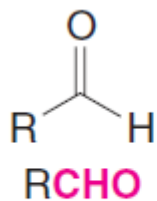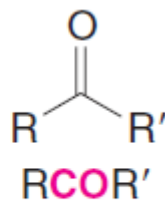# *Aldehydes and Ketones Nucleophilic Addition to the Carbonyl Group*

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

RCHO
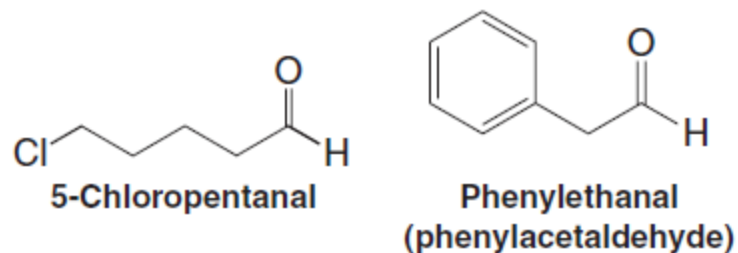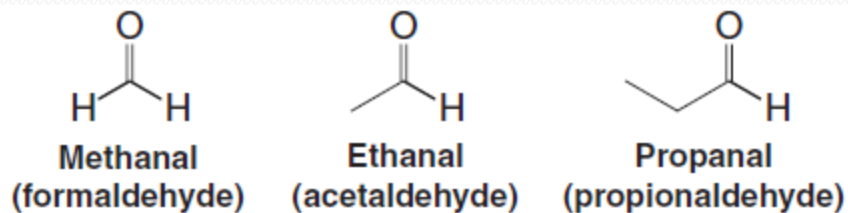General formulas
for an aldehyde

RCOR′
General formulas
for a ketone

Nomenclature of Aldehydes and Ketones

Aliphatic aldehydes are named substitutively in the IUPAC system by replacing the final **-e** of the name of the corresponding alkane with **–al** Since the aldehyde group must be at an end of the carbon chain, there is no need to indicate its position. When other substituents are present the carbonyl group carbon is assigned position 1. Many aldehydes also have common names; these are given below in parentheses. These common names are derived from the common names for the corresponding carboxylic acids and some of them are retained by the IUPAC as acceptable names

Methanal
(formaldehyde)

Ethanal
(acetaldehyde)

Propanal
(propionaldehyde)

5-Chloropentanal

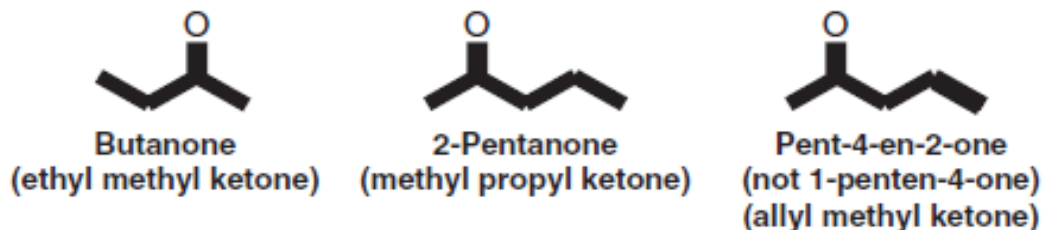**Phenylethanal**
(phenylacetaldehyde)

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

Benzenecarbaldehyde
(benzaldehyde)

Cyclohexanecarbaldehyde

2-Naphthalenecarbaldehyde
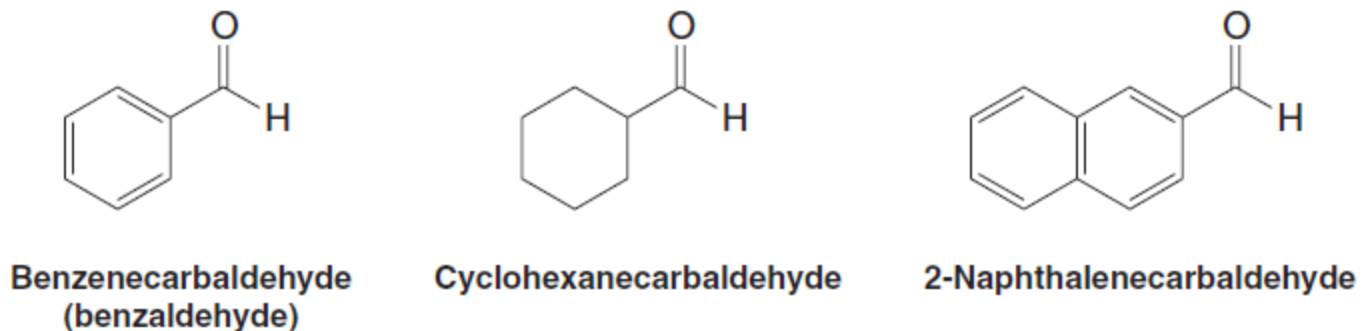
The common name *benzaldehyde* is far more frequently used than benzenecarbaldehyde for C_6H_5CHO, and it is the name we shall use in this text.
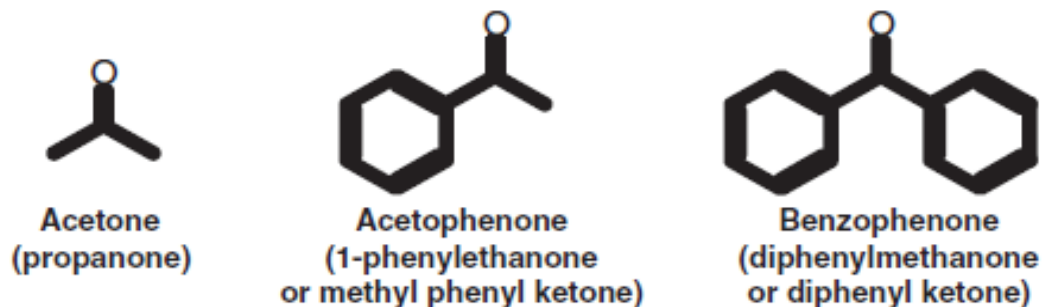
- Aliphatic ketones are named substitutively by replacing the final **-e** of the name of the corresponding alkane with **-one**.

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

Butanone
(ethyl methyl ketone)

2-Pentanone
(methyl propyl ketone)

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

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

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

Acetone
(propanone)

Acetophenone
(1-phenylethanone
or methyl phenyl ketone)

Benzophenone
(diphenylmethanone
or diphenyl ketone)

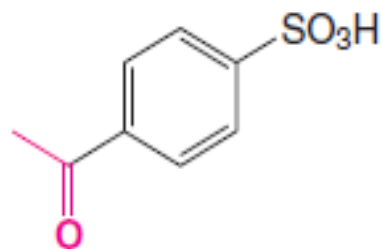When it is necessary to name the H group as a prefix, it is the **methanoyl** or **formyl**

group. The group is called the **ethanoyl** or **acetyl group** (often abbreviated as Ac).

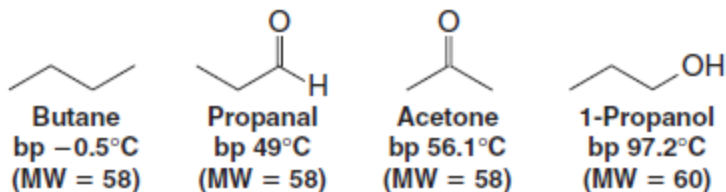When R groups are named as substituents, they are called **alkanoyl** or **acyl groups**.
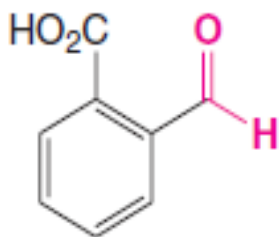
**2-Methanoylbenzoic acid**
(*o*-formylbenzoic acid)

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

Physical Properties

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

Butane
bp −0.5°C
(MW = 58)

Propanal
bp 49°C
(MW = 58)

Acetone
bp 56.1°C
(MW = 58)

1-Propanol
bp 97.2°C
(MW = 60)

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

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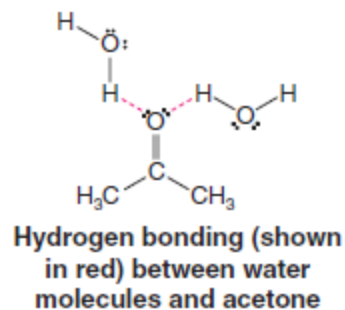
Synthesis of Aldehydes

Aldehydes by Oxidation of 1° Alcohols

● The oxidation state of an aldehyde lies between that of a 1° alcohol and a carboxylic acid

1° Alcohol → Aldehyde → Carboxylic acid
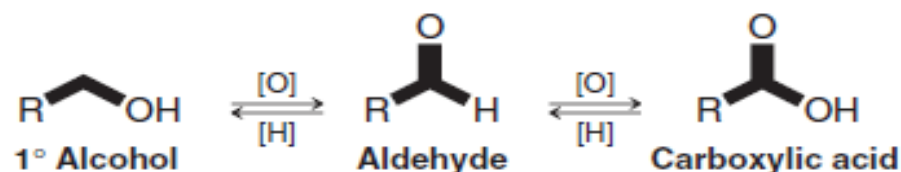
Aldehydes can be prepared from 1° alcohols by oxidation with pyridinium chlorochromate ($C_5H_5NH^+CrO_3Cl^-$, or PCC):
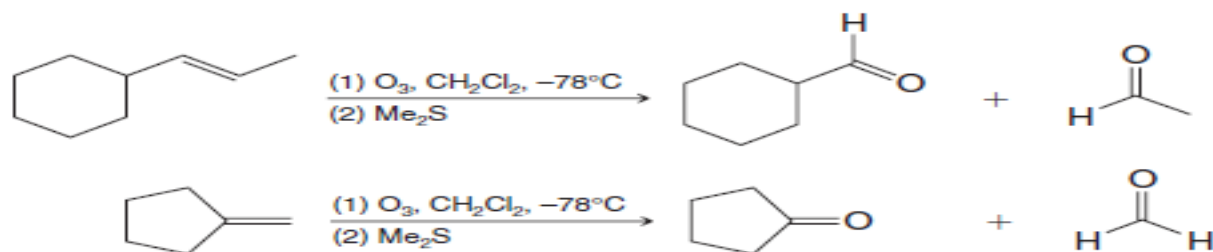

1° Alcohol → Aldehyde
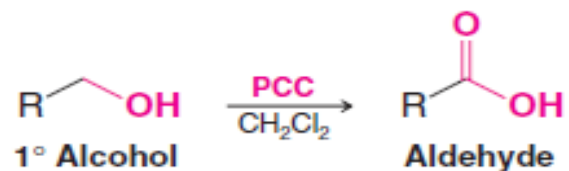
An example of the use of PCC in the synthesis of an aldehyde is the oxidation of 1-heptanol to heptanal:

1-Heptanol $\xrightarrow[CH_2Cl_2]{PCC}$ Heptanal (93%)
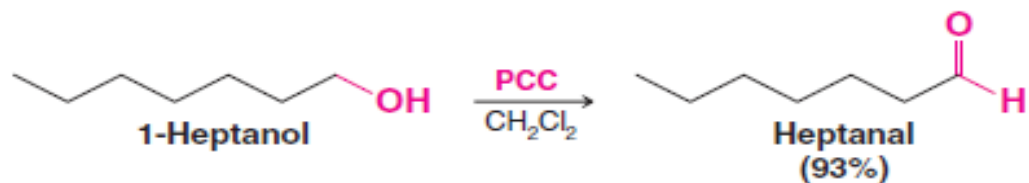
Aldehydes by Ozonolysis of Alkenes

- Alkenes can be cleaved by ozonolysis of their double bond The products are aldehydes and ketones.


Aldehydes by Reduction of Acyl Chlorides, Esters, and Nitriles

Theoretically, it ought to be possible to prepare aldehydes by reduction of carboxylic acids. In practice, this is not possible with the reagent normally used to reduce a carboxylic acid, lithium aluminum hydride (LiAlH$_4$ or LAH).

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

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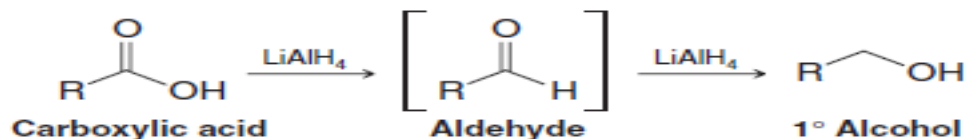

The secret to success here is not to use a carboxylic acid itself, but to use a derivative of a carboxylic acid that is more easily reduced, and an aluminum hydride derivative that is less reactive than LAH.

- Acyl chlorides (RCOCl), esters (RCO$_2$R'), and nitriles (RCN) are all easily prepared from carboxylic acids (Chapter 17), and they all are more easily reduced.

- Two derivatives of aluminum hydride that are less reactive than LAH, in part because they are much more sterically hindered, are **lithium tri-*tert*-butoxy-aluminum hydride** and **diisobutylaluminum hydride (DIBAL-H):**
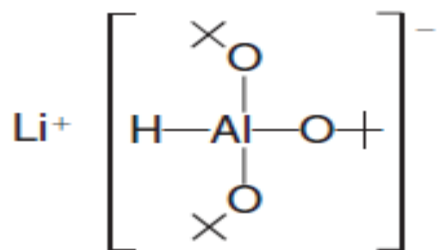
Lithium tri-*tert*-butoxy-aluminum hydride
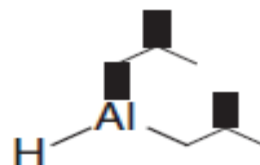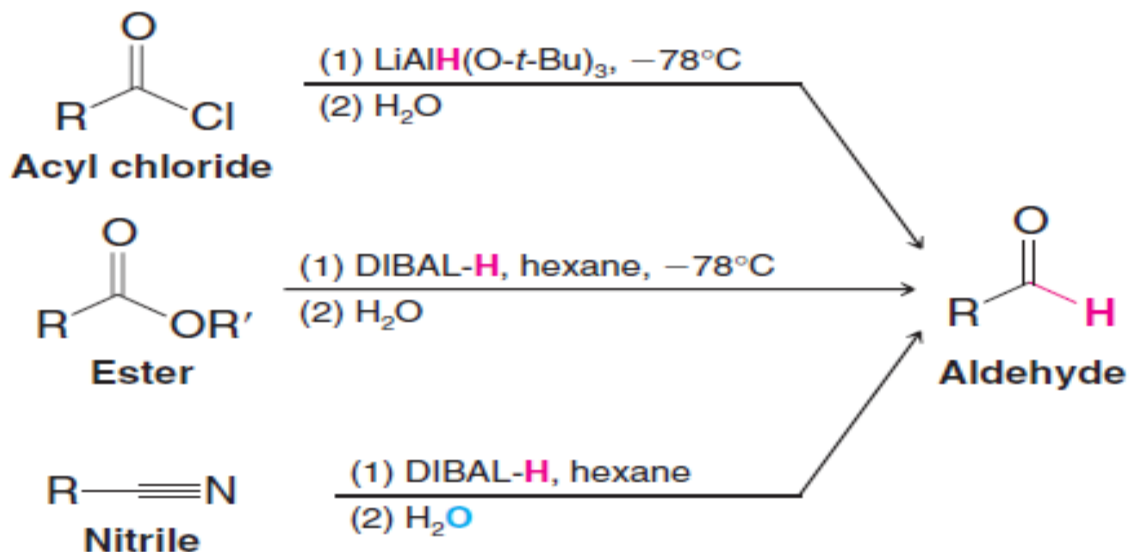
Diisobutylaluminum hydride (abbreviated *i*-Bu₂AlH or DIBAL-H)

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

Acyl chloride
(1) LiAlH(O-*t*-Bu)₃, −78°C
(2) H₂O

Ester
(1) DIBAL-H, hexane, −78°C
(2) H₂O

Nitrile
(1) DIBAL-H, hexane
(2) H₂O

Aldehyde

Aldehydes from Acyl Chlorides: RCOCl → RCHO

- Acyl chlorides can be reduced to aldehydes by treating them with LiAlH[OC(CH$_3$)$_3$]$_3$, lithium tri-*tert*-butoxyaluminum hydride, at $-78°C$.

- Carboxylic acids can be converted to acyl chlorides by using SOCl$_2$
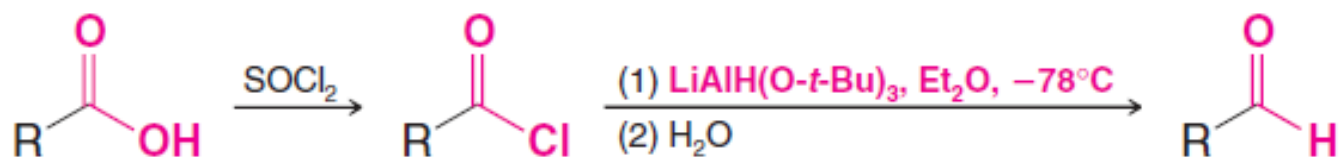
The following is a specific example:

3-Methoxy-4-methylbenzoyl chloride　　　　　　　**3-Methoxy-4-methylbenzaldehyde**
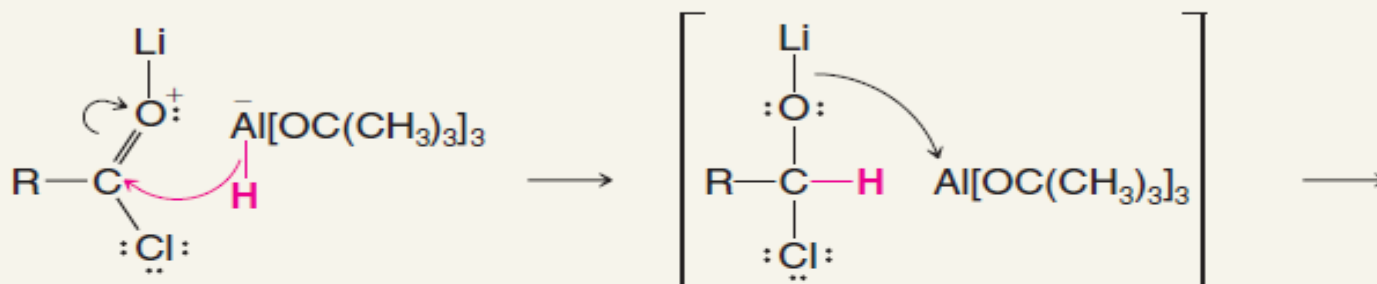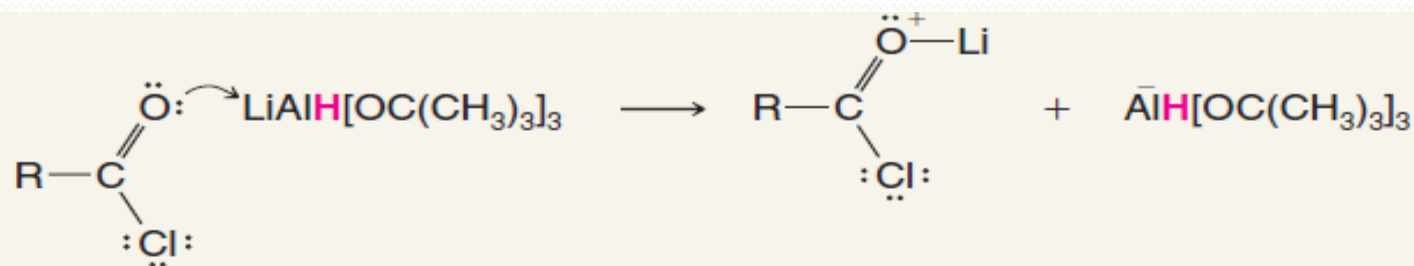
Transfer of a hydride ion to the carbonyl carbon brings about the reduction.
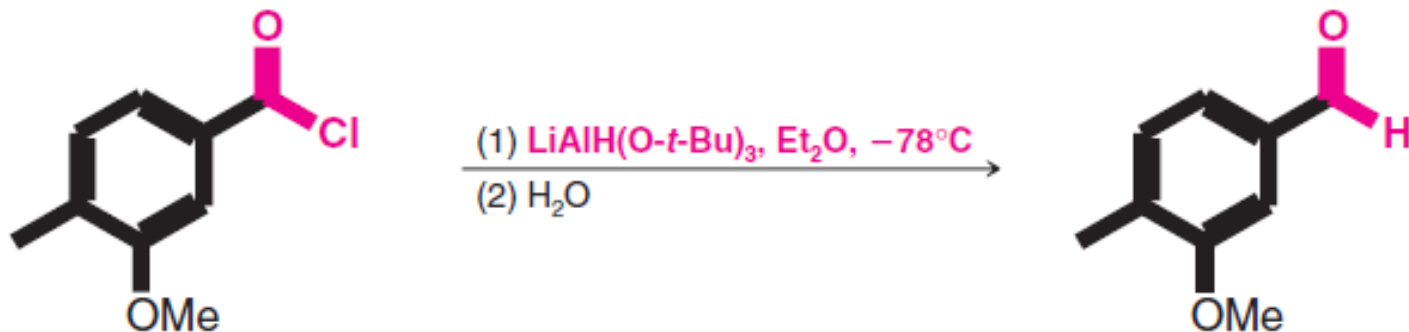
Acting as a Lewis acid, the aluminum atom accepts an electron pair from oxygen.
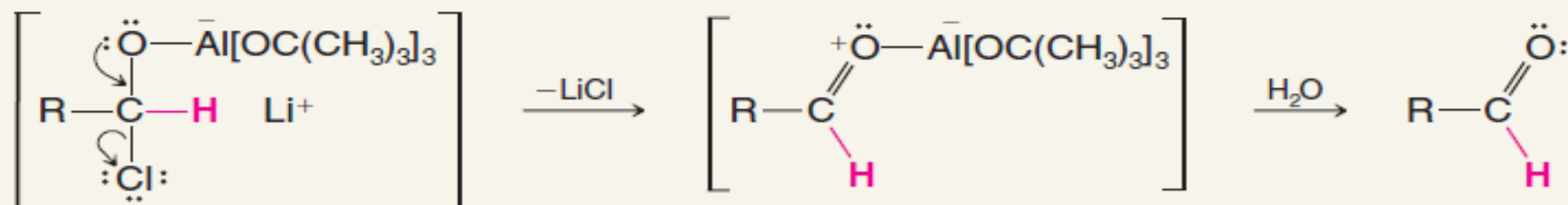
This intermediate loses a chloride ion as an electron pair from the oxygen assists.

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

Reduction of an Ester to an Aldehyde
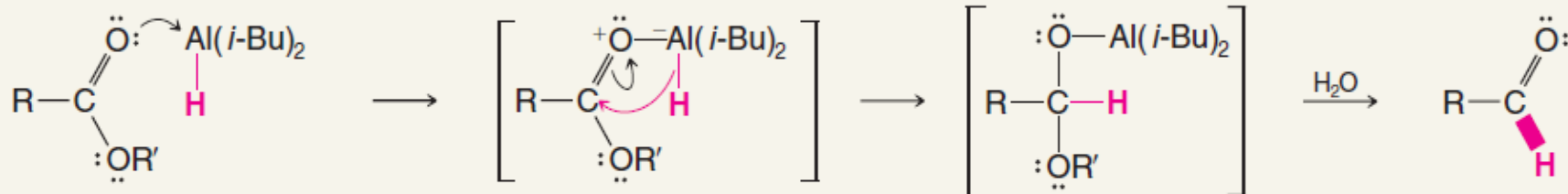
The aluminum atom accepts an electron pair from the carbonyl oxygen atom in a Lewis acid-base reaction.

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

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

Reduction of a Nitrile to an Aldehyde
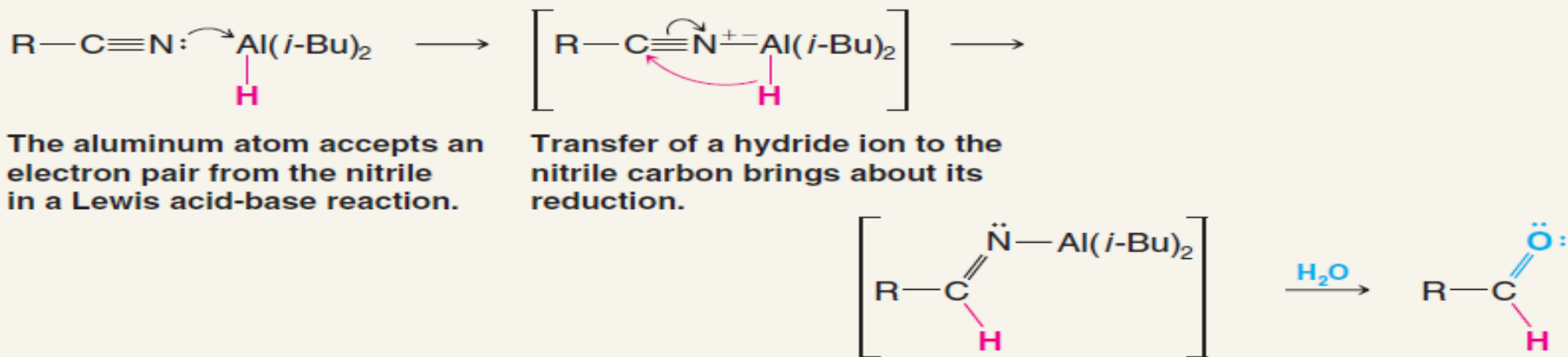
The aluminum atom accepts an electron pair from the nitrile in a Lewis acid-base reaction.

Transfer of a hydride ion to the nitrile carbon brings about its reduction.
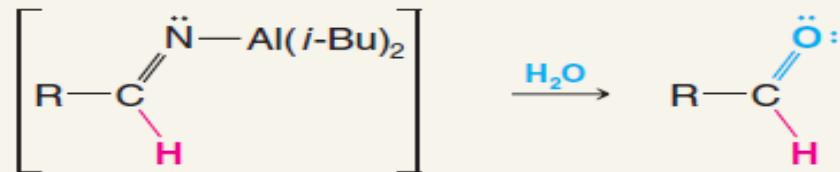
Addition of water at the end of the reaction hydrolyzes the aluminum complex and produces the aldehyde.

The following specific examples illustrate these syntheses:
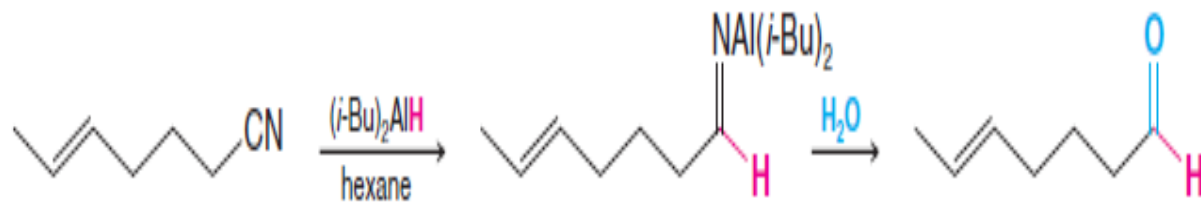
Ketones from Alkenes, Arenes, and 2° Alcohols

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

1. Ketones (and aldehydes) by ozonolysis of alkenes
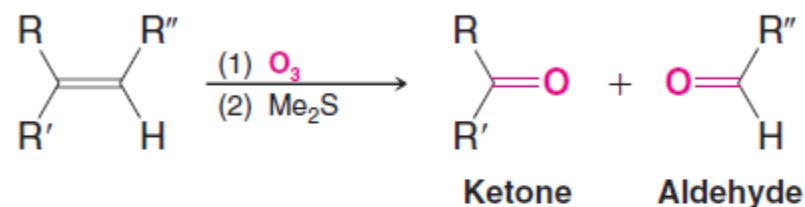
2. Ketones from arenes by Friedel–Crafts acylations
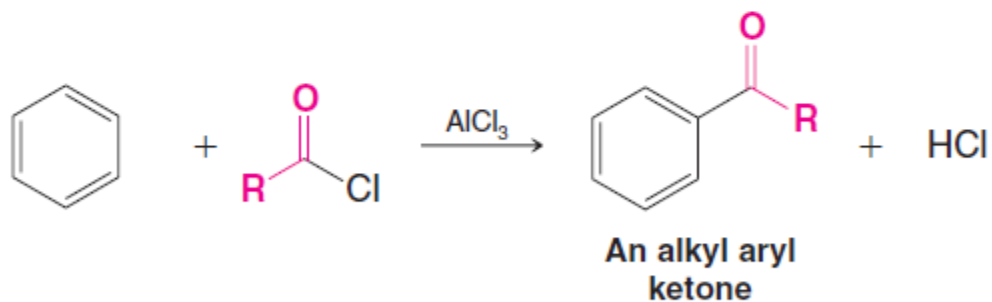
3. Ketones from secondary alcohols by oxidation
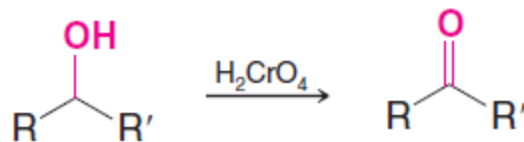
Ketones from Nitriles

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

General Reactions

$$R—{\equiv}N \ + \ R'—MgX \longrightarrow \underset{R}{\overset{N^-Mg^+X}{\big\|}}R' \xrightarrow{H_3O^+} \underset{R}{\overset{O}{\big\|}}R' \ + \ NH_4^+ \ + \ Mg^{2+} \ + \ X^-$$

$$R—{\equiv}N \ + \ R'—Li \longrightarrow \underset{R}{\overset{N^- \ Li^+}{\big\|}}R' \xrightarrow{H_3O^+} \underset{R}{\overset{O}{\big\|}}R' \ + \ NH_4^+ \ + \ Li^+$$
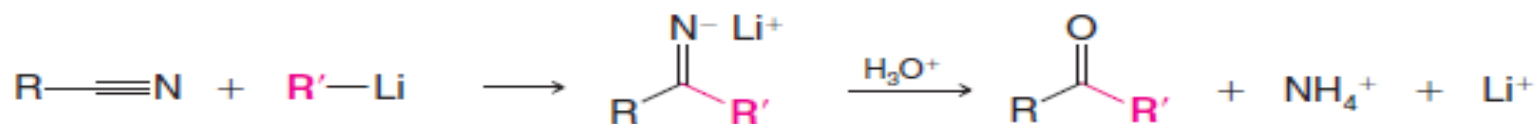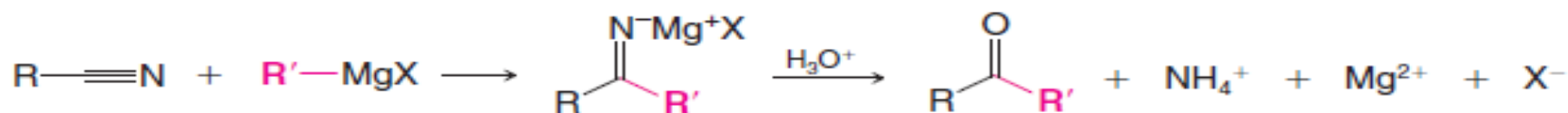
Specific Examples
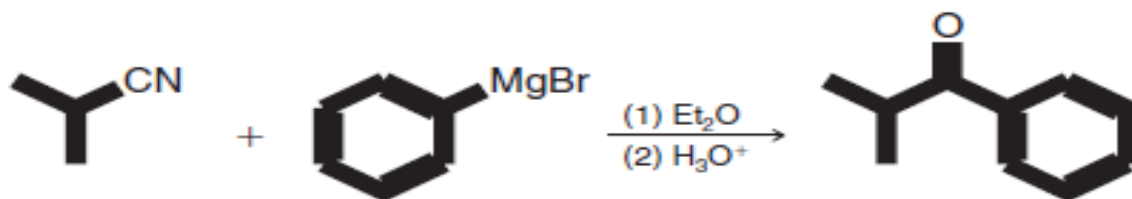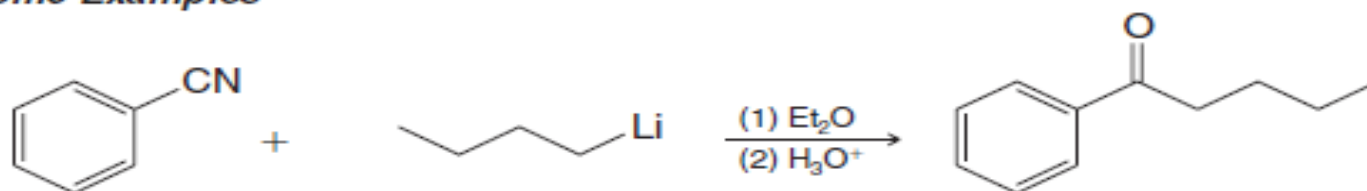
2-Cyanopropane

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

Acid-Catalyzed Nucleophilic Addition to an Aldehyde or Ketone

Step 1
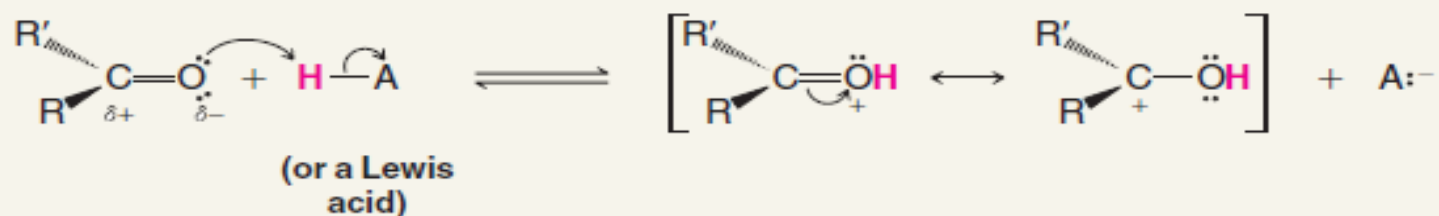
(or a Lewis acid)

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

Step 2
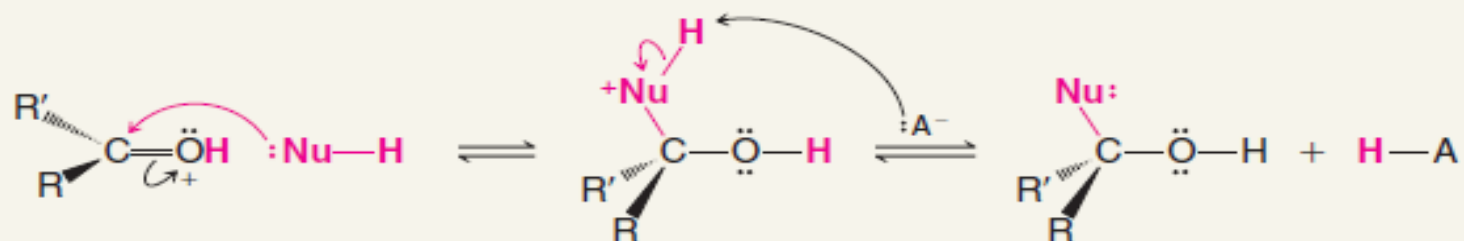
In the first of these two steps, the oxonium cation accepts the electron pair of the nucleophile. In the second step, a base removes a proton from the positively charged atom, regenerating the acid.

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

Relative Reactivity: Aldehydes versus Ketones

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

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

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

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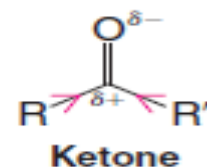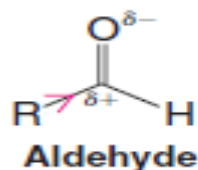
The Ketone carbonyl carbon is less positive because it has two electron-releasing alkyl groups.

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

The Addition of Alcohols: Hemiacetals and Acetals

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

Hemiacetals

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

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

Hemiacetal Formation

Aldehyde (or ketone)	Alcohol	Hemiacetal (usually too unstable to isolate)

In this step the alcohol attacks the carbonyl carbon.

In two intermolecular steps, a proton is removed from the positive oxygen and a proton is gained at the negative oxygen.
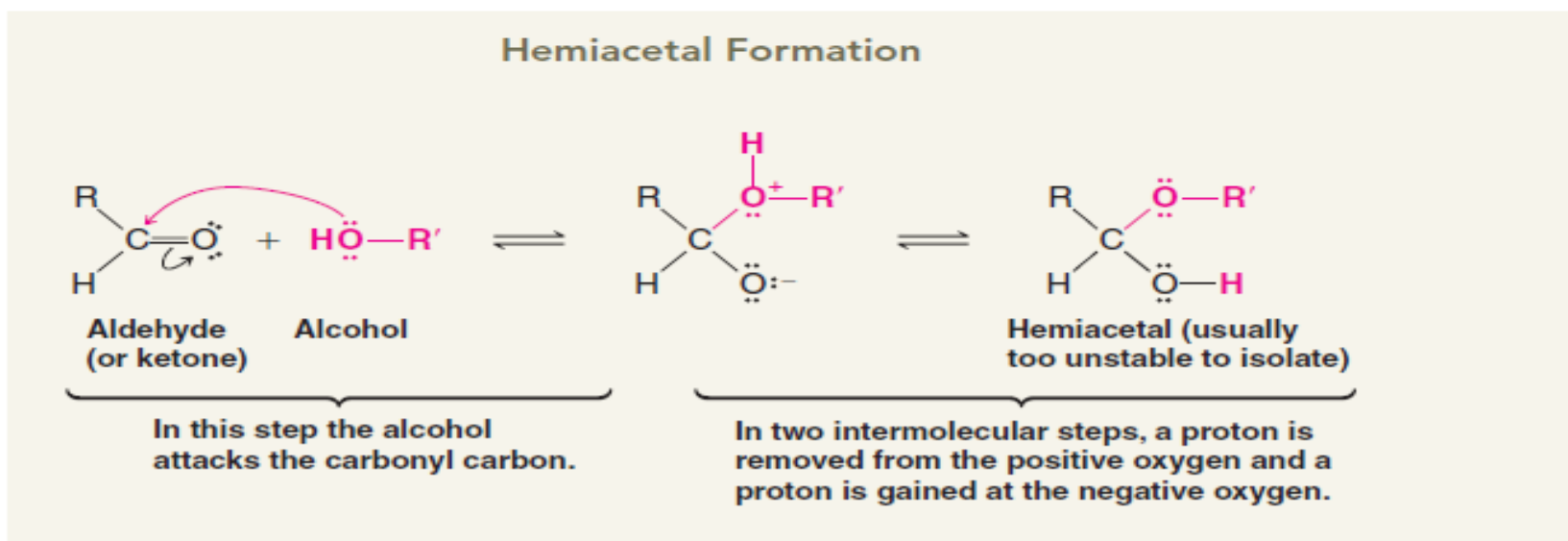
Acid-Catalyzed Hemiacetal Formation
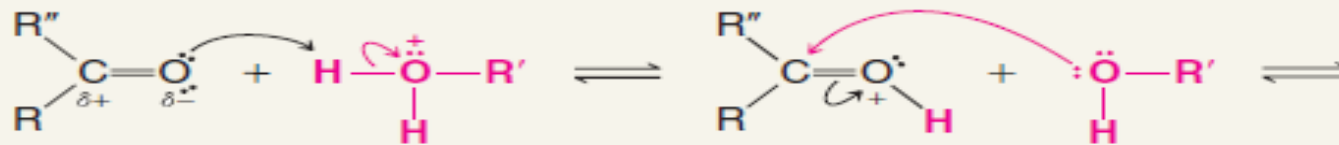
(R" may be H)

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

An alcohol molecule adds to the carbon of the oxonium cation.
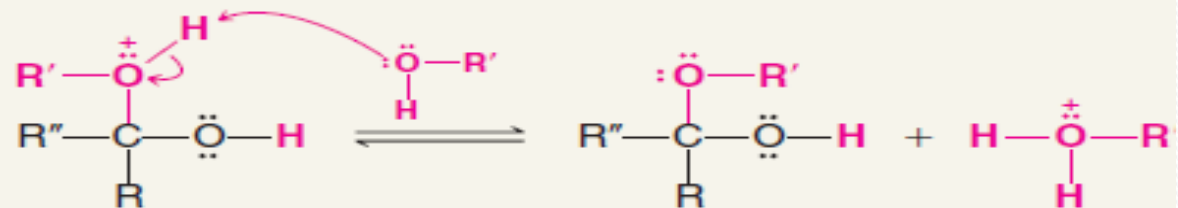
The transfer of a proton from the positive oxygen to another molecule of the alcohol leads to the hemiacetal.

Base-Catalyzed Hemiacetal Formation
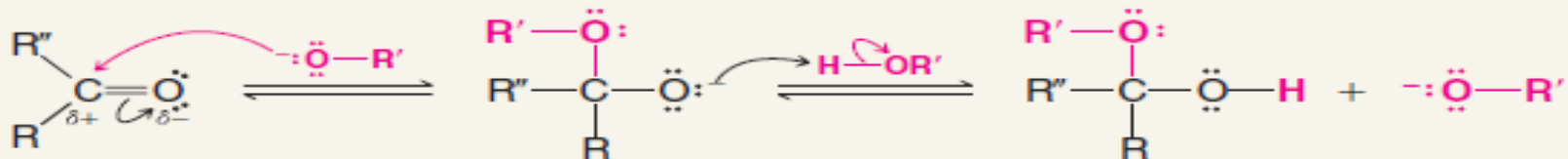
(R" may be H)

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

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

Acetals

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

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

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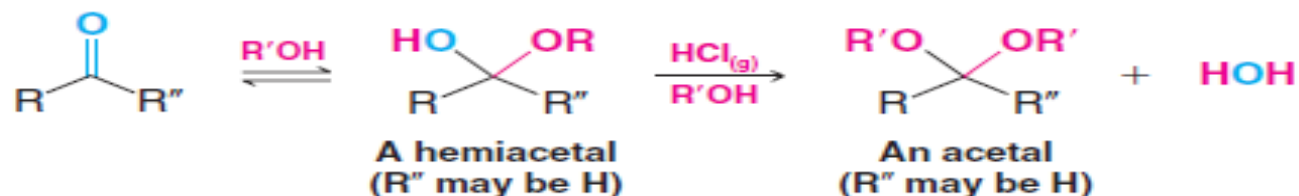
An acetal
(R″ may be H)

Shown below is the structural formula for sucrose (table sugar). Sucrose has two acetal groupings. Identify these.
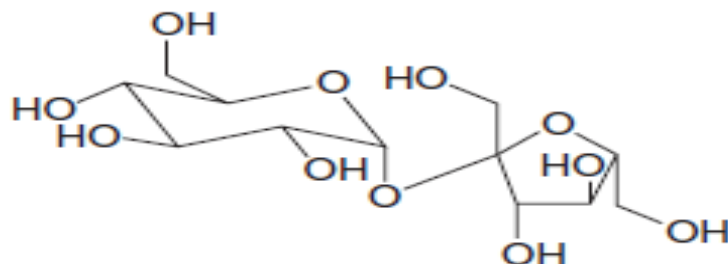
- The mechanism for acetal formation involves acid-catalyzed formation of the hemiacetal, then an acid-catalyzed elimination of water, followed by a second *addition* of the alcohol and loss of a proton.

- All steps in the formation of an acetal from an aldehyde are reversible.

Acid-Catalyzed Acetal Formation

Proton transfer to the carbonyl oxygen

Nucleophilic addition of the first alcohol molecule

Proton removal from the positive oxygen results in formation of a hemiacetal.
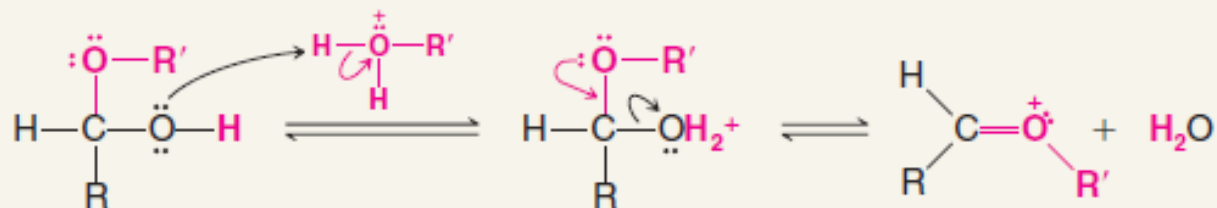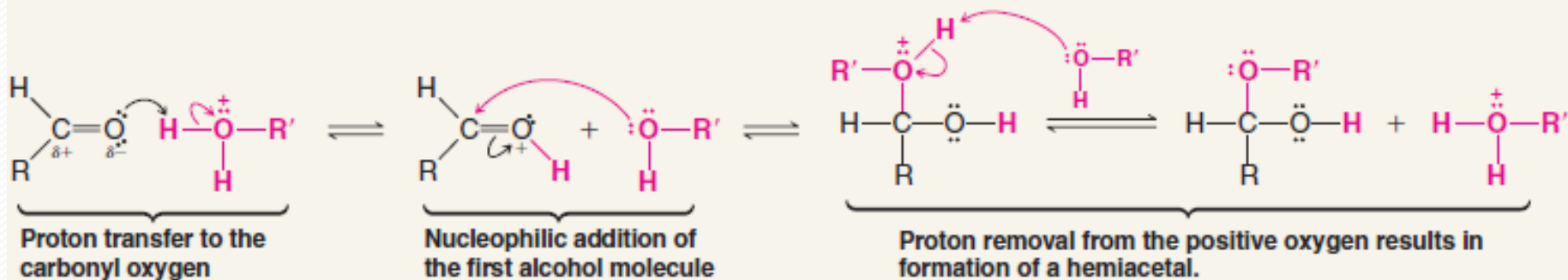
Protonation of the hydroxyl group leads to elimination of water and formation of a highly reactive oxonium cation.
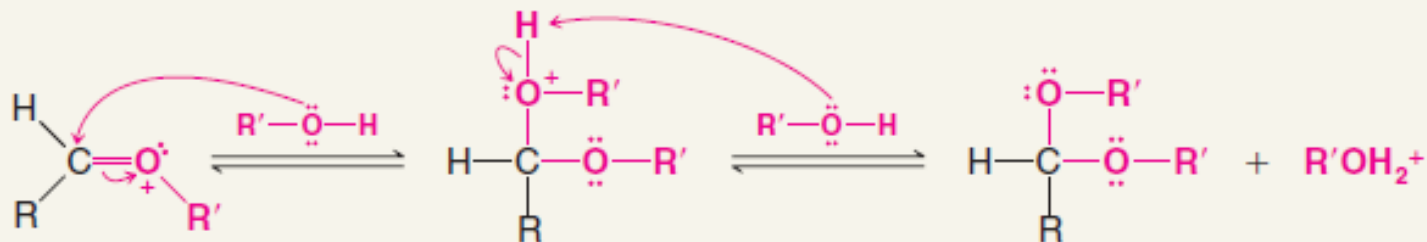
Attack on the carbon of the oxonium ion by a second molecule of the alcohol, followed by removal of a proton, leads to the acetal.

Acetals Are Used as Protecting Groups

- Although acetals are hydrolyzed to aldehydes and ketones in aqueous acid, *acetals are stable in basic solutions*:
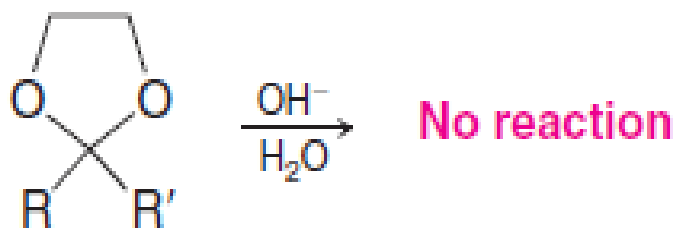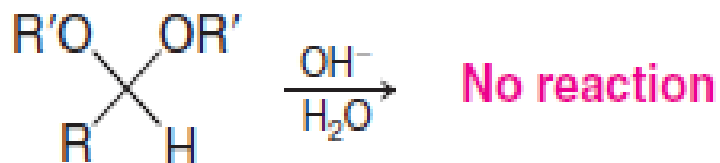
- Acetals are used to protect aldehydes and ketones from undesired reactions in basic solutions.

The Addition of Primary and Secondary Amines

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

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

From a 1° amine

From a 2° amine

Imine

Enamine

$$R^1, R^2, R^3 = C \text{ or } H;$$
$$R^4, R^5 = C$$

Imine Formation

Aldehyde or ketone + **1° Amine** ⇌ **Dipolar intermediate** ⇌ **Aminoalcohol**
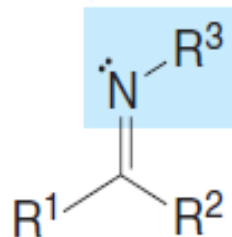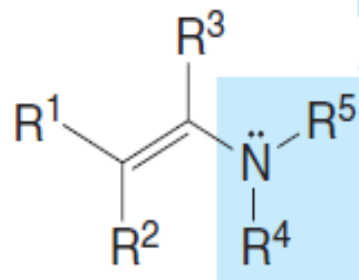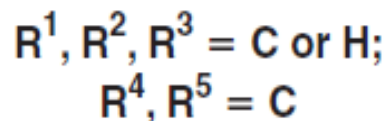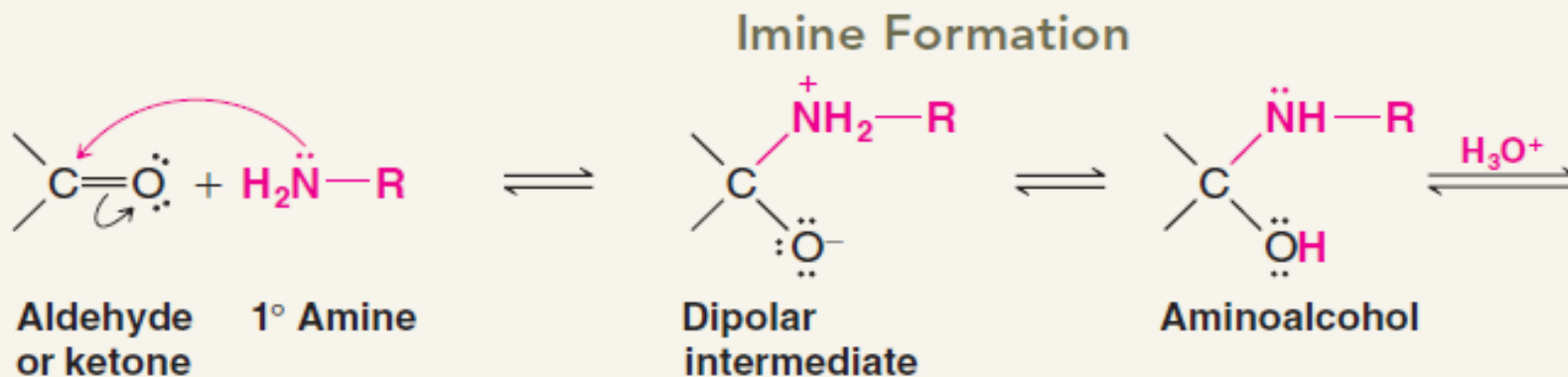
The amine adds to the carbonyl group to form a dipolar tetrahedral intermediate.

Intermolecular proton transfer from nitrogen to oxygen produces an aminoalcohol.

Protonated aminoalcohol $\xrightarrow{-H_2O}$ **Iminium ion** ⇌ **Imine [(E) and (Z) isomers]** + H_3O^+
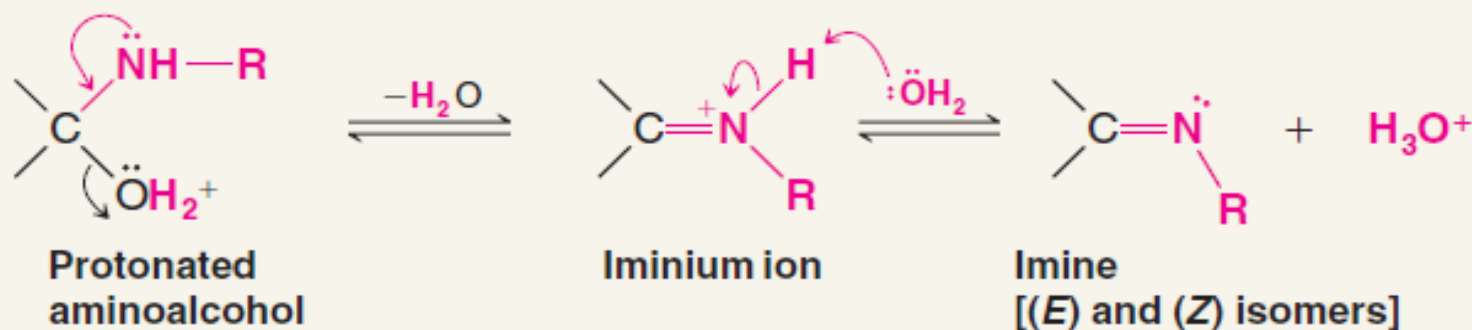
Protonation of the oxygen produces a good leaving group. Loss of a molecule of water yields an iminium ion.

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

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

Oximes and Hydrazones

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

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

Reactions of Aldehydes and Ketones with Derivatives of Ammonia

1. Imine formation—reaction with a primary amine

Aldehyde or ketone   A 1° amine   An imine [(E) and (Z) isomers]

2. Oxime formation—reaction with hydroxylamine

Aldehyde or ketone   Hydroxylamine   An oxime [(E) and (Z) isomers]

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

$$\text{C=O} + H_2NNH_2 \longrightarrow \text{C=N}\overset{NH_2}{\underset{..}{}} + H_2O$$

Aldehyde or ketone   Hydrazine   A hydrazone

$$\text{C}\blacksquare\text{O} + H_2NNHC_6H_5 \longrightarrow \text{C=NNHC}_6H_5 + H_2O$$

Phenylhydrazine   A phenylhydrazone

$$\text{C=O} + H_2NNH-\underset{NO_2}{\underset{|}{\bigcirc}}-NO_2 \longrightarrow \text{C=NNH}-\underset{NO_2}{\underset{|}{\bigcirc}}-NO_2 + H_2O$$

2,4-Dinitrophenylhydrazine   A 2,4-dinitrophenylhydrazone
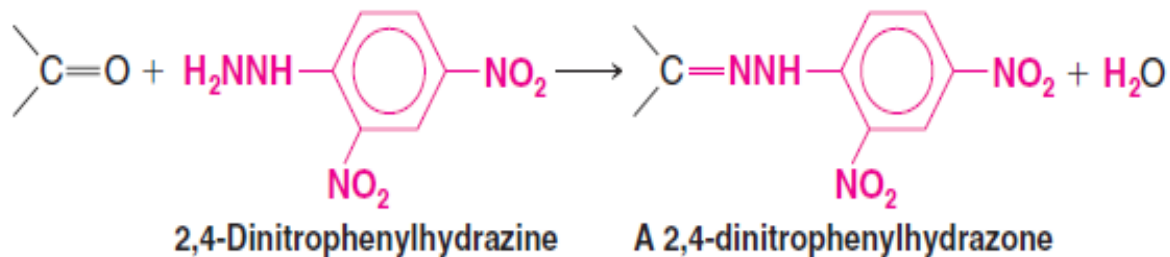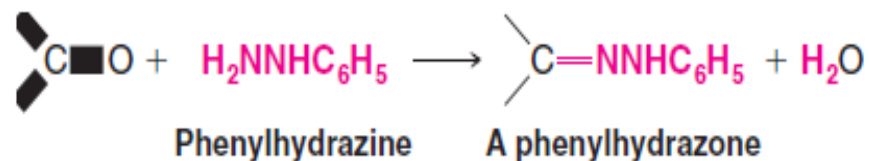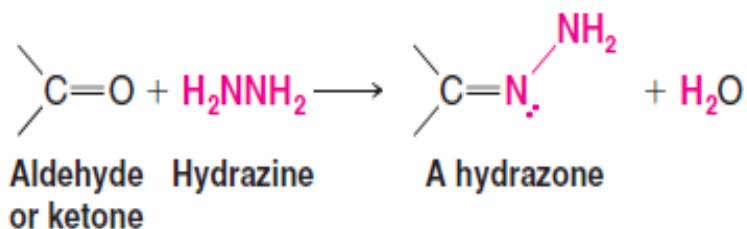
4. Enamine formation—reaction with a secondary amine

$$-\underset{H}{\underset{|}{C}}-\overset{\overset{..O..}{||}}{C}- + H-\overset{R}{\underset{R}{\underset{|}{\overset{|}{\ddot{N}}}}}-R \xrightleftharpoons{\text{cat. HA}} \text{C=C}\overset{R}{\underset{R}{\overset{|}{\underset{}{N}}}} + HOH$$

Secondary amine   Enamine

Enamine Formation

Step 1

Aldehyde or ketone   Secondary amine   Aminoalcohol intermediate

Step 2

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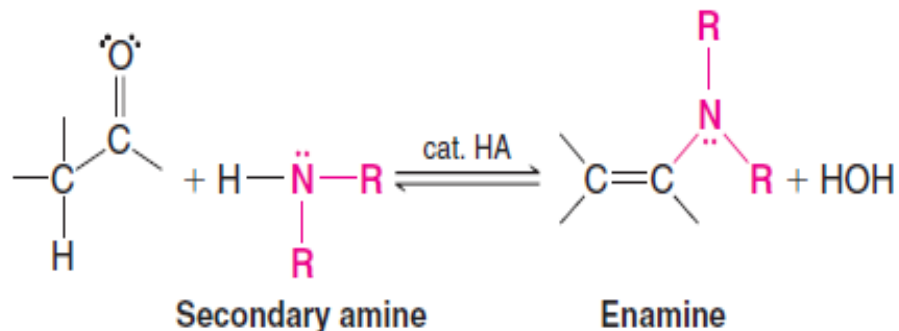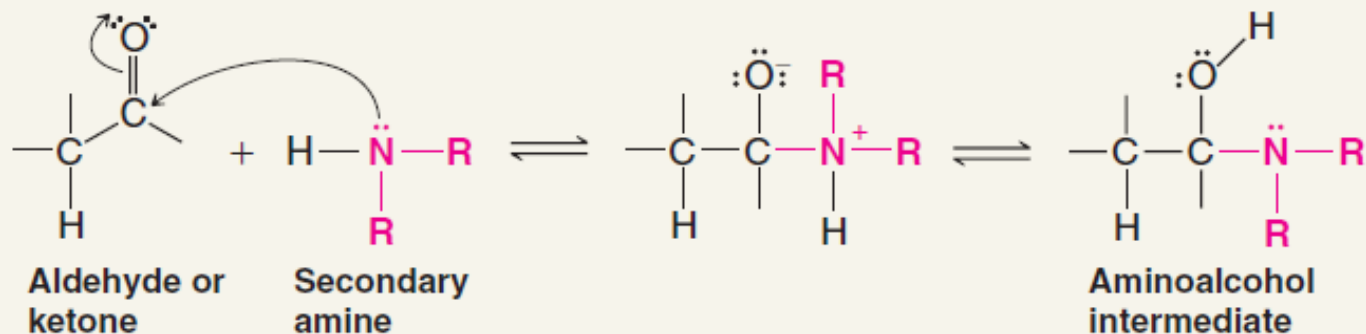
The aminoalcohol intermediate is protonated by the catalytic acid. Contribution of an unshared electron pair from the nitrogen atom and departure of a water molecule lead to an iminium cation intermediate.

Step 3

Enamine

The Addition of Hydrogen Cyanide: Cyanohydrins

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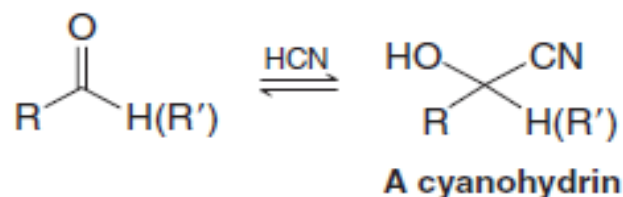
A cyanohydrin

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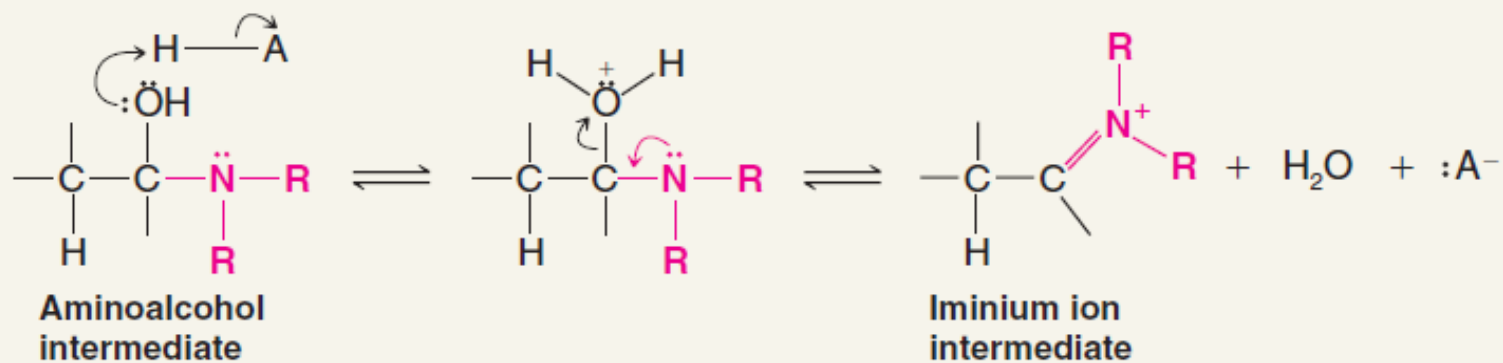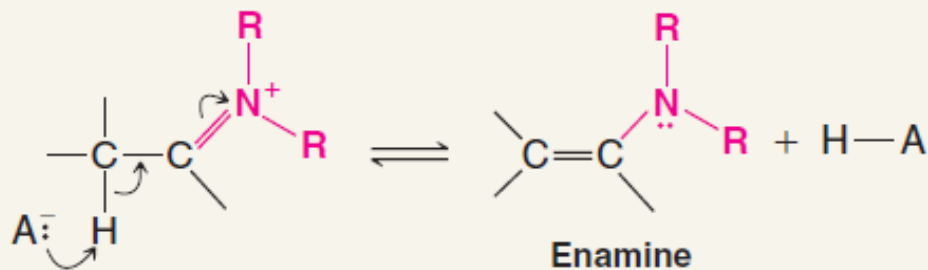eak acidity of HCN ($pK_a \sim 9$) provides only a small concentration of the nucleophilic cyanide anion. The following is a mechanism for formation of a cyanohydrin.

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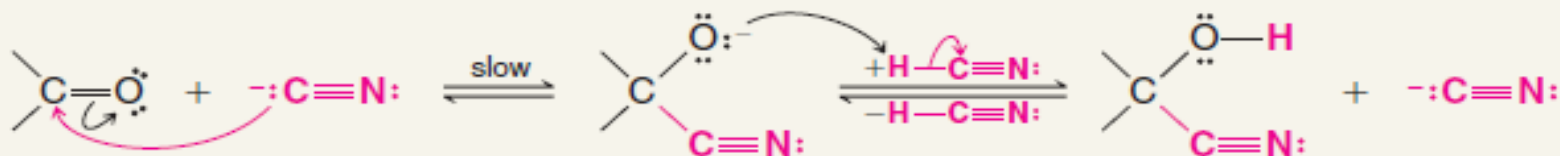
Great care must be taken when working with hydrogen cyanide due to its high toxicity and volatility. Reactions involving HCN must be conducted in an efficient fume hood.

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

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

α-**Hydroxy acid**

α,β-**Unsaturated acid**
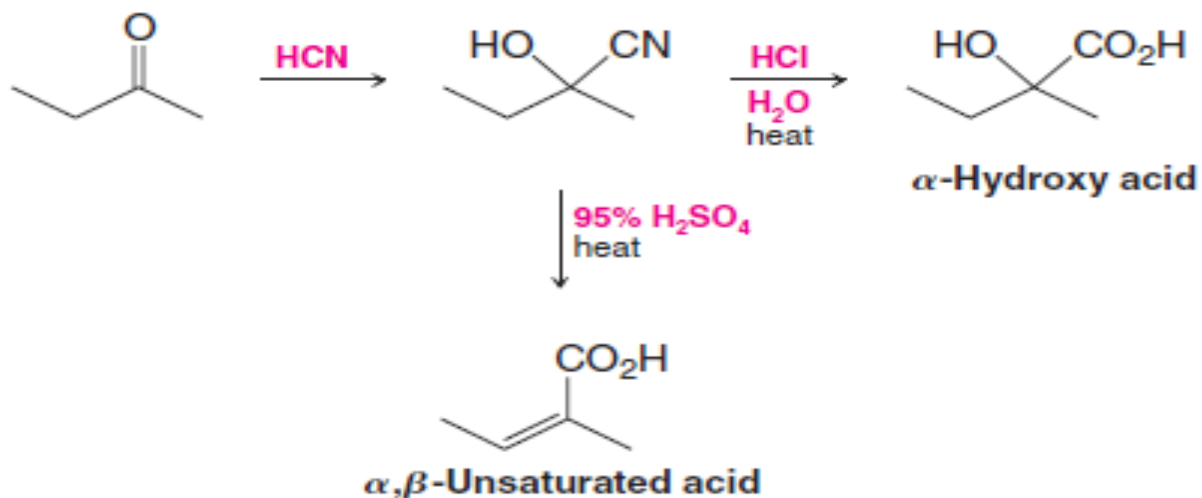
- Reduction of a cyanohydrin with lithium aluminum hydride gives a β-aminoalcohol
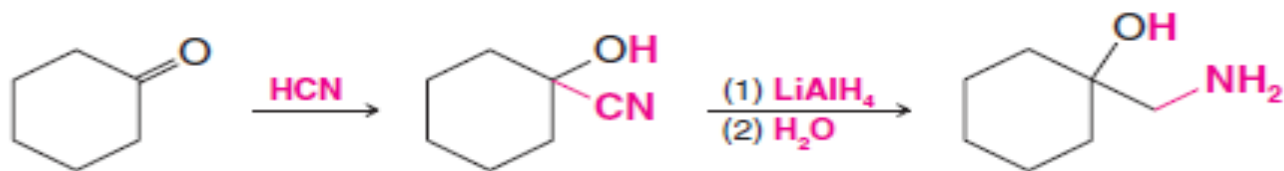
The Addition of Ylides: The Wittig Reaction

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

The Wittig reaction has proved to be a valuable method for synthesizing alkenes. The ylide required for the reaction is a molecule with no net charge but which has a negative carbon atom adjacent to a positive heteroatom, which in the Wittig reaction is a phosphorus atom. Phosphorus ylides are also called phosphoranes.

$$
\underset{\substack{\text{Aldehyde or}\\\text{ketone}}}{\overset{\displaystyle R}{\underset{\displaystyle R'}{>}}C=O} \;+\; \underset{\substack{\text{Phosphorus ylide}\\\text{(or phosphorane)}}}{(C_6H_5)_3\overset{+}{P}-\overset{..}{\overset{-}{C}}\overset{R''}{\underset{R'''}{<}}} \;\longrightarrow\; \underset{\subs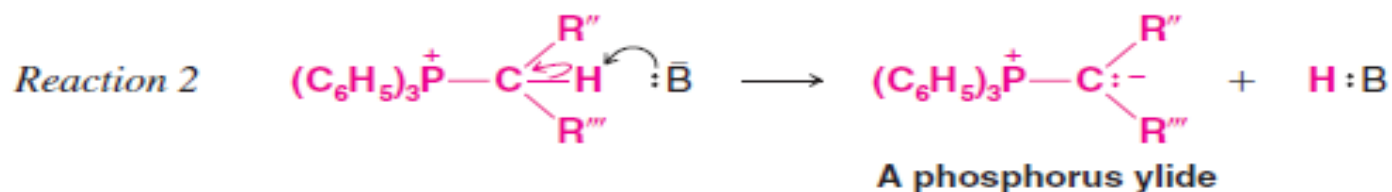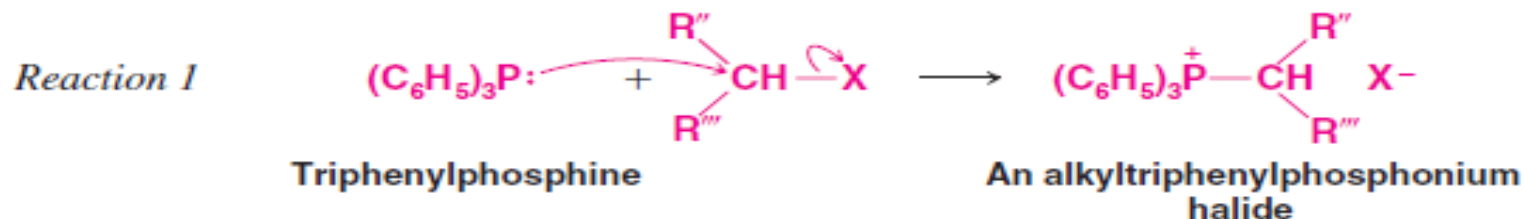tack{\text{Alkene}\\ [(E)\text{ and }(Z)\text{ isomers}]}}{\overset{\displaystyle R}{\underset{\displaystyle R'}{>}}C=C\overset{R''}{\underset{R'''}{<}}} \;+\; \underset{\substack{\text{Triphenyl-}\\\text{phosphine oxide}}}{O=P(C_6H_5)_3}
$$

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

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

General Reaction

Reaction 1

$(C_6H_5)_3P\colon\ \ \ +\ \ \underset{R'''}{\overset{R''}{>}}CH-X\ \ \longrightarrow\ \ (C_6H_5)_3\overset{+}{P}-\underset{R'''}{\overset{R''}{C}}H\ \ \ X^-$

Triphenylphosphine

An alkyltriphenylphosphonium halide

Reaction 2

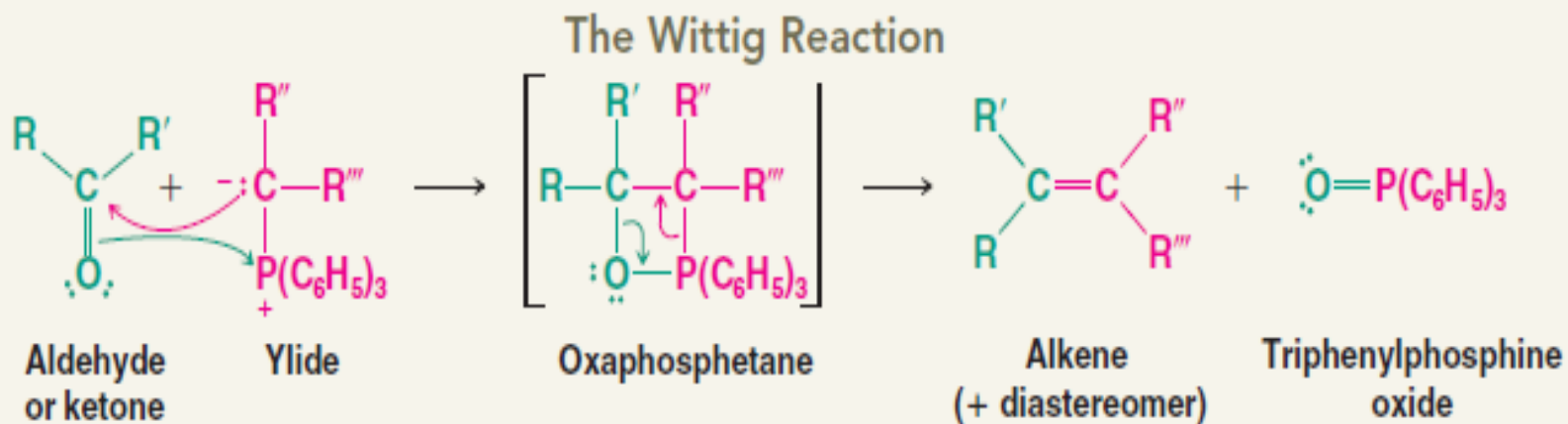$(C_6H_5)_3\overset{+}{P}-\underset{R'''}{\overset{R''}{C}}H\ \ \ \colon\bar{B}\ \ \longrightarrow\ \ (C_6H_5)_3\overset{+}{P}-\underset{R'''}{\overset{R''}{C}}\colon^-\ \ \ +\ \ \ H\colon B$

A phosphorus ylide

Specific Example

Reaction 1

$(C_6H_5)_3P\colon\ \ \ +\ \ \ CH_3Br\ \ \xrightarrow[C_6H_6]{}\ \ (C_6H_5)_3\overset{+}{P}-CH_3\ \ Br^-$

Methyltriphenylphosphonium bromide
(89%)

Reaction 2

$(C_6H_5)_3\overset{+}{P}-CH_3\ \ \ +\ \ \ C_6H_5Li\ \ \longrightarrow\ \ (C_6H_5)_3\overset{+}{P}-CH_2\colon^-\ \ +\ \ C_6H_6\ \ +\ \ LiBr$
Br^-
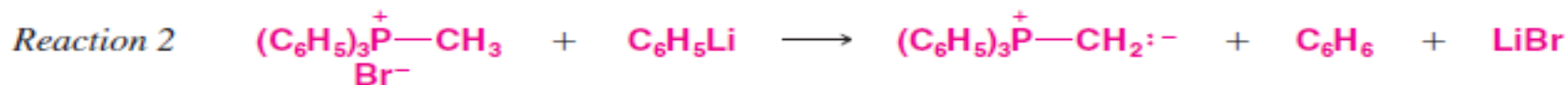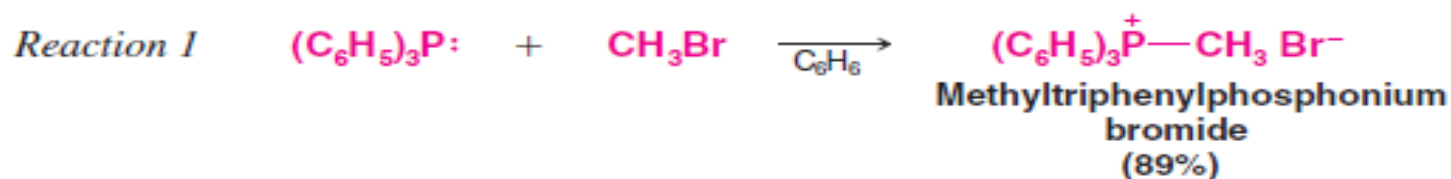
The first reaction is a nucleophilic substitution reaction. Triphenylphosphine is an excellent nucleophile and a weak base. It reacts readily with 1° and 2° alkyl halides by an S_N2 mechanism to displace a halide ion from the alkyl halide to give an alkyltriphenylphosphonium salt. The second reaction is an acid–base reaction. A strong base (usually an alkyllithium or phenyllithium) removes a proton from the carbon that is attached to phosphorus to give the ylide.

The Wittig Reaction

Aldehyde or ketone + Ylide ⟶ Oxaphosphetane ⟶ Alkene (+ diastereomer) + Triphenylphosphine oxide

Specific Example

Methylenecyclohexane
(86% from cyclohexanone
and methyltriphenylphosphonium
bromide)