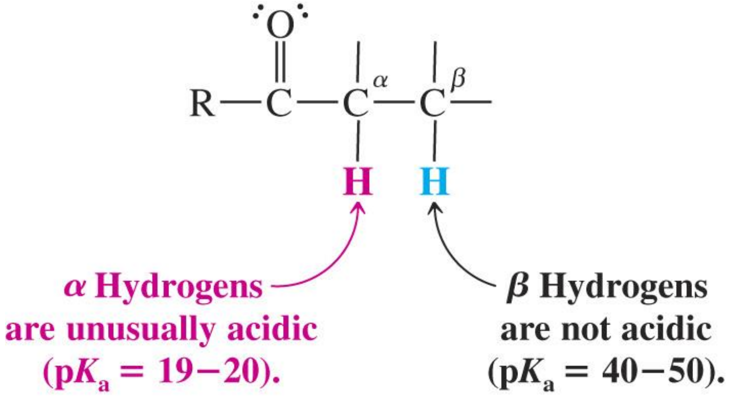
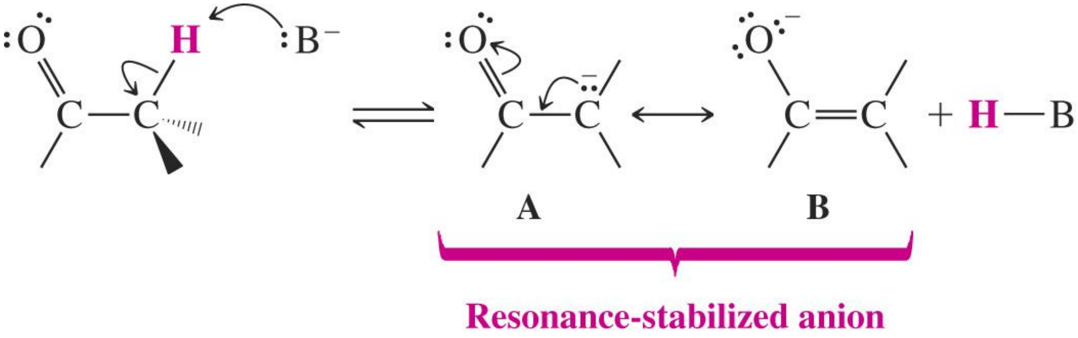
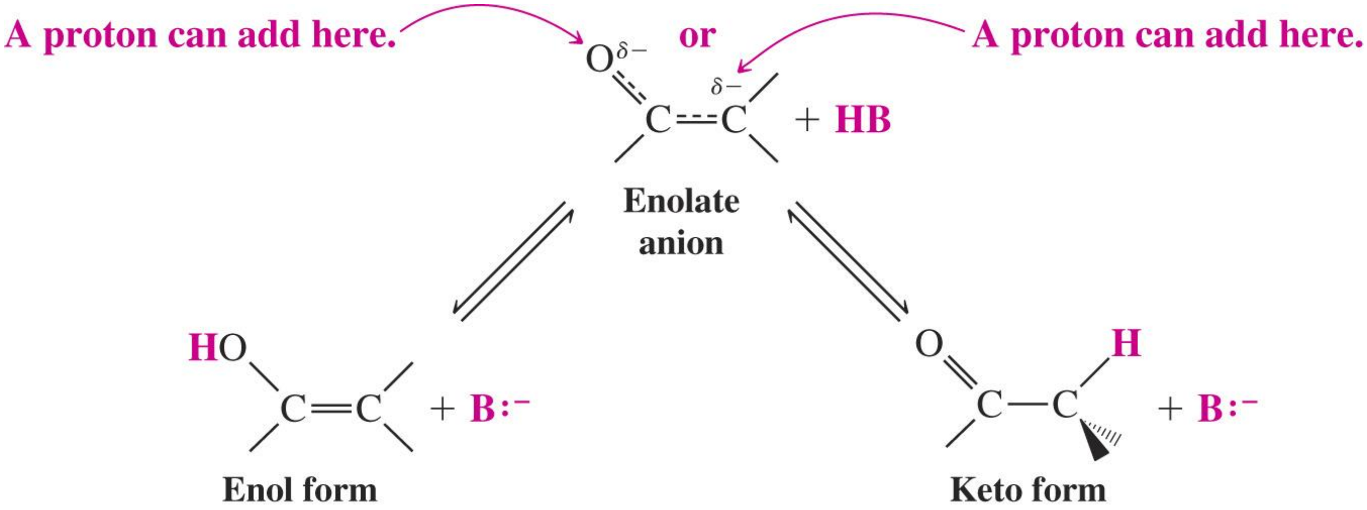
Capítulo 17
Aldeídos e cetonas
II.Reações Aldólicas

- **A acidez dos hidrogenios α de compostos carbonílicos: ânion enolato**
  - **Hidrogenios nos carbonos α a carbonila são ácidos**
    - **Os anions resultantes são estabilizados por ressonancia com a carbonila**



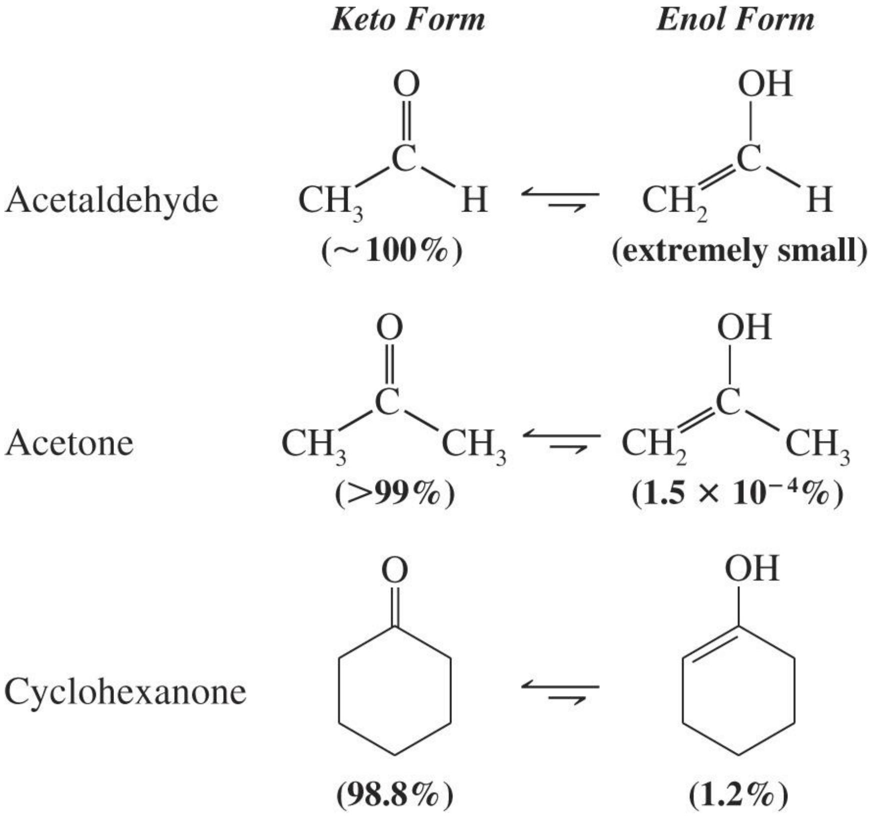


- **O anion enolato pode ser protonado no carbono ou no oxigênio**
  - **O enol resultante e a forma ceto da carbonila são revesíveis e interconversíveis**

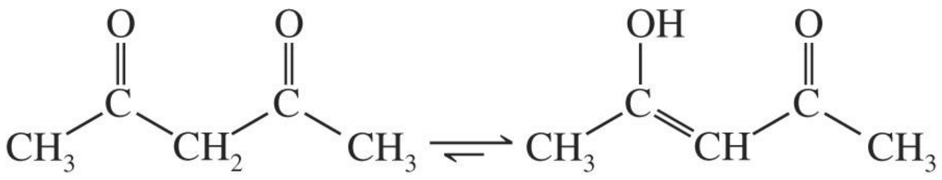


Tautômeros Ceto enólicos

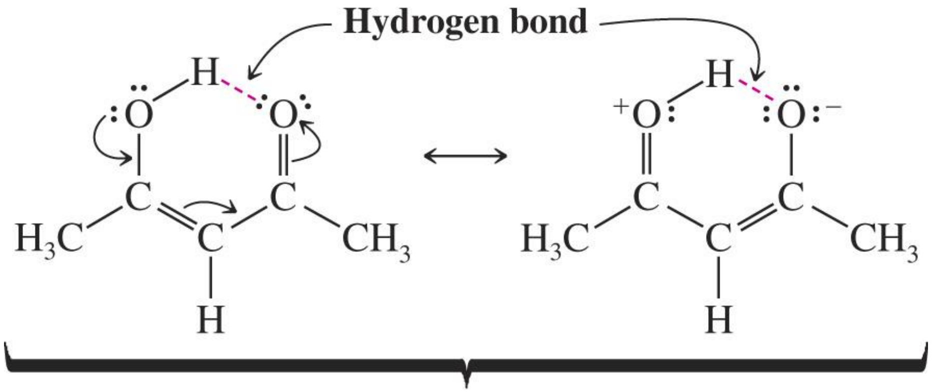
- **Tautômeros Ceto-Enolicos são isômeros constitucionais que se interconvertem com traços de ácido ou base.**
- **A maioria das cetonas e aldeidos existem na forma ceto devido a maior força da dupla ligação carbono-oxigênio relativa a a ligação dupla carbono-carbono**



è **Compostos β-Dicarbonilicos existem primariamente na forma enólica. O enol é mais estável porque tem um sistema conjugado π e o enol está estabilizado através da ligação de hidrogênio**


Pentane-2,4-dione (24%)

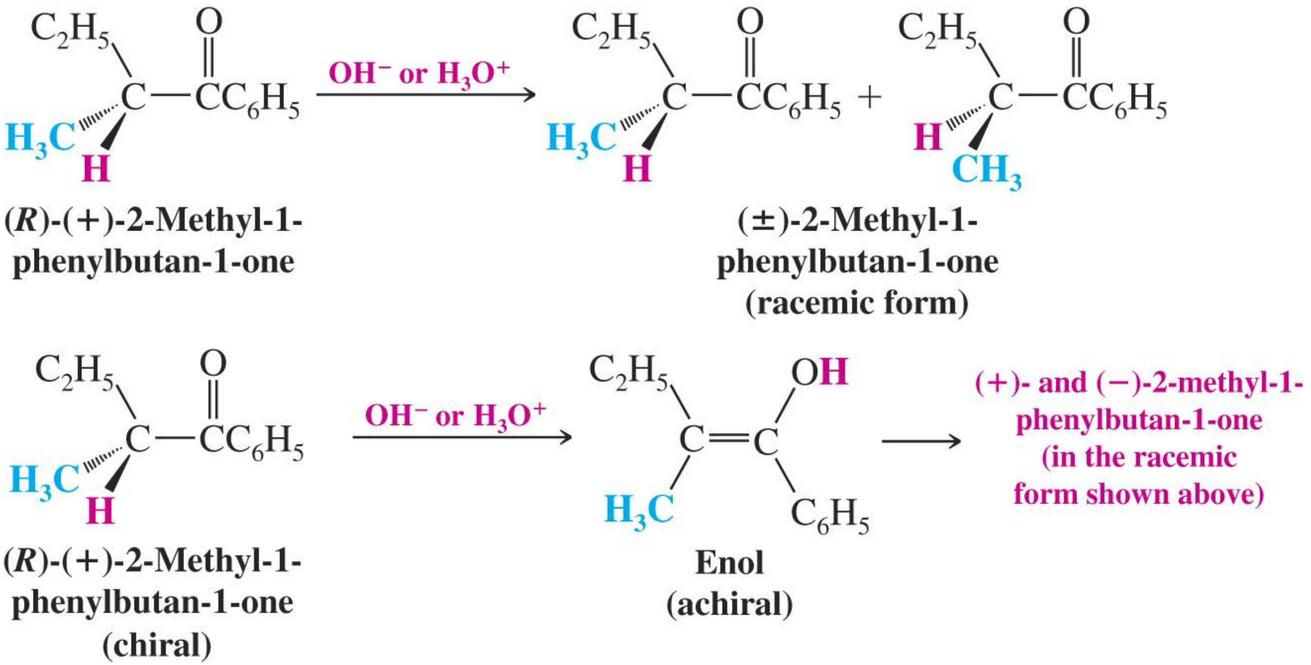
Enol form (76%)



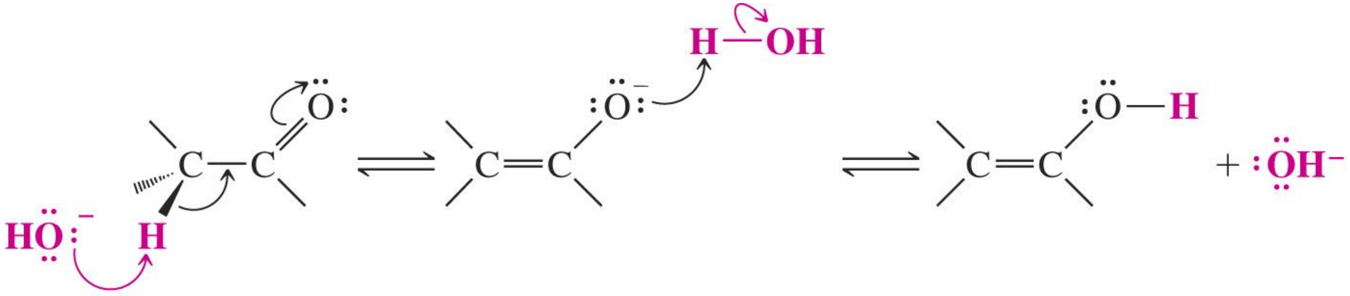
Resonance stabilization of the enol form

♦ Reações via Enois e Anions Enolatos

- **Racemização**
  - **Um aldeido oticamente ativo ou uma cetona com um centro assimétrico no carbono-α pode racemizar na presença de ácido ou base catalíticos. O intermediario enol ou enolato não possue centro asssimetrico na posição α**

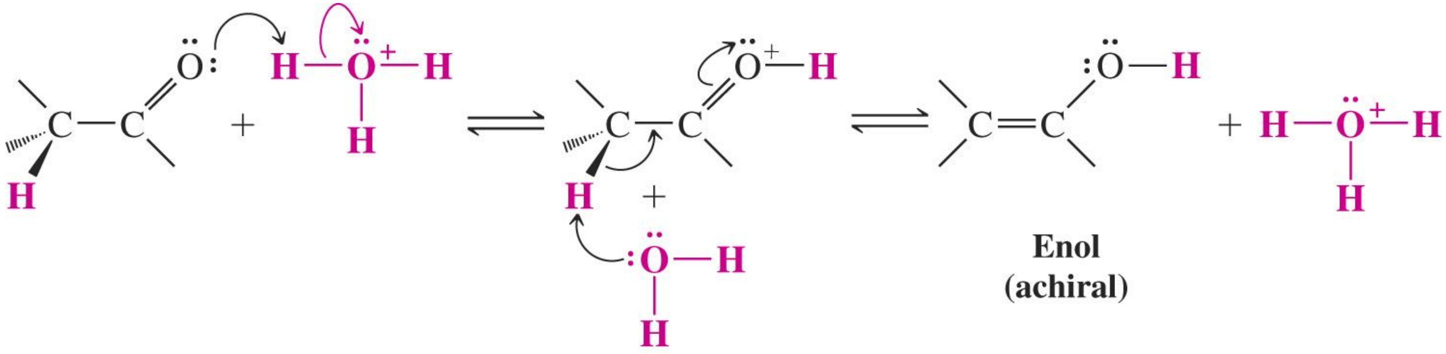


Os mecanismos das racemizaçõese ácidas e básicas são indicadas abaixo



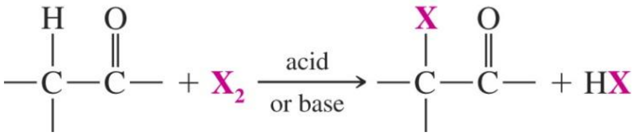
Enolate anion
(achiral)

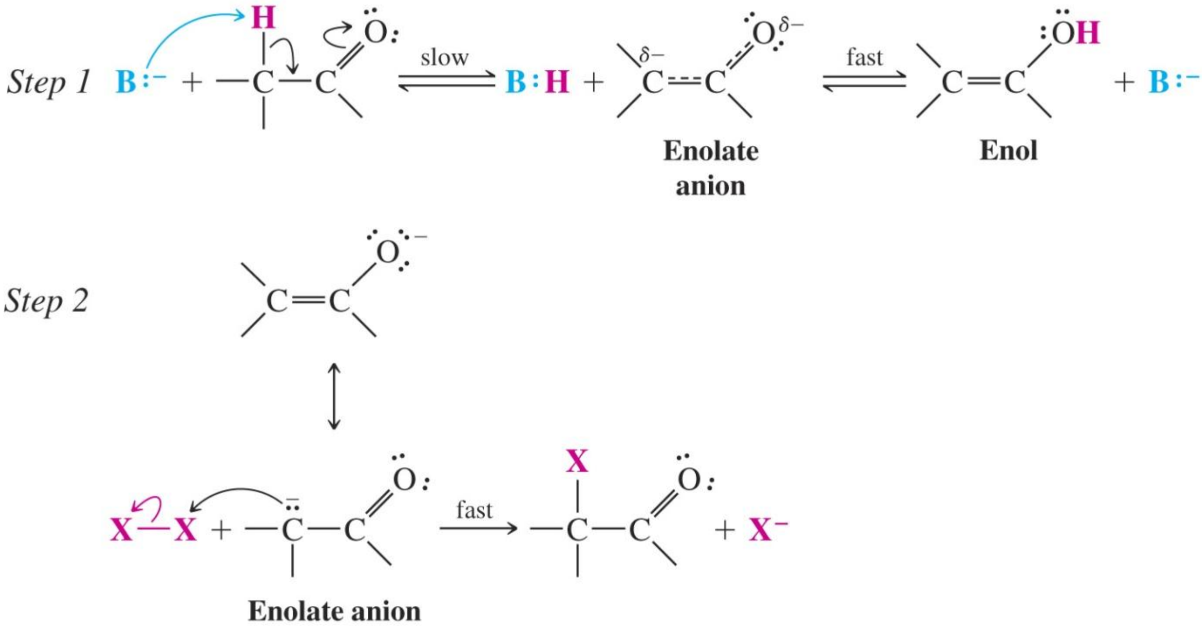
Enol
(achiral)



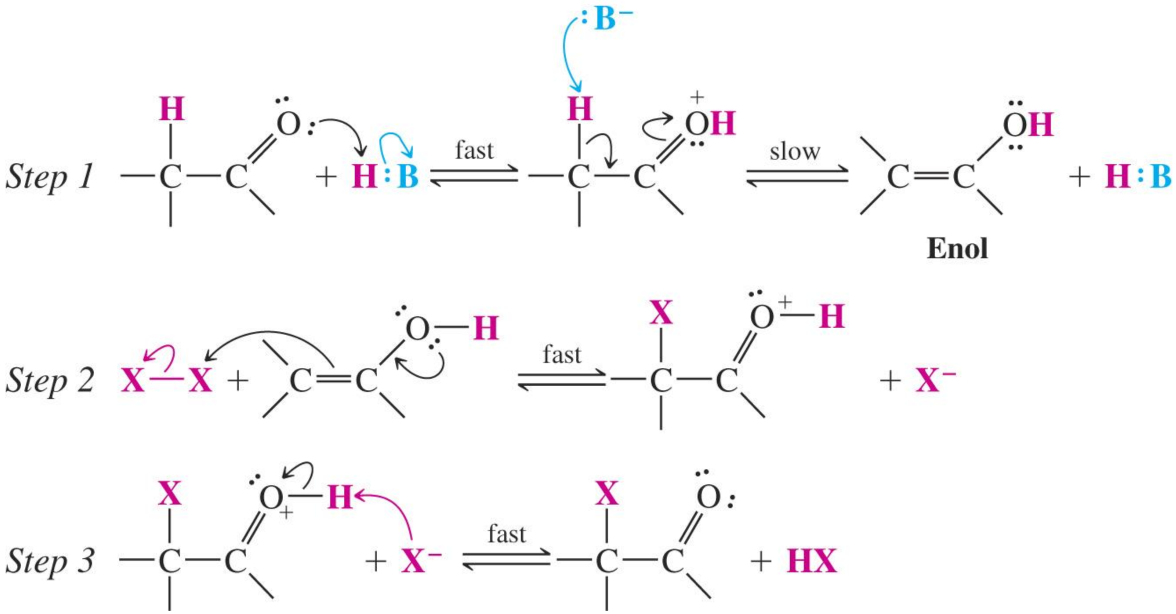
Enol
(achiral)

- **Halogenação de cetonas**
  - Cetonas podem ser halogenadas na posição α na presença de ácido ou base e X_2
  - Halogenação promovida por base ocorre via enolato

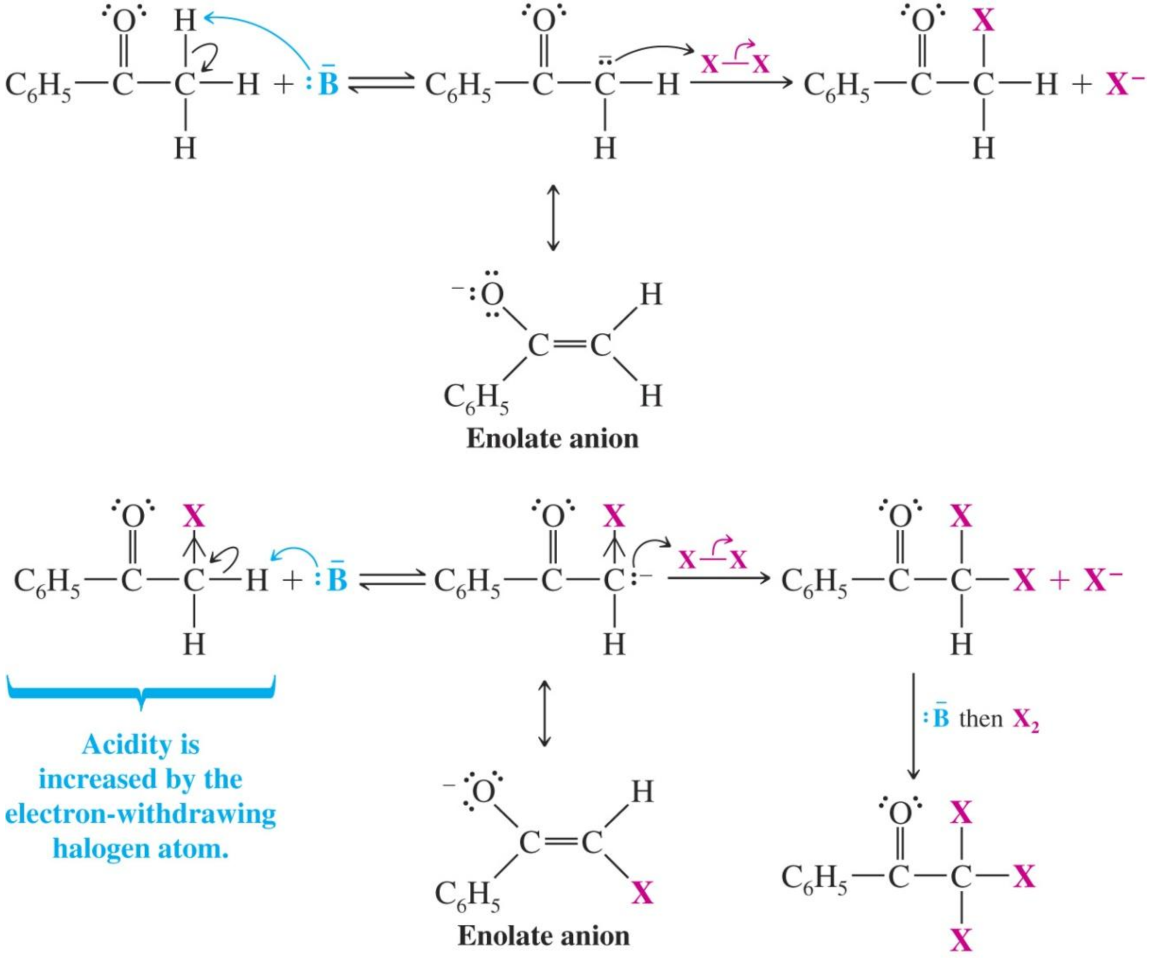




Halogenação catalisada por ácido procede via enol

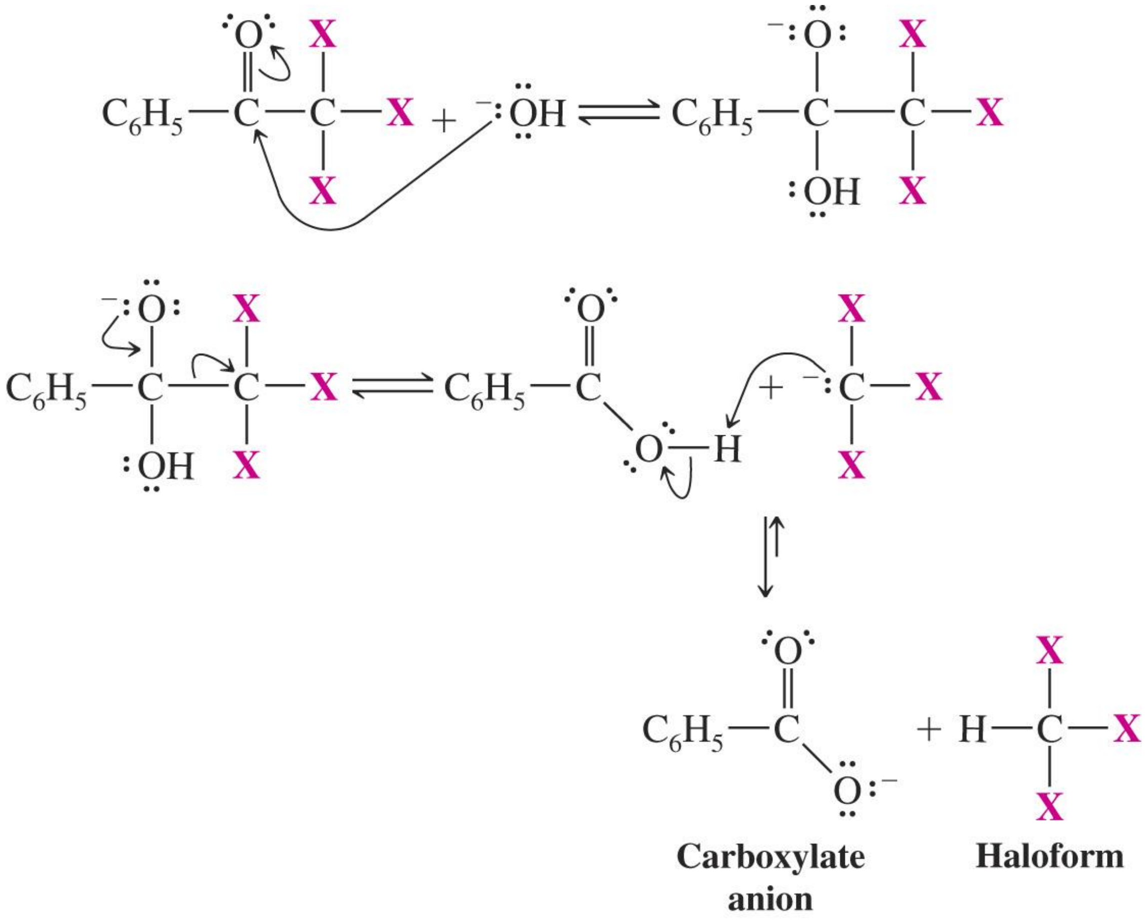


- **Reação do Haloformio**
  - **Metil cetonas reagem com X_2 na presença de base**
    - » Insert mechanism page 777



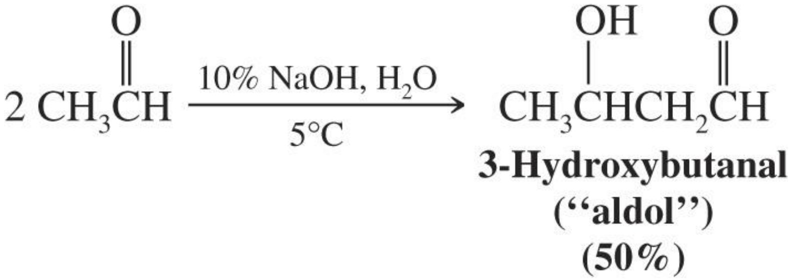
Resultando em carboxilato e haloformio (CX_3H)

O anion trialometil é um bom grupo de saida e tem a carga estabilizada pelos 3 halogênios



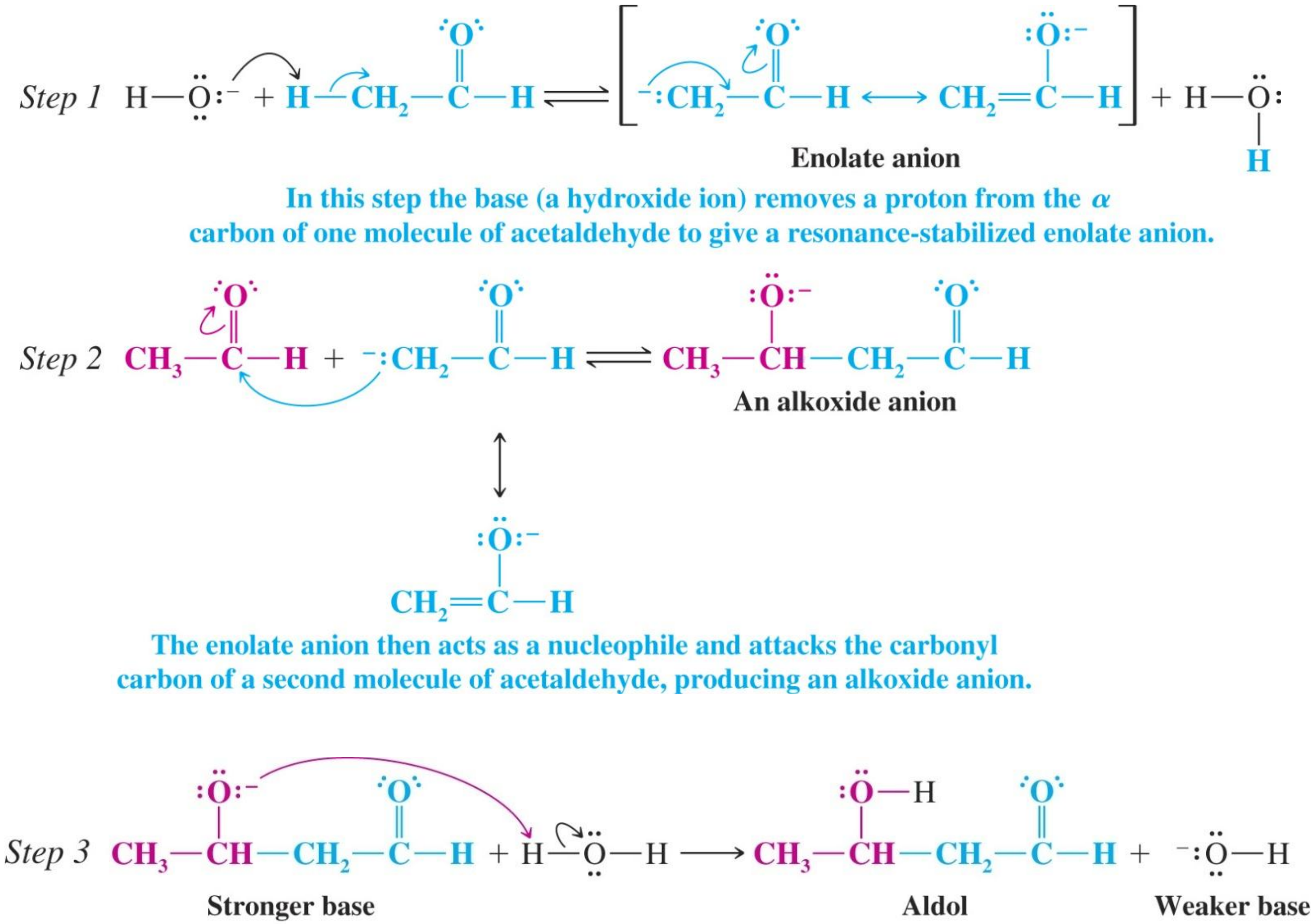
♦ Reação Aldólica: Adição de anions Enolatos a Aldeidos e Cetonas

Acetaldeido dimeriza na presença de hidróxido de sódio diluido a temperatura ambiente. O produto é denominado de aldol (aldeido e álcool)



$$2\ CH_3\overset{\overset{O}{\|}}{C}H \xrightarrow[5°C]{10\%\ NaOH,\ H_2O} CH_3\overset{\overset{OH}{|}}{C}HCH_2\overset{\overset{O}{\|}}{C}H$$

O mecanismo procede via anion enolato



$$\text{H—}\ddot{\text{O}}\text{:}^- + \text{H—CH}_2\text{—}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{—H} \rightleftharpoons \left[{}^-\text{:CH}_2\text{—}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{—H} \longleftrightarrow \text{CH}_2\text{=}\overset{\text{O}^-}{\overset{|}{\text{C}}}\text{—H} \right] + \text{H—}\ddot{\text{O}}\text{—H}$$

In this step the base (a hydroxide ion) removes a proton from the α carbon of one molecule of acetaldehyde to give a resonance-stabilized enolate anion.

$$\text{CH}_3\text{—}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{—H} + {}^-\text{:CH}_2\text{—}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{—H} \rightleftharpoons \text{CH}_3\text{—}\overset{\text{O}^-}{\overset{|}{\text{CH}}}\text{—CH}_2\text{—}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{—H}$$

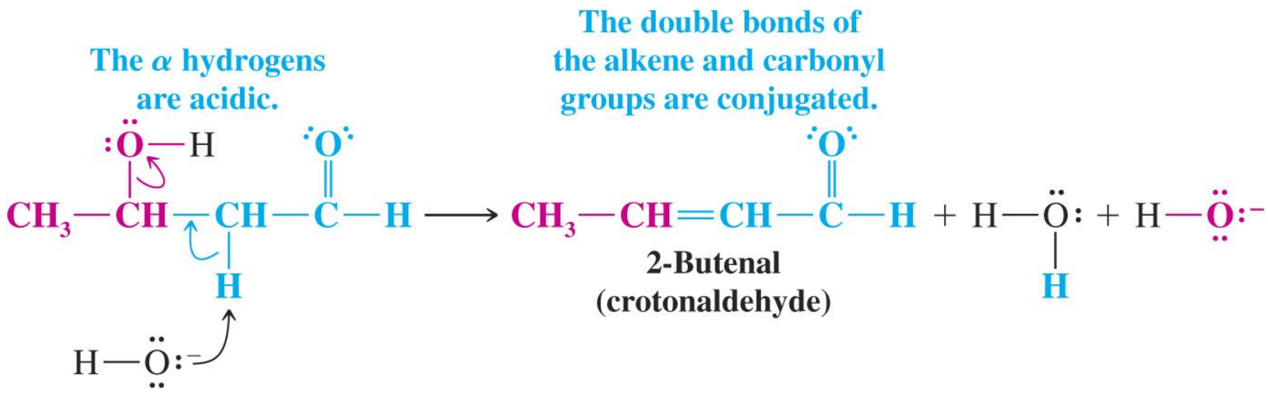
$$\text{CH}_2\text{=}\overset{\text{O}^-}{\overset{|}{\text{C}}}\text{—H}$$

The enolate anion then acts as a nucleophile and attacks the carbonyl carbon of a second molecule of acetaldehyde, producing an alkoxide anion.

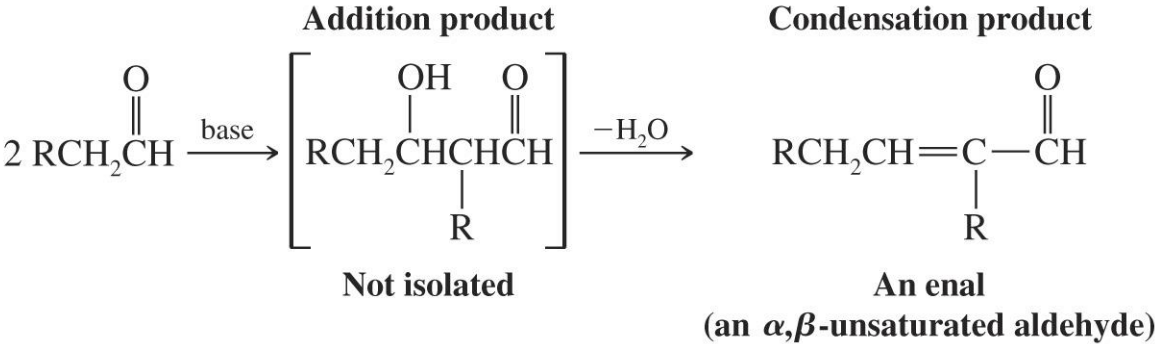
$$\text{CH}_3\text{—}\overset{\text{O}^-}{\overset{|}{\text{CH}}}\text{—CH}_2\text{—}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{—H} + \text{H—}\ddot{\text{O}}\text{—H} \longrightarrow \text{CH}_3\text{—}\overset{\text{OH}}{\overset{|}{\text{CH}}}\text{—CH}_2\text{—}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{—H} + {}^-\text{:}\ddot{\text{O}}\text{—H}$$

The alkoxide anion now removes a proton from a molecule of water to form the aldol.

- **Desidratação do produto aldólico**
  - **If the aldol reaction mixture is heated, dehydration to an α,β-unsaturated carbonyl compound takes place**
    - **Dehydration is favorable because the product is stabilized by conjugation of the alkene with the carbonyl group**

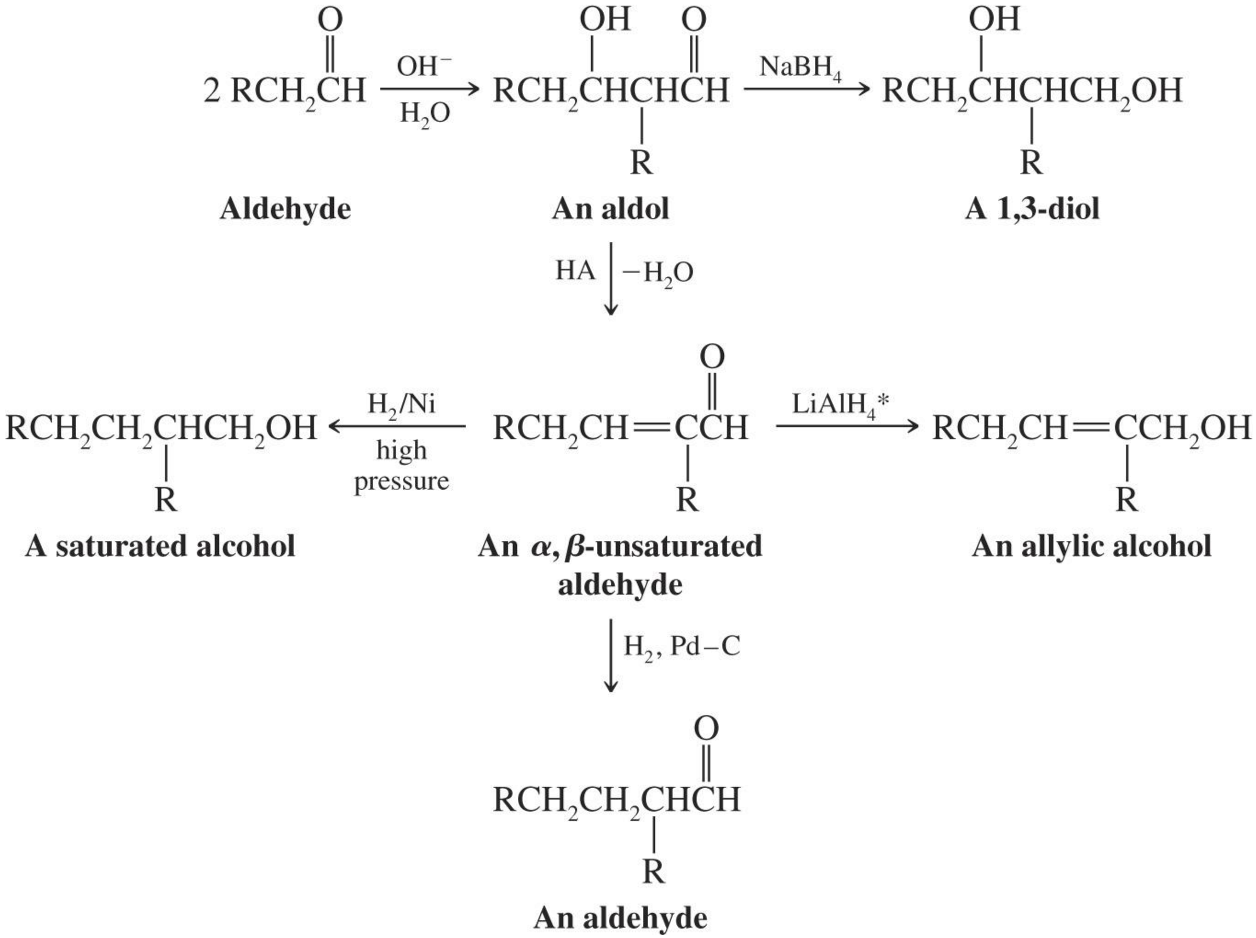


  - **In some aldol reactions, the aldol product cannot be isolated because it is rapidly dehydrated to the α,β-unsaturated compound**



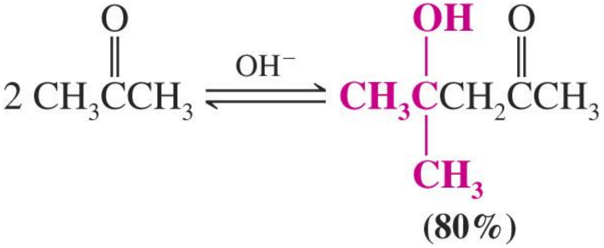
- **Aplicações sintéticas**

  Reações aldólicas permite fazer a ligação entre duas moléculas pequena gerando uma nova ligação carbono-carbono



Reações aldólicas com cetonas são desfavorecidas pois o equilíbrio favorece a cetona de partida

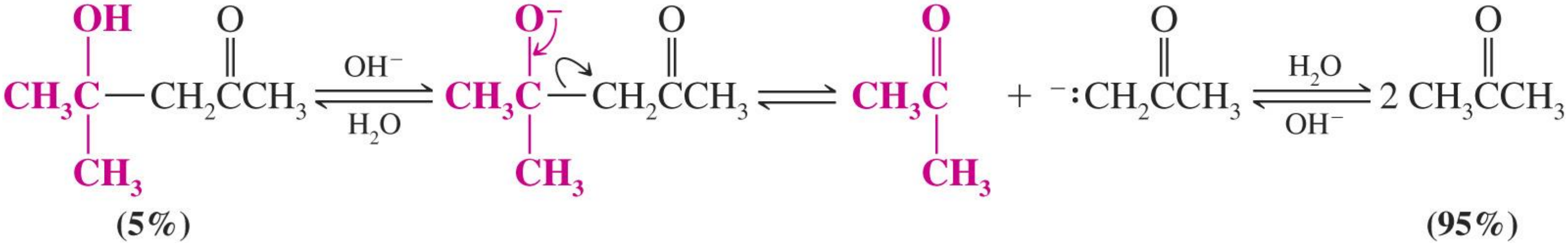
- H **TUso de equipamento para retirar o produto do meio de reação permite obter o aldol em bons rendimentos**



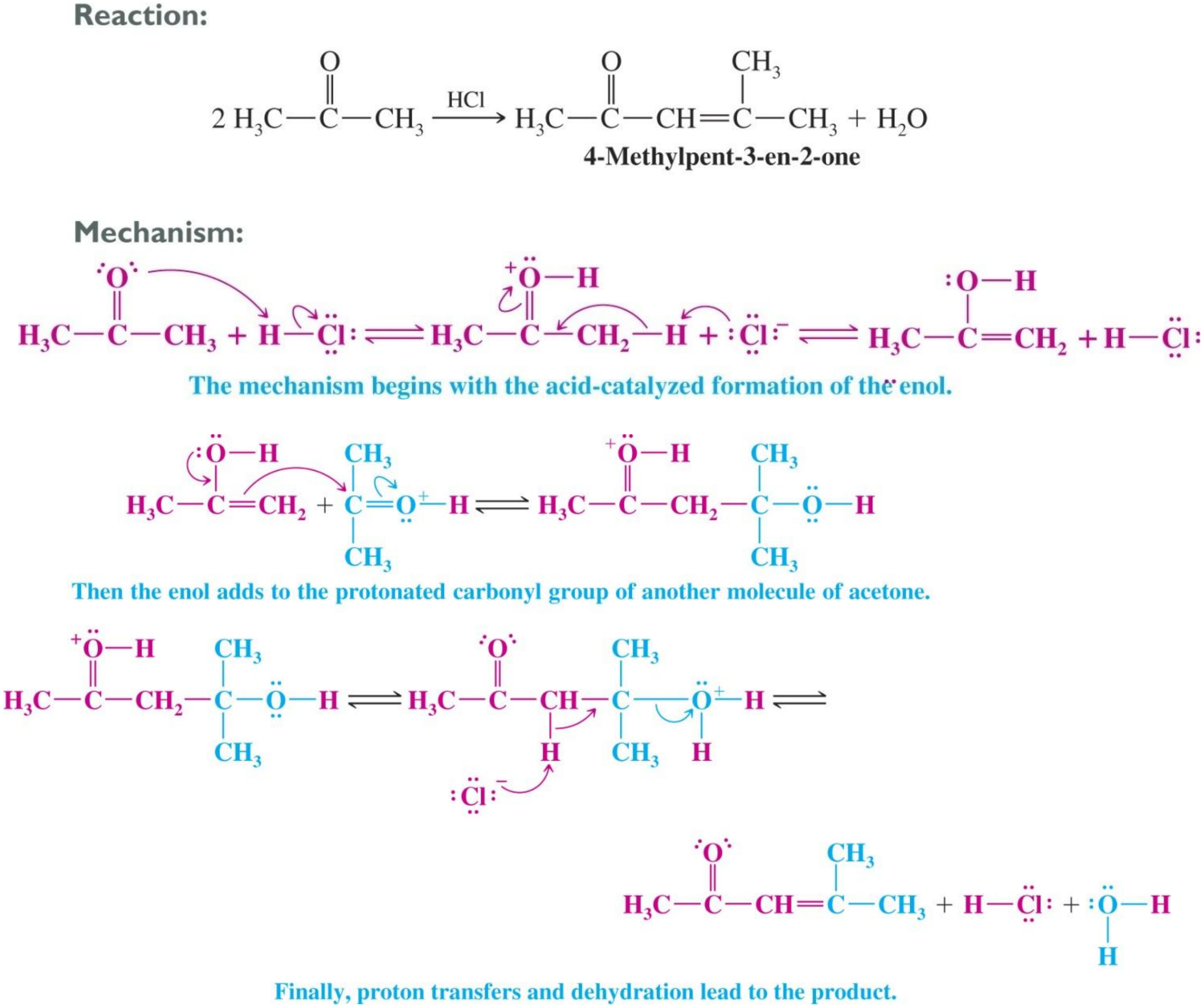
- **A reversibilidade das adições aldólicas**

Produtos de adição aldólica sofrem reações *retro-aldolicas na*

(80%)



- **Condensação aldólica catalisada por ácido**
- **Esta reação leva ao produto de desidratação**



Reaction:

$$2\ H_3C-\overset{\overset{\displaystyle O}{\|}}{C}-CH_3 \xrightarrow{HCl} H_3C-\overset{\overset{\displaystyle O}{\|}}{C}-CH=\overset{\overset{\displaystyle CH_3}{|}}{C}-CH_3 + H_2O$$

4-Methylpent-3-en-2-one

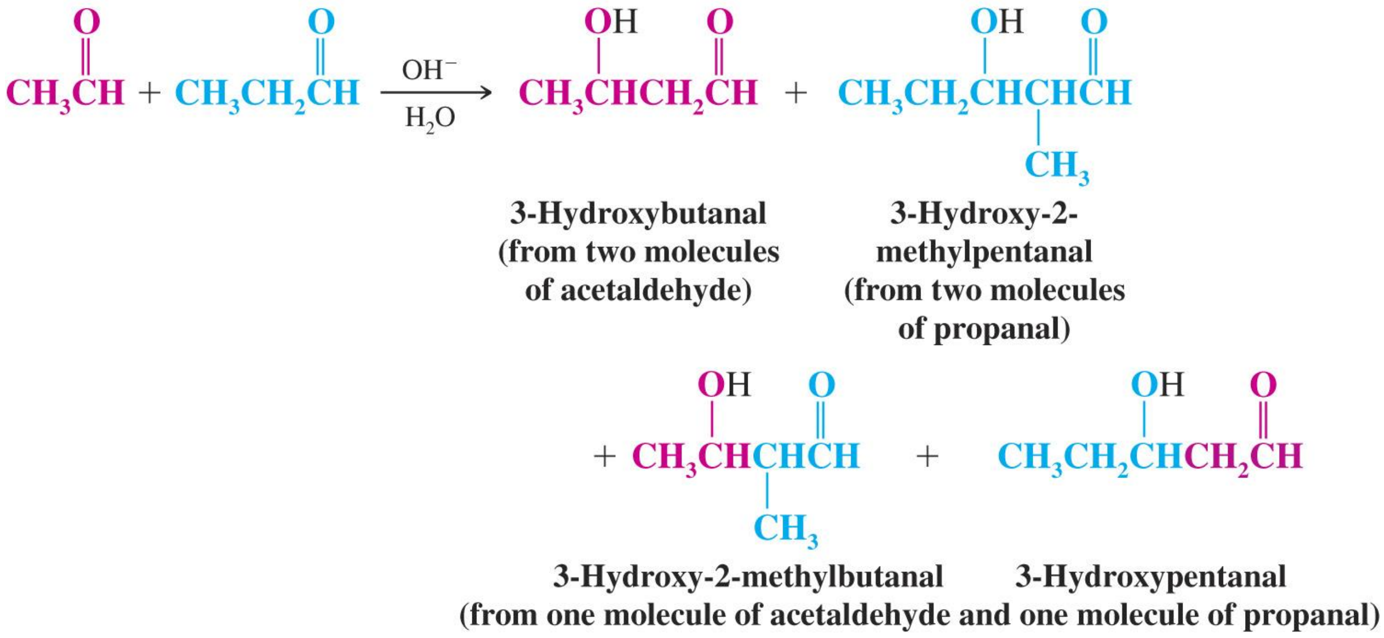
Mechanism:

The mechanism begins with the acid-catalyzed formation of the enol.

Then the enol adds to the protonated carbonyl group of another molecule of acetone.

Finally, proton transfers and dehydration lead to the product.

- **Reações Aldol Cruzadas ocorrem com dois aldeidos diferentes e não são práticas pois geram misturas de produtos**



$$CH_3\overset{\overset{O}{\|}}{C}H + CH_3CH_2\overset{\overset{O}{\|}}{C}H \xrightarrow[H_2O]{OH^-} CH_3\overset{\overset{OH}{|}}{C}HCH_2\overset{\overset{O}{\|}}{C}H + CH_3CH_2\overset{\overset{OH}{|}}{C}H\underset{\underset{CH_3}{|}}{C}H\overset{\overset{O}{\|}}{C}H$$

$$+ CH_3\overset{\overset{OH}{|}}{C}H\underset{\underset{CH_3}{|}}{C}H\overset{\overset{O}{\|}}{C}H + CH_3CH_2\overset{\overset{OH}{|}}{C}HCH_2\overset{\overset{O}{\|}}{C}H$$

3-Hydroxybutanal (from two molecules of acetaldehyde)

3-Hydroxy-2-methylpentanal (from two molecules of propanal)

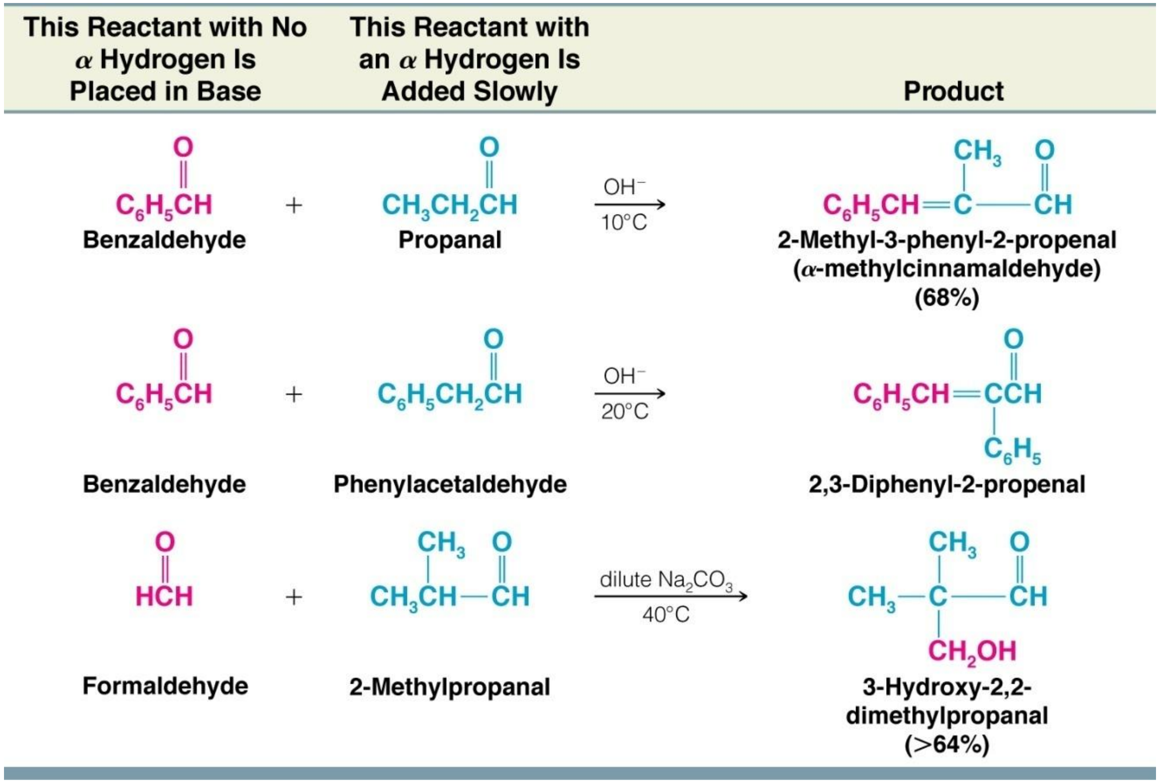
3-Hydroxy-2-methylbutanal

3-Hydroxypentanal

(from one molecule of acetaldehyde and one molecule of propanal)

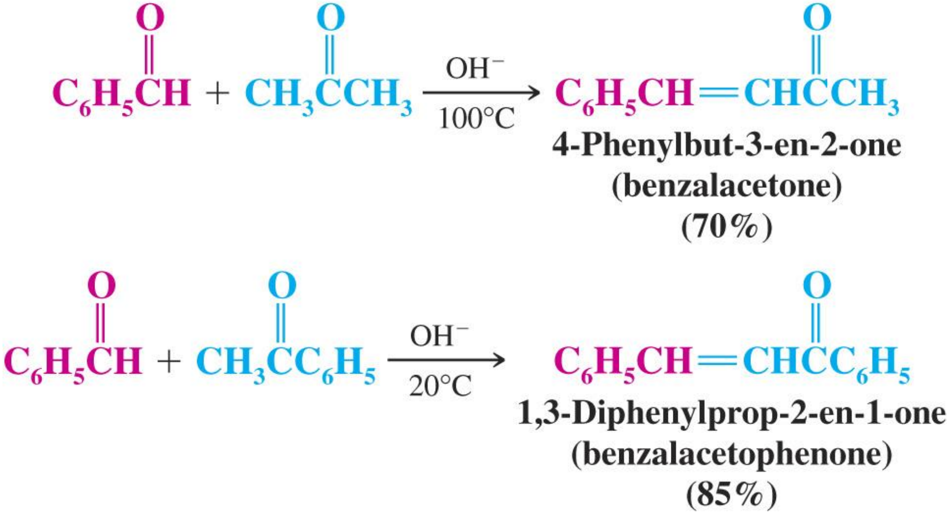
- **Reações aldólicas cruzadas praticas são aquelas em que um dos aldeido não possue hidrogênio α. O aldeido sem hidrogênio no carbono α é adicionado em meio básico e depois adiciona-se o segundo aldeido**

Desidratação corre imediatamente se houver conjugão



This Reactant with No α Hydrogen Is Placed in Base		This Reactant with an α Hydrogen Is Added Slowly		Product
$C_6H_5\overset{O}{\overset{\|}{C}}H$ Benzaldehyde	+	$CH_3CH_2\overset{O}{\overset{\|}{C}}H$ Propanal	$\xrightarrow[10°C]{OH^-}$	$C_6H_5CH{=}\overset{CH_3}{\overset{\|}{C}}{-}\overset{O}{\overset{\|}{C}}H$ 2-Methyl-3-phenyl-2-propenal (α-methylcinnamaldehyde) (68%)
$C_6H_5\overset{O}{\overset{\|}{C}}H$ Benzaldehyde	+	$C_6H_5CH_2\overset{O}{\overset{\|}{C}}H$ Phenylacetaldehyde	$\xrightarrow[20°C]{OH^-}$	$C_6H_5CH{=}\underset{C_6H_5}{\underset{\|}{C}}\overset{O}{\overset{\|}{C}}H$ 2,3-Diphenyl-2-propenal
$H\overset{O}{\overset{\|}{C}}H$ Formaldehyde	+	$CH_3\overset{CH_3}{\overset{\|}{C}}H{-}\overset{O}{\overset{\|}{C}}H$ 2-Methylpropanal	$\xrightarrow[40°C]{\text{dilute } Na_2CO_3}$	$CH_3{-}\underset{CH_2OH}{\underset{\|}{\overset{CH_3}{\overset{\|}{C}}}}{-}\overset{O}{\overset{\|}{C}}H$ 3-Hydroxy-2,2-dimethylpropanal (>64%)

- **Reação de Claisen-Schmidt são reações aldólicas cruzadas com cetonas**
  - **O produto da condensação da cetona não predomina pois não é favorecido pelo equilibrio**

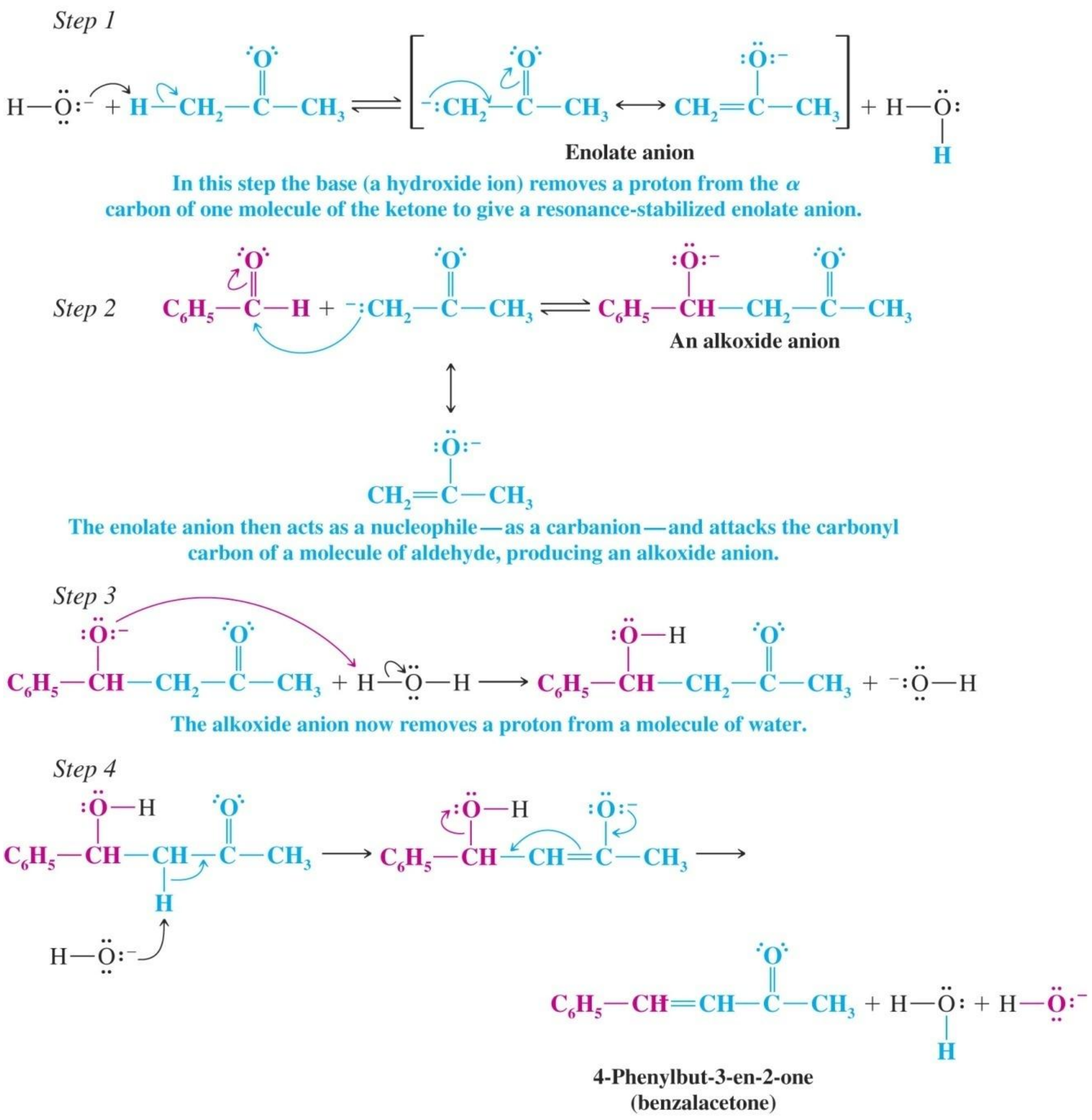


$$C_6H_5\overset{\overset{\displaystyle O}{\|}}{C}H + CH_3\overset{\overset{\displaystyle O}{\|}}{C}CH_3 \xrightarrow[100°C]{OH^-} C_6H_5CH{=}CH\overset{\overset{\displaystyle O}{\|}}{C}CH_3$$

4-Phenylbut-3-en-2-one
(benzalacetone)
(70%)

$$C_6H_5\overset{\overset{\displaystyle O}{\|}}{C}H + CH_3\overset{\overset{\displaystyle O}{\|}}{C}C_6H_5 \xrightarrow[20°C]{OH^-} C_6H_5CH{=}CH\overset{\overset{\displaystyle O}{\|}}{C}C_6H_5$$

1,3-Diphenylprop-2-en-1-one
(benzalacetophenone)
(85%)



In this step the base (a hydroxide ion) removes a proton from the α carbon of one molecule of the ketone to give a resonance-stabilized enolate anion.

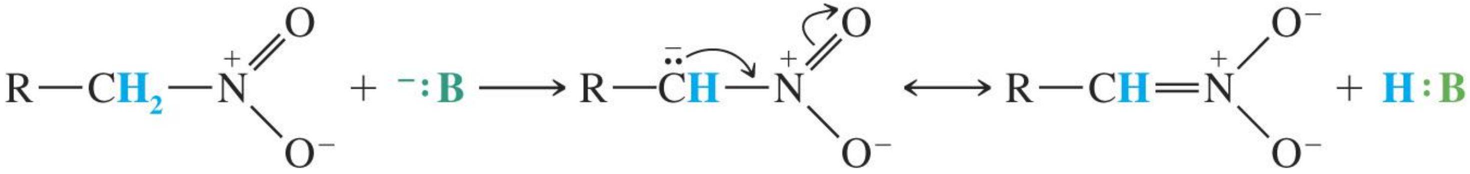
The enolate anion then acts as a nucleophile—as a carbanion—and attacks the carbonyl carbon of a molecule of aldehyde, producing an alkoxide anion.

The alkoxide anion now removes a proton from a molecule of water.

Dehydration produces the conjugated product.

- **Condensação com Nitroalcanos**

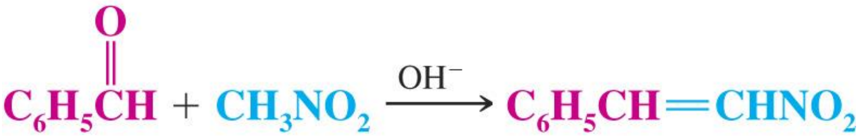
  Os hidrogênios α dos nitroalkanos são fracamente acidos (p*K*a = 10) pois os anions resultante são estabilizados por ressonancia



Resonance-stabilized anion

  Anions Nitroalcanos podem sofrer condensação do tipo aldol com aldeidos e cetonas

  O grupo nitro pode ser reduzido a amina



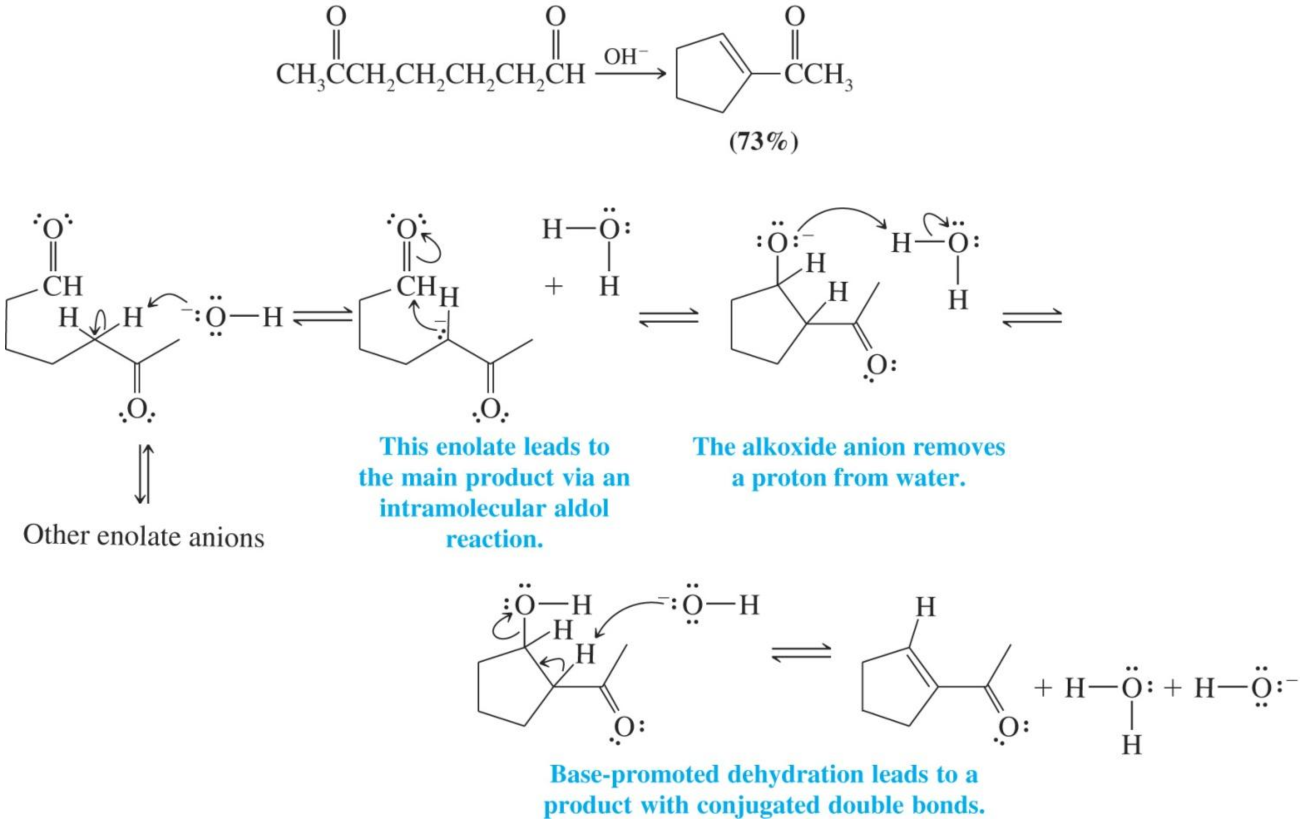
$$C_6H_5\overset{\overset{O}{\|}}{C}H + CH_3NO_2 \xrightarrow{OH^-} C_6H_5CH{=}CHNO_2$$

$$C_6H_5CH{=}CHNO_2 \xrightarrow{H_2,\ Ni} C_6H_5CH_2CH_2NH_2$$

♦ Ciclização via Condensação Aldólica

Reação intramolecular dos compostos dicarbonílicos procedem preferencialmente via aneis de cinco e seis membros

Na reação abaixo a carbonila do aldeido é atacada preferencialmente por sofrer menor repulsão eletronica e impedimento estéreo do que a cetona



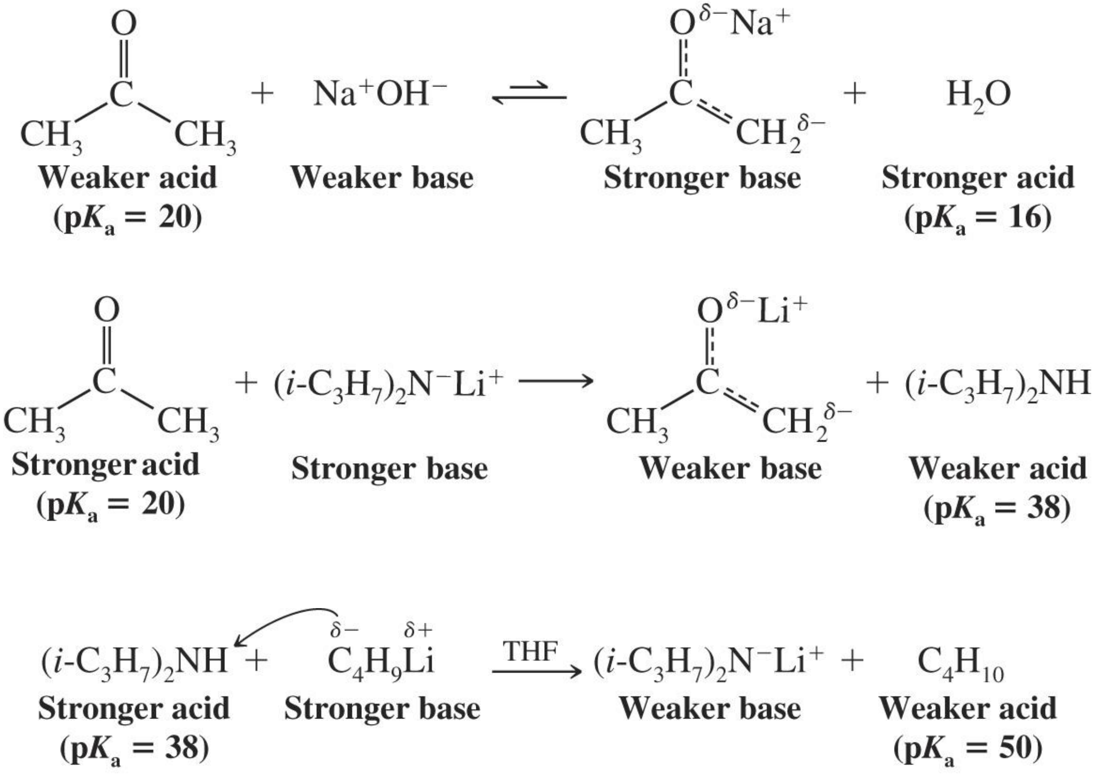
This enolate leads to the main product via an intramolecular aldol reaction.

The alkoxide anion removes a proton from water.

Base-promoted dehydration leads to a product with conjugated double bonds.

♦ Enolatos de Litio

- Na presença de uma base forte como amideto de diisopropil lítio (LDA), a formação do enolato é favorecida
  - Bases fracas como ´hidróxido de só dio produzem somente pequenas quantidades de enolatos.



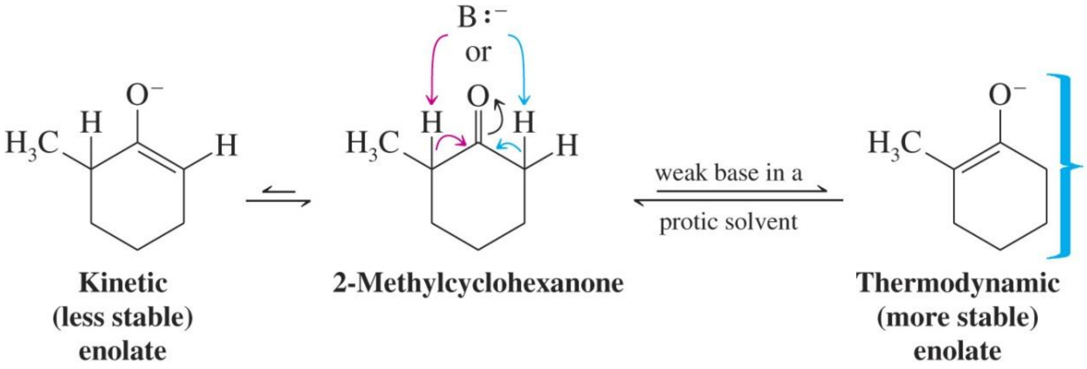
- **Regiosseletividade da Formação dos Enolatos**

  CetonaS não simétricas podem formar dois enolatos distintos.

  <u>Enolato termodinâmico ,o mais substituido e</u>

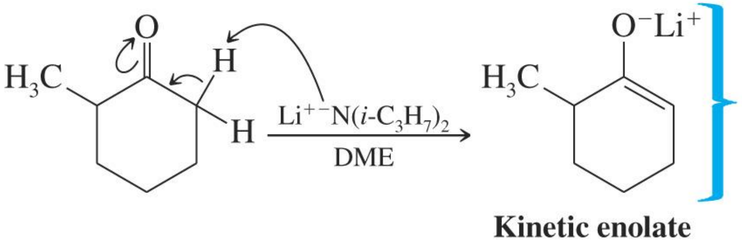
  one with the more highly substituted double bond

  - H **A weak base favors the thermodynamic enolate because an equilibrium between the enolates is estabilished**



This enolate is more stable because the double bond is more highly substituted. It is the predominant enolate at equilibrium.

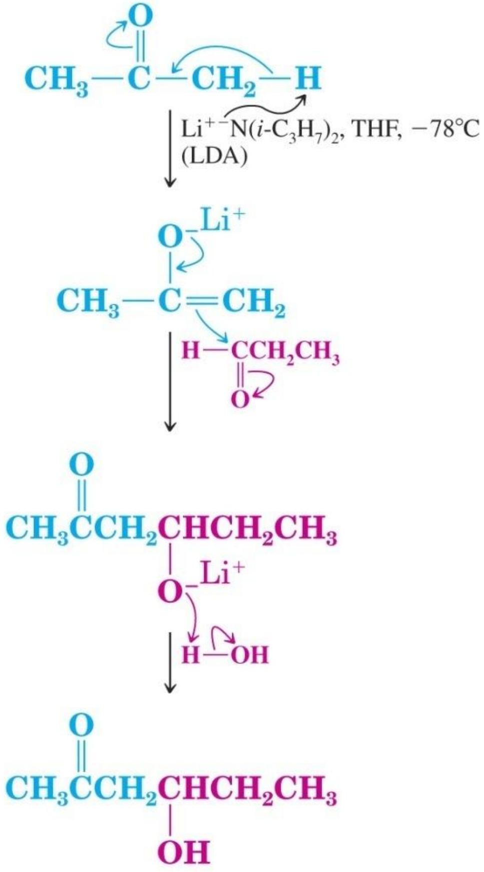
- è **The <u>kinetic enolate</u> is the enolate formed fastest and it usually is the enolate with the least substituted double bond**
  - H **A strong, sterically hindered base such as lithium diisopropyl amide favors formation of the kinetic enolate**



This enolate is formed faster because the hindered strong base removes the less-hindered proton faster.

Lithium Enolates in Directed Aldol Reactions

- Crossed aldol reactions proceed effectively when a ketone is first deprotonated with a strong base such as LDA and the aldehyde is added slowly to the enolate

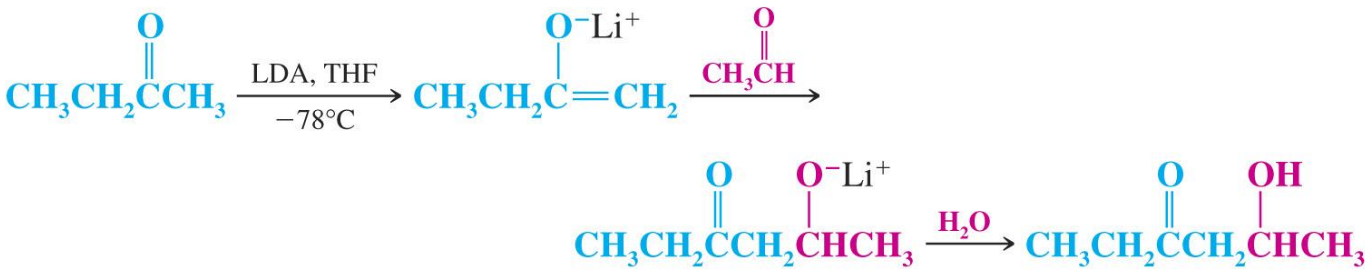


The ketone is added to LDA, the strong base, which removes an α hydrogen from the ketone to produce an enolate.

The aldehyde is added and the enolate reacts with the aldehyde at its carbonyl carbon.

An acid–base reaction occurs when water is added at the end, protonating the lithium alkoxide.

- **An unsymmetrical ketone can be selectively deprotonated with LDA to form the kinetic enolate and this will react with an aldehyde to give primarily one product**



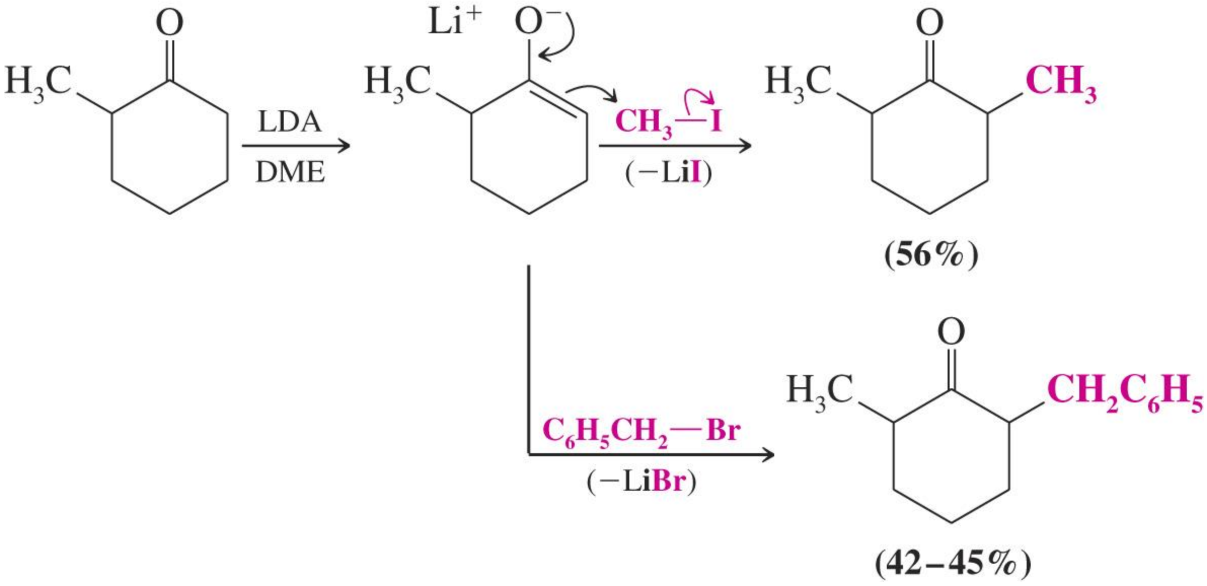
$$CH_3CH_2\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow[-78^\circ C]{\text{LDA, THF}} CH_3CH_2\overset{O^-Li^+}{\overset{|}{C}}{=}CH_2 \xrightarrow{CH_3\overset{O}{\overset{\|}{C}}H}$$

$$CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2\overset{O^-Li^+}{\overset{|}{C}}HCH_3 \xrightarrow{H_2O} CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2\overset{OH}{\overset{|}{C}}HCH_3$$

(75%)

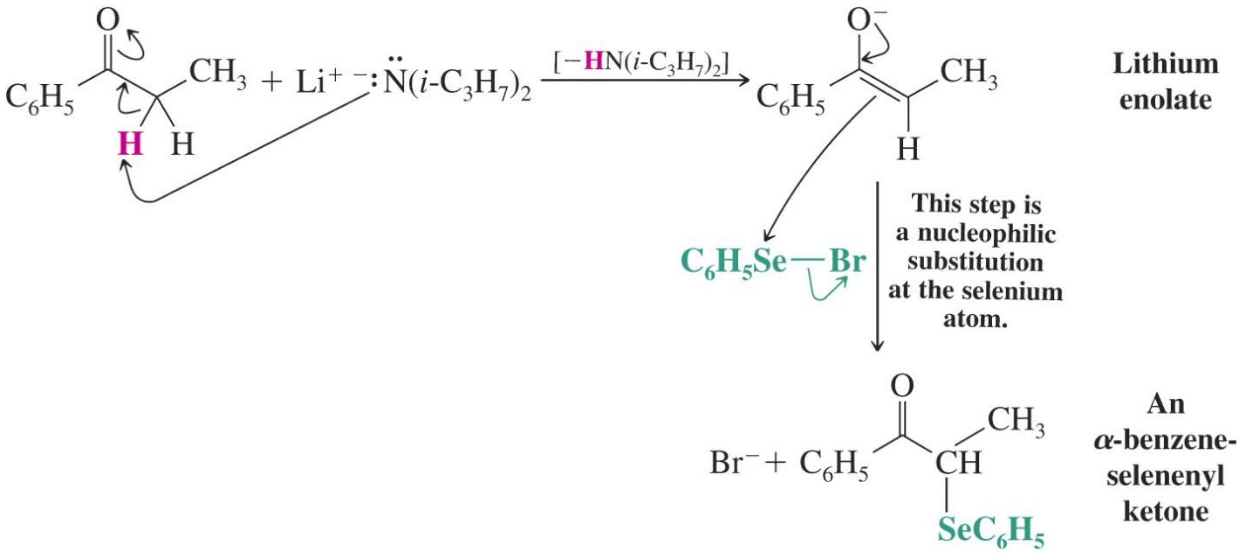
A single crossed aldol product results.

- **Direct Alkylation of Ketones via Lithium Enolates**
  - **Enolates can also be alkylated with primary alkyl halides via an S_N2 reaction**
    - **Unsymmetrical ketones can be alkylated at the least substituted position if LDA is used to form the kinetic enolate**

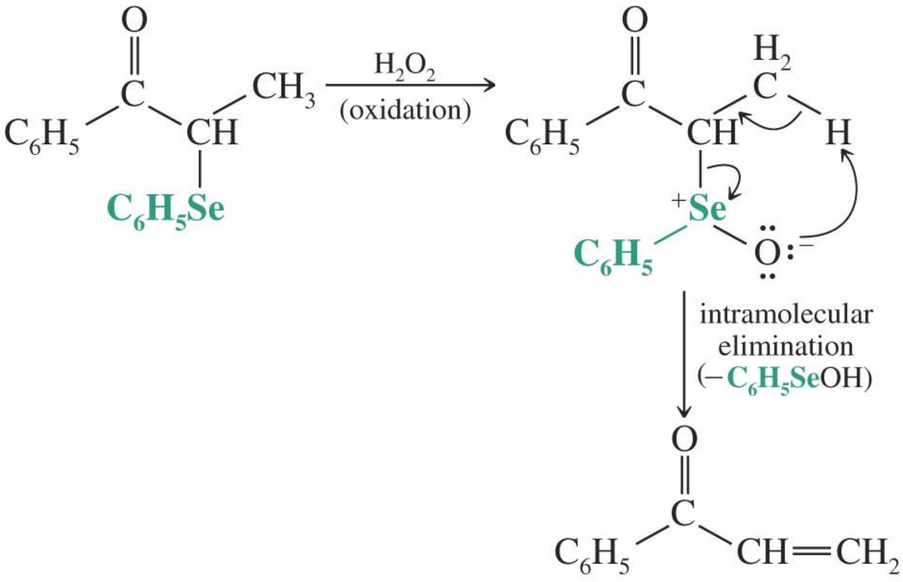


♦ α-Selenation: A Synthesis of α,β-Unsaturated Carbonyl Compounds

- è A lithium enolate can be selenated with benzeneselenyl bromide

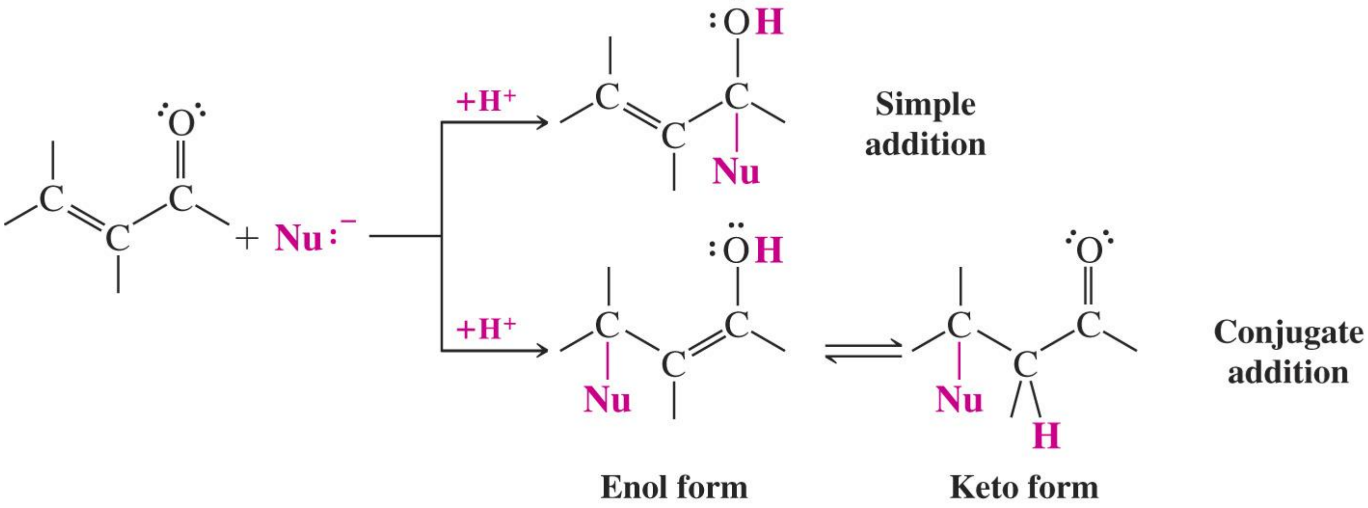


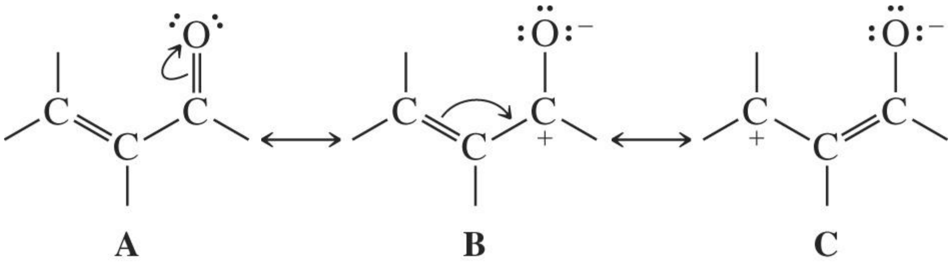
- **The α-selenyl ketone is converted to the α,β-unsaturated carbonyl compound by reaction with hydrogen peroxide**
  - **Elimination of the selenoxide produces the unsaturated carbonyl**



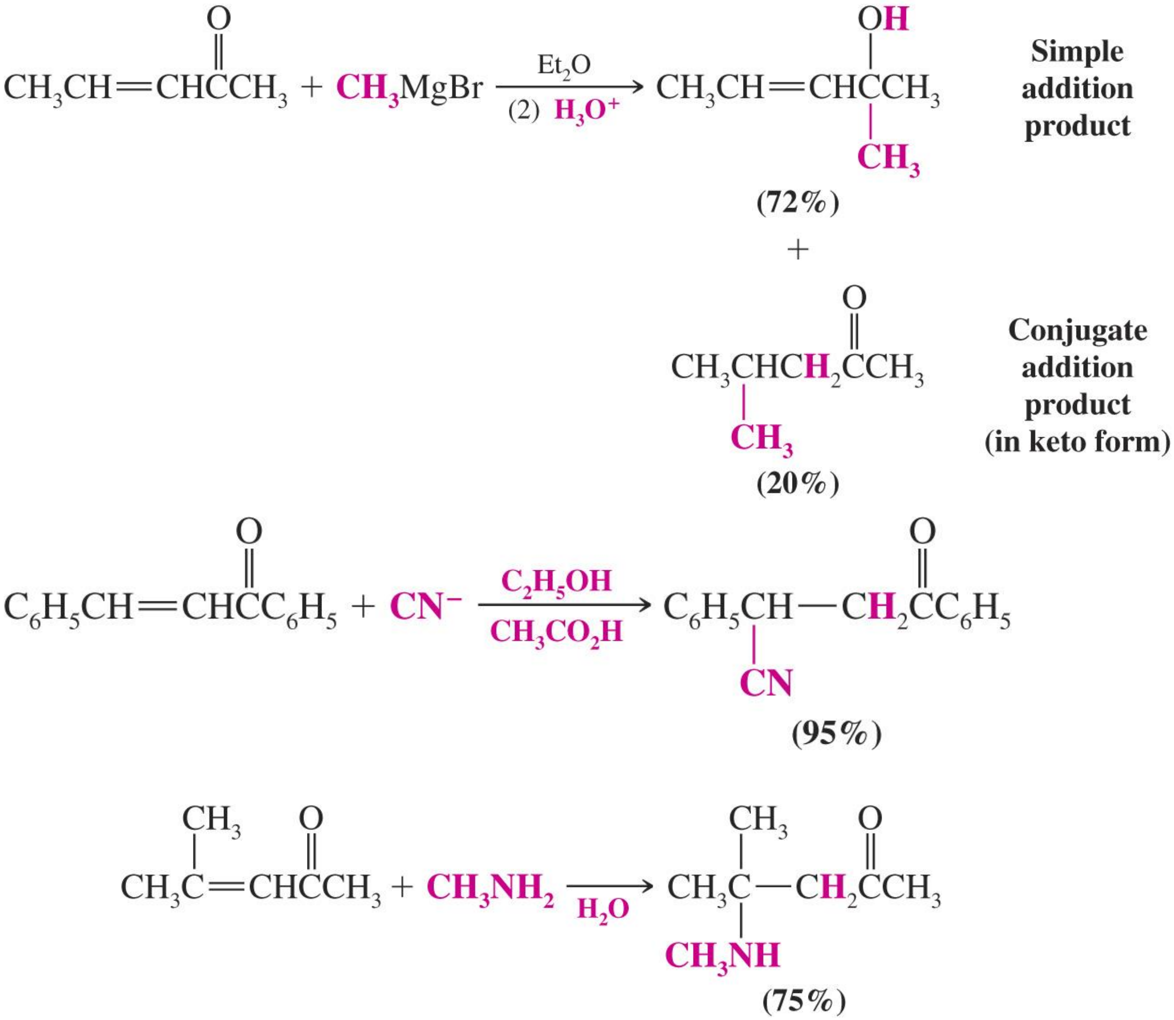
♦ Additions to *α,β*-Unsaturated Aldehydes and Ketones

- è *α,β*-Unsaturated aldehydes and ketones can react by simple (1,2) or conjugate (1,4) addition
  - H Both the carbonyl carbon and the β carbon are electrophilic and can react with nucleophiles





- **Stronger nucleophiles such as Grignard reagents favor 1,2 addition whereas weaker nucleophiles such as cyanide or amines favor 1,4 addition**



$$CH_3CH{=}CH\overset{O}{\overset{\|}{C}}CH_3 + CH_3MgBr \xrightarrow[(2)\ H_3O^+]{Et_2O} CH_3CH{=}CH\underset{CH_3}{\overset{OH}{C}}CH_3$$

(72%)

Simple addition product

+

$$CH_3\underset{CH_3}{CH}CH_2\overset{O}{\overset{\|}{C}}CH_3$$

(20%)

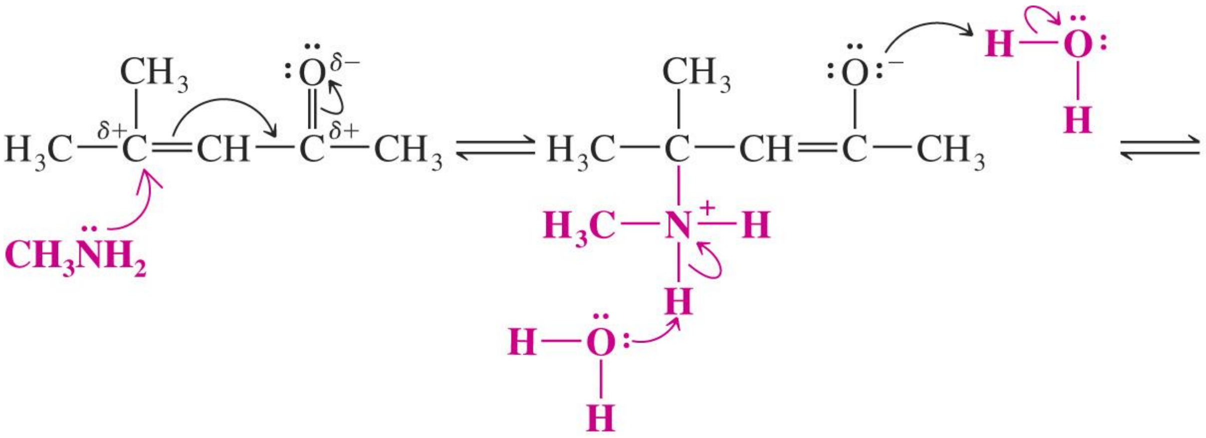
Conjugate addition product (in keto form)

$$C_6H_5CH{=}CH\overset{O}{\overset{\|}{C}}C_6H_5 + CN^- \xrightarrow[CH_3CO_2H]{C_2H_5OH} C_6H_5\underset{CN}{CH}{-}CH_2\overset{O}{\overset{\|}{C}}C_6H_5$$

(95%)

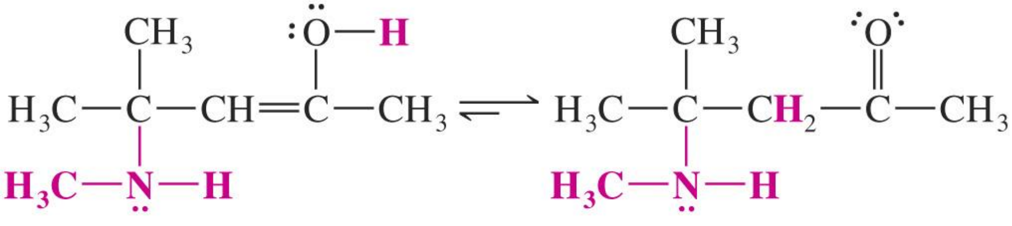
$$CH_3\overset{CH_3}{C}{=}CH\overset{O}{\overset{\|}{C}}CH_3 + CH_3NH_2 \xrightarrow[H_2O]{} CH_3\underset{CH_3NH}{\overset{CH_3}{C}}{-}CH_2\overset{O}{\overset{\|}{C}}CH_3$$

(75%)



The nucleophile attacks the partially positive β carbon.

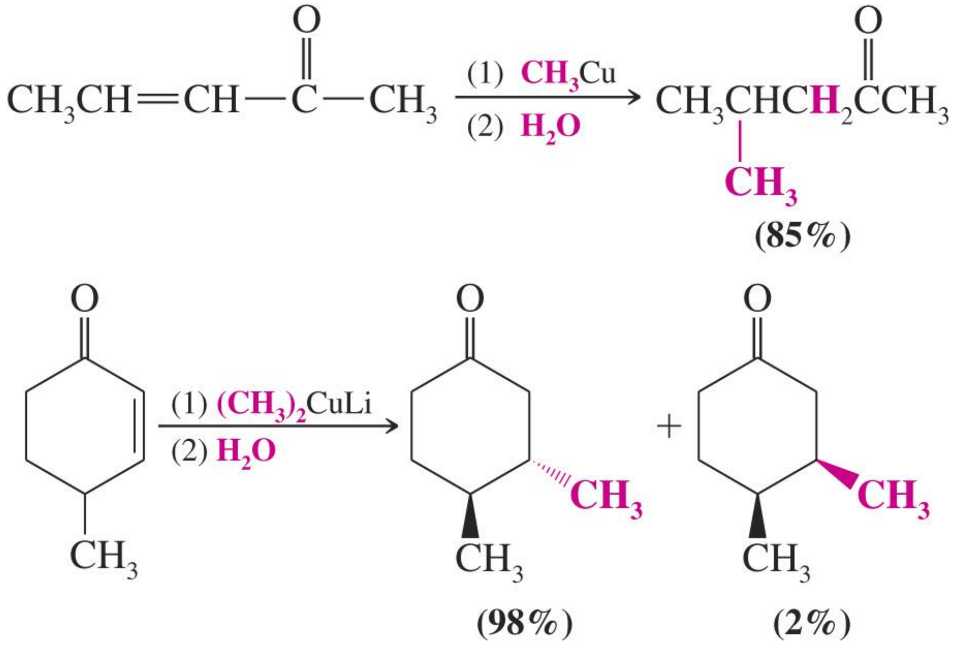
In two separate steps, a proton is lost from the nitrogen atom and a proton is gained at the oxygen.



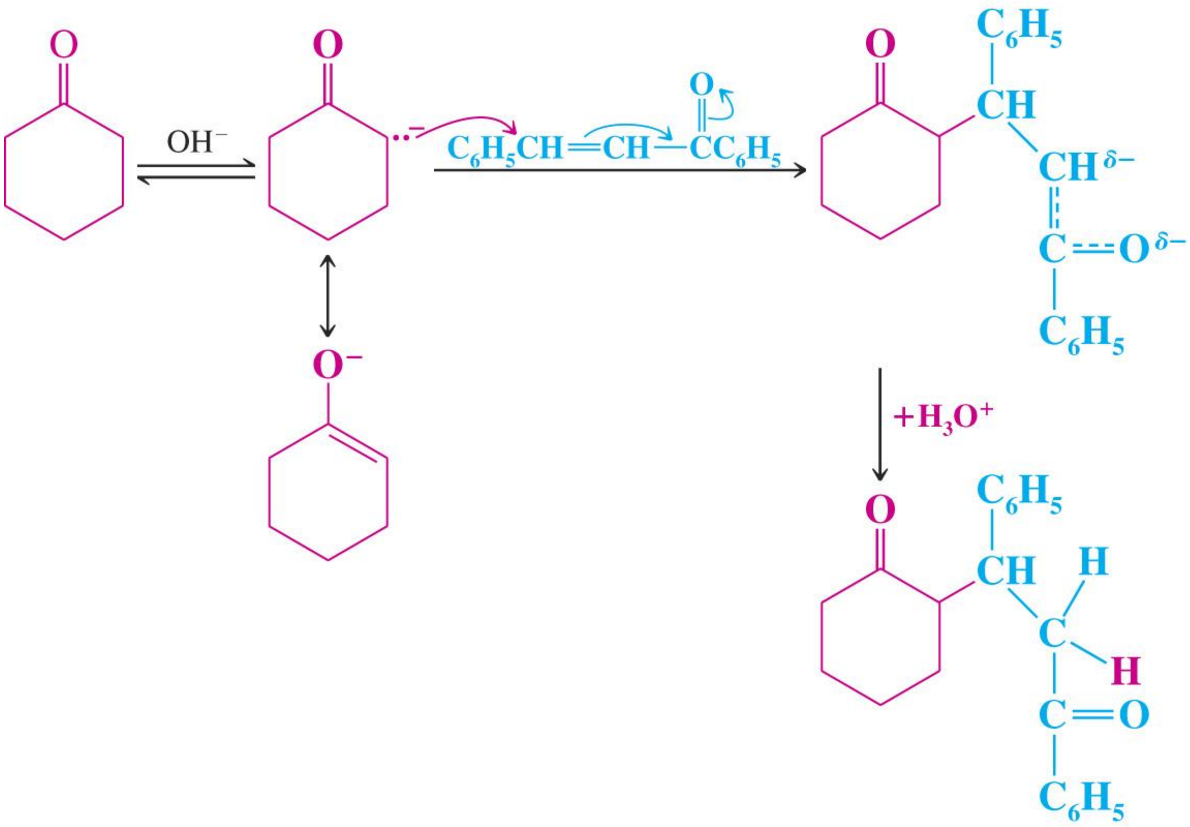
Enol form

Keto form

- **Conjugate Addition of Organocopper Reagents**
  - **Organocopper reagents add almost exclusively in a conjugate manner to α,β-unsaturated aldehydes and ketones**



- **Michael Additions**
  - è **Addition of an enolate to an α,β-unsaturated carbonyl compound usually occurs by conjugate addition**
  - è **This reaction is called a Michael addition**



- **A Robinson annulation can be used to build a new six-membered ring on an existing ring**
  - **Robinson annulation involves a Michael addition followed by an aldol condensation to close the ring**