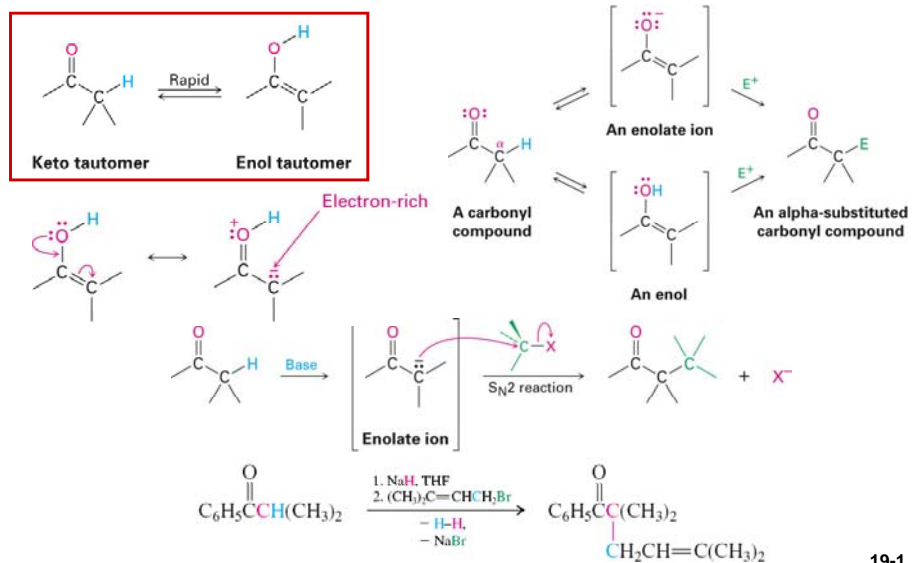
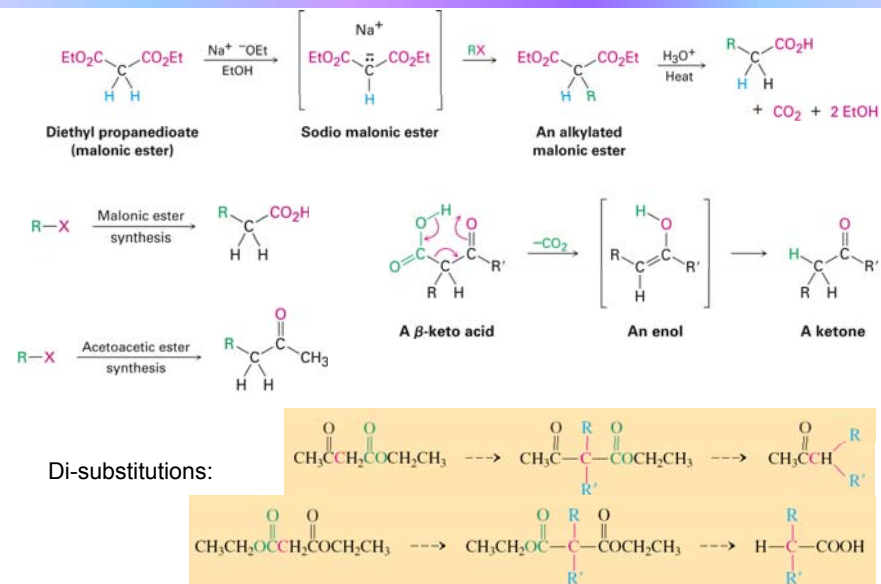


# Review of Keto-Enol Tautomerism and $\alpha$ -Substitution of Carbonyl Groups



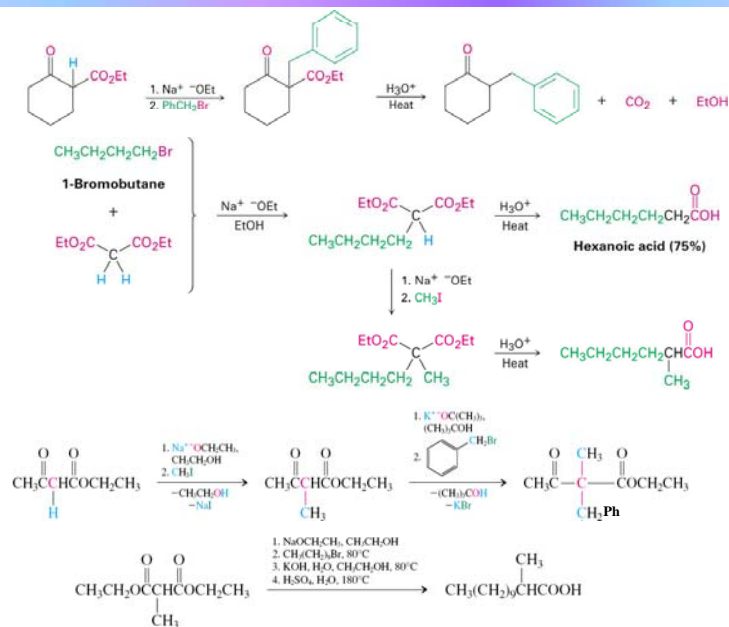
19-1

# Malonic and Acetoacetic Ester Syntheses



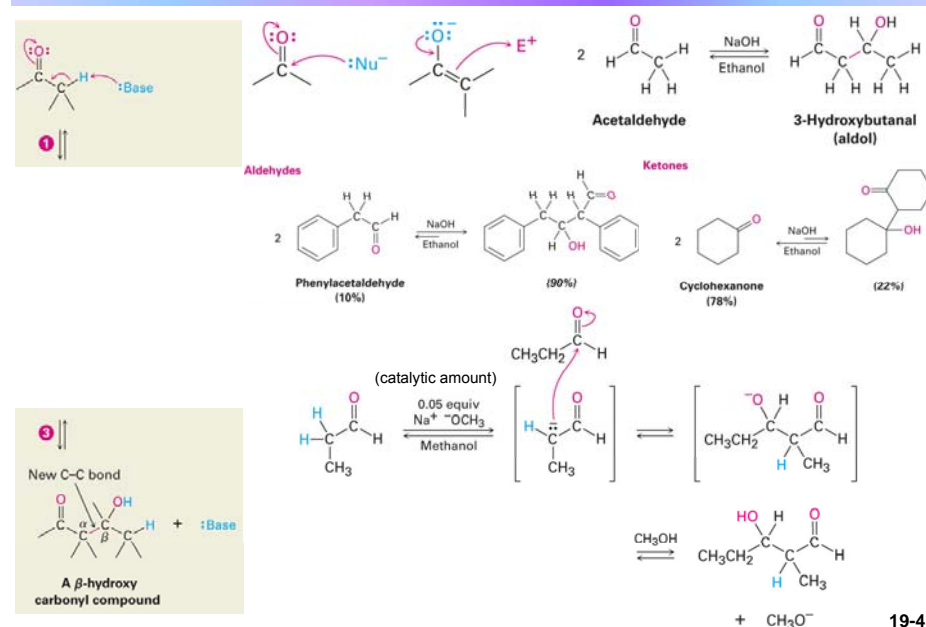
19-2

# Examples of Malonic and Acetoacetic Ester Synthesis



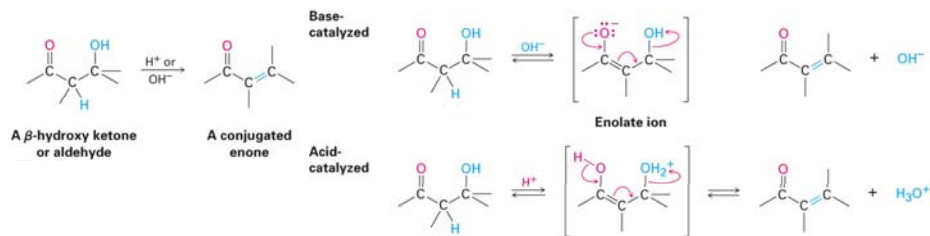
19-3

# Attack by Enolates on the Carbonyl: Aldol Condensation

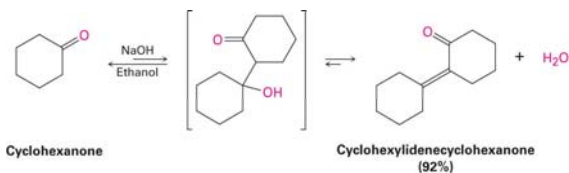


19-4

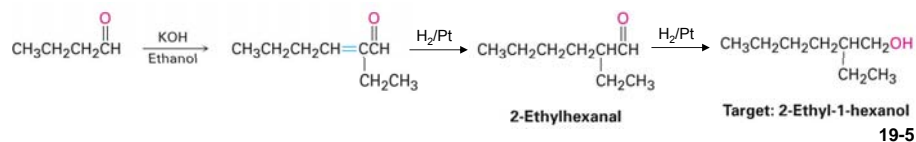
## Dehydration of Aldols



Dehydration Drives a Ketone Condensation

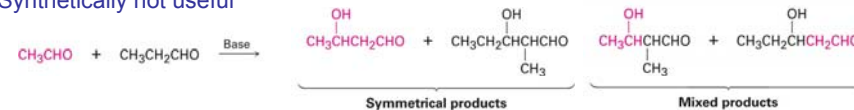


Application of Aldol Condensation

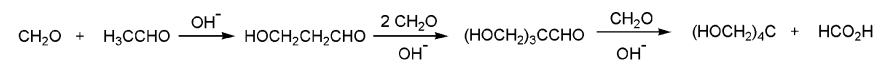


## Mixed Aldol Reactions

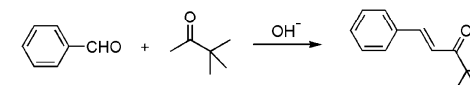
Synthetically not useful



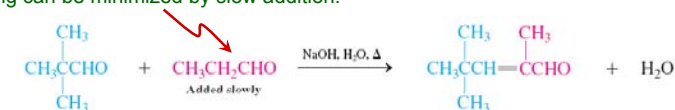
useful mixed aldol reactions



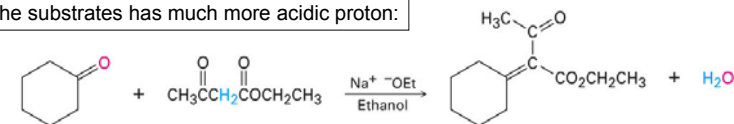
Aldehydes without  $\alpha$ -hydrogen as nucleophile acceptors:



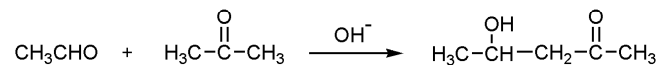
Homo-coupling can be minimized by slow addition.



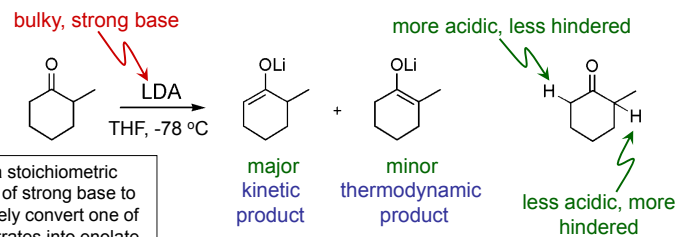
One of the substrates has much more acidic proton:



## Mixed Aldol Reactions

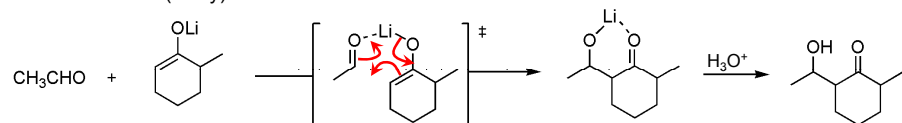


(realized by slow addition of acetaldehyde into acetone and base solution; self-condensation of acetone is reversible and unfavorable)

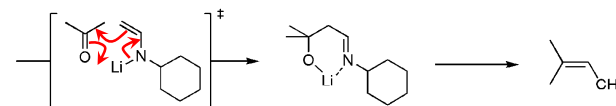
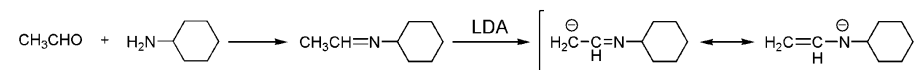


Use a stoichiometric amount of strong base to completely convert one of the substrates into enolate.

strong bases: **LDA, Ph<sub>3</sub>CNa, NaH, NaNH<sub>2</sub>**, etc. (bulky)



## Mixed Aldol and Mannich Reaction



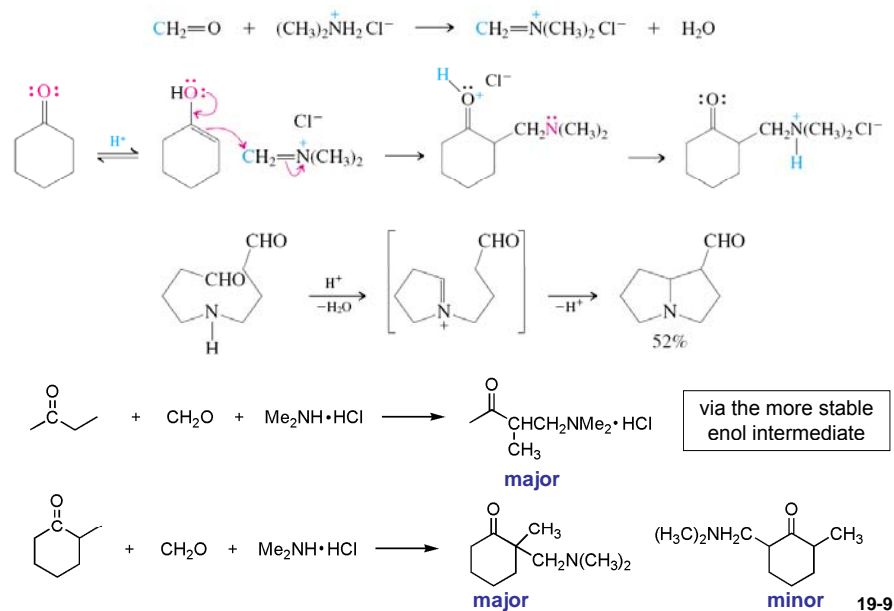
Aldehydes are protected before it is made into lithium salts; in the form of imine, it is less reactive and not attacked by carboanion.



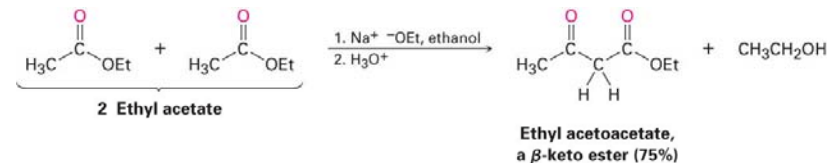
Mannich Reaction



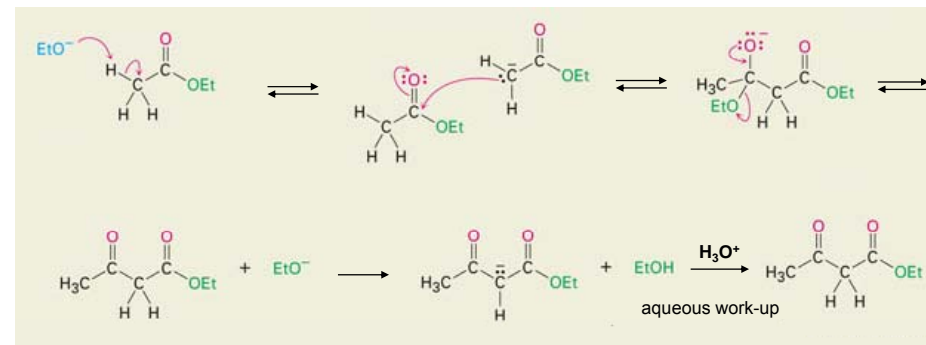
## Mechanism and Application of Mannich Reaction



## Claisen Condensation



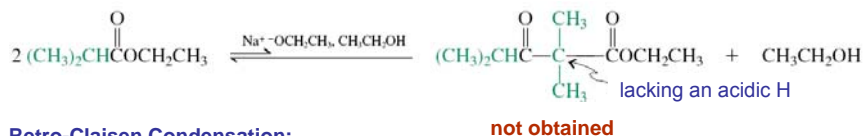
Mechanism:



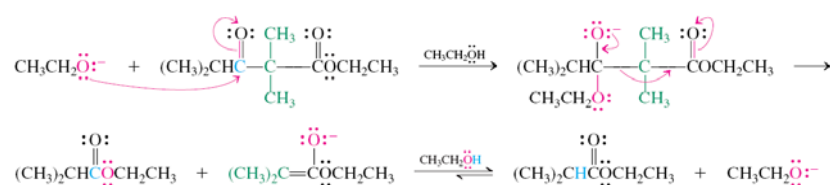
Deprotonation of keto-ester drives the equilibrium.

19-10

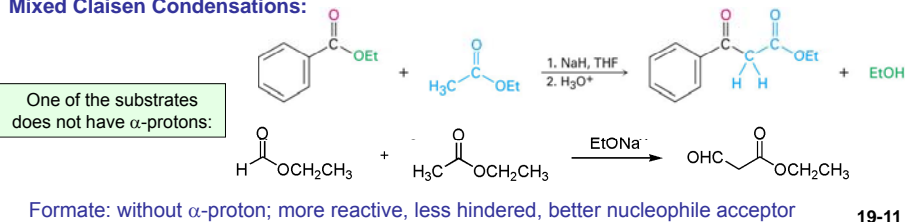
## Retro- and Mixed Claisen Condensation



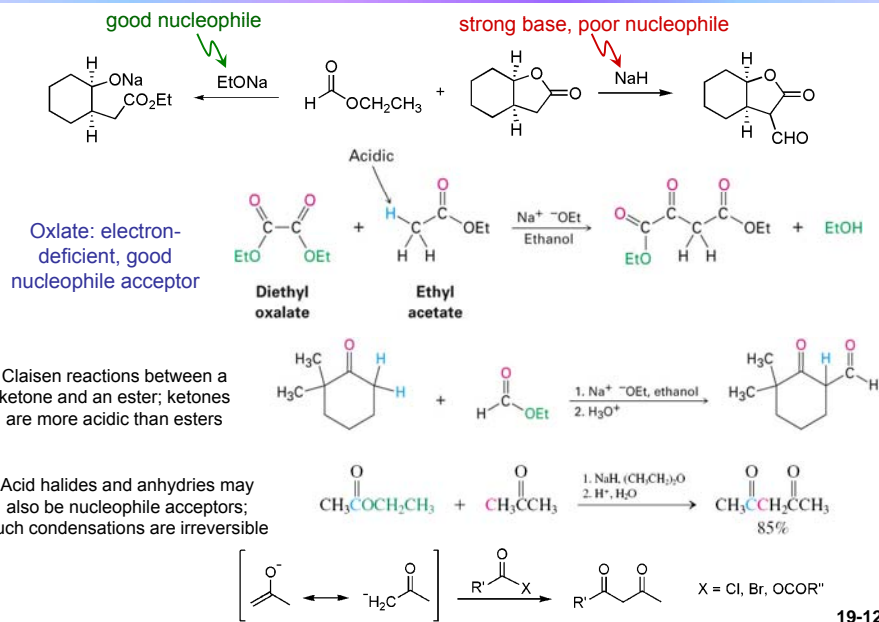
Retro-Claisen Condensation:



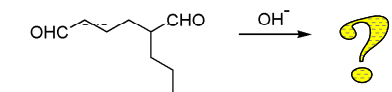
Mixed Claisen Condensations:



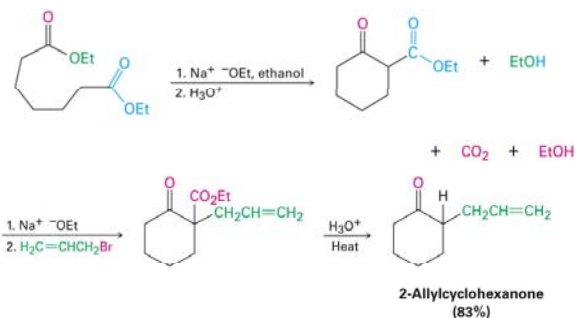
## Mixed Claisen Condensation



## Intramolecular Aldol and Claisen Condensations



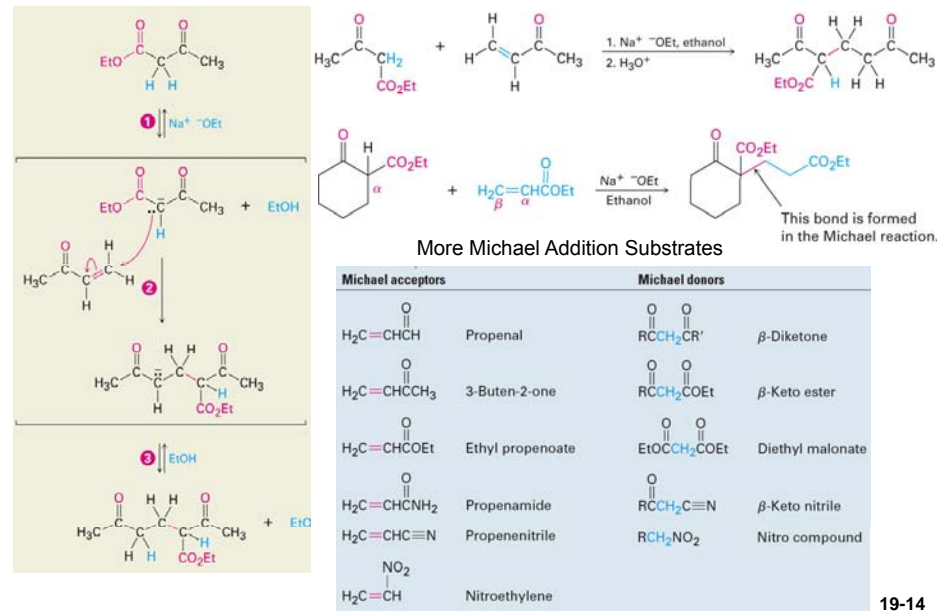
more compounds with acidic  $\alpha$ -protons



Structure	pK <sub>a</sub>
<chem>CC(=O)CC(=O)C</chem>	9
<chem>NC(=O)CC(=O)C</chem>	9
<chem>CC(=O)CC(=O)OCC</chem>	11
<chem>NC(=O)CCN</chem>	13
<chem>CC(=O)CC(=O)OCC</chem>	13

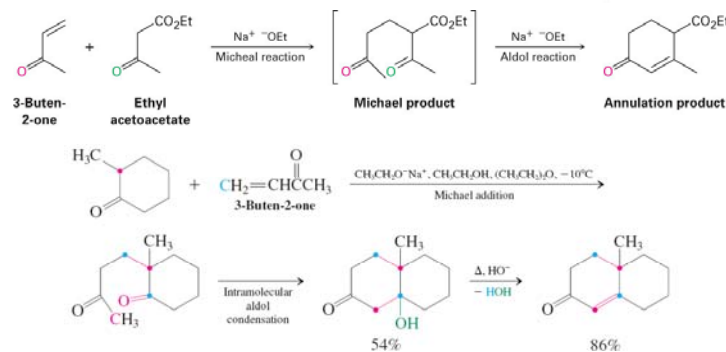
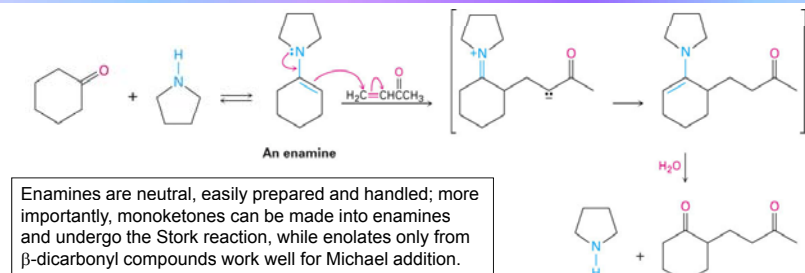
19-13

## Conjugate Carbonyl Addition: the Michael Addition



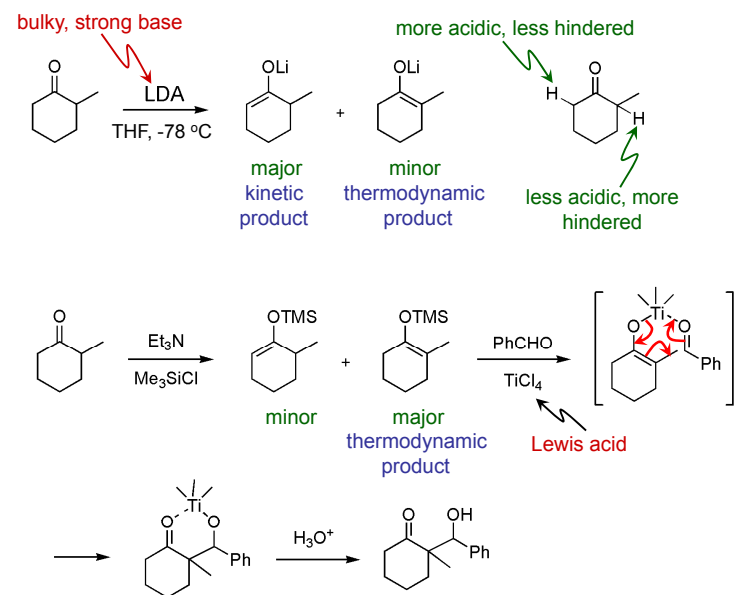
19-14

## The Stork Reaction and Robinson Annulation Reaction



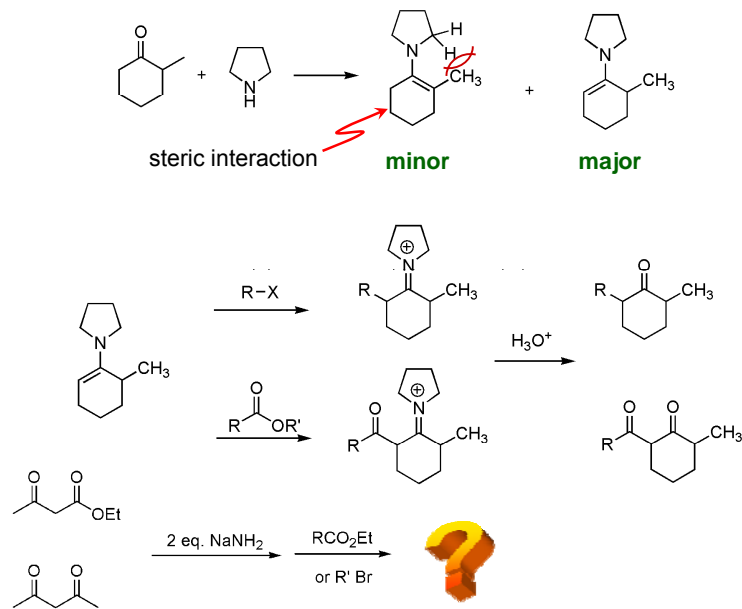
19-15

## Enolization of Asymmetric Ketones



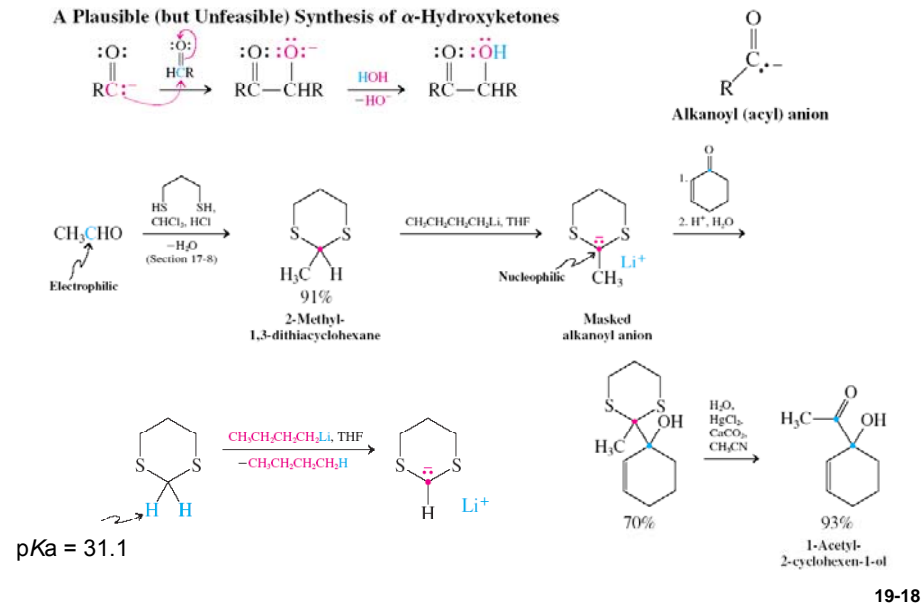
19-16

## Enamine Alkylation and Acylation

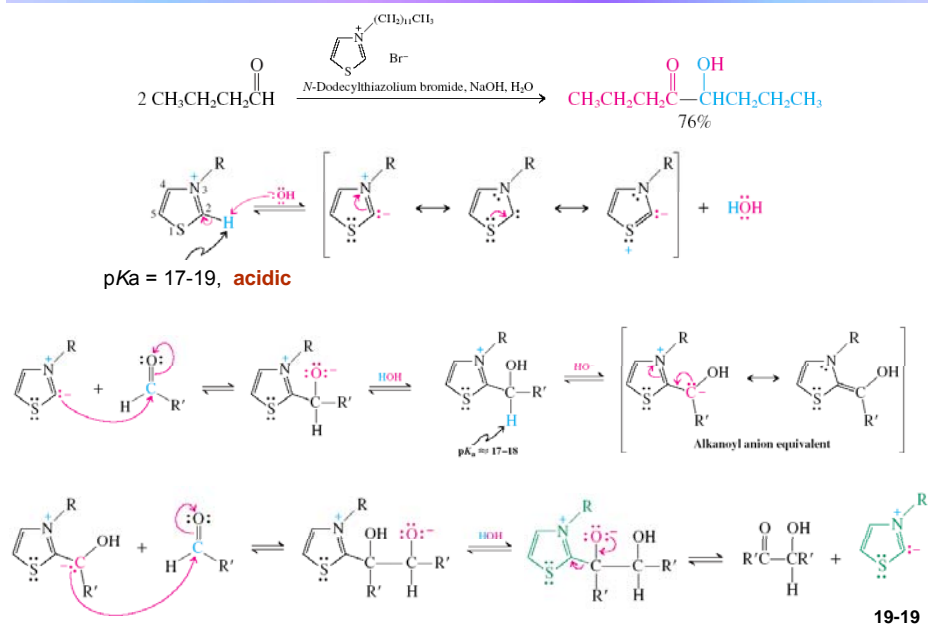


## Acyl Anion Equivalents

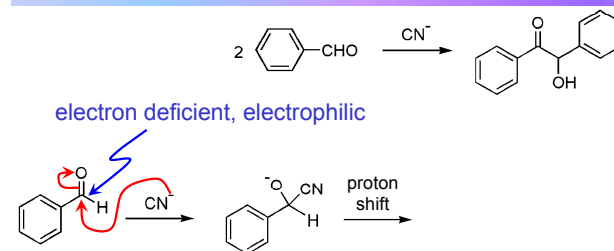
A Plausible (but Unfeasible) Synthesis of  $\alpha$ -Hydroxyketones



## Thiazolium Salt Catalyze Aldehyde Coupling



## Benzoin Condensation



**Umpolung or polarity inversion** in organic chemistry is the chemical modification of a functional group with the aim of the reversal of polarity of that group.

Besides the above 3 examples, find another case of umpolung of carbon atom in our lecture notes.