

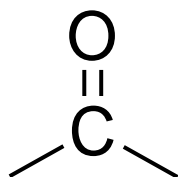
3. Reactions of carbonyl groups

3.1 Addition reaction

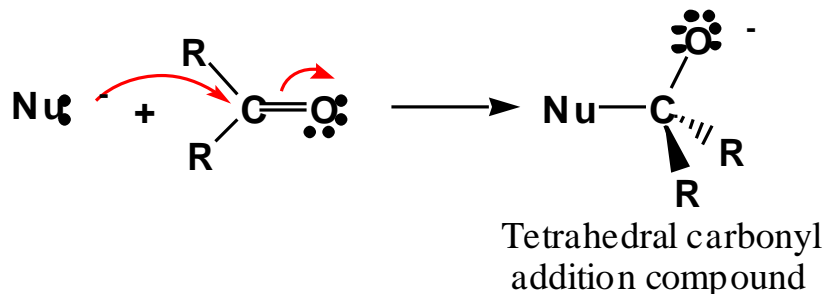
3. Reactions of carbonyl groups

Addition reaction

- “carbonyl” functional group

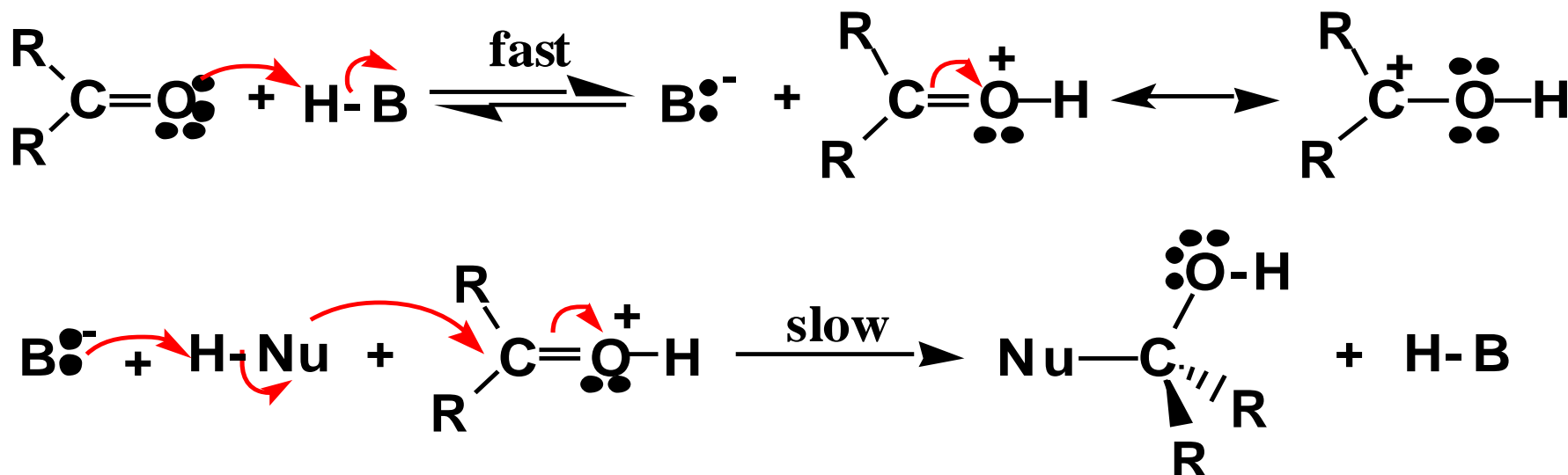


- One of the most common reaction themes of a carbonyl group is addition of a nucleophile to form a tetrahedral carbonyl addition compound.



Reaction Themes

- A second common theme is reaction with a proton or other Lewis acid to form a resonance-stabilized cation.
 - Protonation increases the electron deficiency of the carbonyl carbon and makes it more reactive toward nucleophiles.



Addition of C Nucleophiles

- Addition of carbon nucleophiles is one of the most important types of nucleophilic additions to a C=O group.
- A new carbon-carbon bond is formed in the process.
- Four common types of carbon nucleophiles are:

RMgX
A Grignard reagent

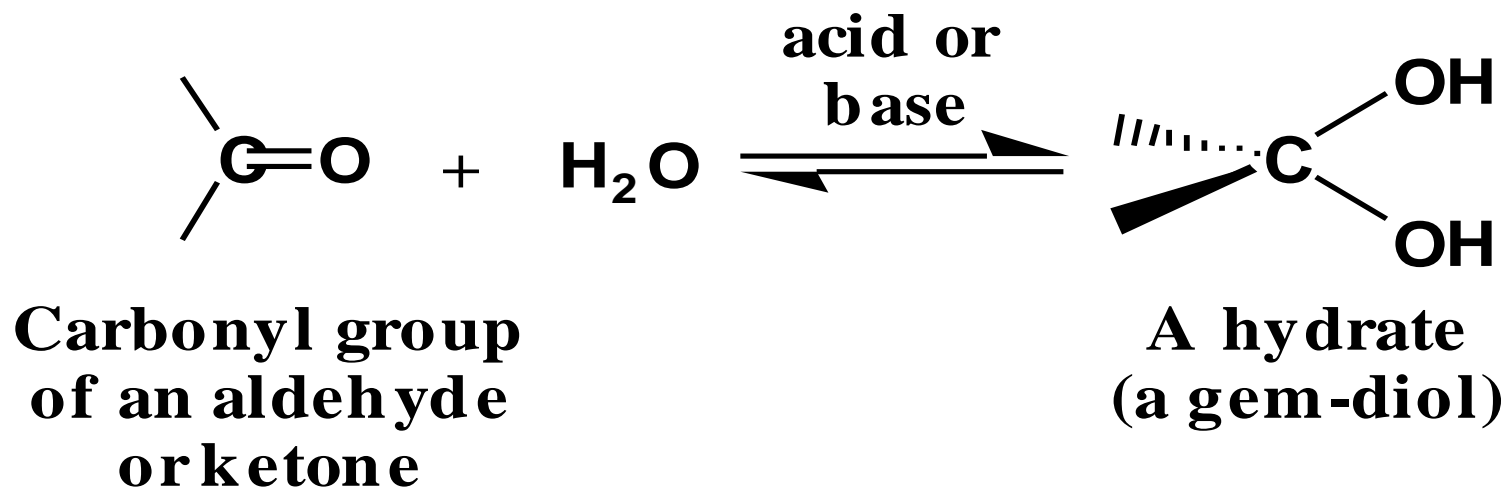
RLi
An organolithium reagent

$\text{RC}\equiv\text{C}:\text{ }^-$
An alkyne anion

$:\text{C}\equiv\text{N}:$
Cyanide ion

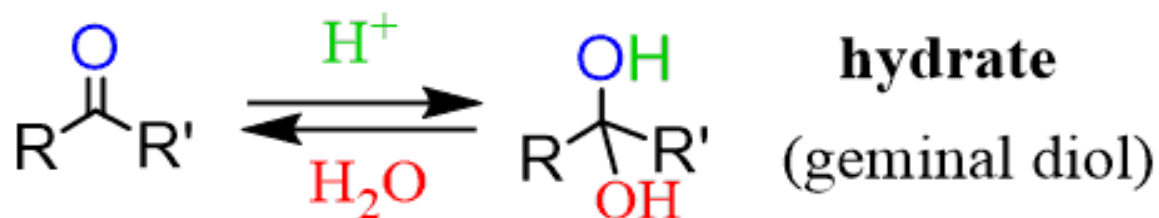
Hydrates

- Addition of water (hydration) to the carbonyl group of an aldehyde or ketone gives a geminal diol, commonly referred to as a gem-diol.
- A gem-diol is also referred to as a hydrate.

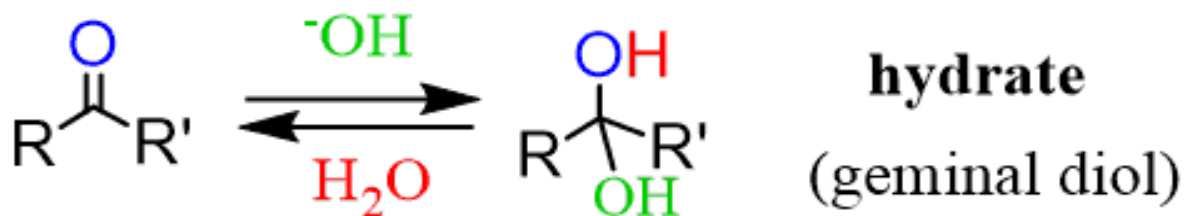


Aldehydes and Ketones:

Reaction with Water produces a Hydrate



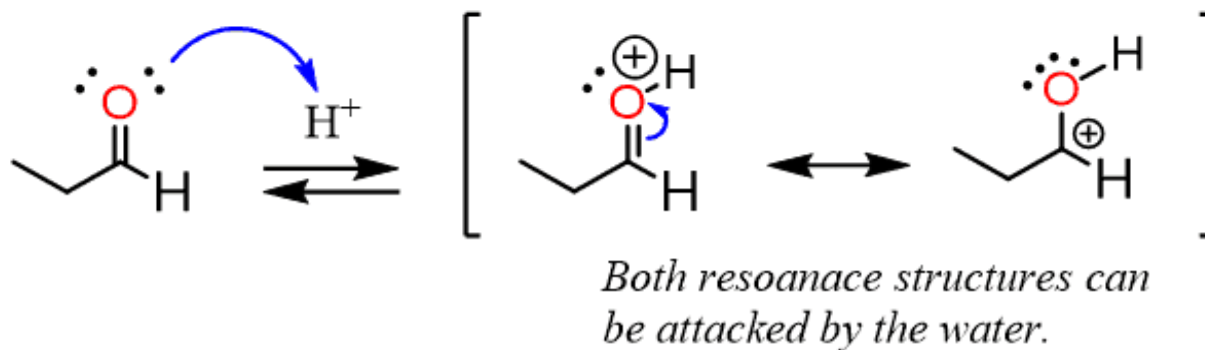
Acid-Catalyzed Addition of water



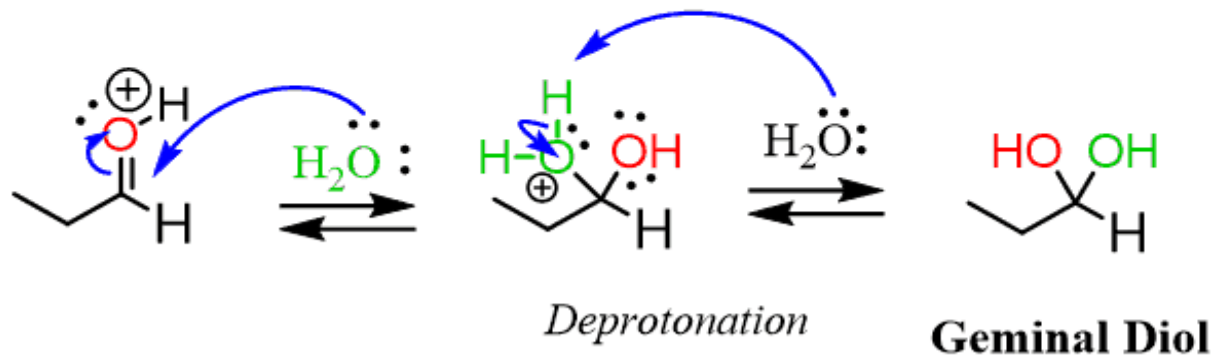
Base-Catalyzed Addition of water

Acid-Catalyzed Hydration of Aldehydes and Ketones

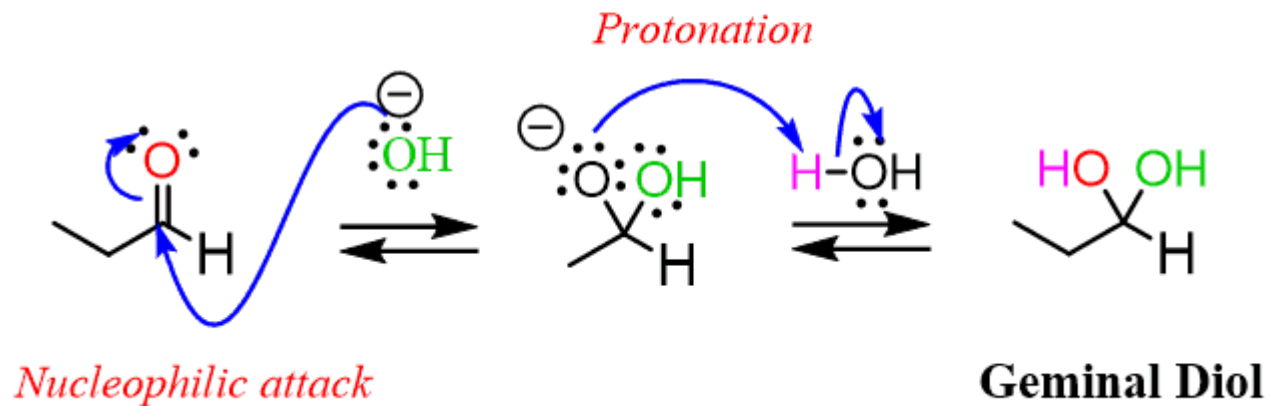
Step 1. Protonation of carbonyl



Step 2. Nucleophilic Addition

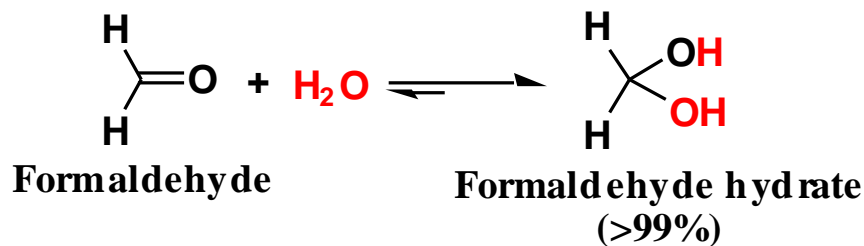


Base-Catalyzed Hydration of Aldehydes and Ketones

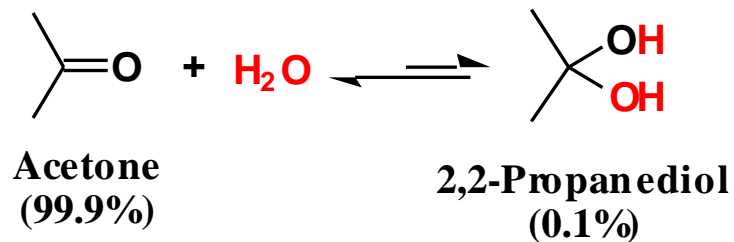


Hydrates

- When formaldehyde is dissolved in water at 20°C, the carbonyl group is more than 99% hydrated.

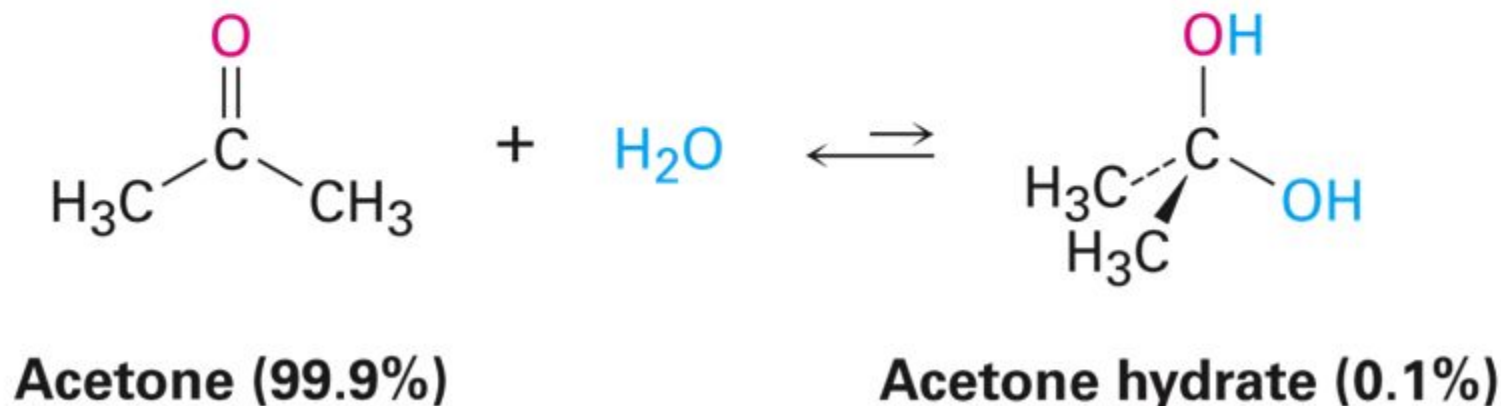


- The equilibrium concentration of a hydrated ketone is considerably smaller.



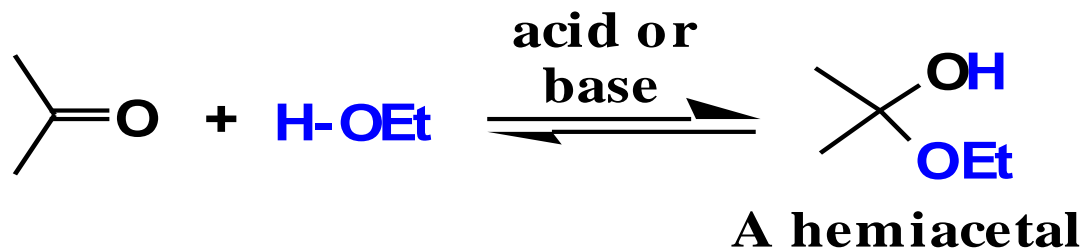
Nucleophilic Addition: Hydration

- Aldehydes and ketones react with water to yield 1,1-diols or geminal diols
- Hydration is reversible
- Equilibrium depends on structure of carbonyl compound



Hemi-acetals

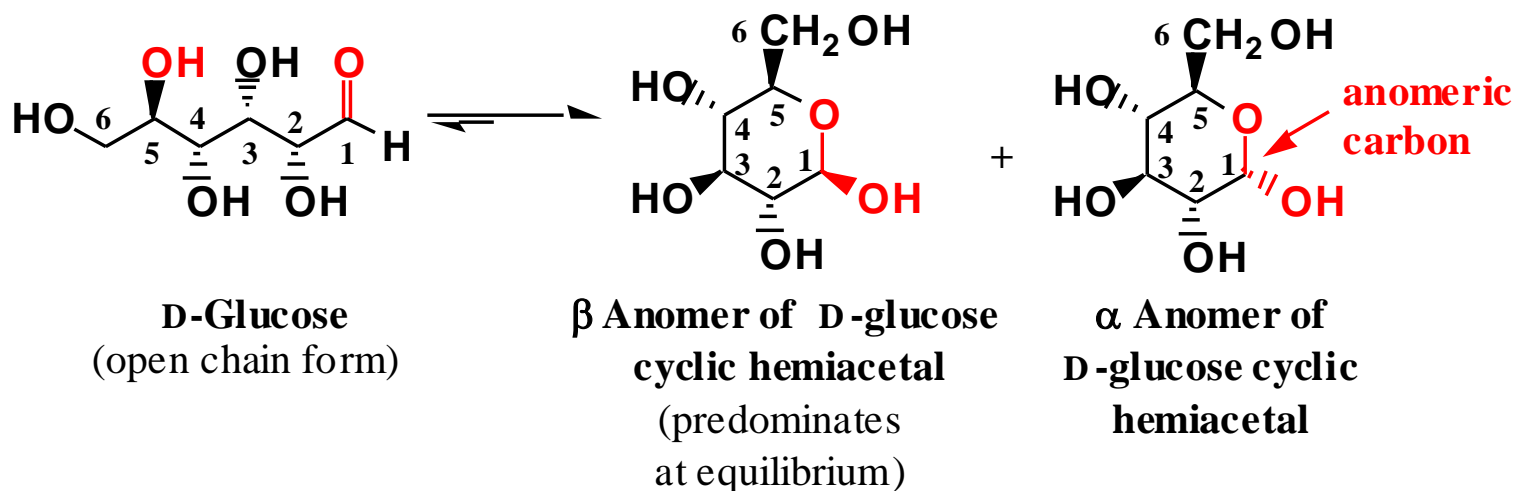
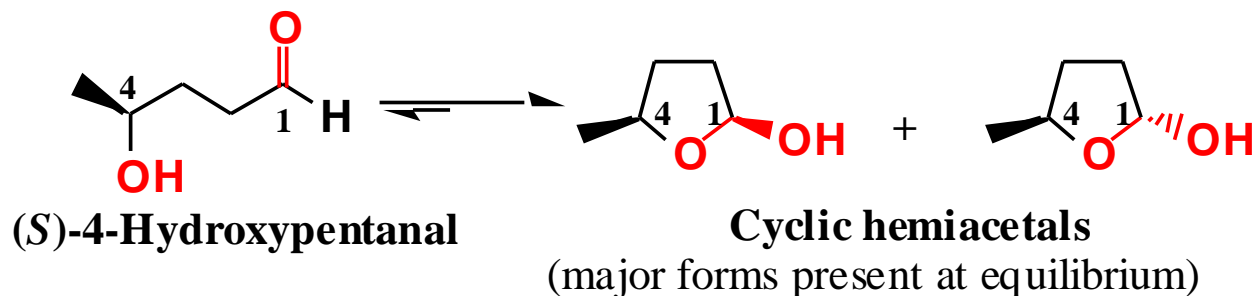
- Addition of one molecule of alcohol to the C=O group of an aldehyde or ketone gives a hemiacetal.
- **Hemiacetal:** A molecule containing an -OH and an -OR or -OAr bonded to the same carbon.



- Hemiacetals are only minor components of an equilibrium mixture, except where a five- or six-membered ring can form.

Hemiacetals

- Hemiacetals are only minor components of an equilibrium mixture, except where a five- or six-membered ring can form.

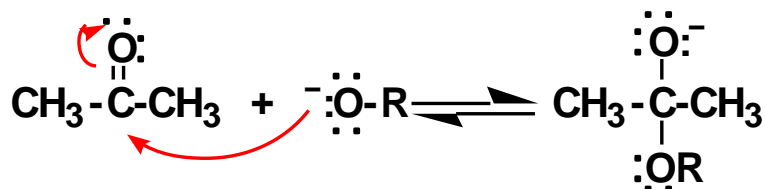


Hemiacetals

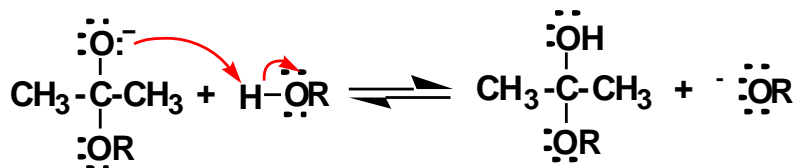
- Formation of a hemiacetal is base catalyzed
 - Step 1: Proton transfer from HOR gives an alkoxide.



- Step 2: Attack of RO^- on the carbonyl carbon.



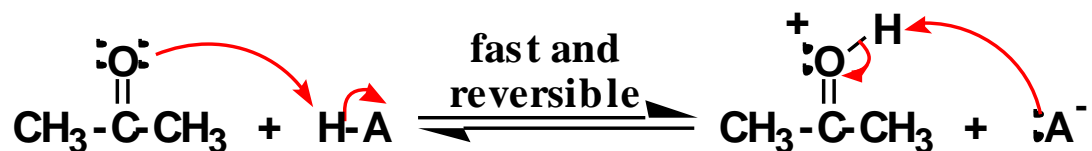
- Step 3: Proton transfer from the alcohol to O^- gives the hemiacetal and generates a new base catalyst.



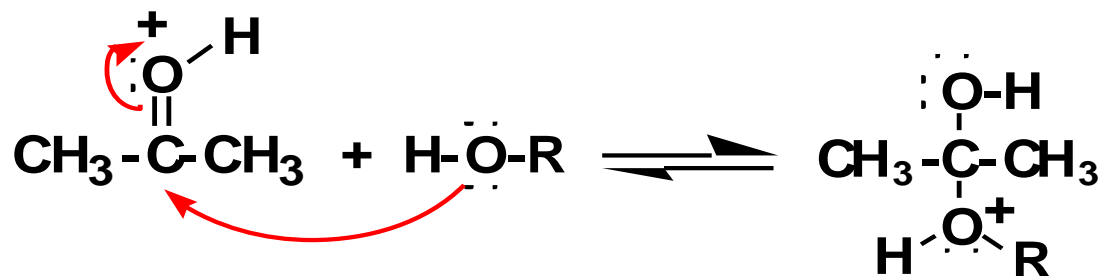
Hemiacetals

- Formation of a hemiacetal is also acid catalyzed.

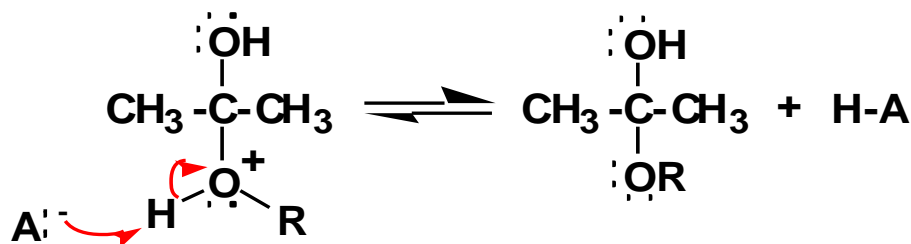
Step 1: Proton transfer to the carbonyl oxygen.



Step 2: Attack of ROH on the carbonyl carbon.



Step 3: Proton transfer from the oxonium ion to A⁻ gives the hemiacetal and generates a new acid catalyst.



Cyanohydrin

- HCN adds to the C=O group of an aldehyde or ketone to give a cyanohydrin.
- Cyanohydrin:** A molecule containing an -OH group and a -CN group bonded to the same carbon

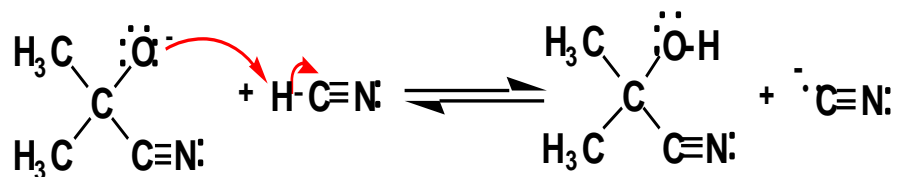


**2-Hydroxypropanenitrile
(Acetaldehyde cyanohydrin)**

- Mechanism of cyanohydrin formation
 - Step 1: Nucleophilic addition of cyanide

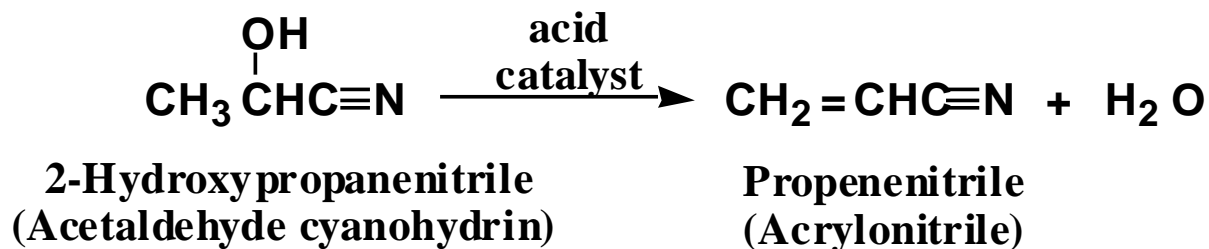


- Step 2: Proton transfer gives the cyanohydrin and regenerates cyanide ion nucleophile.

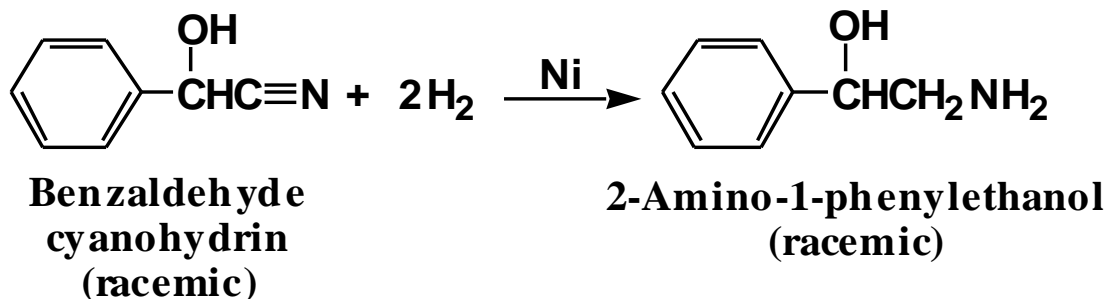


Cyanohydrins

- **Acid-catalyzed dehydration gives an alkene.**

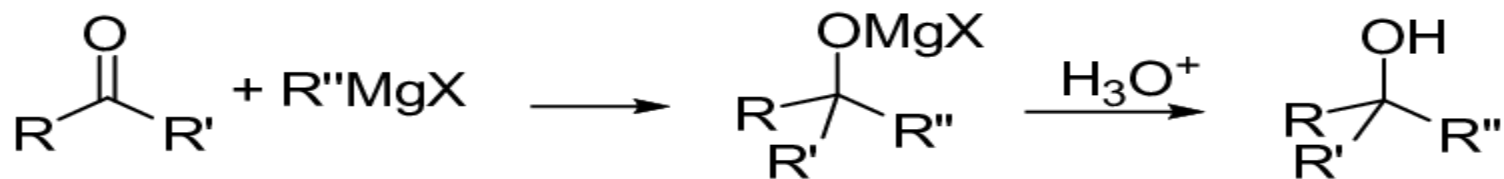


- **Catalytic reduction of the cyano group gives a 1° amine.**



Addition of Grignard Reagents

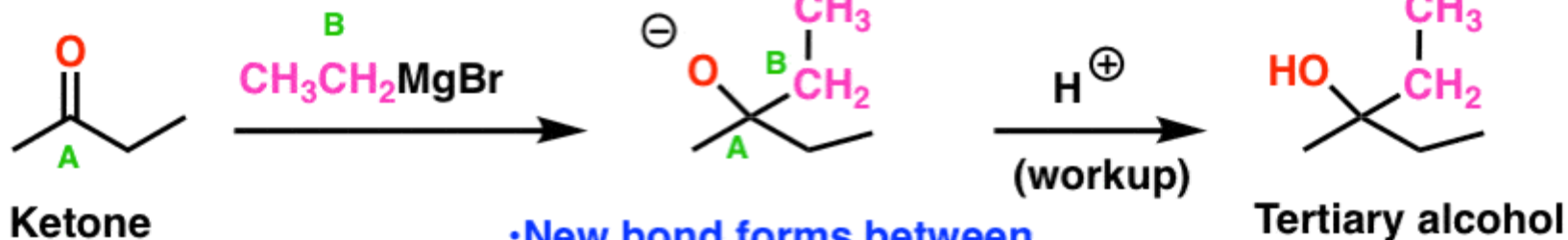
- Given the difference in electronegativity between carbon and magnesium, the C-Mg bond is polar covalent, with C δ^- and Mg δ^+ .
 - A Grignard reagent behaves as a carbanion.
- **Carbanion:** An anion in which carbon has an unshared pair of electrons and bears a negative charge.
 - A carbanion is a good nucleophile and adds readily to the carbonyl group of aldehydes and ketones.
 - Addition of a Grignard reagent to formaldehyde followed by treatment with H_3O^+ gives a 1° alcohol.



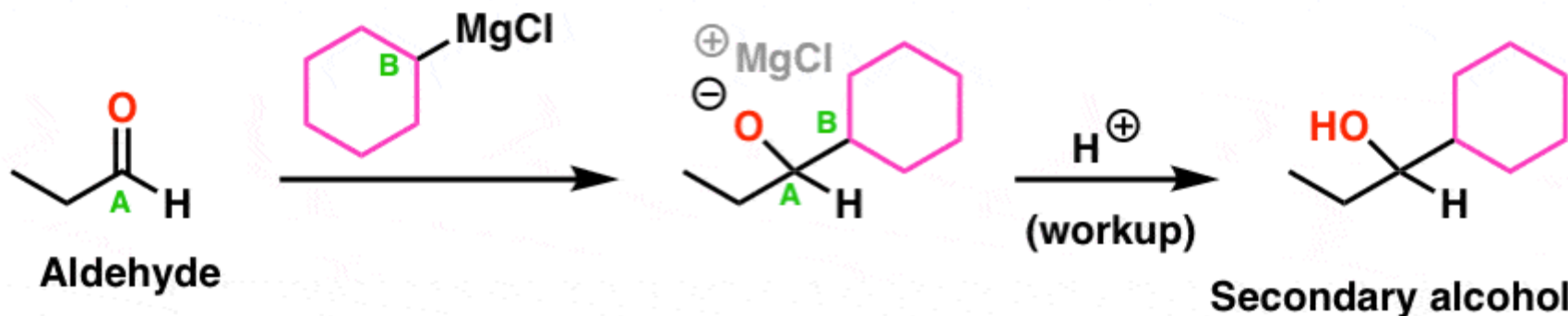
R, R' = H, alkyl, aryl

R'' = alkyl, aryl

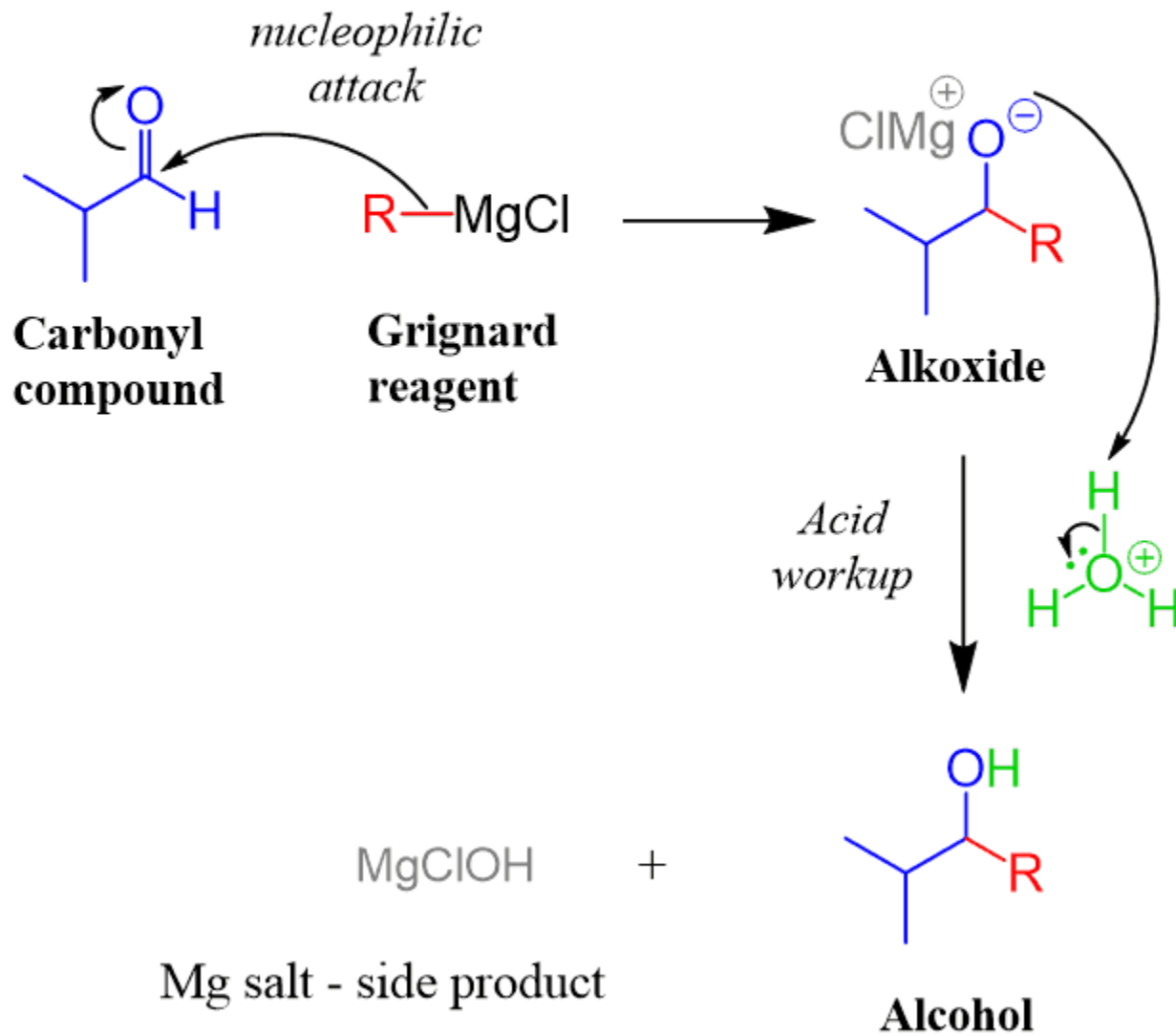
Examples:



- New bond forms between Carbon A and Carbon B
- Carbon A to Oxygen π bond breaks

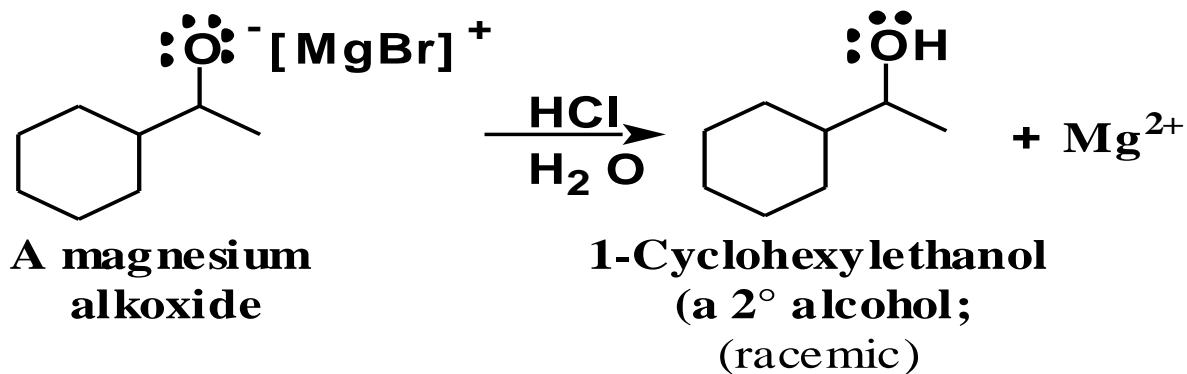
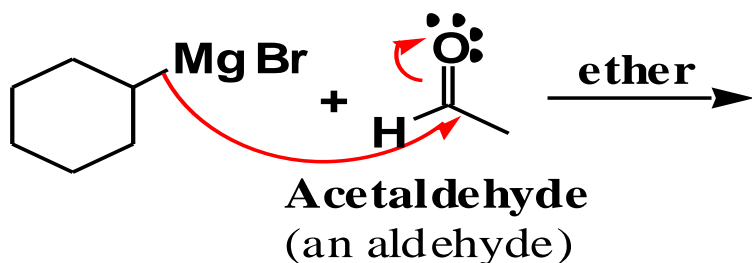


The Mechanism of Grignard reaction with an Aldehyde



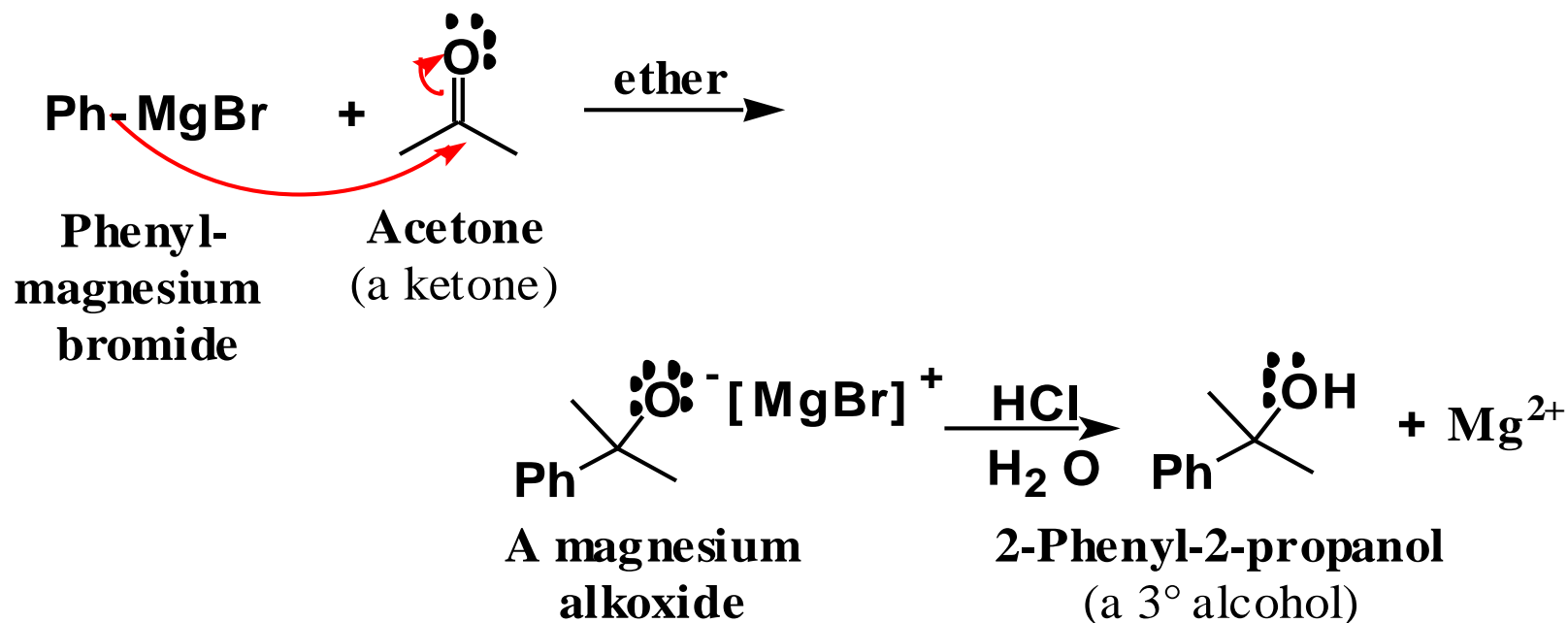
Addition of Grignard Reagents

– Addition to any other RCHO gives a 2° alcohol.



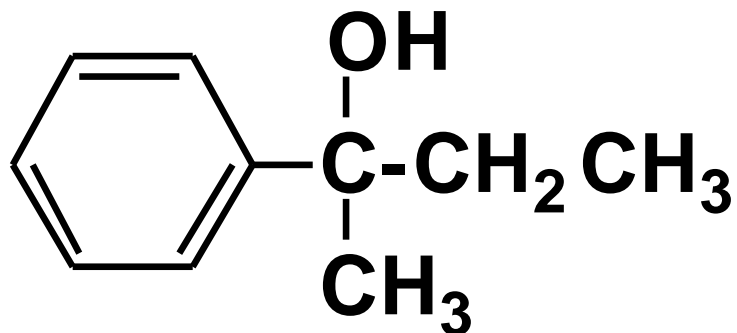
Addition of Grignard Reagents

- Addition to a ketone gives a 3° alcohol.



Addition of Grignard Reagents

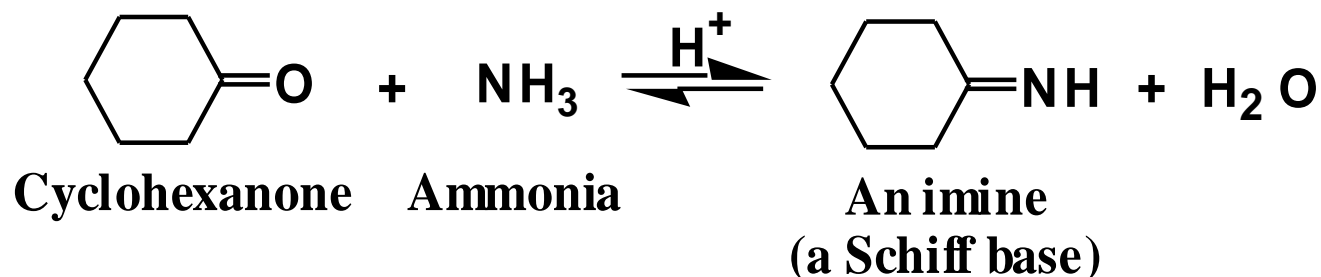
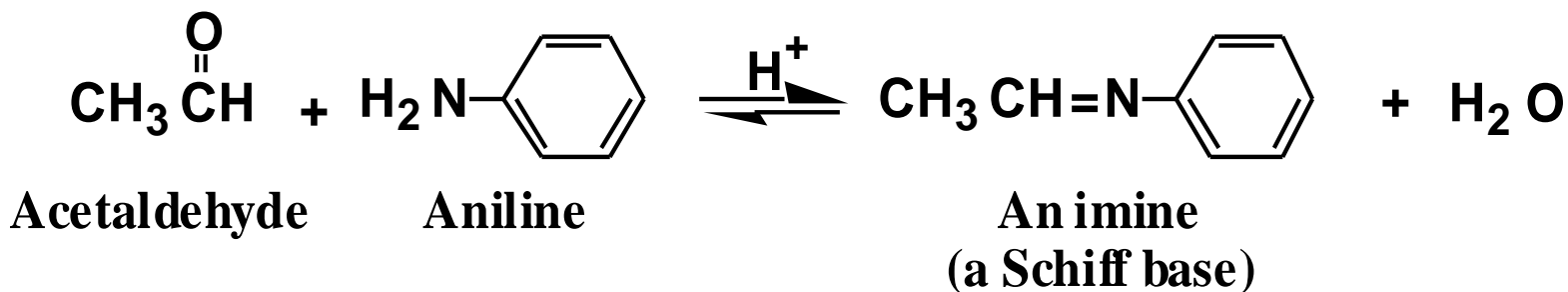
Problem: 2-Phenyl-2-butanol can be synthesized by three different combinations of a Grignard reagent and a ketone. Show each combination.



3.2 Addition-Elimination Reactions

Imines and related compounds

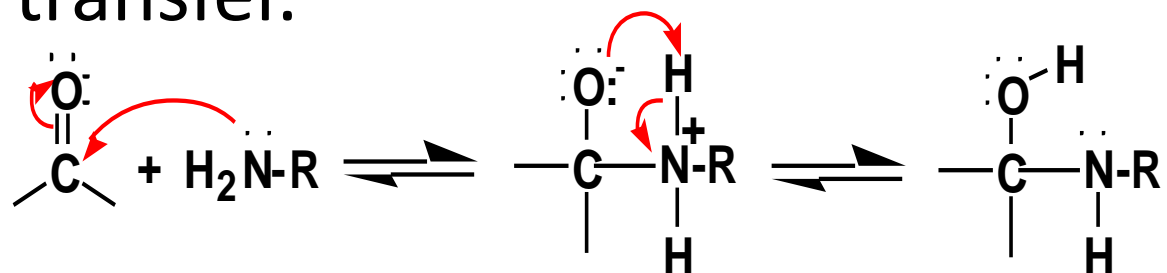
- Ammonia, 1° aliphatic amines, and 1° aromatic amines react with the C=O group of aldehydes and ketones to give imines (Schiff bases).



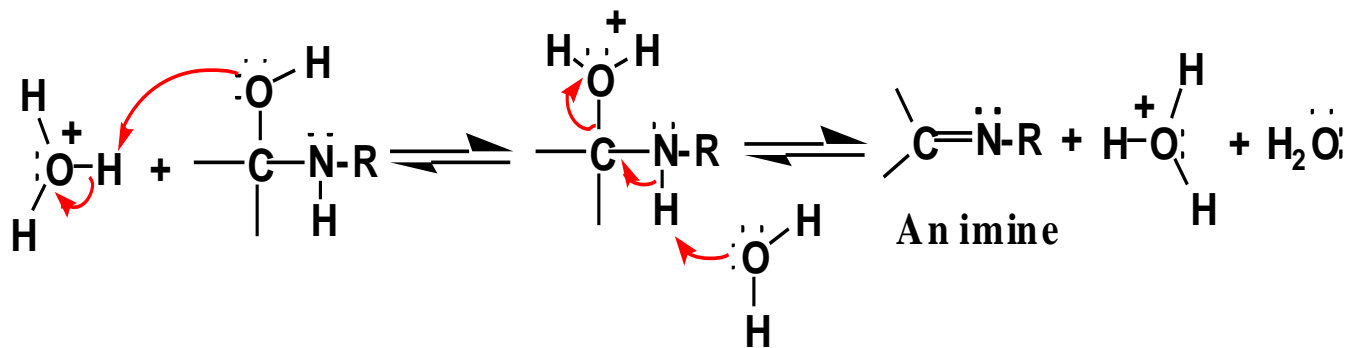
Imines and related compounds

- Formation of an imine occurs in two steps:

Step 1: Carbonyl addition followed by proton transfer.

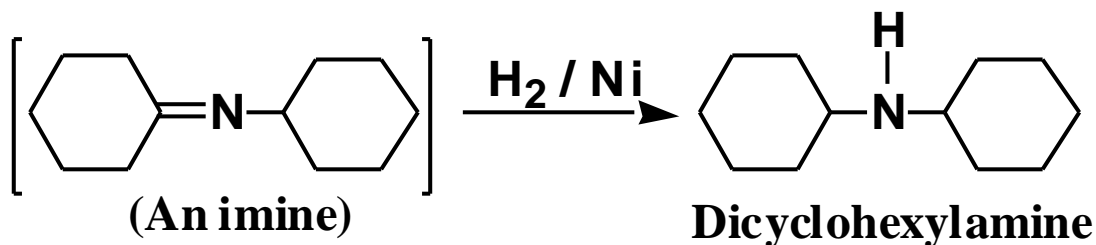
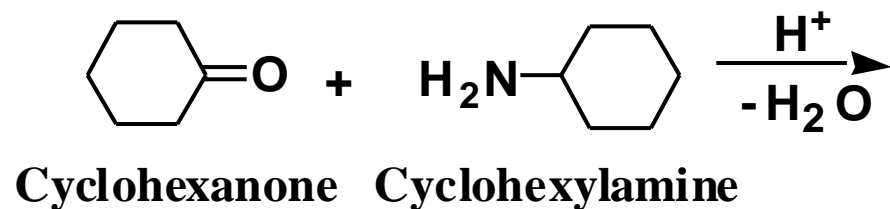


Step 2: Loss of H_2O and proton transfer



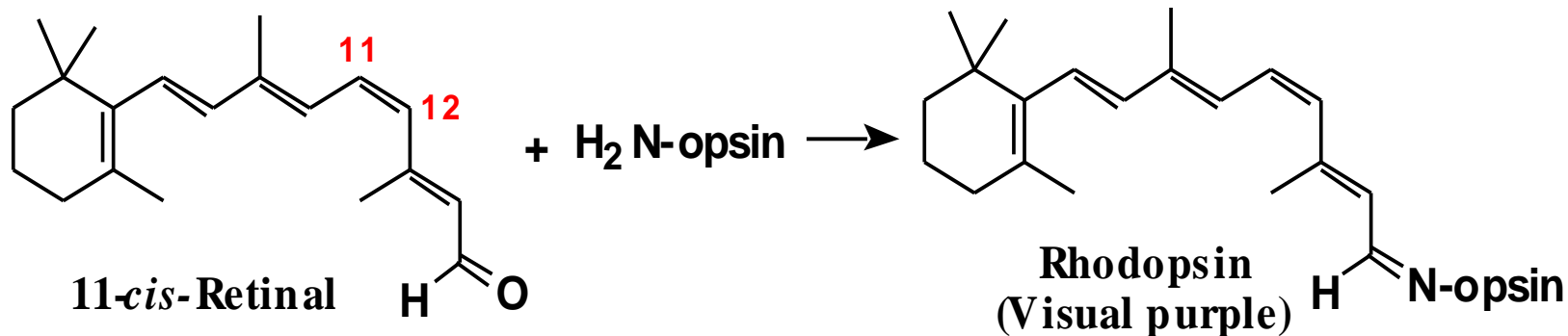
Imines and related compounds

- A value of imines is that the carbon-nitrogen double bond can be reduced to a carbon-nitrogen single bond.



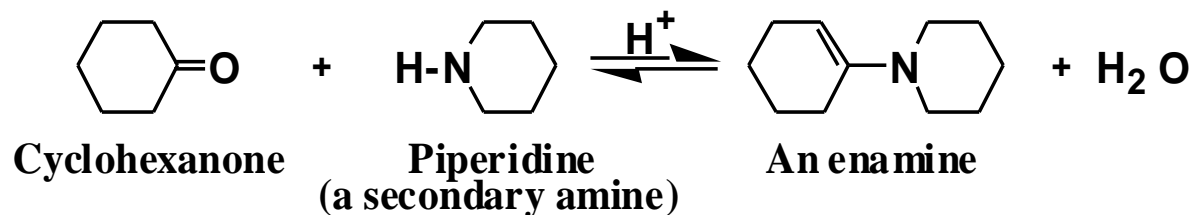
Imines and related compounds

- Rhodopsin (visual purple) is the imine formed in the eye between 11-*cis*-retinal (vitamin A aldehyde) and the protein opsin.



Imines and related compounds

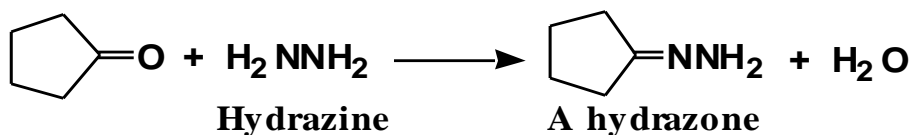
- Secondary amines react with the C=O group of aldehydes and ketones to form enamines.

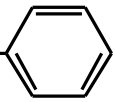
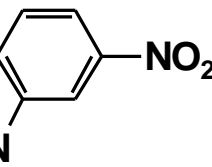


- The mechanism of enamine formation involves formation of a tetrahedral carbonyl addition compound followed by its acid-catalyzed dehydration.

Imines and related compounds

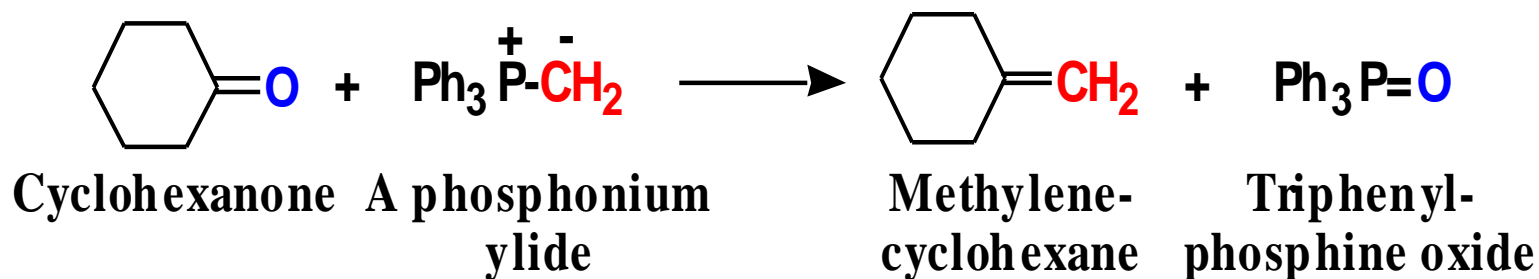
- The carbonyl groups of aldehydes and ketones react with hydrazine in a manner similar to their reactions with 1° amines.



| Reagent, H ₂ N-R | Name of Reagent | Name of Derivative Formed |
|--|----------------------------|----------------------------|
| H ₂ N-OH | Hydroxylamine | Oxime |
| H ₂ N-NH-  | Phenylhydrazine | Phenylhydrazone |
| H ₂ N-NH-  | 2,4-Dinitrophenylhydrazine | 2,4-Dinitrophenylhydrazone |
| H ₂ N-NHC(=O)NH ₂ | Semicarbazide | Semicarbazone |

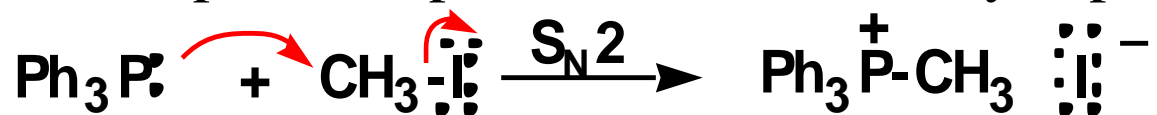
Wittig Reaction

- The Wittig reaction is a very versatile synthetic method for the synthesis of alkenes from aldehydes and ketones.



Phosponium Ylides

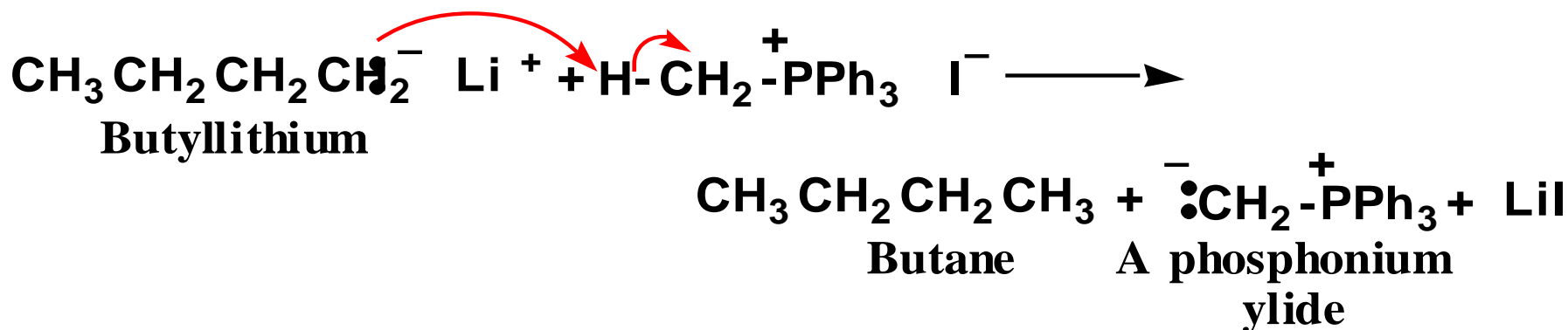
- Phosponium ylides are formed in two steps:
- Step 1: Nucleophilic displacement of iodine by triphenylphosphine.



Triphenylphosphine

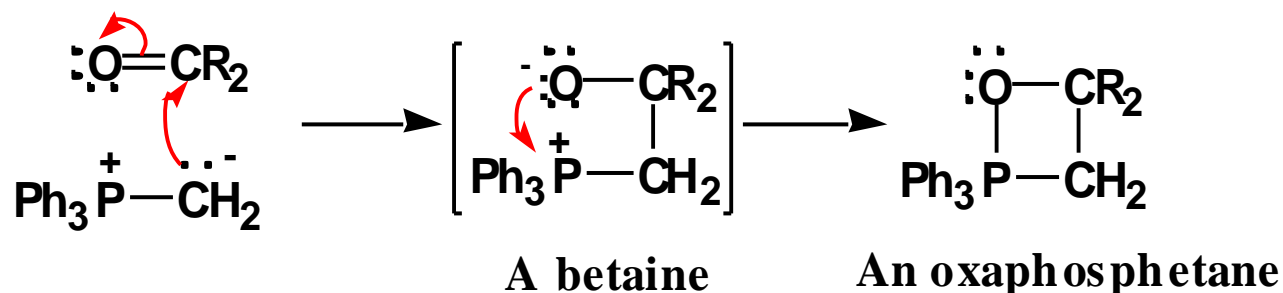
Methyltriphenylphosponium iodide

- Step 2: Treatment of the phosponium salt with a very strong base, such as BuLi, NaH, or NaNH₂

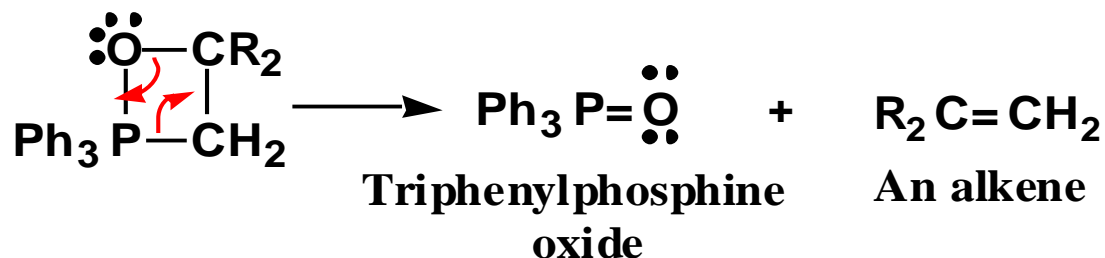


Wittig Reaction-mechanism

- Phosphonium ylides react with aldehydes and ketones to give alkenes.
 - Step 1: Nucleophilic addition of the ylide to the electrophilic carbonyl carbon.

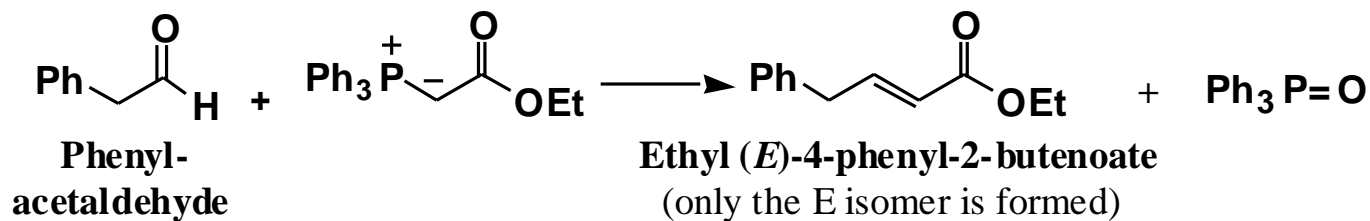
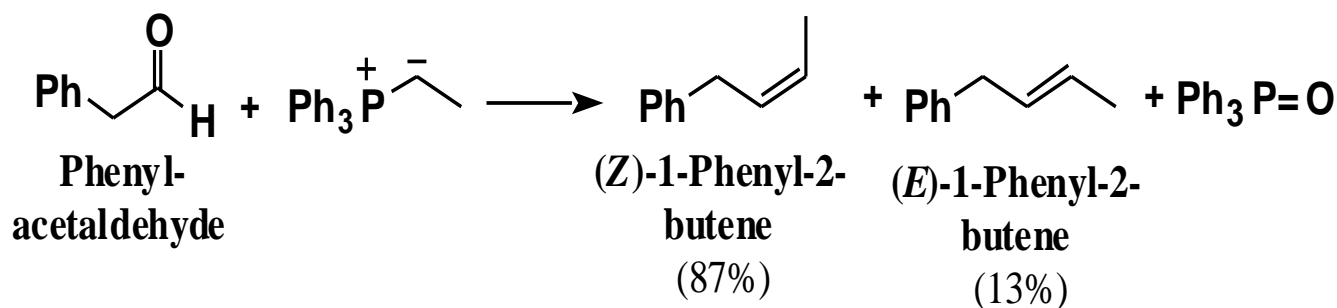
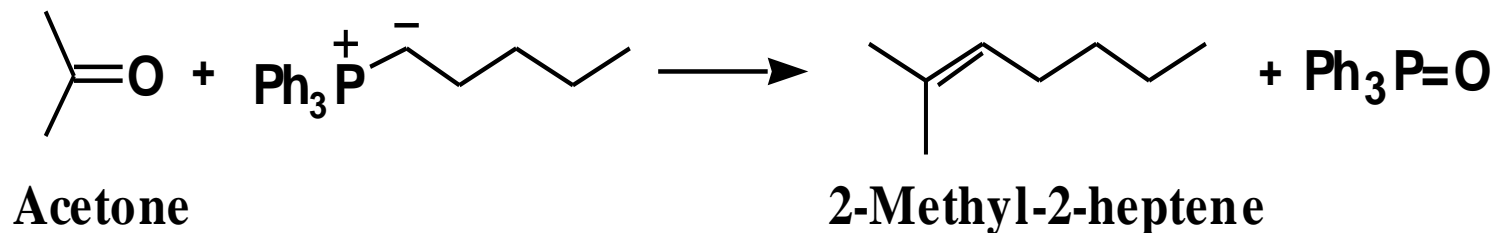


- Step 2: Decomposition of the oxaphosphatane.



Wittig Reaction-examples

Examples:



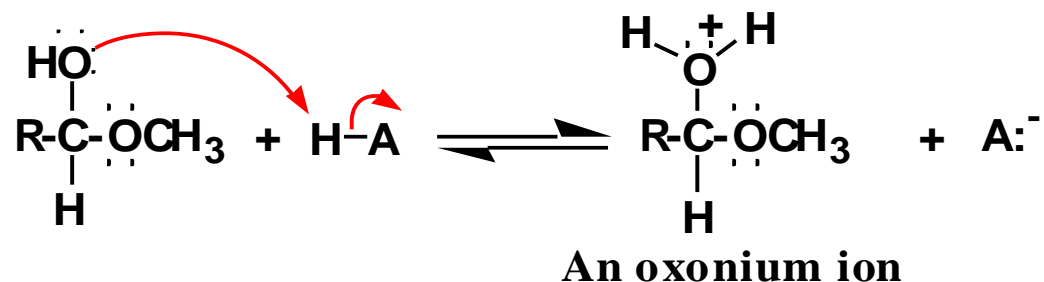
Acetals

- Hemiacetals react with alcohols to form acetals.
- **Acetal:** A molecule containing two -OR or -OAr groups bonded to the same carbon.

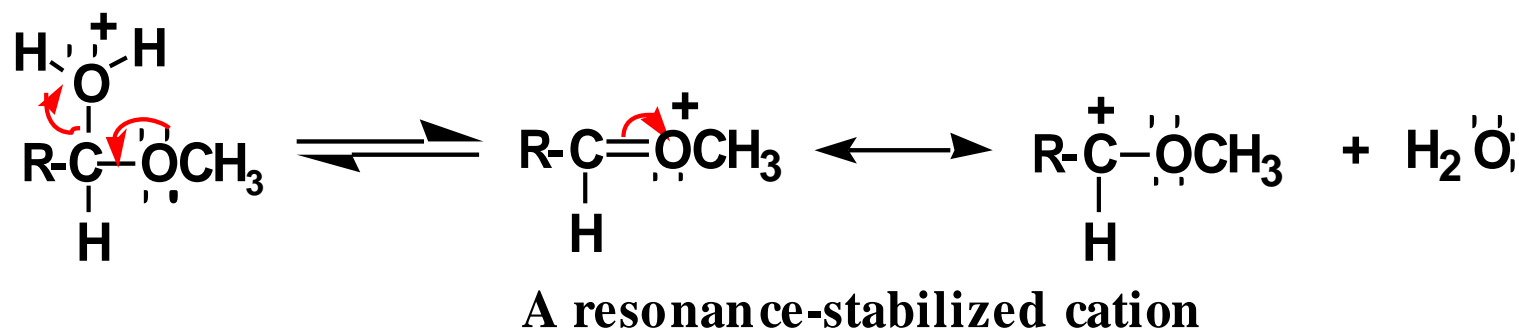


Acetals

Step 1: Proton transfer from HA gives oxonium ion.

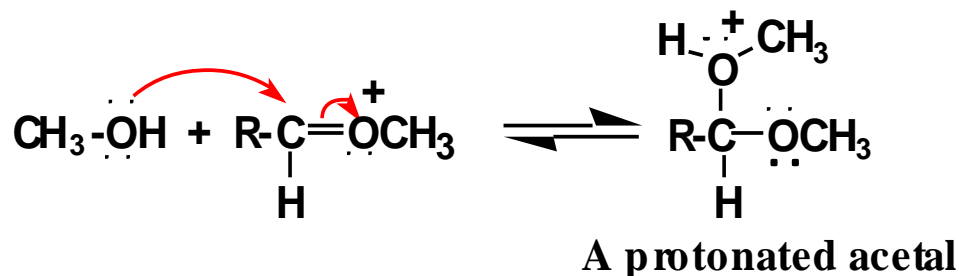


Step 2: Loss of water gives resonance-stabilized cation.

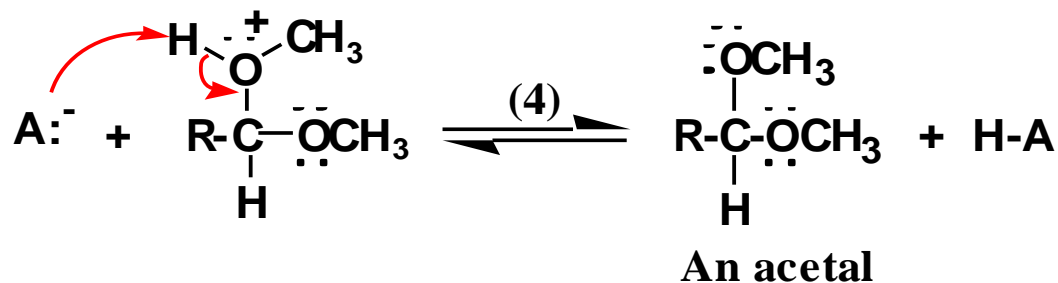


Loss of water gives resonance-stabilized cation.

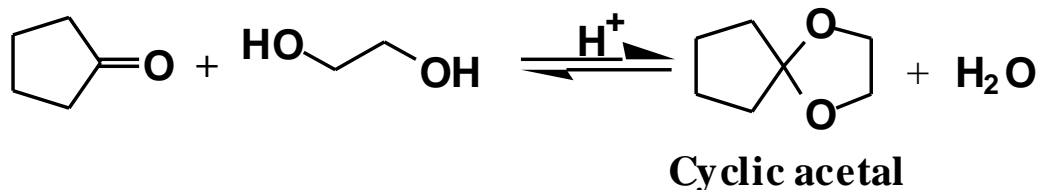
Step 3: Reaction of the cation with methanol gives the conjugate acid of the acetal.



Step 4: Proton transfer to A⁻ gives the acetal and generates a replacement acid catalyst.



- With ethylene glycol and other glycols, the product is a five-membered cyclic acetal.



Ester hydrolysis and formation

- Esters occur in nature, low molecular weight esters are fairly volatile
- possess pleasing odors
- prepared using

1. From carboxylic acids

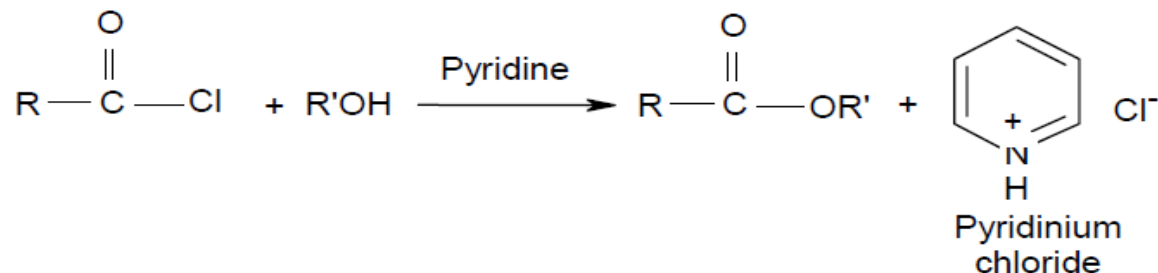
- Alcohols and carboxylic acids react in the presence of an acid catalyst to form an ester and water
- reaction is called as the Fischer esterification



Ester hydrolysis and formation

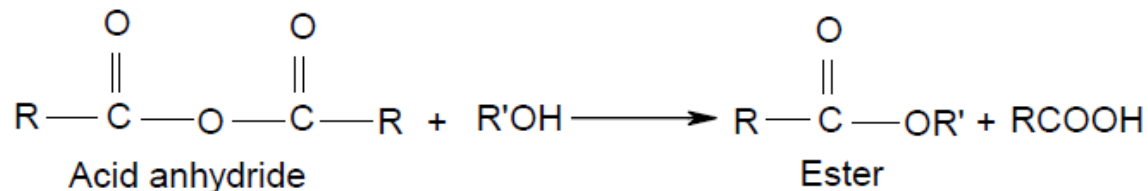
2. From acyl chloride

- reaction of alcohols with acyl chlorides by nucleophilic acyl substitution yields esters
- in the presence of a weak base such as pyridine



3. From anhydrides of carboxylic acids

- The transfer of an acyl group from an acid anhydride to an alcohol is a common method used for the preparation of esters.

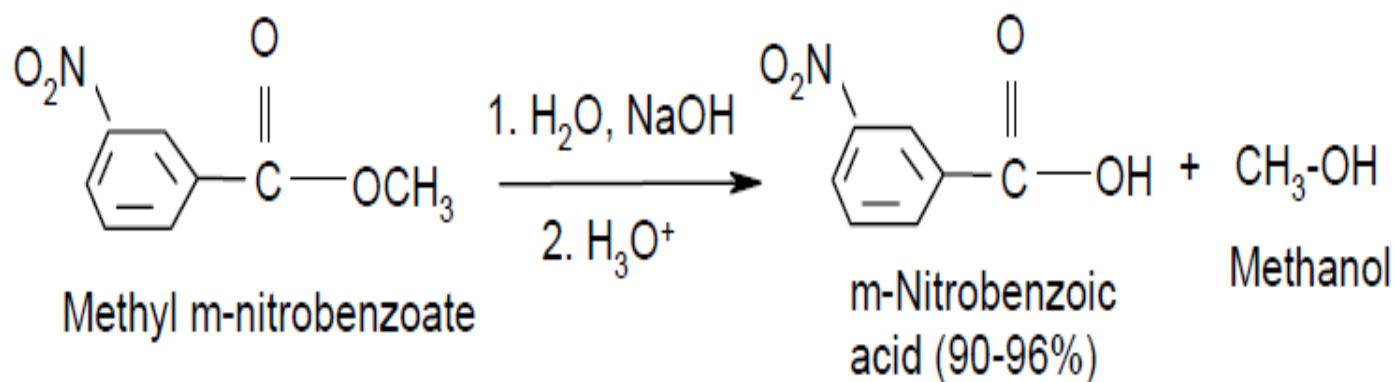


- a catalyst, which is normally an acid (H₂SO₄) or base (pyridine).

Ester hydrolysis and formation

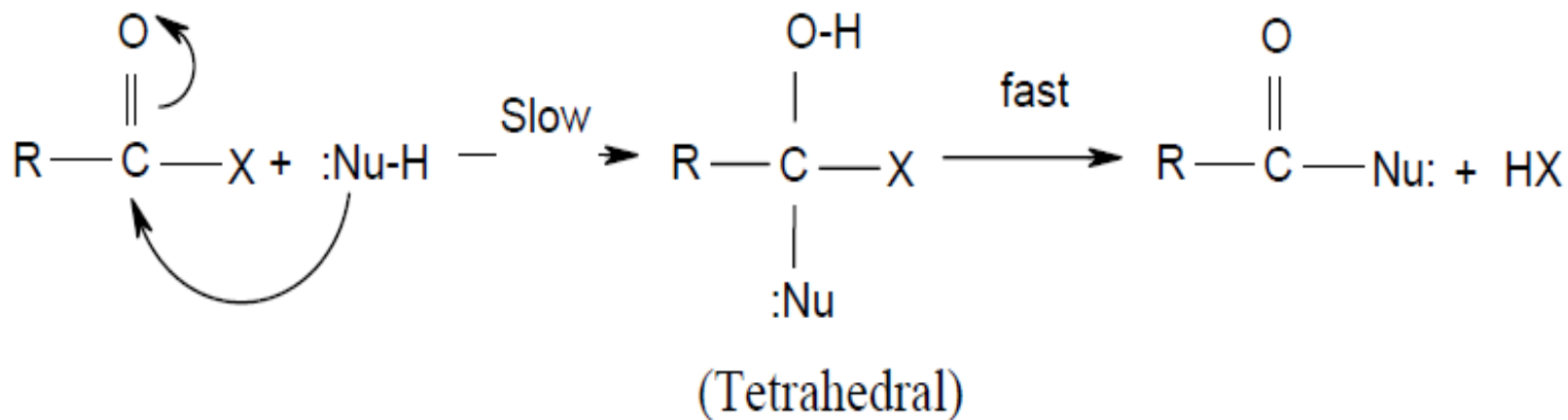
Ester hydrolysis

- catalyzed either by using acids or by bases
- Acid catalyzed hydrolysis is considered as the reverse of the Fischer esterification
- Base catalyzed hydrolysis is irreversible



Reactions of acid chlorides

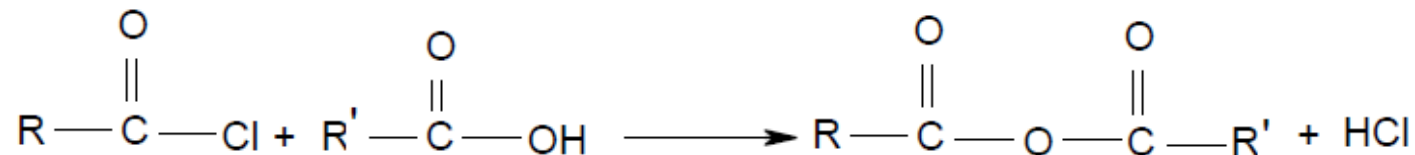
- The treatment of an acyl chloride with an appropriate nucleophile may lead to an acid anhydride, an ester, an amide and carboxylic acid.
- nucleophilic acyl substitution follows a two-step mechanism and involves the formation of a tetrahedral intermediate.



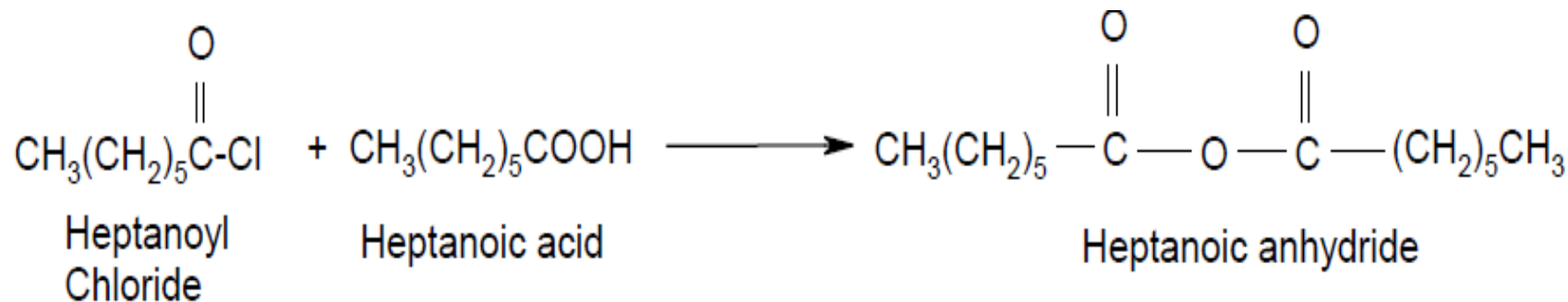
Reactions of acid chlorides

1. Reactions with carboxylic acids

- reaction of acyl chlorides with carboxylic acids yields an acid anhydride.
- pyridine is normally added as a catalyst.
- The base also neutralizes the hydrogen chloride formed.



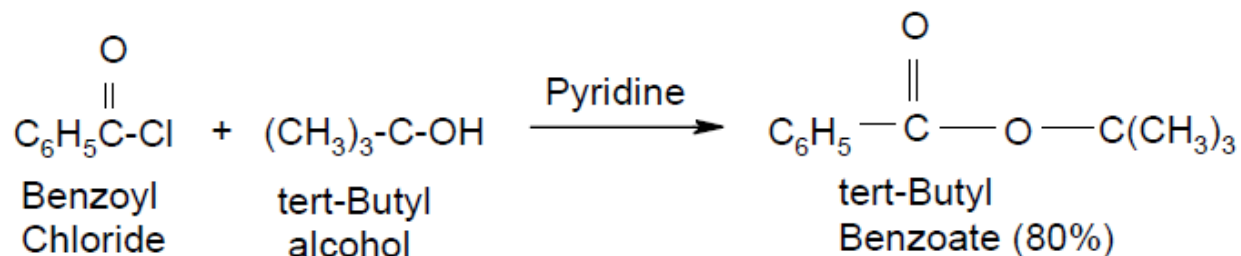
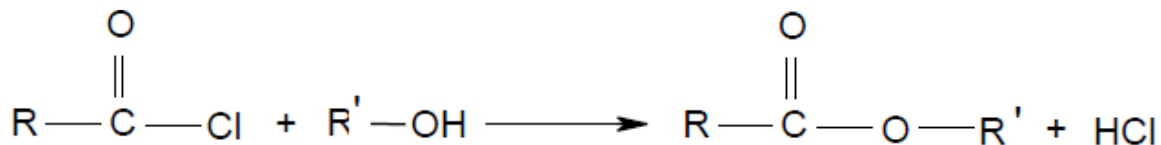
- example



Reactions of acid chlorides

2. Reaction with alcohols

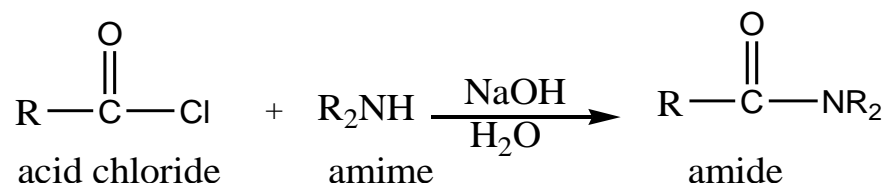
- The reaction of acyl chlorides with alcohols gives esters.
- The reaction is typically carried out in the presence of small amount of pyridine.



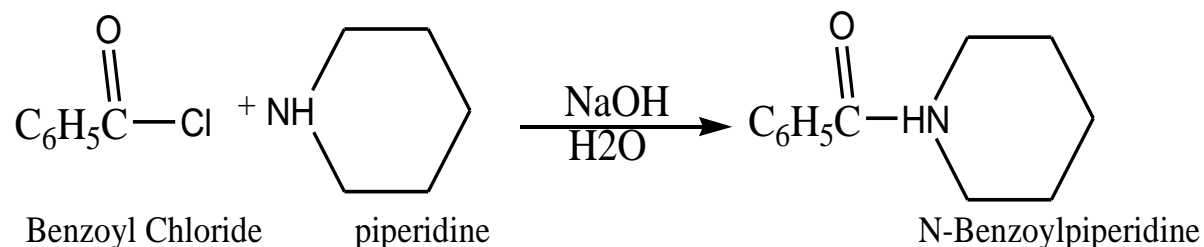
Reactions of acid chlorides

3. Reaction with ammonia and amines

- The reaction of acyl chlorides with ammonia and amines leads to the formation of amides.
- A base such as NaOH is normally added to neutralize the hydrogen chloride produced.



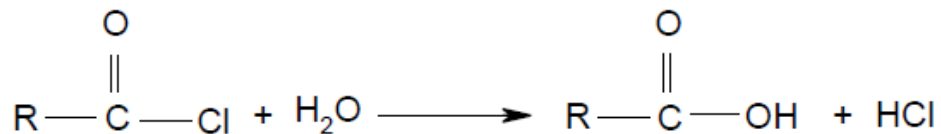
- **Example**



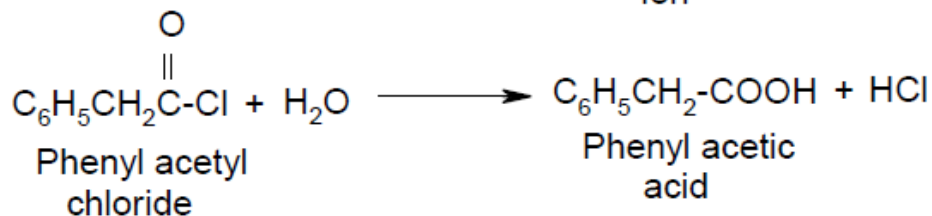
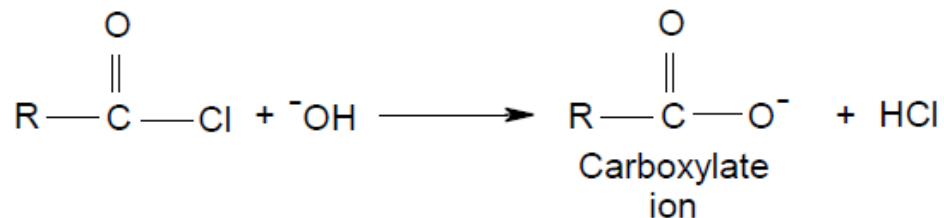
Reactions of acid chlorides

4. Hydrolysis of acid chloride

- hydrolysis of acyl chlorides yields carboxylic acids
- In basic medium, the product acid is converted to its carboxylate salt.

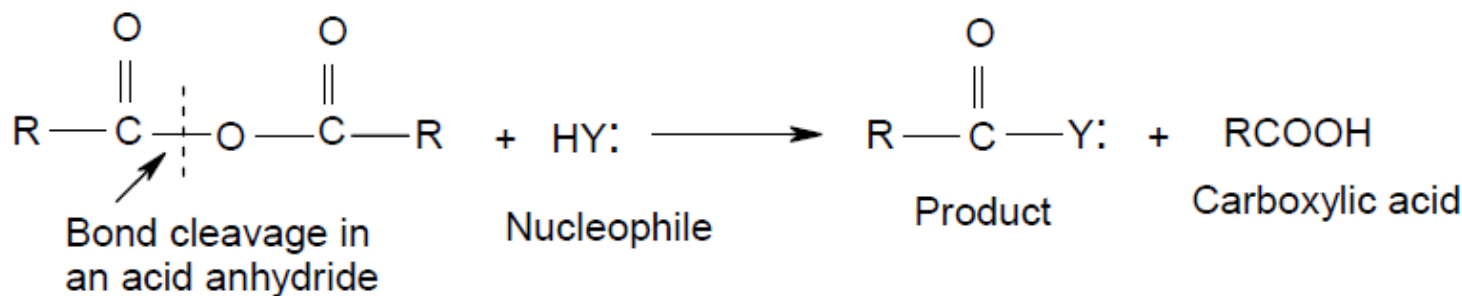


In basic medium



Reactions of acid anhydride

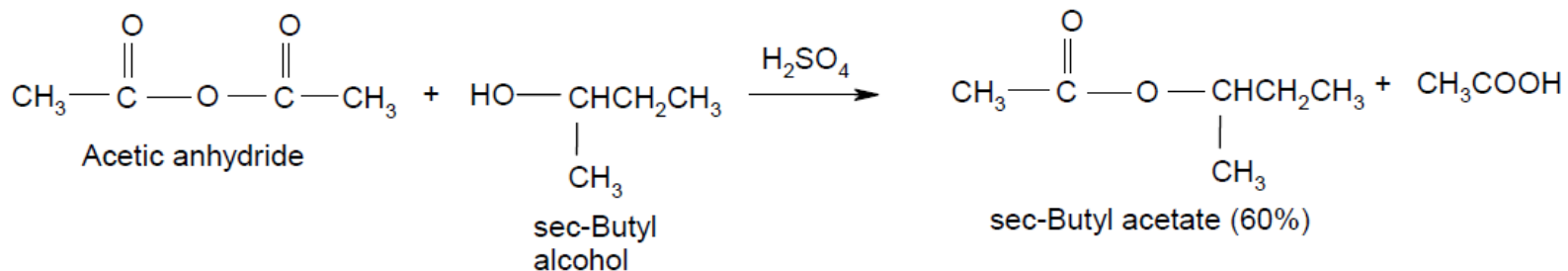
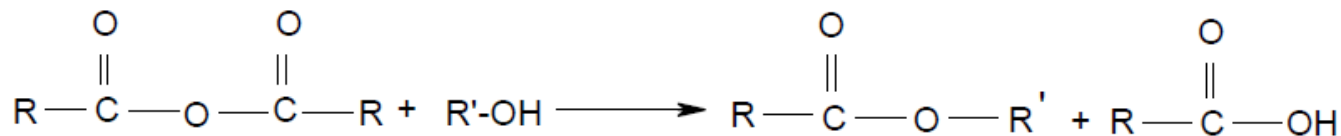
- The nucleophilic substitution in acid anhydrides involves cleavage of C-O bond between central oxygen and one of the carbonyl groups.
- The result is that one acyl group is transferred to an attacking nucleophile; whereas, the other acyl group retains its single bond to oxygen and becomes the acyl group of a carboxylic acid



Reactions of acid anhydride

1. Reaction with alcohols

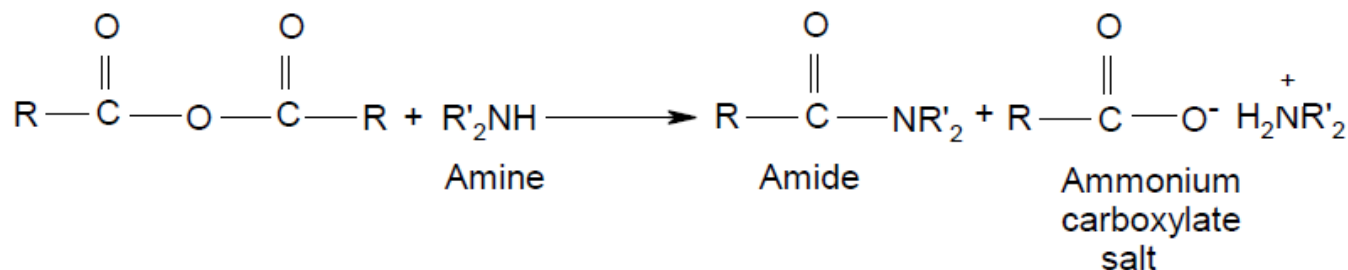
- leads to the formation of esters.
- The catalyst used is pyridine or small amount of acid
- An acyl group of acetic anhydride is incorporated into the ester whereas the other becomes the acyl group of an acetic acid molecule.



Reactions of acid anhydride

2.Reaction with ammonia and amines

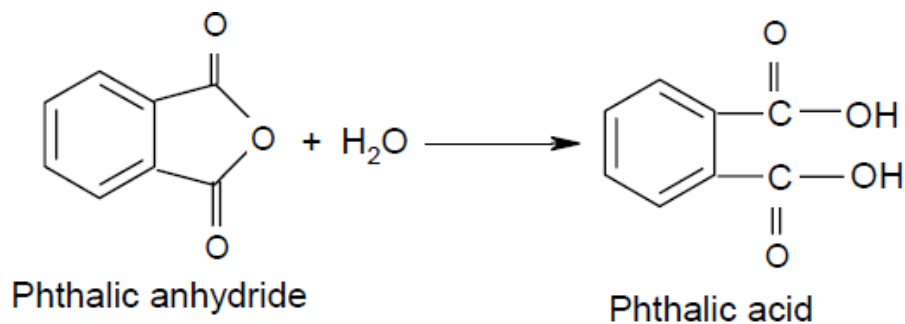
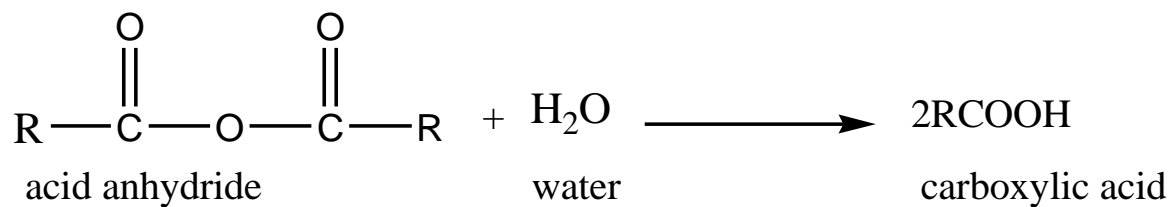
- The reaction of acid anhydrides with ammonia or amines gives amides.
- the reaction requires two mole equivalents of amine.
- One of the acyl groups of acetic anhydride is incorporated into the amide
- the other become s the acyl group of the amine salt of acetic acid



Reactions of acid anhydride

3. Hydrolysis

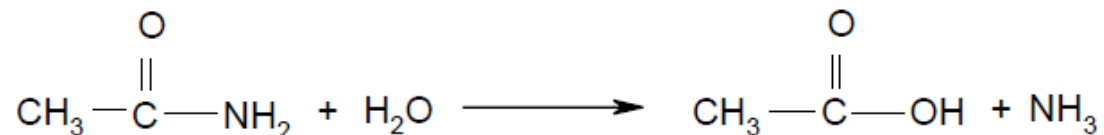
- Acid anhydrides on reaction with water yields two moles of a carboxylic acid.



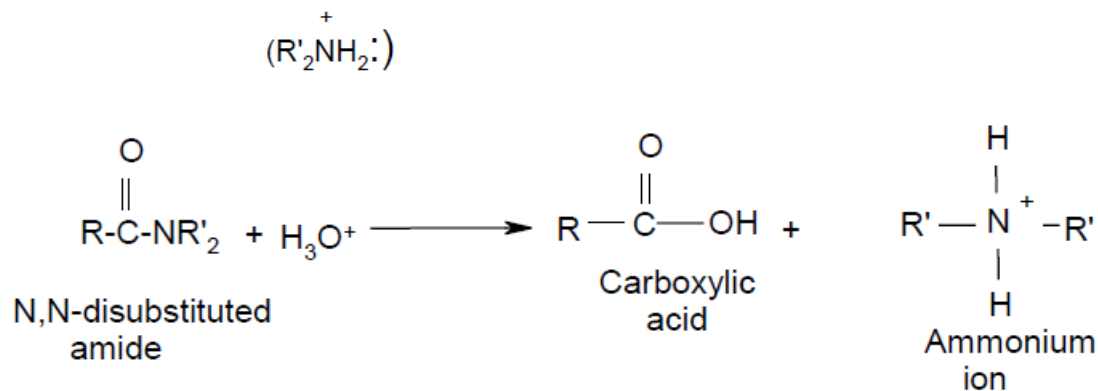
Reactions of amides

1. Hydrolysis

- hydrolysed by acid, alkali and even by water.

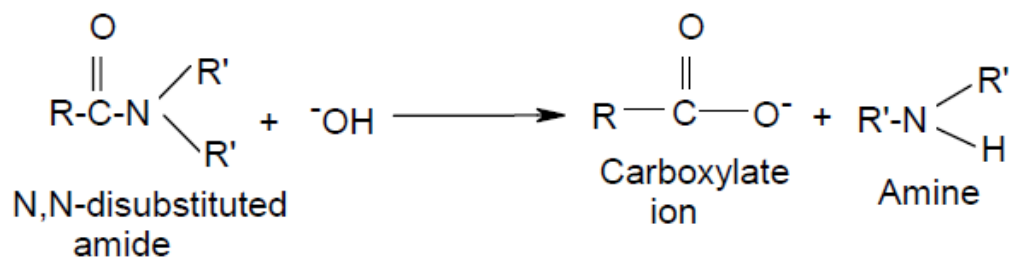


- If hydrolysis is carried out in acidic medium, the amine formed is protonated giving an ammonium ion.



Reactions of amides

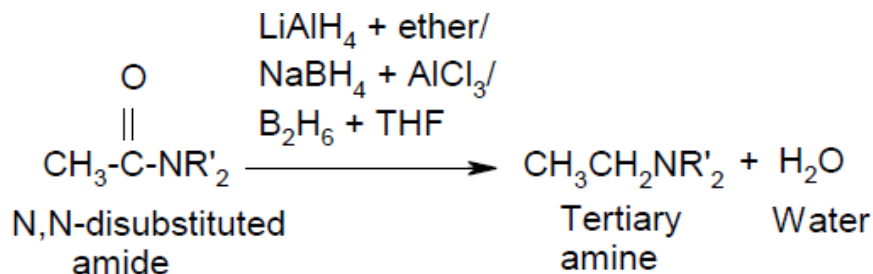
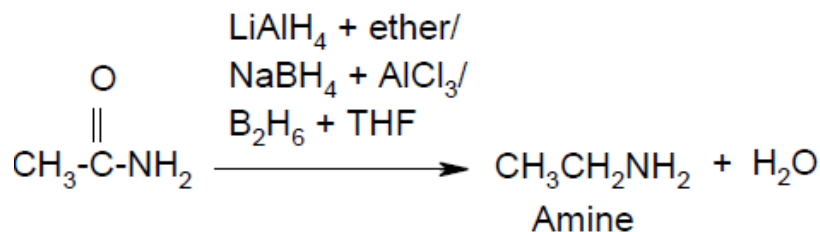
- Whereas in basic medium, the carboxylic acid gets deprotonated, and a carboxylate ion is formed.



Reactions of amides

2. Reduction

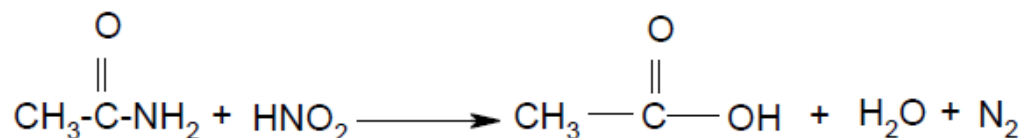
- The reduction of amides with different reducing agents like LiAlH_4 in ether, NaBH_4 in AlCl_3 and B_2H_6 in THF give amines along with water.
- Thus $>\text{C}=\text{O}$ group is reduced to $-\text{CH}_2$.



Reactions of amides

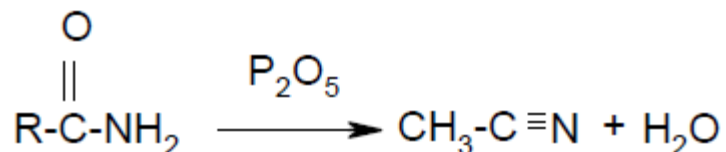
3. Reaction with HNO_2

- treatment of amides with nitrous acid gives carboxylic acids along with nitrogen gas and water.



4. Dehydration

- Loss of water molecule occurs in presence of P_2O_5 and nitriles are produced



3.3 Enolization -ketonization

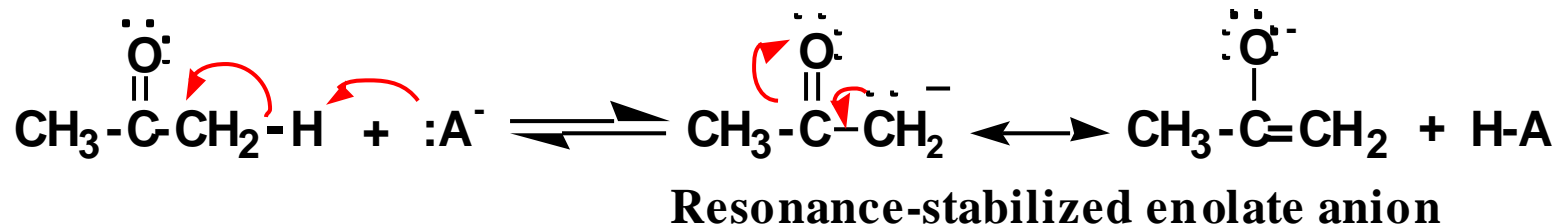
Enolization -ketonization

- Hydrogens alpha to a carbonyl group are more acidic than hydrogens of alkanes, alkenes, and alkynes but less acidic than the hydroxyl hydrogen of alcohols

| Type of Bond | p K _a |
|---|------------------|
| CH ₃ CH ₂ O-H | 16 |
| $\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3 \text{C} \text{CH}_2 \end{array}$ -H | 20 |
| CH ₃ C≡C-H | 25 |
| CH ₂ = CH-H | 44 |
| CH ₃ CH ₂ -H | 51 |

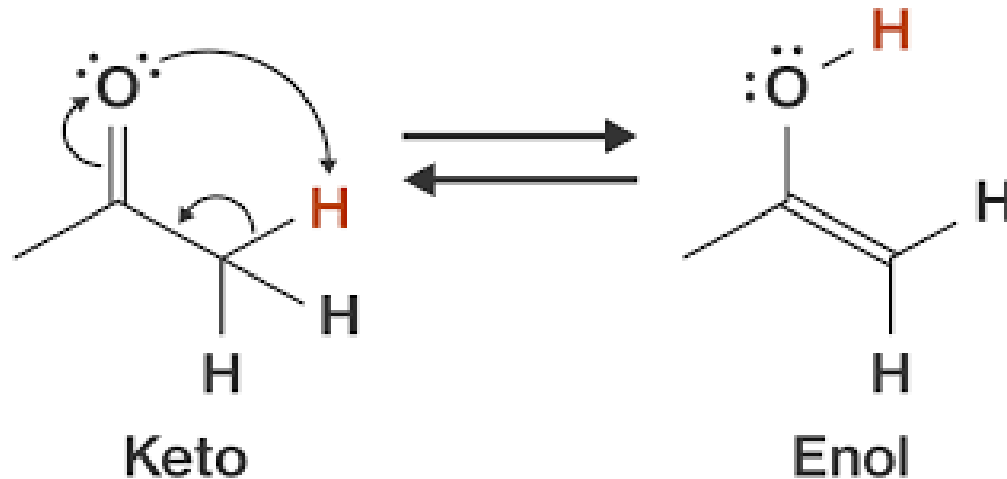
Enolization -ketonization

- α -Hydrogens are more acidic because the enolate anion is stabilized by:
 1. Delocalization of its negative charge.
 2. The electron-withdrawing inductive effect of the adjacent electronegative oxygen

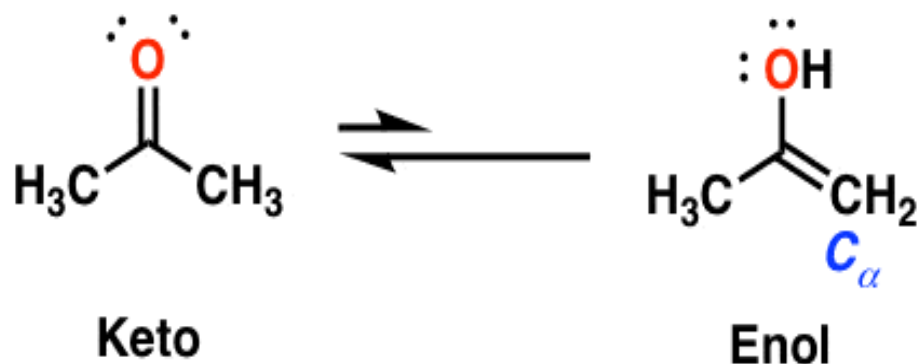


keto–enol tautomerism

- keto–enol tautomerism refers to a **chemical equilibrium between a keto form (a ketone or an aldehyde) and an enol (an alcohol).**
- The keto and enol forms are said to be tautomers of each other.



Keto-Enol Tautomerism



Electrophilic!

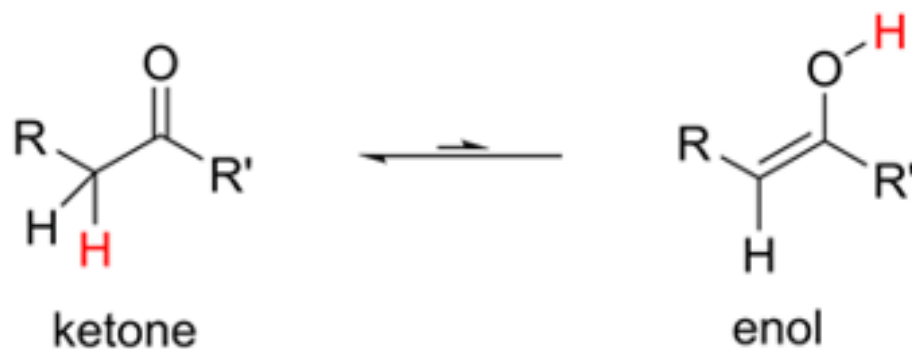
- reacts with nucleophiles at carbonyl carbon
- acidic at α -carbon
- hydrogen bond acceptor

Nucleophilic!

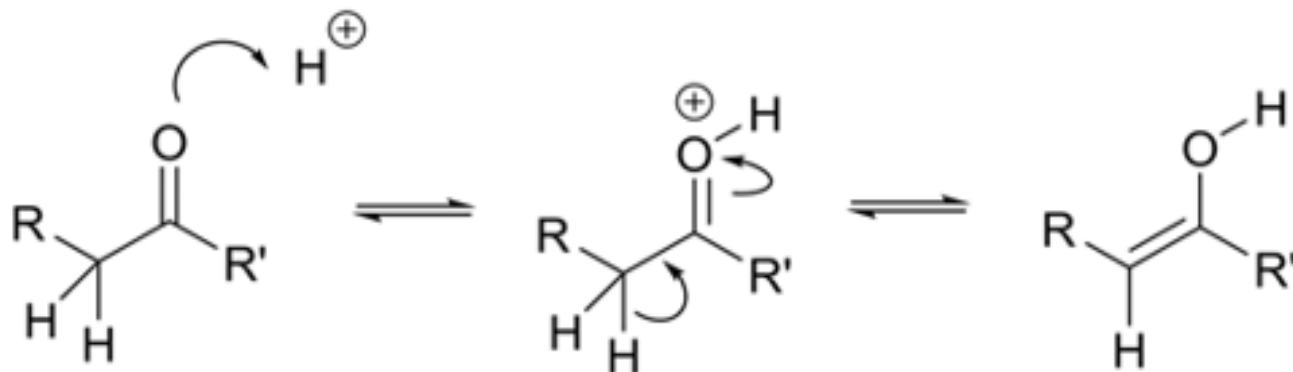
- reacts with electrophiles at α -carbon
- acidic at oxygen ($\text{O}-\text{H}$)
- hydrogen bond donor **and** acceptor

- Equilibrium between isomers (not resonance)
- Under most conditions, keto form is favored (6600:1 for acetone)
- Important for aldehydes, ketones, but not so much for carboxylic acids, esters and amides under normal conditions (>10 million : 1 keto: enol)

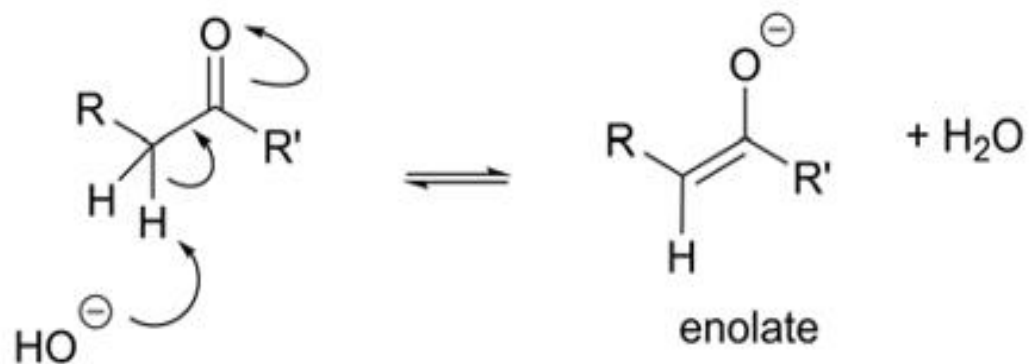
A)



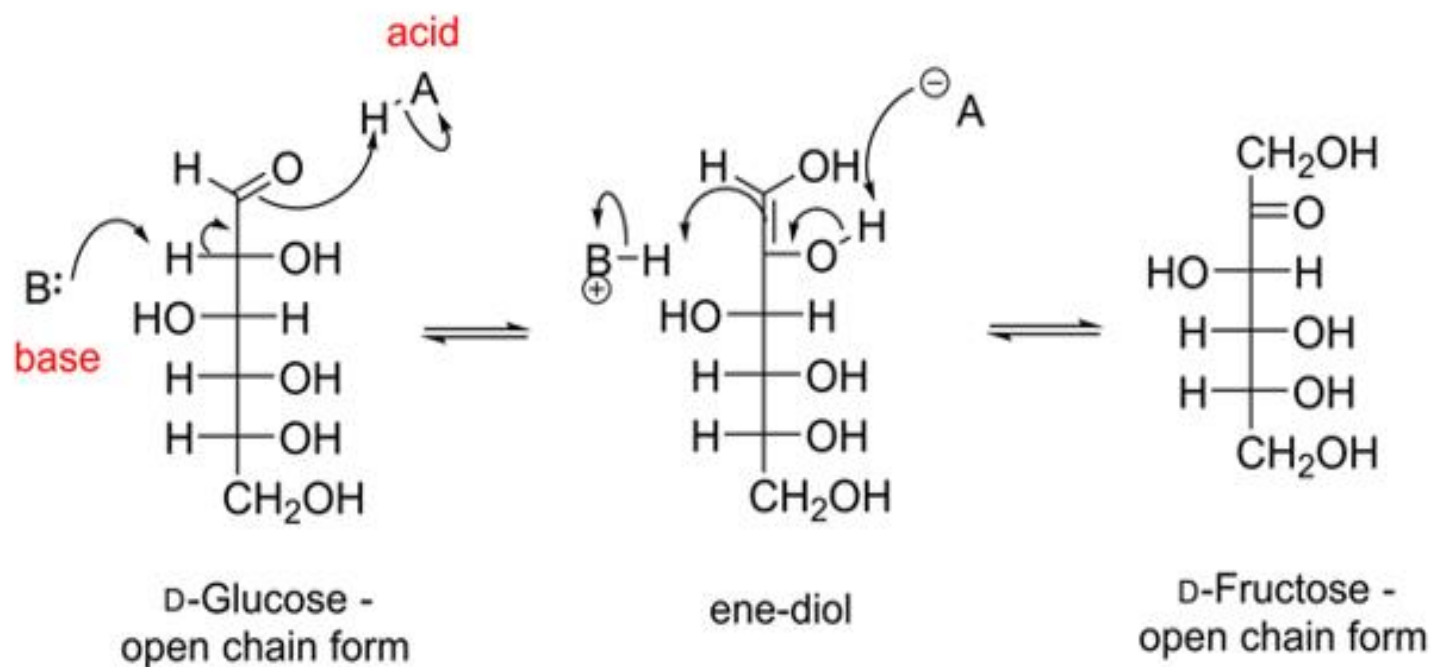
Mechanism with acid catalysis:



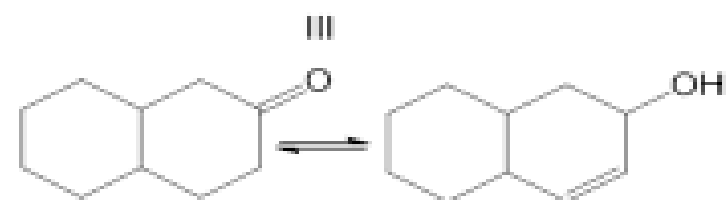
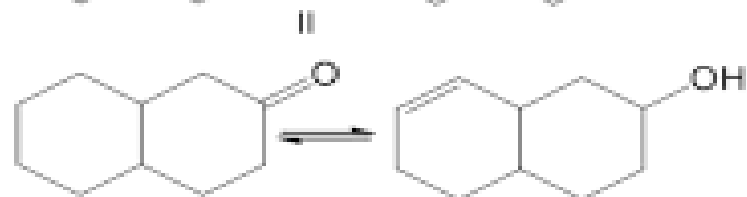
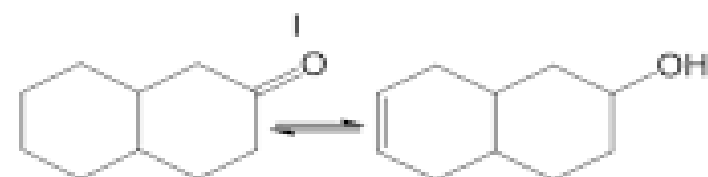
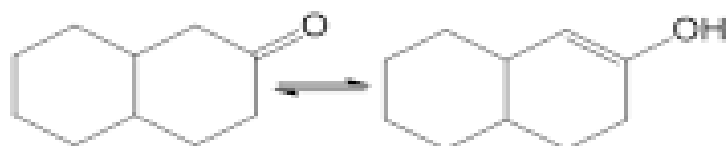
Mechanism with base catalysis:



B)



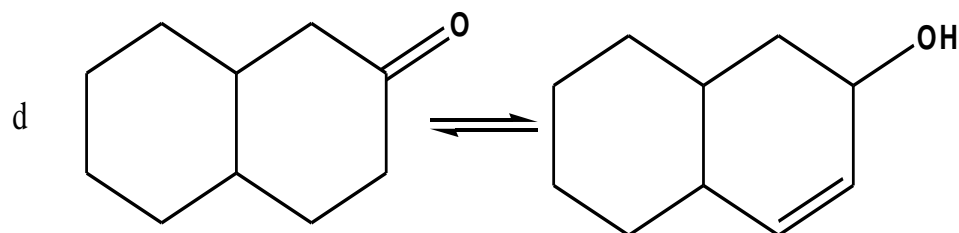
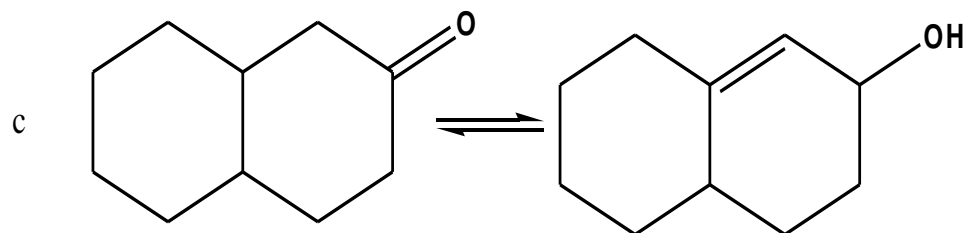
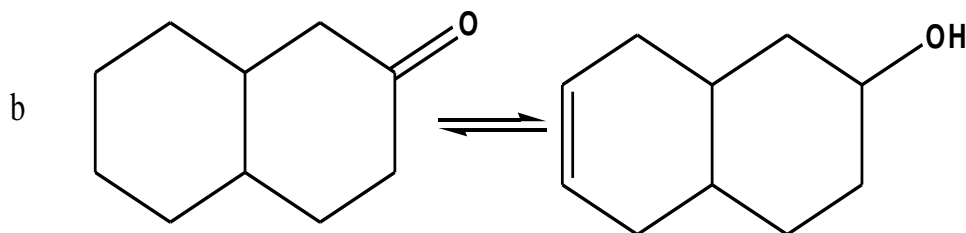
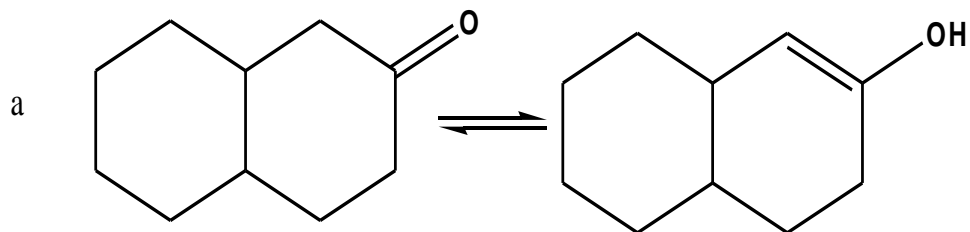
Which of the following is a keto-enol tautomeric pair?



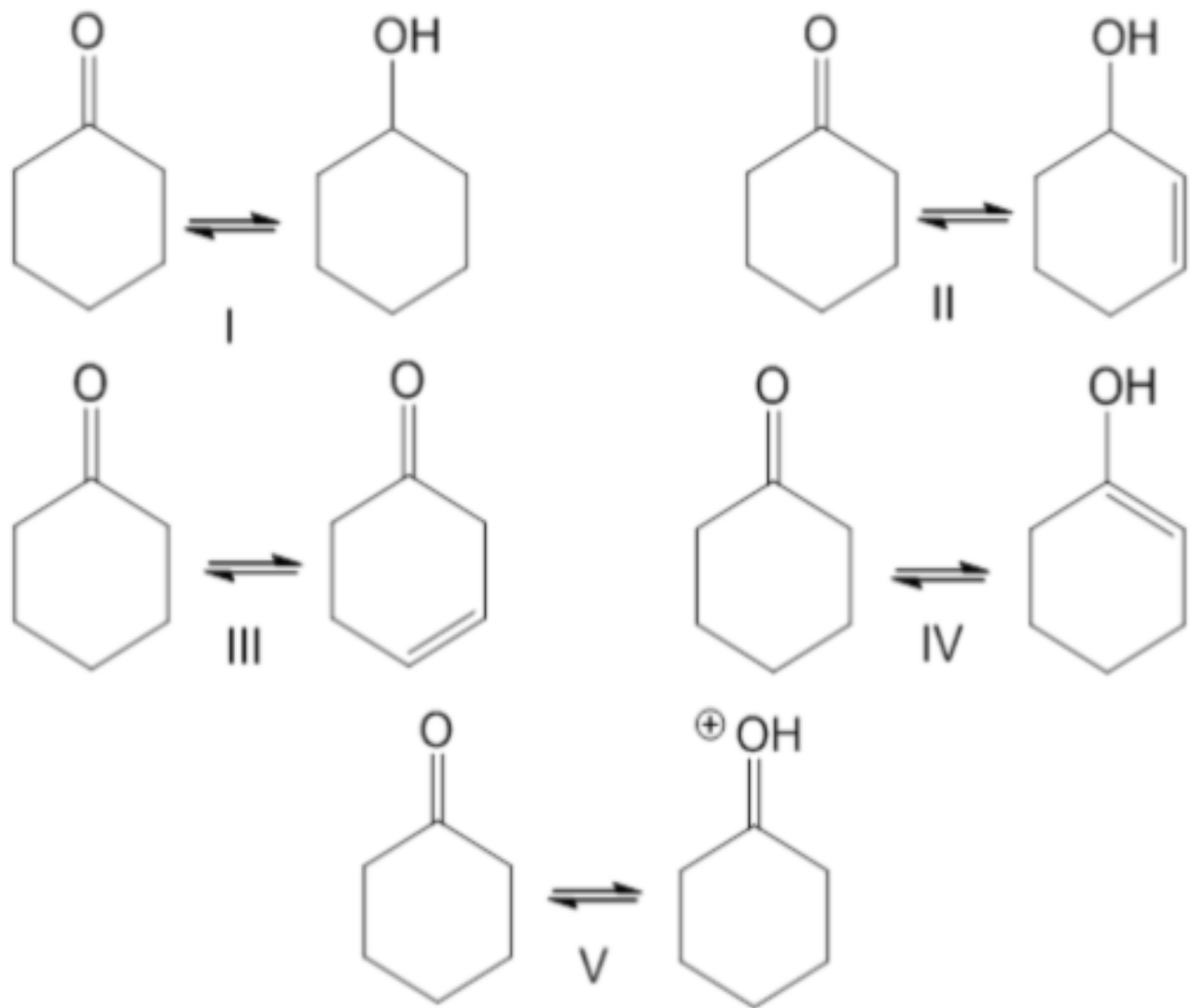
IV

- **Problem** : Select keto enol tautomer pairs among the following

1)

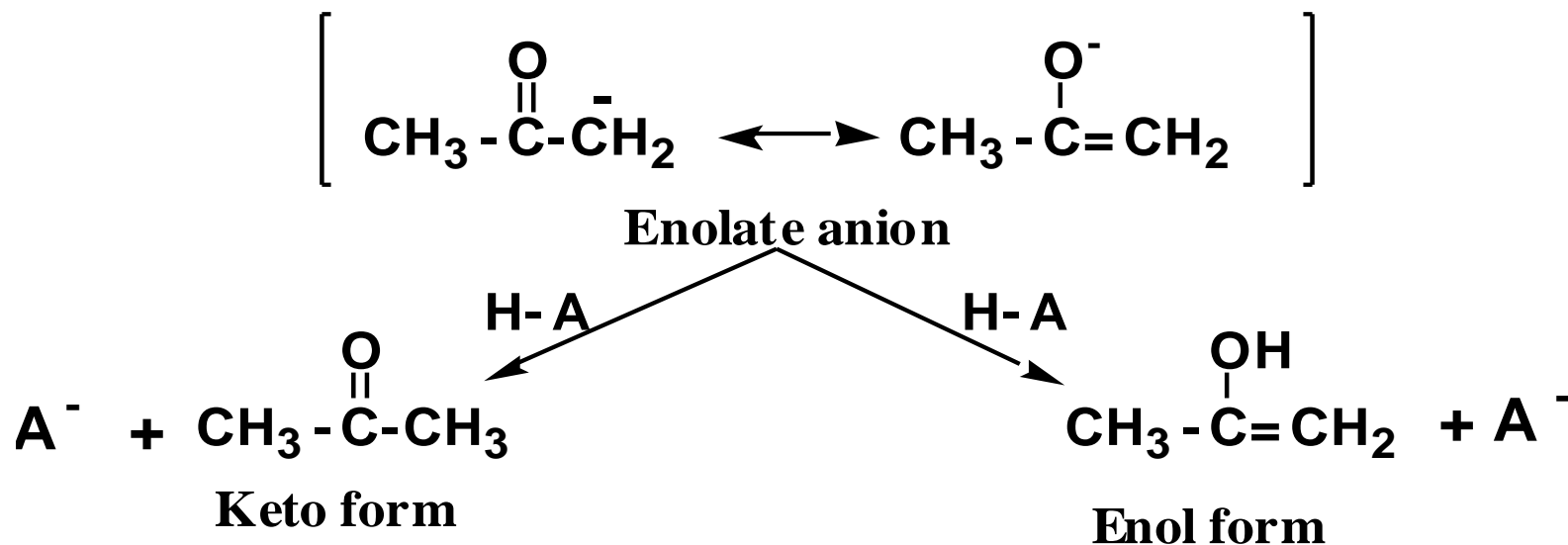


2)



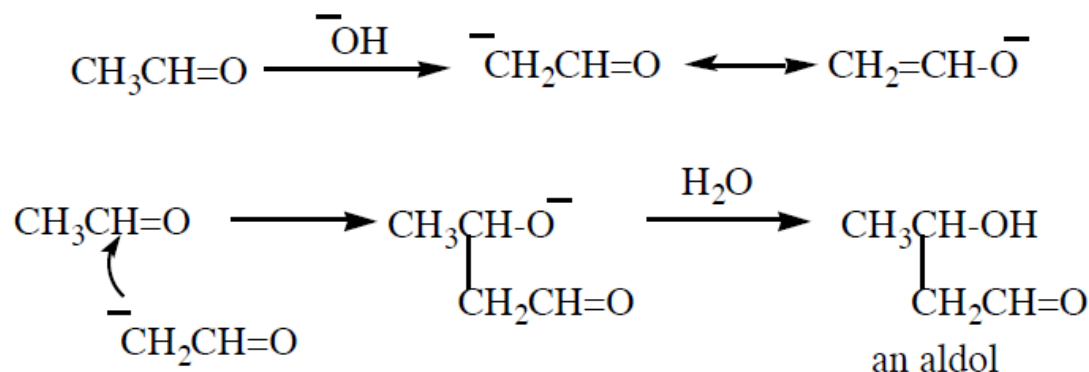
Enolization -ketonization

- Protonation of the enolate anion on oxygen gives the enol form; protonation on carbon gives the keto form.



Aldol and related condensation

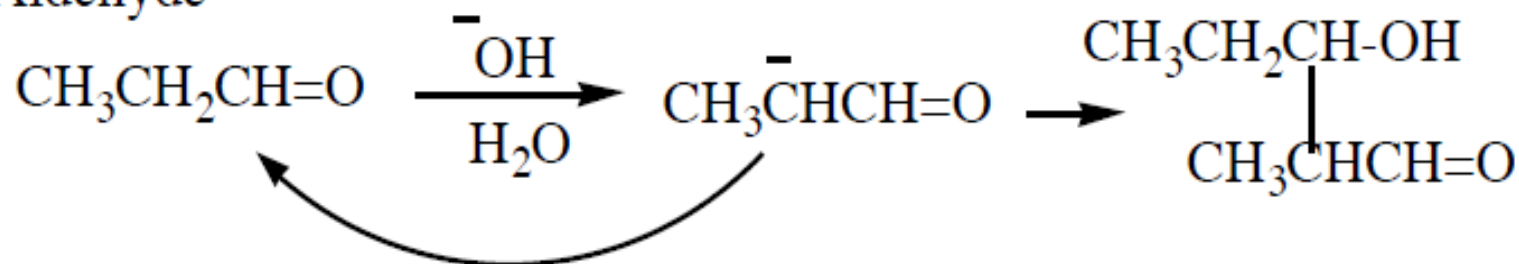
- aldehyde or ketone that has a hydrogen next to the carbonyl group, can form an enolate in basic solution
- the enolate can react by nucleophilic addition at the carbonyl group of another molecule.
- is known as the **Aldol Condensation**
- The product is called an aldol.



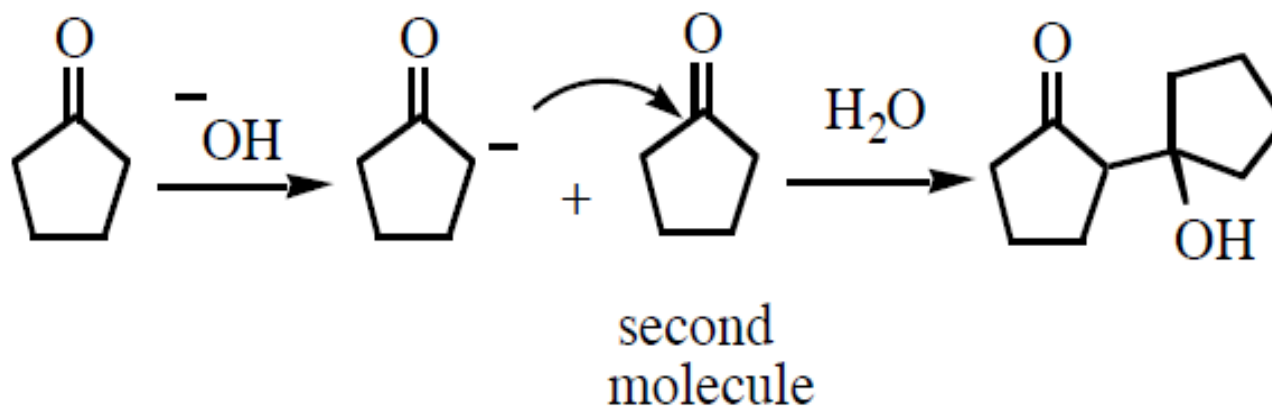
Aldol and related condensation

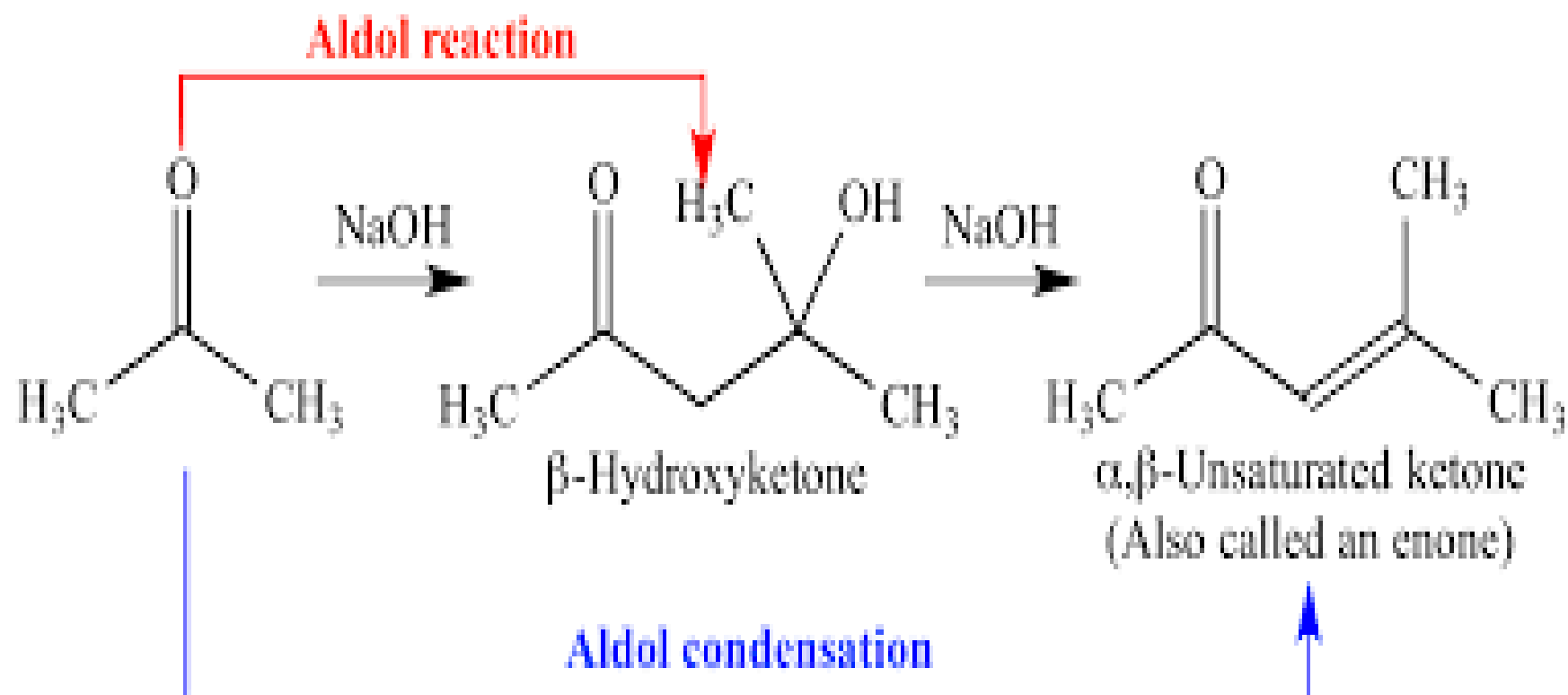
- Example

Aldehyde



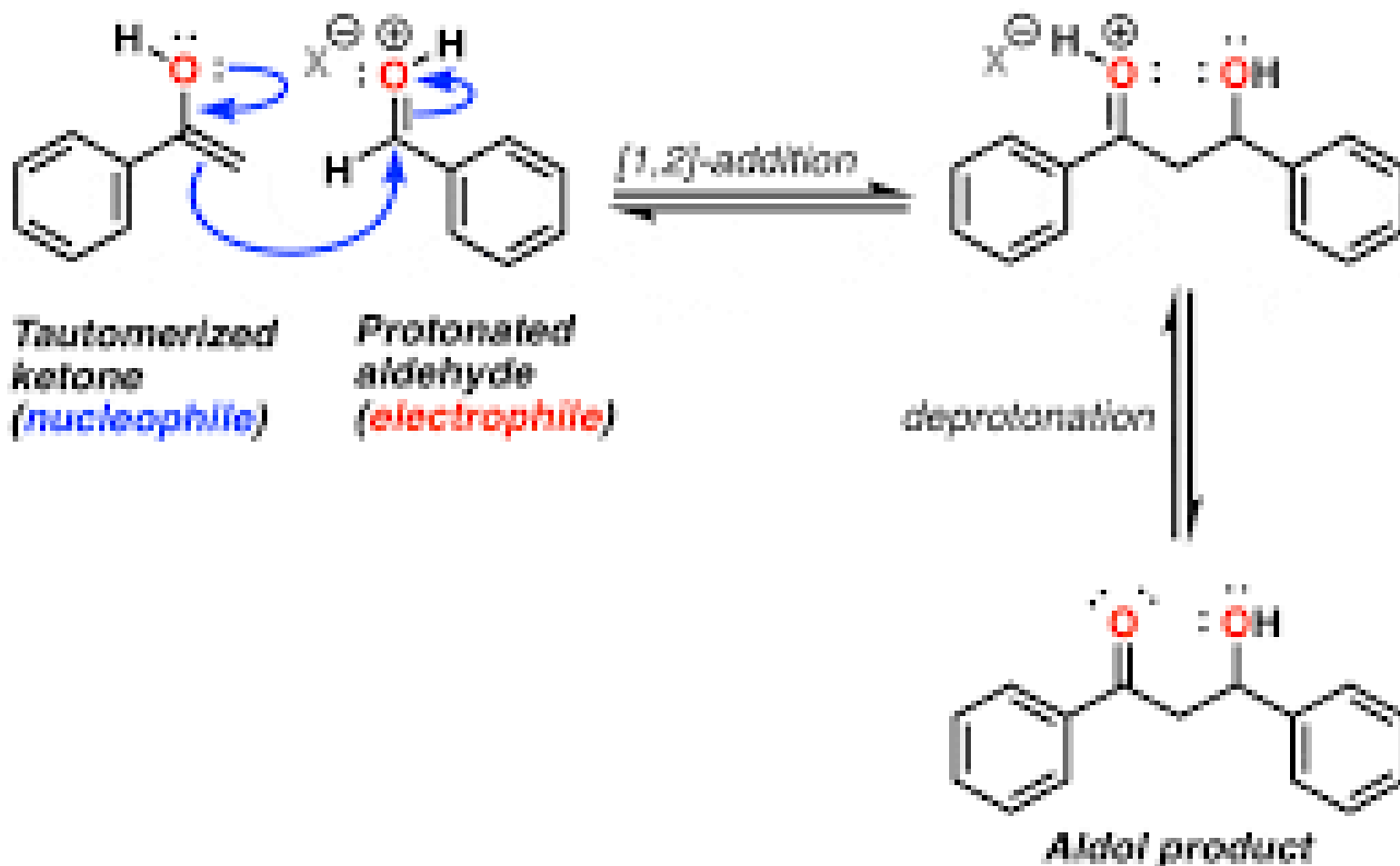
Ketone





Acid catalyzed aldol condensation

How it works:

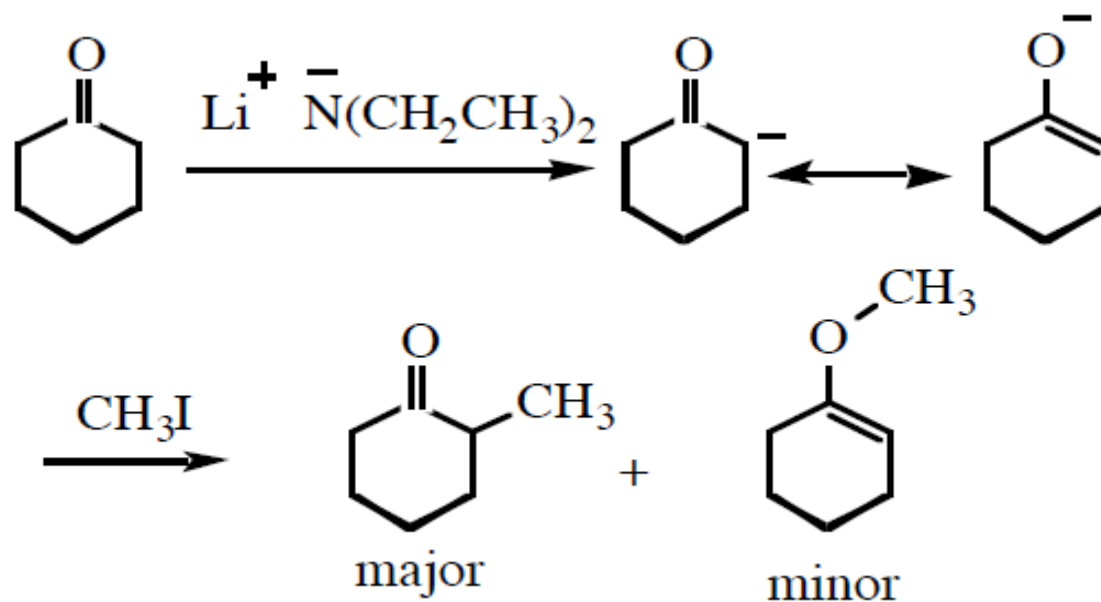


Aldol condensation and related reactions

Alkylation at alpha carbon

- When strong anhydrous bases such as sodium hydride, sodamide or lithium diethylamide $\text{LiN}(\text{C}_2\text{H}_5)_2$, are used to prepare the enolate anions at low temperatures,
- The resulting enolate reacts very slowly with carbonyl groups and can be used as nucleophiles in the $\text{S}_{\text{N}}2$ reaction with primary alkyl halides.

- In the resonance stabilized enolate, a negative charge exists on both a carbon and an oxygen. Both sites are possible nucleophiles
- but the carbon nucleophile predominates , but minor products from O-alkylation are found.



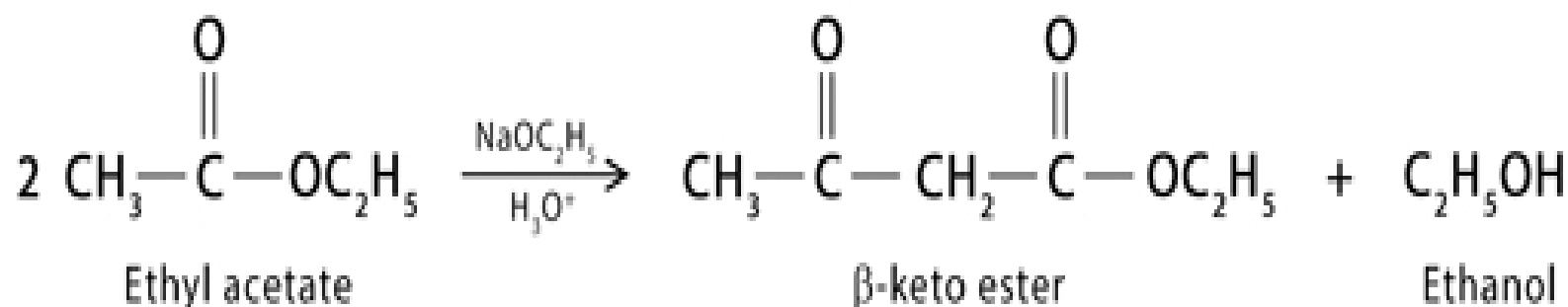
Aldol and related condensation

Claisen Condensation

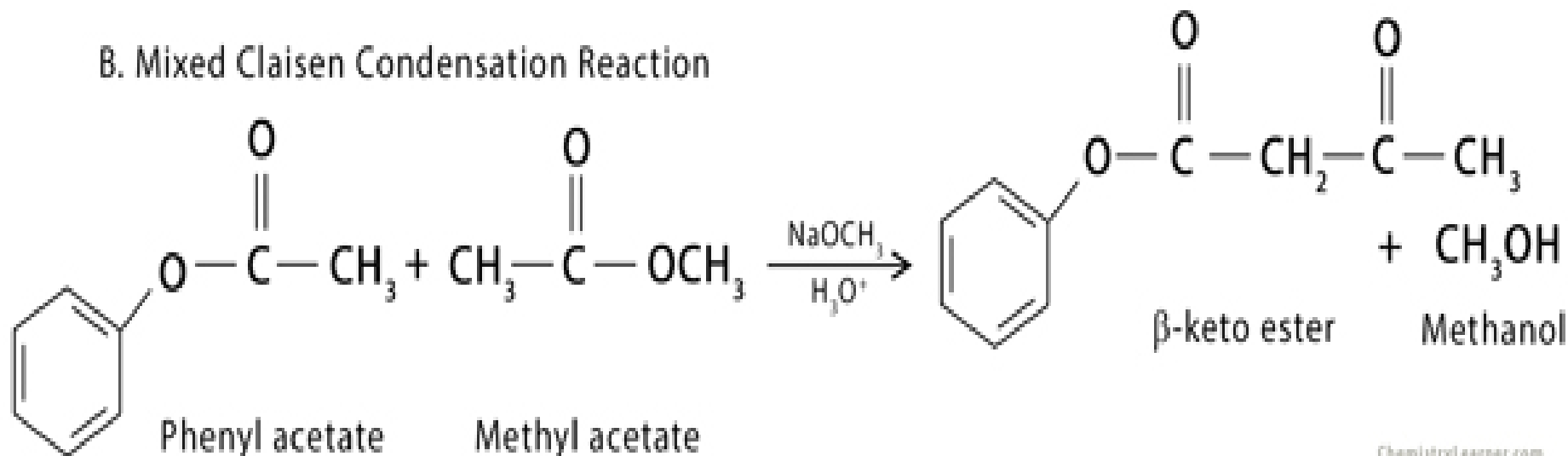
- Esters, like aldehydes and ketones, give an aldol-type reaction
- hydrogen of the ester is removed by base to give the enolate.
- The resulting product is a β -ketoester.
- The reaction is known as the **Claisen condensation**.

Examples of Claisen Condensation Reaction

A. General Claisen Condensation Reaction

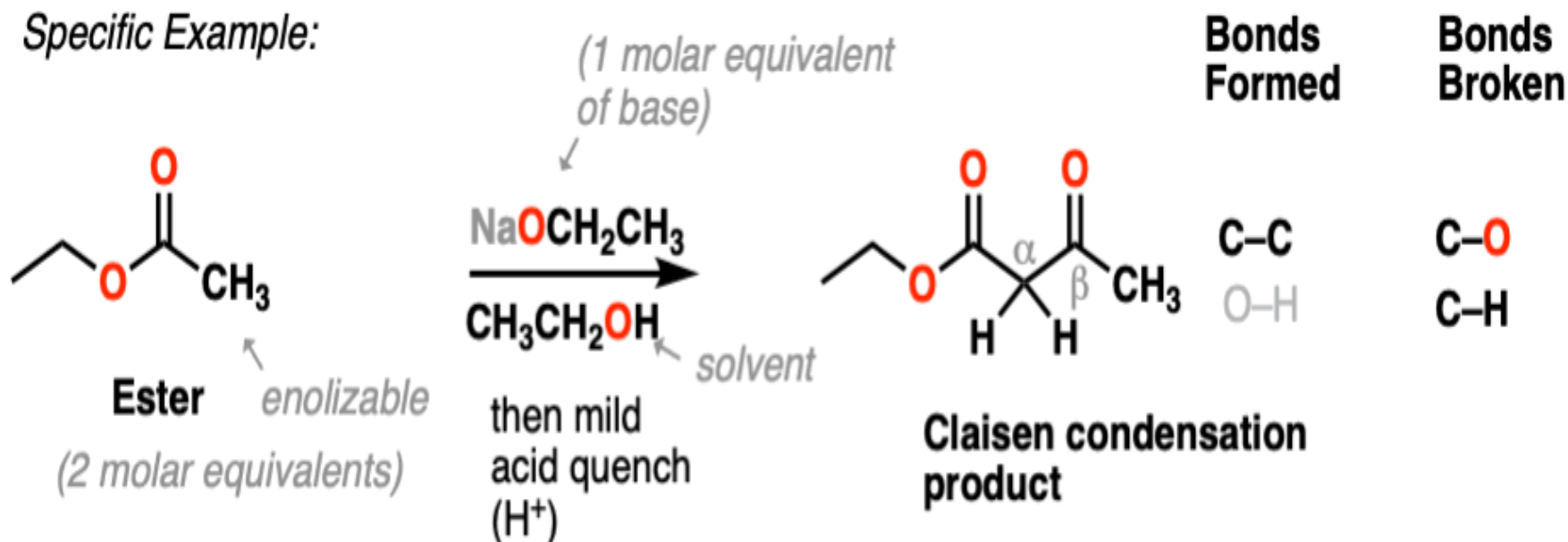


B. Mixed Claisen Condensation Reaction



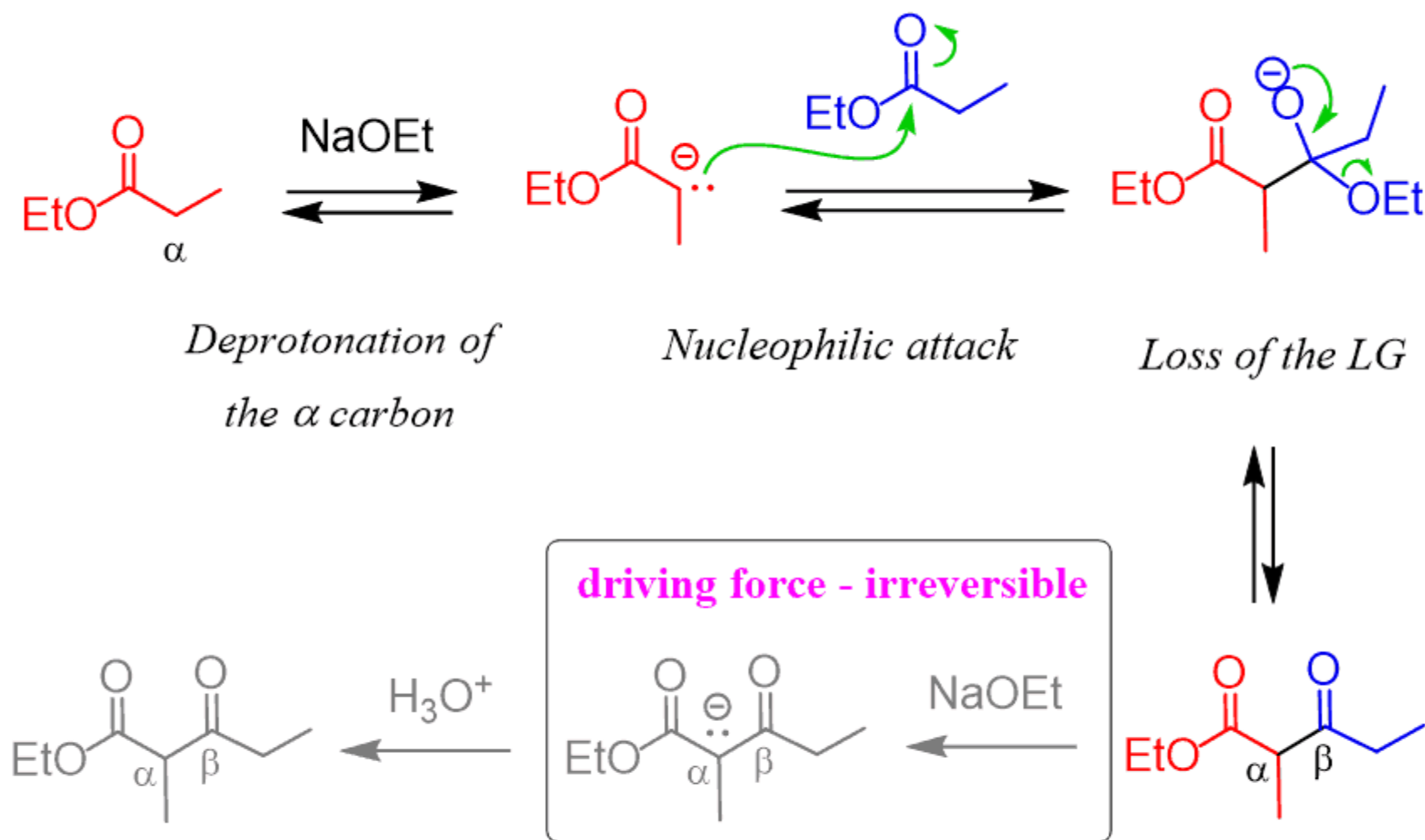
The Claisen Condensation

Specific Example:



- If two different esters are used, the reaction is called a "crossed" Claisen condensation
- If the two esters are attached through a carbon chain, an *intramolecular* reaction is possible, which is often called the "Dieckmann condensation".

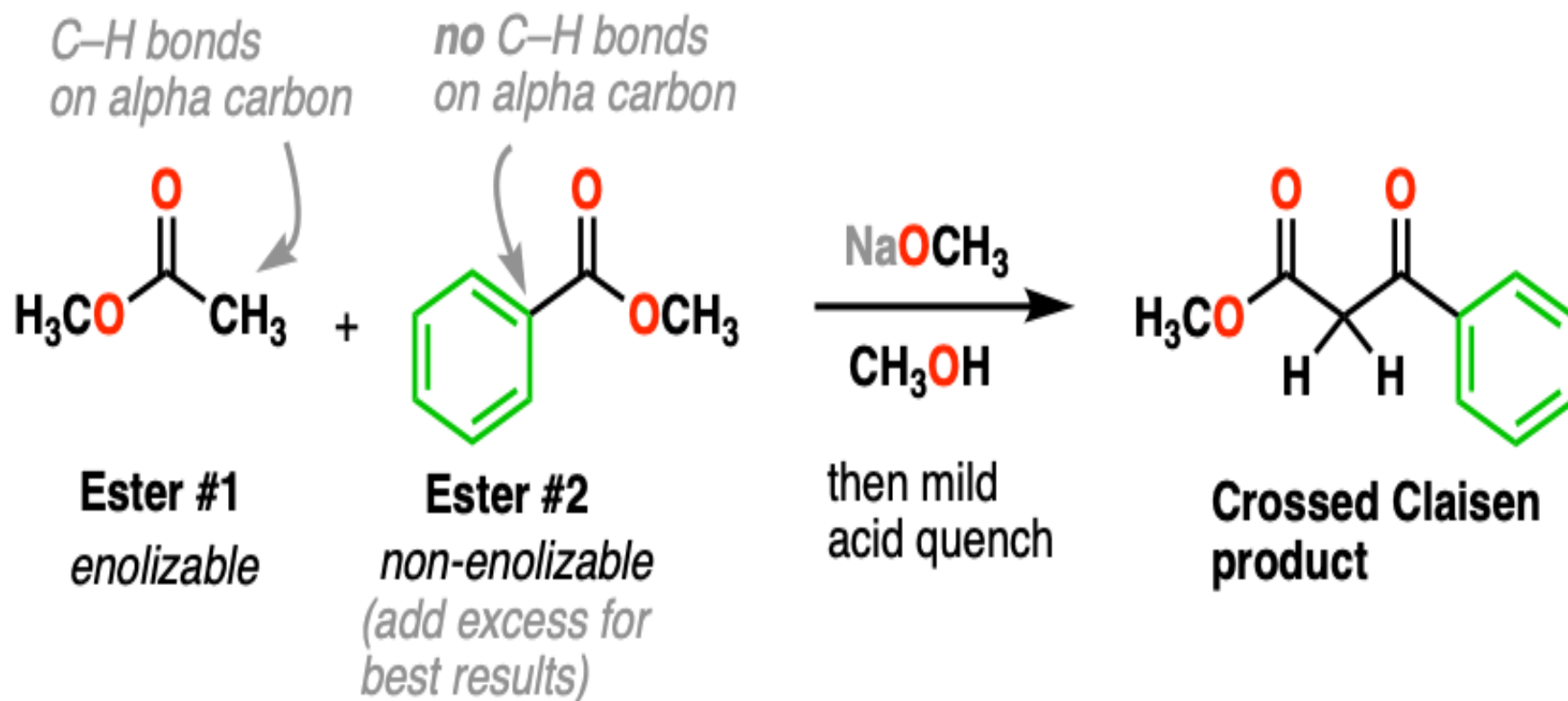
The Mechanism of Claisen Condensation



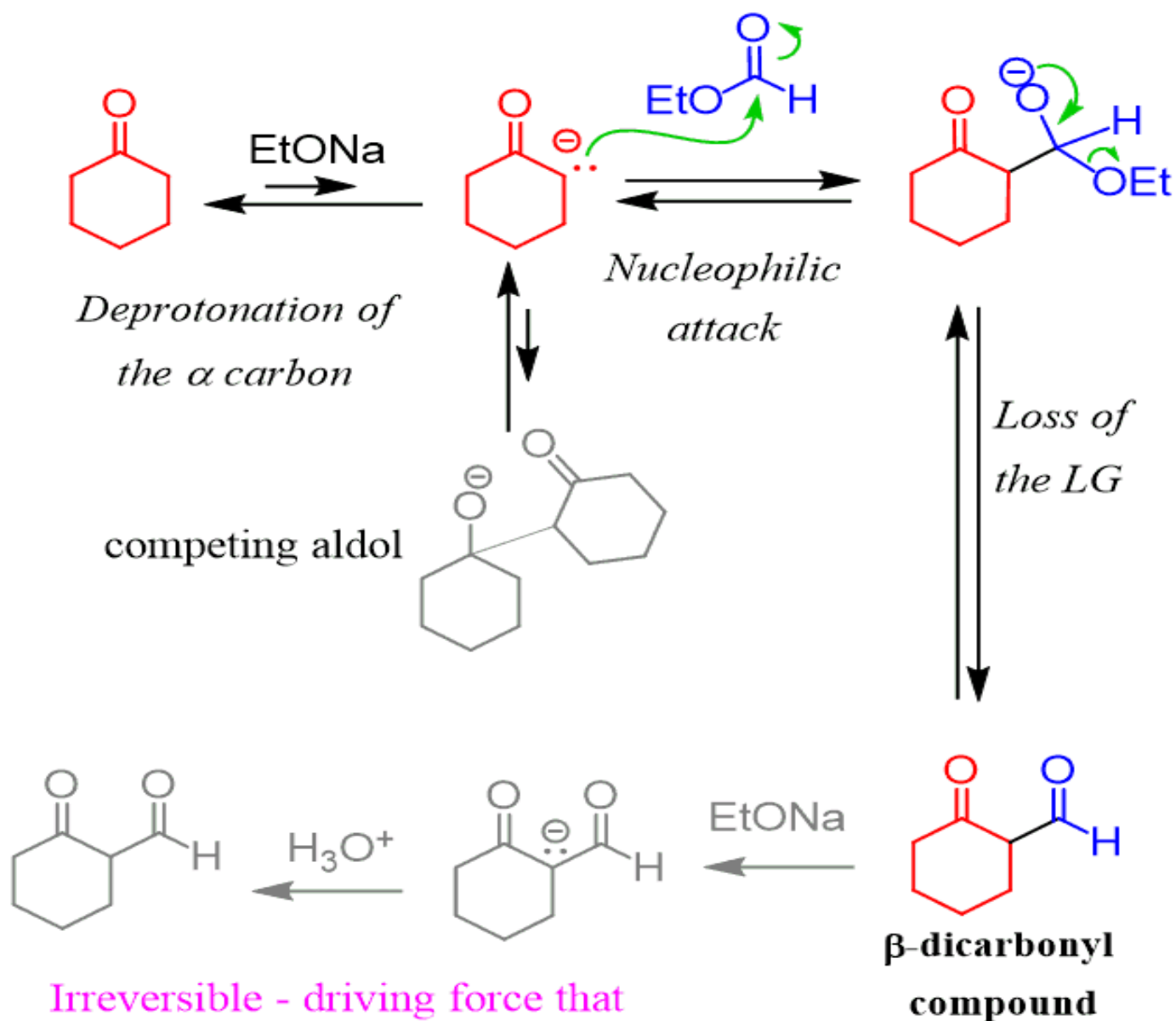
The β -keto ester has a very acidic proton which is removed by the base. Therefore, an acidic workup is needed.

a β -keto ester

A “Crossed” Claisen Condensation Joins Two *Different* Esters



Crossed Claisen Reaction with Ketones using Ethyl Formate

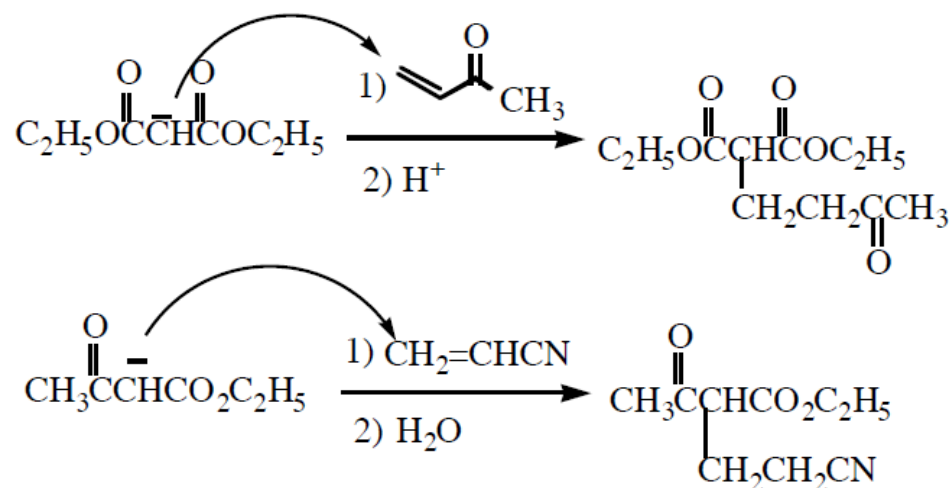


Aldol and related condensation

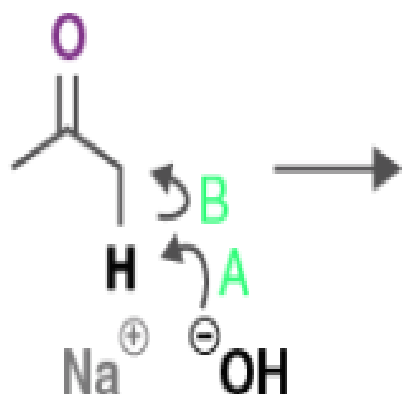
The Michael Reaction

Enolate Addition

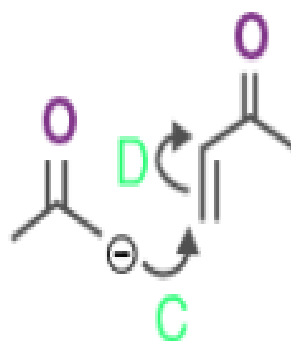
- Enolates may also be alkylated with α,β -unsaturated carbonyl substrates.
- The enolate adds in the 1,4 fashion to give a unit extended by three carbon atoms in a process known as the Michael reaction.
- Many α,β -unsaturated carbonyl systems may be prepared by the dehydration of aldol products.



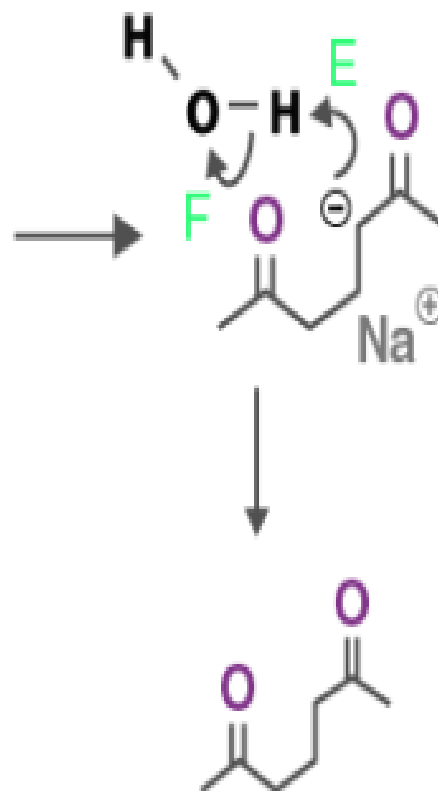
Step 1:
Deprotonation
(enolate formation)



Step 2:
1, 4-addition



Step 3: Protonation



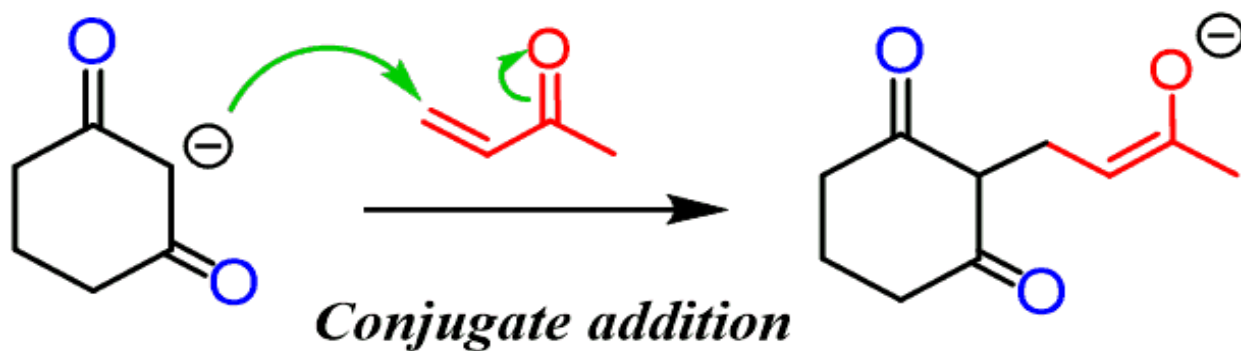
Bonds formed

A O-H
C C-C
E C-H

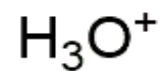
Bonds Broken

B C-H
D C-C(x)
F O-H

Michael Addition Mechanism



protonation



Note :KET= keto enol tautomer

