Compounds containing carbonyl group.

1. Aldehydes

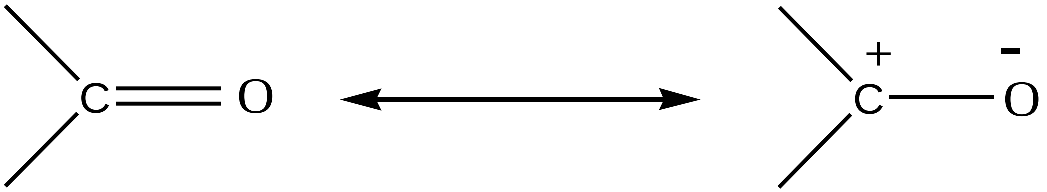
2. Ketones

3. Carboxylic acids and their derivatives.

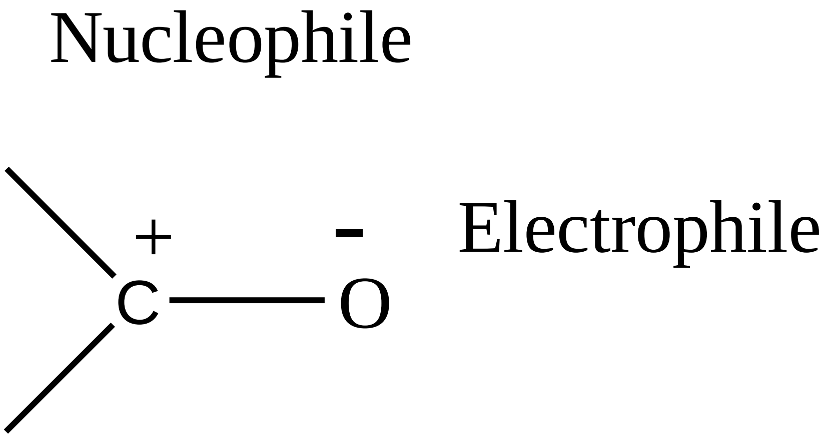
Carbonyl group

Carbonyl group is **POLAR**

(due to strong **electronegative oxygen atom**)



Characteristic feature



Electrophilic carbon reacts with- Nucleophile or base

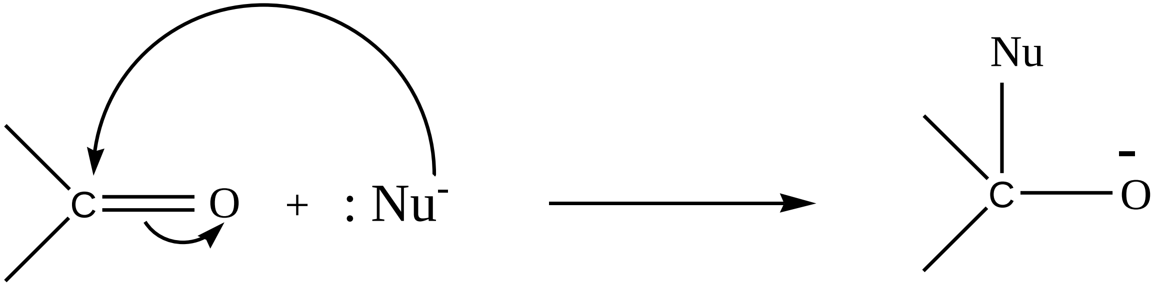
Nucleophilic Oxygen reacts with- acid or electrophile

Chemistry of carbonyl compounds (Aldehydes and Ketones)

Two ways

(i) First way: (Nucleophilic addition)

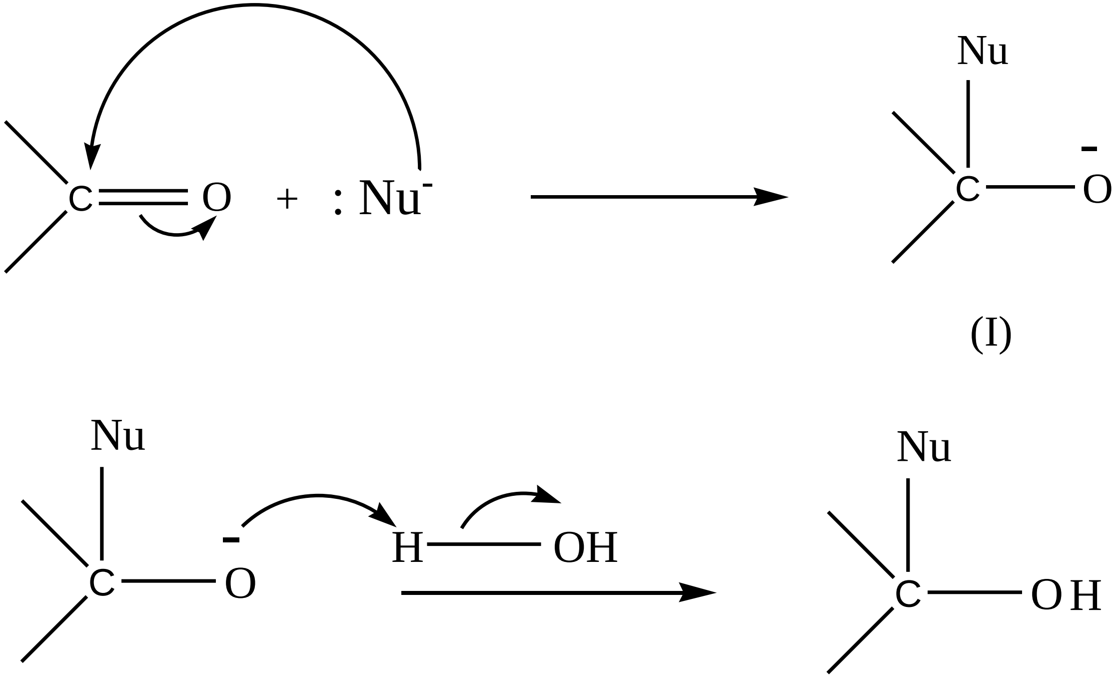
(a) **Direct attack of Nucleophile** at electron deficient carbon atom of carbonyl group



(I)

(b) Thus formed Species (I) Picks up proton to give addition product i.e. Nucleophilic addition product.

Nucleophilic addition reaction- Characteristic reaction of carbonyl compounds



(I)

(I)

Nucleophilic Addition Product

Reactivity of Carbonyl Compound

Reactivity of carbonyl compounds toward these reactions depends upon three factors:

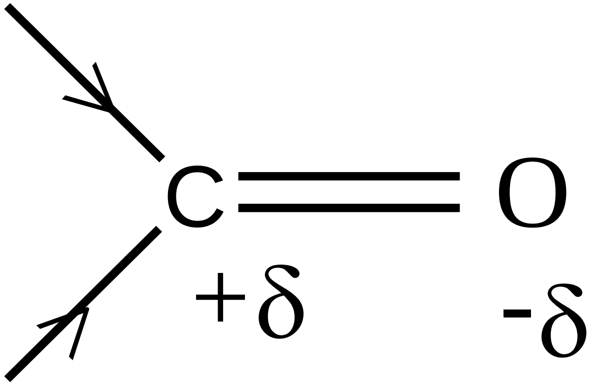
1. Electronic factor
2. Steric hindrance factor
3. Resonance factor

1. Electronic factor (+I and –I effect)

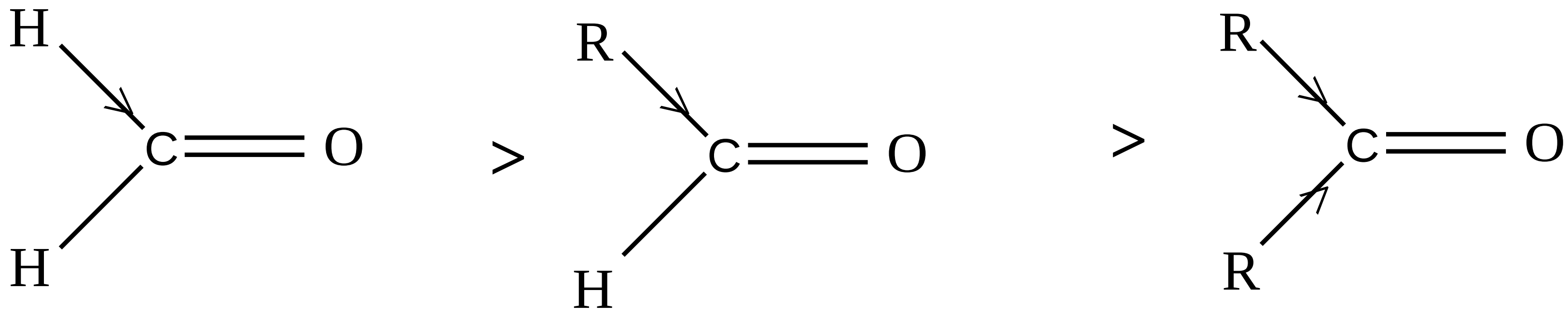
\# Electron donating group attached to carbonyl group has +I effect on carbonyl carbon.

\# It results in decrease in electrophilicity of carbonyl carbon.

\# Reactivity (towards nucleophile) decreases.



(A) Example: Effect of electron releasing group **(+I effect)** on order of reactivity of carbonyl compounds

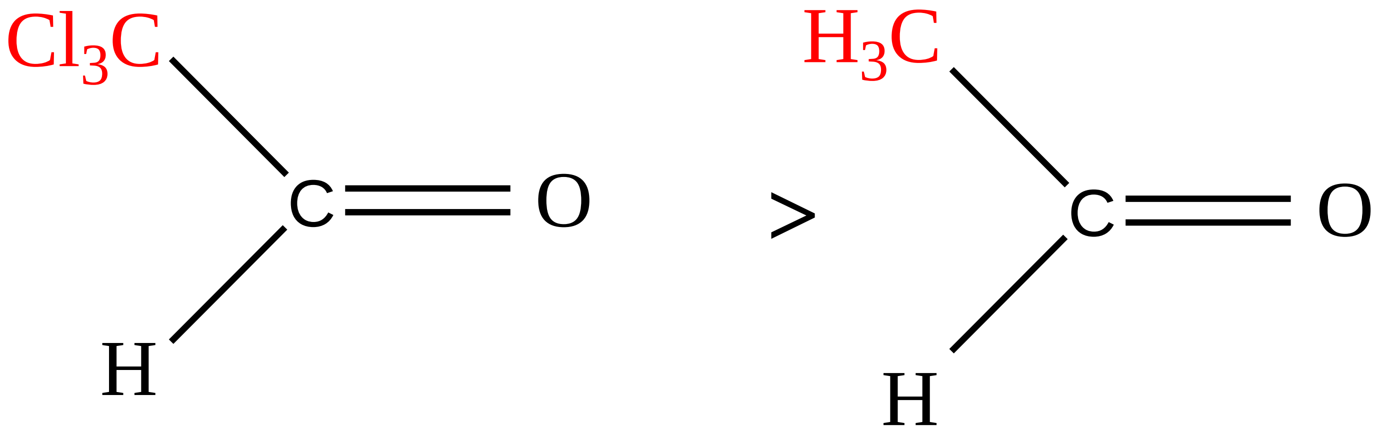


(B) Effect of Electron withdrawing group:

Electron withdrawing group increase the electrophilicity of Carbonyl carbon due to –I effect.

Result: Reactivity of carobonyl compound (toward nucleophile) increases.

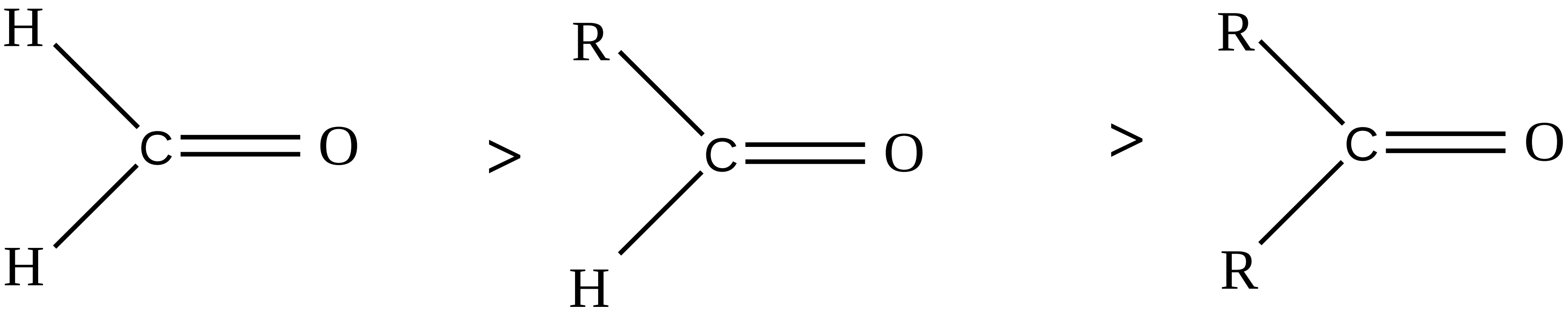
Example of -I effect



2. Steric hindrance

Same effect occurs as with **electron donating groups**

(both factors work simultaneously)



3. Resonance factor

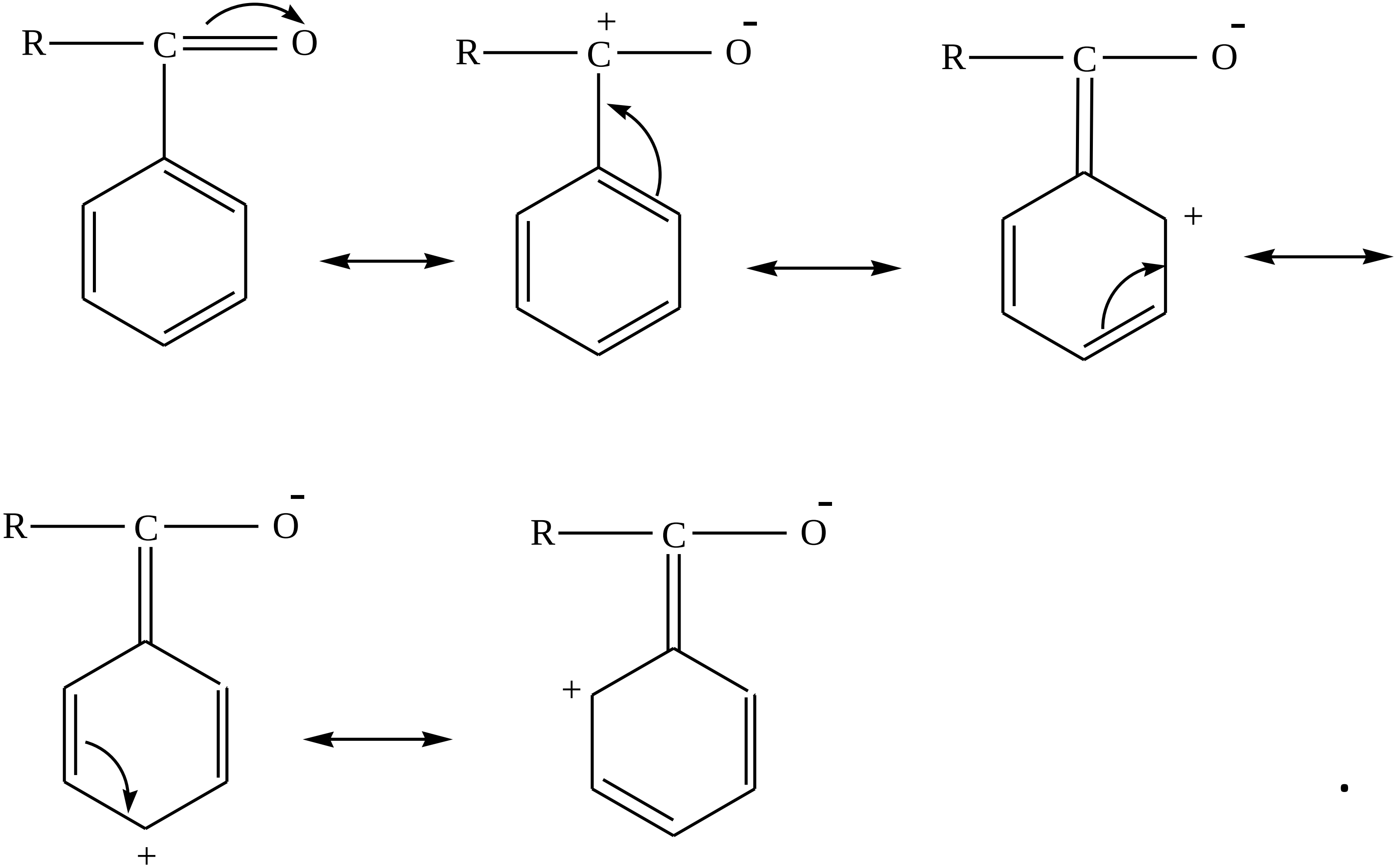
Aromatic aldehyde and ketones are less reactive

than their aliphatic analogues.

Reason: electron donating resonance effect
(+R effect)

+R effect in aromatic aldehyde/ketone

(**elecrophilicity** of carbonyl carbon **decreases**)
So **reactivity** towards nucleophile **decreases**.



Types of Nucleophilic addition reaction of aldehydes and Ketones

Two types:

- 1. **Nucleophilic addition reactions**

  (Without elimination)

- 2. **Nucleophilic addition with elimination**.

Examples of Simple Nucleophilic addition reactions

(Without elimination)

1. Addition of **sodium bisulphite**

2. Addition of **HCN**

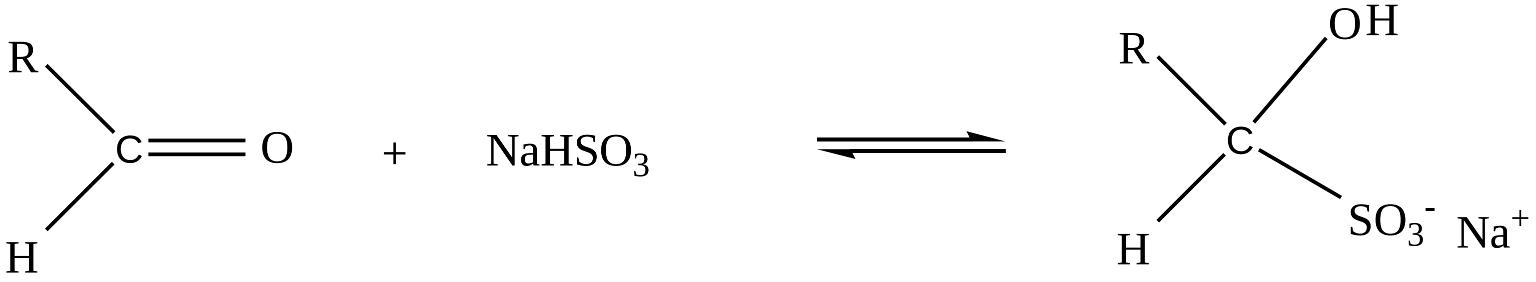
3. Addition of **Grignard reagent**

4. Addition of **Alcohol**

1. Addition of sodium bisulphite

Aldehydes or Ketones react with Sodium bisulphite to give **crystalline adduct**

These adducts are called **as** **sodium bisulphite addition compounds**



Sodium bisulphite addition compound

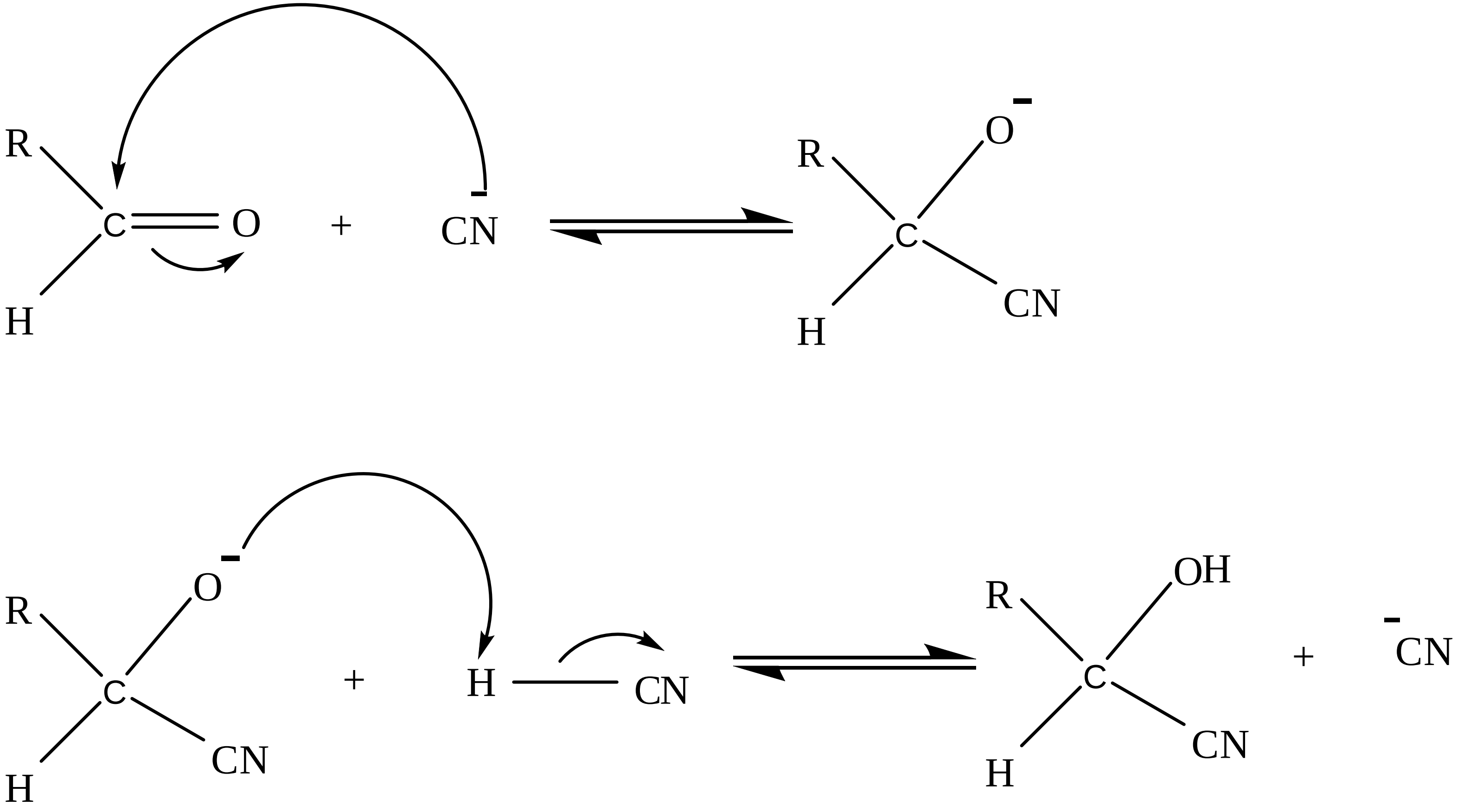
Conversion of crystalline **bisulphite addition compounds**
to
carbonyl compounds

Original Aldehydes or Ketones can be regenerated from **crystalline bisulphite addition compounds** on heating with dil. acid or aq. Alkali.

2. Addition of HCN

Aldehyde or Ketone $\xrightarrow{\text{HCN}}$ **Cyanohydrin**

Mechanism:



Addition of Grignard reagent

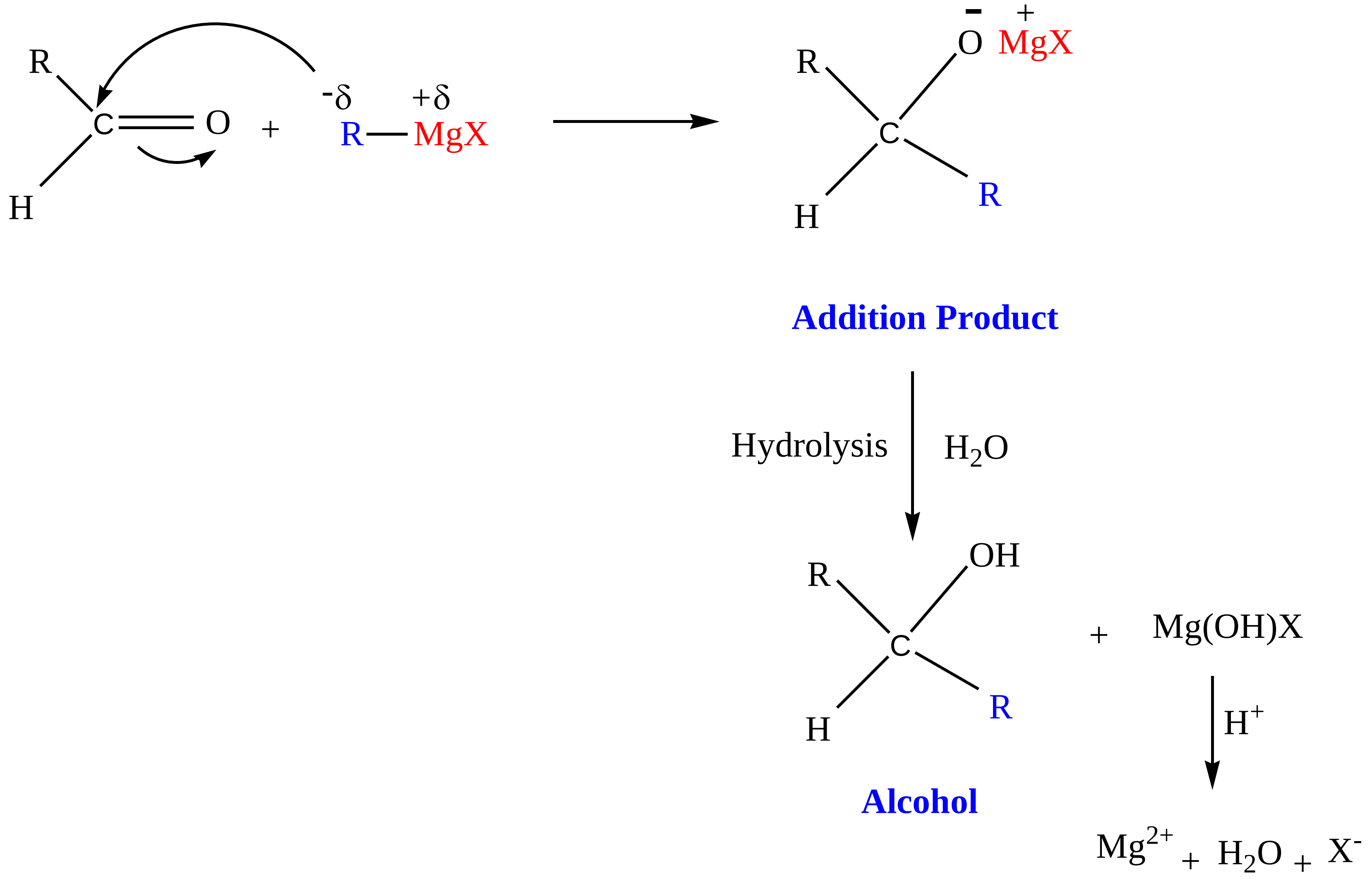
Grignard reagent (RMgX) and **Organolithium (RLi)** compounds are Strong Nucleophile

Both add easily to Aldehyde/Ketone.

Addition product is hydrolyzed with **dil. acid** to give **alcohol** (final product).

This reaction is an important tool for the formation of carbon–carbon bonds.

Mechanism



Addition Product

Hydrolysis

H_2O

Alcohol

+ Mg(OH)X

H^+

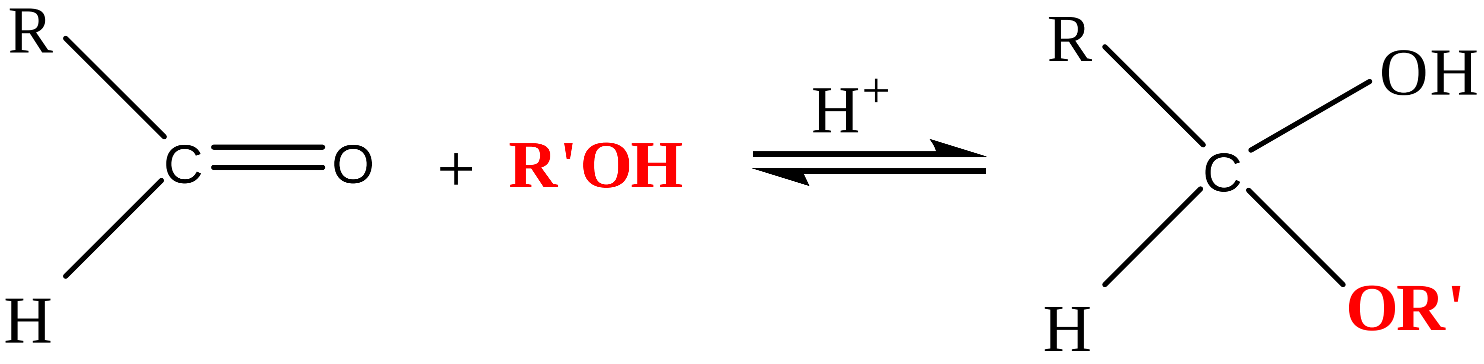
$Mg^{2+} + H_2O + X^-$

Addition of alcohol to carbonyl compound

Alcohol adds **to aldehyde** to give **Hemiacetal**

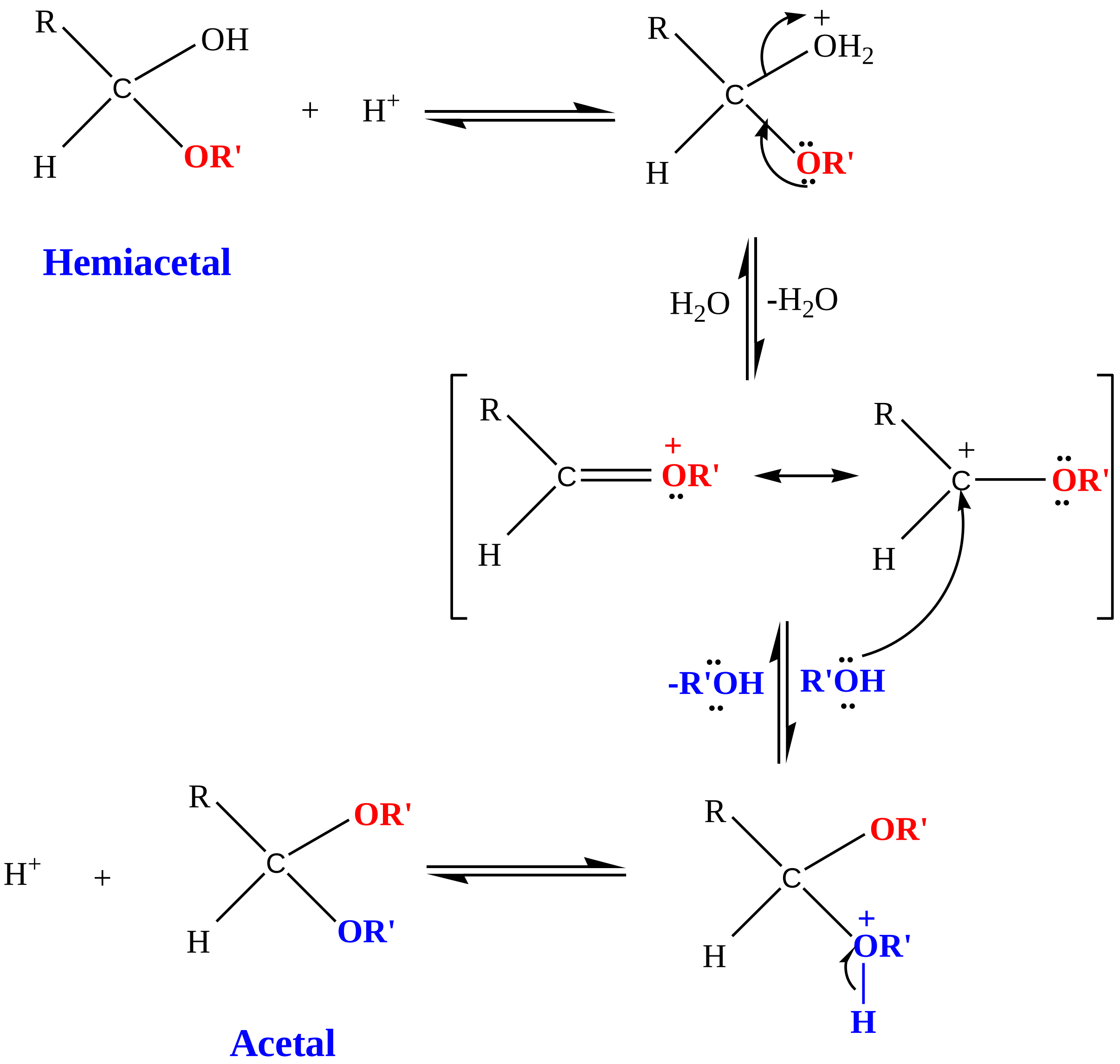
Hemiacetal then get converted into **Acetal**.

Acid catalyzed - **Hemiacetal** formation



Hemiacetal

2nd part of reaction: Acid catalyzed conversion of Hemiacetal to Acetal



Acidic Hydrolysis of Acetal

- **Acidic hydrolysis** of **acetal** in presence of

  excess of water will give

  the **carbonyl compound** back

Addition of water to carbonyl group

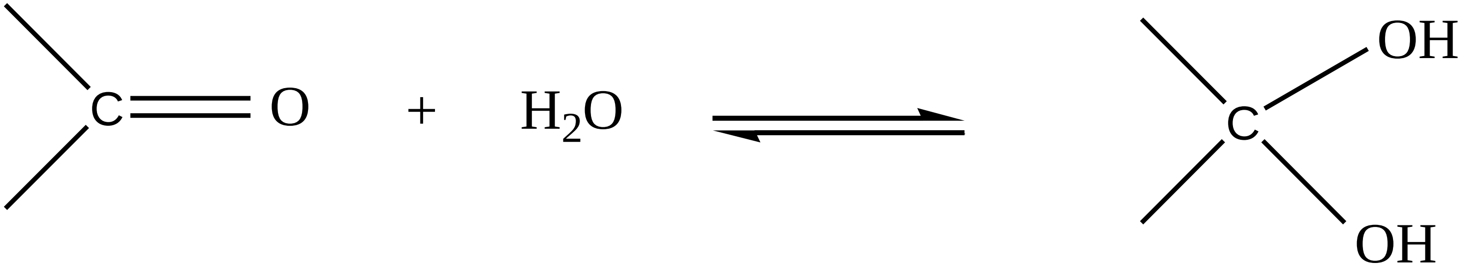
Carbonyl group (of aldehyde and ketone)

+

Water

↓

gem-diol



gem-diol

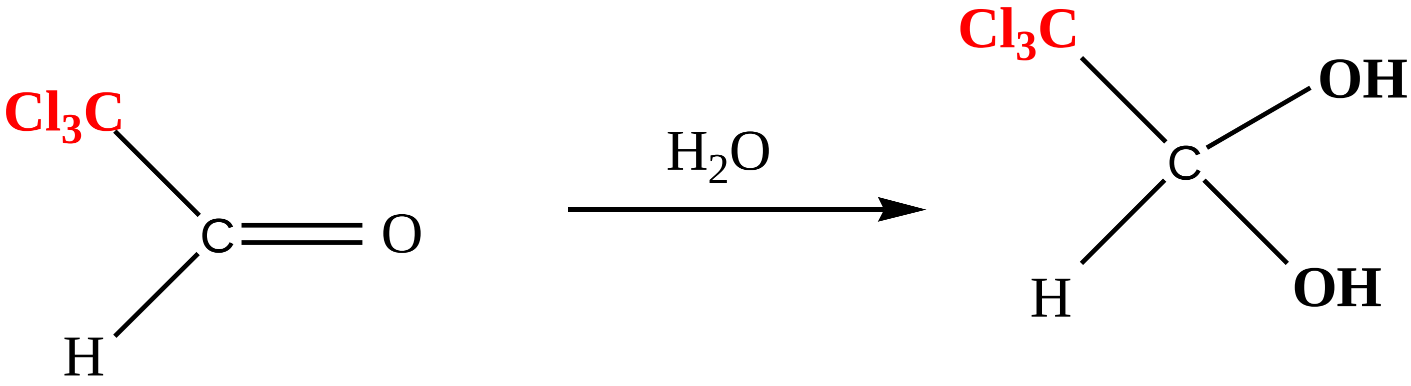
(too unstable to be isolated)

Can gem-diols be isolated? Give example.

If gem-diols **are stable**,

then they **can be isolated.**

Example:



Chloral hydrate

Reason of its stability:

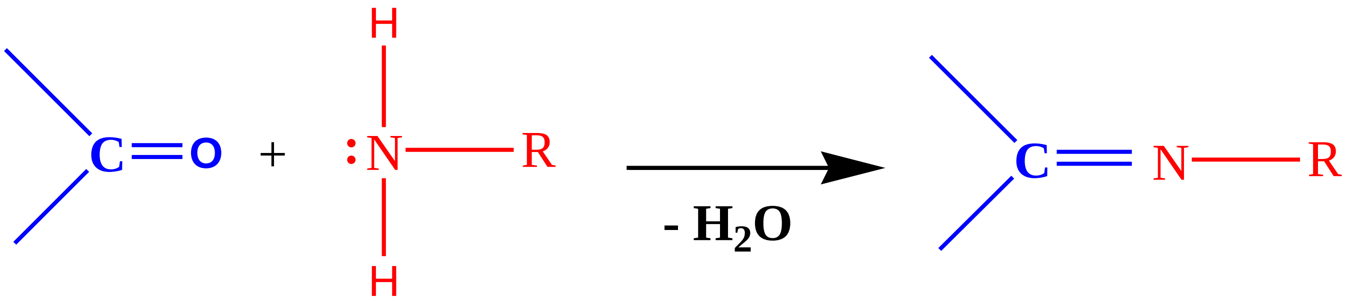
combined electron withdrawing effect of the substituents

This **effect prevent departure of hydroxide ion from hydrate** to regenerate carbonyl compound.

(Nucleophilic Addition-elimination reactions of aldehydes and Ketones)

Addition of derivative of ammonia (H_2N-R) to aldehyde and ketone

(Addition elimination reactions of ketone and aldehyde)



(**Reaction Type:** **Addition-elimination reactions of aldehyde/ketone)**

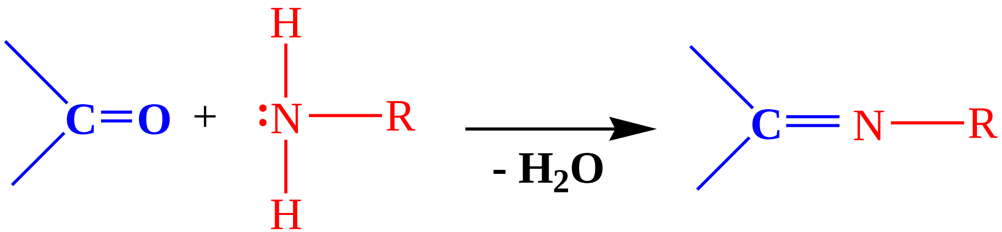
(H_2N-R = derivative of ammonia)

where R = -OH, $-NH_2$, -NHPh, $-NHCONH_2$

Product

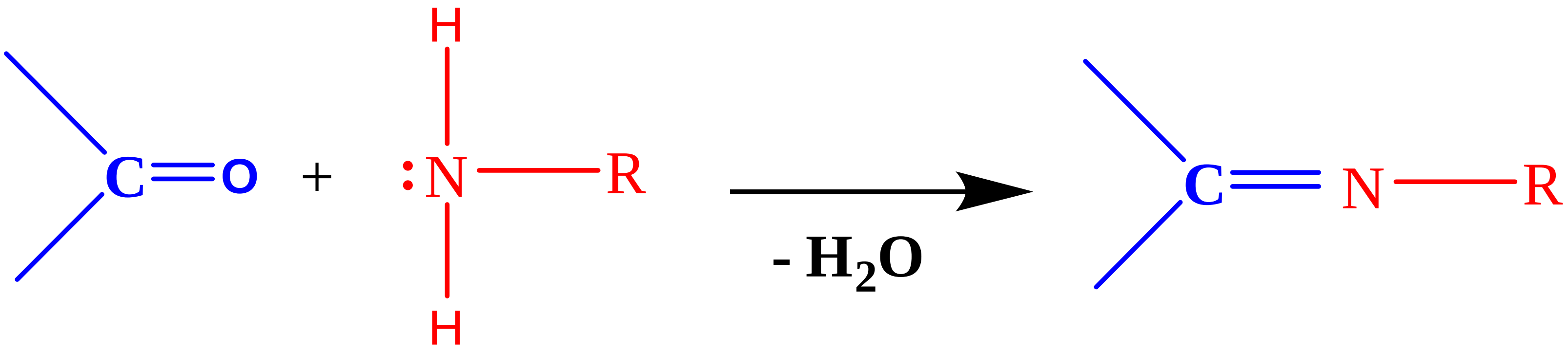
- Aldehydes and Ketones react with a range of **primary amine derivatives** to give **substituted imines**.

- However, the product **with ammonia are too unstable to be isolated** but this unstable product **can be reduced *in situ* to amines.**



R	Reagent	Product (Reagent + Carbonyl Compound)
-OH	$H_2N\text{-}OH$ (Hyroxylamine)	**Oxime**
$-NH_2$	$H_2N\text{-}NH_2$ (Hydrazine)	**Hydrazone**
-NHPh	$PhNHNH_2$ (Phenylhydrazine)	**Phenylhydrazone**
$-NHCONH_2$	$NH_2NHCONH_2$ (Semicarbazide)	**Semicarbazone**

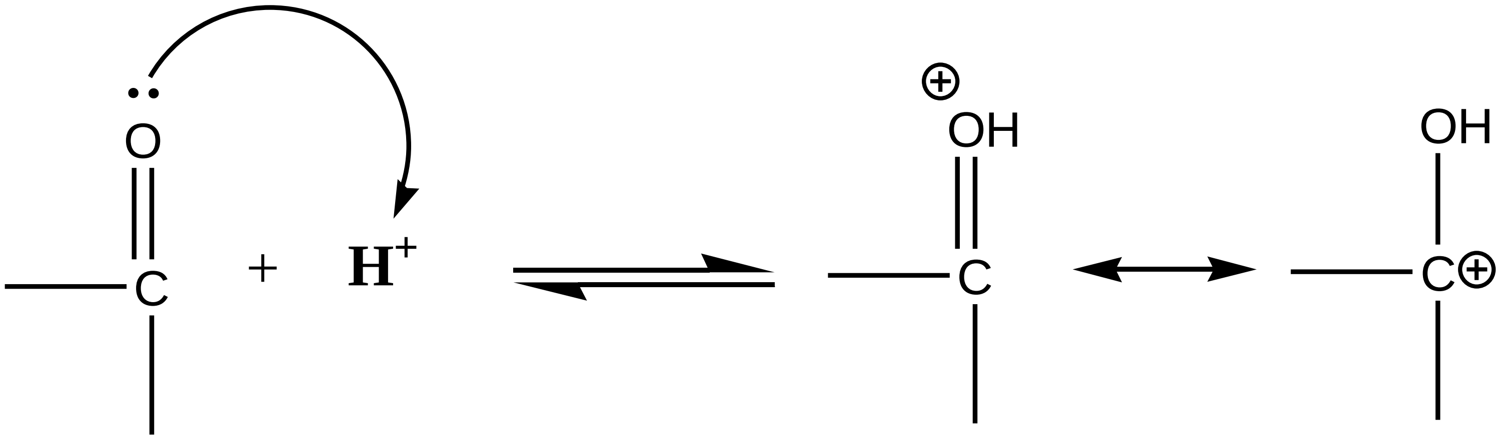
Reaction



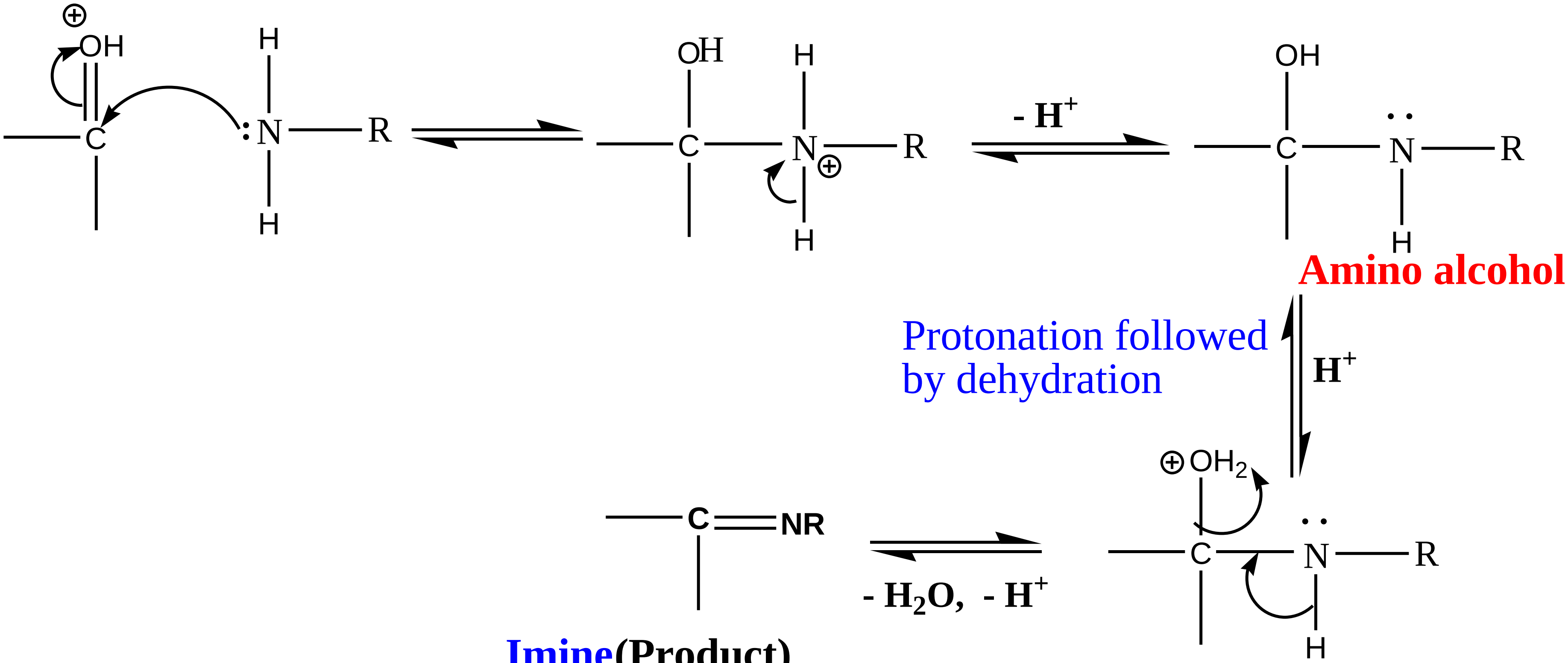
An Imine or a Schiff's base

Mechanism of imine formation

- 1st step- Protonation of carbonyl oxygen



2nd step- attack of nucleophile (1° amine) on carbonyl carbon



Amino alcohol

Protonation followed by dehydration

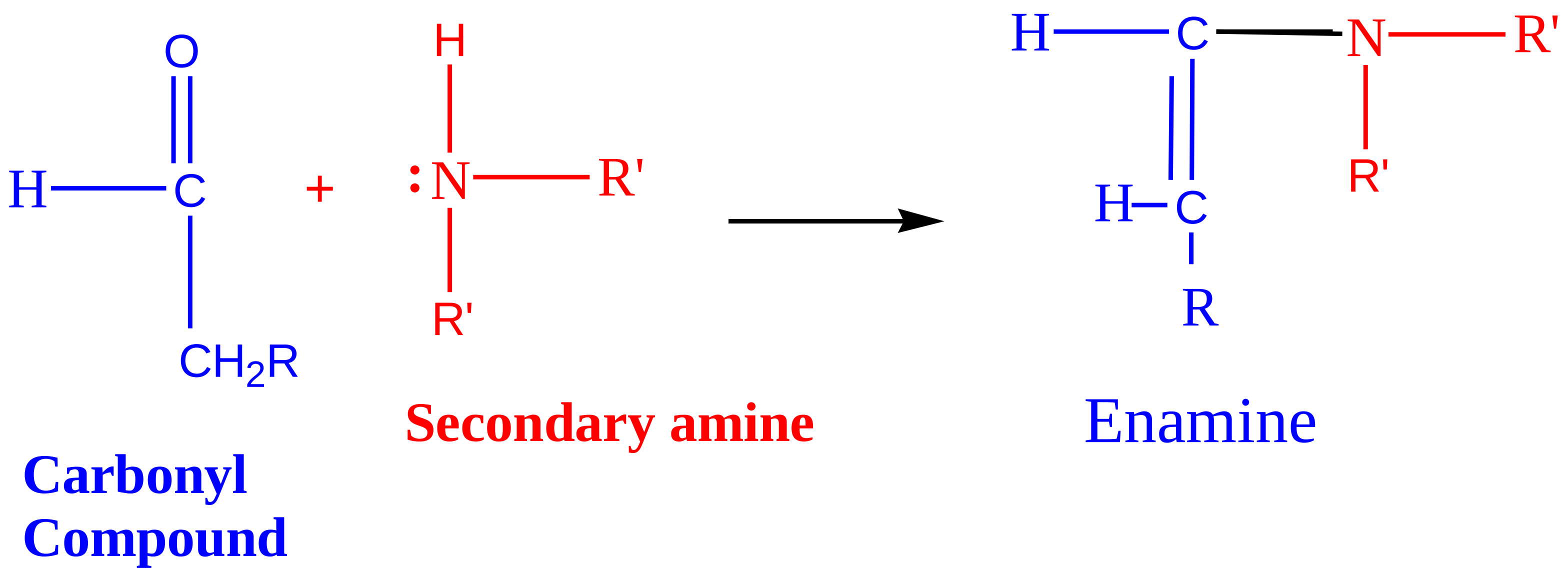
Imine(Product)

Primary amine **vs** Secondary amine

Primary amine + Aldehyde/Ketone = **Substituted imine**

Secondary amine + Aldehyde/Ketone = **enamine**

Secondary amine + Aldehyde/Ketone = enamine



Carbonyl Compound

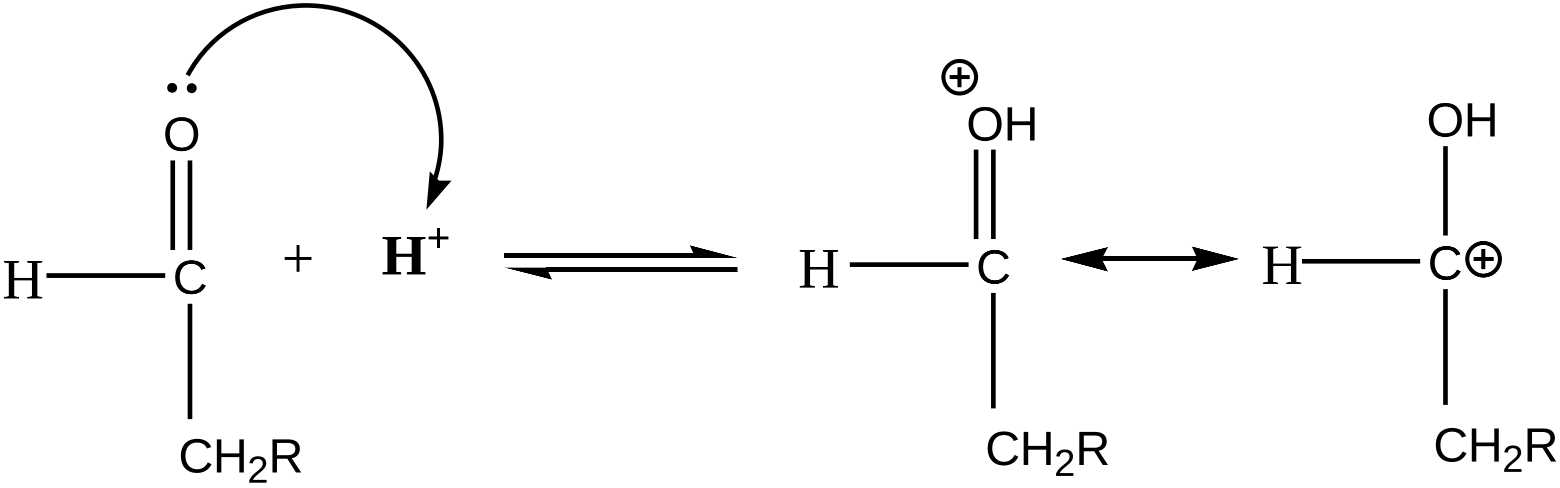
Secondary amine

Enamine

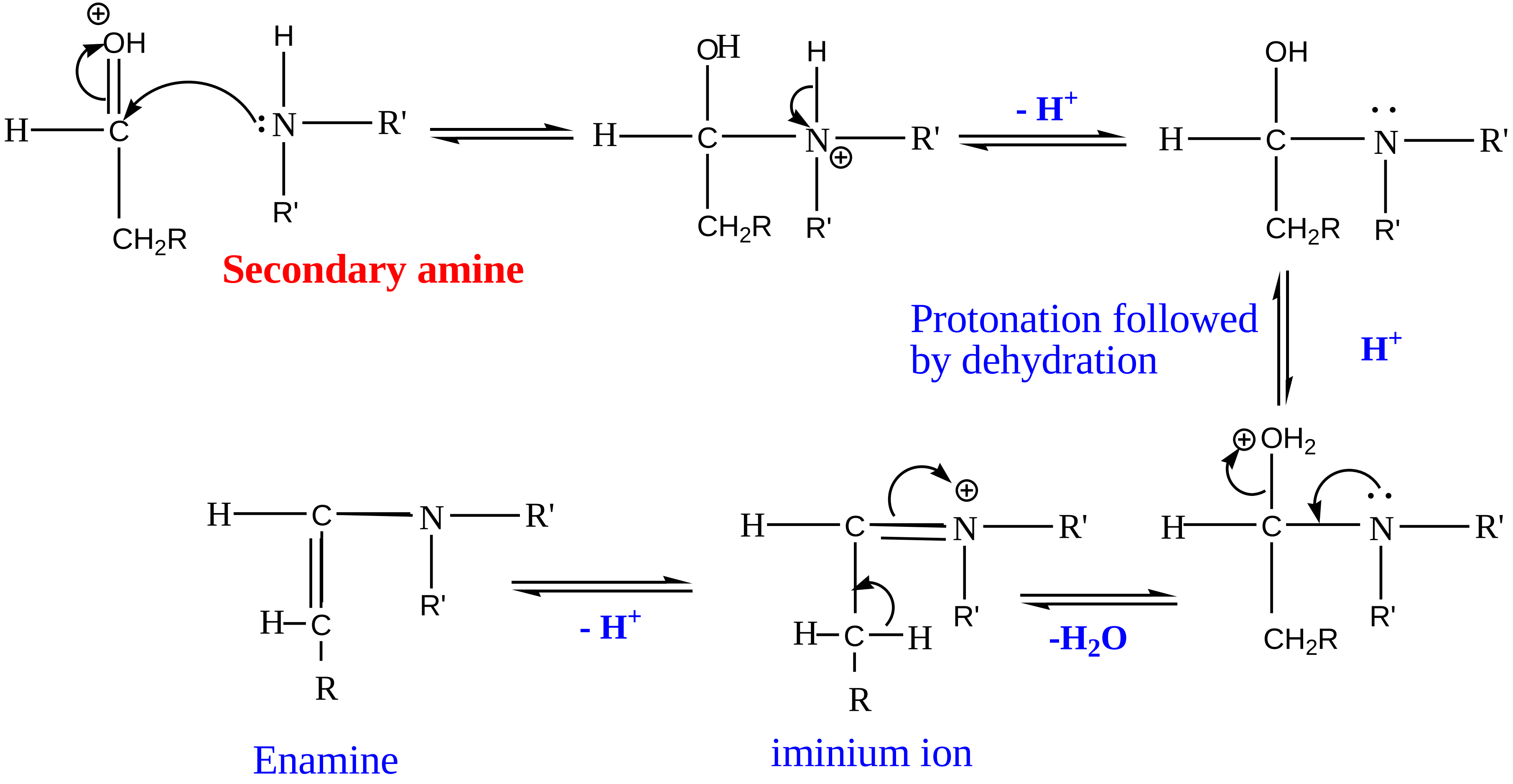
The products are called enamines because they are "alkene amines"

Mechanism for enamine formation

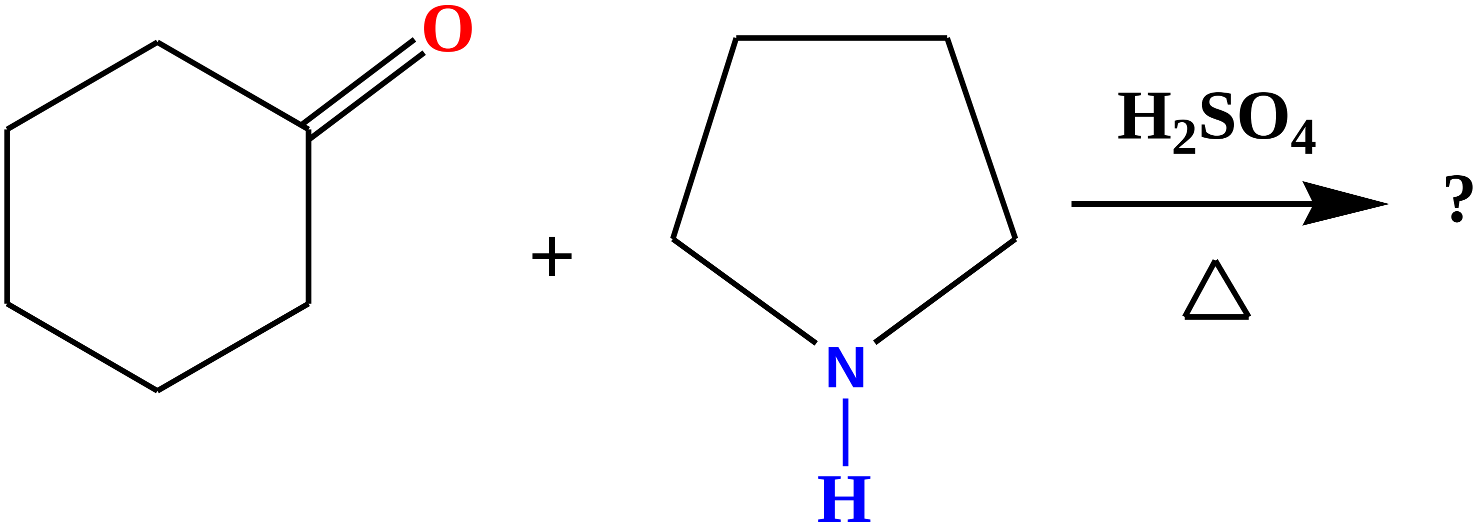
- 1st step- Protonation of carbonyl oxygen



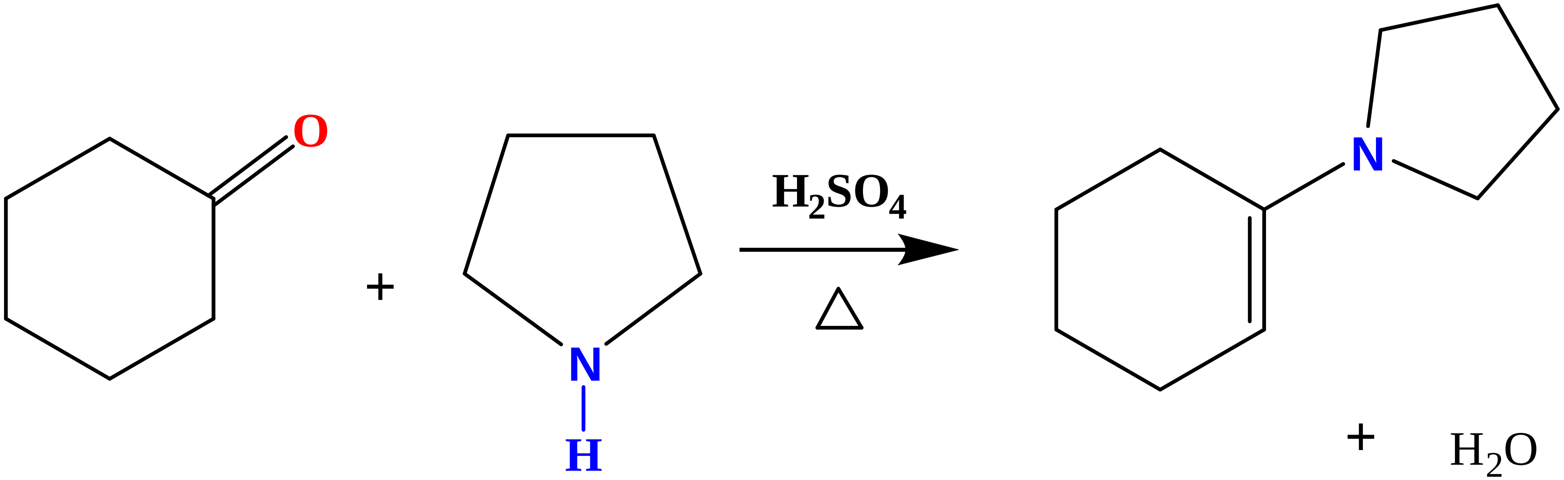
2nd step- attack of nucleophile (2° amine) on carbonyl carbon



Guess the product?



Example of enamine formation



Reactions of Grignard reagent with acids and their derivatives

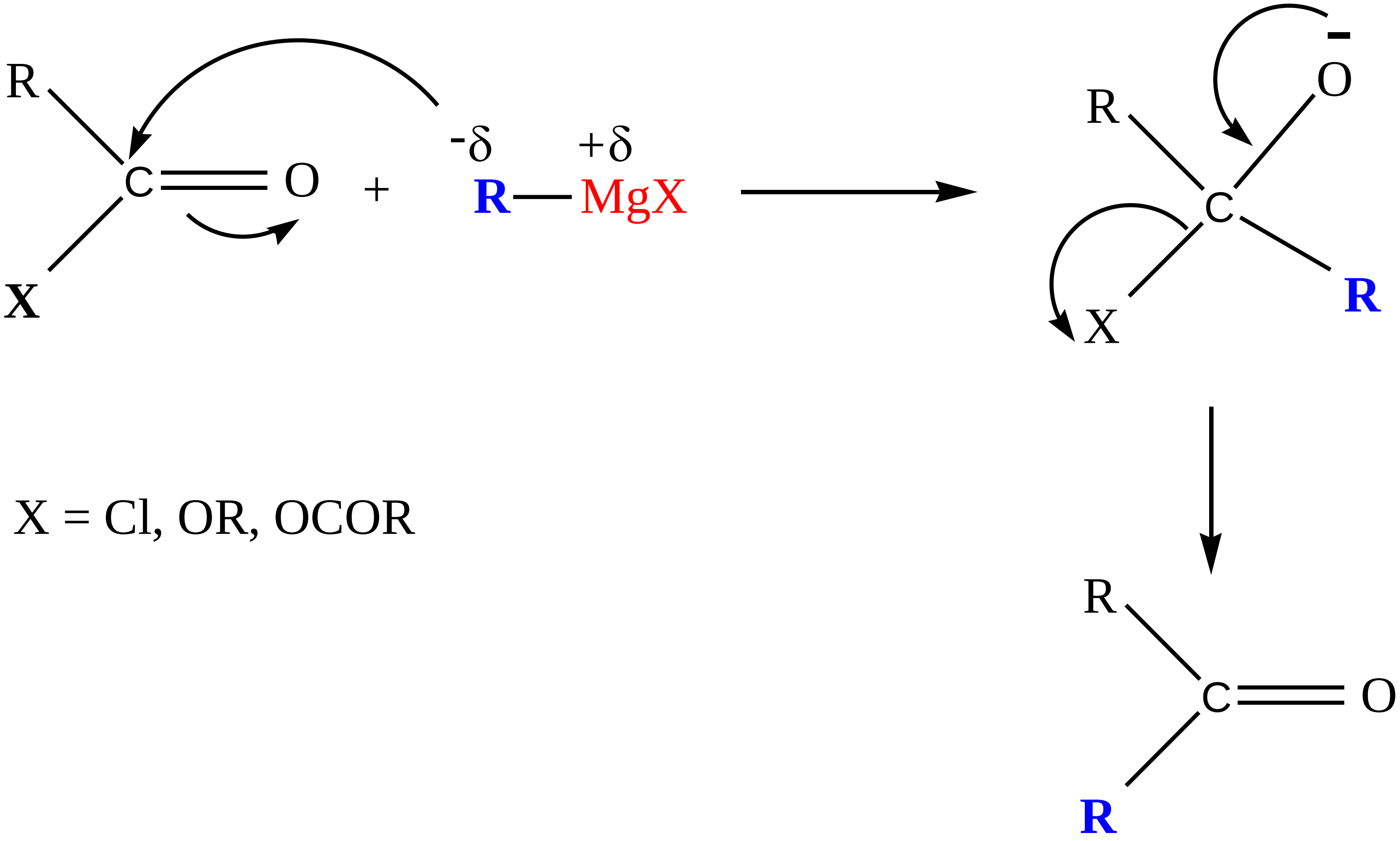
Addition of **Grignard reagent** to aldehyde and ketone

- Addition to **HCHO** = **Primary alcohol**
- Addition to **other aldehydes** = **Secondary alcohol**
- Addition to **Ketone**= **Tertiary alcohol**

Addition of **Grignard reagent** to carboxylic acid derivatives

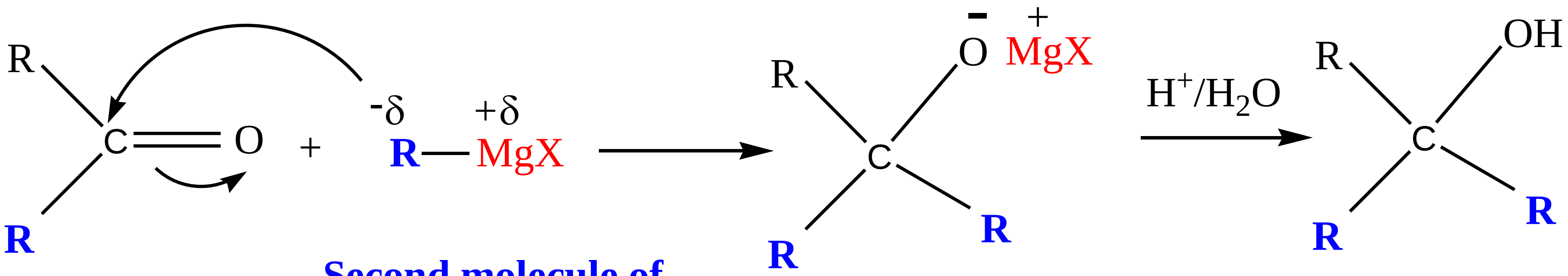
- Addition to **Acid chloride** = **Tertiary alcohol**
- Addition to **Ester** = **Tertiary alcohol**
- Addition to **Nitrile** = **Ketone**

Addition of **Grignard reagent** to carboxylic acid derivatives



X = Cl, OR, OCOR

Ketone thus formed further reacts with Grignard reagent to form tert. Alcohol as **final product**

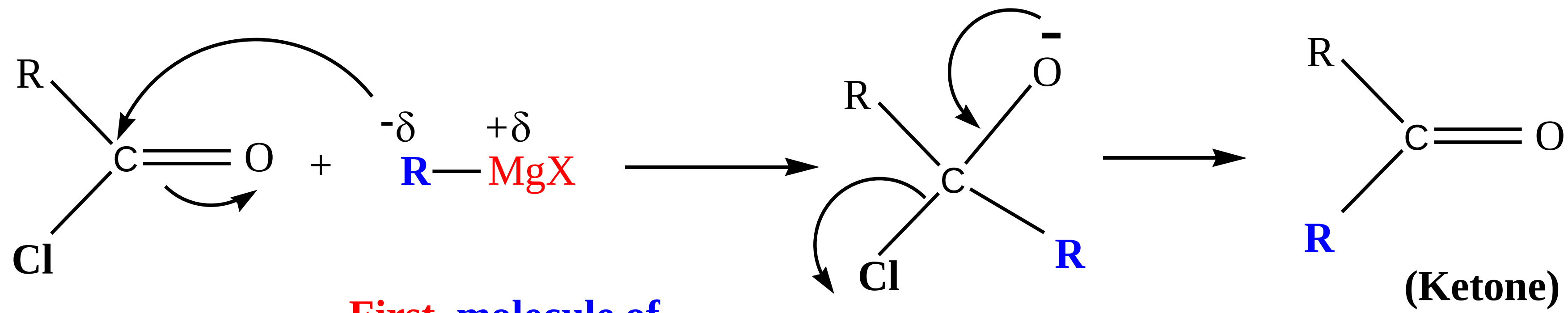


(Ketone)

Second molecule of Grignard reagent

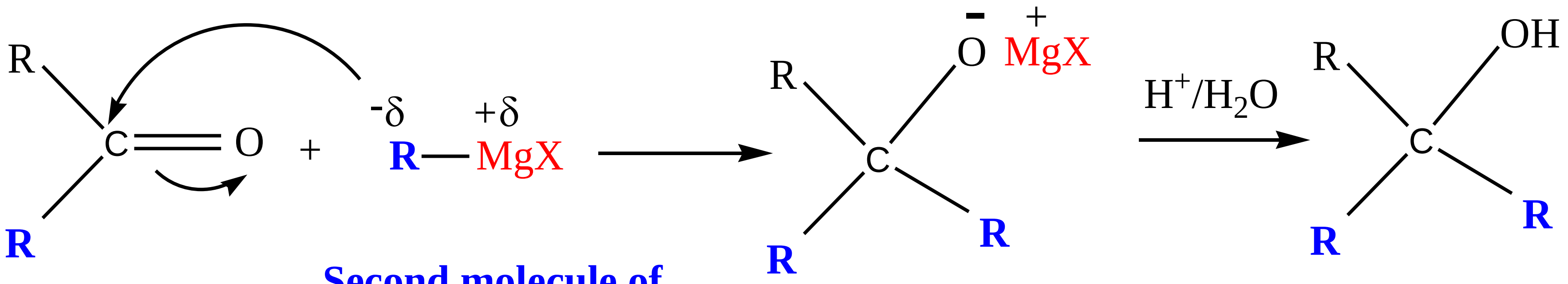
tertiary alcohol

E.g. Acid Chloride + Grignard reagent



Acid Chloride

First molecule of Grignard reagent



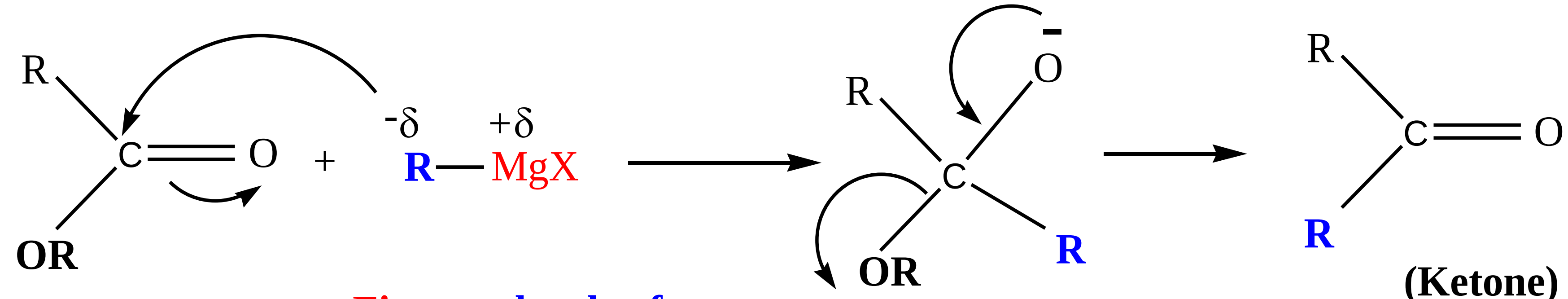
(Ketone)

Second molecule of Grignard reagent

tertiary alcohol

$$Mg(OH)X \xrightarrow{H^+} Mg^{2+} + H_2O + X^-$$

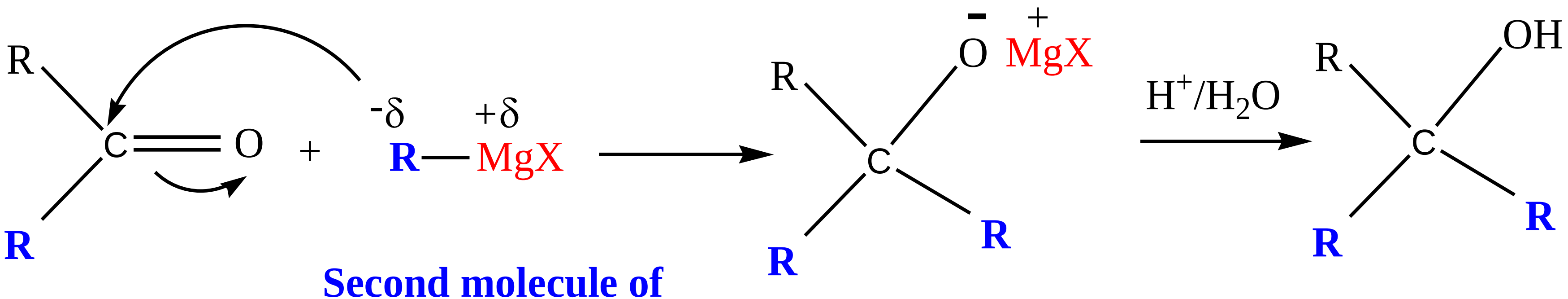
Ester + Grignard reagent



(Ketone)

First molecule of Grignard reagent

Ester



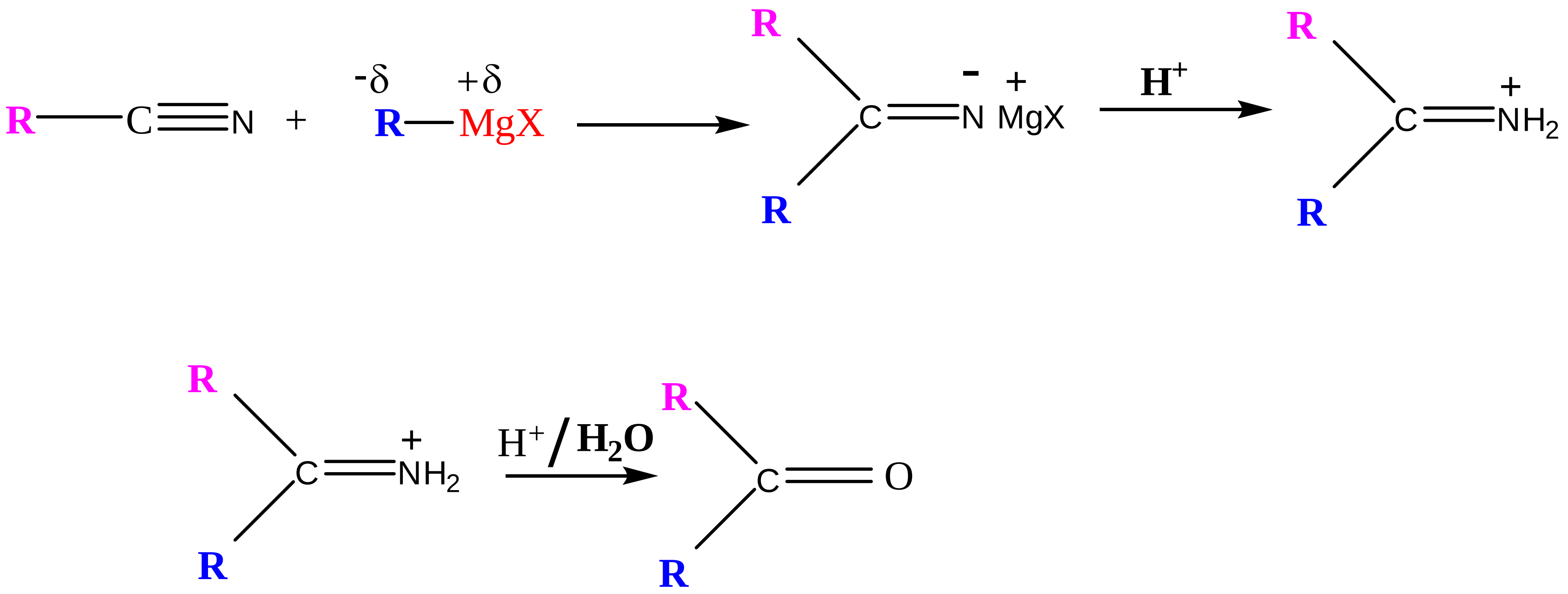
(Ketone)

Second molecule of Grignard reagent

tertiary alcohol

$$Mg(OH)X \xrightarrow{H^+} Mg^{2+} + H_2O + X^-$$

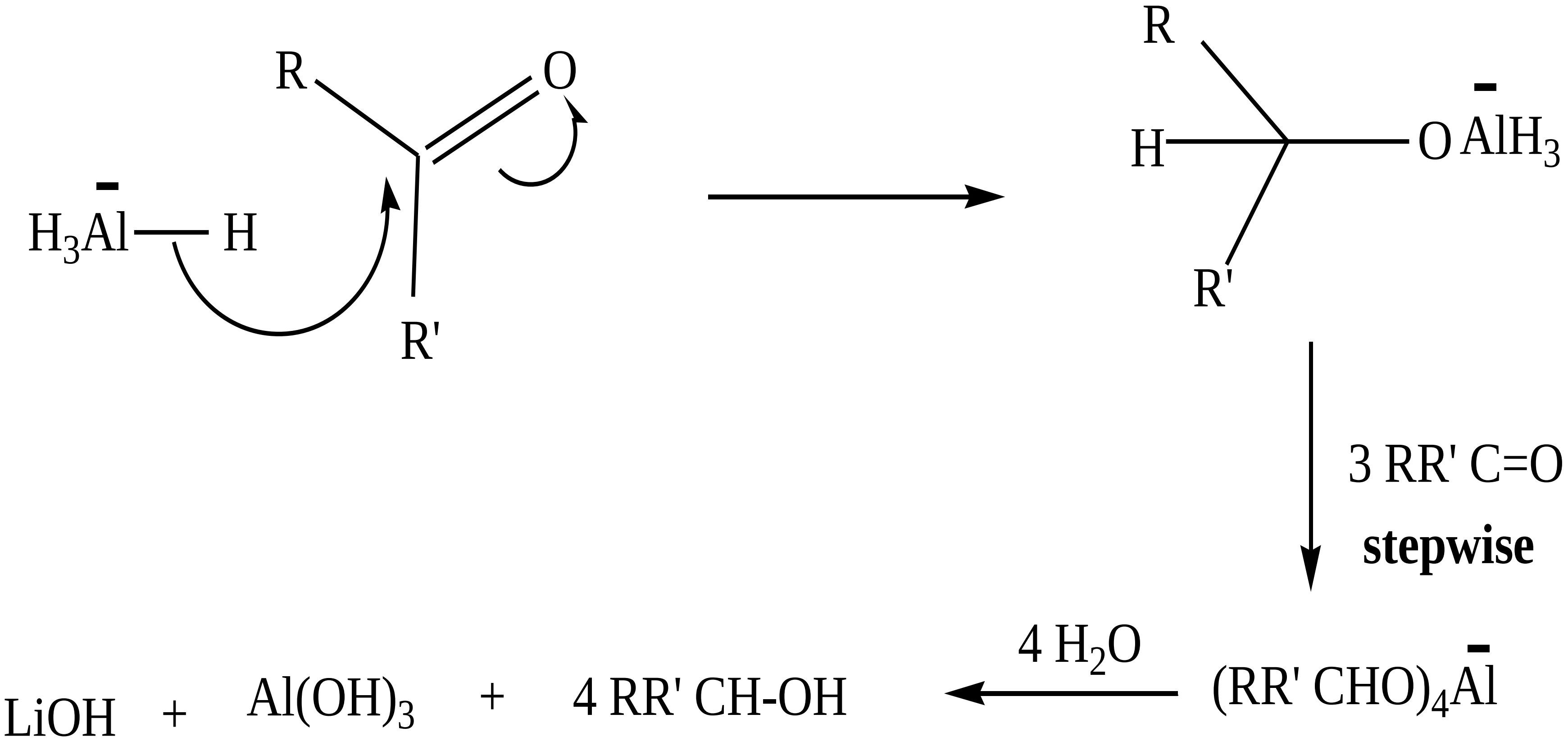
Nitrile + Grignard reagent = Ketone



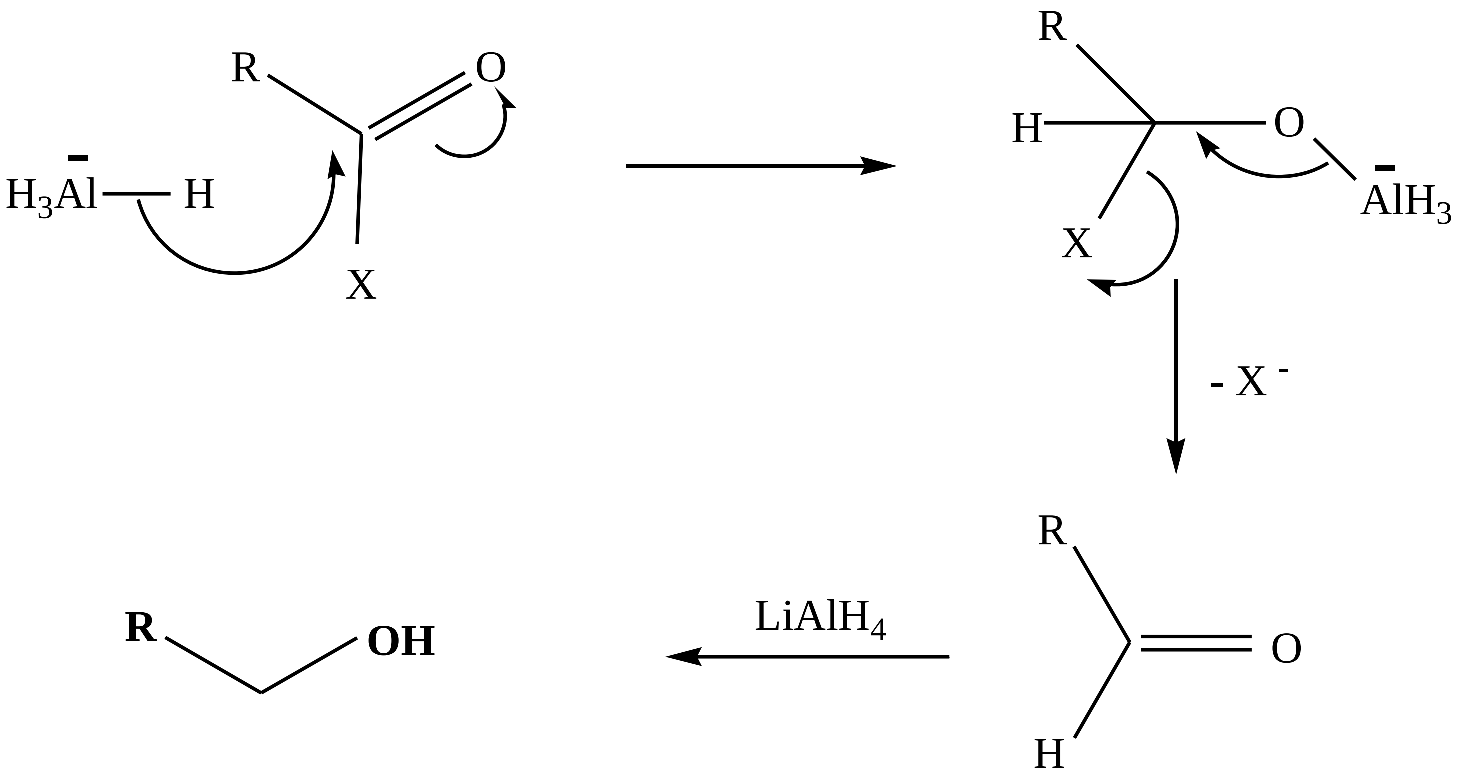
That is why all **reagents and solvent (Apparatus also)** used in reactions of **Grignard reagent must be dry (i.e. moisture free)**.

Reaction of carbonyl group with Hydride donor

1. Reduction by $LiAlH_4$



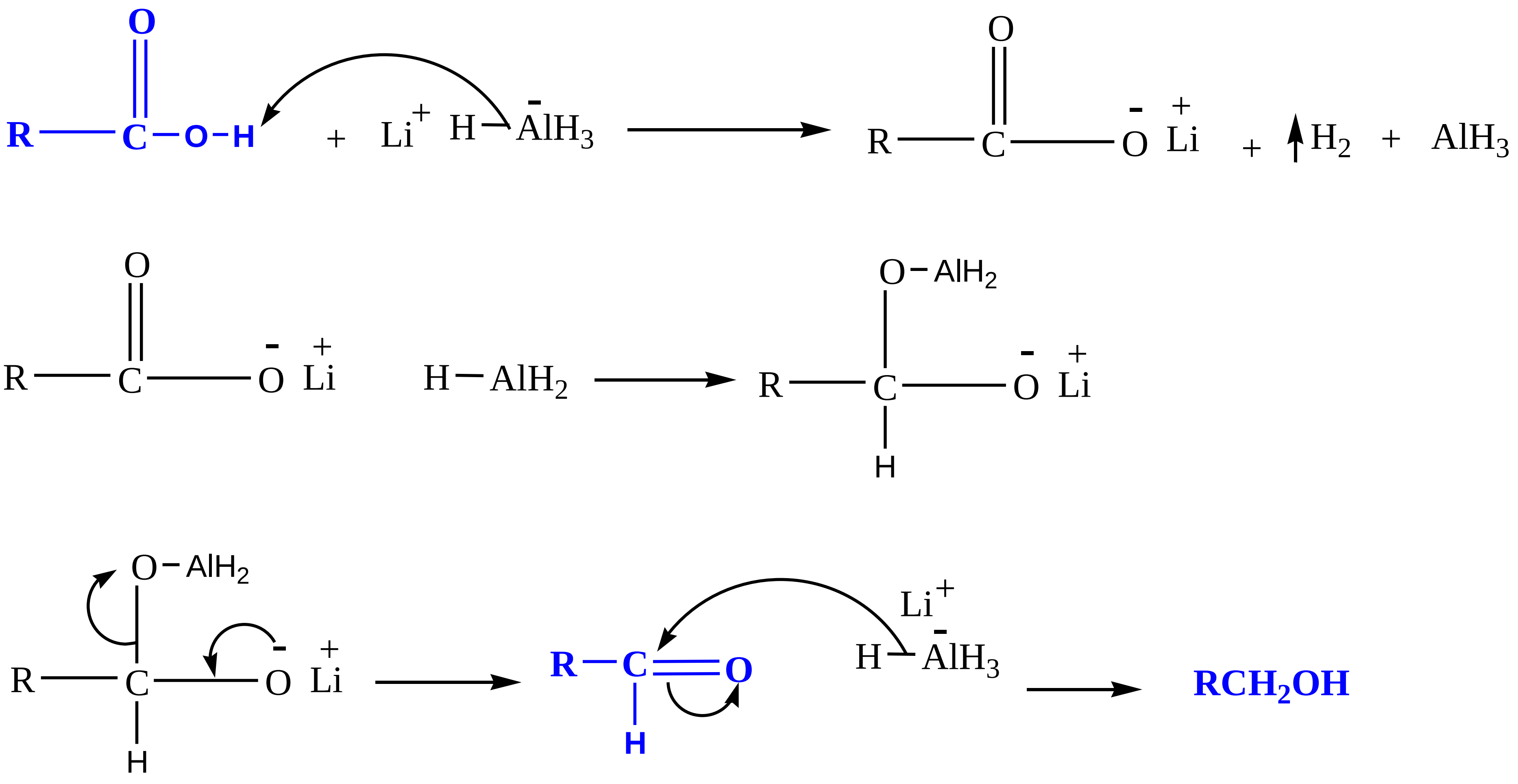
Mechanism (Ester/Anhydride/Acid Chloride to **alcohol**)



X = -OR (ester), -OCOR(anhydride), Halogen (acid chloride)

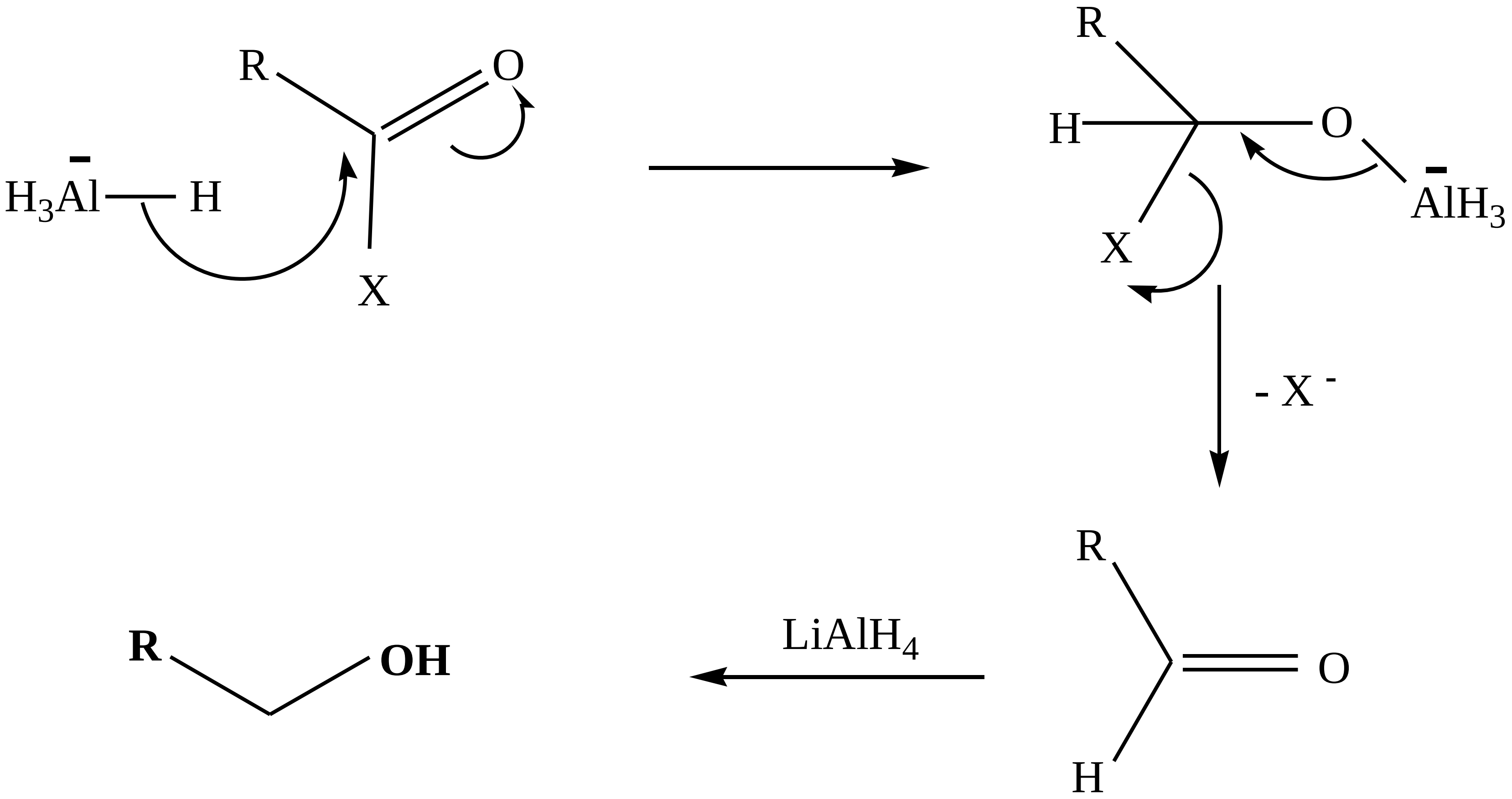
Mechanism for reduction of Carboxylic Acid by LAH

$$\mathrm{RCOOH} \xrightarrow[\text{(ii) } H_2O]{\text{(i) } LiAlH_4} \mathrm{RCH_2OH}$$

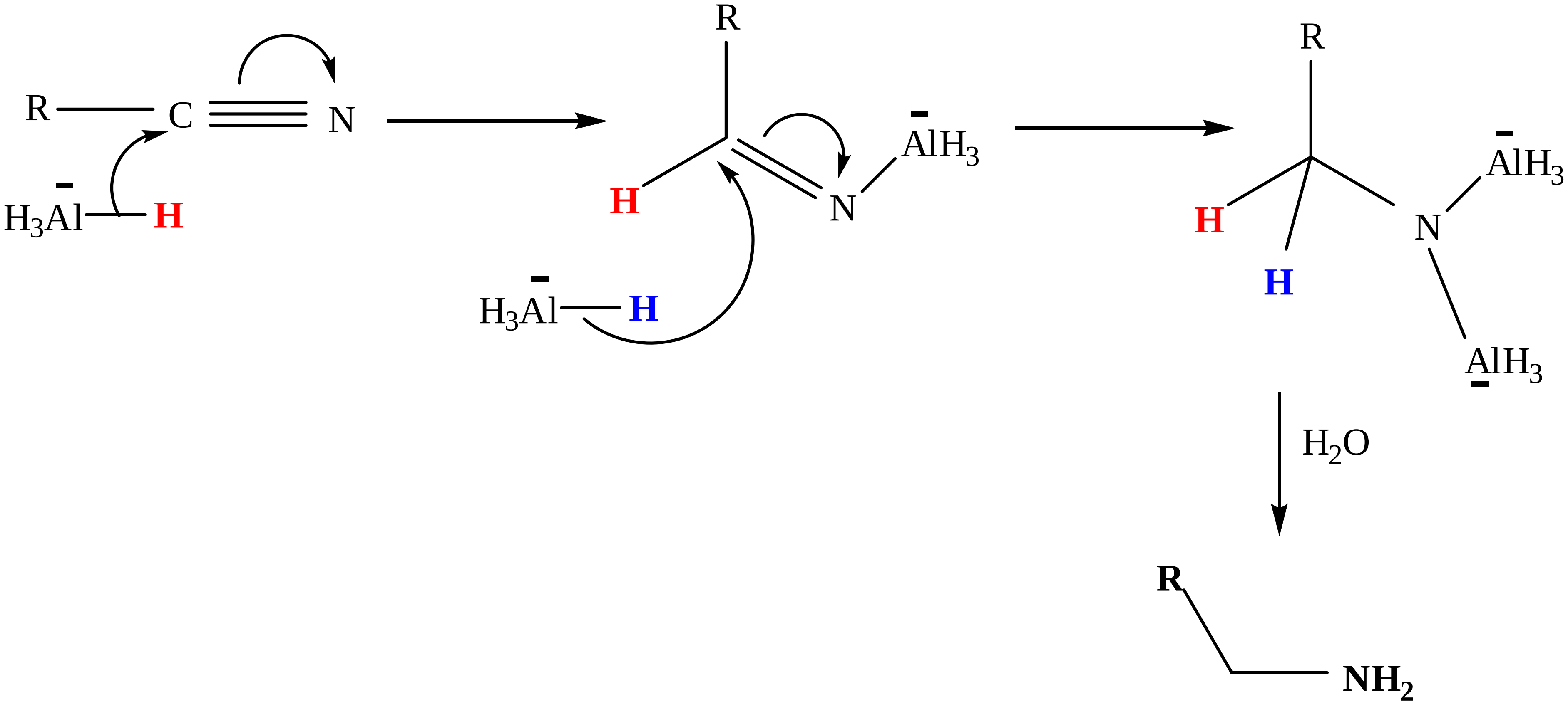


Reduction of **acid chloride**, **ester**, **anhydride to alcohol**) (X= Cl, **OR**, OCOR respectively)

(**X**$^-$ = good leaving group)



Mechanism (Nitrile to Amine)

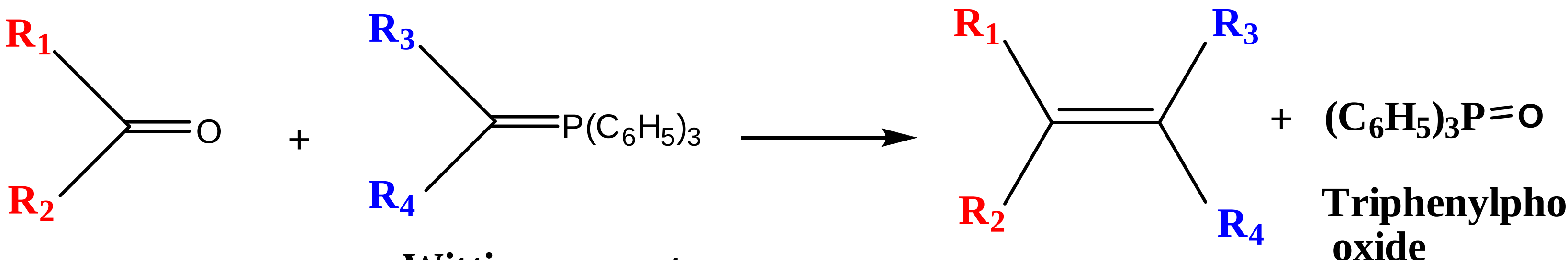


Wittig reaction

Aldehyde/Ketone +

alkylidenetriphenylphosphoranes = **Alkene**

Wittig reaction



Aldehyde / Ketone

Witting reagent

Alkylidenetriphenylphosphorane

substituted alkene

Triphenylphosphine oxide

[(E) and (Z) isomers]

In **Wittig reaction** **Phosphorus Ylide** is used.

(Preparation of **Phosphorus Ylide**)

Alkyl halide (1° or 2°) + **Triphenylphosphine**

↓

Alkyltriphenyl Phosphonium Salt

↓ **Strong base (n- butyllithium)**

Alkylidenetriphenylphosphorane

(Phosphorus Ylide)

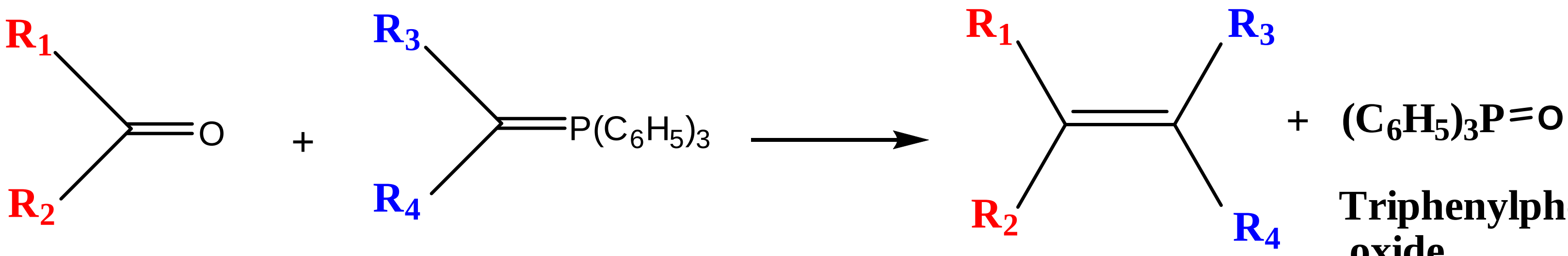
(wittig reagent)

Base used to abstract proton from phosphonium salt

The **phosphonium salts** are most often **converted to the ylides** by treatment with a **strong base** such as:

n- butyllithium,
sodium amide,
sodium hydride or
a **sodium alkoxide**,

Mechanism of Witting reaction



Aldehyde / Ketone

Witting reagent

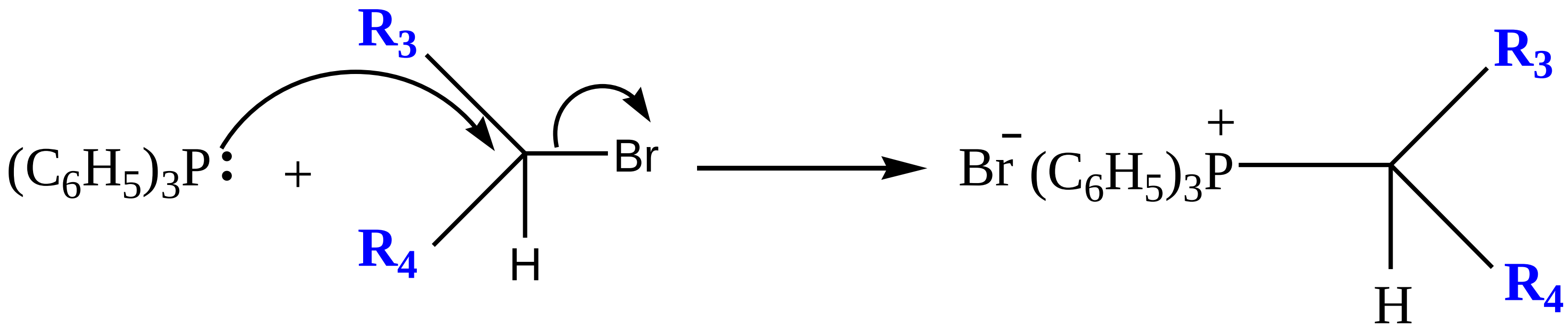
Alkylidenetriphenylphosphorane

Triphenylphosphine oxide

substituted alkene

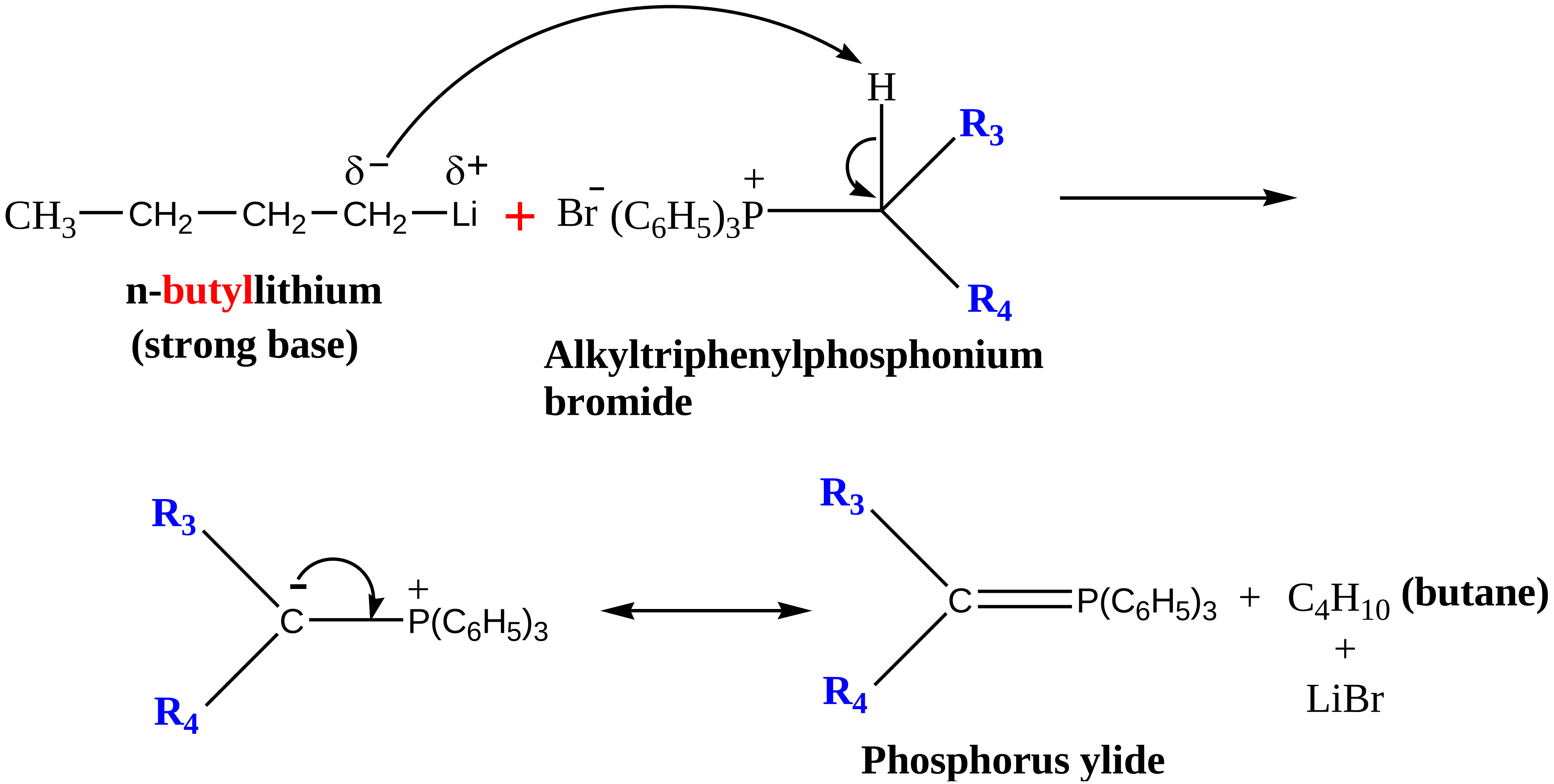
[(E) and (Z) isomers]

Preparation of witting reagent for this reaction

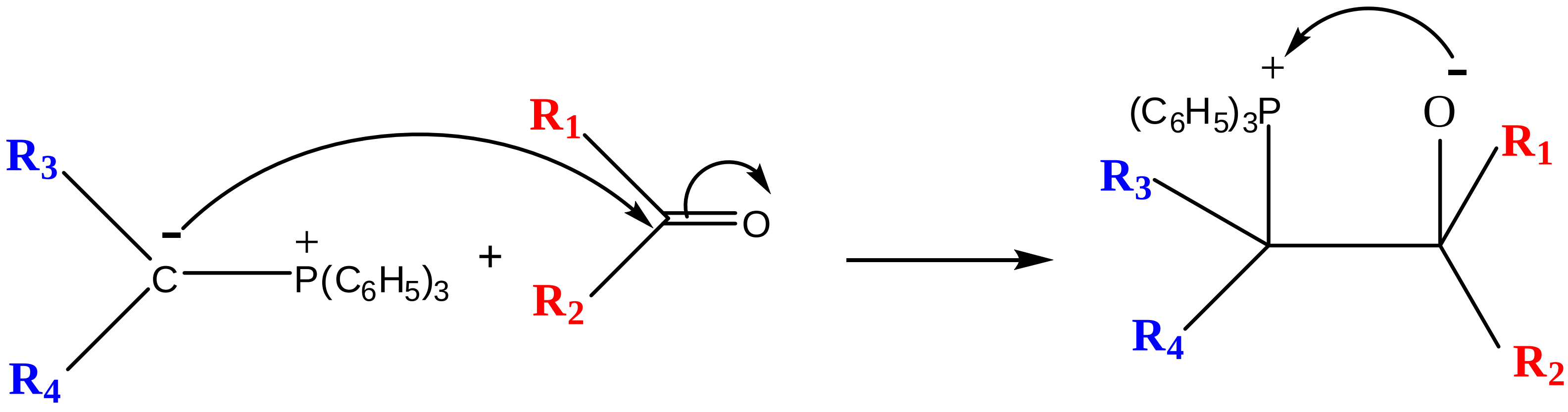


Triphenylphosphine **Alkyl halide**

Alkyltriphenylphosphonium bromide


CH3–CH2–CH2–CH2–Li
δ−
δ+
+
Br− (C6H5)3P+
H
R3
R4
n-butyllithium
(strong base)
Alkyltriphenylphosphonium
bromide
R3
R4
C
−
+
P(C6H5)3
R3
R4
C=P(C6H5)3
+ C4H10 (butane)
+
LiBr
Phosphorus ylide

Attack of phosphorus ylide on carbonyl carbon of aldehyde or ketone

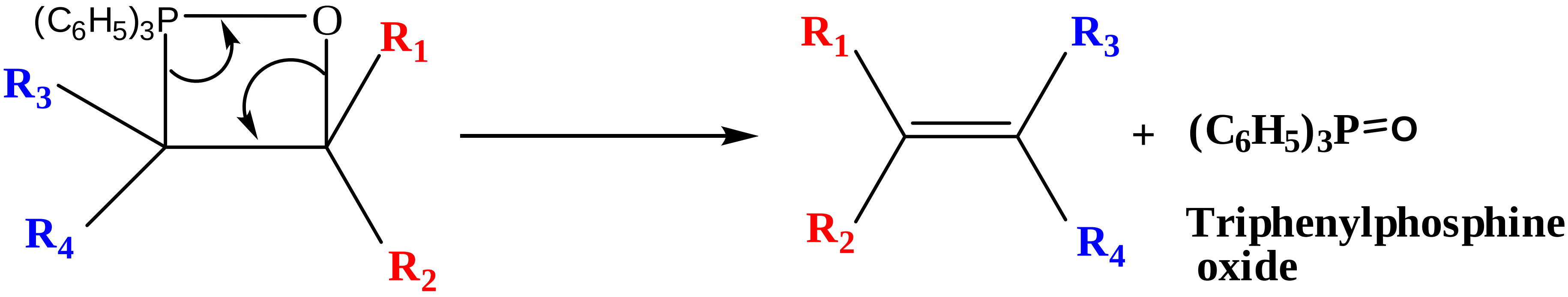


Phosphorus ylide

Aldehyde / Ketone

Betaine

unstable intermediate with separated charges



Triphenylphosphine
oxide

Unstable Four membered
cyclic intermediate

(Oxaphosphetane)

substituted alkene

Driving force of this reaction

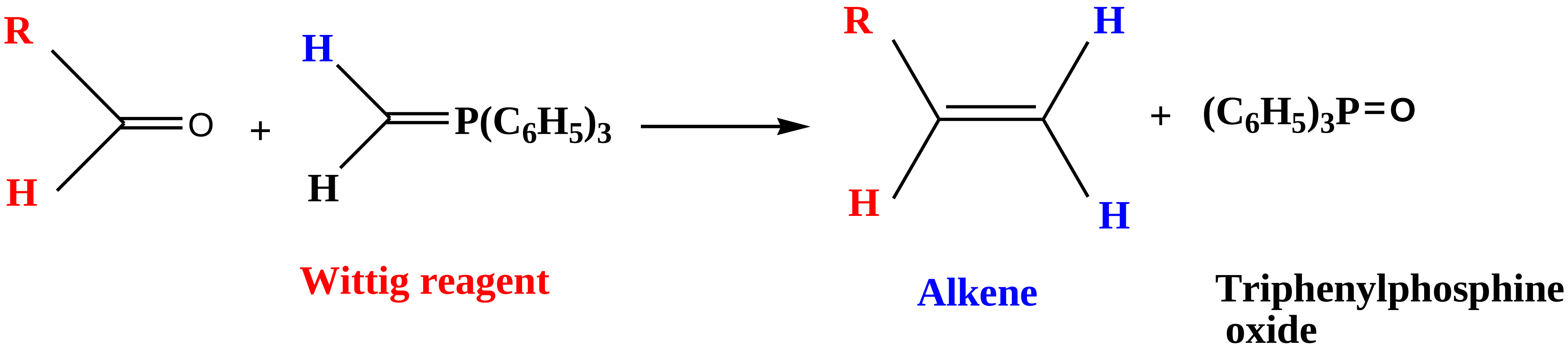
Four membered cyclic intermediate is converted into alkene and **stable molecule of triphenylphosphine oxide** (strong P=O bond is formed in it)

Driving force: Formation of **strong Phosphorus-Oxygen bond**

at the expense of

weak Carbon-Phosphorus bond

Example



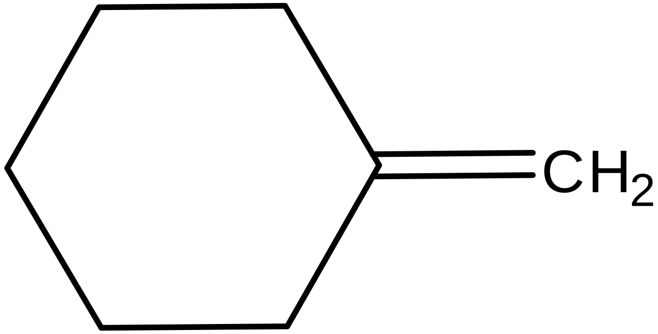
How will you **prepare wittig reagent** for above reaction?

Also write down **mechanism** of this reaction?

Problem

How will you prepare **methylenecyclohexane** from **cyclohexanone** using wittig reaction?

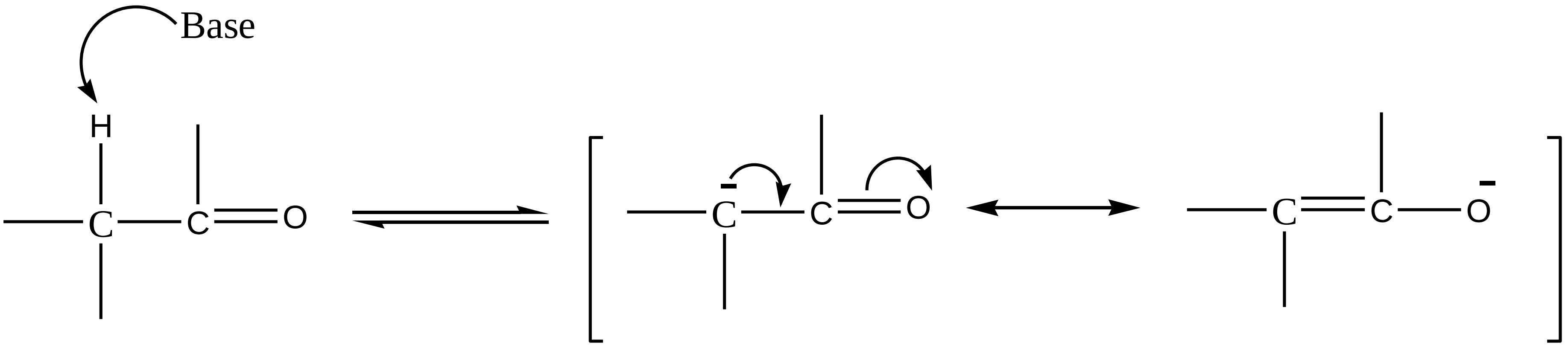
- **Also outline the synthesis of wittig regent involved in this reaction.**



methylenecyclohexane

Addition of carbanion to carbonyl group. (Aldol Addition)

Carbanion is generated by abstraction of acidic alpha hydrogen by strong base.



Carbonyl compound having **α - hydrogen**

Resonance stabilized carbanion

Main features of such reactions

1. Thus formed carbanion is **resonance stabilized.**
2. It behaves as **Nucleophile**
3. It **attacks on carbonyl carbon of second molecule** of carbonyl compound.

Aldol Addition

- **Aldehydes** having **α-hydrogens** undergo **self condensation** in presence of **base** (dil. NaOH) to give **β-hydroxyaldehyde** .
- This **product** is called as **ALDOL** as it contains both **aldehyde** and **alcohol group**.
- This type of reaction is called **Aldol addition** or **Aldol reaction**.

Aldol Addition

It is condensation between two molecules of an aldehyde (**having α-hydrogen)**

or

condensation between two molecules of a ketone **(having α-hydrogen)**

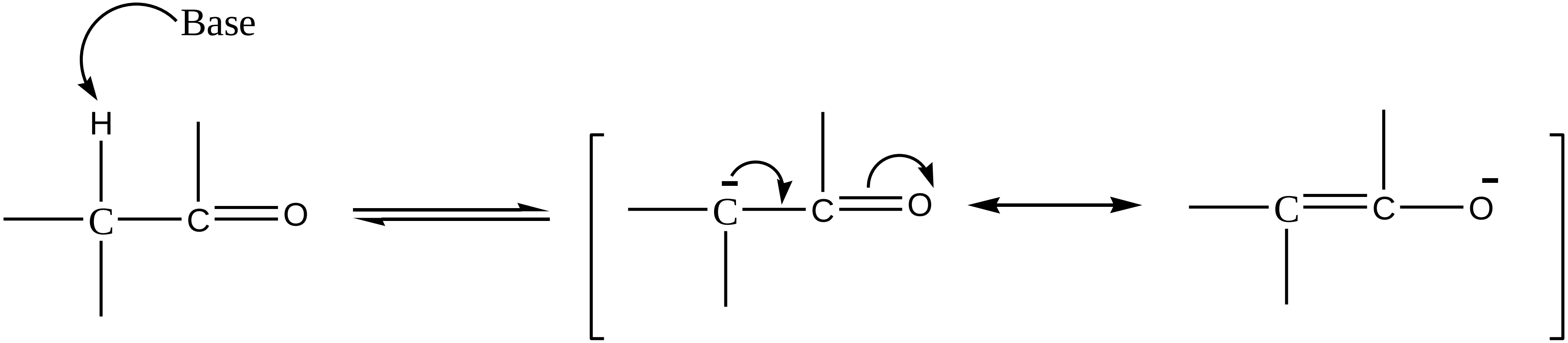
in presence of a base (dil. NaOH)

Product: β-hydroxyaldehyde or β-hydroxyketone

(in Aldol Addition)

Key step

Abstraction of acidic alpha hydrogen of carbonyl compound by base to generate carbanion.



Carbonyl compound having α - hydrogen

Resonance stabilized carbanion

Carbanion thus formed is resonance stabilized.

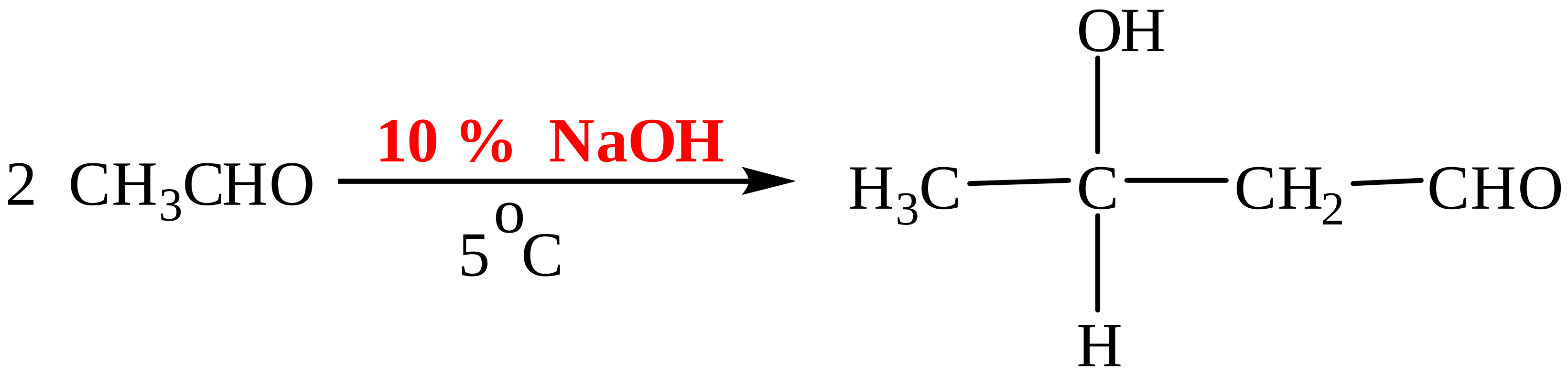
2nd step

Carbanion thus formed attack on carbonyl carbon of second molecule of carbonyl compound.

So, an **anion** (species with -ve charge on oxygen) is formed,

which **takes proton** from **solvent/water** **to give product** in next step.

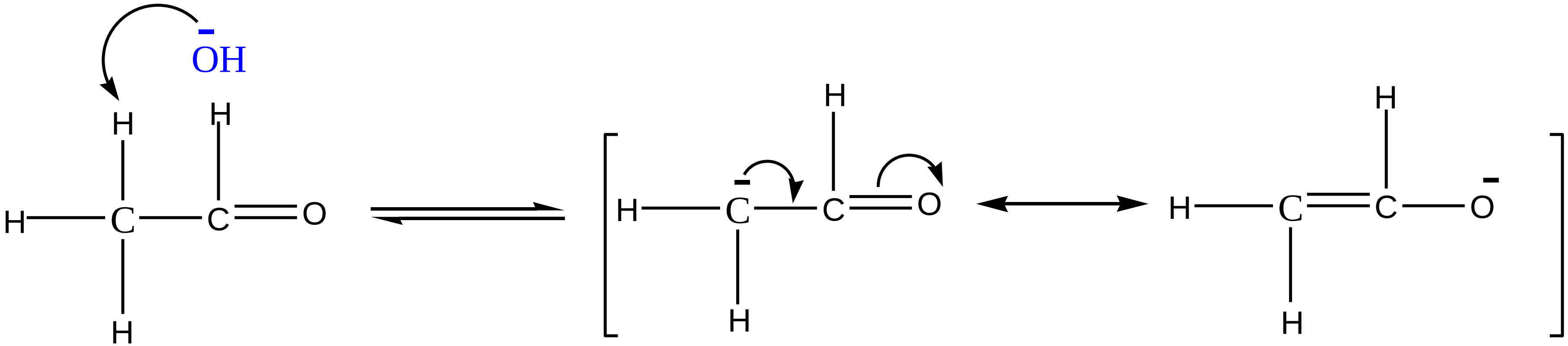
Example: Reaction between two molecules of **acetaldehyde**.



$$2\ CH_3CHO \xrightarrow[5\ ^{o}C]{10\ \%\ NaOH} H_3C-\overset{OH}{\underset{H}{C}}-CH_2-CHO$$

3-hydroxybutanal (Aldol)

Mechanism of reaction

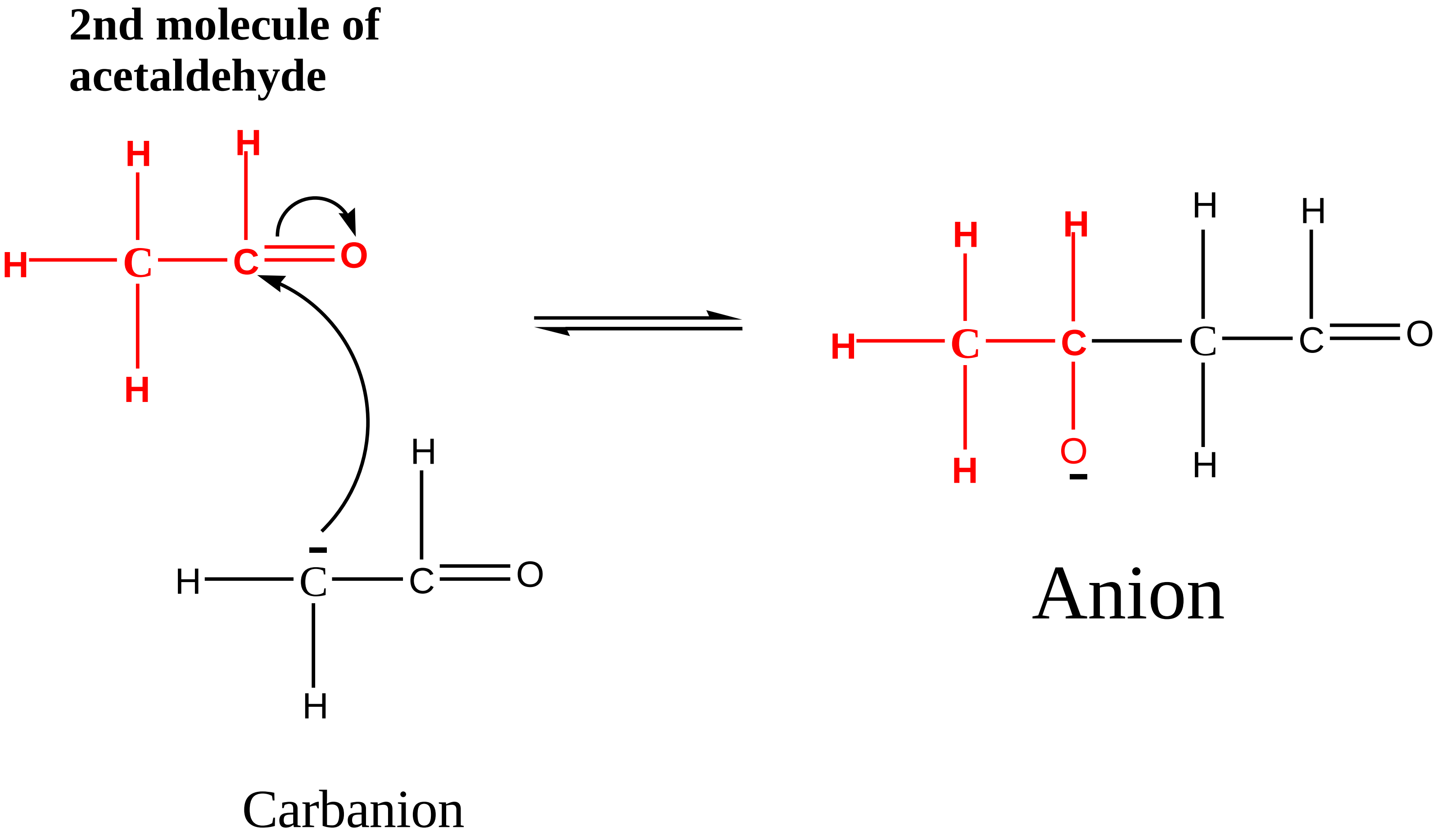


Resonance stabilized carbanion

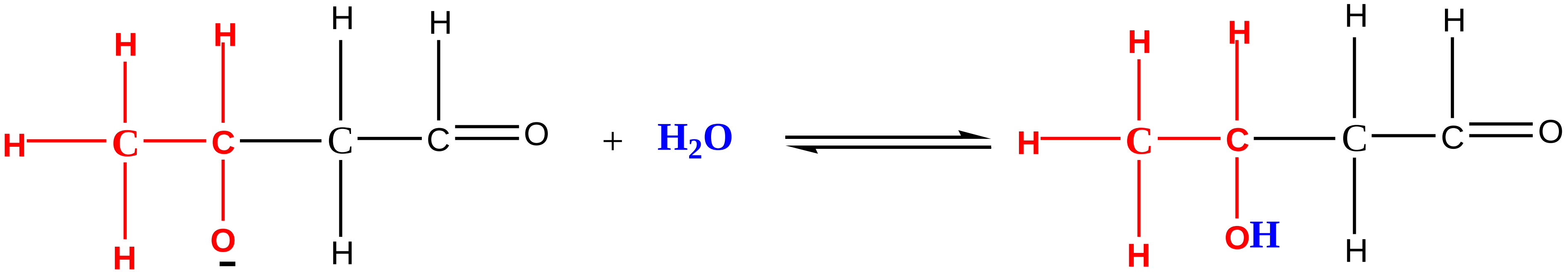
Base abstracts
alpha hydrogen

+ H_2O

2nd step: carbanion attack on carbonyl carbon of 2nd molecule of acetaldehyde



3rd step: Anion thus formed takes proton from water to form product.



Anion

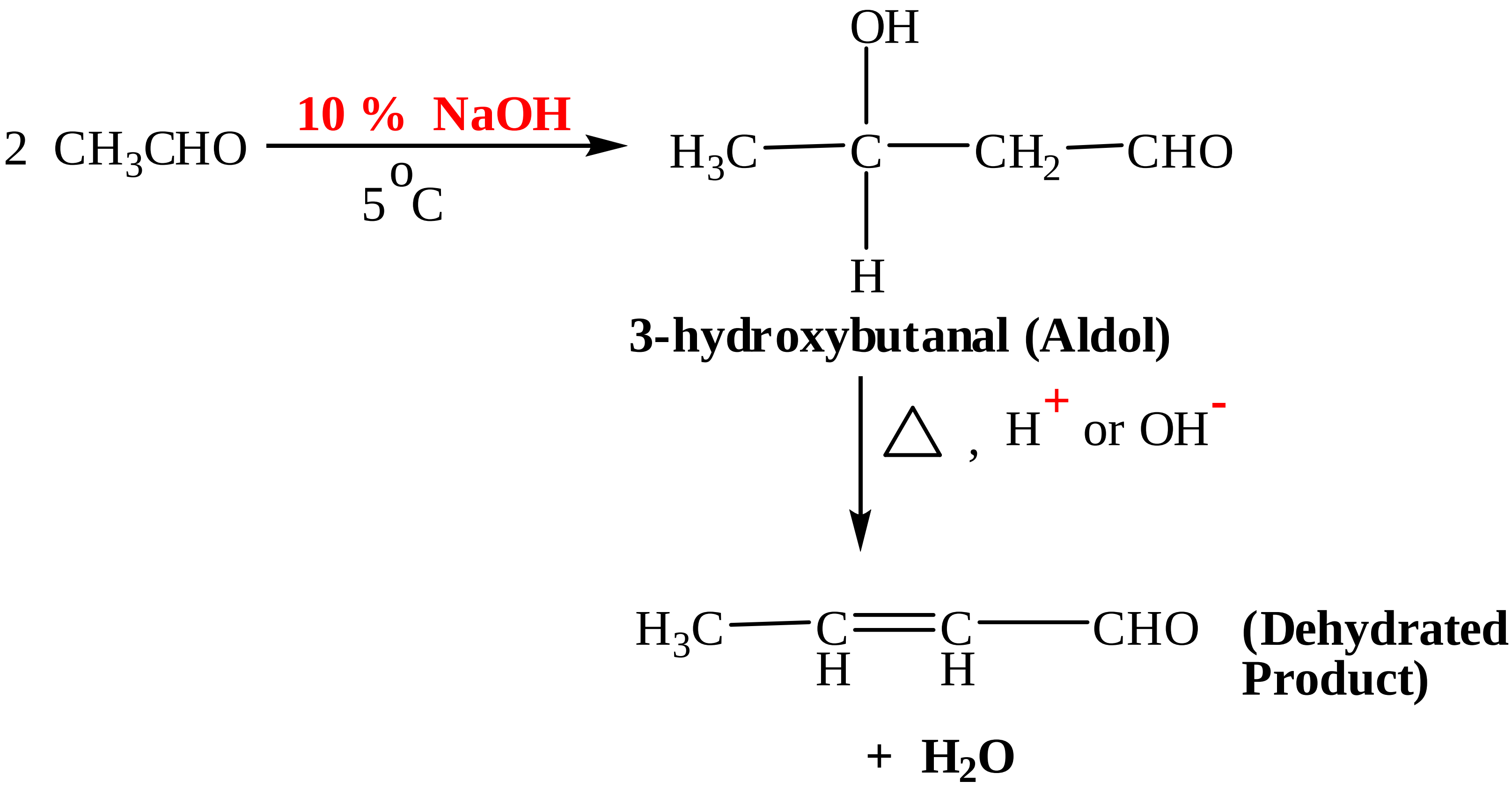
β - hydroxyaldehyde

+ $^{-}$OH

Dehydration of Aldol Addition Product

- If the **Aldol product** is **heated in presence of base or acid**, it undergoes **dehydration** to give **dehydrated product** i.e. **α,β-unsaturated carbonyl compound** .

Dehydration of Aldol Product after heating either in presence of base or acid



$$2\ CH_3CHO \xrightarrow[5\,^{o}C]{10\ \%\ \ NaOH} H_3C-\overset{OH}{\underset{H}{C}}-CH_2-CHO$$

3-hydroxybutanal (Aldol)

Δ , H^{+} or OH^{-}

$$H_3C-\underset{H}{C}=\underset{H}{C}-CHO$$

(Dehydrated Product)

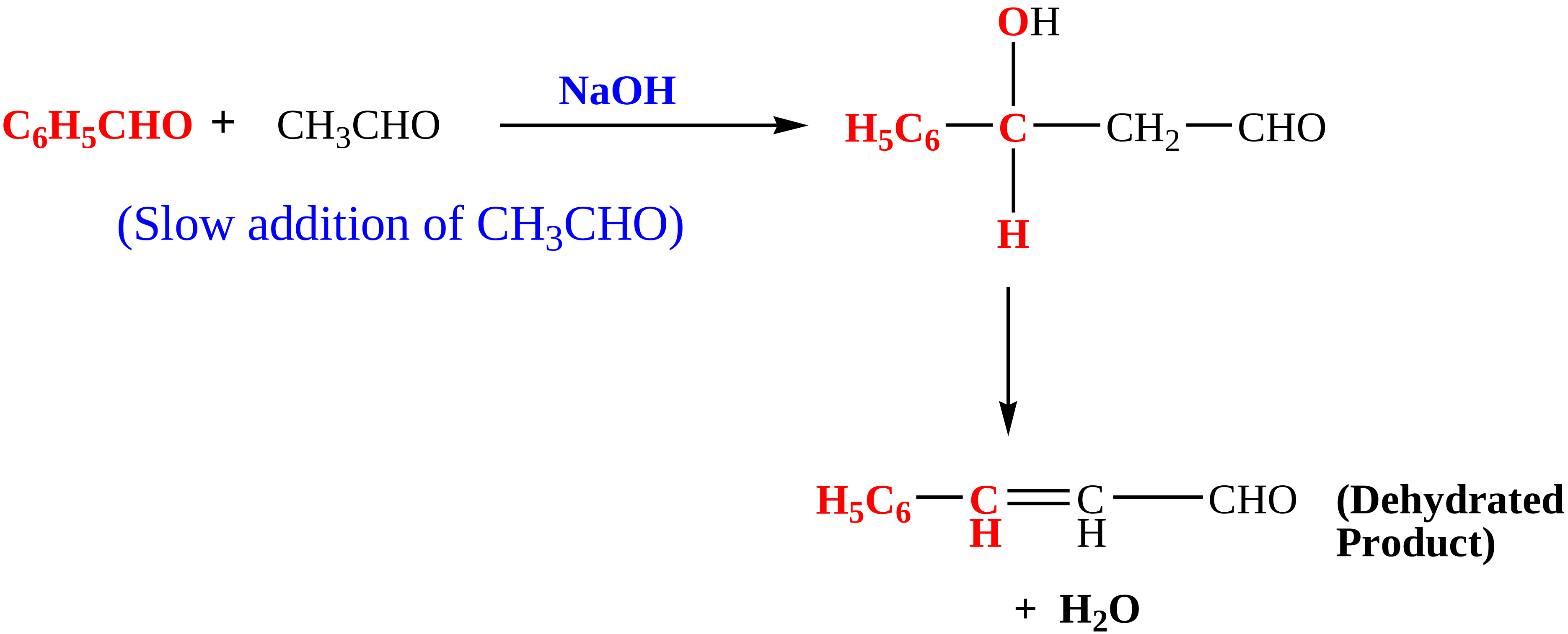
+ H_2O

Aldol Condensation

- **After dehydration** reaction is known as **Aldol Condensation** instead of **Aldol addition**.
- In some reaction, **dehydration occurs so readily** that **aldol addition product is not isolated** rather a **dehydrated product is isolated**.
- So, **Aldol condensation** occurs instead of **aldol addition.**

Example of Aldol Condensation

Reaction between **Benzaldehyde** and **Acetaldehyde**



$$C_6H_5CHO + CH_3CHO \xrightarrow{NaOH} H_5C_6-\underset{H}{\overset{OH}{C}}-CH_2-CHO$$

(Slow addition of CH_3CHO)

$$\downarrow$$

$$H_5C_6-\underset{H}{C}=\underset{H}{C}-CHO$$

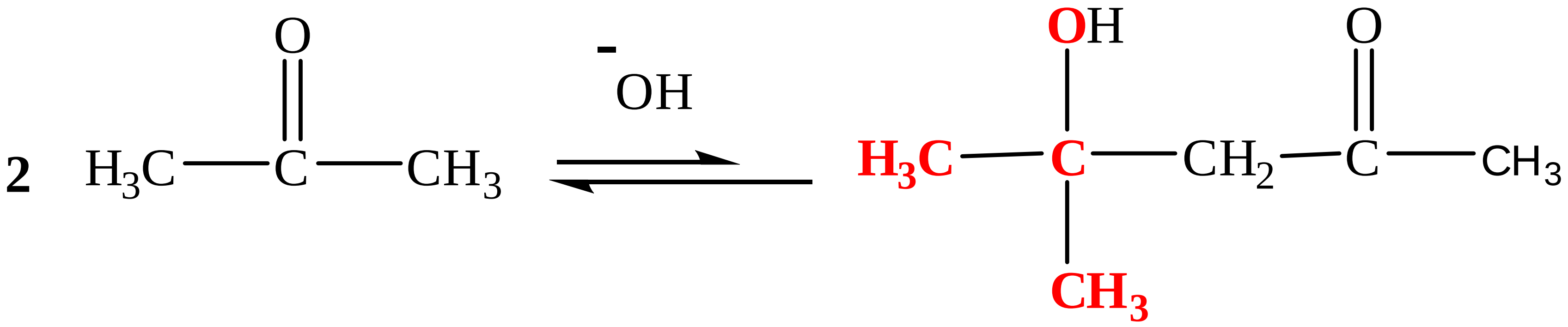
(Dehydrated Product)

$$+\ H_2O$$

Why dehydration occurs readily

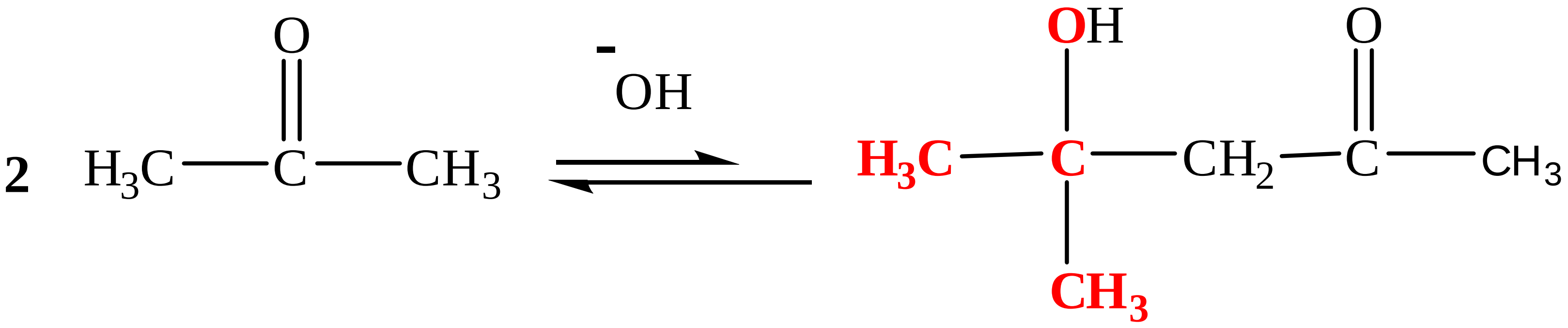
- Here dehydration occurs readily, as **double bond formed in dehydrated aldol will be in conjugation with aromatic ring** (**a stable product**).
- So **extended conjugation** is reason for the dehydration of aldol.

Reaction between two molecules of acetone

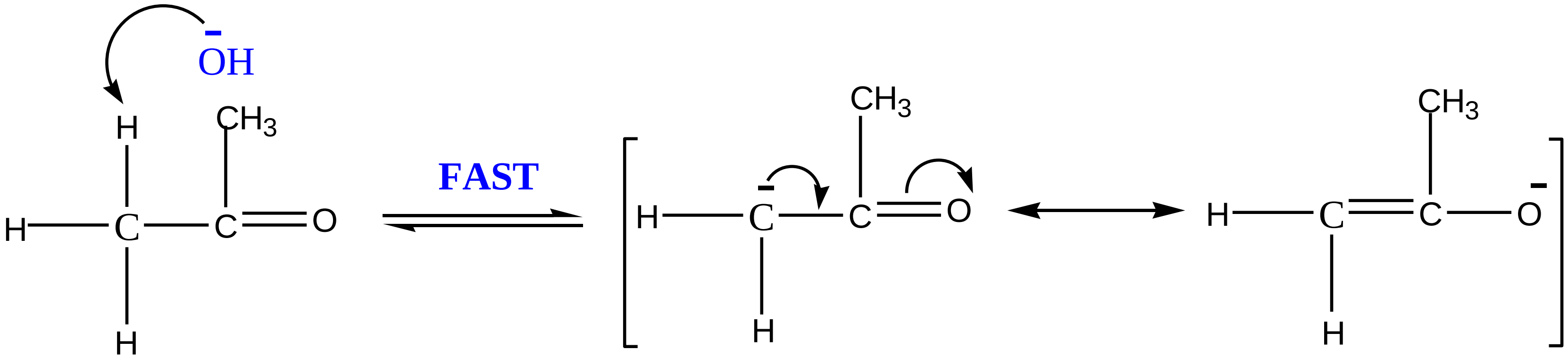


$$2\ H_3C-\overset{\overset{\displaystyle O}{\|}}{C}-CH_3 \xrightleftharpoons{^{-}OH} H_3C-\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle OH}{|}}{C}}-CH_2-\overset{\overset{\displaystyle O}{\|}}{C}-CH_3$$

Mechanism of reaction



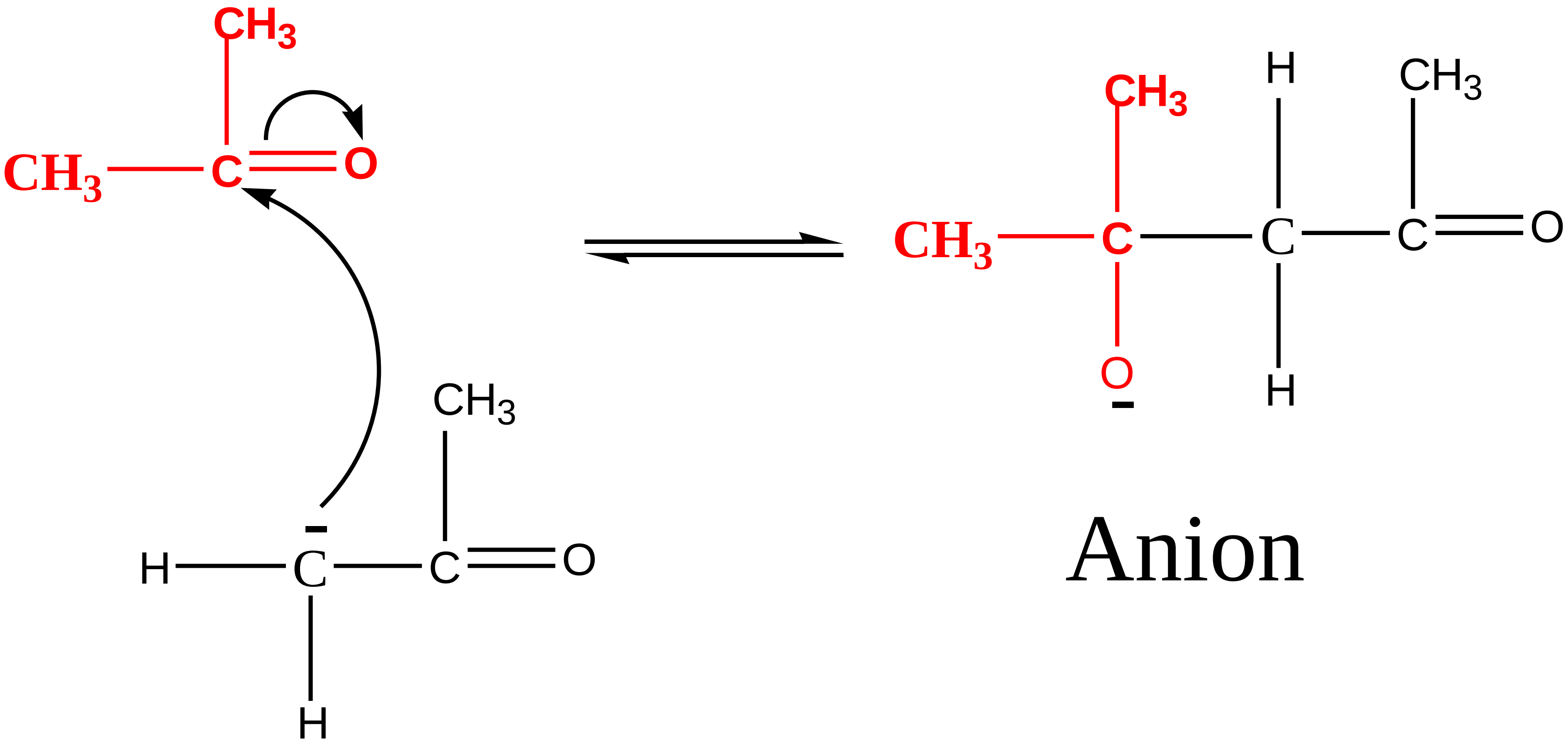
$$2\ H_3C-\overset{\overset{O}{\|}}{C}-CH_3 \xrightleftharpoons{^{-}OH} H_3C-\overset{\overset{OH}{|}}{\underset{\underset{CH_3}{|}}{C}}-CH_2-\overset{\overset{O}{\|}}{C}-CH_3$$



Base abstracts
alpha hydrogen

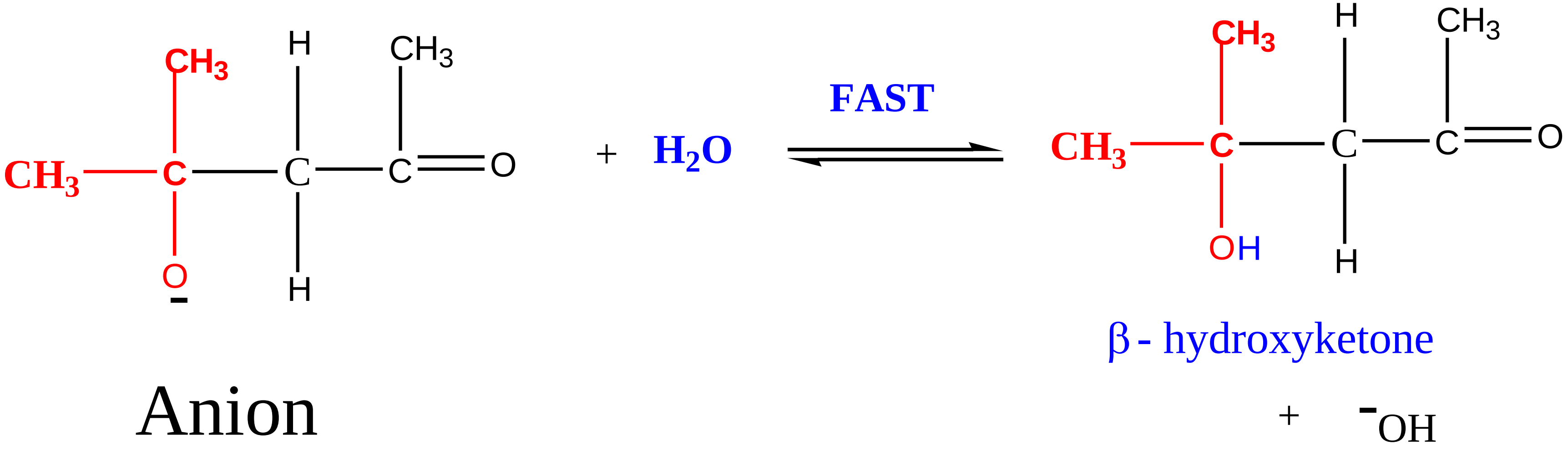
Resonance stabilized carbanion

+ H_2O



Carbanion

Anion



Anion

β - hydroxyketone

Crossed aldol condensation

Occurs between two different carbonyl compounds.

A+B (A and B are different aldehydes)
A+B (A and B are different Ketones)
A+B (A = aldehyde; B=Ketone or vice versa)

If both have alpha-hydrogens, then

All possible products are formed (i.e. four products)

However, if one of the carbonyl compound does not have α-hydrogen, then crossed aldol condensation is of great **synthetic utility**.

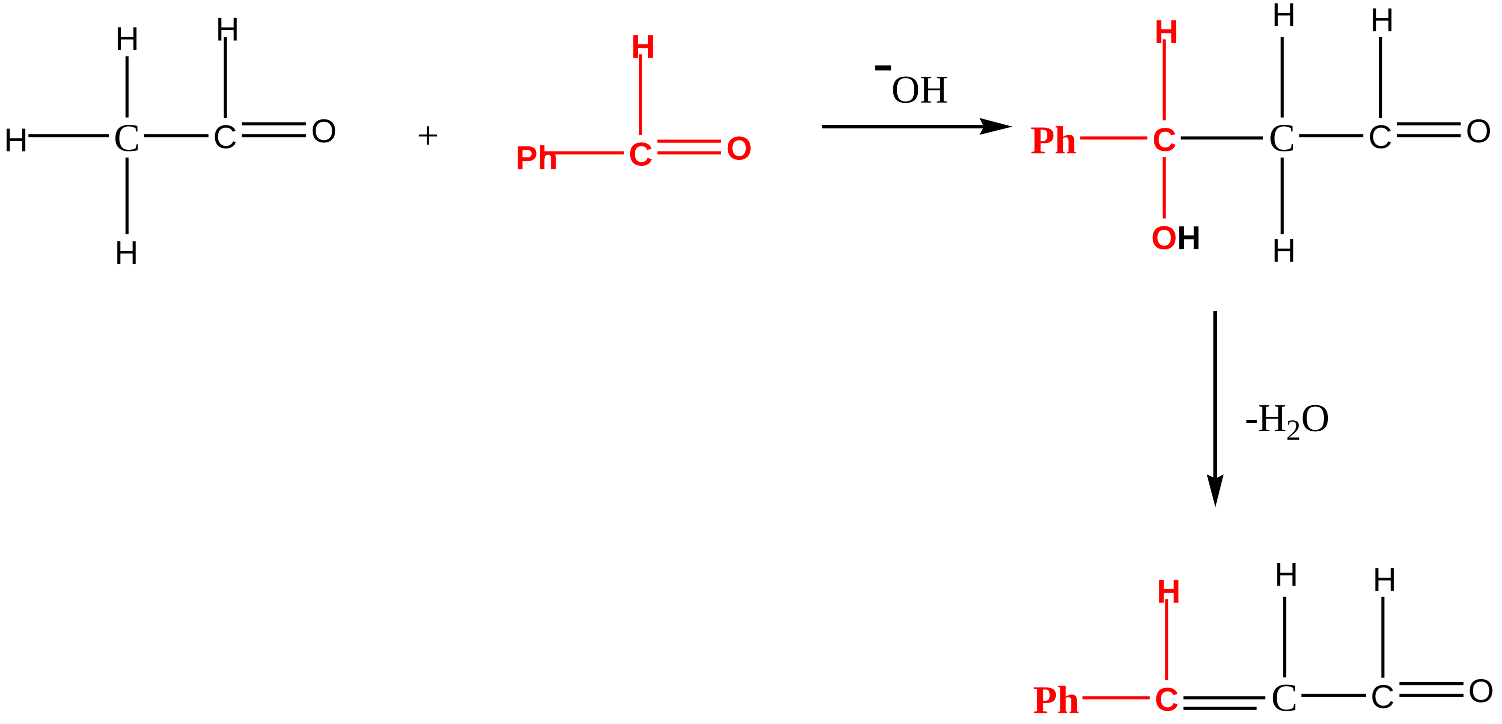
In this case,

Carbanion is formed from carbonyl compound having alpha hydrogen.

This carbanion attack on carbonyl carbon of compound **having no alpha hydrogen (taken in excess)**.

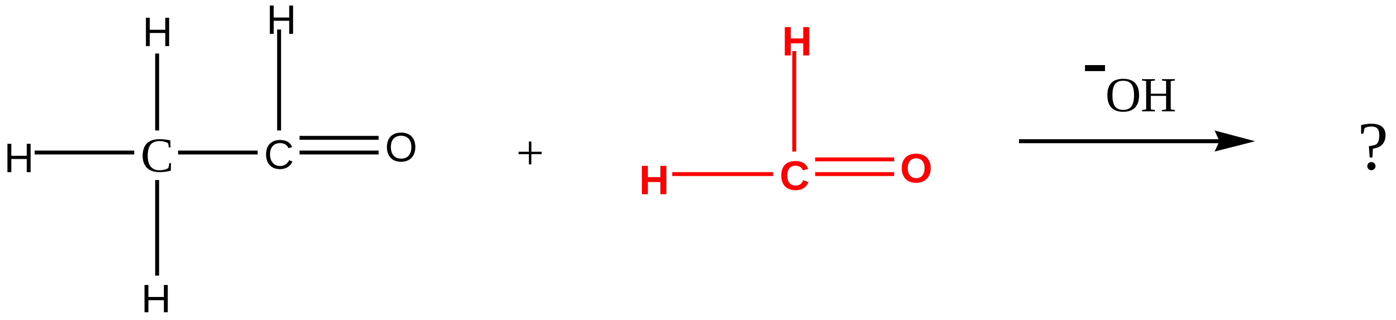
Carbonyl compound **with alpha-hydrogen** is added slowly to basic solution of Carbonyl compound **without alpha-hydrogen**

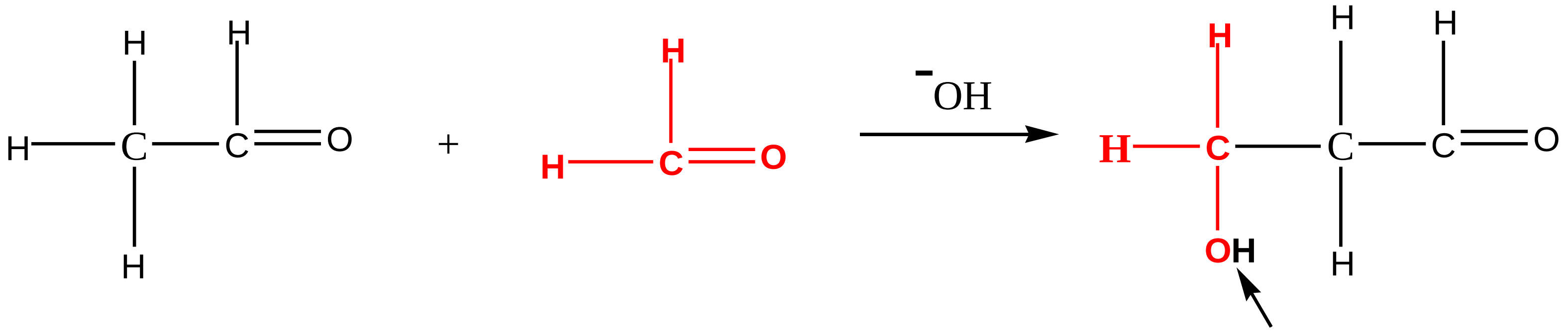
Example of Crossed Aldol Condensation



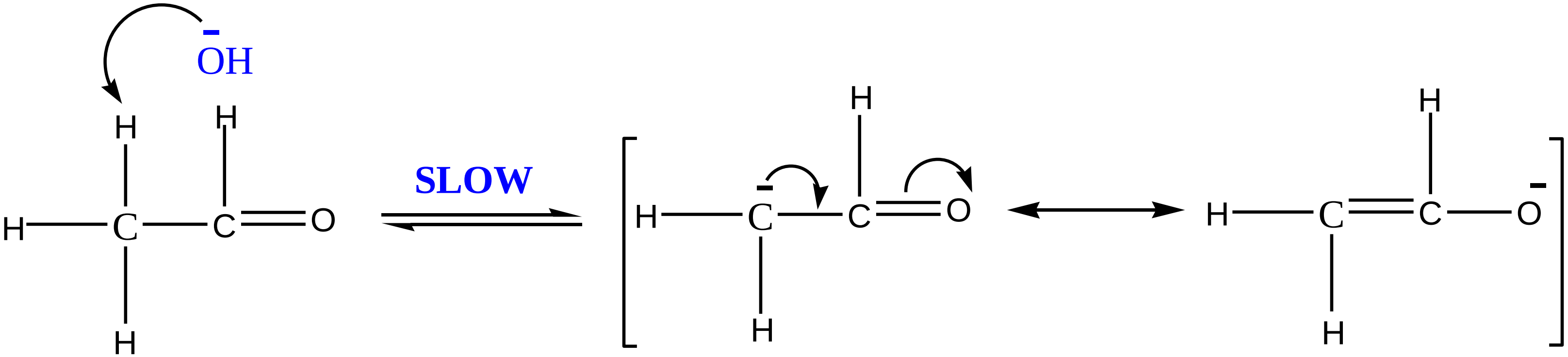
Dehydrated product

Another Example of crossed aldol condensation
Reaction between formaldehyde and acetaldehyde





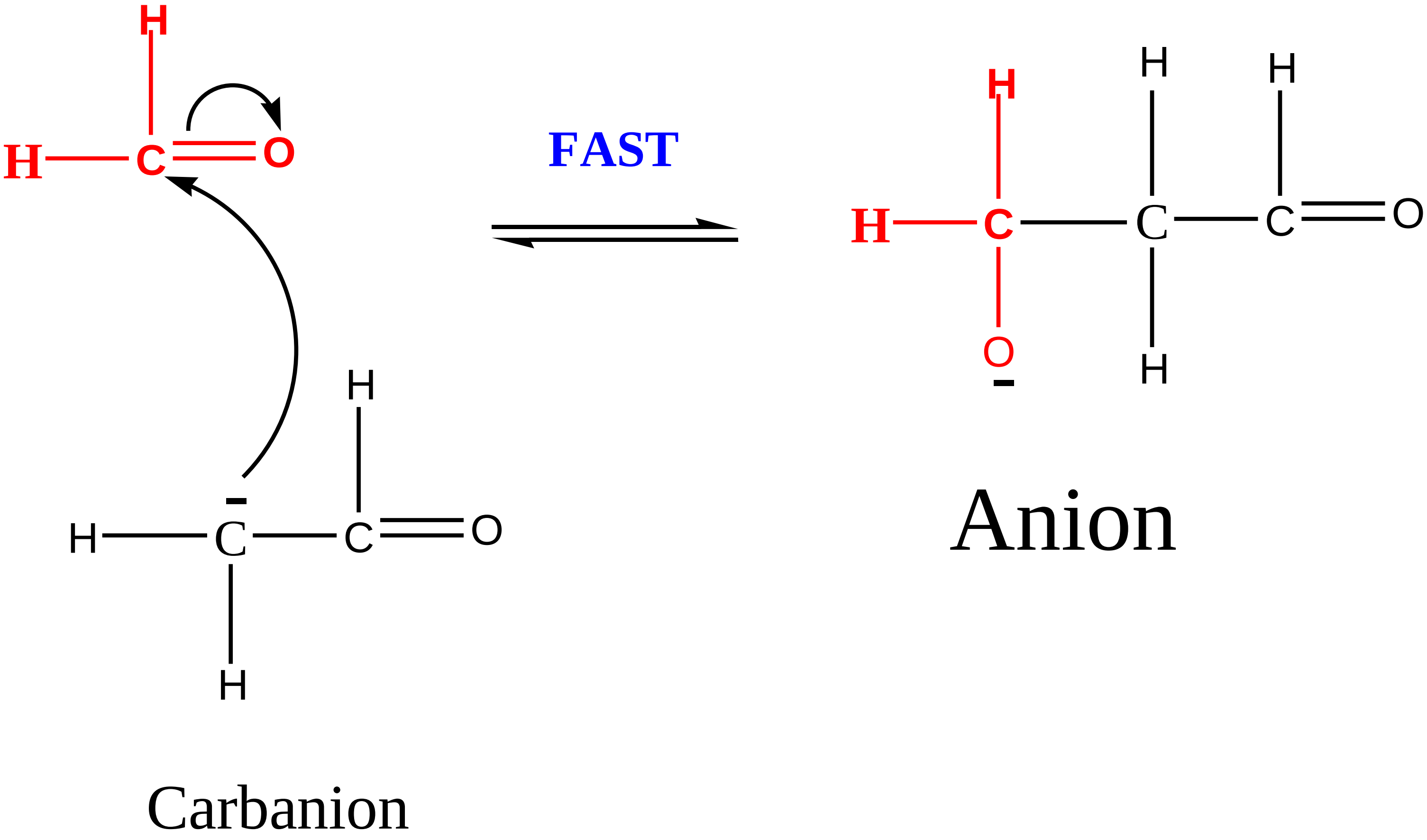
Hydogen comes from water

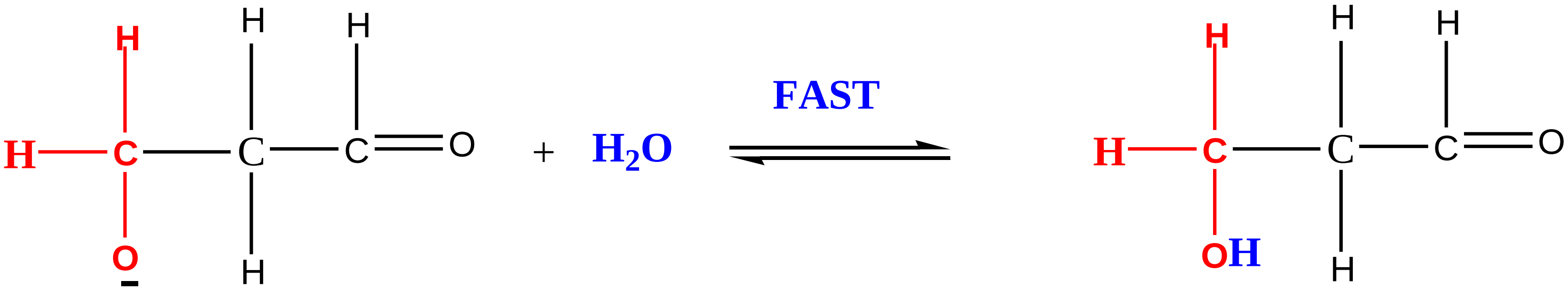


Base abstracts alpha hydrogen

Resonance stabilized carbanion

$+ \; H_2O$


H
H
C
O
FAST
H
H
H
H
C
C
C
O
O
-
H
C
C
O
-
H
H
Anion
Carbanion



Anion

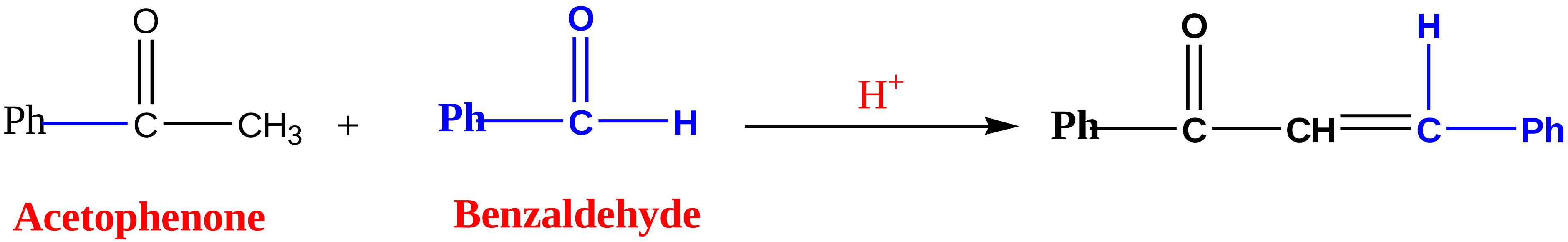
β - hydroxyaldehyde

+ $^{-}$OH

Acid catalyzed aldol condensation

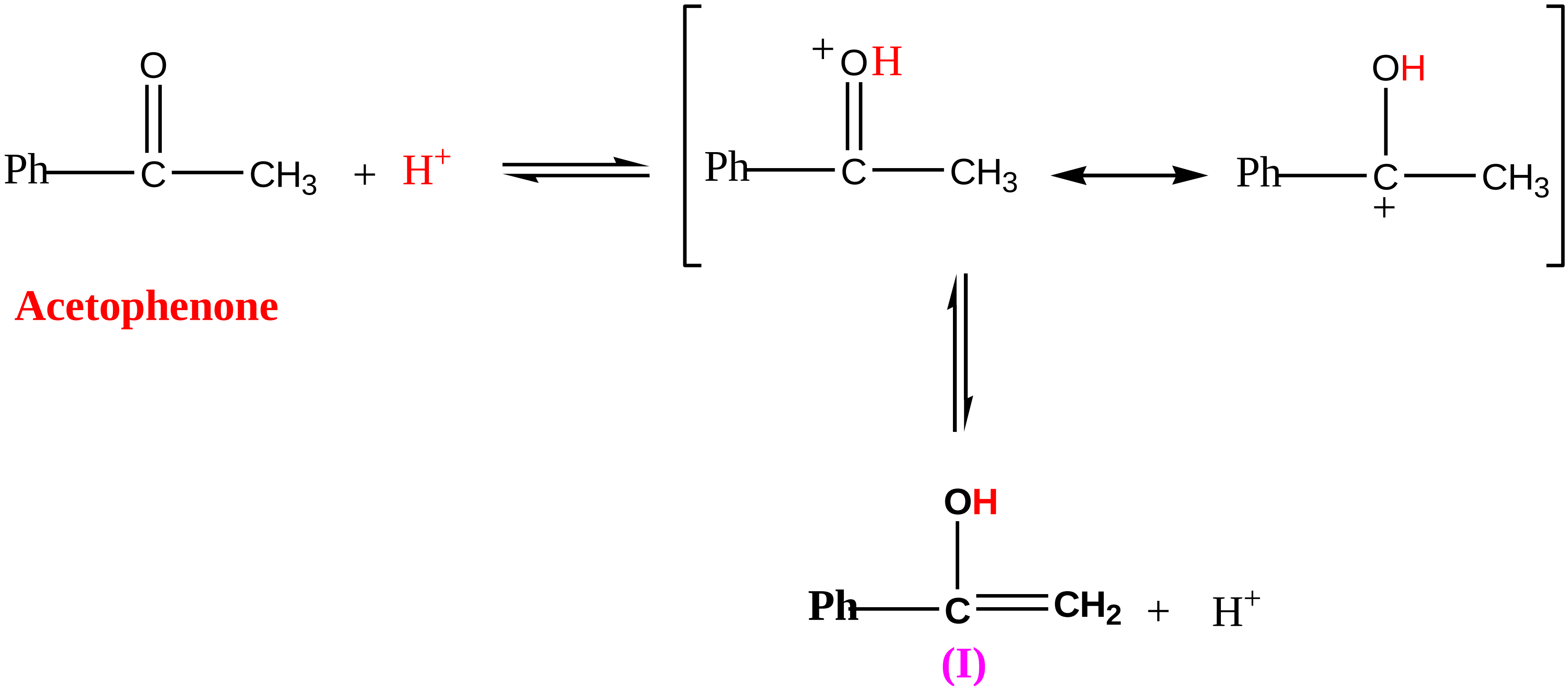
- In such reactions, **aldol** is not final product.
- **α,β-unsaturated aldehyde** or **α,β-unsaturated ketone** is the final product.
- Because **aldol** formed **readily undergo dehydration** in **presence of acid**.

Example: Acid catalyzed aldol condensation



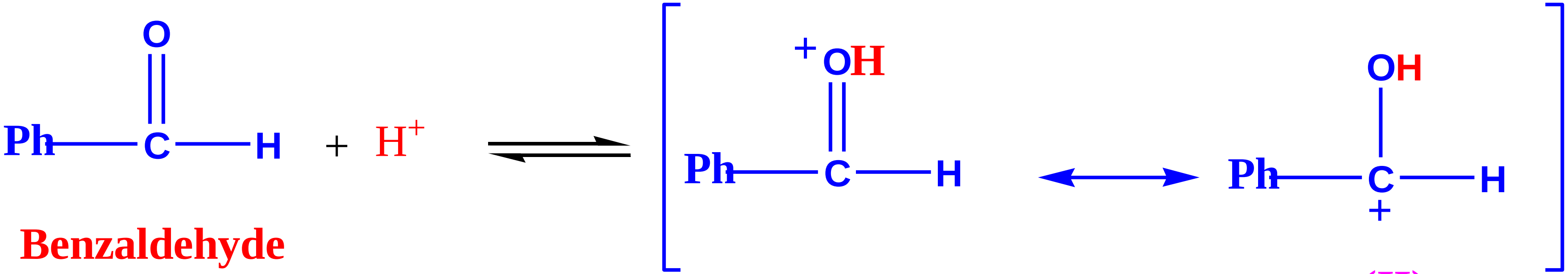
Mechanism of acid catalyzed condensation

(Both **acetophenone** and **Benzaldehyde** get protonated.



Acetophenone

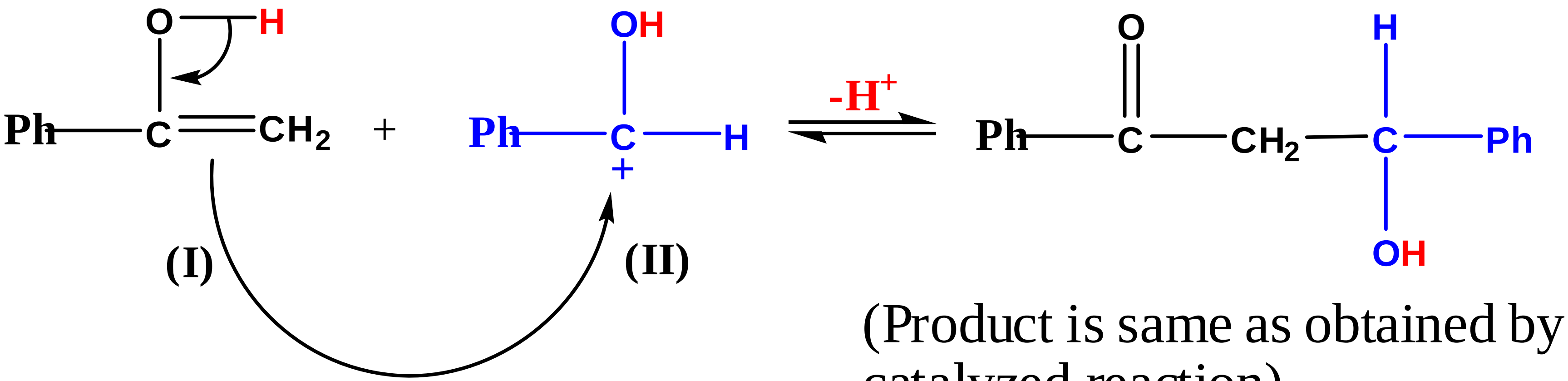
(I)



Benzaldehyde

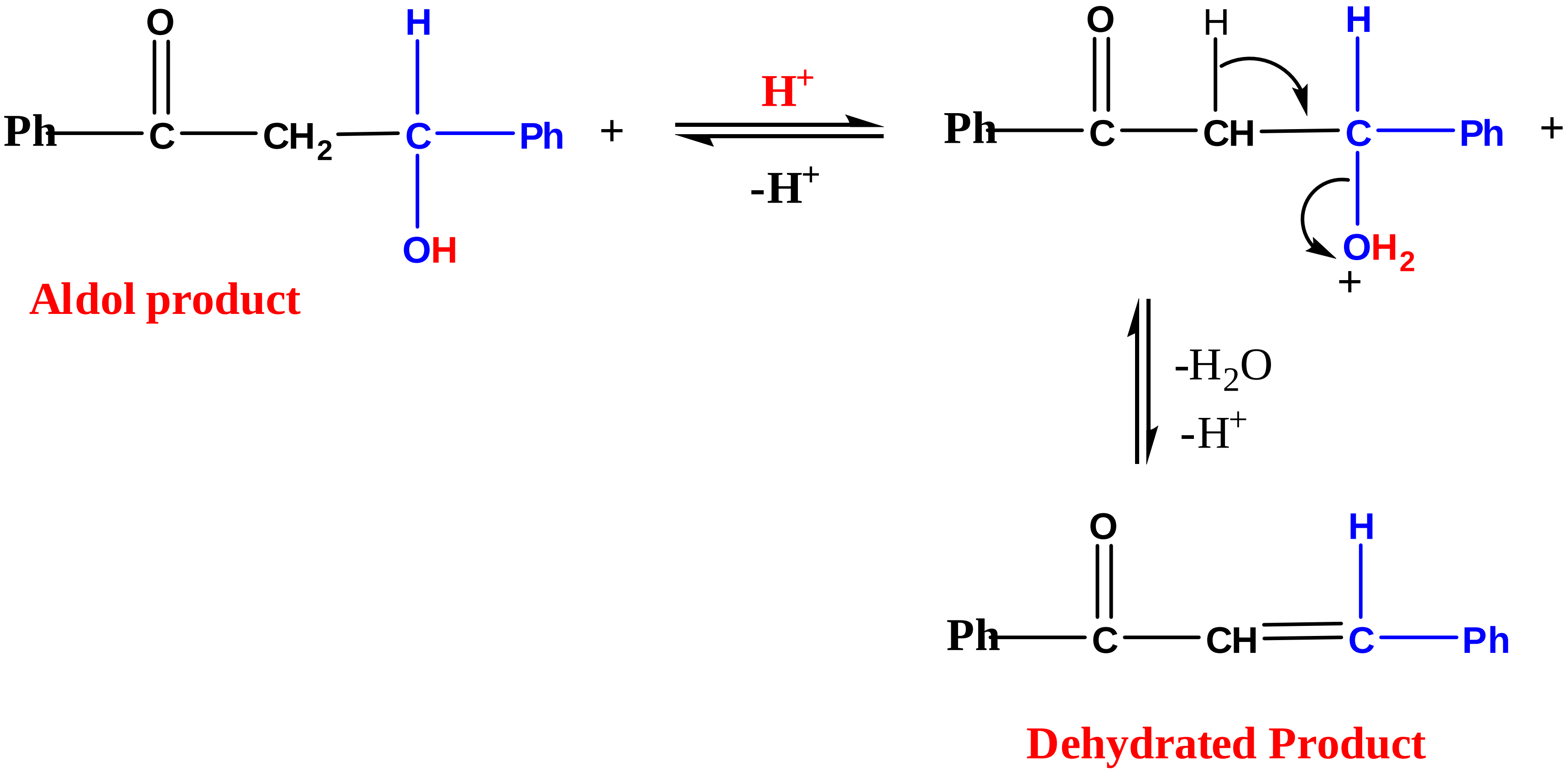
(II)

Attack of enol of acetophenone on carbonyl carbon of Benzaldehyde



(Product is same as obtained by base catalyzed reaction)

Aldol products are usually dehydrated under acidic condition to give dehydrated product



Aldol product

Dehydrated Product

Perkin Condensation

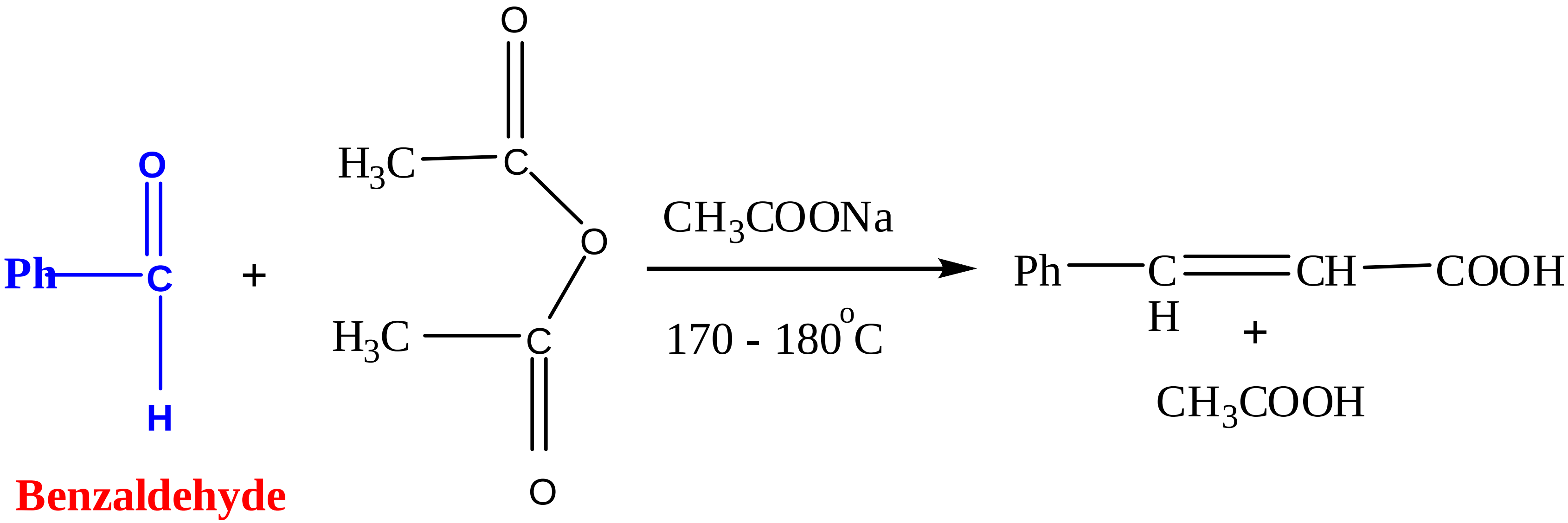
Aromatic aldehyde + **Acid anhydride**

↓ **Salt of carboxylic acid related to anhydride (used as base)**

Cinnamic acid (Product)

(However, other bases like pyridine, quinoline and triethylamine may be used as catalyst)

Example: Perkin condensation between Benzaldehyde and Acetic anhydride.

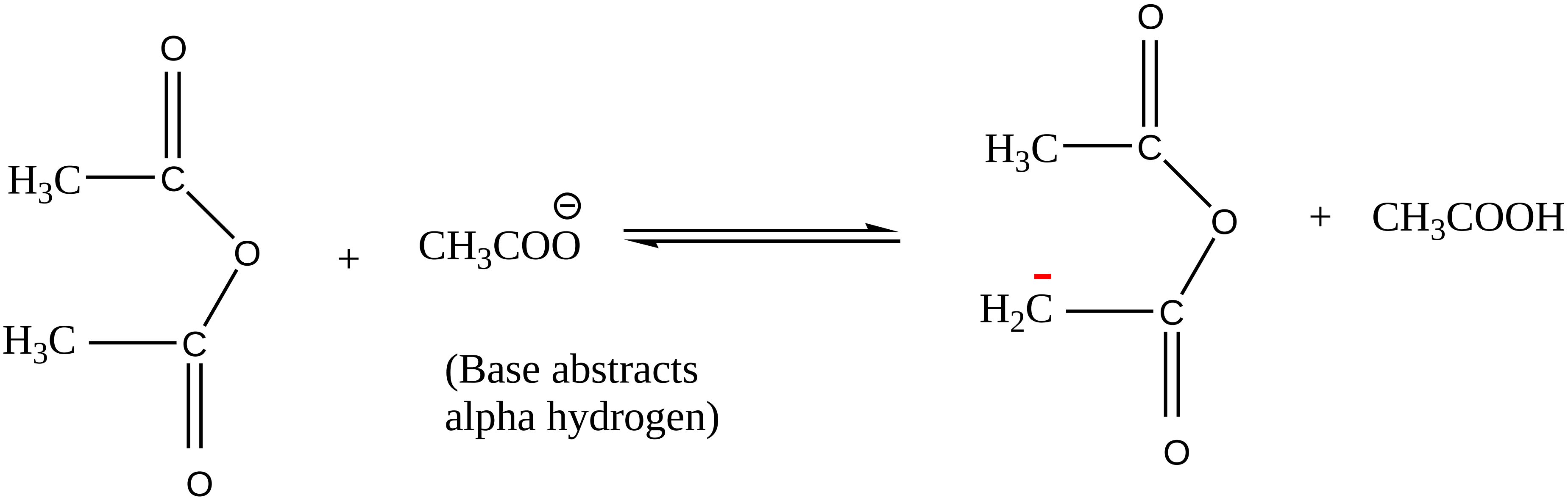


Benzaldehyde

Acetic anhydride

Mechanism:

First step: Generation of Carbanion



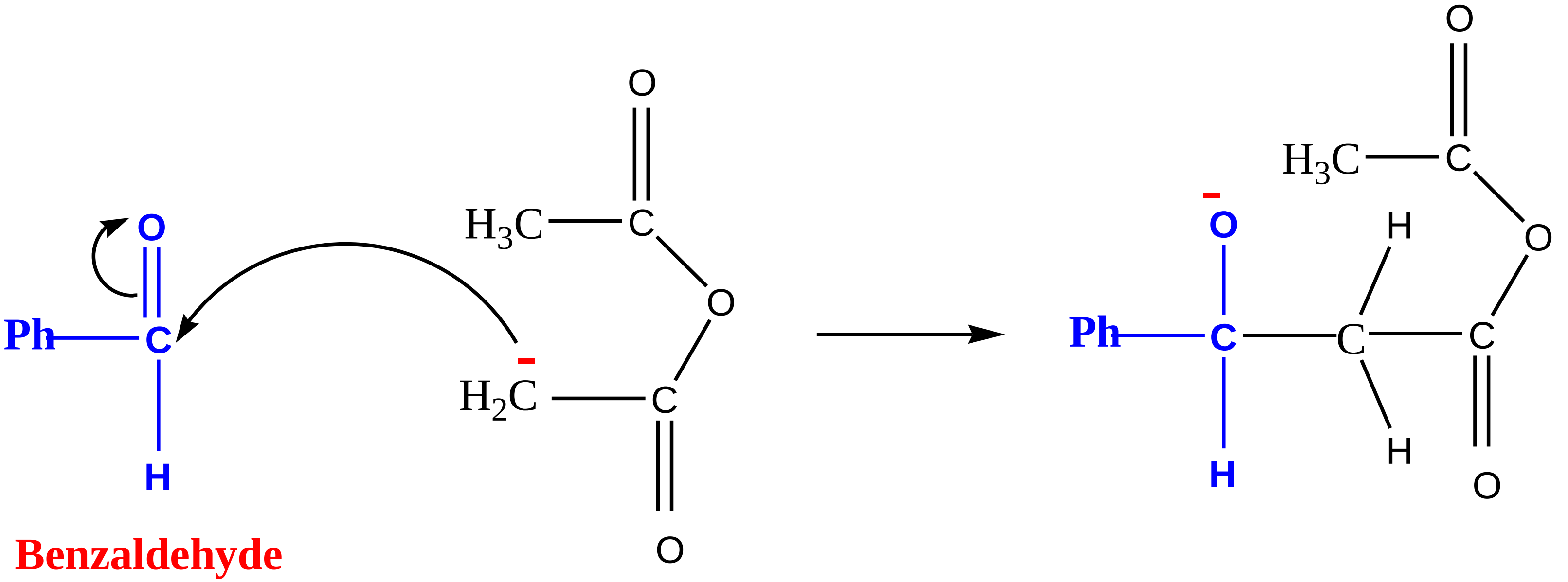
(Base abstracts alpha hydrogen)

Acetic anhydride

(alpha hydrogens)

Carbanion is formed by abstraction of alpha hydrogen

Carbanion attack on carbonyl carbon of benzaldehyde to form an anion.

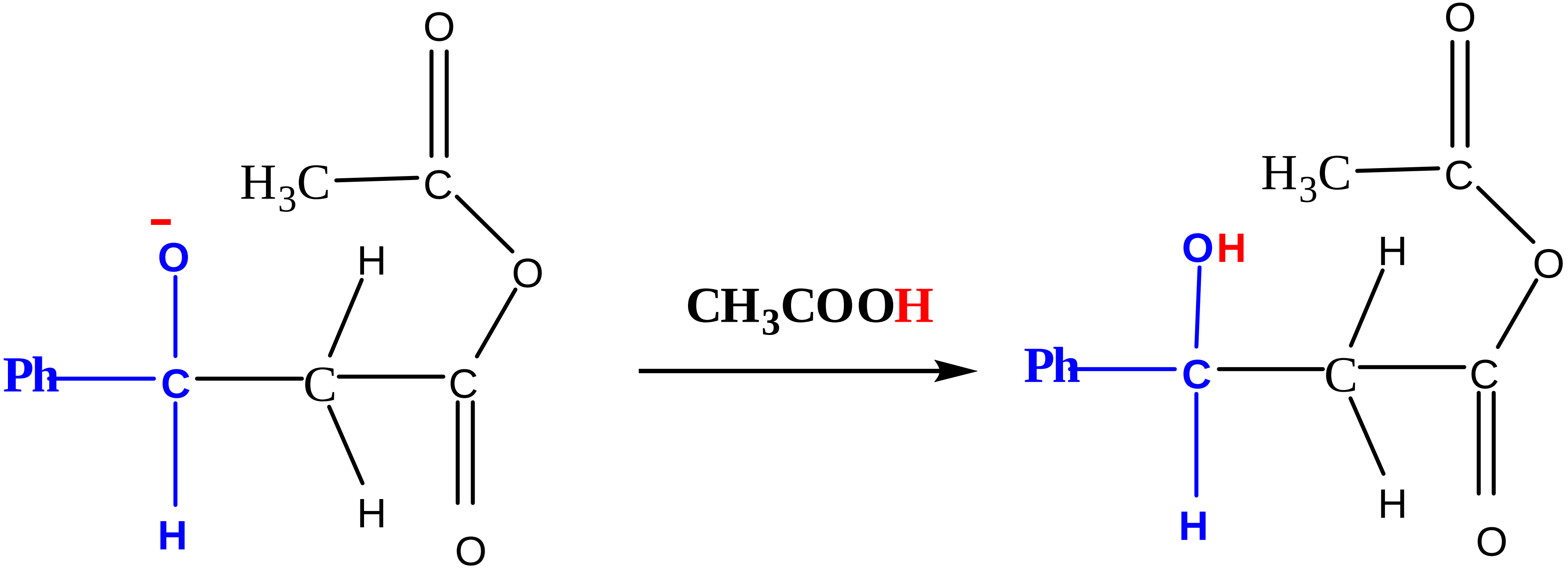


Benzaldehyde

Anion is formed

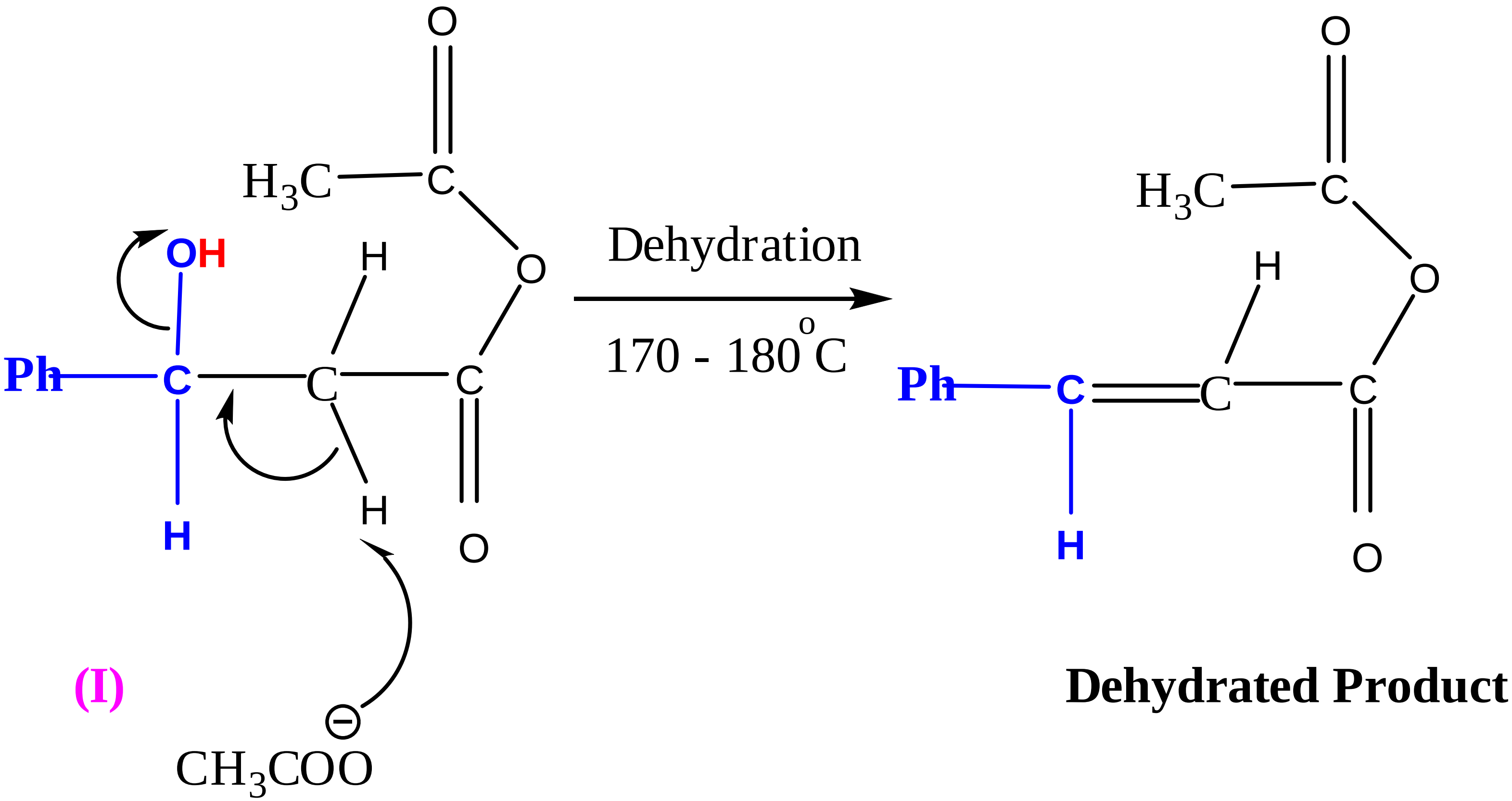
(Carbanion attacks on carbonyl carbon of benzaldehyde)

Next step : Anion so formed takes up proton from acid

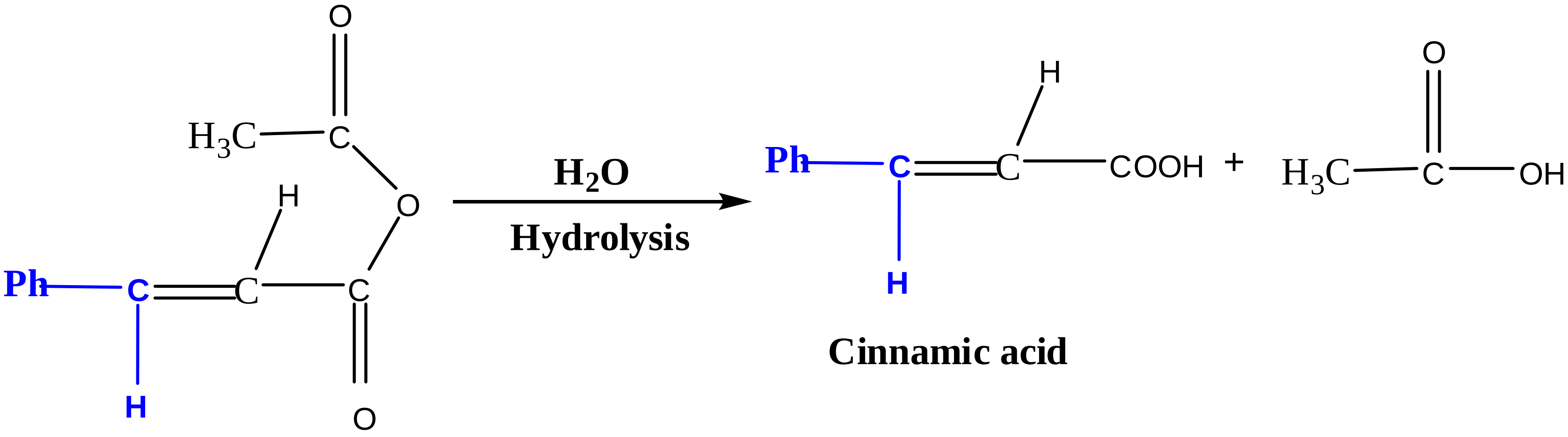


(I)

The product thus formed undergo **dehydration**



Dehydrated product give Cinnamic acid upon **hydrolysis**

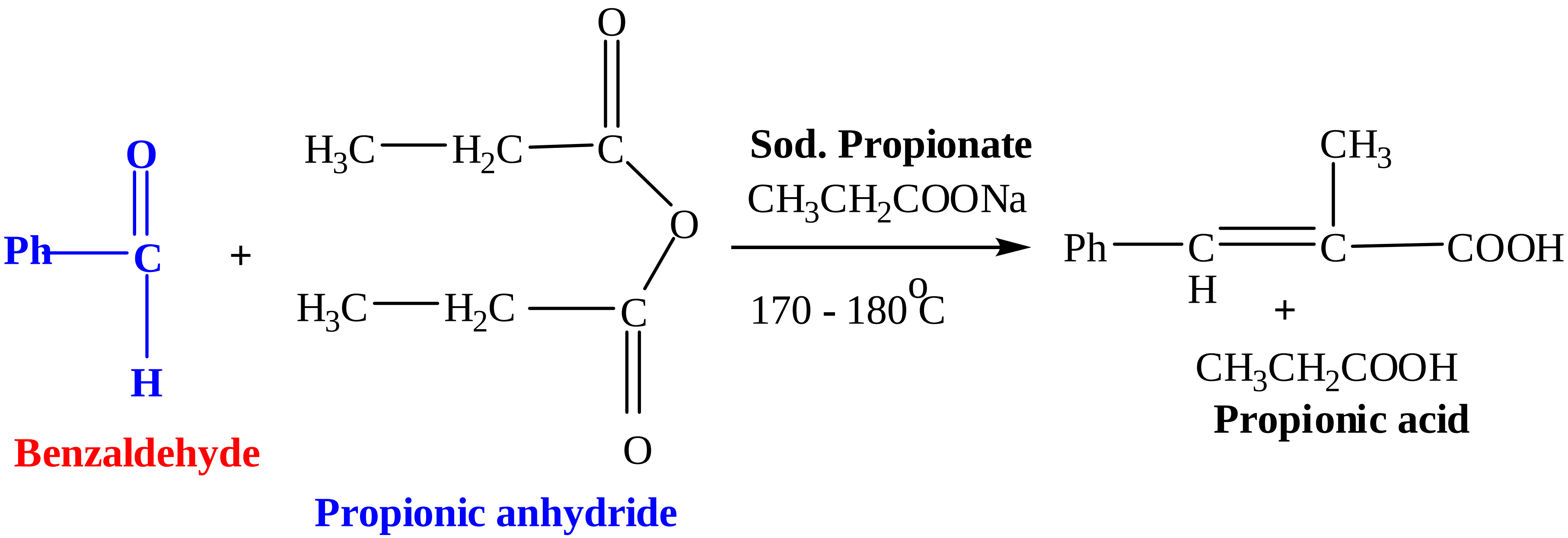


Cinnamic acid

Dehydrated Product

(On pouring the hot mixture in water, the mixed hydride is hydrolyzed)

Another example:



Main features of reaction:

1. **Prolonged heating** is required (5 hours) as **weak base (acetate ion)** has to react with **weak acid (anhydride)**

(The **α-hydrogen of acid anhydride** is **weakly acidic** like those of aldehyde and ketone)

2. Acid anhydride should have at least

two alpha-hydrogens

(necessary for generation of carbanion and dehydration)

When anhydride with **one alpha-hydrogen** is used ,

Then **no dehydration is possible** and **aldol type product is isolated.**

Benzoin condensation

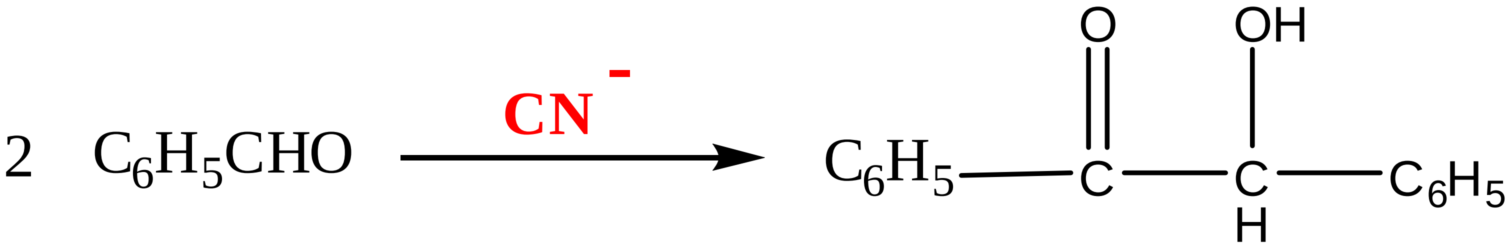
(Self condensation of aromatic aldehyde in presence of CN^-)

Dimerization of two aromatic aldehydes in presence of **cyanide ion**.

Aromatic aldehydes in presence of **cyanide ion** undergo **self condensation** to form **α-hydroxyketone**

Product = **α-hydroxyketone** (Commonly known as **Benzoin**)

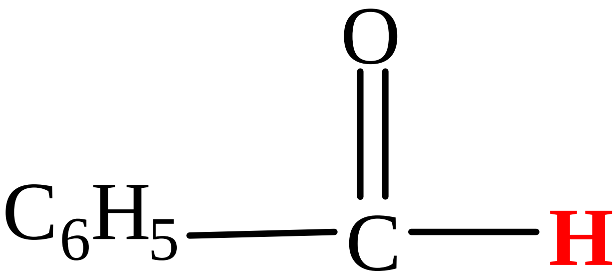
Reaction



$$2\ C_6H_5CHO \xrightarrow{CN^-} C_6H_5-\overset{O}{\overset{\|}{C}}-\underset{H}{\overset{OH}{\overset{|}{C}}}-C_6H_5$$

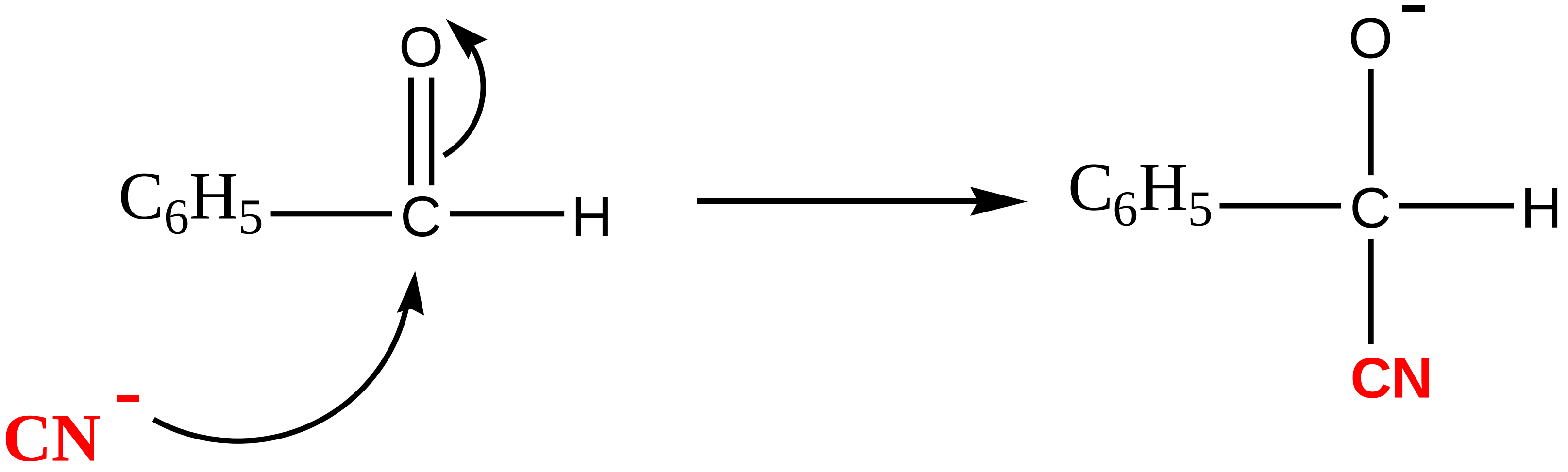
Benzoin

Hydrogen atom attached to Carbonyl group is **not acidic enough** to be removed easily by **Cyanide ion**.

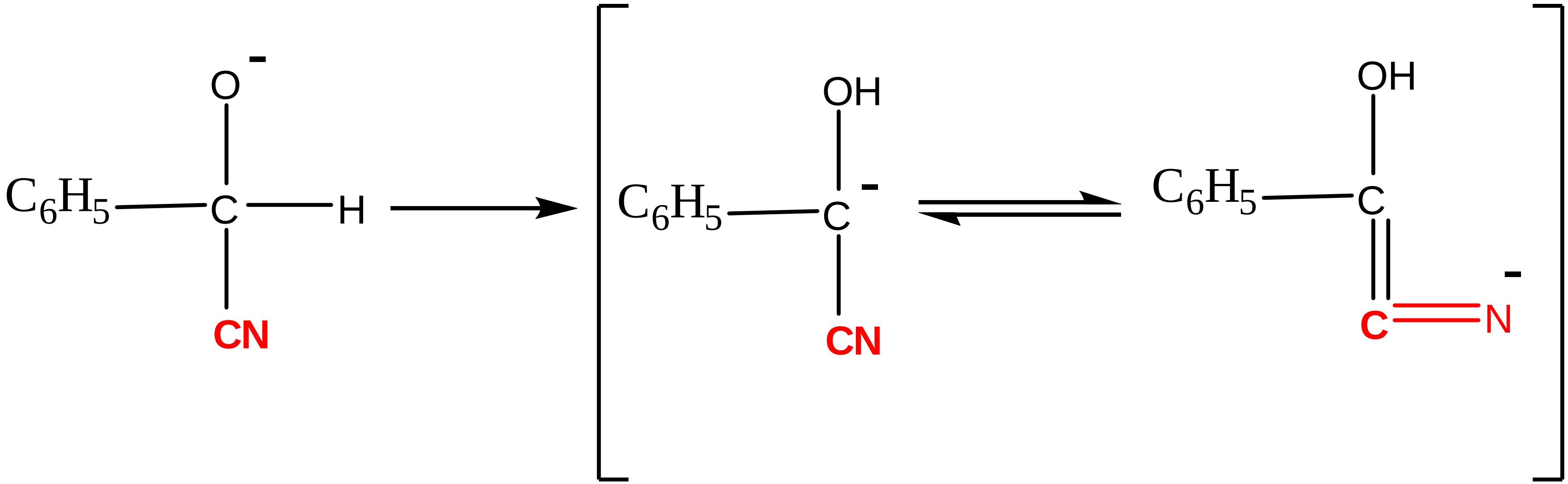


$$C_6H_5-\overset{\overset{\displaystyle O}{\|}}{C}-H$$

After attack of Cyanide ion at carbonyl carbon, its (hydrogen) position becomes **alpha to CN group** and becomes relatively **more acidic.**

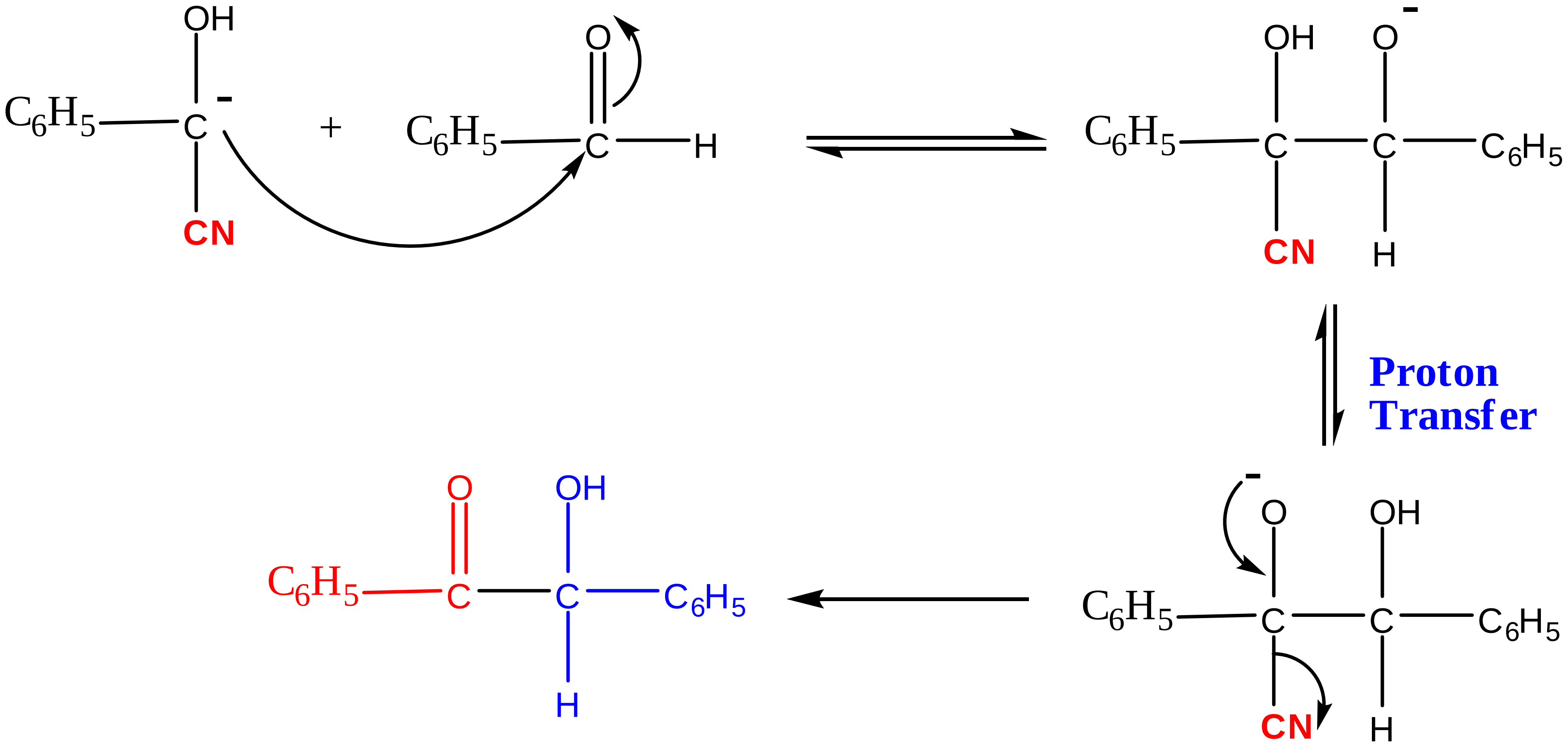


Proton transfer to Oxygen



The driving force for this proton tranfer is formation of resonance stabilized carbanion

Carbanion thus formed attack on **second molecule** of Benzaldehyde



Benzoin condensation is not catalyzed by Hydroxide ion or bases in general, but specifically catalyzed by Cyanide ion

Reasons:

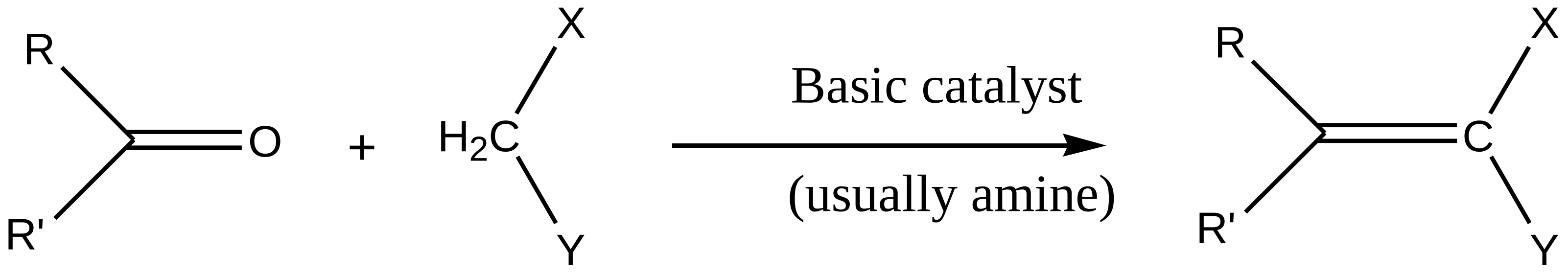
1. Its capability to stabilize the carbanion.

2. Its good nucleophilicity.

3. It departs very easily in the last step to give product.

Knoevenagel Condensation

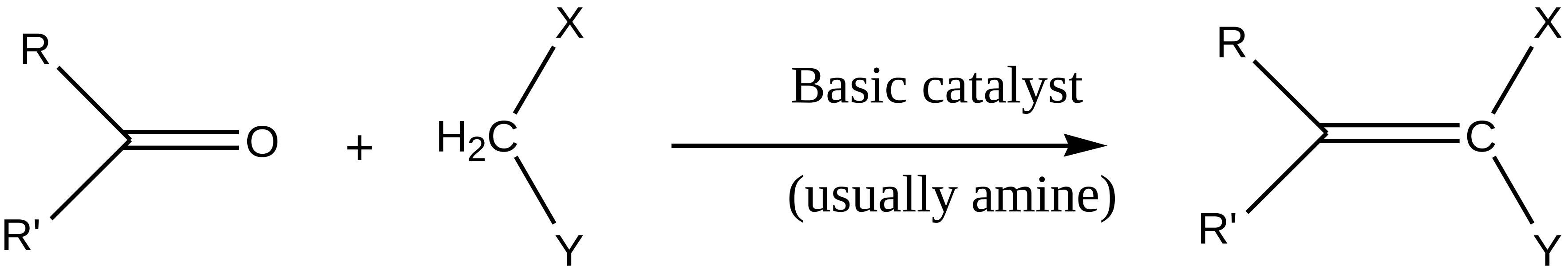
Aldehyde / Ketone **(aliphatic or aromatic)** + Compound having active methylene group $\xrightarrow[\textbf{usually amine}]{\textbf{Base}}$ α,β - unsaturated product



X and Y are activating groups

e.g. $COCH_3$, $COOC_2H_5$, CN , NO_2

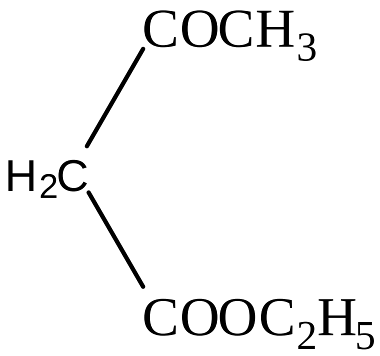
Reaction:



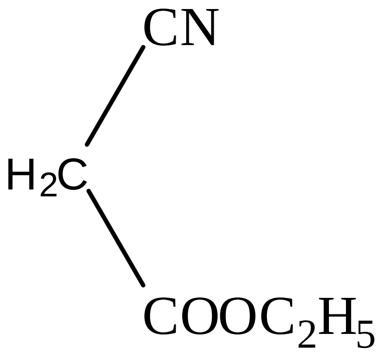
X and Y are activating groups

e.g. $COCH_3$, $COOC_2H_5$, CN , NO_2

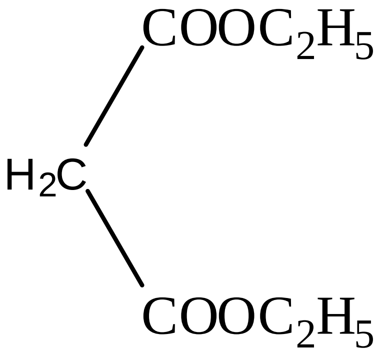
Examples of compounds containing active methylene group



Ethyl acetoacetate

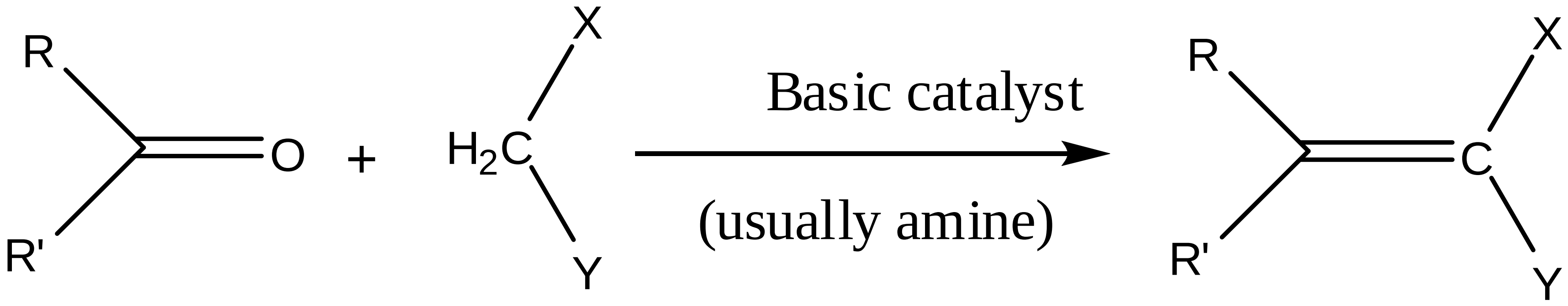


Ethyl cyanoacetate

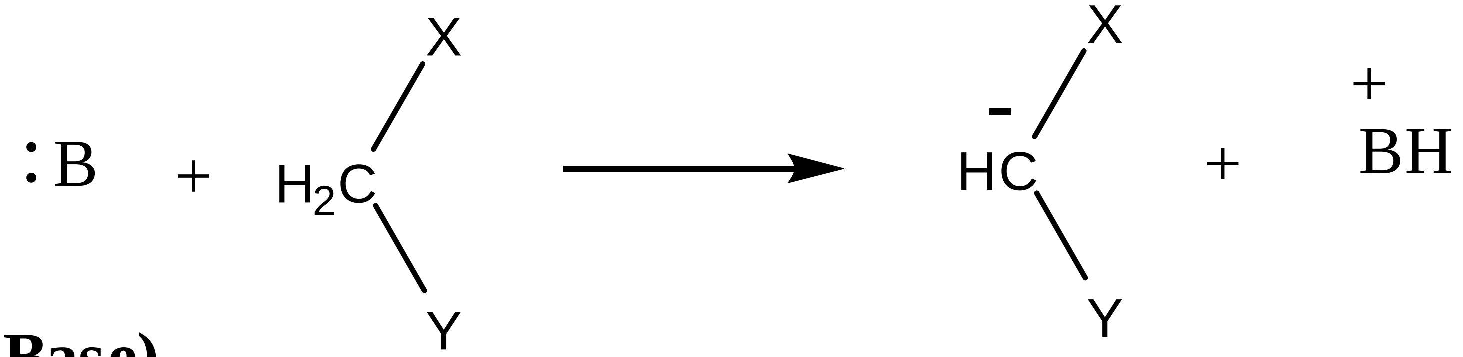


Malonoic ester

Mechanism of Reaction



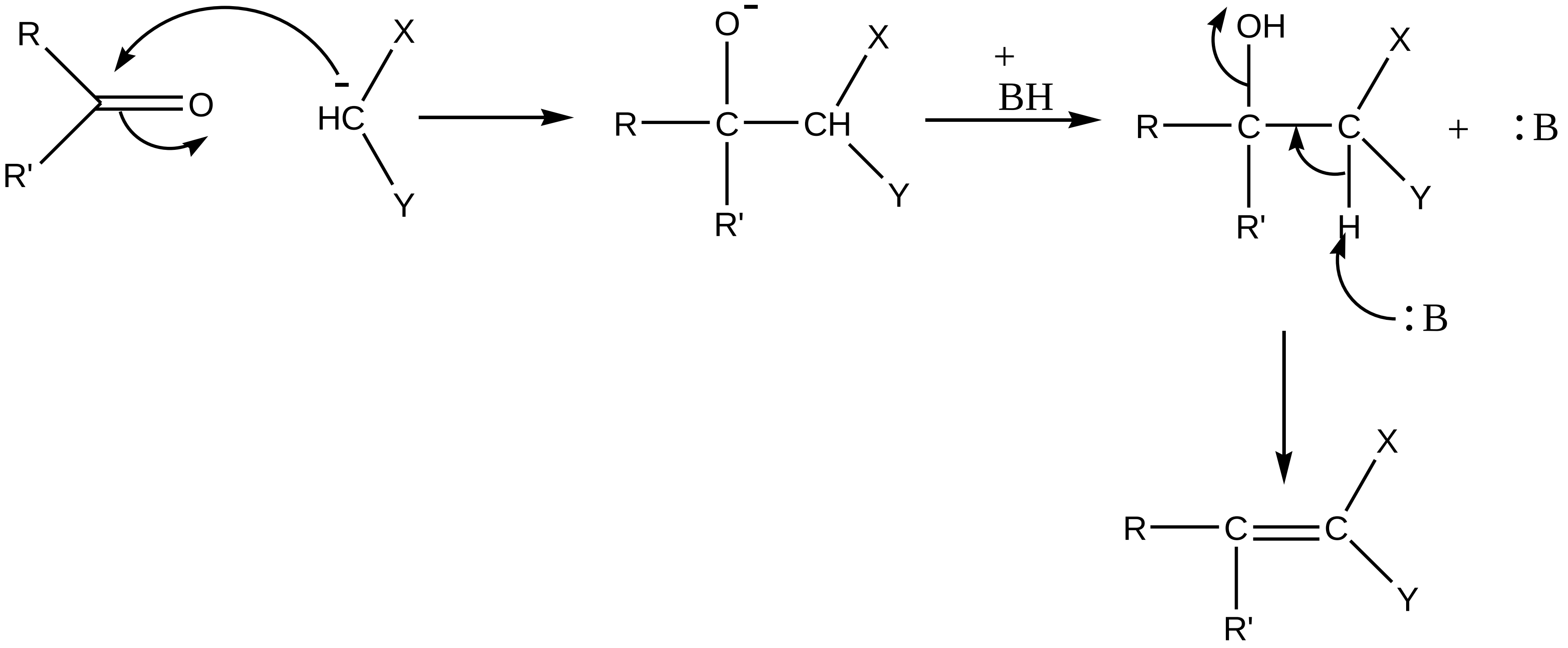
Mechanism: 1st step



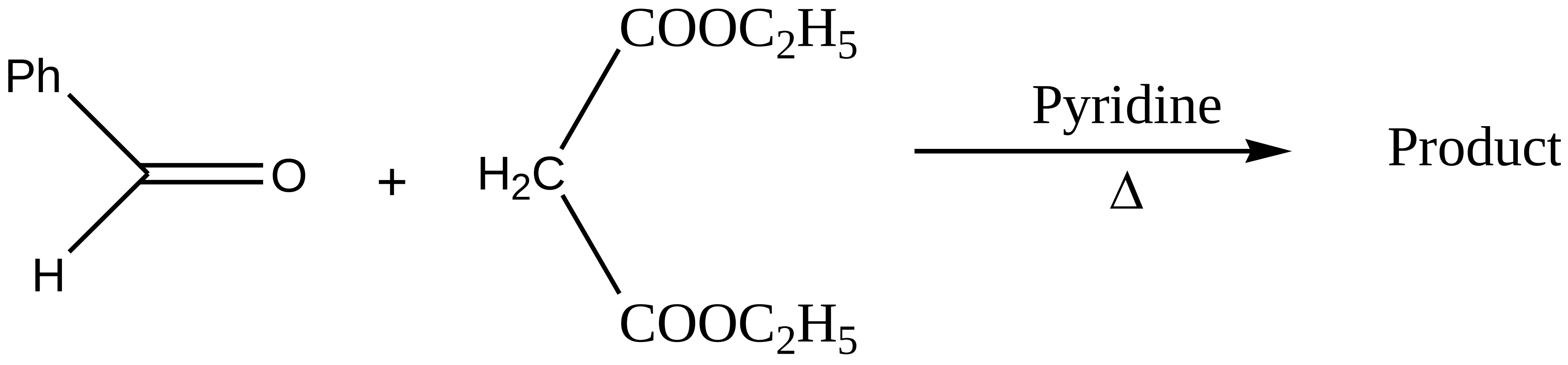
(Base)

Carbanion

(resonanace stabilized)



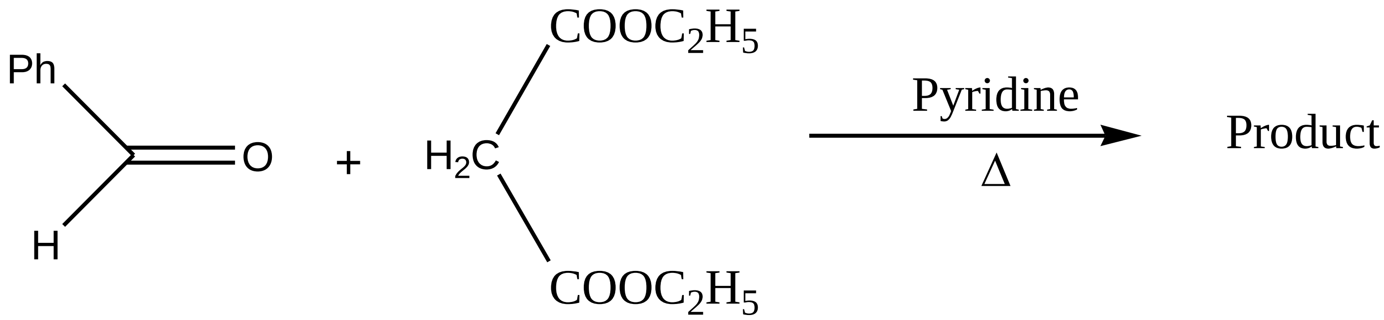
α, β - unsaturated compound



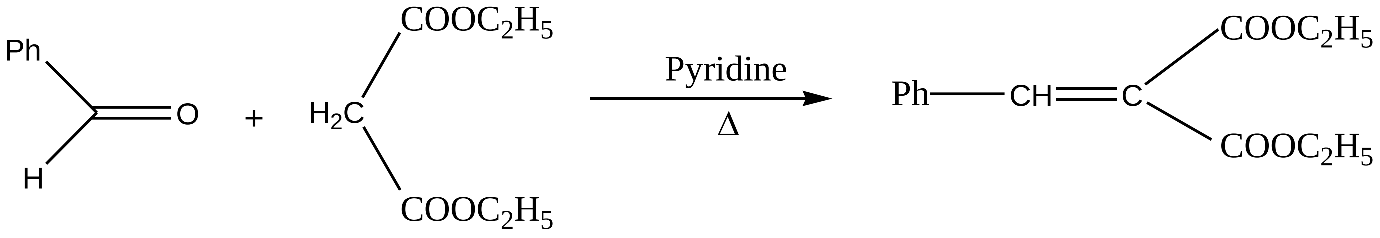
Benzaldehyde

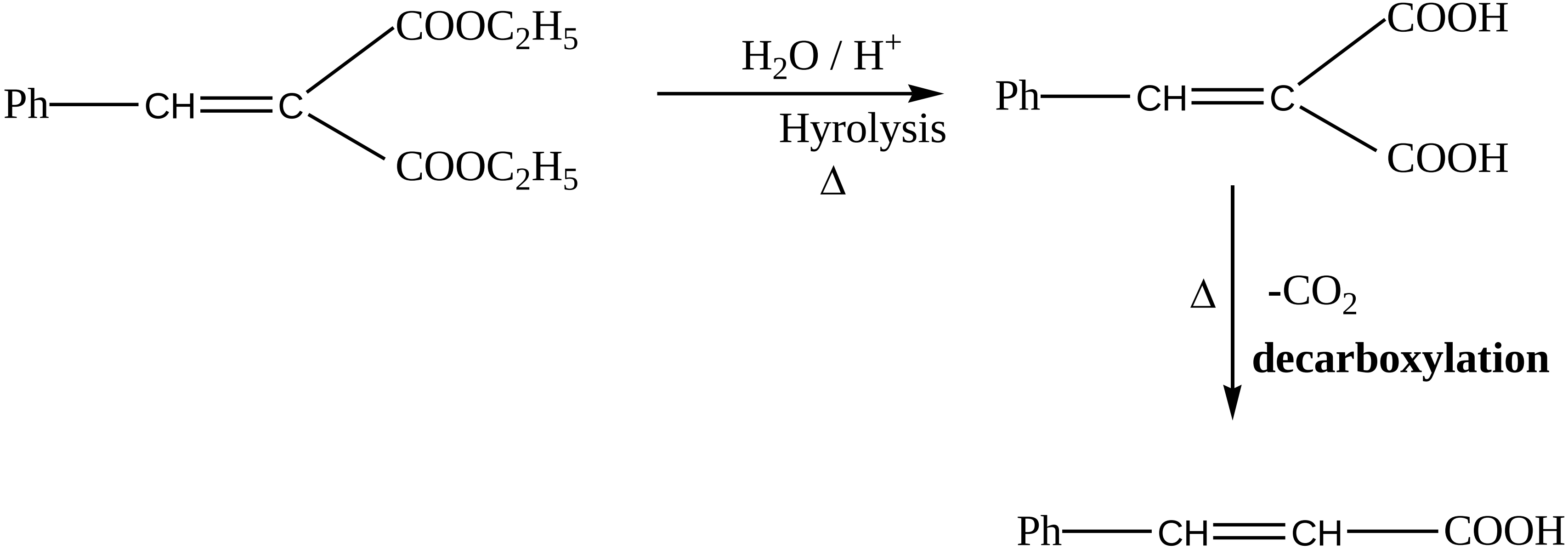
Malonoic ester

Example:

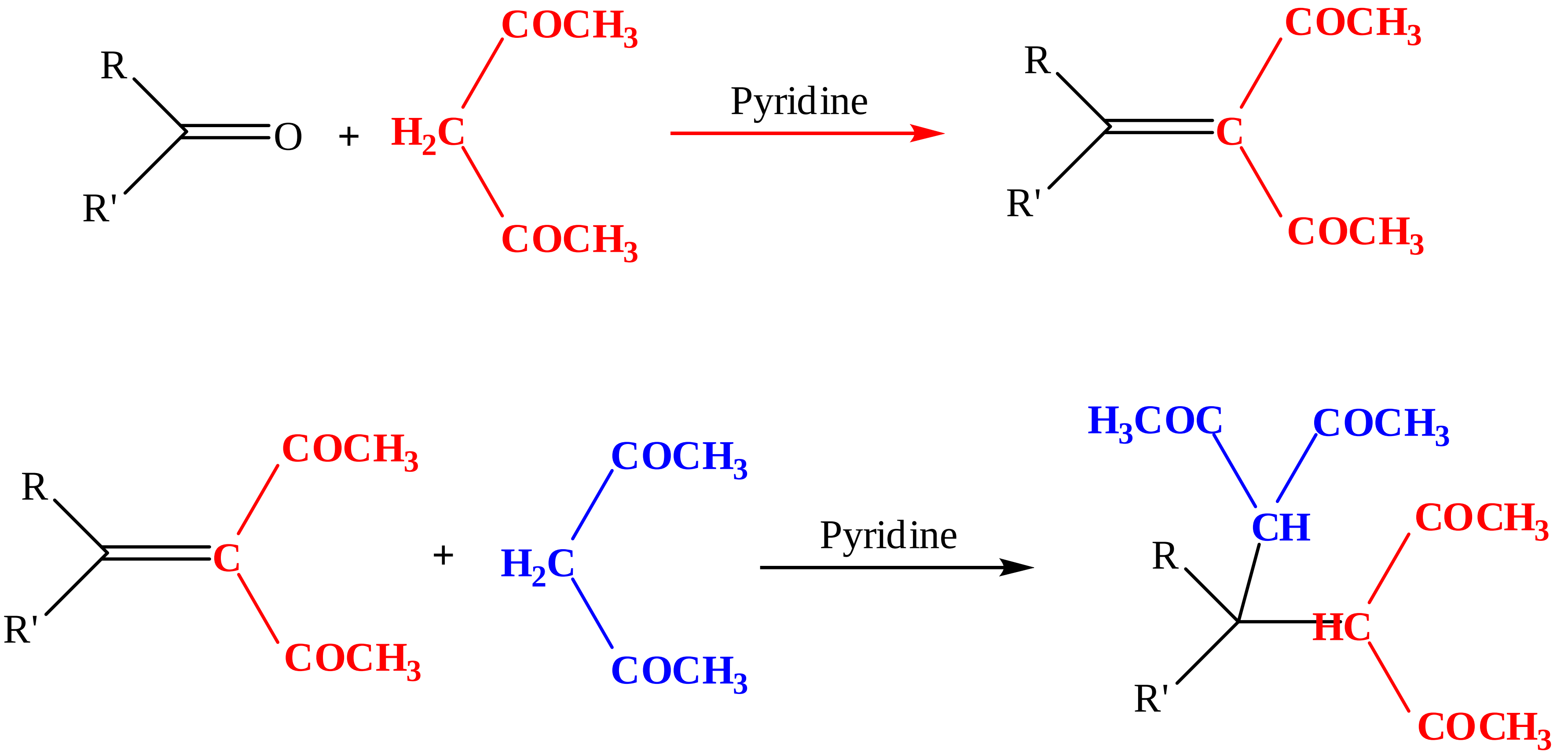


Application of this reaction to form Cinnamic acid




Ph
CH
C
COOC2H5
COOC2H5
H2O / H+
Hyrolysis
Δ
Ph
CH
C
COOH
COOH
Δ
-CO2
decarboxylation
Ph
CH
CH
COOH

Knoevenagel Condensation sometimes may be followed by Michael addition reaction.



Addition of **Organozinc compound** to carbonyl carbon of aldehyde and ketone

(Reformatsky Reaction)

Reaction of α-bromoester with an aldehyde or ketone

in presence of Zn metal

to give β-hydroxy ester is called Reformatsky reaction.

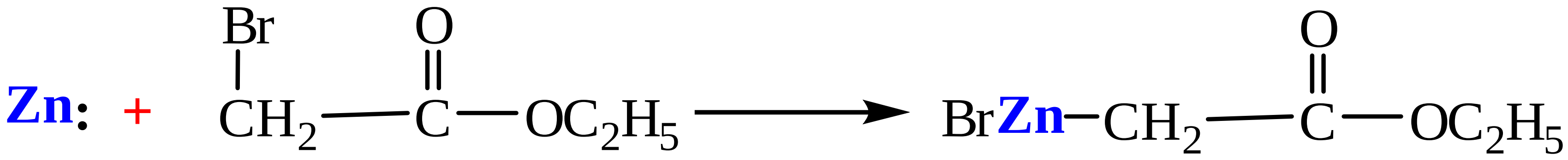
Reformatsky reaction

Zinc + **alpha**-haloester $\longrightarrow$ Organozinc intermediate

Organozinc intermediate + Carbonyl compound $\longrightarrow$ β- hydroxy ester

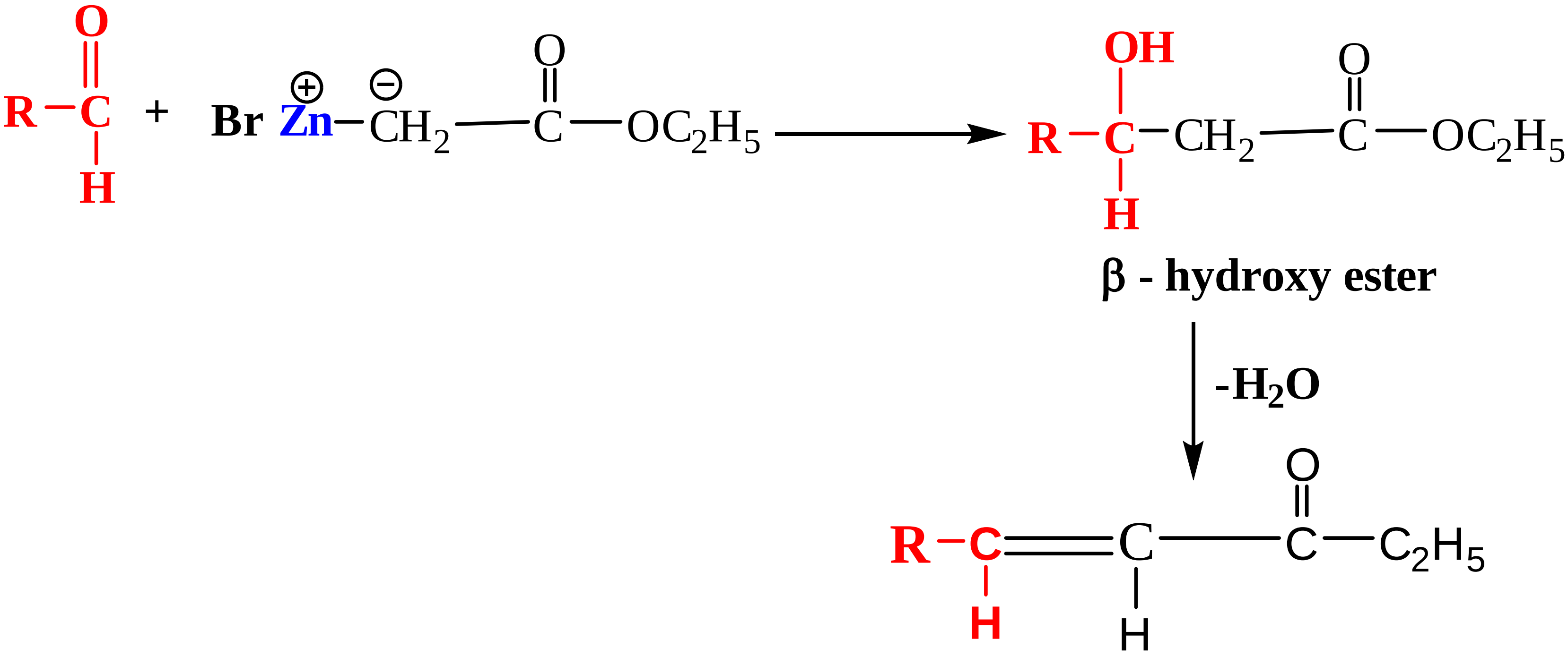
β- hydroxy ester $\xrightarrow[\mathbf{-\ H_2O}]{}$ α , β -unsaturated ester

Mechanism



$$\mathrm{Zn}\!: + \overset{\mathrm{Br}}{\overset{|}{\mathrm{CH_2}}}-\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-\mathrm{OC_2H_5} \longrightarrow \mathrm{BrZn}-\mathrm{CH_2}-\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-\mathrm{OC_2H_5}$$

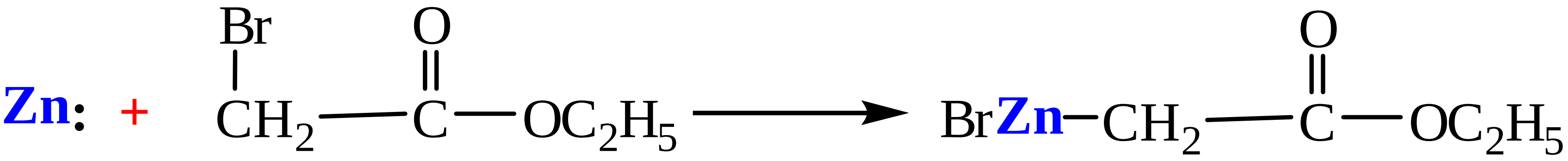
Reaction



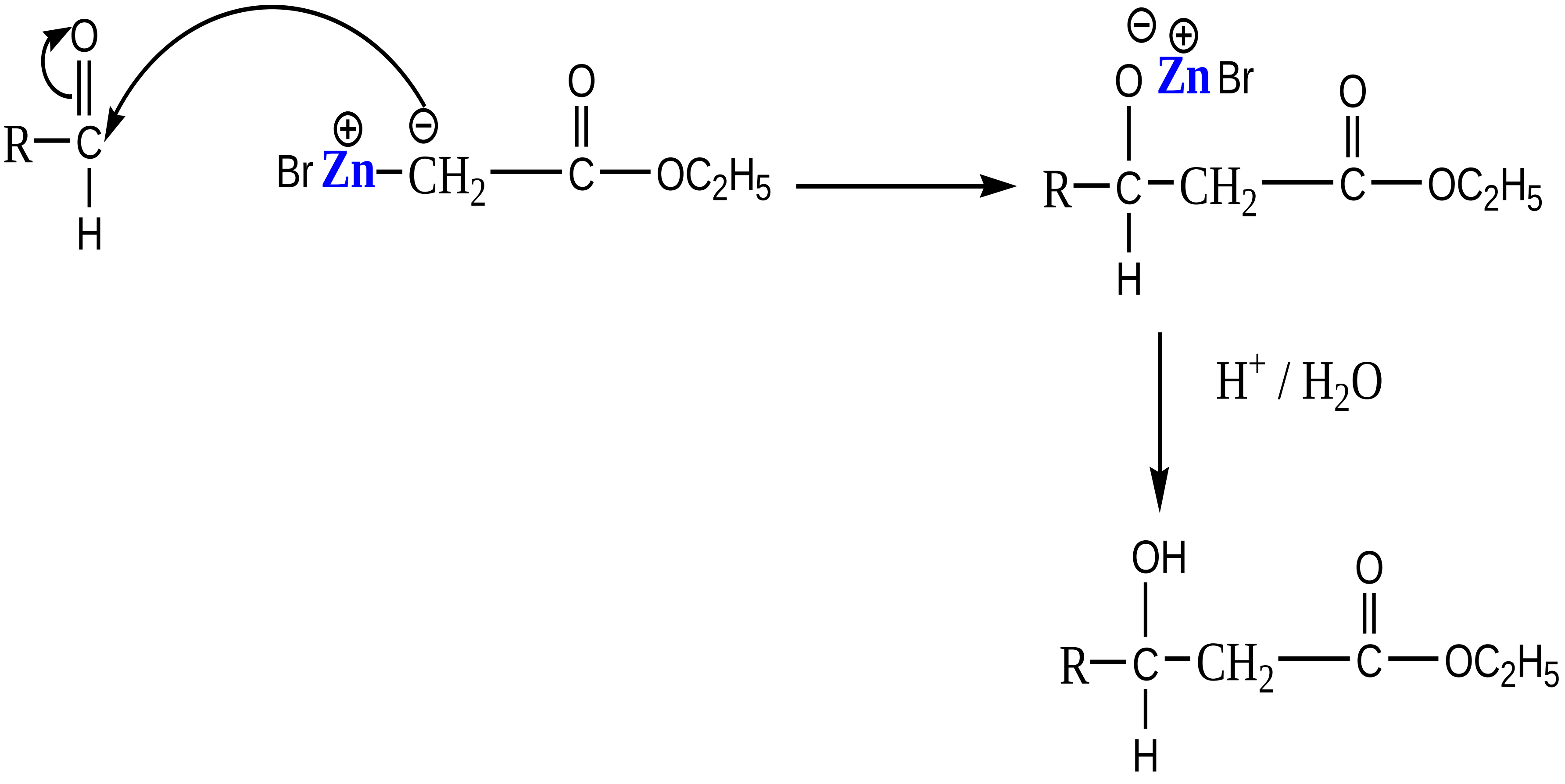
β - hydroxy ester

α , β -unsaturated ester

Mechanism of Reaction



$$\text{Zn:} + \underset{\text{CH}_2}{\overset{\text{Br}}{|}} - \overset{\overset{\text{O}}{\|}}{\text{C}} - \text{OC}_2\text{H}_5 \longrightarrow \text{BrZn} - \text{CH}_2 - \overset{\overset{\text{O}}{\|}}{\text{C}} - \text{OC}_2\text{H}_5$$



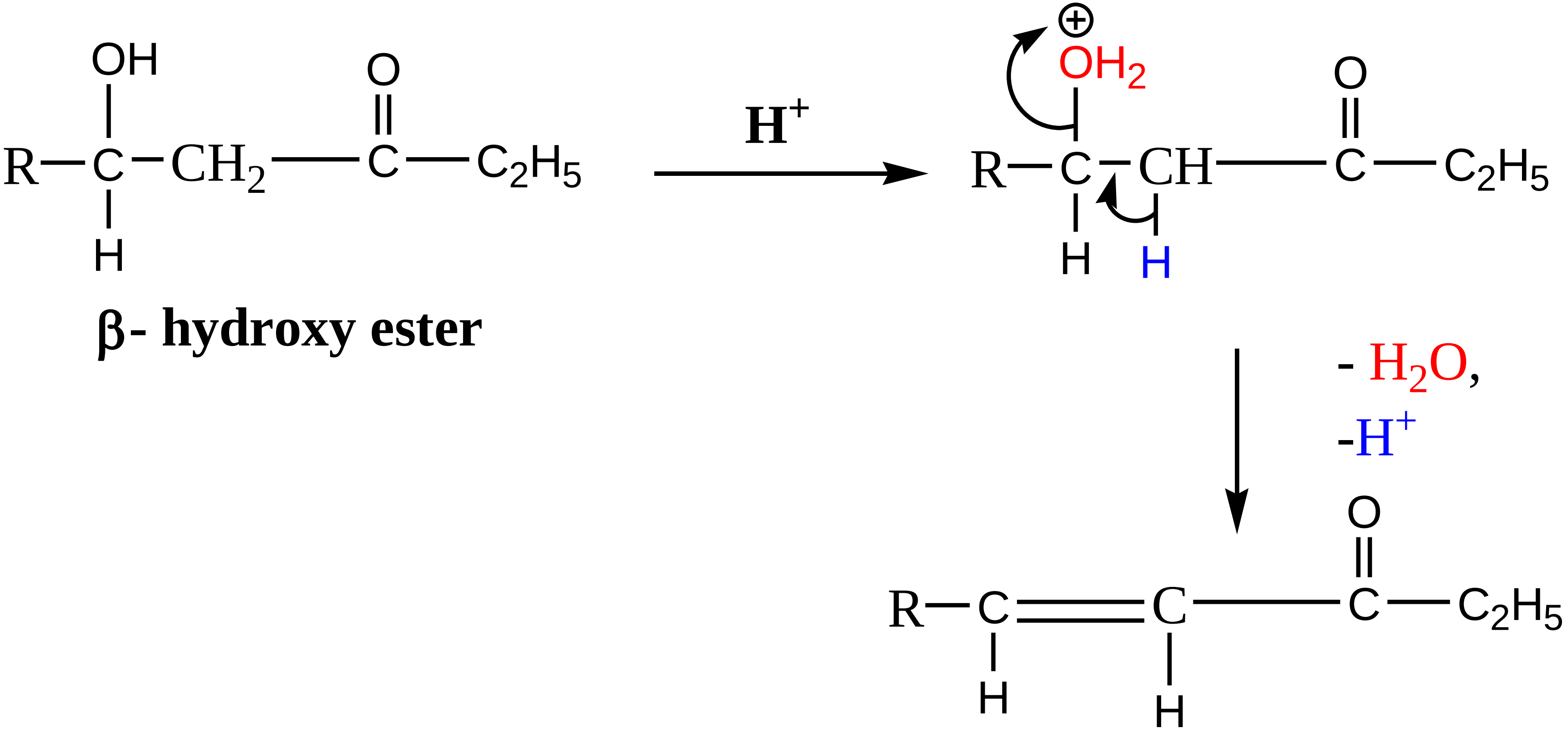
β- hydroxy ester

Next step - Dehydration

β-hydroxy ester is the product,

which undergo **acid catalyzed dehydration** to

give **α,β–unsaturated ester**



β- hydroxy ester

α , β -unsaturated ester

Drawback of Reformatsky reaction

Side product may be formed.

Side product = β- ketoester

Self condensation of α- haloester give = β- ketoester

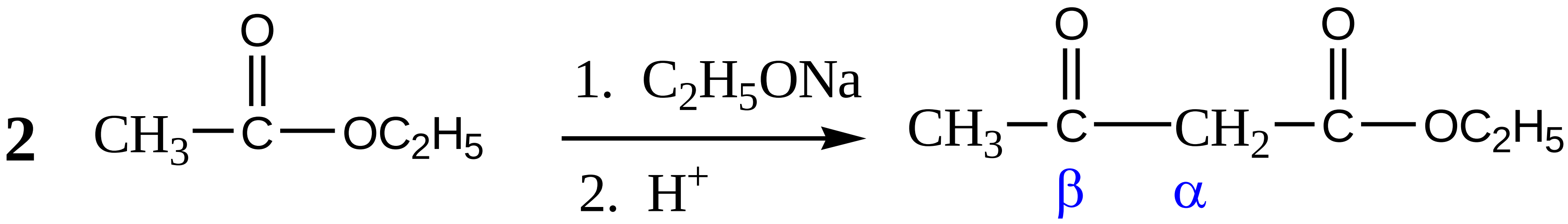
This side reaction occurs in case of sterically hindered ketone; as in such cases organozinc intermediate **reacts perforce** with its own ester group **rather than hindered keto group** and give product **β- ketoester.**

Therefore, Reformatsky reaction best proceeds with aldehydes, methyl ketones and cyclic ketones.

Claisen condensation: The synthesis of β-keto ester

Esters having α-hydrogen on treatment with strong base (e.g. C_2H_5ONa) undergo **self condensation**

Product = **β – ketoester**



$$2\ CH_3-\overset{\overset{O}{\|}}{C}-OC_2H_5 \xrightarrow[2.\ H^+]{1.\ C_2H_5ONa} CH_3-\overset{\overset{O}{\|}}{C}-CH_2-\overset{\overset{O}{\|}}{C}-OC_2H_5$$

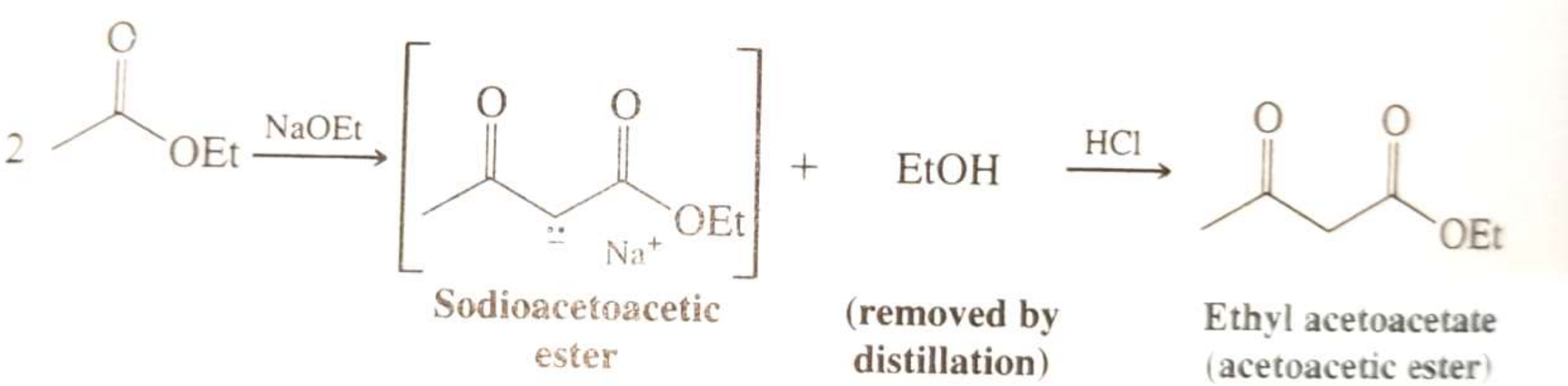
Ethyl acetate

(ester having alpha-hydrogen)

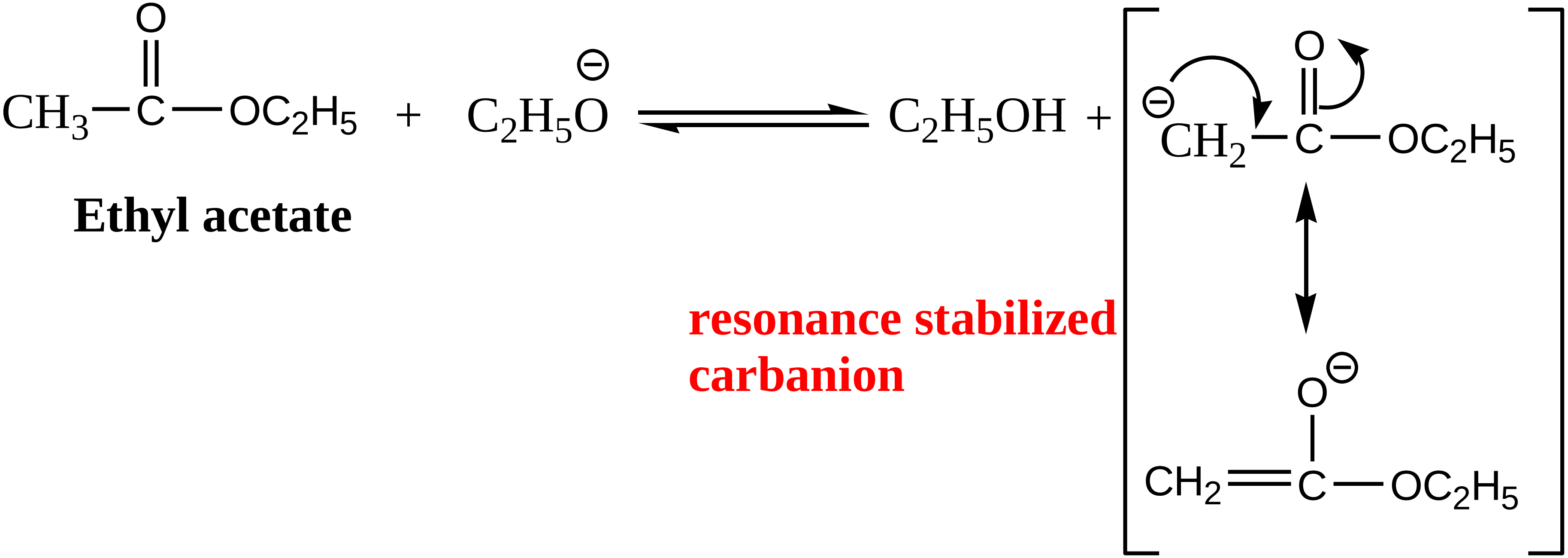
ethyl acetoacetate

β -Ketoester

- When **ethyl acetate** reacts with **sodium ethoxide**, it undergoes a **condensation reaction**.
- **After acidification**, the product formed is a **β-keto ester i.e. Ethylacetoacetate** (commonly called as **acetoacetic ester**)



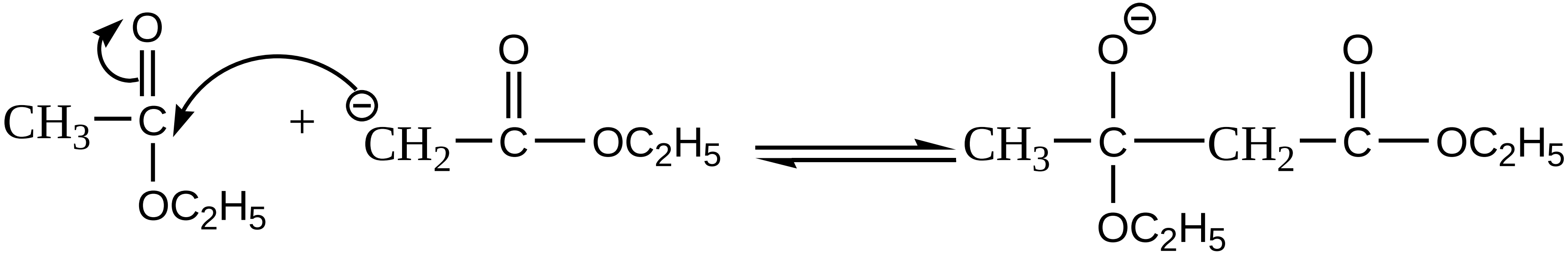
Mechanism

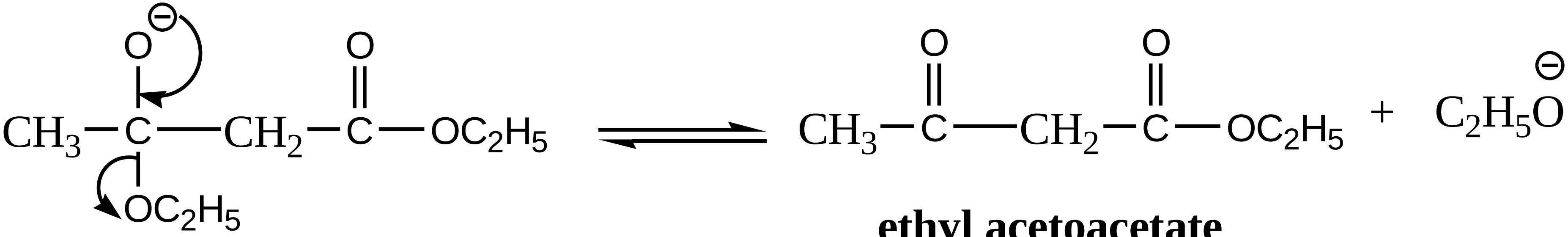


Ethyl acetate

resonance stabilized carbanion

Attack of carbanion on 2nd molecule of ester





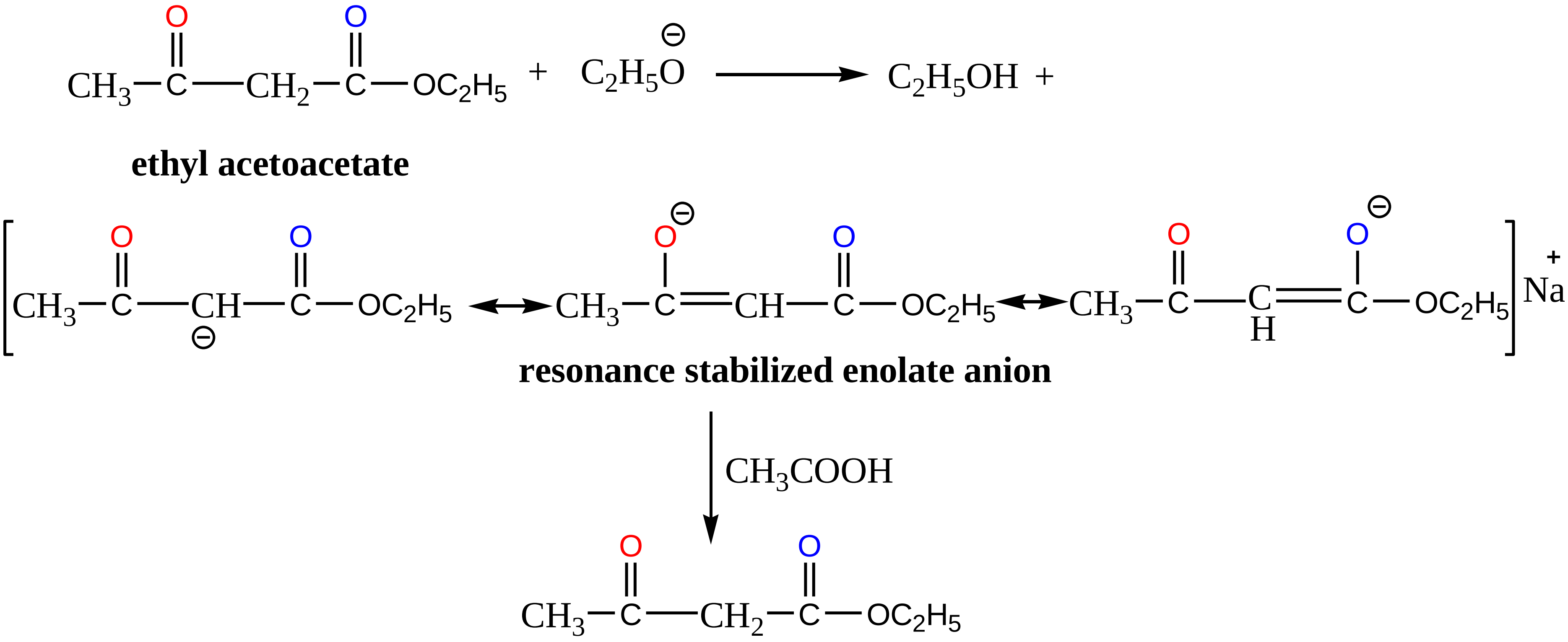
ethyl acetoacetate

Shifting of equilibrium in forward direction

- Here all the **three steps are in equilibrium state.**

- Hence **excess of sodium ethoxide** is used to force the equilibrium **to shift in forward direction** **through formation of** **enolate anion**(by abstraction of 2nd α-hydrogen) in fourth step.

Fourth step: formation of enolate anion (stable) which favours the equilibrium in forward direction



$CH_3-CO-CH_2-CO-OC_2H_5 + C_2H_5O^{\ominus} \longrightarrow C_2H_5OH +$

ethyl acetoacetate

resonance stabilized enolate anion

Na^+

CH_3COOH

$CH_3-CO-CH_2-CO-OC_2H_5$

So for the success of **Claisen condensation** **two α-hydrogens** are necessary.

Otherwise **enolate ion in fourth step will not be formed.**

If this enolate anion is not formed, **then equilibrium will not be shifted in forward direction and**

reaction will not succeed.

Crossed Claisen condensation

Claisen condensation between **two different esters** **(both having α-hydrogen)**

= **4 different products** (β- ketoester) are formed.

This reaction is of **little synthetic importance**.

However, If **One ester** is **without α-hydrogen**

(Example: **ester of** HCOOH, Oxalic acid, Benzoic acid)

(taken in excess)

+

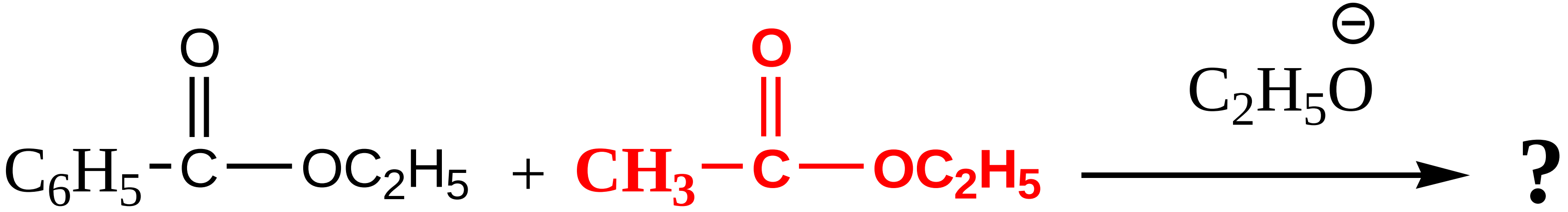
2nd ester is **with α-hydrogen**

(added slowly to ester without α-hydrogen)

↓

Single Product is obtained

Example: (ethyl benzoate in excess (no α-H) + ethyl acetate)

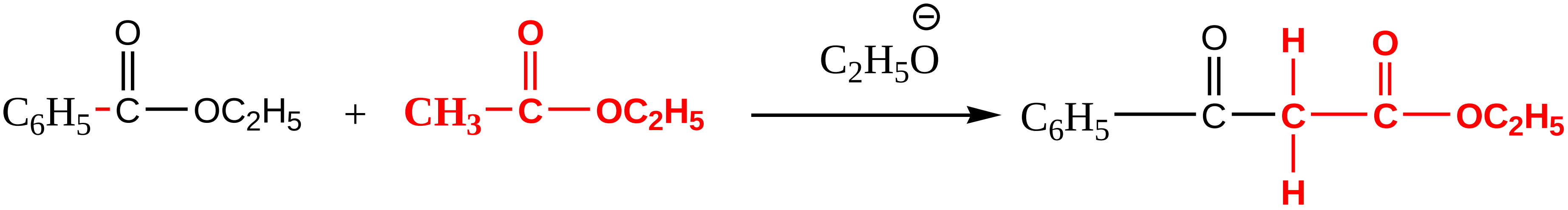


$$C_6H_5-\overset{\overset{O}{\|}}{C}-OC_2H_5 + CH_3-\overset{\overset{O}{\|}}{C}-OC_2H_5 \xrightarrow{C_2H_5\overset{\ominus}{O}} ?$$

Ester without α-hydrogen serves as **carbanion acceptor** **(as it can not form carbanion)**.

(carbanion is formed by abstraction of α - hydrogen of 2nd ester)

second ester with α-hydrogen, does not undergo self condensation as it is added slowly to the reaction mixture slowly and only **single product** is formed.



$$C_6H_5-\overset{\overset{\displaystyle O}{\|}}{C}-OC_2H_5 + CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-OC_2H_5 \xrightarrow{C_2H_5O^{\ominus}} C_6H_5-\overset{\overset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle H}{|}}{\overset{\overset{\displaystyle H}{|}}{C}}-\overset{\overset{\displaystyle O}{\|}}{C}-OC_2H_5$$

Dieckman Reaction (intramolecular Claisen condensation)

(By Dieckman)

Cyclic **β-ketoester** are synthesized by

intramolecular **Claisen condensation** of

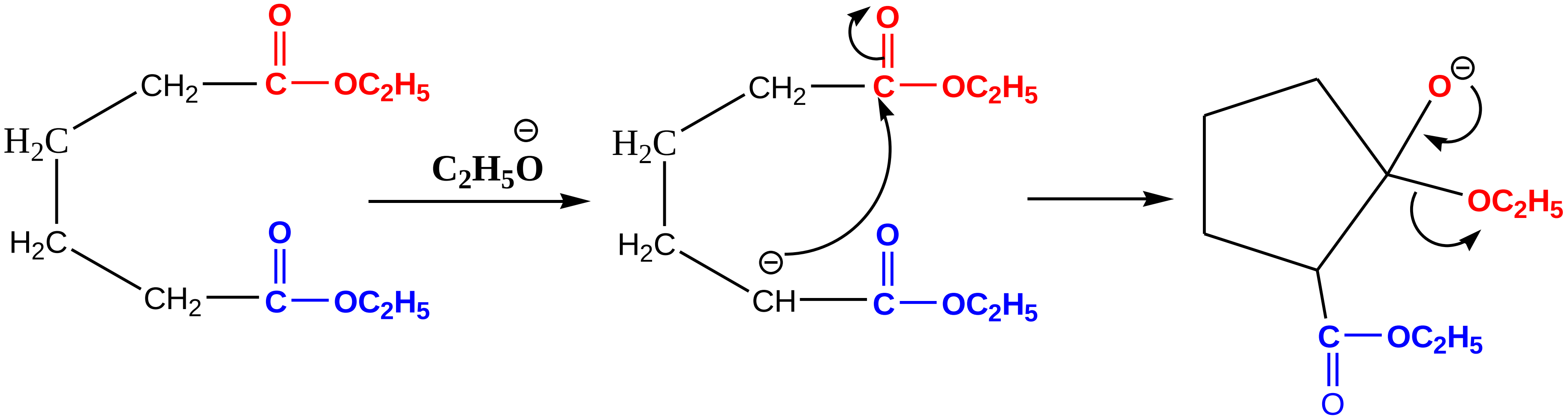
esters of dicarboxylic acids

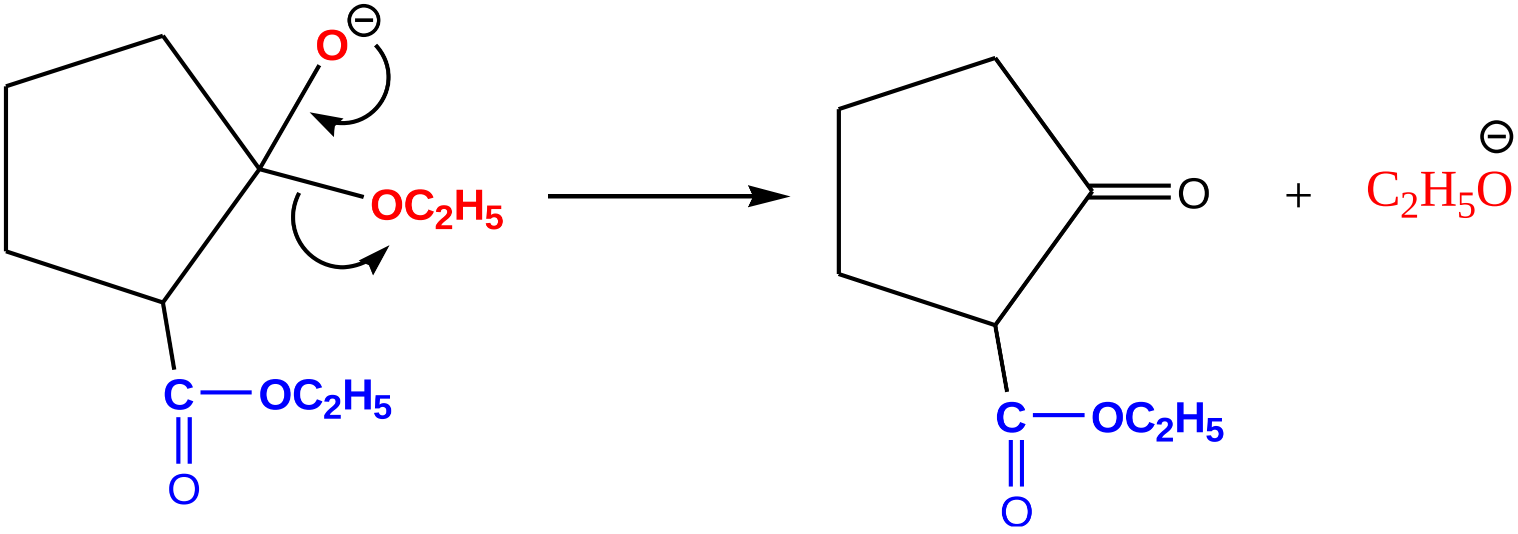
(e.g. **esters of** 1,6- and 1,7-dicarboxylic acids).

Main features of reaction

- **Carbanion is formed** by abstraction of α -hydrogen of one ester
- **This carbanion attack on carbonyl carbon** of 2nd ester **in the same molecule**
- Subsequent **expulsion of alkoxide** ion gives product.

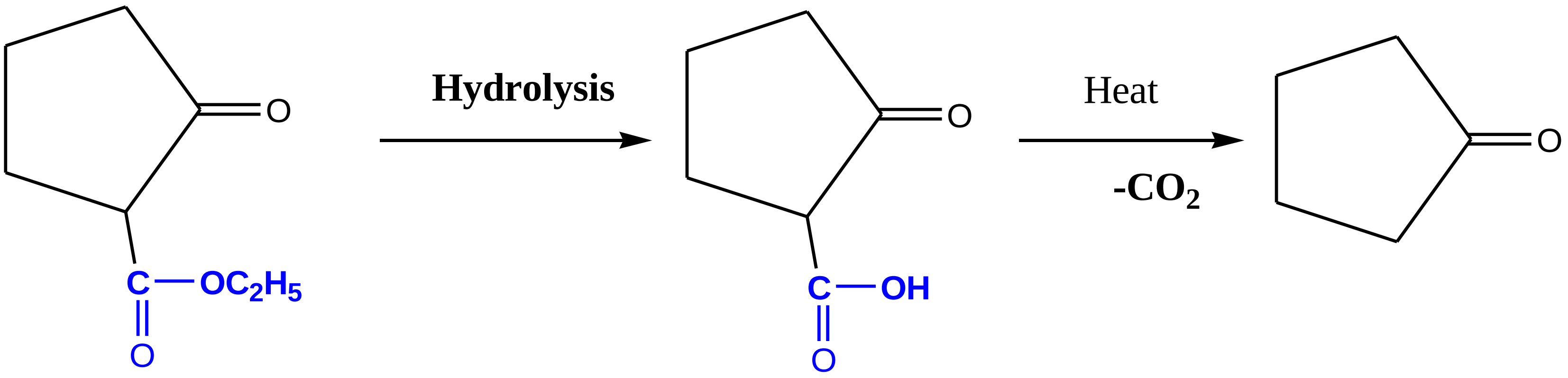
Example: Dieckman Reaction of diethyl adipate (stable 5-membered ring is formed)




O
OC2H5
C
OC2H5
O
O
+
C2H5O
C
OC2H5
O

This reaction can be used for preparation of cyclic ketone

This compound on **hydrolysis** followed by **decarboxylation** gives cyclic ketone.



Beta - keto acid

Mannich Reaction

Compound with active hydrogen

+

HCHO

+

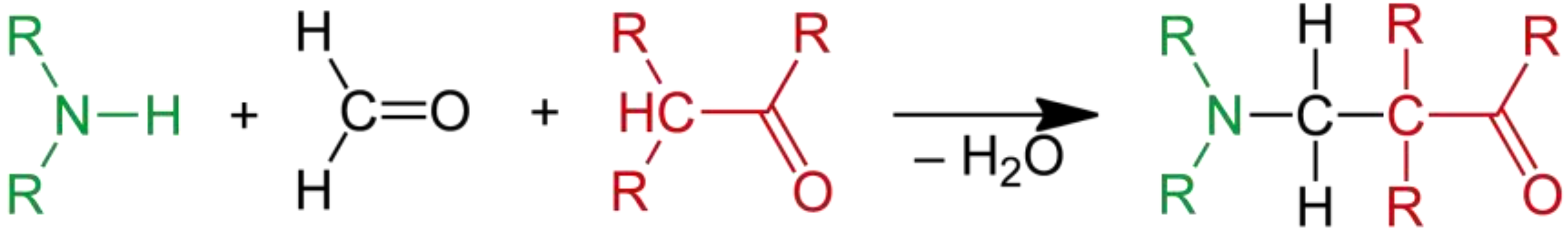
NH_3 / Primary amine / Secondary amine

↓

β -amino carbonyl compound

(Mannich base)

Three components of the reaction



Product of reaction

The final product is a **β-amino-carbonyl compound .**

This **product** is also known as a **Mannich base**.

Mannich reaction

The **Mannich reaction** is an example

of nucleophilic addition of an **amine** to

a carbonyl group

followed by **dehydration** to form Schiff base.

2nd step

The **Schiff base** act as an electrophile

In second step,

Schiff base (Compounds containing C=N bond) reacts

with a **compound containing an acidic proton** (which is, or had become an enol).

Two steps of Mannich reaction

1st step:

HCHO + Ammonia/ 1° or 2° amine = **Iminium ion** (electrophile)

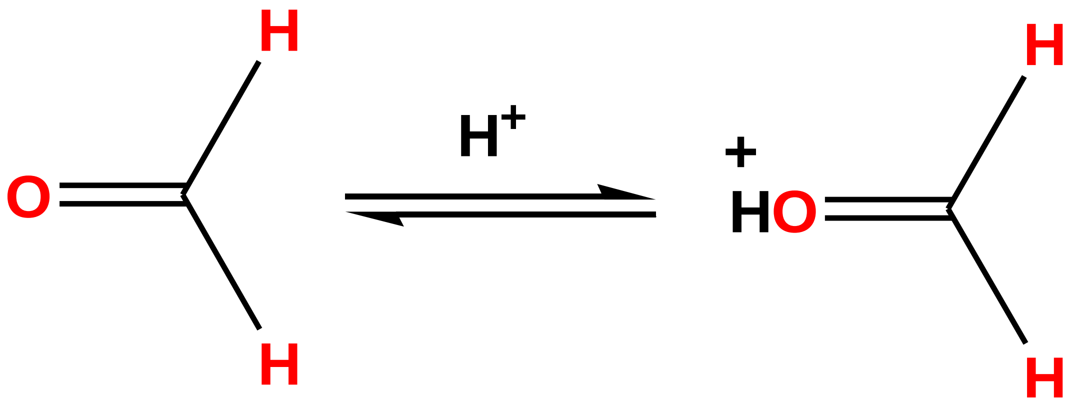
2nd step :

Iminium ion + **enol form** of carbonyl compound

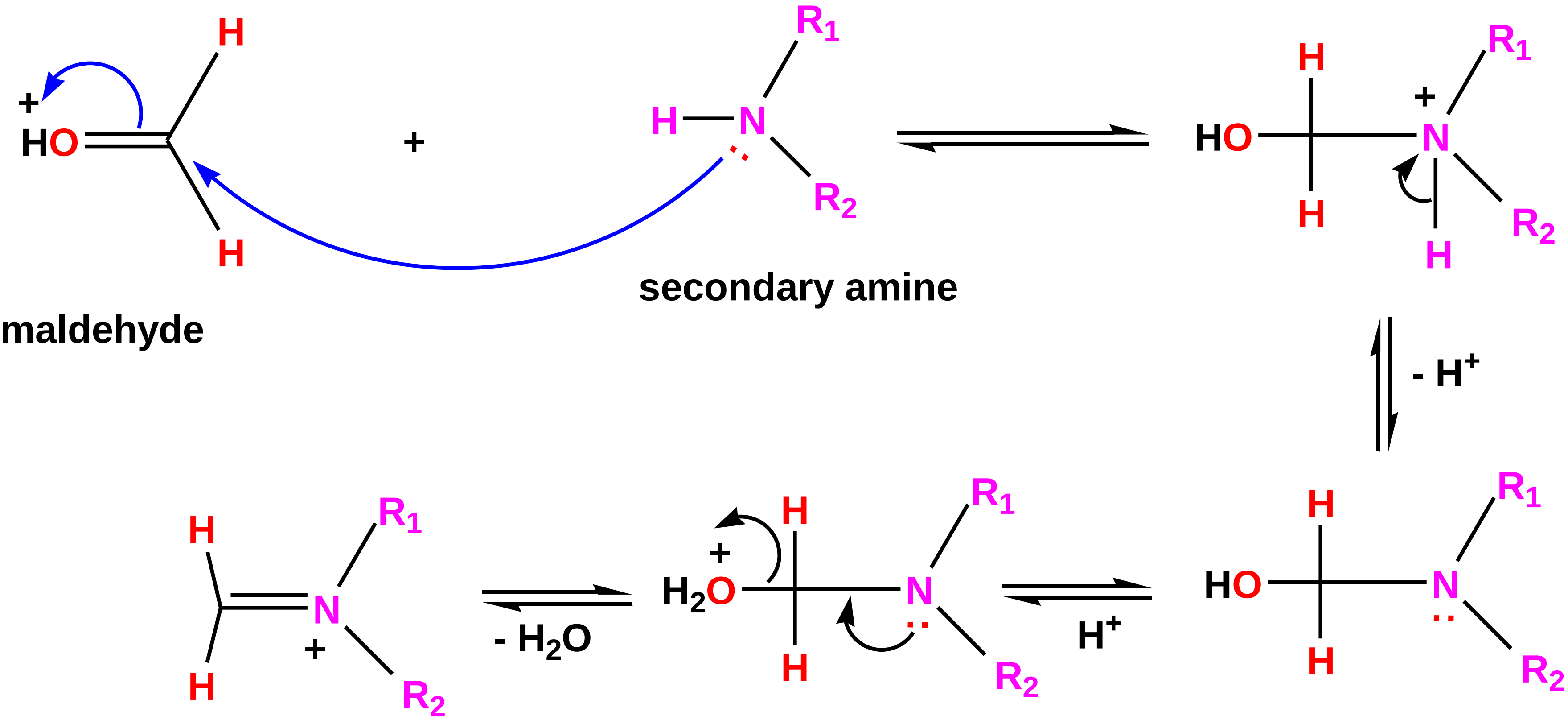
= **Product**

Reaction mechanism

First step: **Amine** and **HCHO** condense in presence of H^+ to form **iminium cation**



Nucleophilic addition of amine to HCHO form iminium ion



Formaldehyde

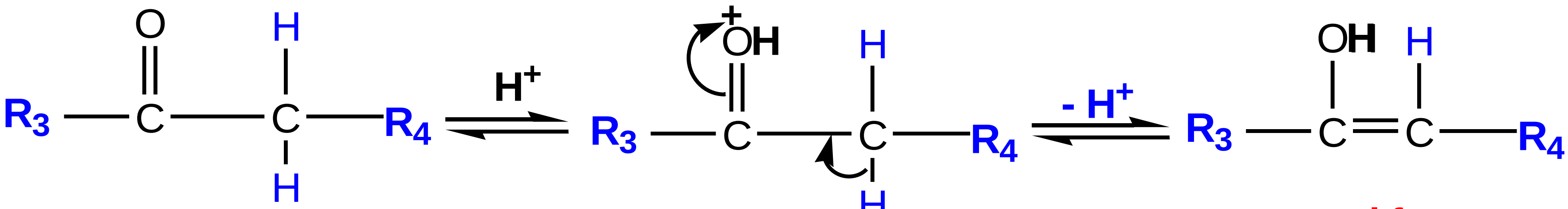
secondary amine

Iminium ion

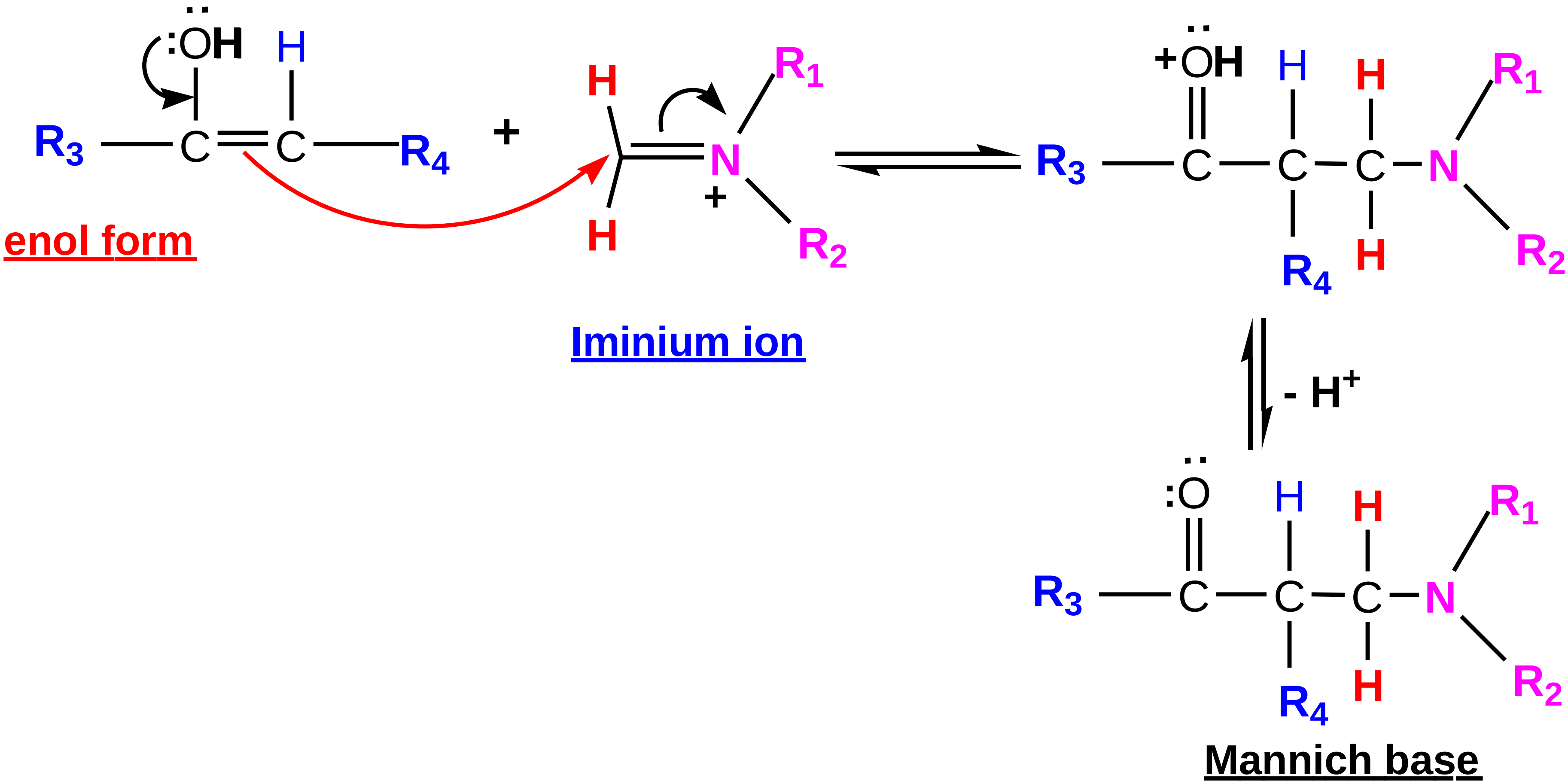
2nd step: In presence of acid, ketone get tautomerized

to enol form,

which attack on iminium cation to form mannich base



enol form


:ÖH
H
R3
C
C
R4
enol form
+
H
H
N
+
R1
R2
Iminium ion
+ÖH
H
H
R3
C
C
C
N
R1
R2
R4
H
- H+
:Ö
H
H
R3
C
C
C
N
R1
R2
R4
H
Mannich base

Main features of Mannich reaction

- In the Mannich reaction, ammonia or primary or secondary amines are employed.
- **Tertiary amines lack** an **N-H proton** to form the **intermediate** imine.
- Among amines **secondary amine** is preferred.

Why 2° amine is preferred

Because with **ammonia** **and** **primary amines**, **reaction may proceed further**

(i.e. Mannich base formed can react with HCHO again leading to same course of reaction to form new imine)

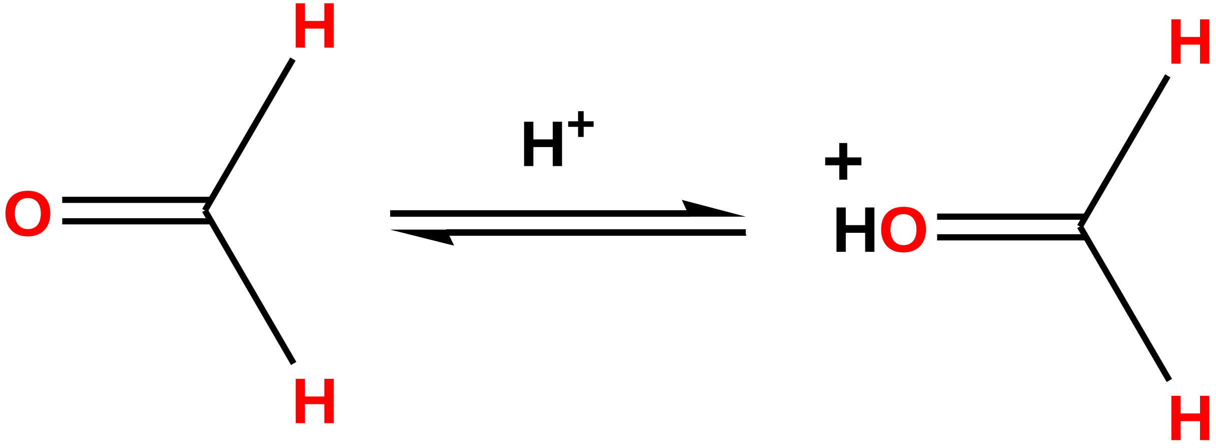
as Mannich base formed still contains **hydrogen on nitrogen atom.**

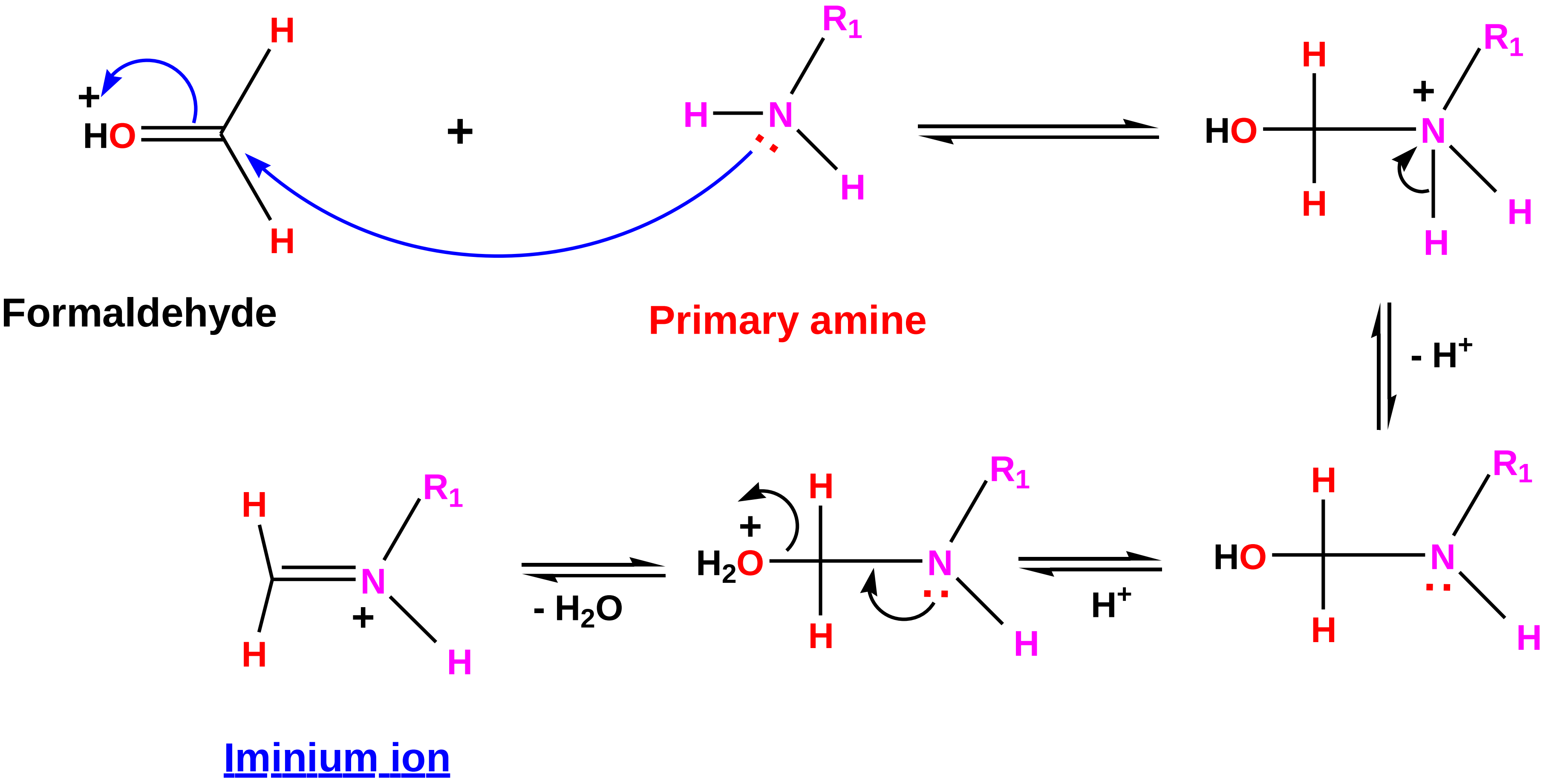
But in case of **Mannich base** formed from secondary amine **there is no hydrogen on Nitrogen.**

Mannich reaction with **primary amine**

Mannich reaction with **primary amine**

First step: Formation of iminium ion (Primary amine + HCHO)



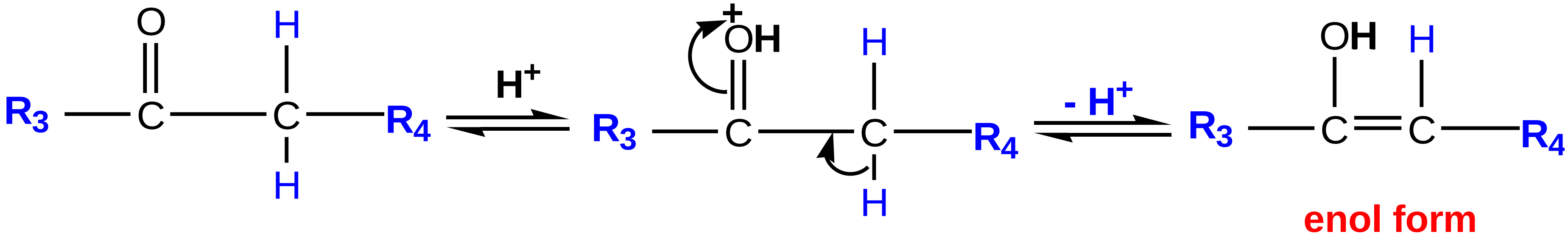


Formaldehyde

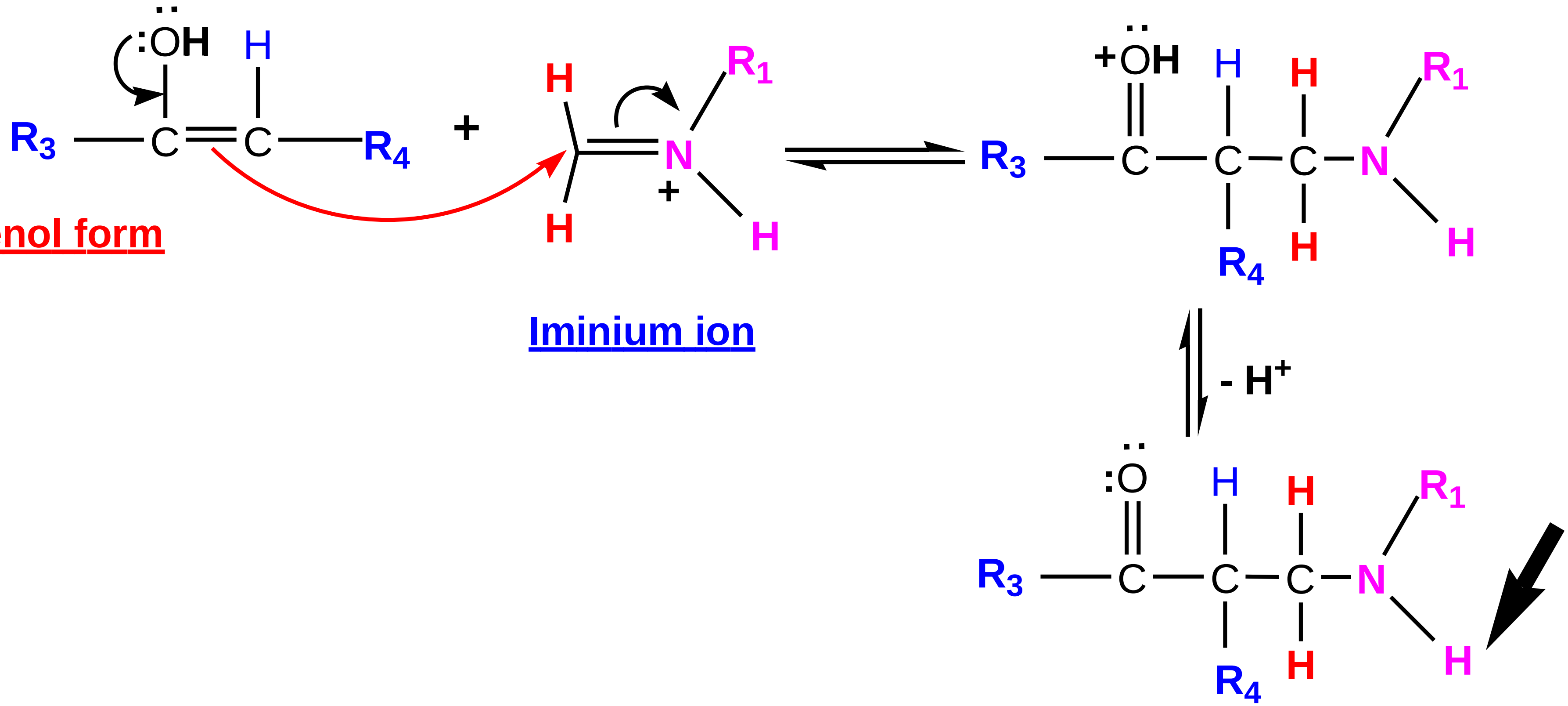
Primary amine

Iminium ion

2nd step: Attack of enol on iminium ion



enol form



enol form

Iminium ion

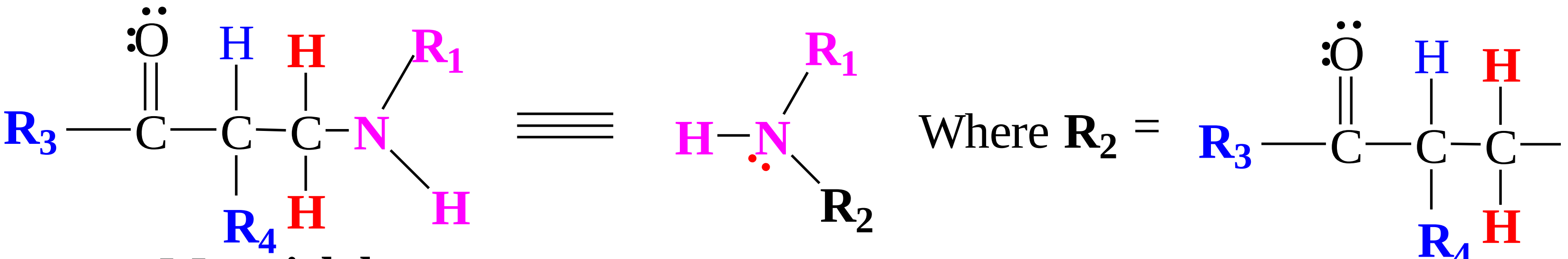
Mannich base

(still have H attached to N)

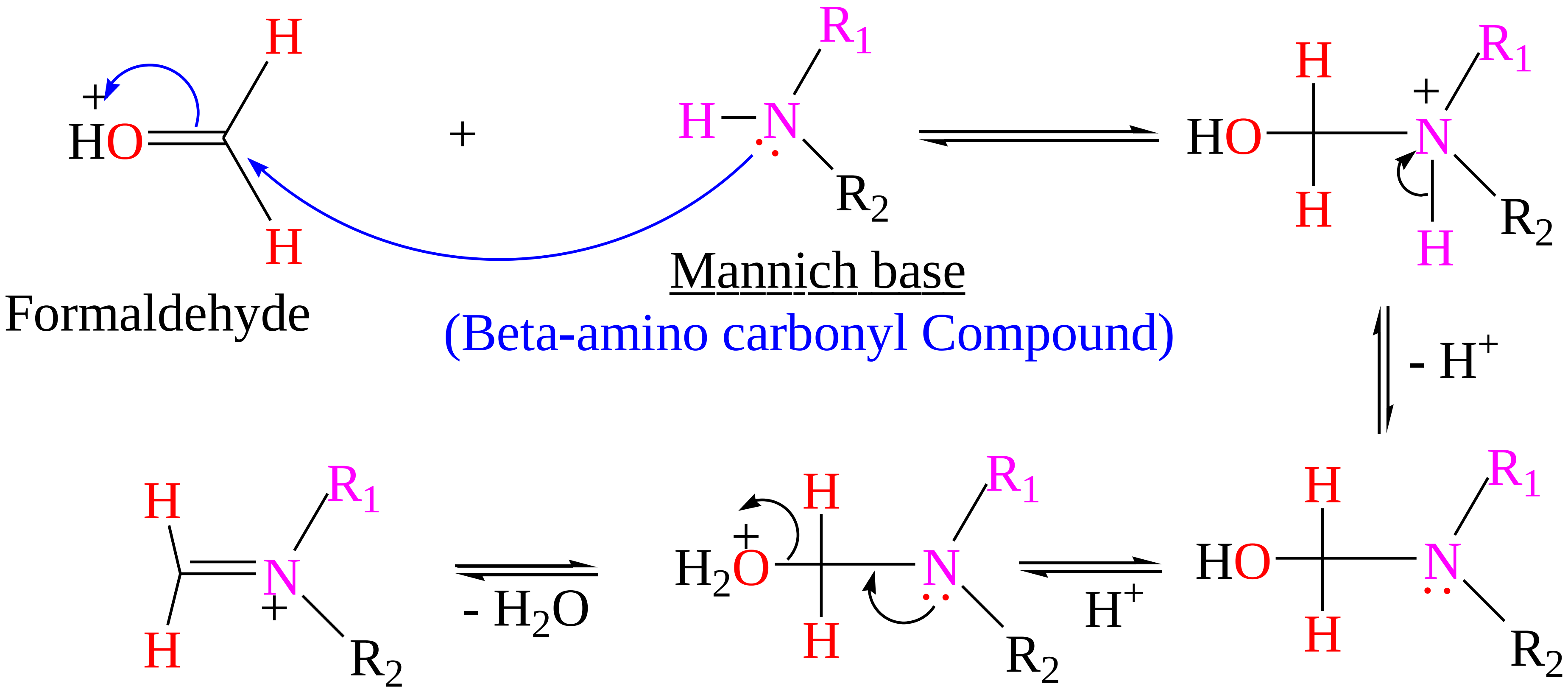
(So can react further with HCHO)

Mannich base so formed still has <u>active hydrogen</u> attached to Nitrogen,

So, it can react further with HCHO to form new iminium ion



<u>Mannich base</u>



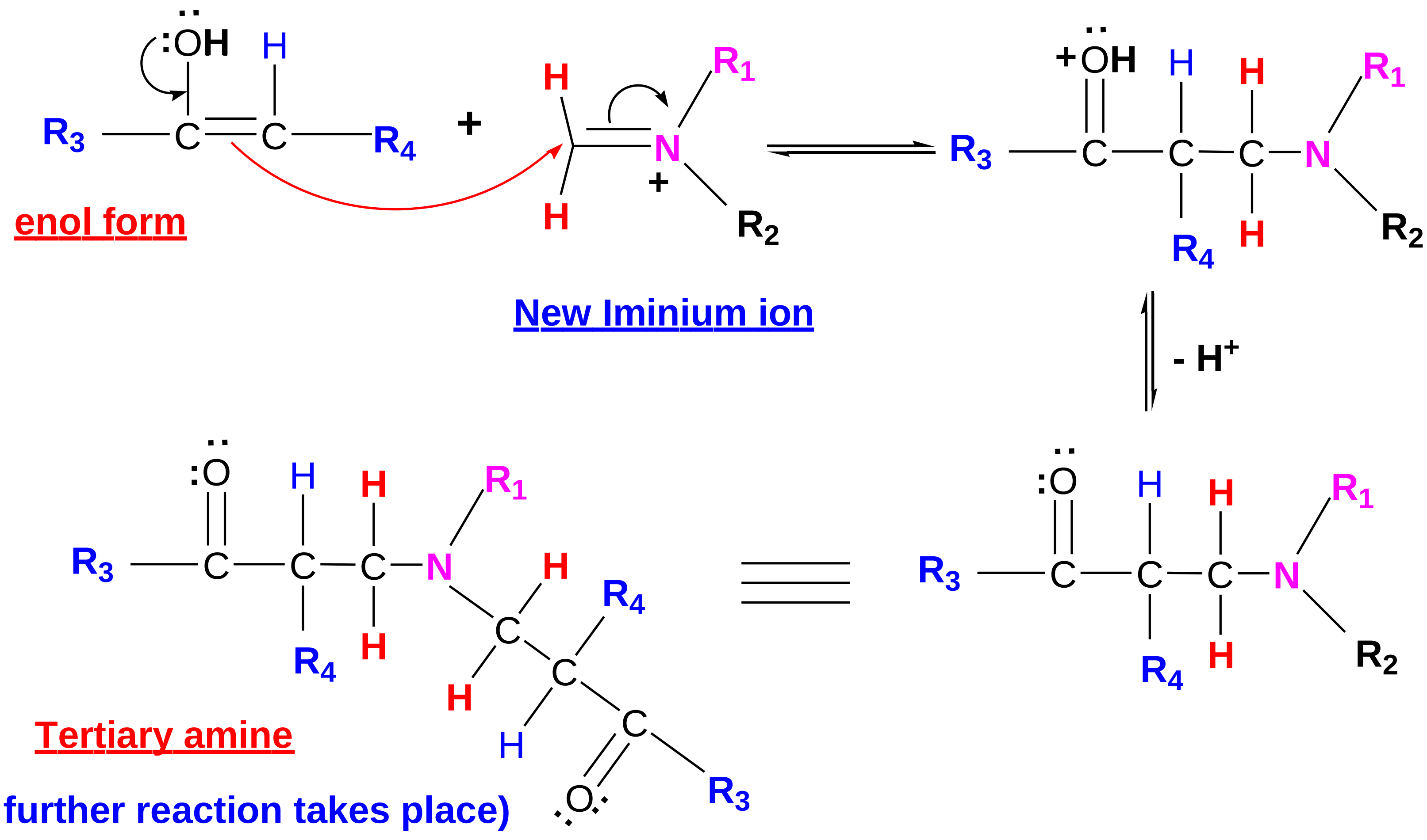
Formaldehyde

Mannich base

(Beta-amino carbonyl Compound)

New Iminium ion

2nd step: final product is **tertiary amine** without any Hydrogen attached to Nitrogen



enol form

New Iminium ion

Tertiary amine

(So, no further reaction takes place)

Mannich Reaction With **Ammonia**

Similarly with **ammonia,**

three successive reactions occur to give

tertiary amine as final products.

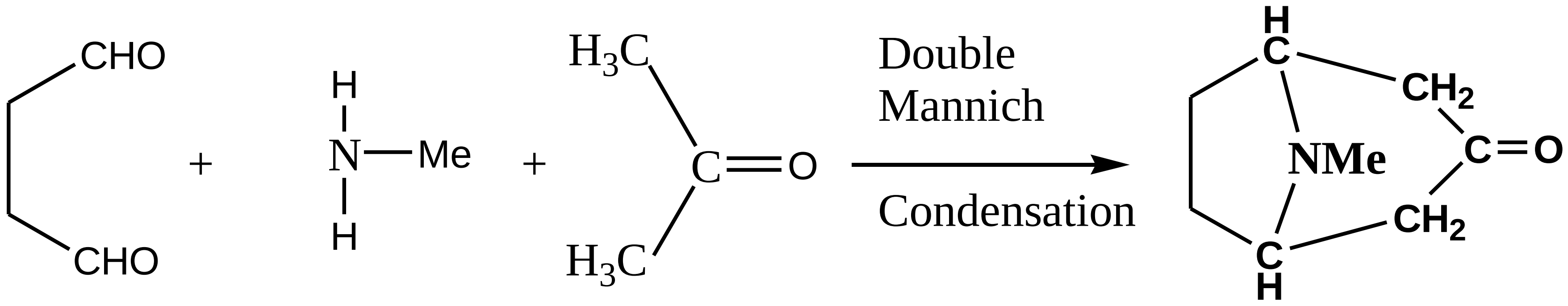
Application of Mannich reaction

Many important **natural products** especially **alkaloids**, have been synthesized by this reaction.

Example: Robinson synthesis of **Tropinone (alkaloid)** by a **double Mannich condensation** from **succinaldehyde**.

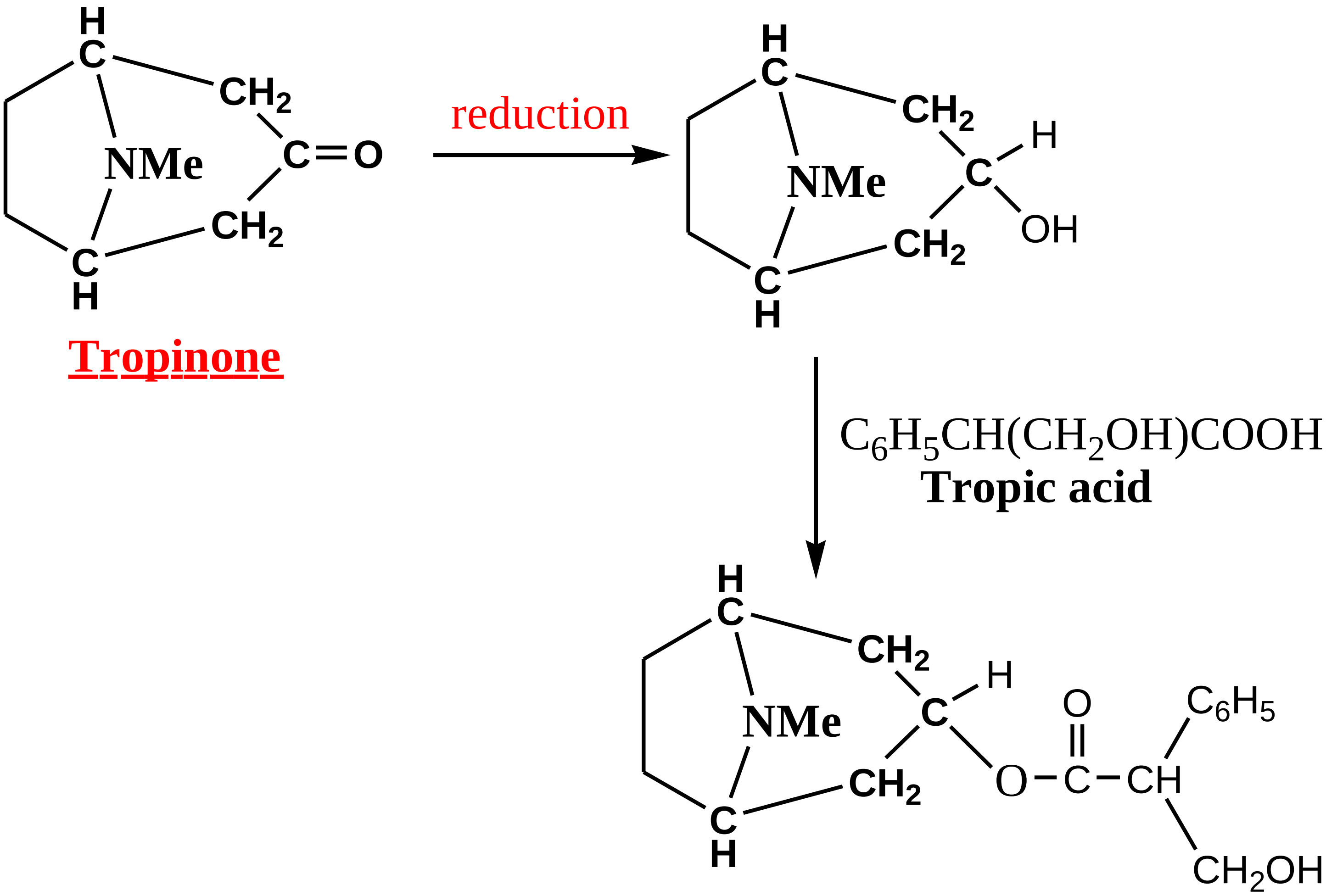
Atropine is synthesized from **Tropinone**.

Synthesis of Tropinone



Tropinone

Synthesis of Atropine



Tropinone

reduction

$C_6H_5CH(CH_2OH)COOH$

Tropic acid

Atropine

Ammonolysis of Ester

(Conversion of an ester to an Amide)

Reaction:

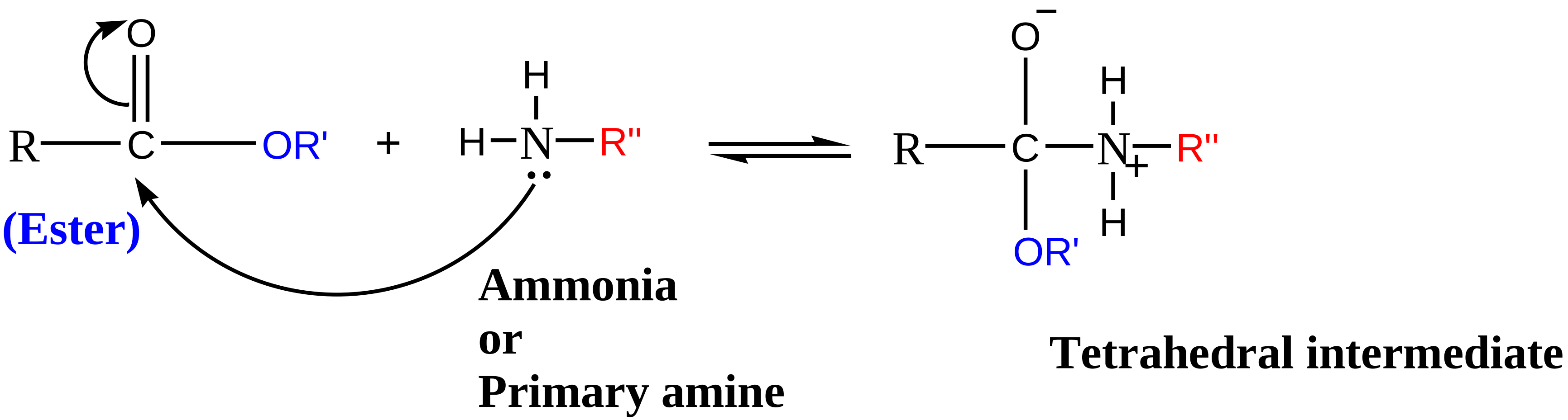
Ester + Ammonia / Primary amine

↓

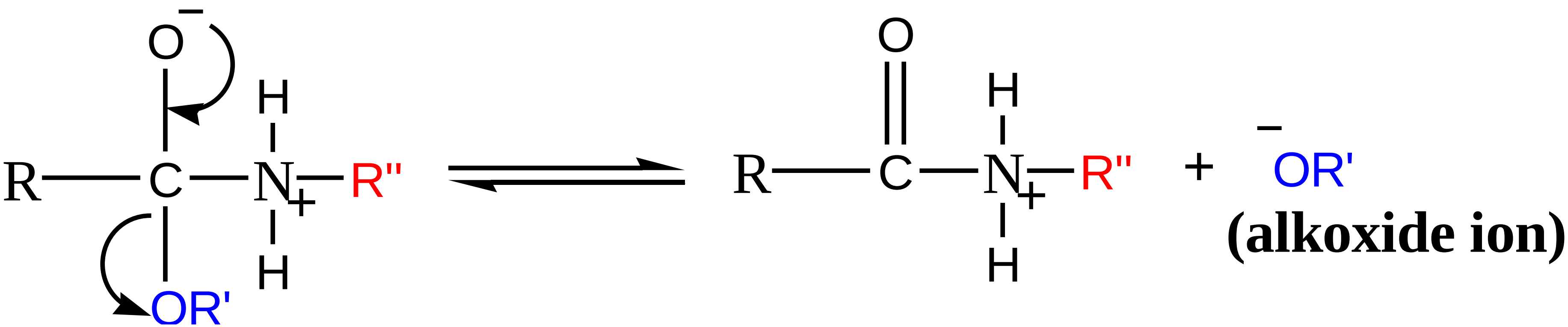
<u>Amide</u> + Alcohol

Three steps of reaction

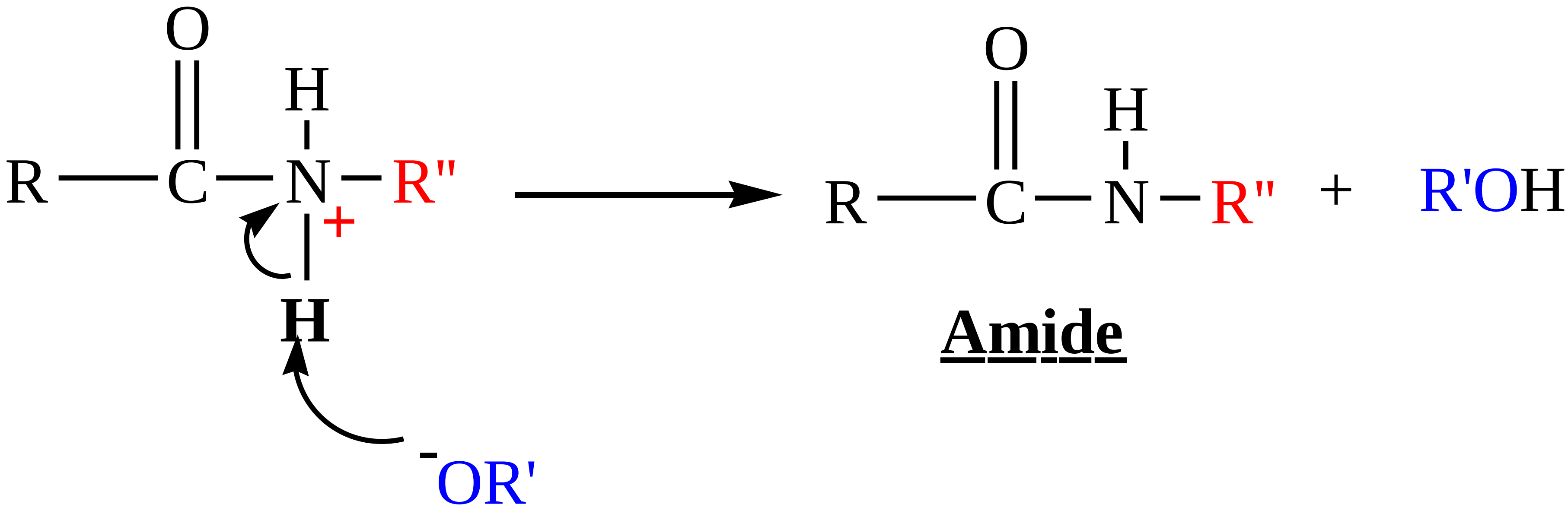
Step – 1: Addition of Nucleophile (Ammonia/primary or secondary amine) to ester



Step –II : Elimination of leaving group

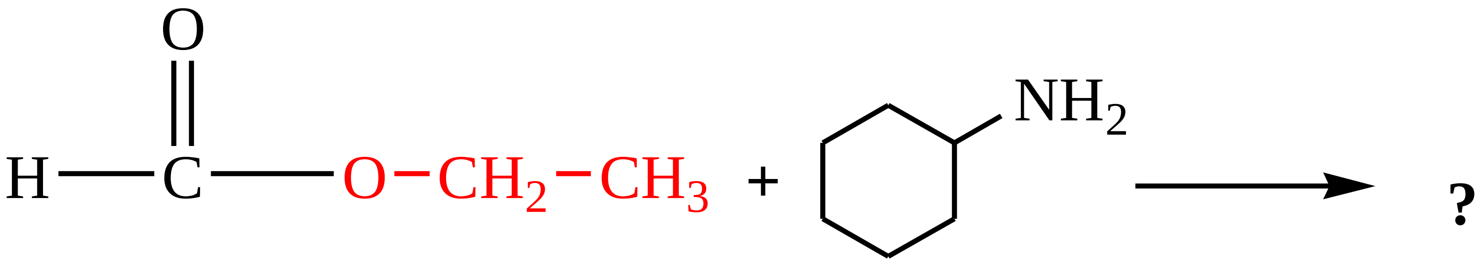


Step-III : Loss of proton



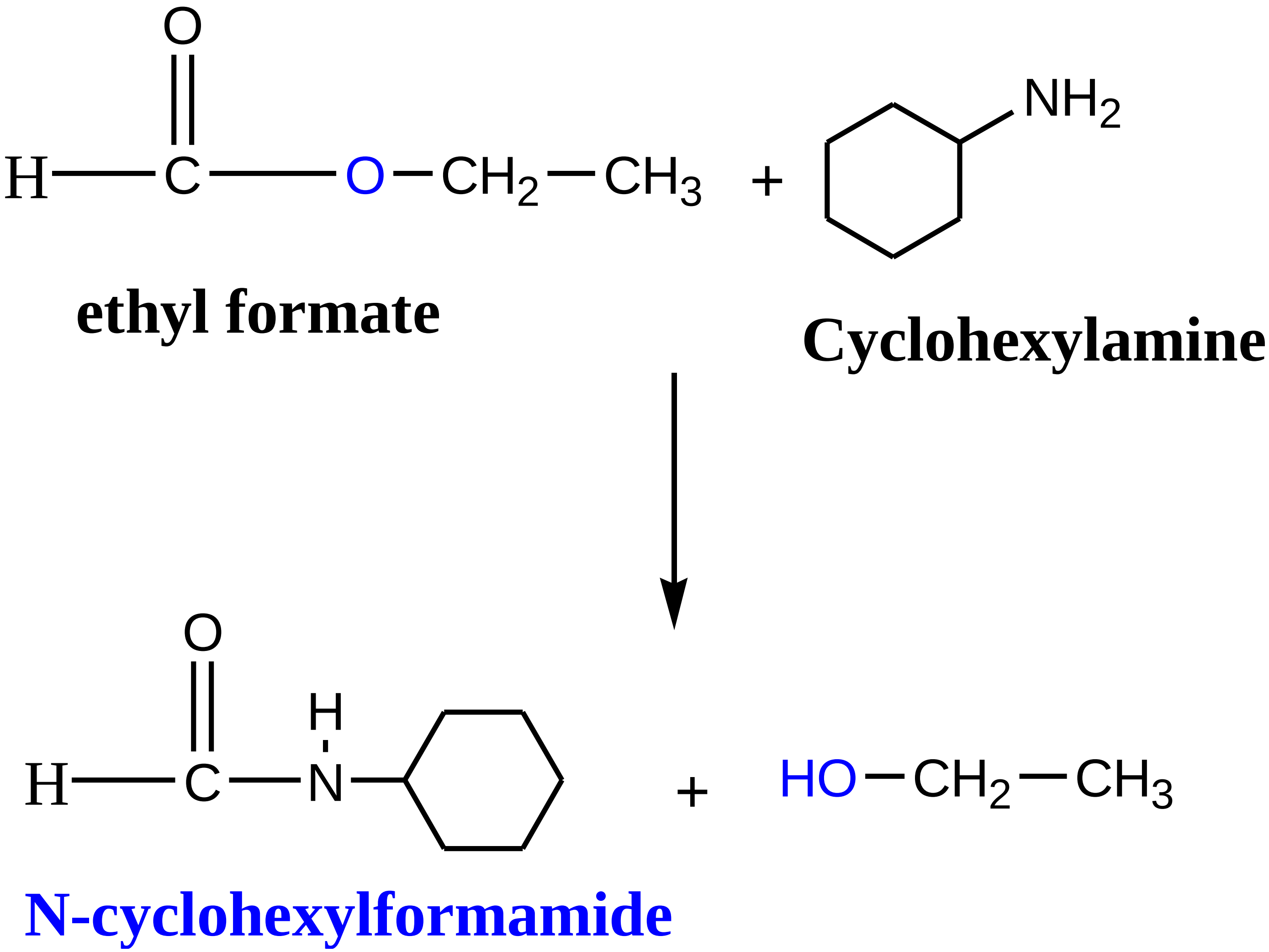
Amide

Example



ethyl formate

Cyclohexylamine


ethyl formate
Cyclohexylamine
N-cyclohexylformamide

Ester hydrolysis

Ingold short hand notations

A = Acidic medium

B = Basic medium

Ac = Acyl cleavage

AL = Alkyl cleavage

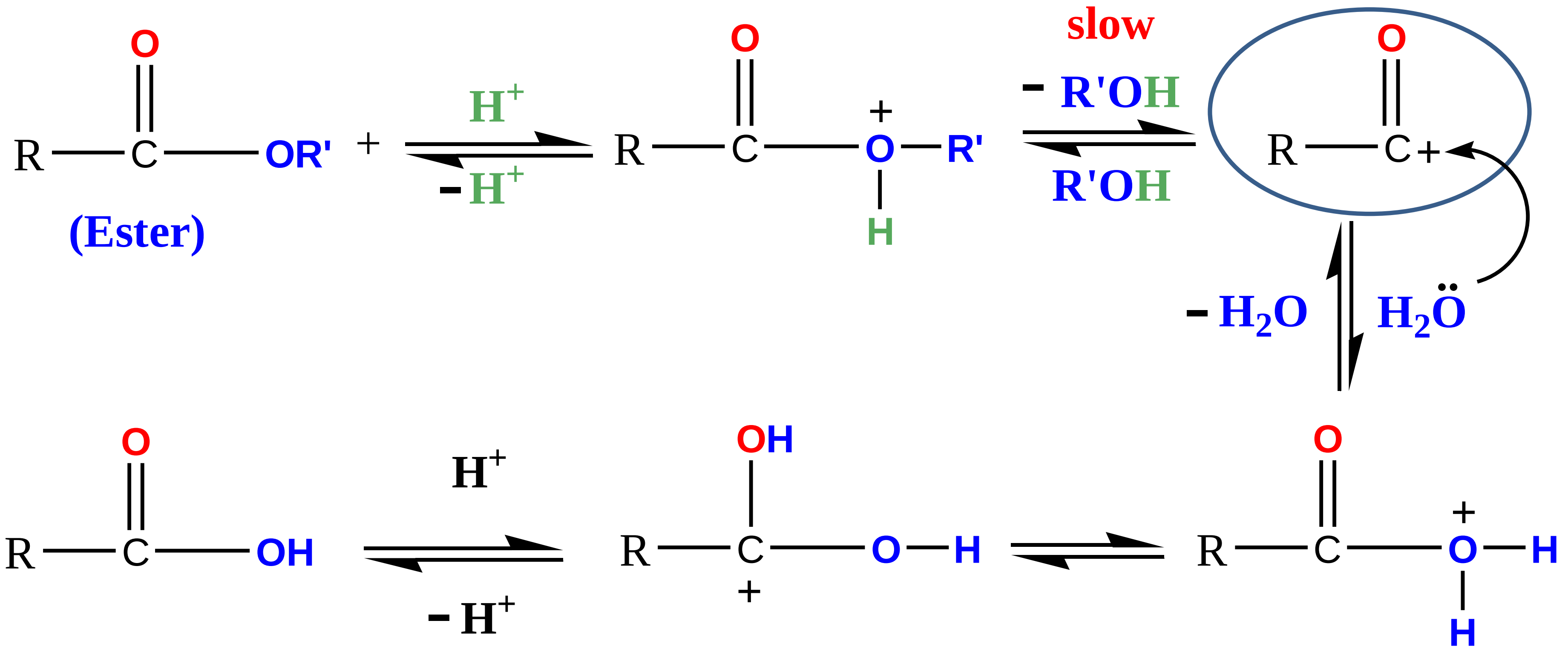
1 or 2 = Molecularity of reaction

BAC^{2} = **bimolecular basic hydrolysis** of an ester which proceed through cleavage of **acyl-oxygen bond**

Medium	Cleavage		Type	
Acidic	Acyl	AAC^{1}	SN^{1}	Mechanism 1
		AAC^{2}	**Tetrahedral**	**Mechanism 2**
		AAL^{1}	SN^{1}	Mechanism 3
		AAL^{2}	SN^{2}	Mechanism 4
Basic	Acyl	BAC^{1}	SN^{1}	Mechanism 5
		BAC^{2}	**Tetrahedral**	**Mechanism 6**
		BAL^{1}	SN^{1}	Mechanism 7
		BAL^{2}	SN^{2}	Mechanism 8

AAC¹ (rare mechanism)

(occurs where R group is bulky)



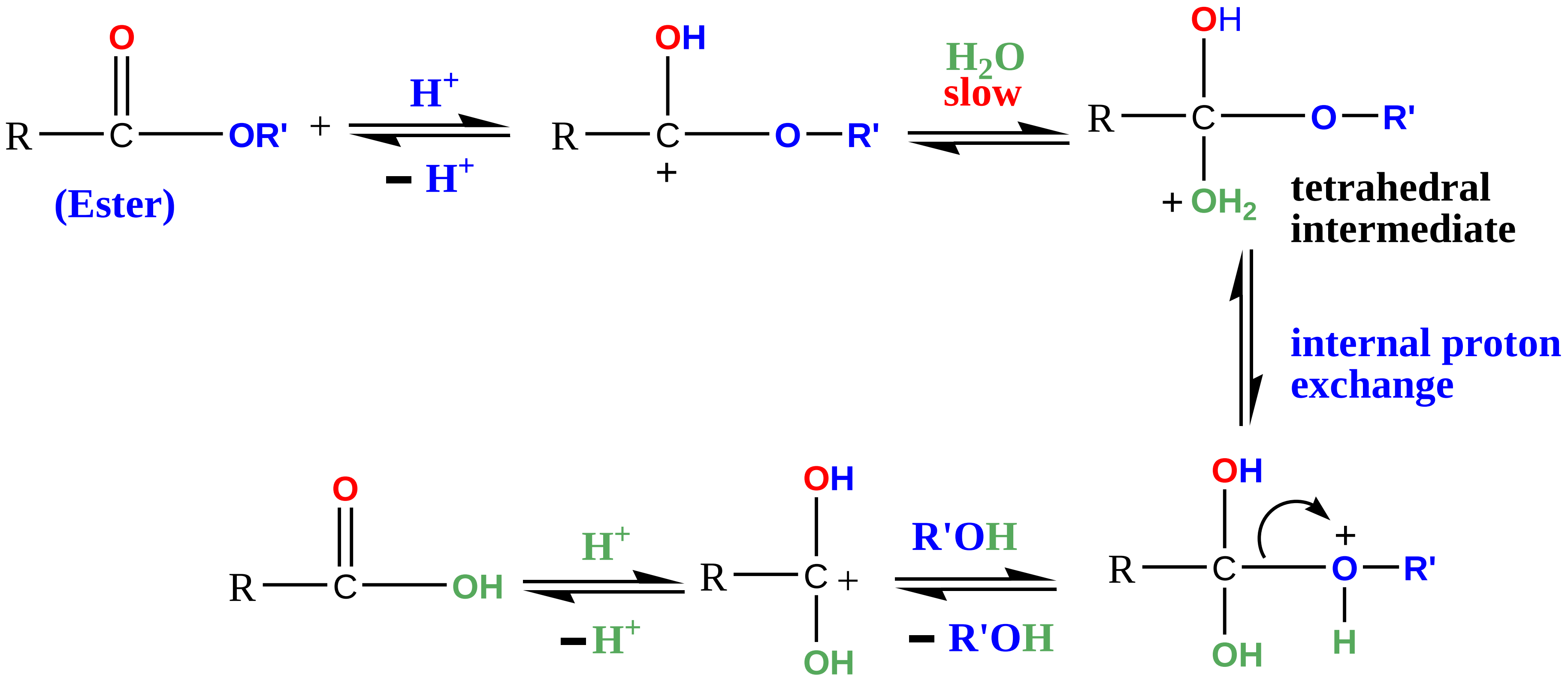
- There are many physical evidences that show **Protonation in esters occurs on** carbonyl oxygen and not on alkyl oxygen.

- However this mechanism proceeds through the protonation of ether oxygen.

- **This mechanism is rare** and is being found where, **R is very bulky group** , so that **bimolecular attack ($A_{AC}2$)** is sterically hindered

This mechanism has been demonstrated by **esters of 2,4,6-trimethyl benzoic acid (bulky group).**

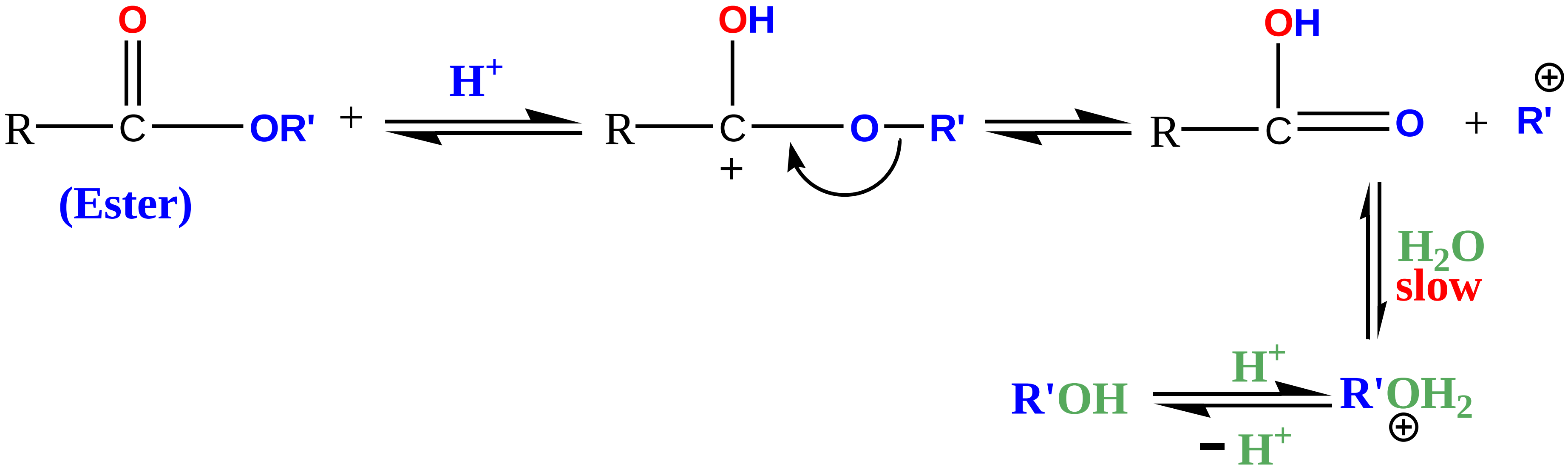
AAC^2 (Most common mechanism for acid catalysis)



* This mechanism proceeds through the **protonation of carbonyl oxygen** **which is most likely to occur.**

* This is **most common** mechanism **for acid catalysis**

AAL1 (This mechanism occurs when R' comes out as stable carbocation)



This mechanism occurs when R’ comes out as

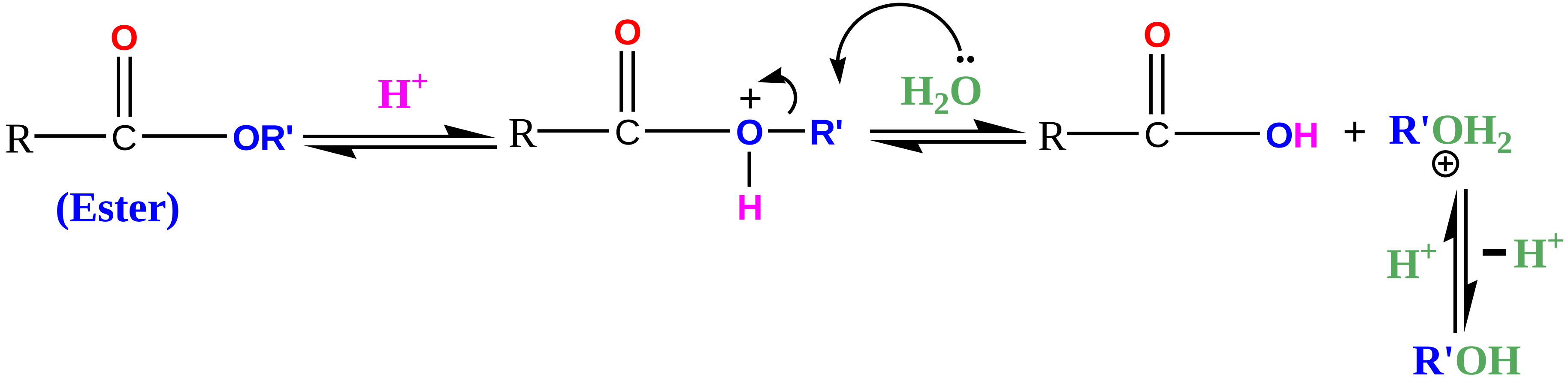
stable carbocation

i.e. R’ is tert. alkyl, allylic, Benzylic

(in allylic and benzylic system carbocation is

resonance stabilized)

AAL^2 (Very rare) . Because it requires water (weak nucleophile) to be nucleophile in SN^2 process and it requires nucleophilic attack of water on alkyl carbon rather than carbonyl carbon)



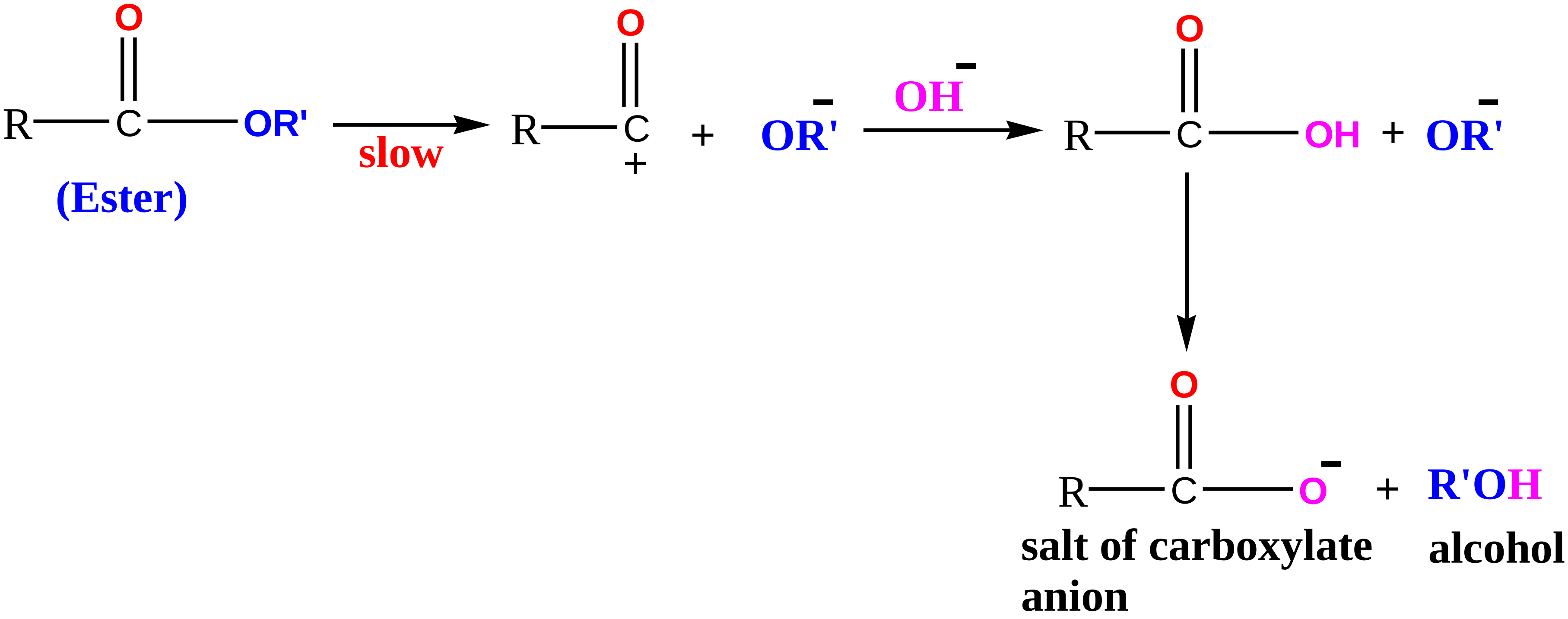
Protonation occurs on alkyl oxygen.

Here R’ does not comes out as carbocation. (as it is S_N2 process)

$A_{AL}2$ mechanism is Very rare because it requires water (weak nucleophile) to be nucleophile in S_N2 process

This mechanism has been reported in acid cleavage of γ-lactones .

B_{AC}^{1} (This mechanism has not been observed)

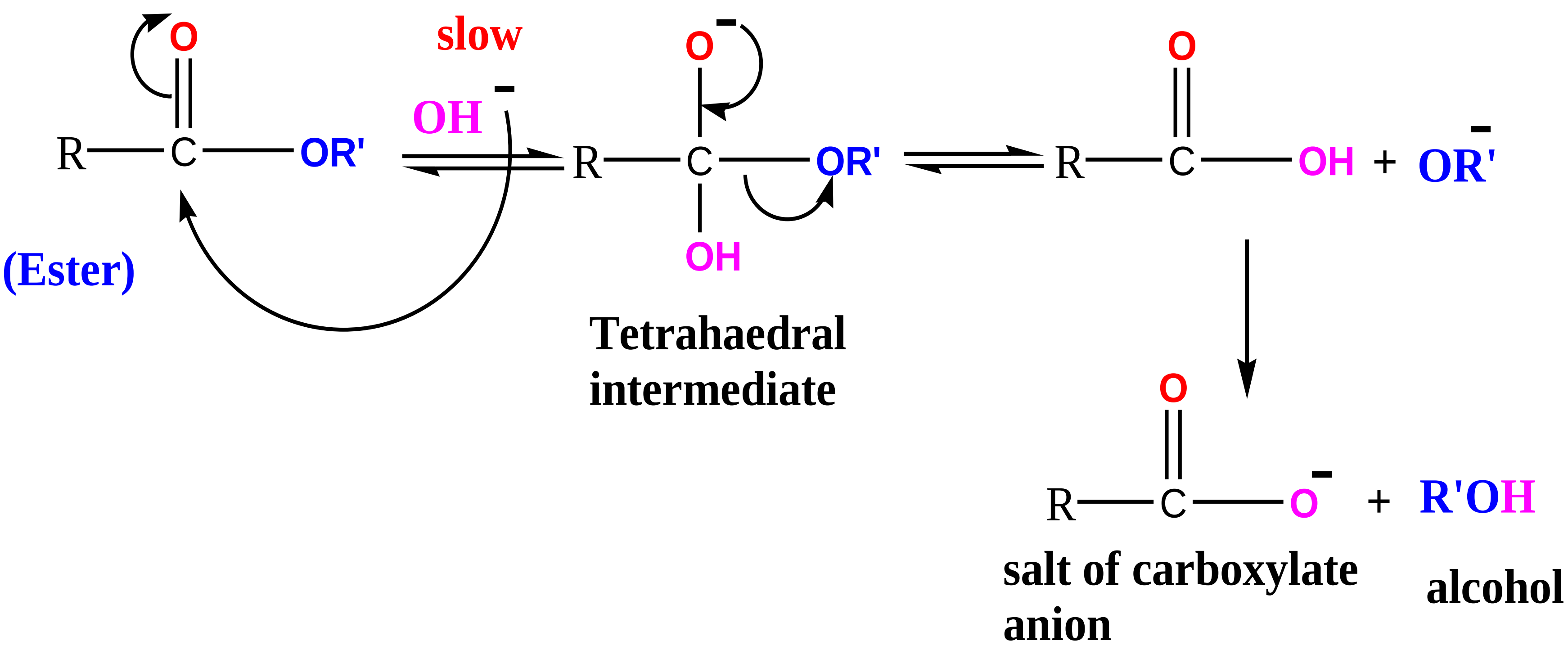


$$R{-}C({=}O){-}OR' \xrightarrow{\text{slow}} R{-}\overset{+}{C}({=}O) + {}^{-}OR' \xrightarrow{OH^{-}} R{-}C({=}O){-}OH + {}^{-}OR' \longrightarrow R{-}C({=}O){-}O^{-} + R'OH$$

Out of **eight mechanisms**, **seven have actually been observed** in hydrolysis of carboxylic acid esters.

The **one** which **has not been observed** is **$B_{AC}1$ mechanism.**

BAC^2 (most common mechanism for base catalysis) **(irreversible hydrolysis)**

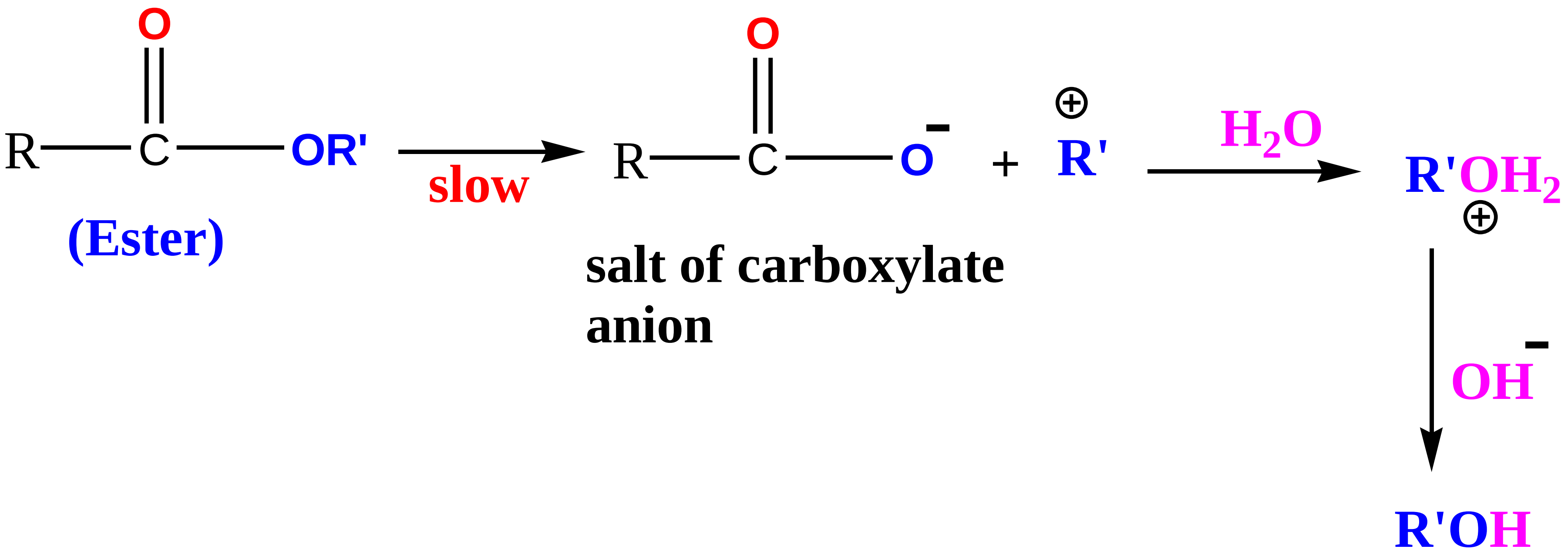


- This is **most common** mechanism for base catalysis

- This **mechanism include formation of**

  tetrahedral intermediate as in **AAC^{2} mechanism.**

BAL^1 (occurs where R’ comes off as a stable carbocation)



- Same as in AAL^1

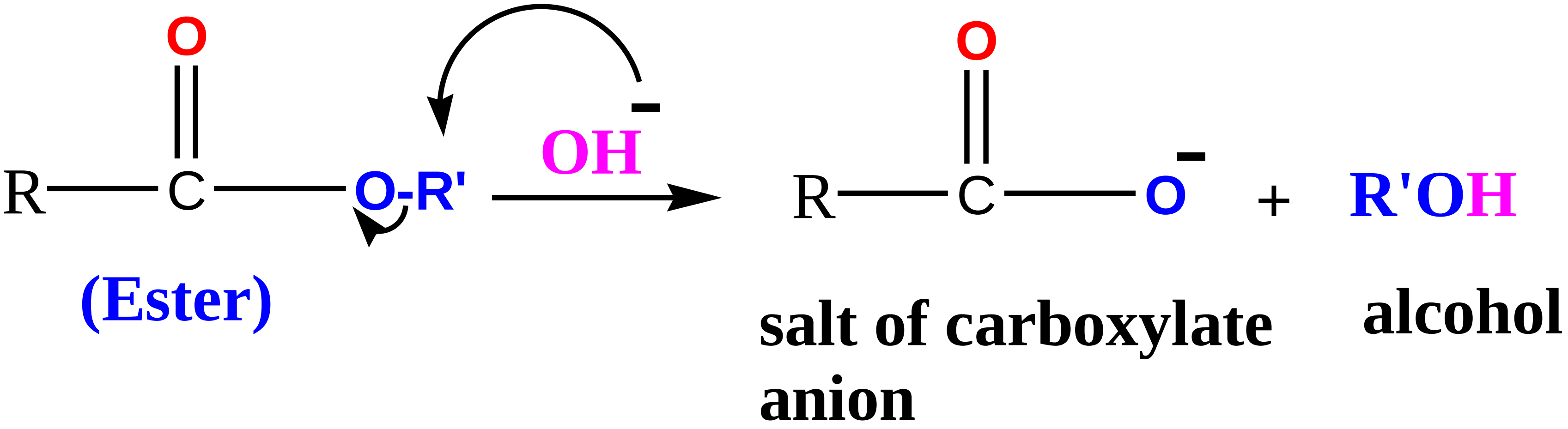
- In this mechanism also, R’ comes out as **carbocation**.

- **So like AAL^1**, this mechanism occurs where **R’ is a stable carbocation.**

  i.e. R’ is tert. alkyl, allylic, Benzylic cation

  (in allylic and benzylic system carbocation is resonance stabilized)

B$_{AL}^{2}$ (very rare as it requires nucleophilic attack of base on alkyl carbon rather than carbonyl carbon)



B_{AL}^{2} mechanism is also Very rare like A_{AL}^{2} because

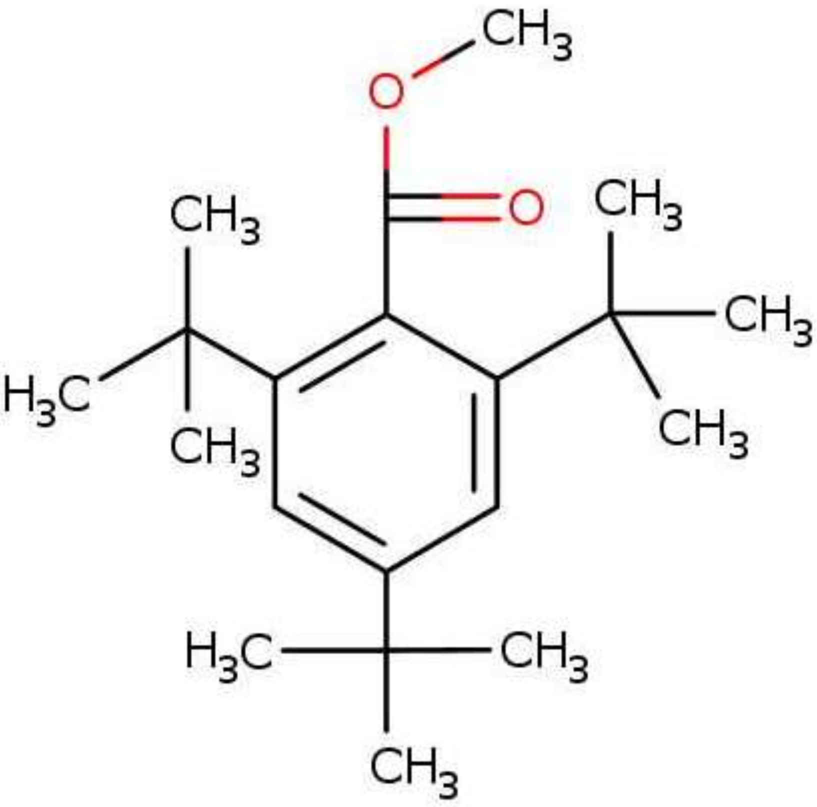
it requires OH^- to attack on alkyl carbon (in presence of more electrophilic carbonyl carbon)

- This mechanism has been reported in **hydrolysis of β-lactones** **(cyclic ester -4 membered ring)**

  (because cleavage of **C-O bond in the transition state opens four membered ring** and relieves strain)

- This mechanism is also seen in **alkaline hydrolysis** of **methyl** **2,4,6-tri-tertiary butyl benzoate**

methyl 2,4,6-tri-tertiary butyl benzoate



Summary

Acid catalyzed hydrolysis of ester is **reversible**

Basic hydrolysis of esters avoids equilibrium.

Base catalyzed reactions are not shown with reversible arrows, since **they are reversible only in theory not in practice**

Basic hydrolysis of esters is called **saponification**.

Saponification term comes **from alkaline hydrolysis of fat** (triacyl glycerol) which results in formation of **soap** **(sodium salt of higher fatty acid)**.

Basic hydrolysis of esters gives **sodium salt of carboxylic acid.**

Among the **acid catalyzed mechanism**,

A_{AC}^{2} and A_{AL}^{1} are the most common mechanisms.

A_{AL}^{1} : occurs where R’ of RCOOR’ comes out as a stable carbocation.

A_{AC}^{2}: most practically possible.

A_{AC}^{1}: **rare**, found in ester with **sterically hindered R.**

A_{AL}^{2}: **more rare**.

Among the **base catalyzed mechanism**,

BAC^{1}: has **never** been **observed**

BAC^{2} : most universal

BAL^{1} : R’ comes out as a **stable carbocation**

BAL^{2}: Very rare (occurs under neutral or weakly basic condition- as it involves attack of OH^{-} on alkyl carbon rather than carbonyl carbon)

Out of eight mechanisms

B_{AC}^2 and A_{AC}^2 are **most common** mechanism.

Both involve acyl cleavage