

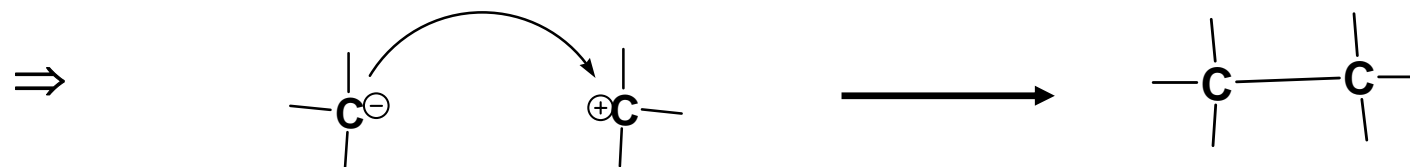
Chapter 20 Enolates / other Carbanions

C-C bond formation is very important

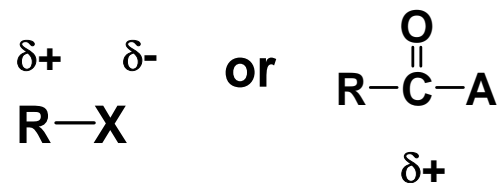
⇒ larger, more complex organic molecule can be made from smaller ones

How?

carbon nucleophile + carbon electrophile



Carbon electrophile:

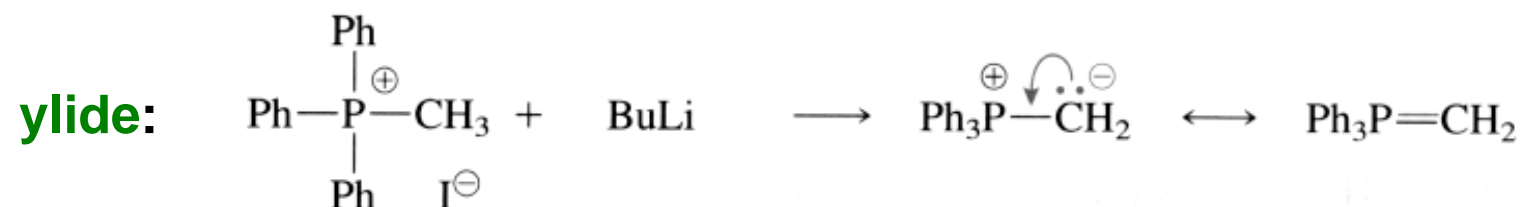
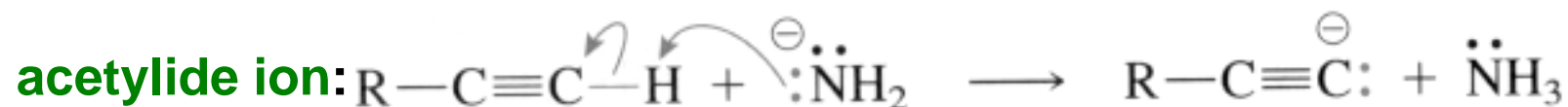


⇒ abundant

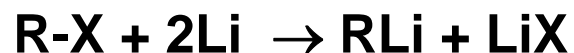
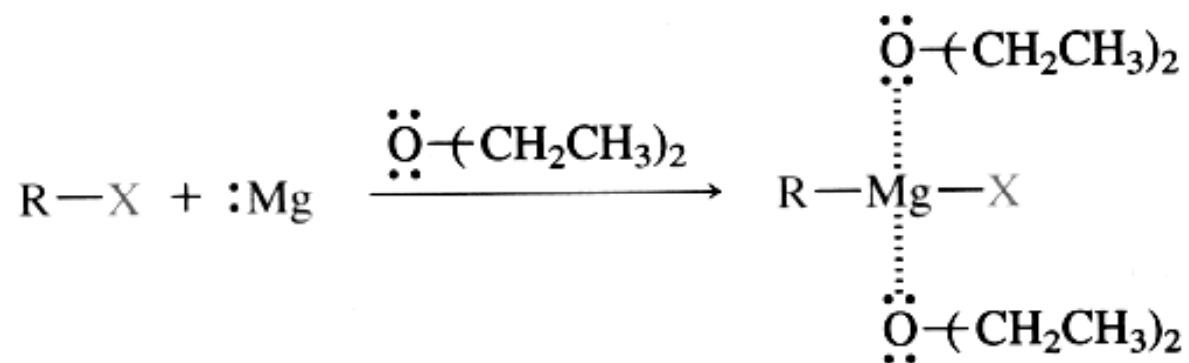
How about carbon nucleophile?

⇒ **limited**

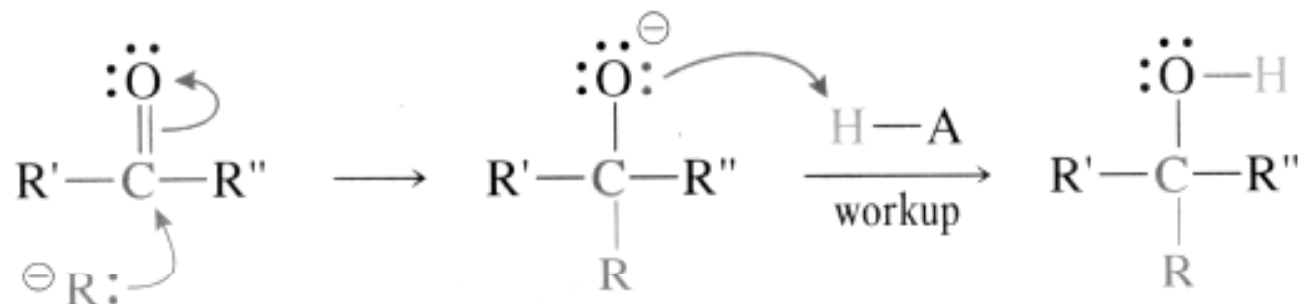
Ex) cyanide ion: $M^+ \text{ } ^- \text{CN}$



Grignard reagent and organo metallic compound:

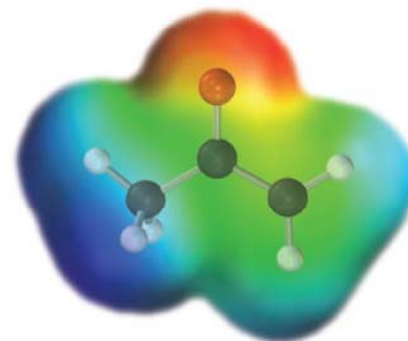
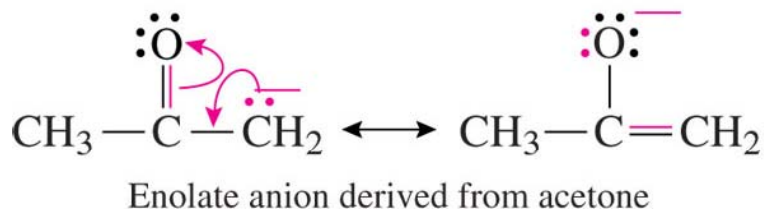


⇒ Grignard reagent and organometallic compound are not useful for S_N2 reactions because they are too reactive.

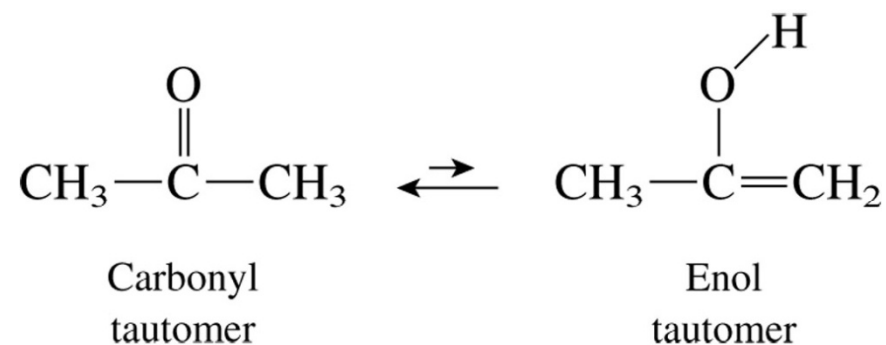


For the S_N2 enolates are used

Because they are not as reactive as organometallic compounds, then C-C bond through S_N2 can be formed



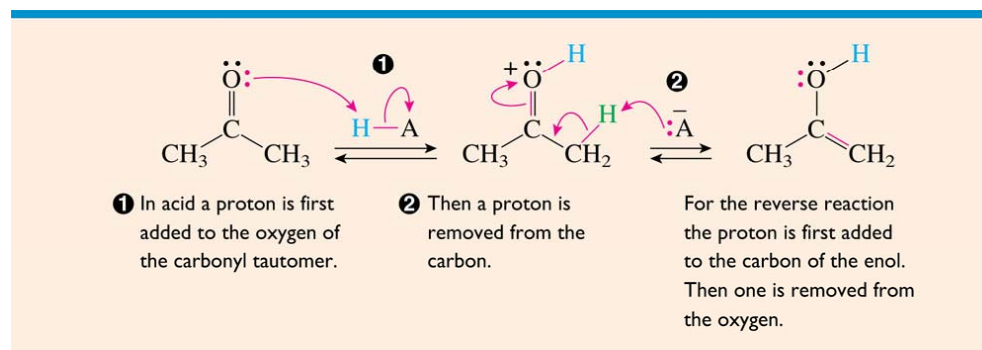
20.1 Enols and Enolate Anions



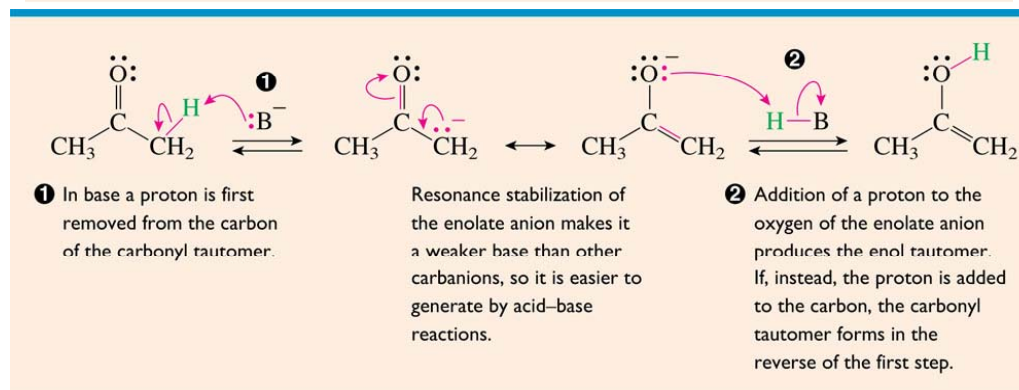
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⇒ both are possible under acidic and basic conditions

In acidic condition

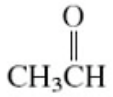
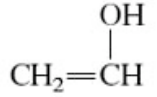
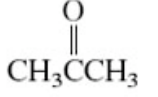
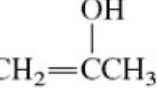
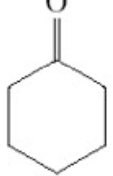
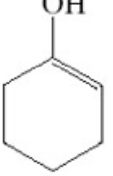
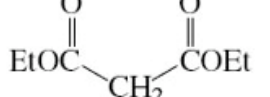
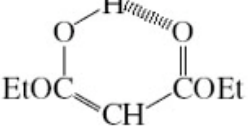
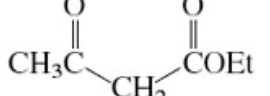
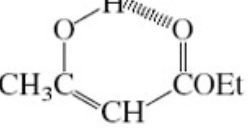
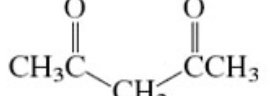
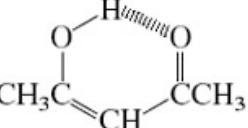


In basic condition



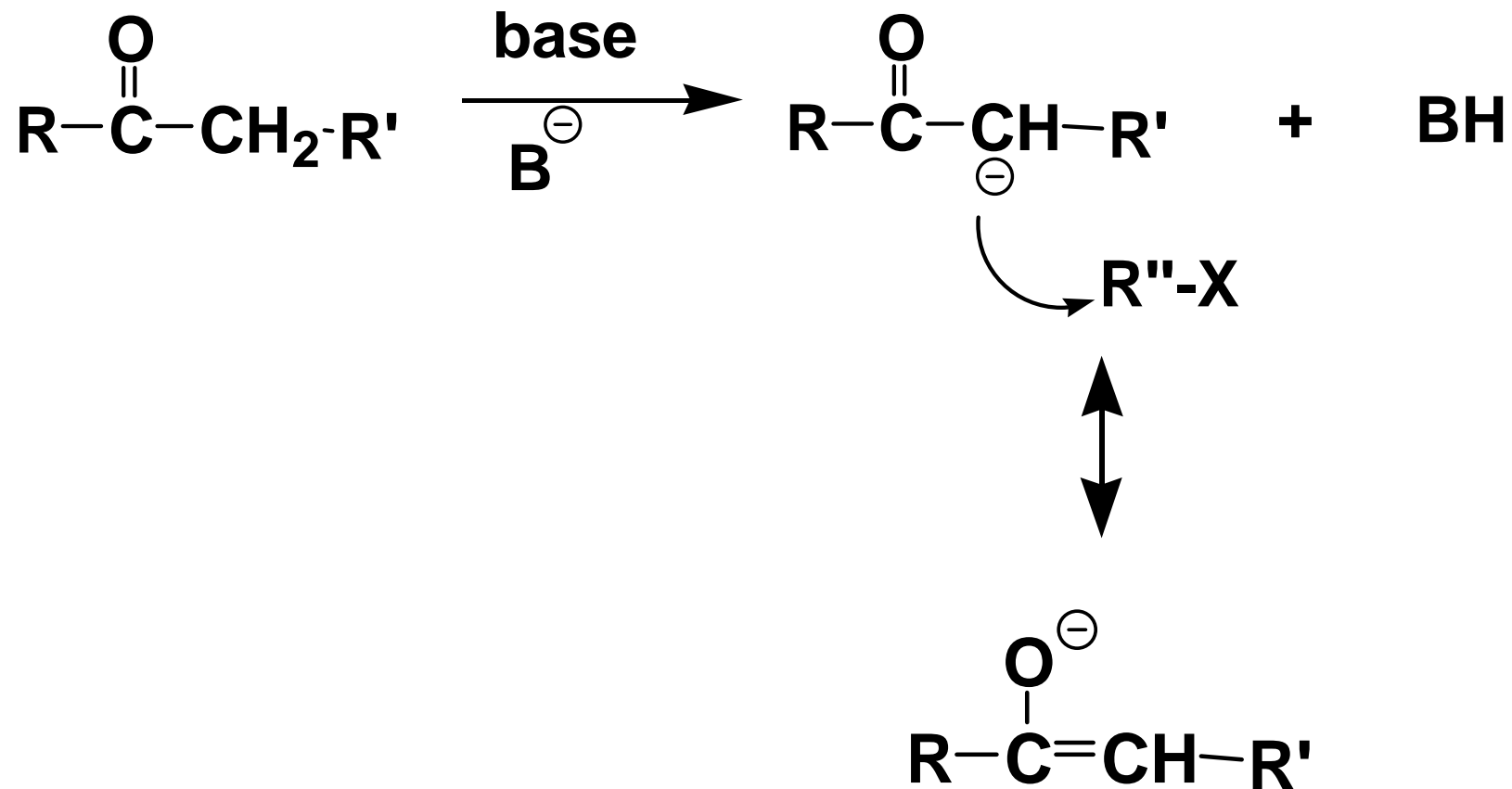
Equilibrium constants of carbonyl and enol tautomers for base condition

Table 20.1 Equilibrium Constants for Carbonyl-Enol Tautomerization

Carbonyl Tautomer	Enol Tautomer	$K = \frac{[\text{Enol}]}{[\text{Carbonyl}]}$	Enol Present
		6×10^{-7}	0.00006%
		5×10^{-9}	0.0000005%
		1×10^{-8}	0.000001%
		8×10^{-5}	0.008%
		9×10^{-2}	8%
		3	76%

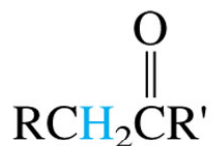
Higher value for α, ω -dicarbonyl compounds
diketone > ketoester > diester

What kinds of base can we use?

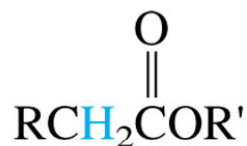


Use base whose pK_a s of conjugate acids are greater than those of the carbonyl base !

For



Ketone
(or aldehyde)
 $\text{p}K_a = 20$



Ester
 $\text{p}K_a = 25$



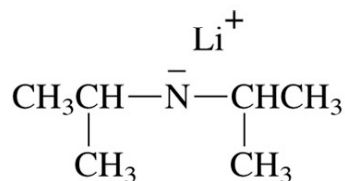
Nitrile
 $\text{p}K_a = 25$

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Use compounds whose $\text{p}K_a$ s of conjugate acids are greater than 30 such as



Sodium amide
 $\text{p}K_a = 38$



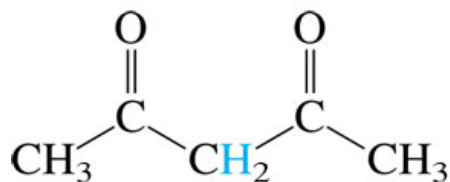
Lithium diisopropylamide
(LDA)
 $\text{p}K_a = 38$



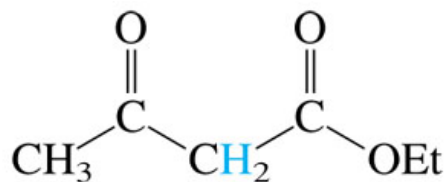
Sodium hydride
 $\text{p}K_a = 35$

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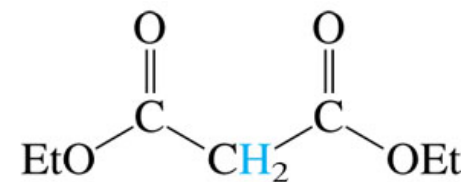
For



2,4-Pentanedione
 $\text{p}K_a = 9$



Ethyl acetoacetate
 $\text{p}K_a = 11$



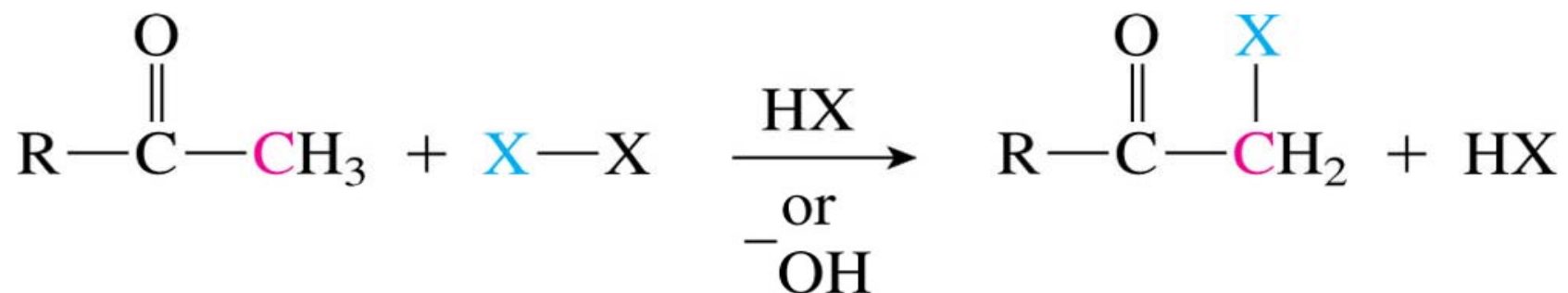
Diethyl malonate
 $\text{p}K_a = 13$

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Ethoxide can be used ($\text{p}K_a \sim 16$)

20.2 Halogenation of the α -Carbon

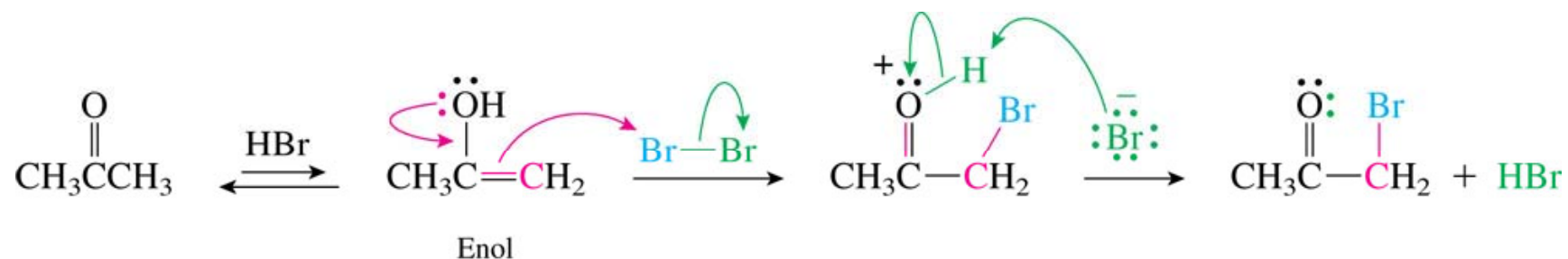
The reaction of an aldehyde or ketone with Cl_2 , Br_2 , or I_2 , under either acid or basic condition



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Both acidic and basic conditions can be used

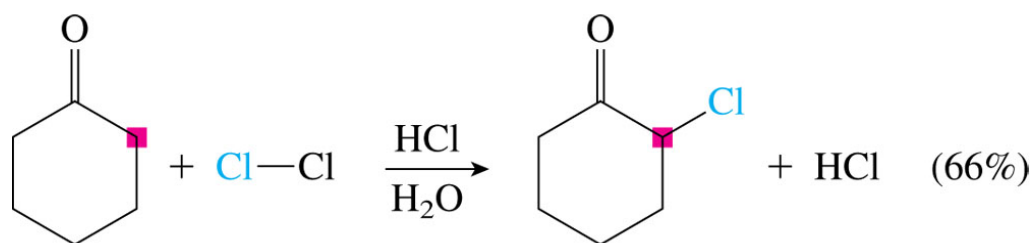
Under acidic conditions



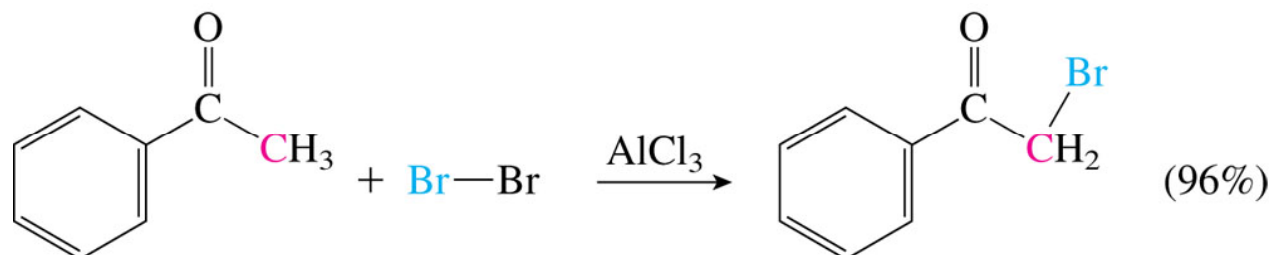
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The presence of the halogens retards the enolation, so the addition of single halogen is possible

Examples

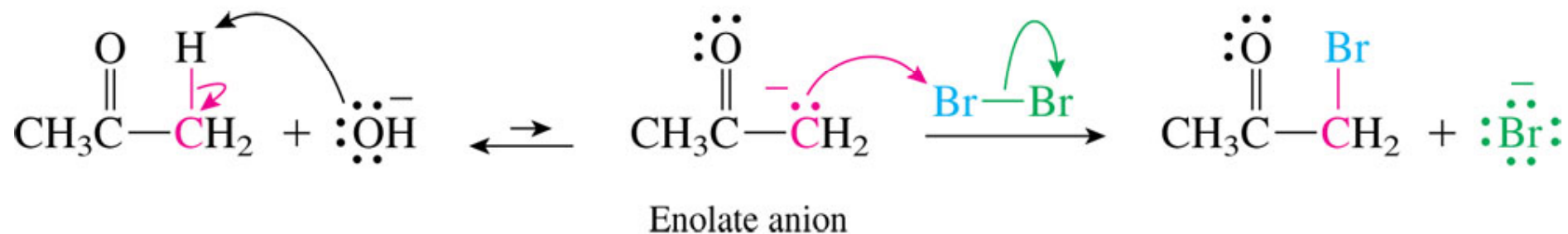


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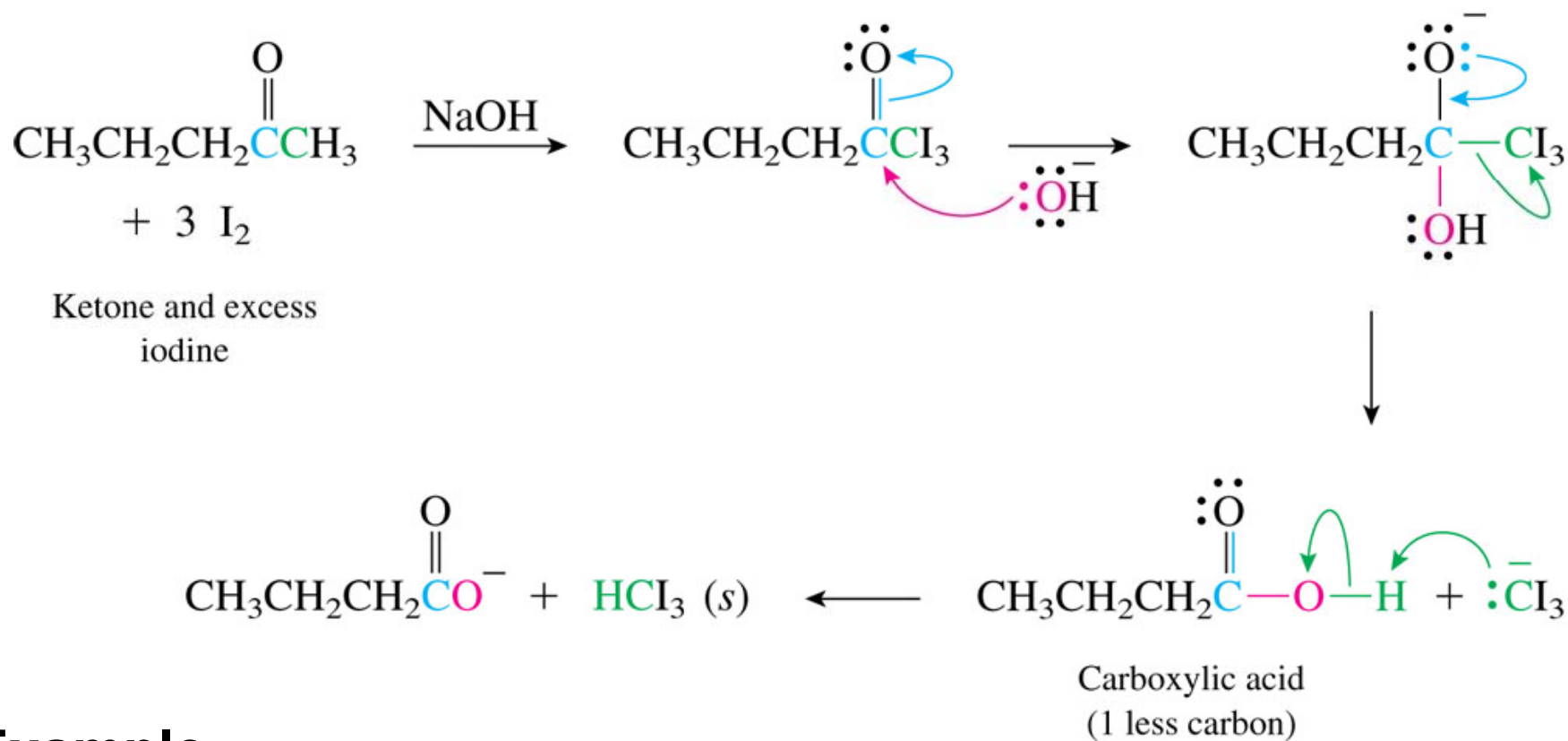
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Under basic conditions



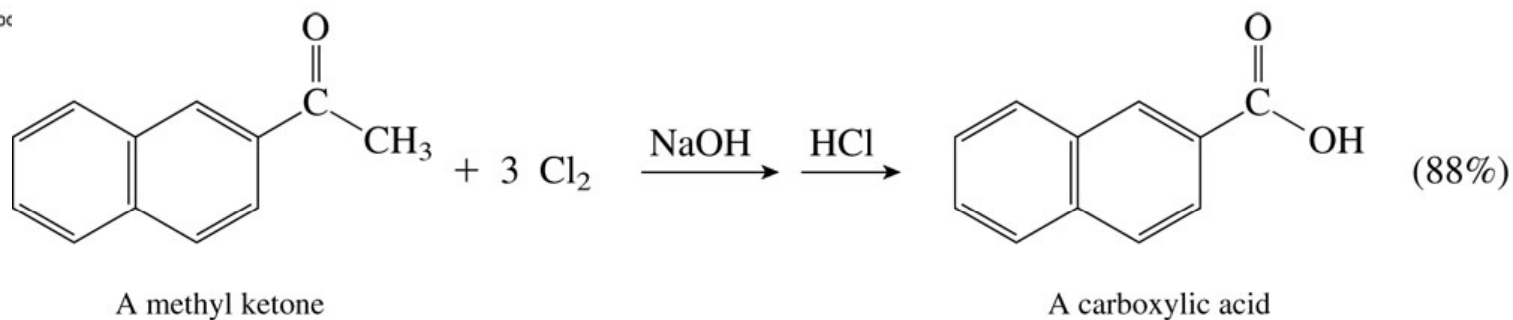
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Haloform Reaction (Iodoform Reaction)



Example

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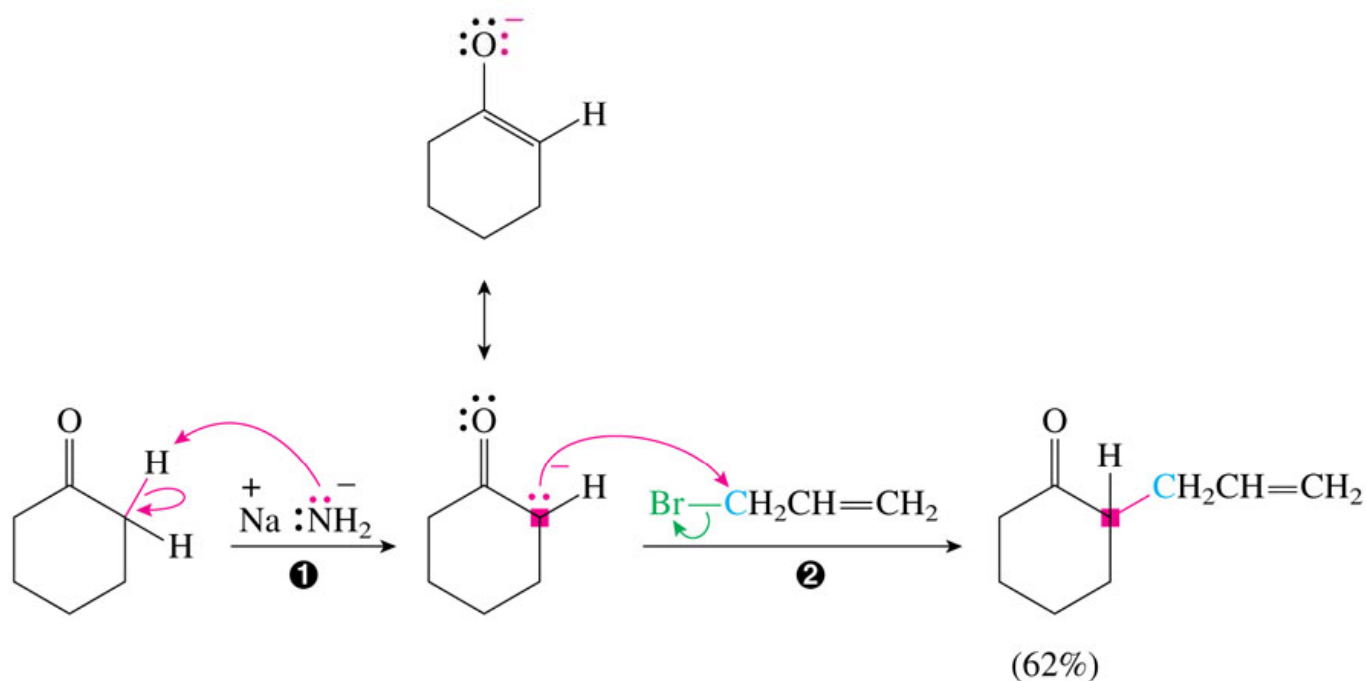


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20.3 Alkylation of Enolate Anions

⇒ Enolates from esters, ketones, and nitriles can be used in S_N2 reactions (alkylations).

Ex)



❶ A strong base must be used to ensure complete deprotonation in this step. The solvent must not have any acidic hydrogens. An ether (diethyl ether, DME, THF, dioxane) or DMF is commonly used.

❷ Because this is an S_N2 reaction, it works only when the leaving group is attached to an unhindered carbon (primary or secondary). When the leaving group is attached to a tertiary carbon, E2 elimination occurs rather than substitution.

⇒ Aldehydes cannot be used in such reactions because they are too reactive (side reactions)

1. Reactions with base

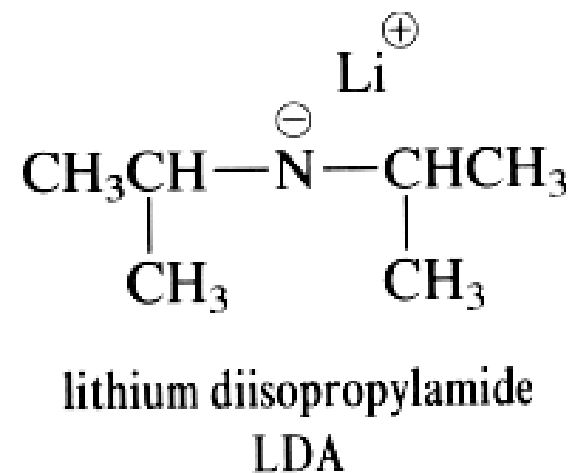


2. Reactions with themselves: Aldol condensation

(later)

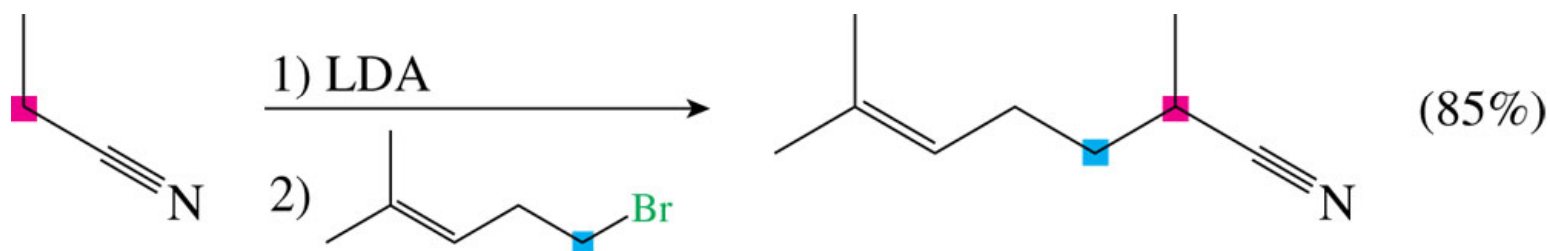
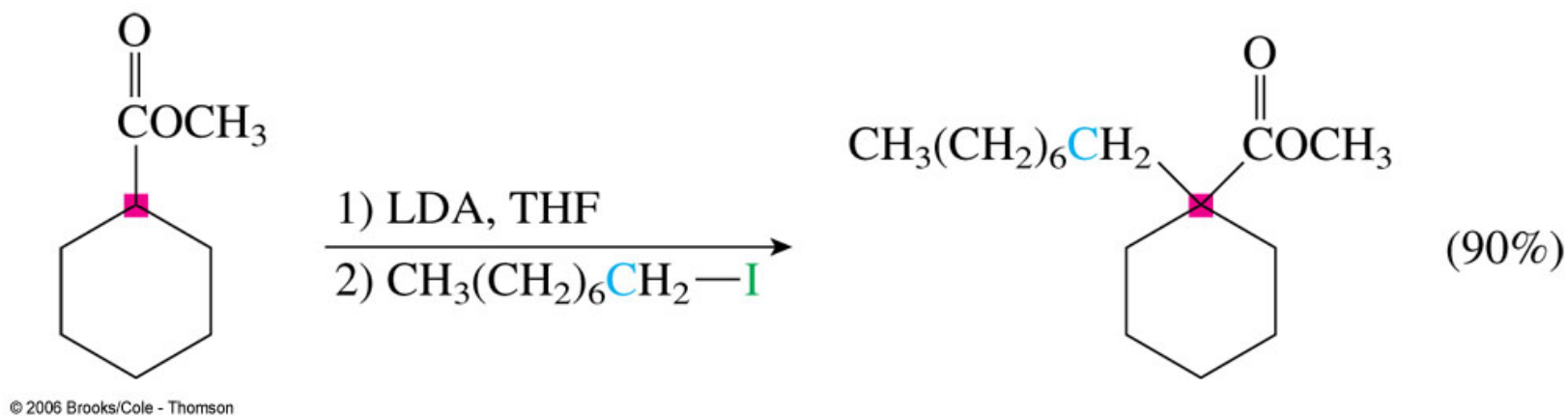
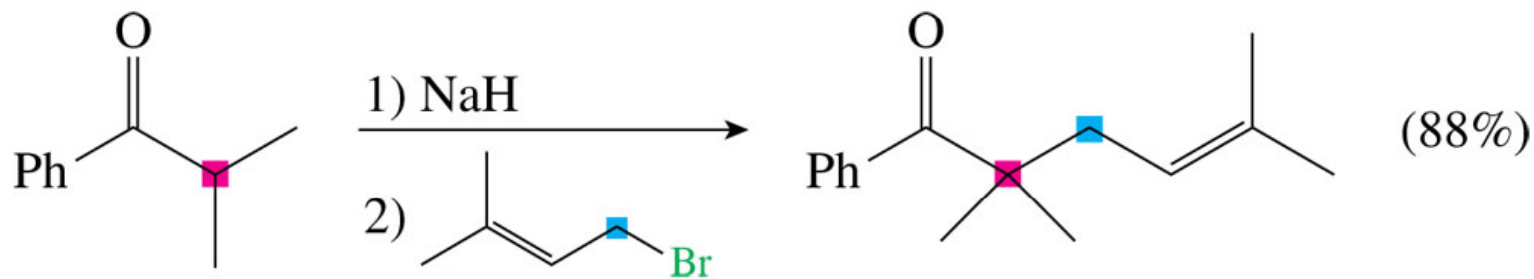
LDA: lithium diisopropylamide

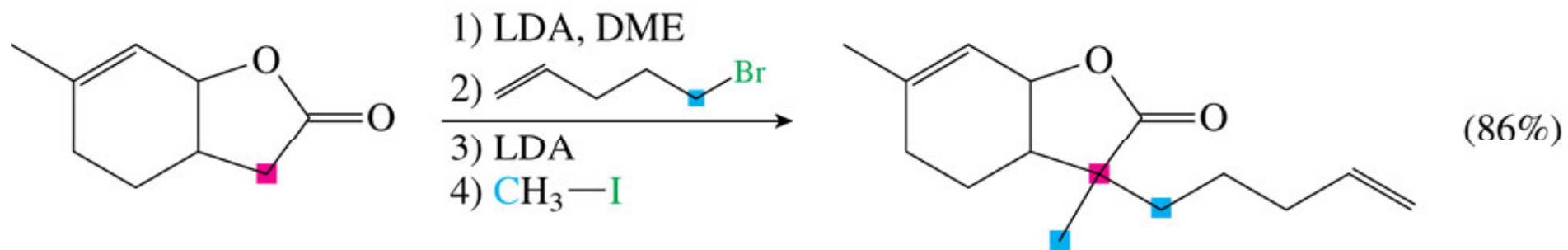
⇒ It is a very strong base but not very nucleophilic due to the steric hindrance



To avoid the formation of two products, deprotonation of the **ketones must produce a single enolate ion.**

Examples





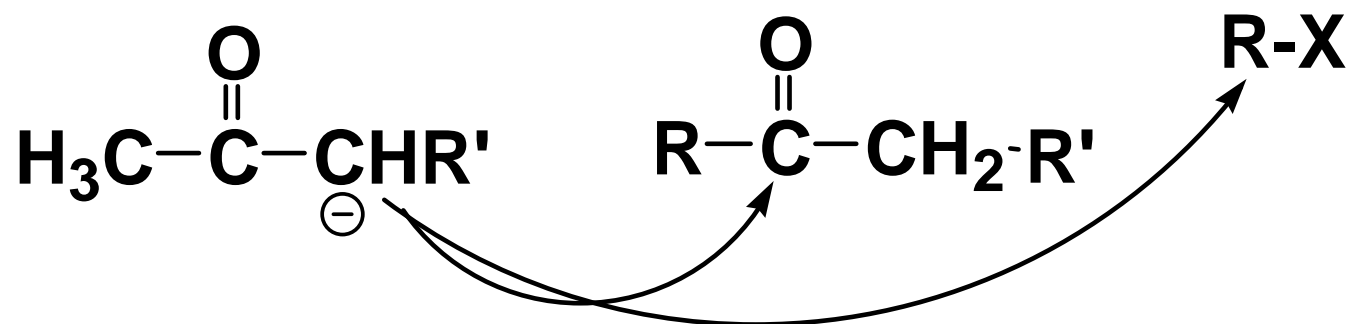
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20.4 Alkylation of More Stabilized Anions

Strong nucleophiles are normally strong bases, then many side reactions are possible.

1. Elimination

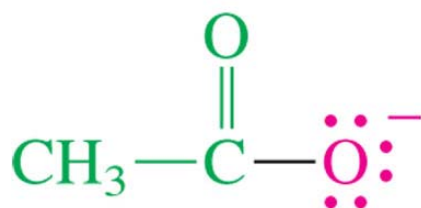
2. Unwanted substitution



Therefore we might need to use less nucleophilic enolates,

Then we might need more steps to, still the yield can be higher due to less side reaction.

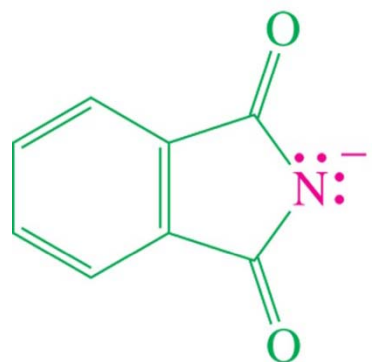
Example



is the synthetic equivalent of



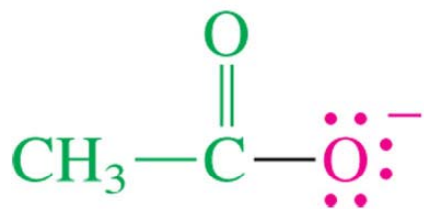
Ch 10.2



is the synthetic equivalent of



Ch 10.6

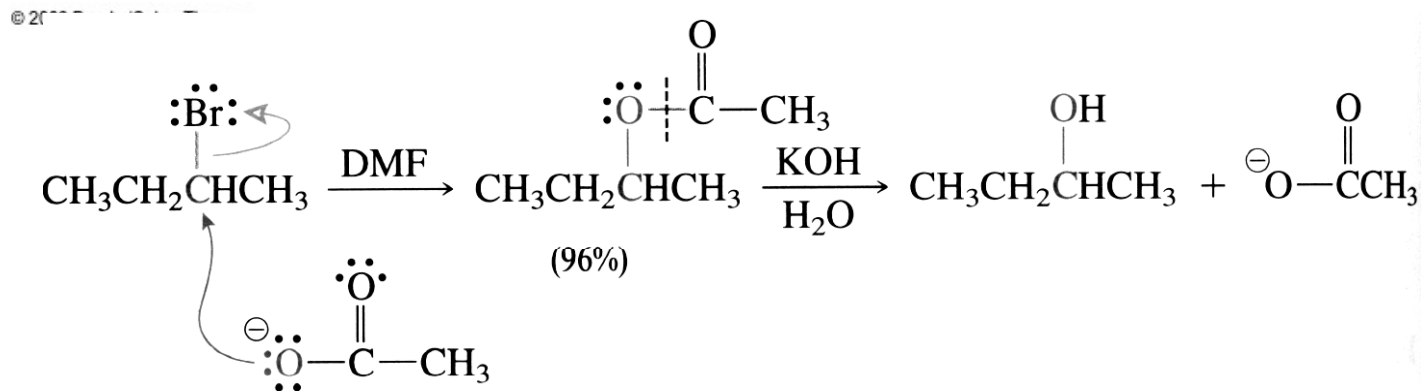
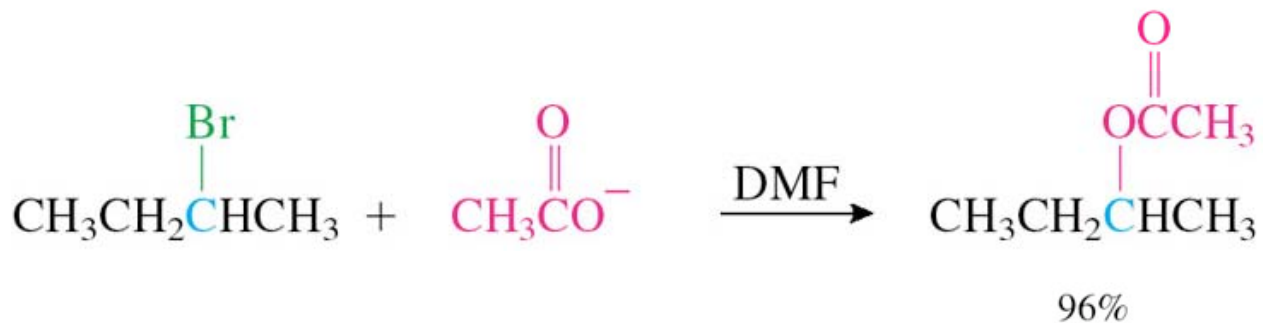
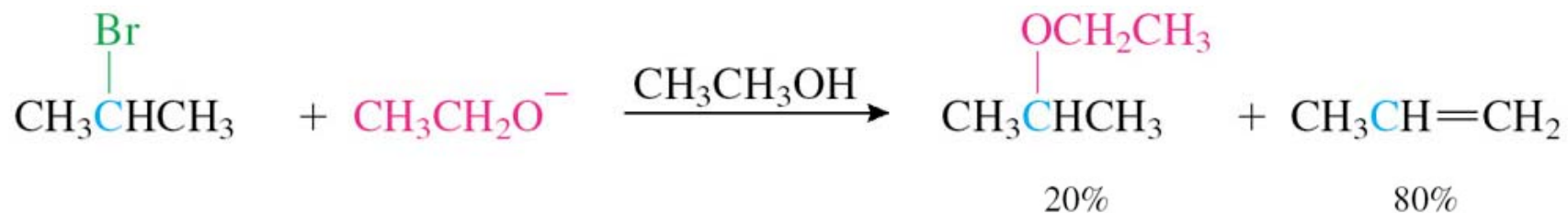


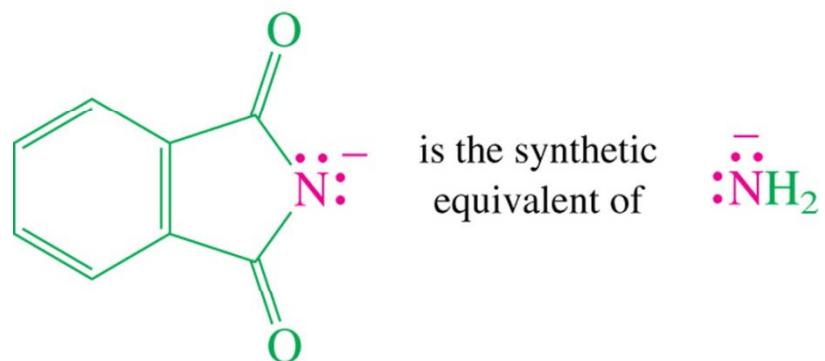
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is the synthetic
equivalent of

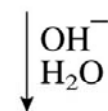
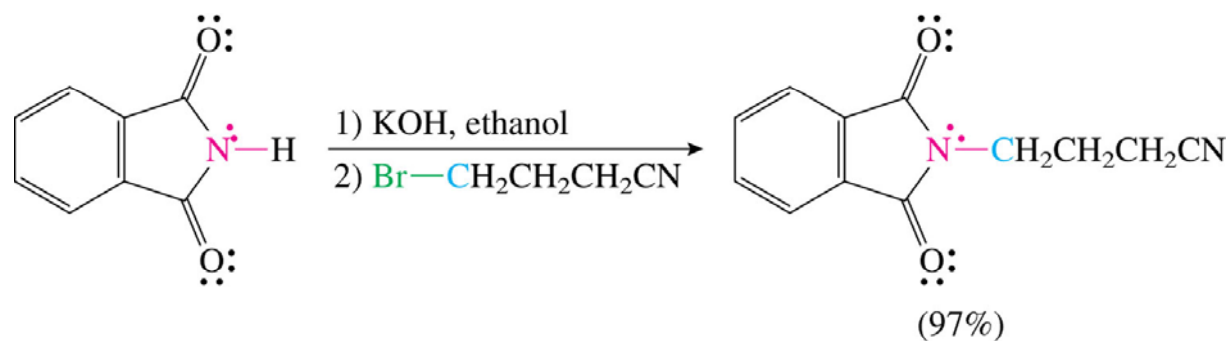


Ch 10.2



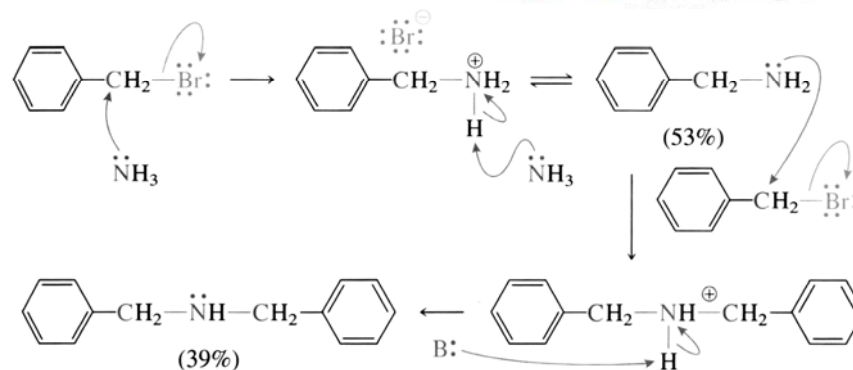


Ch 10.6

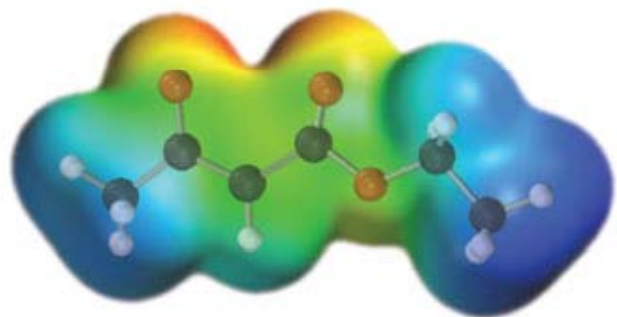


Why?

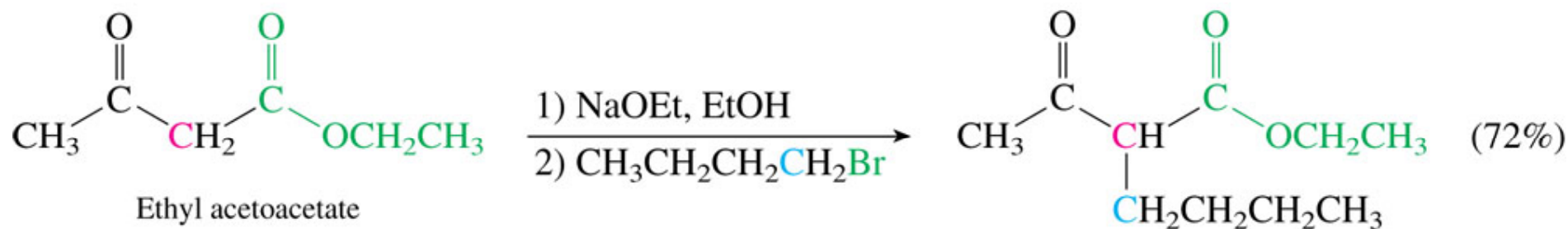
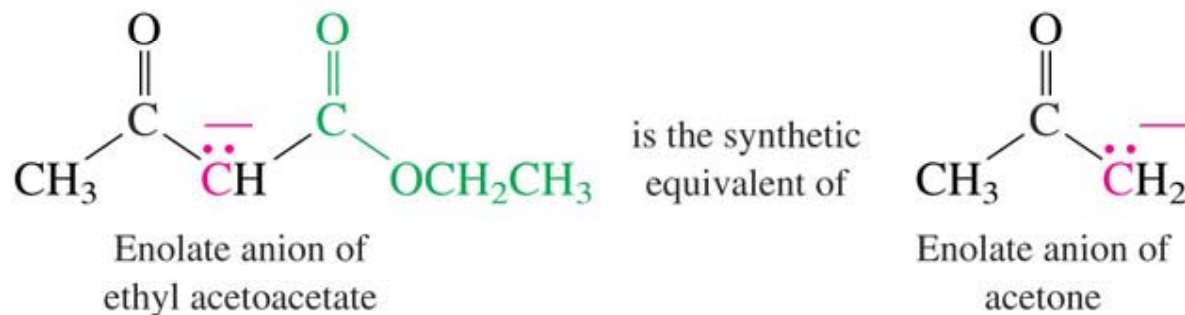
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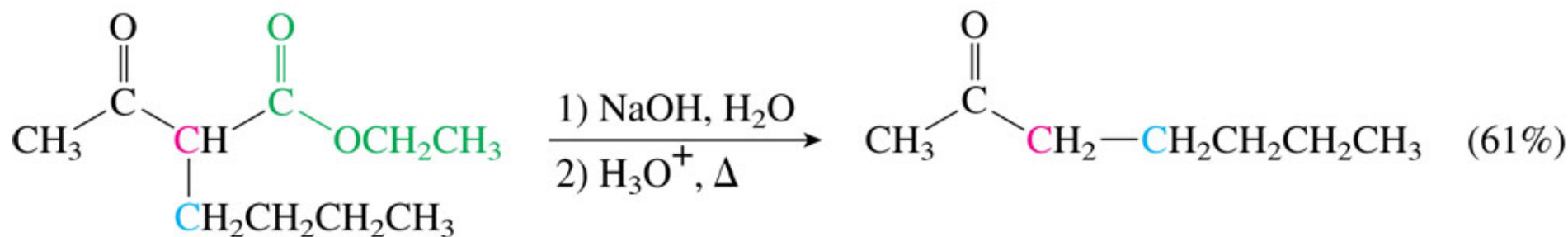
This time, ethyl **acetoacetate** can be used instead of acetone!



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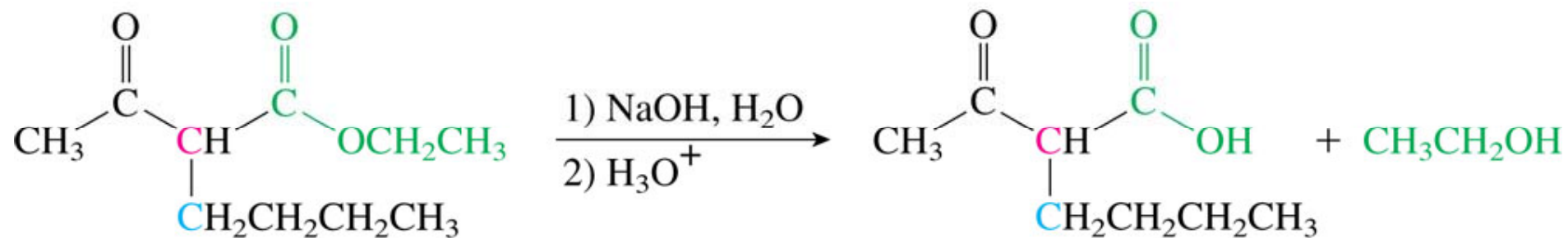


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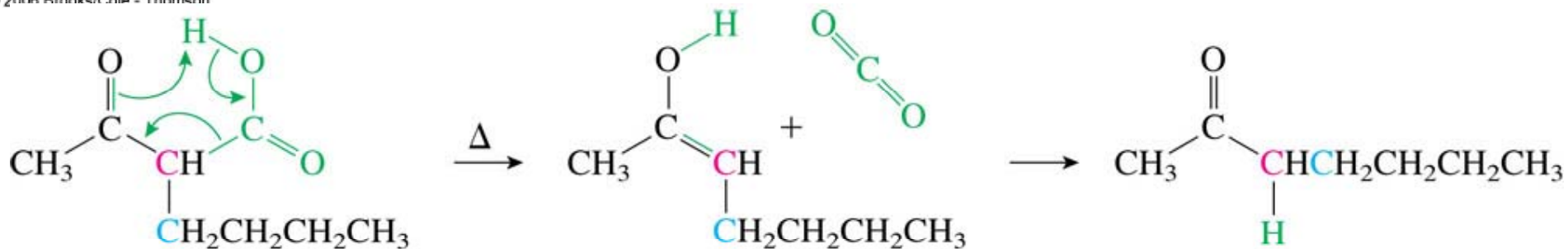
Mechanism



A β -ketoester

A β -ketoacid

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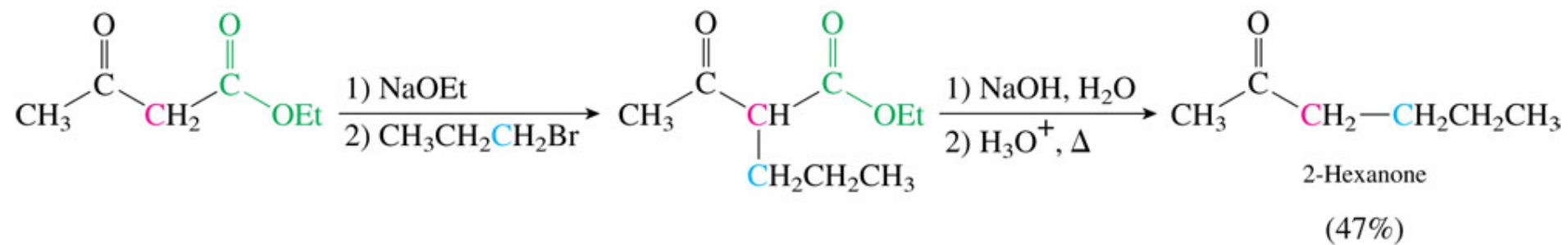


An enol

A methyl ketone

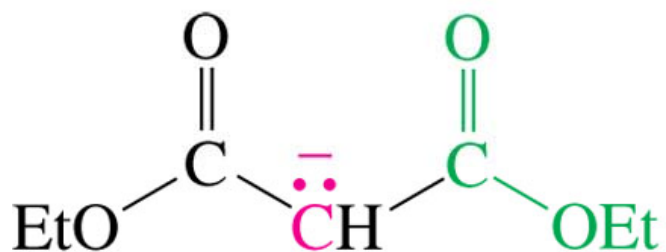
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Example

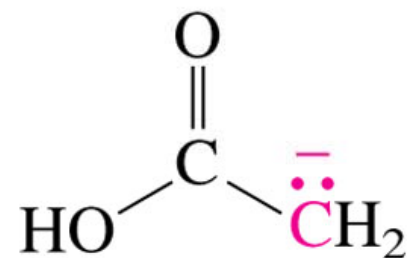


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Diethyl malonate can be used instead of acetic acid



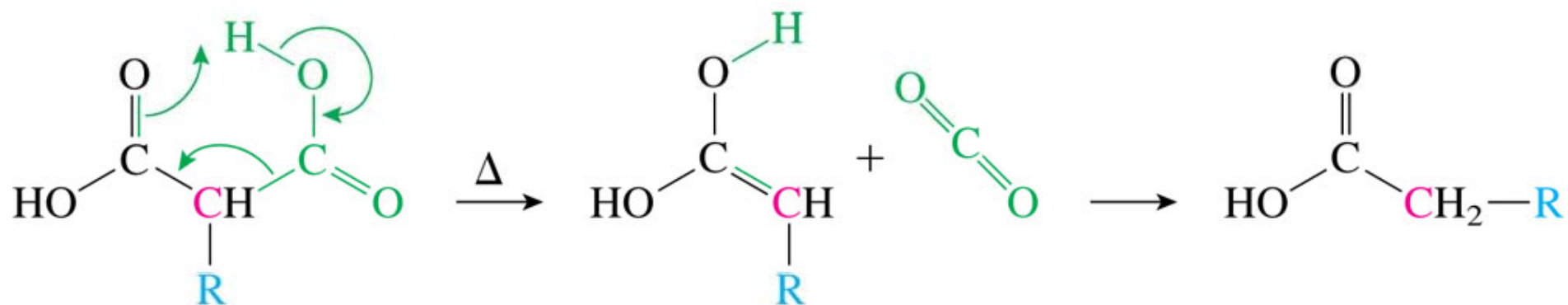
is the synthetic equivalent of



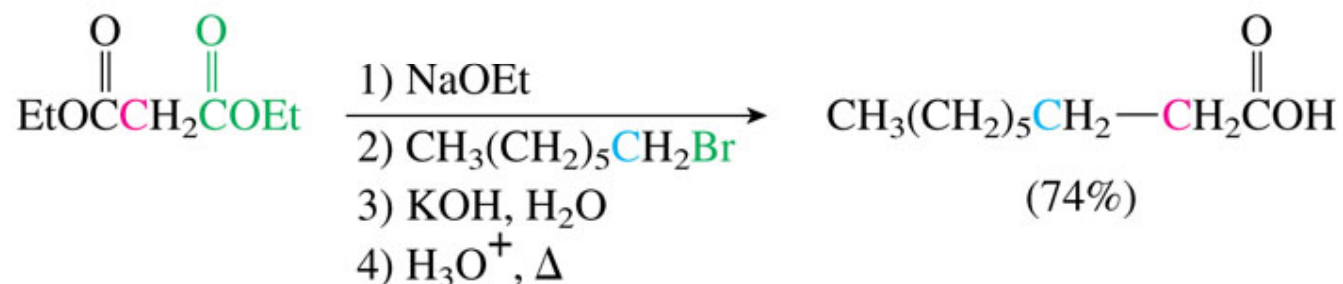
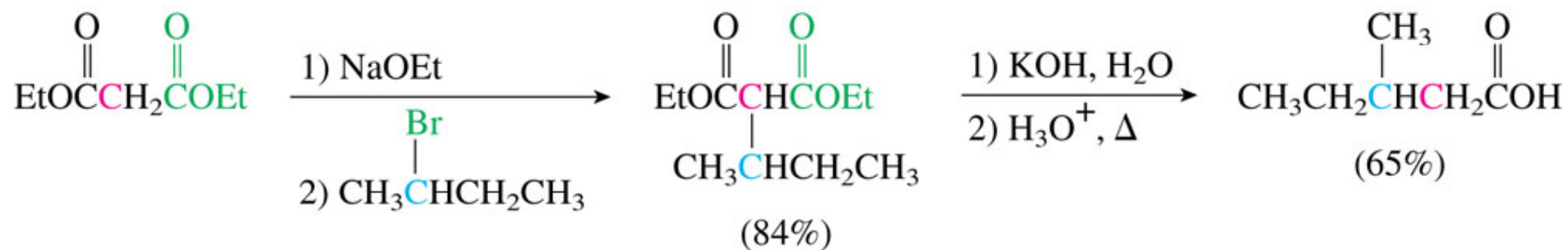
Enolate ion of diethyl malonate

Enolate ion of acetic acid

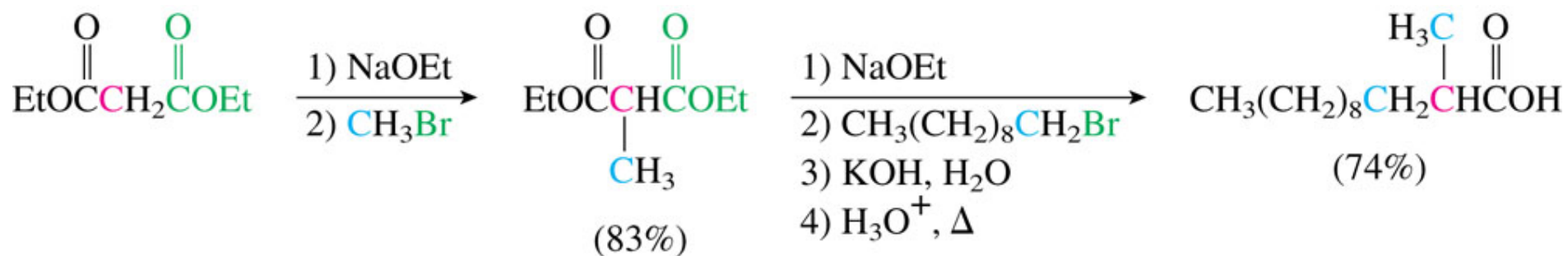
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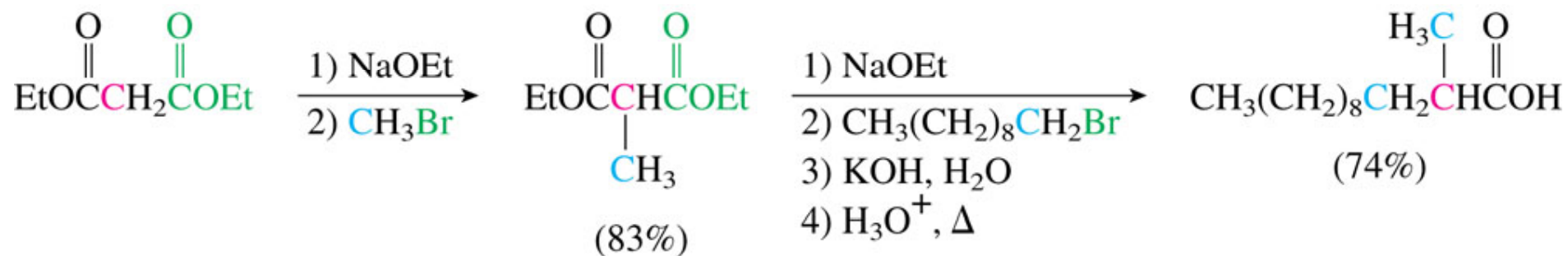
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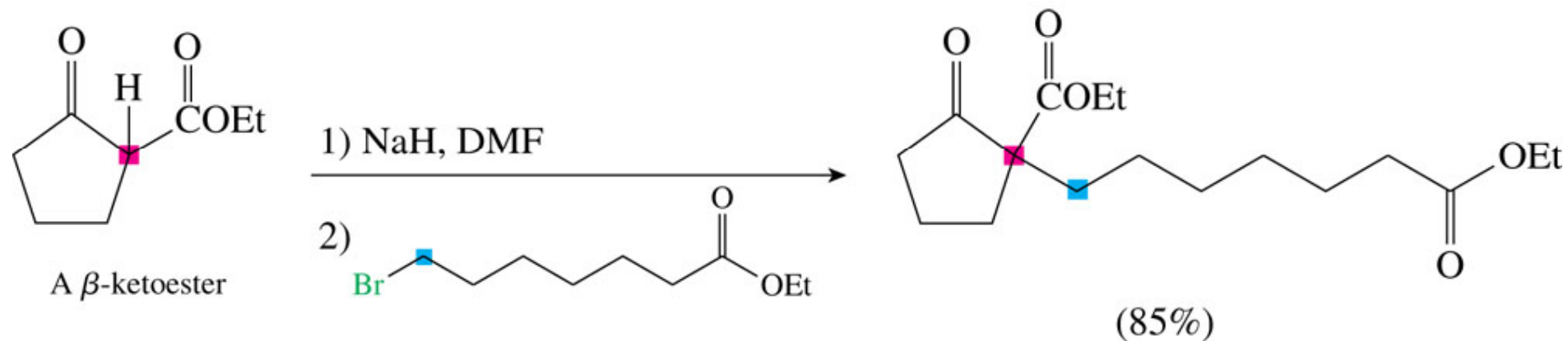
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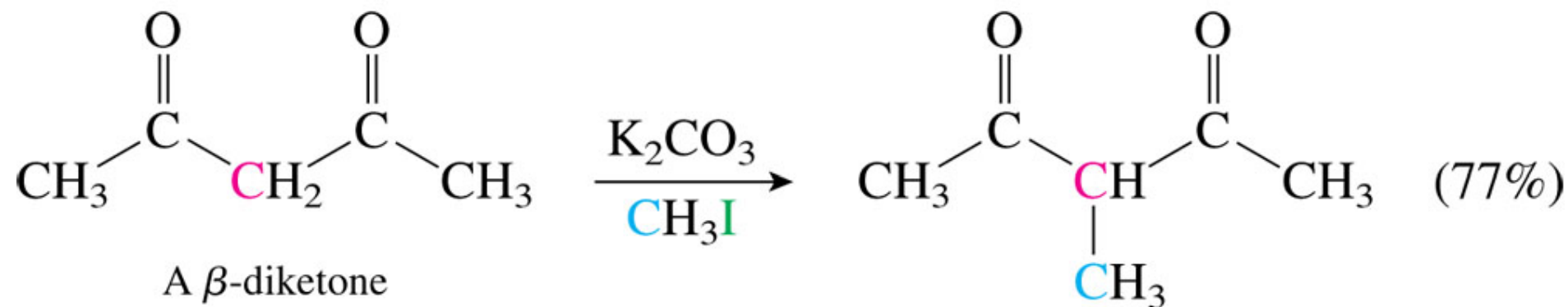
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**Preparation of substituted β -ketoesters, β -diester, and dinitrile
 \Rightarrow without hydrolysis**

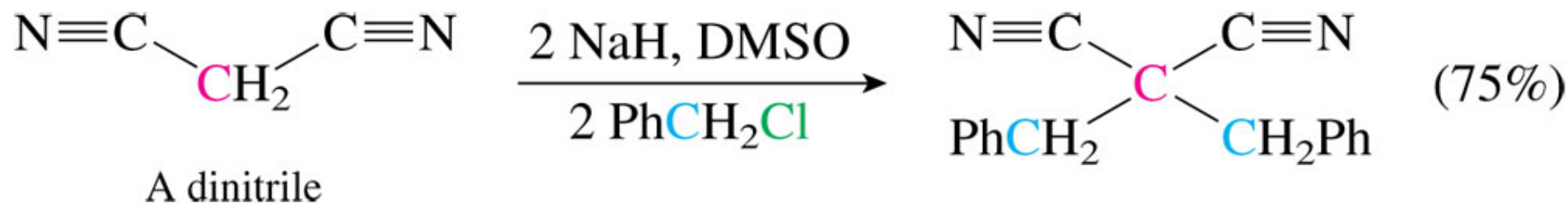
Next page



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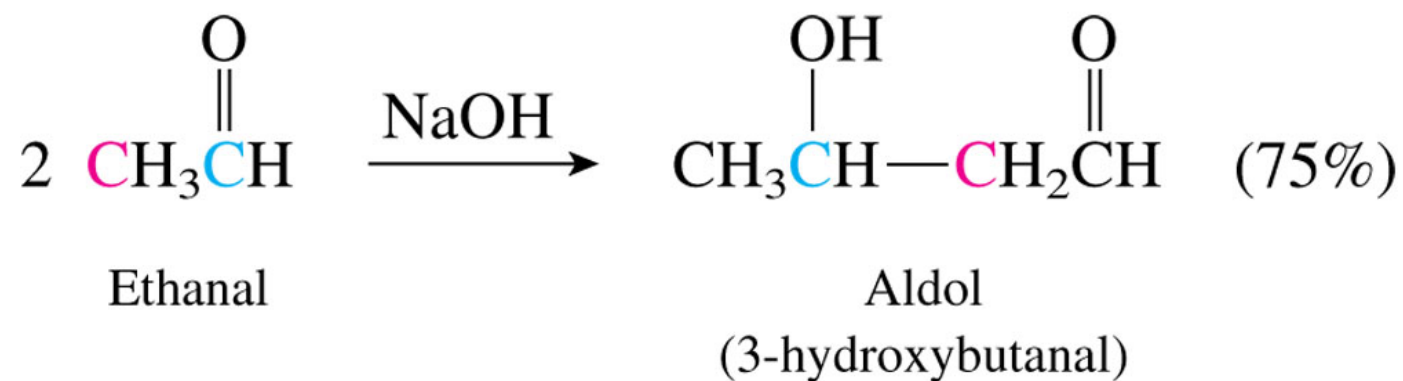


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20.5 The Aldol Condensation



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(aldehyde + base) cannot be used for the alkylation of alkyl halide, because of the aldol condensation!

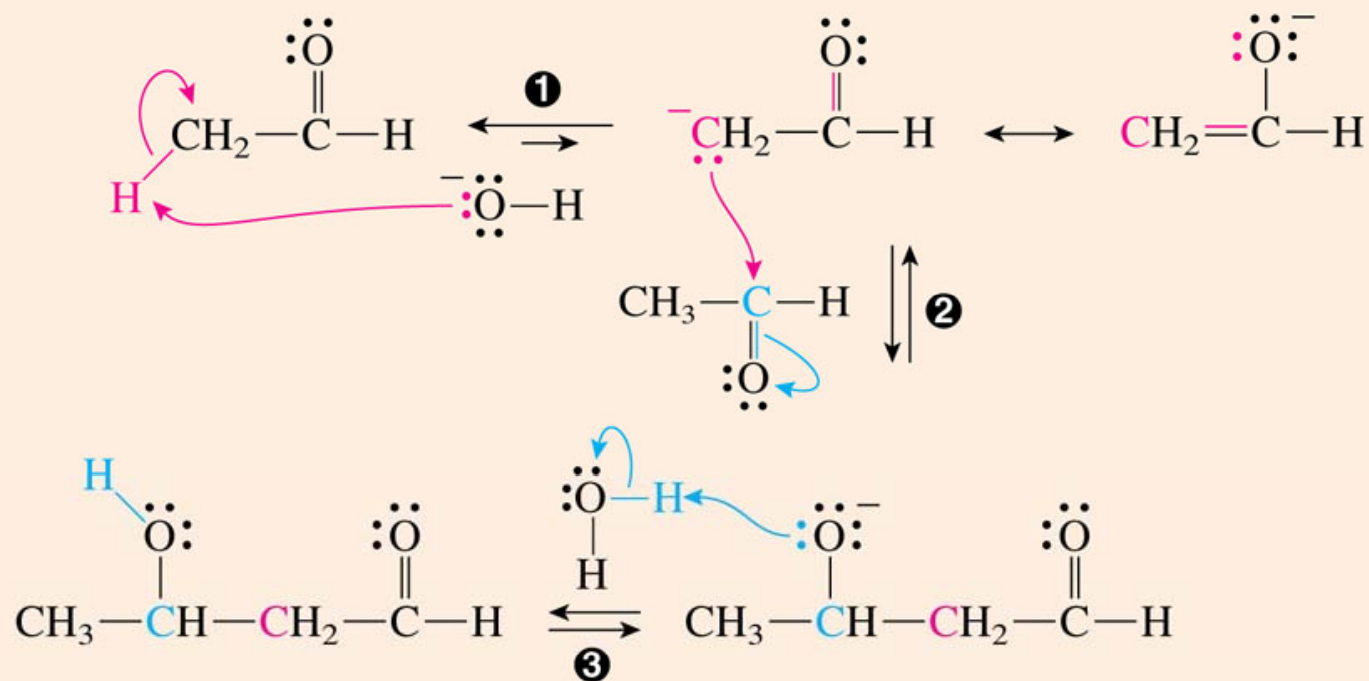
Carbonyl carbon of aldehyde is much more electrophilic than those of ester, ketone, and nitrile!

ester, ketone, and nitrile \Rightarrow S_N2

<Mechanism>

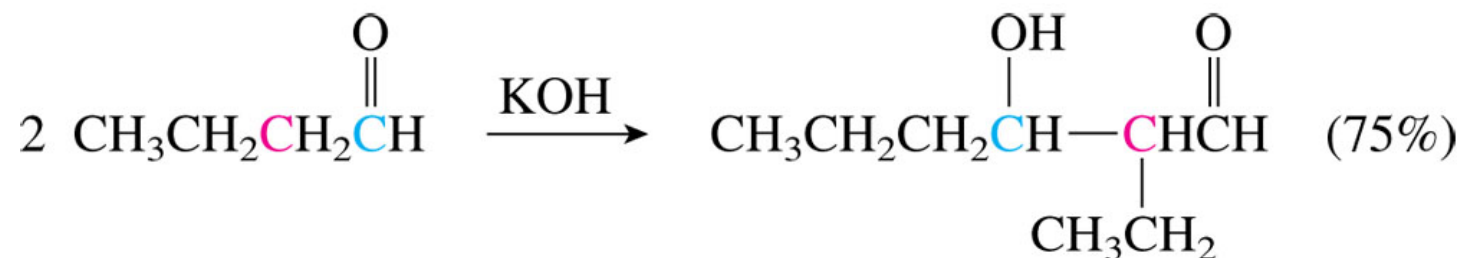
- ❶ The base, hydroxide ion, removes an acidic hydrogen from the α -carbon of the aldehyde. The conjugate base of the aldehyde is a stronger base than hydroxide, so the equilibrium for this first step favors the reactants.

However, enough enolate ion nucleophile is present to react with the electrophilic carbonyl carbon of a second aldehyde molecule.

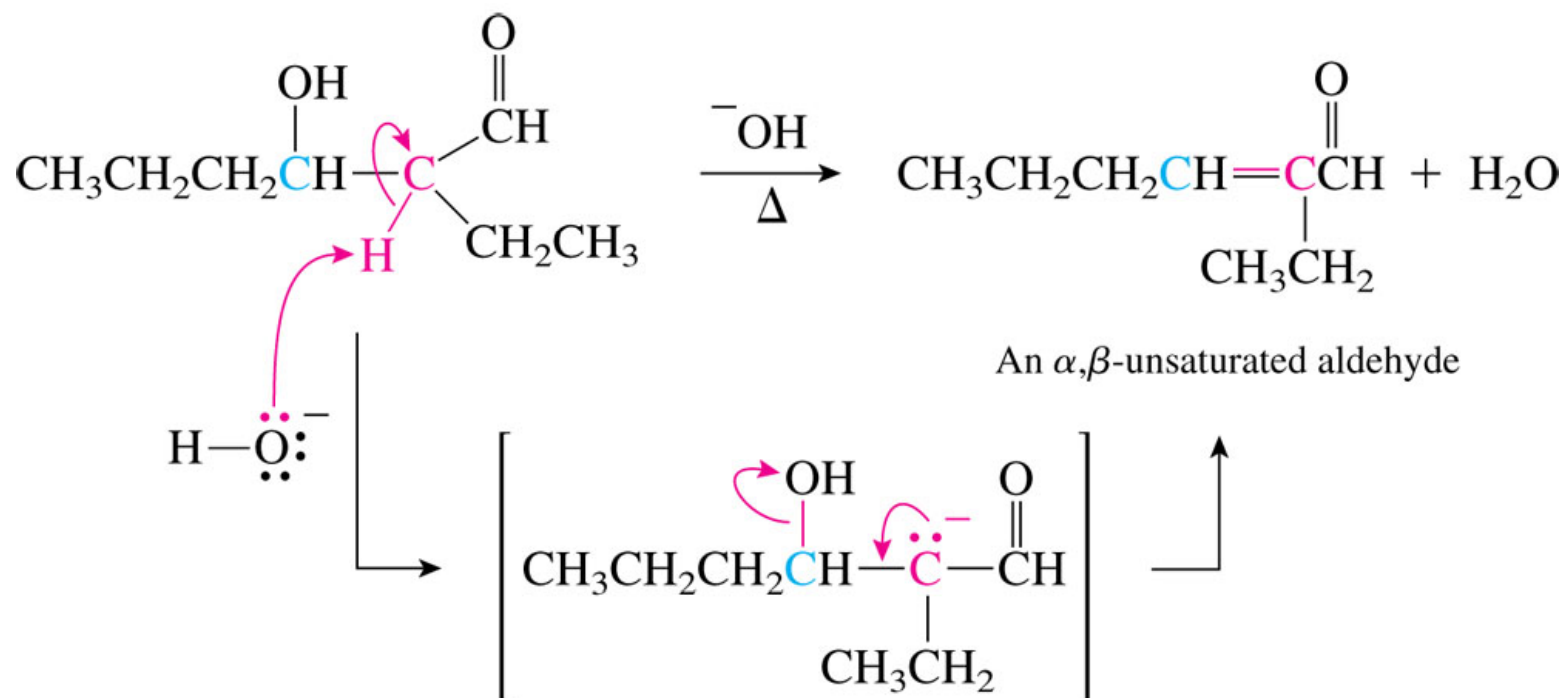


This part of the mechanism is just like the mechanism for the addition reactions of Chapter 18. ❷ The enolate nucleophile adds to the carbonyl carbon of a second aldehyde molecule, and ❸ the negative oxygen removes a proton from water. This step regenerates hydroxide ion, so the reaction is base catalyzed.

If the aldol condensation is conducted under very vigorous conditions (higher temperature, longer reaction time, and/or strong base)



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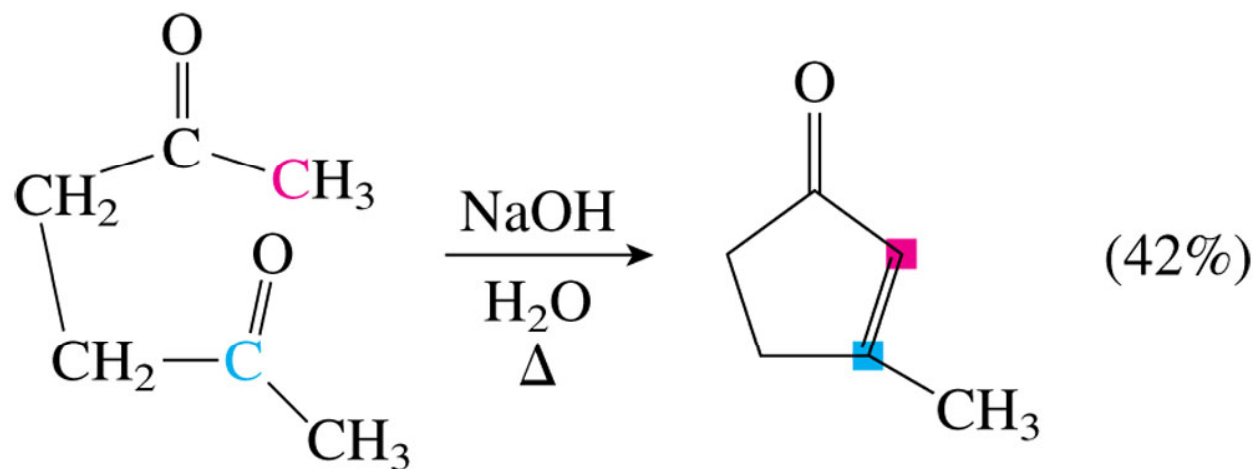


Ketones

As less electrophilic, usually **no aldol condensation**.

However when the product is **5- or 6- membered ring**, then aldol condensation occurs!

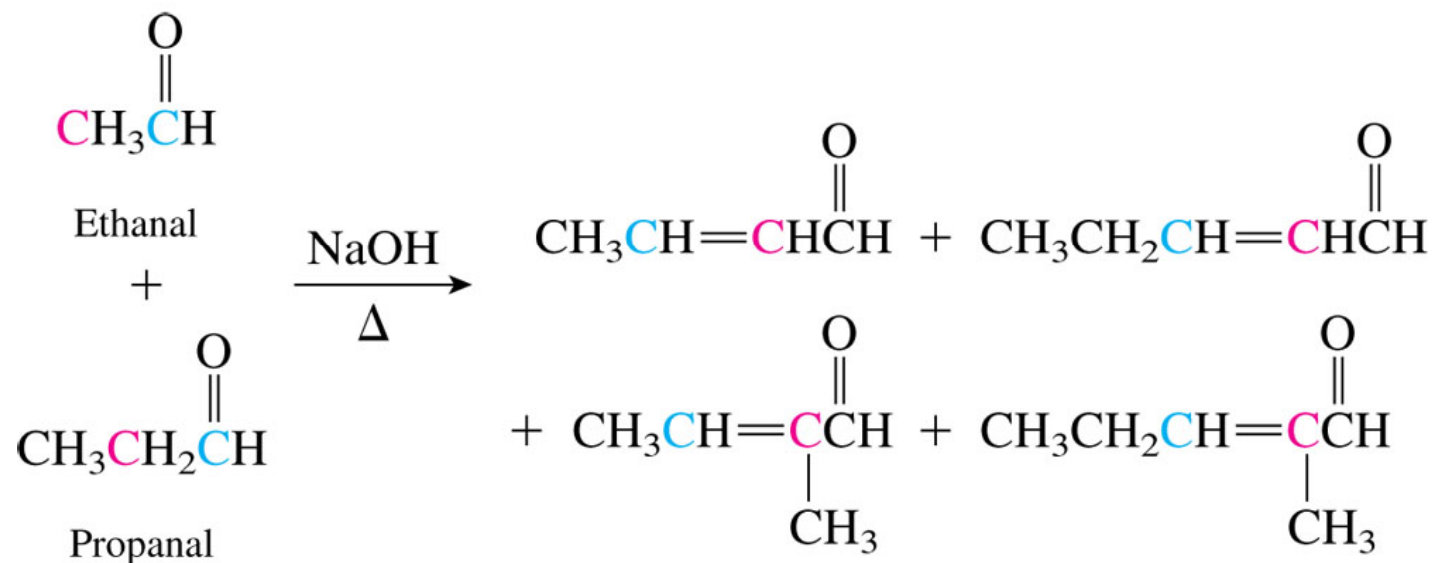
<Example>



A diketone

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Mixed aldol condensation



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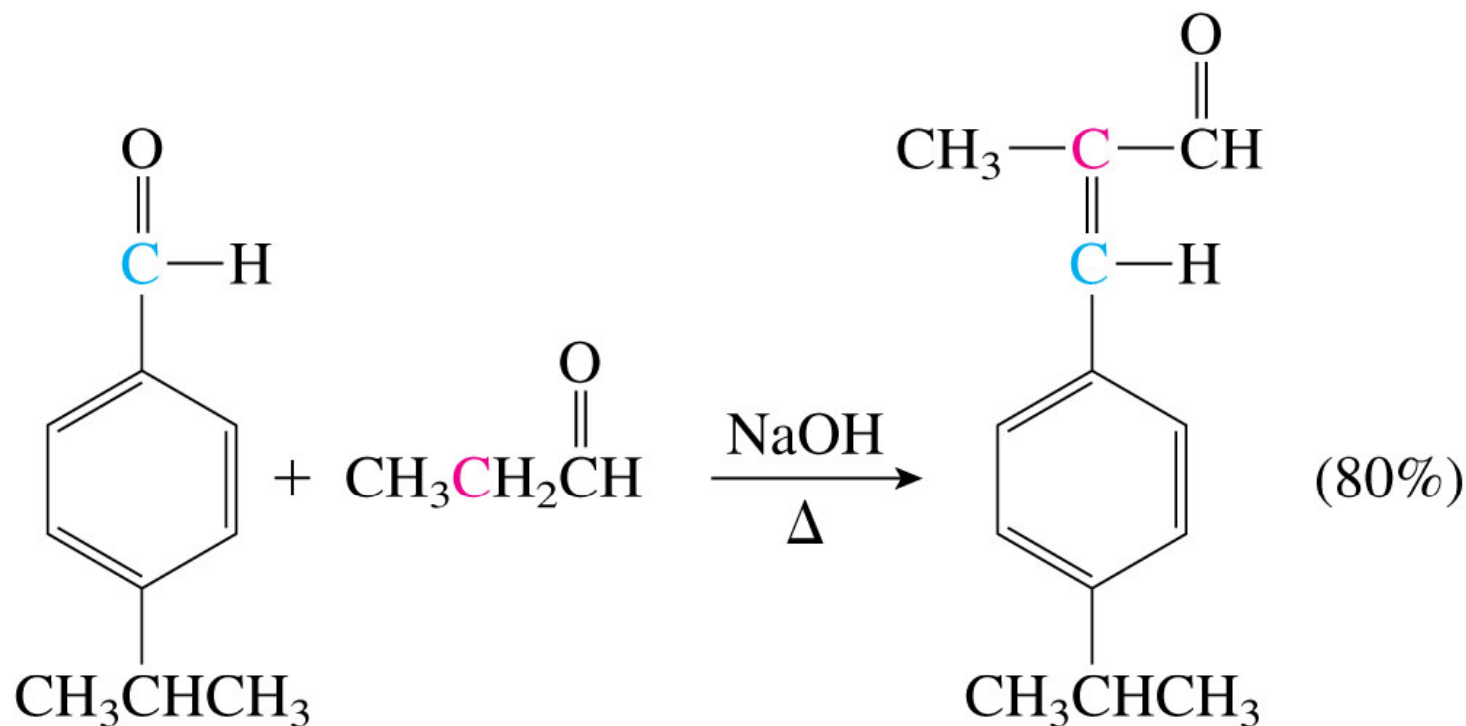
4 products =

2 acidic compounds x 2 electrophilic compounds

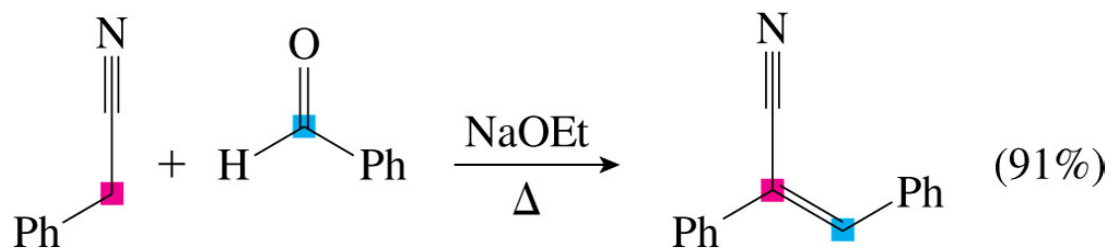
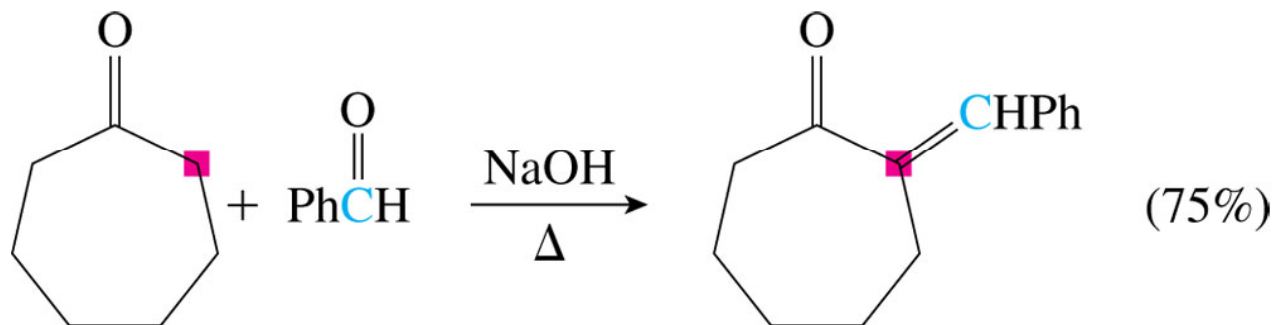
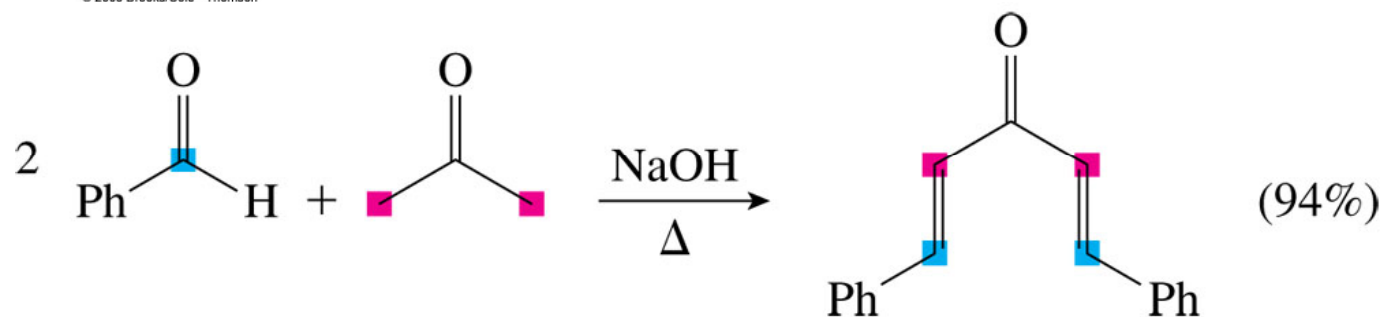
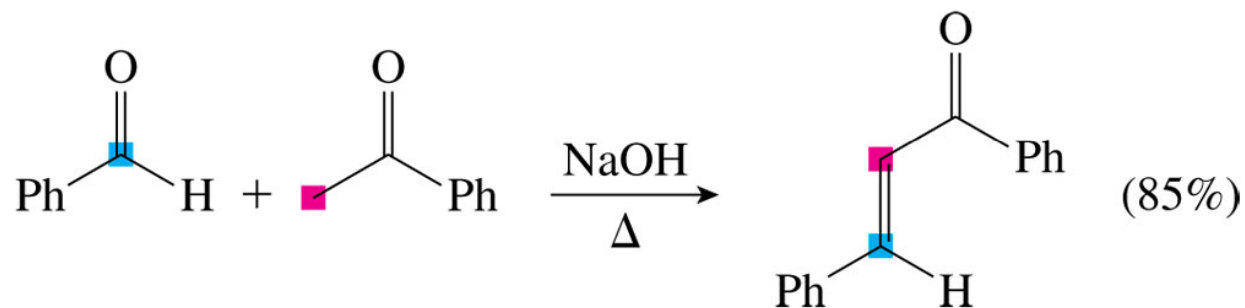
Use **aromatic aldehyde** (only electrophilic)
to get **one product**.

Product is more favorable: conjugation

<Example>

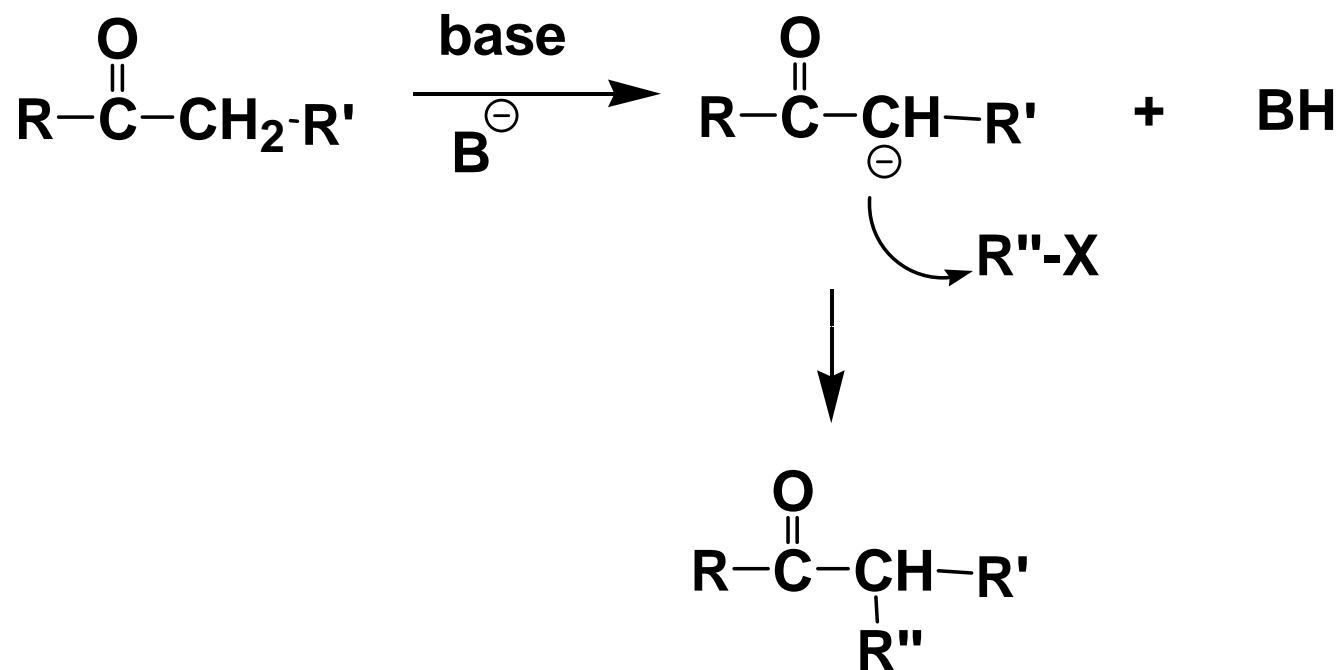


<Examples>



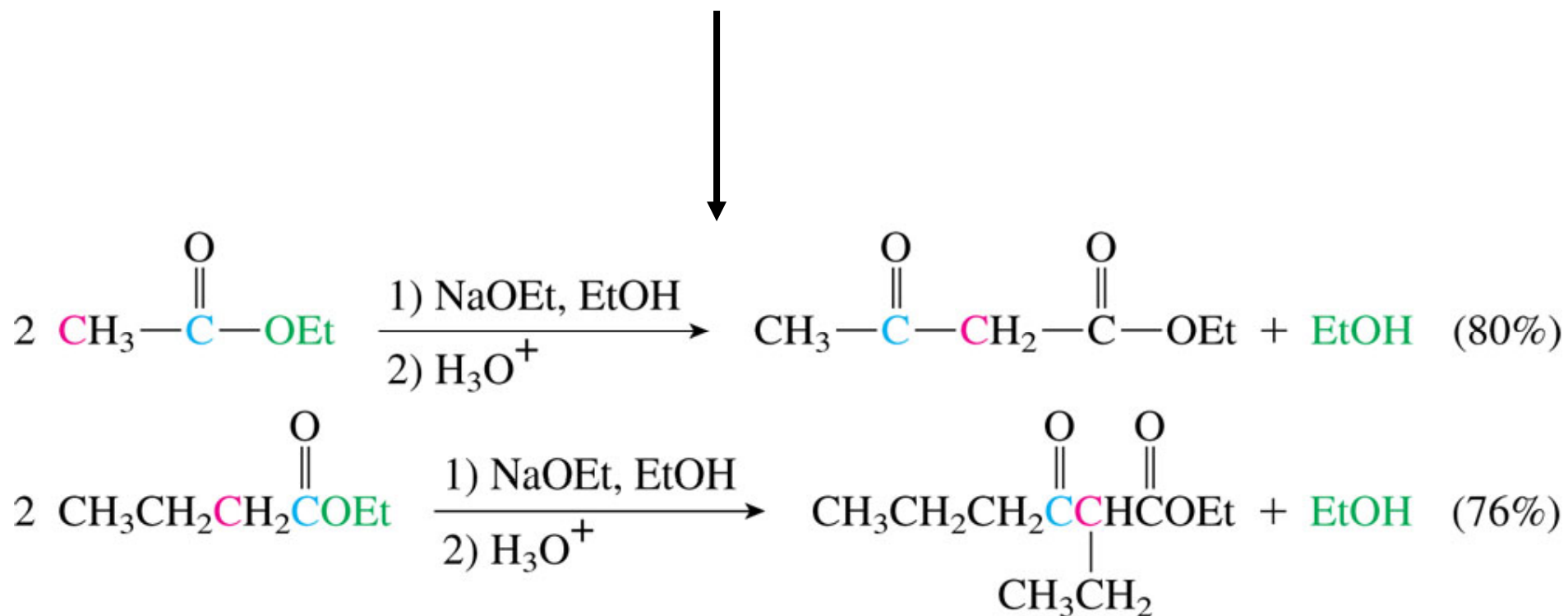
20.6 Ester Condensation

20.3-4: enolates with alkyl halide using weak or strong bases depending on the acidity.



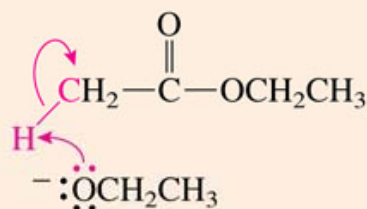
20.5: enolate with aldehyde using weaker bases. ⇒
Aldol condensation

20.6: enolate with ester using weaker bases. ⇒
Ester condensation or Claisen ester condensation

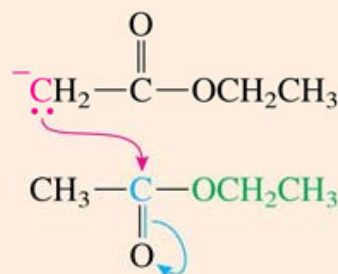


Mechanism of the Claisen Ester Condensation

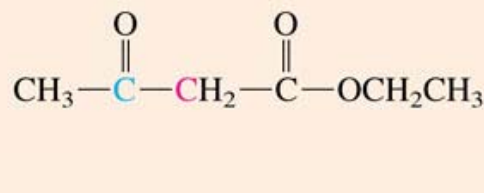
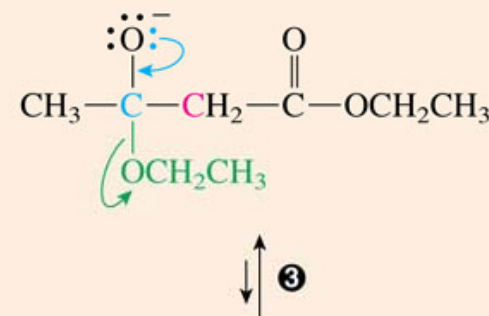
1 The base, ethoxide ion, removes an acidic hydrogen from the α -carbon of the ester.



2 The enolate anion reacts as a nucleophile, attacking the electrophilic carbonyl carbon of another ester molecule. This is another example of the substitution mechanism presented in Chapter 19.

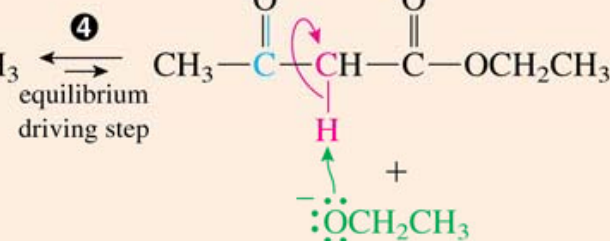


3 Ethoxide ion leaves as the electrons on the oxygen reform the carbonyl double bond.



5 Workup with acid protonates the anion, producing the β -ketoester.

The equilibria for **1**, **2**, and **3** are all unfavorable. However, the formation of the weakest base in this reaction **4**, drives the overall equilibrium to completion. If this step cannot occur, the equilibrium will be unfavorable and the reaction will not occur.

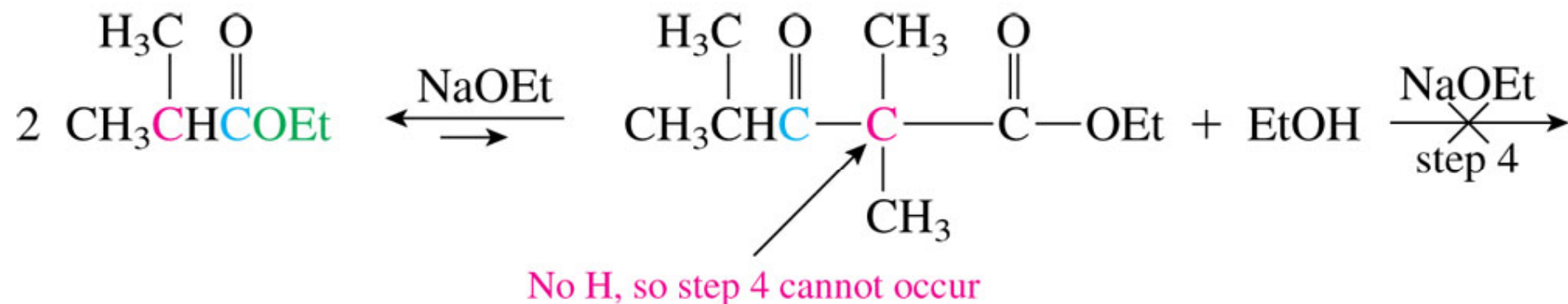


4 The hydrogen on the carbon between the two carbonyl groups of the β -ketoester is quite acidic and is removed by ethoxide ion.

Step 4 is the reason why this reaction is possible

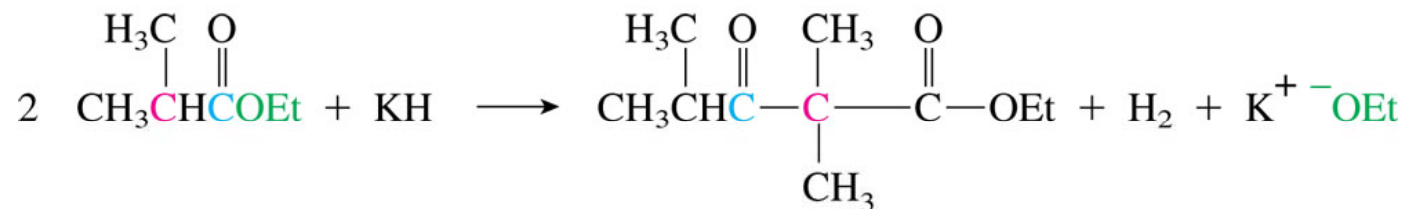
For the compounds with only one on the α -carbon, Step 4 is impossible.

Then the ester condensation is impossible



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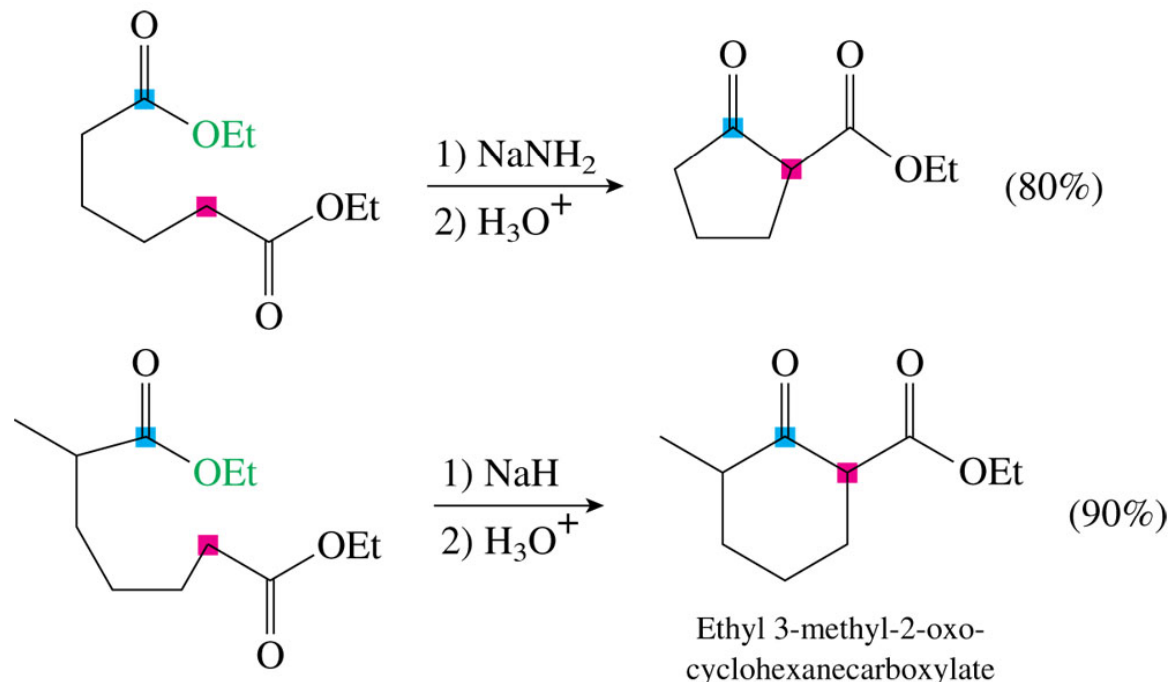
If stronger base is used, then condensation is possible



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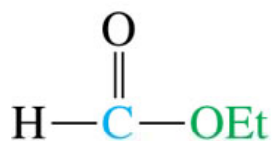
Dieckmann condensatoin

⇒ Intramolecular ester condensation

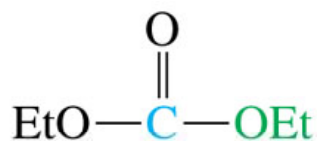


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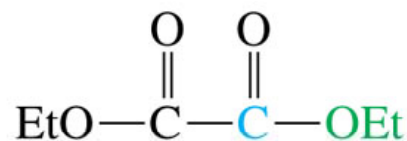
Mixed ester condensation can be prevented if one of the component acts as only electrophile such as



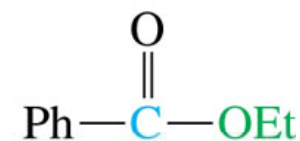
Ethyl formate



Diethyl carbonate

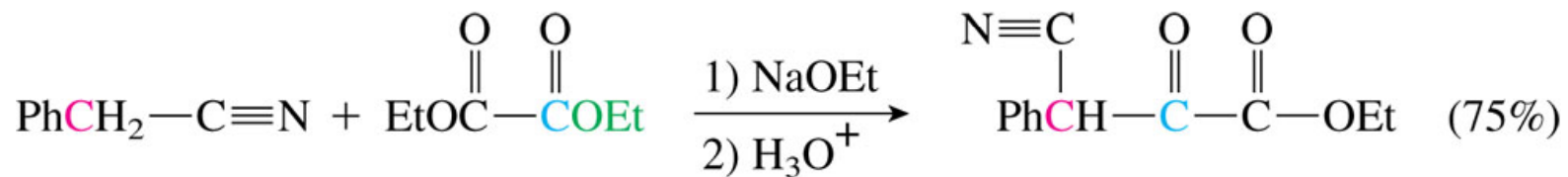
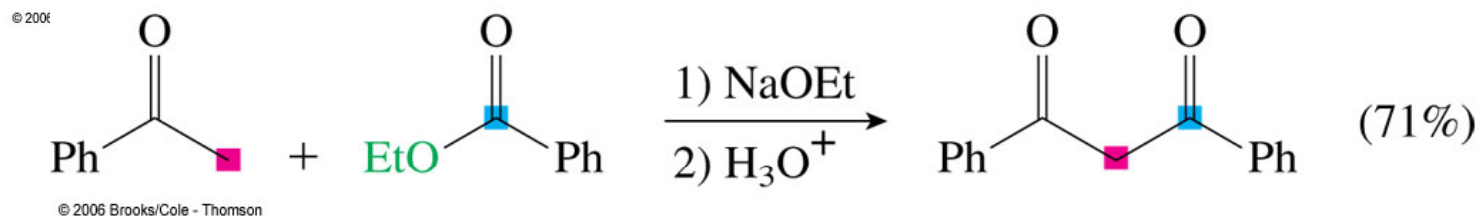
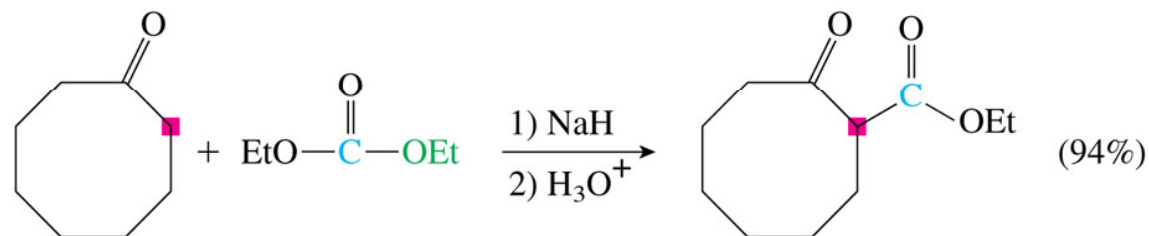
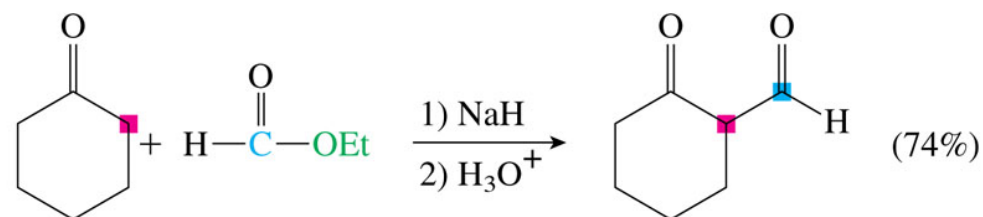
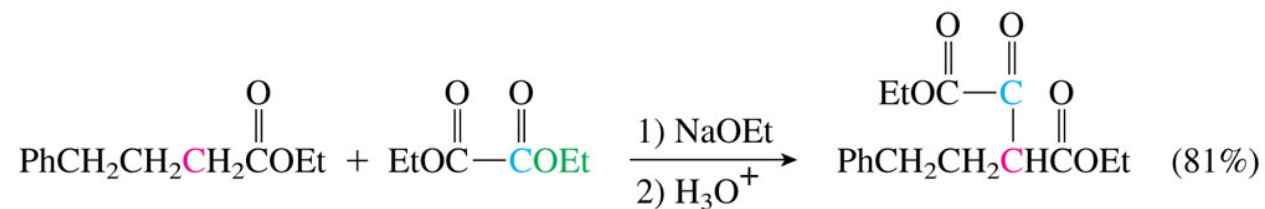


Diethyl oxalate



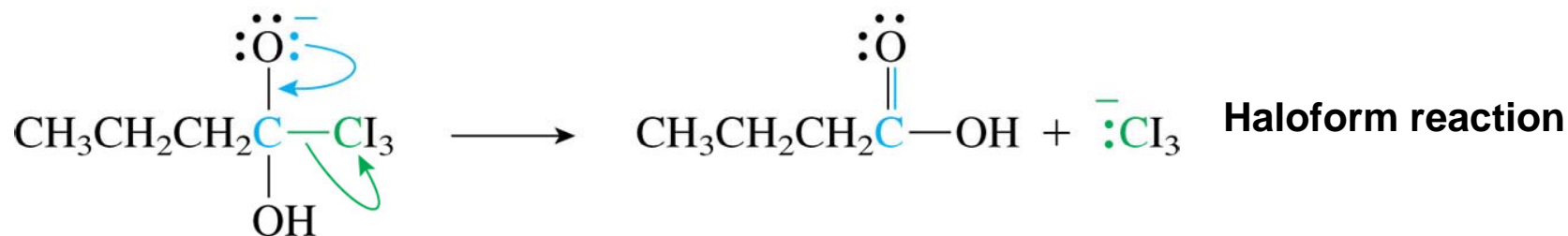
Ethyl benzoate

<Examples>

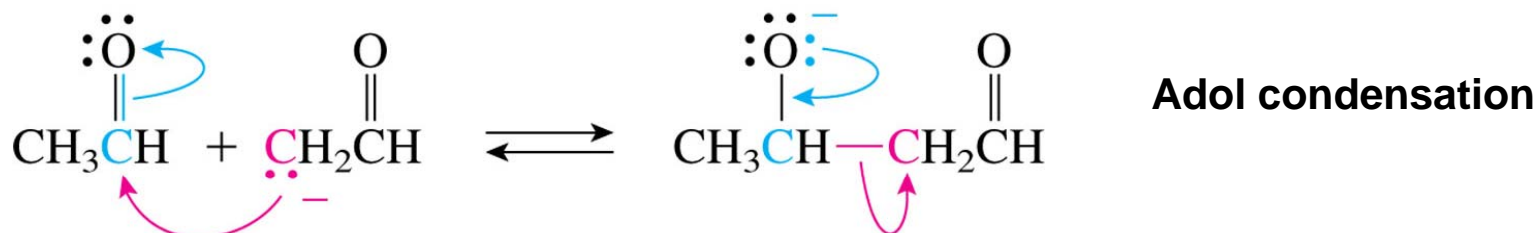


20.7 Carbon and hydrogen leaving groups

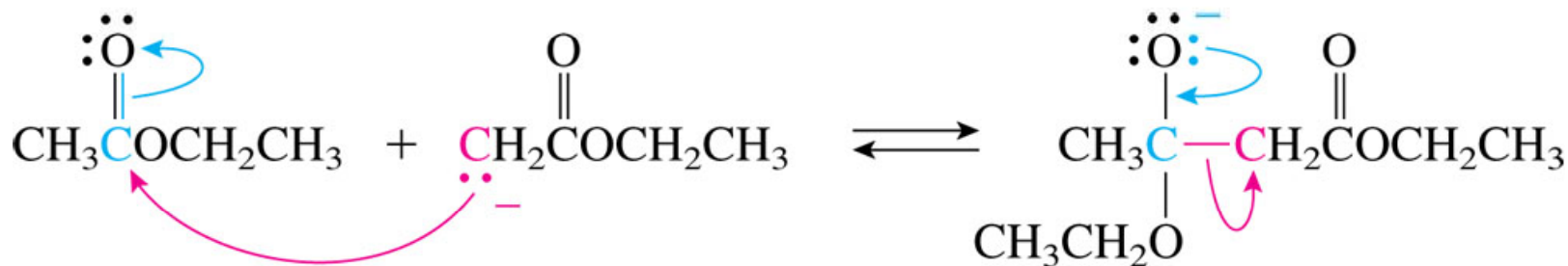
A carbanion as a leaving group



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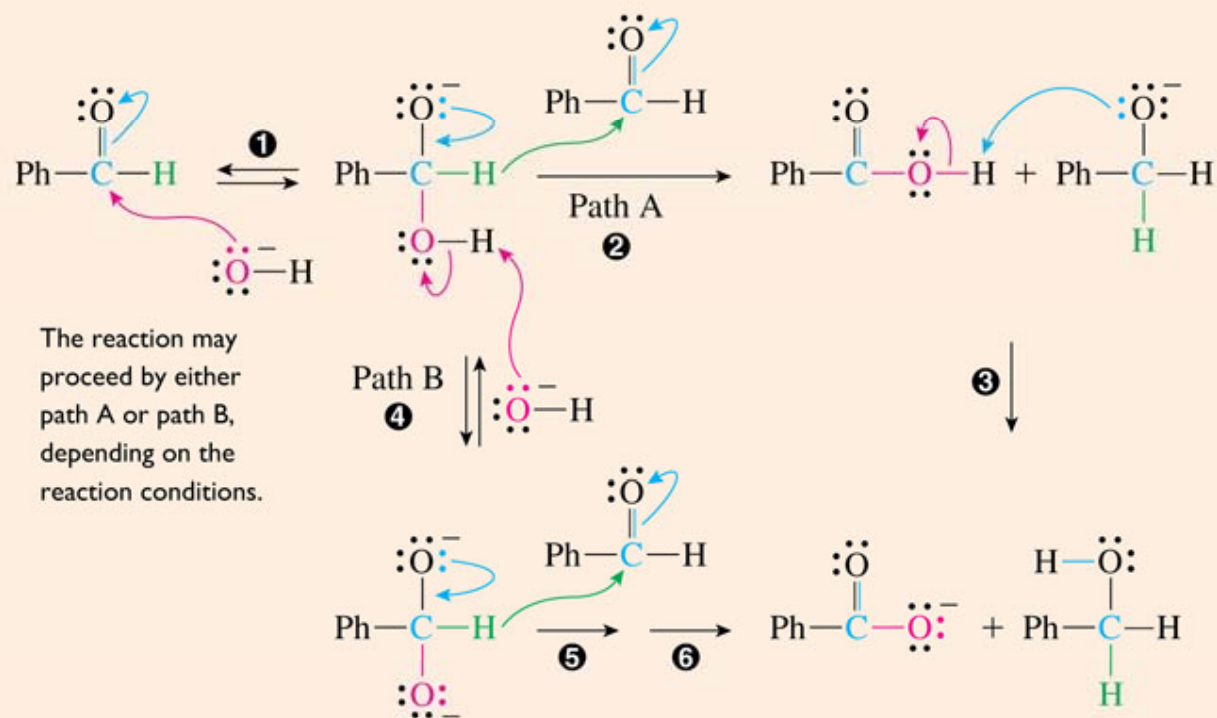
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A hydride as a leaving group, Cannizzaro reaction

❶ The Cannizzaro reaction begins with the attack of the hydroxide ion nucleophile at the electrophilic carbon of the aldehyde, as described in Chapter 18.



The reaction may proceed by either path A or path B, depending on the reaction conditions.

❷ In path A, the electrons on the negative oxygen reform the double bond as hydride leaves. Hydride is too basic to leave by itself, so it is transferred to the electrophilic carbonyl carbon of another aldehyde molecule in a concerted step. This step is relatively slow and occurs only when no other reaction pathways, such as an aldol condensation, are available.

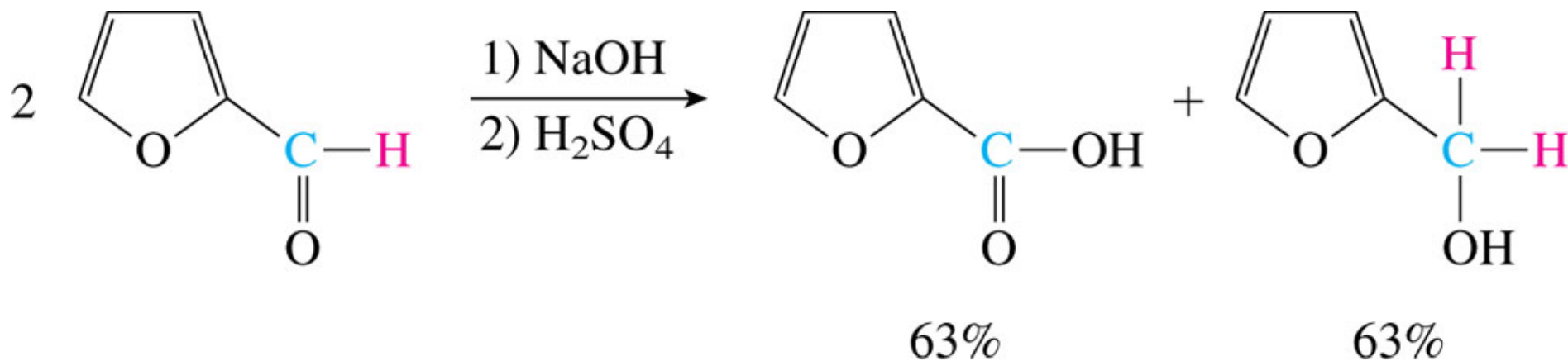
❸ An acid–base step completes the reaction.

❹ In path B, the initial anion loses a proton to the base, forming a dianion.

❺ Transfer of a hydride from the dianion to the second aldehyde molecule leads to the carboxylate anion and the conjugate base of the alcohol, ❻ which then obtains a proton from the solvent. Although the dianion is less stable than the initial anion, it is a stronger hydride donor because of its two negative charges.

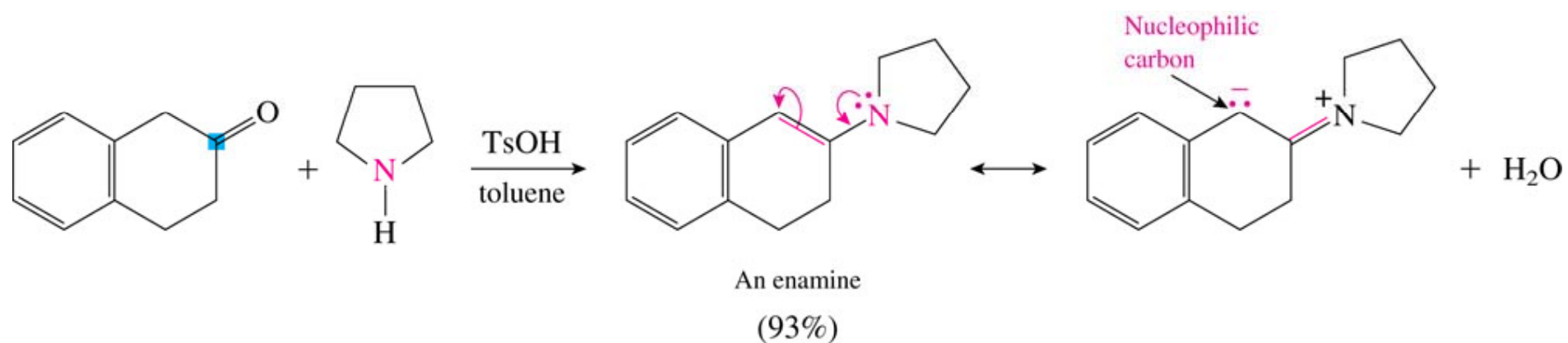
Cannizzaro reaction

example

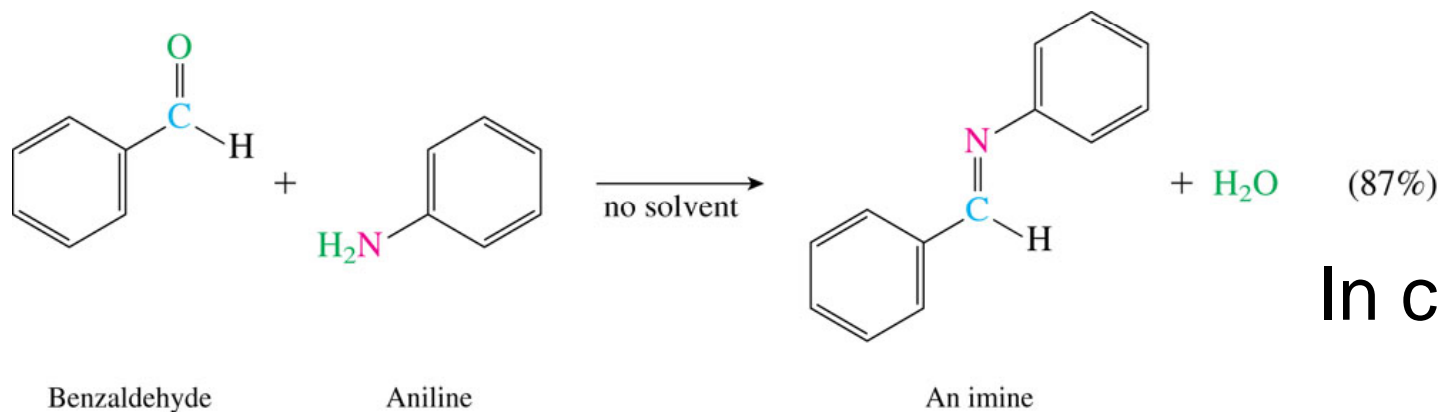


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20.8 Enamines



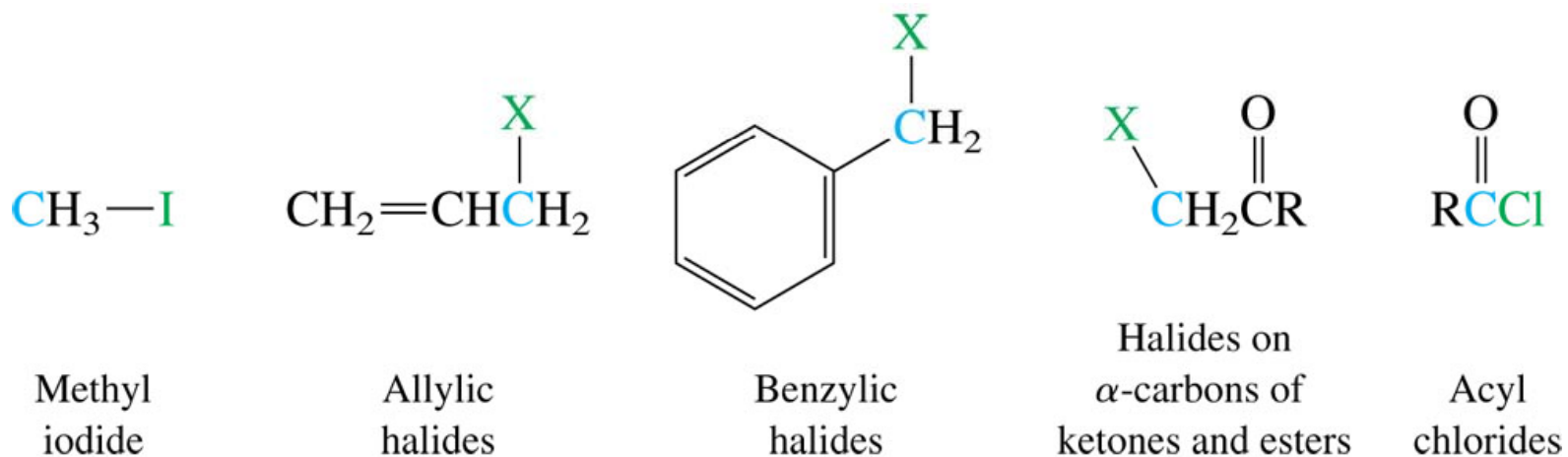
The enamine can be used as a carbon nucleophile !



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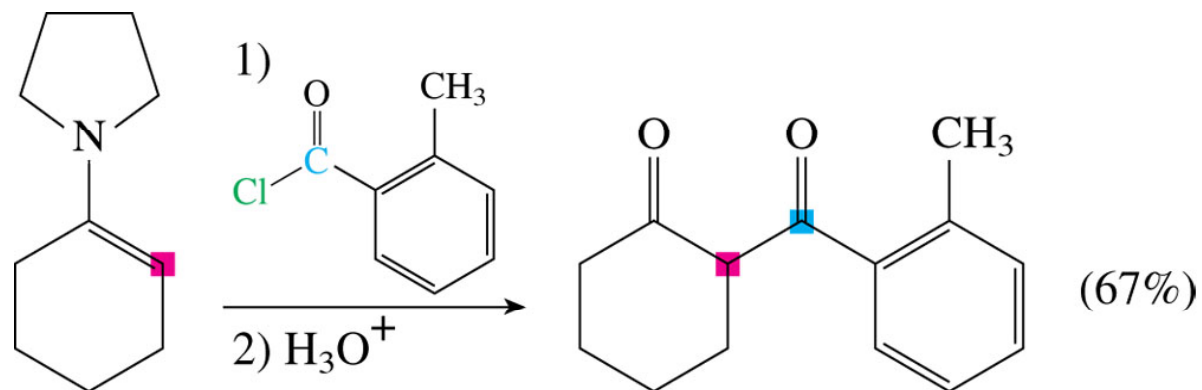
In ch 18.8

α -carbon is nucleophilic, still weaker nucleophile than the enolates. Therefore for S_N2 reaction, the alkyl halide must be very reactive such as:



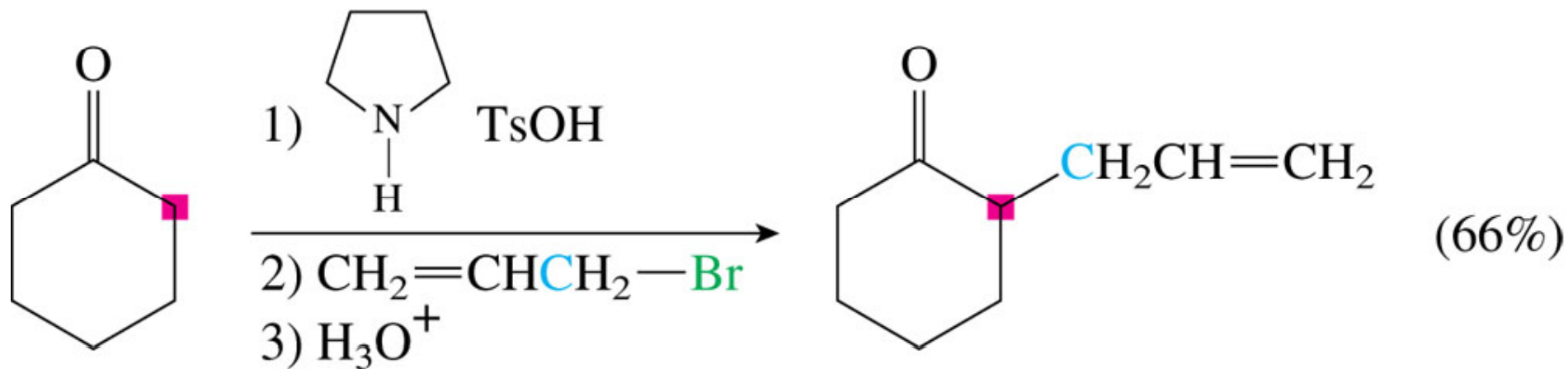
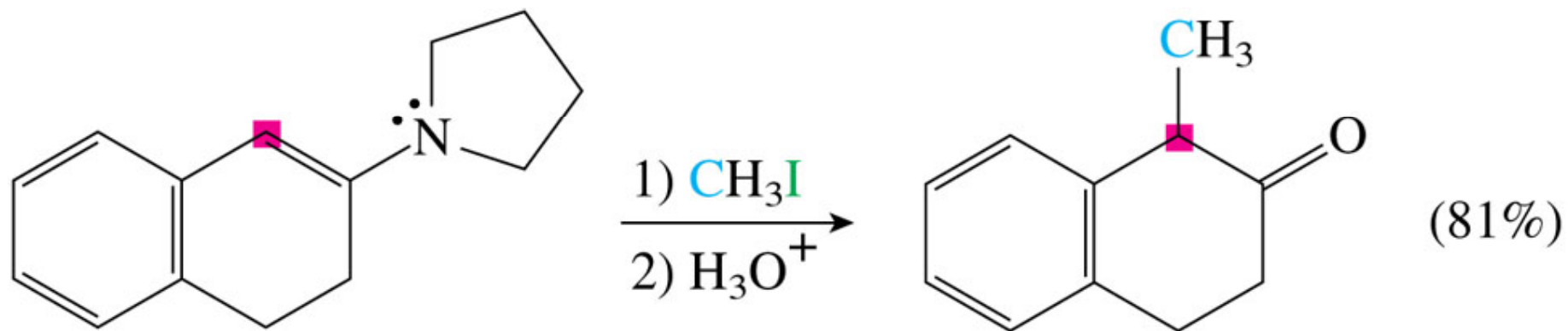
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<Examples>



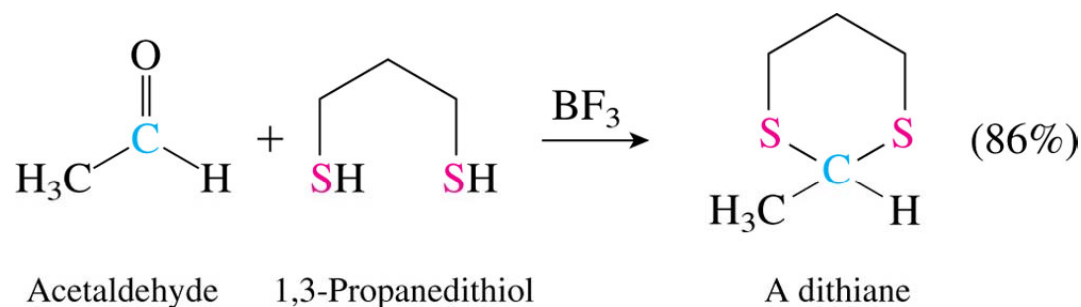
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<Examples>



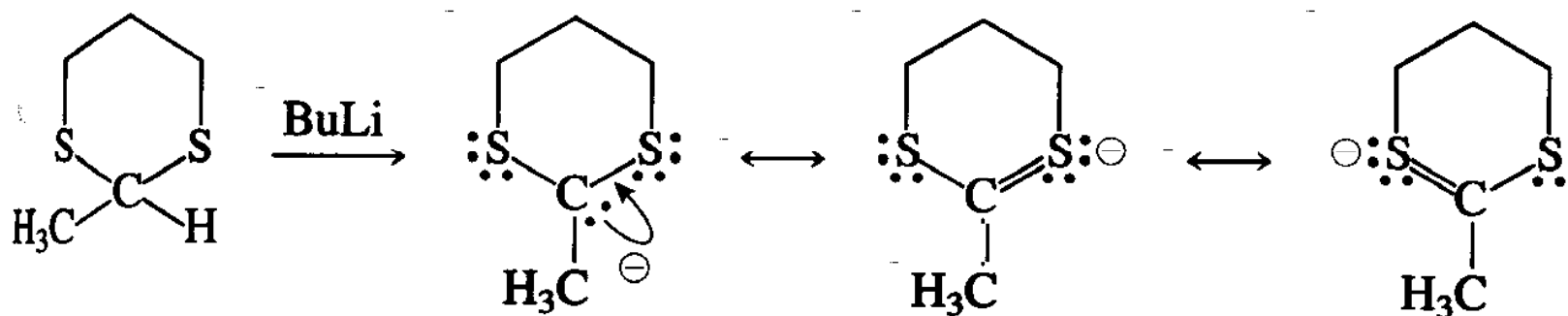
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20.9 Other Carbon Nucleophiles

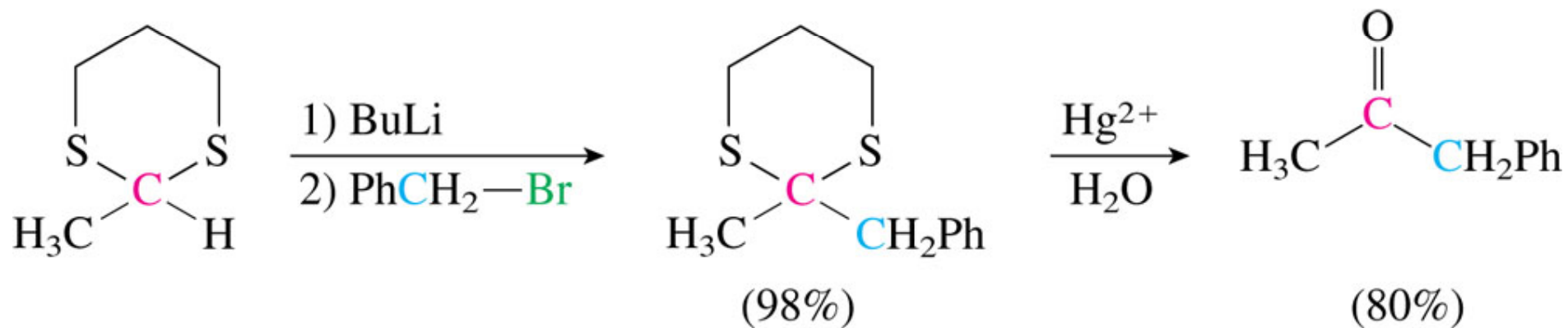


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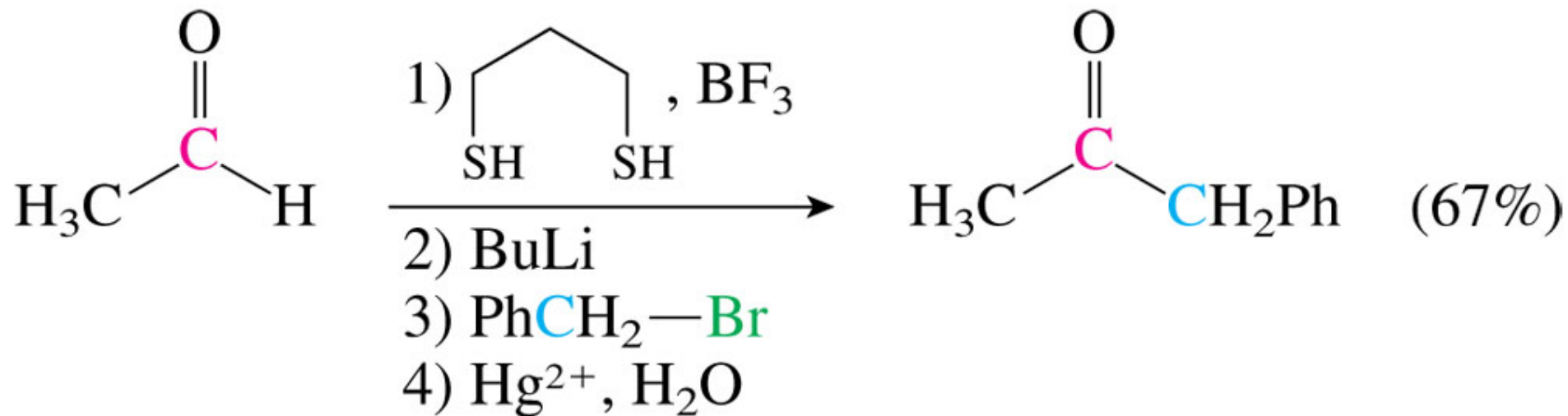
The hydrogen on the carbon attached to the two sulfur atoms is weakly acidic ($pK_a = 31$) and can be removed by reaction with a strong base, such as butyllithium. (Butyllithium is also a nucleophile, and therefore it is not used to generate enolate anions from carbonyl compounds. However, the dithiane is not electrophilic, so butyllithium can be used as the base in this reaction.)



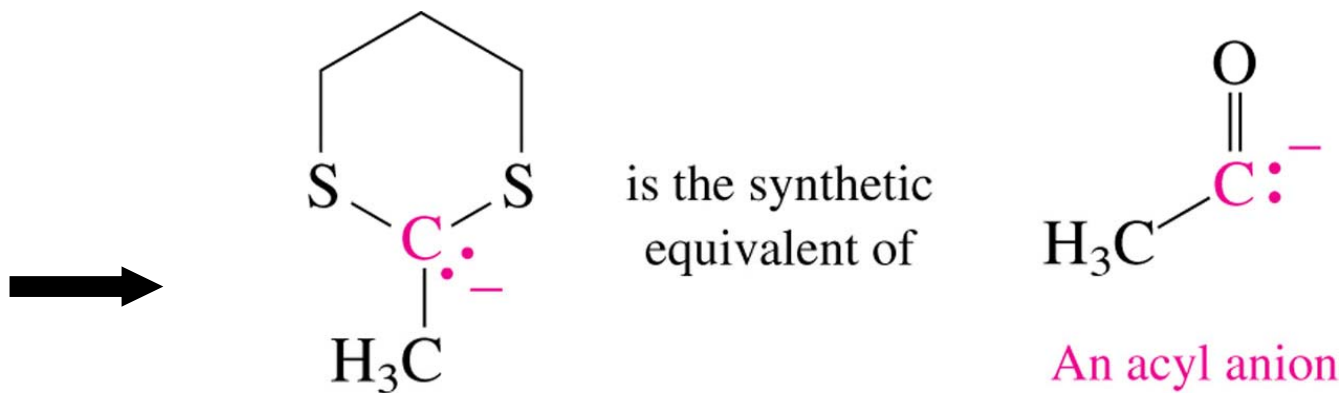
Example reaction



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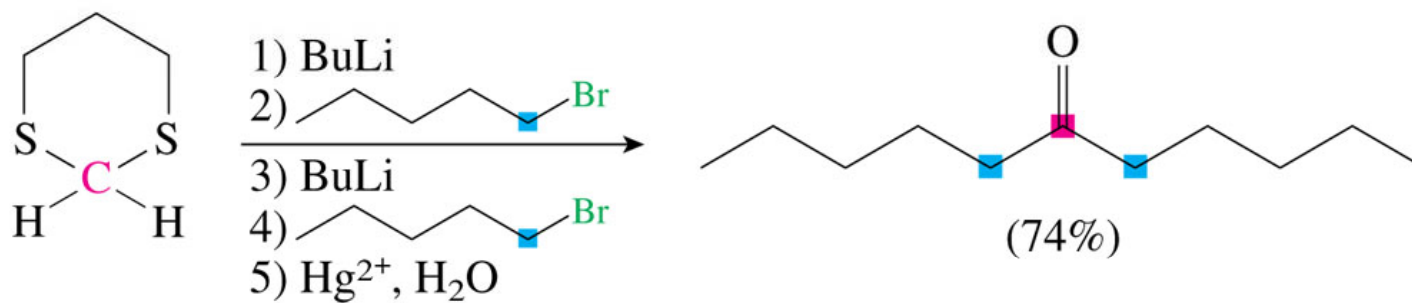
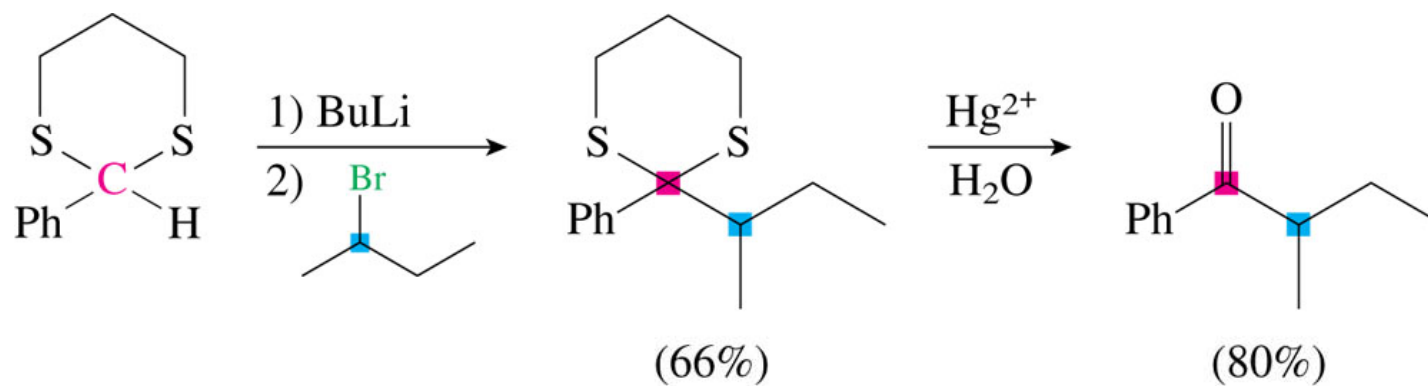


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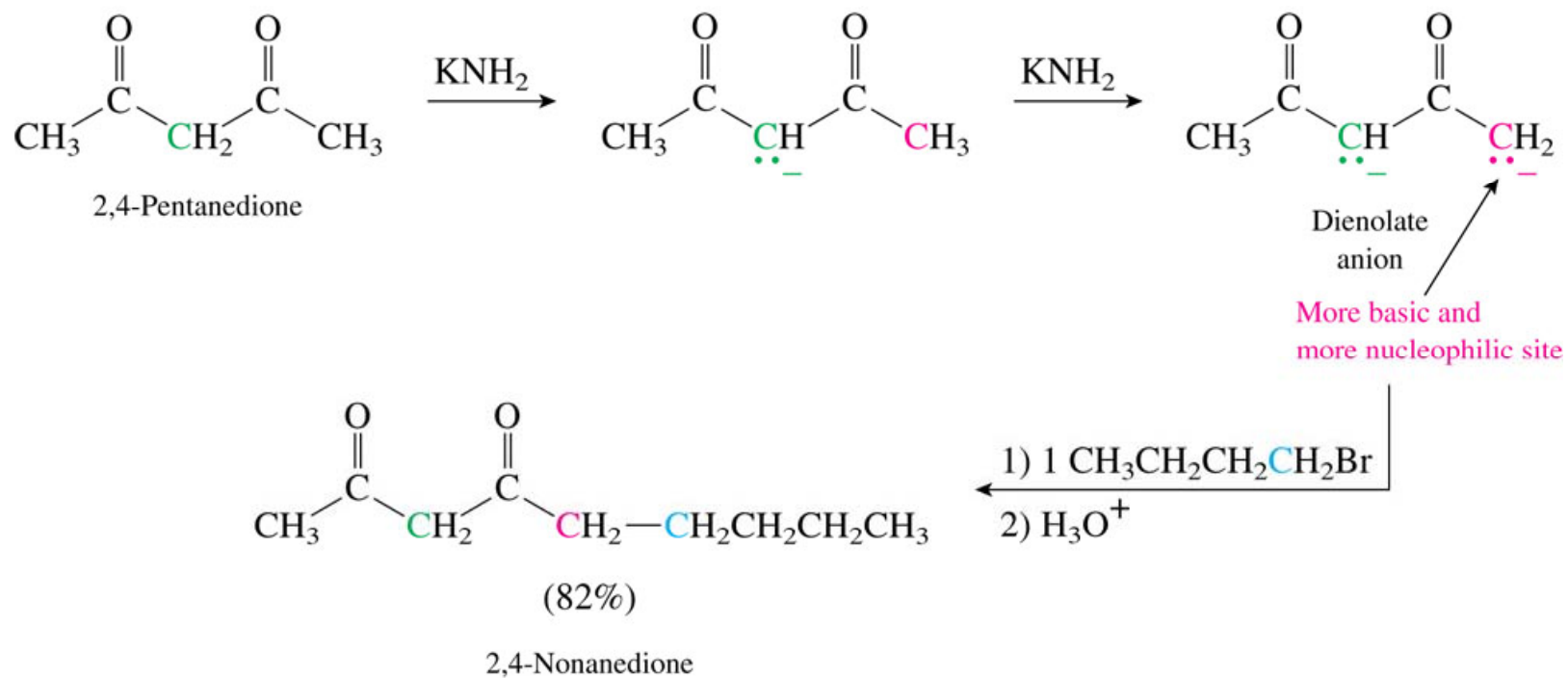
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Example reaction

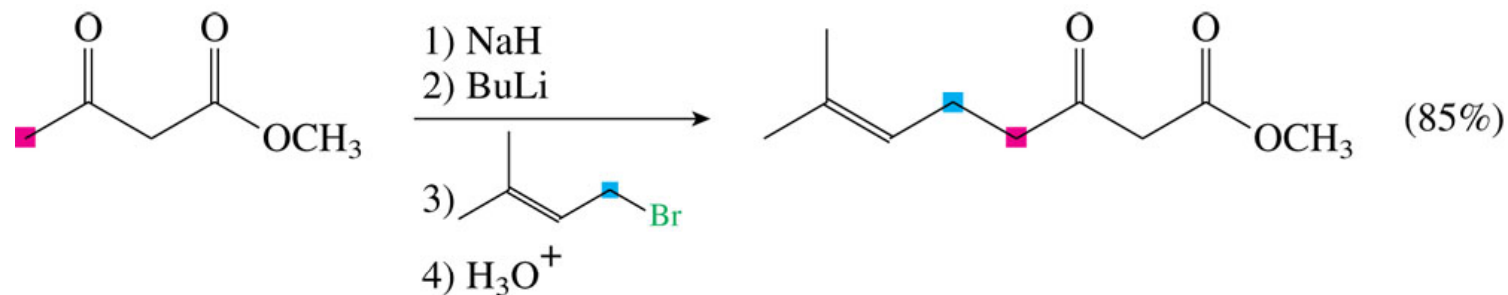


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Other Carbon Nucleophiles



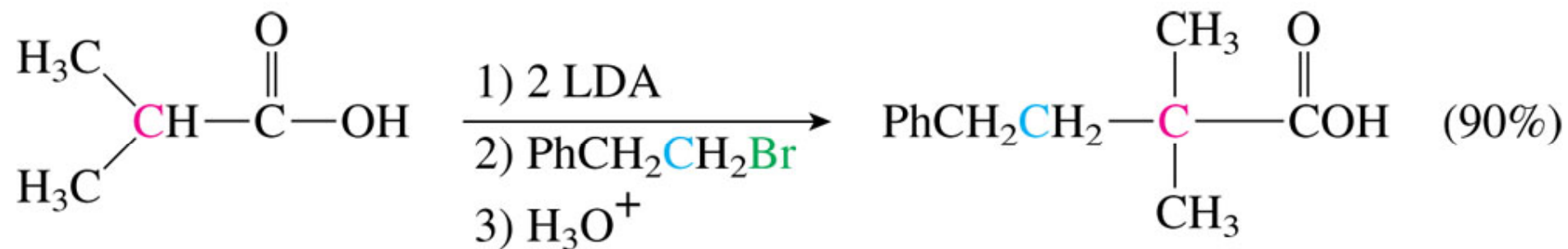
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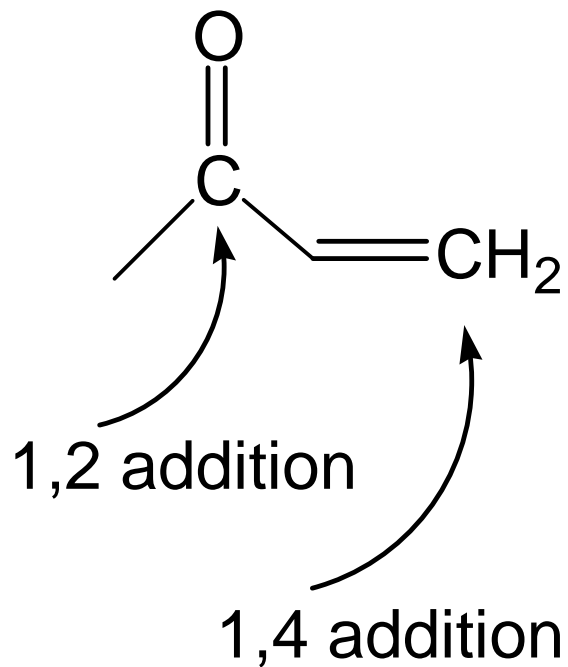
Using two equivalent of LDA

more nucleophilic site is reacted



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20.10 Conjugated Addition



1,2 addition: Grignard reagent, hydride
→ stronger nucleophile

1,4 addition: cyanide, amine
→ less reactive nucleophile
or sterically hindered

See CH 18.10

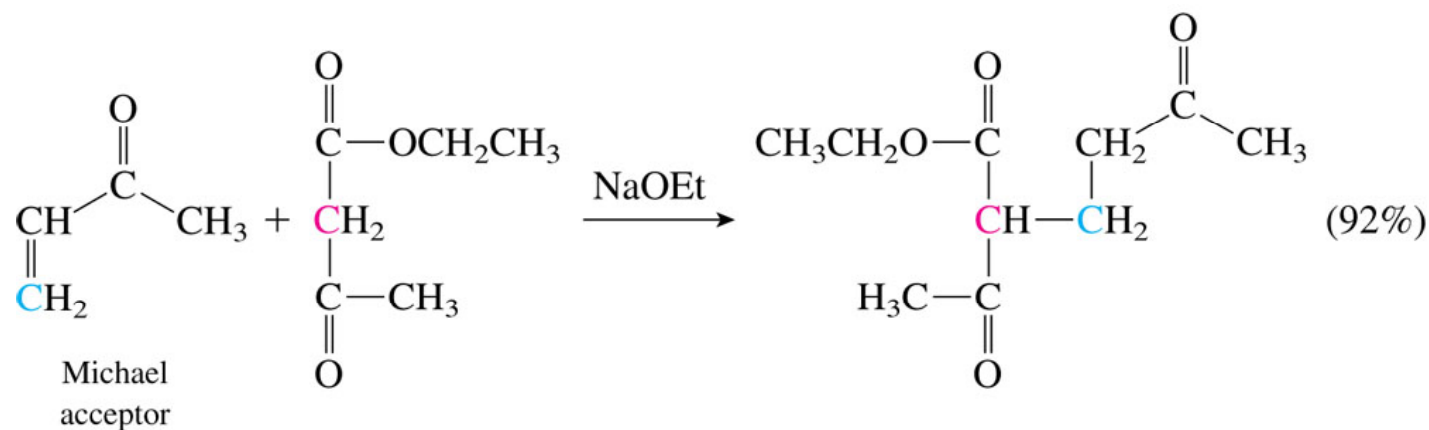
In CH 20 Michael reaction

→ enolate and related carbanion

+

α,β -unsaturated carbonyl compound

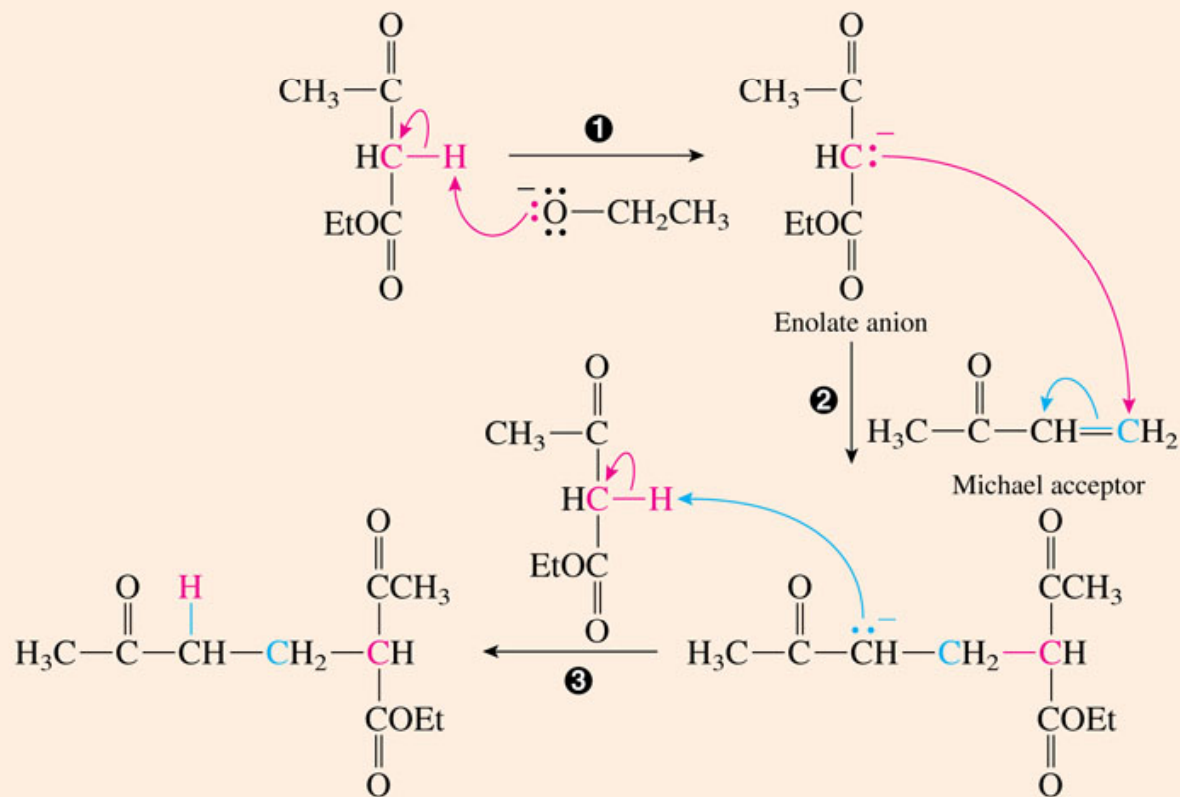
In Michael reaction only catalytic amount of base is needed



Michael reaction mechanism

1 The enolate anion of the β -dicarbonyl compound is generated in the usual manner.

2 The enolate nucleophile adds to the β -carbon of an α,β -unsaturated ketone (or ester or nitrile), which is called the Michael acceptor.

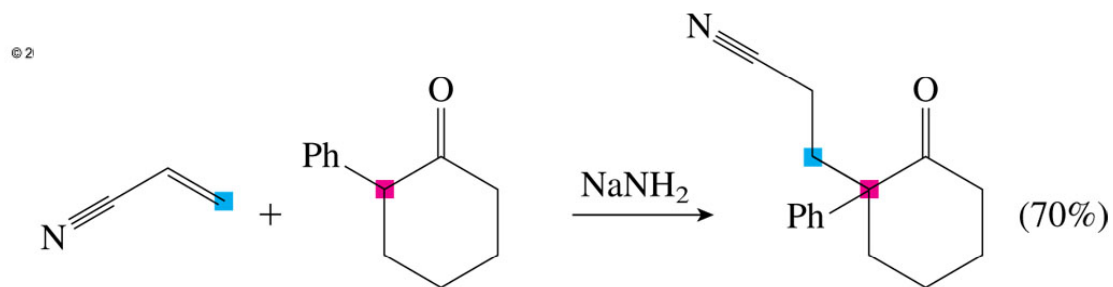
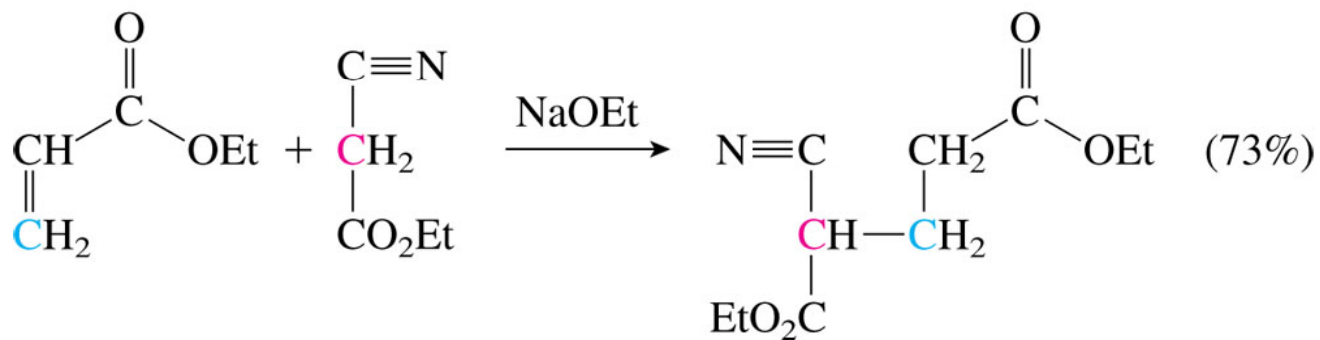
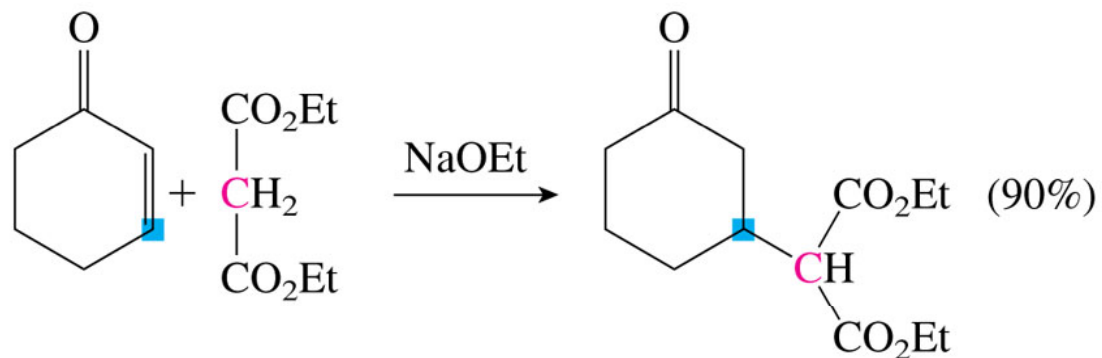


The product, formed in 92% yield in this case, has a bond from the α -carbon of the original enolate ion to the β -carbon of the Michael acceptor.

The product of this addition is an enolate ion.

3 This ion reacts as a base with ethyl acetoacetate to regenerate another enolate ion, so only a catalytic amount of base is needed for the reaction.

Examples of Michael reaction



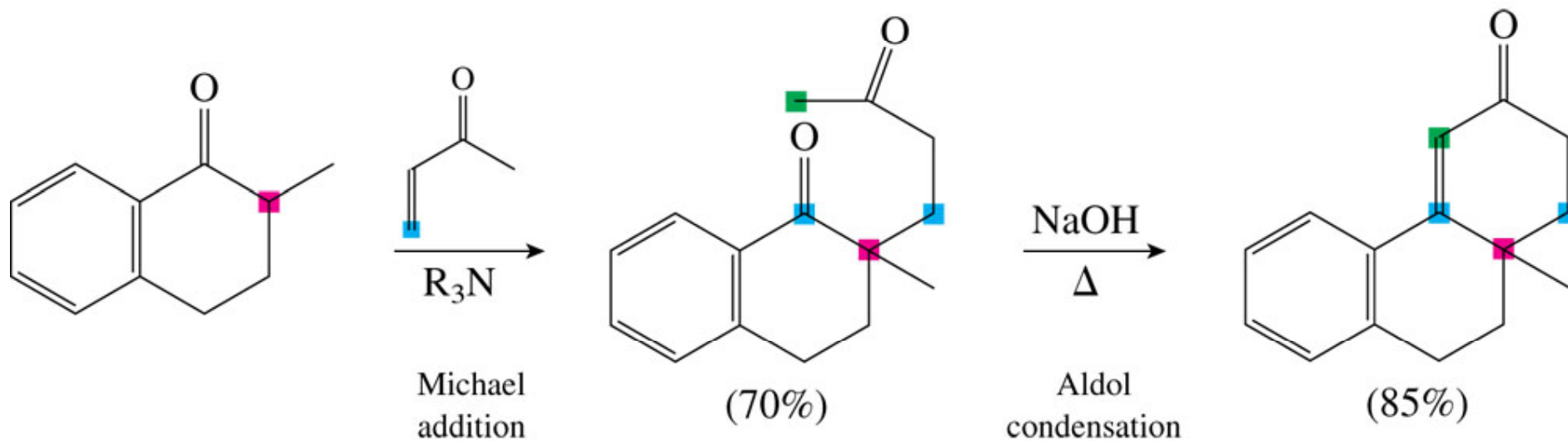
2-Propenenitrile

2-Phenylcyclohexanone

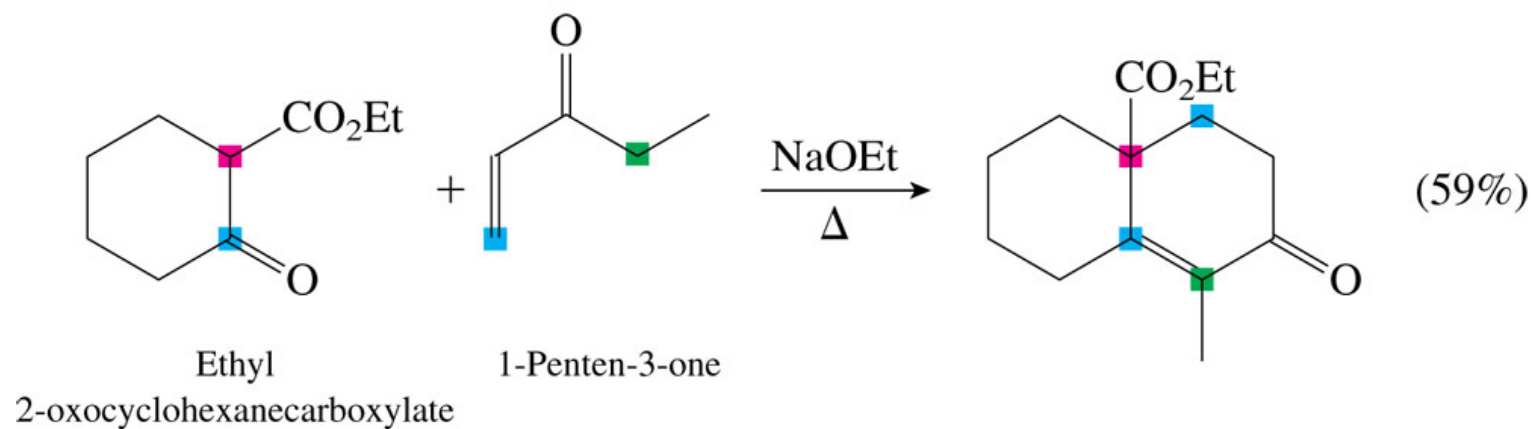
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Robinson annulation

⇒ Michael reaction + aldol condensation



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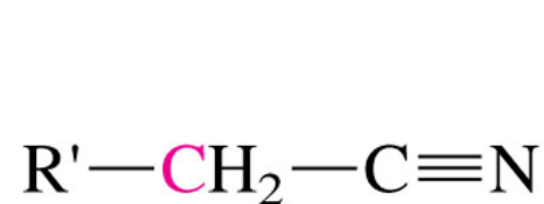
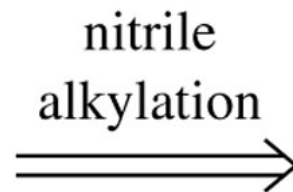
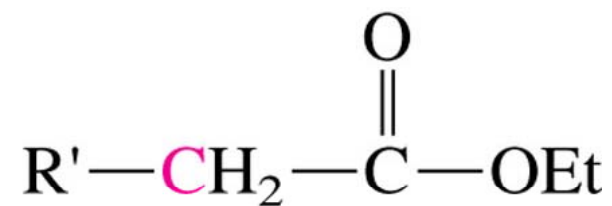
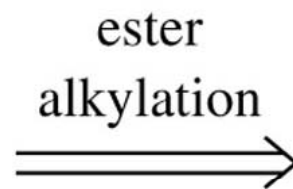
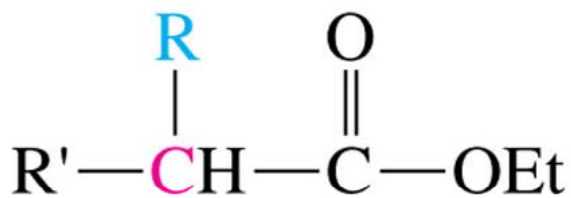
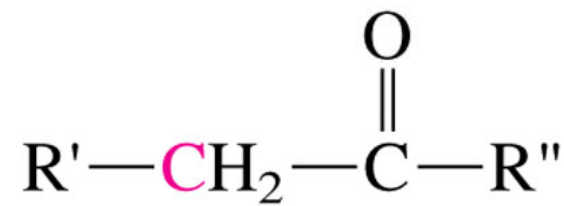
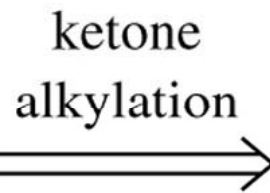
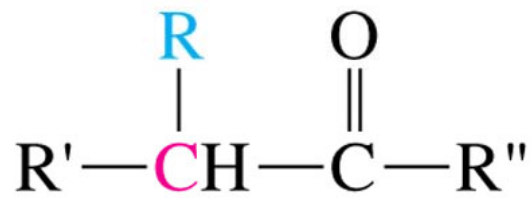
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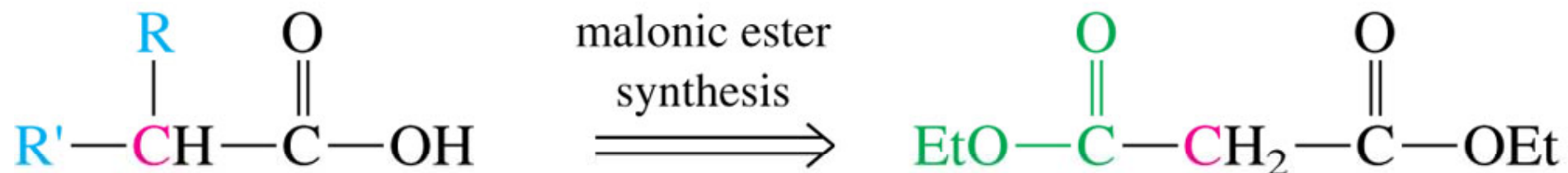
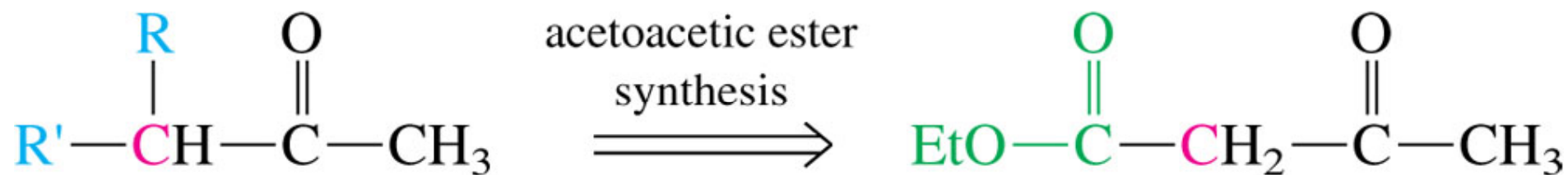
20.11 Synthesis

Retrosynthetic Arrow

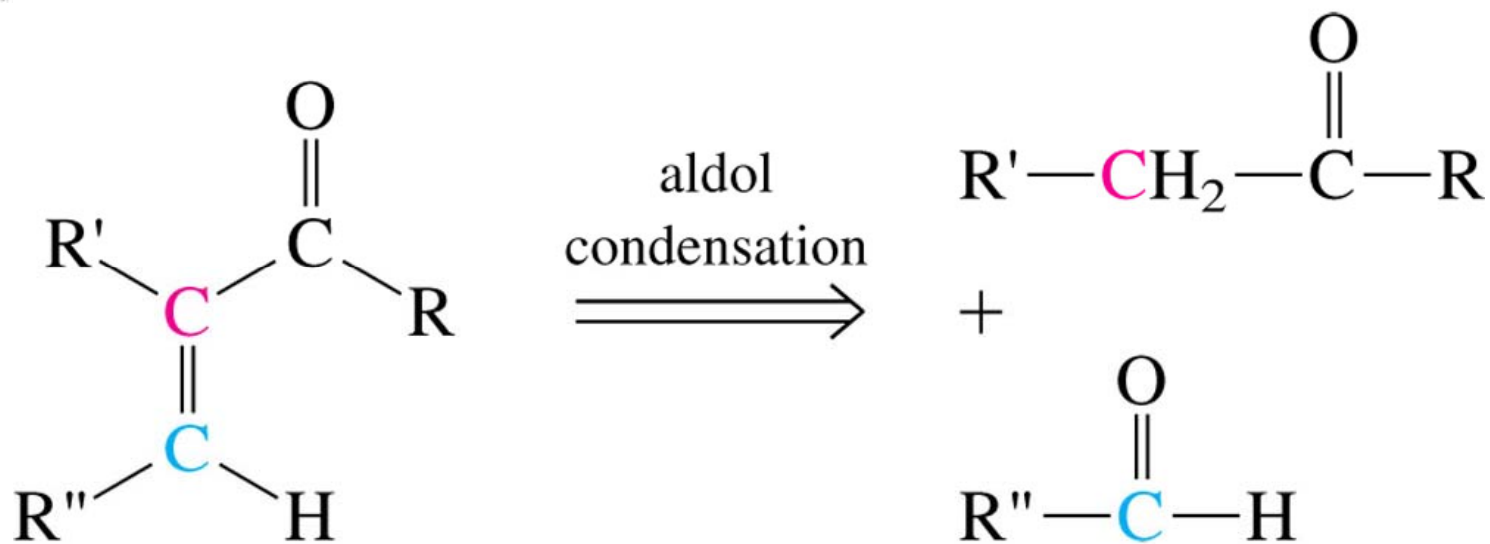
Target Compound

Starting Material

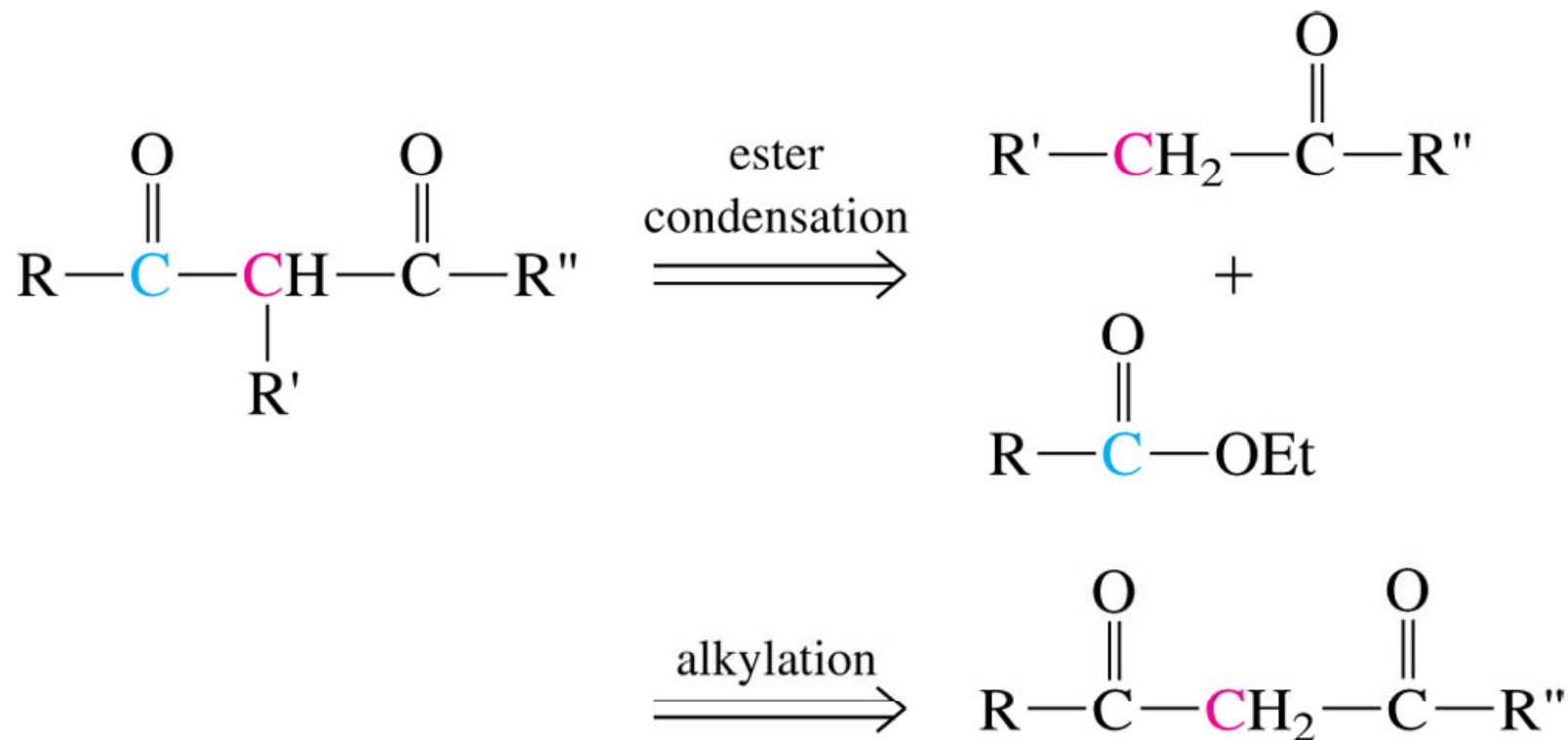




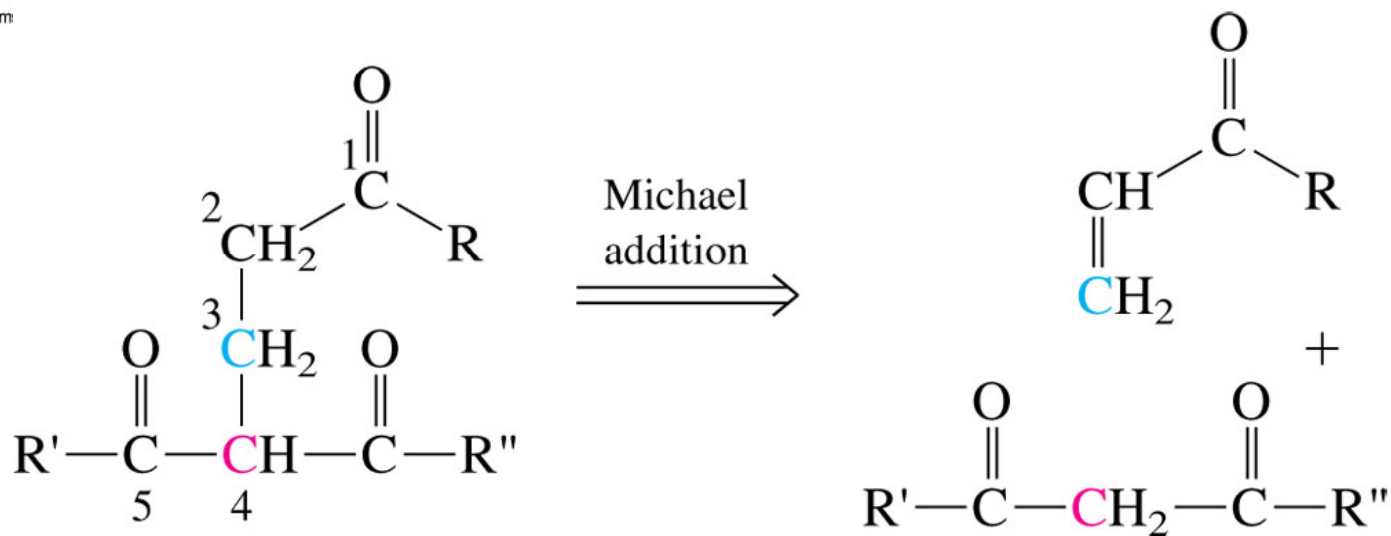
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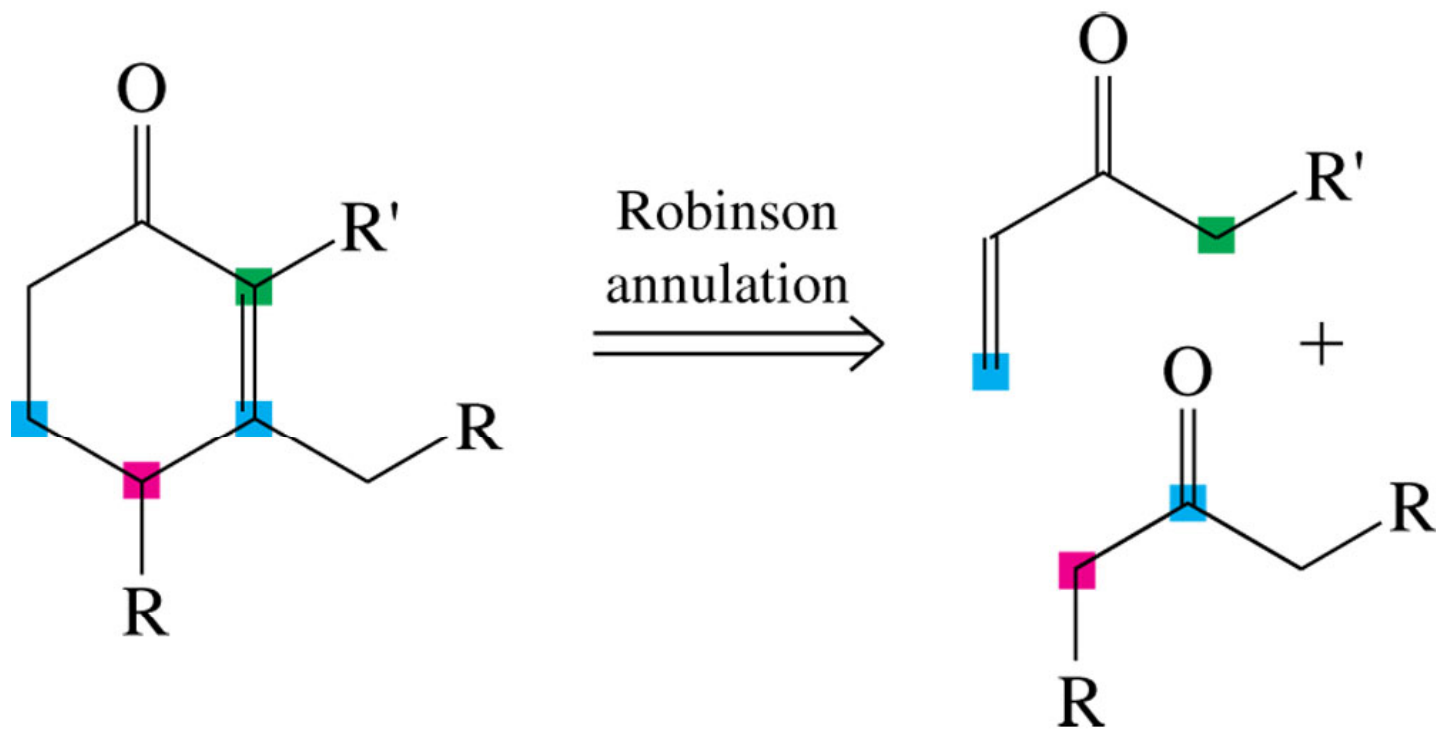


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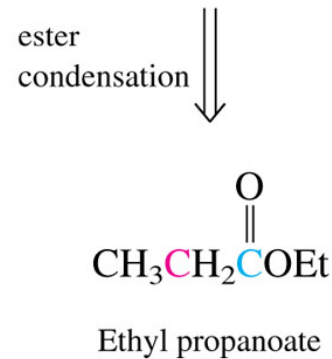
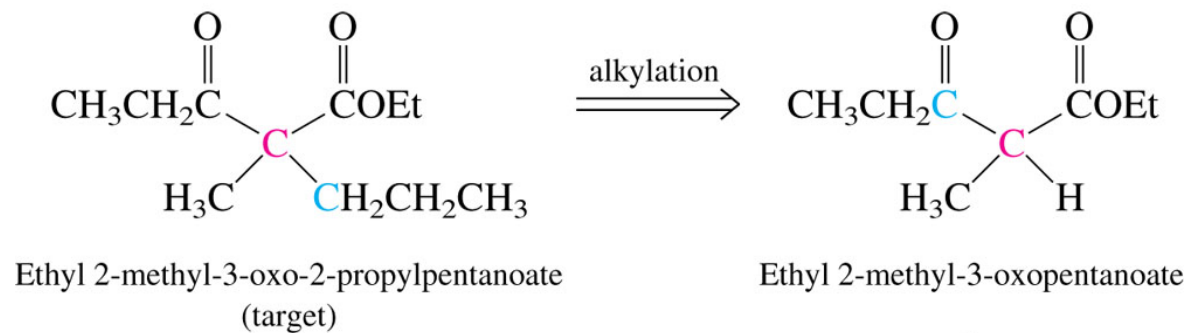


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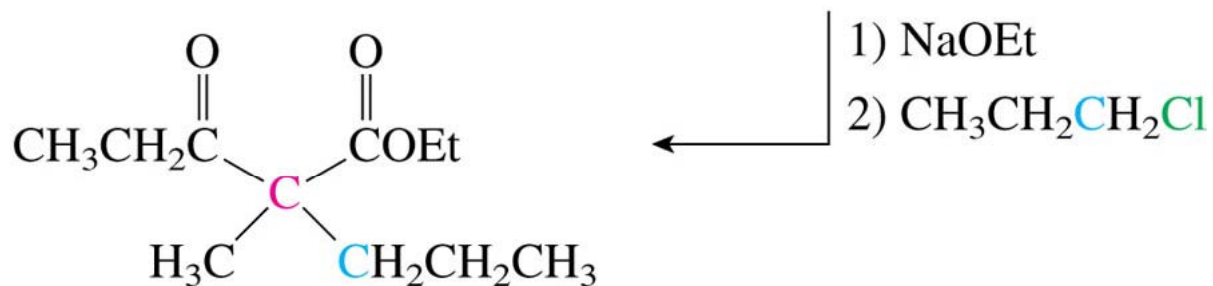
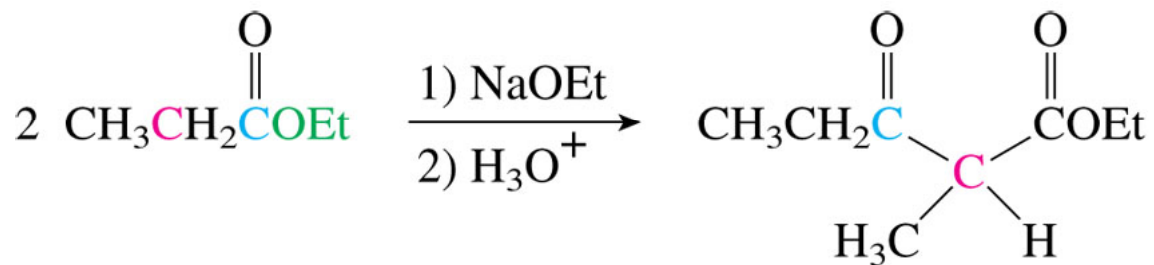




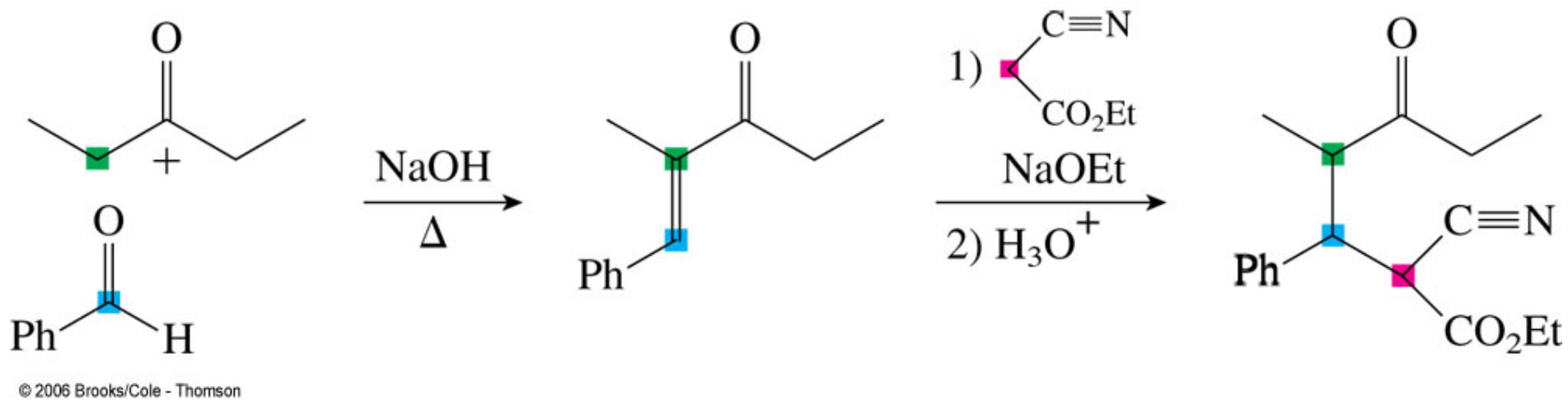
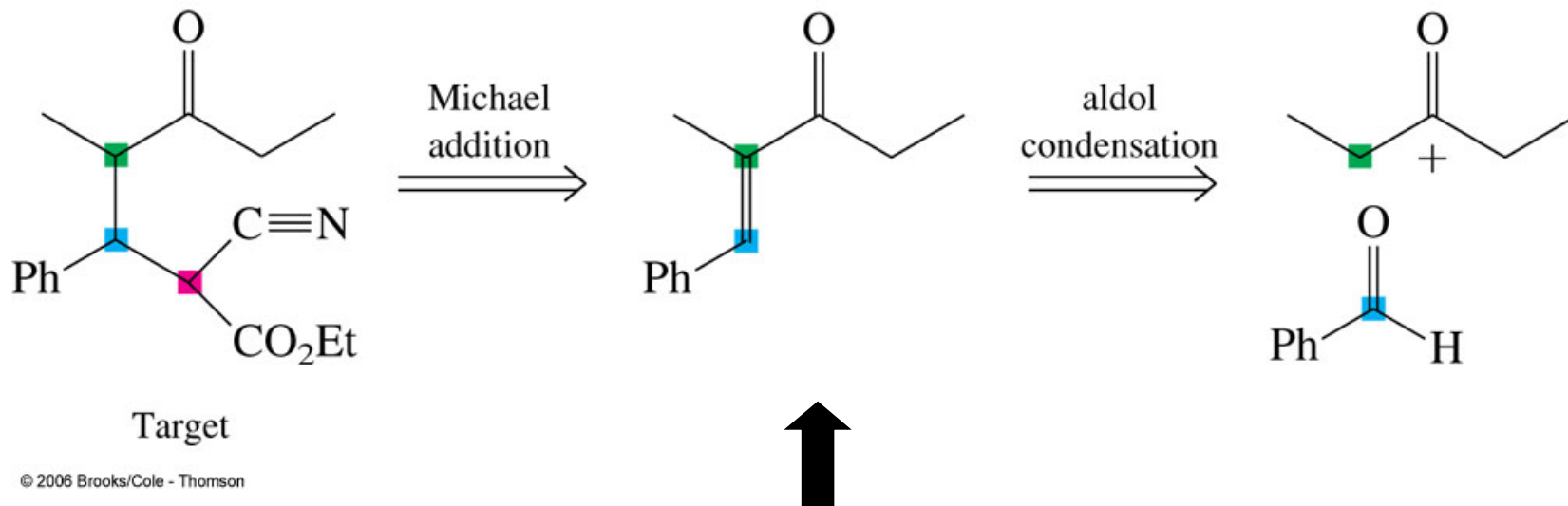
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Other example



Summary

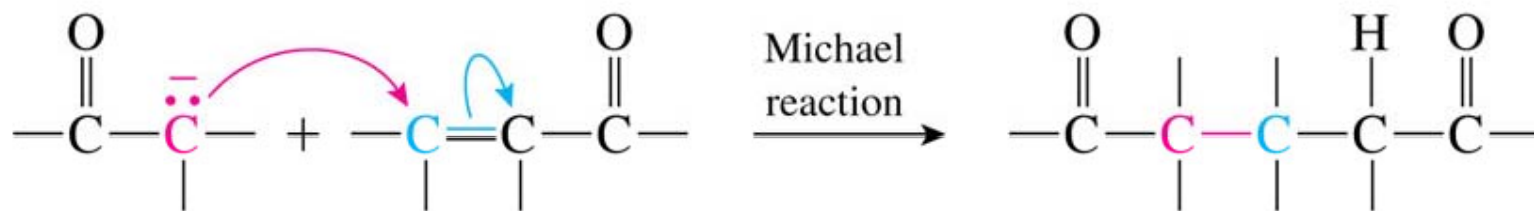
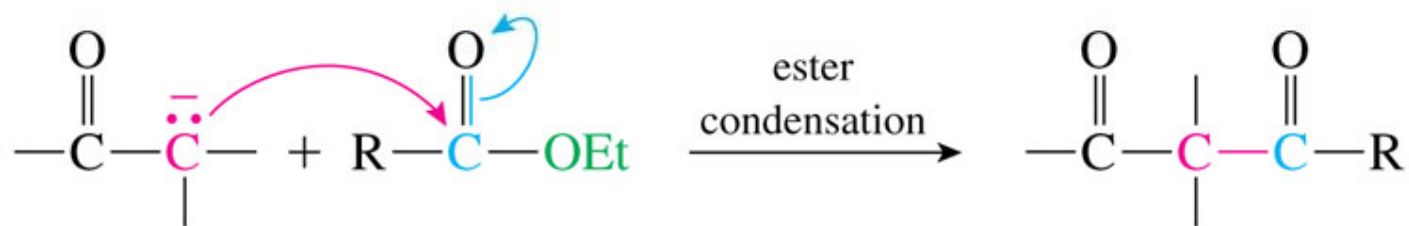
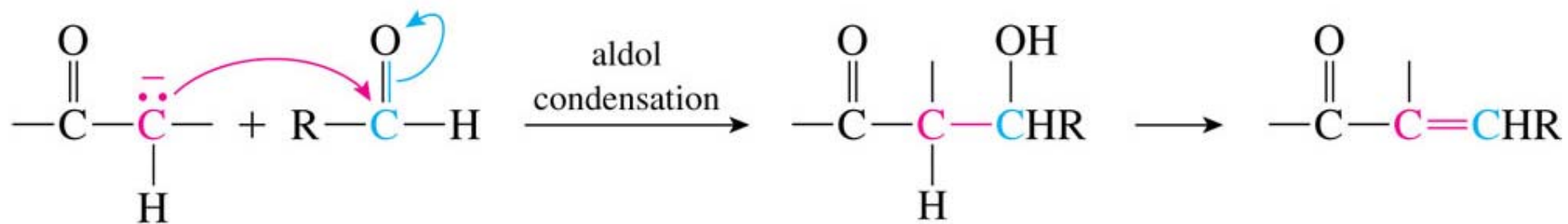


Table 20.2 Carbon Nucleophiles

Nucleophile	Comments
	<p>Because aldehydes are so reactive as electrophiles, enolate anions derived from them are primarily restricted to use in the aldol condensation.</p>
	<p>Enolate anions derived from ketones, esters, and nitriles can be alkylated, used in the aldol or ester condensations, or used in the Michael reaction.</p>
	<p>Enolate anions that are stabilized by two carbonyl groups (or cyano groups) can be alkylated and give excellent yields in the Michael reaction.</p>
	<p>Enamines react only with very reactive electrophiles.</p>
	<p>Dithiane anions are acyl anion equivalents and can be readily alkylated.</p>
	<p>These dianions can be selectively alkylated at the more basic site.</p>

Table 20.3 Electrophiles

Electrophiles	Comments
$\begin{array}{c} \text{H} \\ \\ \text{---C---L} \\ \end{array}$	The carbon must be primary or secondary to use these compounds in an S_N2 reaction. The leaving group can be a halide or a sulfonate group.
$\begin{array}{c} \text{O} \\ \\ \text{R---C---H} \end{array}$	Aldehydes are very reactive electrophiles in the aldol condensation.
$\begin{array}{c} \text{O} \\ \\ \text{R---C---R}' \end{array}$	Ketones are less reactive and are most useful when the aldol condensation is intramolecular.

Table 20.3 Electrophiles—cont'd

Electrophiles	Comments
$\begin{array}{c} \text{O} \\ \\ \text{R---C---OR}' \end{array}$	Esters are useful in the Claisen ester condensation. Most often, $R' = \text{Me}$ or Et .
$\begin{array}{c} \text{O} \\ \\ \text{---C---C---} \\ \\ \text{C} \\ \end{array}$	α,β -Unsaturated compounds are useful in the Michael reaction. A cyano group can be used in place of the carbonyl group.

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