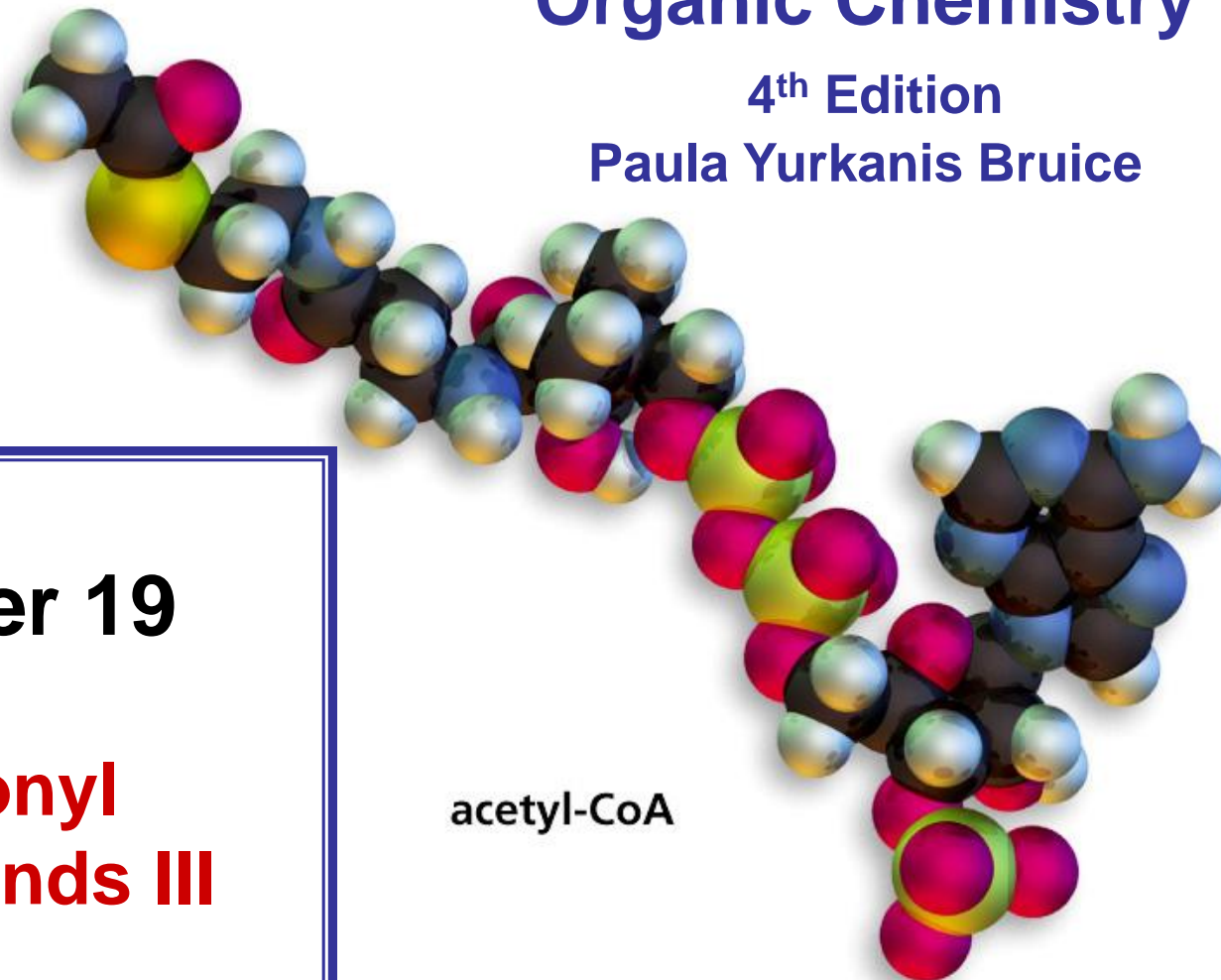


Organic Chemistry

4th Edition

Paula Yurkanis Bruice



acetyl-CoA

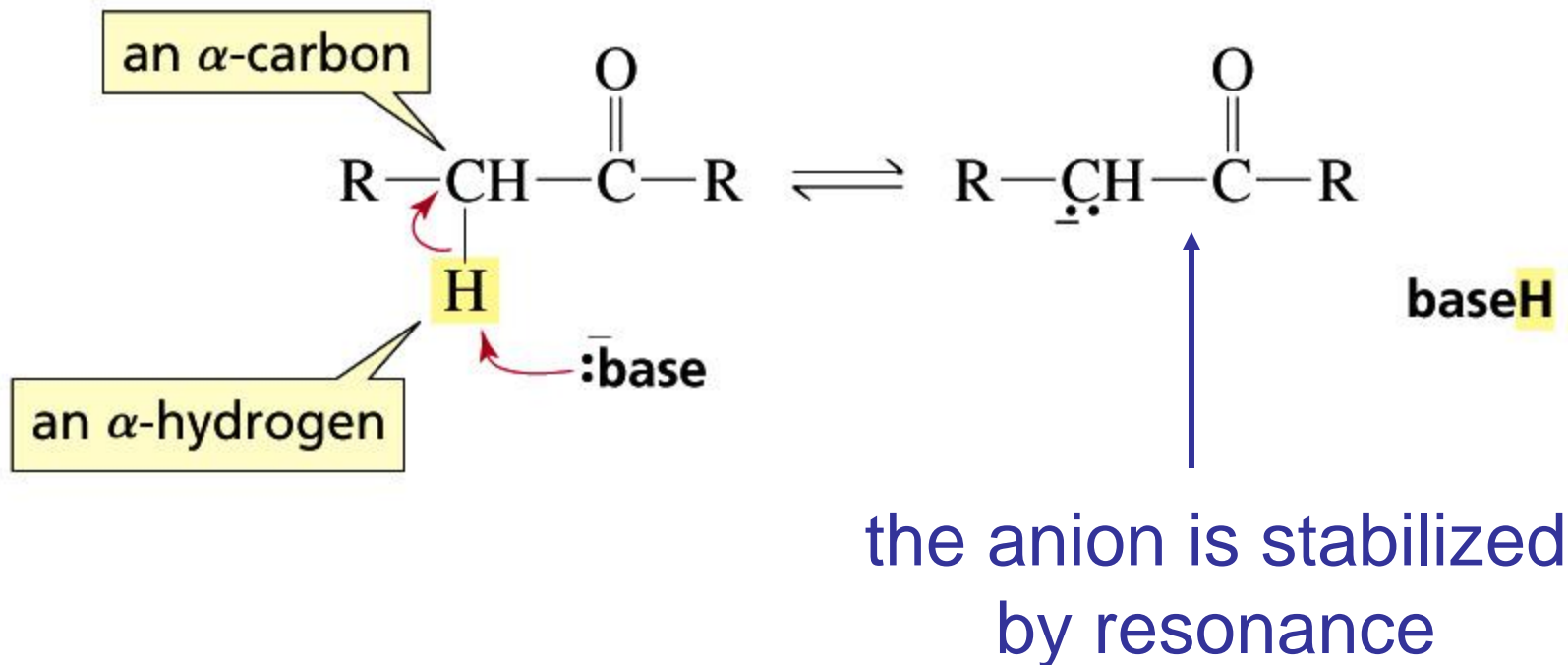
Chapter 19

Carbonyl Compounds III

Reactions at the
 α -Carbon

Disampaikan oleh: Dr. Sri Handayani
2013

The α -Hydrogen Is Acidic

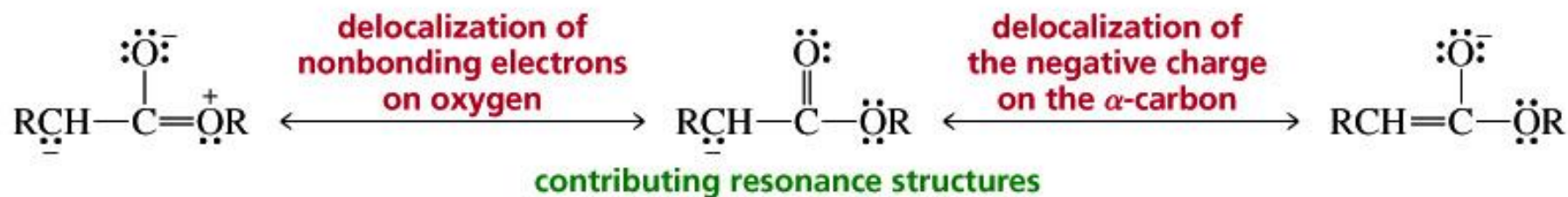


A carbon acid is a compound with a relatively acidic hydrogen bonded to an sp^3 -hybridized carbon

TABLE 19.1 The pK_a Values of Some Carbon Acids

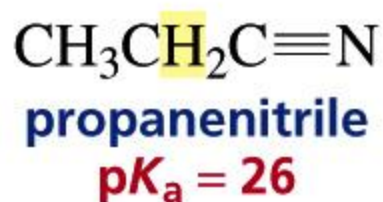
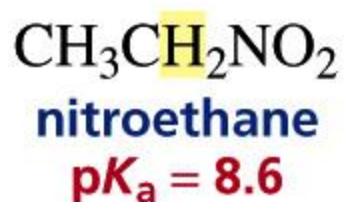
	pK_a		pK_a
$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_2\text{CN}(\text{CH}_3)_2 \\ \\ \text{H} \end{array}$	30	$\begin{array}{c} \text{N}\equiv\text{CCHC}\equiv\text{N} \\ \\ \text{H} \end{array}$	11.8
$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_2\text{COCH}_2\text{CH}_3 \\ \\ \text{H} \end{array}$	25	$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{CH}_3\text{CCHCOCH}_2\text{CH}_3 \\ \\ \text{H} \end{array}$	10.7
$\begin{array}{c} \text{CH}_2\text{C}\equiv\text{N} \\ \\ \text{H} \end{array}$	25	$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{C}_6\text{H}_5\text{CCHCCH}_3 \\ \\ \text{H} \end{array}$	9.4
$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_2\text{CCH}_3 \\ \\ \text{H} \end{array}$	20	$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{CH}_3\text{CCHCCH}_3 \\ \\ \text{H} \end{array}$	8.9
$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_2\text{CH} \\ \\ \text{H} \end{array}$	17	$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{CH}_3\text{CCHCH} \\ \\ \text{H} \end{array}$	5.9
$\begin{array}{c} \text{CH}_3\text{CHNO}_2 \\ \\ \text{H} \end{array}$	8.6	$\begin{array}{c} \text{O}_2\text{NCHNO}_2 \\ \\ \text{H} \end{array}$	3.6

Esters Are Less Acidic Than Aldehydes and Ketones

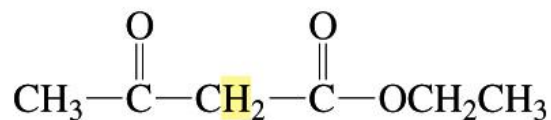


The electrons are not as readily delocalized

In these compounds, the electrons left behind from deprotonation can be delocalized onto a more electronegative atom



The acidity of the α -hydrogens is attributed to charge stabilization by resonance

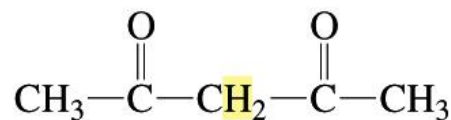


ethyl 3-oxobutyrate

ethyl acetoacetate

a β -keto ester

$\text{p}K_a = 10.7$

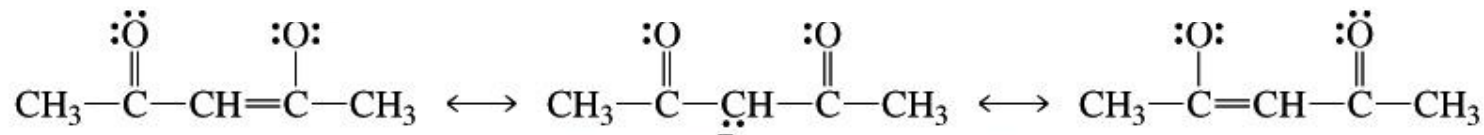


2,4-pentanedione

acetylacetone

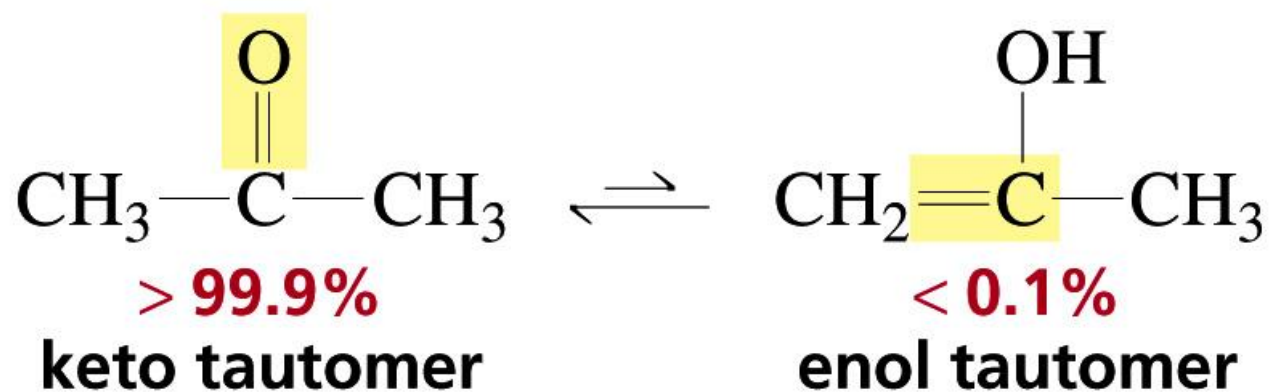
a β -diketone

$\text{p}K_a = 8.9$

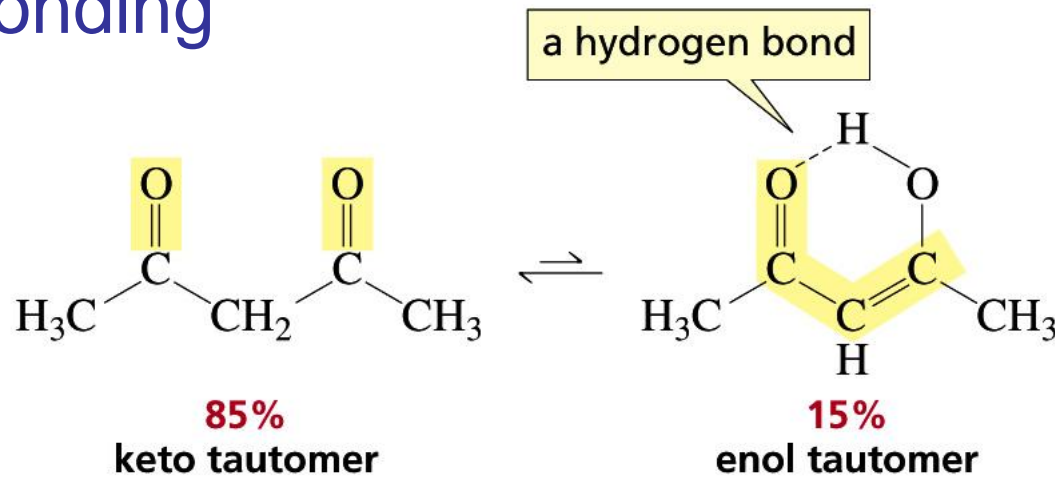


resonance contributors for the 2,4-pentanedione anion

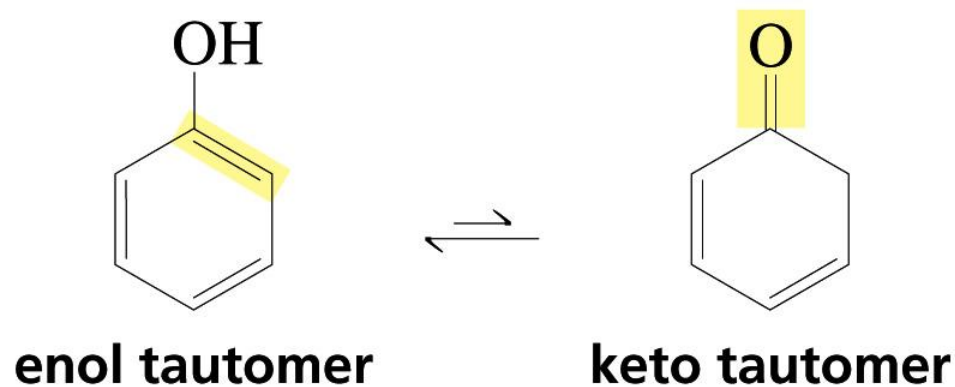
Keto–Enol Tautomerism



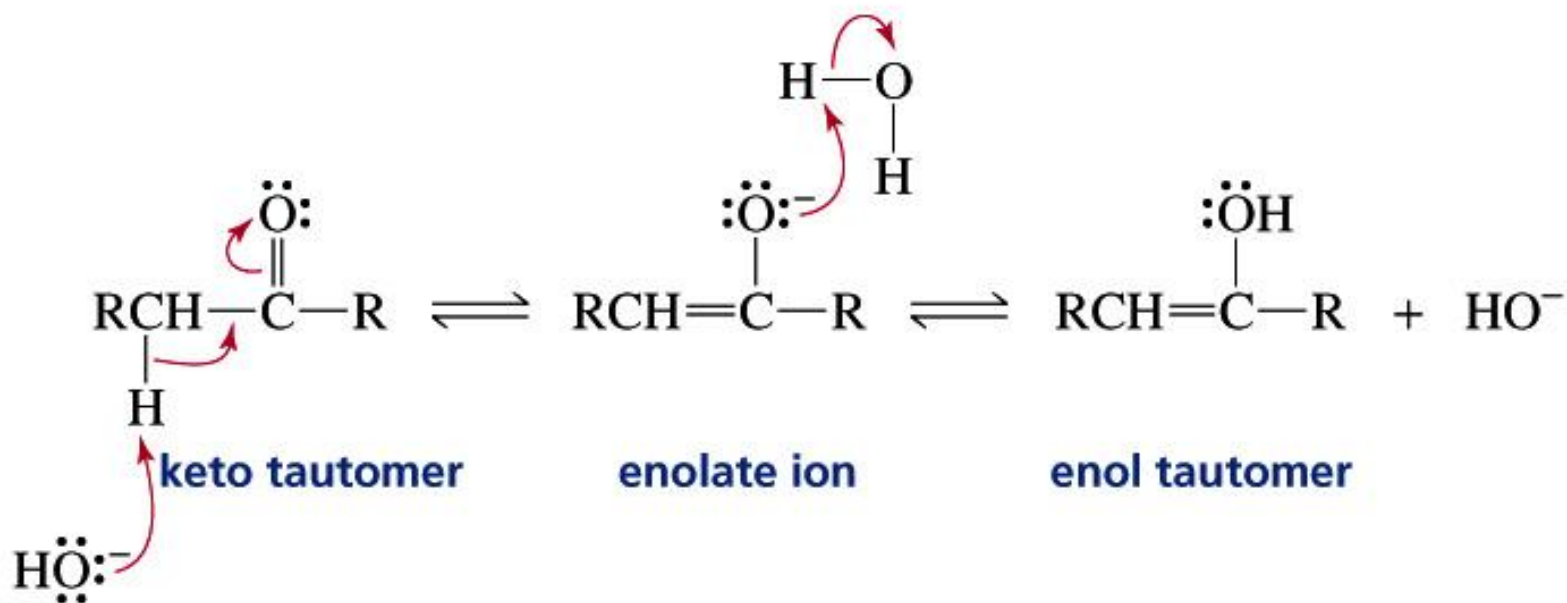
The enol tautomer can be stabilized by intramolecular hydrogen bonding



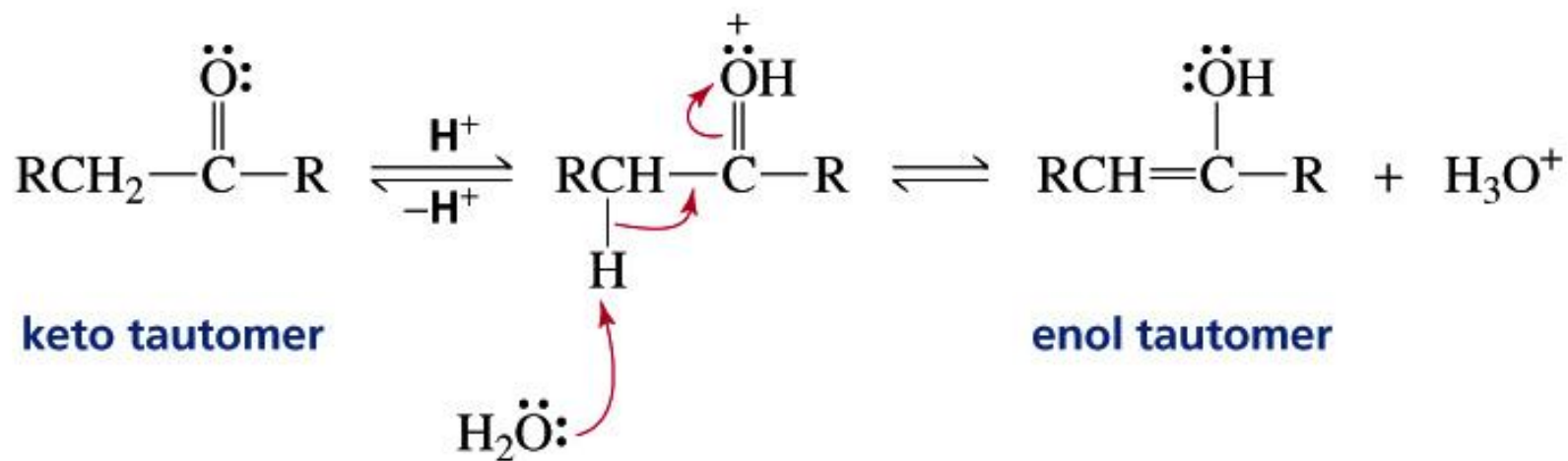
In phenol, the enol tautomer is aromatic



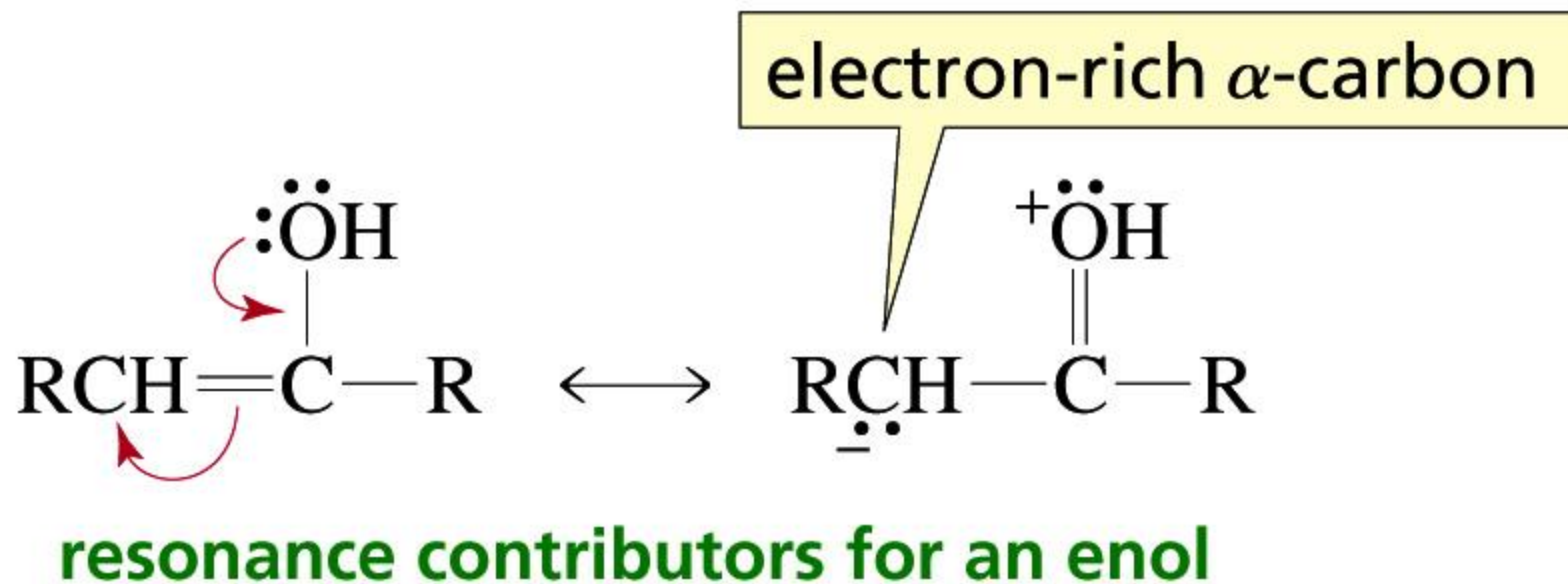
base-catalyzed keto-enol interconversion



acid-catalyzed keto-enol interconversion

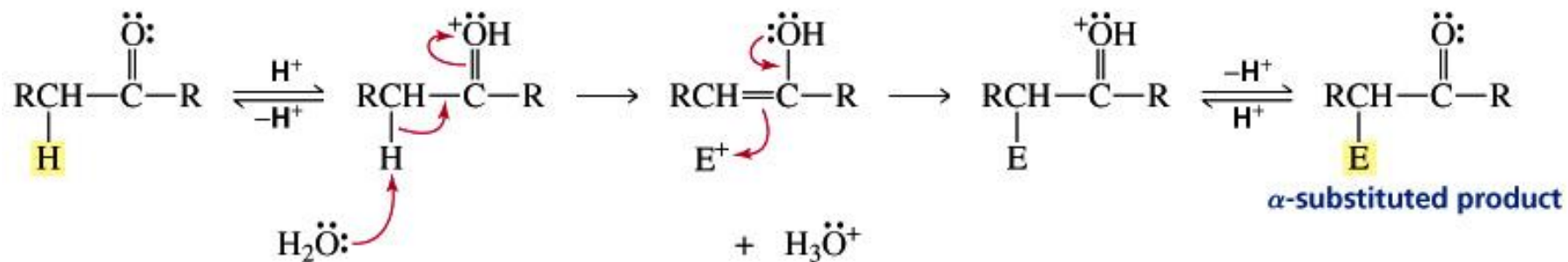


An Enol Is a Better Nucleophile Than an Alkene

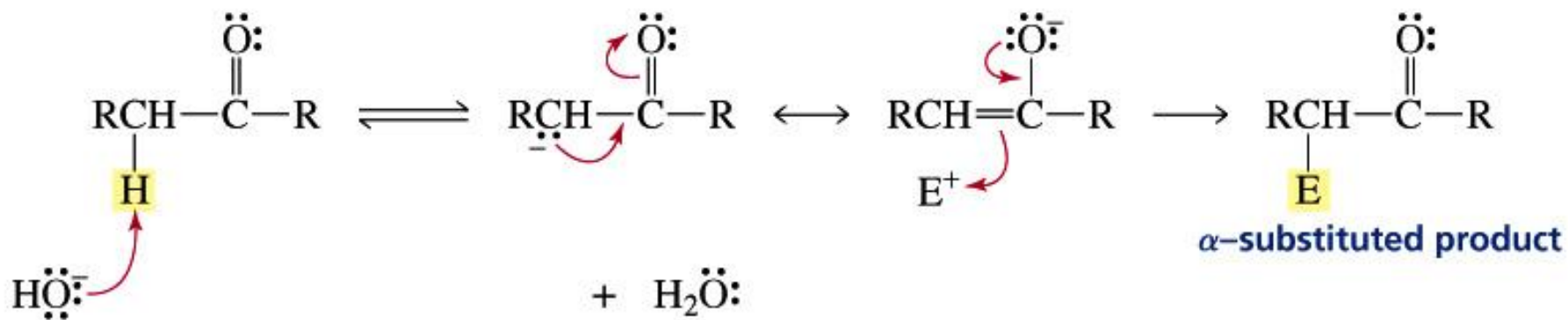


Carbonyl compounds that form enol undergo substitution reactions at the α -carbon: an α -substitution reaction

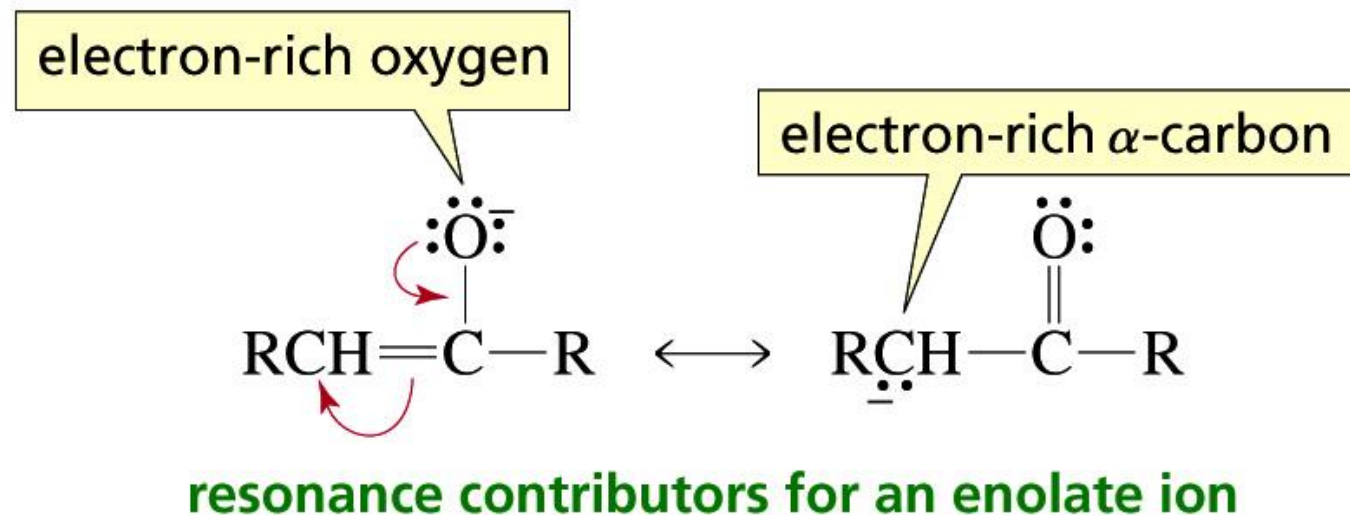
An Acid-Catalyzed α -Substitution Reaction



A Base-Catalyzed α -Substitution Reaction



An Enolate Is an Ambident Nucleophile

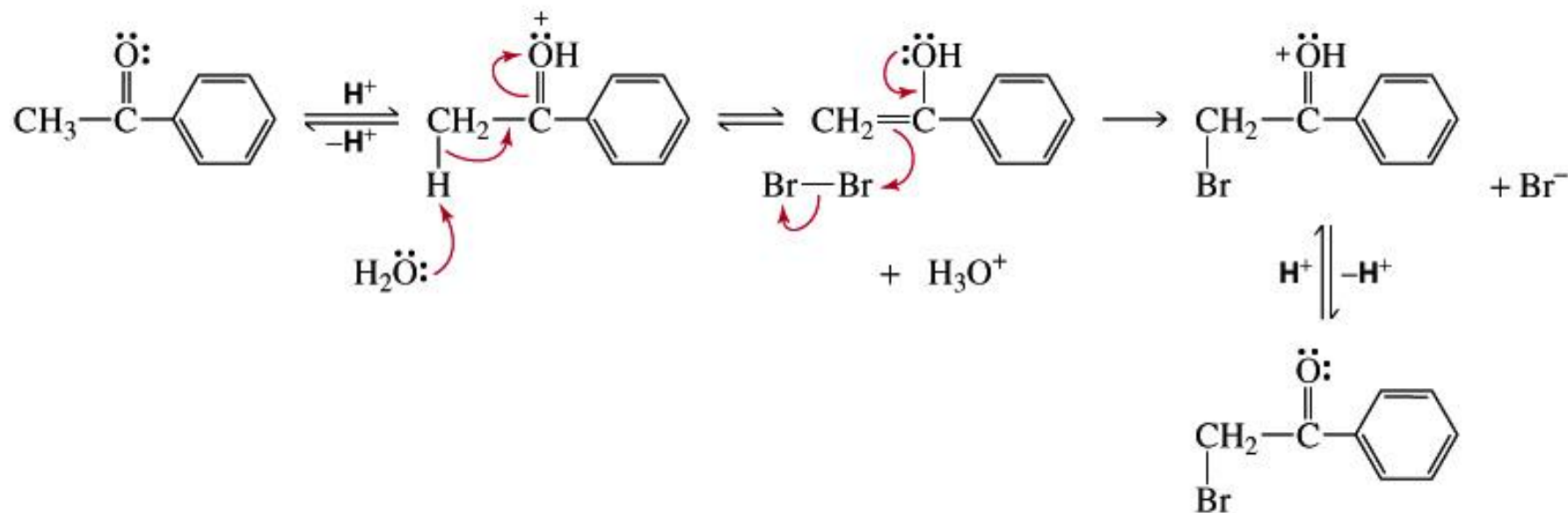


Reaction at the C or O site depends on the electrophile and on the reaction condition

Protonation occurs preferentially on the O site

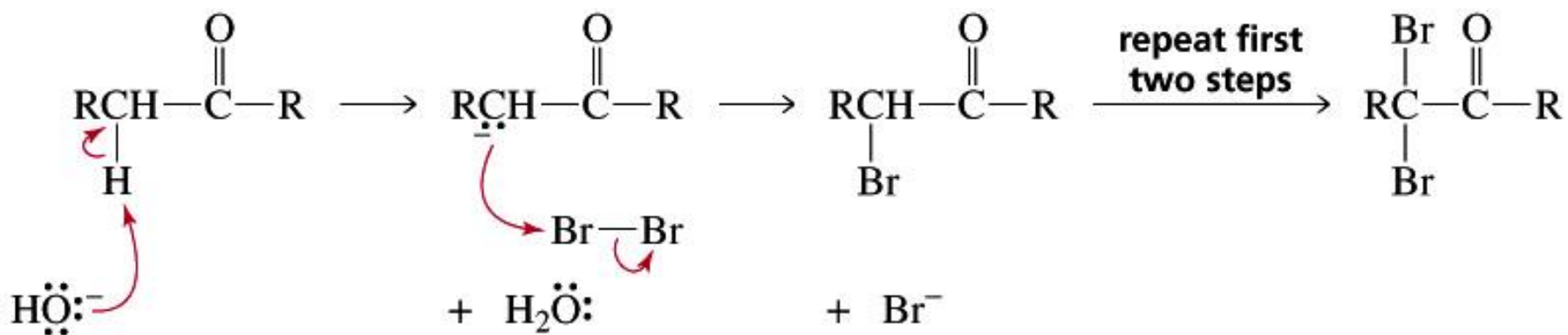
Otherwise, the C site is likely the nucleophile

Acid-Catalyzed Halogenation



Under acidic conditions, one α -hydrogen is substituted for a bromine

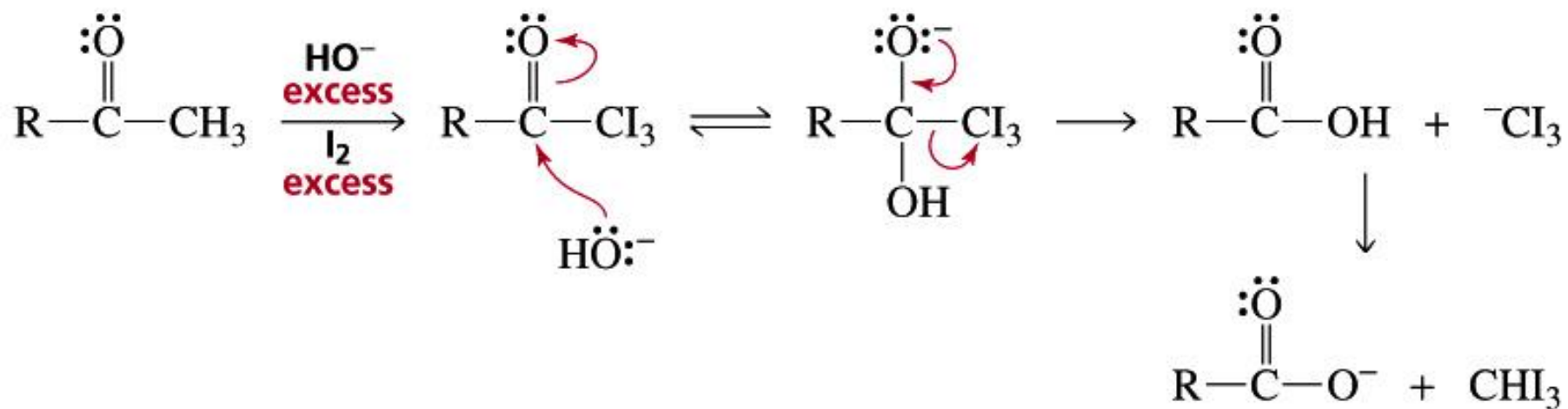
Base-Promoted Halogenation



Under basic conditions, all the α -hydrogens are substituted for bromines

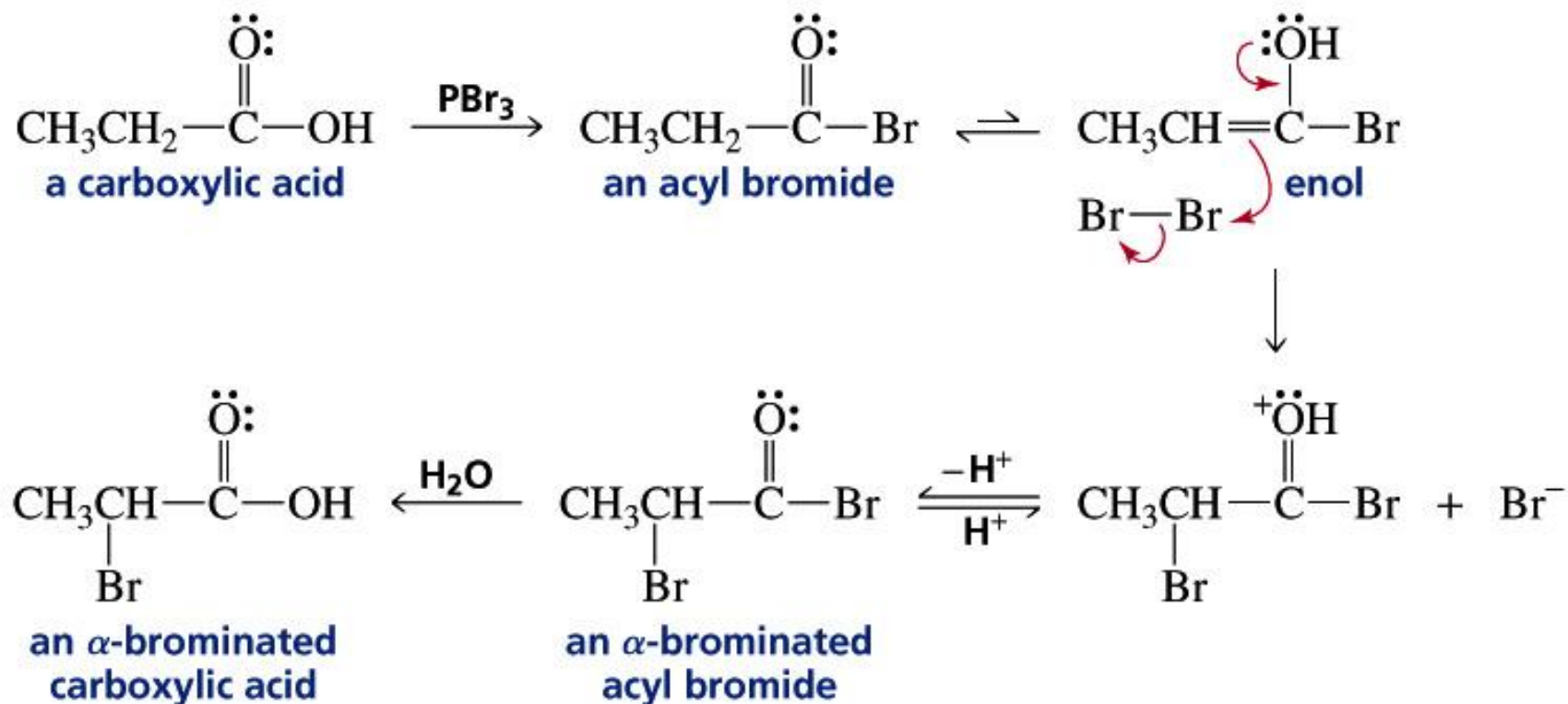
Conversion of a Methyl Ketone to a Carboxylic Acid

the haloform reaction

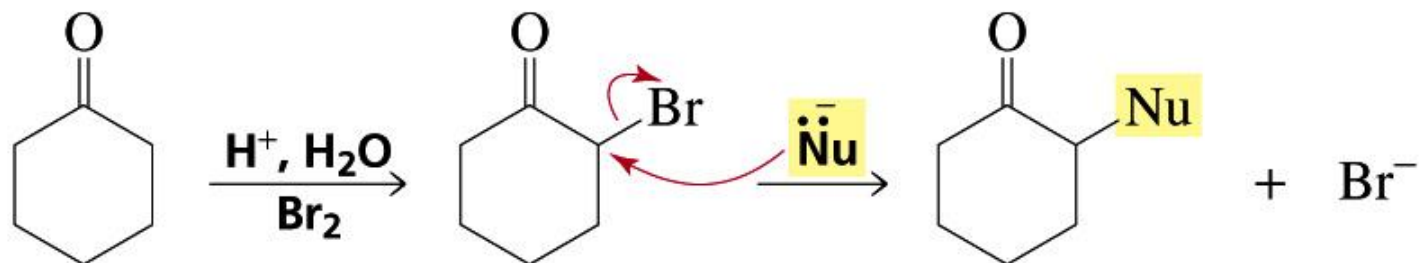


Halogenation of the α -Carbon of Carboxylic Acids

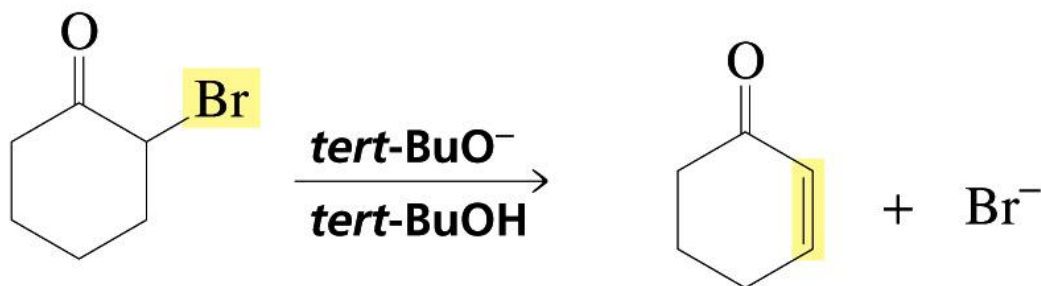
mechanism for the Hell-Volhard-Zelinski reaction



When the α -carbon is halogenated, it becomes electrophilic

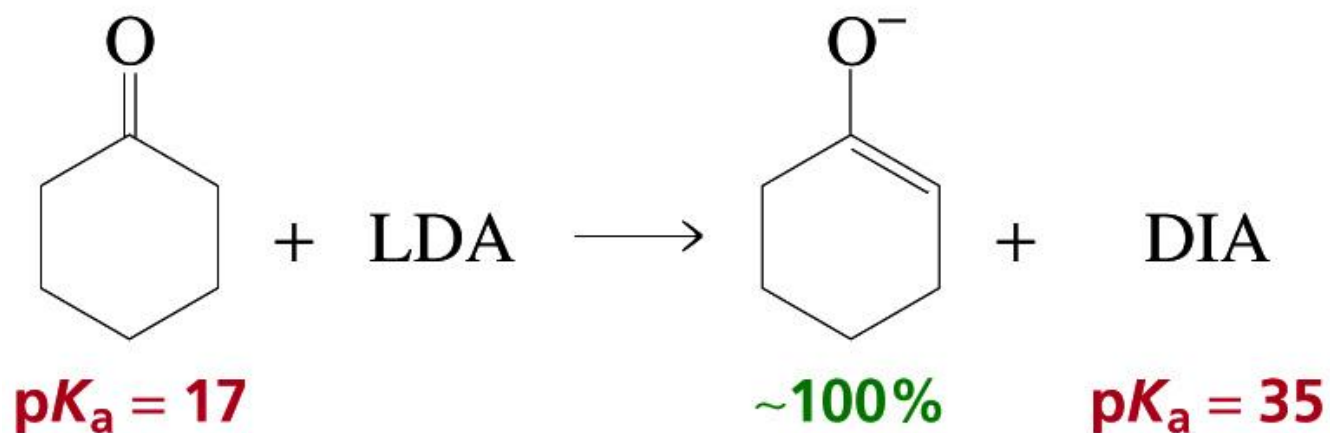
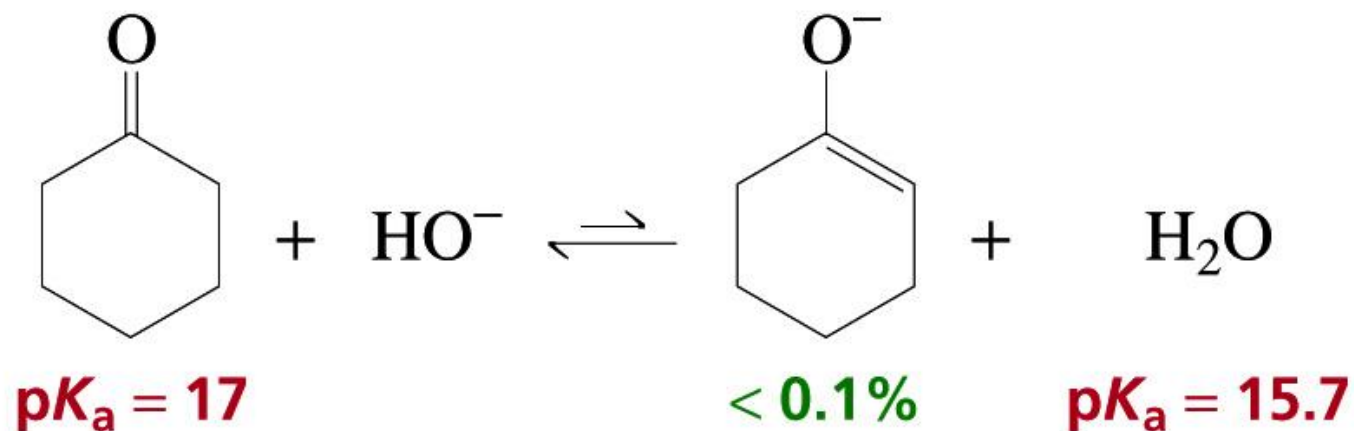


An E2 elimination will occur if a bulky base is used

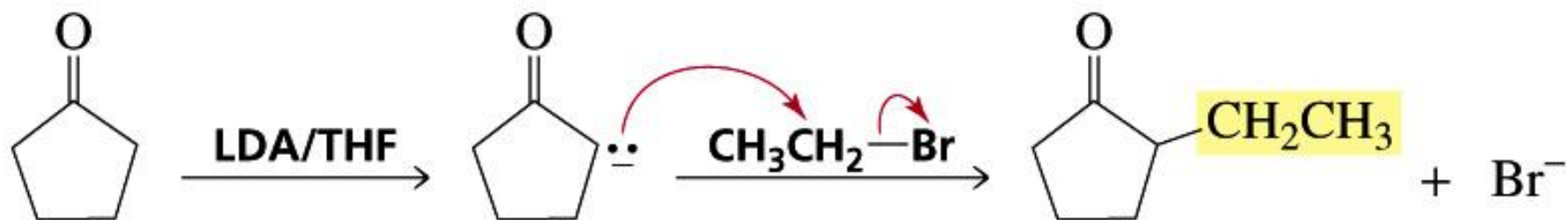


an α,β -unsaturated
carbonyl compound

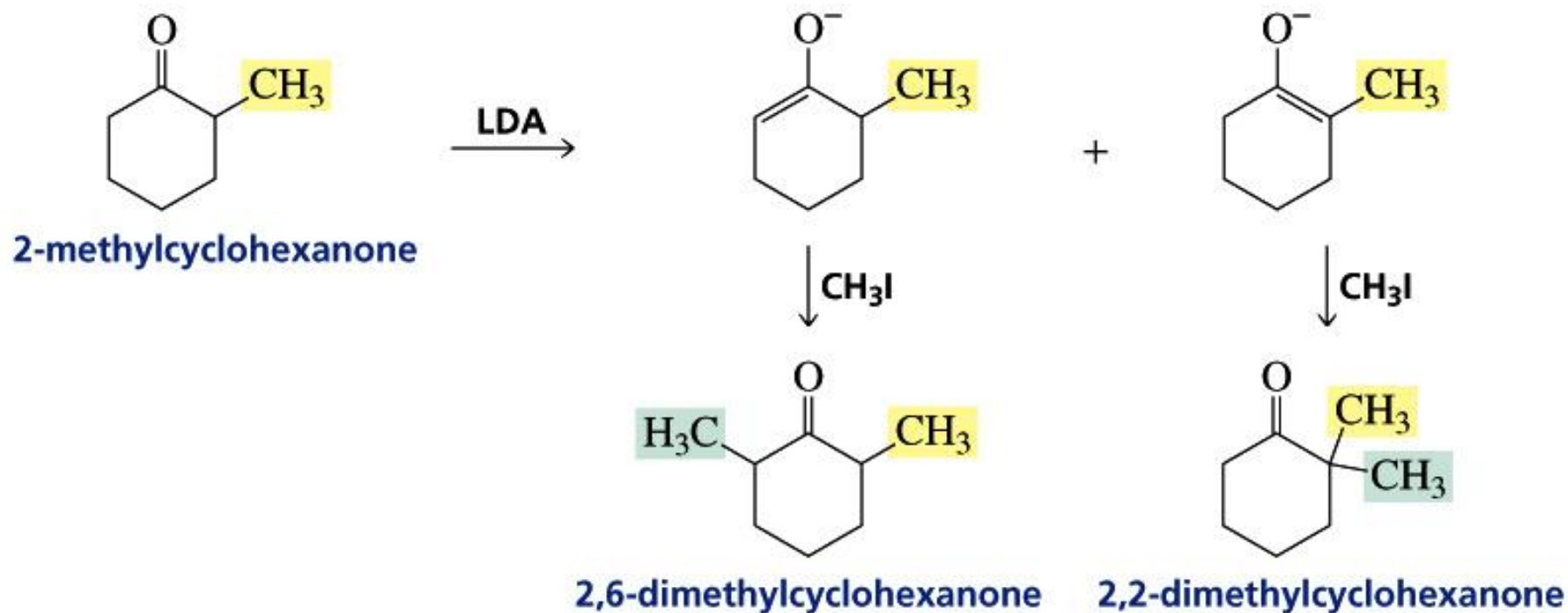
Using LDA to Form an Enolate



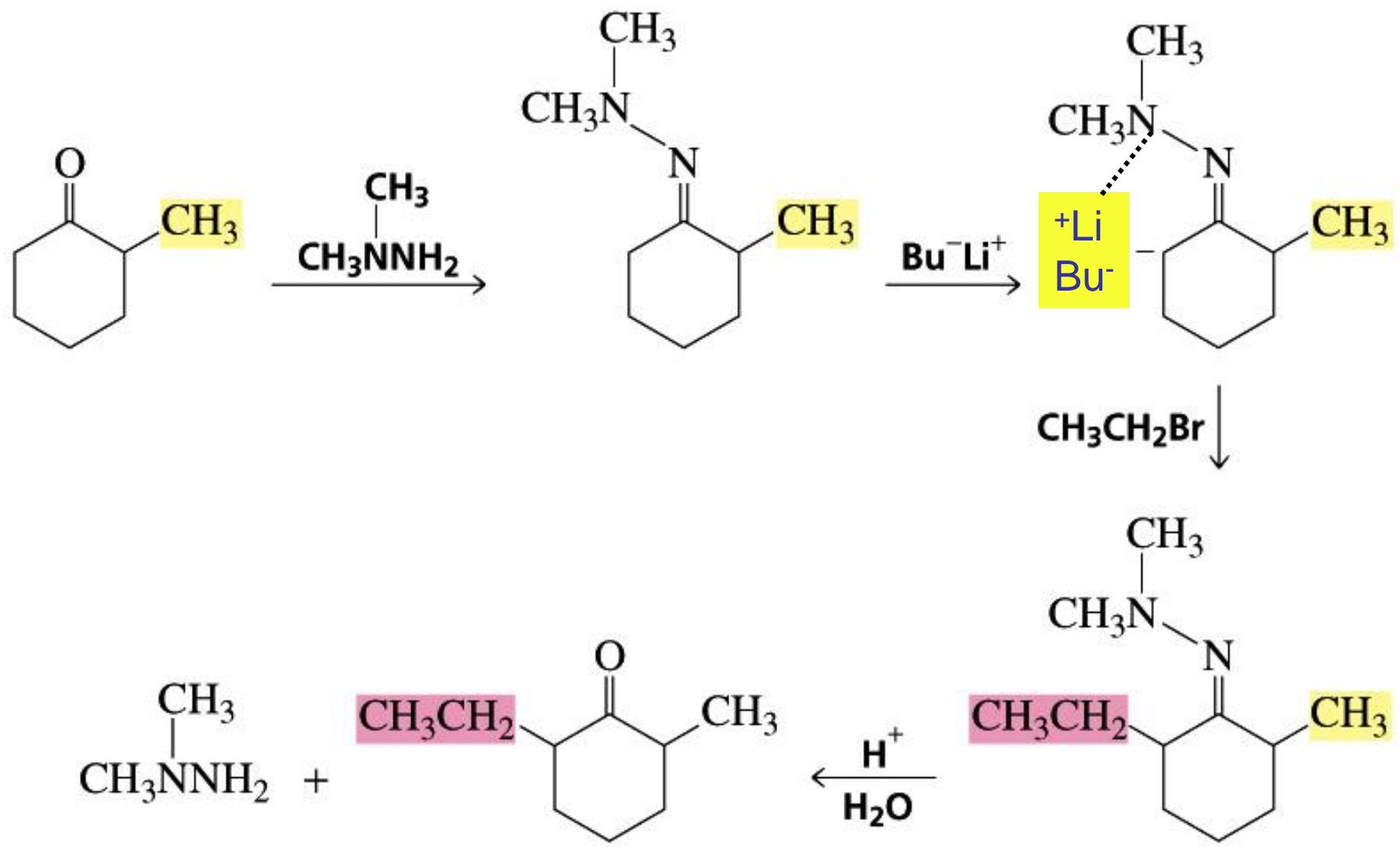
Alkylation of the α -Carbon of Carbonyl Compounds



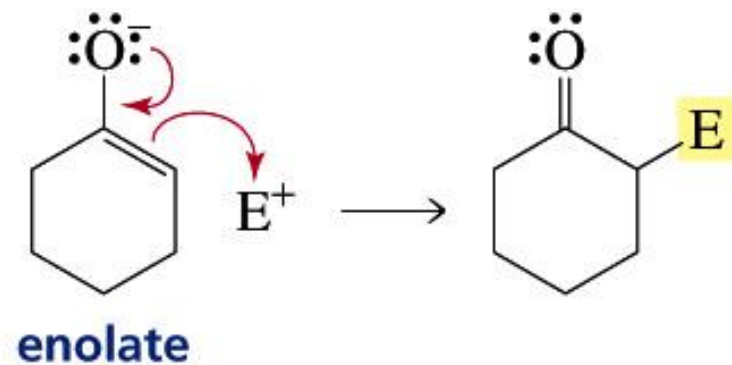
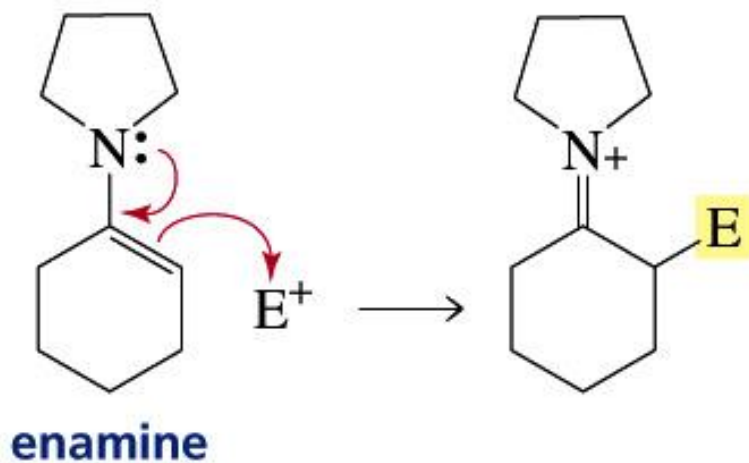
Two different products can be formed if the ketone is not symmetrical

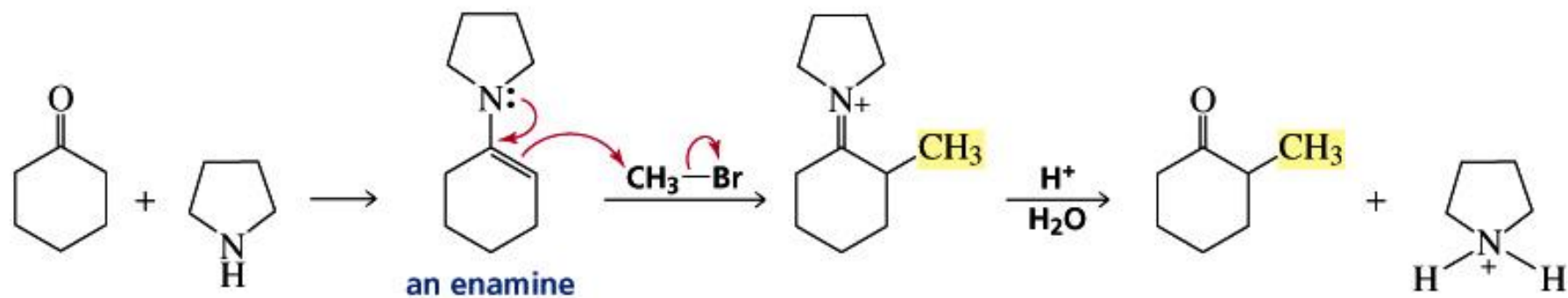


The less substituted α -carbon can be alkylated if ...



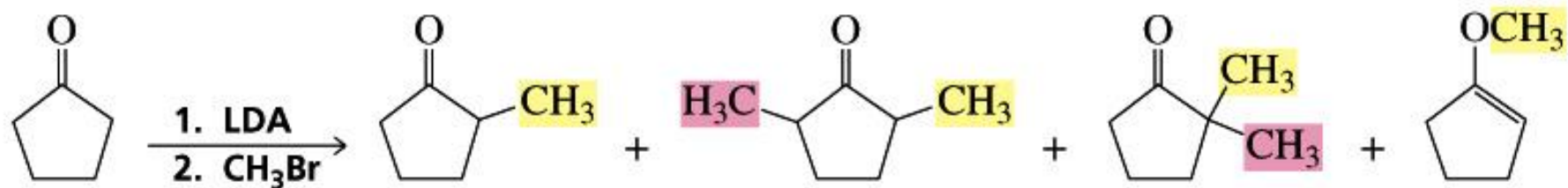
Enamine Reacts with Electrophiles





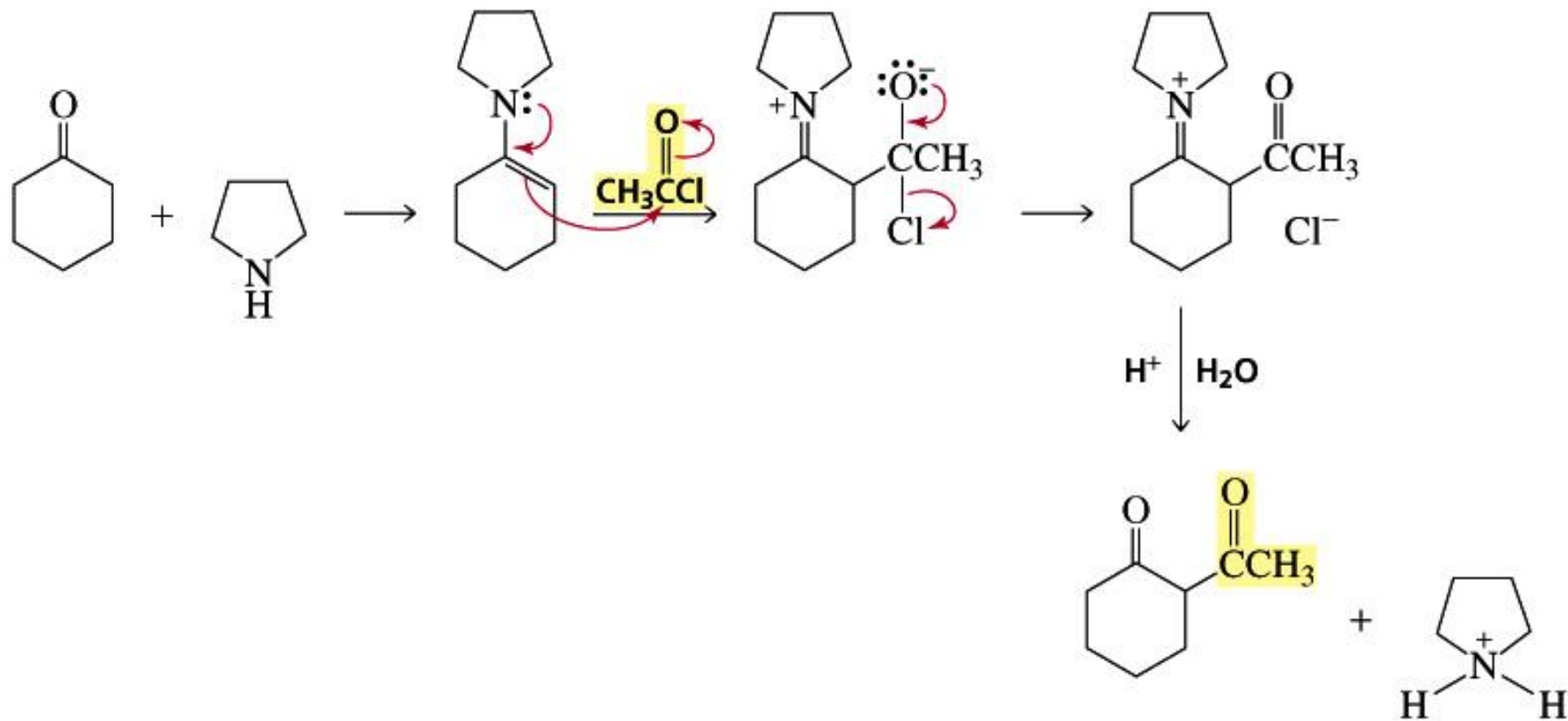
The alkylation step is an $\text{S}_{\text{N}}2$ reaction

Direct alkylation of a carbonyl compound yields several products

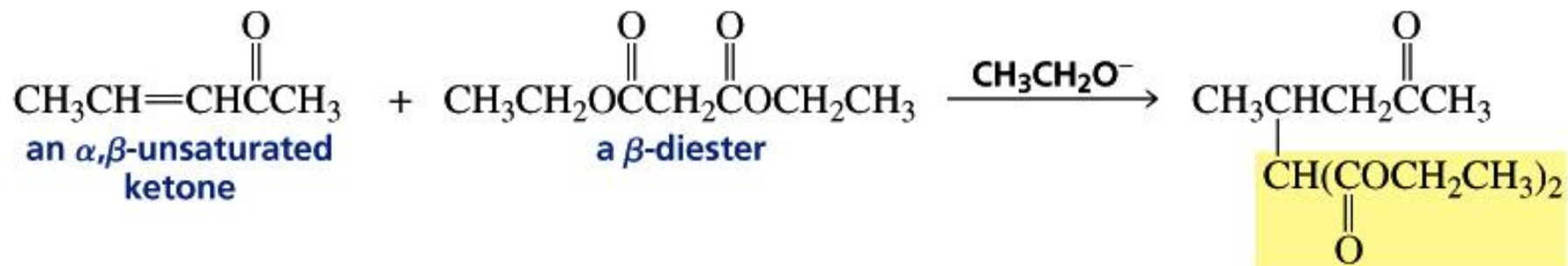
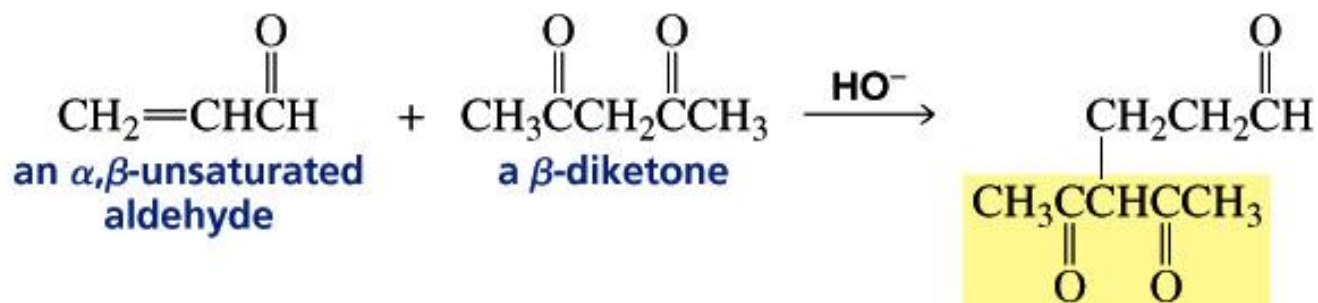


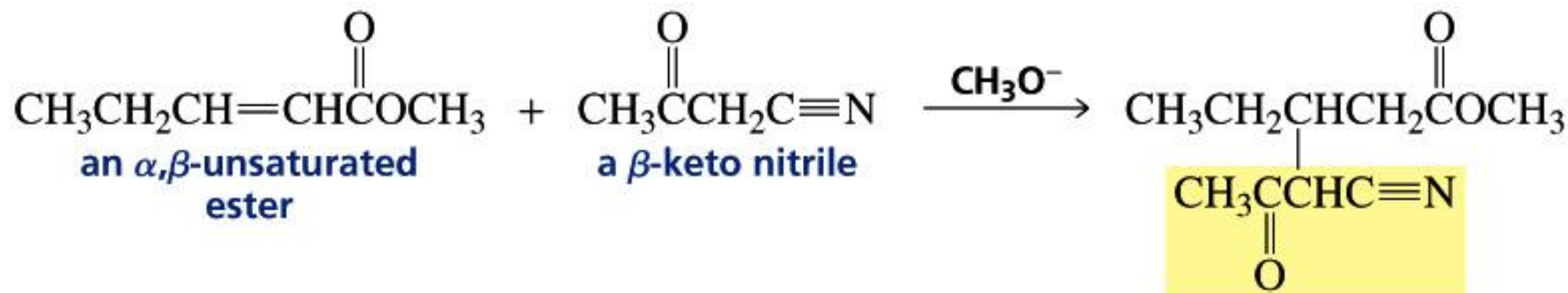
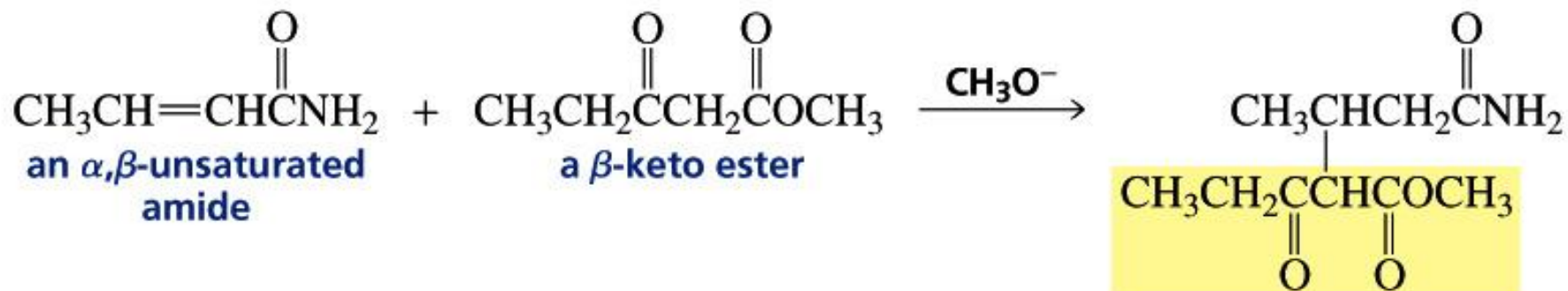
In contrast, alkylation of an aldehyde or a ketone using an enamine intermediate yields the monoalkylated product

Aldehydes and ketones can be acylated via an enamine intermediate

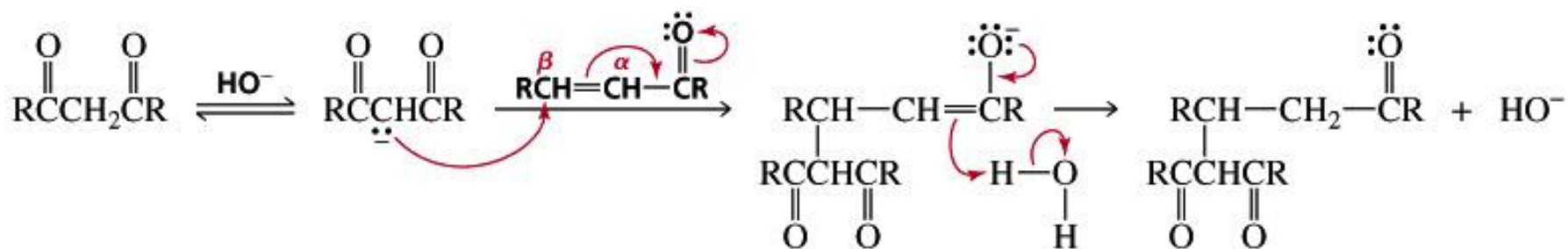


The Michael Addition

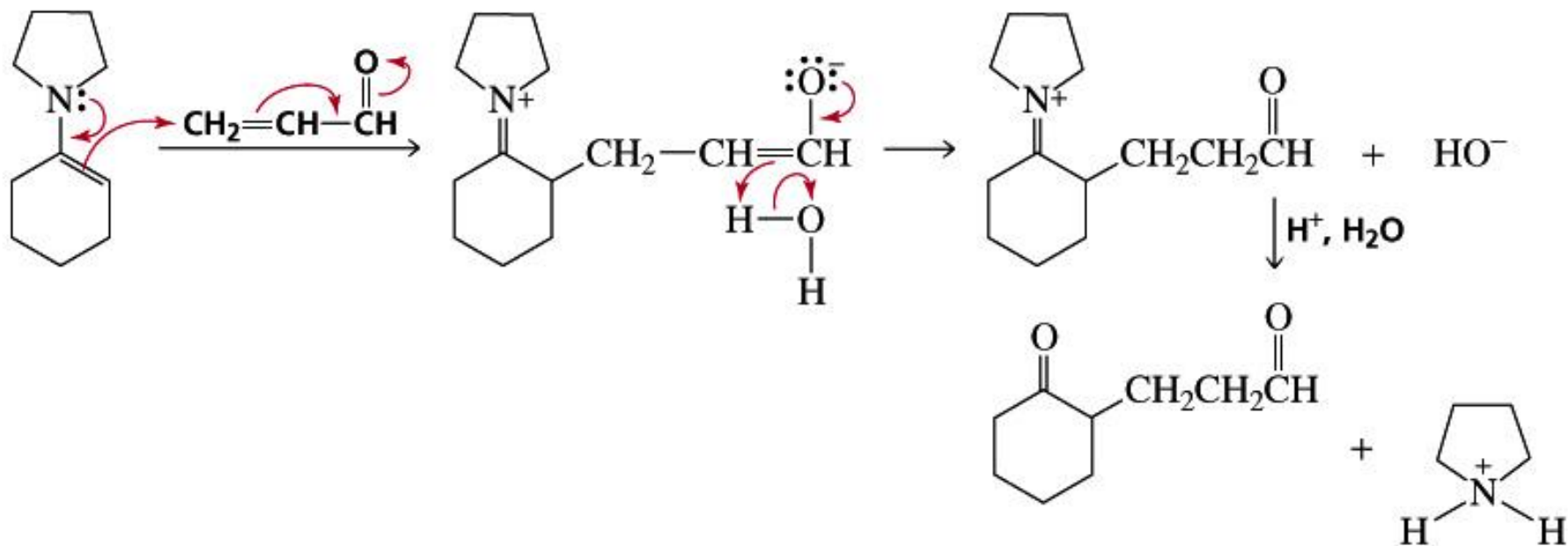




Mechanism of the Michael Reaction

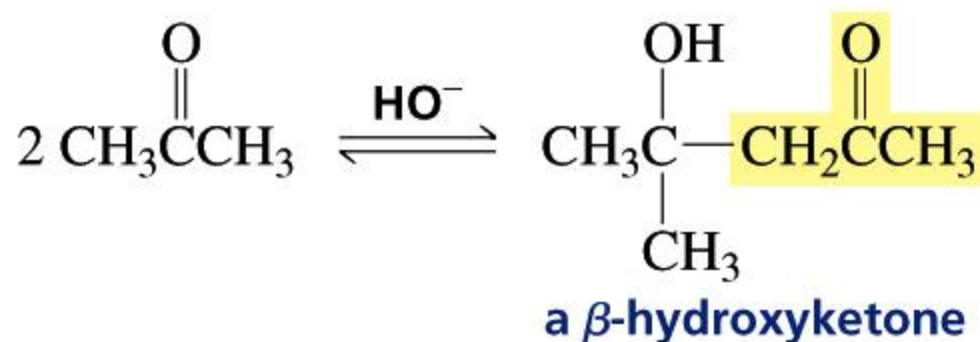
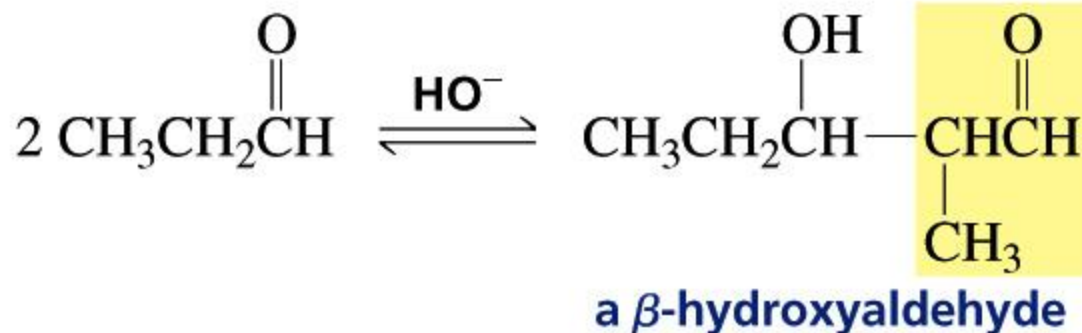


The Stork Enamine Reaction



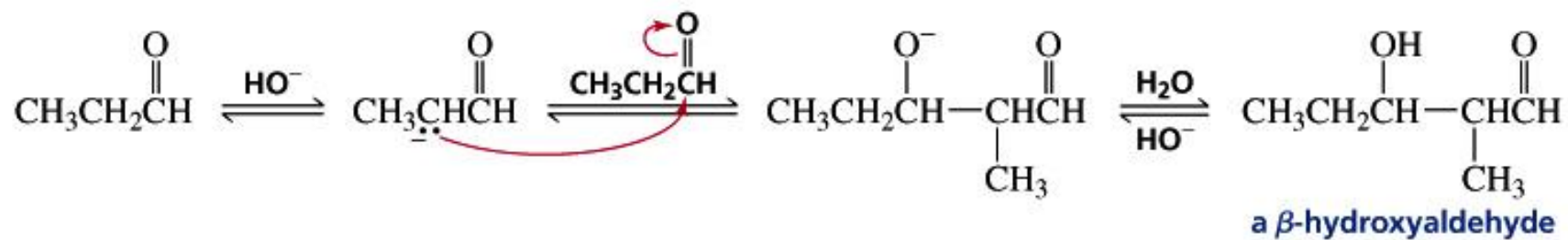
Enamines are used in place of enolates in Michael reactions

aldol additions

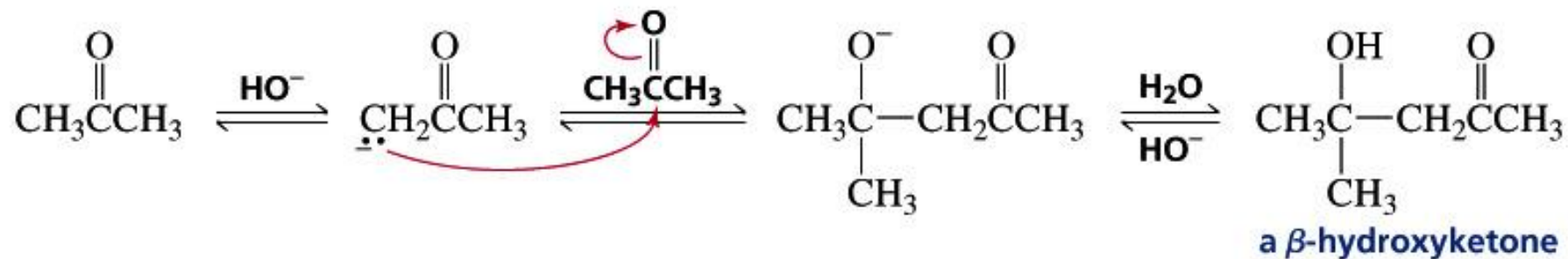


One molecule of a carbonyl compound acts as a nucleophile and the other carbonyl compound acts as an electrophile

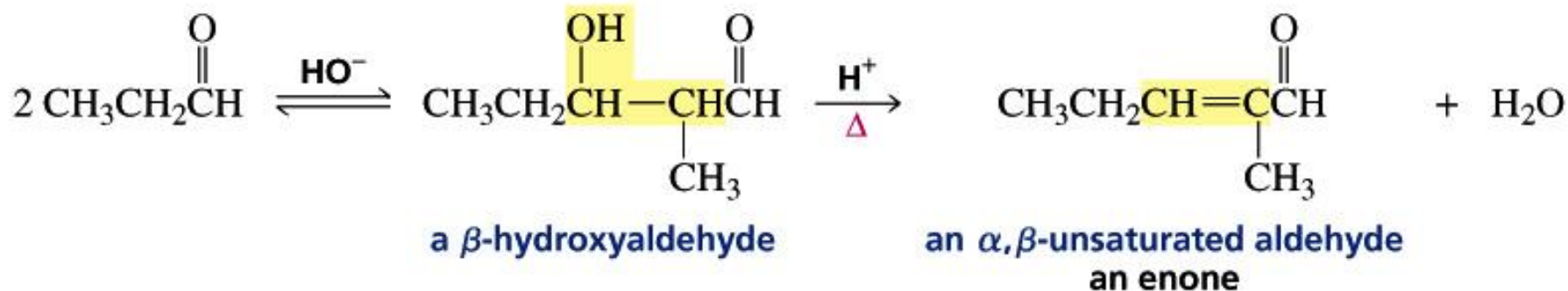
mechanism for the aldol addition

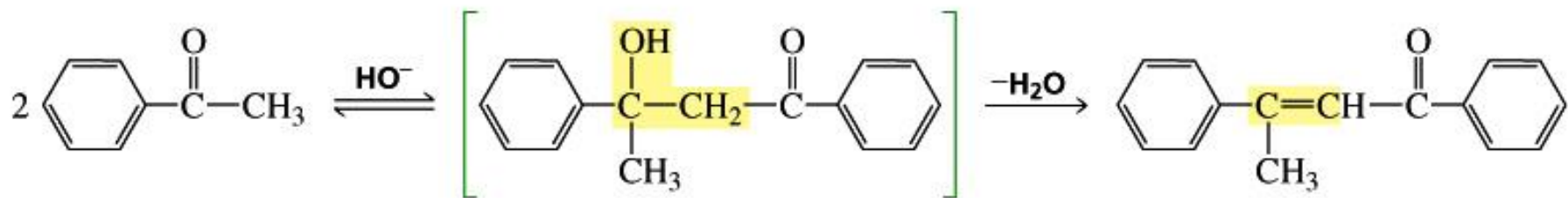


Ketones are less susceptible than aldehydes to attack by nucleophiles

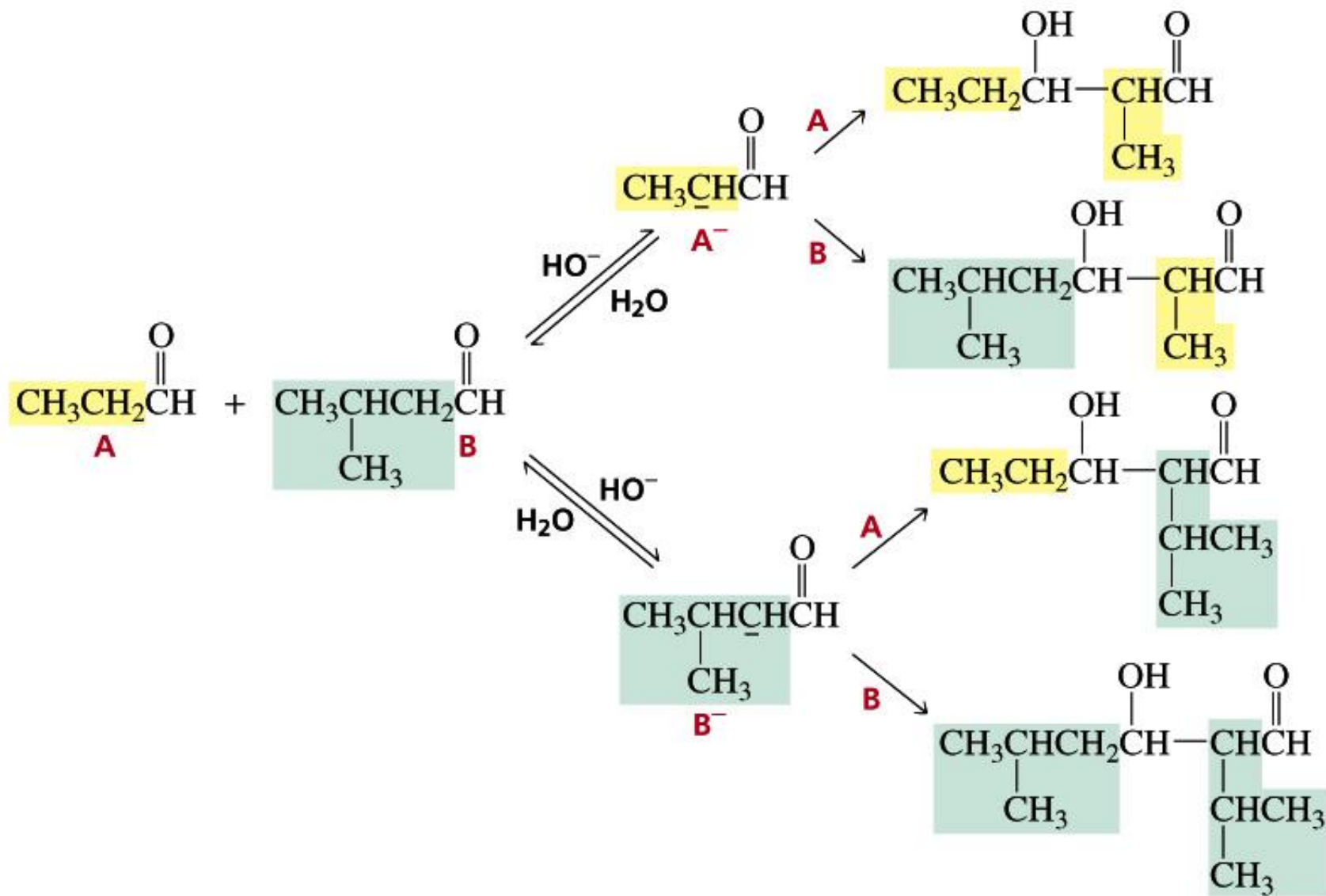


An aldol addition product loses water to form an aldol condensation product

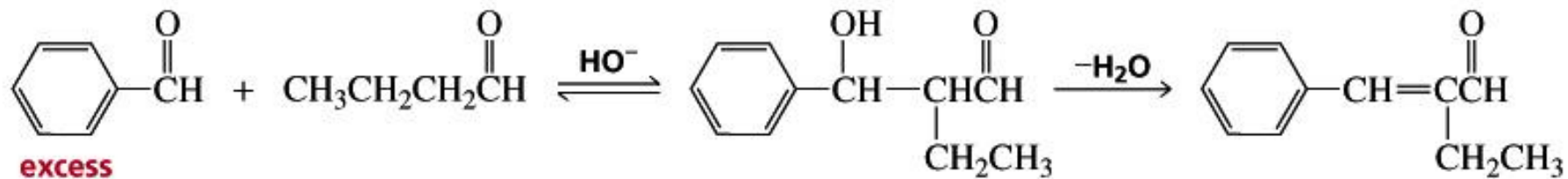




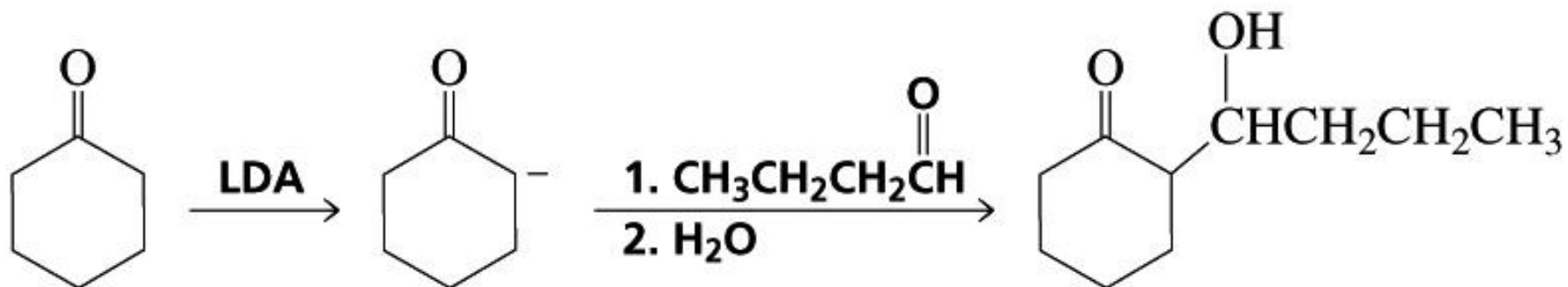
The Mixed Aldol Addition



One product will be formed if one of the carbonyl compounds does not have any α -hydrogen

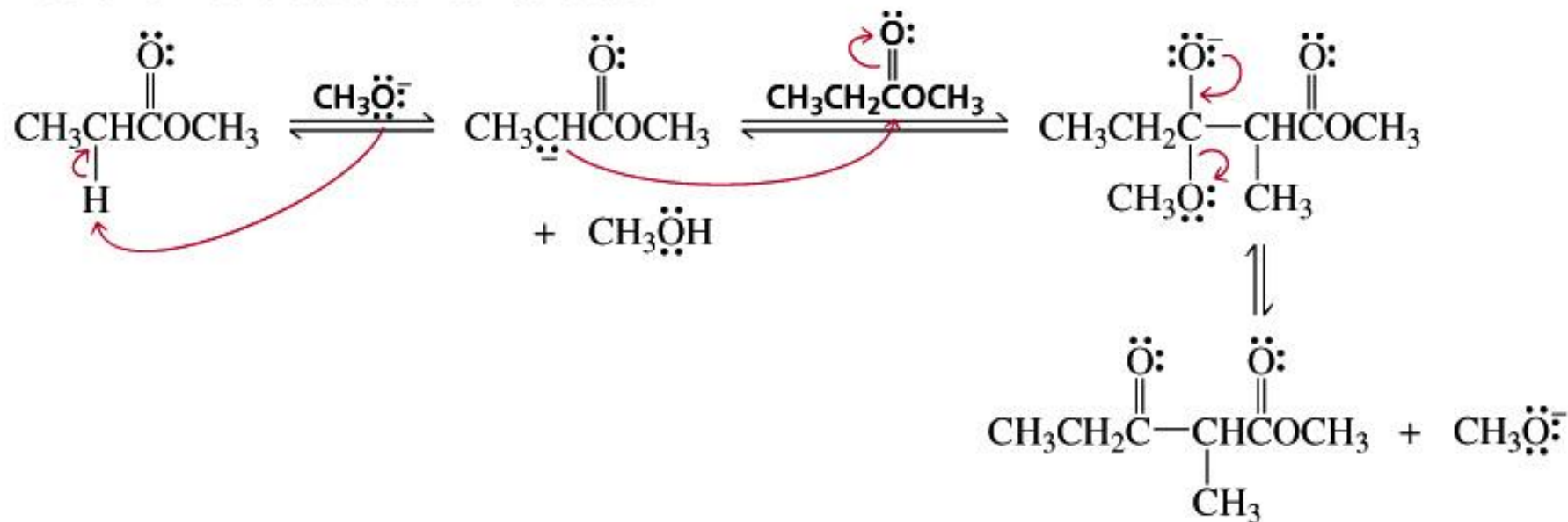


Primarily one product can be formed by using LDA to deprotonate one of the carbonyl compounds



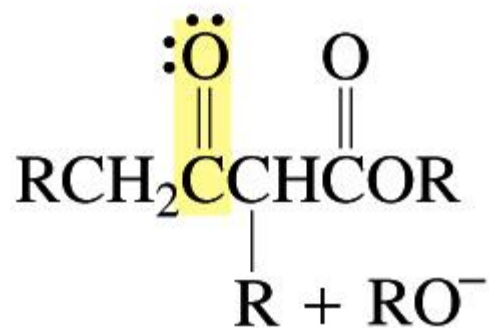
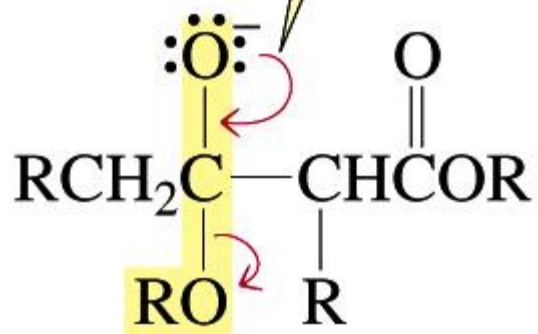
Condensation of Two Ester Molecules

mechanism for the Claisen condensation



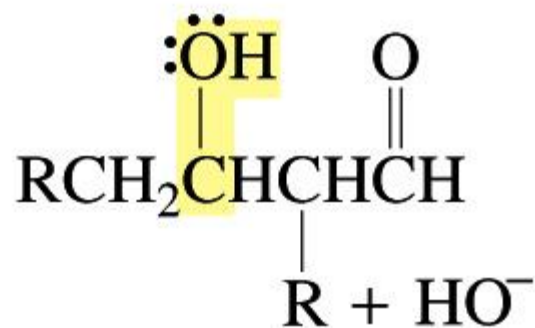
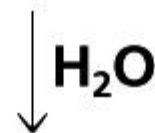
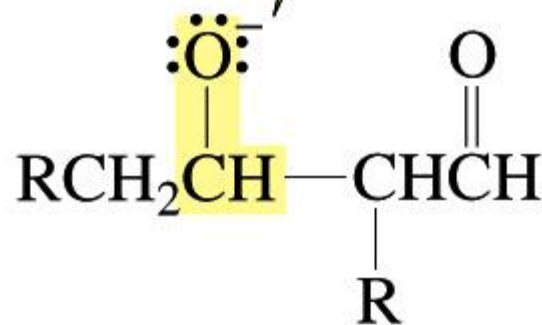
Claisen condensation

formation of a π bond
by expulsion of RO^-

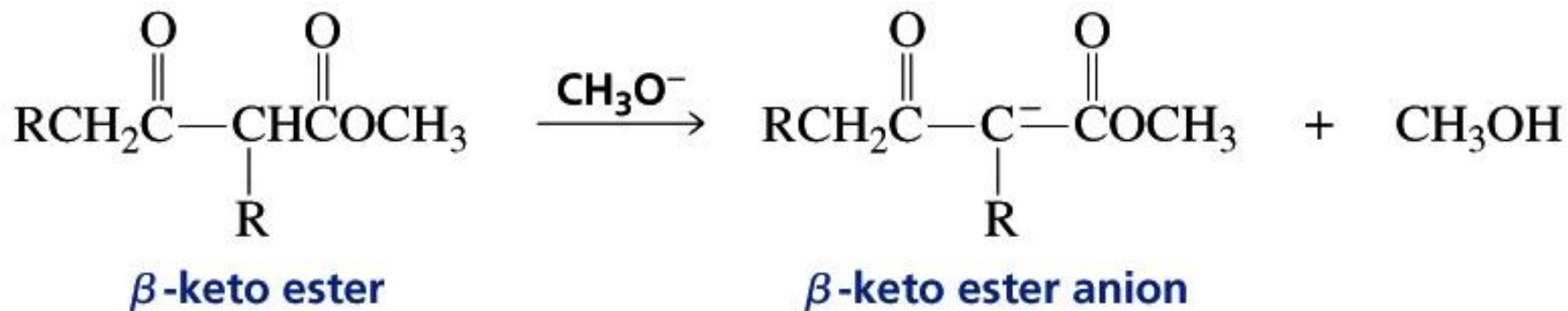
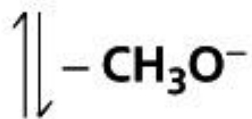
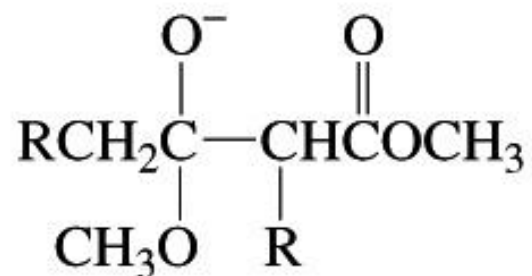


aldol addition

protonation of O^-

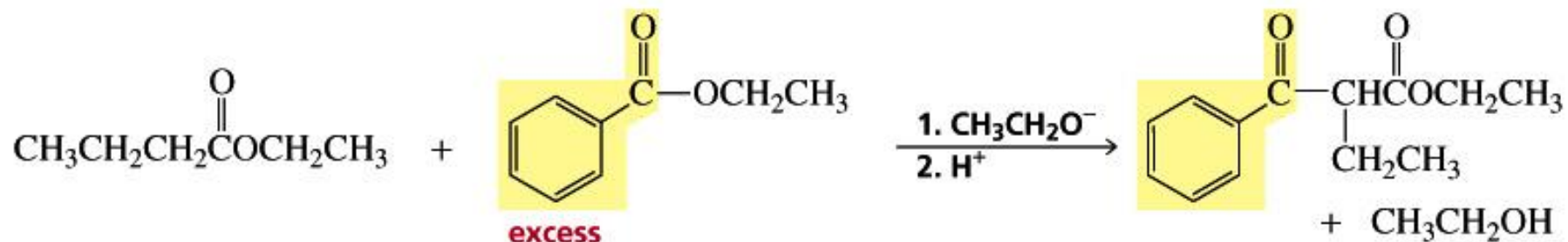


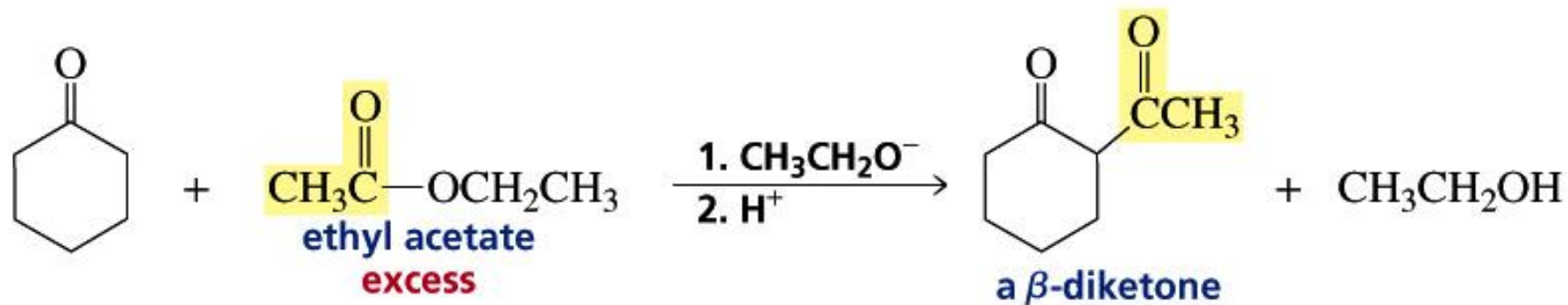
The reaction can be driven to completion by removal of a proton from the β -keto ester



The Claisen condensation requires an ester with two α -hydrogens and an equivalent amount of base

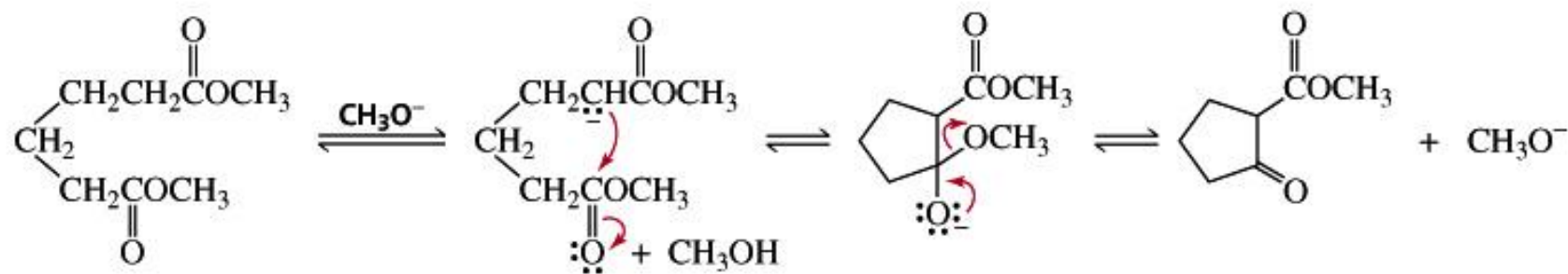
The Mixed Claisen Condensation



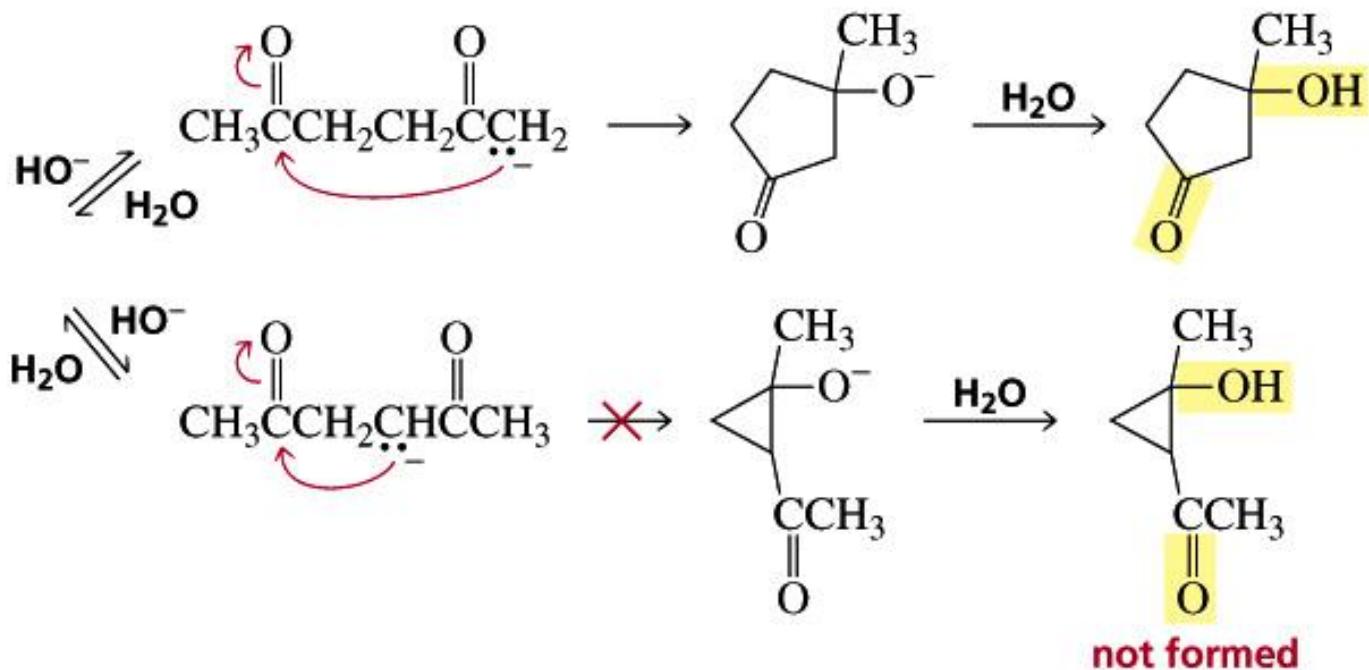
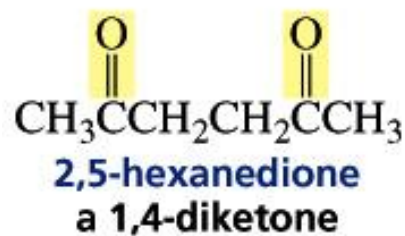


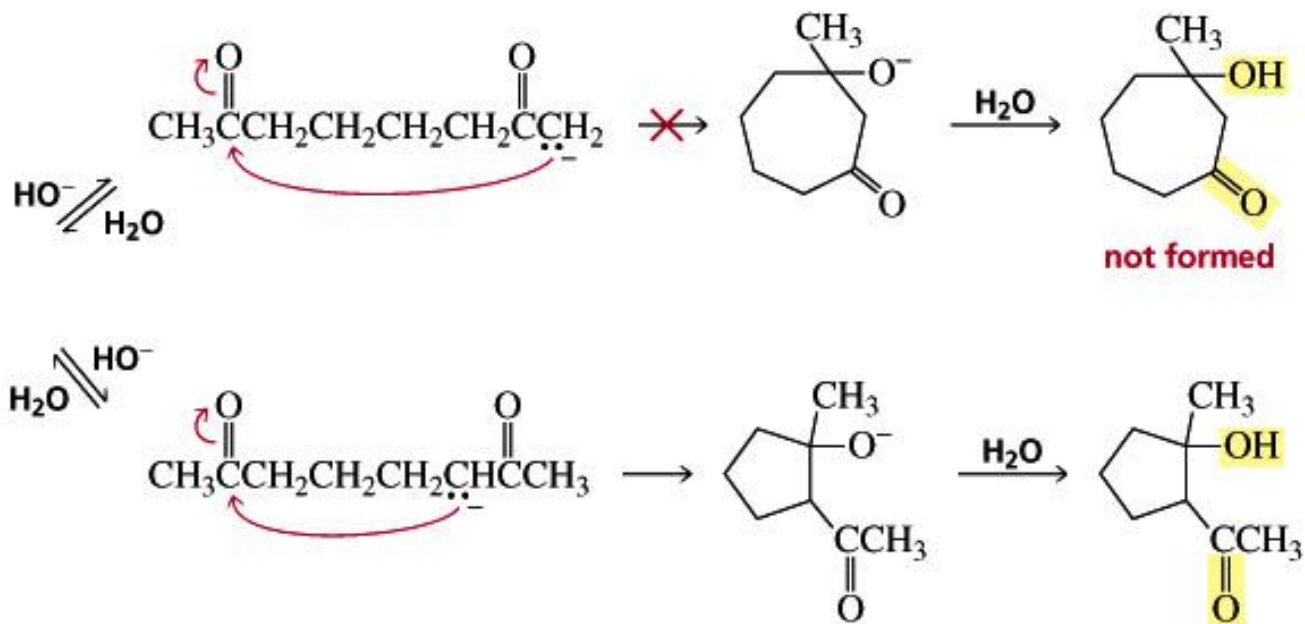
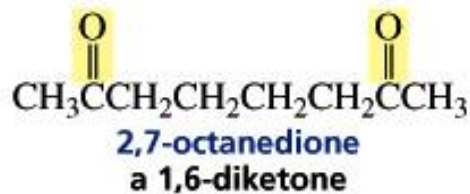
Because of the difference in the acidities of the α -hydrogens in the two carbonyl compounds, primarily one product is obtained

mechanism for the Dieckmann condensation

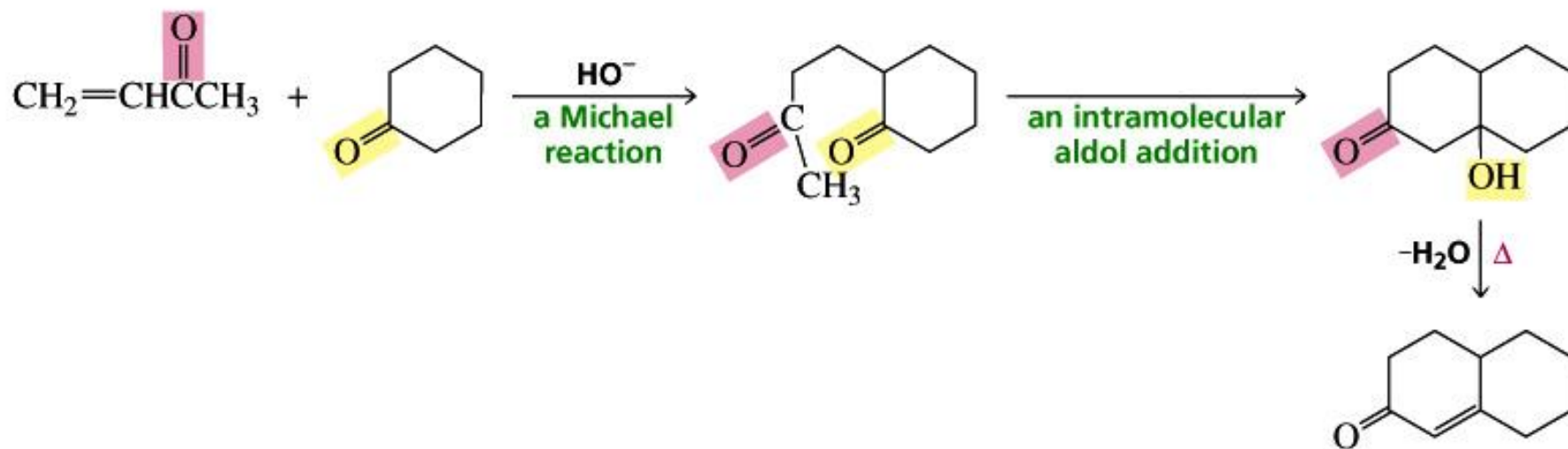


Intramolecular Aldol Additions



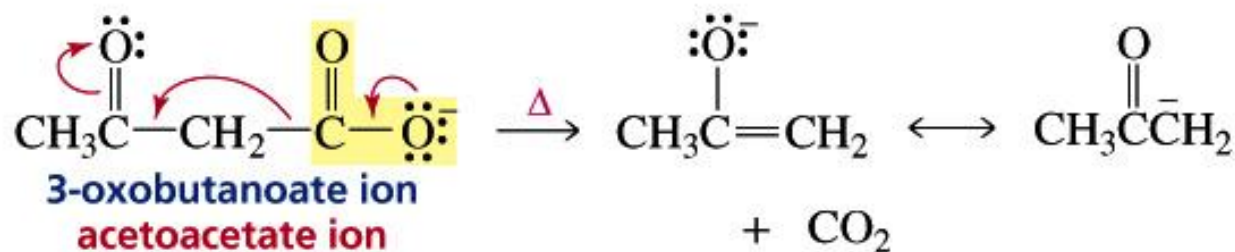


The Robinson Annulation

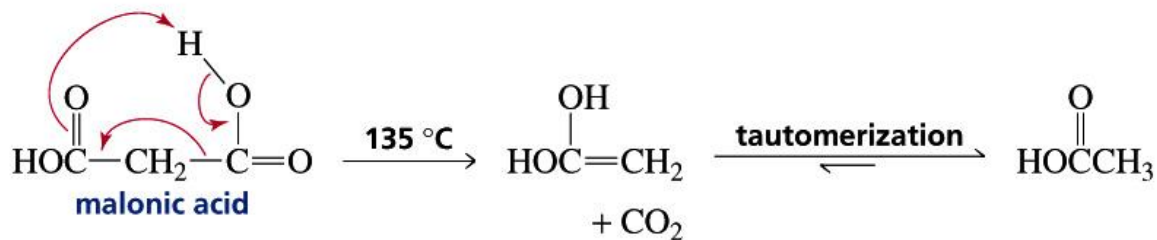
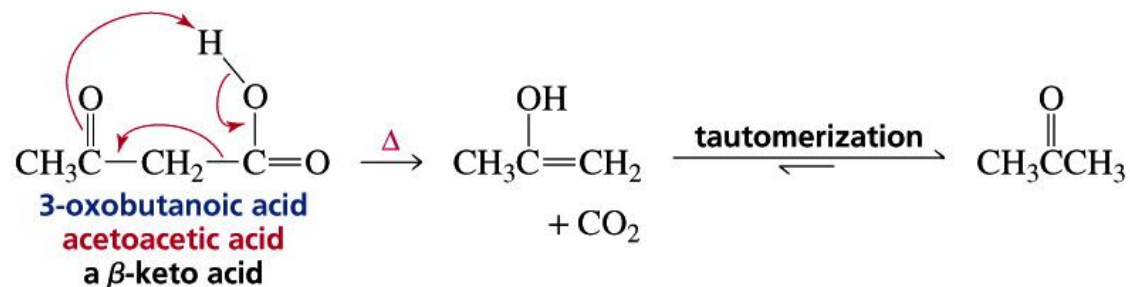


Decarboxylation of 3-Oxocarboxylic Acids

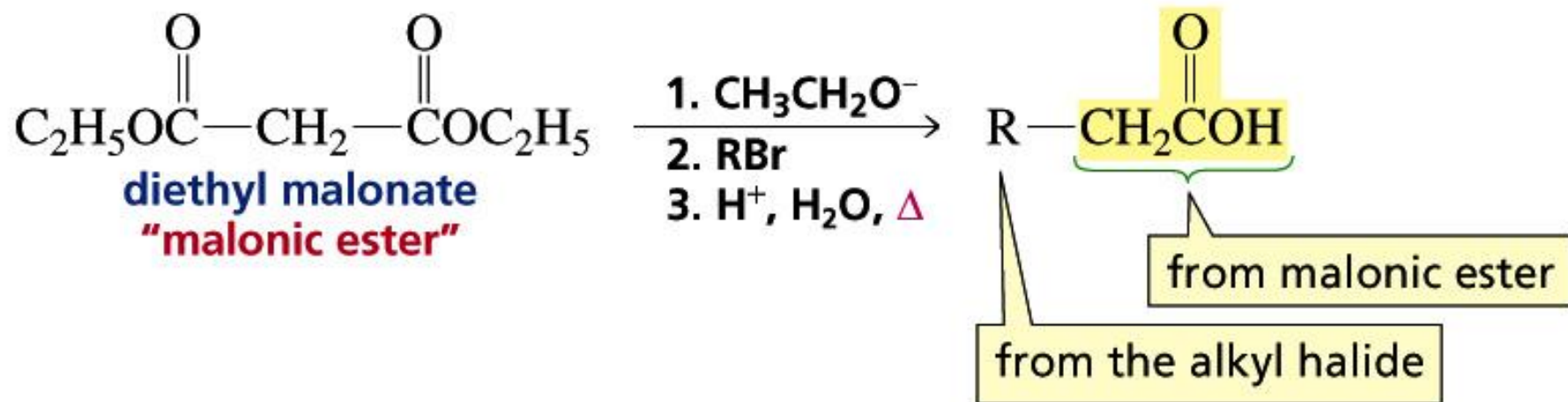
removing CO₂ from an α -carbon

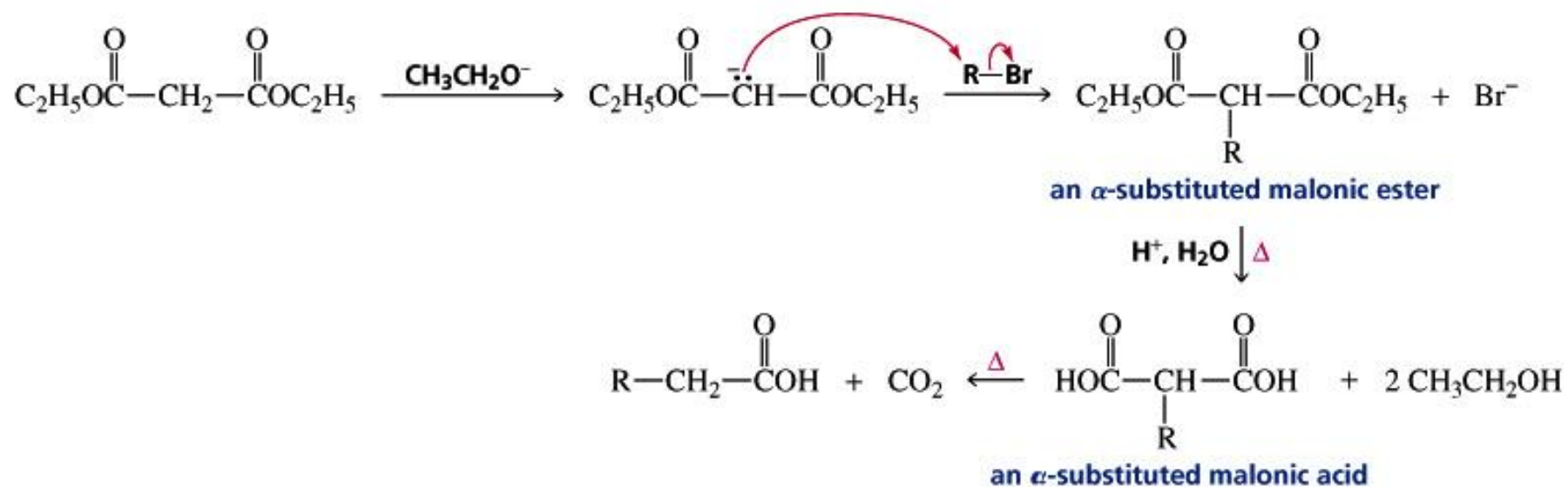


Acid catalyzes the intramolecular transfer of the proton

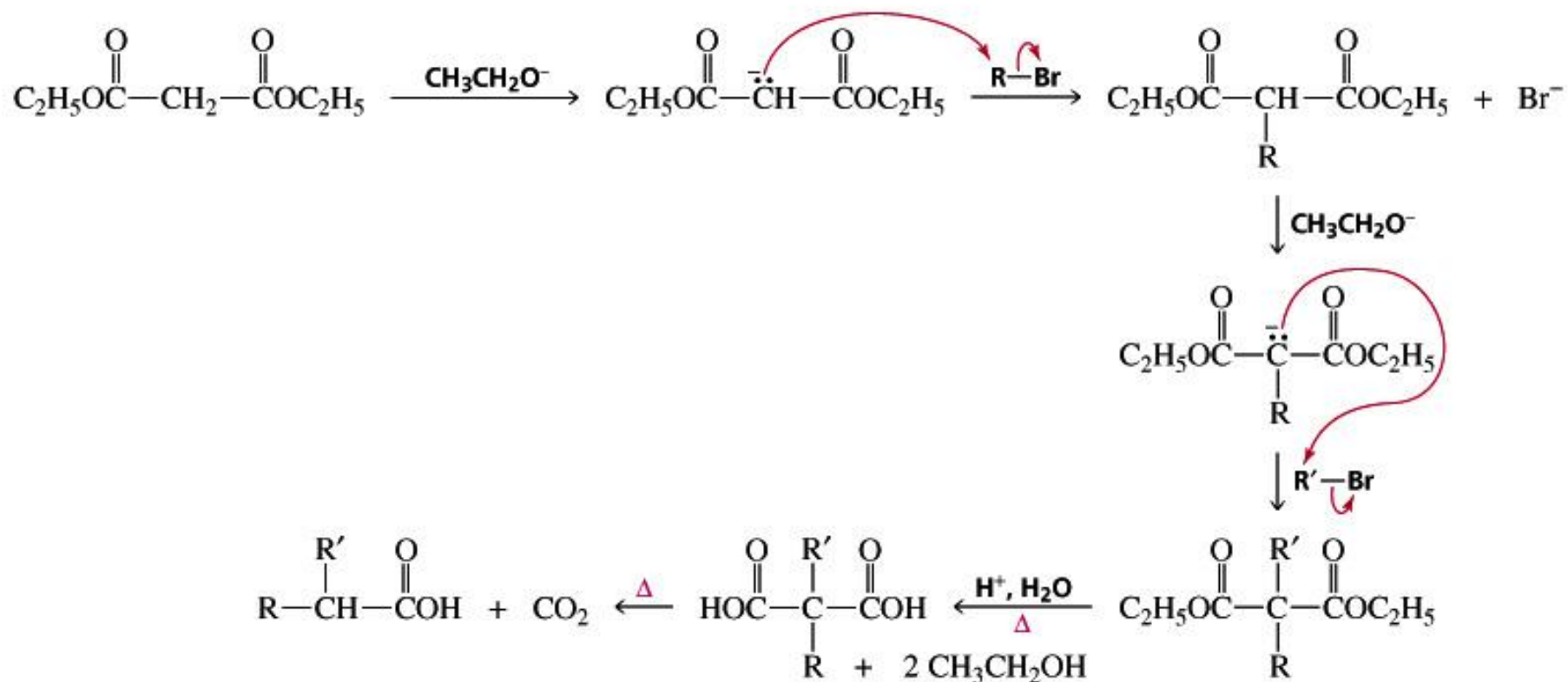


A malonic ester synthesis forms a carboxylic acid with two more carbon atoms than the alkyl halide

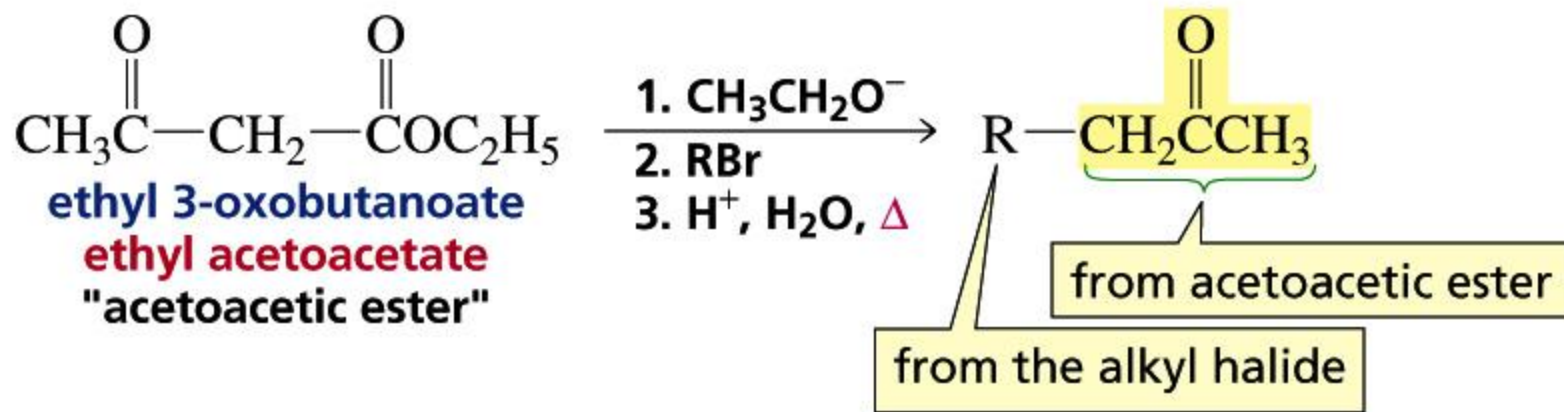


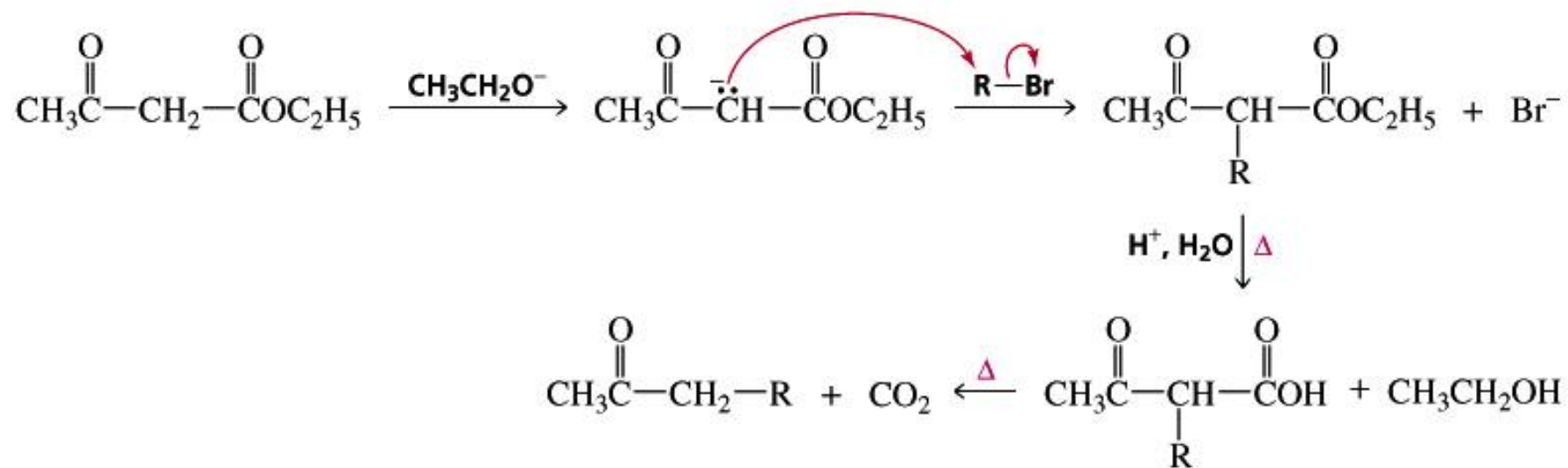


Preparation of Carboxylic Acids with Two Substituents Bonded to the α -Carbon

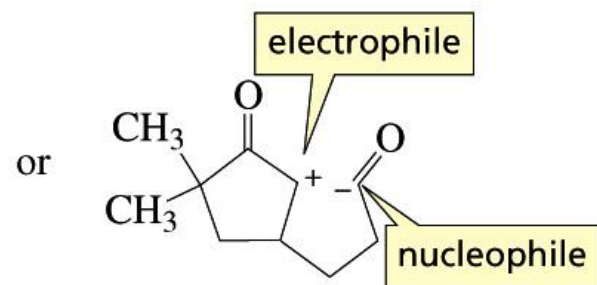
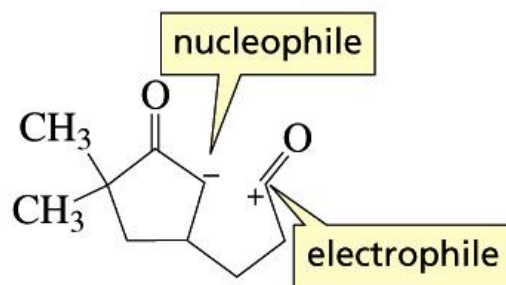
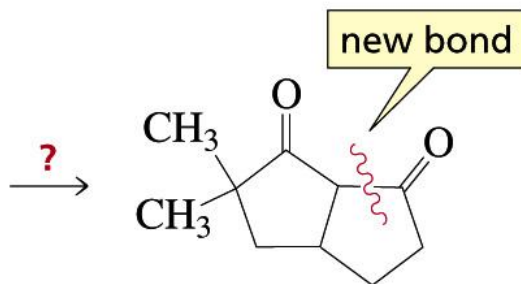
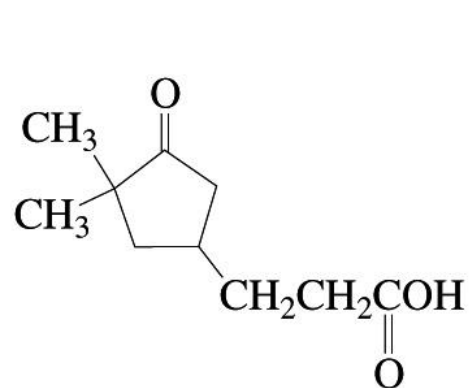


Synthesis of Methyl Ketone by Acetoacetic Ester Synthesis

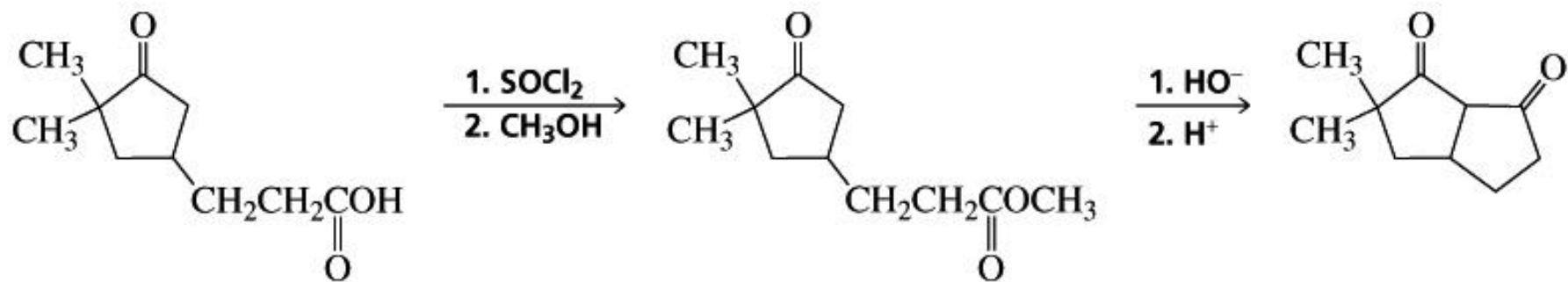




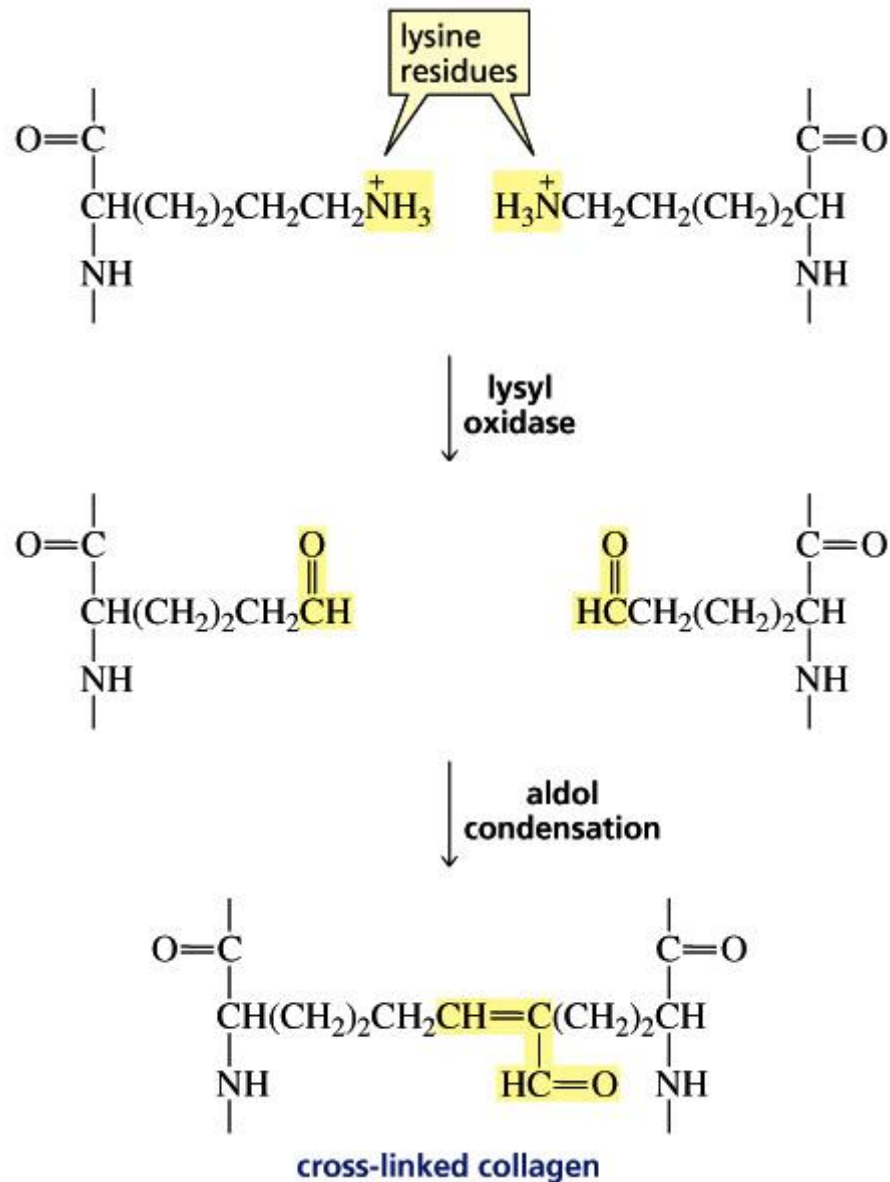
Designing a Synthesis to Make New Carbon–Carbon Bonds



Preparation of the Ester



A Biological Aldol Condensation



A Biological Claisen Condensation

