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

Aldehydes and ketones with enolizable hydrogens (α-H's) undergo a self-reaction to give β-hydroxyaldehydes or β-hydroxyketones in the presence of base. This reaction is called the aldol condensation.

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

Acetaldehyde → 3-Hydroxbutanal, an "aldol"

Requirements for an aldol reaction:

(1) α-H

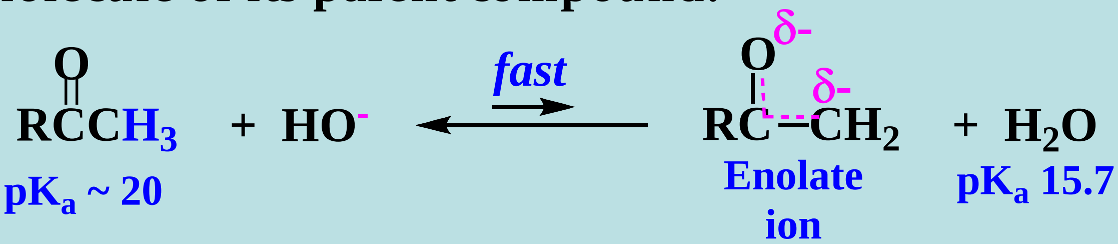
(2) Dilute solution of base, usually HO^-

Types the aldol reaction does not occur with:

$ArCHO$ $\quad$ $HCHO$ $\quad$ $(CH_3)_3\overset{\overset{\displaystyle O}{\|}}{C}CH$ $\quad$ $Ar\overset{\overset{\displaystyle O}{\|}}{C}Ar'$ $\quad$ $Ar\overset{\overset{\displaystyle O}{\|}}{C}CR_3$

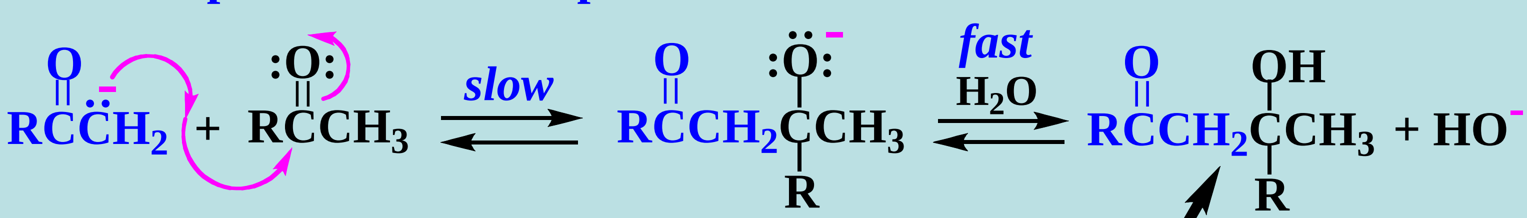
A Mechanism for the Aldol Reaction

In dilute basic solution, an aldehyde or ketone with enolizable-H reacts to produce a low concentration of its enolate ion. This anion is a good nucleophile, and it adds to the carbonyl group of another molecule of its parent compound.



Note: Only a low conc. of the enolate ion is formed.

The nucleophilic addition step:

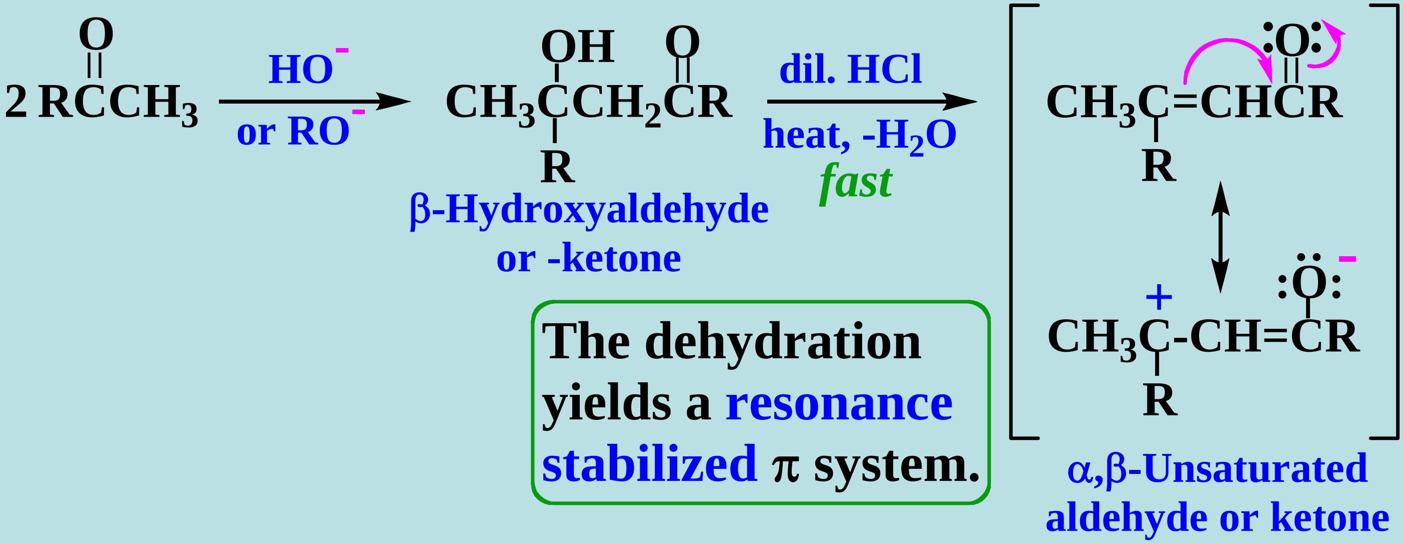


The above scheme for the aldol reaction is reversible. With aldehydes, R=H, the condensation product is favored, but with ketones, the reaction proceeds well only if the product is removed from the basic solution or reacts further by dehydration.

Note the sources of the structural components in the aldol product.

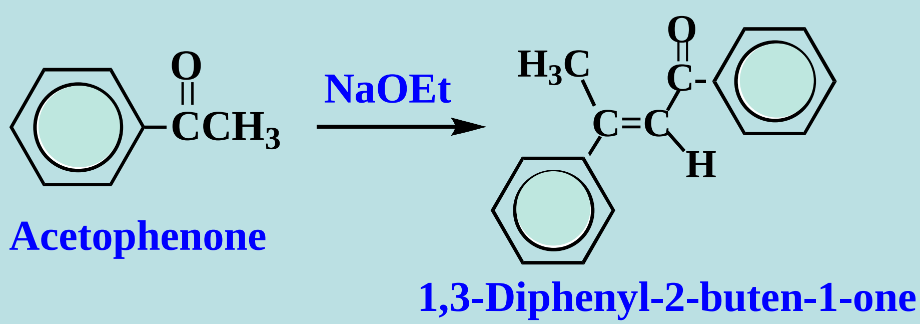
Dehydration of Aldol Products

The β-hydroxyaldehyde and -ketone aldol condensation products dehydrate easily to α,β-unsaturated carbonyl compounds because of the stability inherent in conjugated enone structures.

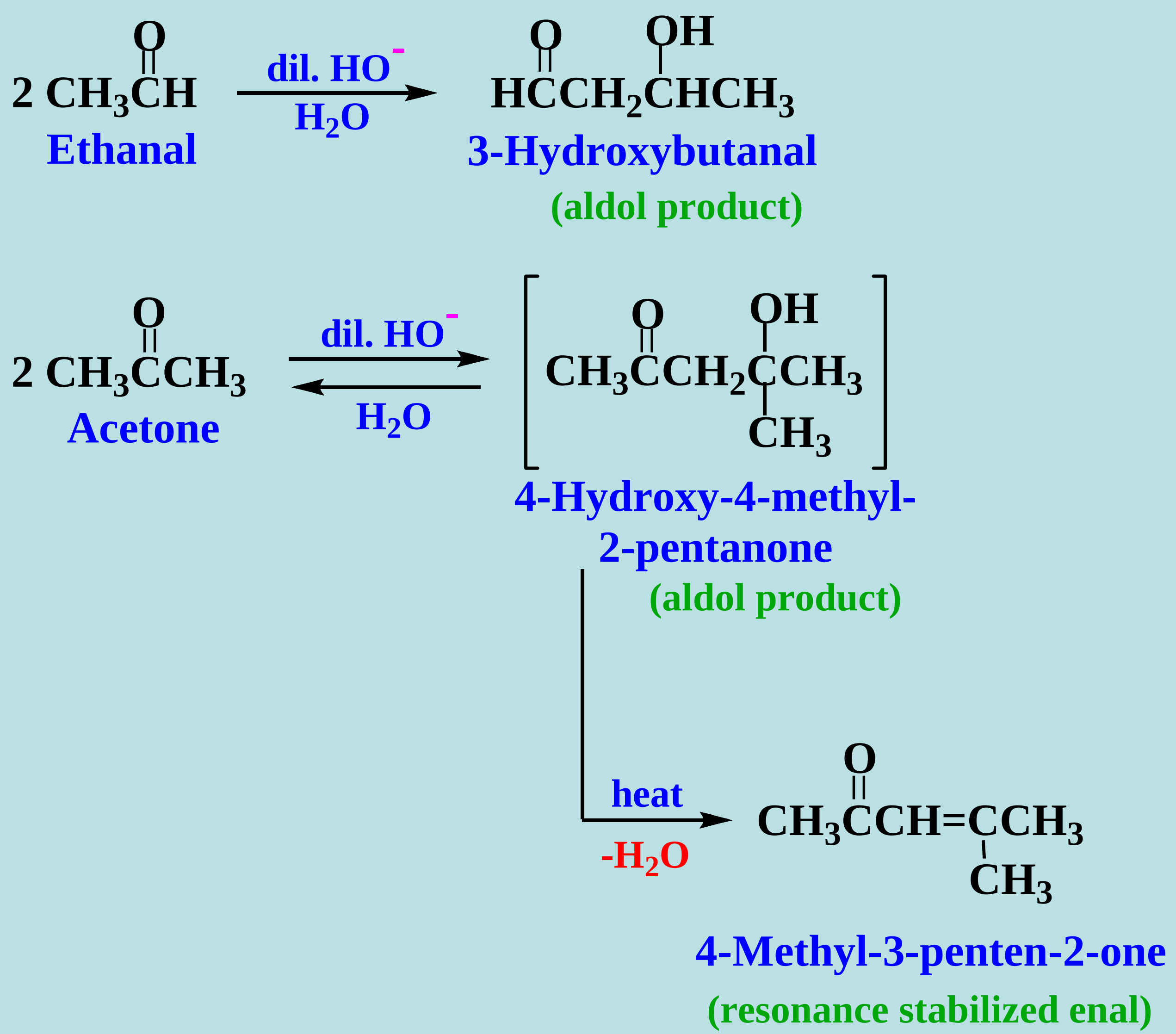


The dehydration yields a resonance stabilized π system.

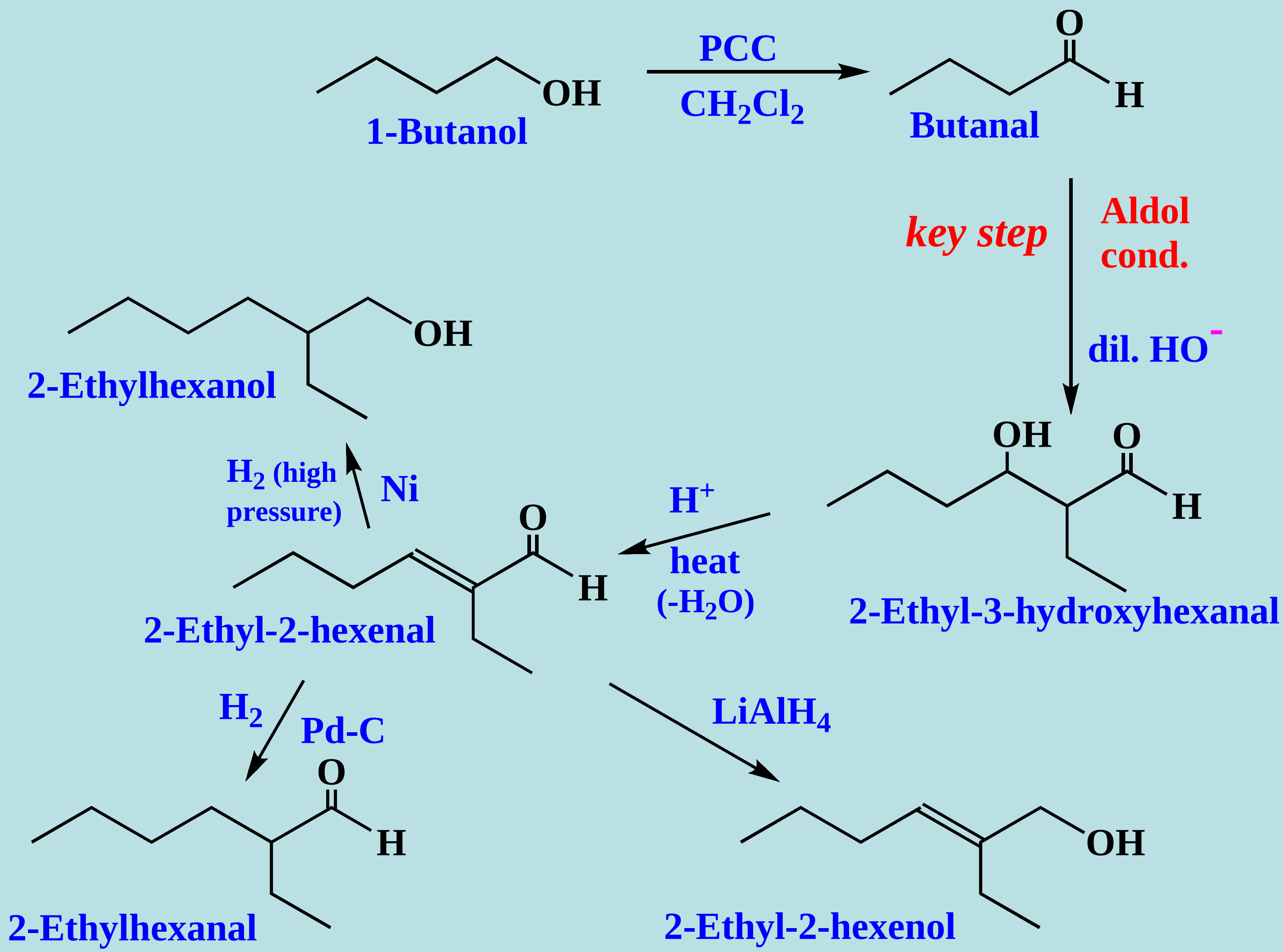
When R = aryl, dehydration occurs during the aldol condensation:



Examples


2 CH3CH(=O)
dil. HO-
H2O
HC(=O)CH2CH(OH)CH3
Ethanal
3-Hydroxybutanal
(aldol product)
2 CH3C(=O)CH3
Acetone
dil. HO-
H2O
CH3C(=O)CH2C(OH)(CH3)CH3
4-Hydroxy-4-methyl-
2-pentanone
(aldol product)
heat
-H2O
CH3C(=O)CH=C(CH3)CH3
4-Methyl-3-penten-2-one
(resonance stabilized enal)

Aldol Condensations in Synthesis: EXAMPLES

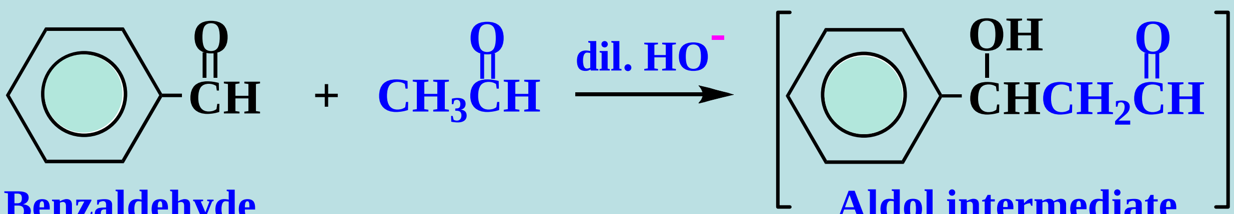


Note that in this scheme, the aldol reaction is the key reaction that leads to five of many possible final products.

The Crossed Aldol Condensation

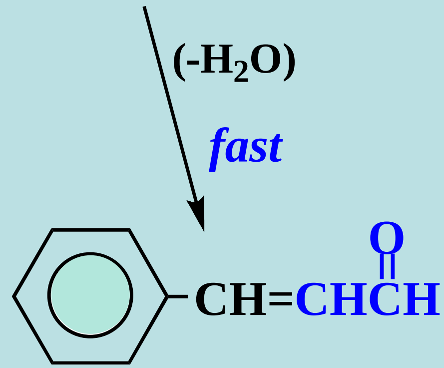
An aldol reaction using two different carbonyl compounds is a crossed aldol condensation. Because of the possibility of four different condensation products, this reaction is not synthetically useful unless it is carefully designed.

A practical synthesis employs only one carbonyl compound that has an α-H, which eliminates two of the products that would be possible if both reactants had an α-H. An example is the crossed aldol condensation of benzaldehyde and acetaldehyde.



Benzaldehyde
(no enolizable H)

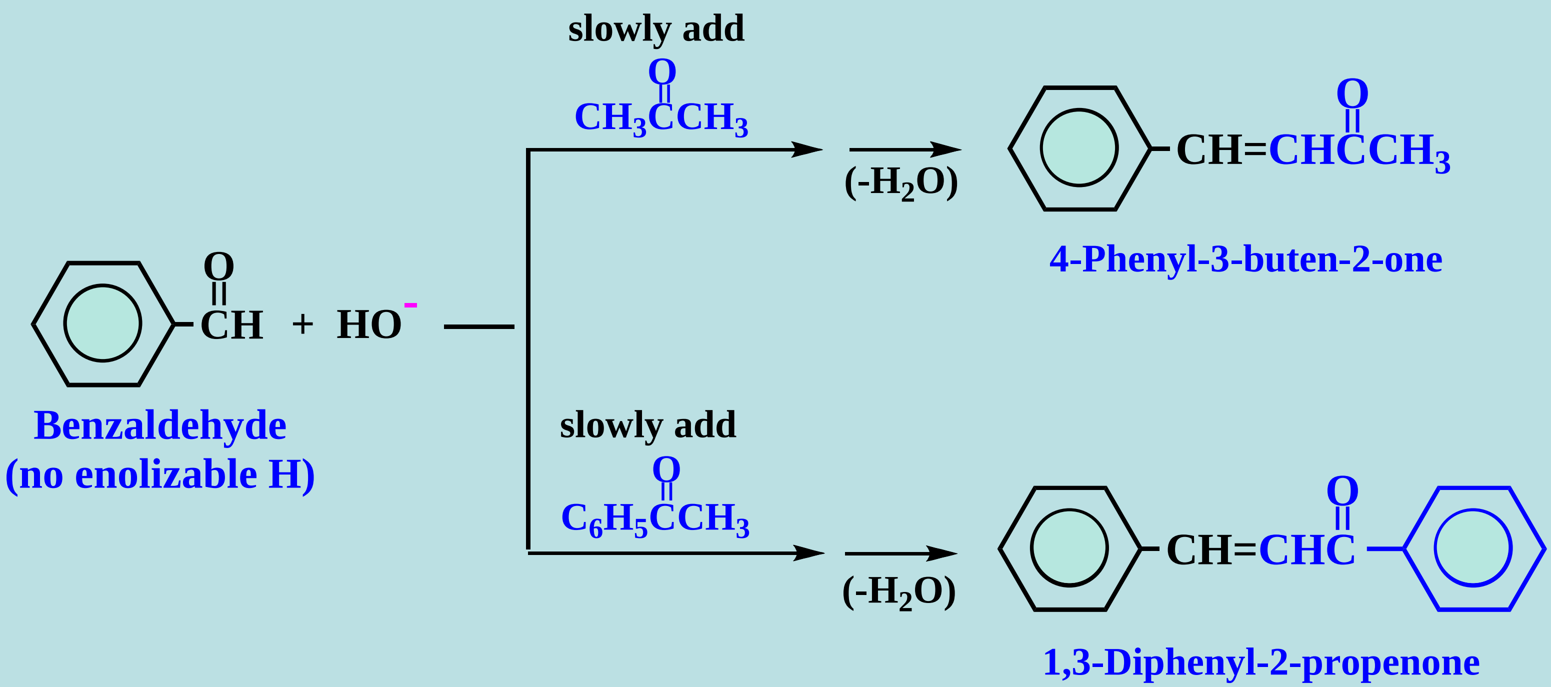
Aldol intermediate



Cinnamaldehyde
(3-phenyl-2-propenal)

To minimize self-condensation of acetaldehyde, this enolizable reactant is slowly added to a mixture of benzaldehyde and dilute HO^-.

Additional examples of crossed aldol reactions using benzaldehyde:

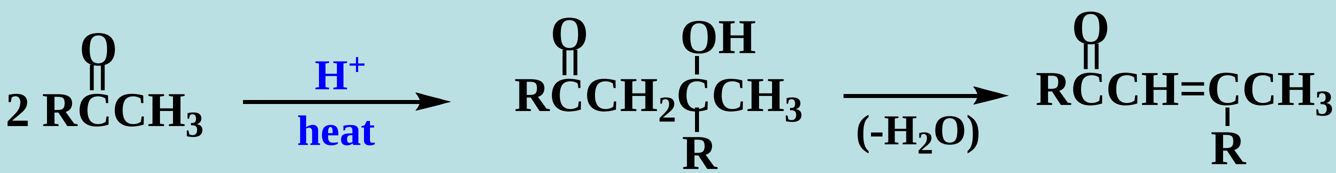


Dehydration of the initial aldol is spontaneous because it results in an extended, resonance stabilized system.

The Acid-Catalyzed Aldol Condensation

The aldol reaction of aldehydes and ketones with enolizable-H also occurs under acid-catalyzed conditions. The nucleophile in the addition reaction is the enol (not the enolate ion), and the rate of the addition step is increased by acid catalysis.

Overall Reaction

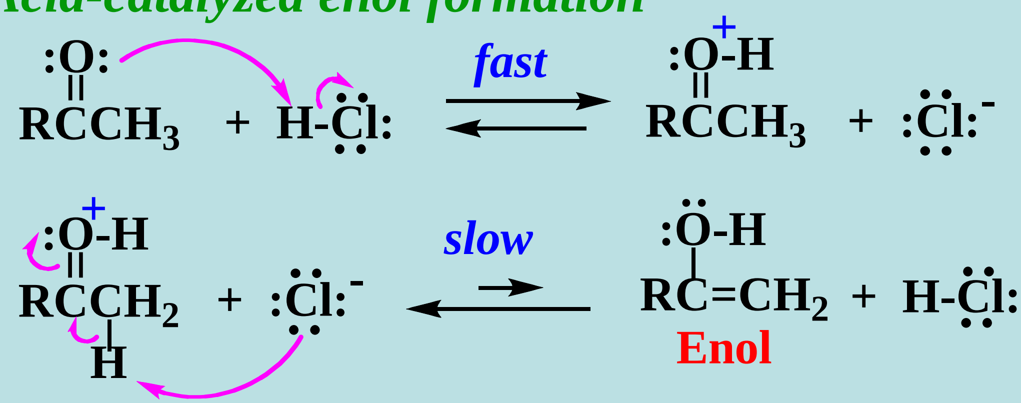


Aldol

The acidic conditions favor dehydration of the aldol condensation product, affording an α,β-unsaturated carbonyl compound, which is resonance stabilized.

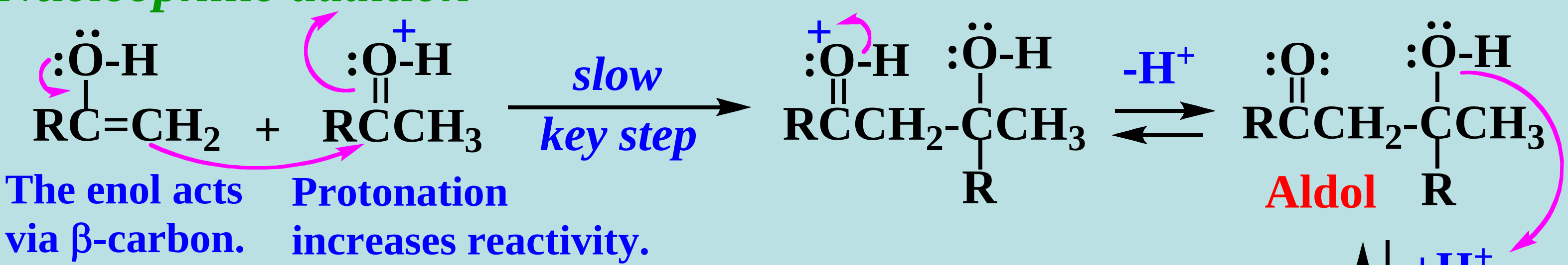
Mechanism of Acid-Catalyzed Aldol Condensation

Acid-catalyzed enol formation

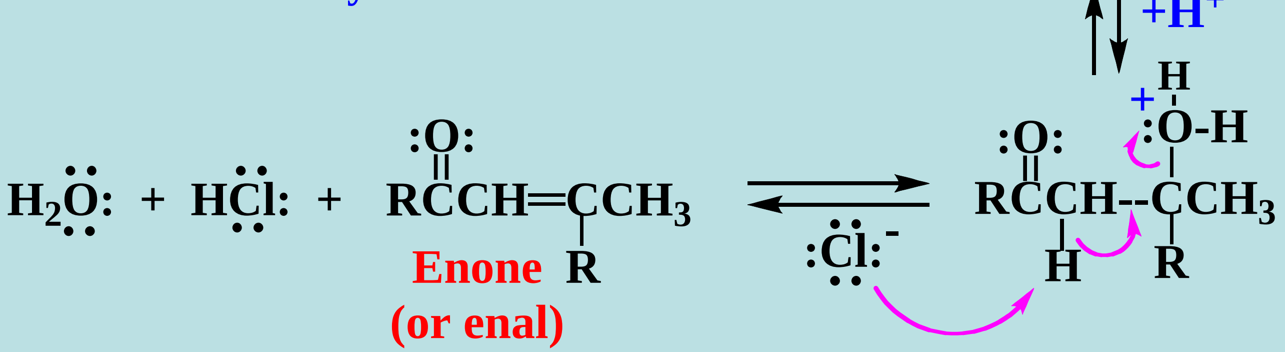


Enol concentration is low, but it is a reactive nucleophile.

Nucleophilic addition



Elimination



Claisen-Schmidt Reactions: α,β-Unsaturated Ketones

Crossed aldol reactions where ketones are one component are called Claisen-Schmidt reactions. These reactions were discovered and developed by two Germans chemists in the 1880s: J. G. Schmidt and Ludwig Claisen.

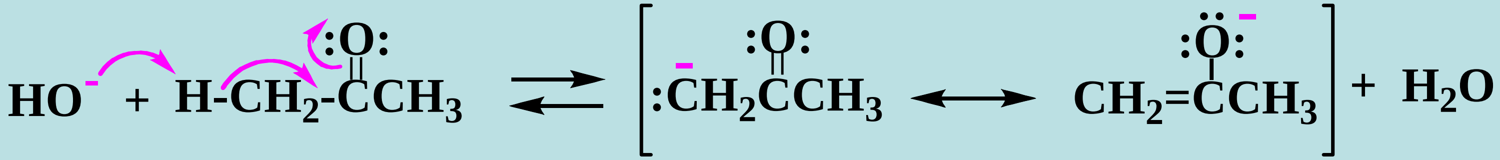
The crossed aldol product is favored over the self-reaction of the ketones because of the irreversibility of the cross product (a conjugated enone), while the self-reaction of the ketones is reversible.

$$C_6H_5\overset{\overset{O}{\|}}{C}H + CH_3\overset{\overset{O}{\|}}{C}CH_3 \xrightarrow[100\ ^oC]{HO^-} C_6H_5CH{=}CH\overset{\overset{O}{\|}}{C}CH_3 + H_2O$$

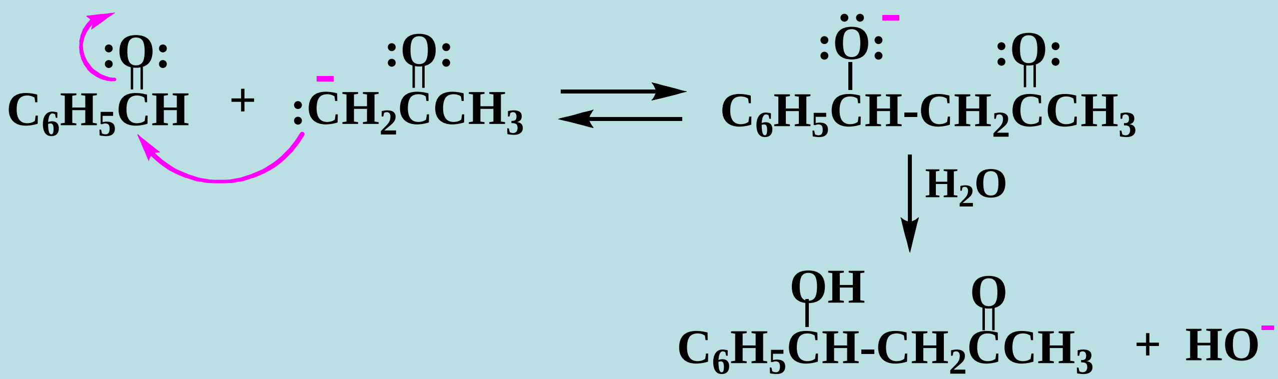
Benzaldehyde **Acetone** **4-Phenyl-3-buten-2-one (benzalacetone) 70%**

A Mechanism for the Claisen-Schmidt Reaction of Benzaldehyde and Acetone

Enolate anion formation

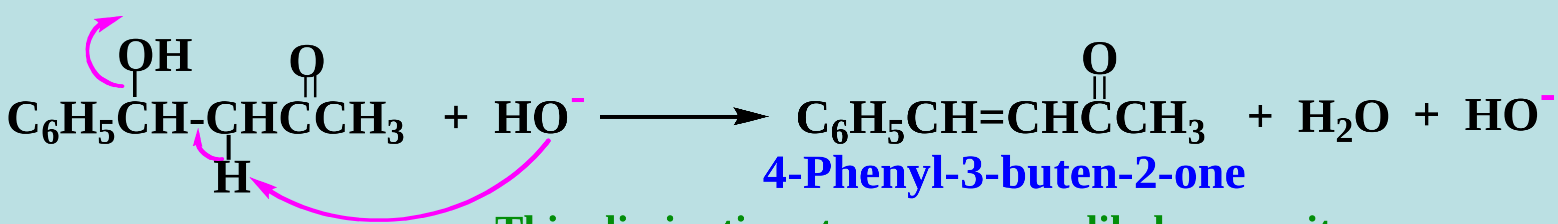


Nucleophilic addition



Aldol

Dehydration

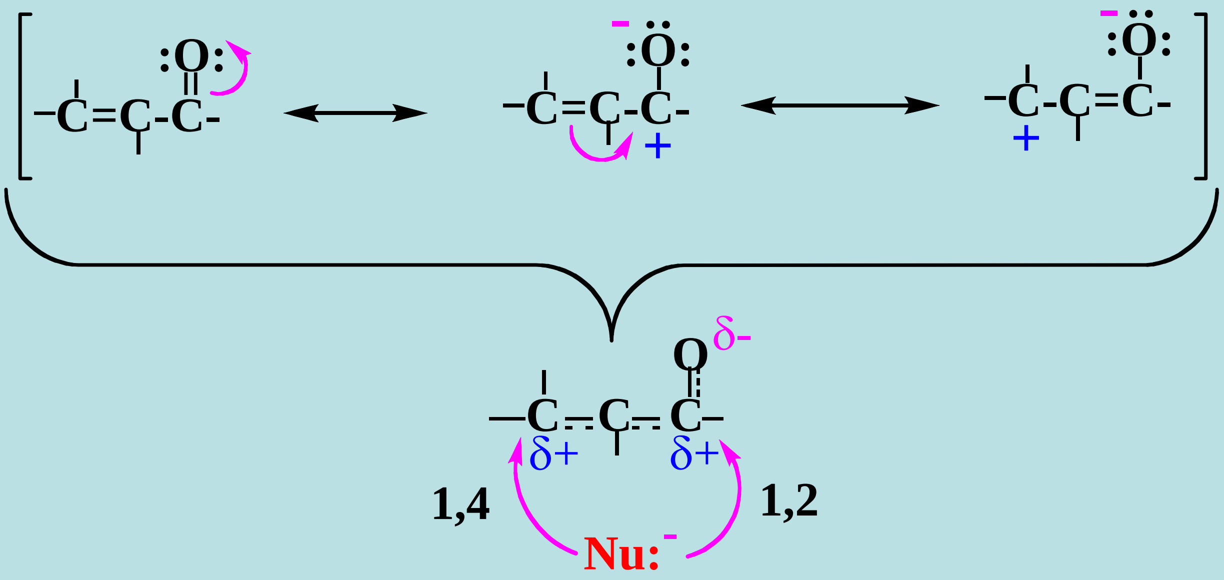


4-Phenyl-3-buten-2-one

This elimination step occurs readily because it extends the conjugated system.

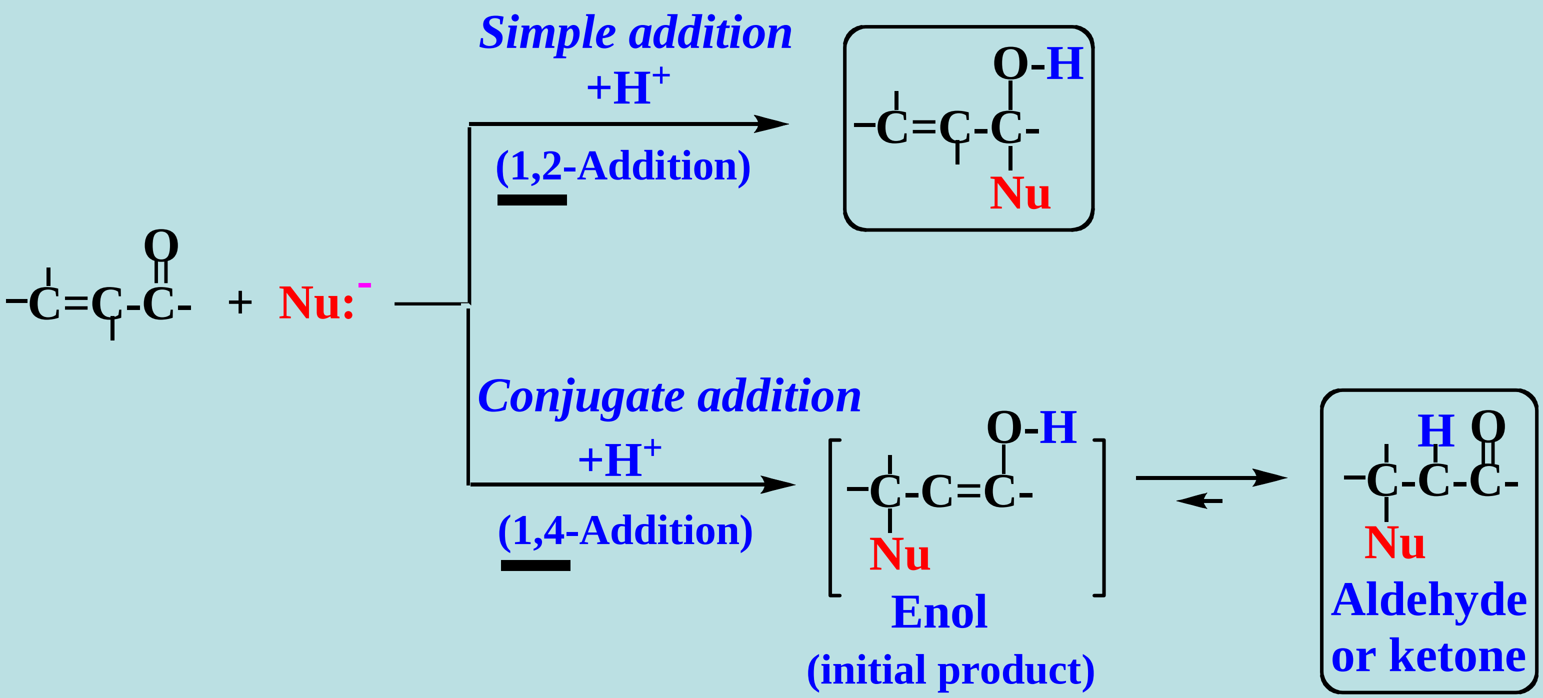
Additions to α,β-Unsaturated Aldehydes and Ketones

α,β-Unsaturated aldehydes and ketones react with nucleophiles by simple (1,2) addition and/or conjugate (1,4) addition. These two modes of reaction are understandable from an examination of the resonance structures for a conjugated enone system that shows two electropositive carbon centers.



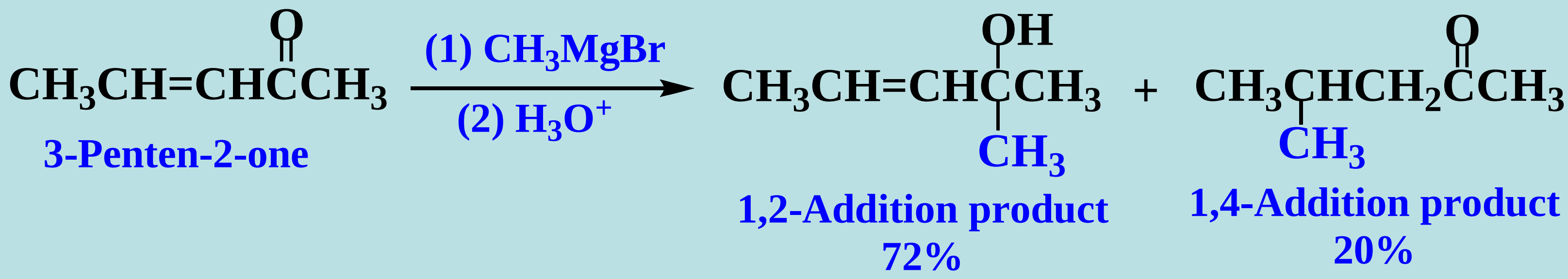
Modes of nucleophilic attack that lead to 1,2- vs. 1,4-addition

Reaction Schemes for Simple and Conjugate Additions

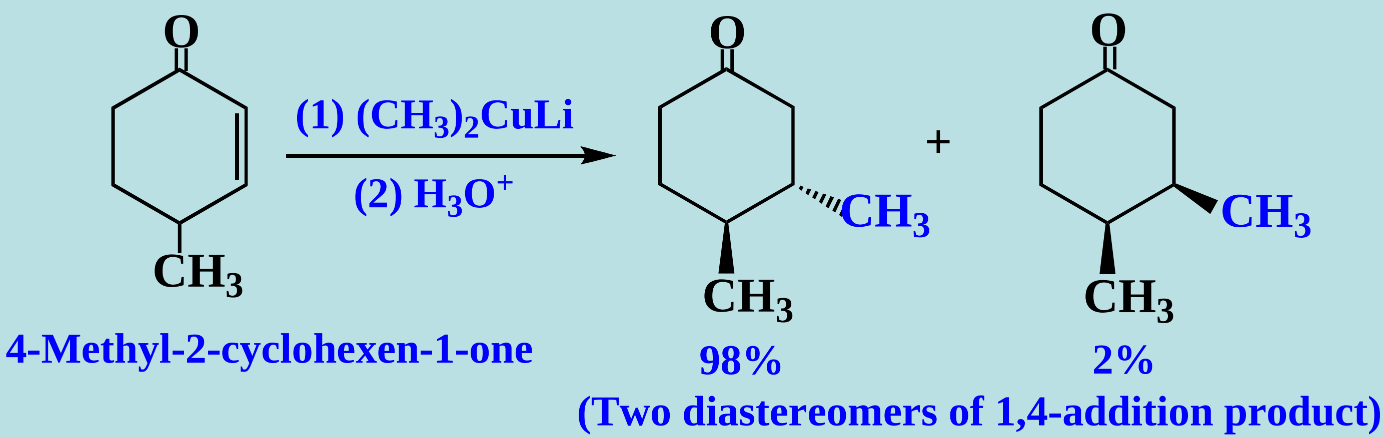


Examples

Often both modes of addition compete, giving a mixture of 1,2- and 1,4-addition products.



While Grignard reagents give mixtures of products from both addition modes, organocopper reagents primarily give 1,4-addition products.

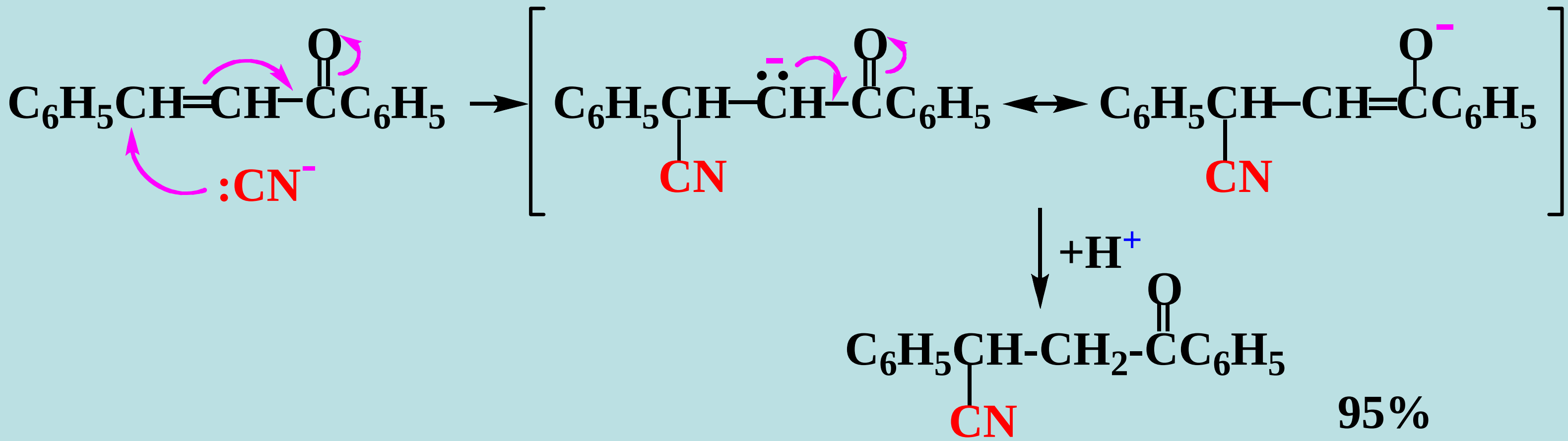


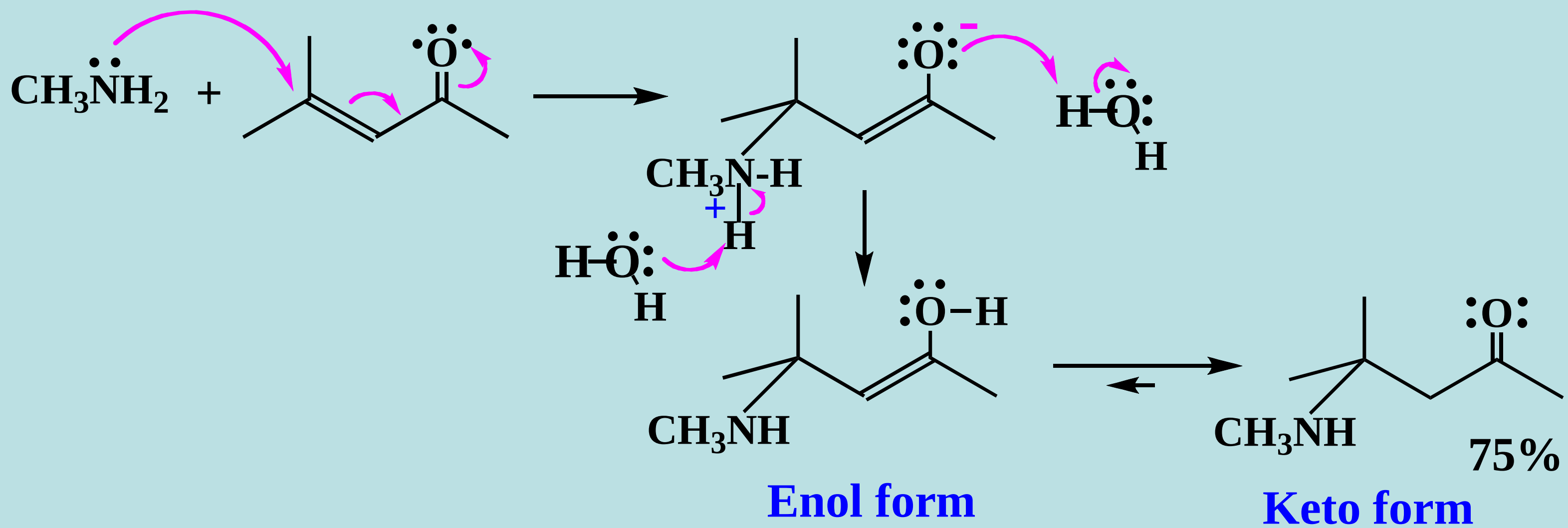
Only products from conjugate addition are found. The predominant diastereomer results from addition from the less hindered side, away from the methyl group in the 4-position. Hydrogen cyanide also adds primarily 1,4.

The Conjugate Addition of HCN and Amines

It is typical of weaker nucleophiles like HCN and amines that they add 1,4 to α,β-unsaturated aldehydes and ketones.

EXAMPLES

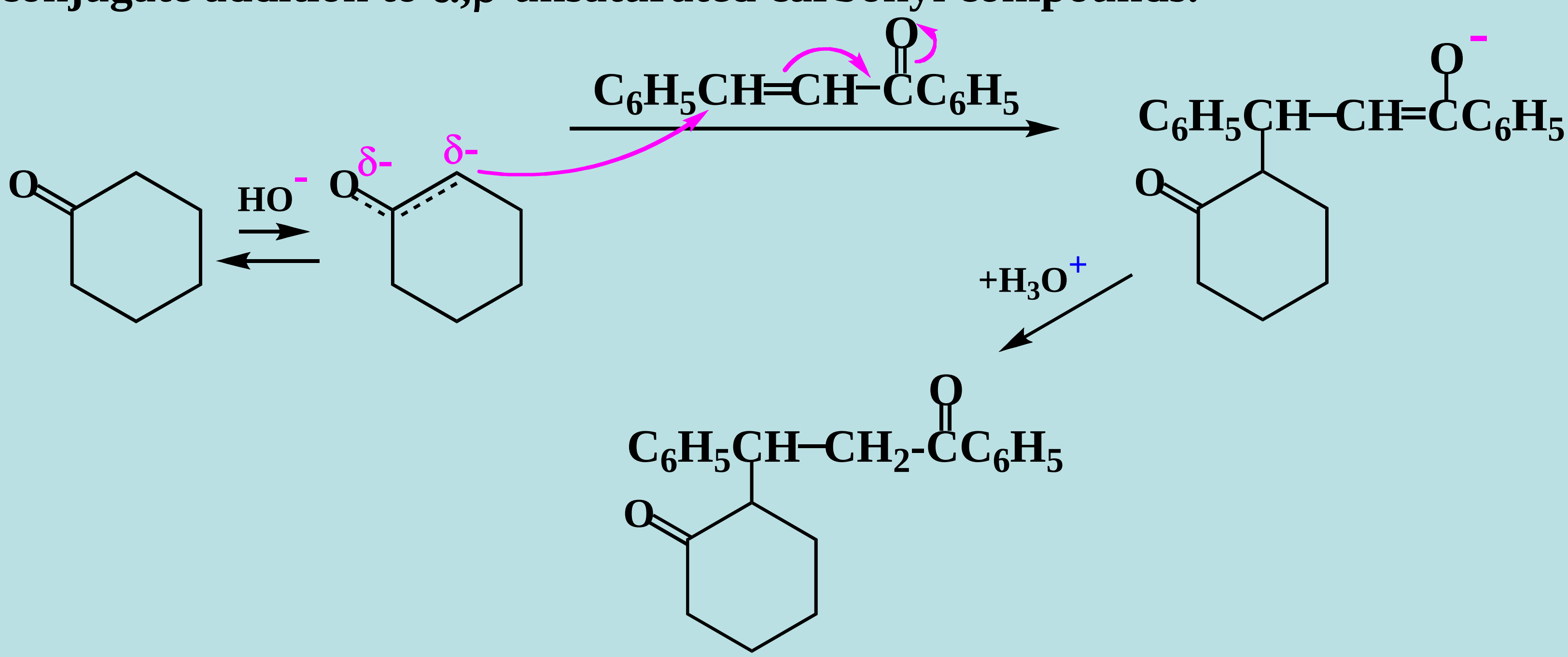




Michael Additions: Conjugate Additions of Enolate Anions

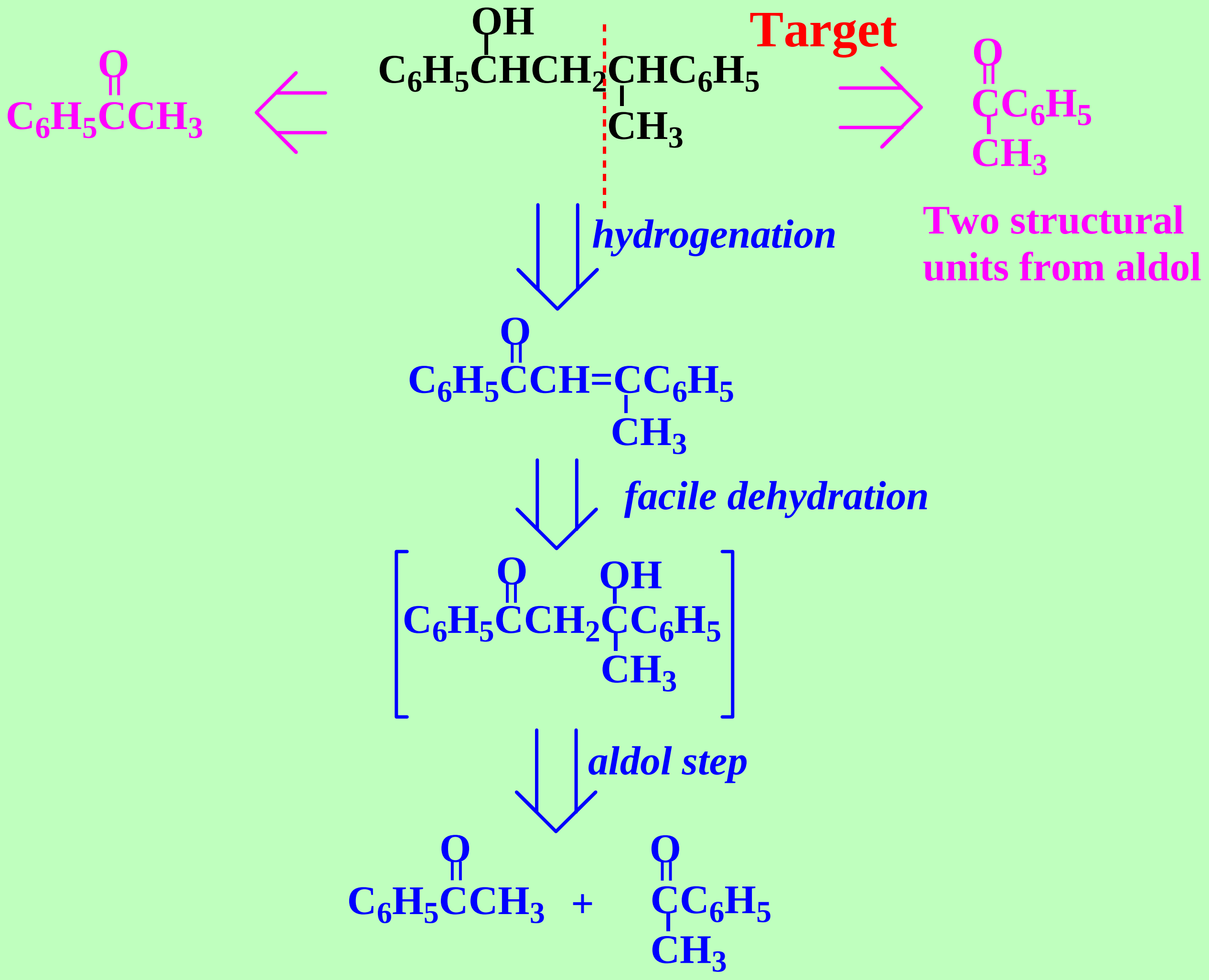
The conjugate additions of enolate anions to α,β-unsaturated carbonyl compounds are called Michael additions in honor of Arthur Michael (1853-1942), a Tufts (and, later, Harvard) professor who studied these reactions.

The enolate anions (nucleophiles) used in Michael additions may be those of simple aldehydes or ketones but often are derived from 1,3-dicarbonyl compounds. The term "Michael addition" is sometimes used for any conjugate addition to α,β-unsaturated carbonyl compounds.



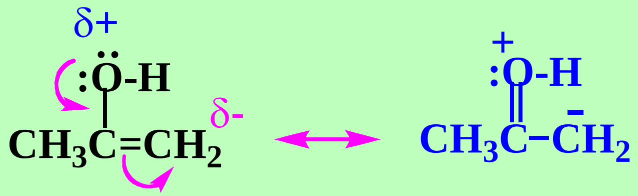
Quiz 17.04

Carry out a retrosynthetic analysis of 1,3-diphenyl-1-butanol that incorporates an aldol condensation step.

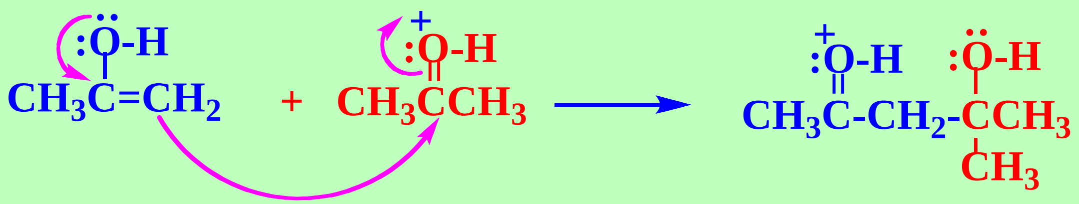


Quiz 17.05

Enols are nucleophiles. Show the polarization of charge in the enol of acetone using its resonance structures and the curved arrow formalism.



Write the equation for the condensation step in the acid-catalyzed aldol reaction of acetone. How does acid increase the rate of this step?



Protonation of the carbonyl enhances its reactivity towards nucleophiles.