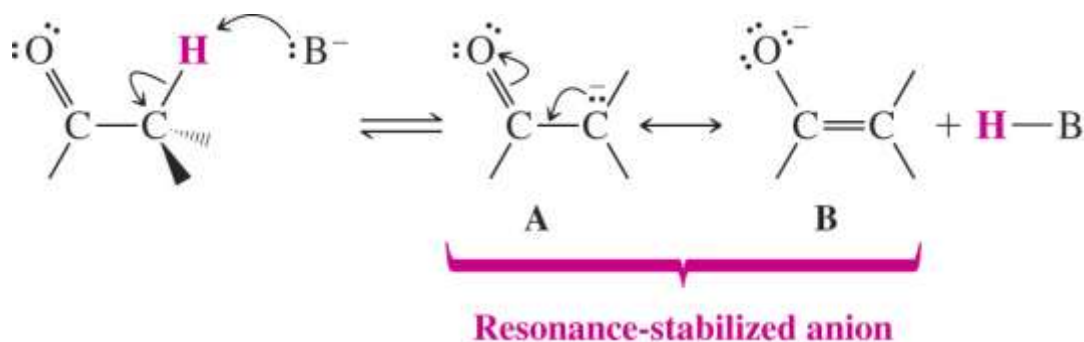
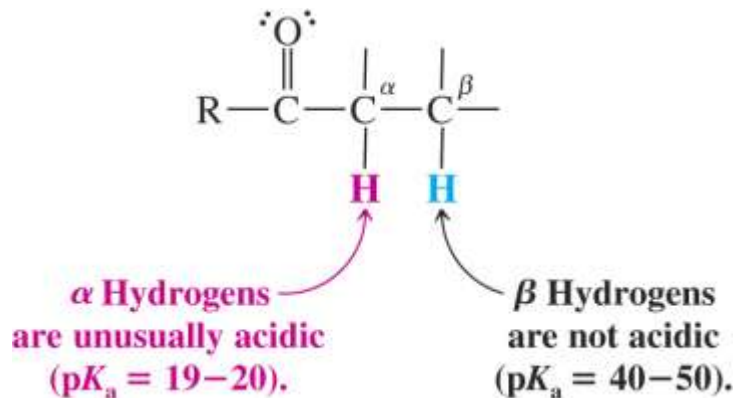


Aldehydes and Ketones : Aldol Reactions

◆ The Acidity of the α Hydrogens of Carbonyl Compounds: Enolate Anions

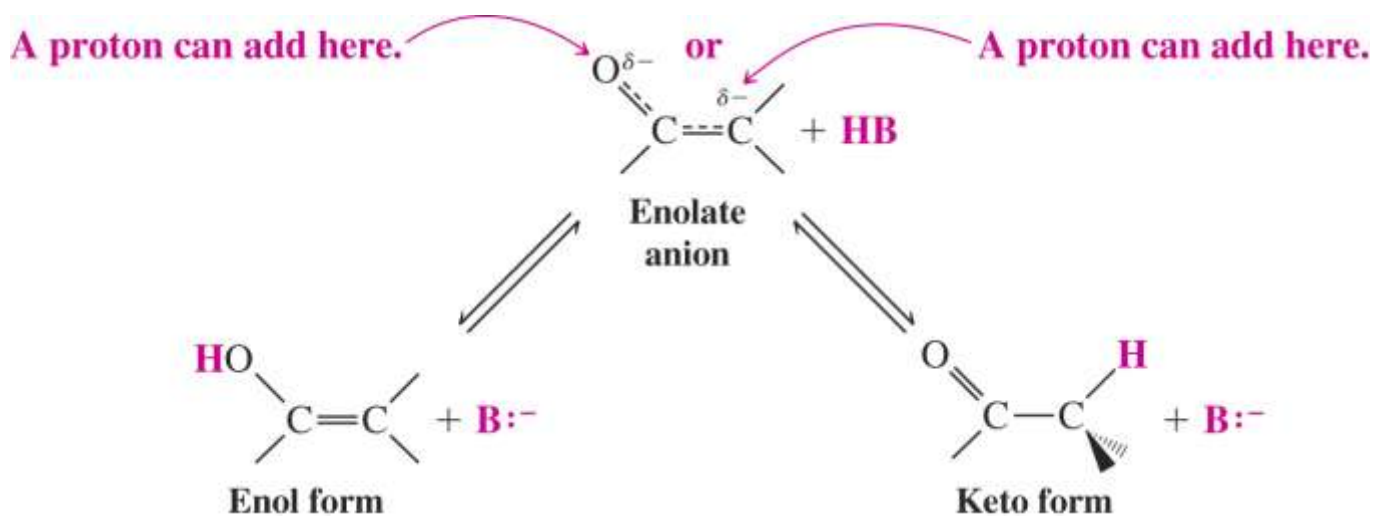
→ Hydrogens on carbons α to carbonyls are unusually acidic

☞ The resulting anion is stabilized by resonance to the carbonyl



- The enolate anion can be protonated at the carbon or the oxygen

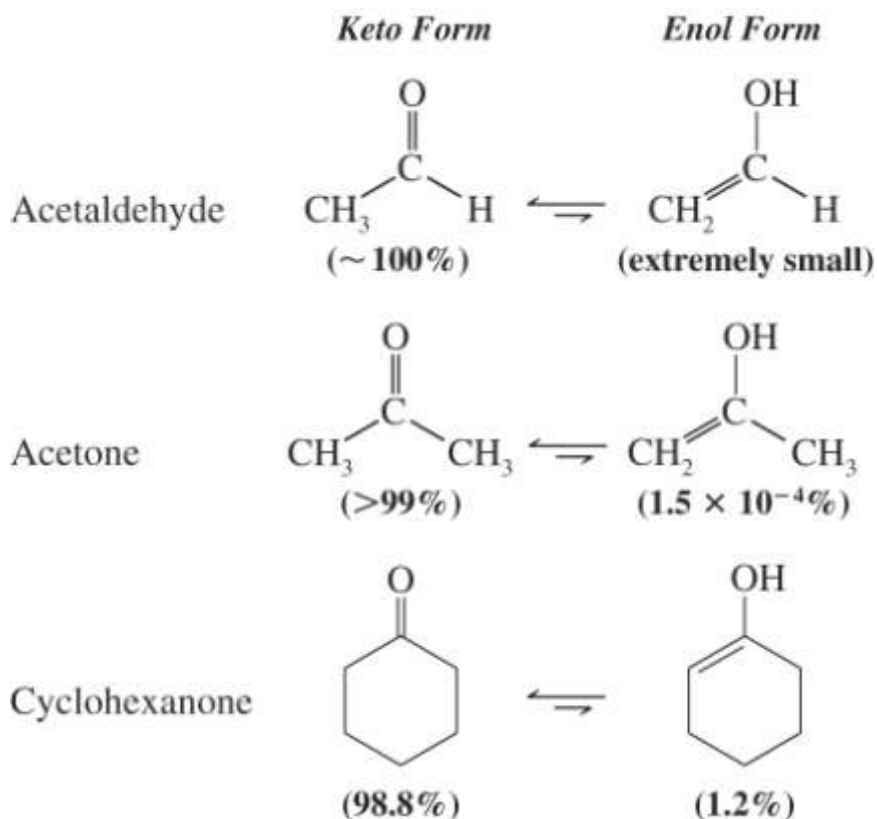
→ The resultant enol and keto forms of the carbonyl are formed reversibly and are interconvertible



◆ Keto and Enol Tautomers

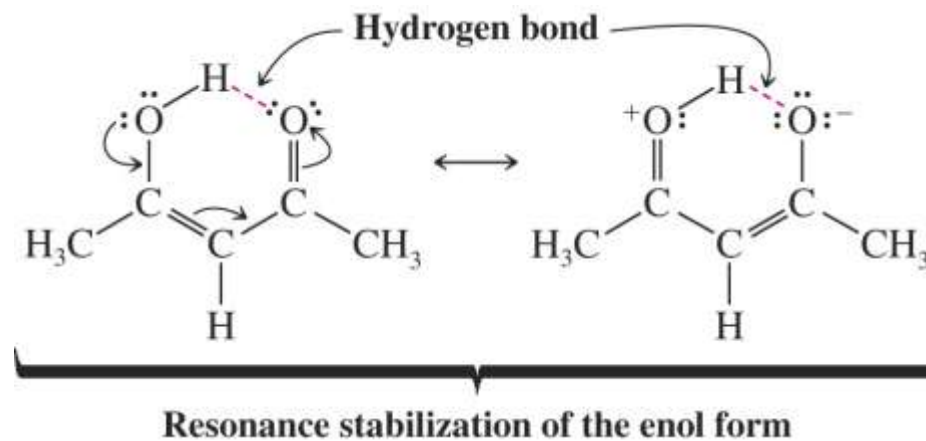
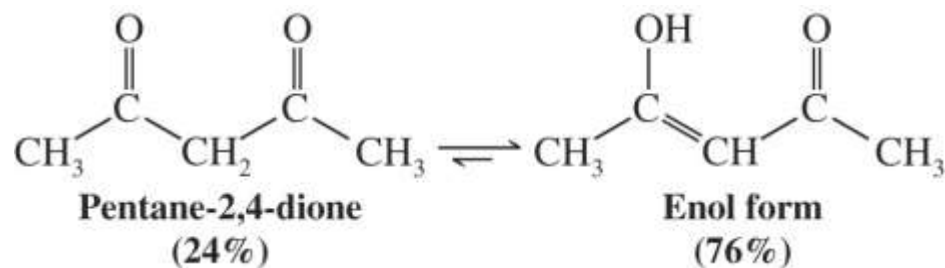
→ Enol-keto tautomers are constitutional isomers that are easily interconverted by a trace of acid or base

- 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



→ β -Dicarbonyl compounds exist primarily in the enol form

- ☞ The enol is more stable because it has a conjugated π system and because of stabilization of the enol through hydrogen bonding

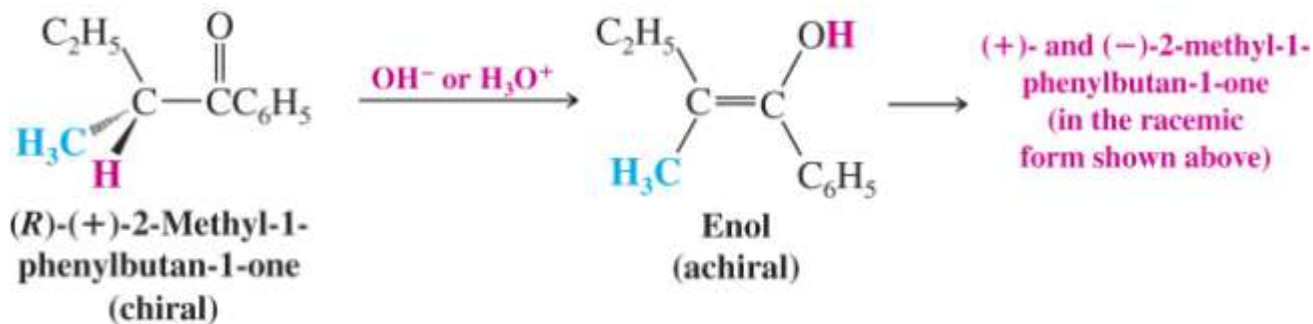
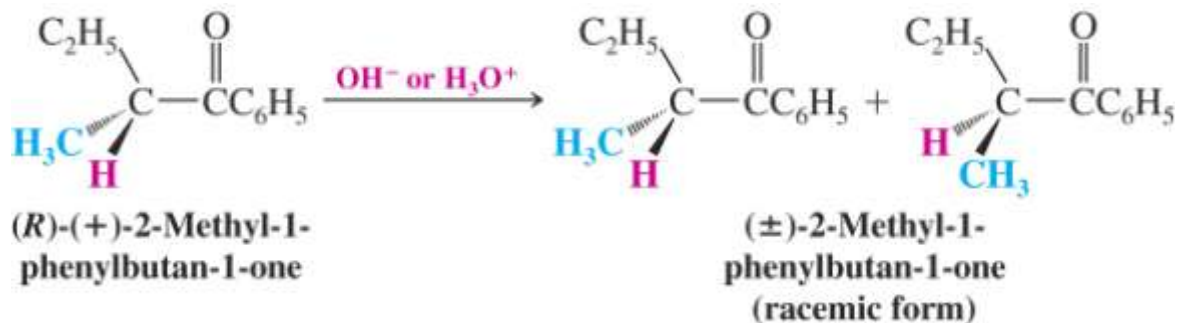


◆ Reactions via Enols and Enolate Anions

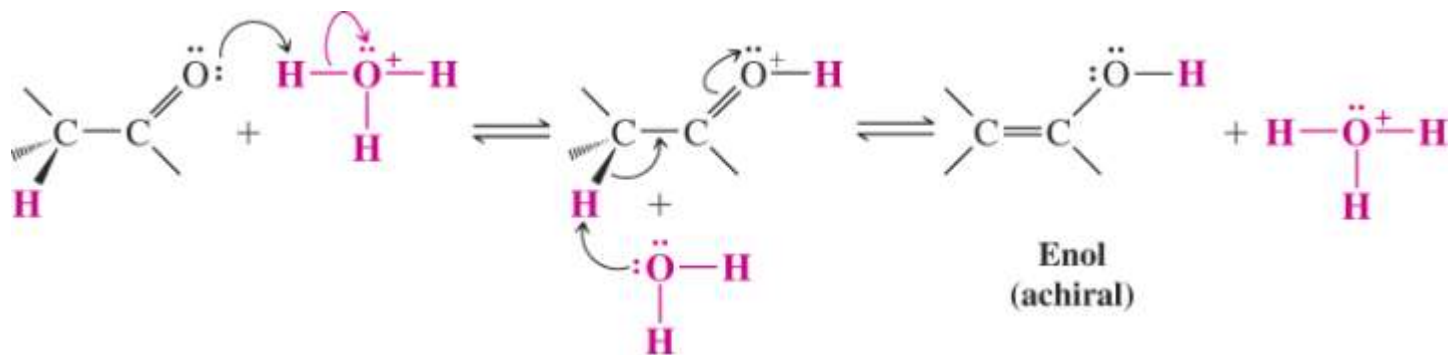
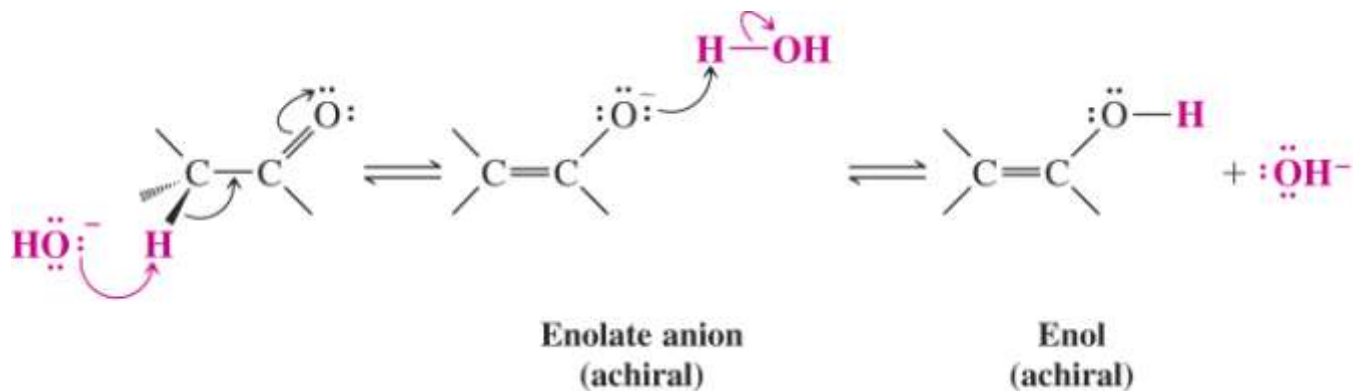
● Racemization

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

☞ The intermediate enol or enolate has no stereocenter at the α position



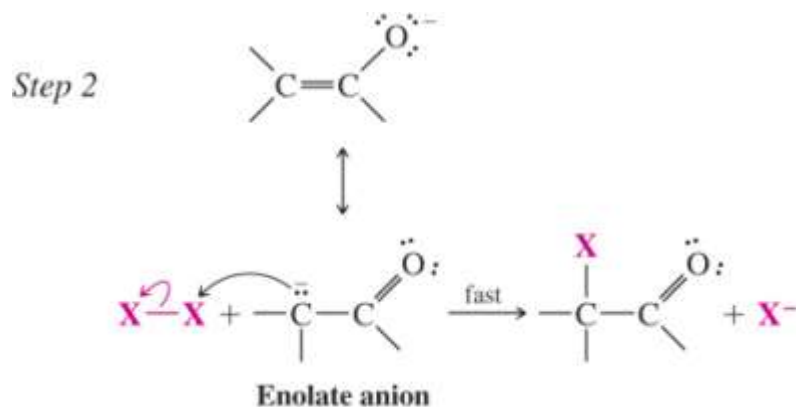
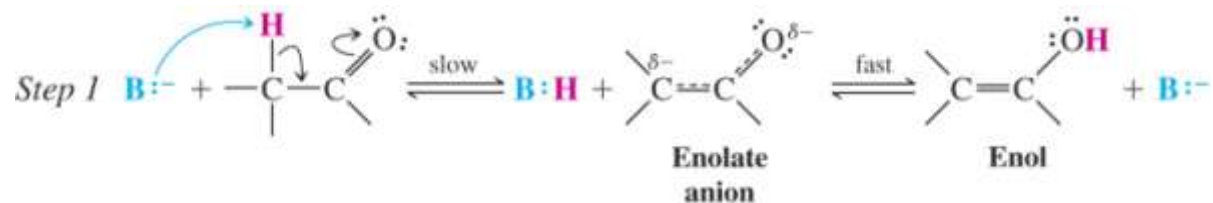
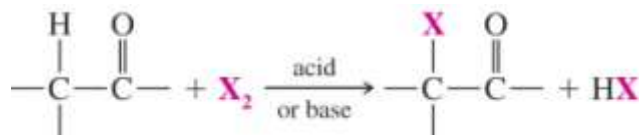
→ The mechanisms of base and acid catalysed racemization are shown below



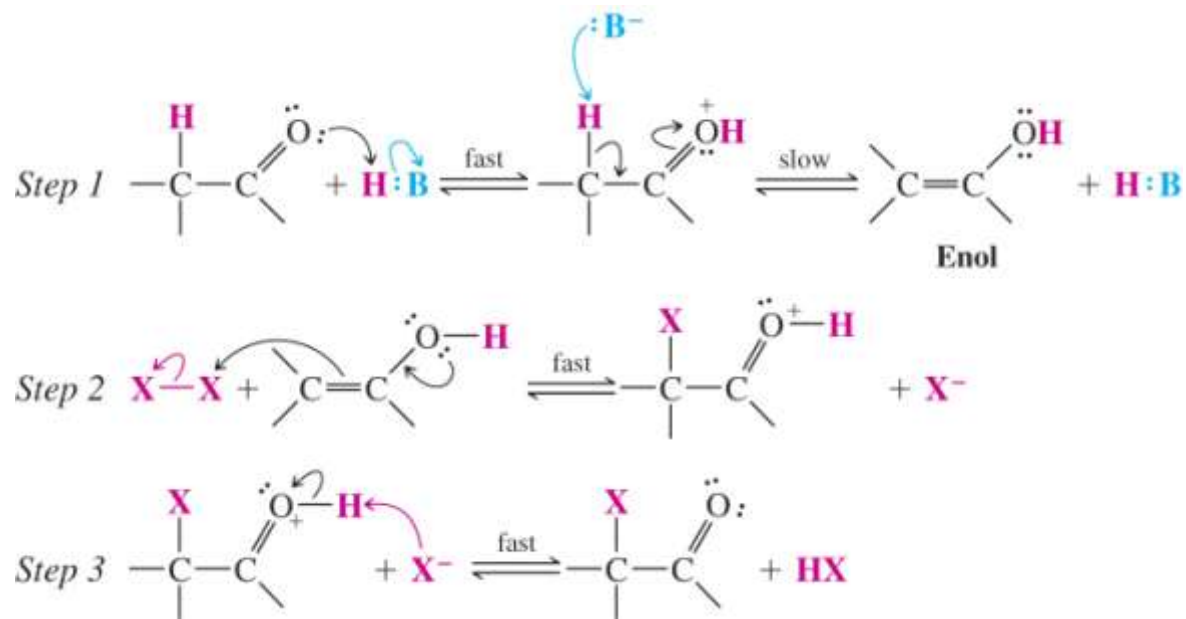
● Halogenation of Ketones

→ Ketones can be halogenated at the α position in the presence of acid or base and X_2

☞ Base-promoted halogenation occurs via an enolate

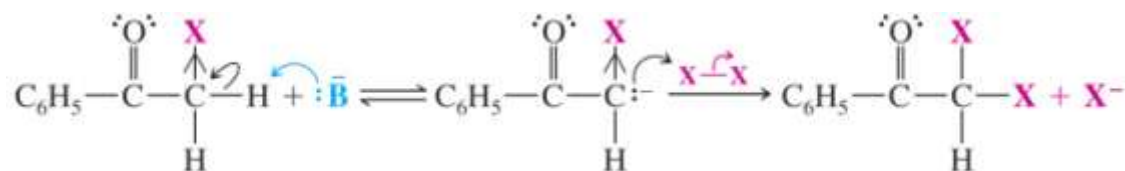
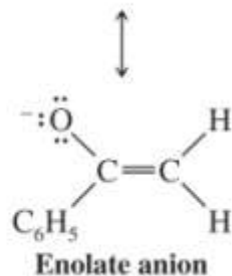
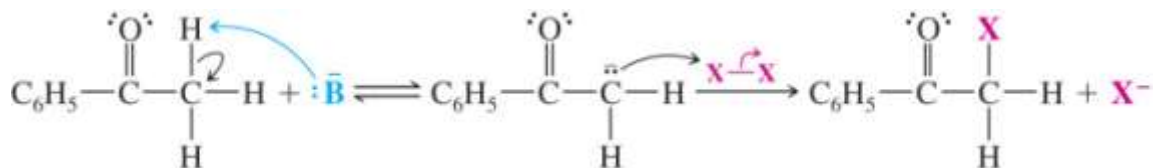


☞ Acid-catalyzed halogenation proceeds via the enol

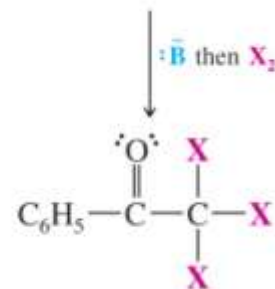
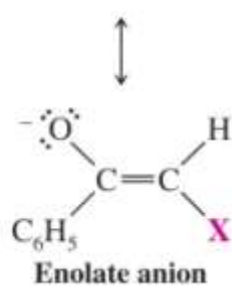


● Haloform Reaction

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

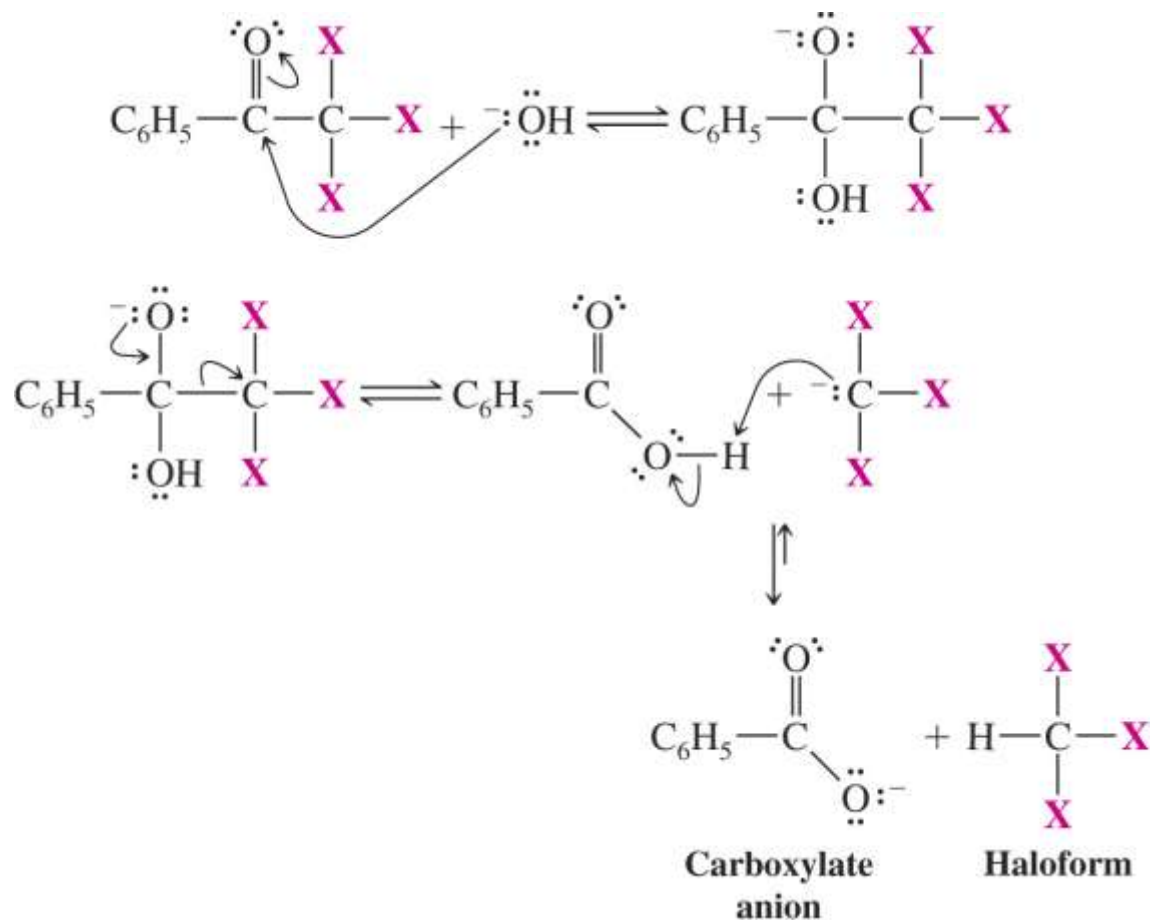


Acidity is increased by the electron-withdrawing halogen atom.



→ When methyl ketones react with X_2 in aqueous hydroxide the reaction gives a carboxylate anion and a haloform (CX_3H)

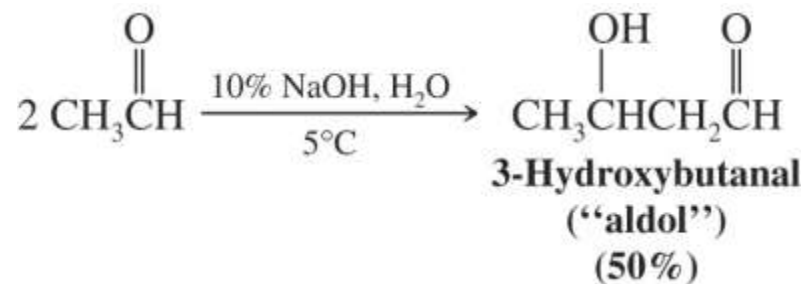
- ☞ The trihalomethyl anion is a relatively good leaving group because the negative charge is stabilized by the three halogen atoms



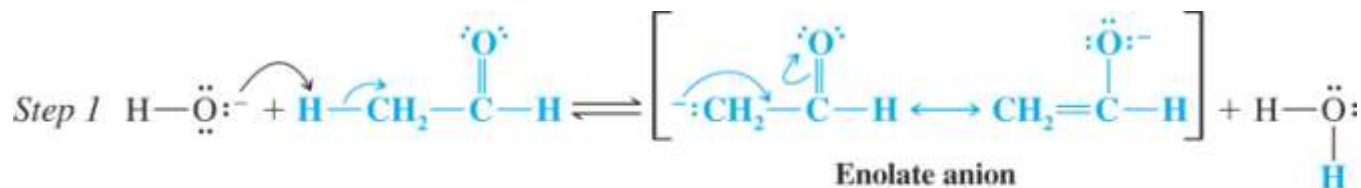
◆ The Aldol Reaction: The Addition of Enolate Anions to Aldehydes and Ketones

→ Acetaldehyde dimerizes in the presence of dilute sodium hydroxide at room temperature

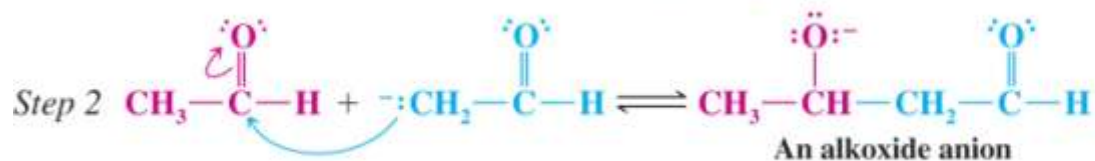
☞ The product is called an aldol because it is both an aldehyde and an alcohol



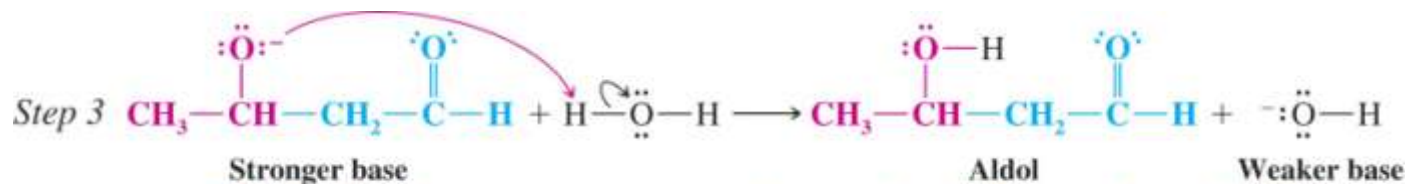
→ The mechanism proceeds through the enolate anion



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.



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

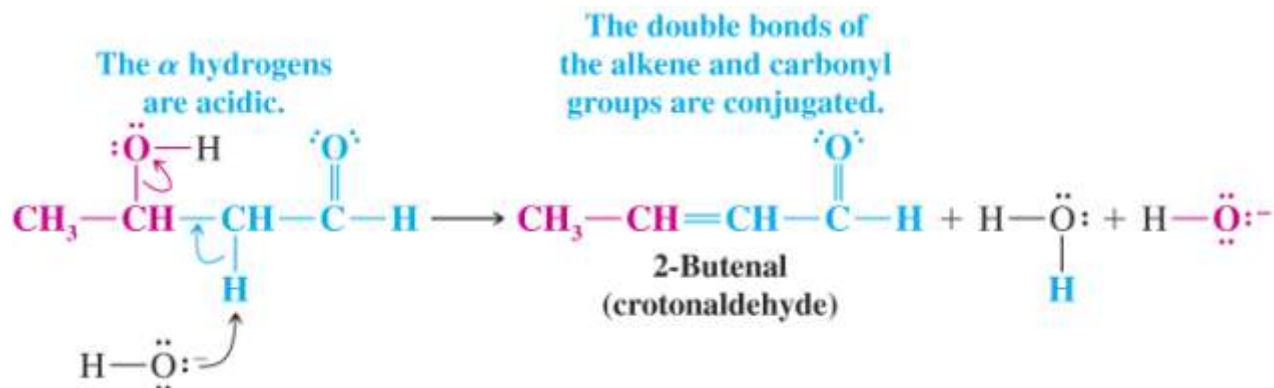


The alkoxide anion now removes a proton from a molecule of water to form the aldol.

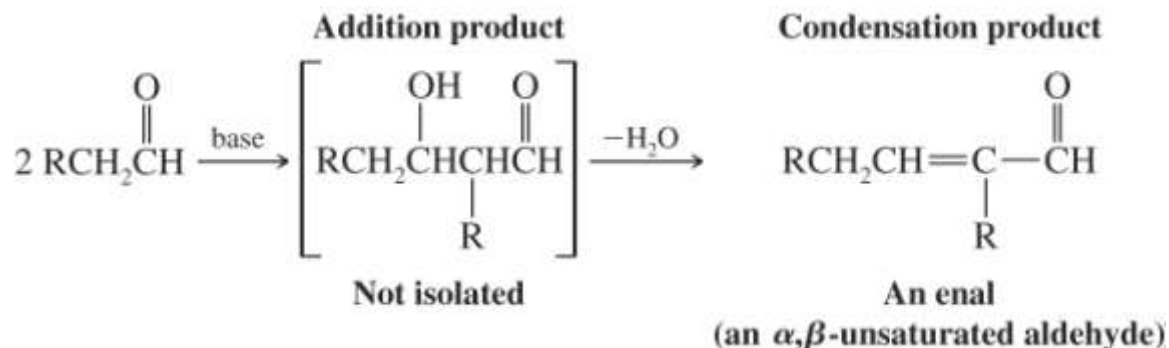
● Dehydration of the Aldol Product

→ 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

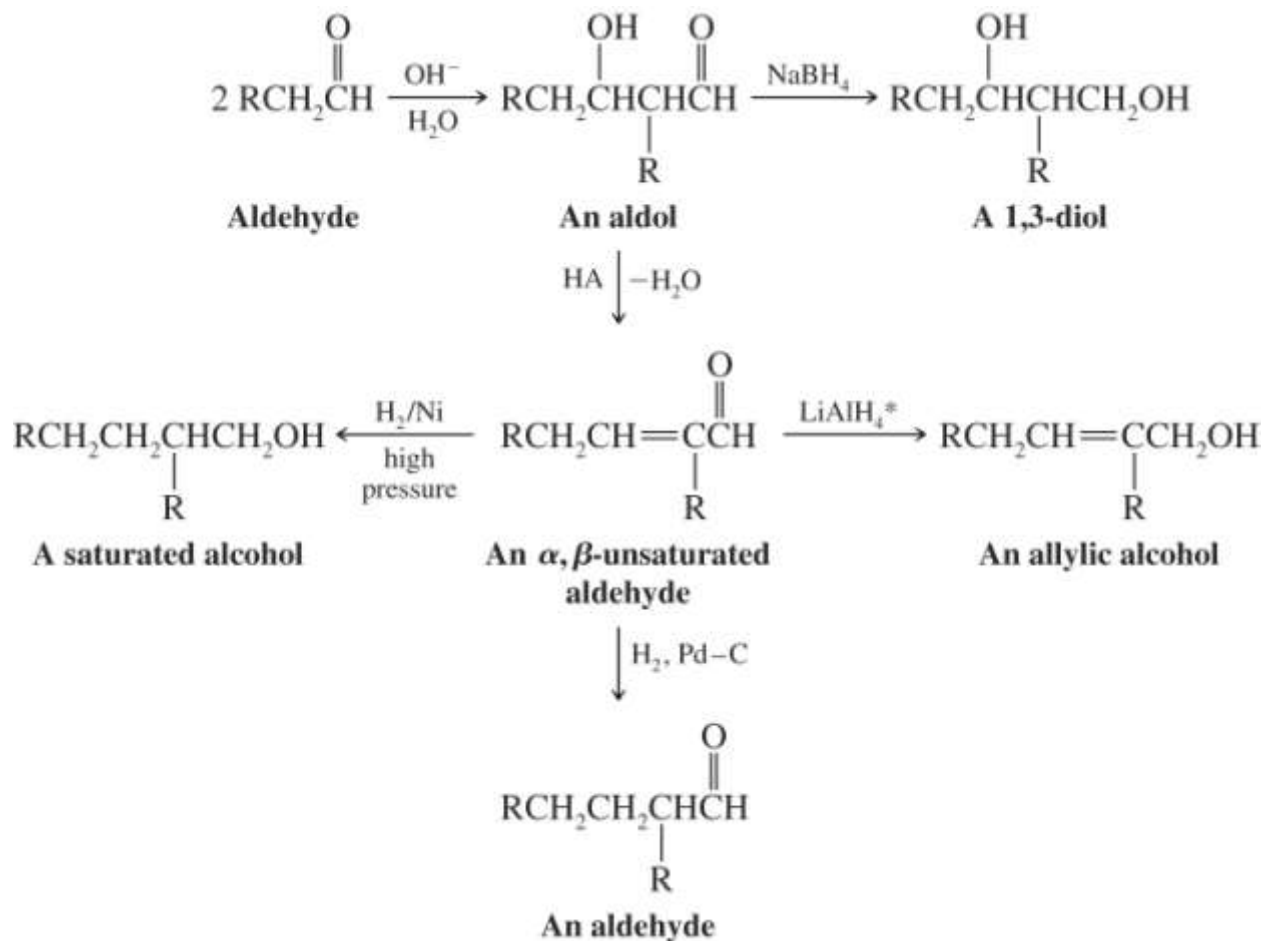


→ In some aldol reactions, the aldol product cannot be isolated because it is rapidly dehydrated to the α,β -unsaturated compound



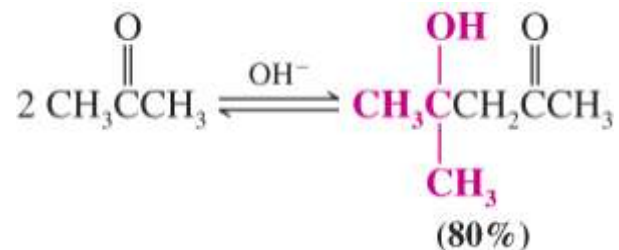
● Synthetic Applications

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



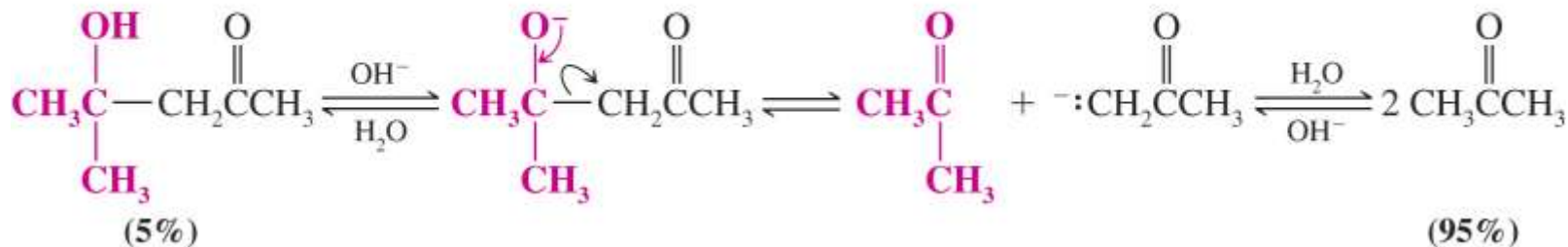
→ Aldol reactions with ketones are generally unfavorable because the equilibrium favors the starting ketone

☞ 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

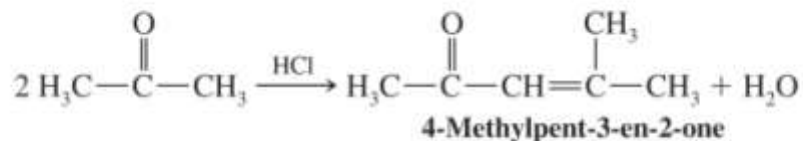
→ Aldol addition products undergo *retro-aldol* reactions in the



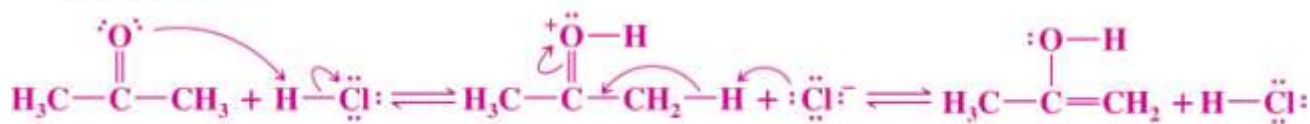
● Acid-Catalyzed Aldol Condensation

→ This reaction generally leads directly to the dehydration product

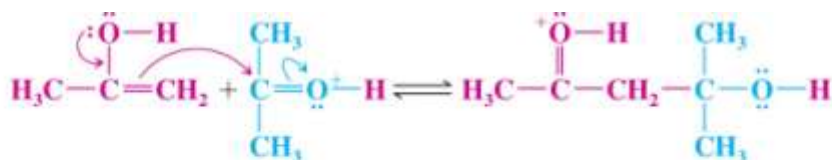
Reaction:



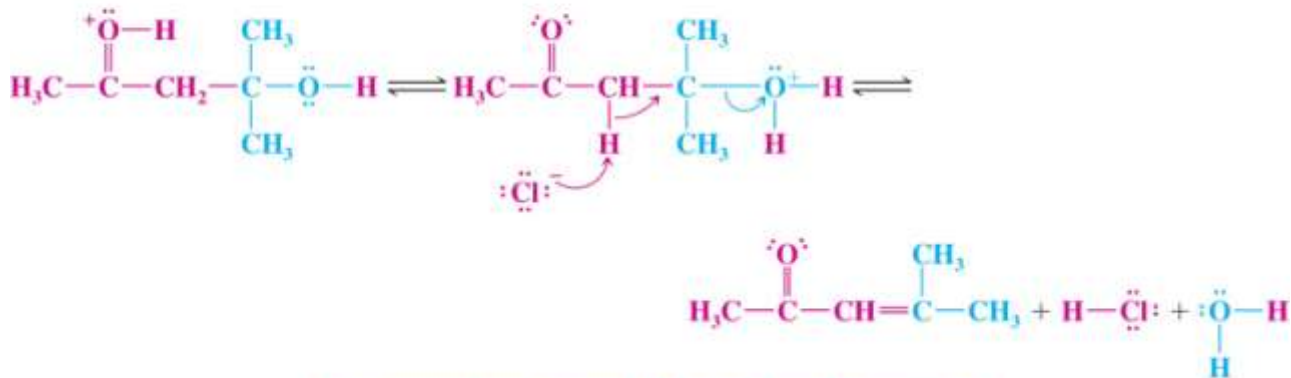
Mechanism:



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



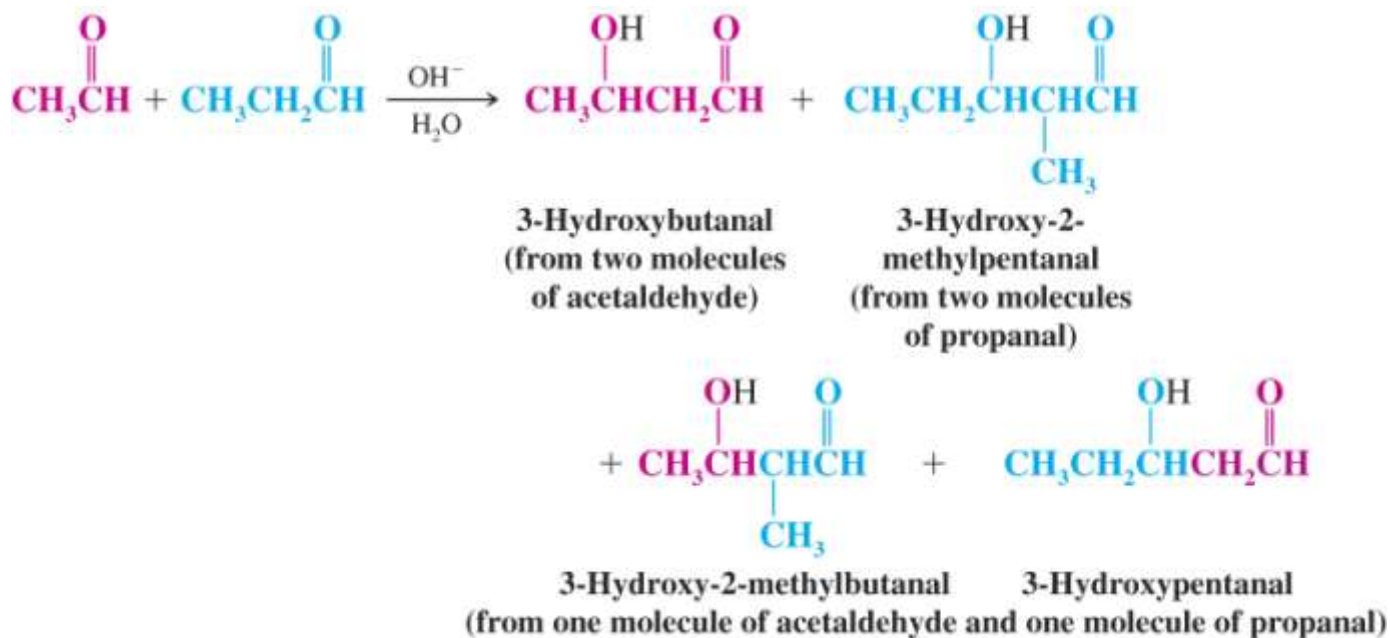
Then the enol adds to the protonated carbonyl group of another molecule of acetone.



Finally, proton transfers and dehydration lead to the product.

◆ Crossed Aldol Reactions

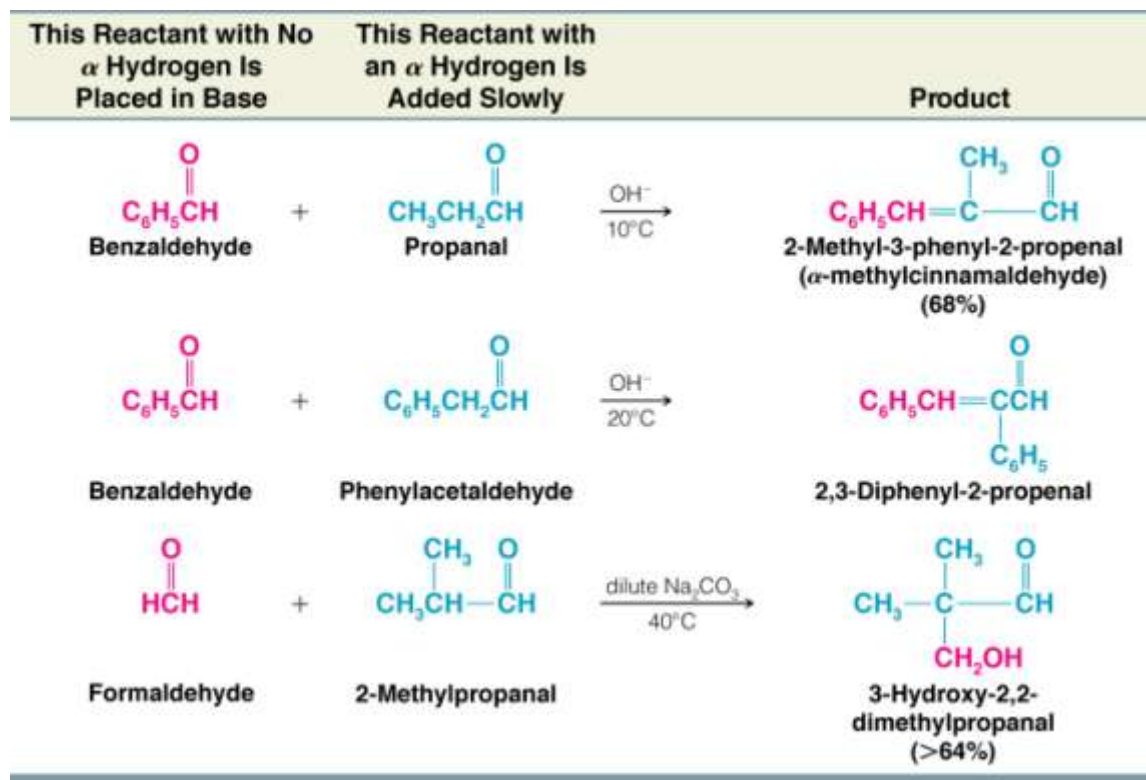
→ Crossed aldol reactions (aldol reactions involving two different aldehydes) are of little use when they lead to a mixture of products



● Practical Crossed Aldol Reactions

→ Crossed aldol reactions give one predictable product when one of the reaction partners has no α hydrogens

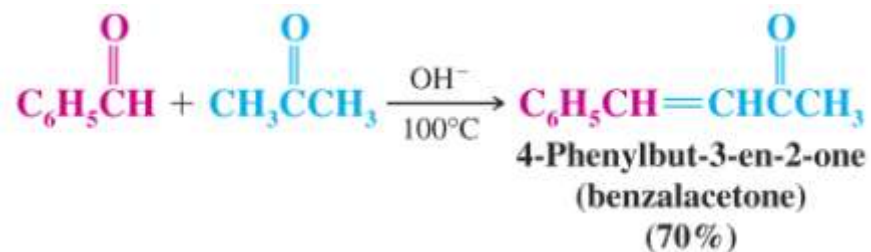
- ☞ The carbonyl compound without any α hydrogens is put in basic solution, and the carbonyl with one or two α hydrogens is added slowly
- ☞ Dehydration usually occurs immediately, especially if an extended conjugated system results



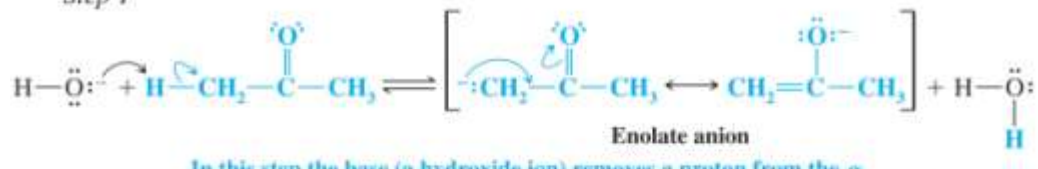
● Claisen-Schmidt Reactions

→ Crossed-aldol reactions in which one partner is a ketone are called Claisen-Schmidt reactions

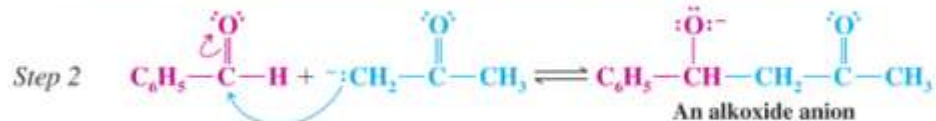
- ⚡ The product of ketone self-condensation is not obtained because the equilibrium is not favorable



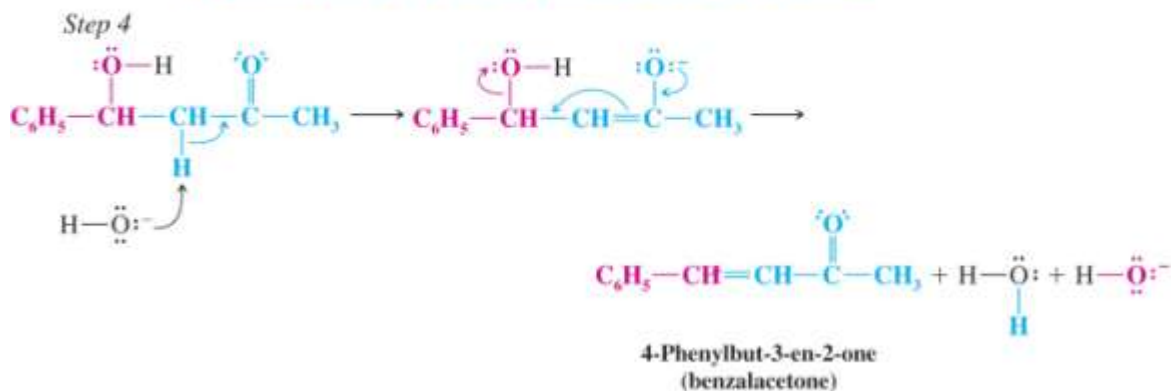
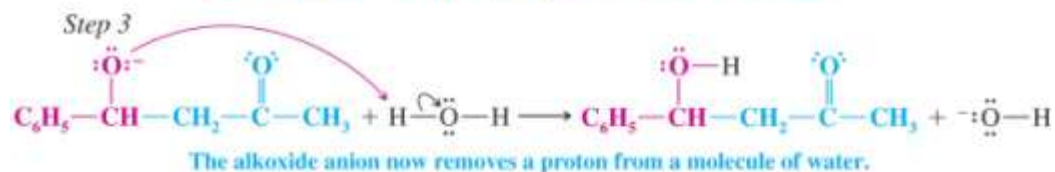
Step 1



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.



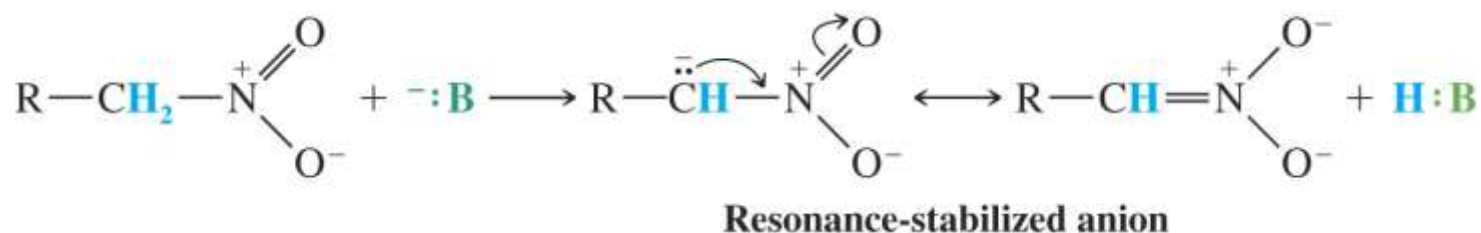
The enolate anion then acts as a nucleophile—as a carbanion—and attacks the carbonyl carbon of a molecule of aldehyde, producing an alkoxide anion.



Dehydration produces the conjugated product.

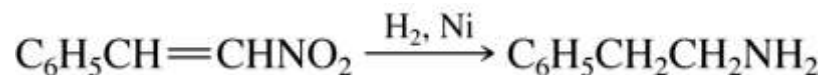
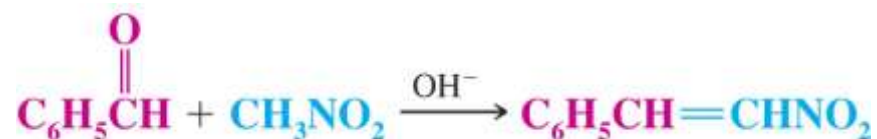
- **Condensation with Nitroalkanes**

→ The α 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

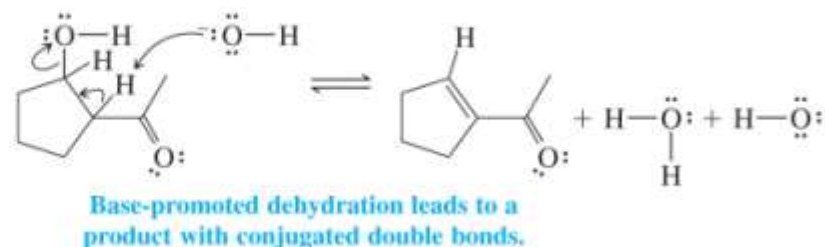
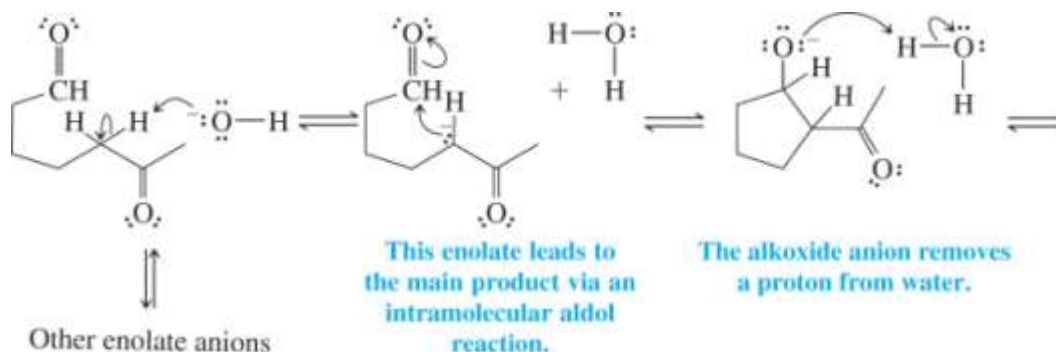
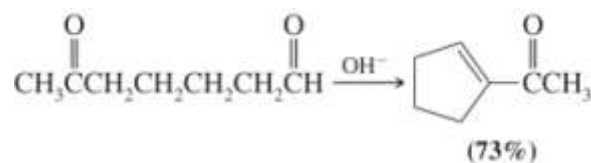
☞ The nitro group can be easily reduced to an amine



◆ Cyclization via Aldol Condensations

→ Intramolecular reaction of dicarbonyl compounds proceeds to form five- and six-membered rings preferentially

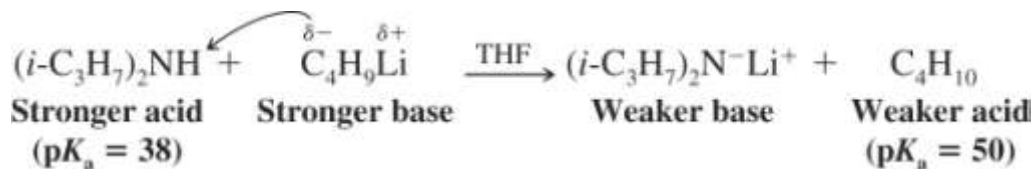
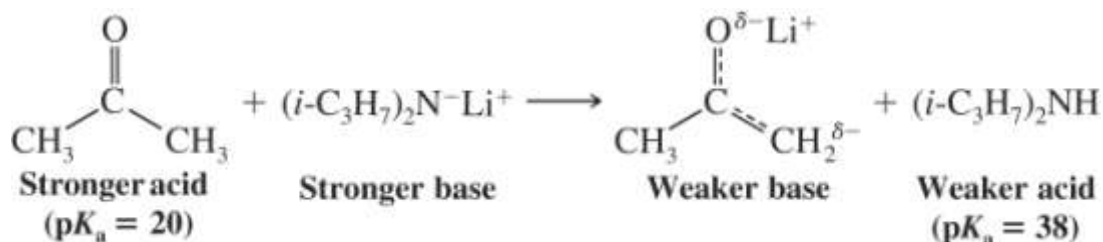
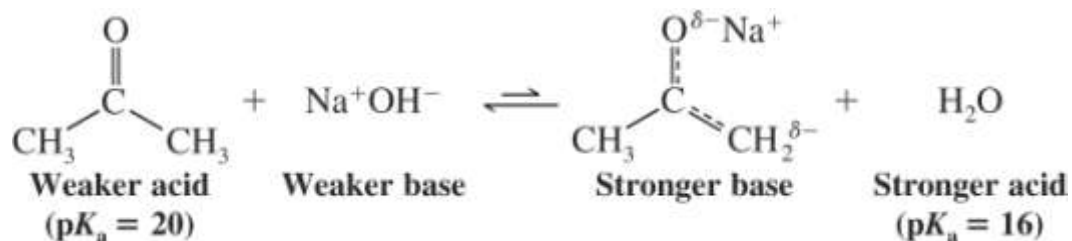
- ☞ In the following reaction the aldehyde carbonyl carbon is attacked preferentially because an aldehyde is less sterically hindered and more electrophilic than a ketone



◆ 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

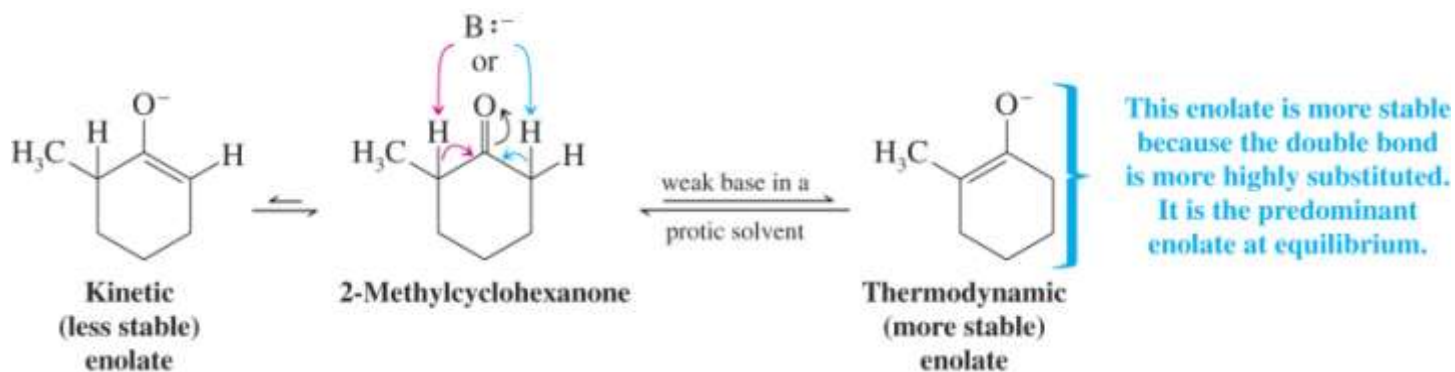


● Regioselective Formation of Enolate Anions

→ Unsymmetrical ketones can form two different enolates

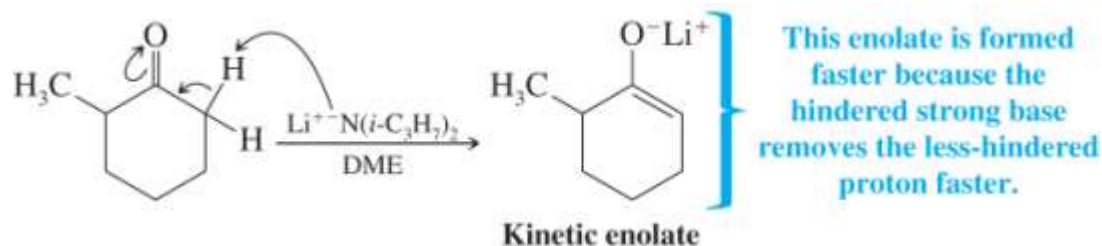
→ The thermodynamic enolate is the most stable enolate *i.e.* the one with the more highly substituted double bond

☞ A weak base favors the thermodynamic enolate because an equilibrium between the enolates is established



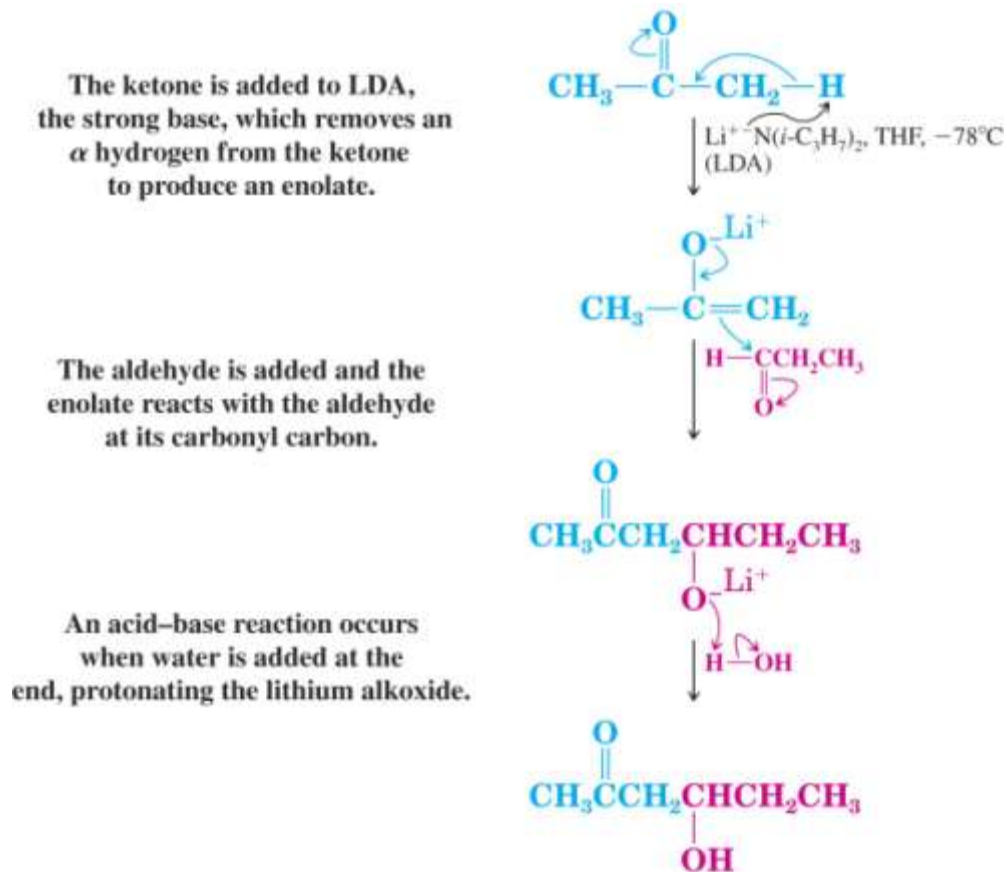
→ The kinetic enolate is the enolate formed fastest and it usually is the enolate with the least substituted double bond

☞ A strong, sterically hindered base such as lithium diisopropyl amide favors formation of the kinetic enolate

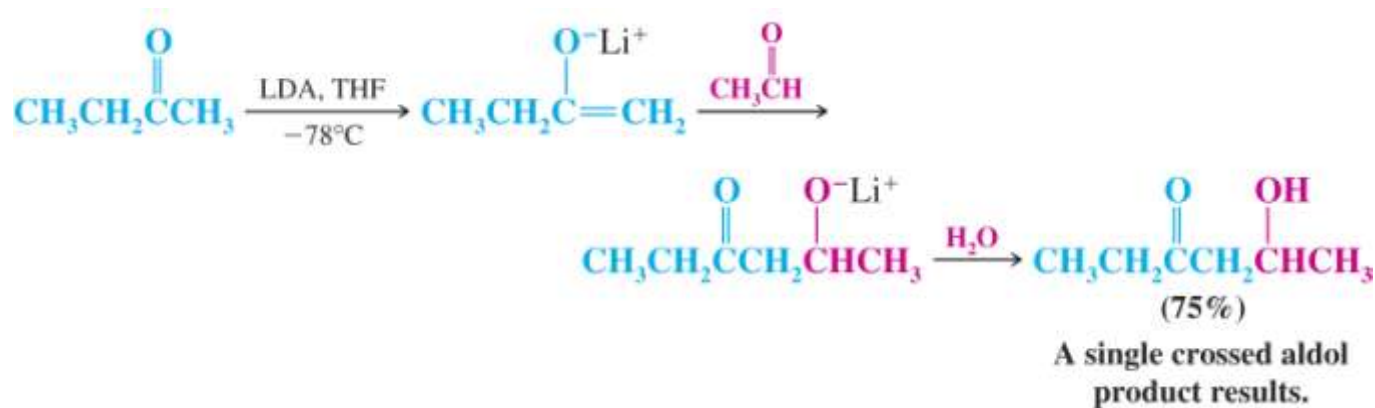


● Lithium Enolates in Directed Aldol Reactions

→ 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



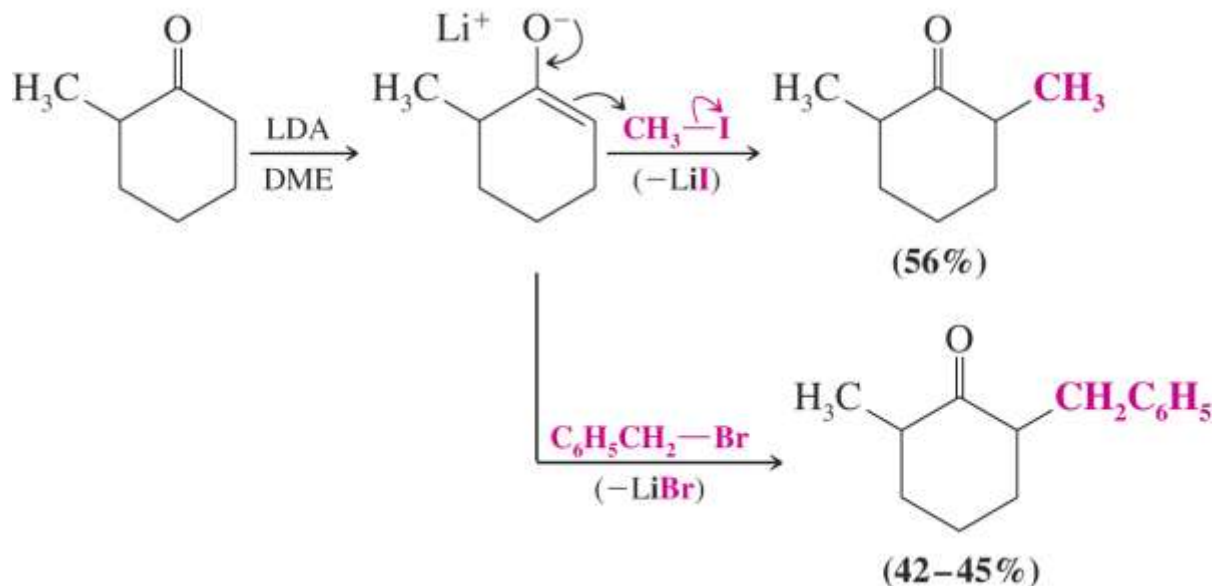
→ An unsymmetrical ketone can be selectively deprotonated with LDA to form the kinetic enolate and this will react with an aldehyde to give primarily one product



● Direct Alkylation of Ketones via Lithium Enolates

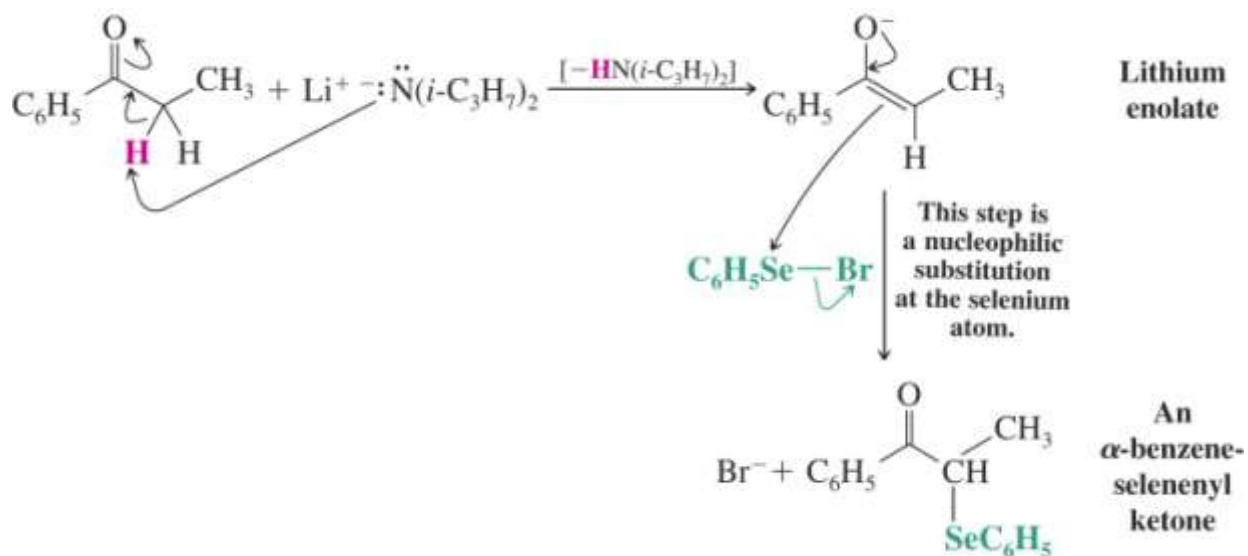
→ Enolates can also be alkylated with primary alkyl halides via an S_N2 reaction

☞ Unsymmetrical ketones can be alkylated at the least substituted position if LDA is used to form the kinetic enolate



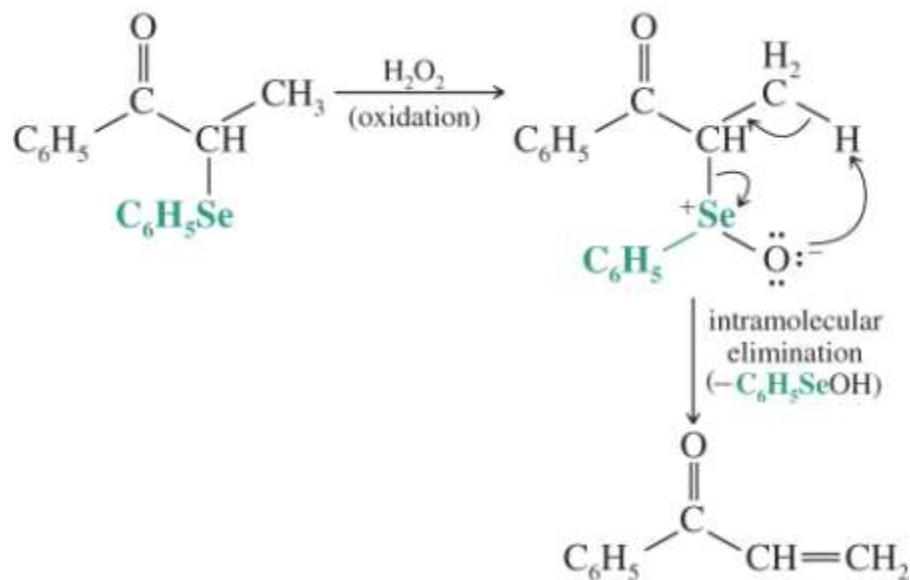
◆ α -Selenation: A Synthesis of α,β -Unsaturated Carbonyl Compounds

→ A lithium enolate can be selenated with benzeneselenenyl bromide



→ The α -selenyl ketone is converted to the α,β -unsaturated carbonyl compound by reaction with hydrogen peroxide

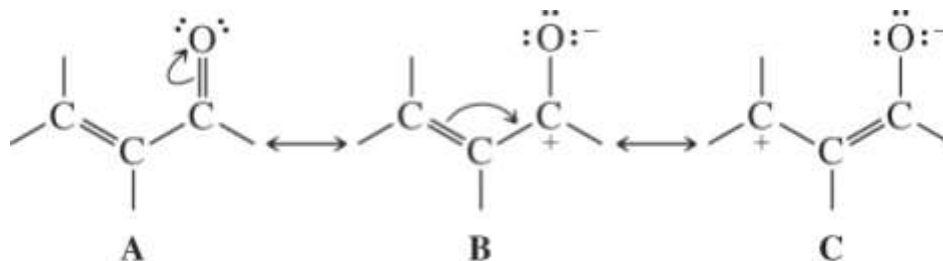
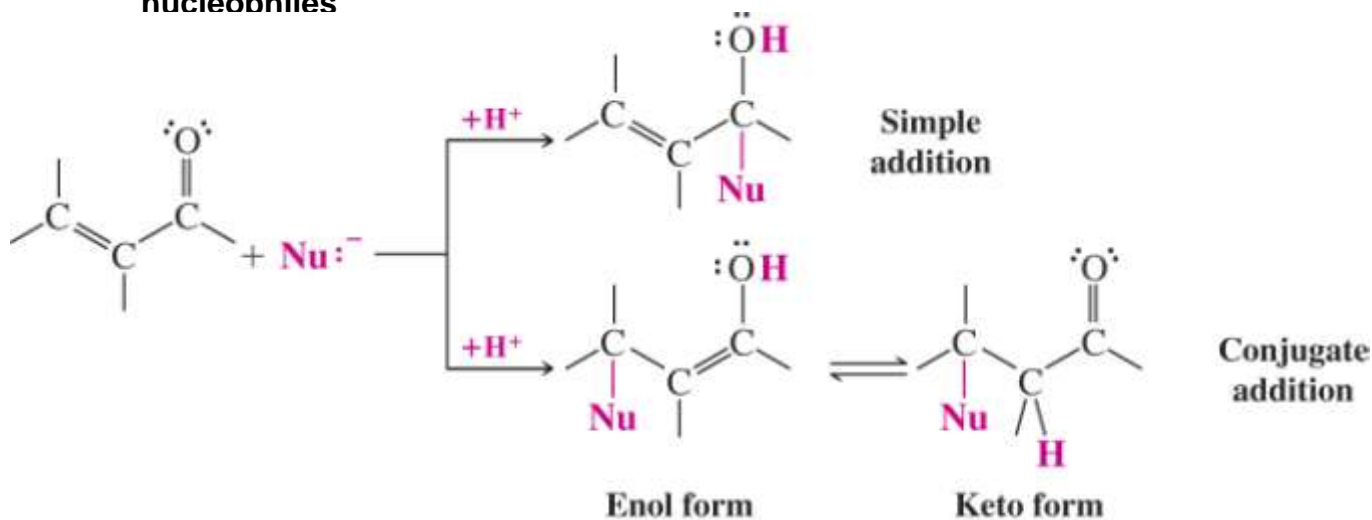
✎ Elimination of the selenoxide produces the unsaturated carbonyl

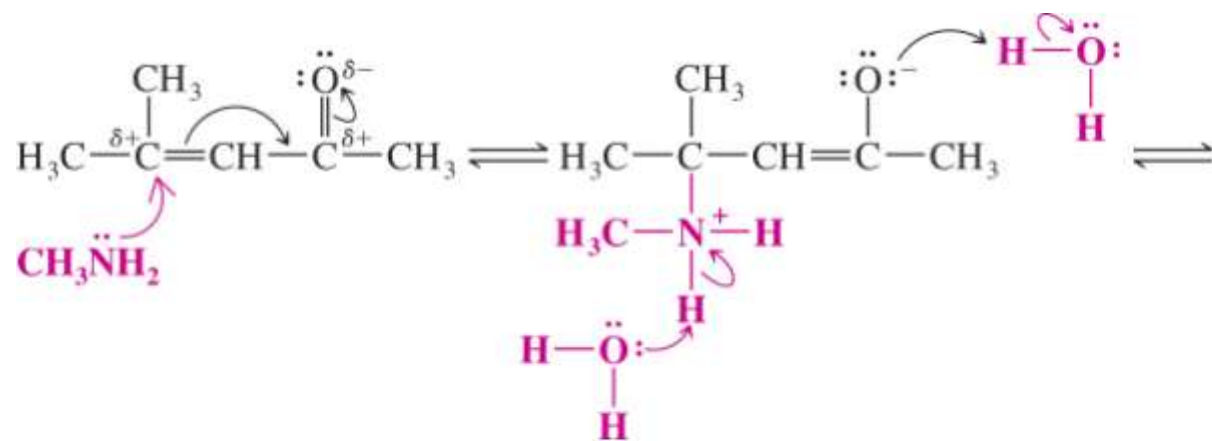


◆ Additions to α,β -Unsaturated Aldehydes and Ketones

→ α,β -Unsaturated aldehydes and ketones can react by simple (1,2) or conjugate (1,4) addition

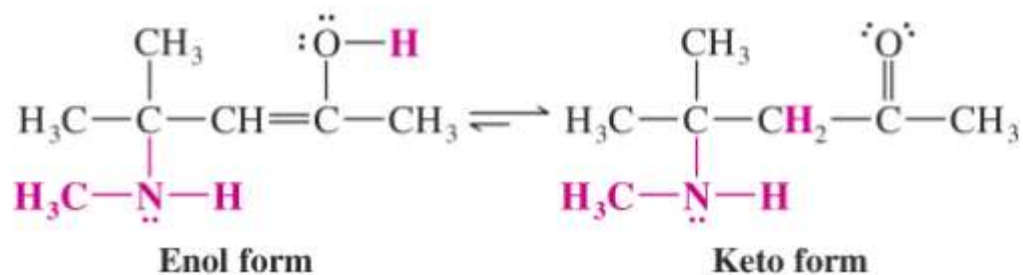
☞ Both the carbonyl carbon and the β carbon are electrophilic and can react with nucleophiles





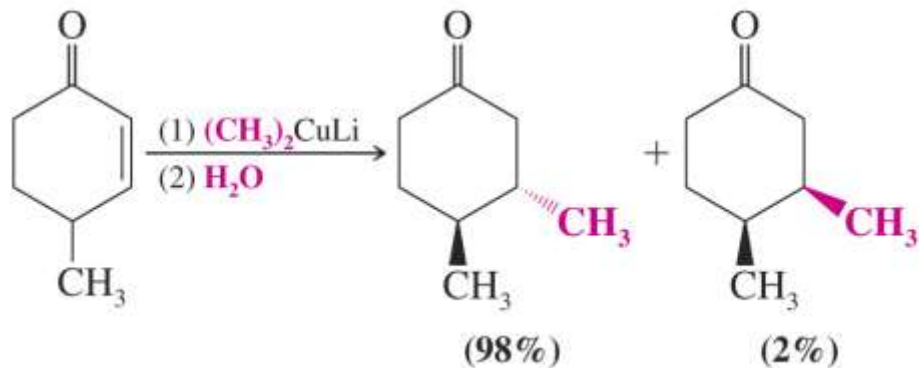
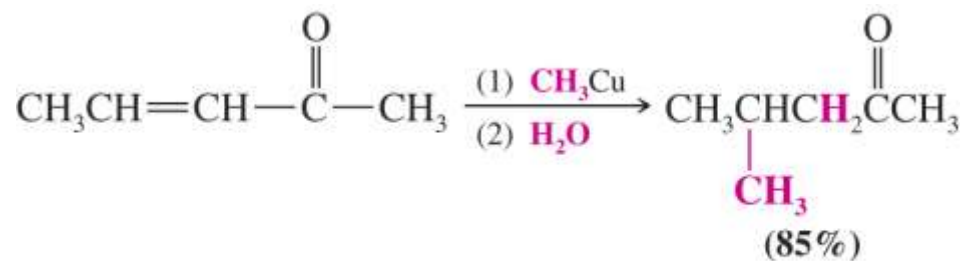
The nucleophile attacks the partially positive β carbon.

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



- **Conjugate Addition of Organocopper Reagents**

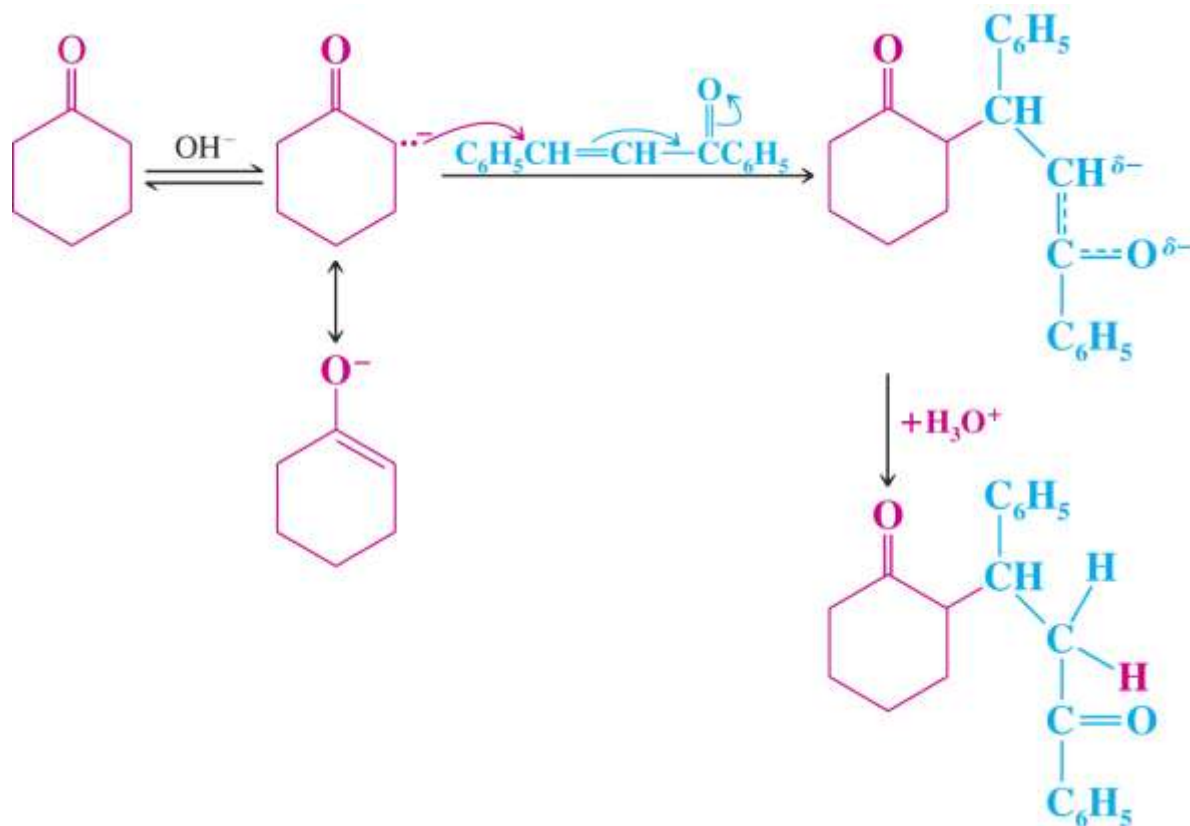
→ Organocopper reagents add almost exclusively in a conjugate manner to α,β -unsaturated aldehydes and ketones



● Michael Additions

→ Addition of an enolate to an α,β -unsaturated carbonyl compound usually occurs by conjugate addition

→ 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

