

# Organic Chemistry II / CHEM 252

## Chapter 17 – Aldehydes and Ketones II. Aldol Reactions

Bela Torok

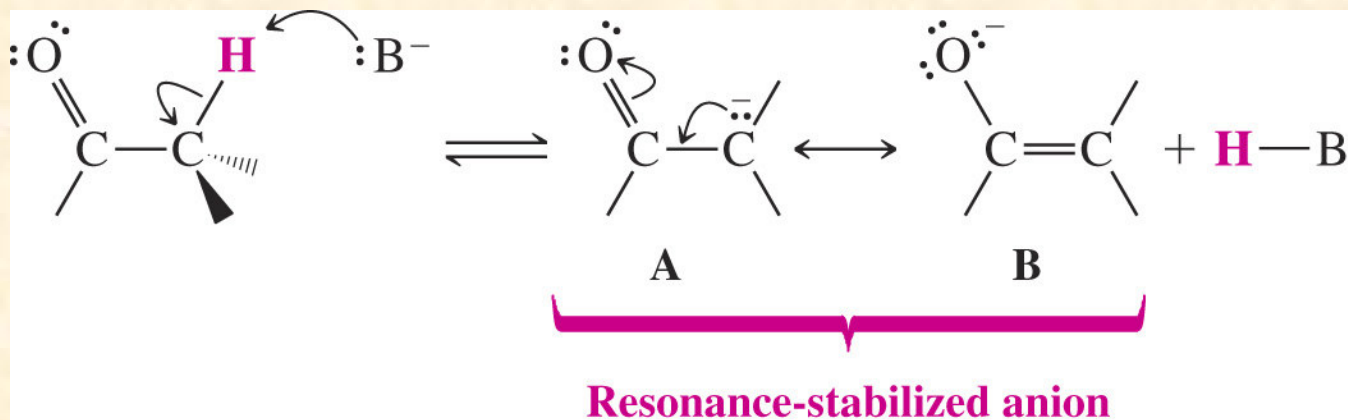
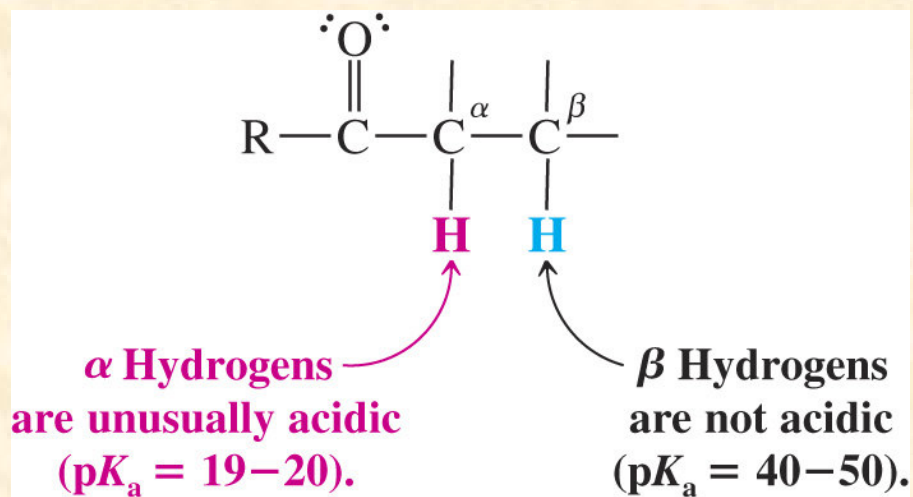
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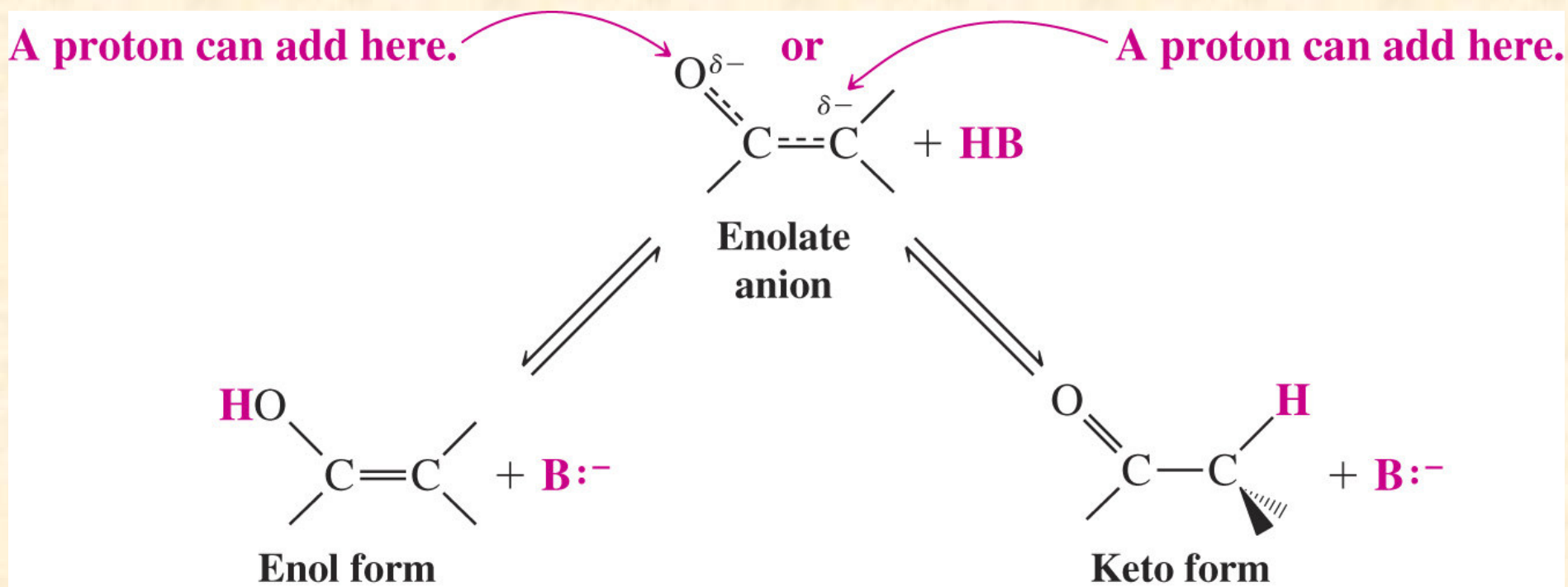
# Acidity of Carbonyl Compounds

- The Acidity of the  $\alpha$  Hydrogens of Carbonyl Compounds: Enolate Anions
  - Hydrogens on carbons  $\alpha$  to carbonyls are unusually acidic
    - The resulting anion is stabilized by resonance to the carbonyl



# Acidity of Carbonyl Compounds

- The enolate anion can be protonated at the carbon or the oxygen
  - The resultant enol and keto forms of the carbonyl are formed reversibly and are interconvertible

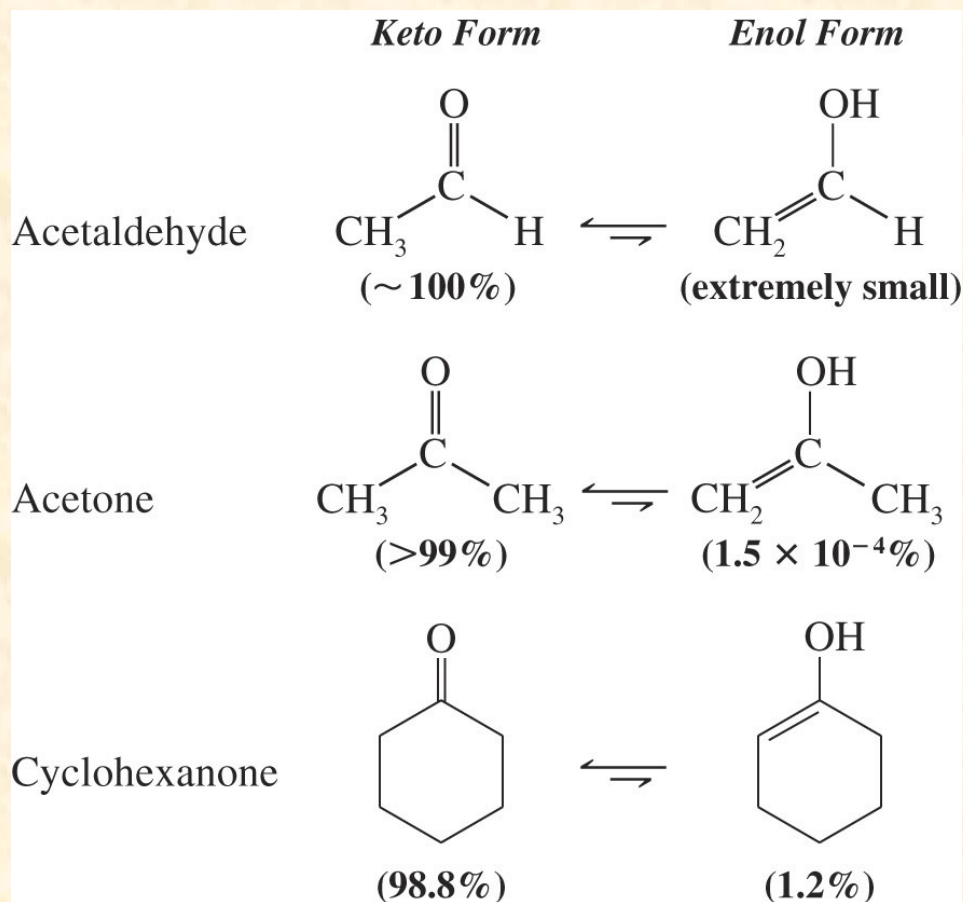


# Keto-Enol Tautomerism

- Keto and Enol Tautomers

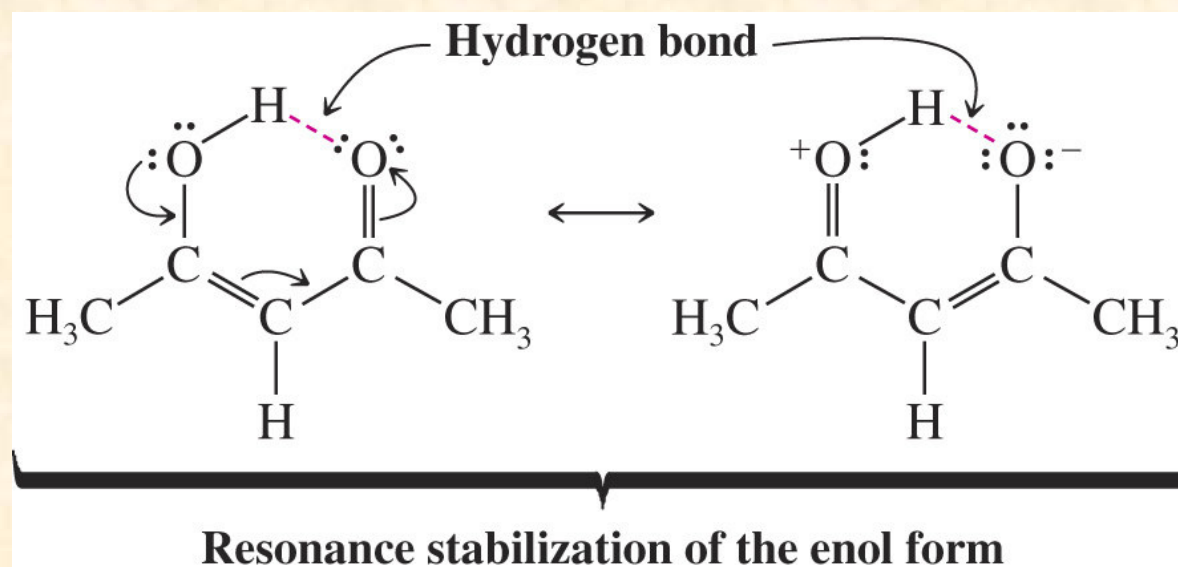
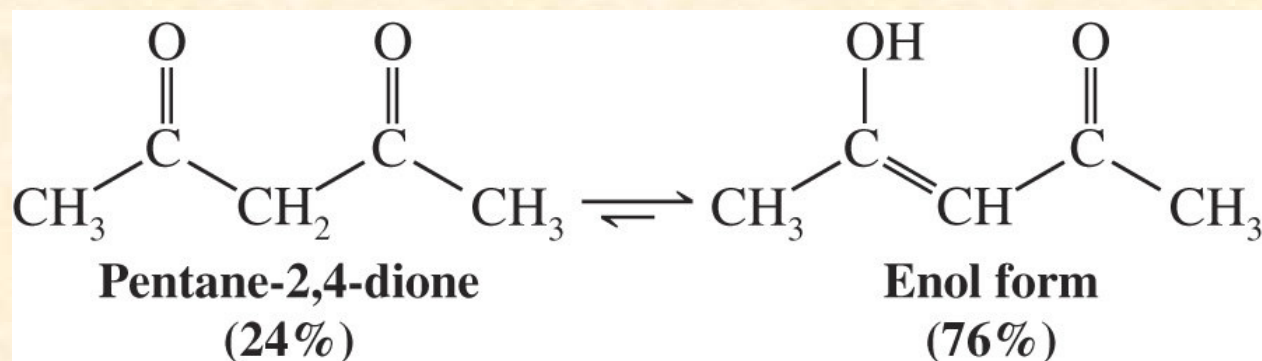
- Enol-keto tautomers are constitutional isomers that are easily interconverted by a trace of acid or base

- Most aldehydes and ketones exist primarily in the keto form because of the greater strength of the carbon-oxygen double bond relative to the carbon-carbon double bond



# Keto-Enol Tautomerism

- $\beta$ -Dicarbonyl compounds exist primarily in the enol form
  - The enol is more stable because it has a conjugated  $\pi$  system and because of stabilization of the enol through hydrogen bonding

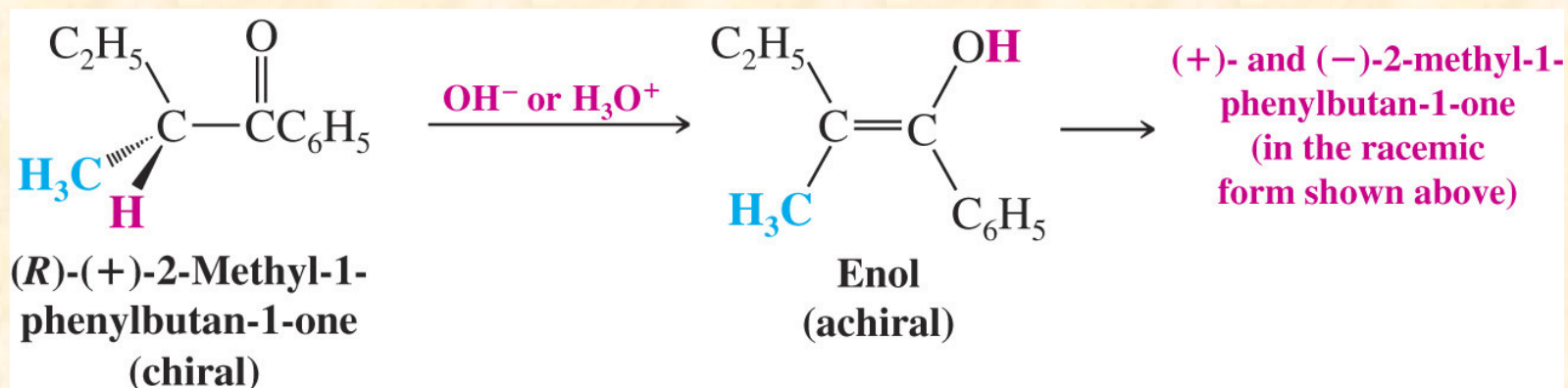
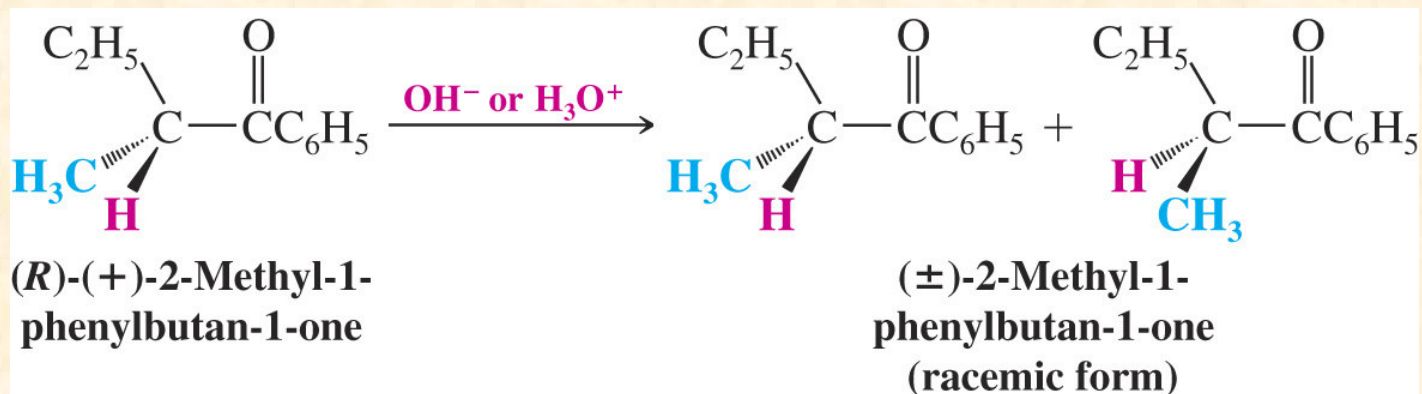


# Reactions via Enols/Enolate Ions

## – Racemization

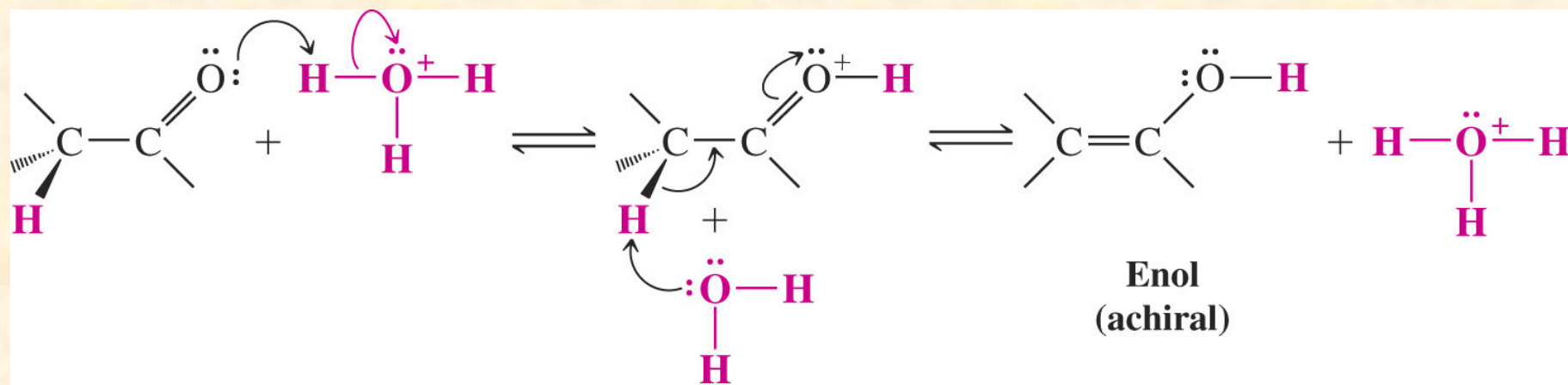
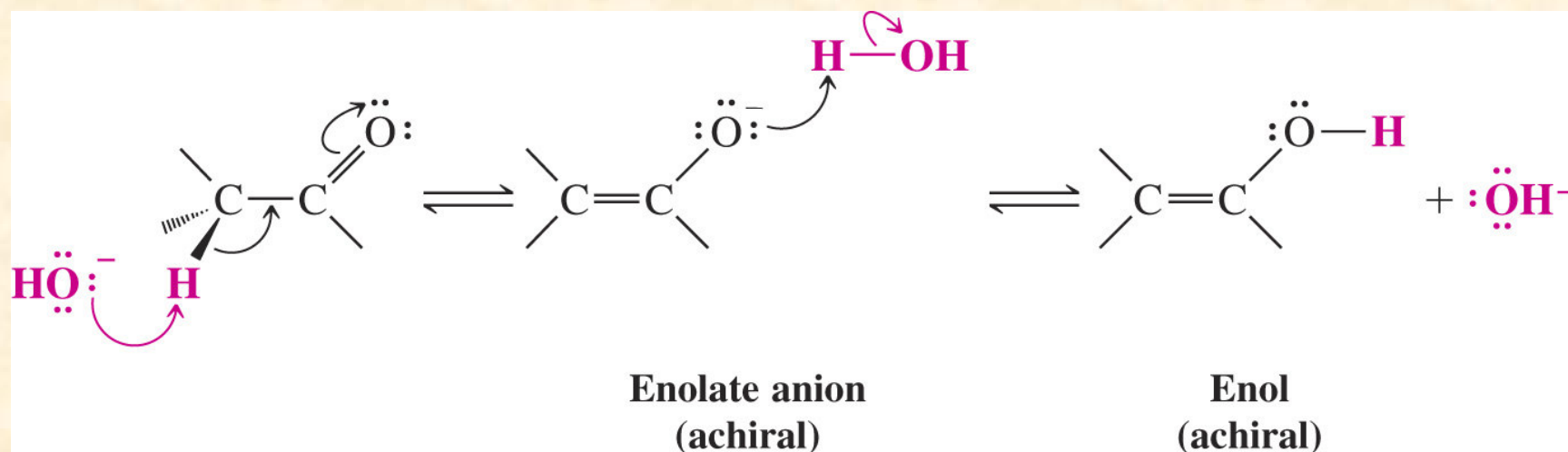
- An optically active aldehyde or ketone with a stereocenter at the  $\alpha$ -carbon can racemize in the presence of catalytic acid or base

- The intermediate enol or enolate has no stereocenter at the  $\alpha$  position



# Reactions via Enols/Enolate Ions

- The mechanisms of base and acid catalysed racemization are shown below



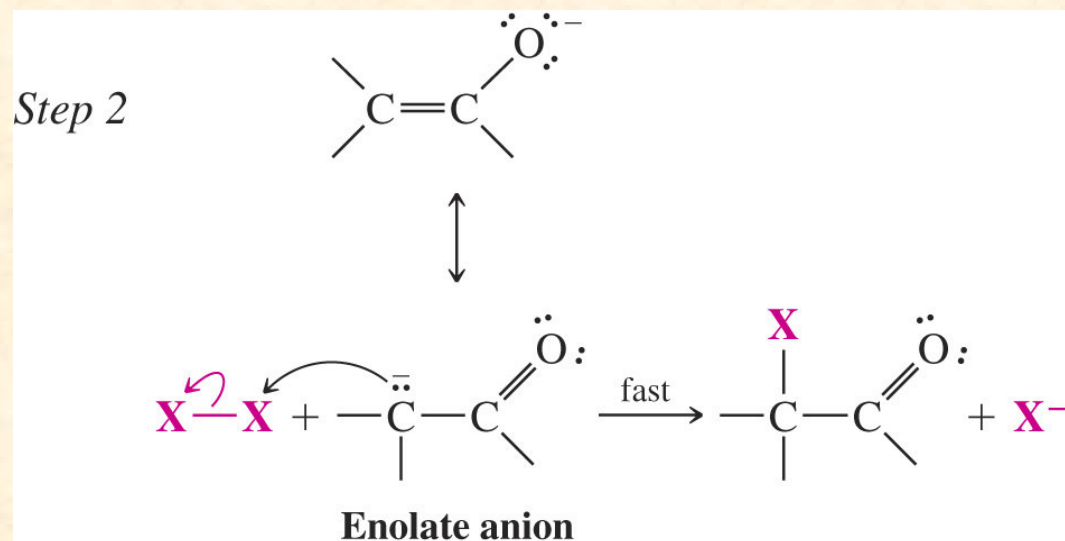
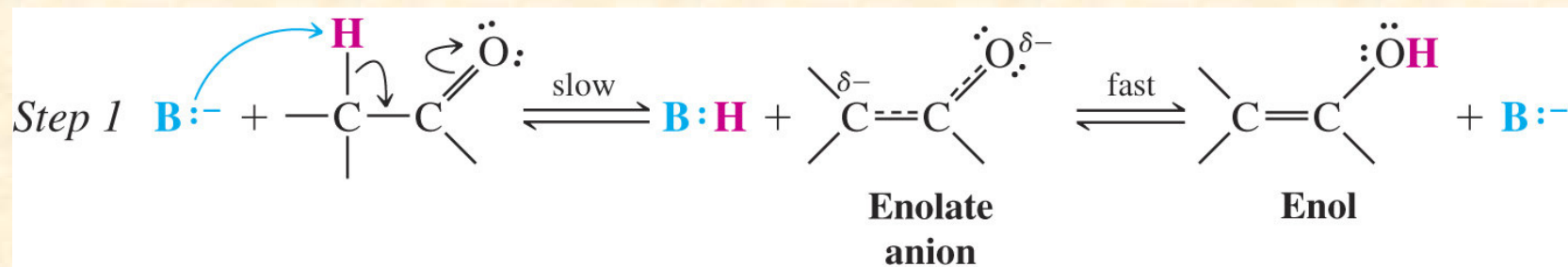
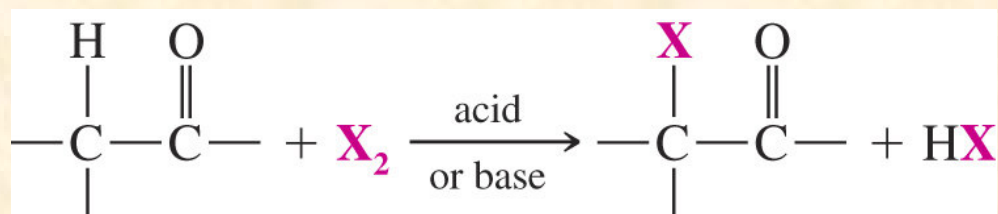


# Reactions via Enols/Enolate Ions

## – Halogenation of Ketones

- Ketones can be halogenated at the  $\alpha$  position in the presence of acid or base and  $X_2$

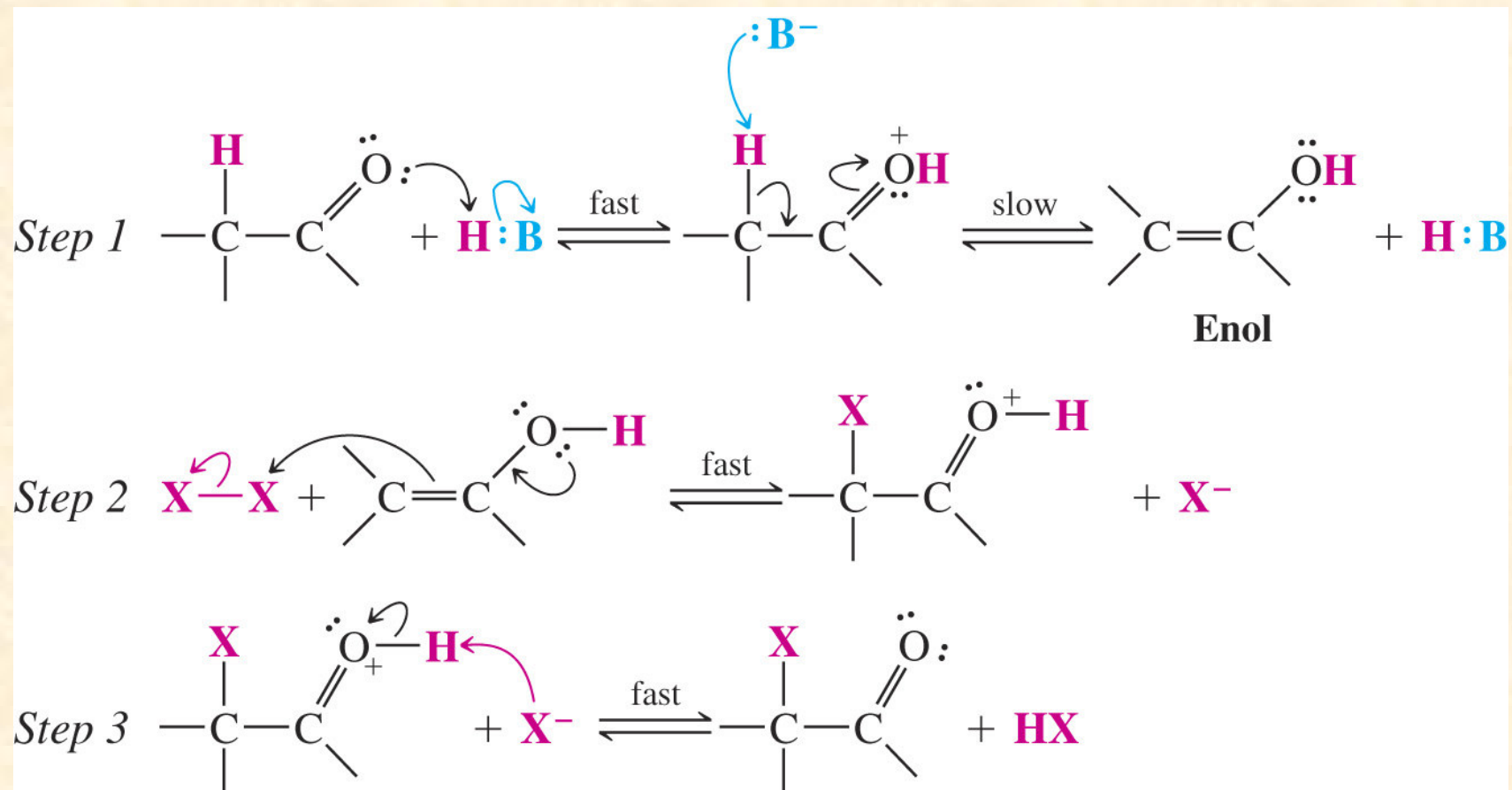
– Base-promoted halogenation occurs via an enolate





# Reactions via Enols/Enolate Ions

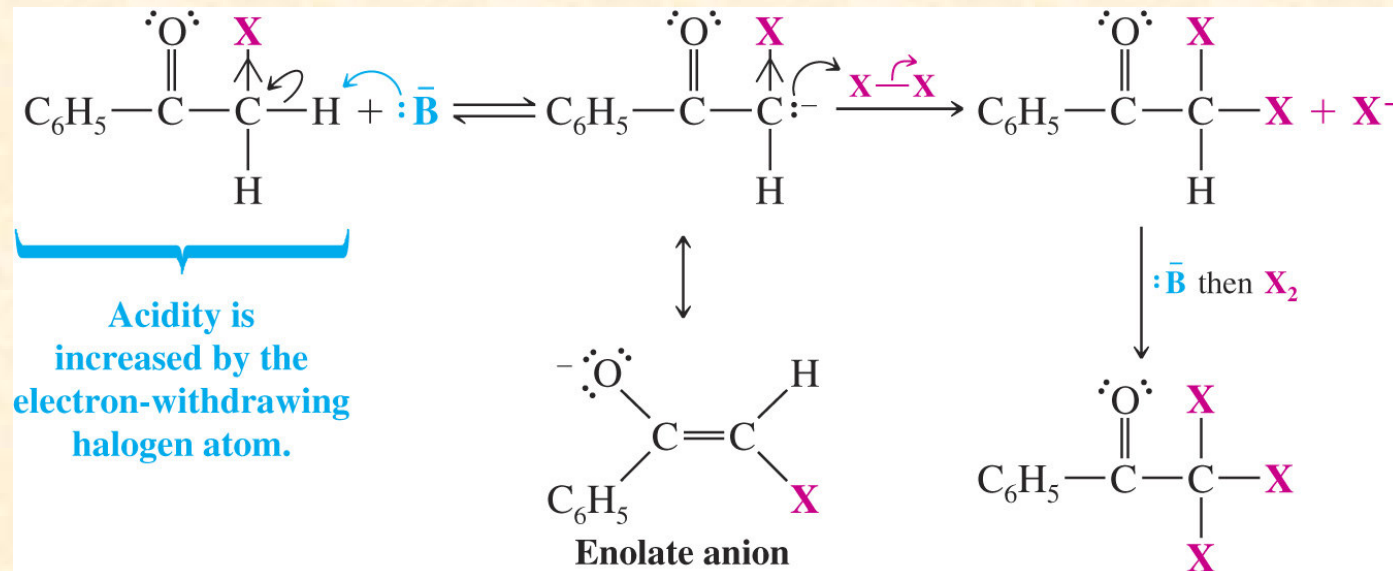
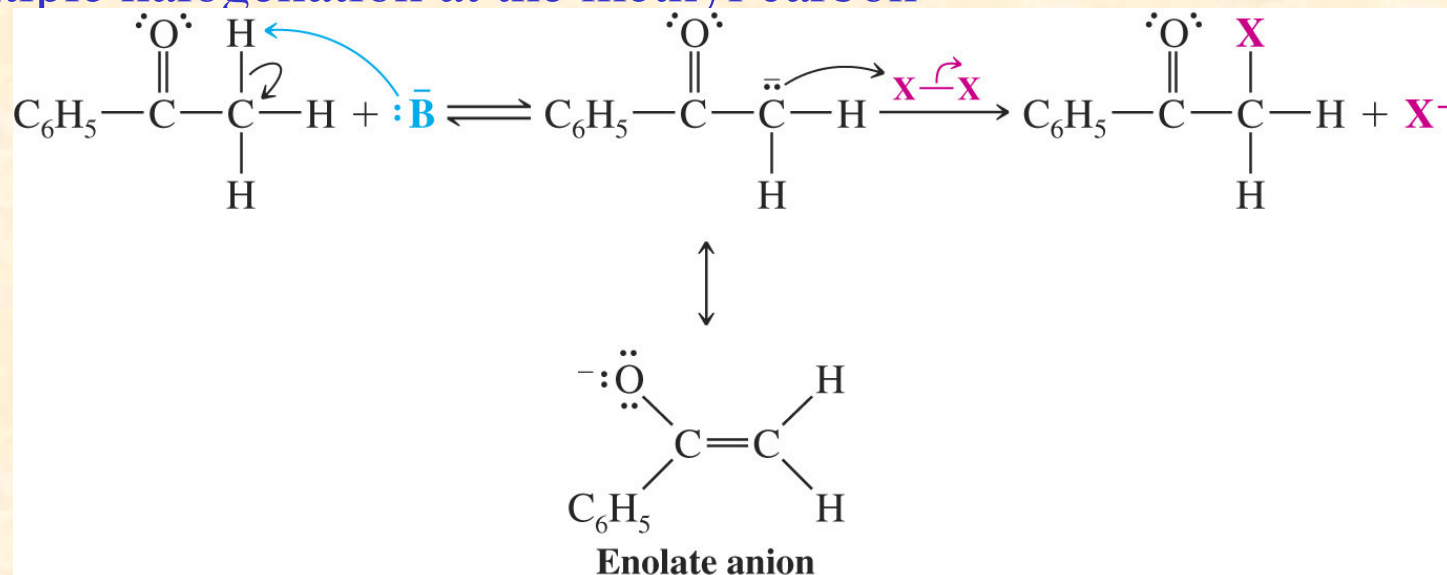
- Acid-catalyzed halogenation proceeds via the enol



# Reactions via Enols/Enolate Ions

## – Haloform Reaction

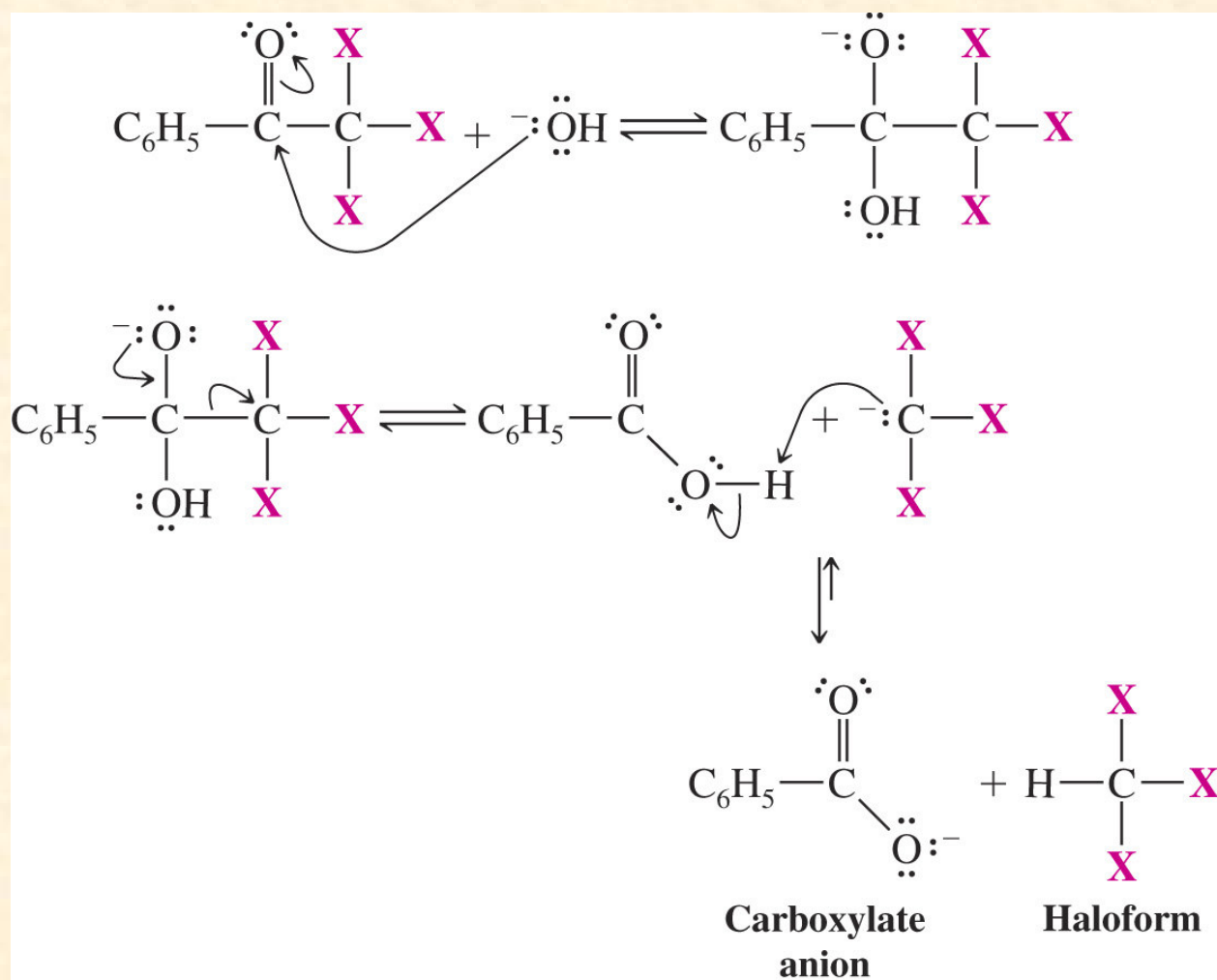
- Reaction of methyl ketones with  $X_2$  in the presence of base results in multiple halogenation at the methyl carbon



Acidity is increased by the electron-withdrawing halogen atom.

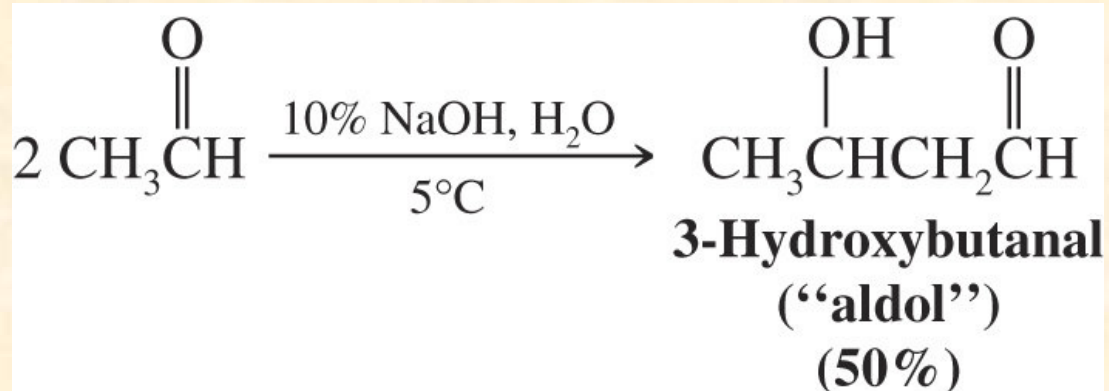
# Reactions via Enols/Enolate Ions

- When methyl ketones react with  $X_2$  in aqueous hydroxide the reaction gives a carboxylate anion and a haloform ( $CX_3H$ )
  - The trihalomethyl anion is a relatively good leaving group (the negative charge is stabilized by the three halogen atoms)



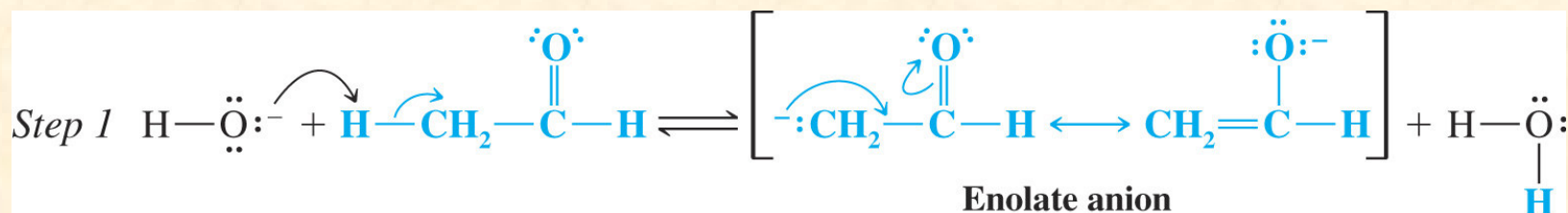
# The Aldol Reaction

- The Aldol Reaction: The Addition of Enolate Anions to Aldehydes and Ketones
  - Acetaldehyde dimerizes in the presence of dilute sodium hydroxide at room temperature
    - The product is called an aldol because it is both an aldehyde and an alcohol

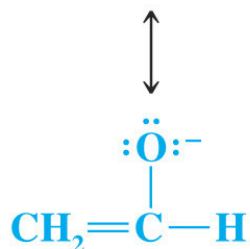
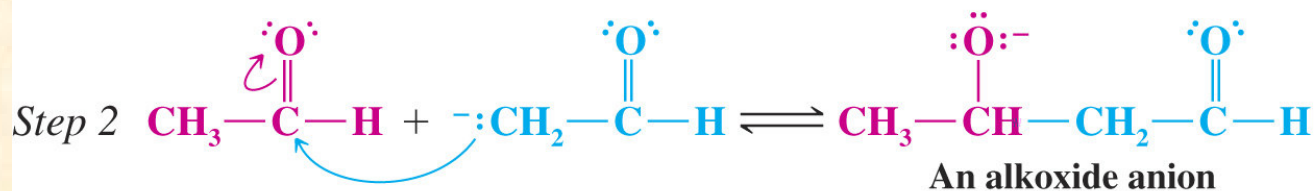


# The Aldol Reaction

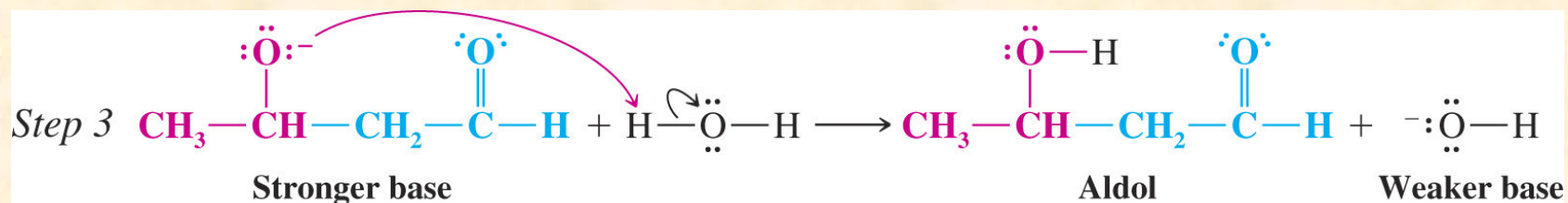
- The mechanism proceeds through the enolate anion



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



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

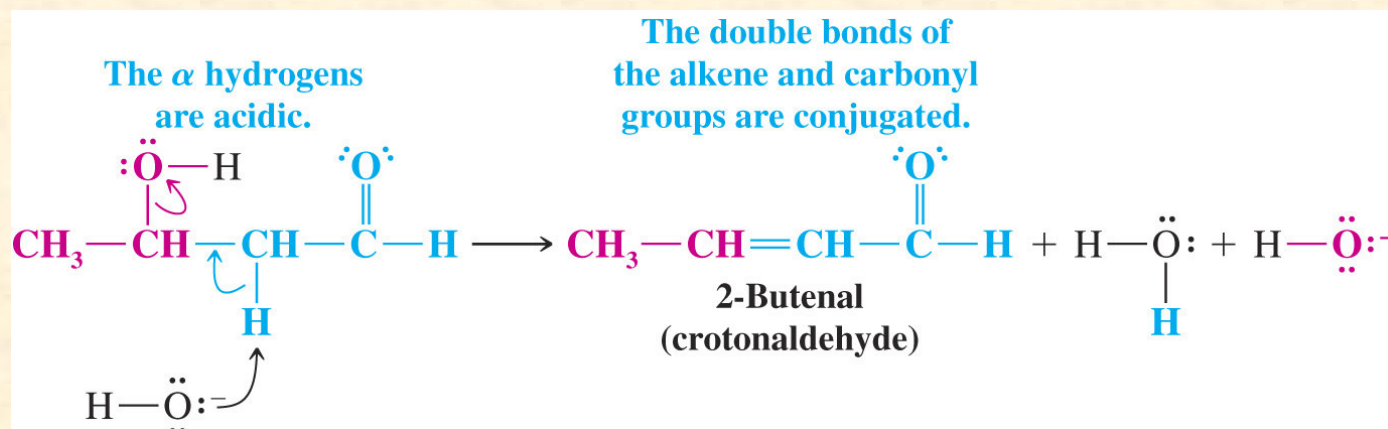


The alkoxide anion now removes a proton from a molecule of water to form the aldol.

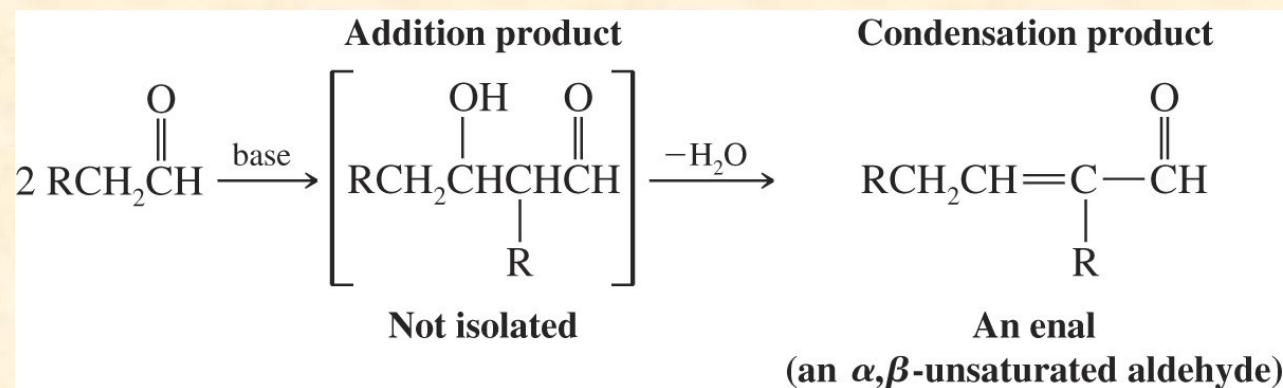
# The Aldol Reaction

## – Dehydration of the Aldol Product

- If heated, dehydration to an  $\alpha,\beta$ -unsaturated carbonyl compound occurs
  - 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  $\alpha,\beta$ -unsaturated compound

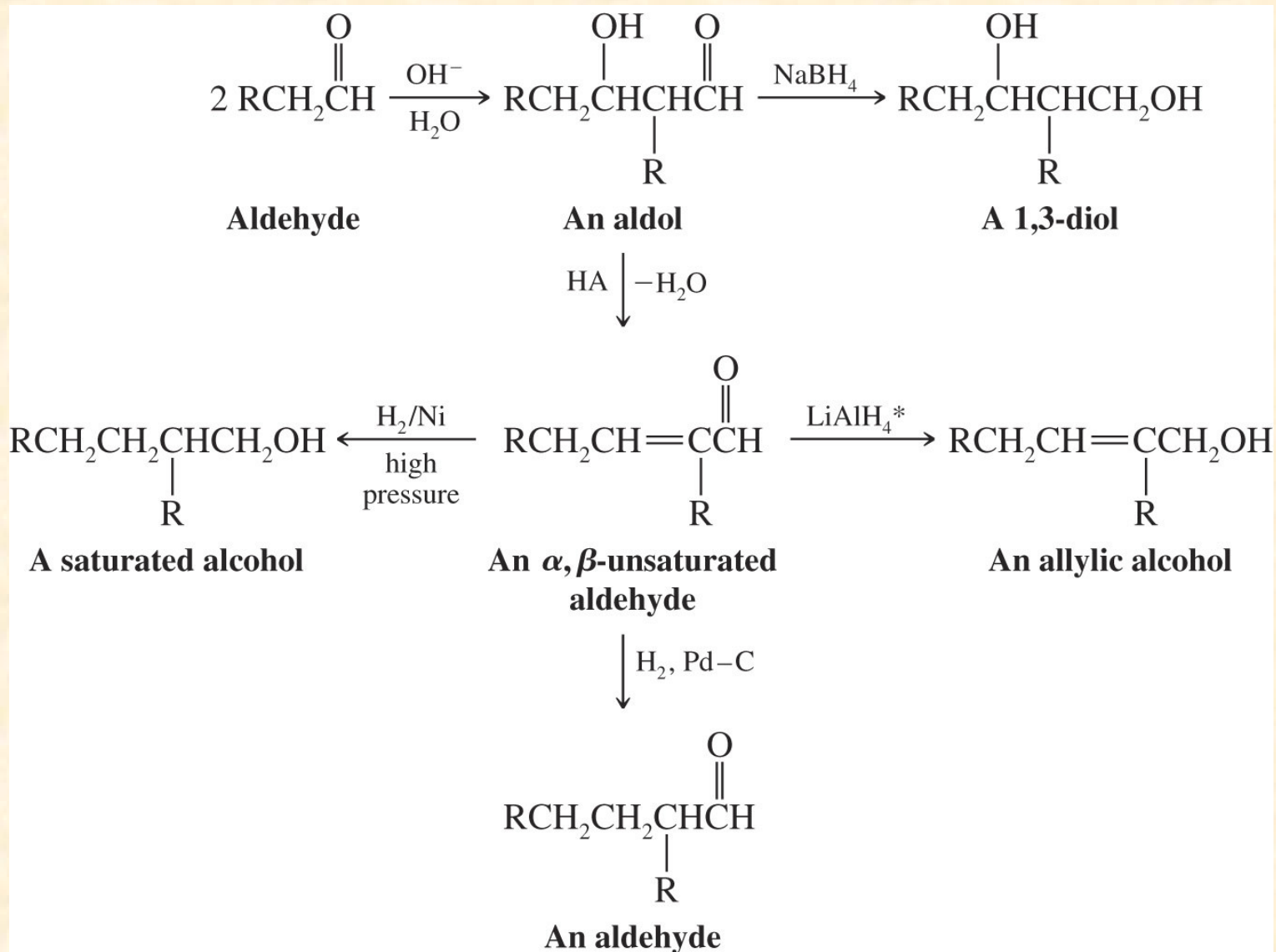




# The Aldol Reaction

## – Synthetic Applications

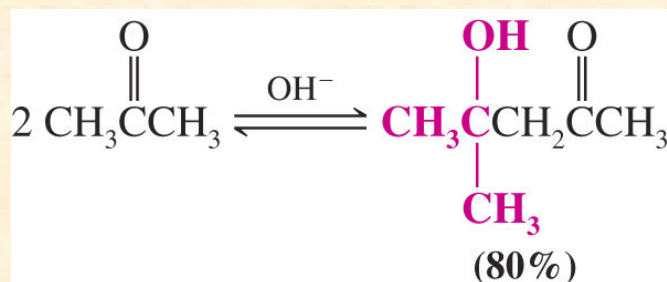
- The aldol reaction links two smaller molecules and creates a new carbon-carbon bond





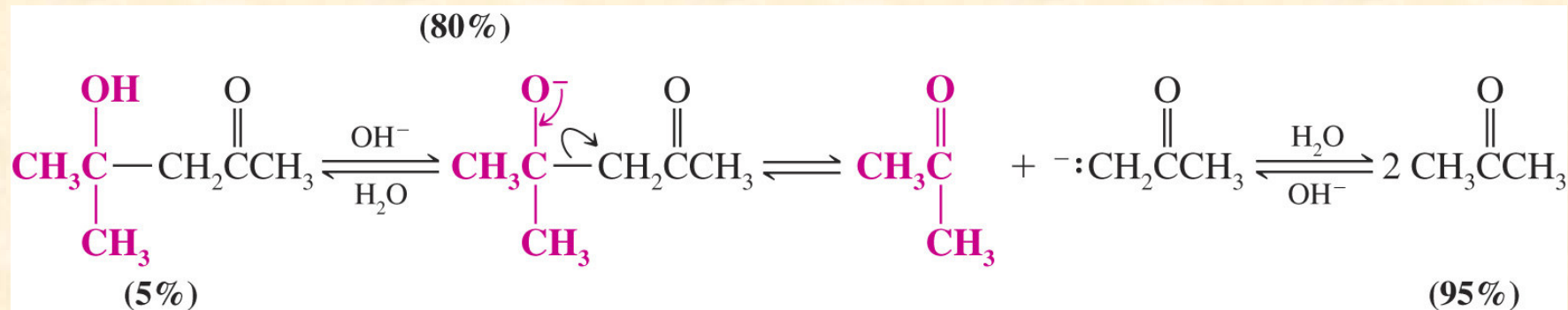
# The Aldol Reaction

- Aldol reactions with ketones are generally unfavorable because the equilibrium favors the starting ketone
  - The use of a special apparatus which removes product from the reaction mixture allows isolation of a good yield of the aldol product of acetone



## – The Reversibility of Aldol Additions

- Aldol addition products undergo *retro-aldol* reactions in the presence of strong base

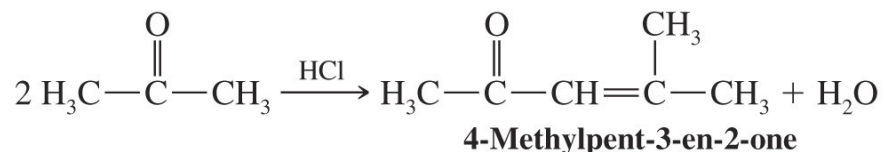


# The Aldol Reaction

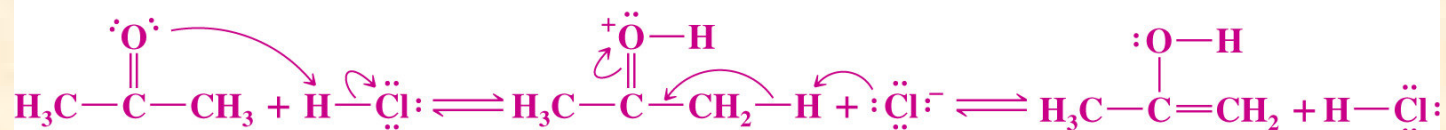
## – Acid-Catalyzed Aldol Condensation

- This reaction generally leads directly to the dehydration product

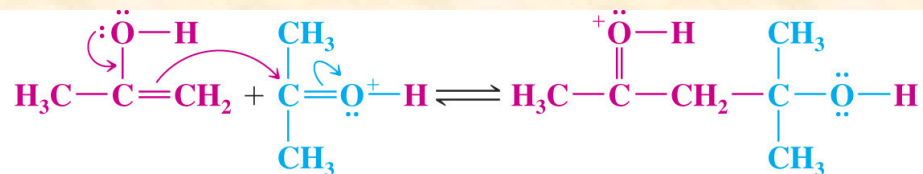
Reaction:



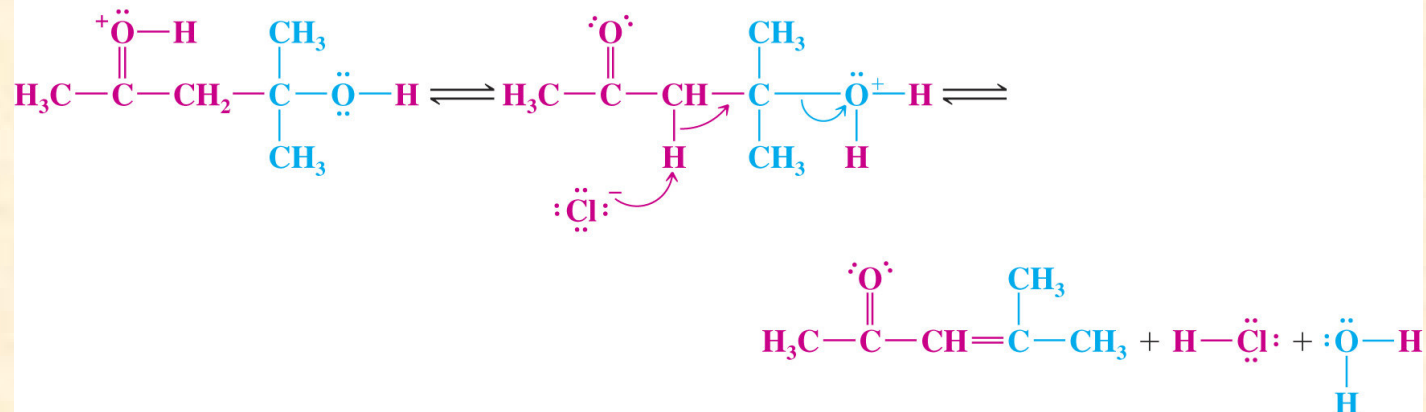
Mechanism:



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.

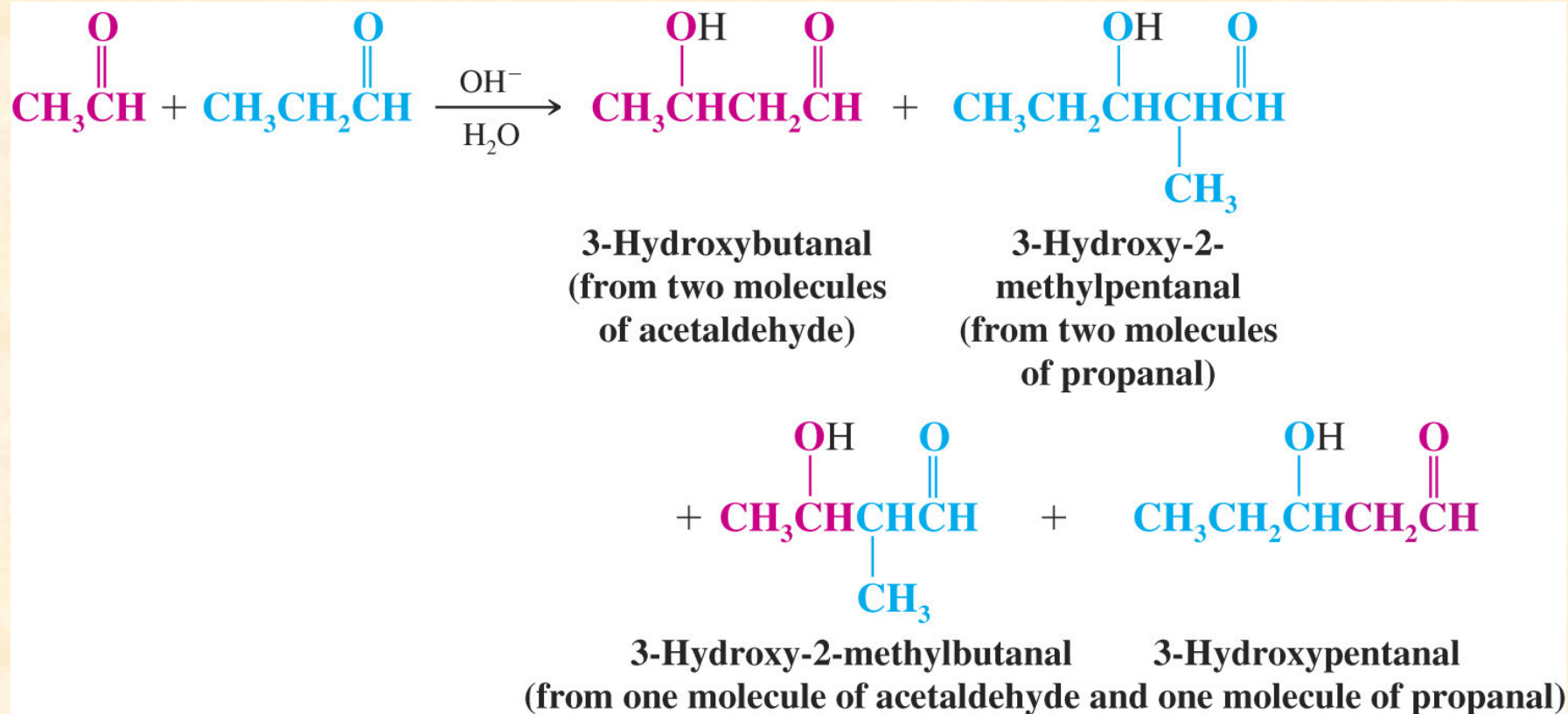


Finally, proton transfers and dehydration lead to the product.

# The Aldol Reaction

- Crossed Aldol Reactions

- Crossed aldol reactions (aldol reactions involving two different aldehydes) are of little use when they lead to a mixture of products



# The Aldol Reaction

## – Practical Crossed Aldol Reactions

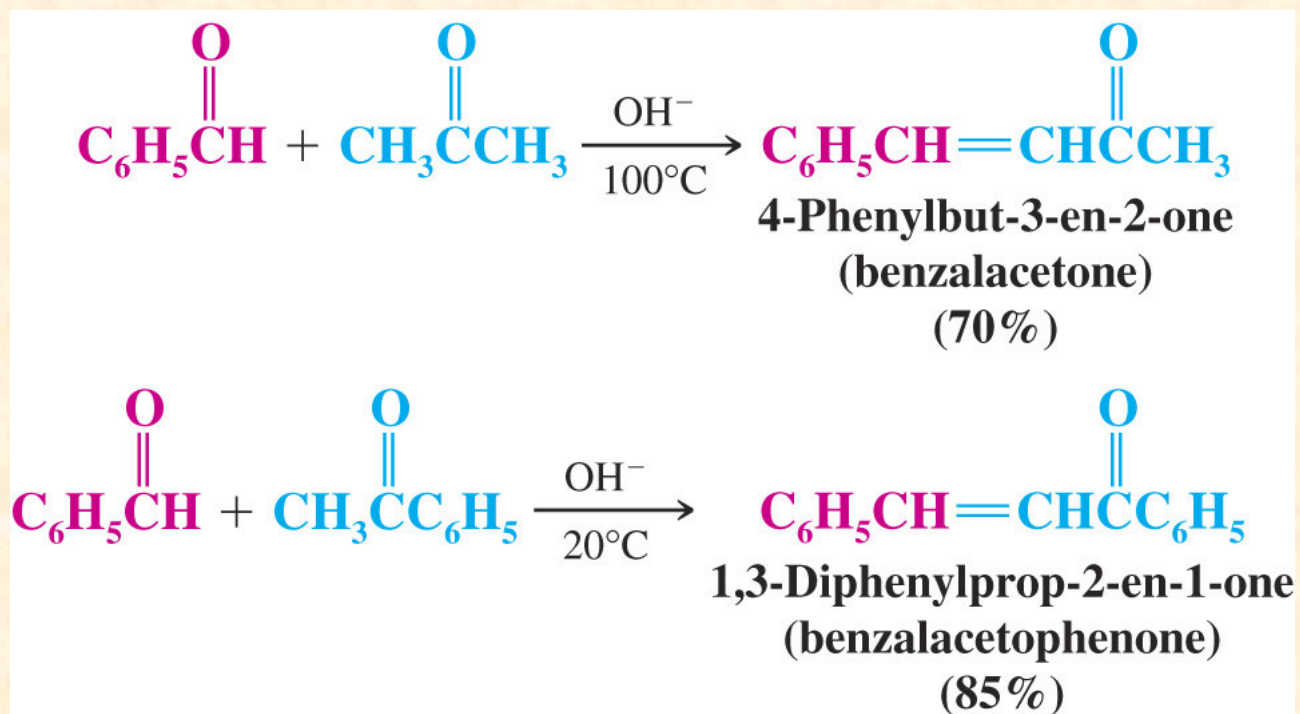
- Crossed aldol reactions give one predictable product when one of the reaction partners has no  $\alpha$  hydrogens
  - The carbonyl compound without any  $\alpha$  hydrogens is put in basic solution, and the carbonyl with one or two  $\alpha$  hydrogens is added
  - Dehydration usually occurs immediately

This Reactant with No $\alpha$ Hydrogen Is Placed in Base	This Reactant with an $\alpha$ Hydrogen Is Added Slowly	Product
$\text{C}_6\text{H}_5\text{CH}=\text{O}$ <p>Benzaldehyde</p>	$\text{CH}_3\text{CH}_2\text{CH}=\text{O}$ <p>Propanal</p>	$\text{C}_6\text{H}_5\text{CH}=\text{C}(\text{CH}_3)\text{CH}=\text{O}$ <p>2-Methyl-3-phenyl-2-propenal (<math>\alpha</math>-methylcinnamaldehyde) (68%)</p>
$\text{C}_6\text{H}_5\text{CH}=\text{O}$ <p>Benzaldehyde</p>	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}=\text{O}$ <p>Phenylacetaldehyde</p>	$\text{C}_6\text{H}_5\text{CH}=\text{C}(\text{C}_6\text{H}_5)\text{CH}=\text{O}$ <p>2,3-Diphenyl-2-propenal</p>
$\text{HCH}=\text{O}$ <p>Formaldehyde</p>	$\text{CH}_3\text{CH}(\text{CH}_3)\text{CH}=\text{O}$ <p>2-Methylpropanal</p>	$\text{CH}_3\text{C}(\text{CH}_3)(\text{CH}_2\text{OH})\text{CH}=\text{O}$ <p>3-Hydroxy-2,2-dimethylpropanal (&gt;64%)</p>

# The Aldol Reaction

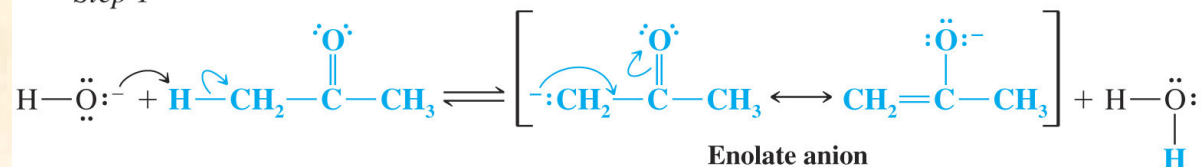
## – Claisen-Schmidt Reactions

- Crossed-aldol reactions in which one partner is a ketone are called Claisen-Schmidt reactions
  - The product of ketone self-condensation is not obtained because the equilibrium is not favorable

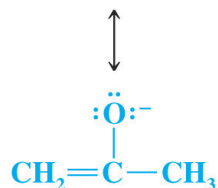
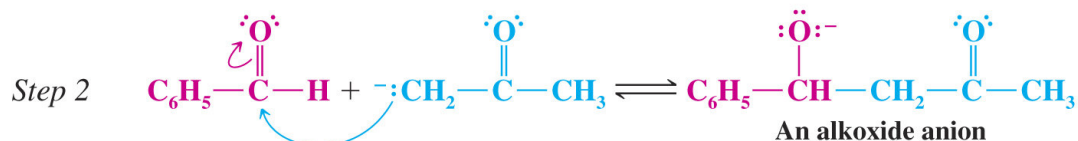


# The Aldol Reaction

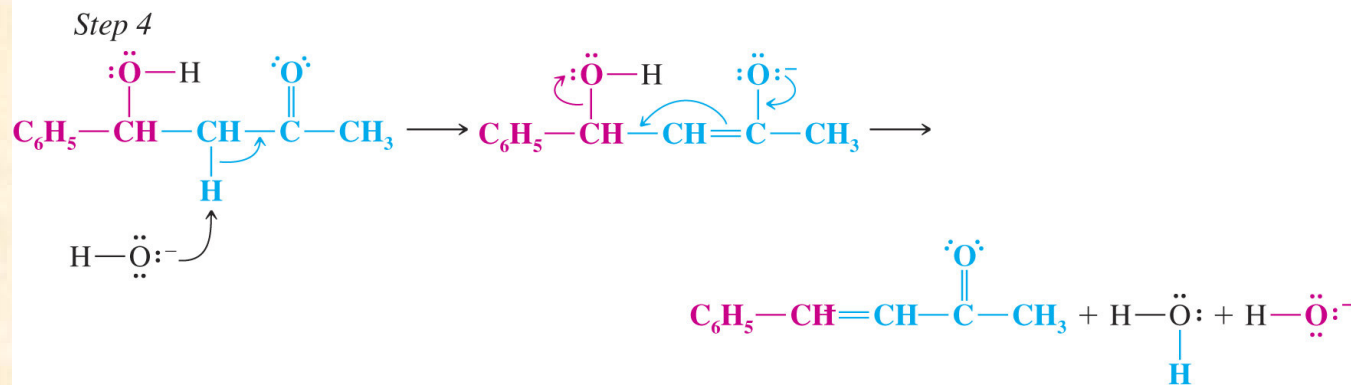
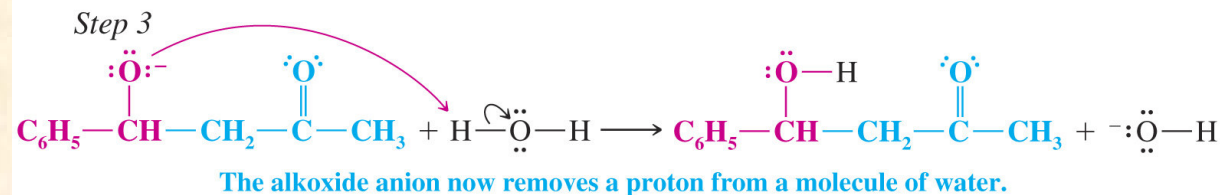
Step 1



In this step the base (a hydroxide ion) removes a proton from the  $\alpha$  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.



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

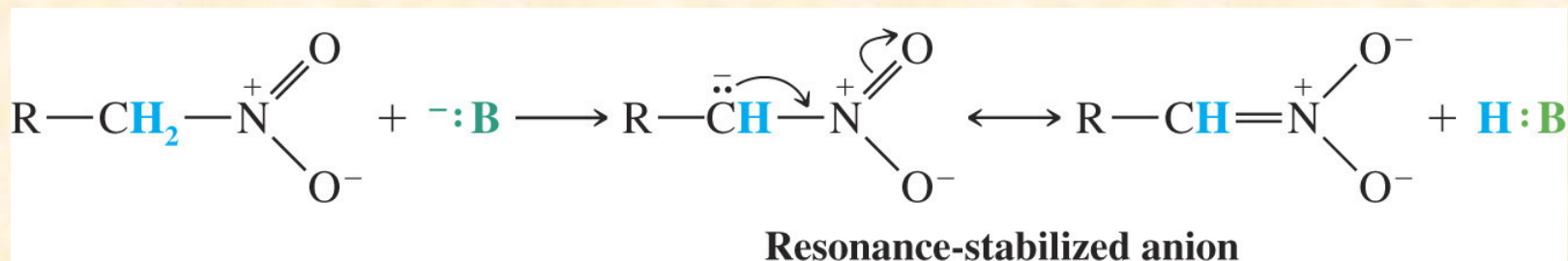
Dehydration produces the conjugated product.



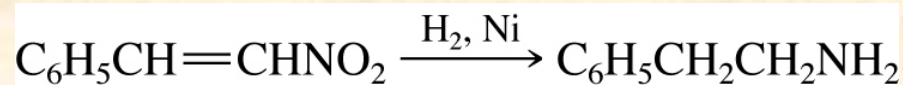
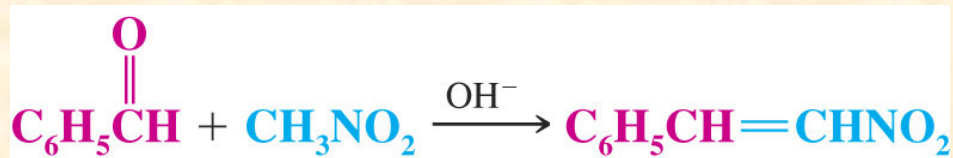
# The Aldol Reaction

## – Condensation with Nitroalkanes

- The  $\alpha$  hydrogens of nitroalkanes are weakly acidic ( $pK_a = 10$ ) because the resulting anion is resonance stabilized



- Nitroalkane anions can undergo aldol-like condensation with aldehydes and ketones
  - The nitro group can be easily reduced to an amine

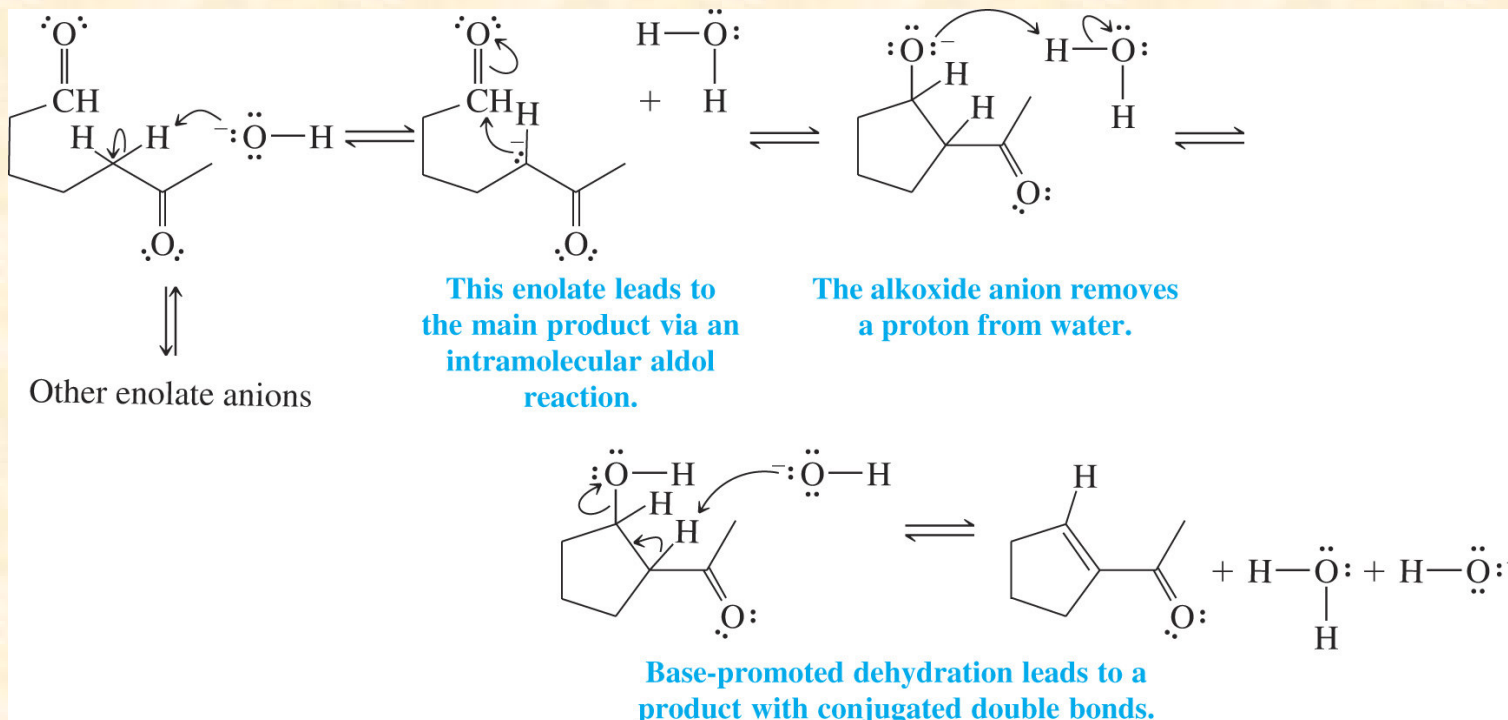
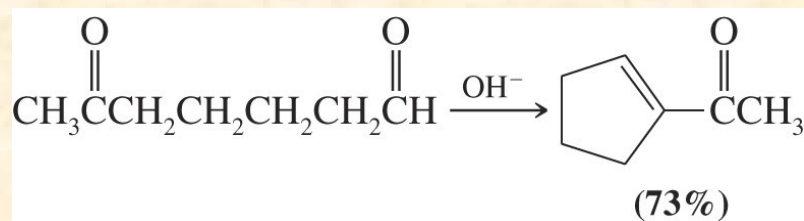




# The Aldol Reaction

## Cyclization via Aldol Condensations

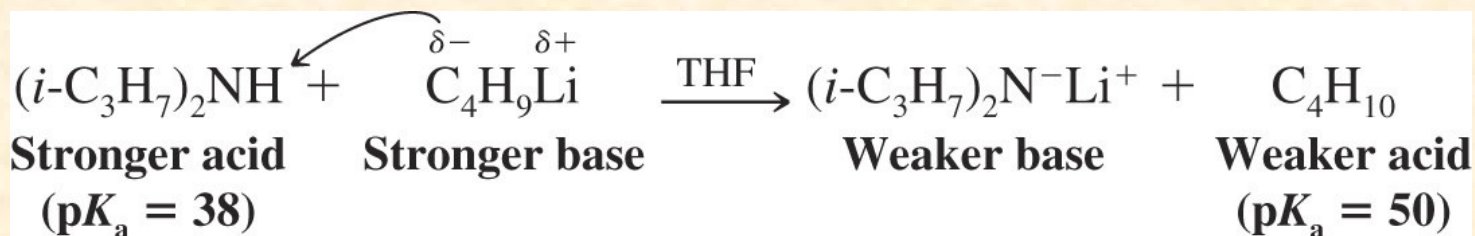
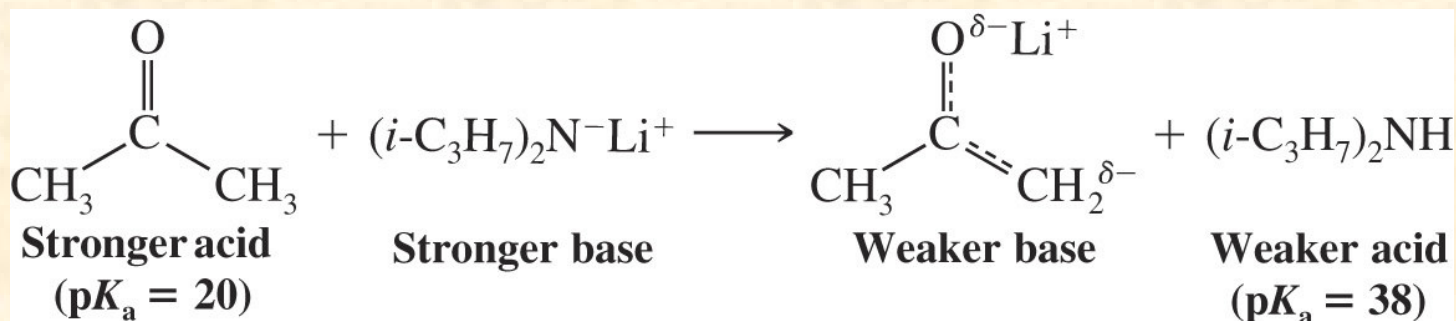
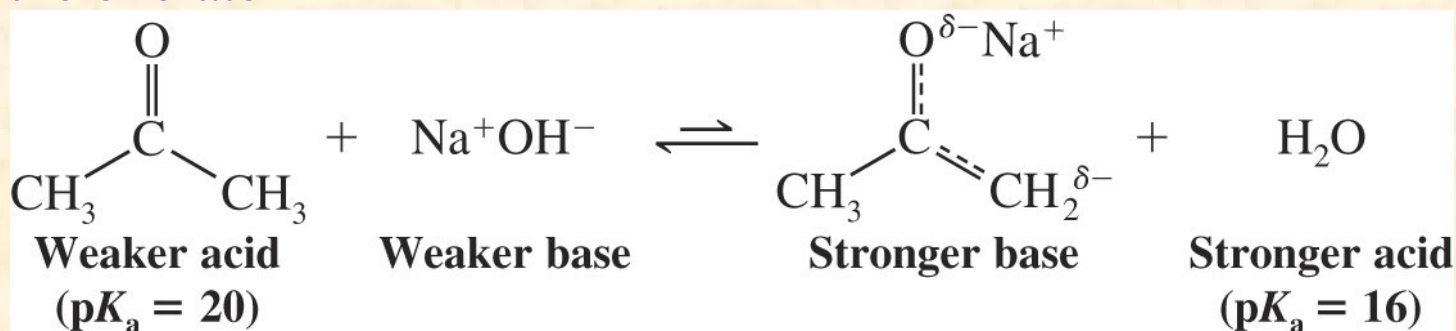
- Intramolecular reaction of dicarbonyl compounds proceeds to form five- and six-membered rings preferentially
  - the aldehyde carbon is attacked preferentially because an aldehyde is less sterically hindered and more electrophilic than a ketone



# The Aldol Reaction

## Lithium Enolates

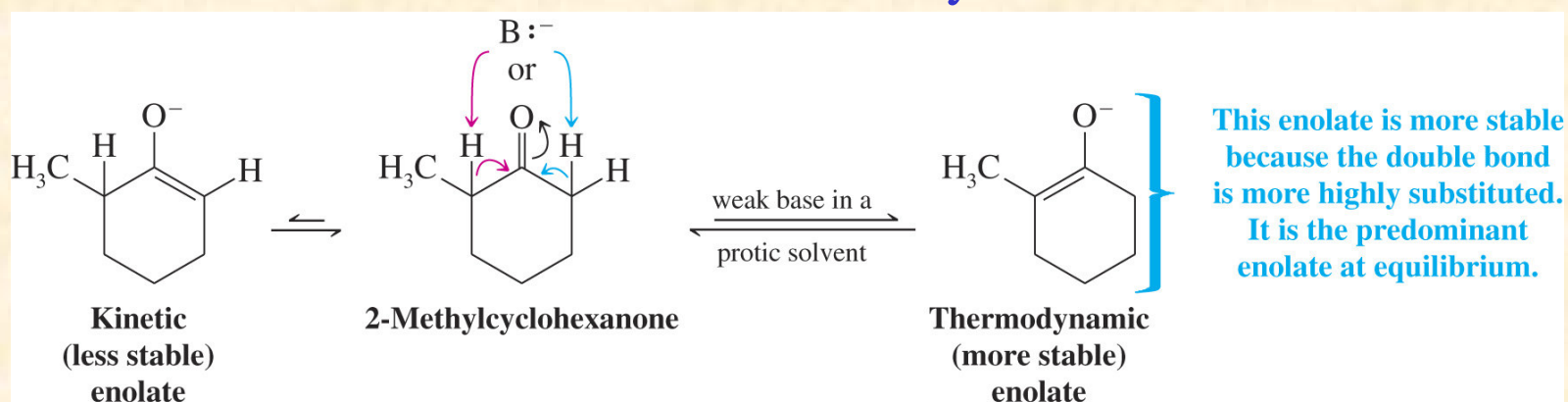
- In the presence of a very strong base such as lithium diisopropyl amide (LDA), enolate formation is greatly favored
  - Weak bases such as sodium hydroxide produce only a small amount of the enolate



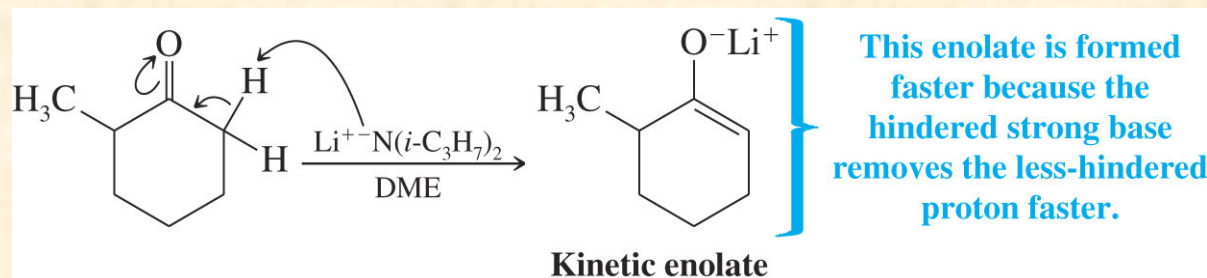
# The Aldol Reaction

## – Regioselective Formation of Enolate Anions

- Unsymmetrical ketones can form two different enolates
- The thermodynamic enolate is the most stable enolate *i.e.* the one with the more highly substituted double bond
  - A weak base favors the thermodynamic enolate



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



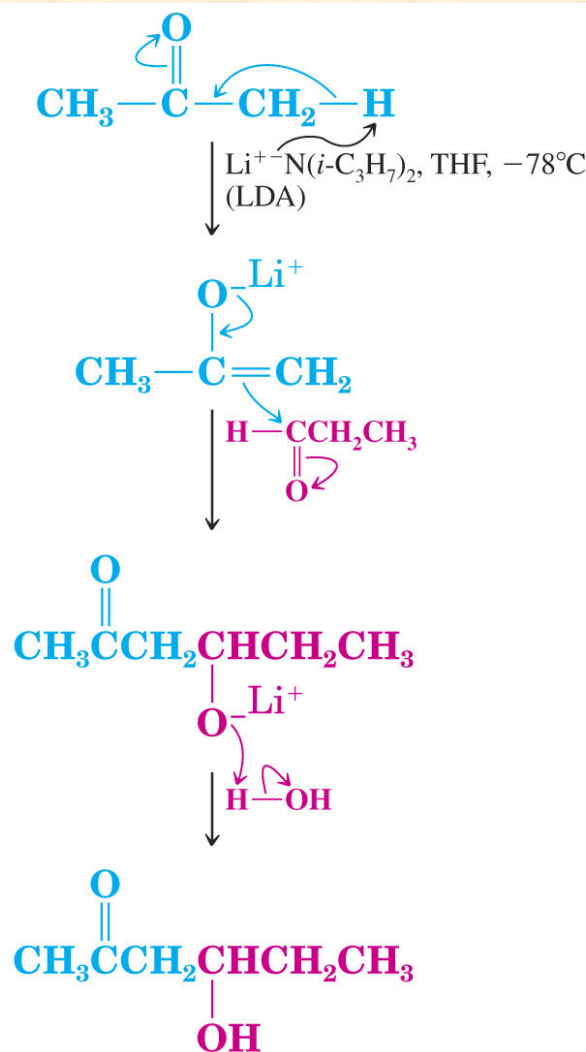
# The Aldol Reaction

- 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  $\alpha$  hydrogen from the ketone to produce an enolate.

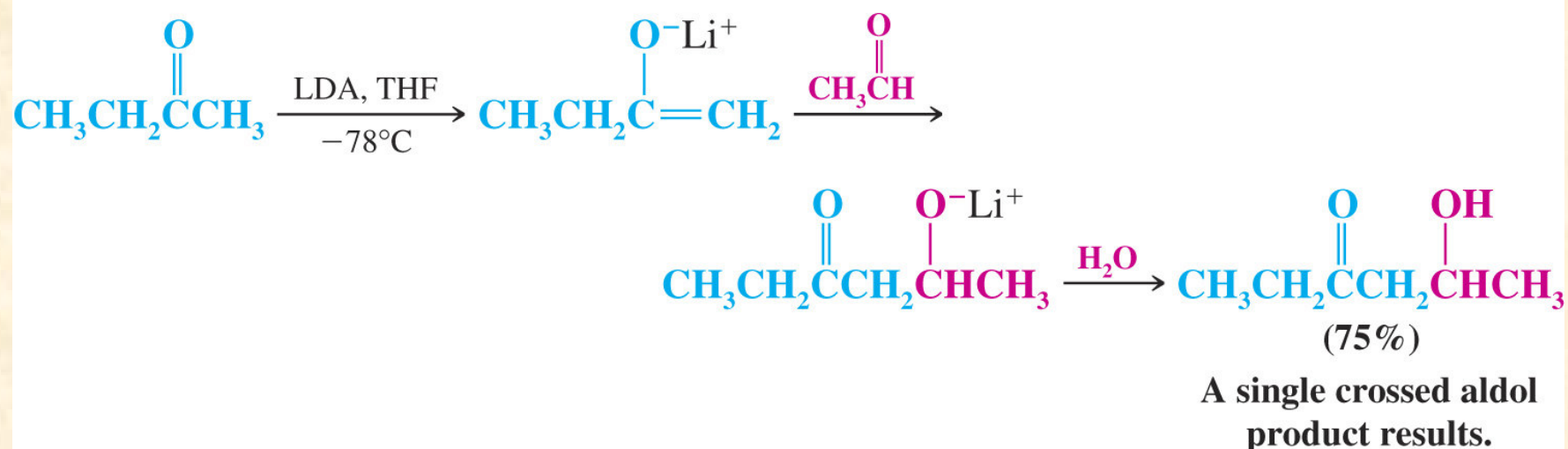
The aldehyde is added and the enolate reacts with the aldehyde at its carbonyl carbon.

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



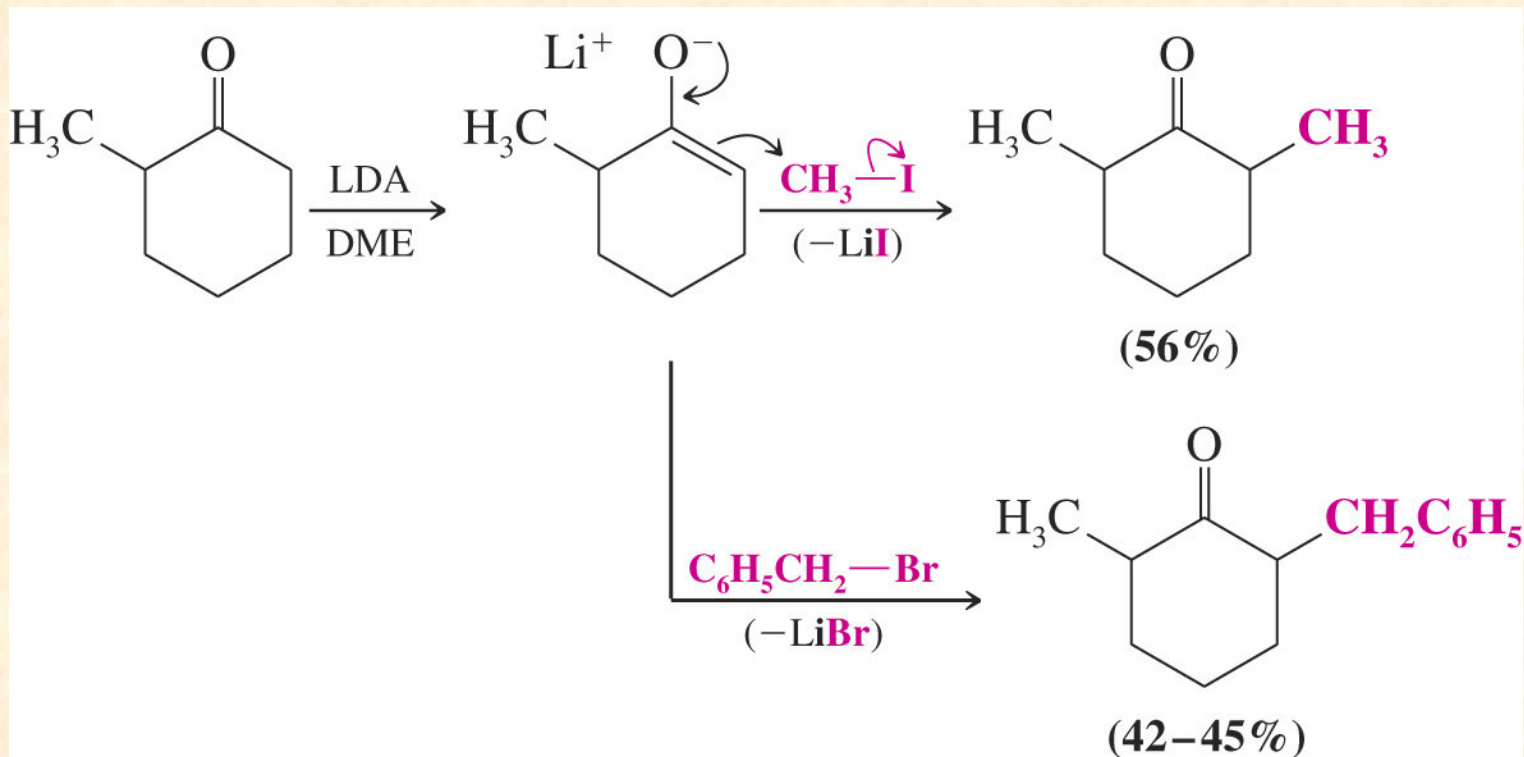
# The Aldol Reaction

- 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



# The Aldol Reaction

- 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

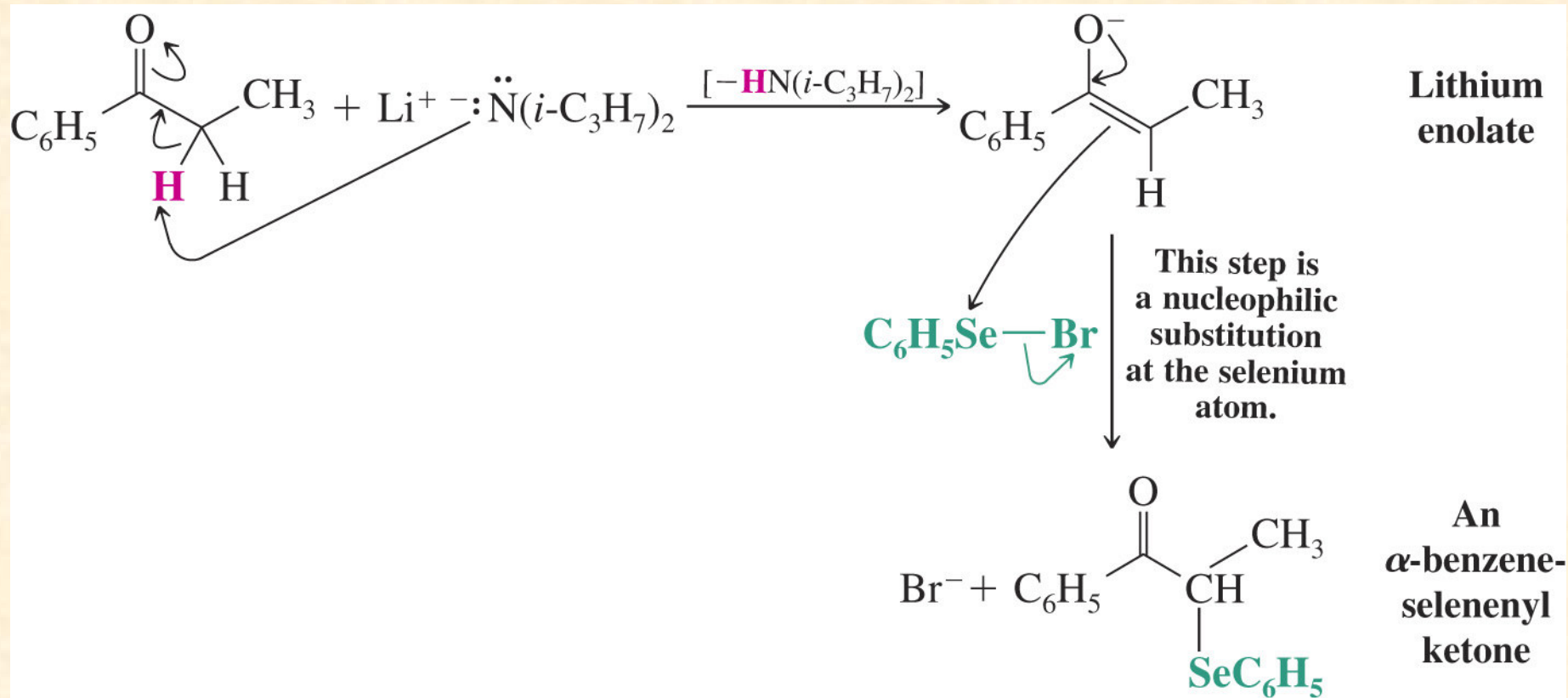




# The Aldol Reaction

## $\alpha$ -Selenation: A Synthesis of $\alpha,\beta$ -Unsaturated Carbonyl Compounds

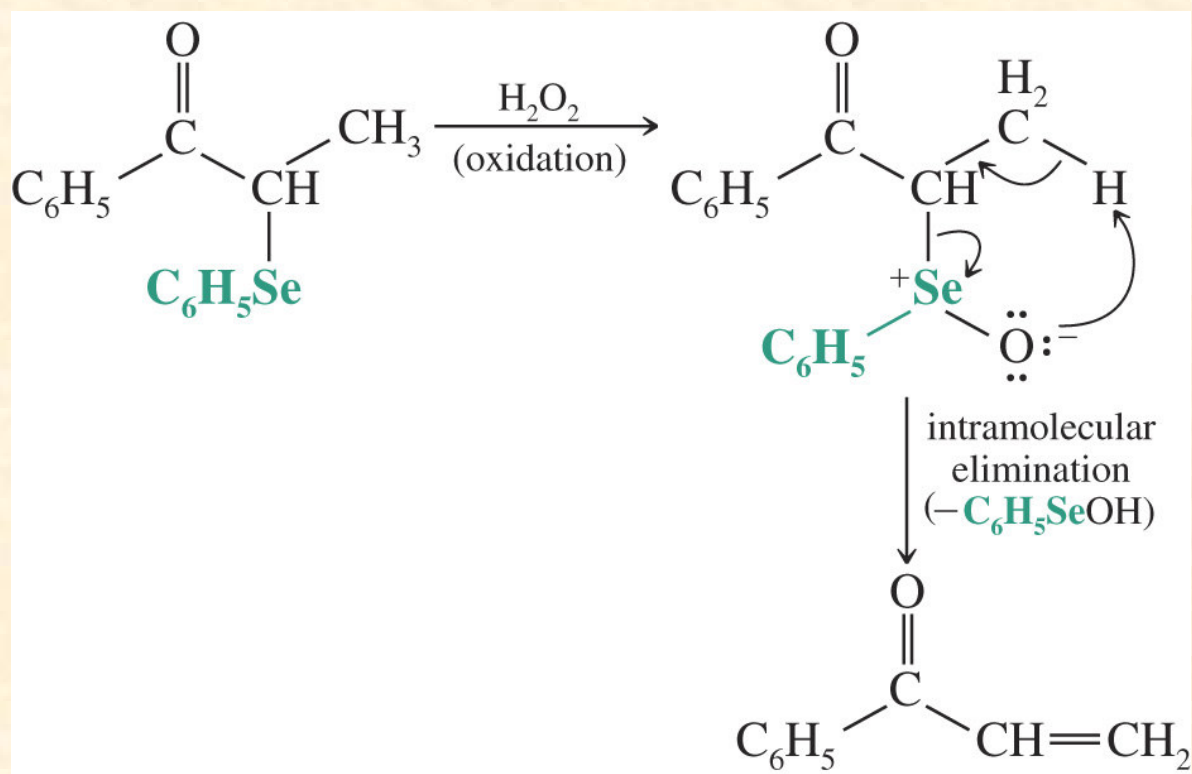
- A lithium enolate can be selenated with benzeneselenenyl bromide





# The Aldol Reaction

- The  $\alpha$ -selenyl ketone is converted to the  $\alpha,\beta$ -unsaturated carbonyl compound by reaction with hydrogen peroxide
  - Elimination of the selenoxide produces the unsaturated carbonyl

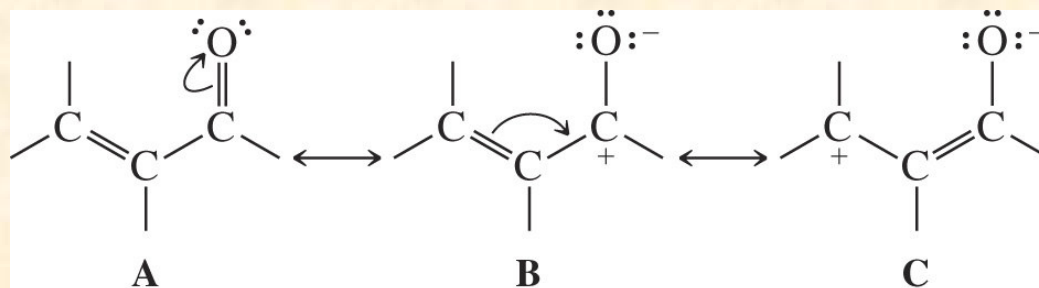
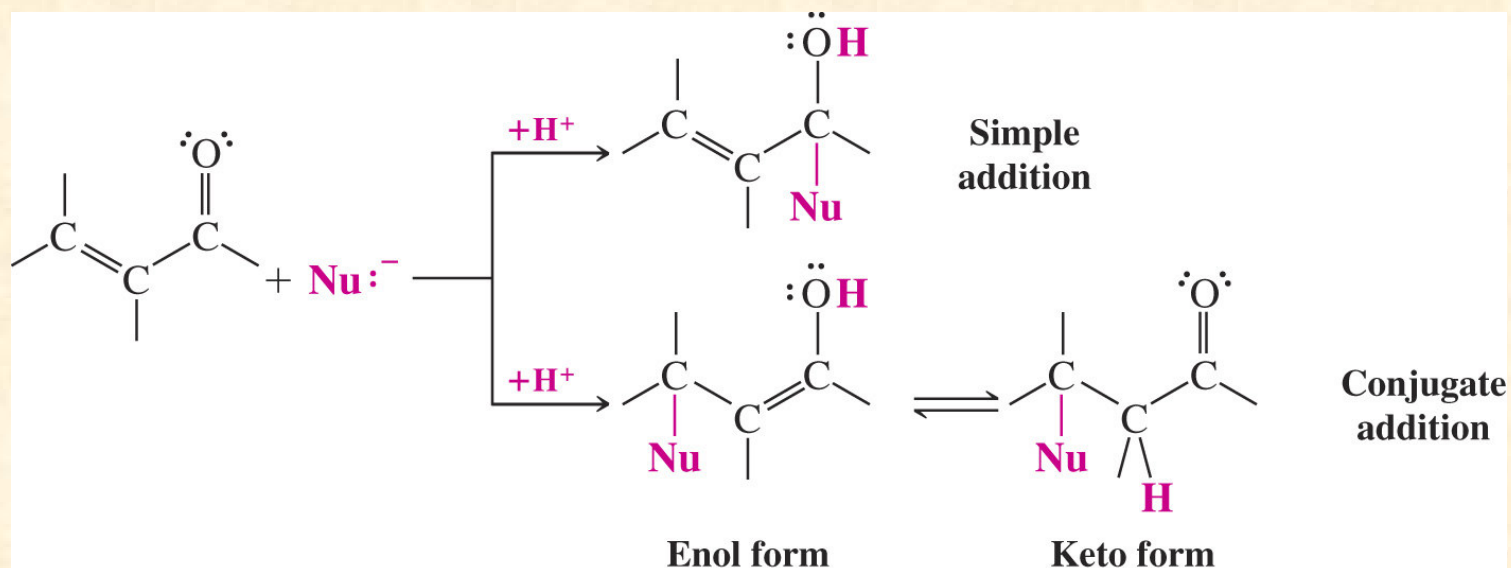


# Additions to $\alpha,\beta$ -Unsaturated Carbonyls

- Additions to  $\alpha,\beta$ -Unsaturated Aldehydes and Ketones

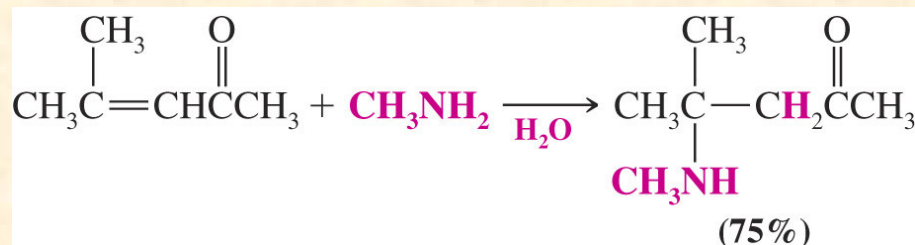
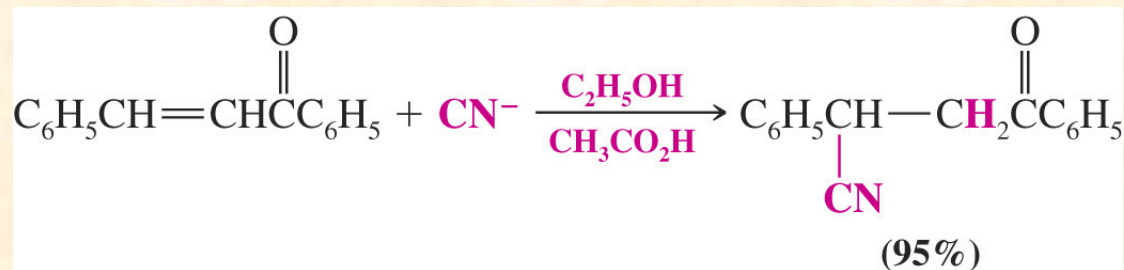
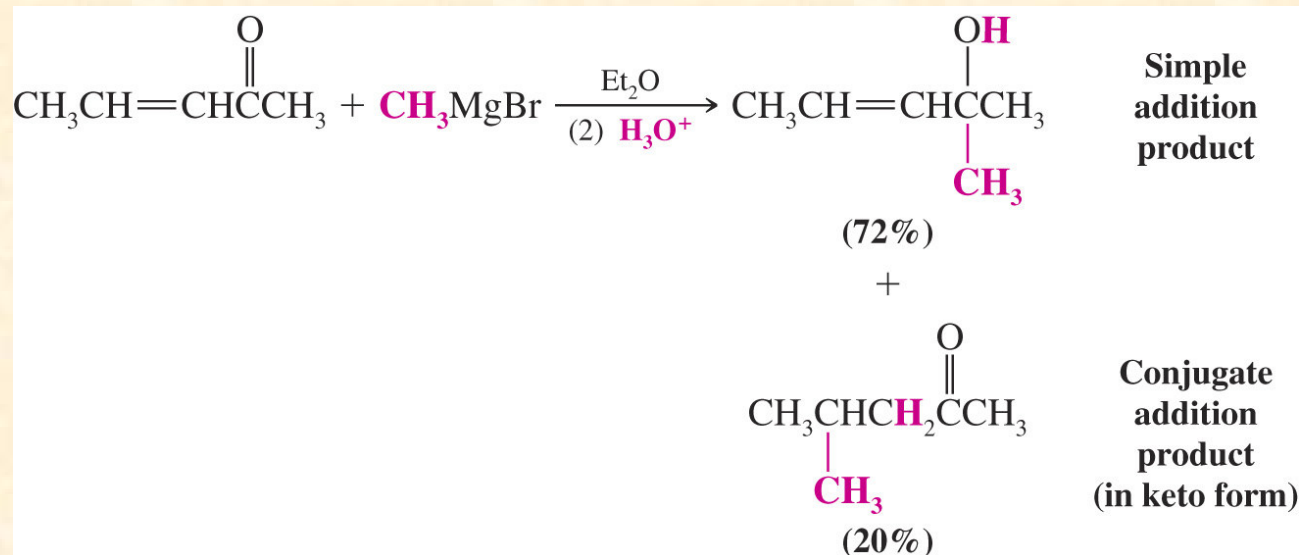
$\alpha,\beta$ -Unsaturated aldehydes and ketones can react by simple (1,2) or conjugate (1,4) addition

- Both the carbonyl carbon and the  $\beta$  carbon are electrophilic and can react with nucleophiles

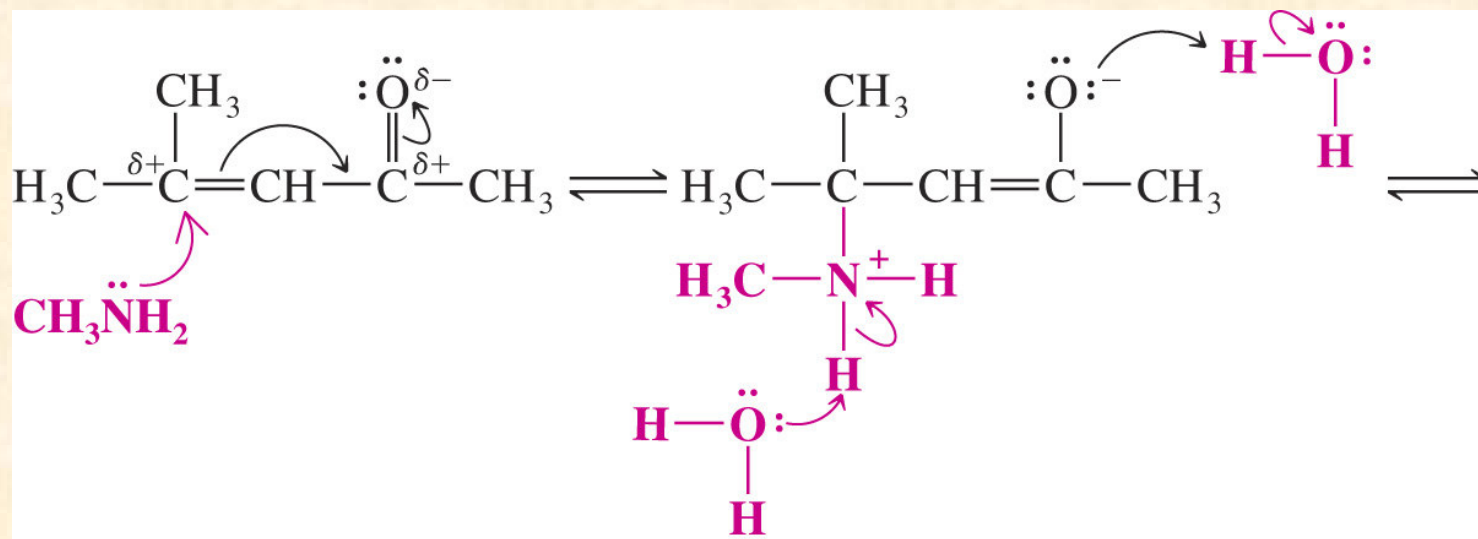


# Additions to $\alpha,\beta$ -Unsaturated Carbonyls

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

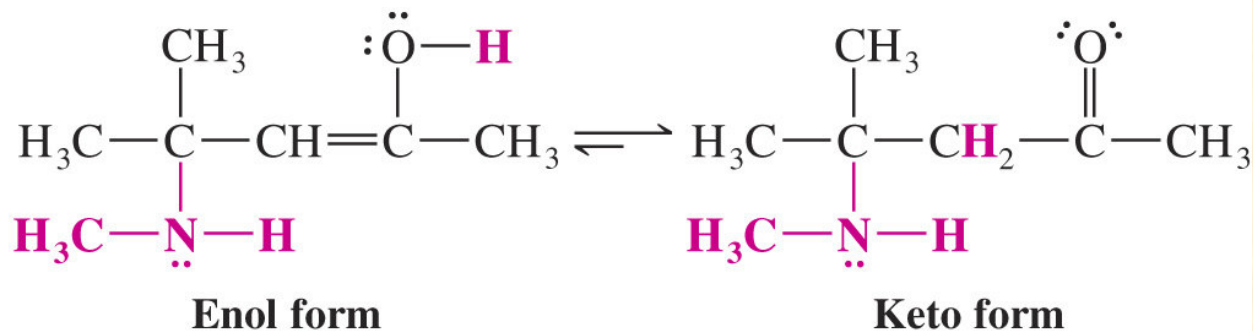


# Additions to $\alpha,\beta$ -Unsaturated Carbonyls



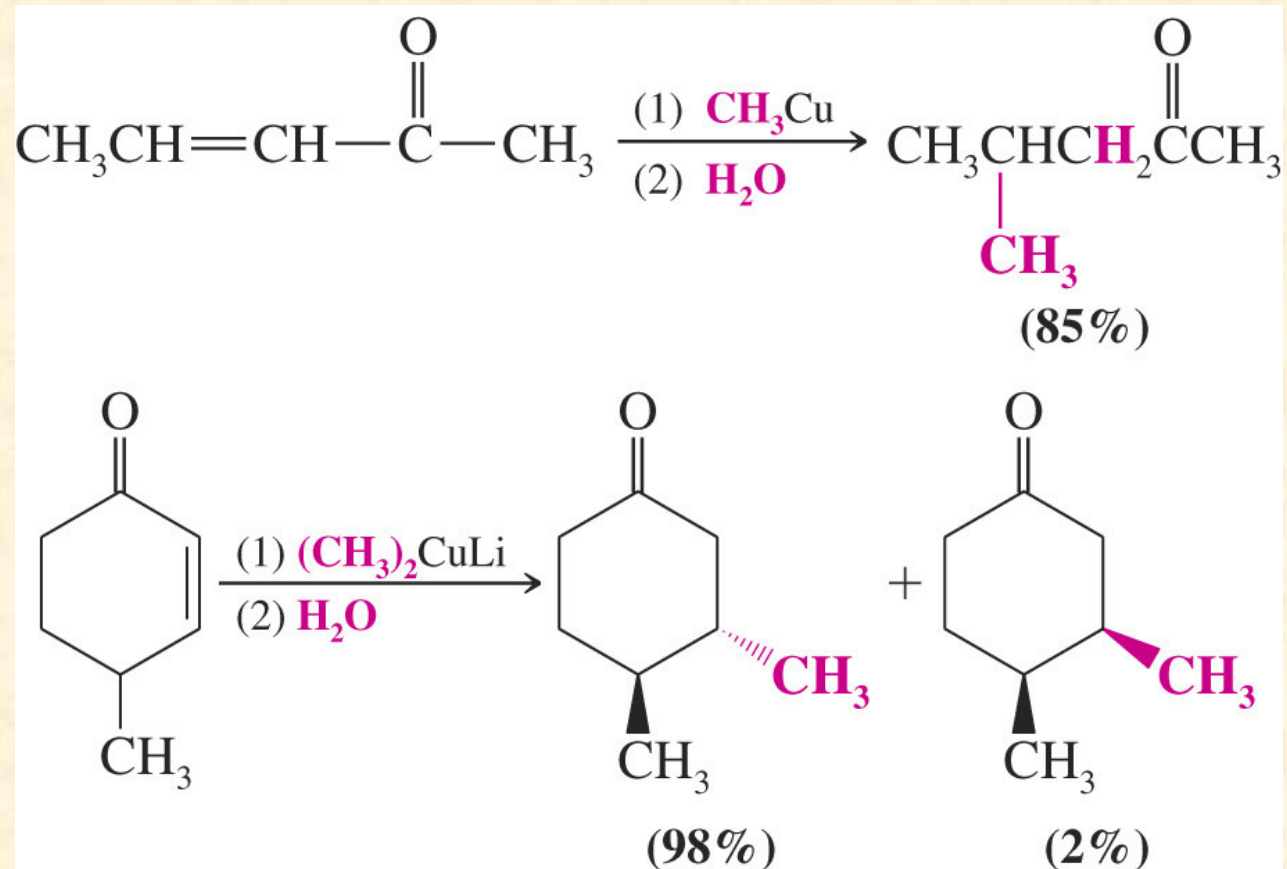
The nucleophile attacks the partially positive  $\beta$  carbon.

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



# Additions to $\alpha,\beta$ -Unsaturated Carbonyls

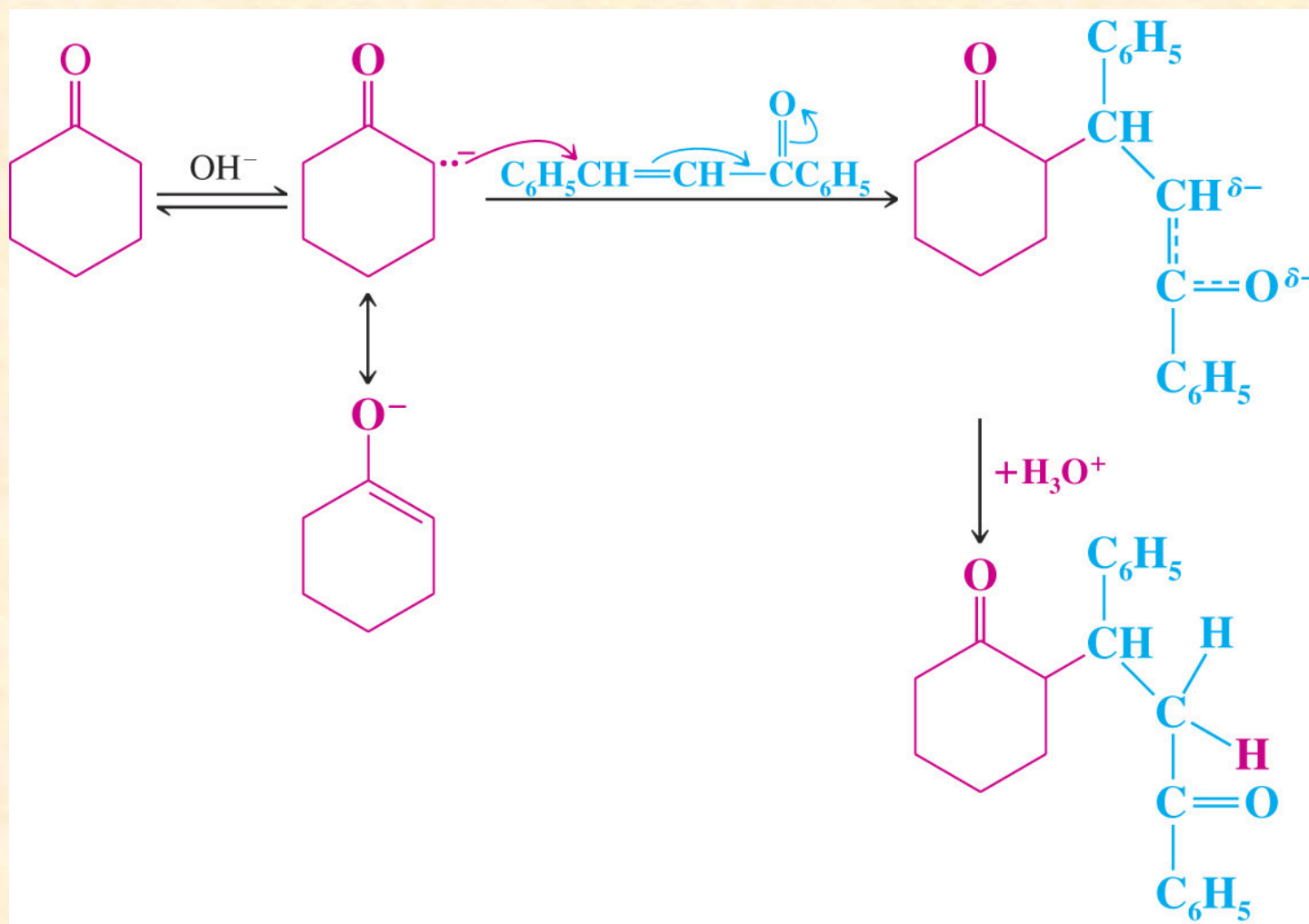
- Conjugate Addition of Organocopper Reagents
  - Organocopper reagents add almost exclusively in a conjugate manner to  $\alpha,\beta$ -unsaturated aldehydes and ketones



# Michael Addition

## – Michael Additions

- Addition of an enolate to an  $\alpha,\beta$ -unsaturated carbonyl compound usually occurs by conjugate addition
- This reaction is called a Michael addition





# Robinson Annulation

- 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

