



# Organic Chemistry II / CHEM 252

## Chapter 16 – Aldehydes and Ketones I. Nucleophilic Addition to the Carbonyl Group

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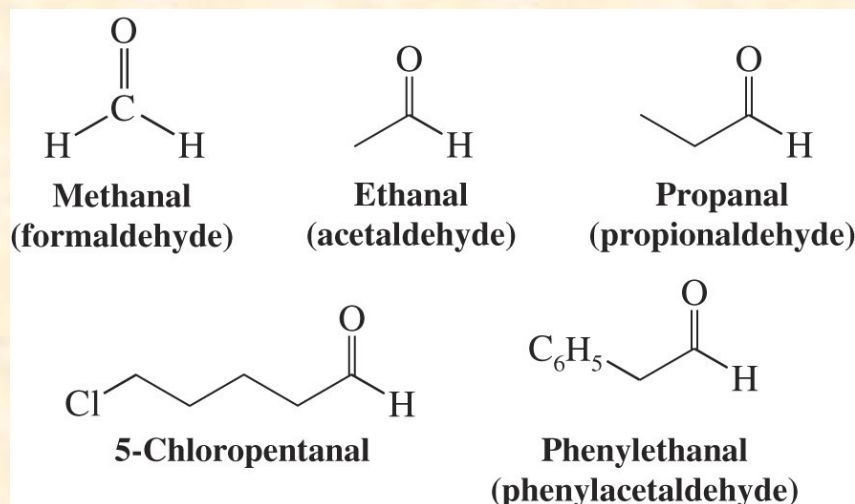
University of Massachusetts Boston

Boston, MA

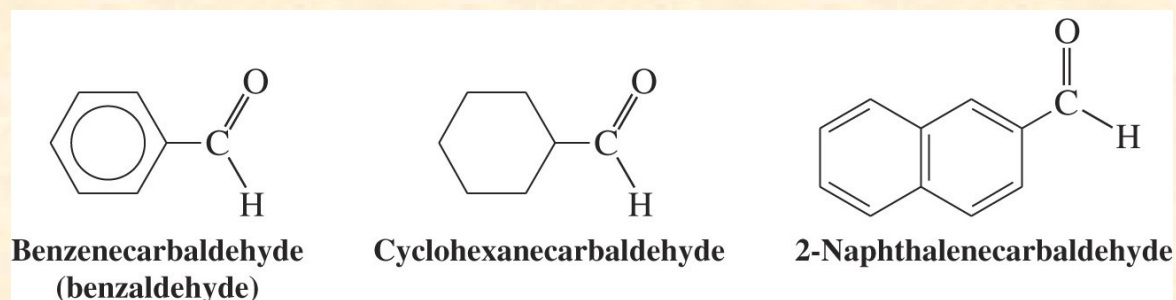
# Nomenclature

Aldehydes: replace the -e of the corresponding parent alkane with -al

- The aldehyde functional group is always carbon 1 and need not be numbered, some of the common names are shown in parenthesis

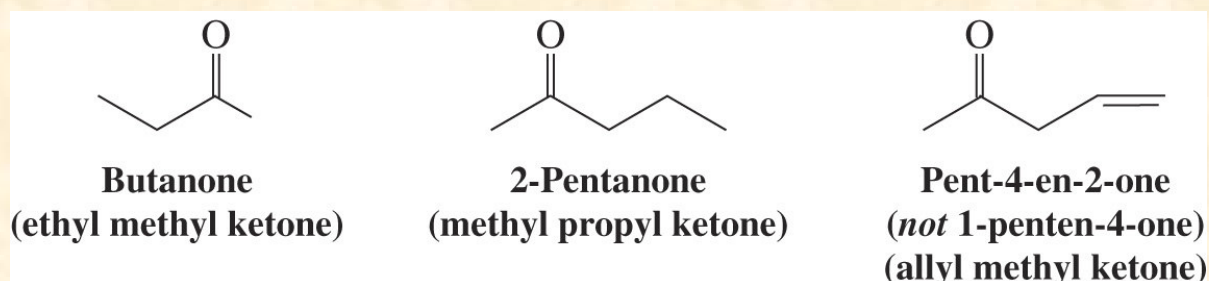


- Aldehydes bonded to a ring are named using the suffix carbaldehyde
  - Benzaldehyde is used more commonly than benzenecarbaldehyde

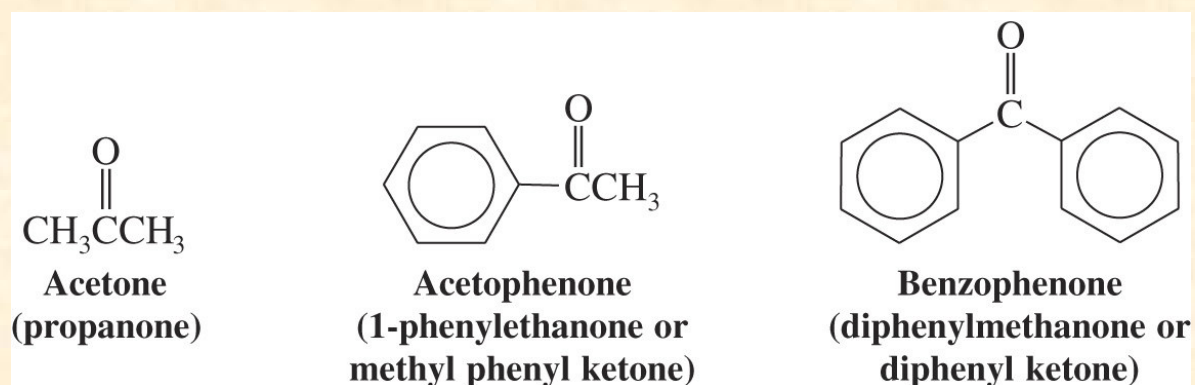


# Nomenclature

- Ketones: replacing the -e of the corresponding parent alkane with -one
  - The parent chain is numbered to give the ketone carbonyl the lowest possible number
  - In common nomenclature simple ketones are named by preceding the word ketone with the names of both groups attached to the ketone carbonyl

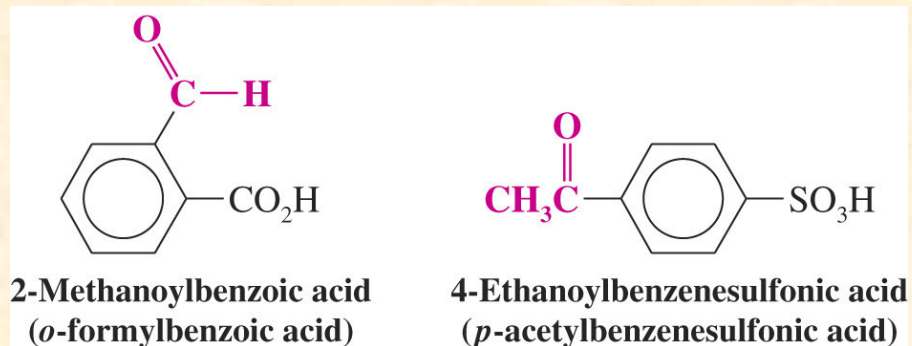


- Common names of ketones that are also IUPAC names are shown below



# Nomenclature

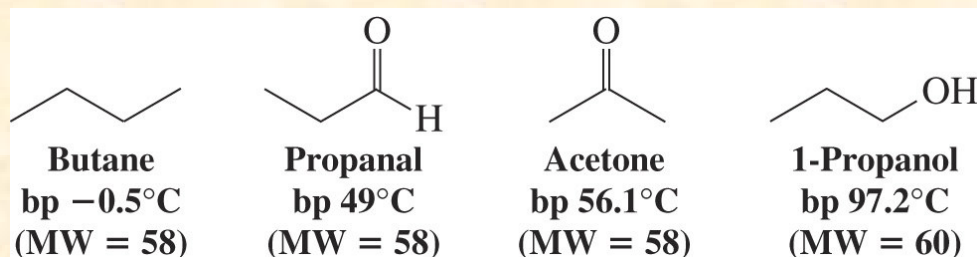
- The methanoyl or formyl group (-CHO) and the ethanoyl or acetyl group (-COCH<sub>3</sub>) are examples of acyl groups



# Physical Properties

Aldehydes (or ketones) cannot hydrogen bond to each other

- They rely only on intermolecular dipole-dipole interactions and have lower boiling points than the corresponding alcohols

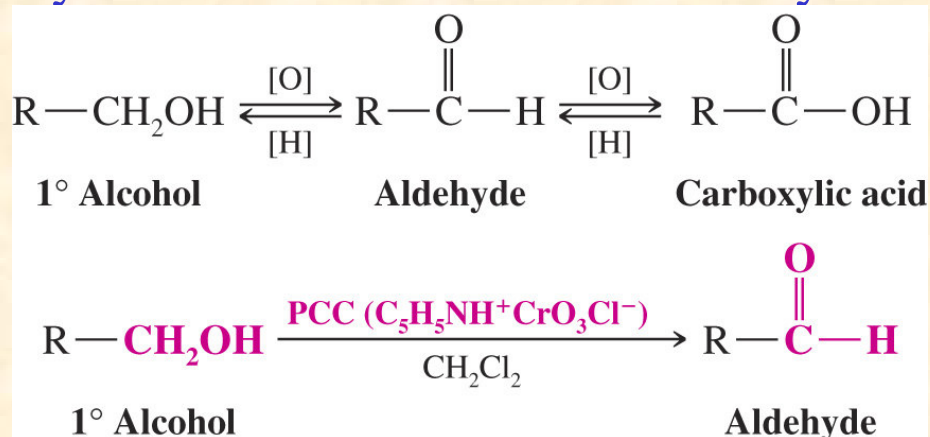


- Aldehydes and ketones can form hydrogen bonds with water and smaller aldehydes and ketones have appreciable water solubility

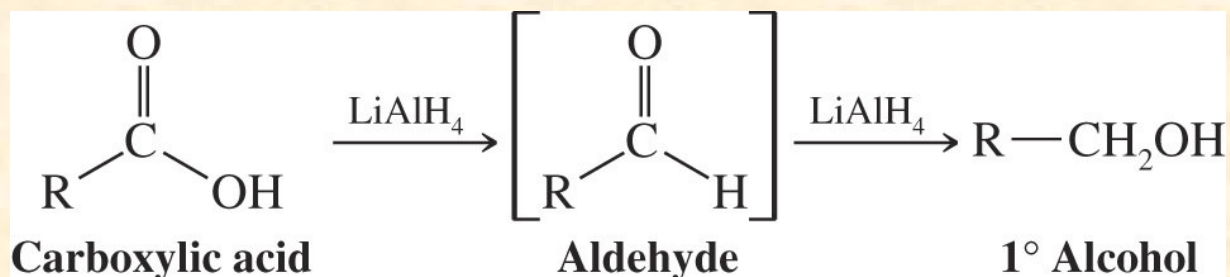
Formula	Name	mp ( $^{\circ}\text{C}$ )	bp ( $^{\circ}\text{C}$ )	Solubility in Water
HCHO	Formaldehyde	-92	-21	Very soluble
CH <sub>3</sub> CHO	Acetaldehyde	-125	21	$\infty$
CH <sub>3</sub> CH <sub>2</sub> CHO	Propanal	-81	49	Very soluble
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> CHO	Butanal	-99	76	Soluble
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> CHO	Pentanal	-91.5	102	Slightly soluble
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub> CHO	Hexanal	-51	131	Slightly soluble
C <sub>6</sub> H <sub>5</sub> CHO	Benzaldehyde	-26	178	Slightly soluble
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CHO	Phenylacetaldehyde	33	193	Slightly soluble
CH <sub>3</sub> COCH <sub>3</sub>	Acetone	-95	56.1	$\infty$
CH <sub>3</sub> COCH <sub>2</sub> CH <sub>3</sub>	Butanone	-86	79.6	Very soluble
CH <sub>3</sub> COCH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	2-Pentanone	-78	102	Soluble
CH <sub>3</sub> CH <sub>2</sub> COCH <sub>2</sub> CH <sub>3</sub>	3-Pentanone	-39	102	Soluble
C <sub>6</sub> H <sub>5</sub> COCH <sub>3</sub>	Acetophenone	21	202	Insoluble
C <sub>6</sub> H <sub>5</sub> COC <sub>6</sub> H <sub>5</sub>	Benzophenone	48	306	Insoluble

# Synthesis of Aldehydes

- Aldehydes by Oxidation of 1° Alcohols
  - Primary alcohols are oxidized to aldehydes by PCC

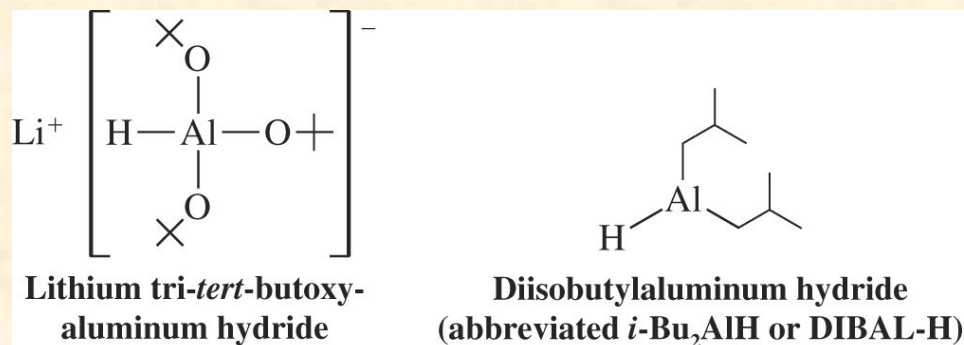


- Aldehydes by Reduction of Acyl Chlorides, Esters and Nitriles
  - Reduction of carboxylic acid to aldehyde is impossible to stop at the aldehyde stage
    - Aldehydes are much more easily reduced than carboxylic acids

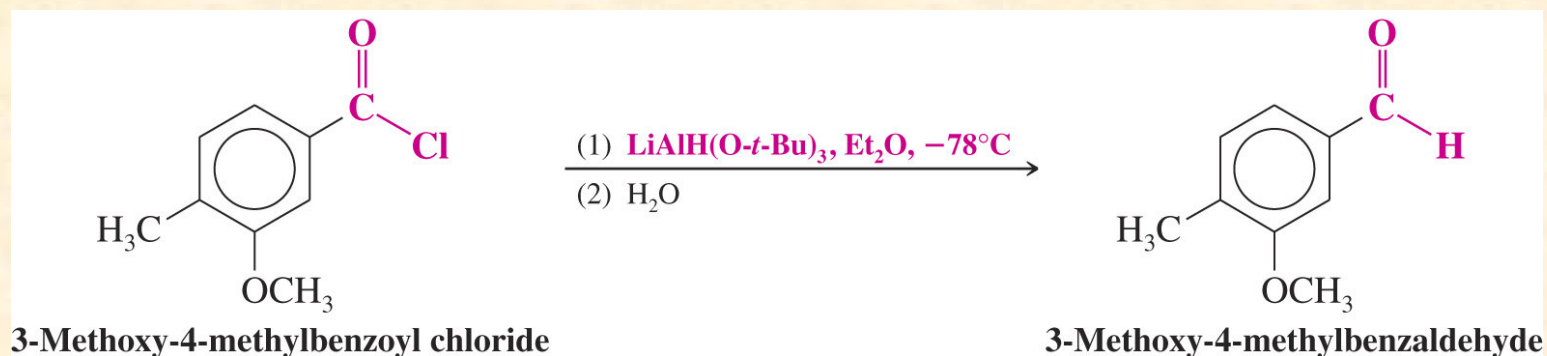
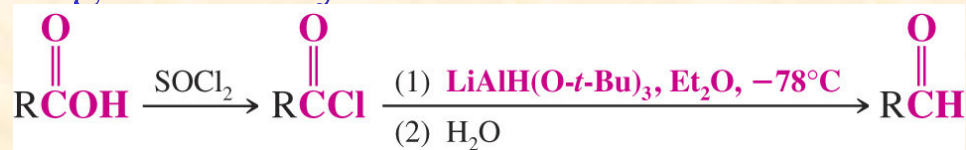


# Synthesis of Aldehydes

- Reduction to an aldehyde: a more reactive carboxylic acid derivatives such as an acyl chloride, ester or nitrile and a less reactive hydride source
  - The use of a sterically hindered and therefore less reactive aluminum hydride reagent is important

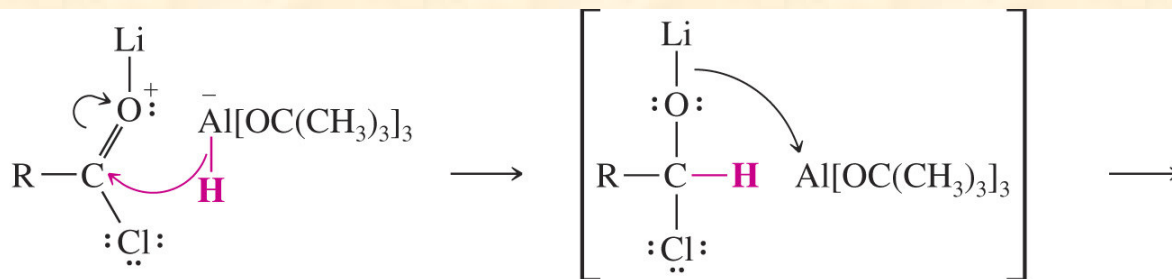
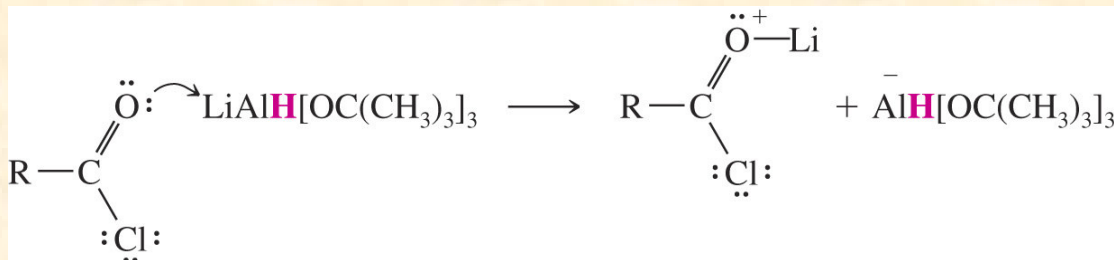


- Acid chlorides react with lithium tri-*tert*-butoxyaluminum hydride at low temperature to give aldehydes



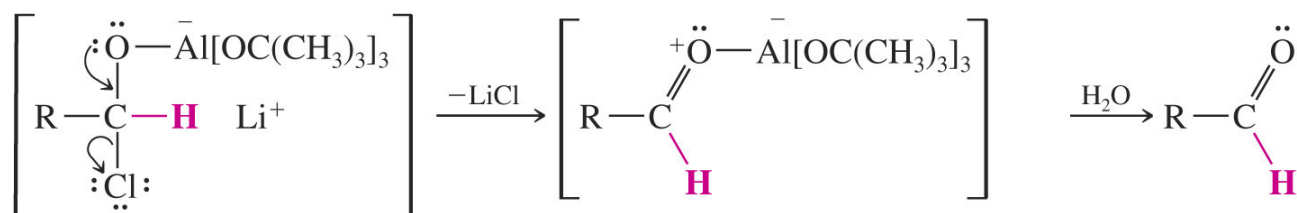
# Synthesis of Aldehydes

- Hydride is transferred to the carbonyl carbon
  - As the carbonyl re-forms, the chloride (which is a good leaving group) leaves



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

Acting as a Lewis acid, the aluminum atom accepts an electron pair from oxygen.



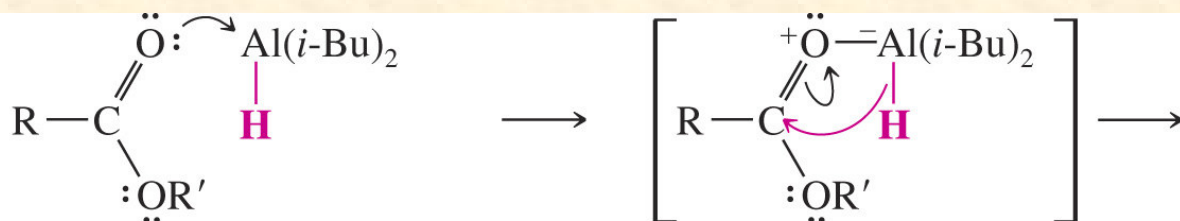
This intermediate loses a chloride ion as an electron pair from the oxygen assists.

The addition of water causes hydrolysis of this aluminum complex to take place, producing the aldehyde. (Several steps are involved.)



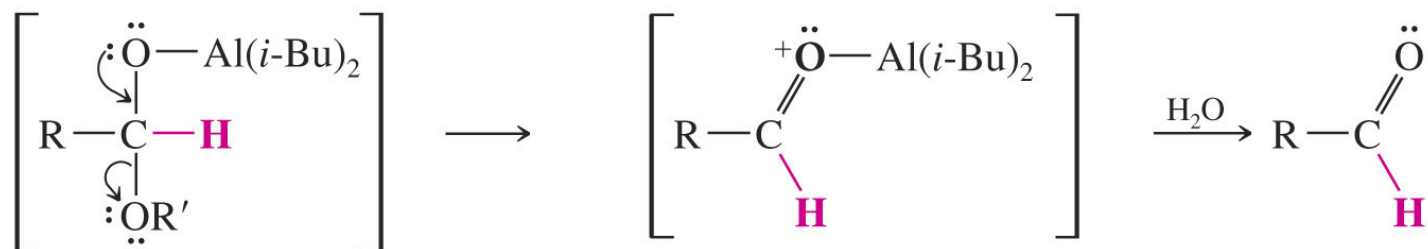
# Synthesis of Aldehydes

- Reduction of an ester to an aldehyde can be accomplished at low temperature using DIBAL-H
  - As the carbonyl re-forms, an alkoxide leaving group departs



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

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



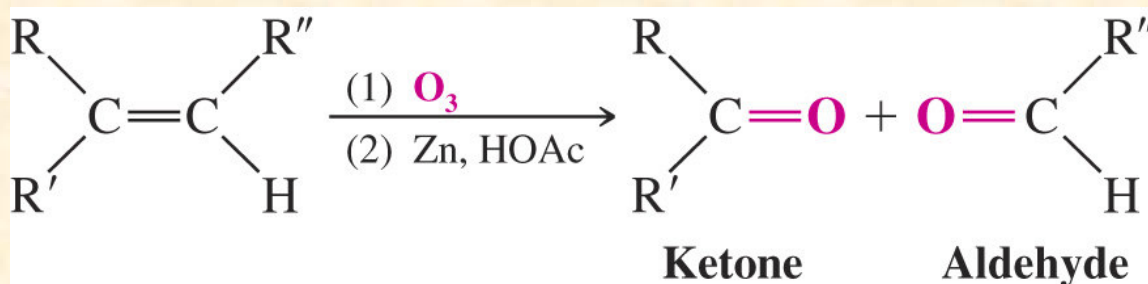
This intermediate loses an alkoxide ion as an electron pair from the oxygen assists.

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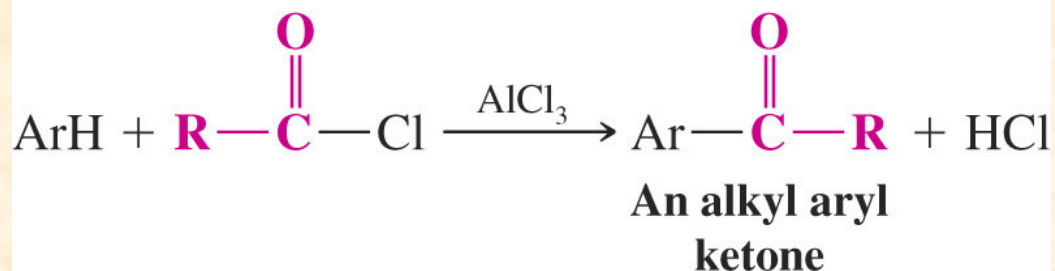
# Synthesis of Ketones

## – Ketones from Alkenes, Arenes, and 2° Alcohols

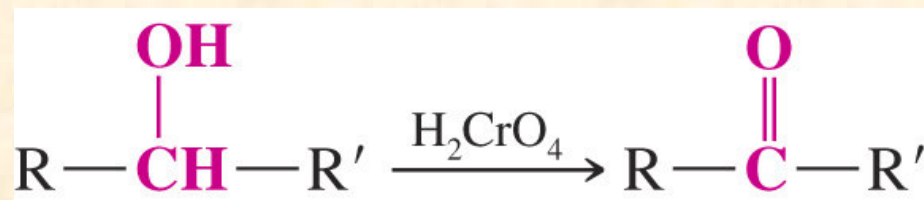
- Ketones can be made from alkenes by ozonolysis



- Aromatic ketones can be made by Friedel-Crafts Acylation



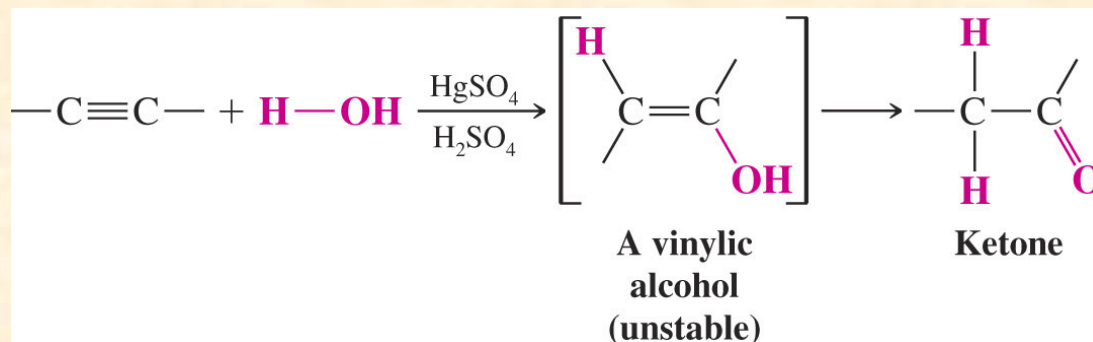
- Ketones can be made from 2° alcohols by oxidation



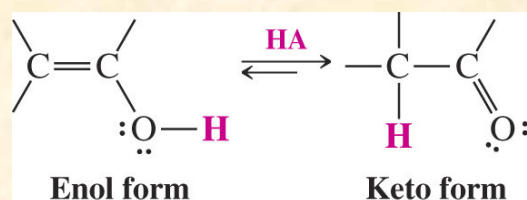
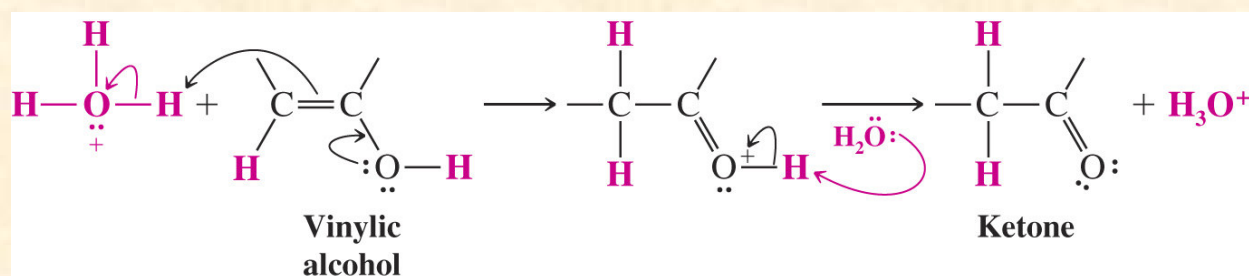
# Synthesis of Ketones

## – Ketones from Alkynes

- Markovnikov hydration of an alkyne initially yields a vinyl alcohol (enol) which then rearranges rapidly to a ketone (keto)

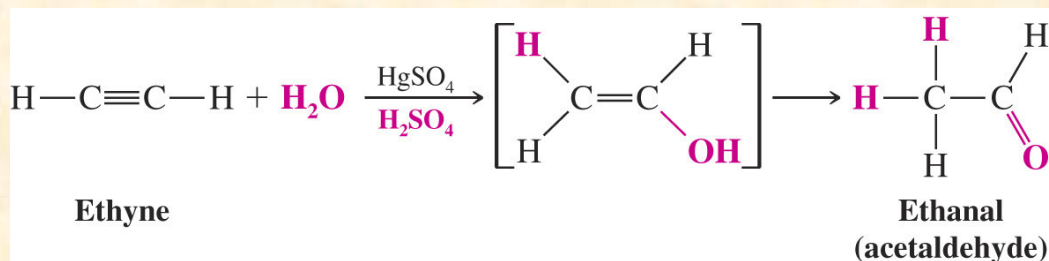
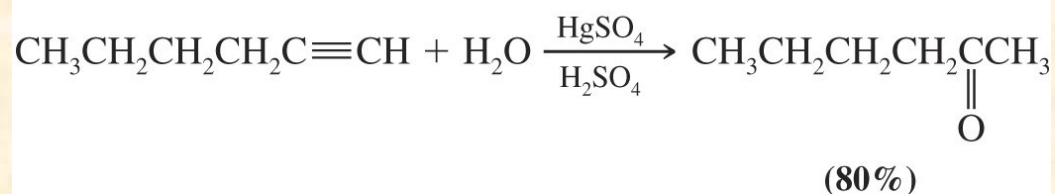
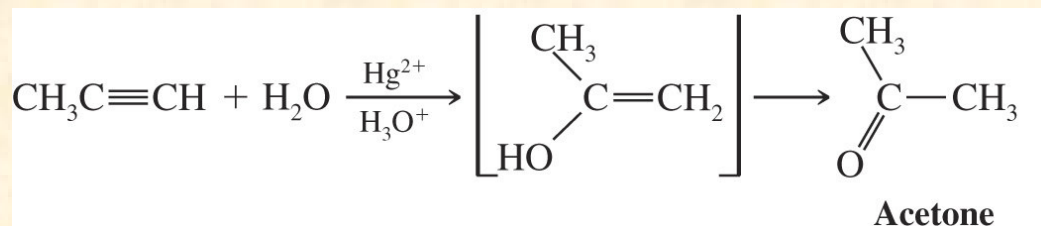


- The rearrangement is called a keto-enol tautomerization (Section 17.2)
  - This rearrangement is an equilibrium which usually favors the keto form



# Synthesis of Ketones

- Terminal alkynes yield ketones because of the Markovnikov regioselectivity of the hydration
  - Ethyne yields acetaldehyde
  - Internal alkynes give mixtures of ketones unless they are symmetrical

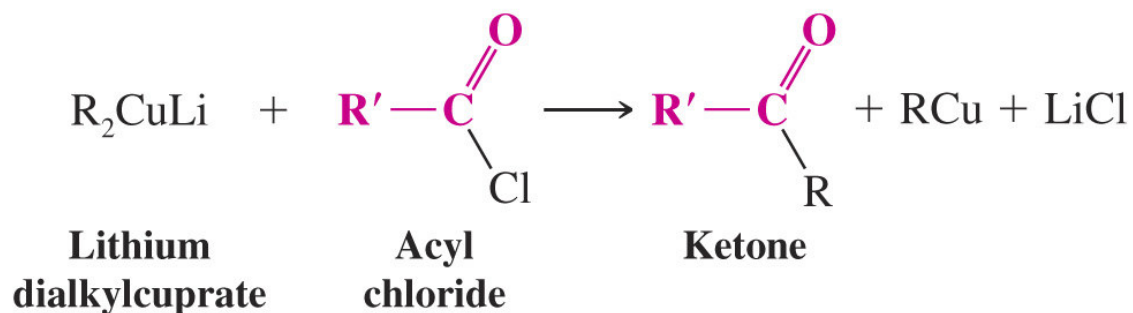


# Synthesis of Ketones

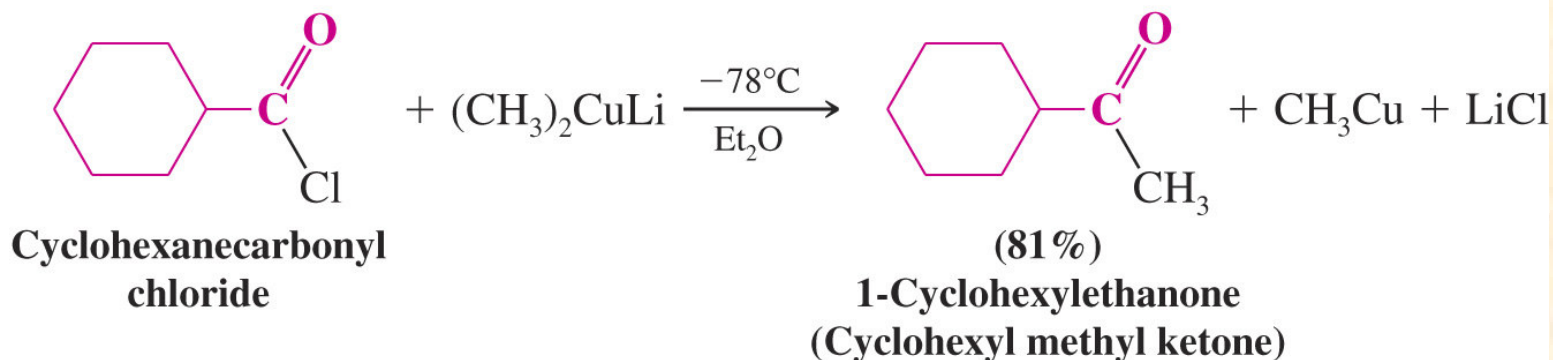
## – Ketones from Lithium Dialkylcuprates

- An acyl chloride can be coupled with a dialkylcuprate to yield a ketone (a variation of the Corey-Posner, Whitesides-House reaction)

### General Reaction



### Specific Example

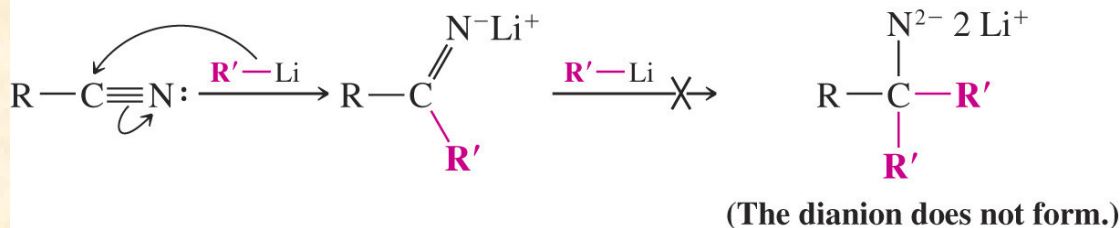
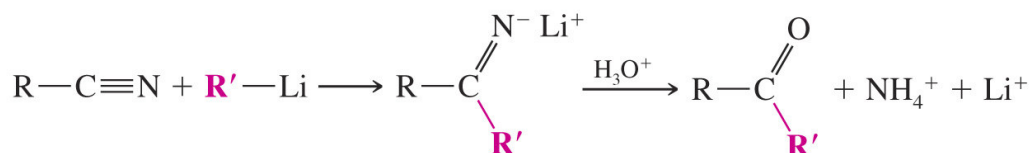
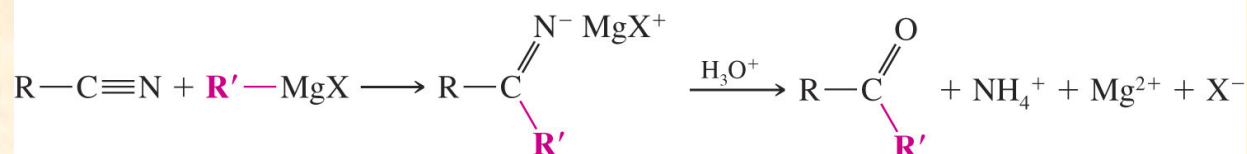


# Synthesis of Ketones

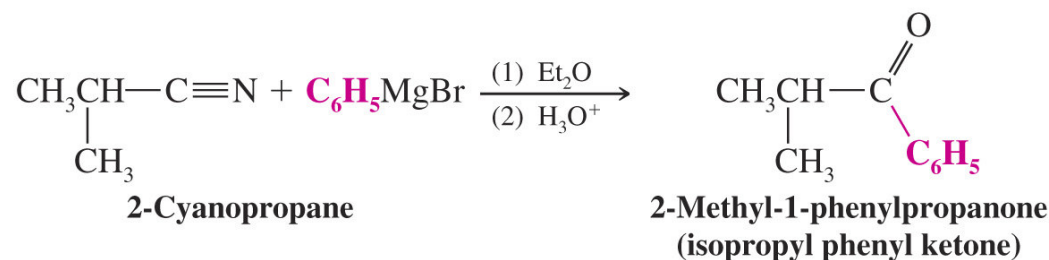
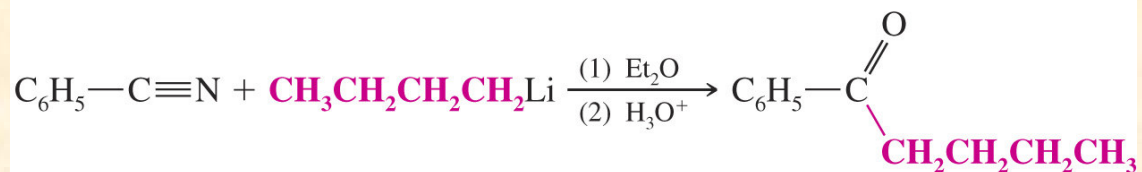
## – Ketones from Nitriles

- Organolithium and Grignard reagents add to nitriles to form ketones
  - Addition does not occur twice - two negative charges on the N

### General Reactions



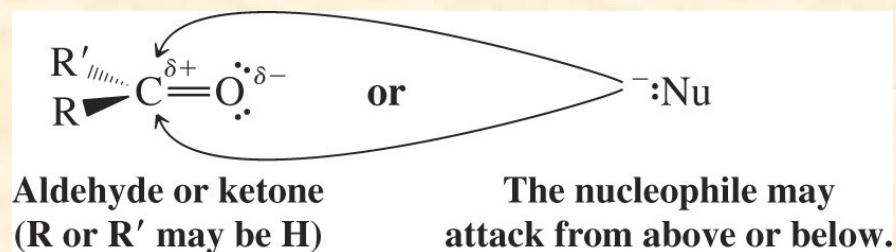
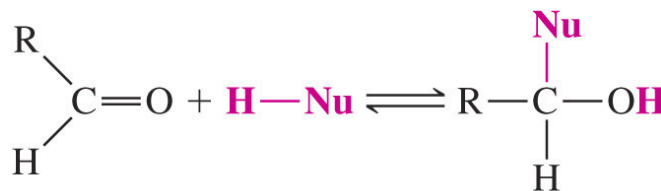
### Specific Examples



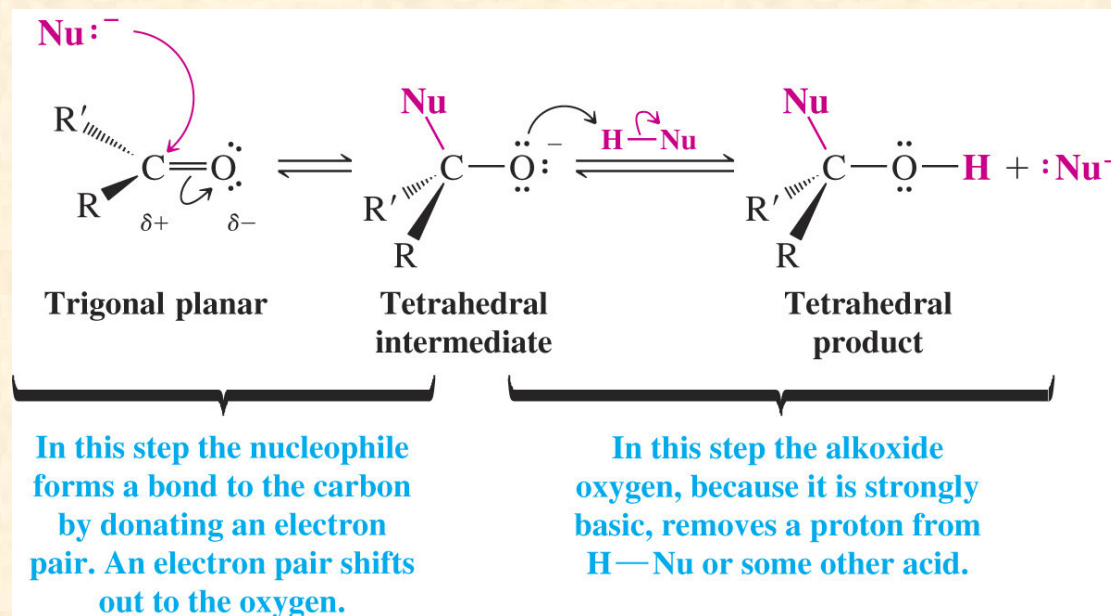
# Nucleophilic Addition to the Carbonyl Group

- Addition of a nucleophile to a carbonyl carbon occurs because of the  $\delta^+$  charge at the carbon

## General Reaction



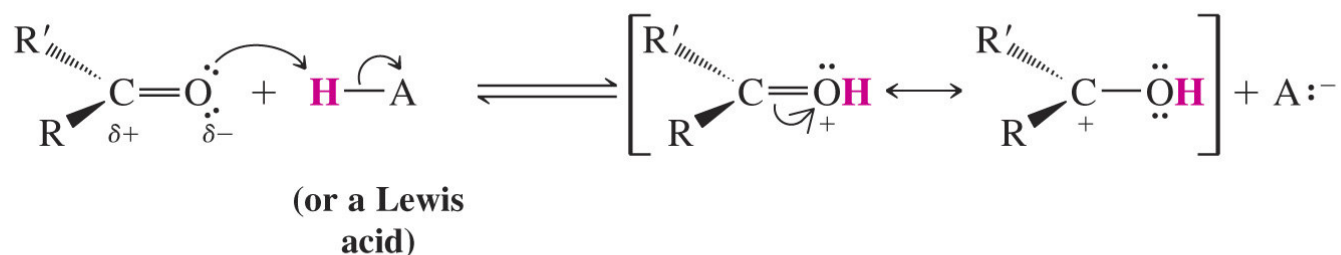
- Addition of strong nucleophiles such as hydride or Grignard reagents result in formation of a tetrahedral alkoxide intermediate
  - The carbonyl  $\pi$  electrons shift to oxygen to give the alkoxide
  - The carbonyl carbon changes from trigonal planar to tetrahedral



# Nucleophilic Addition to the Carbonyl Group

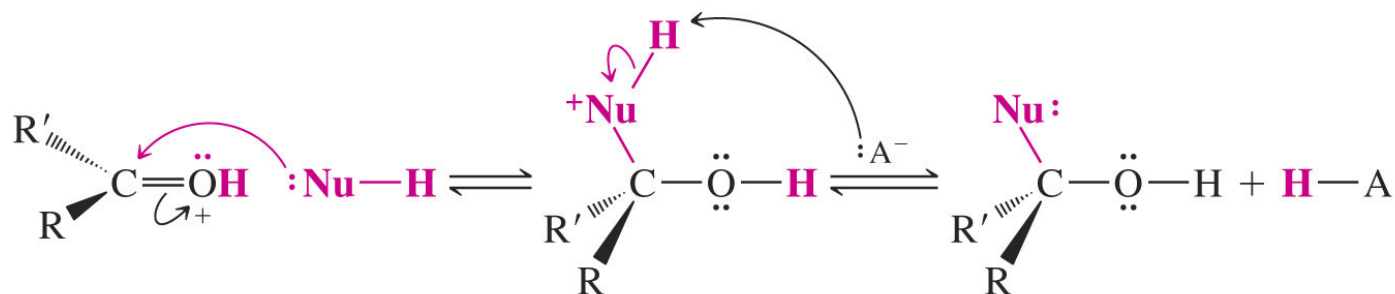
- An acid catalyst is used to facilitate reaction of weak nucleophiles with carbonyl groups
  - Protonating the carbonyl oxygen enhances the electrophilicity of the carbon

Step 1



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

Step 2



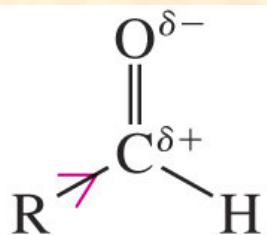
In the first of these two steps, the oxonium cation accepts the electron pair of the nucleophile. In the second step, a base removes a proton from the positively charged atom, regenerating the acid.



# Nucleophilic Addition to the Carbonyl Group

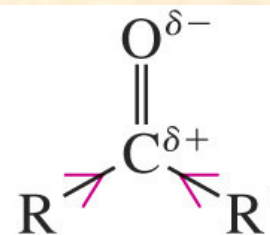
## – Relative Reactivity: Aldehydes versus Ketones

- Aldehydes are generally more reactive than ketones
  - The tetrahedral carbon resulting from addition to an aldehyde is less sterically hindered than the tetrahedral carbon resulting from addition to a ketone
  - Aldehyde carbonyl groups are more electron deficient because they have only one electron-donating group attached to the carbonyl carbon



**Aldehyde**

**Carbonyl carbon is more positive.**



**Ketone**

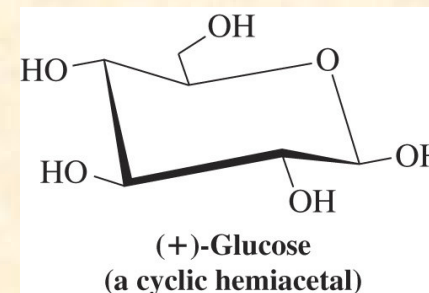
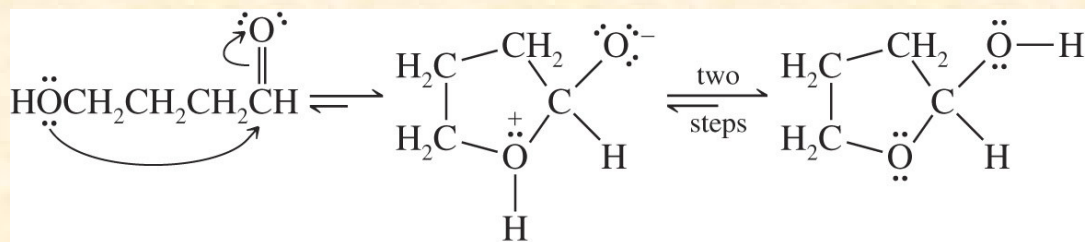
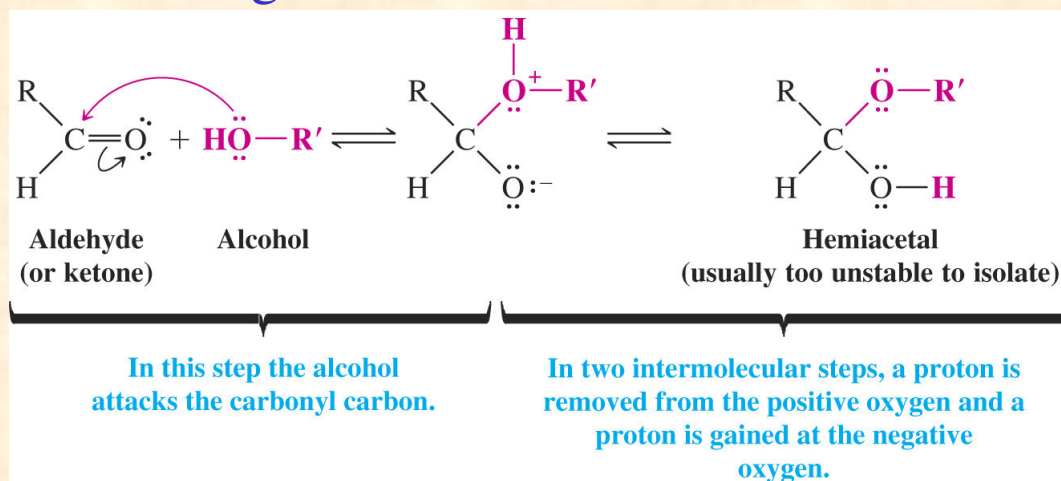
**Carbonyl carbon is less positive.**

# Reactions of Carbonyl Compounds

## The Addition of Alcohols: Hemiacetals and Acetals

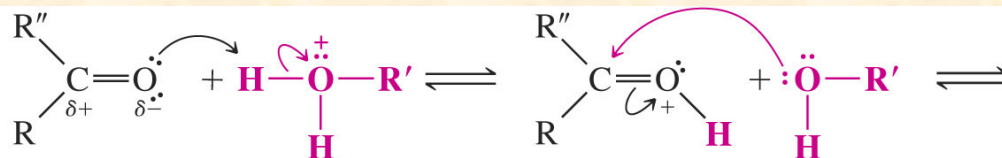
### Hemiacetals

- An aldehyde or ketone dissolved in an alcohol will form an equilibrium mixture containing the corresponding hemiacetal
  - A hemiacetal has a hydroxyl and alkoxy group on the same carbon
  - Acylic hemiacetals - not stable, however, cyclic five- and six-membered ring hemiacetals are



# Reactions of Carbonyl Compounds

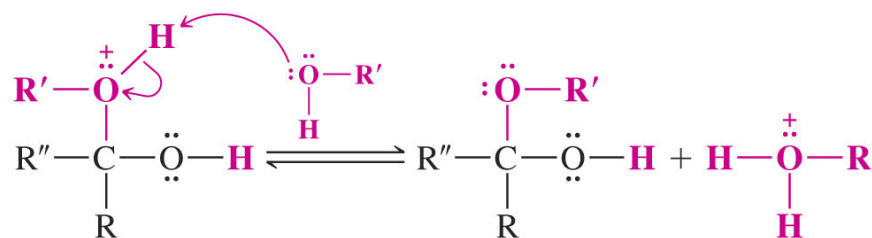
- Hemiacetal formation is catalyzed by either acid or base



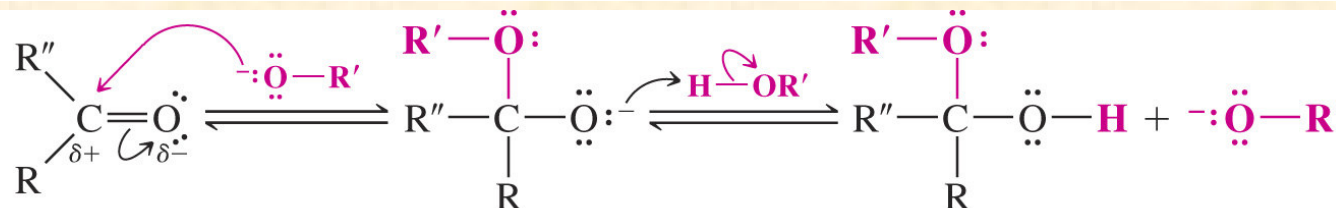
(R'' may be H)

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

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



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



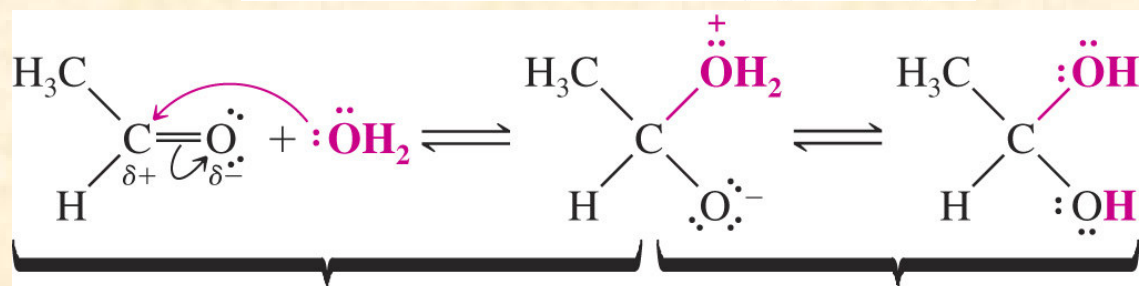
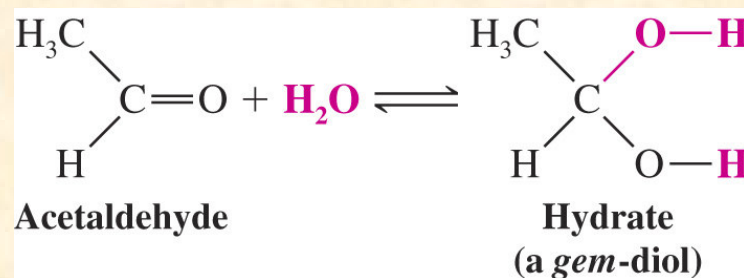
(R'' may be H)

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

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

# Reactions of Carbonyl Compounds

- Dissolving aldehydes (or ketones) in water causes formation of an equilibrium between the carbonyl compound and its hydrate
  - The hydrate is also called a *gem*-diol (*gem* *i.e.* geminal, indicates the presence of two identical substituents on the same carbon)
  - The equilibrium favors a ketone over its hydrate because the tetrahedral ketone hydrate is sterically crowded



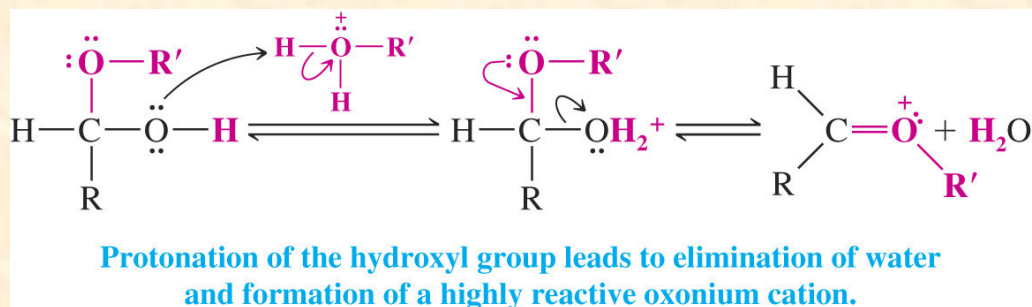
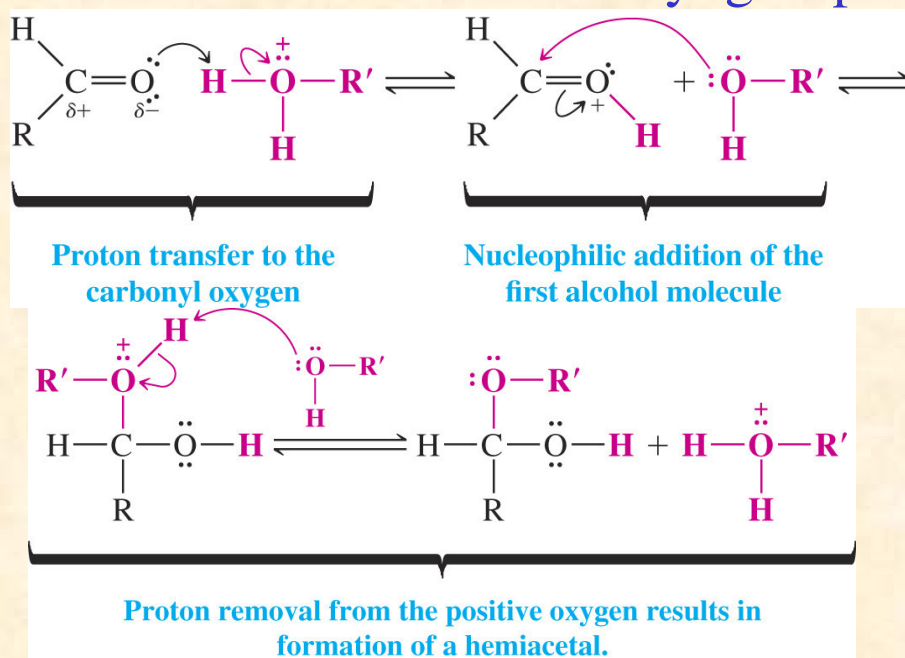
In this step water attacks the carbonyl carbon atom.

In two intermolecular steps a proton is lost from the positive oxygen atom and a proton is gained at the negative oxygen atom.

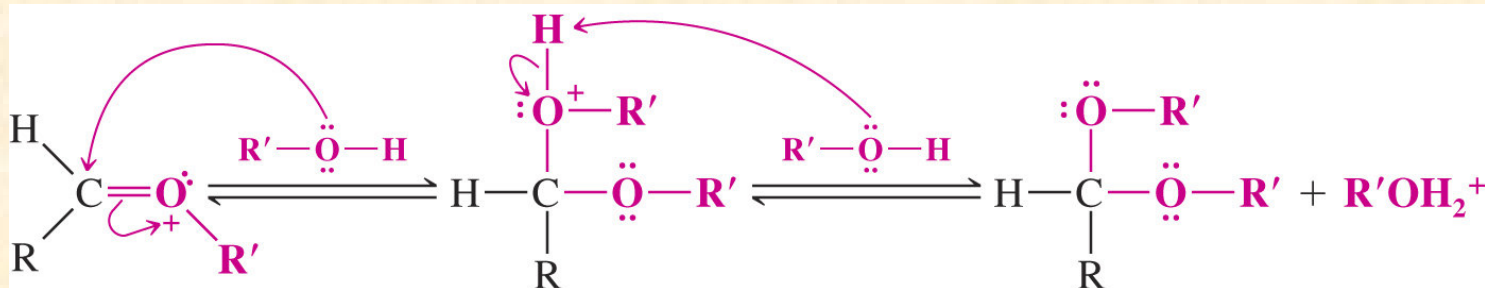
# Reactions of Carbonyl Compounds

## – Acetals

- An aldehyde (or ketone) in the presence of excess alcohol and an acid catalyst will form an acetal
  - Formation of the acetal proceeds via the corresponding hemiacetal
  - An acetal has two alkoxy groups bonded to the same carbon

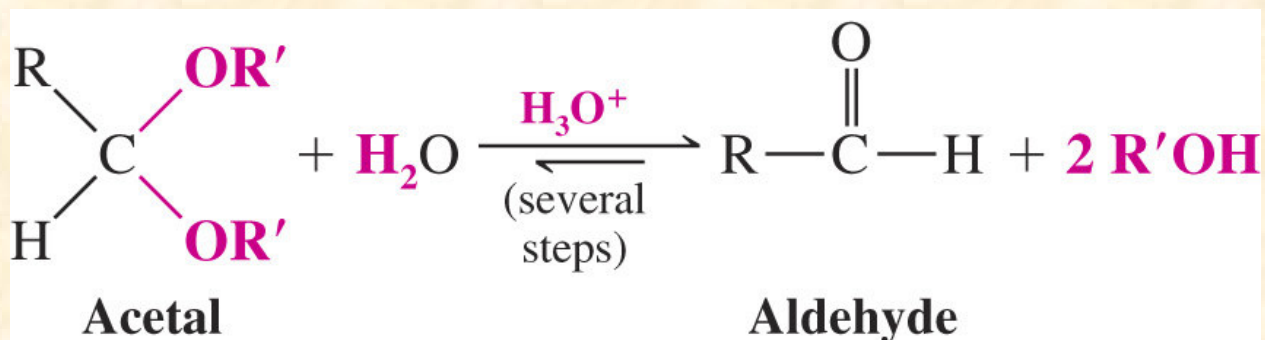


# Reactions of Carbonyl Compounds



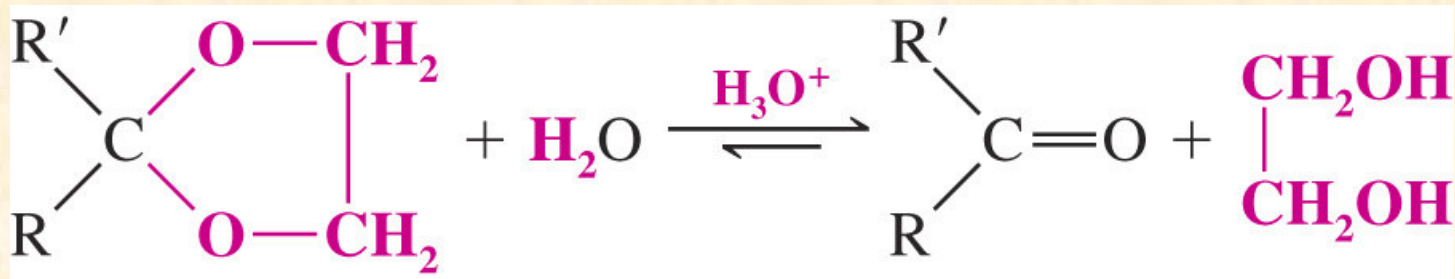
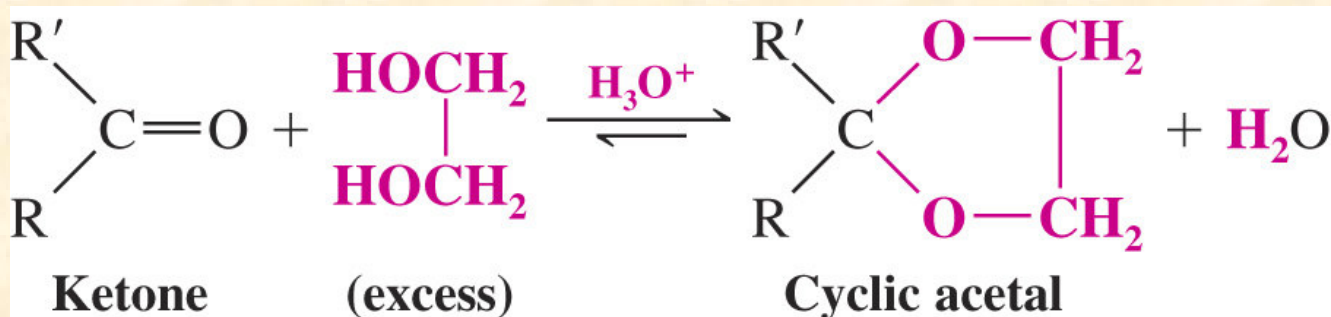
Attack on the carbon of the oxonium ion by a second molecule of the alcohol, followed by removal of a proton, leads to the acetal.

- Acetals are stable when isolated and purified
  - Acetal formation is reversible
    - An excess of water in the presence of an acid catalyst will hydrolyze an acetal to the corresponding aldehyde (or ketone)



# Reactions of Carbonyl Compounds

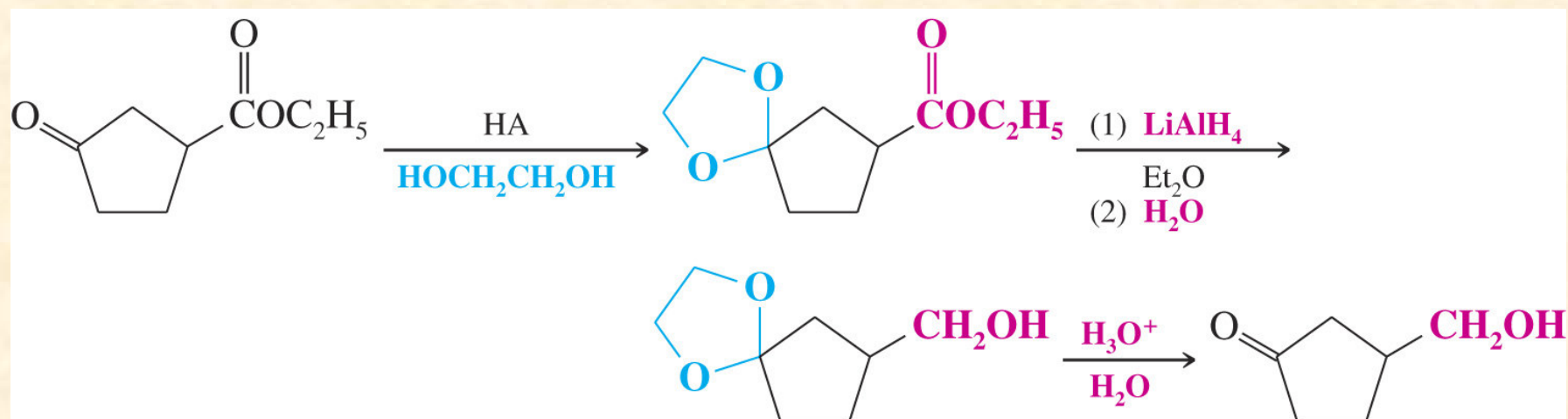
- Acetal formation from ketones and simple alcohols is less favorable than formation from aldehydes
  - Formation of cyclic 5- and 6- membered ring acetals from ketones is, however, favorable
  - Such cyclic acetals are often used as protecting groups for aldehydes and ketones
  - These protecting groups can be removed using dilute aqueous acid



# Reactions of Carbonyl Compounds

## – Acetals as Protecting Groups

- Acetal protecting groups are stable to most reagents except aqueous acid
- Example: An ester can be reduced in the presence of a ketone protected as an acetal

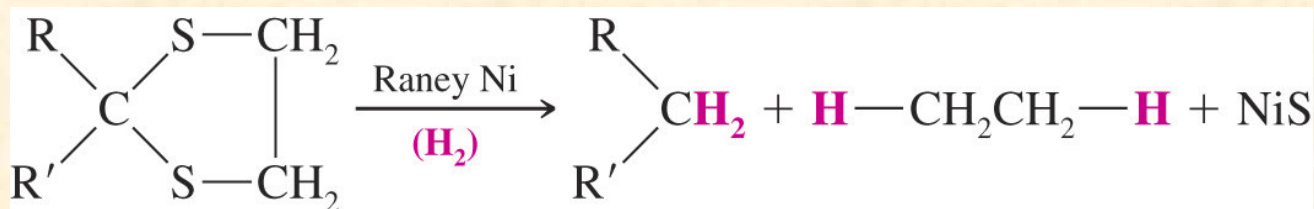
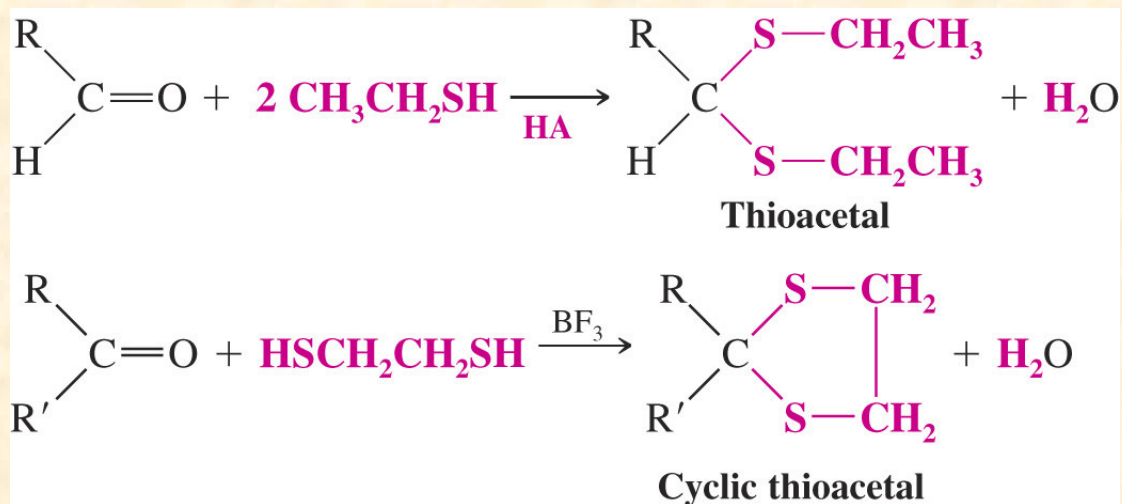




# Reactions of Carbonyl Compounds

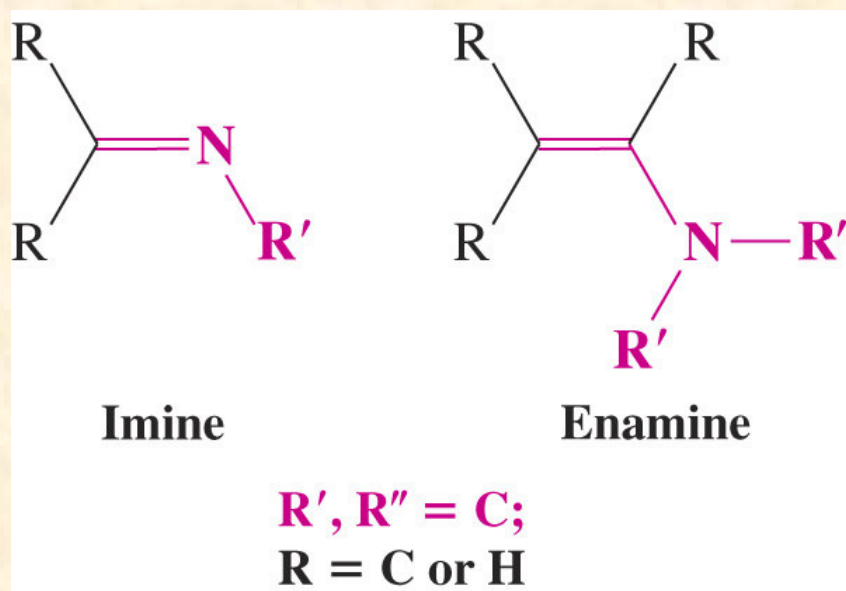
## – Thioacetals

- Thioacetals can be formed by reaction of an aldehyde or ketone with a thiol
  - Thioacetals can be converted to  $\text{CH}_2$  groups by hydrogenation using a catalyst such as Raney nickel
  - This sequence provides a way to remove an aldehyde or ketone carbonyl oxygen



# Reactions of Carbonyl Compounds

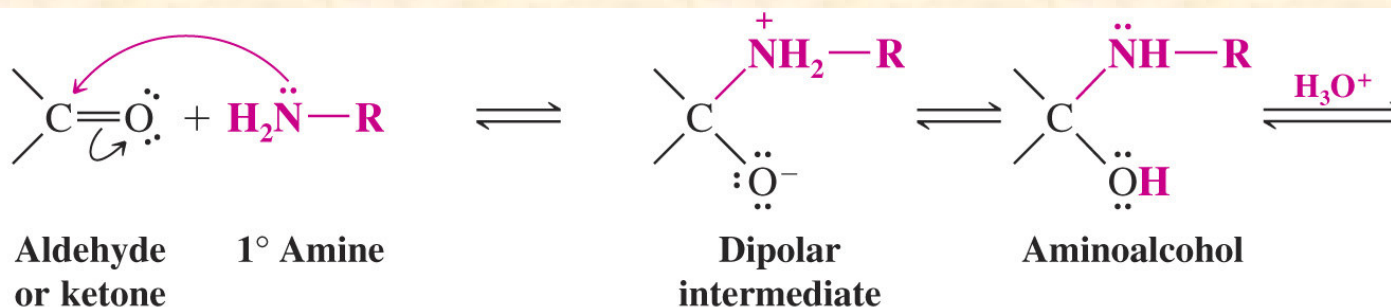
- The Addition of Primary and Secondary Amines
  - Aldehydes and ketones react with primary amines (and ammonia) to yield imines
    - They react with secondary amines to yield enamines



# Reactions of Carbonyl Compounds

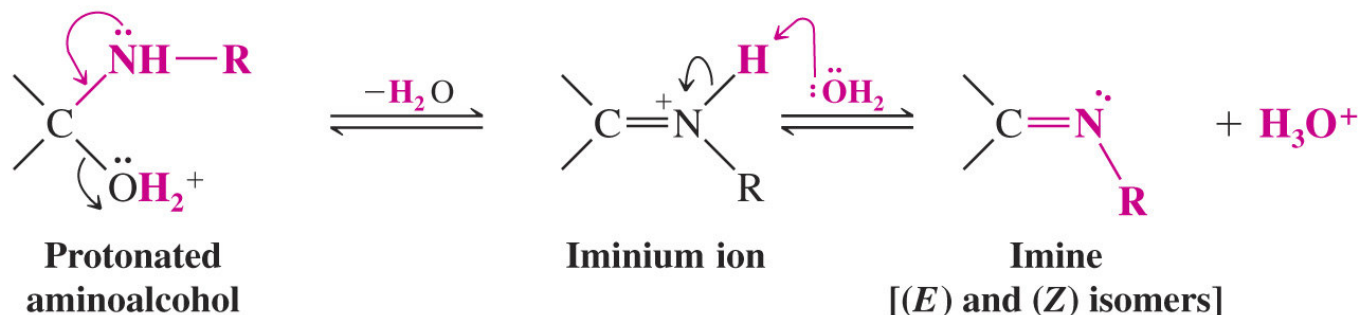
## – Imines

- These reactions occur fastest at pH 4-5
  - Mild acid facilitates departure of the hydroxyl group from the aminoalcohol intermediate without also protonating the nitrogen of the amine starting compound



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

Intermolecular proton transfer from nitrogen to oxygen produces an aminoalcohol.



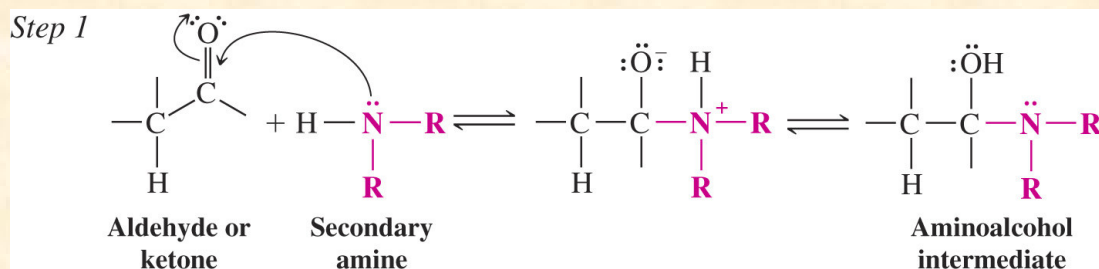
Protonation of the oxygen produces a good leaving group. Loss of a molecule of water yields an iminium ion.

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

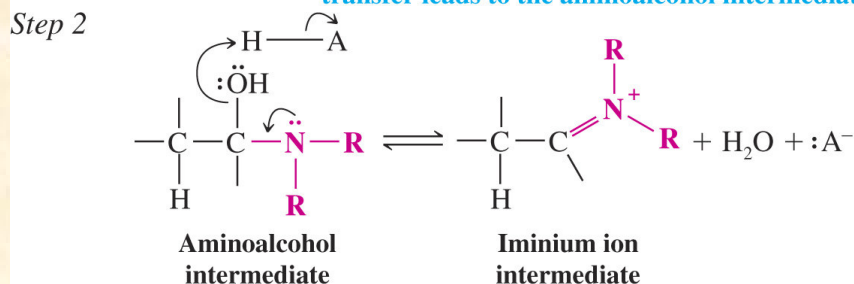
# Reactions of Carbonyl Compounds

## – Enamines

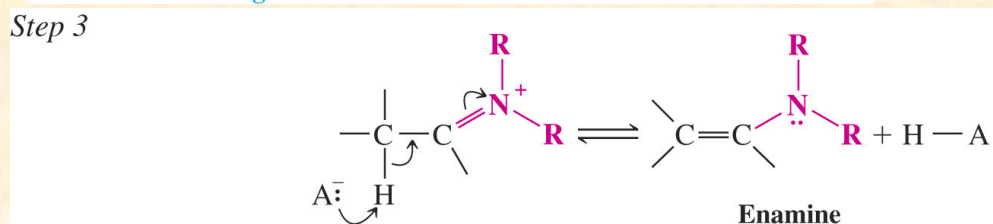
- Secondary amines cannot form a neutral imine by loss of a second proton on nitrogen - An enamine is formed instead



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



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

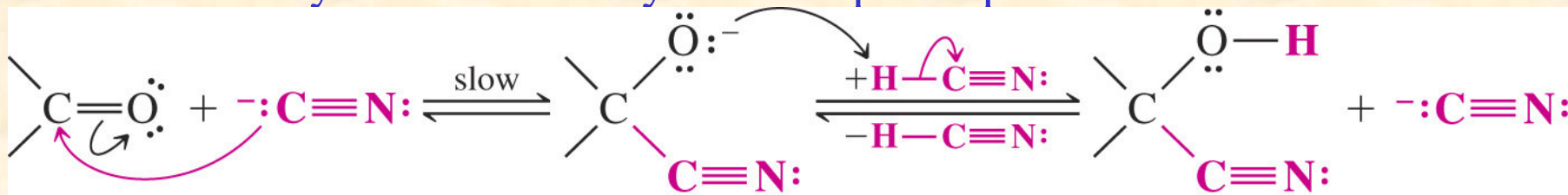


A proton is removed from the carbon adjacent to the iminium group. Proton removal occurs from the carbon because there is no proton to remove from the nitrogen of the iminium cation (as there would have been if a primary amine had been used). This step forms the enamine, neutralizes the formal charge,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

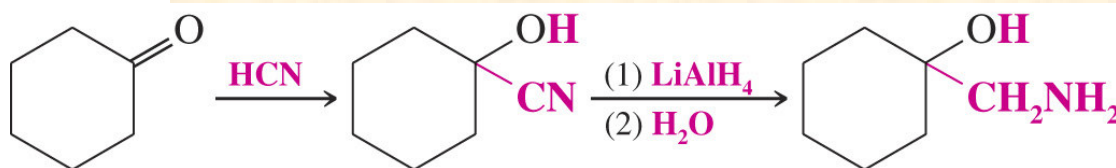
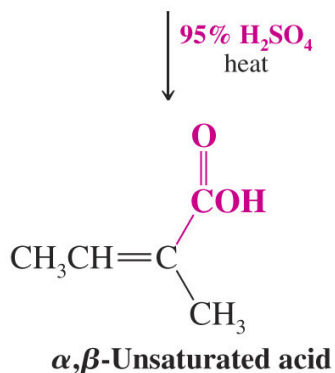
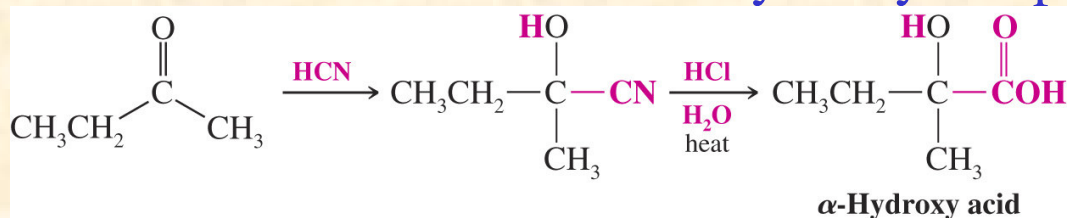
# Reactions of Carbonyl Compounds

## The Addition of Hydrogen Cyanide

- Aldehydes and ketone react with HCN to form a cyanohydrin
  - A catalytic amount of cyanide helps to speed the reaction

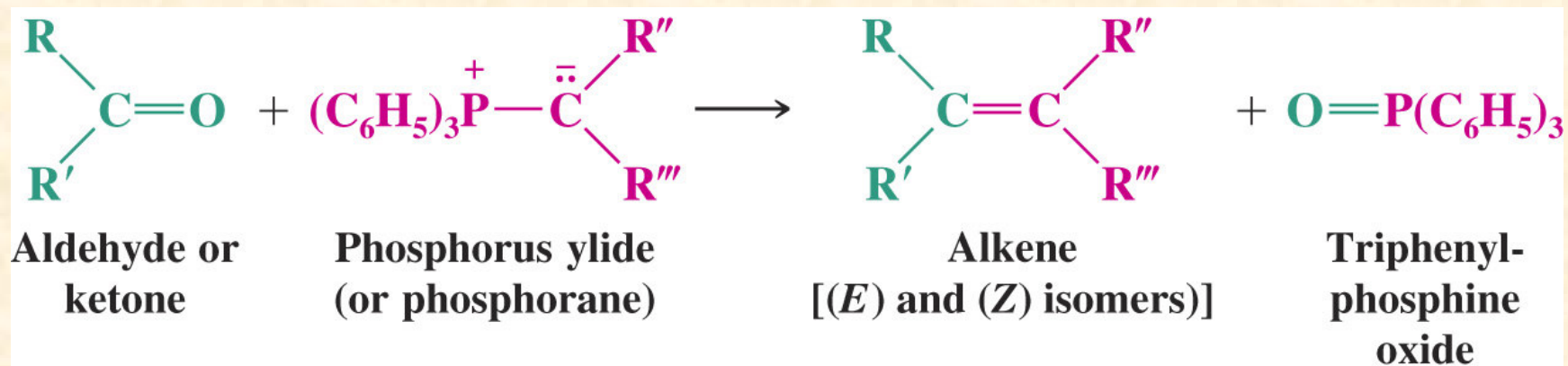


- The cyano group can be hydrolyzed or reduced
  - Hydrolysis of a cyanohydrin produces an  $\alpha$ -hydroxycarboxylic acid
  - Reduction of a cyanohydrin produces a  $\beta$ -aminoalcohol



# Reactions of Carbonyl Compounds

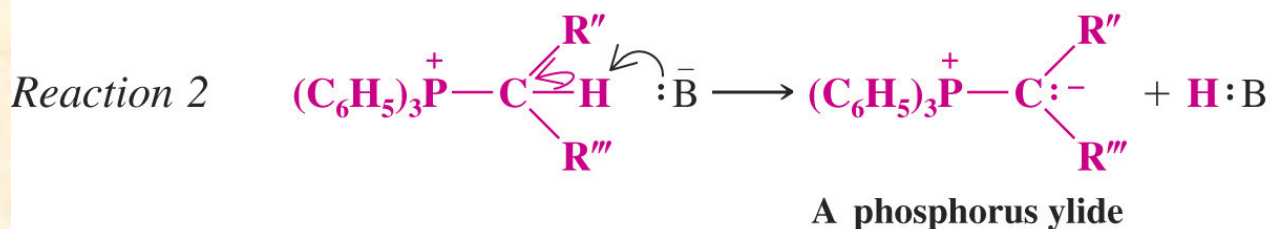
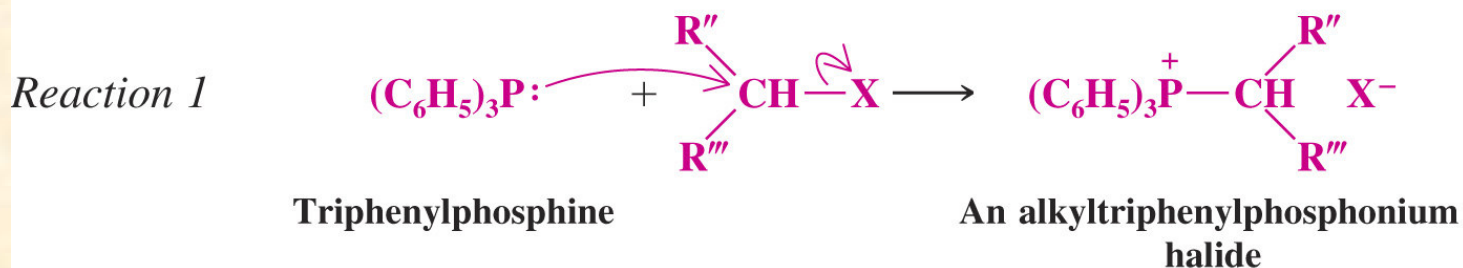
- The Addition of Ylides: The Wittig Reaction
  - Aldehydes and ketones react with phosphorous ylides to produce alkenes
    - An ylide is a neutral molecule with adjacent positive and negative charges



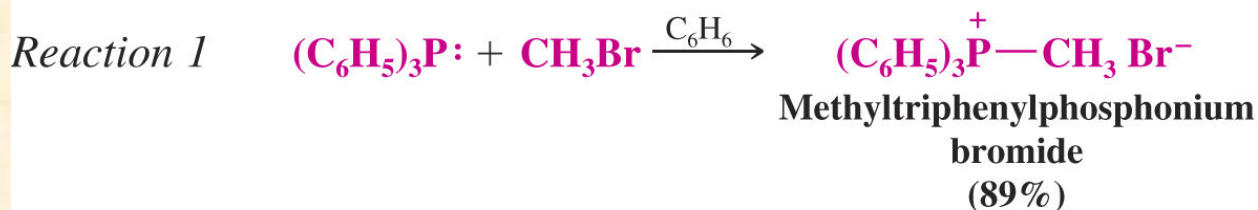
# Reactions of Carbonyl Compounds

- Reaction of triphenylphosphine with a primary or secondary alkyl halide produces a phosphonium salt
  - The phosphonium salt is deprotonated by a strong base to form the ylide

## General Reaction

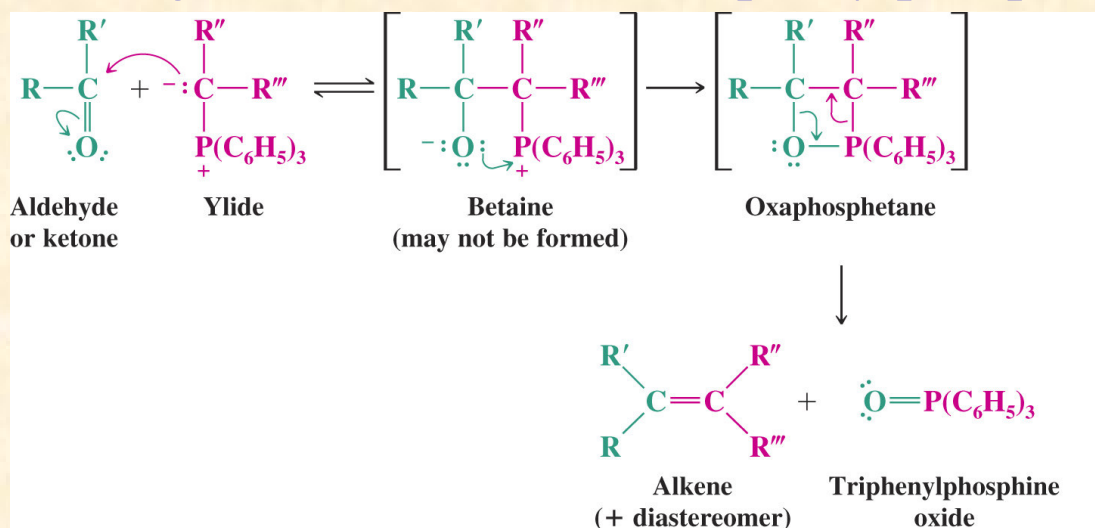


## Specific Example

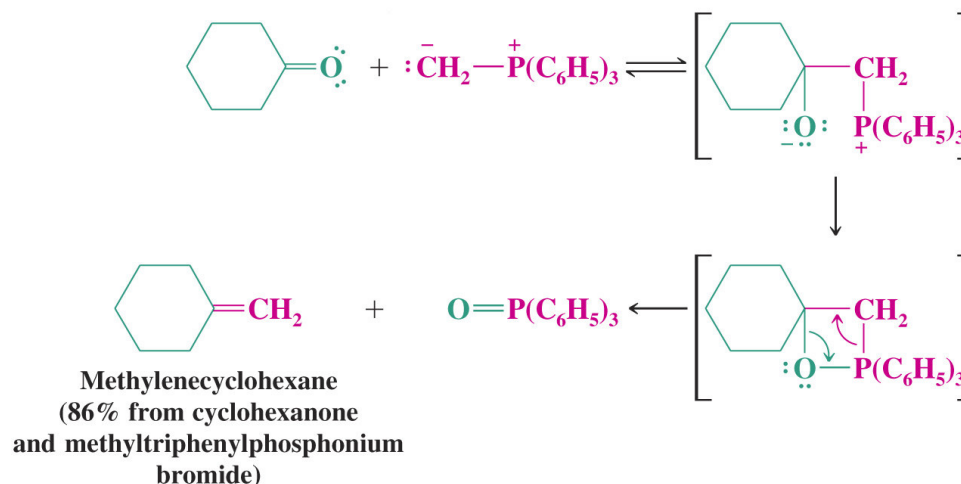


# Reactions of Carbonyl Compounds

- Addition of the ylide to the carbonyl leads to formation of an oxaphosphetane, that rearranges to the alkene and  $\text{Ph}_3\text{P}=\text{O}$ 
  - The driving force for the last reaction is formation of the very strong P-O double bond in triphenylphosphine oxide



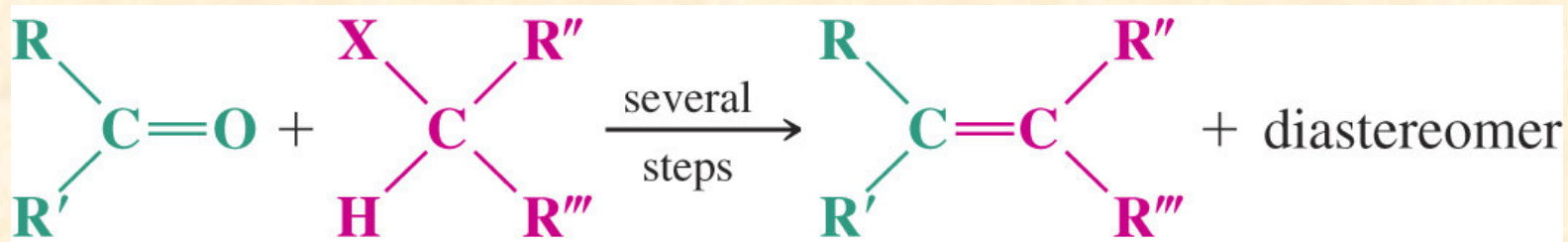
## Specific Example





# Reactions of Carbonyl Compounds

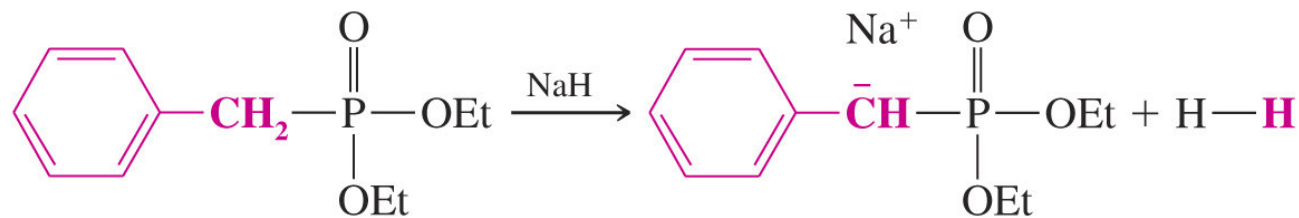
- The overall result of a Wittig reaction is formation of a C=C bond from a C=O bond



# Reactions of Carbonyl Compounds

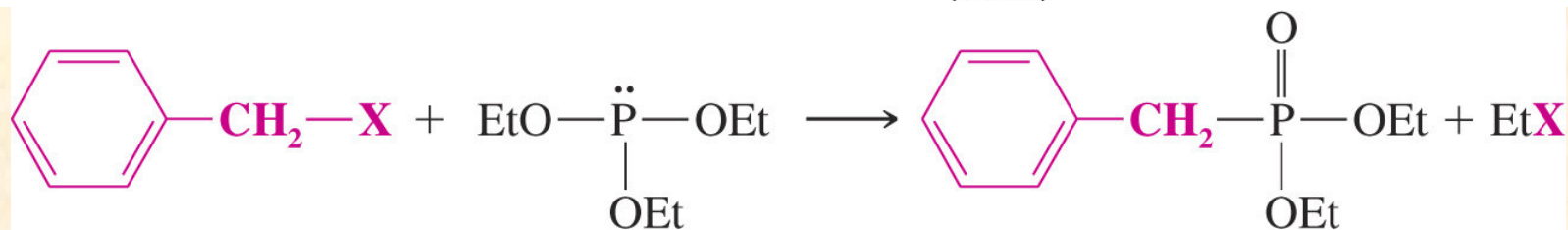
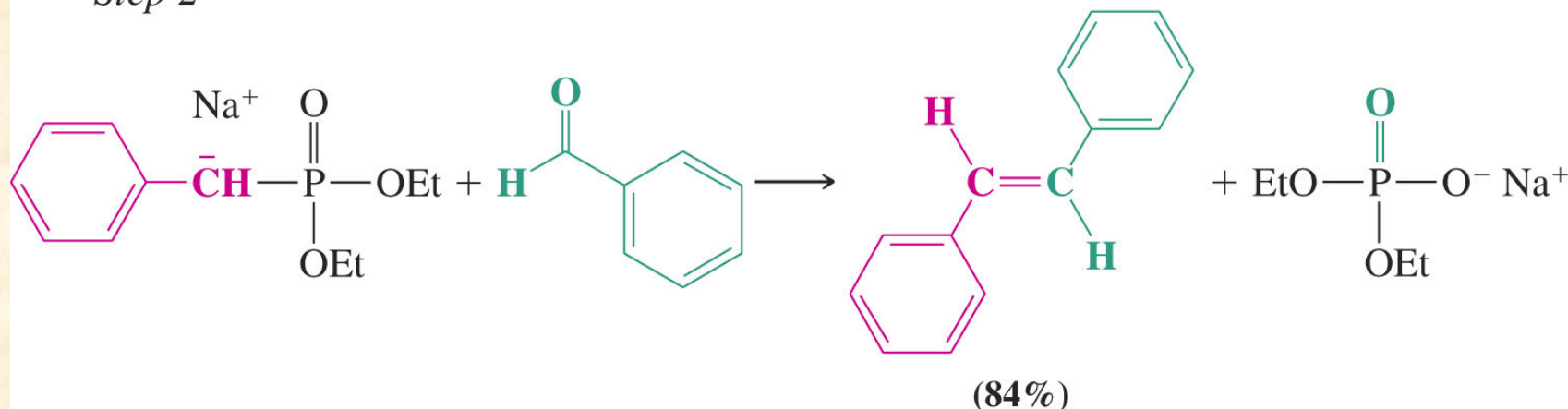
- The Horner-Wadsworth-Emmons reaction employs a phosphonate ester and generally leads to formation of an (*E*)-alkene

Step 1



A phosphonate ester

Step 2

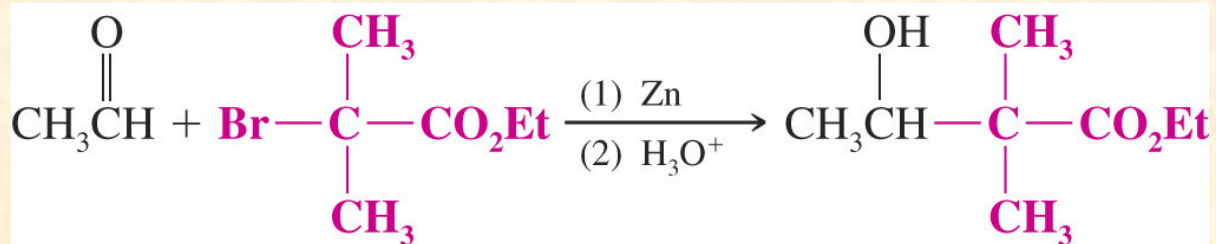
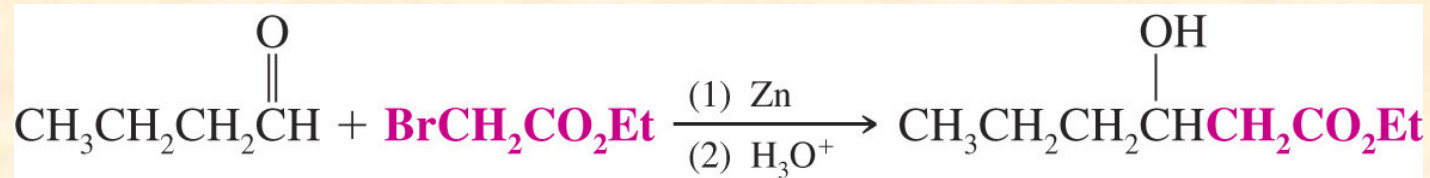
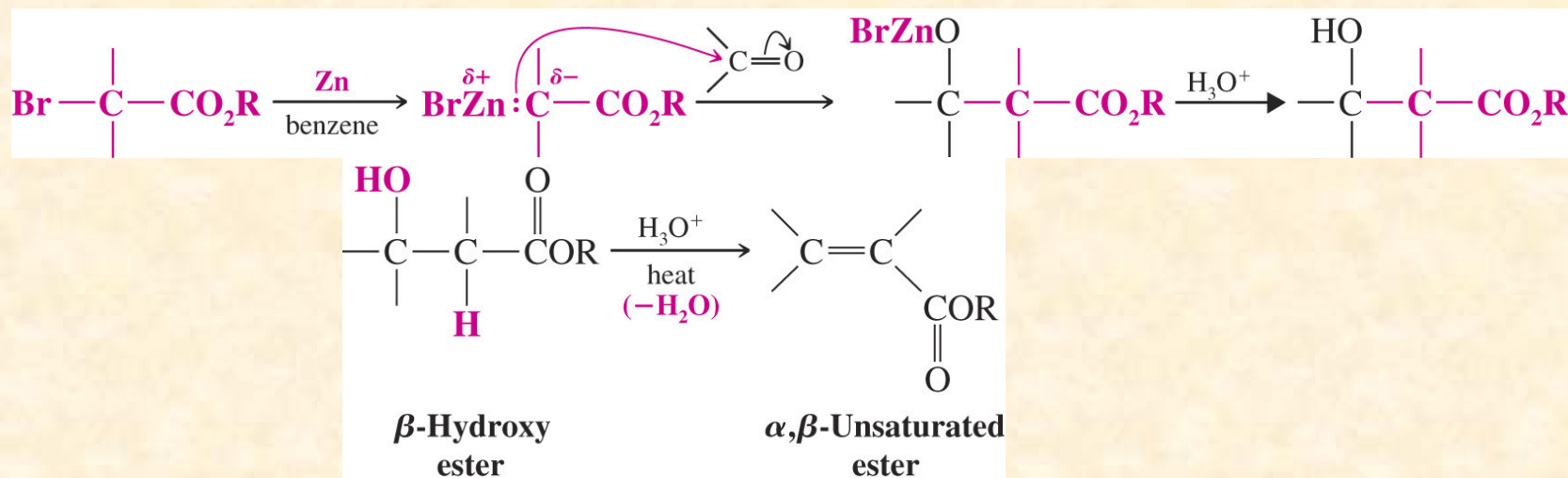


Triethyl phosphite

# Reactions of Carbonyl Compounds

## The Addition of Organometallic Reagents: The Reformatsky Reaction

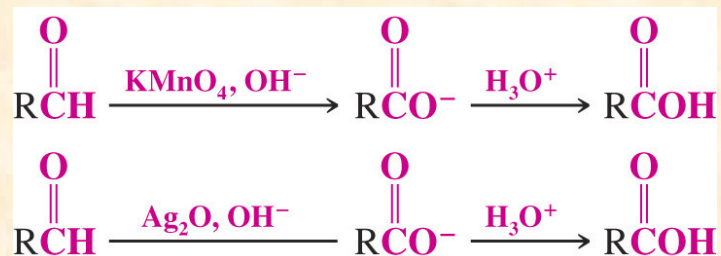
- Addition of an organozinc reagent to an aldehyde or ketone
  - The organozinc reagent is made from an  $\alpha$ -bromo ester; the reaction gives a  $\beta$ -hydroxy ester
  - The  $\beta$ -hydroxyester is easily dehydrated to an  $\alpha,\beta$ -unsaturated



# Reactions of Carbonyl Compounds

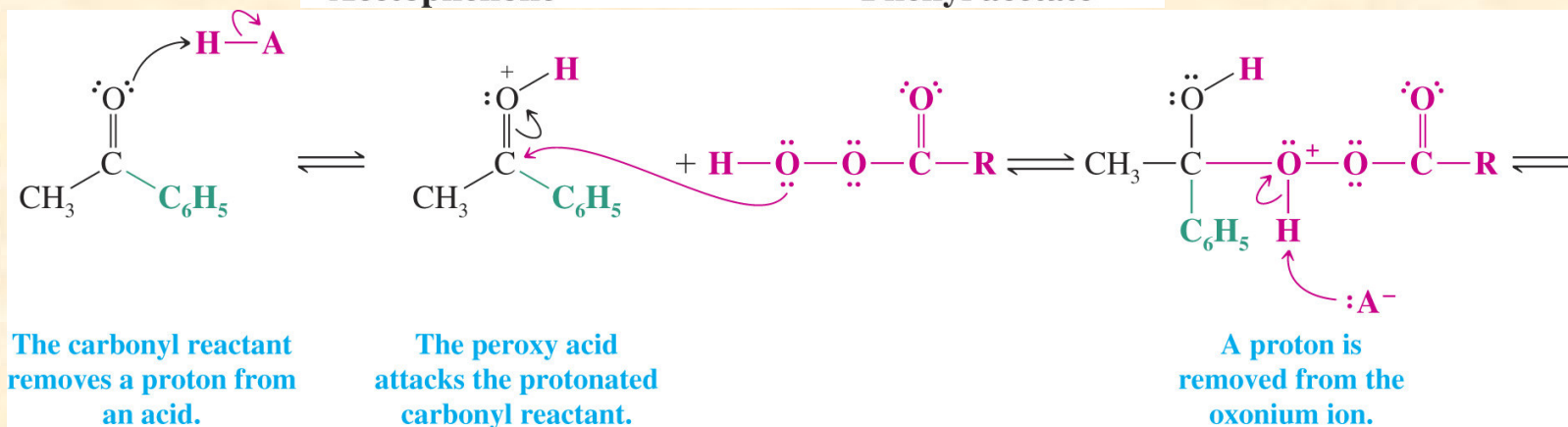
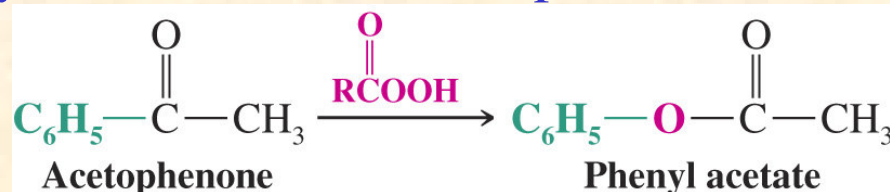
## Oxidation of Aldehydes and Ketones

- Aldehydes are generally much more easily oxidized than ketones

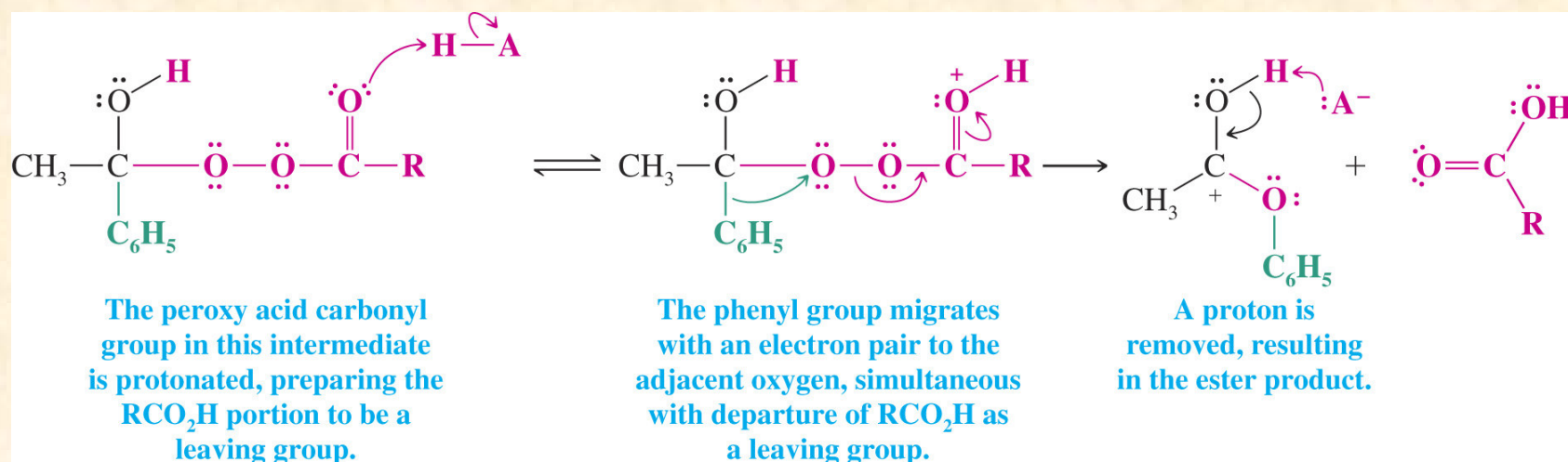


## The Baeyer-Villiger Oxidation of Aldehydes and Ketones

- Insertion of an oxygen atom adjacent to a ketone or aldehyde carbonyl
  - Oxidation of a ketone yields an ester
  - A peroxyacid such as *m*-chloroperbenzoic (MCPBA) acid is used



# Reactions of Carbonyl Compounds



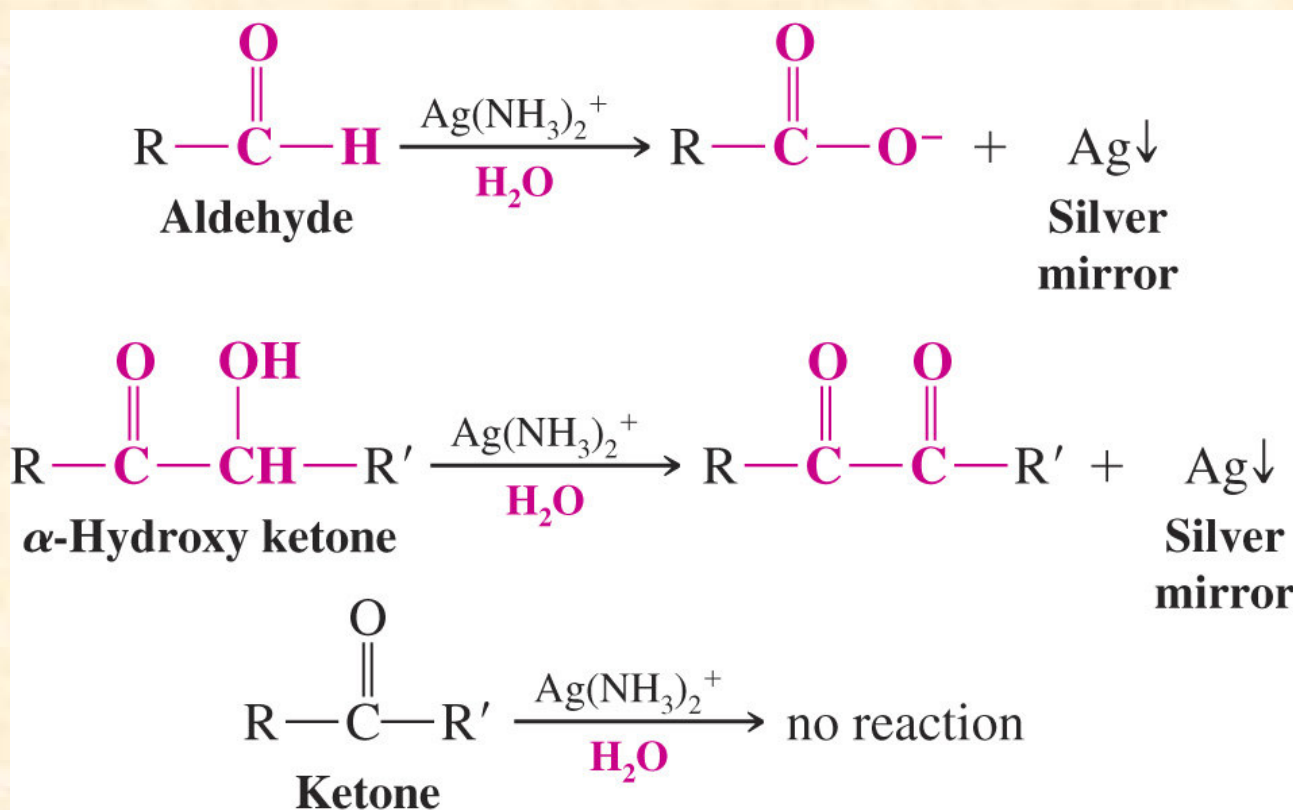
- The migratory aptitude of a group attached to a carbonyl is  $\text{H} > \text{phenyl} > 3^\circ \text{ alkyl} > 2^\circ \text{ alkyl} > 1^\circ \text{ alkyl} > \text{methyl}$

# Reactions of Carbonyl Compounds

## Chemical Analysis of Aldehydes and Ketones

### Tollens' Test (Silver Mirror Test)

- Aldehydes and ketones can be distinguished from each other on the basis of the Tollens test
  - The presence of an aldehyde results in formation of a silver mirror (by oxidation of the aldehyde and reduction of the silver cation)
  - $\alpha$ -Hydroxyketones also give a positive Tollens' test

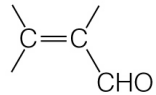
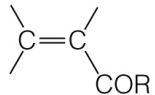


# Spectroscopic Properties

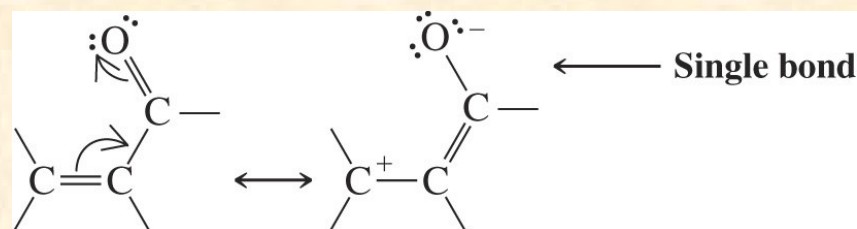
## Spectroscopic Properties of Aldehydes and Ketones

### – IR Spectra of Aldehydes and Ketones

- Aldehydes and ketones have strong carbonyl stretching frequencies in the 1665-1780  $\text{cm}^{-1}$  region

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

- Conjugation shifts the IR frequency about 40  $\text{cm}^{-1}$  lower because the carbonyl has less double bond character
  - Single bonds stretch more easily than double bonds



- Vibrations of the C-H bond in an aldehyde gives two weak but characteristic bands at 2700-2775 and 2820-2900  $\text{cm}^{-1}$

# Spectroscopic Properties

- NMR Spectra of Aldehydes and Ketones
  - $^{13}\text{C}$  NMR Spectra - carbonyl carbons give characteristic signals at  $\delta$  180-220
  - $^1\text{H}$  NMR Spectra - Aldehyde protons give sharp signals at  $\delta$  9-12
    - The aldehyde proton often shows coupling to the protons on the  $\alpha$ -carbon
    - Protons on the  $\alpha$  carbon generally appear at  $\delta$  2.0-2.3

