



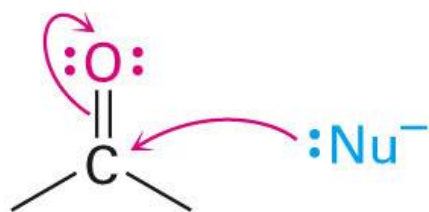
Carbonyl Condensation Reactions

Based on McMurry's *Organic Chemistry*, 7th edition
By **Jalal Hasan Mohammed**



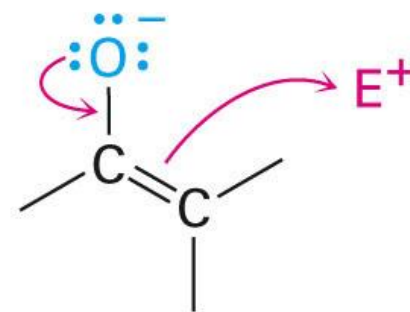
Condensation Reactions

- Carbonyl compounds are *both* the electrophile and nucleophile in carbonyl condensation reactions



**Electrophilic carbonyl group
reacts with nucleophiles.**

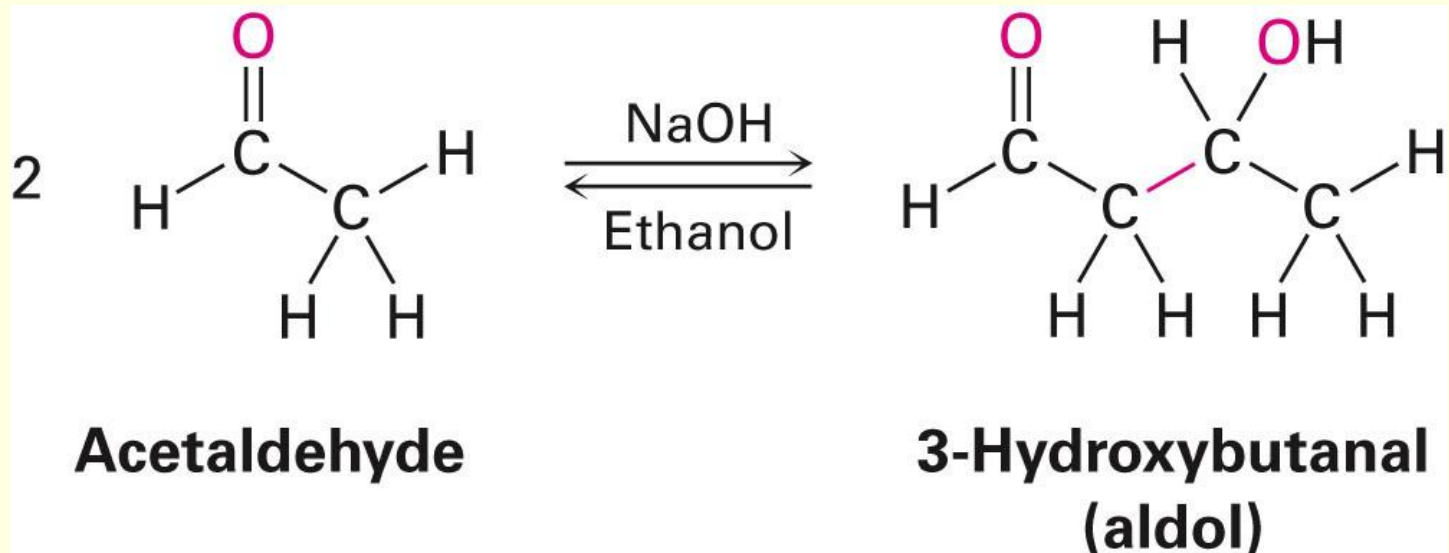
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**Nucleophilic enolate ion
reacts with electrophiles.**

Carbonyl Condensation: The Aldol Reaction

- Acetaldehyde reacts in basic solution (NaOEt, NaOH) with another molecule of acetaldehyde
- The β -hydroxy aldehyde product is *aldol* (*aldehyde* + *alcohol*)
- This is a general reaction of aldehydes and ketones

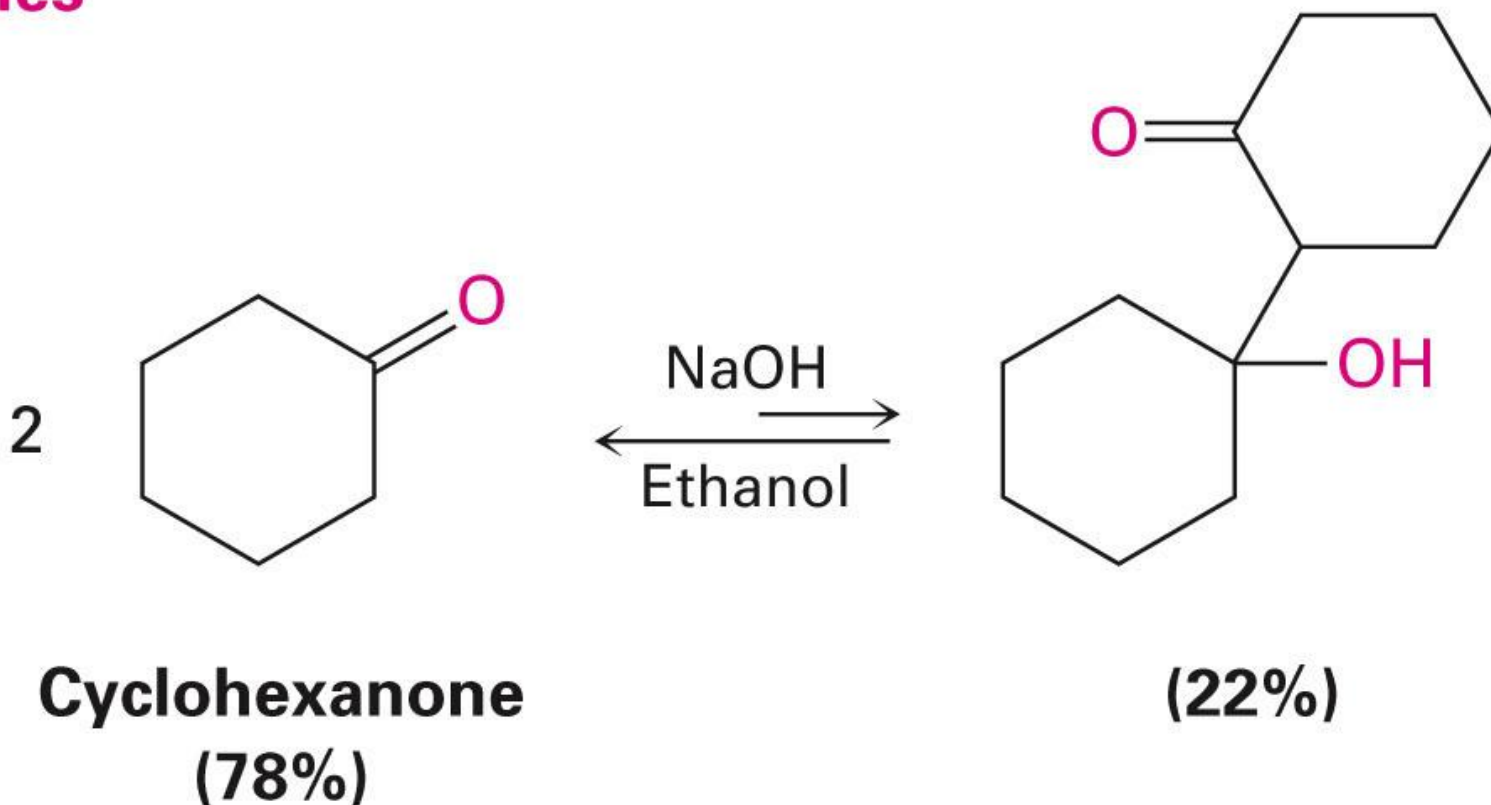


The Equilibrium of the Aldol

- The aldol reaction is reversible, favoring the condensation product only for aldehydes with no α substituent
- Steric factors are increased in the aldol product

Aldehydes and Ketones and the Aldol Equilibrium

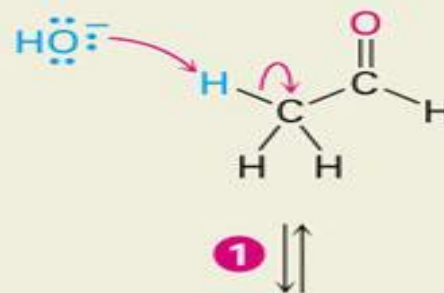
Ketones



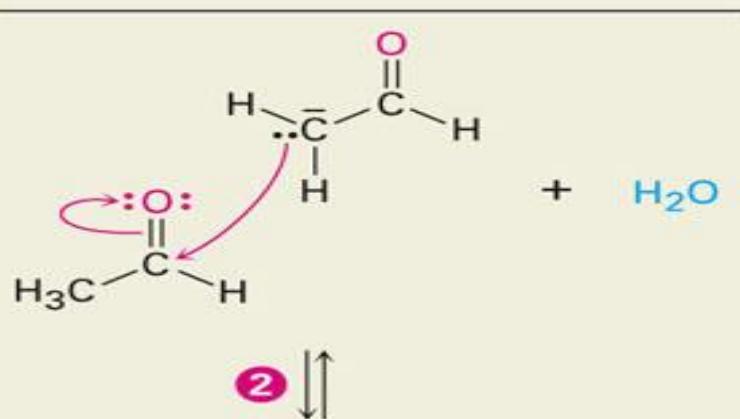
Mechanism of Aldol Reactions

- Aldol reactions, like all carbonyl condensations, occur by nucleophilic addition of the enolate ion of the donor molecule to the carbonyl group of the acceptor molecule
- The addition intermediate is protonated to give an alcohol product

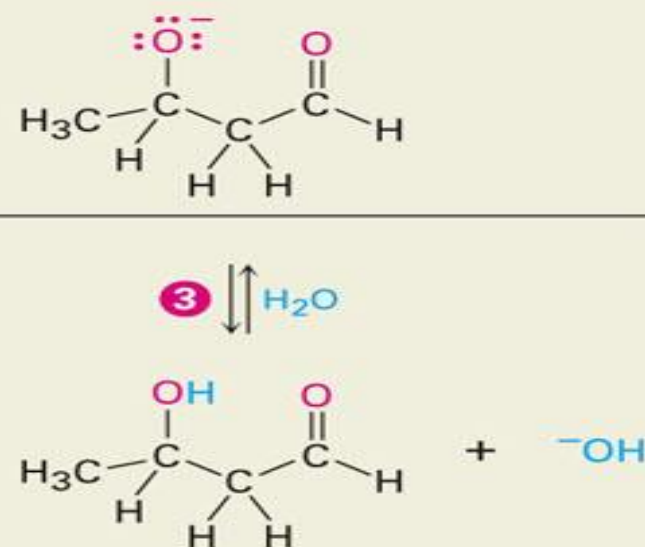
- 1** Base removes an acidic alpha hydrogen from one aldehyde molecule, yielding a resonance-stabilized enolate ion.



- 2** The enolate ion attacks a second aldehyde molecule in a nucleophilic addition reaction to give a tetrahedral alkoxide ion intermediate.

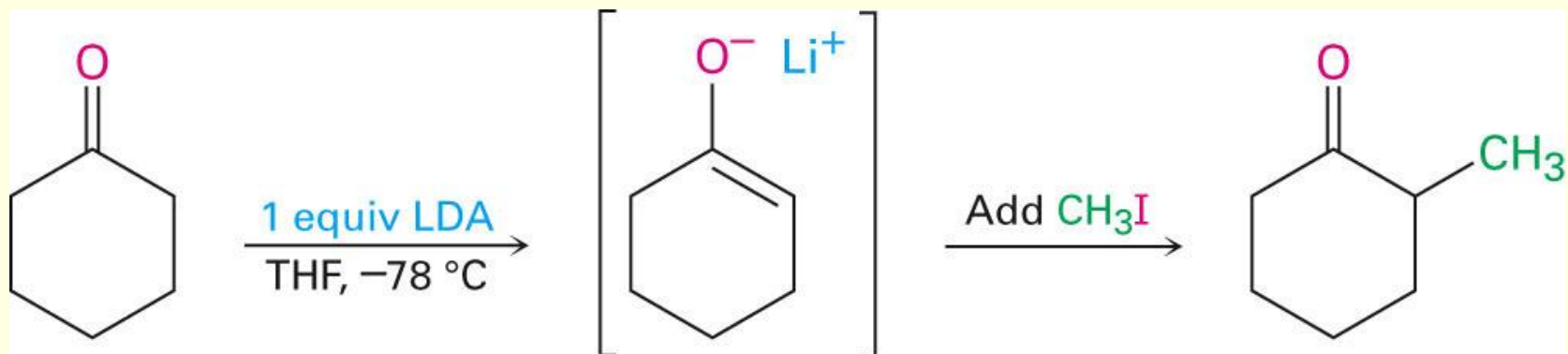


- 3** Protonation of the alkoxide ion intermediate yields neutral aldol product and regenerates the base catalyst.



Carbonyl Condensation versus Alpha-Substitution

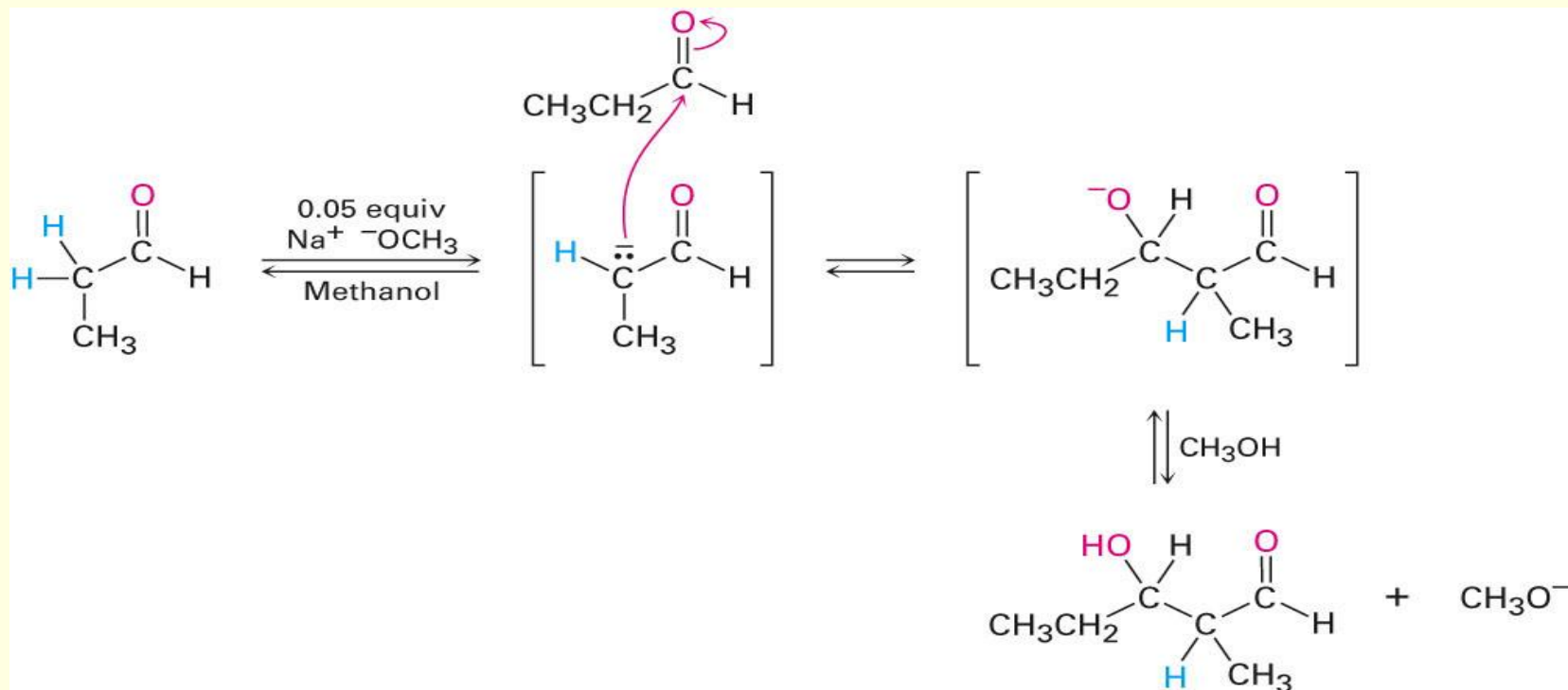
- Carbonyl condensations and α substitutions both involve formation of enolate ion intermediates
- Alpha-substitution reactions are accomplished by converting all of the carbonyl compound to enolate form so it is not an electrophile
- Immediate addition of an alkyl halide to completes the alkylation reaction



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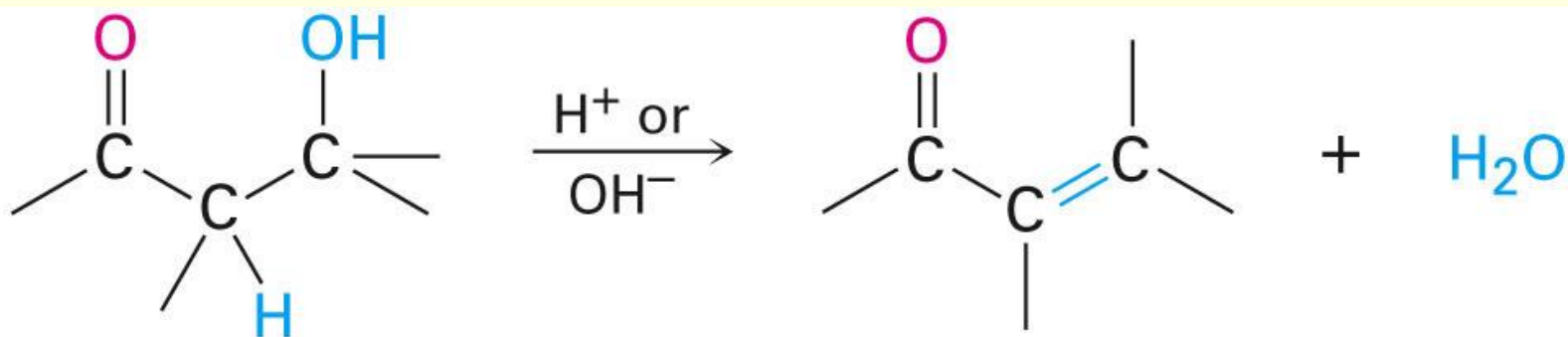
Conditions for Condensations

- A small amount of base is used to generate a small amount of enolate in the presence of unreacted carbonyl compound
- After the condensation, the basic catalyst is regenerated



Dehydration of Aldol Products: Synthesis of Enones

- The β -hydroxy carbonyl products dehydrate to yield conjugated enones
- The term “condensation” refers to the net loss of water and combination of 2 molecules



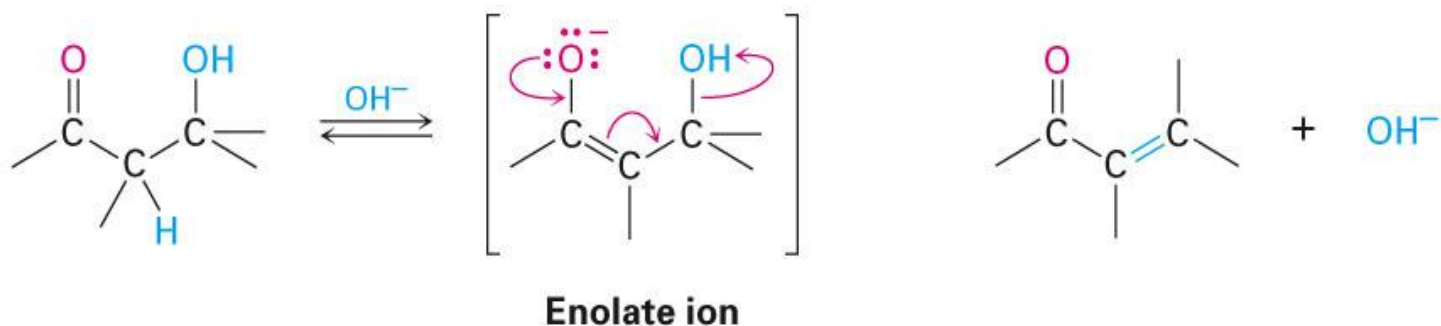
**A β -hydroxy ketone
or aldehyde**

**A conjugated
enone**

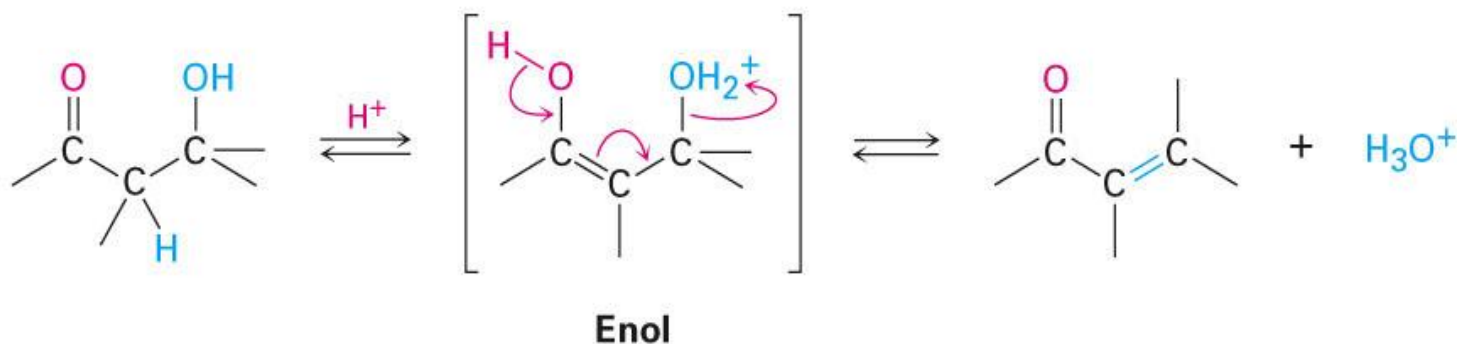
Dehydration of β -Hydroxy Ketones and Aldehydes

- The α hydrogen is removed by a base, yielding an enolate ion that expels the $-\text{OH}$ leaving group
- Under *acidic* conditions the $-\text{OH}$ group is protonated and water is expelled

Base-catalyzed

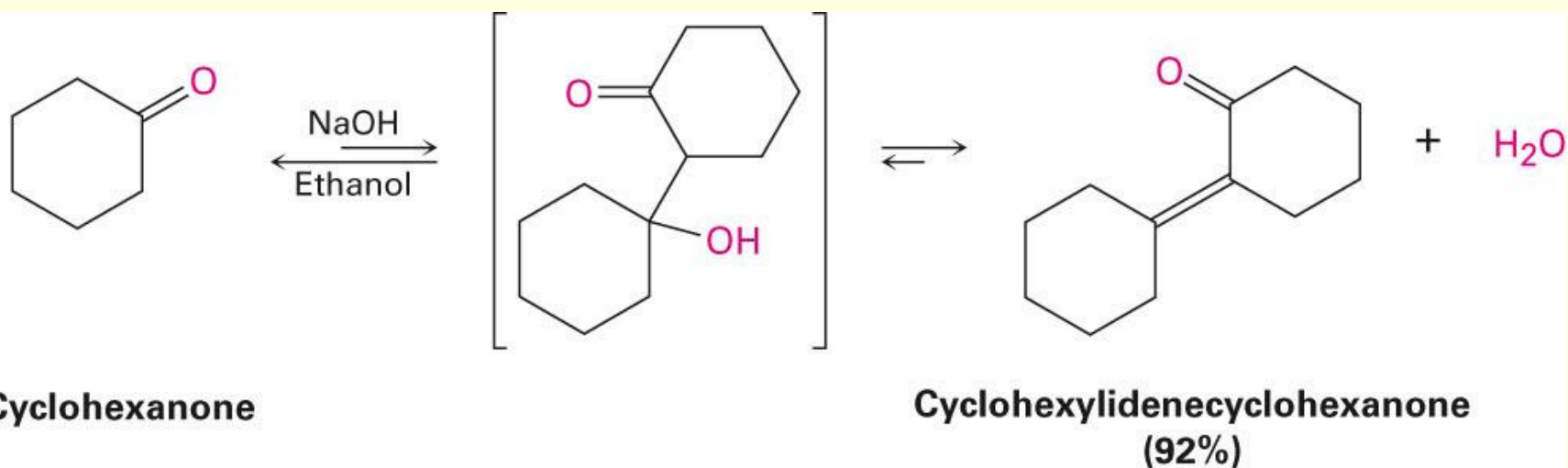


Acid-catalyzed



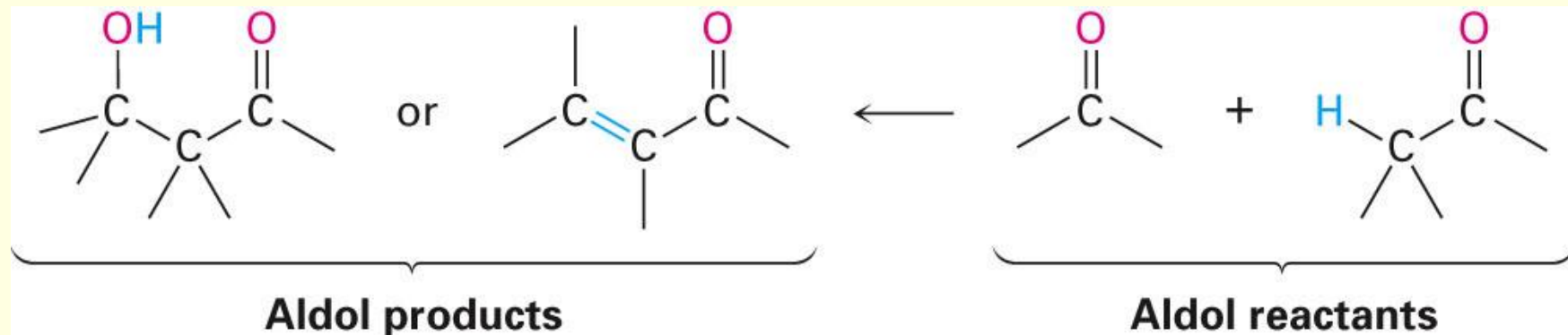
Driving the Equilibrium

- Removal of water from the aldol reaction mixture can be used to drive the reaction toward products
- Even if the initial aldol favors reactants, the subsequent dehydration step pushes the reaction to completion



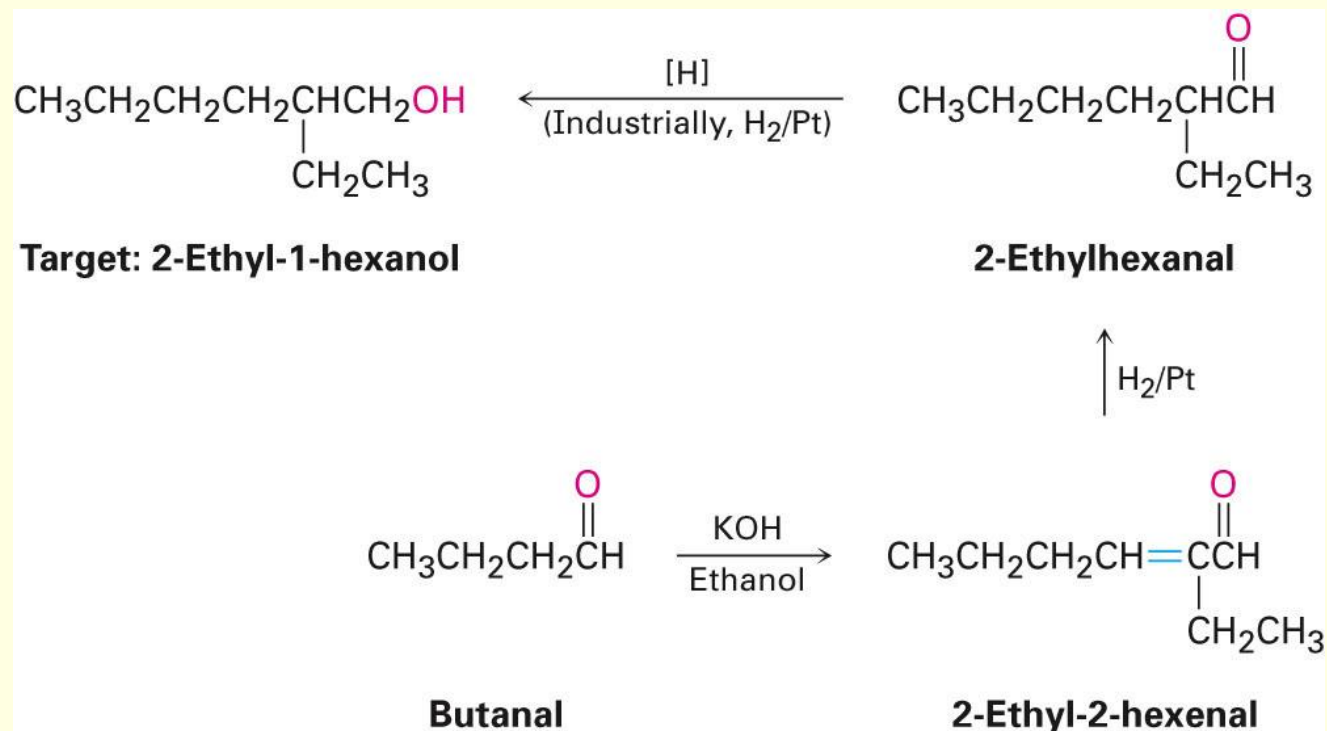
Using Aldol Reactions in Synthesis

- If a desired molecule contains either a β -hydroxy carbonyl or a conjugated enone, it might come from an aldol reaction



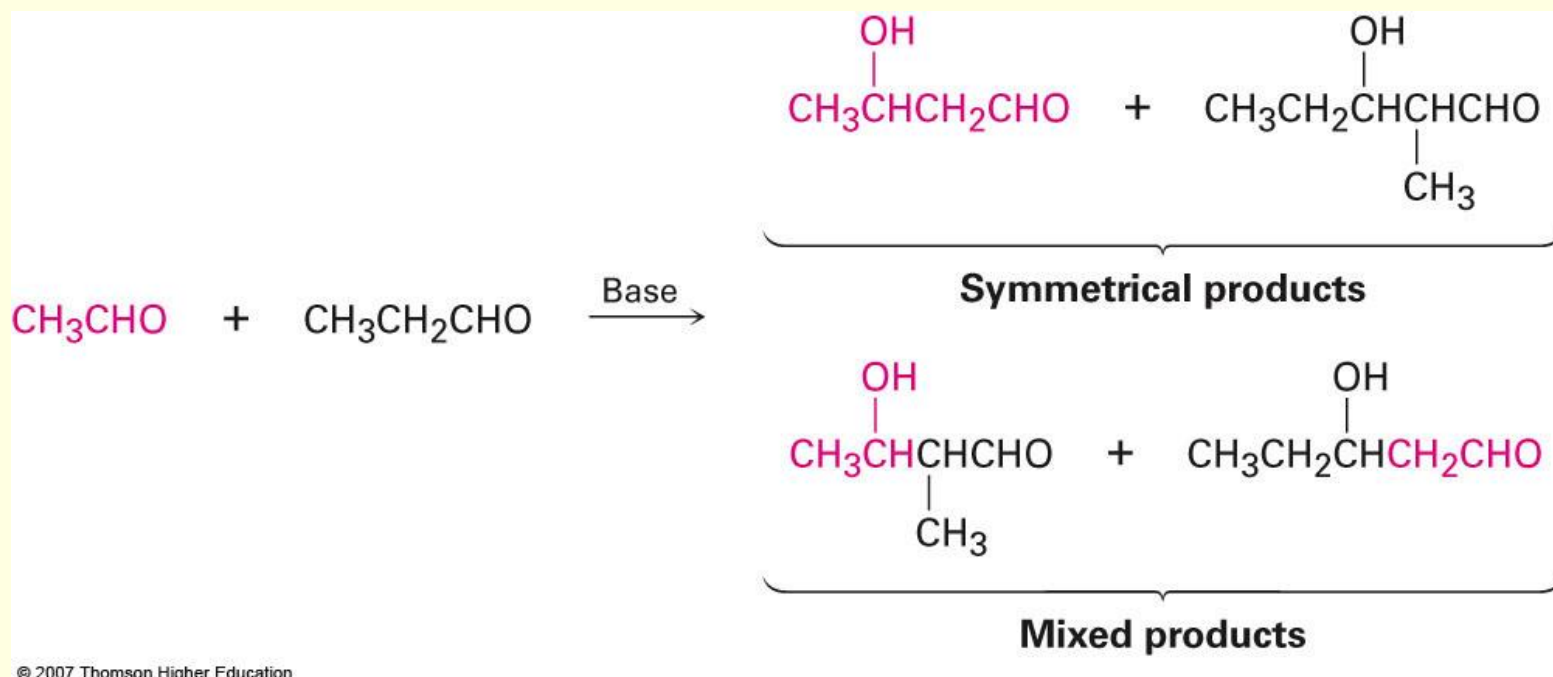
Extending the Synthesis

- Subsequent transformations can be carried out on the aldol products
- A saturated ketone might be prepared by catalytic hydrogenation of the enone product



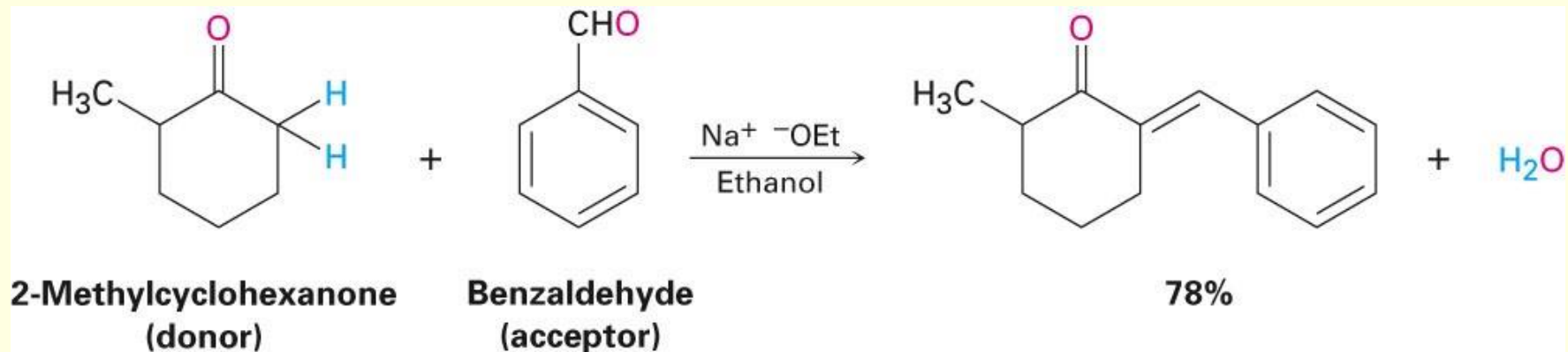
Mixed Aldol Reactions

- A mixed aldol reaction between two similar aldehyde or ketone partners leads to a mixture of four possible products
- This is not useful



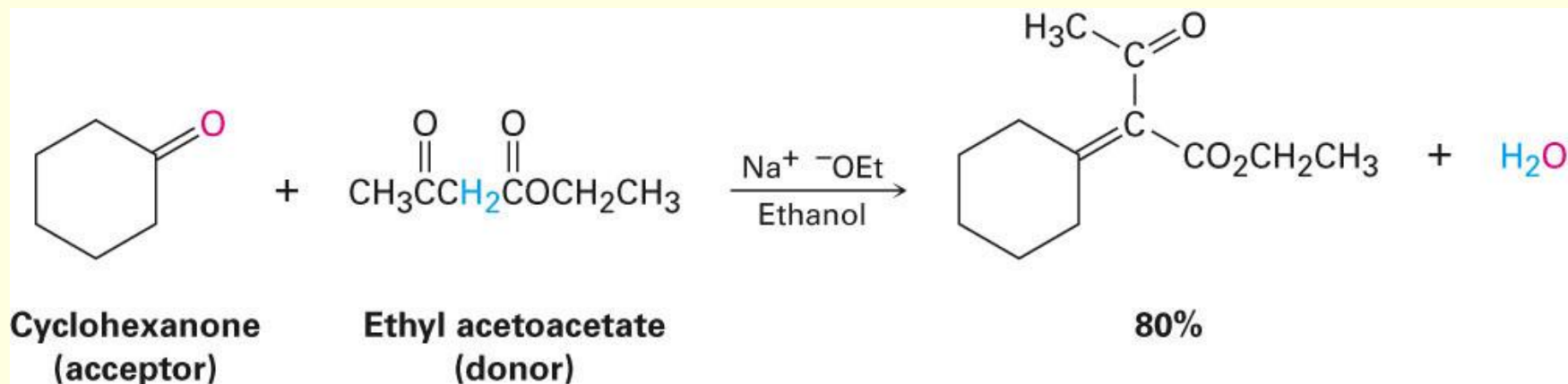
Practical Mixed Aldols

- If one of the carbonyl partners contains no α hydrogens and the carbonyl is unhindered (such as benzaldehyde and formaldehyde) it is a good electrophile and can react with enolates, then a mixed aldol reaction is likely to be successful
- 2-methylcyclohexanone gives the mixed aldol product on reaction with benzaldehyde



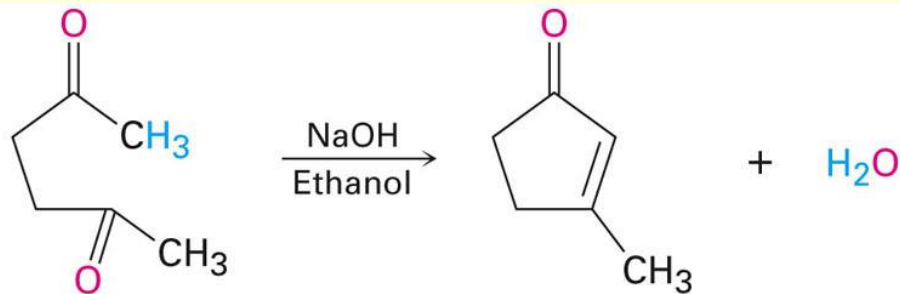
Mixed Aldols With Acidic Carbonyl Compounds

- Ethyl acetoacetate is completely converted into its enolate ion under less basic conditions than monocarbonyl partners
- Aldol condensations with ethyl acetoacetate occur preferentially to give the mixed product



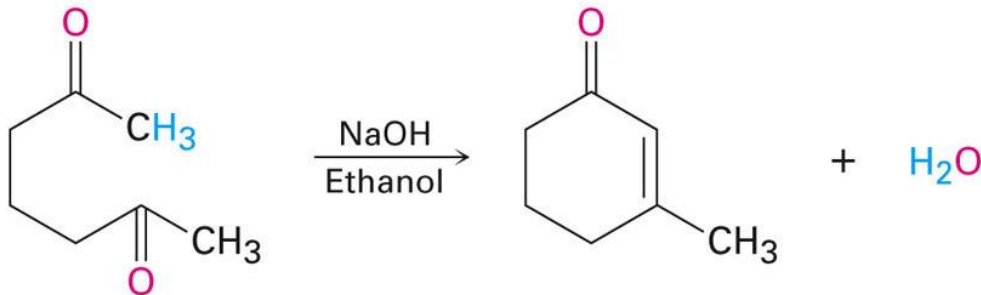
Intramolecular Aldol Reactions

- Treatment of certain *dicarbonyl* compounds with base produces cyclic products by intramolecular reaction



2,5-Hexanedione
(a 1,4-diketone)

3-Methyl-2-cyclopentenone

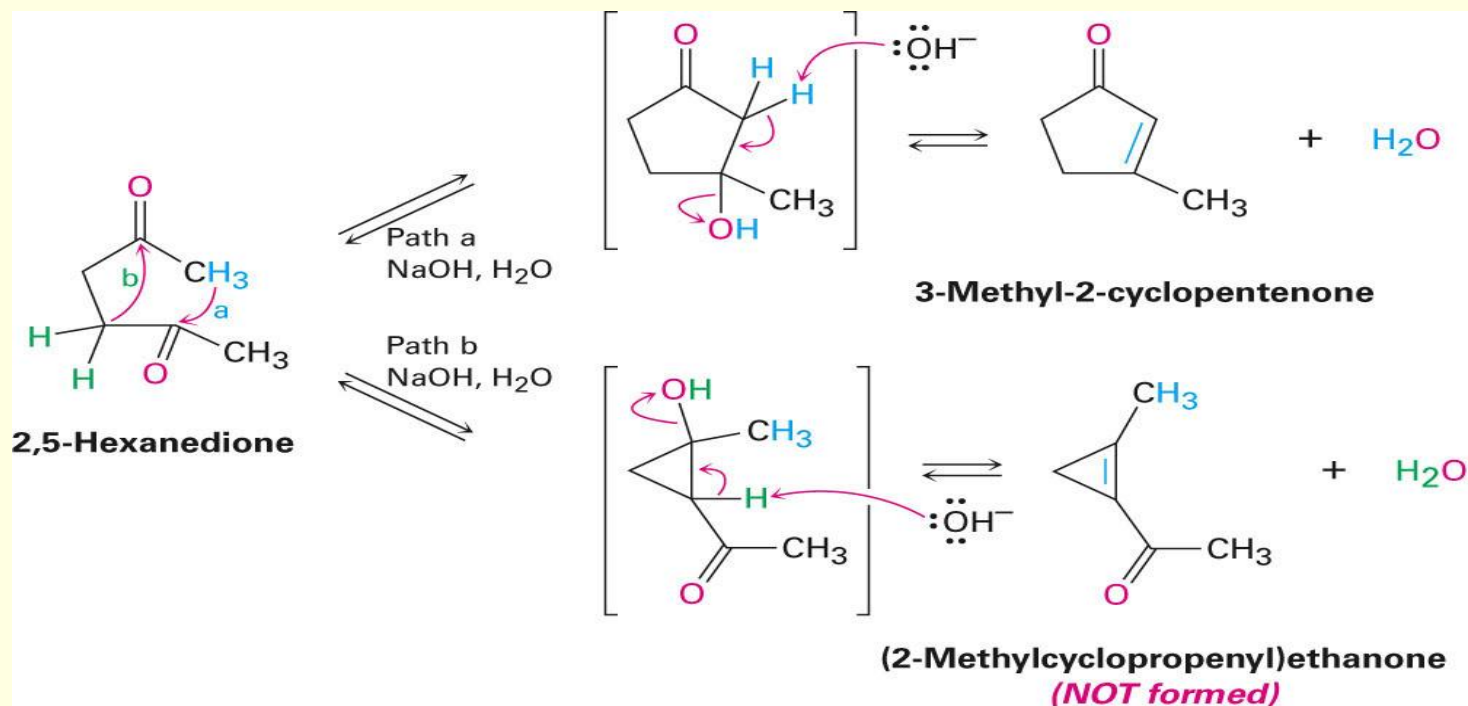


2,6-Heptanedione
(a 1,5-diketone)

3-Methyl-2-cyclohexenone

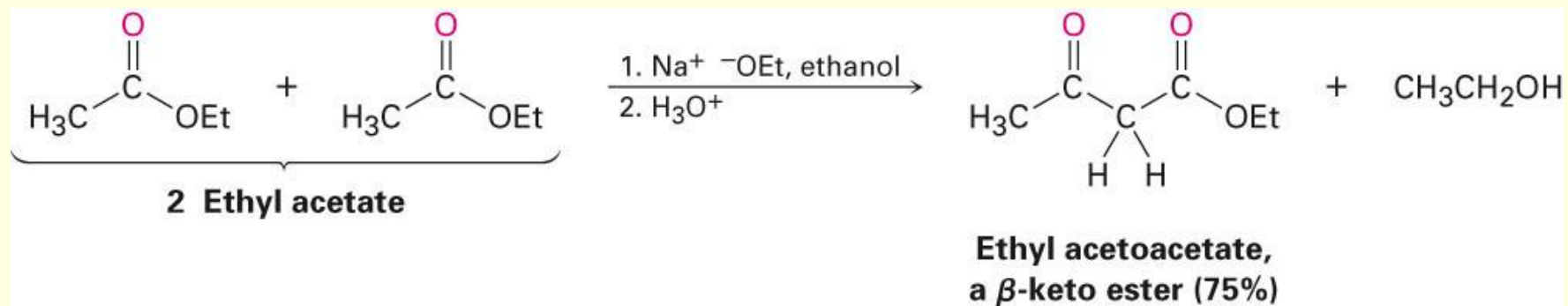
Mechanism of Intramolecular Aldol Reactions

- Both the nucleophilic carbonyl anion donor and the electrophilic carbonyl acceptor are now in the same molecule.
- The least strained product is formed because the reaction is reversible



The Claisen Condensation Reaction

- Reaction of an ester having an α hydrogen with 1 equivalent of a base to yield a β -keto ester



Mechanism of the Claisen Condensation

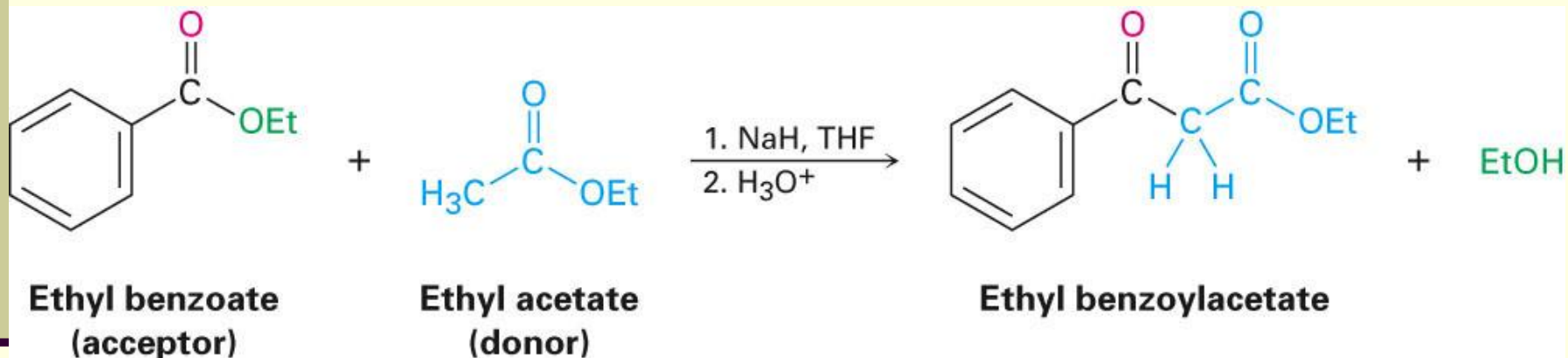
- Similar to aldol condensation: nucleophilic acyl substitution of an ester enolate ion on the carbonyl group of a second ester molecule

Features of the Claisen Condensation

- If the starting ester has more than one acidic hydrogen, the product β -keto ester has a doubly activated proton that can be abstracted by base
- Requires a full equivalent of base rather than a catalytic amount
- The deprotonation drives the reaction to the product

Mixed Claisen Condensations

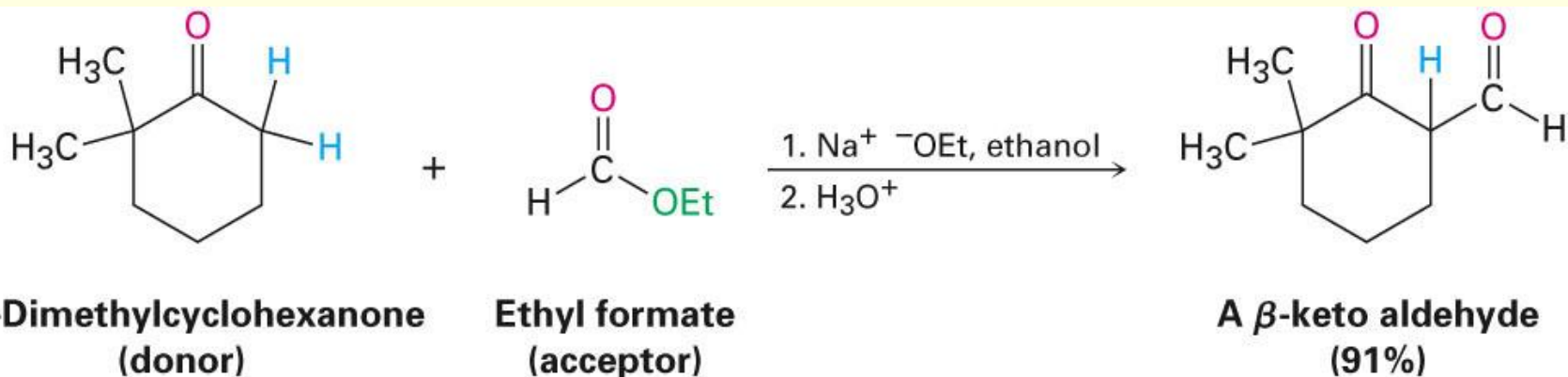
- Successful when one of the two esters acts as the electrophilic acceptor in reactions with other ester anions to give mixed β -keto esters



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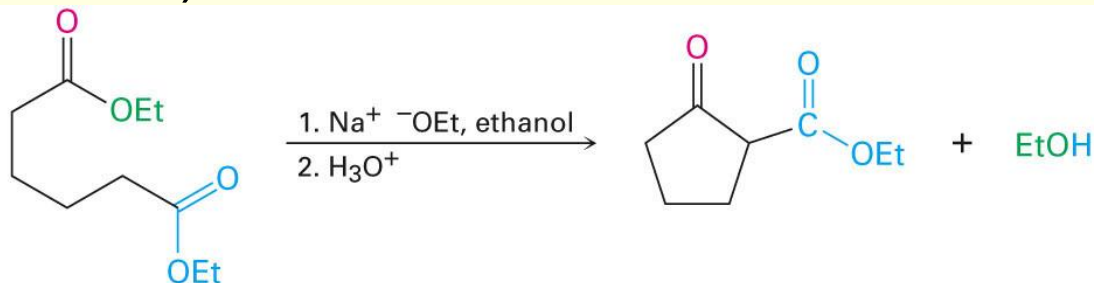
Esters and Ketones

- Reactions between esters and ketones, resulting in β -diketones
- Best when the ester component has no α hydrogens and can't act as the nucleophilic donor



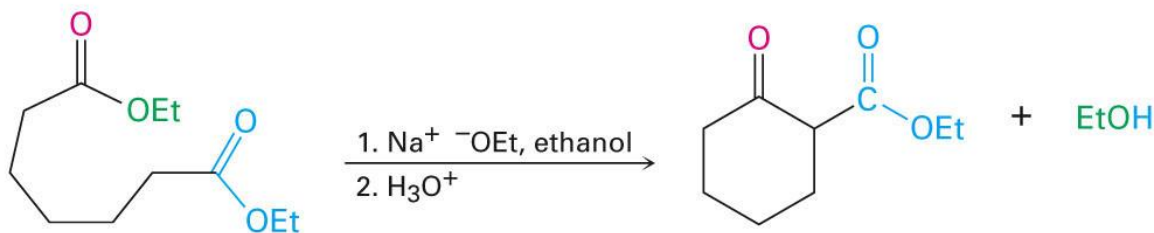
Intramolecular Claisen Condensations: The Dieckmann Cyclization

- Intramolecular Claisen condensation
- Best with 1,6-diester (product: 5-membered β -ketoester) and 1,7-diester (product: 6-membered β -ketoester)



Diethyl hexanedioate
(a 1,6-diester)

Ethyl 2-oxocyclopentanecarboxylate
(82%)

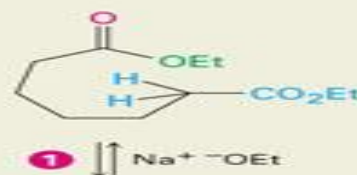


Diethyl heptanedioate
(a 1,7-diester)

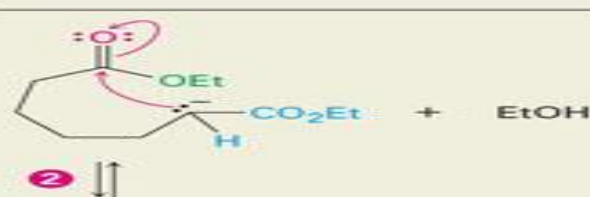
Ethyl 2-oxocyclohexanecarboxylate

Mechanism of the Dieckmann Cyclization

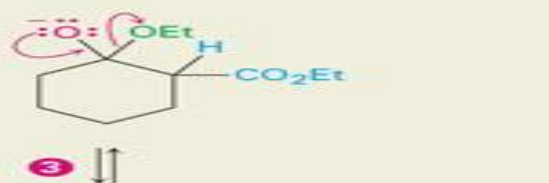
1 Base abstracts an acidic α proton from the carbon atom next to one of the ester groups, yielding an enolate ion.



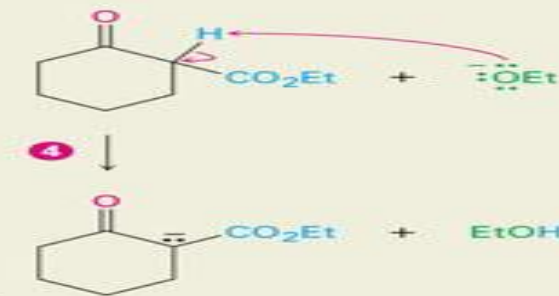
2 Intramolecular nucleophilic addition of the ester enolate ion to the carbonyl group of the second ester at the other end of the chain then gives a cyclic tetrahedral intermediate.



3 Loss of alkoxide ion from the tetrahedral intermediate forms a cyclic β -keto ester.



4 Deprotonation of the acidic β -keto ester gives an enolate ion . . .

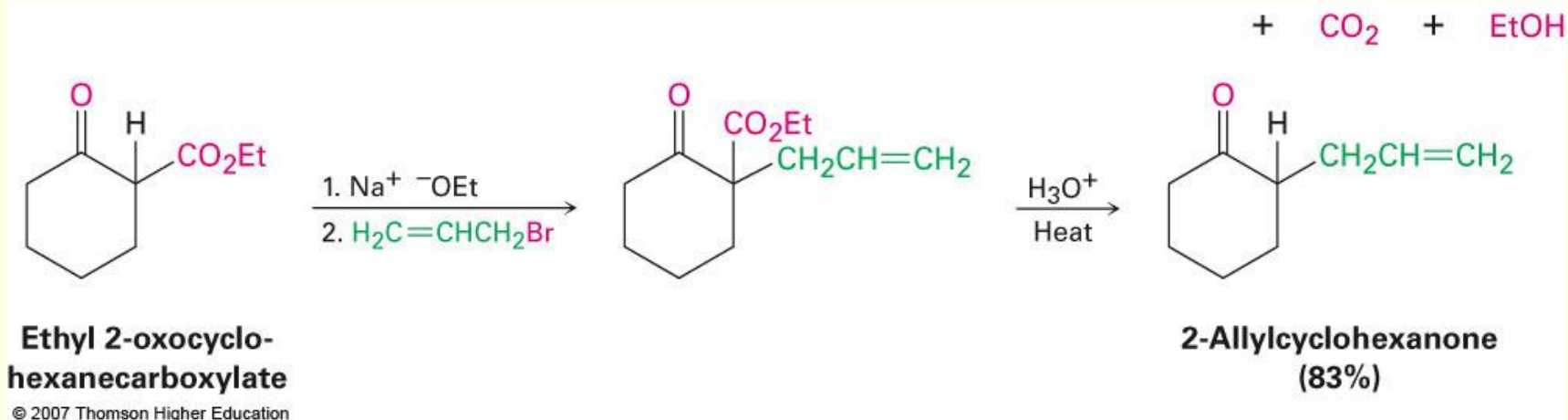


5 . . . which is protonated by addition of aqueous acid at the end of the reaction to generate the neutral β -keto ester product.



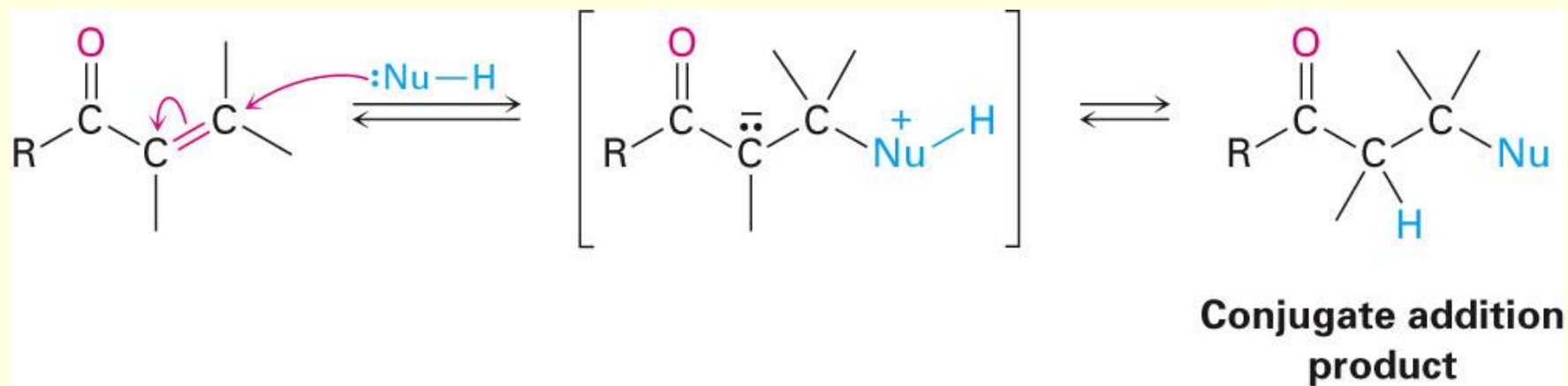
Alkylation of Dieckmann Product

- The cyclic β -keto ester can be further alkylated and decarboxylated as in the acetoacetic ester synthesis



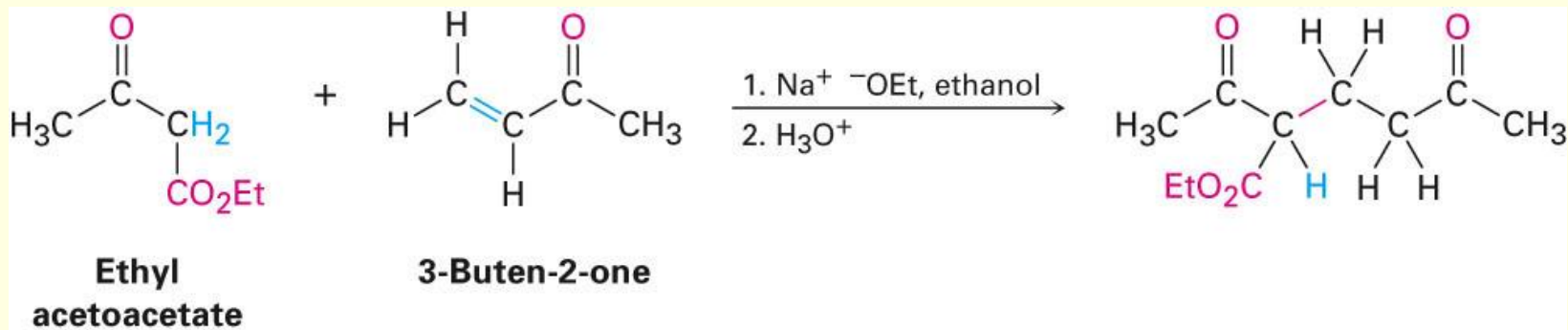
Conjugate Carbonyl Additions: The Michael Reaction

- Enolates can add as nucleophiles to α,β -unsaturated aldehydes and ketones to give the conjugate addition product



Best Conditions for the Michael Reaction

- When a particularly stable enolate ion
- Example: Enolate from a β -keto ester or other 1,3-dicarbonyl compound adding to an unhindered α,β -unsaturated ketone



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Mechanism of the Michael Reaction

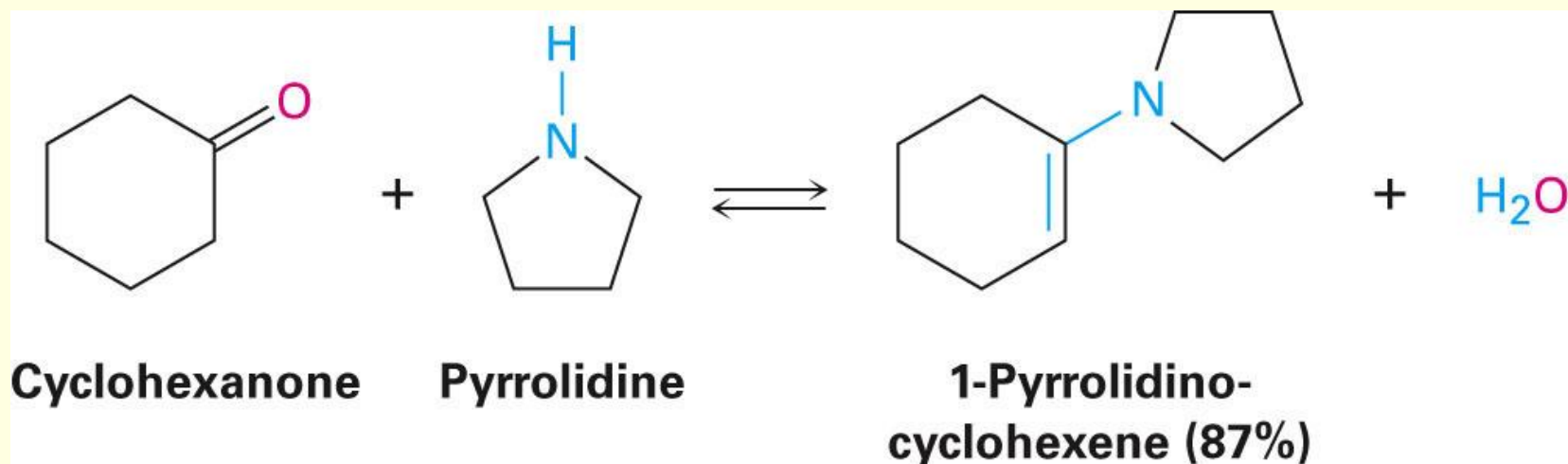
- Nucleophilic addition of an enolate ion donor to the β carbon of an α,β -unsaturated carbonyl acceptor

Generality of the Michael Reaction

- Occurs with a variety of α,β -unsaturated carbonyl compounds (aldehydes, esters, nitriles, amides, and nitro compounds)
- Donors include β -diketones, β -keto esters, malonic esters, β -keto nitriles, and nitro compounds
- See Table 23.1

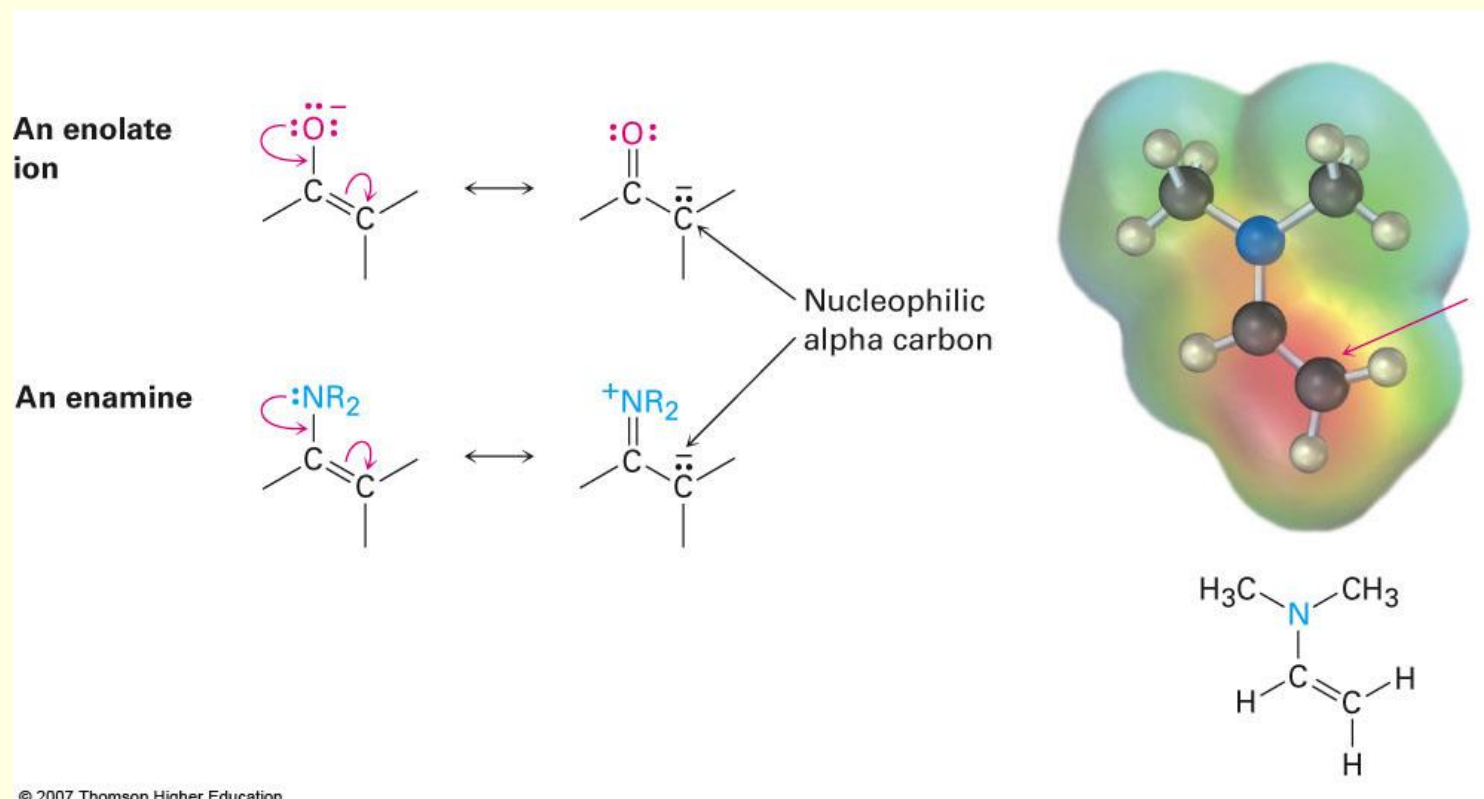
Carbonyl Condensations with Enamines: The Stork Reaction

- Enamines are equivalent to enolates in their reactions and can be used to accomplish the transformations under milder conditions
- Enamines are prepared from a ketone and a secondary amine



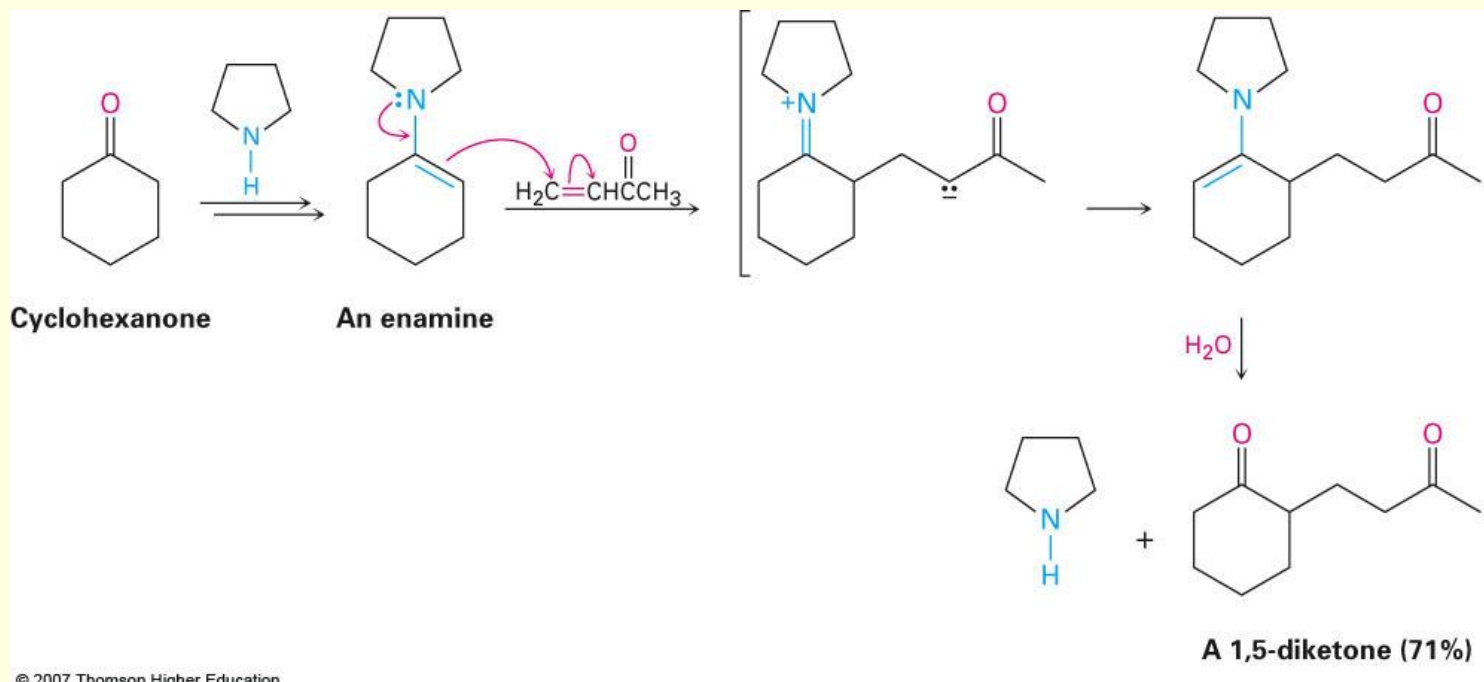
Enamines Are Nucleophilic

- Overlap of the nitrogen lone-pair orbital with the double-bond π orbitals increases electron density on the α carbon atom



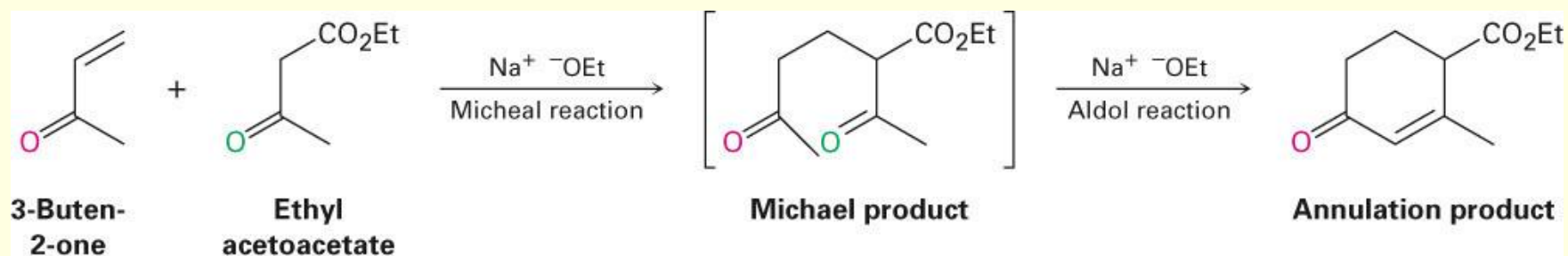
Enamine Addition and Hydrolysis

- Enamine adds to an α,β -unsaturated carbonyl acceptor
- The product is hydrolyzed to a 1,5-dicarbonyl compound



The Robinson Annulation Reaction

- A two-step process: combines a Michael reaction with an intramolecular aldol reaction
- The product is a substituted 2-cyclohexenone



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Some Biological Carbonyl Condensation Reactions

- Malonyl ACP is decarboxylated and enolate is formed
- Enolate is added to the carbonyl group of another acyl group through a thioester linkage to a synthase
- Tetrahedral intermediate gives acetoacetyl ACP

