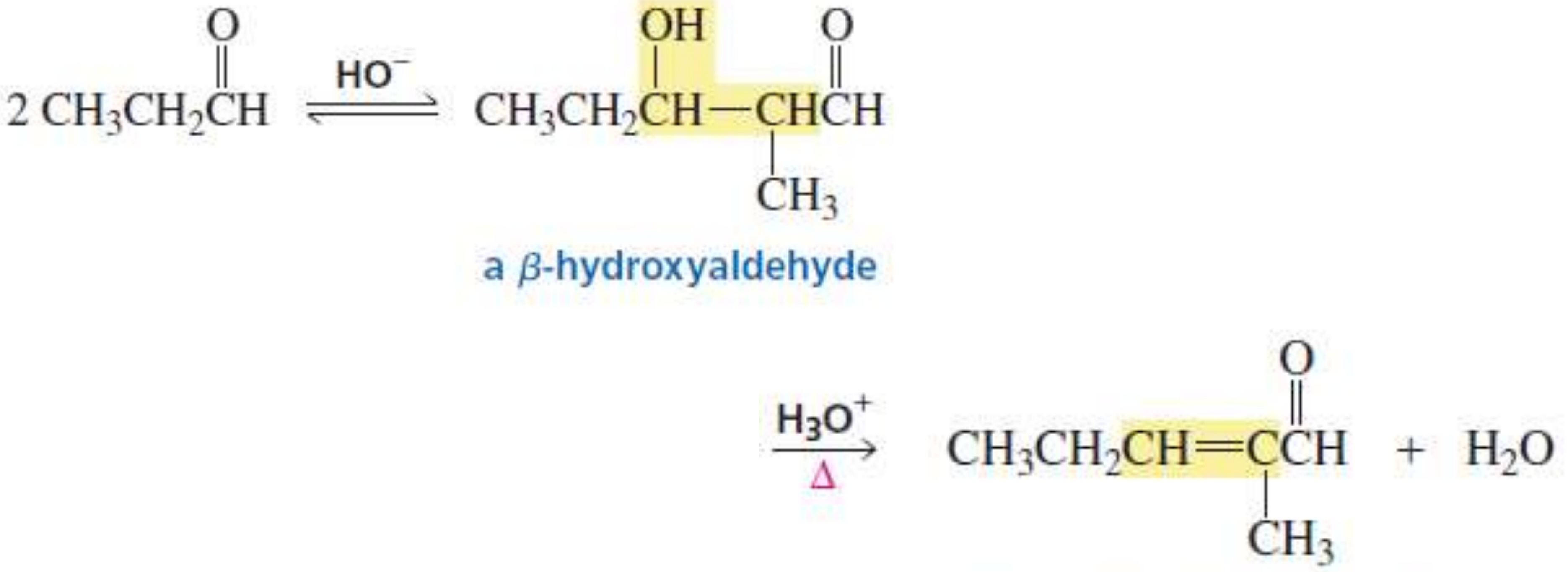


$$CH_3\overset{\overset{O}{\|}}{C}CH_3 \xrightleftharpoons{HO^-} {}^{-}\ddot{C}H_2\overset{\overset{O}{\|}}{C}CH_3 \xrightleftharpoons{CH_3\overset{\overset{O}{\|}}{C}CH_3}$$

$$CH_3\overset{\overset{O^-}{|}}{\underset{\underset{CH_3}{|}}{C}}-CH_2\overset{\overset{O}{\|}}{C}CH_3 \xrightleftharpoons[HO^-]{H_2O} CH_3\overset{\overset{OH}{|}}{\underset{\underset{CH_3}{|}}{C}}-CH_2\overset{\overset{O}{\|}}{C}CH_3$$

a β-hydroxyketone

Dehydration of Aldol Addition Products: Formation of α,β–Unsaturated Aldehydes and Ketones



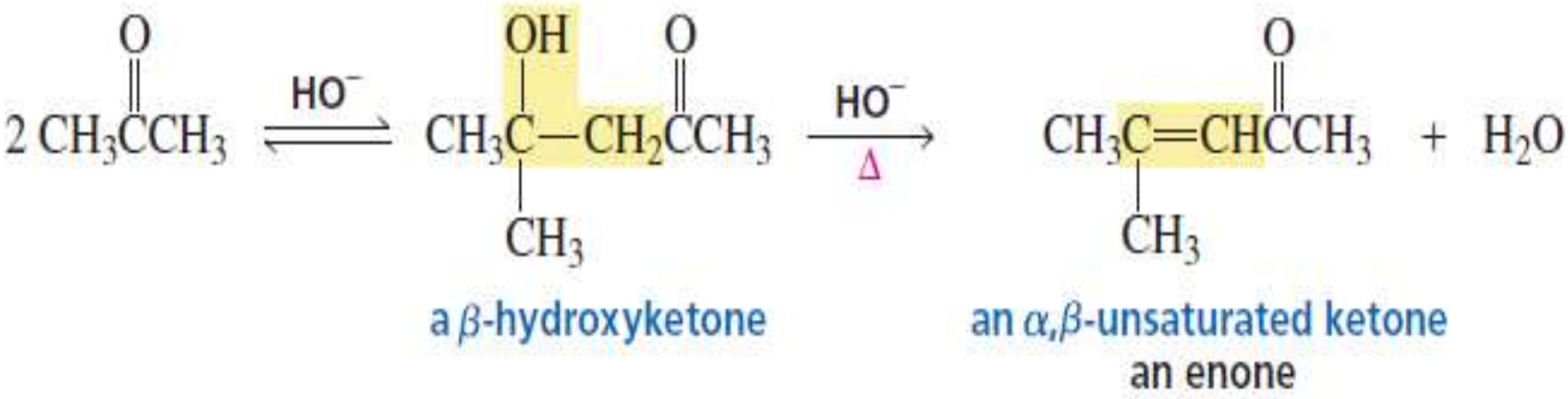
$$2\ CH_3CH_2\overset{O}{\overset{\|}{C}}H \xrightleftharpoons{HO^-} CH_3CH_2\overset{OH}{\overset{|}{C}}H-\underset{CH_3}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}H$$

a β-hydroxyaldehyde

$$\xrightarrow[\Delta]{H_3O^+} CH_3CH_2CH=\underset{CH_3}{\underset{|}{C}}\overset{O}{\overset{\|}{C}}H + H_2O$$

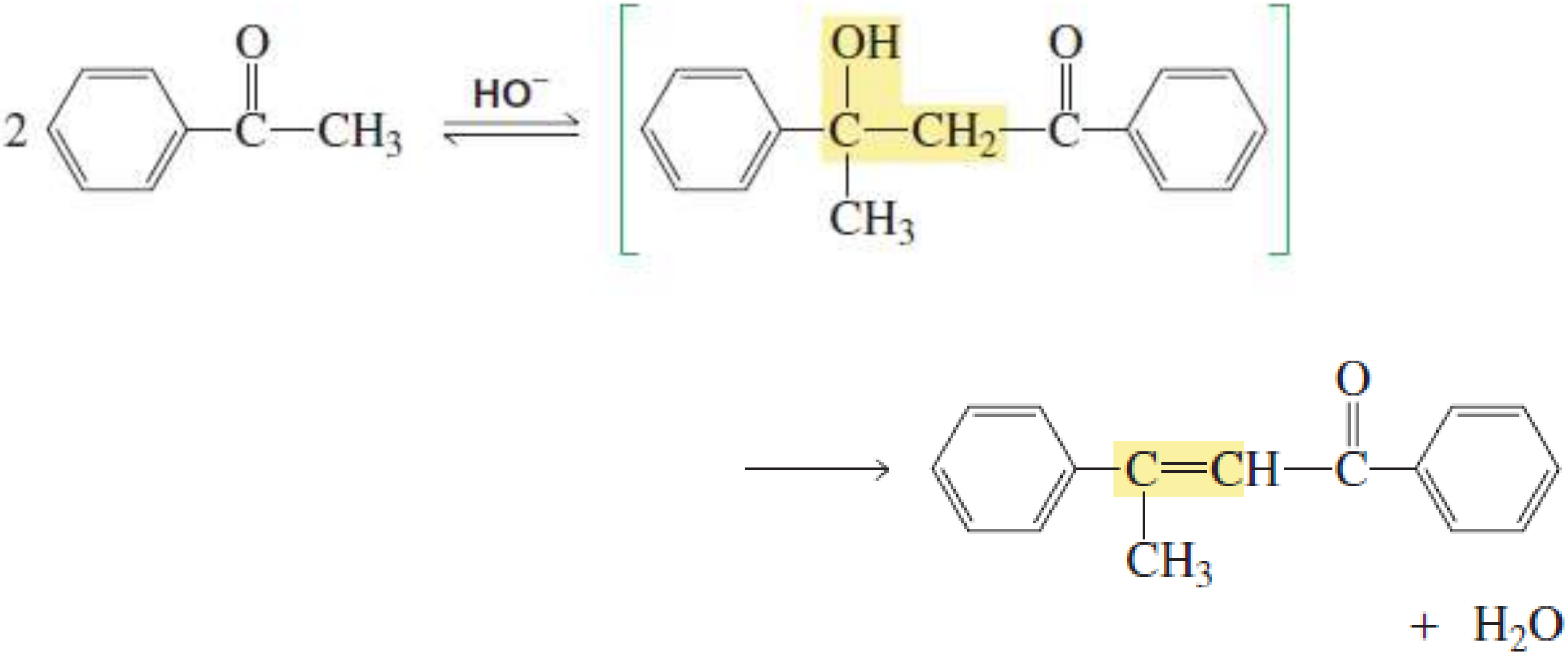
an α,β-unsaturated aldehyde

Dehydration of Aldol Addition Products: Formation of α,β–Unsaturated Aldehydes and Ketones



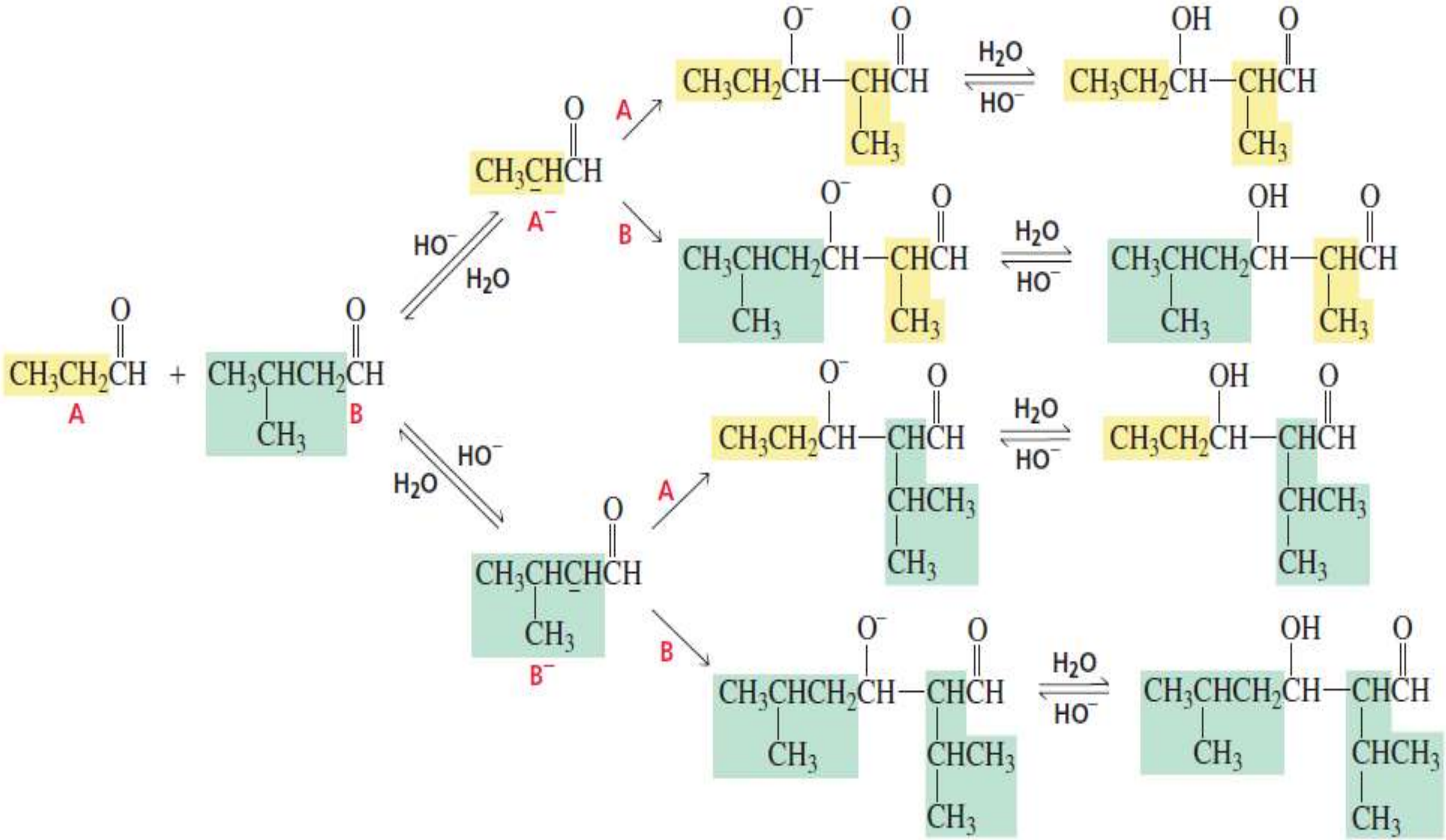
$$2\,CH_3\overset{\overset{O}{\|}}{C}CH_3 \xrightleftharpoons{HO^-} CH_3\underset{\underset{CH_3}{|}}{\overset{\overset{OH}{|}}{C}}-CH_2\overset{\overset{O}{\|}}{C}CH_3 \xrightarrow[\Delta]{HO^-} CH_3\underset{\underset{CH_3}{|}}{C}=CH\overset{\overset{O}{\|}}{C}CH_3 + H_2O$$

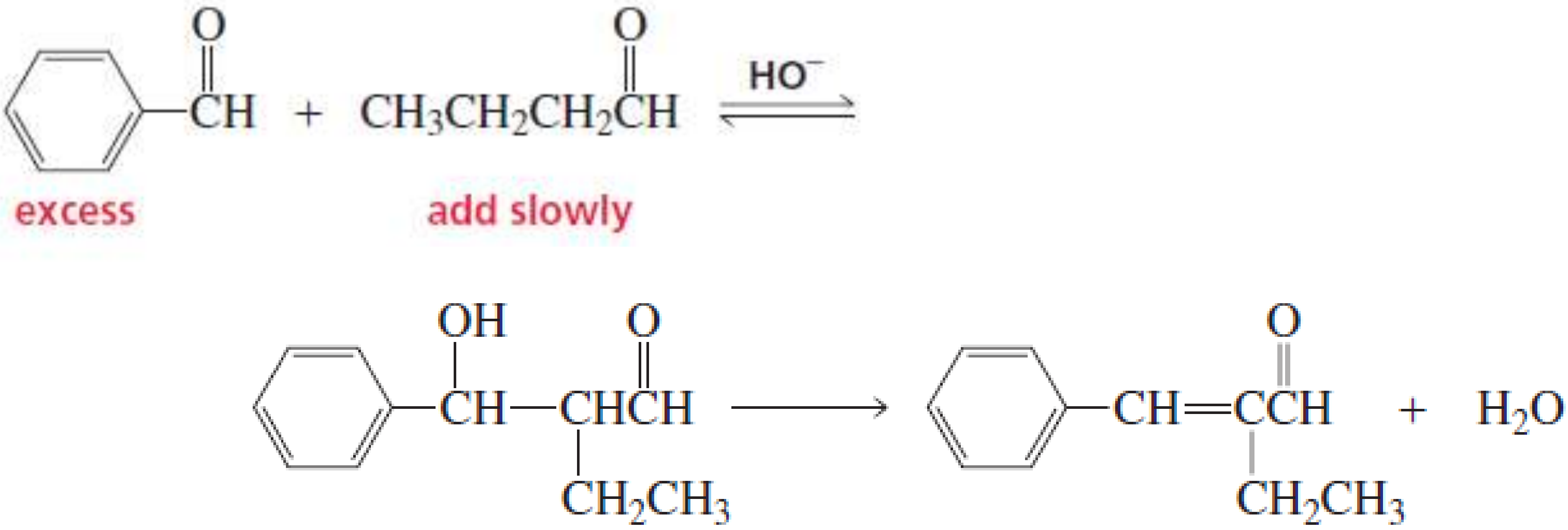
Dehydration of Aldol Addition Products: Formation of α,β–Unsaturated Aldehydes and Ketones



The Mixed Aldol Addition

- If two different carbonyl compounds are used in an aldol addition, four products canbe formed because each enolate can react both with another molecule of the carbonyl compound from which the enolate was formed and with the other carbonyl compound. In the following example, both carbonyl compound A and carbonyl compound B can lose a proton from an α-carbon to form enolates A- and B-; A- can react with either A or B, and can react with either A or B: The preceding reaction is called a **mixed aldol addition or a crossed aldol addition**. The four products have similar physical properties, making them difficult to separate. Consequently, a mixed aldol addition that forms four products is not a synthetically useful reaction.

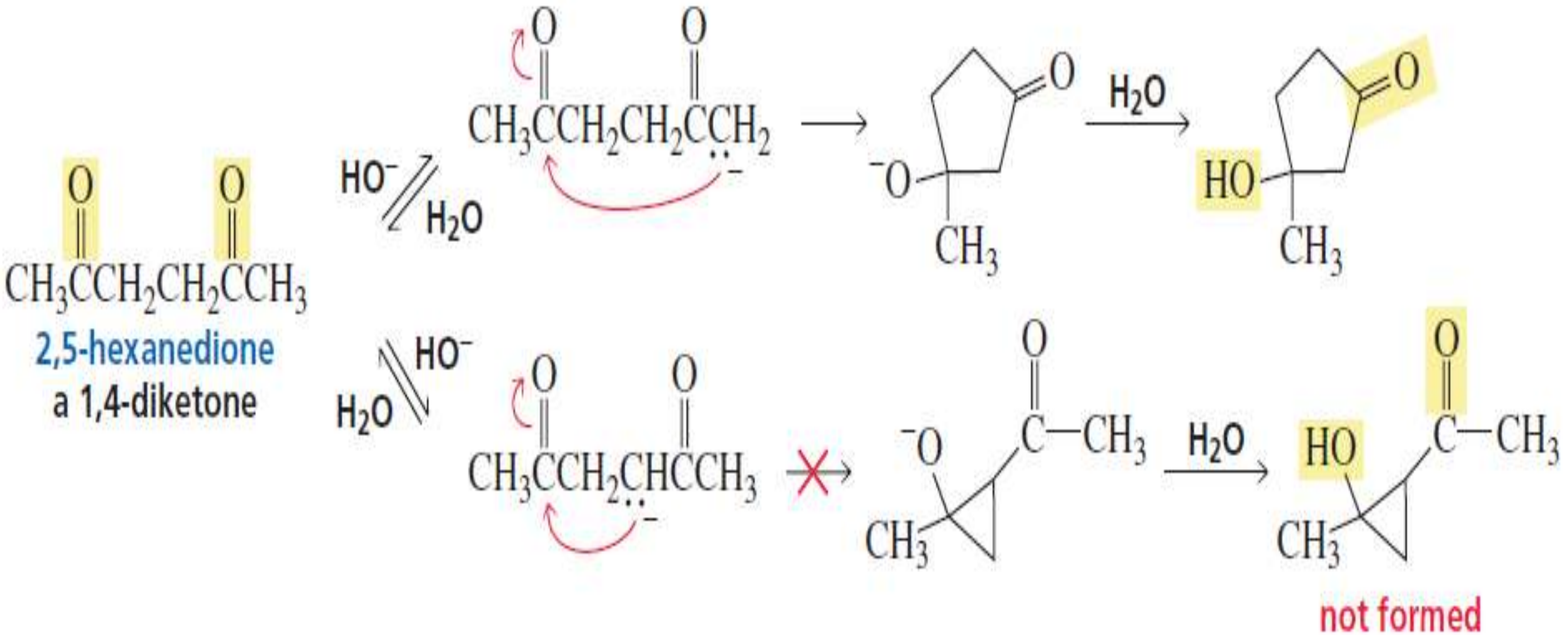

CH3CH2CH(=O)
A
+
CH3CHCH2CH(=O) with CH3 branch
B
HO⁻
H2O
CH3C̲HCH(=O)
A⁻
CH3CHC̲HCH(=O) with CH3 branch
B⁻
A
B
O⁻
O
CH3CH2CH—CHCH with CH3
OH
CH3CHCH2CH—CHCH with CH3 and CH3
CH3CH2CH—CHCH with CHCH3 and CH3
CH3CHCH2CH—CHCH with CH3 and CHCH3, CH3


O
CH
+
O
CH3CH2CH2CH
HO−
excess
add slowly
OH
O
CH—CHCH
CH2CH3
O
CH═CCH
CH2CH3
+
H2O

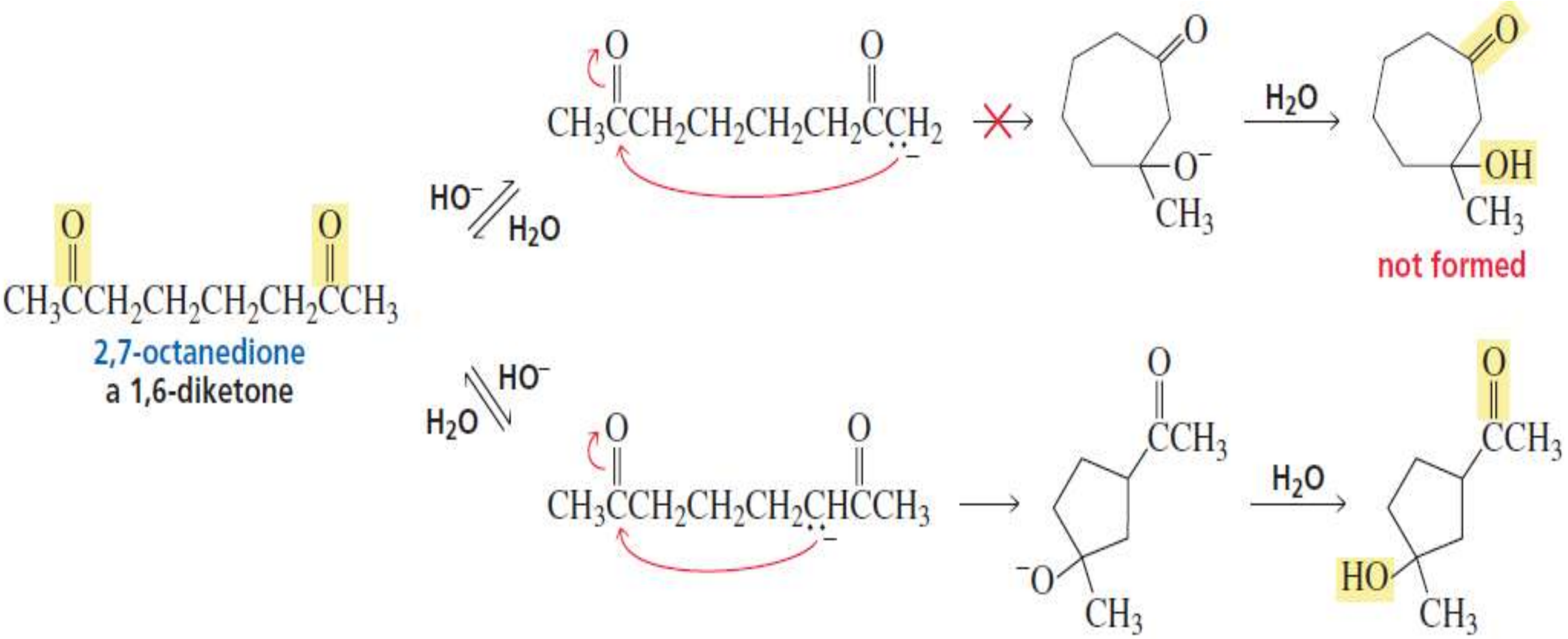
Intramolecular Aldol Additions

- Because a 1,4-diketone has two different sets of two different intramolecular addition products can potentially form—one with a five-membered ring, the other with a three-membered ring. The greater stability of five- and six-membered rings causes them to be formed preferentially (Section 2.11). In fact, the five membered ring product is the only product formed from the intramolecular aldol addition of a 1,4-diketone.

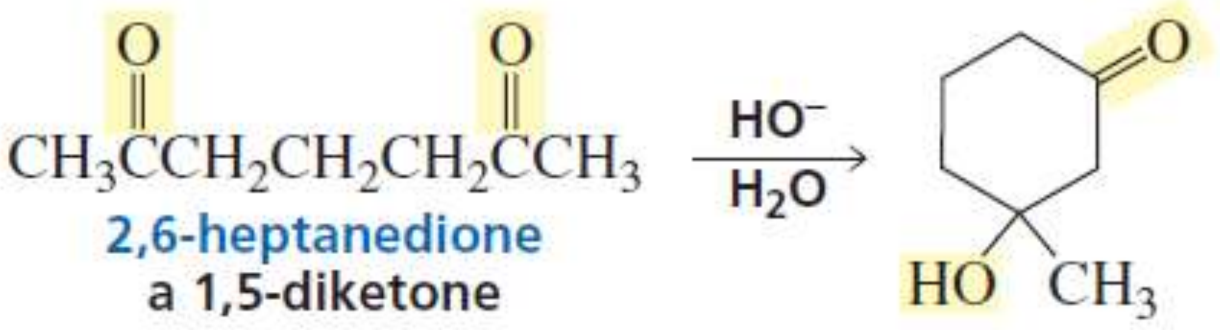
Intramolecular Aldol Additions



Intramolecular Aldol Additions



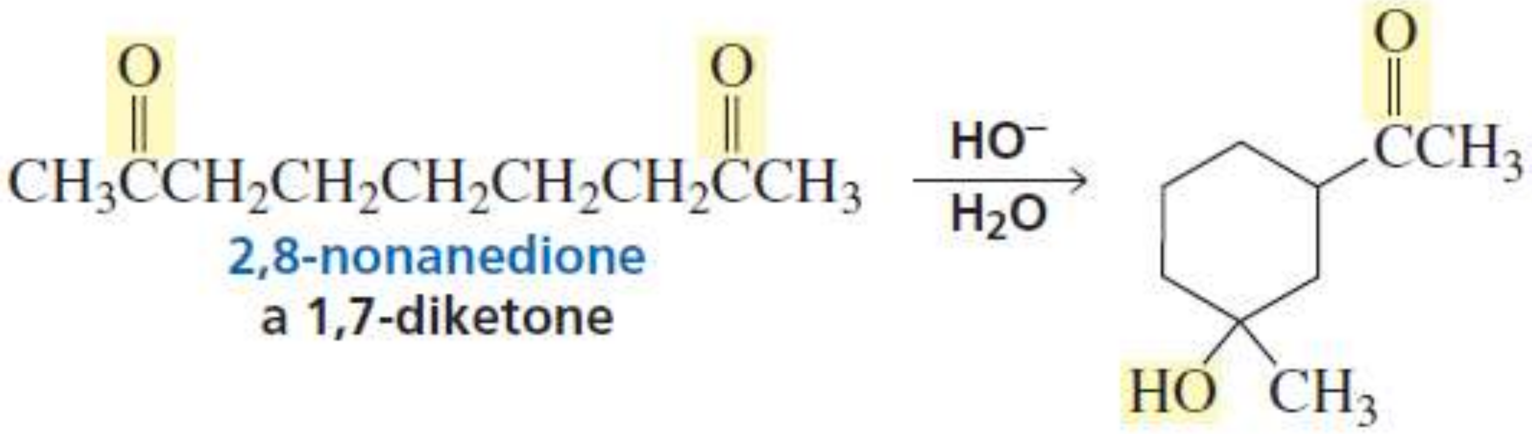
Intramolecular Aldol Additions



$$CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow[H_2O]{HO^-}$$

2,6-heptanedione

a 1,5-diketone



$$CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow[H_2O]{HO^-}$$

2,8-nonanedione

a 1,7-diketone