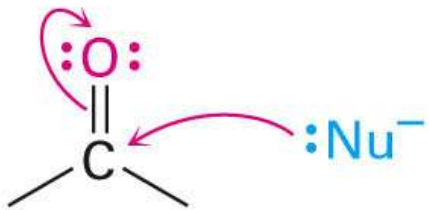
열번째주

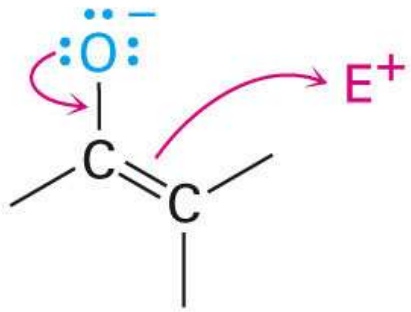
Carbonyl Condensation Reactions (1)

Condensation Reactions

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



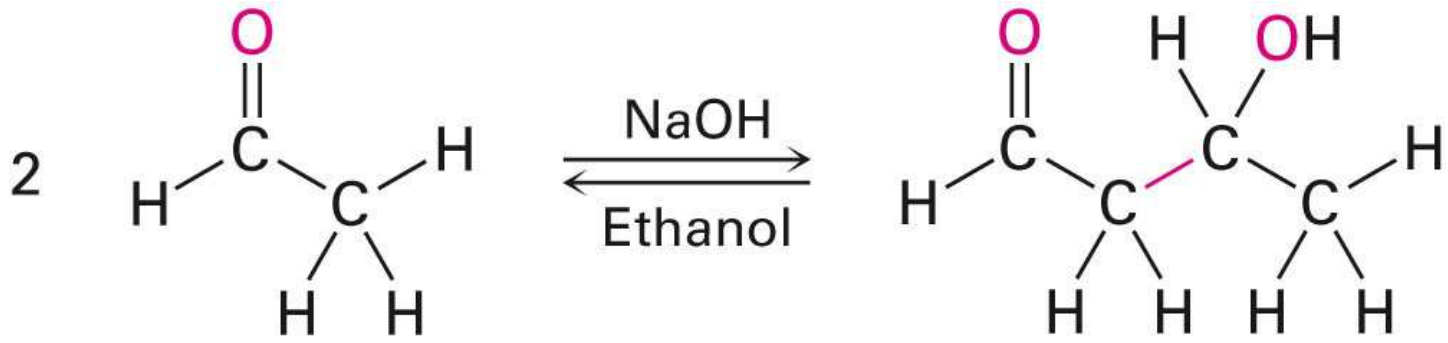
Electrophilic carbonyl group reacts with nucleophiles.



Nucleophilic enolate ion reacts with electrophiles.

Carbonyl Condensation: The Aldol Reaction

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

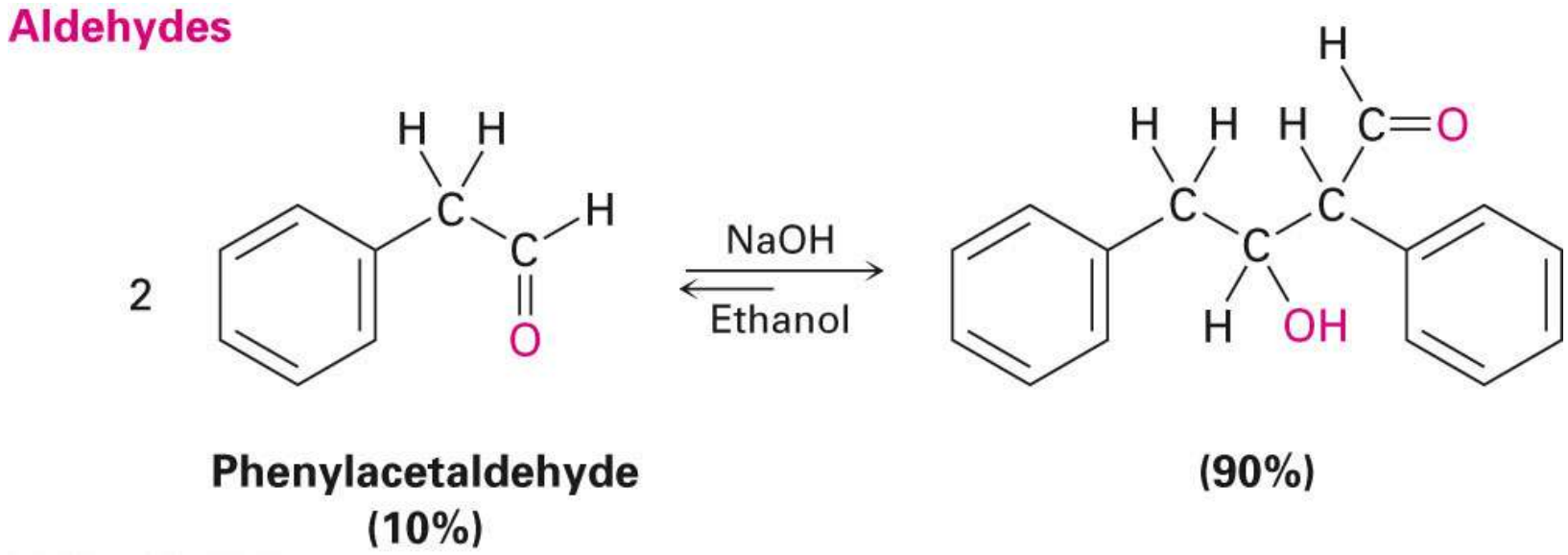


Acetaldehyde

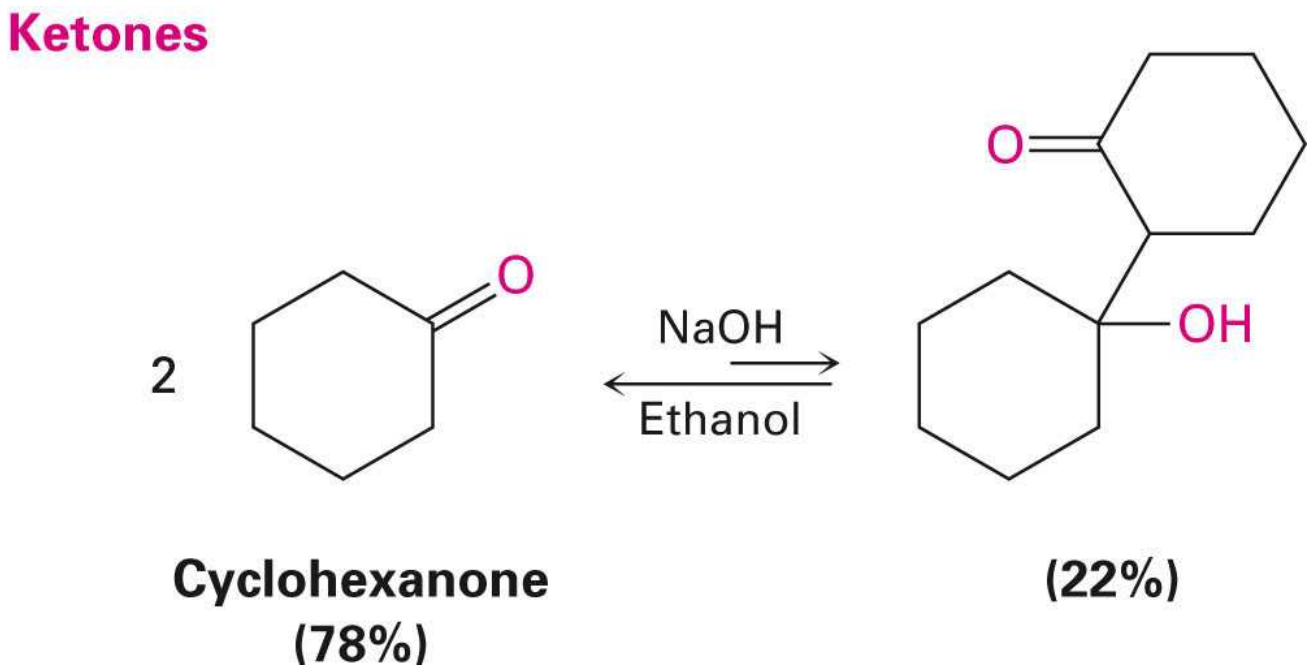
3-Hydroxybutanal (aldol)

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



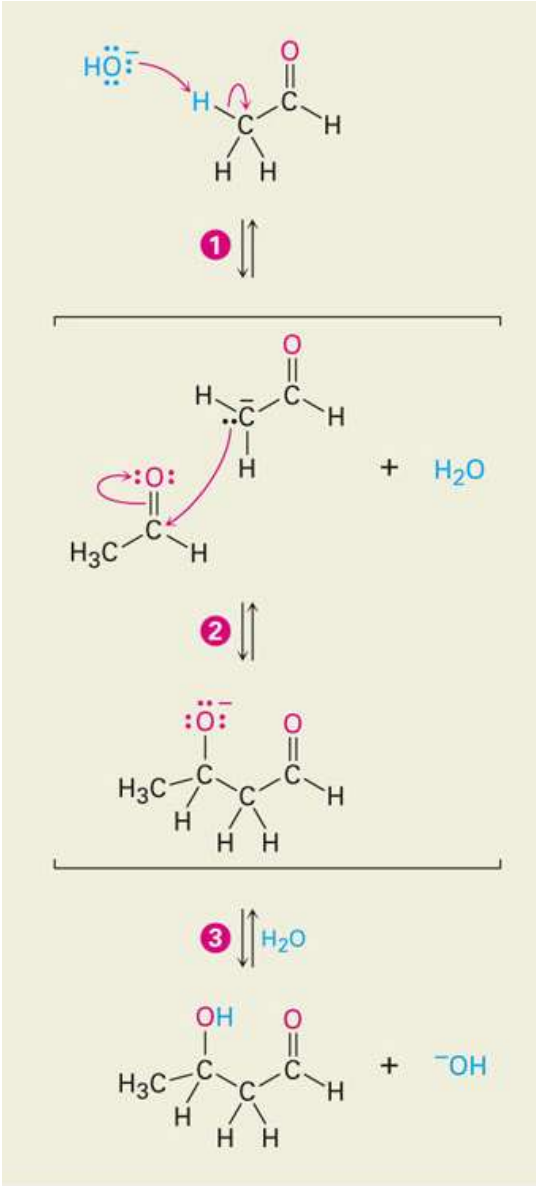
Aldehydes and Ketones and the Aldol Equilibrium



Mechanism of Aldol Reactions

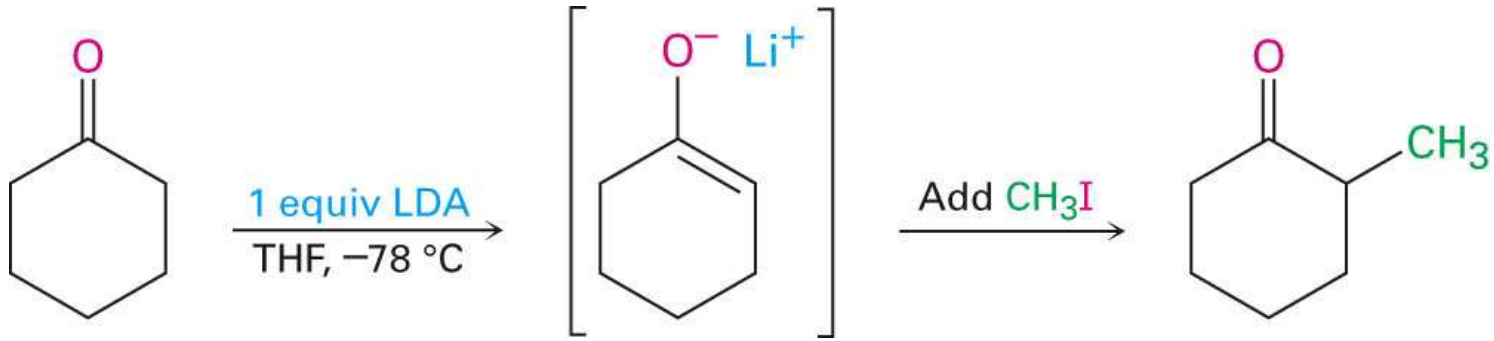
- Aldol reactions, like all carbonyl condensations, occur by nucleophilic addition of the enolate ion of the donor molecule to the carbonyl group of the acceptor molecule

- The addition intermediate is protonated to give an alcohol product



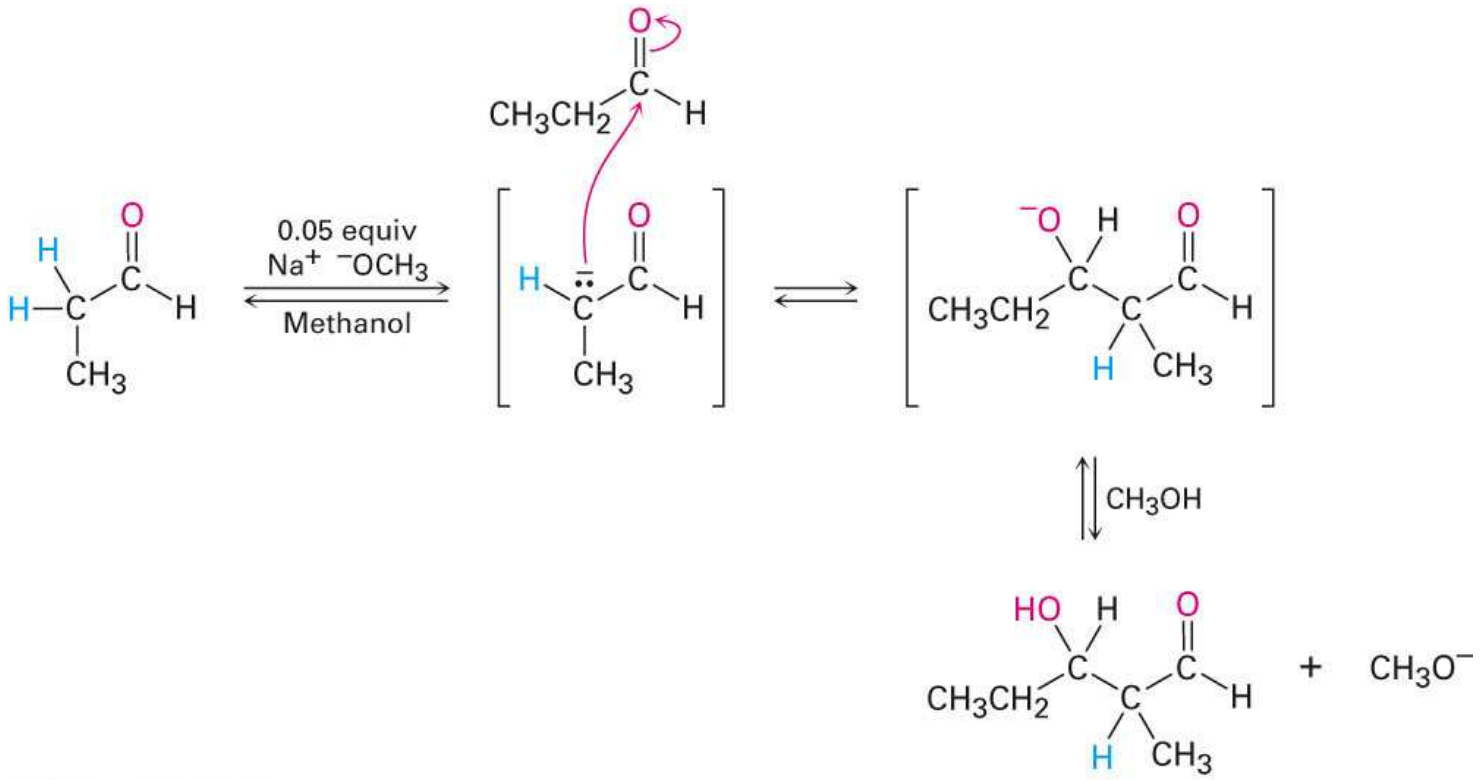
Carbonyl Condensation *vs* Alpha-Substitution

- 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



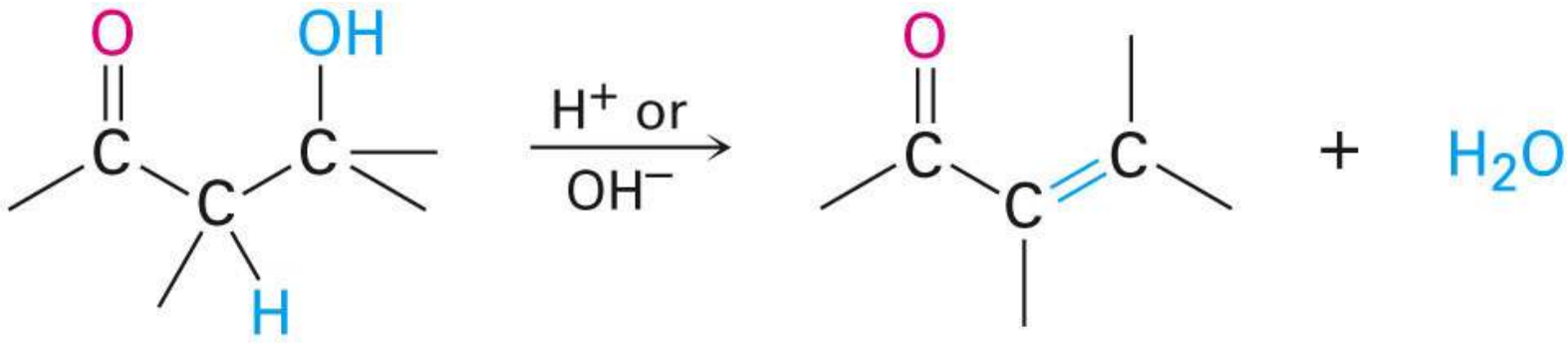
Conditions for Condensations

- 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

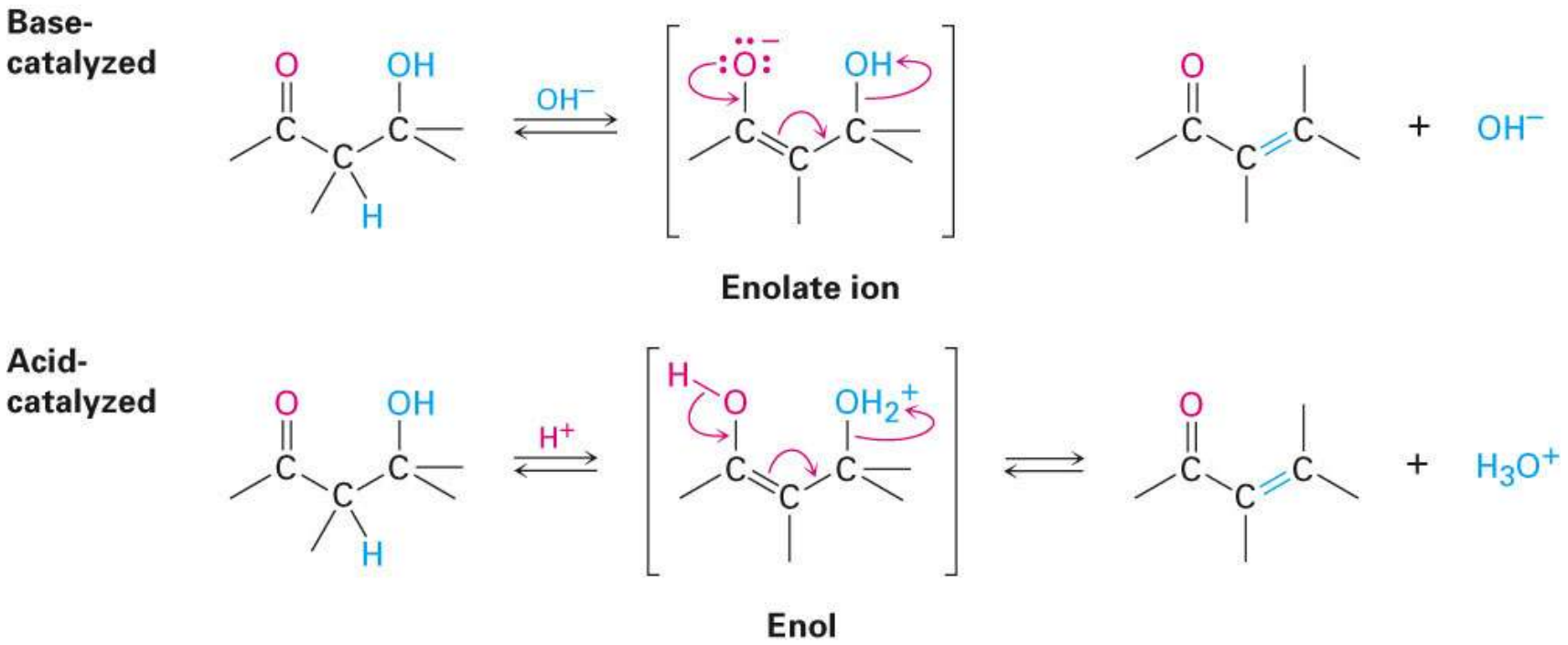


A β-hydroxy ketone or aldehyde

A conjugated enone

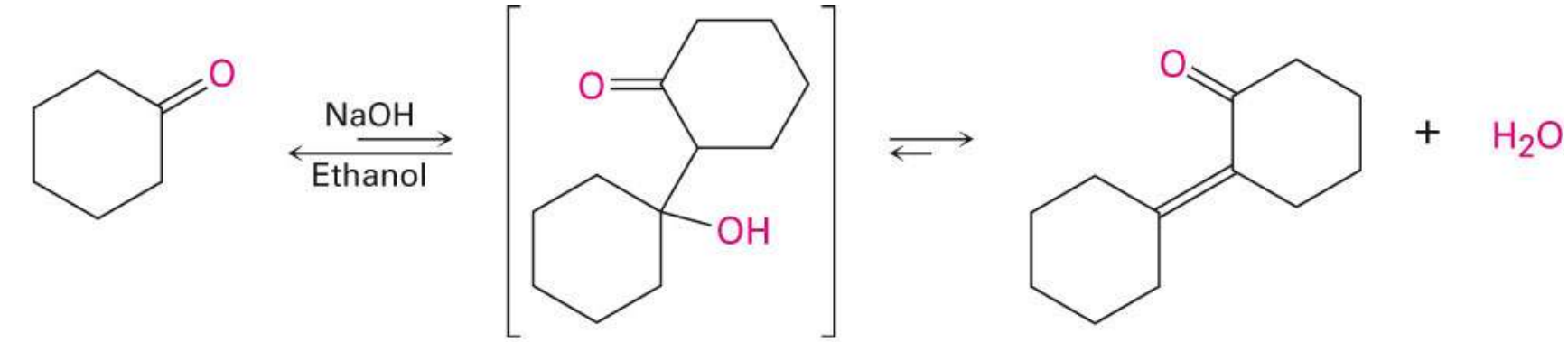
Dehydration of β-Hydroxy Ketones and Aldehydes

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



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

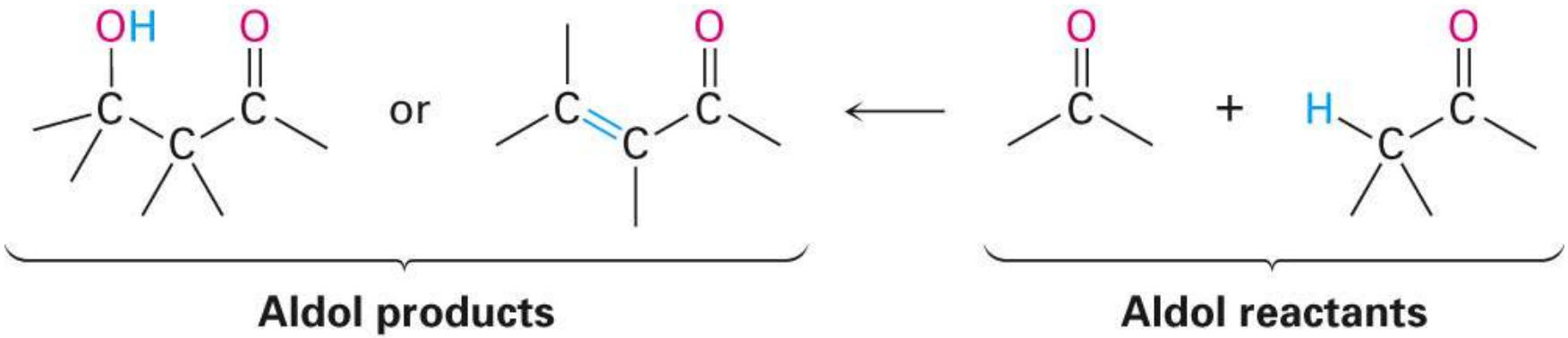


Cyclohexanone

Cyclohexylidenecyclohexanone (92%)

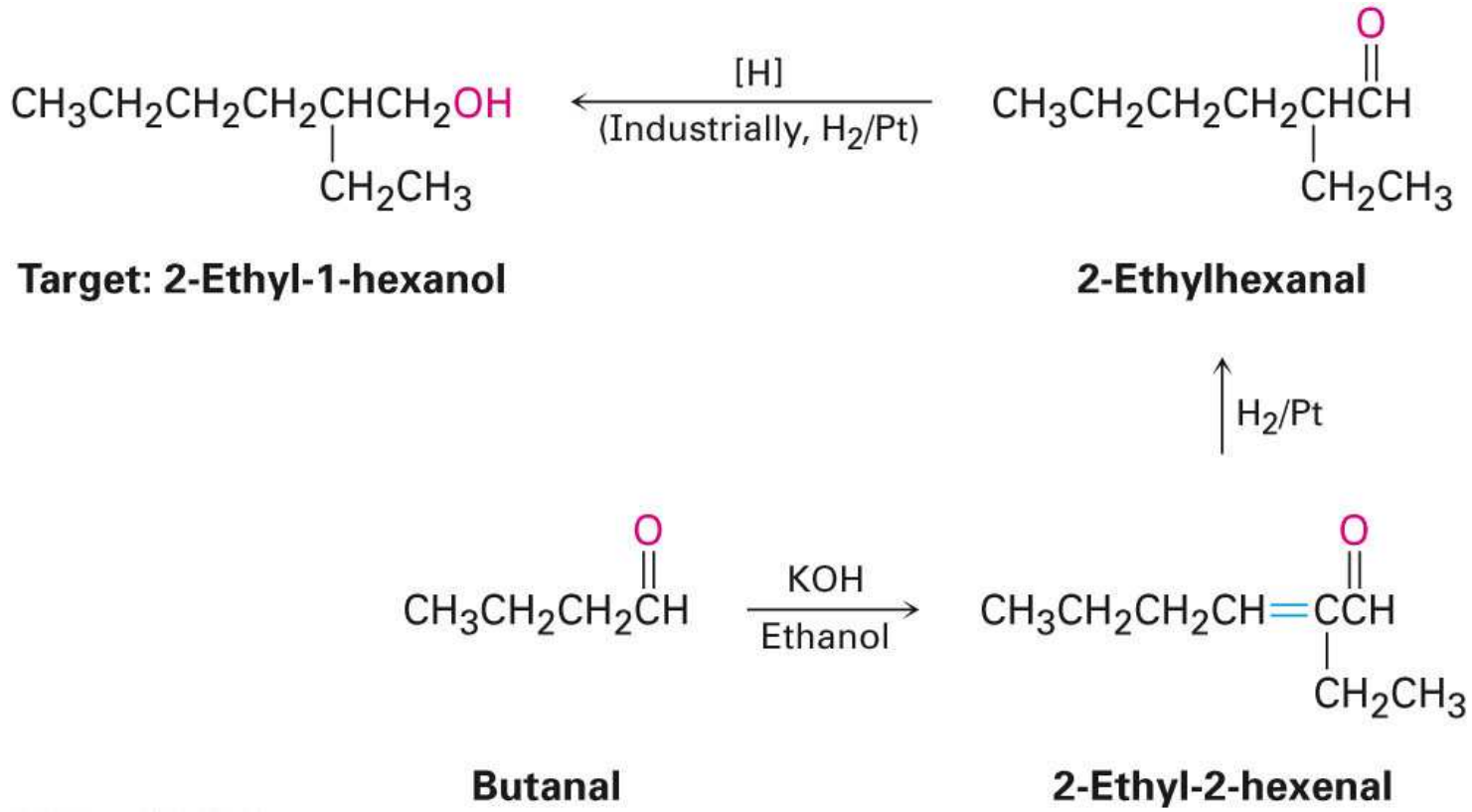
Using Aldol Reactions in Synthesis

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



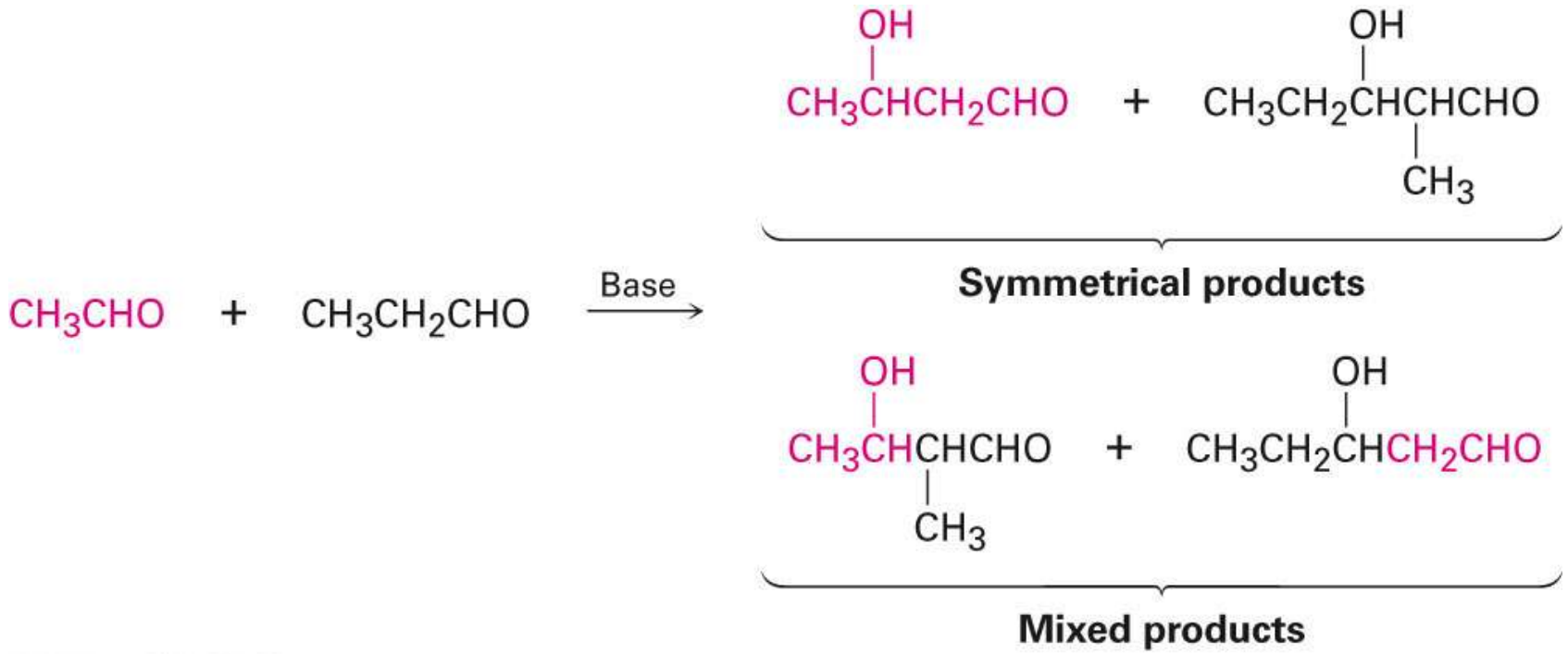
Extending the Synthesis

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



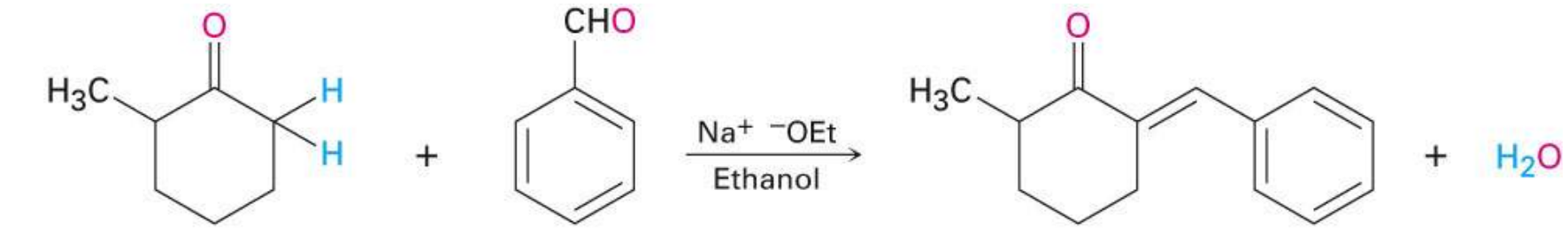
Mixed Aldol Reactions

- 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

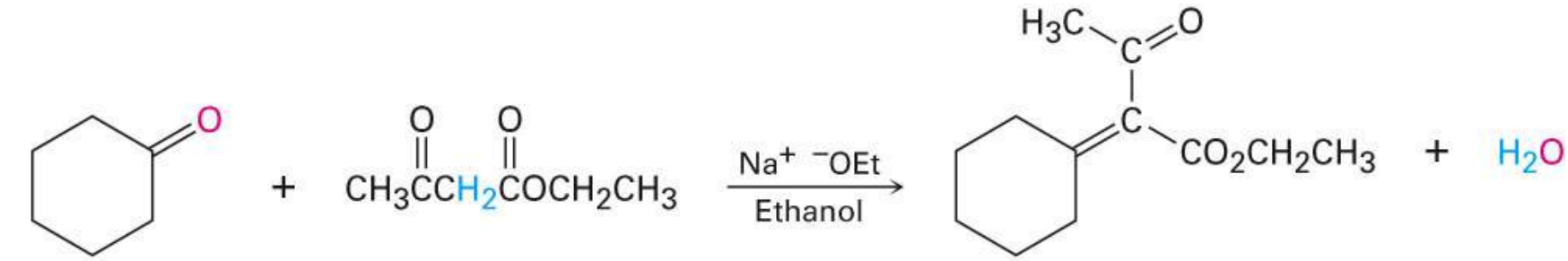
- If one of the carbonyl partners contains no α hydrogens and the carbonyl is unhindered (such as benzaldehyde and formaldehyde) it is a good electrophile and can react with enolates, then a mixed aldol reaction is likely to be successful.
- 2-Methylcyclohexanone gives the mixed aldol product on reaction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



2-Methylcyclohexanone (donor) **Benzaldehyde (acceptor)** **78%**

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



Cyclohexanone (acceptor) **Ethyl acetoacetate (donor)** **80%**