

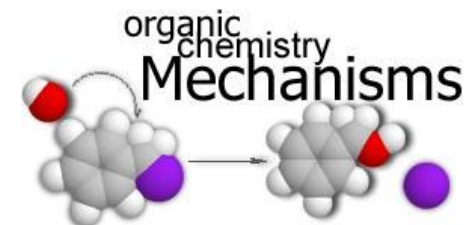
CHEM 344

ORGANIC REACTION MECHANISM

FOR CHEMISTRY' STUDENTS, COLLEGE OF SCIENCE

PRE-REQUISITES COURSE; CHEM 241

CREDIT HOURS; 2 (2+0+0)



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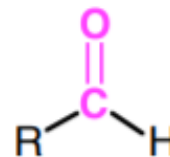
Addition to the Carbonyl Group

Nucleophilic Addition Reactions

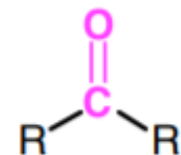
CARBONYL COMPOUNDS

- **Carbonyl compounds** are molecules that containing the carbonyl group, $C=O$.
- These include:

- Aldehydes



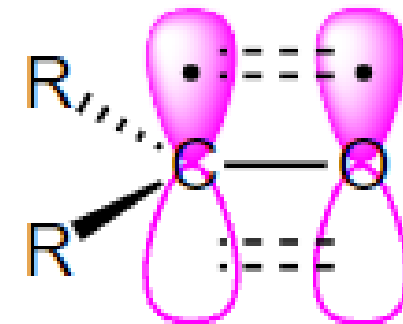
- Ketones



Note: two bonds to heteroatoms

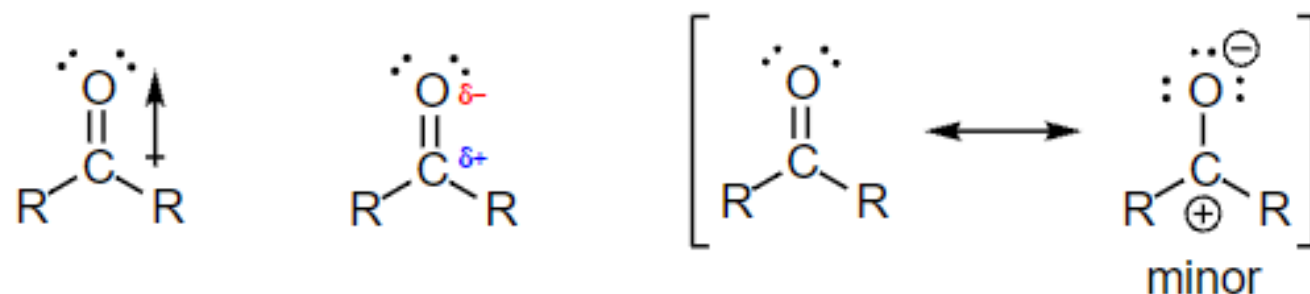
CARBONYL GROUP

- **Carbonyl carbons** are sp^2 hybridized;
 - three sp^2 orbitals (from R groups: C or H) forming three sigma bonds.
 - and an sp^2 hybrid orbital from oxygen.
 - unhybridized $2p$ orbital forms π bond by overlapping with a $2p$ orbital from O.



- The **carbon-oxygen double bond is polar** (*O is more electronegative than C*).

The oxygen is holding a partial negative charge
and the carbonyl carbon with a partial positive charge;



- The **carbon is electron-poor** (*an electrophile*): it attacks by an electron-rich *nucleophilic group*.

NUCLEOPHILIC ADDITION TO CARBONYL GROUP:

GENERAL MECHANISM

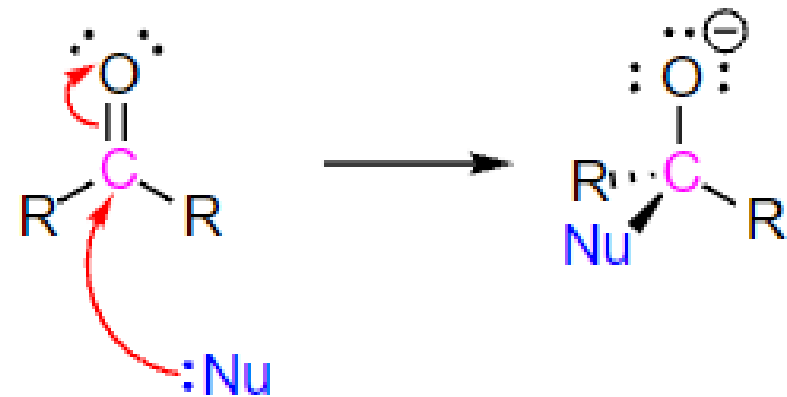
A NUCLEOPHILE

○ In the first step;

- The *nucleophile* forms a bond with the electrophilic C=O carbon atom.

This causes the rehybridization of the carbonyl carbon from sp^2 to sp^3 .

- Electrons in the π bond are pushed up to the electronegative oxygen atom forming a tetrahedral *alkoxide intermediate*.

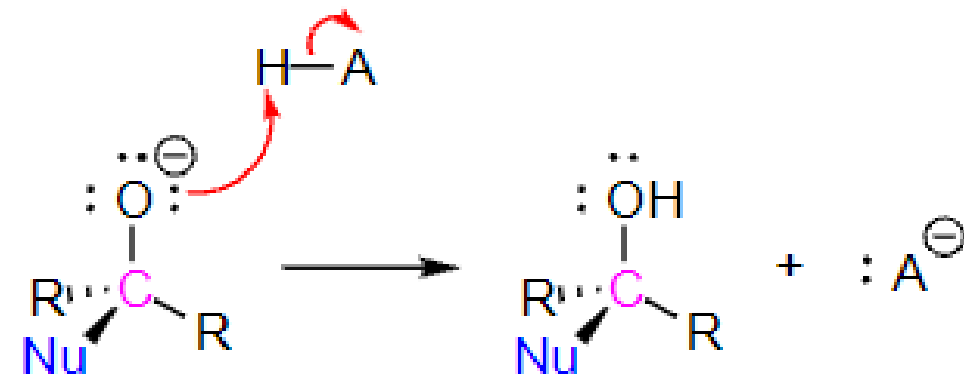


aldehyde or
ketone

tetrahedral alkoxide
intermediate

○ In the second step;

- The alkoxide is protonated by the *addition of an acid* to form *an alcohol*.



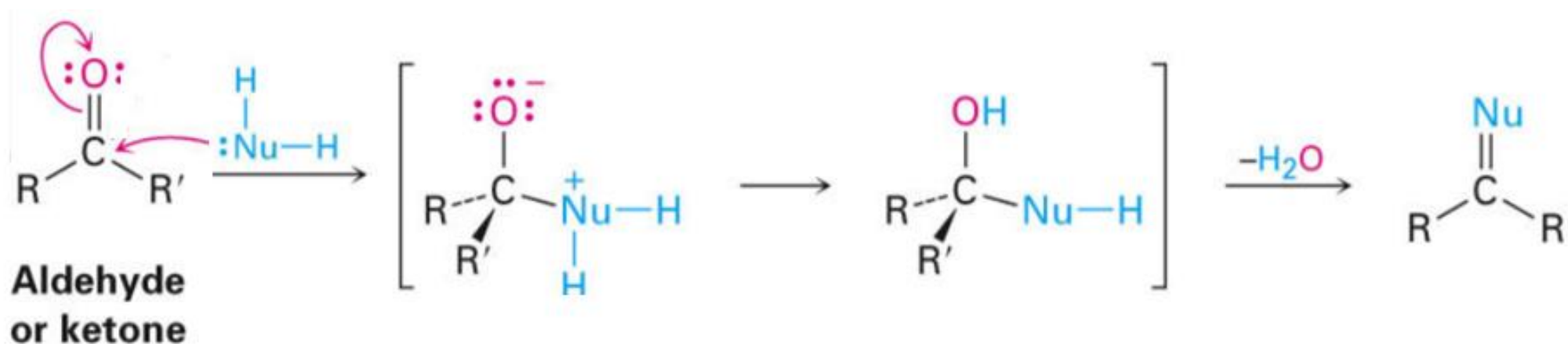
Nucleophilic Addition Reactions of Aldehydes and Ketones, leads to an alcohol product

NUCLEOPHILIC ADDITION TO CARBONYL GROUP:

GENERAL MECHANISM

A NEUTRAL NUCLEOPHILE

- The *presence of an additional hydrogen atom* in the nucleophile allows for the *removal of carbonyl oxygen* to be completely as water and a *C=Nu bond* to be formed

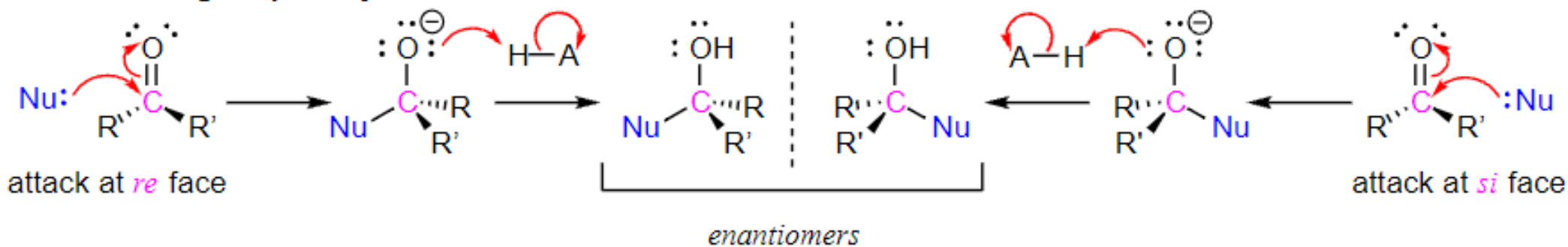


Nucleophilic Addition Reactions of Aldehydes and Ketones, leads to the product with a C= Nu bond.

STEREOCHEMISTRY OF NUCLEOPHILIC ADDITION TO CARBONYL GROUP

- If the **two R groups are not equivalent**;
 - A chiral center is created upon addition of the nucleophile.
 - Reactions of this type often result in a 50:50 racemic mixture of stereoisomers, but it is also possible that one stereoisomer may be more abundant.

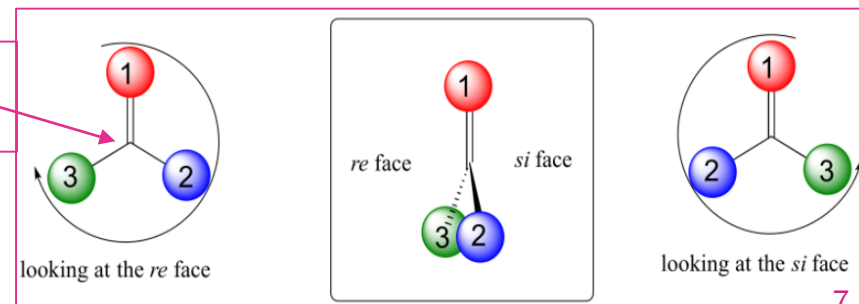
Note: R' is higher priority than R



○ NOTE:

- A 'prochiral' carbon is referred to carbon that can be converted to a chiral center by changing only one of the attached groups.
- Faces are designated by the terms ***re*** (clockwise) and ***si*** (counterclockwise).

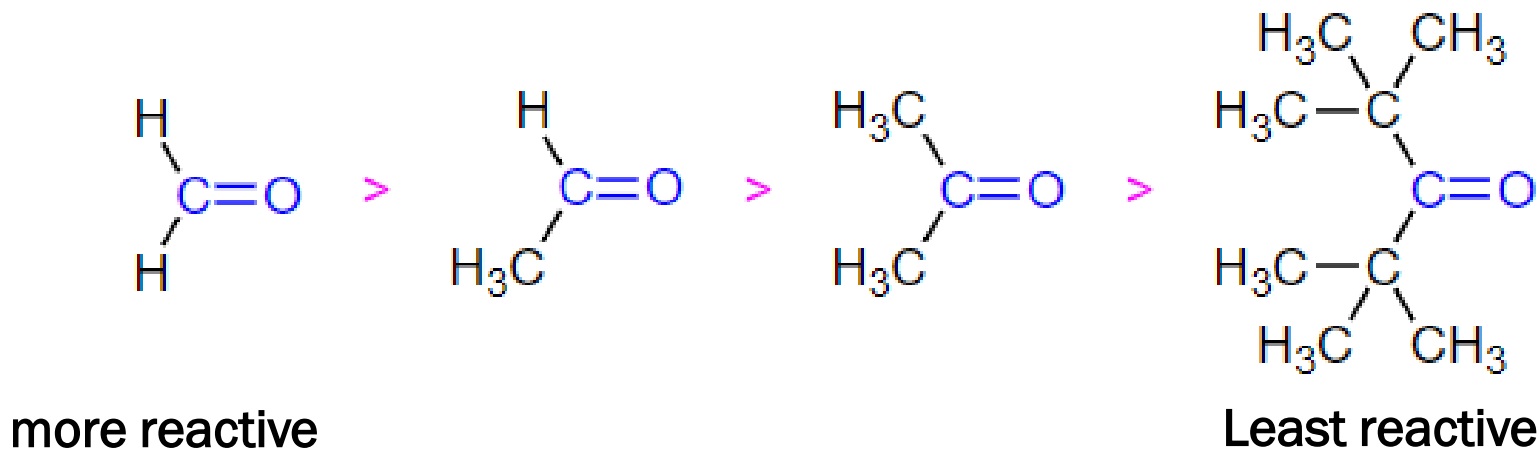
A prochiral
Carbonyl carbon.



RELATIVE REACTIVITY OF ALDEHYDES AND KETONES TO NUCLEOPHILIC ADDITION

➤ Steric Hindrance Effect

- Aldehydes tend to be more reactive than ketones; *Steric hindrance effect*.
 - Nucleophiles have a less sterically hindered path when attacking the carbonyl carbon of an aldehyde.
 - The transition state of the rate determining step for formation of the tetrahedral intermediate is less sterically crowded, lower in energy, and more kinetically favorable for an aldehyde than a ketone.

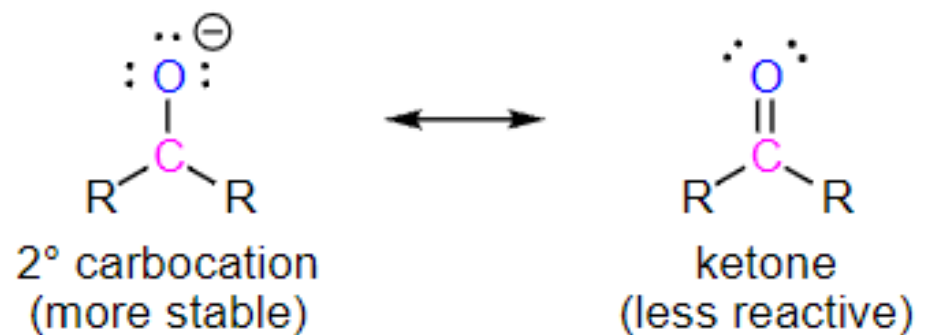
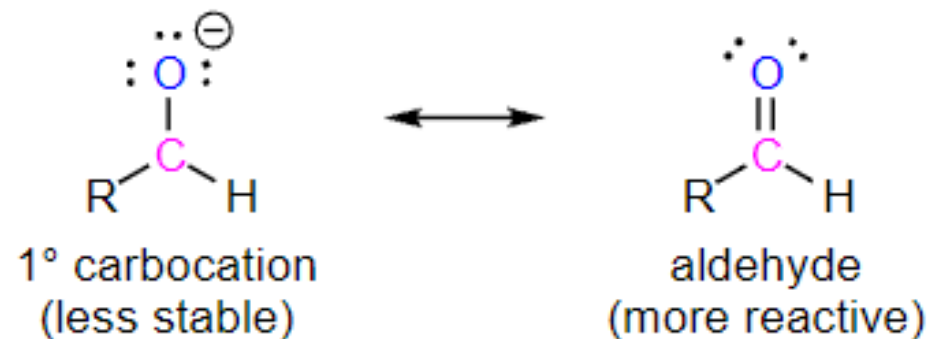


RELATIVE REACTIVITY OF ALDEHYDES AND KETONES TO NUCLEOPHILIC ADDITION

➤ Electrophilicity of Aldehydes and Ketones

○ Aldehydes are more reactive than ketones because

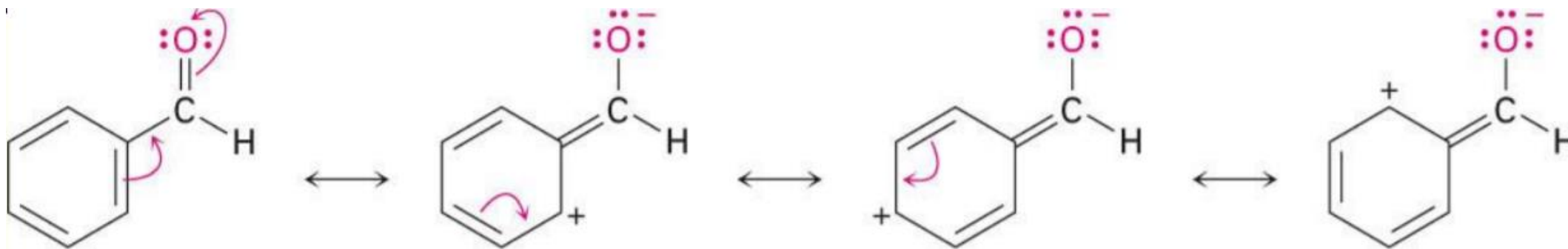
- **Aldehydes** have a greater polarization of the carbonyl bond.
- The **primary carbocation** formed in the polarizing resonance structure of an **aldehyde** is *less stable* and therefore *more reactive*.
- The **secondary carbocation** formed in a similar resonance structure formed by a **ketone** *more stable* and therefore *less reactive*.
- *The stability difference in these resonance structures is due to the extra alkyl group present in the ketone.*



RELATIVE REACTIVITY OF ALDEHYDES AND KETONES TO NUCLEOPHILIC ADDITION

➤ Reactivity of Aromatic Aldehydes

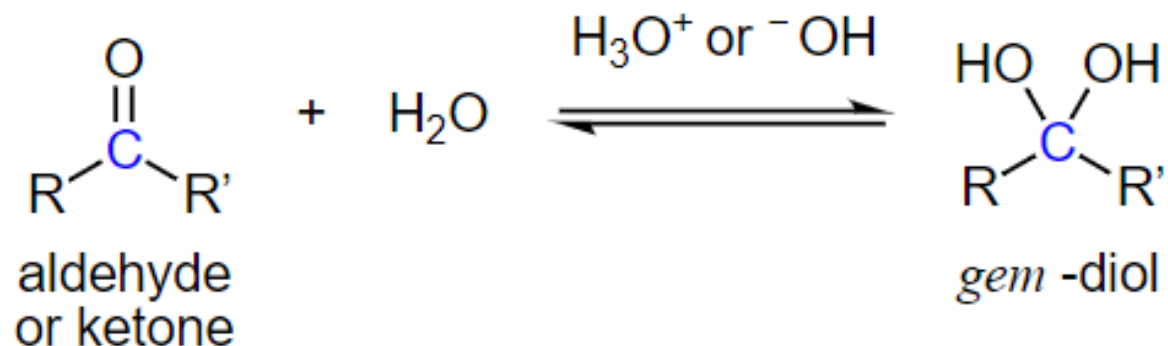
- Aromatic aldehydes are less reactive than aliphatic aldehydes in nucleophilic addition reaction.
- Electron-donating resonance effect of aromatic ring makes C=O less reactive electrophile than the carbonyl group of an aliphatic aldehyde



NUCLEOPHILIC ADDITION OF H₂O:

HYDRATION

- Water adds rapidly to the carbonyl group of aldehydes and ketones establishing a reversible equilibrium with a **hydrate** (*geminal-diol*, *gem-diol*, or *1,1-diol*).

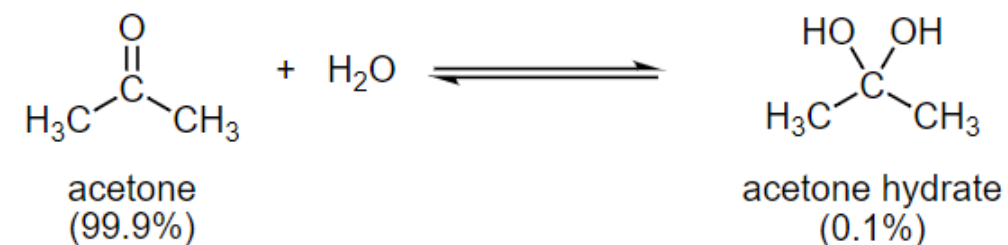
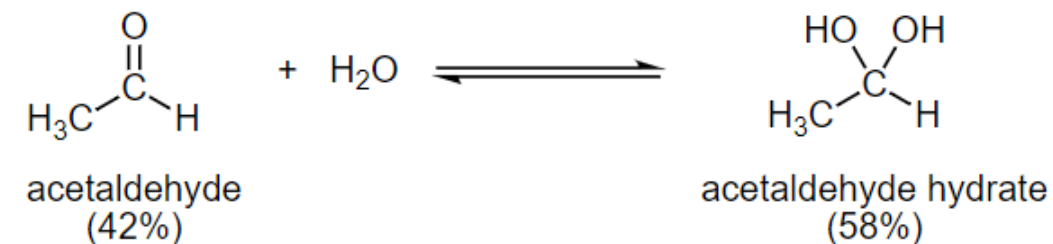
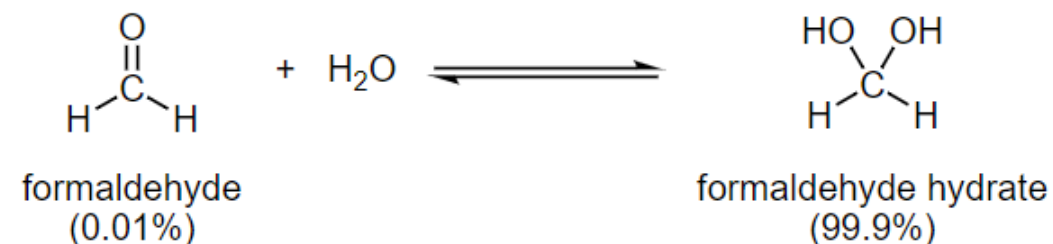


- In most cases the resulting *gem-diol* is unstable relative to the reactants and cannot be isolated.

NUCLEOPHILIC ADDITION OF H₂O: HYDRATION

➤ Factors Affecting the Hydrate Equilibrium

- The equilibrium for hydrate formation depends both on **steric and electrical factors of the carbonyl group**.
- Formaldehyde favors hydrate formation.
- Thus, a solution of formaldehyde in water (**formalin**) is almost exclusively the hydrate, or polymers of the hydrate.
- The addition of **electron donating alkyl groups** stabilized the partial positive charge on the carbonyl carbon and decreases the amount of gem-diol product at equilibrium.

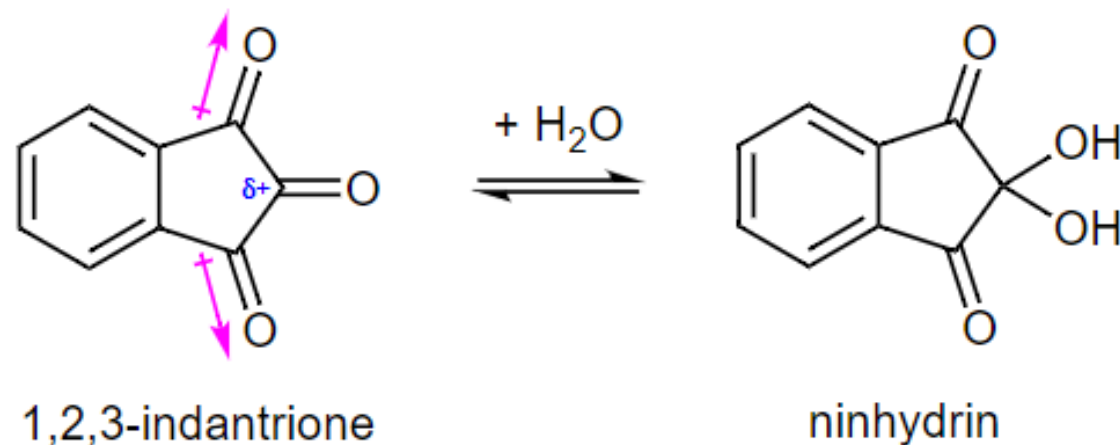
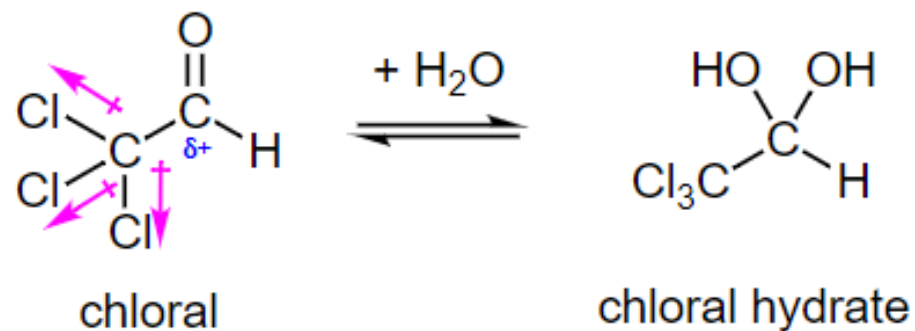


NUCLEOPHILIC ADDITION OF H₂O:

HYDRATION

➤ Factors Affecting the Hydrate Equilibrium

- The addition of strong **electron-withdrawing groups** destabilizes the carbonyl and tends to form stable hydrates.



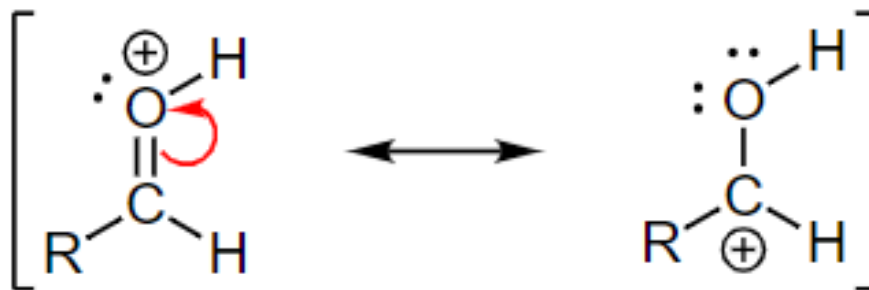
NUCLEOPHILIC ADDITION OF H₂O:

HYDRATION

MECHANISM

- The nucleophilic addition of water to a carbonyl to form a hydrate is usually slow under neutral condition (pH = 7).
- The rate can be significantly increased through the addition of an acid or base as a catalyst.
 - **Basic conditions** speed up the reaction because *hydroxide is a better nucleophile than water*.
 - **Acidic conditions** speed up the reaction because *the carbonyl becomes protonated*.

Protonation increases the polarity of the carbonyl bond which increase the partial positive charge on the carbon making it more electrophilic.

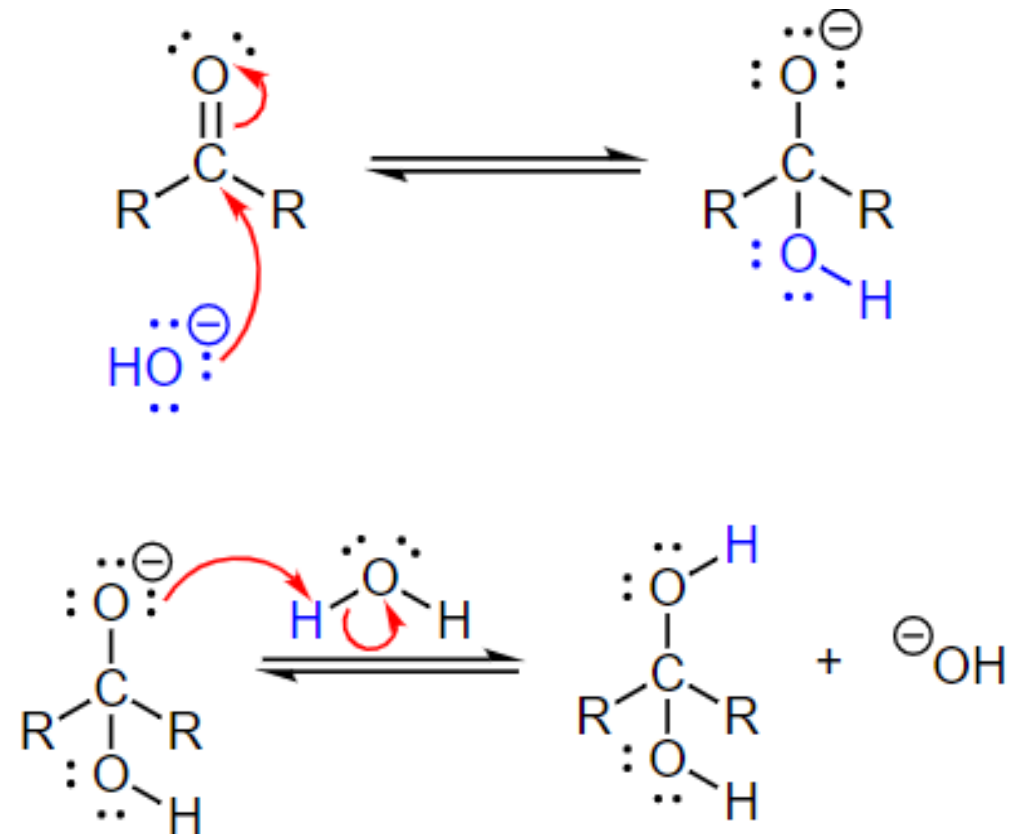


NUCLEOPHILIC ADDITION OF H₂O: HYDRATION

MECHANISM

Basic conditions

- The negatively charged hydroxide forms a single bond with the electrophilic carbonyl carbon.
- This pushes the two electrons of the pi bond onto the electronegative oxygen forming an alkoxide ion intermediate.
- Water acts as an acid and protonates the alkoxide ion to form a neutral hydrate while also regenerating hydroxide.

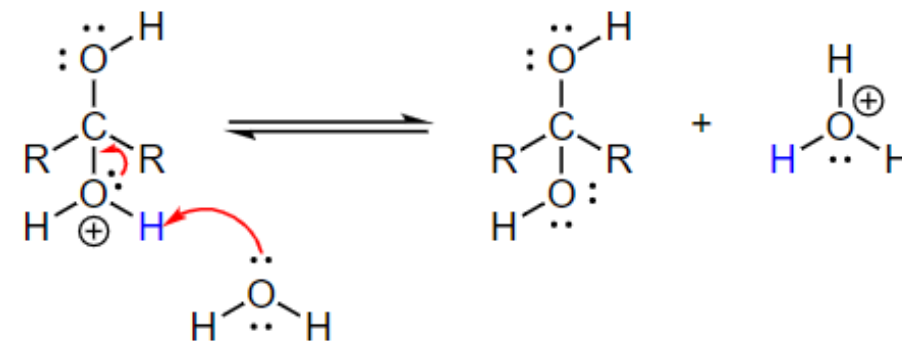
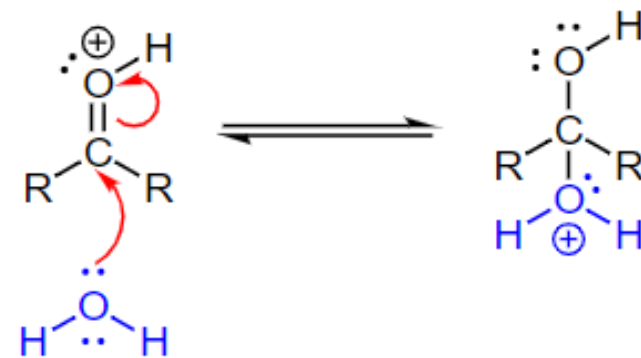
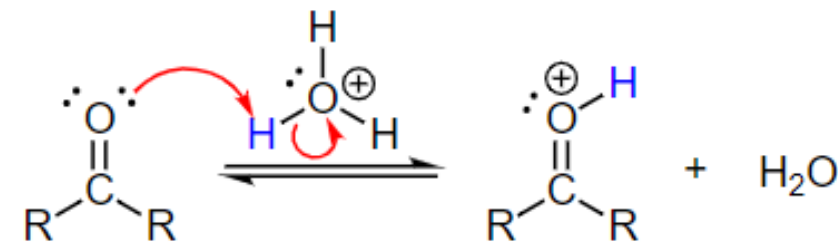


NUCLEOPHILIC ADDITION OF H₂O: HYDRATION

MECHANISM

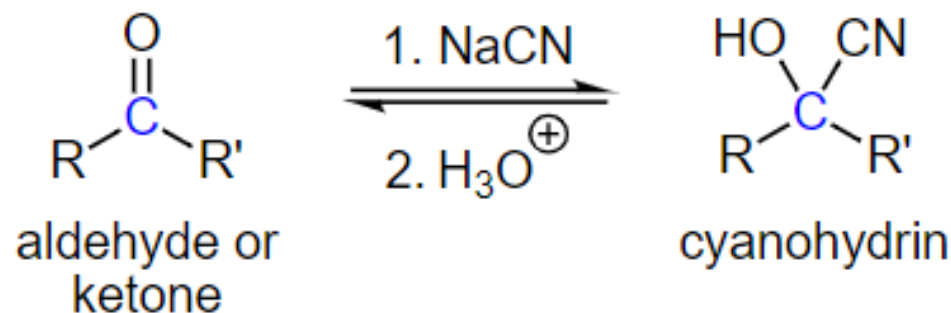
Acidic conditions

- Hydronium protonates the carbonyl oxygen thereby making the carbonyl carbon more electrophilic.
- Water forms a single bond with the electrophilic carbon. This pushes the two electrons in the carbonyl pi bond onto the electronegative oxygen.
- Water acts as a base and deprotonates the intermediate to produce the neutrally charged hydrate while regenerating hydronium.



NUCLEOPHILIC ADDITION OF HCN: CYANOHYDRIN FORMATION

- Hydrogen cyanide ($\text{HC}\equiv\text{N}$), adds reversibly to aldehydes and many ketones forming hydroxyalkanenitrile adducts (**cyanohydrins**).
- **Cyanohydrins** have the structural formula of $\text{R}_2\text{C}(\text{OH})\text{CN}$.
- Cyanohydrin formation is favored for aldehydes, and unhindered cyclic and methyl ketones.



HCN is created *in situ* by adding a strong acid to a mixture of sodium cyanide and the carbonyl compound,

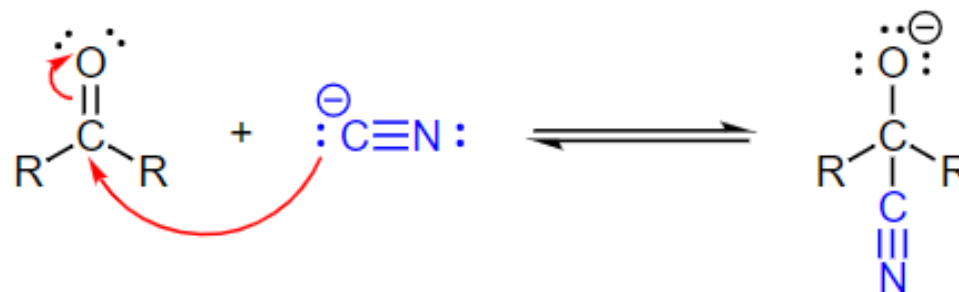
- Cyanohydrin formation is **base-catalyzed** reaction.
Hydrogen cyanide is a weak acid ($\text{p}K_a = 9.25$), and a small amount of a strong base activates hydrogen cyanide by converting it to cyanide ion ($\text{C}\equiv\text{N}^-$, carbon nucleophile).
- **In the absence of base**, the reaction does not proceed, or is at best very slow.

NUCLEOPHILIC ADDITION OF HCN: CYANOHYDRIN FORMATION

MECHANISM

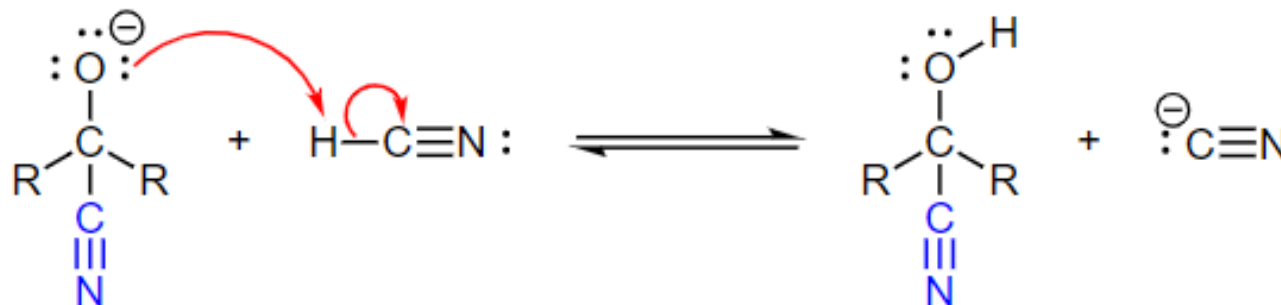
Step 1: Nucleophilic attack

The cyanide ion acts as a nucleophile and forms a C-C bond with the electrophilic carbonyl carbon. The two electrons in the carbonyl pi bond are pushed on to the electronegative oxygen forming a tetrahedral alkoxide ion intermediate.



Step 2: Protonation

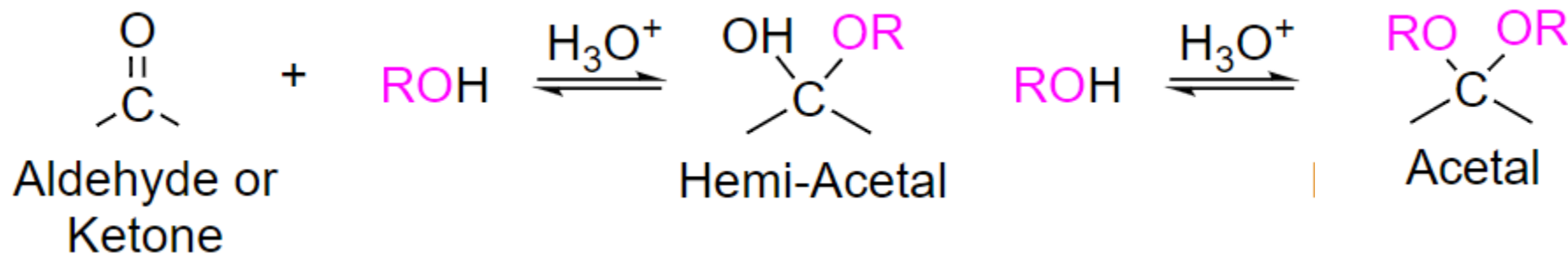
The alkoxide ion is protonated by HCN which regenerates the cyanide ion.



NUCLEOPHILIC ADDITION OF ROH:

ACETAL FORMATION

- Addition of one equivalent of an alcohol to aldehydes and ketones, in the presence of an acid catalyst, form a **hydroxy ether** called a **hemiacetal** (R_2COHOR').
- This reaction can continue by adding another equivalent of an alcohol to form a **diether** called an **acetal** $R_2C(OR')_2$.



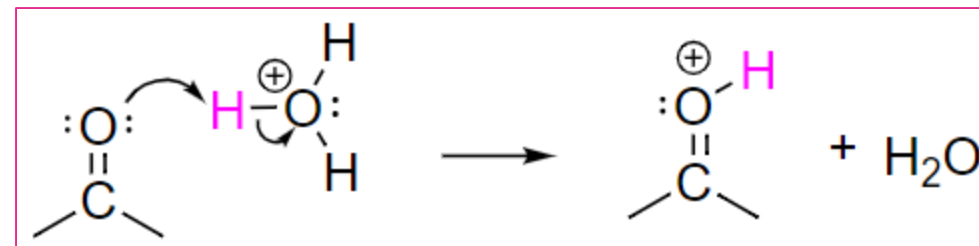
NUCLEOPHILIC ADDITION OF ROH:

ACETAL FORMATION

MECHANISM

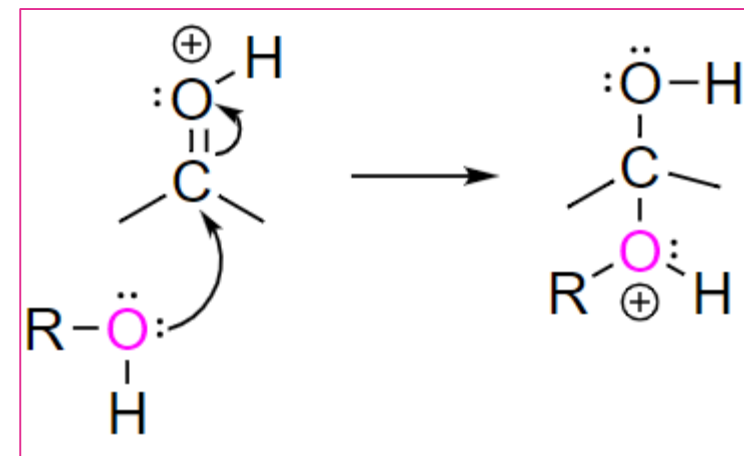
Step 1: Protonation

The acid catalyst **protonates** the carbonyl oxygen, making the **carbonyl carbon more electrophilic**.



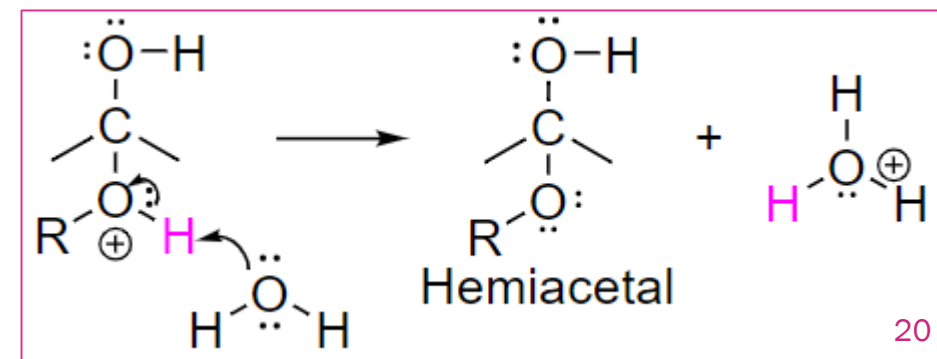
Step 2: Nucleophilic attack

An alcohol undergoes **nucleophilic addition** to the carbonyl producing a **protonated hemiacetal**.



Step 3: Deprotonation

Water acts as base to cause a **deprotonation** creating a **hemiacetal and hydronium**.

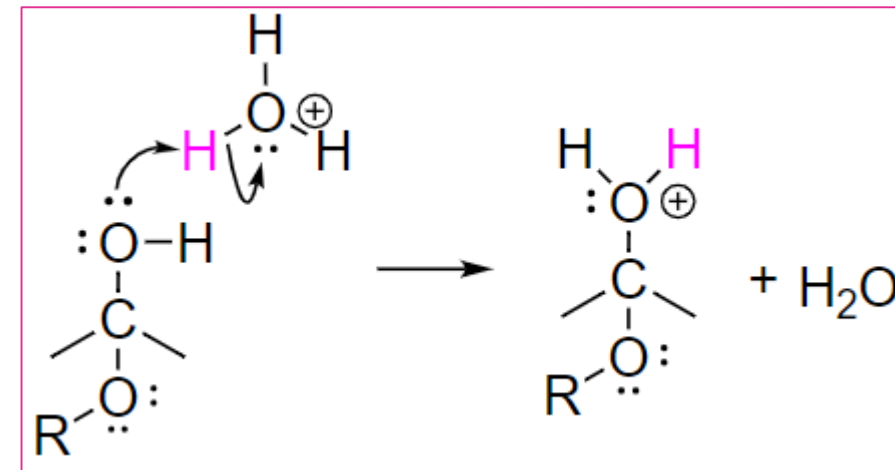


NUCLEOPHILIC ADDITION OF ROH: ACETAL FORMATION

MECHANISM

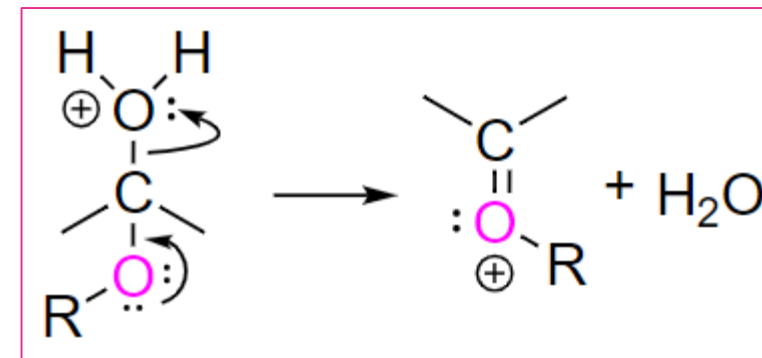
Step 4: Protonation

The OH group of the hemiacetal is **protonated** making it into **a good leaving group**.



Step 5: elimination of water

Lone pair electrons on the ether oxygen reforms the C=O bond causing the **elimination of water** and **producing an oxonium ion**.



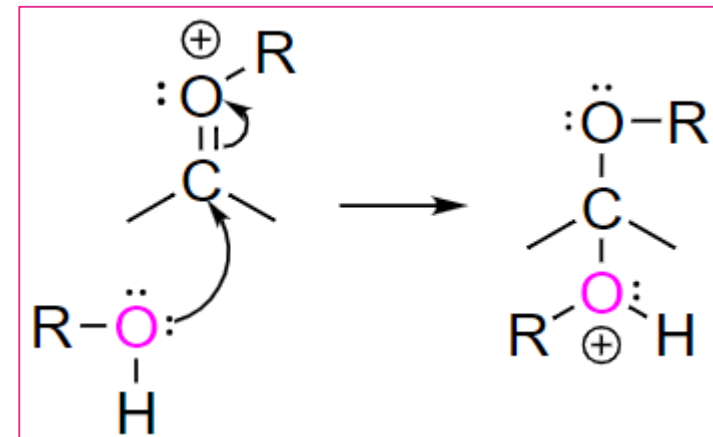
NUCLEOPHILIC ADDITION OF ROH:

ACETAL FORMATION

MECHANISM

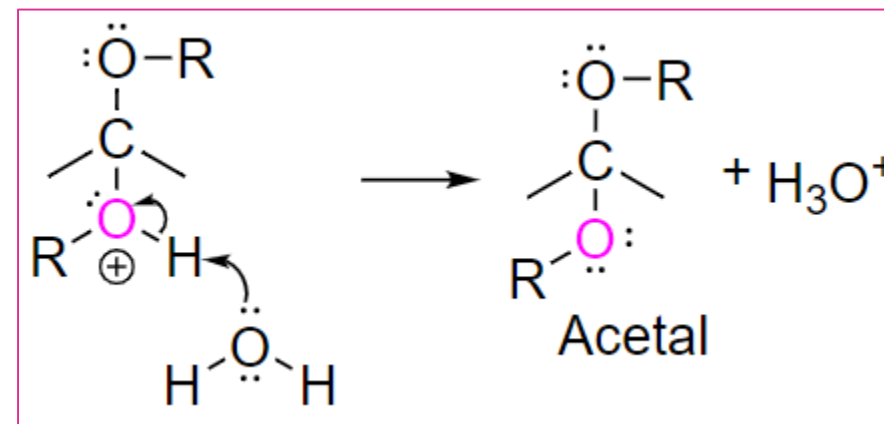
Step 6: Nucleophilic attack

A second alcohol undergoes **nucleophilic addition** to oxonium ion producing a **protonated acetal**.



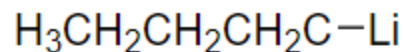
Step 7: Deprotonation

Water acts as a base and causes a **deprotonation**, creating the product **acetal and hydronium**.

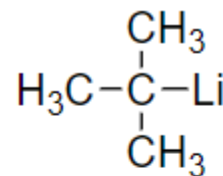


NUCLEOPHILIC ADDITION OF RMgX: ORGANOMETALLIC REACTIONS

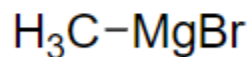
- Lithium and magnesium metals reduce the carbon-halogen bonds of alkyl halides to form **organolithium reagents** and **Grignard reagents** respectively.



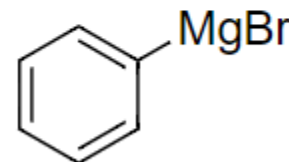
Butyl Lithium



t-Butyl Lithium



Methyl Magnesium Bromide

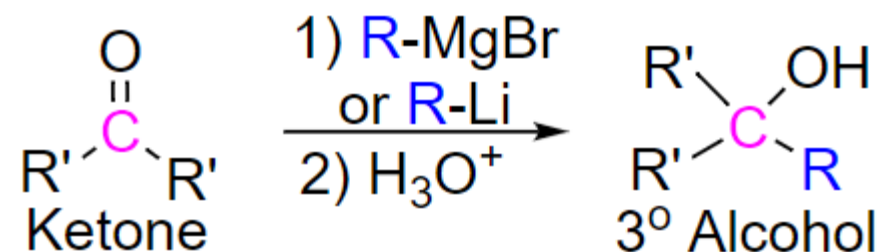
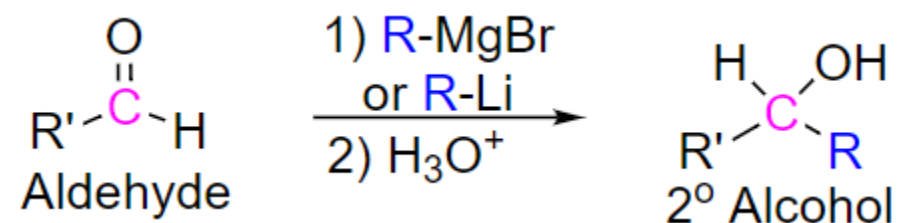
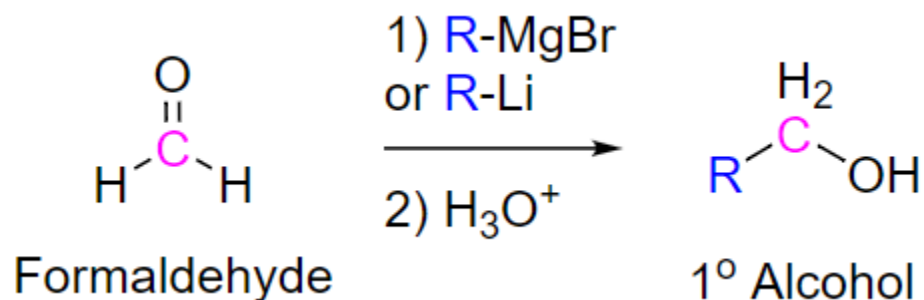


Phenylmagnesium Bromide

- The carbon bonds to the metal and has characteristics similar to a **carbanion (R:-) nucleophile**.
- Grignard and organolithium reagents are powerful bases.*

NUCLEOPHILIC ADDITION OF RMgX: ORGANOMETALLIC REACTIONS

- Aldehydes and ketones will undergo nucleophilic addition with organolithium and Grignard reagent nucleophiles.
- An **alkoxide ion intermediate** is formed which becomes **an alcohol** with subsequent protonation with an acid.



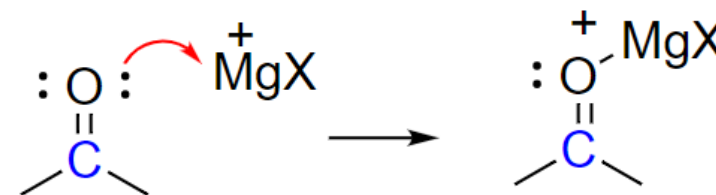
In above examples Formaldehydes is the most reactive one

MECHANISM

NUCLEOPHILIC ADDITION OF RMgX: ORGANOMETALLIC REACTIONS

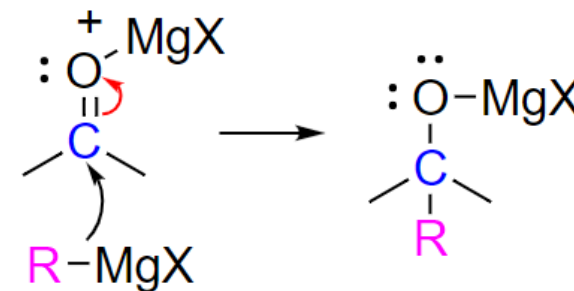
Step 1: Lewis acid-base formation

The mechanism starts with the formation of an acid-base complex between ^+MgX (acts as a Lewis acid) and the carbonyl oxygen.



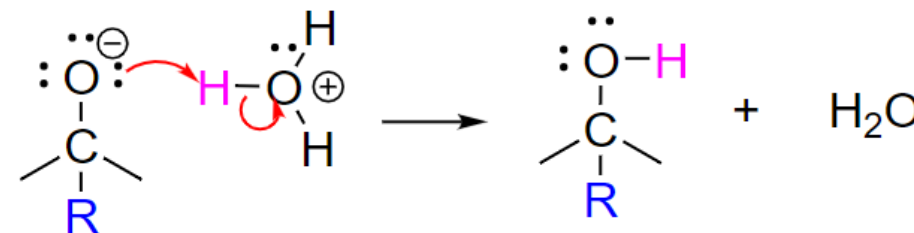
Step 2: Nucleophilic attack

The carbanion nucleophile from the Grignard reagent adds to the electrophilic carbon of the acid-base complex forming a C-C bond forming a tetrahedral magnesium alkoxide intermediate.



Step 3: Protonation

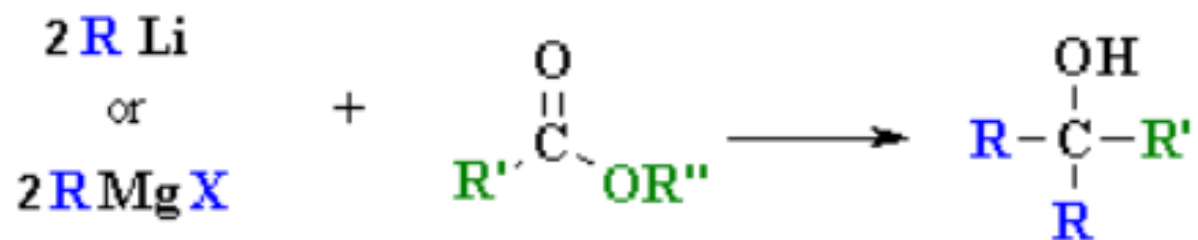
The alkoxide intermediate is converted to an alcohol through addition of an acidic aqueous solution.



NUCLEOPHILIC ADDITION OF RMgX: ORGANOMETALLIC REACTIONS

➤ Reactions of RLi and RMgX with Esters

- Grignard and organolithium reagents are powerful bases and they cannot be used as nucleophiles on compounds which contain acidic hydrogens.
- So, they will act as a base and deprotonate the acidic hydrogen rather than act as a nucleophile and attack the carbonyl.



Reaction usually in Et₂O followed by H₃O⁺ work-up

NUCLEOPHILIC ADDITION OF RMgX: ORGANOMETALLIC REACTIONS

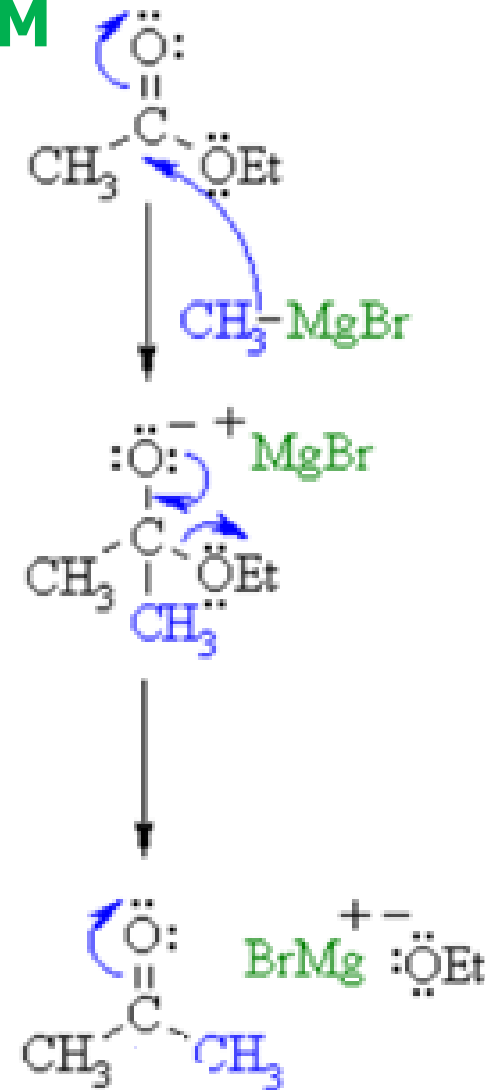
➤ Reactions of RLi and RMgX with Esters: MECHANISM

Step 1:

The nucleophilic **C** in the organometallic reagent adds to the electrophilic **C** in the polar carbonyl group of the ester. Electrons from the **C=O** move to the electronegative **O** creating the **tetrahedral intermediate**, a metal alkoxide complex.

Step 2:

The tetrahedral intermediate collapses and displaces the alcohol portion of the ester as a leaving group, in the form of the alkoxide, **RO⁻**. This produces a *ketone* as an intermediate.



NUCLEOPHILIC ADDITION OF RMgX: ORGANOMETALLIC REACTIONS

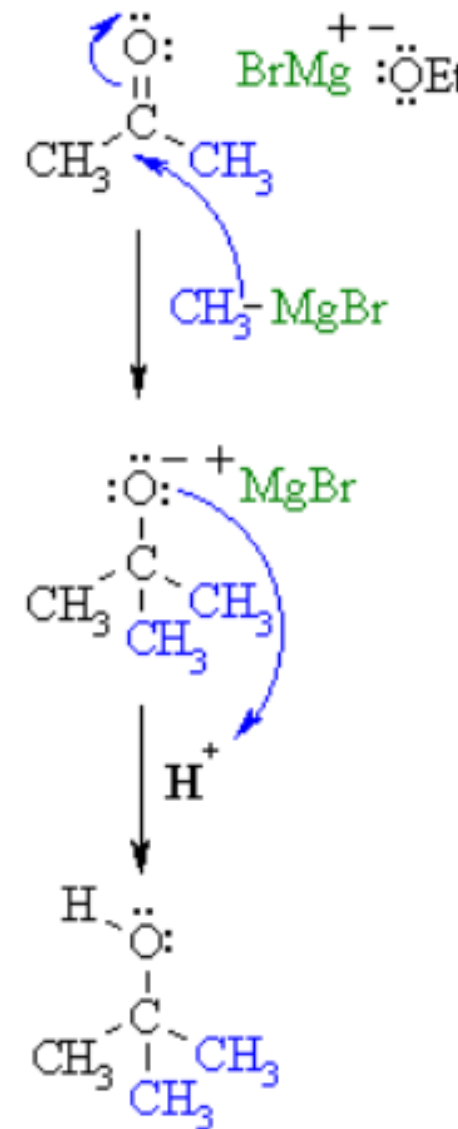
➤ Reactions of RLi and RMgX with Esters: MECHANISM

Step 3:

The nucleophilic **C** in the organometallic reagent adds to the electrophilic **C** in the polar carbonyl group of the ketone. Electrons from the **C=O** move to the electronegative **O** creating an intermediate metal alkoxide complex.

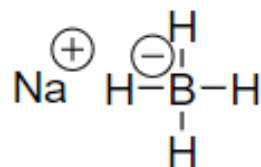
Step 4:

This is the work-up step, a simple acid/base reaction. Protonation of the alkoxide oxygen creates the alcohol product from the intermediate complex.

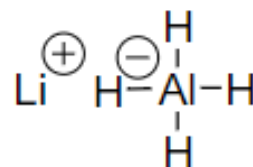


REDUCTION OF CARBONYLS TO ALCOHOLS USING METAL HYDRIDES

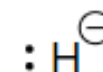
- Hydrogen (e.g. hydride ion) can be used as a nucleophile if it is bonded to a metal.
- The most common sources of the hydride anion (:H^-) are lithium aluminum hydride (LiAlH_4) and sodium borohydride (NaBH_4).



Sodium Borohydride

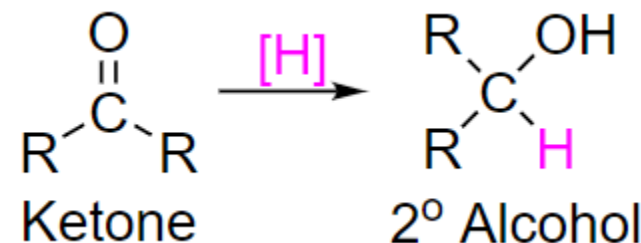
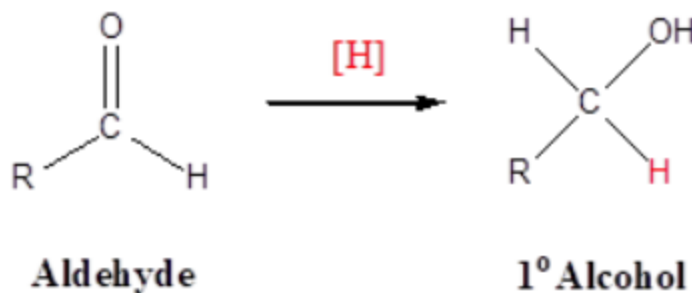


Lithium Aluminum Hydride



Hydride Nucleophile

- Nucleophilic addition of a hydride anion (:H^-) to an aldehyde produce 1° -alcohols and ketones produce 2° -alcohols.

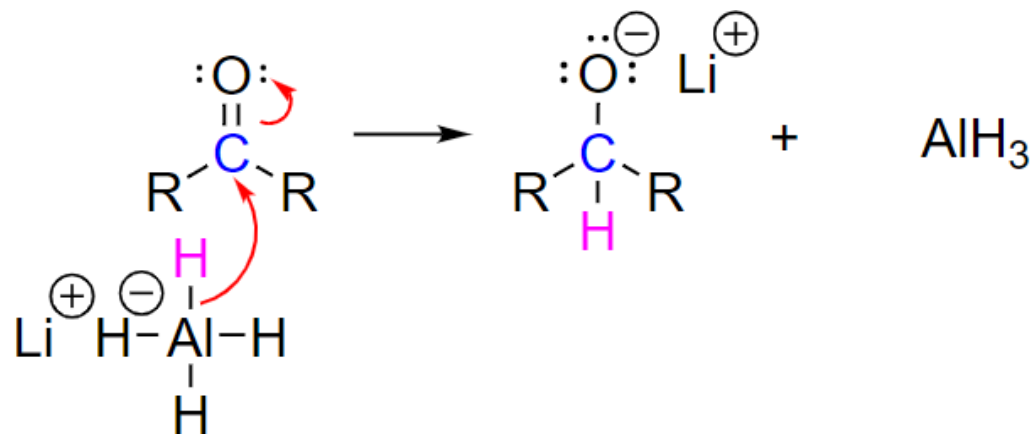


REDUCTION OF CARBONYLS TO ALCOHOLS USING METAL HYDRIDES

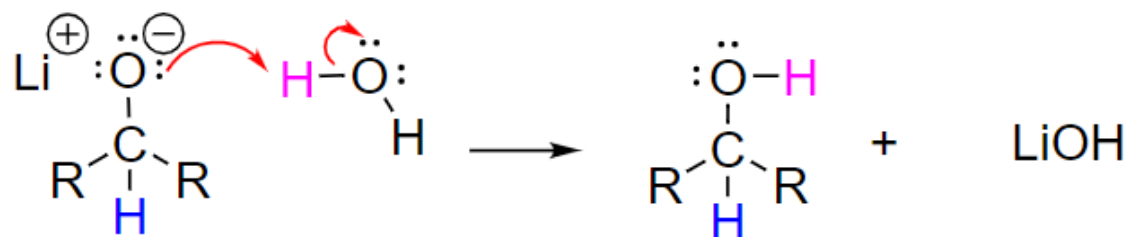
MECHANISM

- The hydride anion undergoes nucleophilic addition to the carbonyl carbon to form a C-H single bond and forming a tetrahedral alkoxide ion intermediate, which on protonation yields the corresponding alcohol.

1) Nucleophilic attack to form a tetrahedral alkoxide intermediate

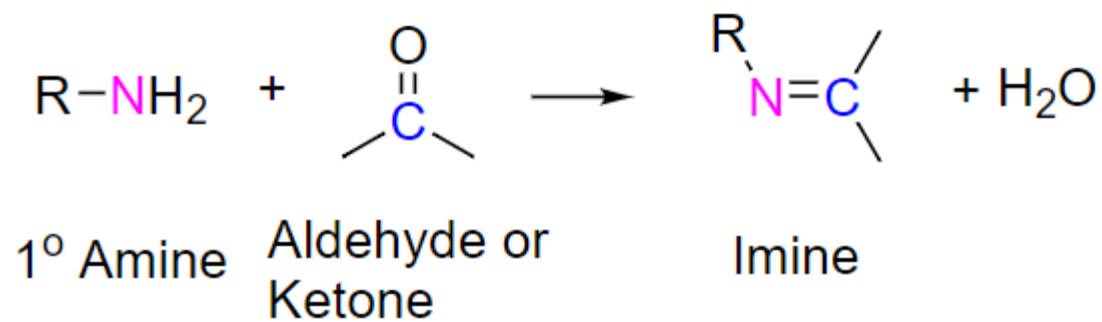


2) Protonation to form an alcohol

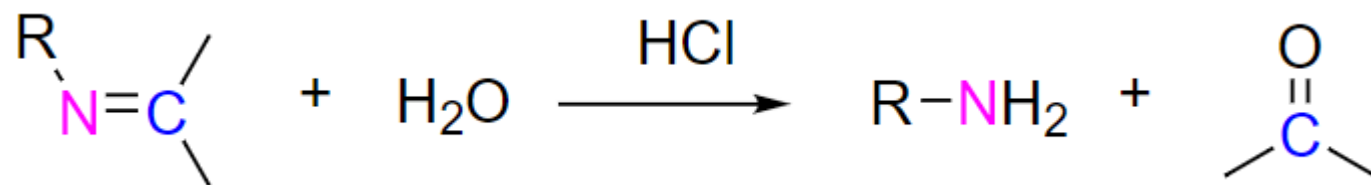


REACTION WITH PRIMARY AMINES TO FORM IMINES

- The reaction of aldehydes and ketones with ammonia or 1°-amines forms imine derivatives (Schiff bases; compounds having a C=N function).
- Water is eliminated in the reaction.



- Imines can be hydrolyzed back to the corresponding 1° amine under acidic conditions.

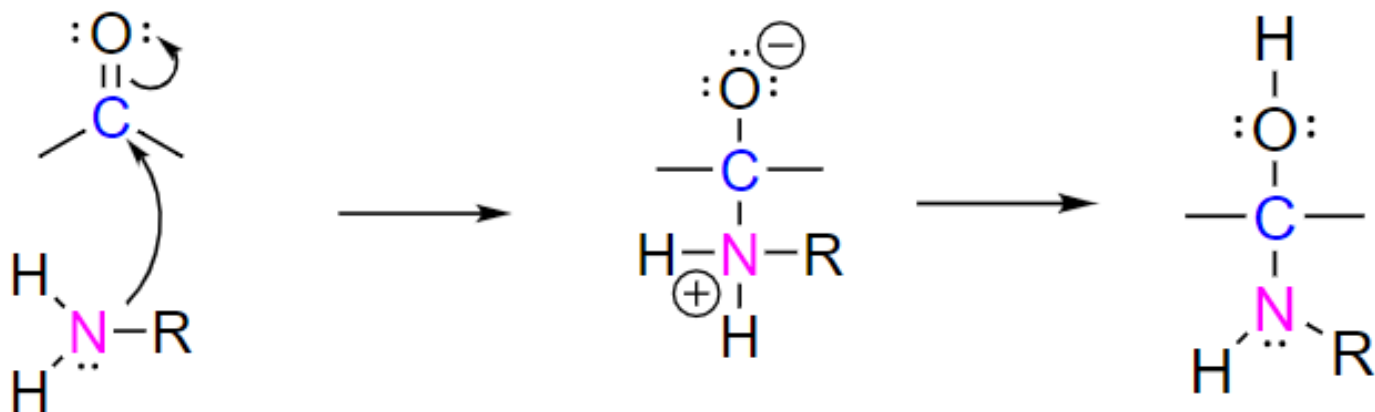


REACTION WITH PRIMARY AMINES TO FORM IMINES

MECHANISM

1) Nucleophilic addition

nucleophilic addition of a primary amine to the carbonyl group of an aldehyde or ketone

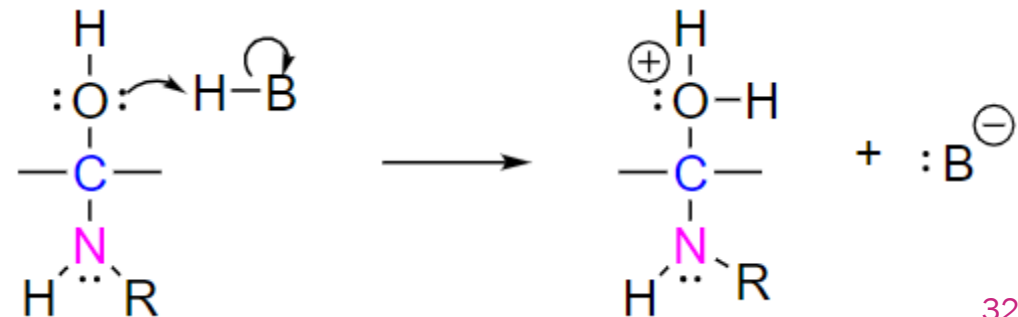


2) Proton transfer

a proton transfer forms a neutral amino alcohol called a carbinolamine

3) Protonation

Acid protonation of the carbinolamine oxygen converts it into a better leaving group

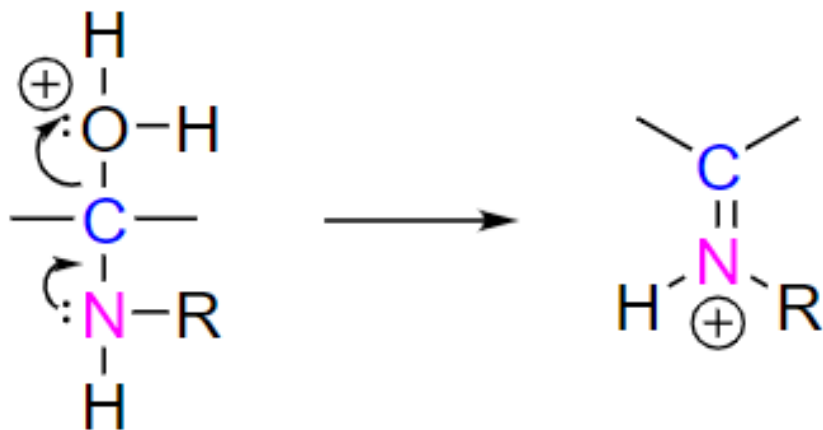


REACTION WITH PRIMARY AMINES TO FORM IMINES

MECHANISM

4) Water is eliminated to form an iminium ion.

better leaving group which is subsequently eliminated as water producing an iminium ion.

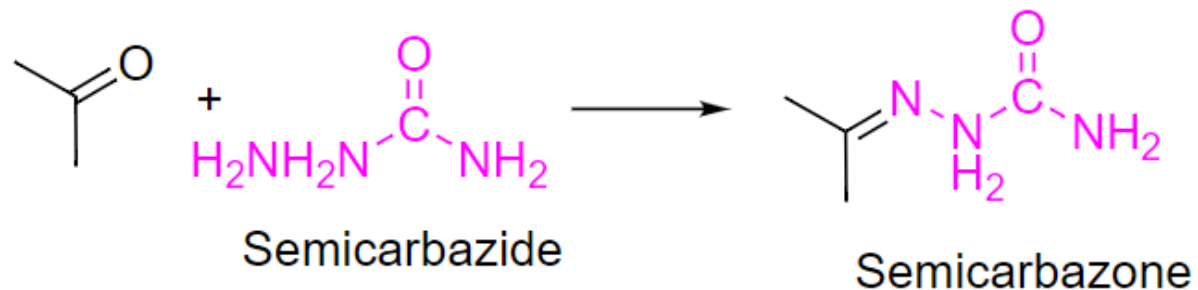
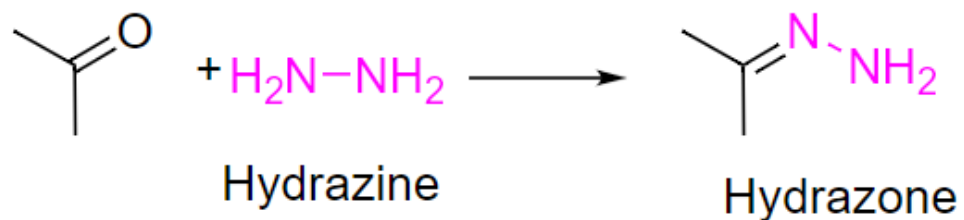
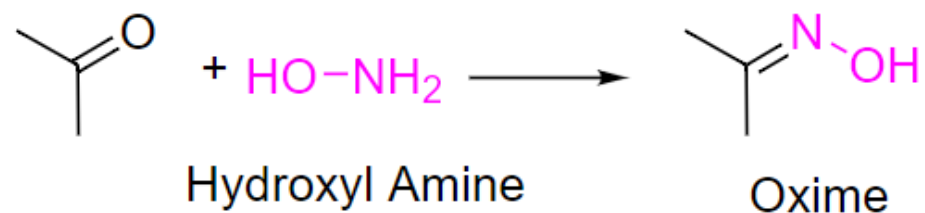
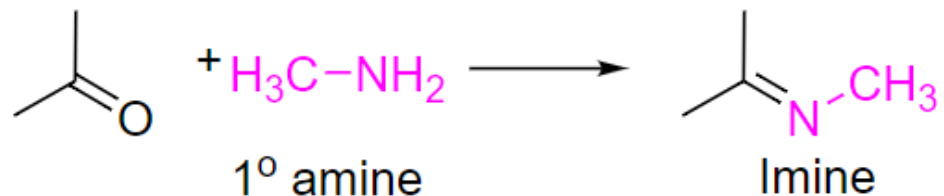


5) Deprotonation

Deprotonation of nitrogen gives the final imine product.

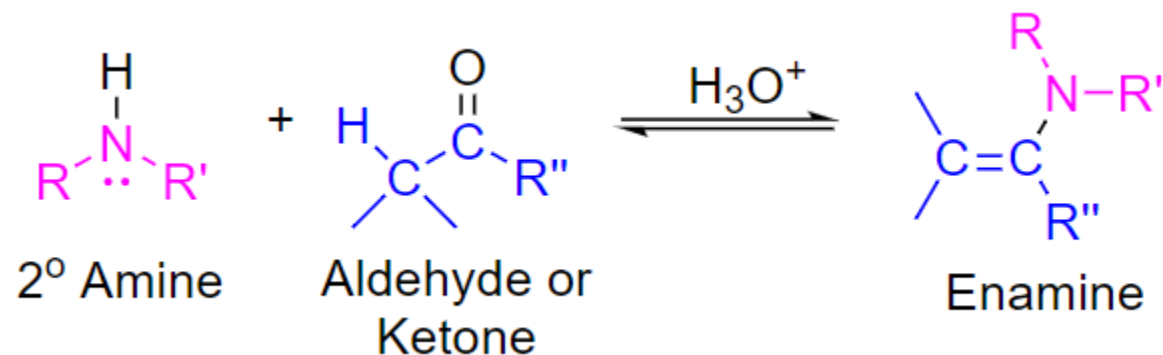


REACTIONS INVOLVING OTHER REAGENTS OF THE TYPE Y-NH₂

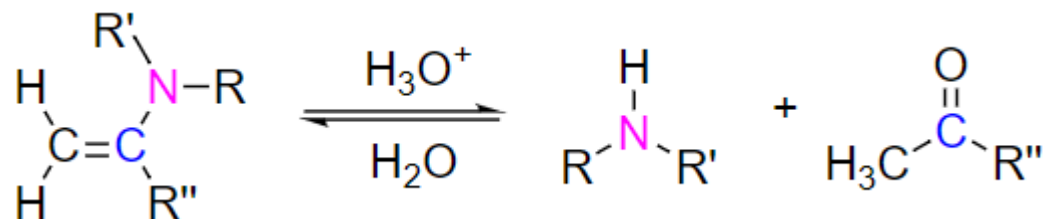


REACTION WITH SECONDARY AMINES TO FORM ENAMINES

- Aldehydes and ketones react with 2°-amines to give products known as **enamines (alkene + amine)**.
- These are acid-catalyzed reversible reactions in which water is lost.



- **Reversibility of Enamines**

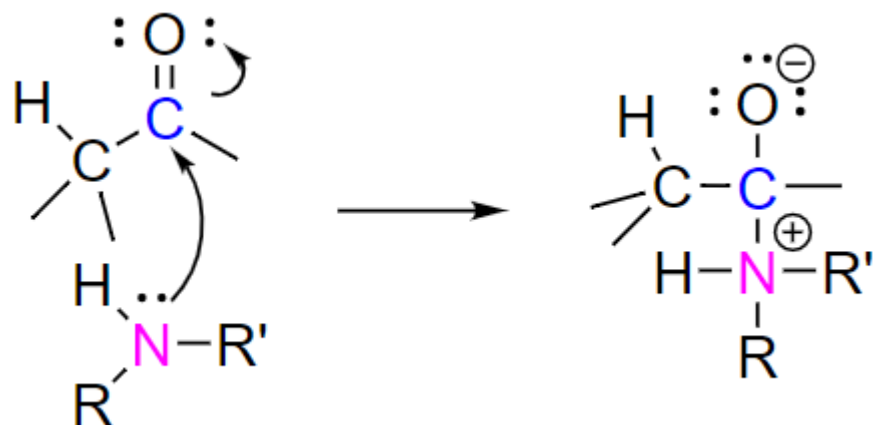


REACTION WITH SECONDARY AMINES TO FORM ENAMINES

MECHANISM

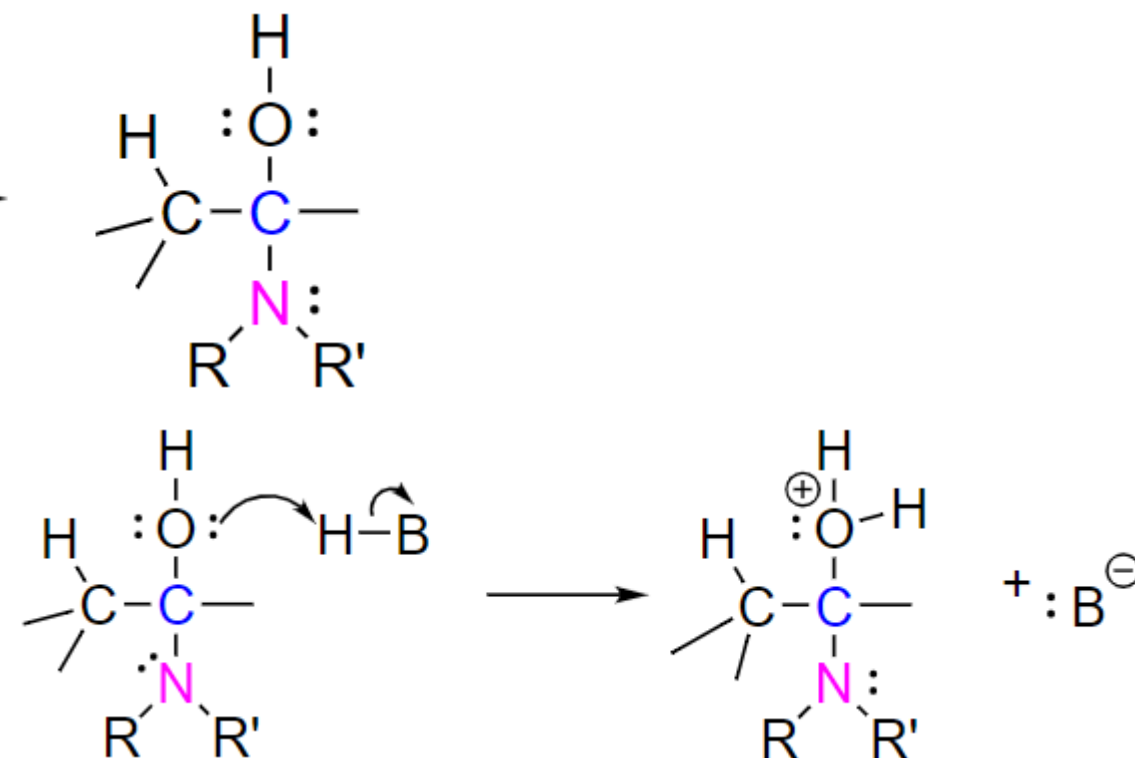
1) Nucleophilic addition

Nucleophilic addition of secondary amine to form a neutral tetrahedral intermediate.



2) A proton transfer

A proton is transferred from the ammonium ion moiety of the tetrahedral intermediate to the alkoxide ion moiety to form a neutral functional group called a carbinolamine.



3) Protonation

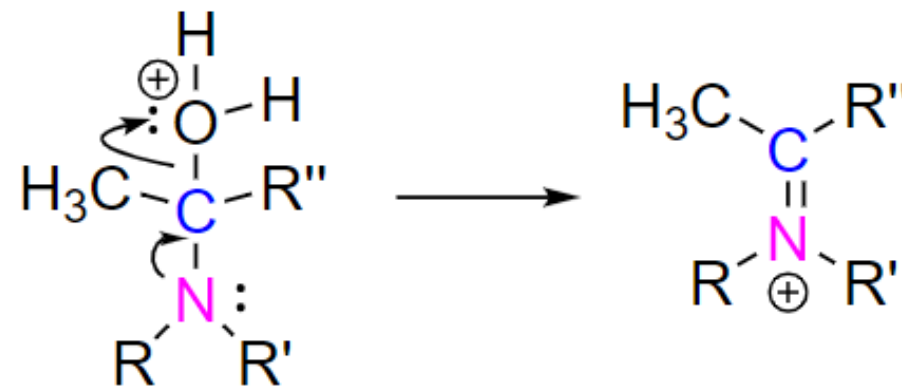
The OH group on the carbinolamine is protonated by hydronium turning it into a good leaving group.

REACTION WITH SECONDARY AMINES TO FORM ENAMINES

MECHANISM

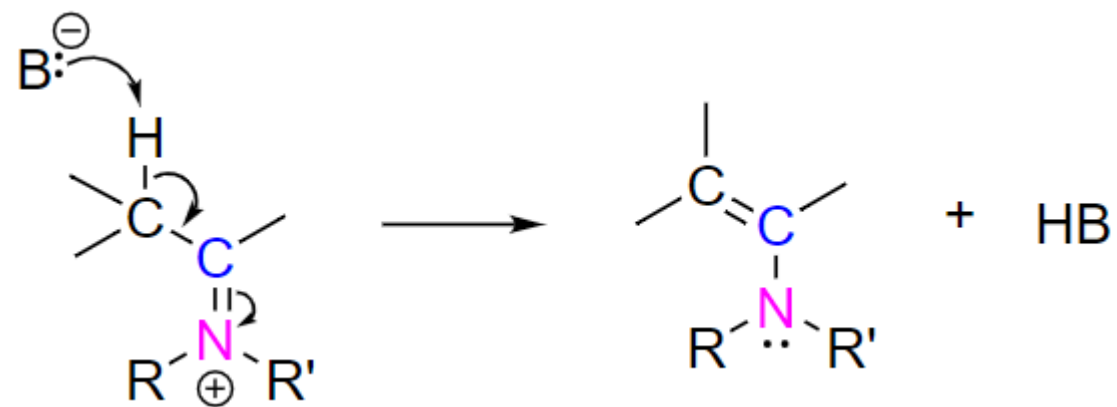
4) Water is eliminated to form an iminium ion.

The lone pair electrons on the nitrogen form the C=N double bond causing water to be eliminated. This forms an iminium ion



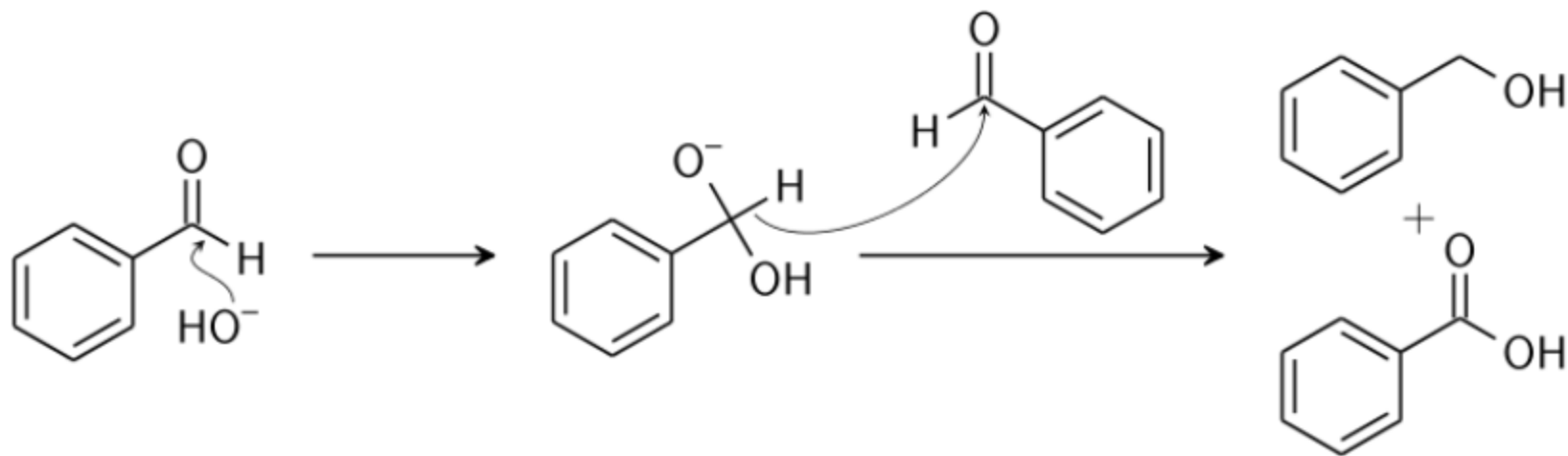
5) Deprotonation

Water (or a base) removes a hydrogen from an adjacent carbon to form an alkene bond (C=N double bond into C=C bond) creating the neutral enamine product and hydronium (or BH).



CANNIZZARO REACTION

- In the presence of concentrated alkali, aldehydes containing **no α -hydrogens** undergo *self oxidation & reduction (Redox)* reaction to yield *a mixture of an alcohol & a salt of carboxylic acid*.

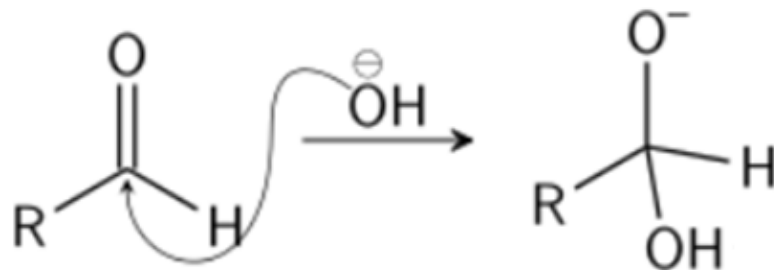


- The oxidation product is a salt of a carboxylic acid and the reduction product is an alcohol.

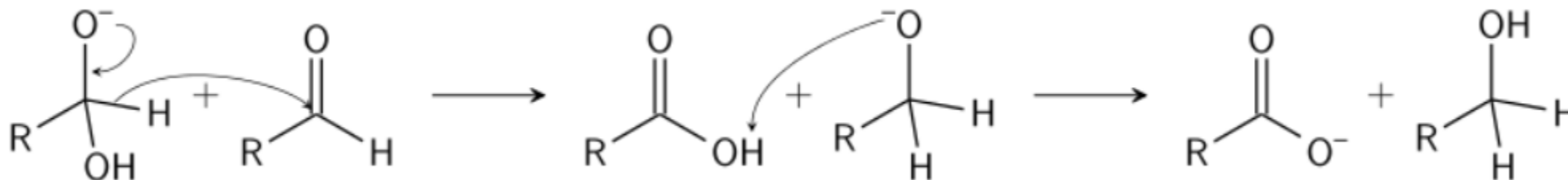
CANNIZZARO REACTION

MECHANISM

- **Nucleophilic addition** of hydroxide to carbonyl group forming a tetrahedral intermediate.



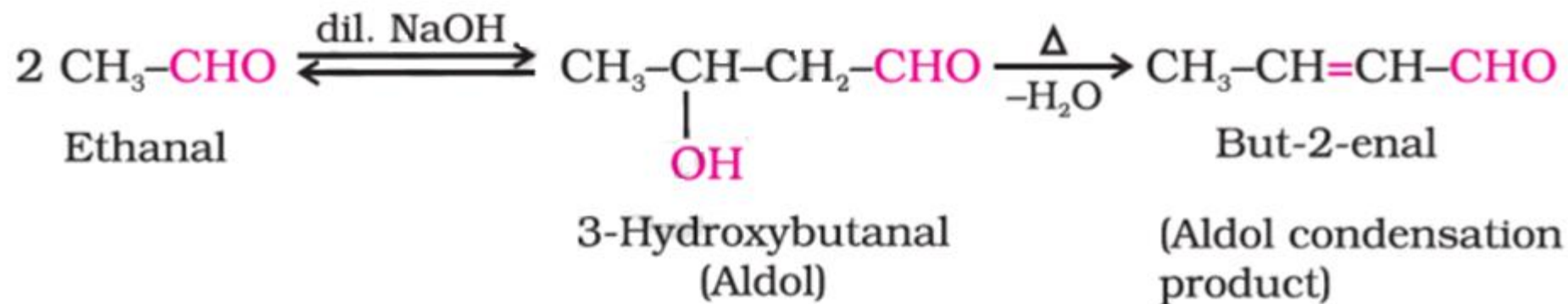
- **Hydride transfer** from the resulting tetrahedral intermediate to attack another carbonyl.



- **In the final step** of the reaction, the acid and alkoxide ions formed exchange a proton.

ALDOL CONDENSATION

- Aldehydes and ketones having **at least one α -hydrogen** undergo a reaction in the presence of dilute alkali as catalyst
- It involves the nucleophilic addition of a ketone enolate to an aldehyde to form a β -hydroxy ketone, or "**aldol**" (**ald**ehyde + **alcoh**ol),

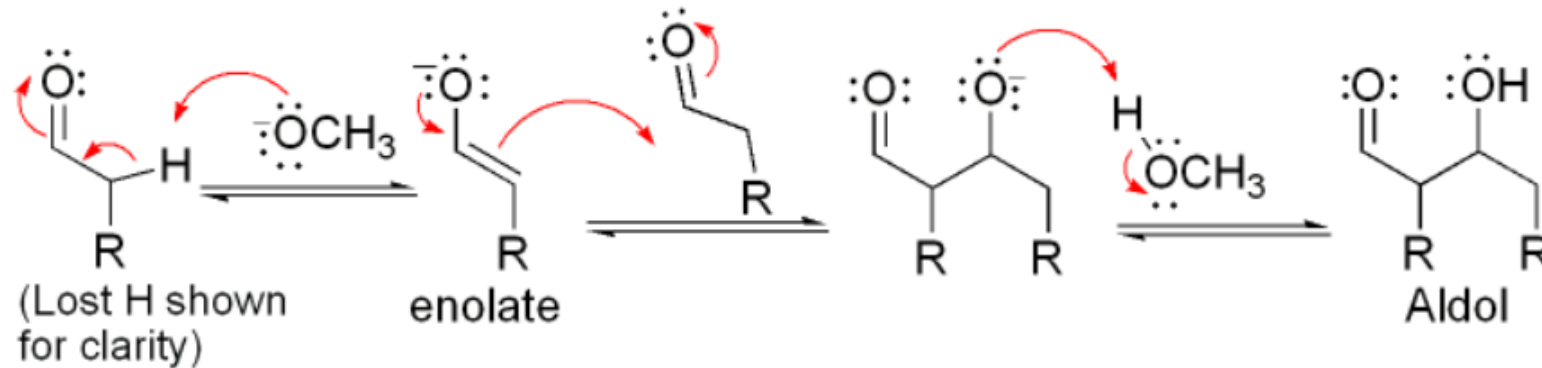


ALDOL CONDENSATION

MECHANISM

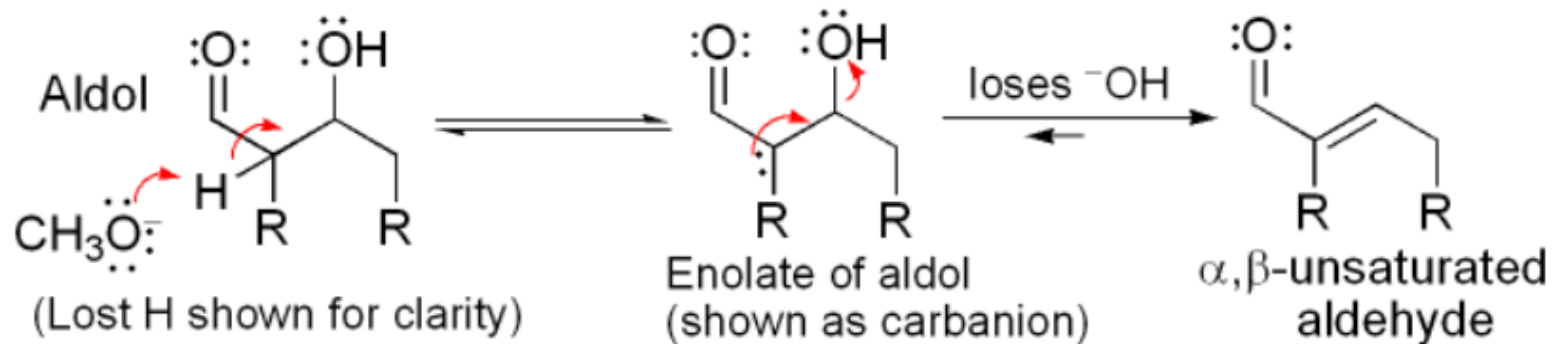
- The first part of this reaction is an **aldol reaction**,

Base catalyzed aldol reaction (shown using $^-\text{OCH}_3$ as base)



- The second part a **dehydration—an elimination reaction** (Involves removal of a water molecule or an alcohol molecule).

Base catalyzed dehydration (sometimes written as a single step)



CONJUGATE ADDITION REACTIONS

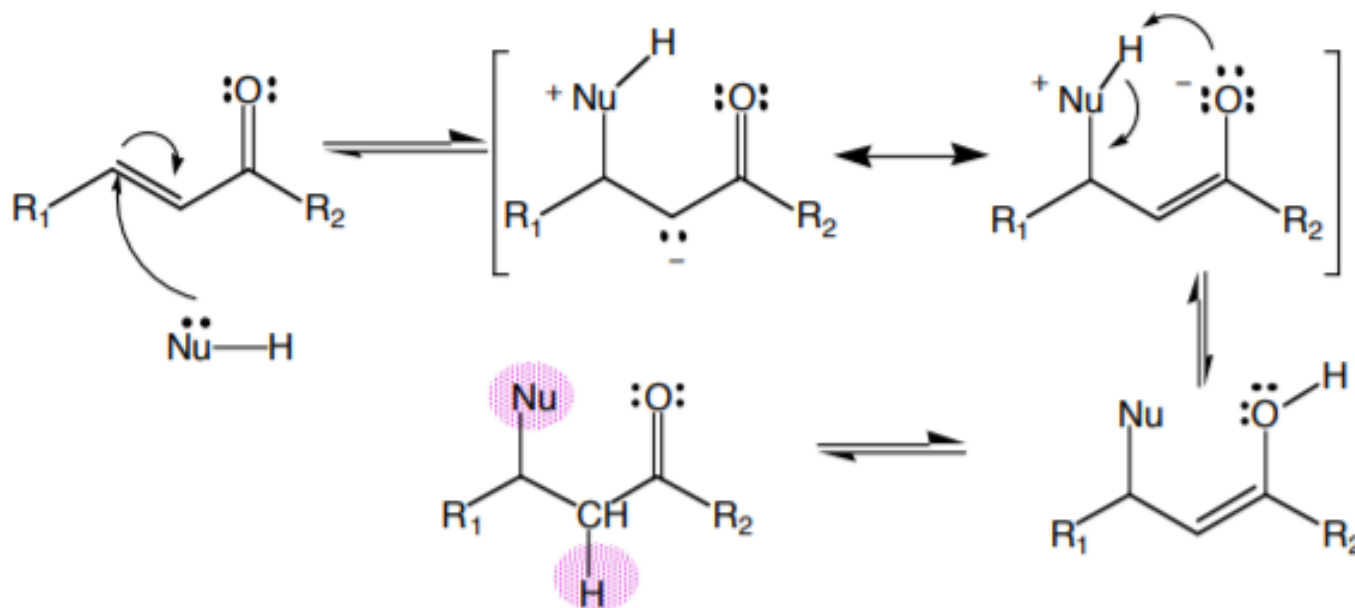
A, B-UNSATURATED CARBONYL COMPOUNDS

- α,β -Unsaturated carbonyl compounds;

These compounds undergo further reactions at the C=C bond which are not found in the reactions of simple alkene compounds.

- Nucleophilic addition to the C=C bond can occur: **why?**

- A **resonance-stabilized enolate** intermediate is formed.
- The overall observed reaction is the **net addition to the double bond**.



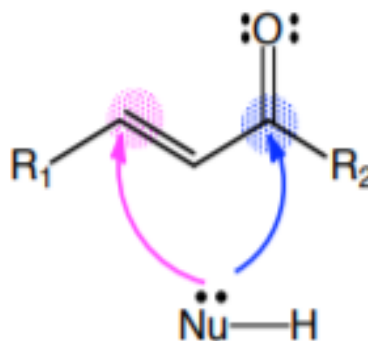
CONJUGATE ADDITION REACTIONS

A, B-UNSATURATED CARBONYL COMPOUNDS

Conjugate Addition vs. Carbonyl Group Reactions

attack at C=C carbon:

conjugate addition



attack at C=O carbon:

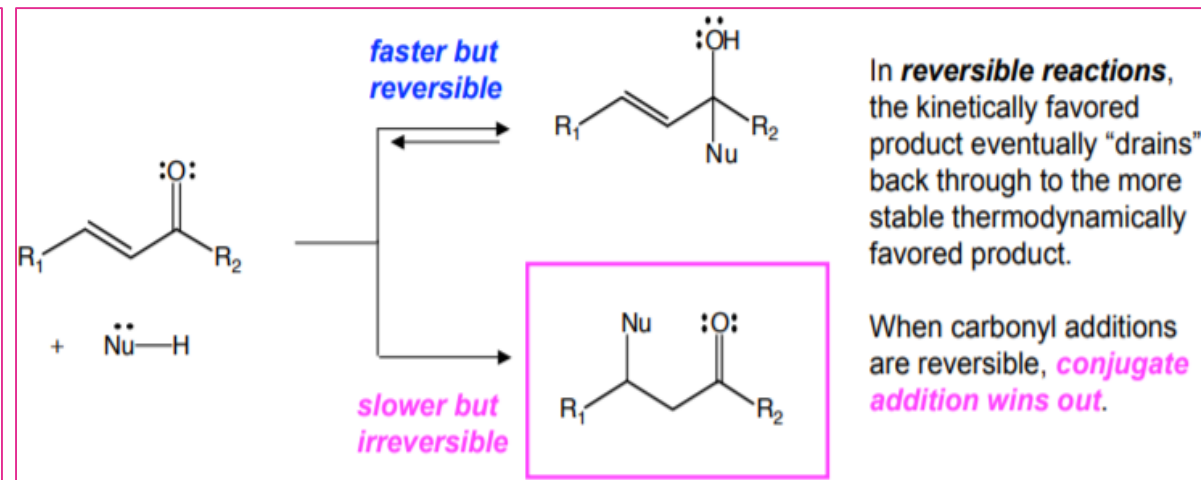
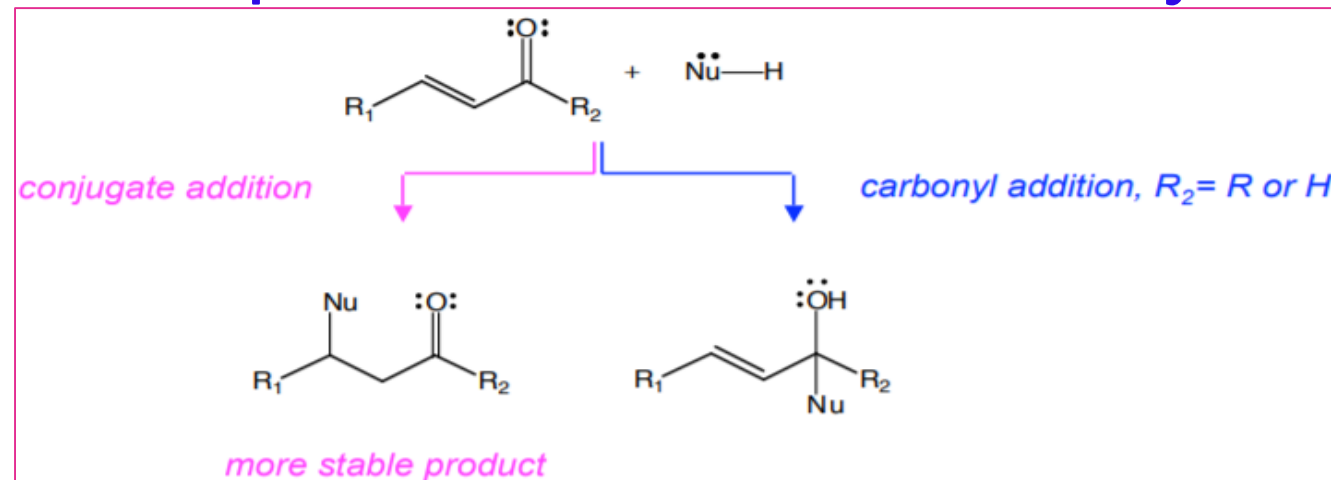
carbonyl addition, $R_2 = R$ or H
carbonyl substitution, $R_2 = OR$

- We must consider both kinetics and thermodynamics to answer this question;
 - **Kinetics:** which reaction is faster?
 - **Thermodynamics:** which reaction gives a more stable product?

CONJUGATE ADDITION REACTIONS

A, B-UNSATURATED CARBONYL COMPOUNDS

Competition in Reactions of Aldehydes and Ketones



○ **Thermodynamics:** Which reaction product is more stable?

- C=O bonds are stronger than C=C bonds.
- **Conjugate addition** retains the stronger C=O bond at the expense of the C=C bond.
- The **conjugate addition product** is more stable and is thermodynamically favored.

○ **Kinetics:** which reaction is faster?

- The addition to the carbonyl carbon proceeds faster (because the carbonyl carbon is a stronger Lewis acid than the C=C carbon)
- Therefore the carbonyl addition reaction usually proceeds faster.

- Reversible carbonyl additions occur with weak bases as nucleophiles (CN^- , amines, enolates derived from β -dicarbonyl compounds).
- When carbonyl additions are irreversible, **carbonyl addition wins out**.