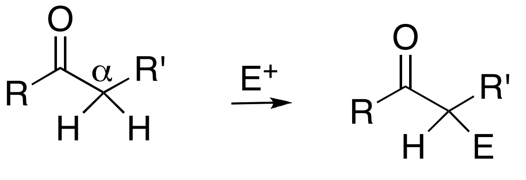
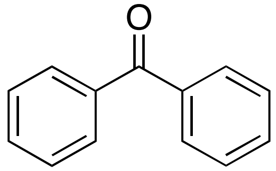
Chapter 23. Carbonyl Alpha Substitution Reactions

Alpha-substitution reactions occur at the position NEXT to the carbonyl group- the α position- and involve substitution of the α-H by an electrophile E through either an ENOL or ENOLATE ION.

The α-C of carbonyls can act as a nucleophile in a number of reactions via either the enol tautomer or via the enolate anion.

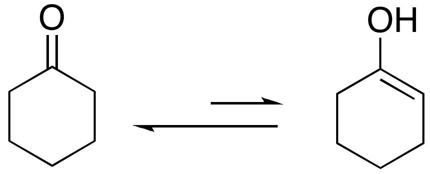




no alpha-proton

Keto-Enol Tautomerization and Enol Reactivity

- S. 8.5: A **ketone** with alpha H is in equilibrium with its corresponding **enol** tautomer: There is a rapid interconversion between the two forms which is a special kind of isomerism called: **tautomerism** (Greek: the same)



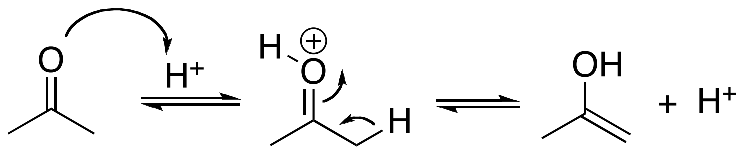
ketone
99.9999%

enol
0.0001%

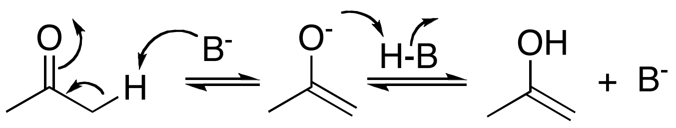
Under most conditions the enol form is present in very small amounts. However, it is very important for synthetic reasons because they are so reactive.

The formation of the enol component is catalyzed by both acids and bases such that it can be present in amounts that allow for synthetically useful reactions:

Acid Catalyzed

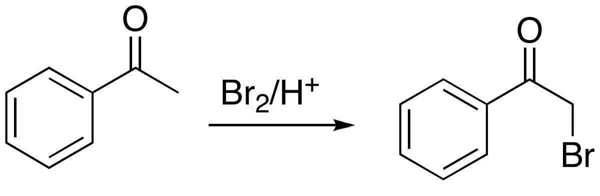


Base Catalyzed

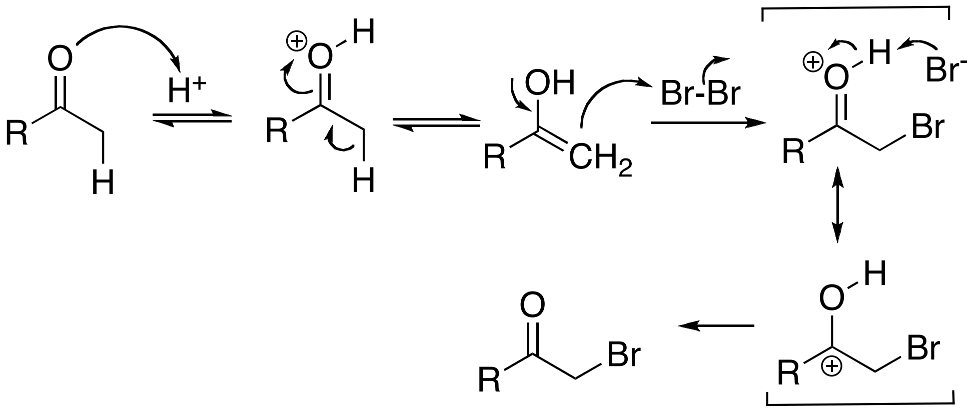


Alpha halogenation of enols

One important reaction of enols: alpha halogenation
Aldehydes and ketones can be halogenated with Cl_2, Br_2, and I_2 under acidic conditions:

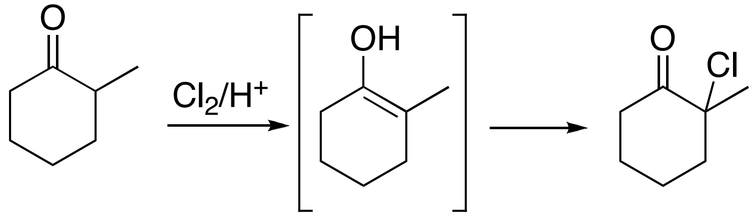


Mechanism:

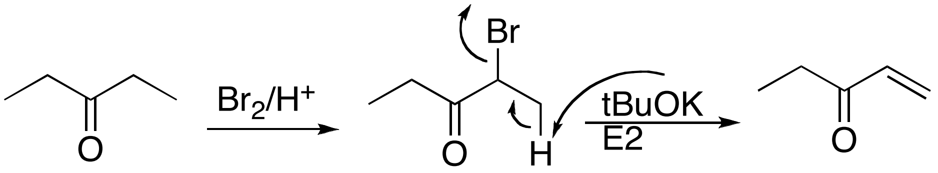


Only ONE alpha-H is replaced by a halogen

If a ketone is unsymmetrically substituted, the halogen is delivered to the more substituted side, via the more substituted and more nucleophilic enol:



Alpha-halogenated ketones and aldehydes are easily converted in their corresponding α,β-unsaturated compounds by elimination:

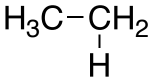


Acidity of Alpha H: Enolate ion formation

- Discuss pKa

$$HA + H_2O \rightleftharpoons A^- + H3O^+$$

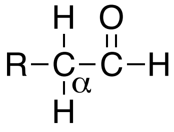
$$Ka = \frac{[A^-][H_3O^+]}{[HA]} \qquad pKa = -logKa$$



$H_3C-\underset{H}{CH_2}$

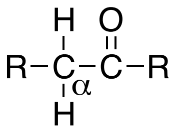
pKa = 60

Difference: ~40 pKa units → ketone is 10^{40} times more acidic than alkane. (USA budget (2006) ~$2 trillion ($10^{12}$))



$R-\underset{H}{\overset{H}{C_{\alpha}}}-\overset{O}{C}-H$

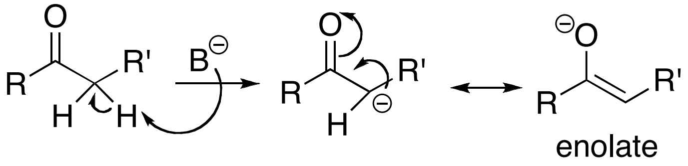
pKa = 17

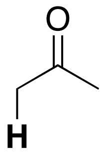


$R-\underset{H}{\overset{H}{C_{\alpha}}}-\overset{O}{C}-R$

pKa = 20

- Lower pKa due to resonance stabilization :

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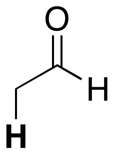
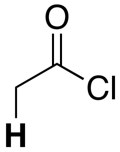
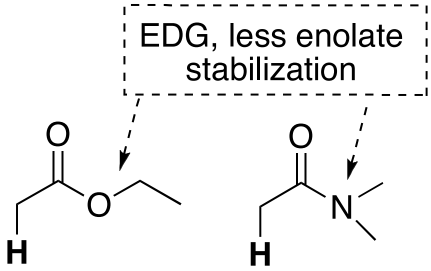
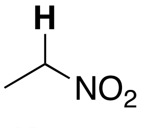

pKa = 17

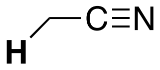

pKa = 16

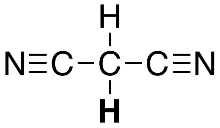


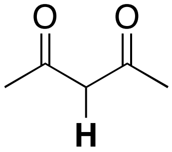
pKa = 25

pKa = 30

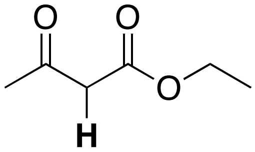

pKa = 8.6


pKa = 25


pKa = 12


2,4 pentane dione

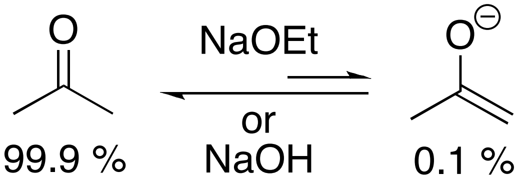
pKa = 9


Ethyl-3-oxobutyrate

pKa = 11

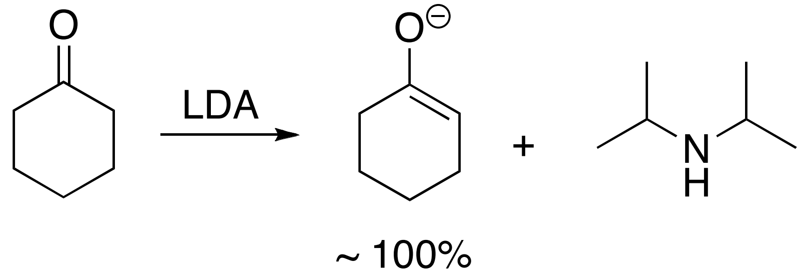
Why higher? Discuss

- Weaker bases, such as NaOH and NaOEt generate an equilibrium mixture of enolate and carbonyl compound:

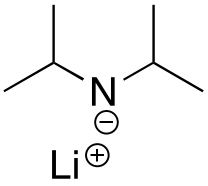


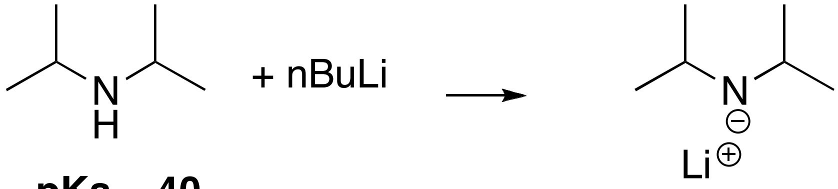
Even though the generated enolate is not much it can still be used in reactions.

- A more powerful base, LDA, can be used to completely convert a ketone or aldehyde to their corresponding enolate:



LDA: lithium diisopropylamide





pKa ~ 40

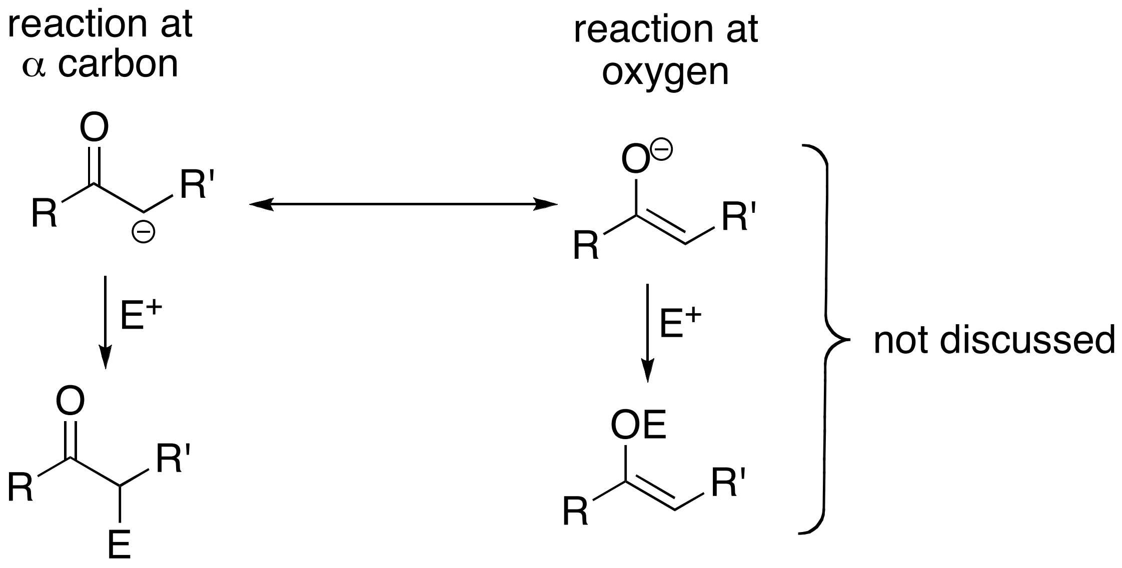
weak acid
conjugated base is strong

bulky base
good base, bad nucleophile

Enolates are more useful than enols for two reasons:

1. Unlike enols, enolates can be generated as stable, pure solutions
2. Due to their negative charge, enolates are more reactive nucleophiles than enols

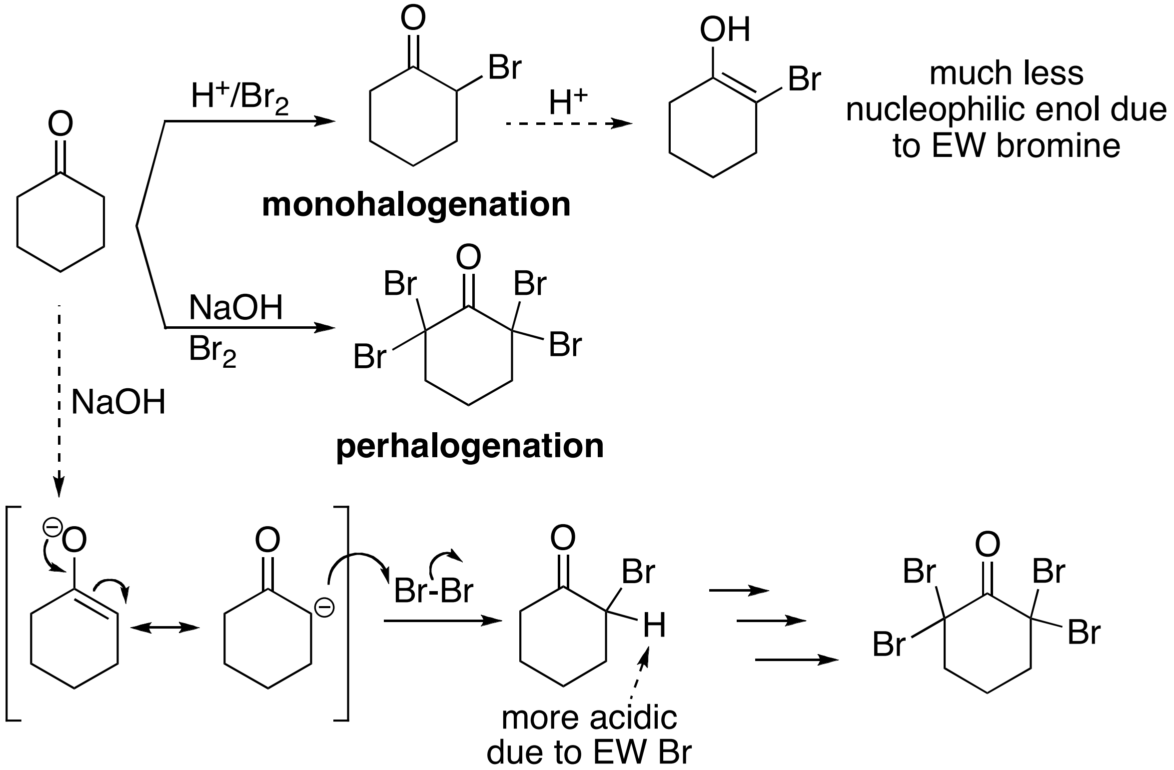
Enolates can react either at the alpha carbon or at the oxygen carbon. (We will only study ***reactions at the alpha carbon***)



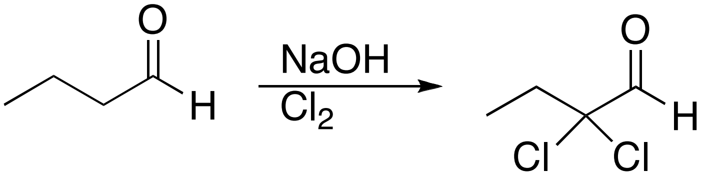
Two reactions of Enolates to discuss:

1. alpha Halogenation

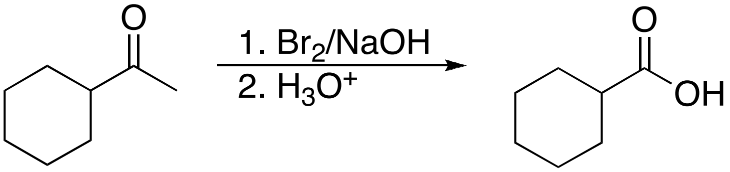
- Already saw enol halogenation (under acidic conditions):
Compare to enolate halogenation (basic conditions):



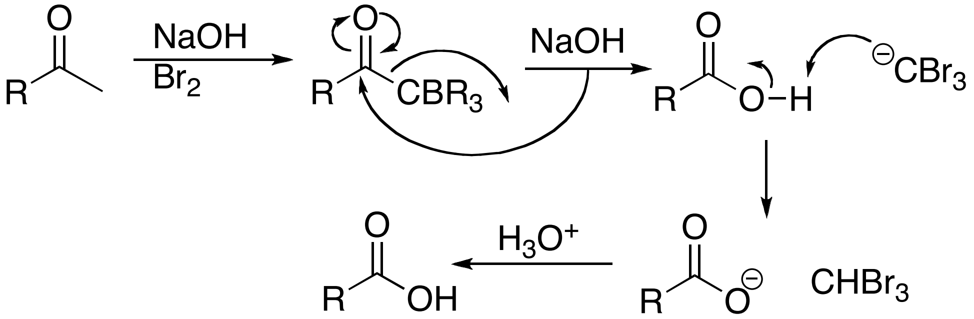
So: Under basic conditions every alpha-H is replaced by a halogen:



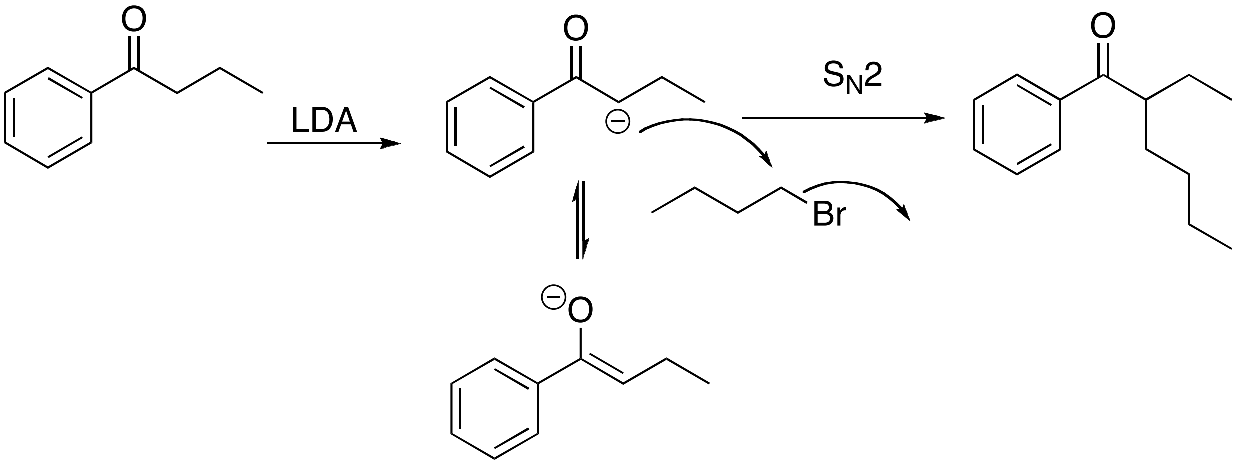
Haloform Reaction: ONLY with methyl ketones, same conditions afford carboxylic acids.



Mechanism

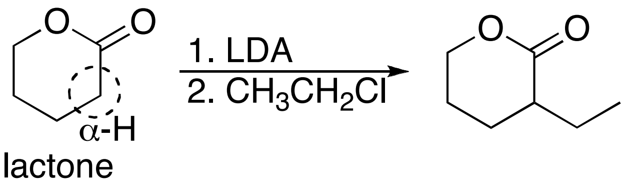


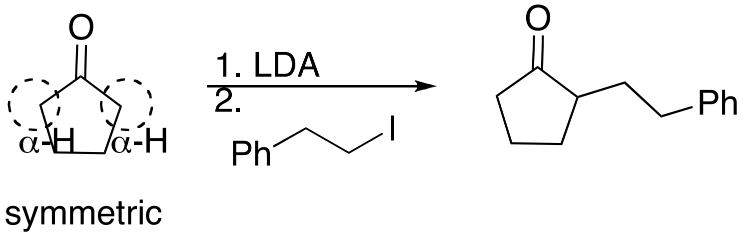
2. Alkylation of Enolate Ions

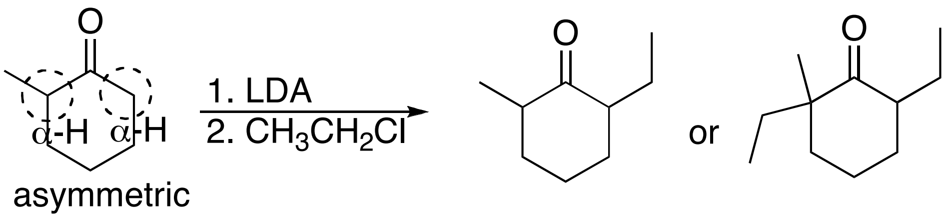


- Aldehydes, Ketones, Lactones, Esters, Nitriles can all be alkylated on the alpha C this way.

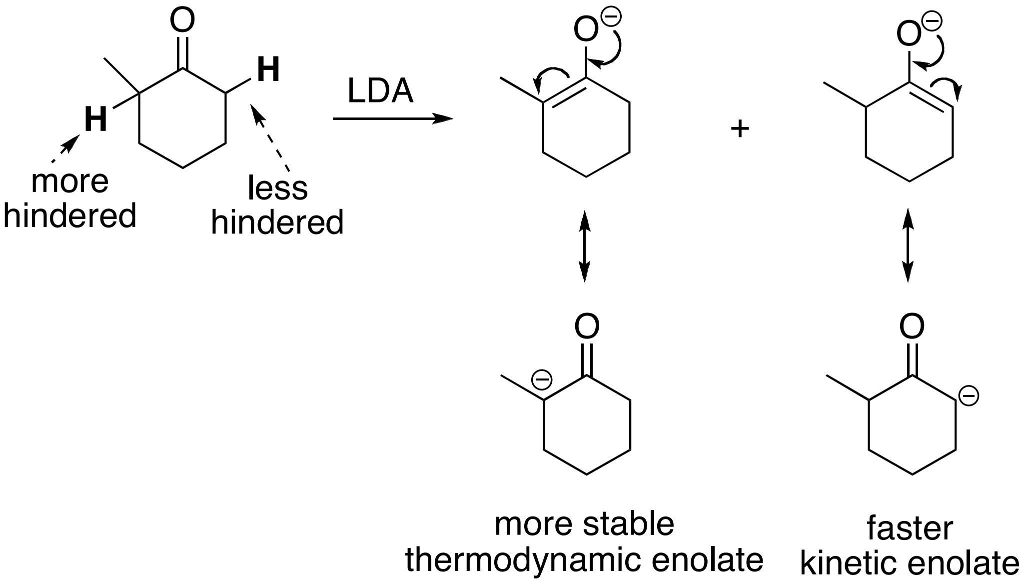
Examples:

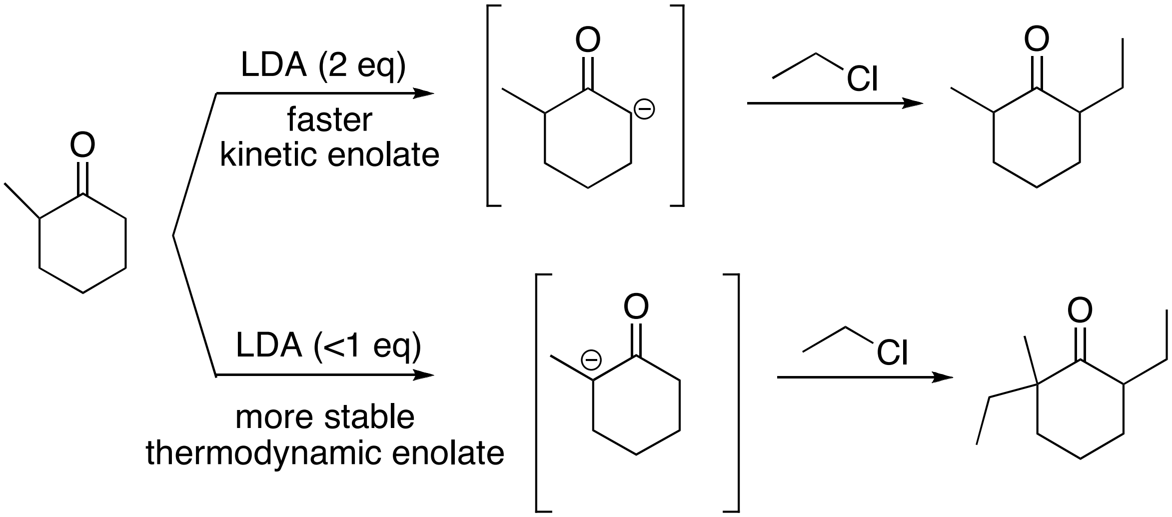






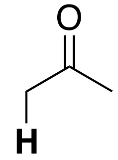
Kinetic vs Thermodynamic Enolate



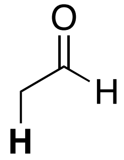


- **Dicarbonyl Compounds**

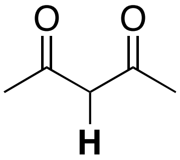
Remember:



pKa = 20

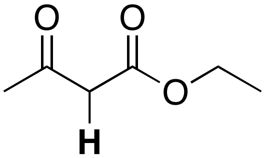


pKa = 17



2,4 pentane dione

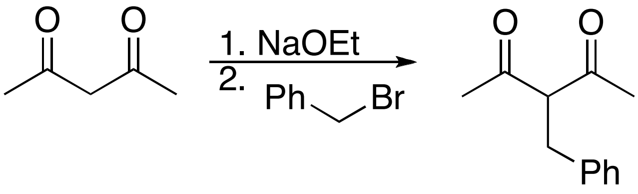
pKa = 9



Ethyl-3-oxobutyrate

pKa = 11

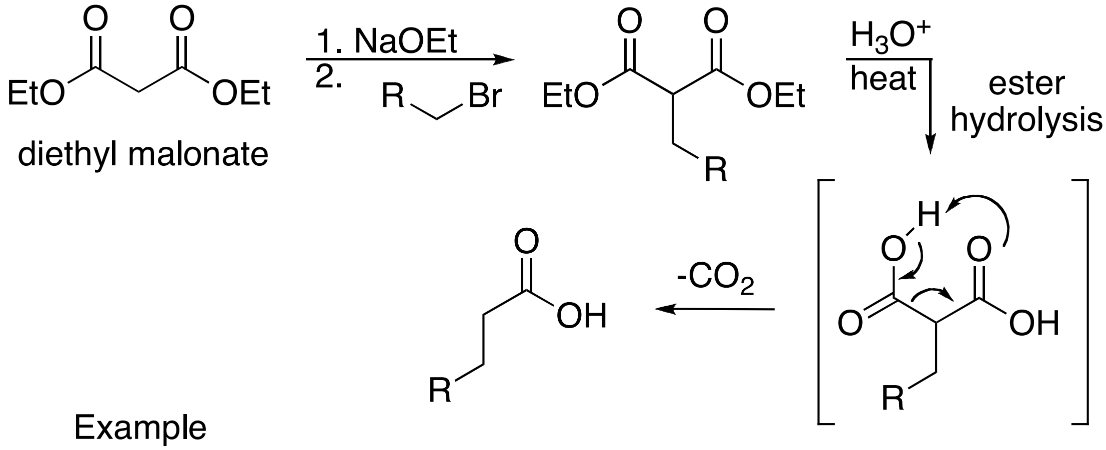
So, dicarbonyl compounds will form enolates easier (no need for strong base like LDA, softer bases (NaOEt, NaOH) would do)



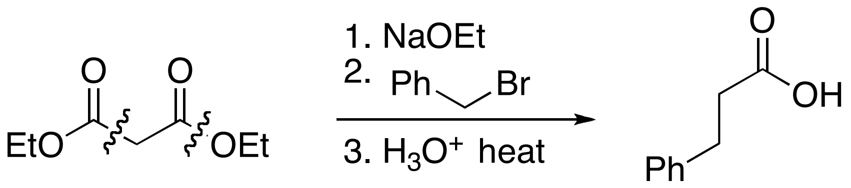
Very useful synthetic indermediates

Two useful reactions (need to memorize the names of the compounds):

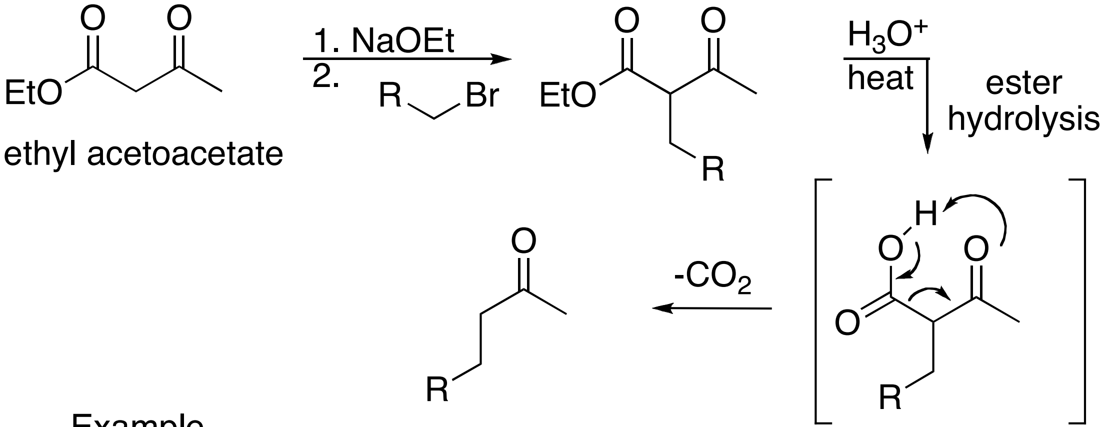
1. The Malonic Ester synthesis (Provides **Carboxylic Acids**)



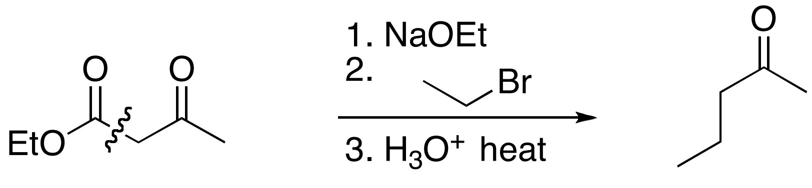
Example



2. The Ethyl Acetoacetate synthesis (Provides **Methyl Ketones**)

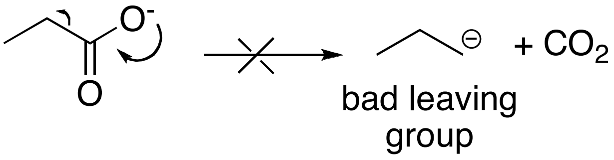


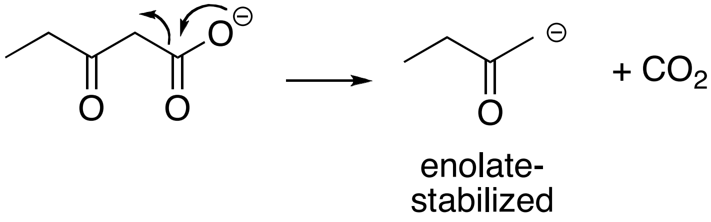
Example



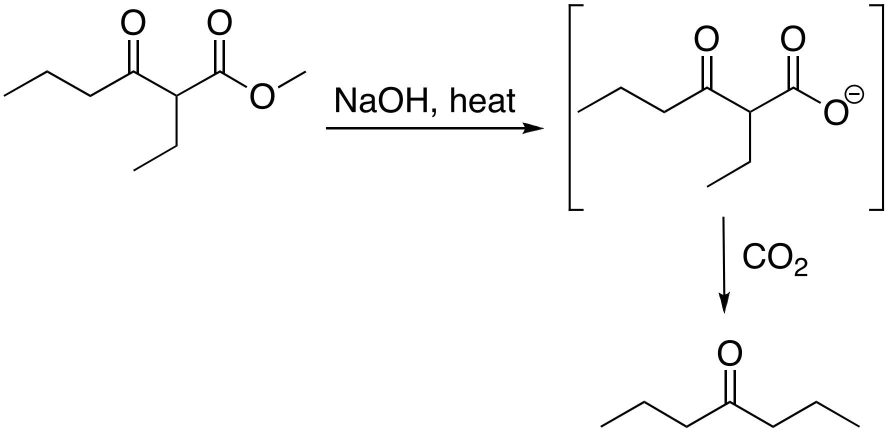
Both reaction proceed through a decarboxylation rxn (loss of CO2)

- 3-oxo-carboxylic acids can decarboxylate if heated under acidic or basic conditions:

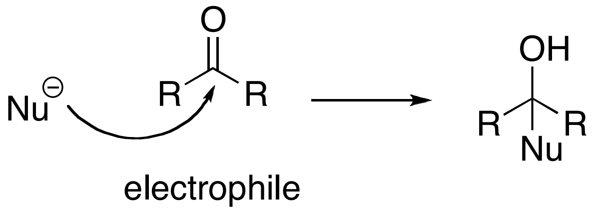


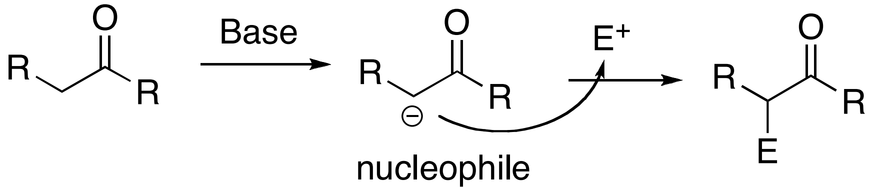


Example:

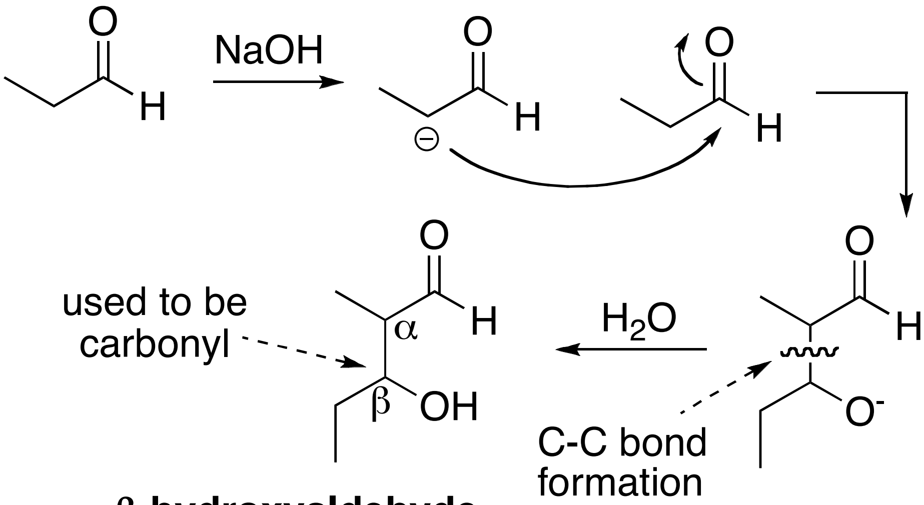


Chapter 24. Carbonyl Condensation Reactions



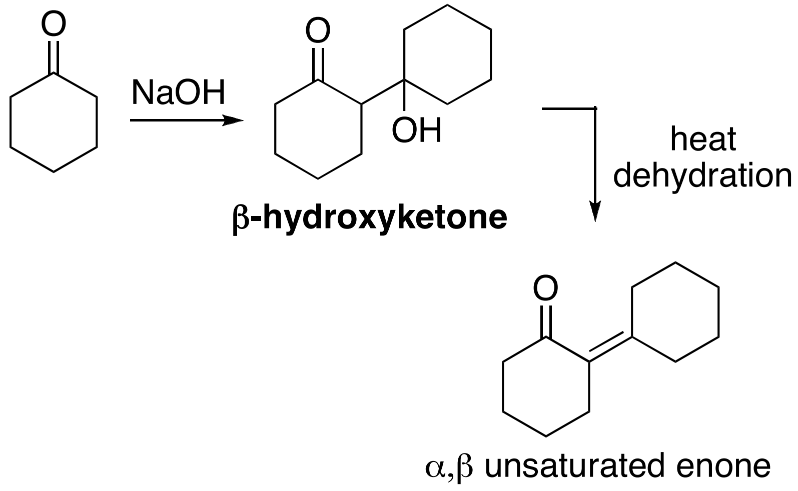


Carbonyls can act as both Electrophiles and Nucleophiles, so:



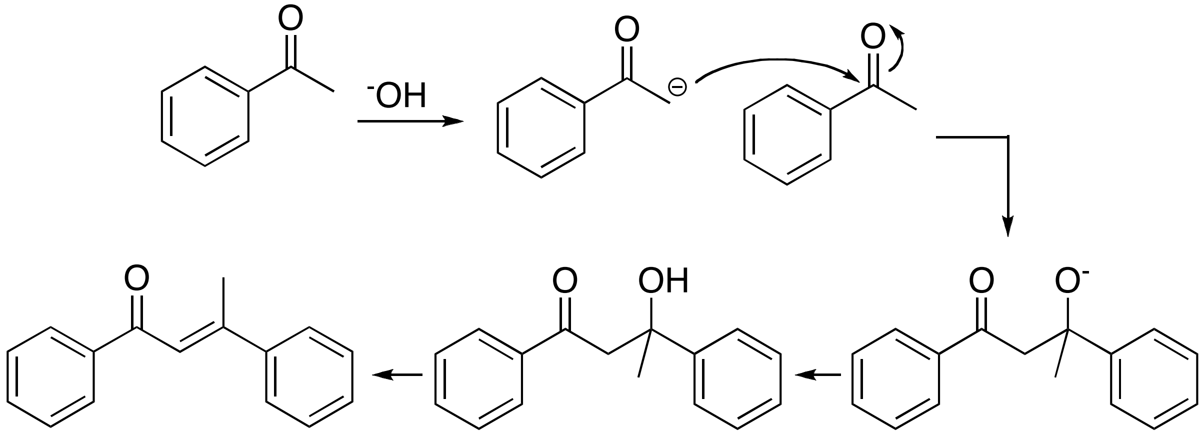
β-hydroxyaldehyde

- Self Aldol Condensation
- Similar rxn with ketones affords beta-hydroxyketones

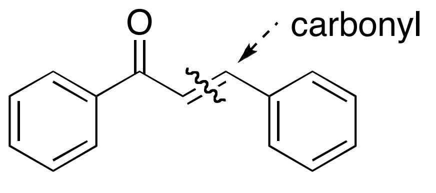


- Hydroxy compounds can dehydrate under acidic conditions, heat
- Aldol products can dehydrate under acidic or basic conditions and heat easier, since the product is a **conjugated system**.

Some Aldol products do not need heat. They dehydrate since they will have extra conjugation.
For example, aromatic systems:

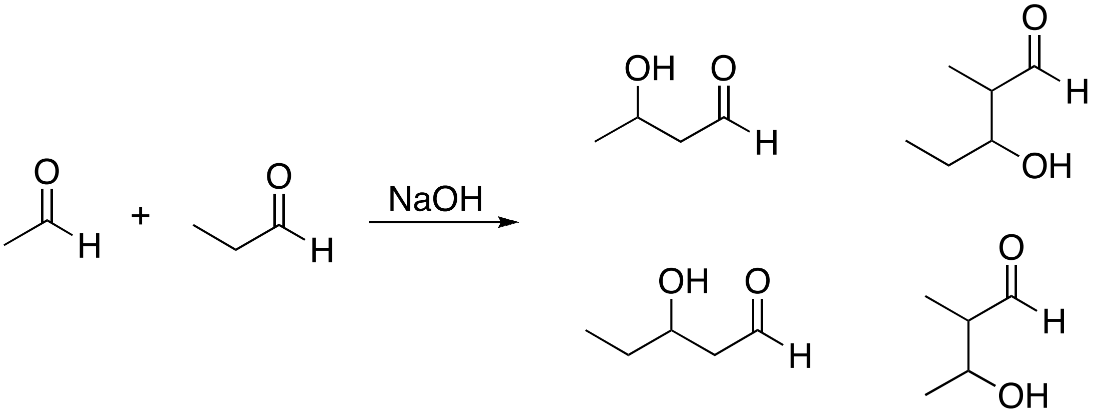


Dehydrated Aldols are called “Aldol Condensations”



Mixed (Crossed) Aldols

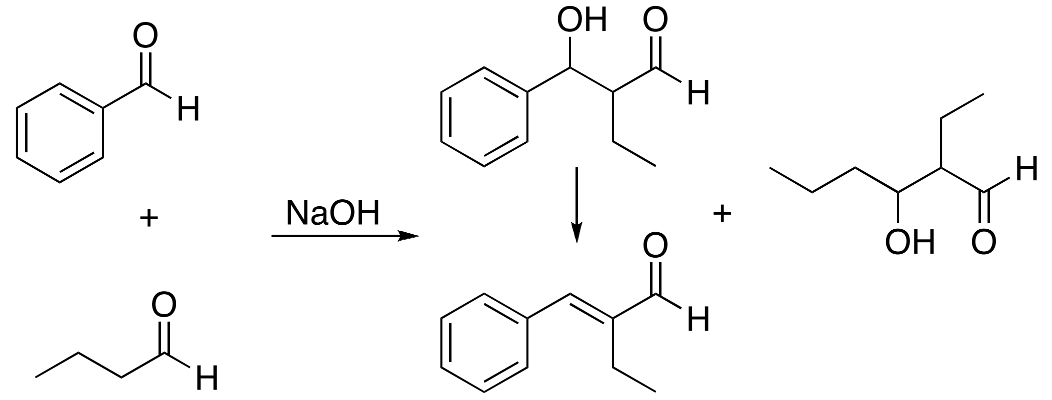
When two non identical carbonyls are used in an aldol rxn
Typically, what is isolated is a statistical mixture of four products: two self-aldol products and two mixed aldol products.



(If asymmetric ketones used, even worse mess!)

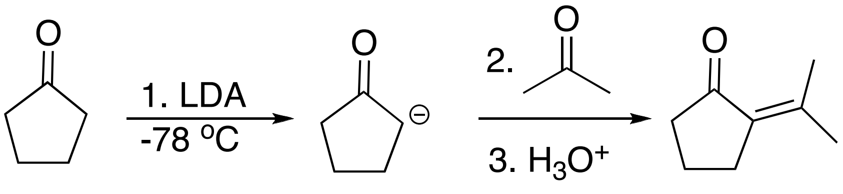
Two possible solutions:

1. If one participant has no α–hydrogens

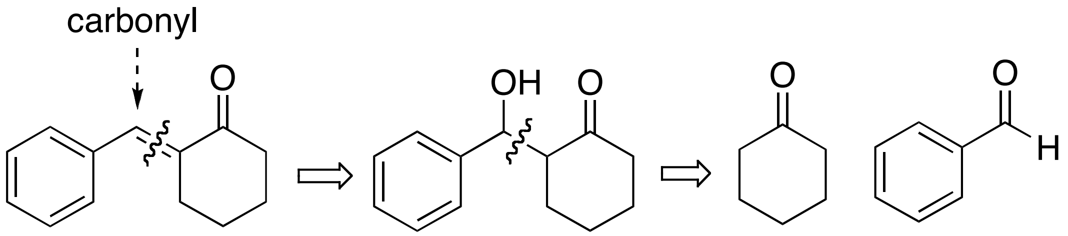


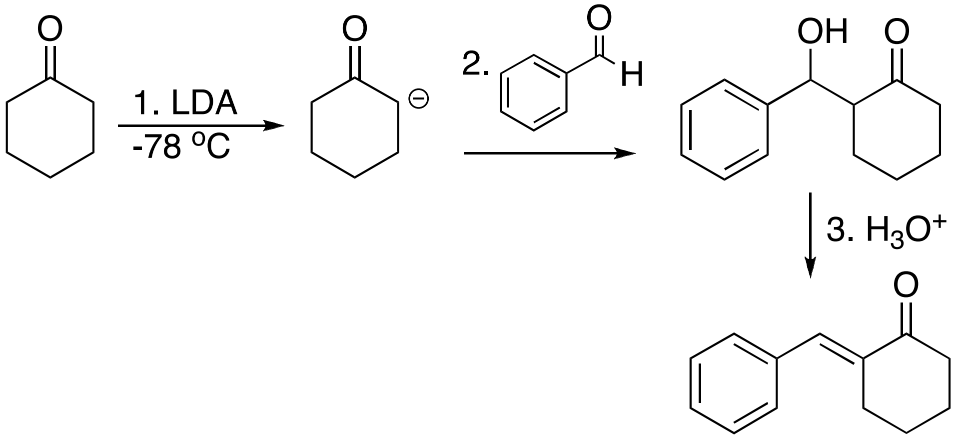
Two products, better yield of 1st if excess benzaldehyde used.

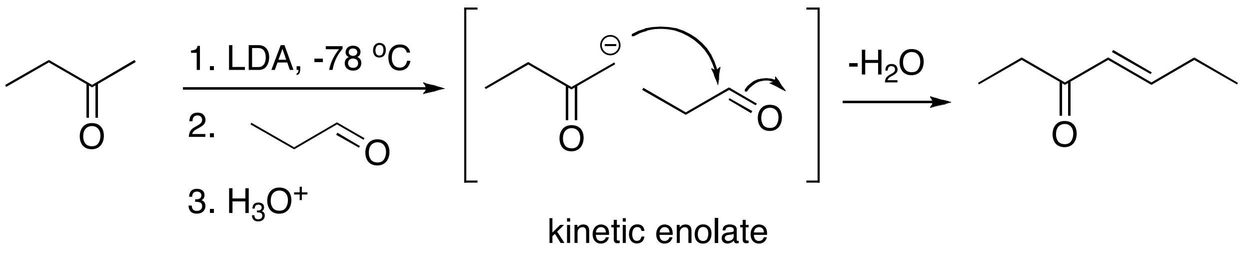
2. **Better solution**: Generate the enolate of one carbonyl compound completely with LDS and then add the 2nd carbonyl compound.



Examples:

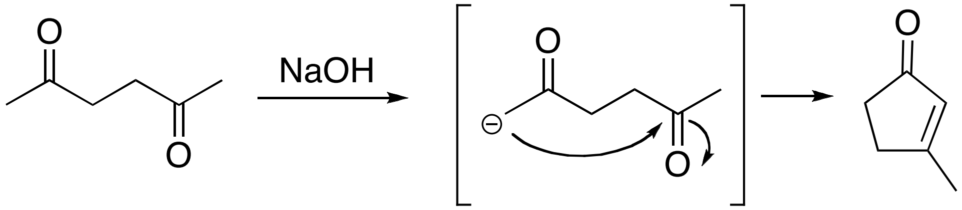






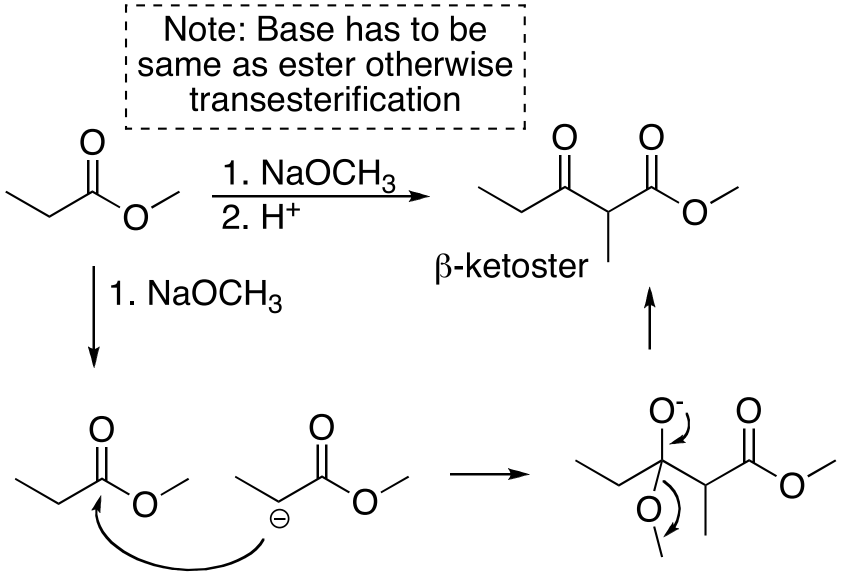
- **Intramolecular Aldol Reactions**

When the same molecule has two aldehydes or ketones
Driving force: Formation of 5 or 6 membered rings.

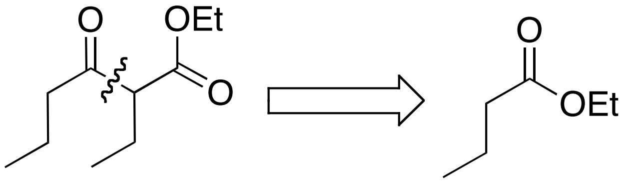


23.8 Claisen Condensation

Condensation of two esters:

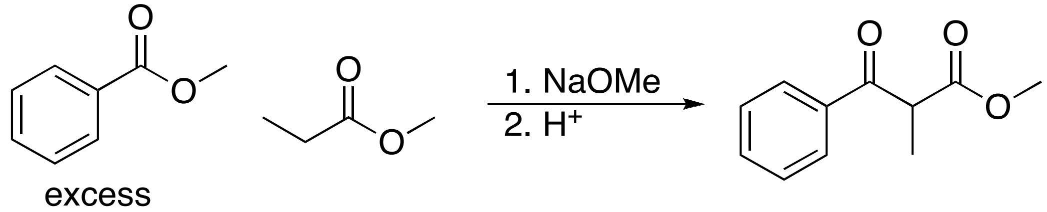

Note: Base has to be same as ester otherwise transesterification

Example:

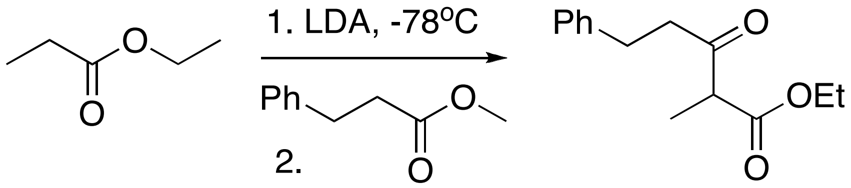


Mixed Claisens:

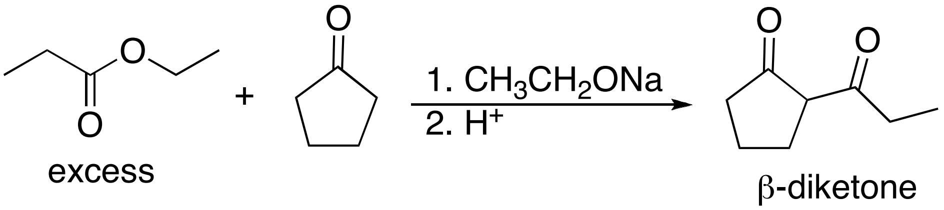
1. Useful only if one of the two esters has no α-H. That ester is used in excess to avoid homocoupling:

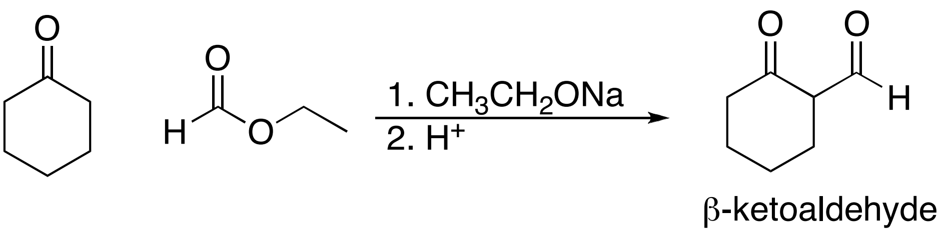


2. Works the best if you 1st generate one enolate and then add the second ester.



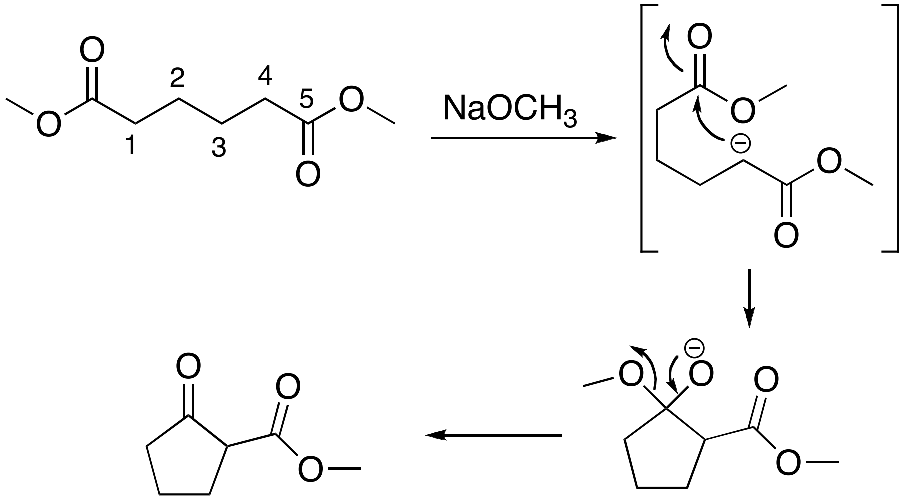
3. Useful if ester is used to condense with ketone/aldehydes (α-H pKa is less), use ester in excess





23.10 Dieckmann Condensation (Intramolecular Claisen)

Diesters can cyclize to form cyclic β-keto esters (5 , 6 m. rings)

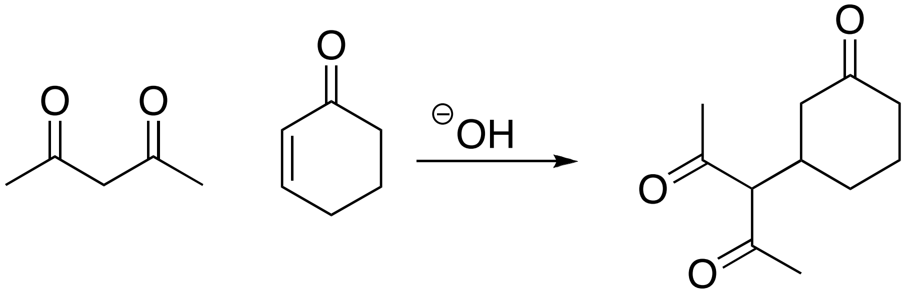


23.11 The Michael Reaction

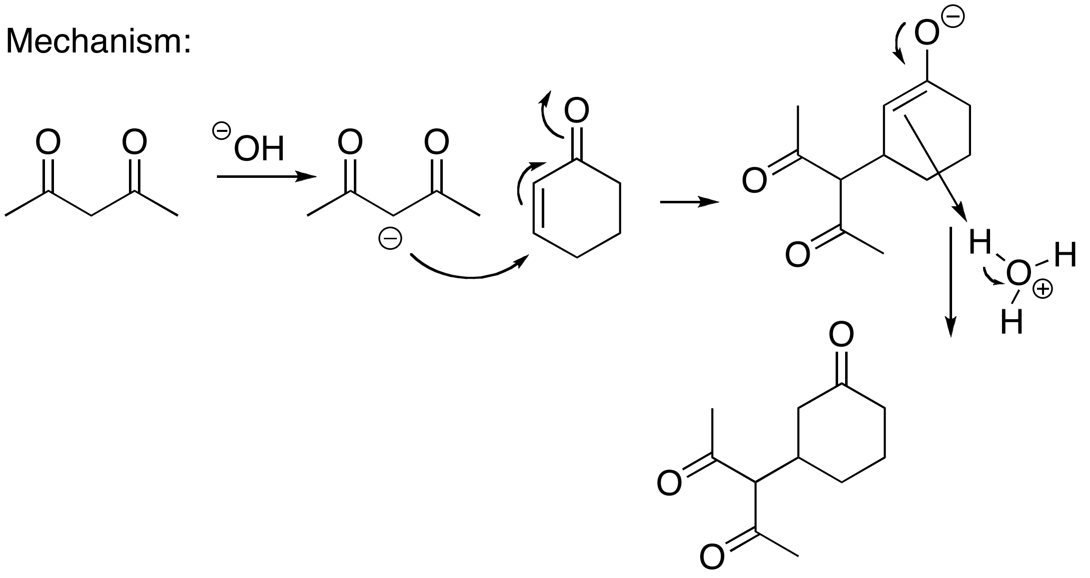
Remember addition to unsaturated compounds:

1,2 for strong bases (Grignard)
1,4 for weaker bases

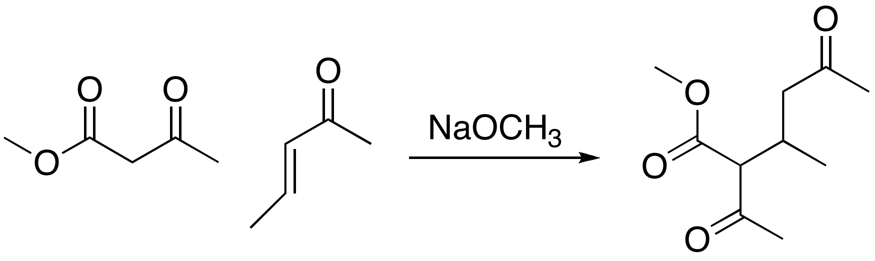
Michael Reaction combines enolate chemistry with the reactivity of α,β-unsaturated carbonyls. Works well with enolates of beta-dicarbonyls, since they are relatively acidic.

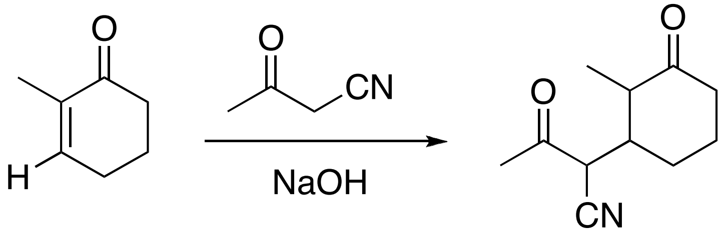


Mechanism:

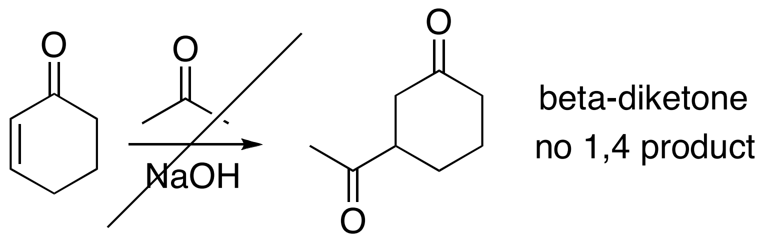


Examples:





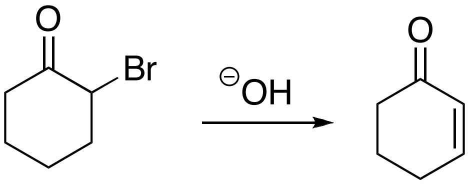
- **1,4 addition does not take place readily with enolates of ketones/aldehydes (too basic).**



(We'll see Stork Enamine Rxn for forming 1,4 diketones, dialdehydes)

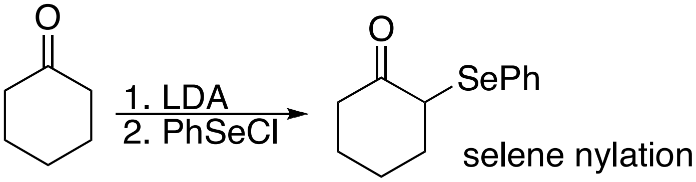
How to prepare α,β unsaturated carbonyls

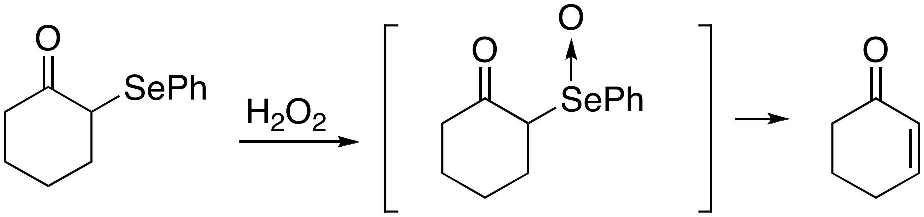
a. Elimination of alpha halogen carbonyls (Not very good)



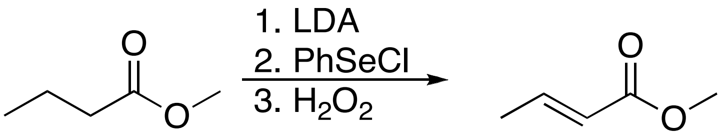
b. Aldol

c. BETTER WAY.



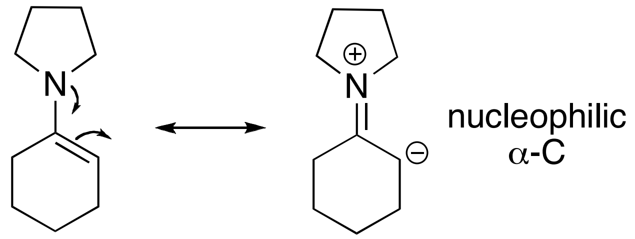


Works well for ketones, esters, nitriles

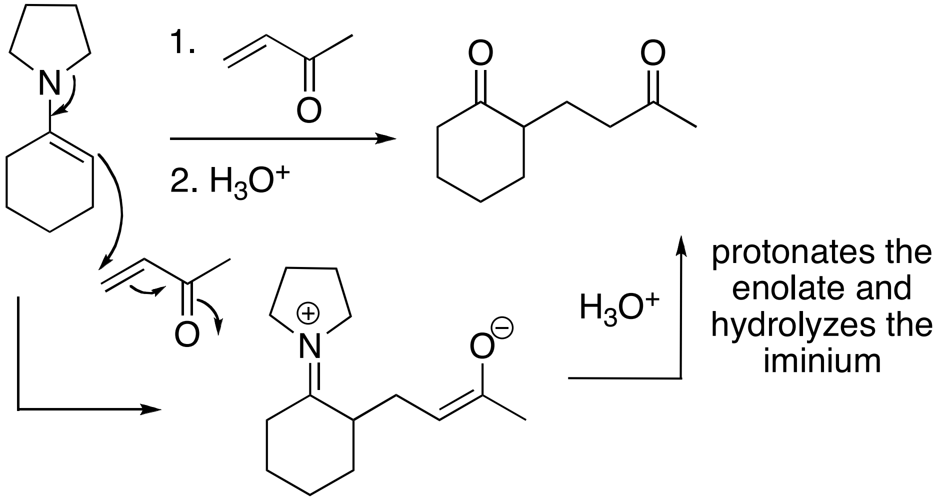


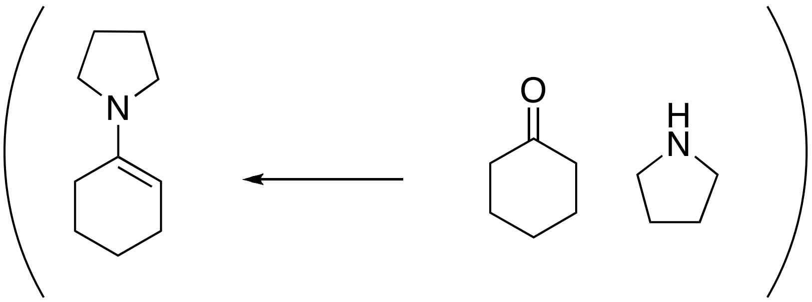
23.12 The Stork Enamine Reaction

Michael rxn with an enamine nucleophile instead of an enolate:



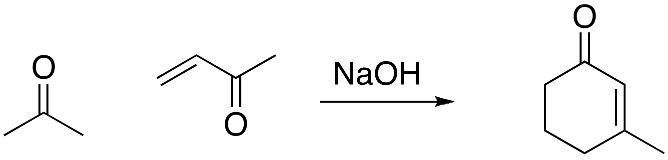
Enamines behave similarly to enolates in that they have a partial negative charge on their alpha-C.



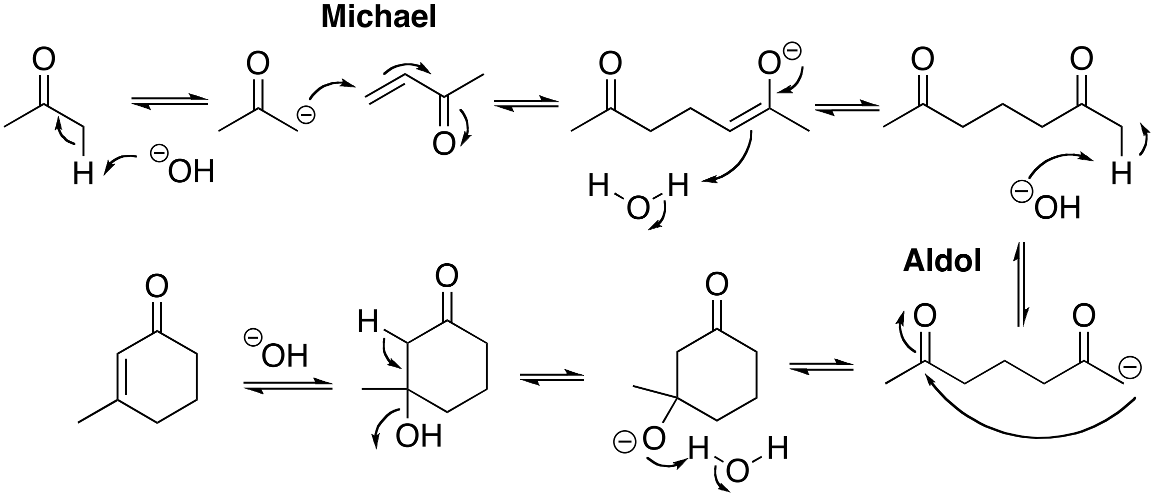


23.13 The Robinson Annulation Reaction

Combination of a Michael Rxn followed by an intramolecular aldol
Always makes six-membered rings, α,β-unsaturated ketones:



mechanism



To analyze a Robinson annulation product:
Cut between β, γ and through double bond