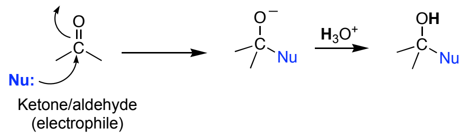
Chapter 23. Carbonyl Condensation Reactions

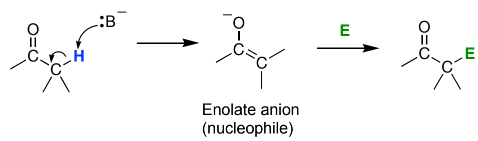
As a result of the large dipole of the carbonyl group:

1. The carbonyl carbon is electrophilic and is the site of addition reactions by nucleophiles;



Chapters 19 & 20

2. The α-protons are acidic and can be deprotonated by strong bases to give an enolate, which are nucleophiles and react with electrophiles.



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23.1 Mechanism of Carbonyl Condensation Reactions
An enolate of one carbonyl (nucleophile) reacts with the carbonyl carbon (electrophile) of a second carbonyl compound (1,2-addition reaction) resulting in the formation of a new C-C bond

General mechanism (Fig. 23.1, page 855):

Nucleophilic carbonyl: aldehydes, ketones, esters, amides and nitrile

Electrophilic carbonyl: aldehydes, ketones, α,β-unsaturated ketones, and esters

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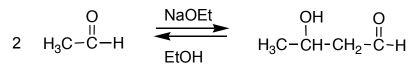
23.2 Condensations of Aldehydes and Ketones: The Aldol Reaction

The base-catalyzed self-condesnation reaction of acetaldehyde gives 3-hydroxybutanal (aldol)



acetaldehyde

3-hydroxybutanal
(β-hydroxy aldehyde)

General mechanism of the aldol reaction (Fig. 23.2, page 857)

The base-catalyzed aldol reaction (NaOEt, EtOH) is reversible

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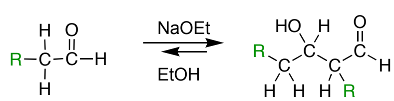
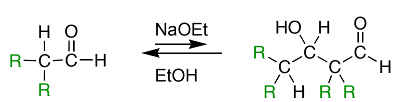
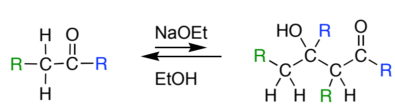
The position of the equilibrium for the aldol reaction is highly dependent on the reaction conditions, substrates, and steric considerations of the aldol product.



aldol reactions involving α-monosubstituted aldehydes are generally favorable



aldol reactions involving α,α-disubstituted aldehydes are generally unfavorable



aldol reactions involving ketones are generally unfavorable

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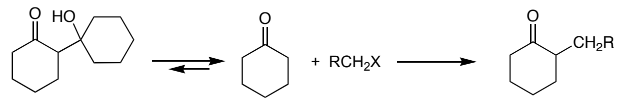
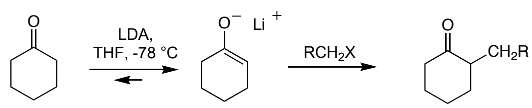
23.3 Carbonyl Condensation Reactions versus Alpha-Substitution Reactions



How do you suppress carbonyl condensation during an α-alkylation reaction??



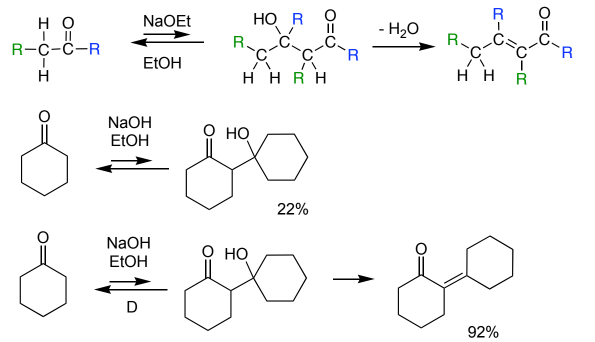
The enolate is discretely and quantitatively generated with LDA at low temperature, then the alkyl halide is added to the solution of the enolate.

23.4 Dehydration of Aldol Products: Synthesis of Enones

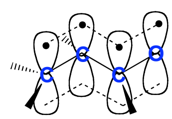
The β-hydroxy carbonyl product of the aldol reaction can undergo dehydration to yield a conjugated enones; this step is irreversible and is catalyzed by either acid or base.

Mechanisms (p. 859)

The aldol reaction can be driven toward products by dehydration



The π-orbitals of the C=C and C=O are in conjugation, which is a stabilizing influence of α,β-unsaturated carbonyls



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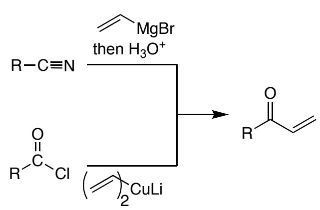
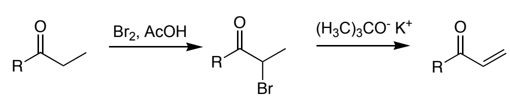
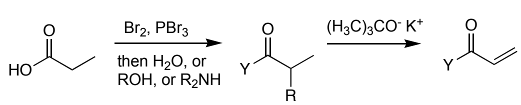
Synthesis of α,β-unsaturated carbonyl compounds



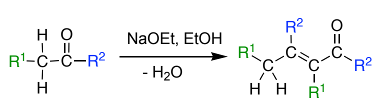
α,β-unsaturated ketones



α,β-unsaturated ketones and aldehydes



α,β-unsaturated acids, esters and amides



α,β-unsaturated ketones, aldehydes and esters

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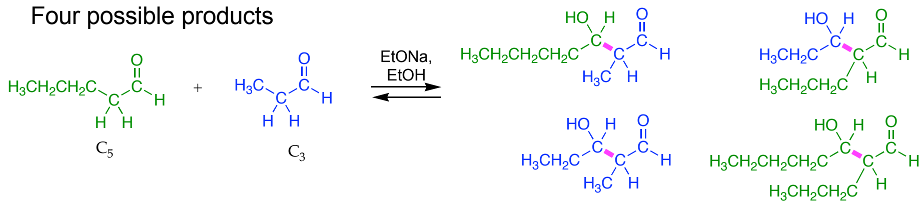
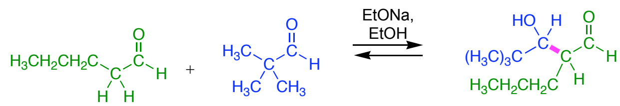
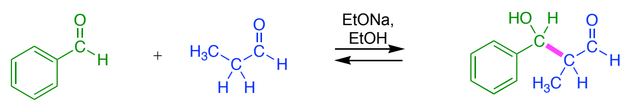
23.6 Mixed Aldol Reactions
Aldol reaction between two different carbonyl compounds

Four possible products



Aldehydes with no α-protons can only act as the electrophile





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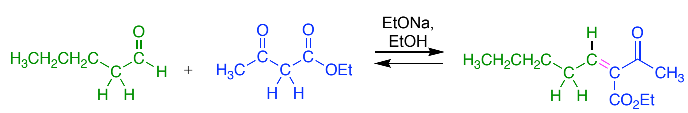
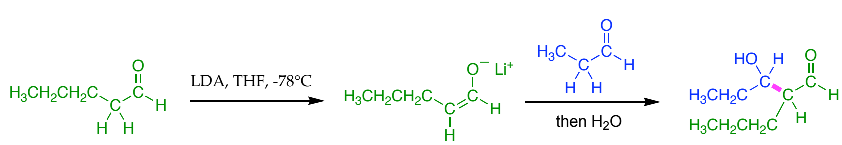
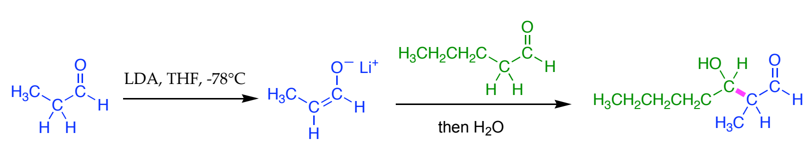
One of the carbonyl compounds is significantly more acidic



Discrete (*in situ*) generation of an enolate with LDA





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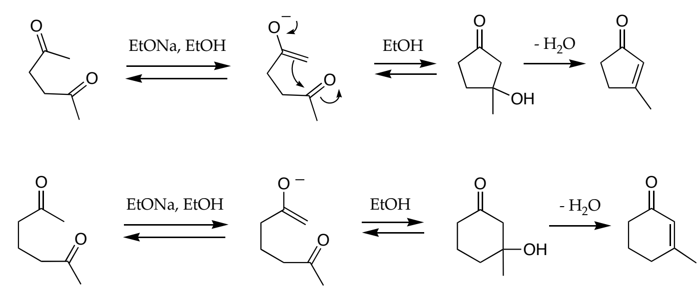
23.7 Intramolecular Aldol Reactions

Treatment of a dicarbonyls compound can lead to an intramolecular aldol condensation. Formation of five- and six-membered rings are favorable.



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More favorable ring sizes (less strained) are made from intramolecular reactions

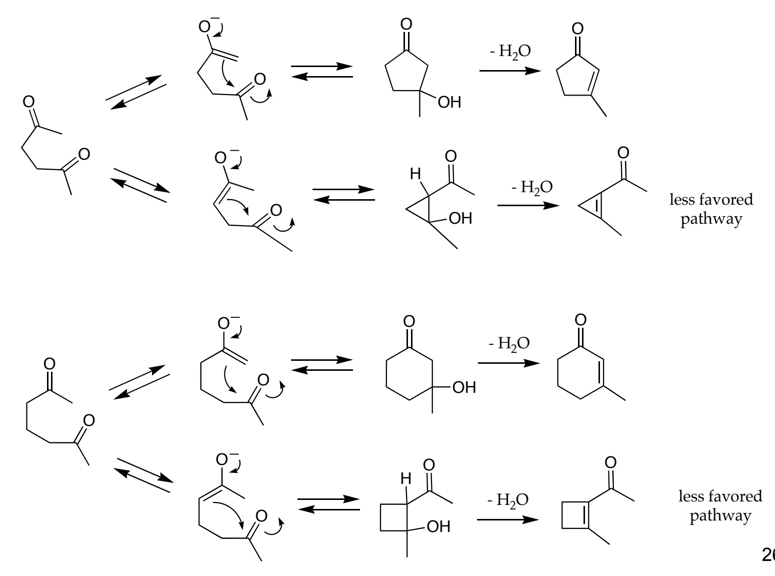

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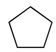
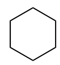
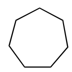
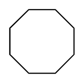
Figure 4.8 (page 111)

	Cycloalkane	Ring Size (n)	ΔH_{comb} KJ/mol	ΔH_{comb} per -CH_2- KJ/mol	Total Strain Energy
Strained rings		3	2090	698	115
		4	2744	686	110
Common rings		5	3220	664	27
		6	3952	659	0
		7	4637	662	27
Medium rings		8	5310	664	42
	Cyclononane	9	5981	665	54
	Cyclodecane	10	6636	664	50
< 12 Large rings	Cyclopentadecane	15	9985	659	0
	Alkane reference			659	0

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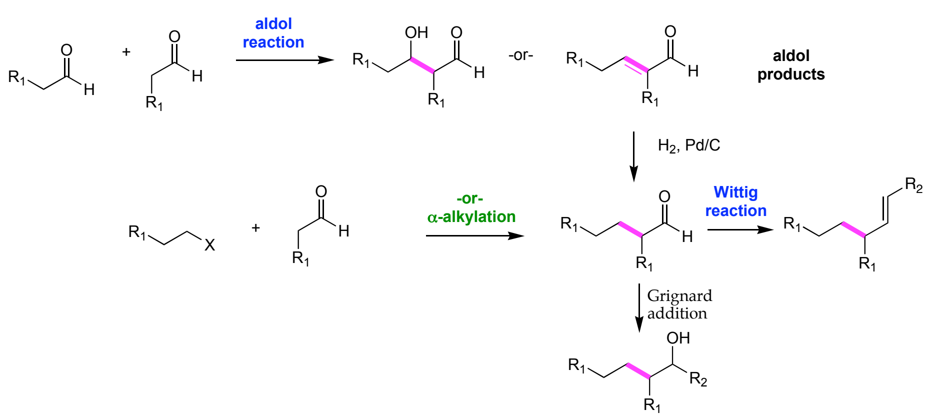
23.5 Using Aldol Reactions in Synthesis

Very important C-C bond forming reaction. Readily make large carbon skeletons from smaller ones



Robert B. Woodward (Harvard): 1965 Nobel Prize in Chemistry

"for his outstanding achievements in the art of organic synthesis"

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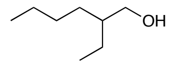
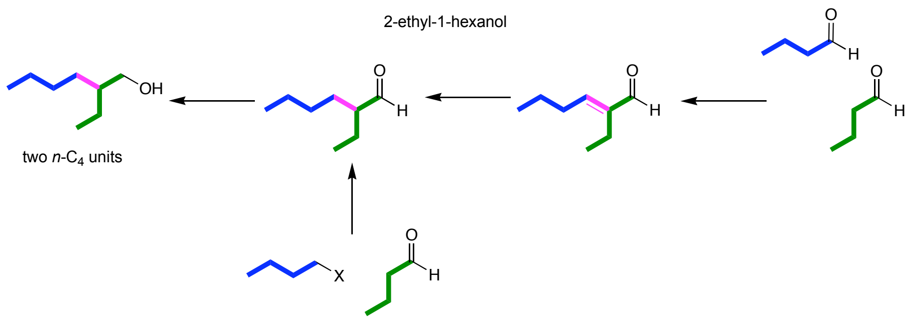


2-ethyl-1-hexanol



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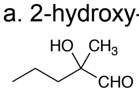
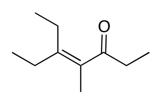
Problem 23.5: Which of the following are aldol condensation products?

a. 2-hydroxy-2-methylpentanal

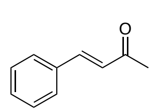


b. 5-ethyl-4-methyl-4-hepten-3-one

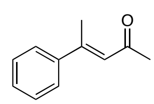


Problem 23.8: Which of the following can probably be prepared by a mixed aldol reaction?

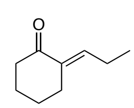
a.



b.



c.



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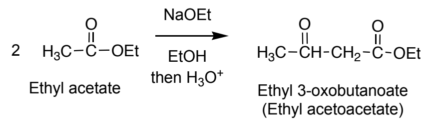
23.8 The Claisen Condensation Reaction
Base catalyzed condensation of two esters to give a β-keto-ester product



Mechanism: has features of the aldol and nucleophilic acyl substitution reactions (Fig. 23.5, page 866)

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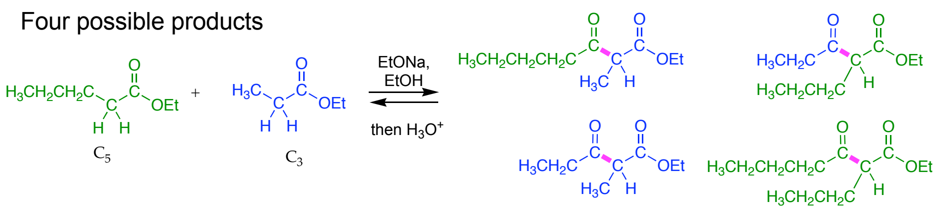
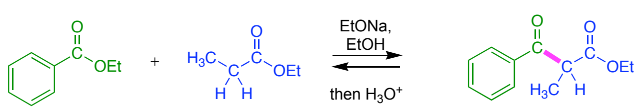
The product β-keto ester product of the Claisen condensation is more acidic than the reactants; deprotonation of the product drives the reaction forward. One full equivalent of base must be used in the Claisen condensation.

23.9 Mixed Claisen Condensation
Strategies are similar to that of the mixed aldol reaction.

Four possible products



Esters with no α-protons can only act as the electrophile



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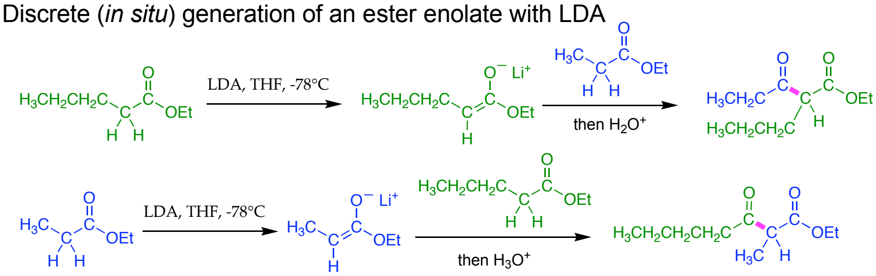
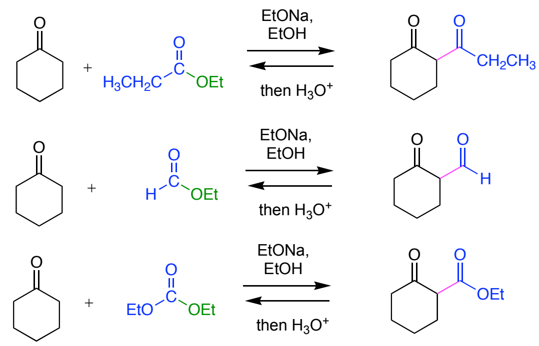
Discrete (*in situ*) generation of an ester enolate with LDA



Mixed Claisen condensations with a ketone enolate and esters



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23.10 Intramolecular Claisen Condensations: The Dieckmann Cyclization

Dieckmann cyclization is an intramolecular Claisen condensation.

Mechanism: same as the Claisen (Fig. 23.6, page 879)

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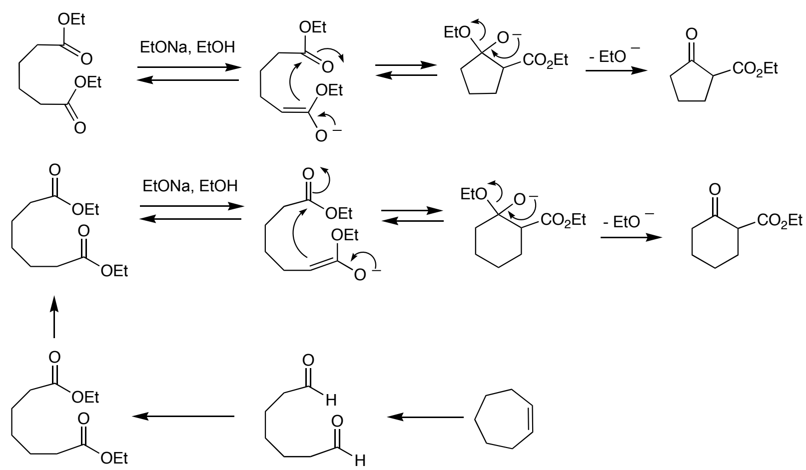
Dieckmann Cyclization works best with 1,6-diesters, to give a 5-membered cyclic β-keto ester product, and 1,7-diesters to give 6-membered cyclic β-keto ester product.



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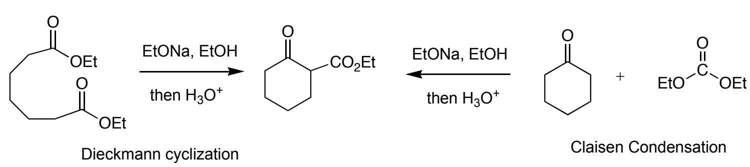
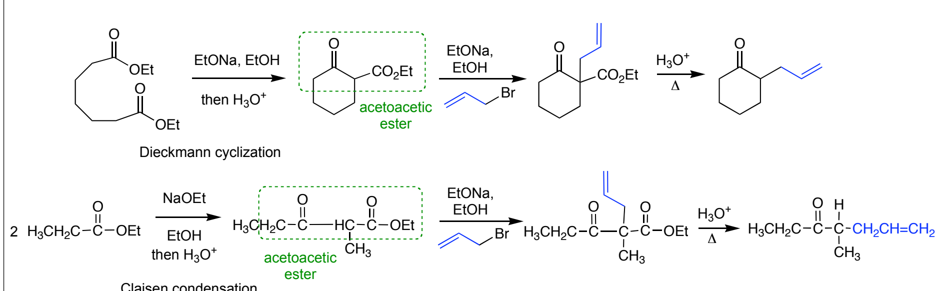


The product of a Claisen condensation or Dieckmann cyclization is an acetoacetic ester (β-keto ester)



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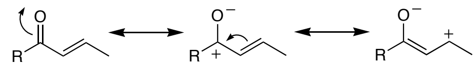
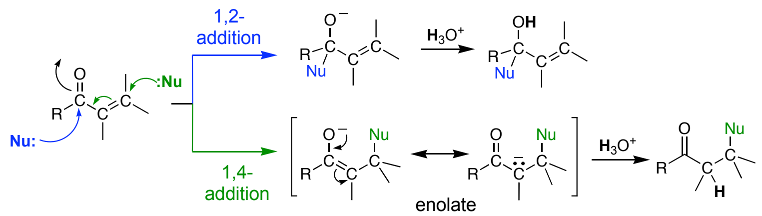
23.11 The Michael Reaction

The conjugate (1,4-) addition of a enolate with an α,β–unsaturated ketone

Recall from Chapter 19.14





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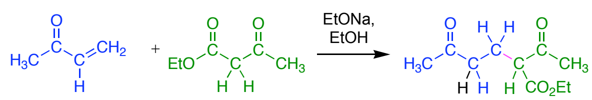
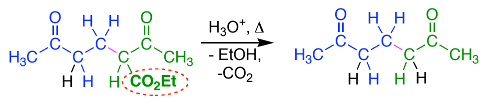
The Michael reaction: works best with enolates of β-dicarbonyls.



Mechanism (Fig 23.7, page 872)

This Michael addition product can be decarboxylated



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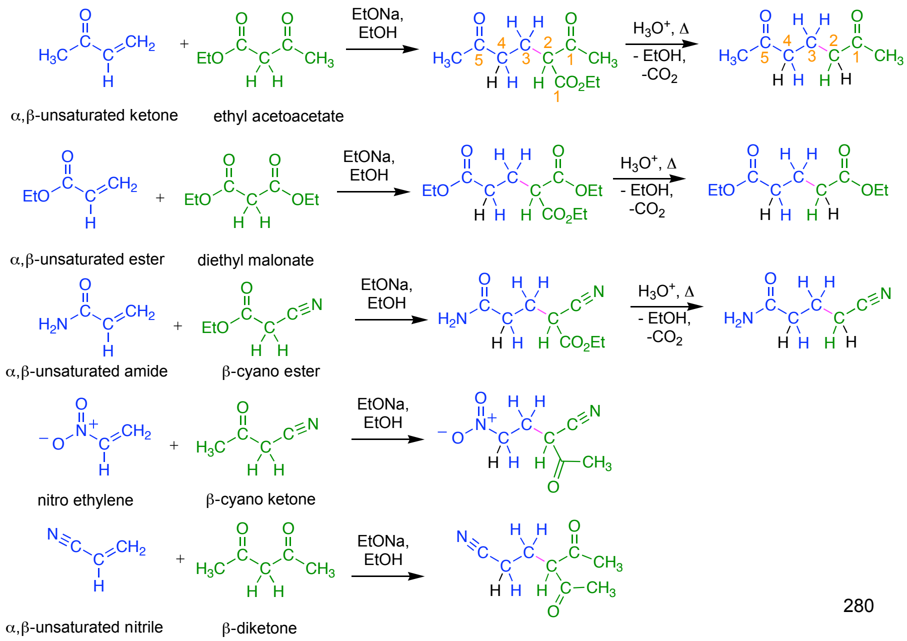
A Michael addition product is a 1,5-dicarbonyl compound



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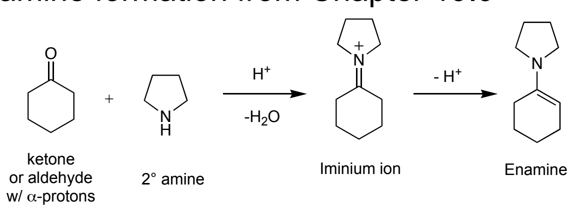
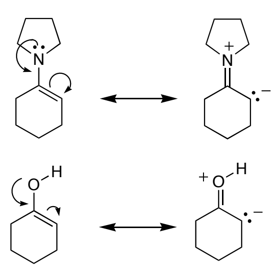
23.12 The Stork Enamine Reaction
recall enamine formation from Chapter 19.9



Enamines are reactive equivalents of enols and enolates



Enamines undergo α-substitution with electrophiles

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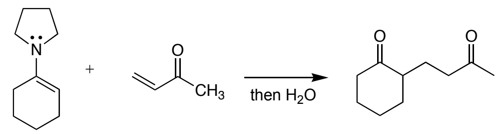
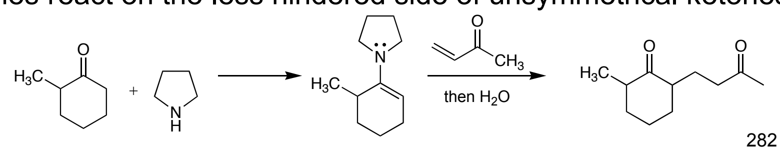
Reaction of enamine with α,β-unsaturated ketones (Michael reaction). Mechanism: Page 875



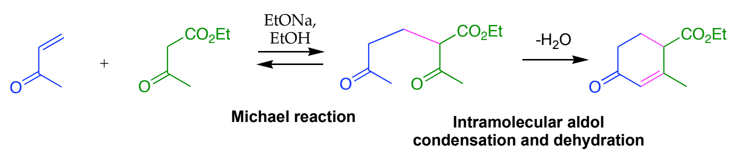
Enamines react on the less hindered side of unsymmetrical ketones

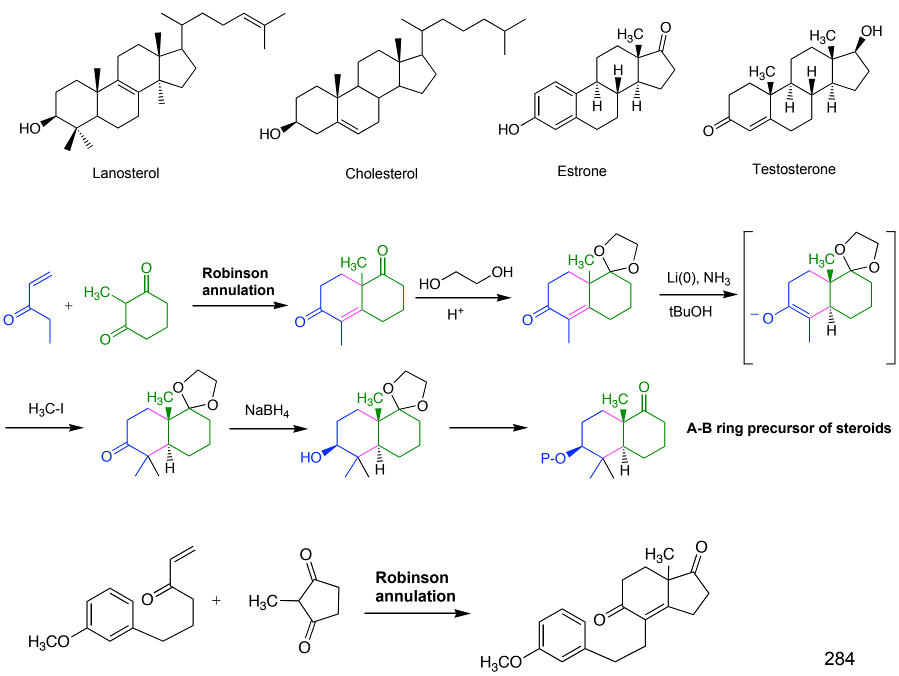


23.13 Carbonyl Condensation Reactions in Synthesis: The Robinson Annulation Reaction

annulation: to build a ring onto a reaction substrate.

Robinson annulation: two stage reaction involving a Michael reaction followed by an intramolecular aldol reaction.





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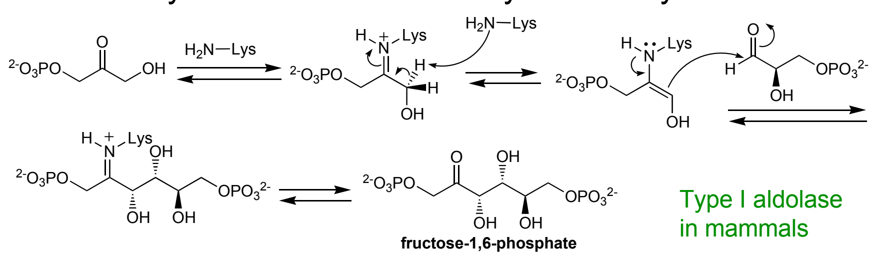
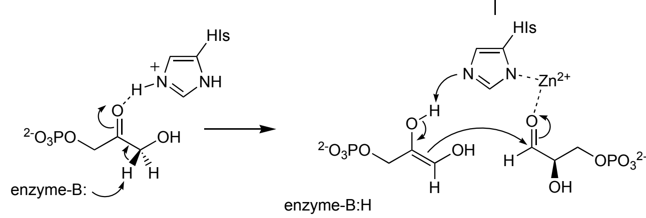
23.14 Biological Carbonyl Condensation Reactions (please read)

Aldolase enzyme: involved in carbohydrate biosynthesis



Type I aldolase
in mammals



Type II aldolase
in yeast and bacteria

Enzymatic Claisen condensations in Chapter 27

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