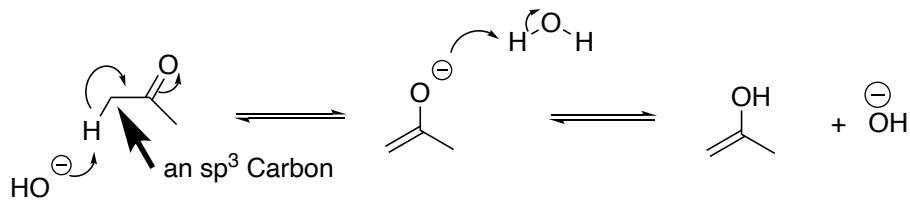


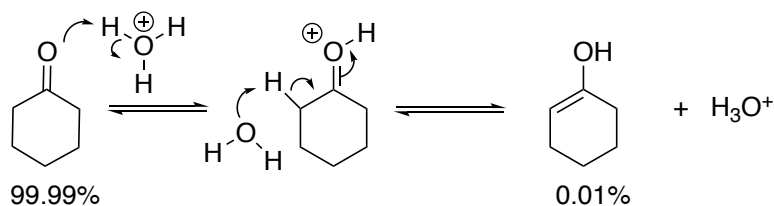
4/22/2024

# CHAPTER 21: CARBONYL CONDENSATION REACTIONS

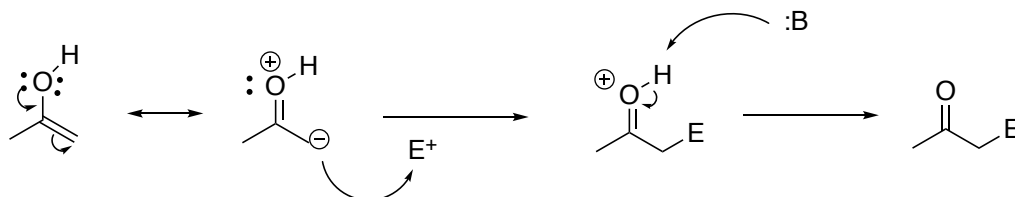
## Base Catalyzed Enolization



## Acid Catalyzed Enolization

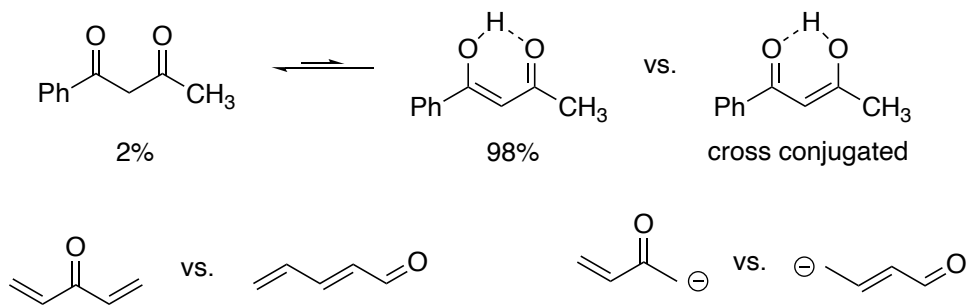


## How do enols react?



Enols are electron-rich and, therefore, react as nucleophiles at the alpha carbon!

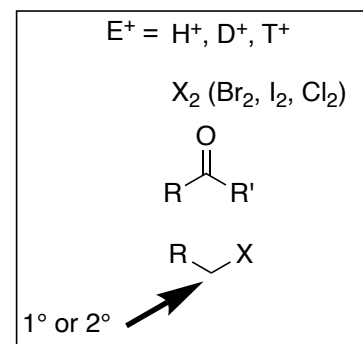
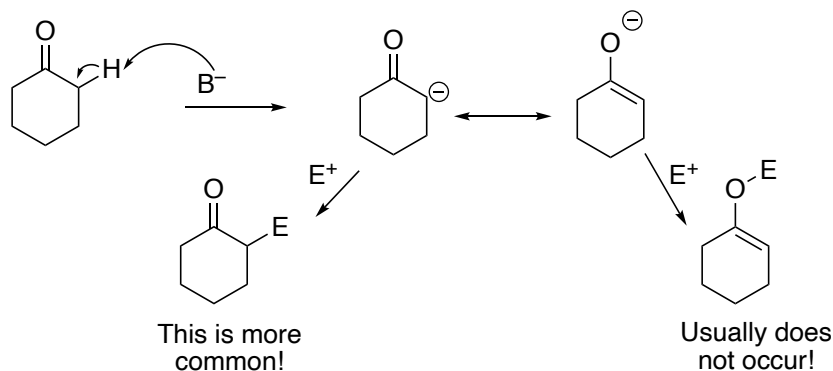
## $\beta$ -dicarbonyl compounds



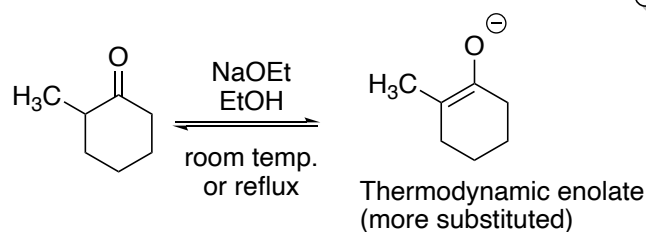
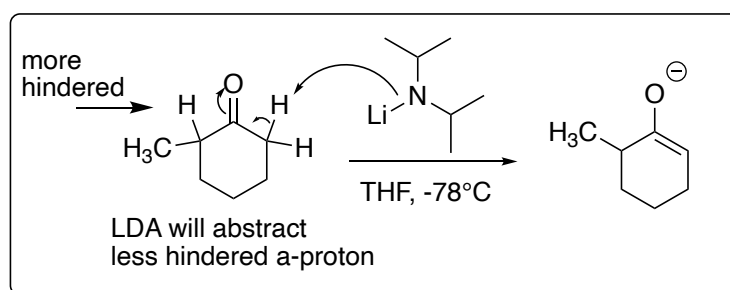
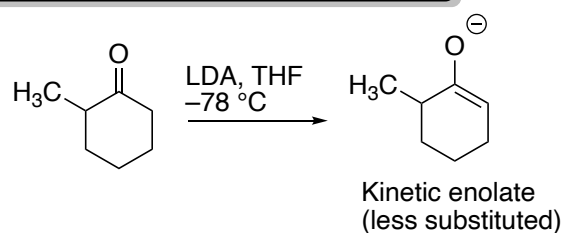
Factors:

- 1) conjugation
- 2) hydrogen bonding

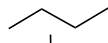
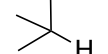
## How do enolates react?



## Thermodynamic vs. Kinetic Enolates

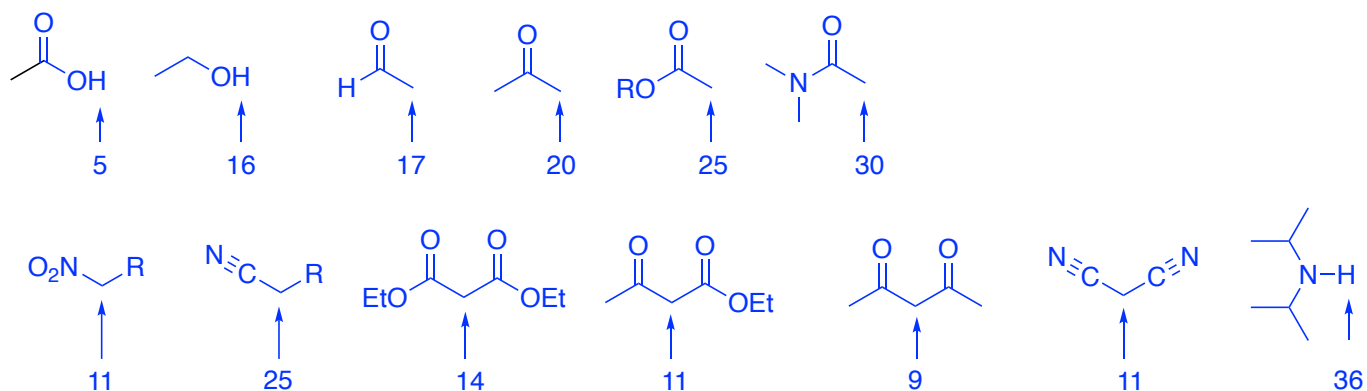


## Bases:

		pKa of conj. Acid			pKa of conj. Acid	
$I^-$	HI	-9	For forming enolates	$HO^-$	$H_2O$	14
$Cl^-$	HCl	-7		$RO^- (NaOEt)$	HOEt	16
$H_2O$	$H_3O^+$	-2		$tBuO^- (KOtBu)$	HOtBu	18
pyridine	pyridine- $H^+$	5		$H^- (NaH)$	$H_2$	36
$Et_3N$	$Et_3NH^+$	10		$H_2N^- (NaNH_2)$	$NH_3$	38
DBU	DBU- $H^+$	13.5		$iPr_2N^- (LiN^iPr_2, LDA)$	HN <sup>i</sup> Pr <sub>2</sub>	40
				$nBu^- (nBuLi)$		50
				$tBu^- (tBuLi)$		51

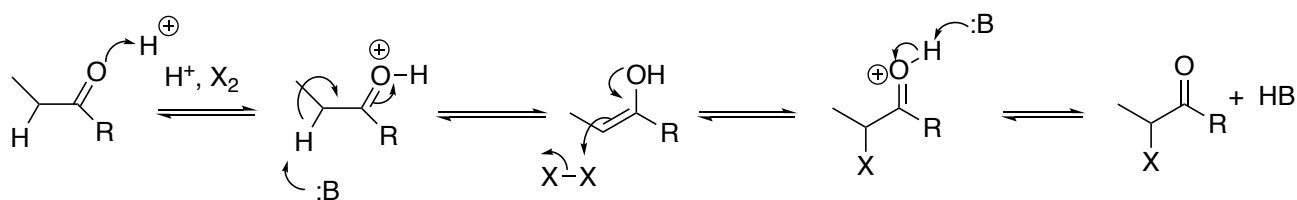
# Show how LDA is made

You need to know your pKa's: Fill them in!

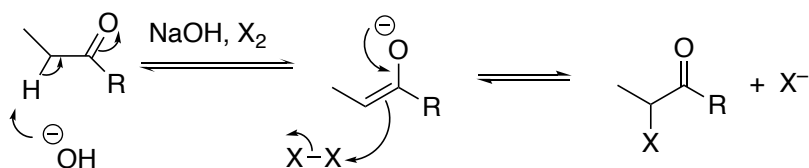


### Halogenation of Ketones

#### Acid Catalyzed Halogenation of Aldehydes and Ketones

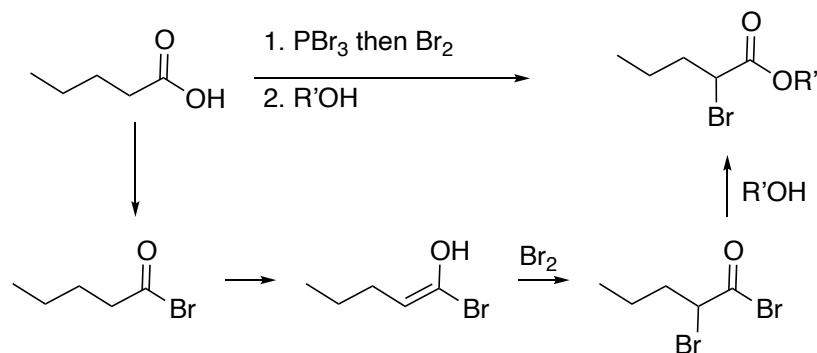


#### Base Promoted Halogenation of Aldehydes and Ketones

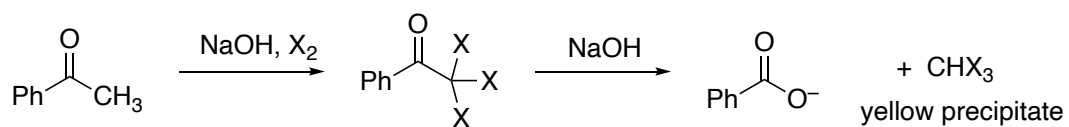


Halogenation in base is hard to stop at one addition!

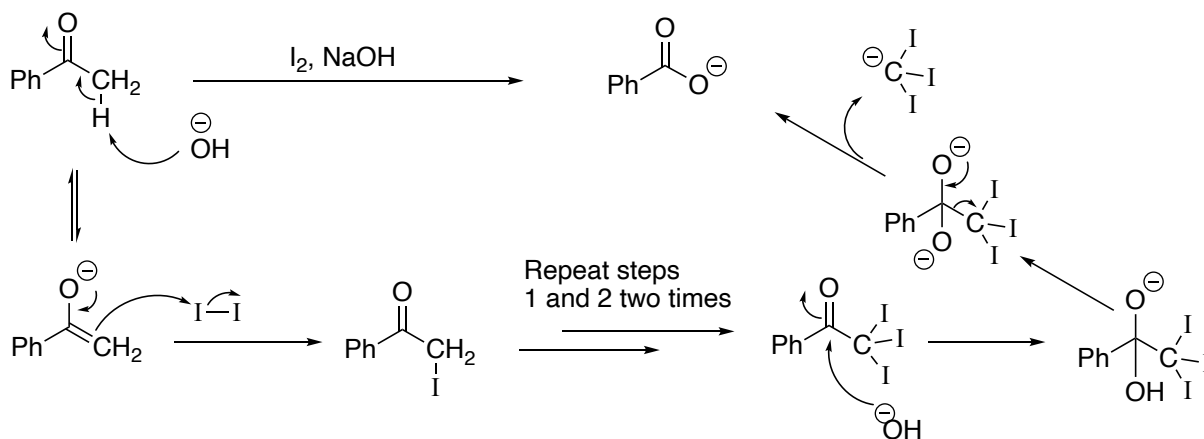
### Hell-Volhard-Zelinsky Reaction



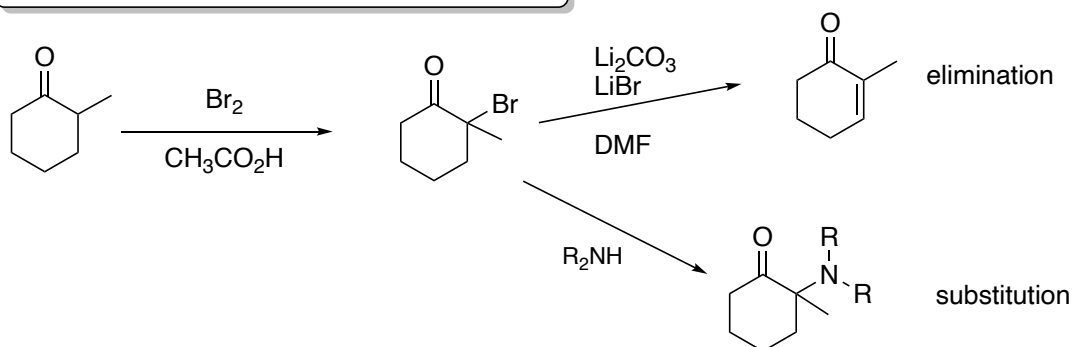
### Haloform Reaction



### Iodoform Reaction: Test for Methyl Ketones MECHANISM



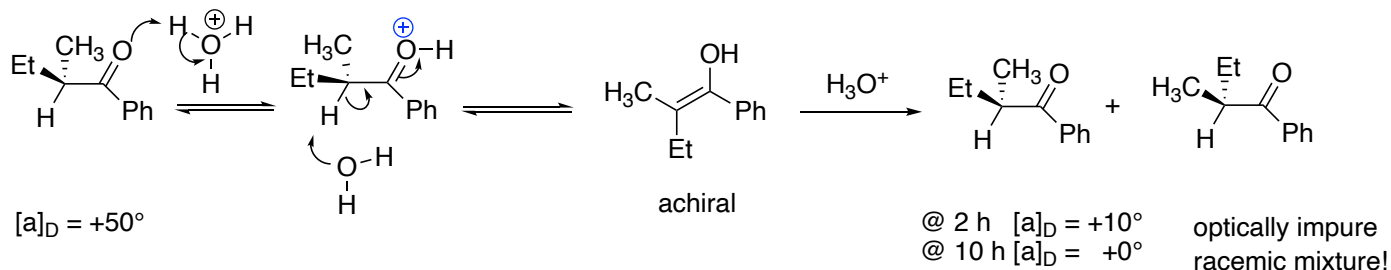
### Reactions of $\alpha$ -halo carbonyl compounds



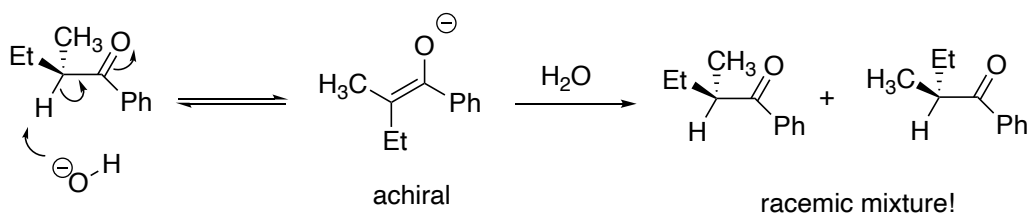
### Epimerization\* via enolization

\*This is called racemization if only 1 stereocenter is present on the substrate

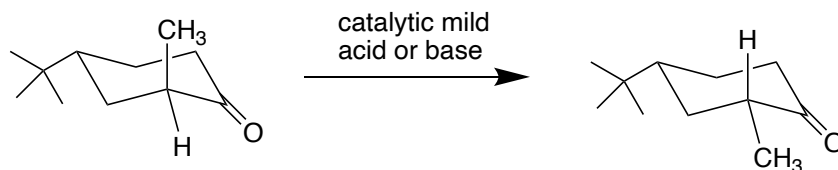
Acid:



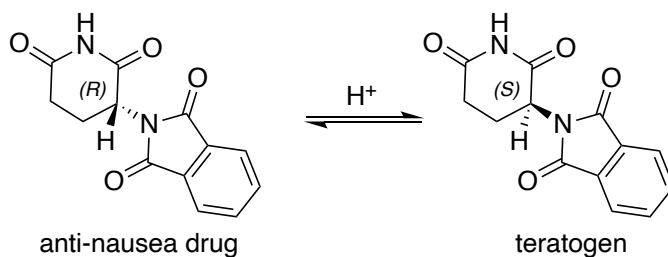
Base:



Example of epimerization:



### Thalidomide (tha-lid-a-mide)

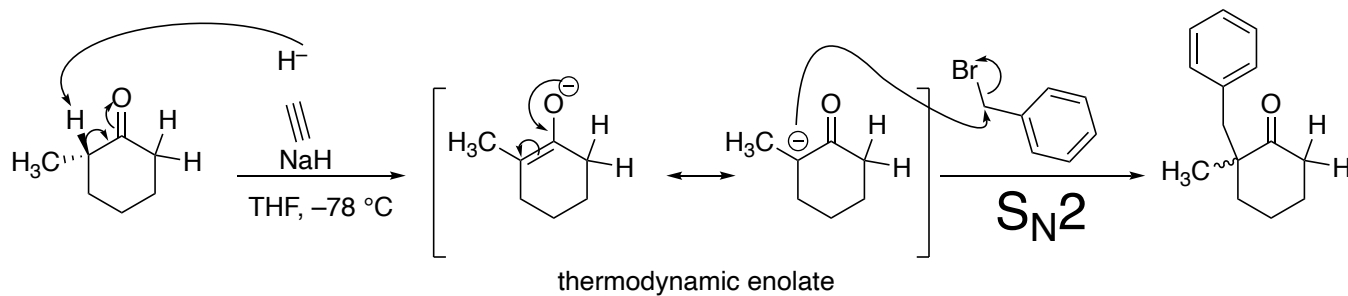
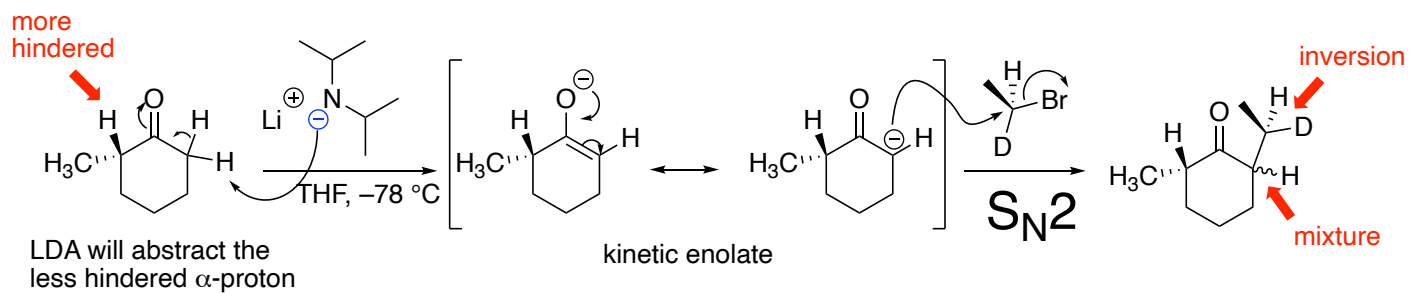


1956 Marked in Europe to woman for morning sickness

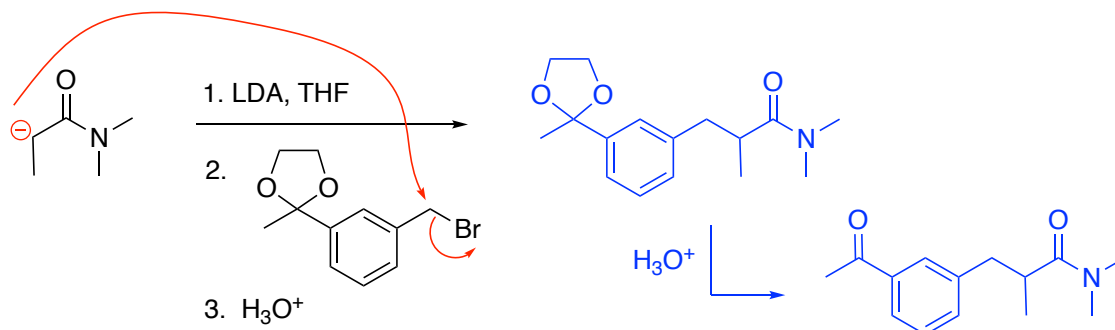
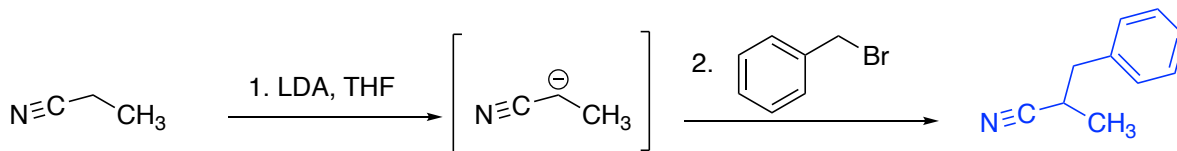
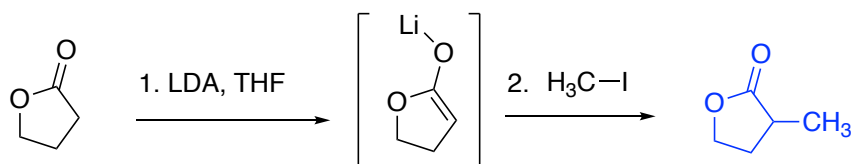
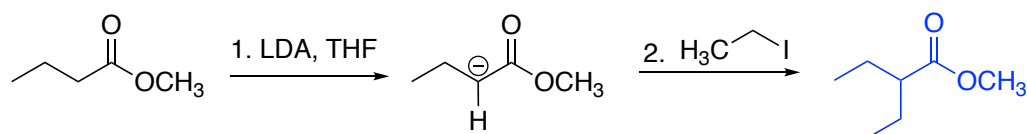
1961 Found that the drug lead to serious birth defects in 12,000 to 20,000 children

1998 FDA approves the drug for leprosy, cancer, and AIDS complications (mandated extremely stringent guidelines for use)

### Enolate Alkylations: The substitution of R for H on the alpha carbon atom

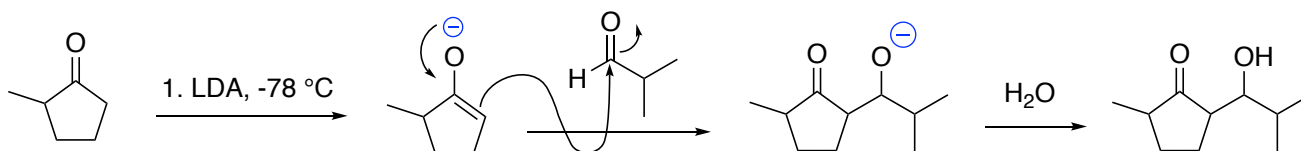


### Direct Alkylation of Esters and Nitriles



### Aldol Reactions-Directed

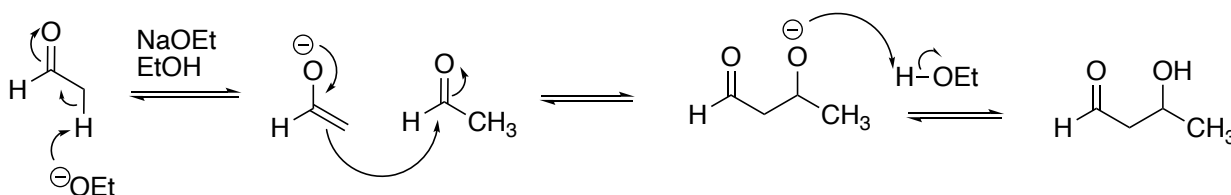
1. Prepare the enolate of one carbonyl component with LDA.
2. Add the second compound containing a carbonyl to the newly formed enolate.
3. Quench with water (carefully!).



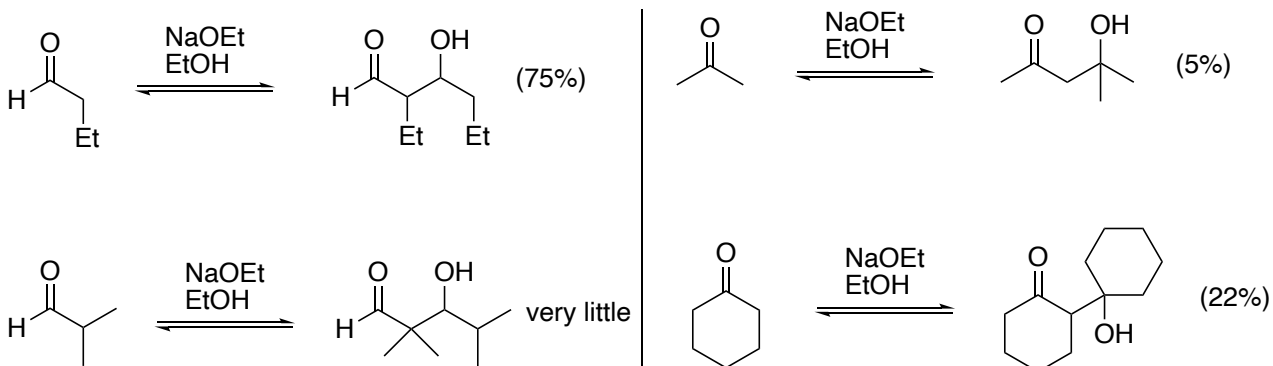
Remember: For LDA, the kinetic enolate is formed.

### Aldol Reactions-“Simple”

The same compound is used to 1) make the enolate nucleophile and 2) serve as the electrophile

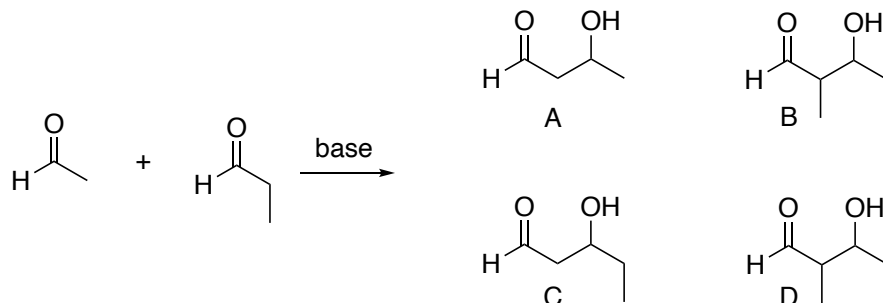


Since this reaction is reversible, the success of the reaction depends on the steric nature of the product. The more crowded it is, the more the equilibrium will shift to the starting materials. In general,  $\alpha$ -branched aldehydes and ketones are poor substrates for condensation in the aldol reaction.

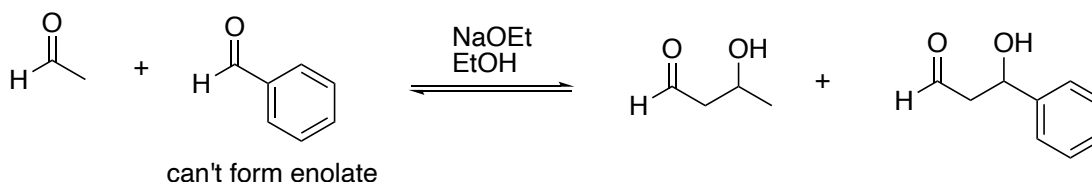


**Aldol Reaction–Mixed**

Aldol reactions between two different enolizable carbonyls is difficult to do without forming a mixture of products. These come from self-condensation and from cross-condensations.

**Limiting the Possibilities in Mixed Aldol Reaction Situations**

A. Use a reaction where one of the carbonyls that does not have enolizable alpha-protons.

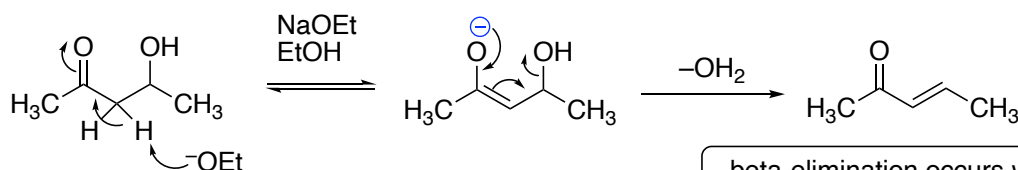


B. Aldehydes (with a protons!) can be hard to enolize and ketones often don't self-condense

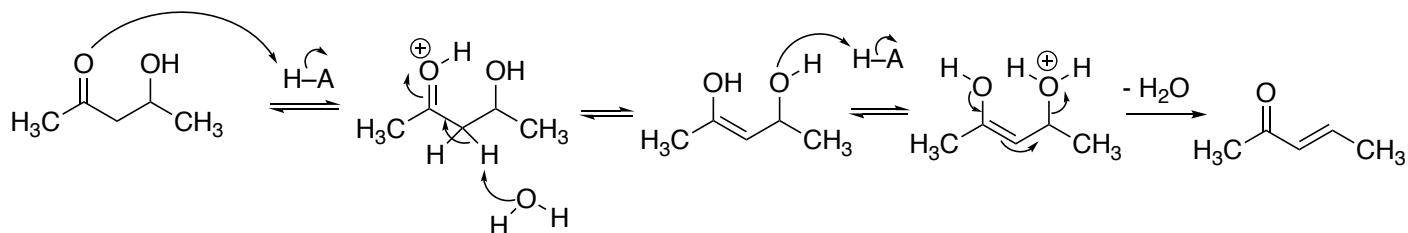
C. The order of addition can help (add the enolizable substrate last)

D. Use a directed aldol reaction (LDA then add aldehyde or ketone) where possible

Trivia: An aldol between a ketone and aldehyde is called the Claisen-Schmidt reaction

**Dehydration of Aldol Products**

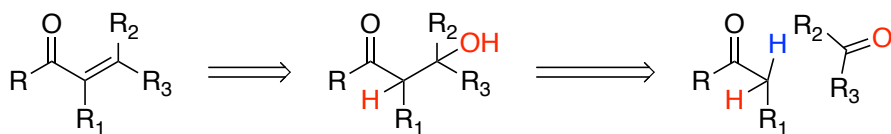
beta-elimination occurs with heat or in cases with extended conjugation. It can be accomplished under acid or base



This dehydration can also be accomplished in acid! Consider a mechanism for that.

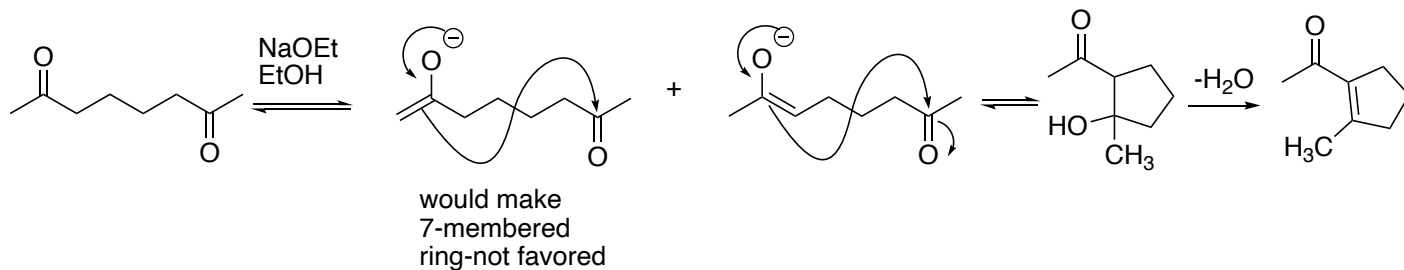
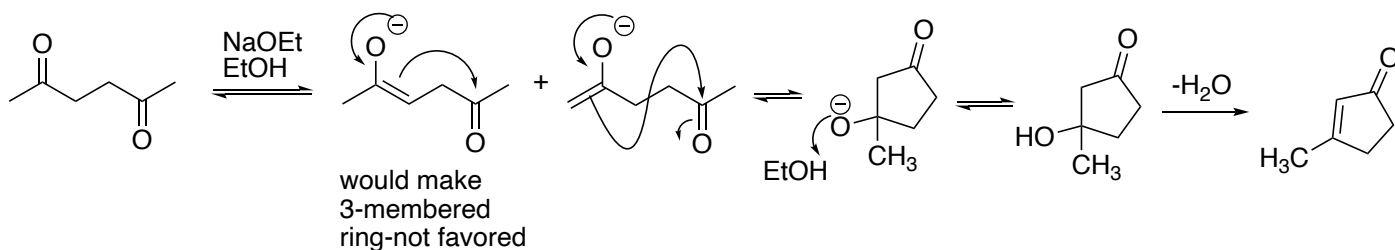


### Retrosynthetic Analysis



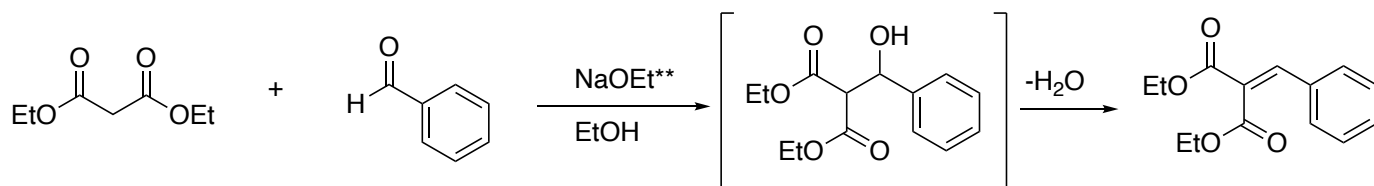
### Intramolecular Aldol Reactions

Molecules containing two carbonyls can undergo aldol condensation reactions within the same molecule (intramolecular) to yield cyclic products. This will take place very readily when forming 5- or 6-membered rings.



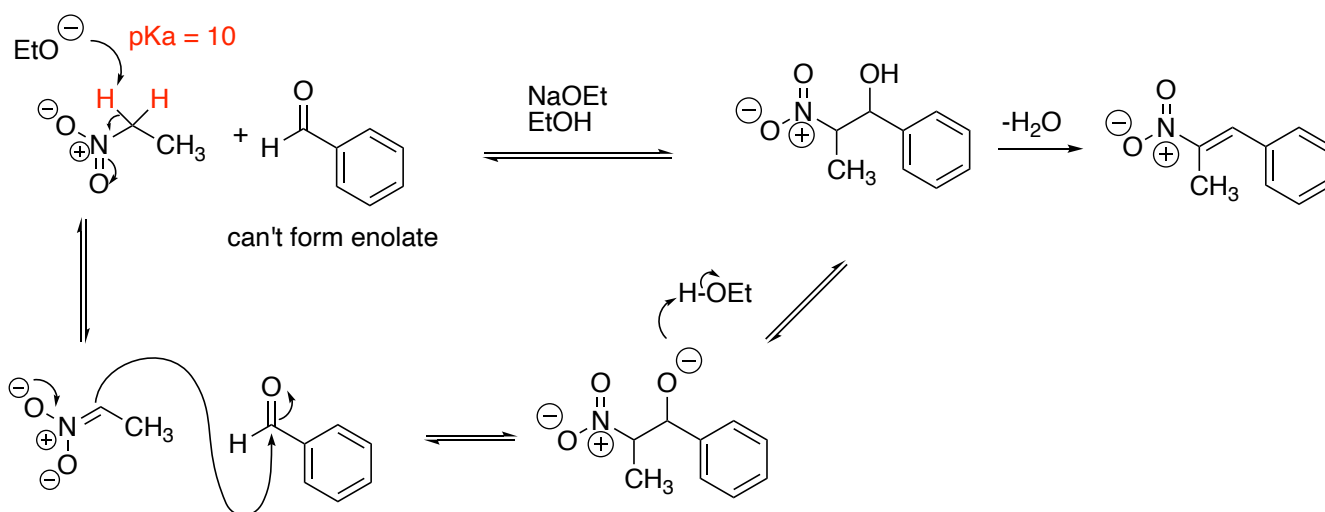
### Mixed Aldol Reactions with 1,3-Dicarbonyl Compounds

1,3-dicarbonyl compounds are also good substrates for aldol reactions as the enolate is more easily generated due to the acidity of the alpha protons. In the example shown below the intermediate beta-hydroxy compound loses water to generate a highly conjugated system.

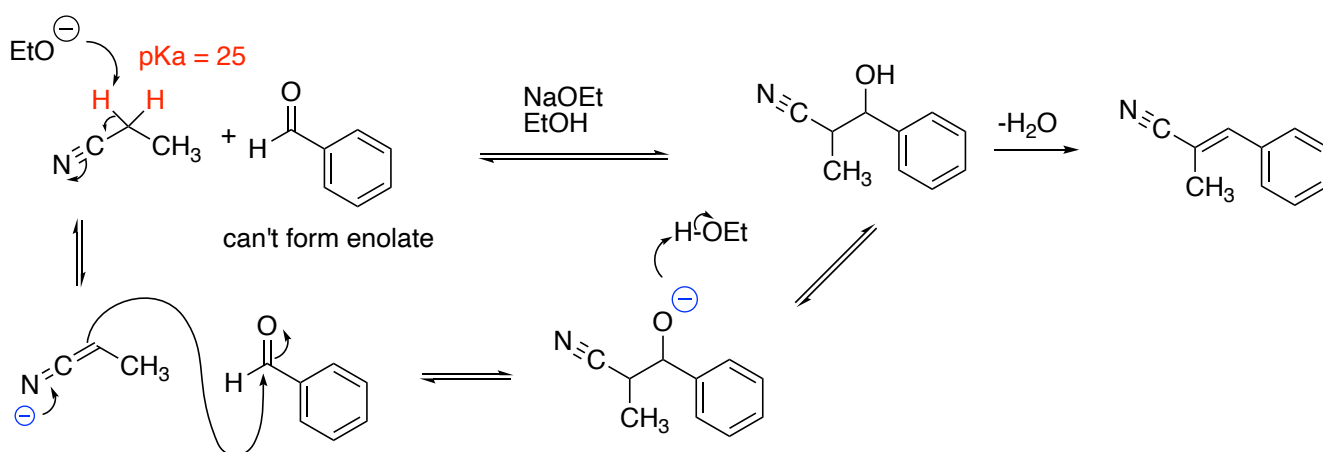


\*\*Note the base NaOEt matches the ester to avoid transesterification

### Aldol Reactions with Nitroalkanes

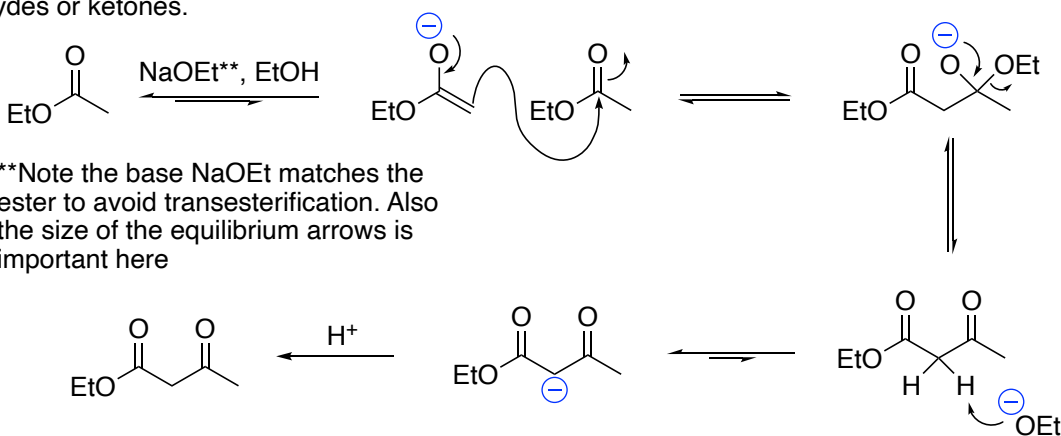


### Aldol Reactions with Nitriles



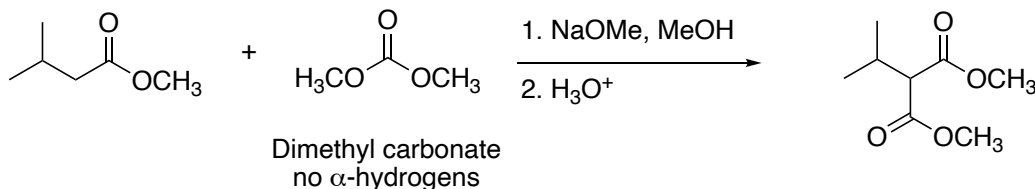
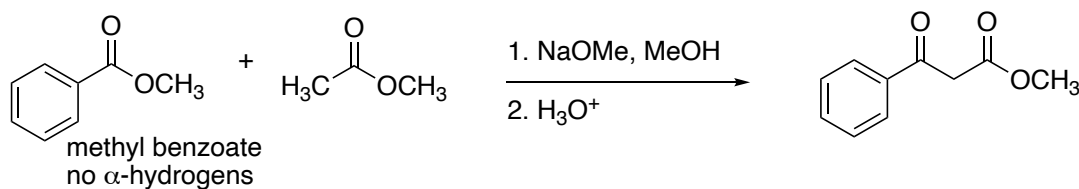
### Claisen Condensation

The Claisen Condensation is very similar to an aldol reaction, except it is carried out with esters rather than aldehydes or ketones.

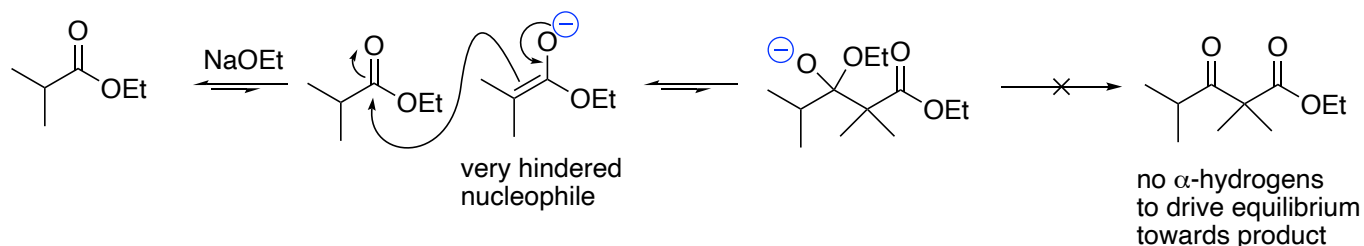


### Crossed Claisen Condensations

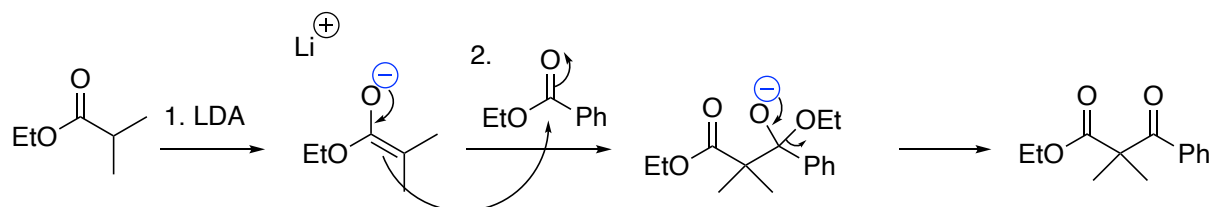
These are possible when one ester component has no  $\alpha$ -hydrogens.



Esters with only one  $\alpha$ -hydrogen cannot be converted to  $\beta$ -Ketoesters because there is no acidic hydrogen left in the final step of the mechanism to pull the equilibrium towards product.

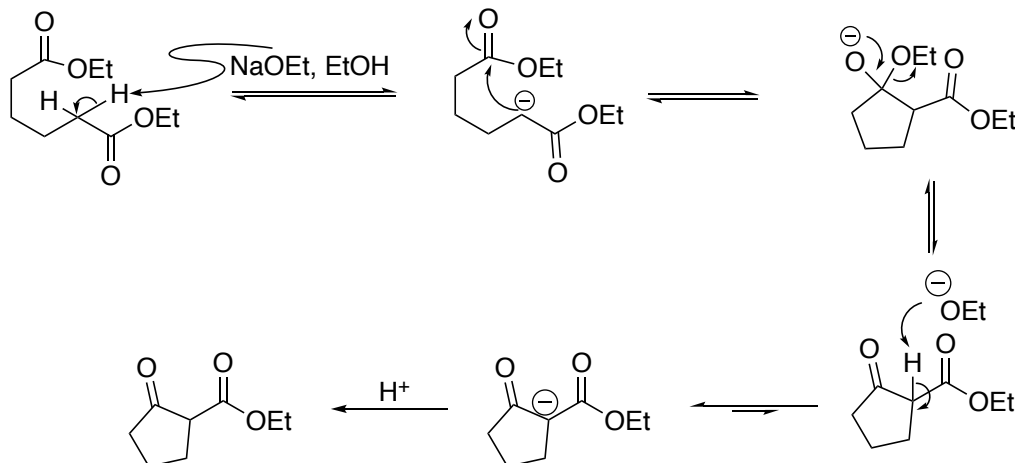


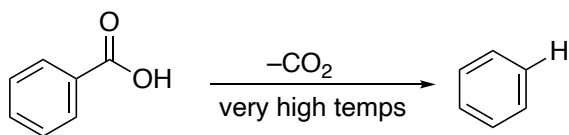
You can get around this problem by using strong bases (i.e. LDA) to form quantitative enolate and then treating the enolate with an ester.



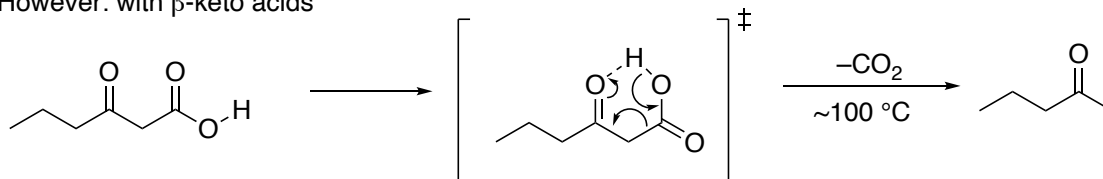
### Dieckmann Cyclization

The Dieckmann Cyclization is just an intramolecular version of the Claisen Condensation.

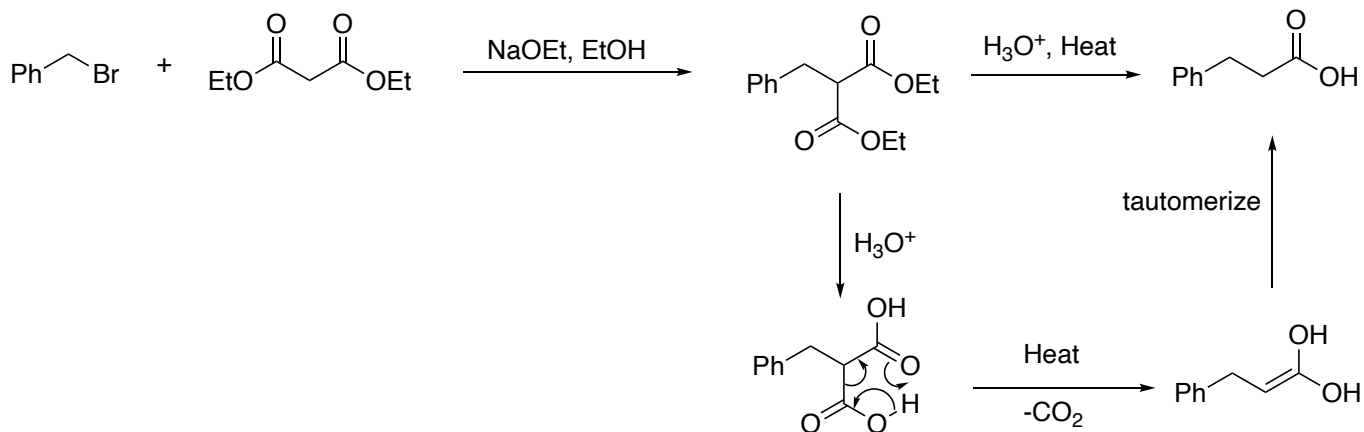
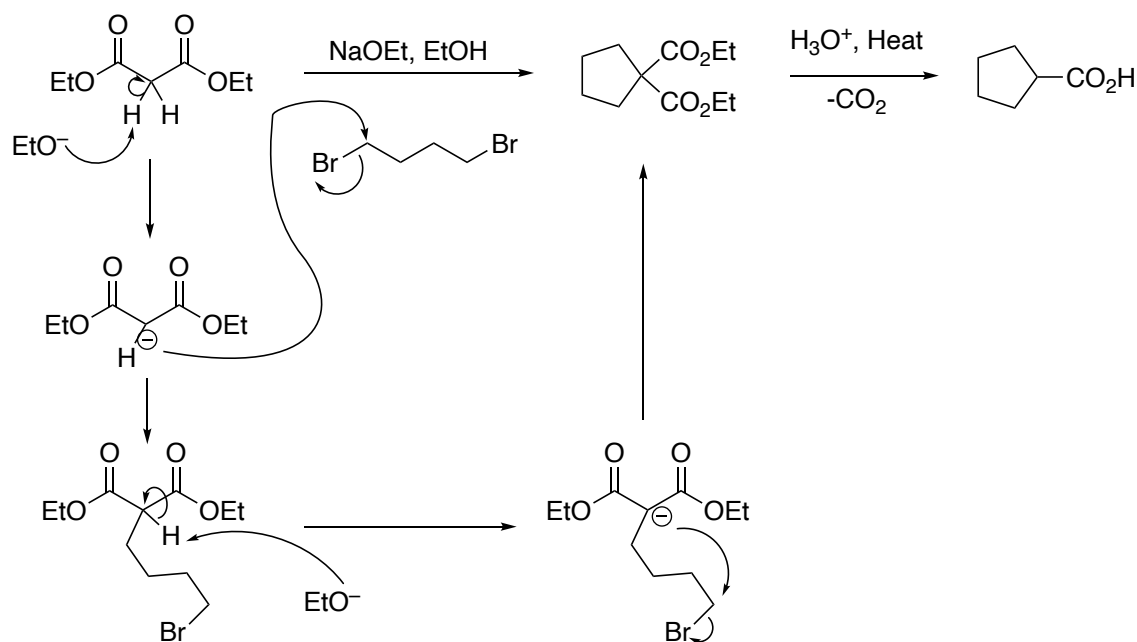


**Decarboxylation**

However: with  $\beta$ -keto acids

**Malonic Ester Synthesis**

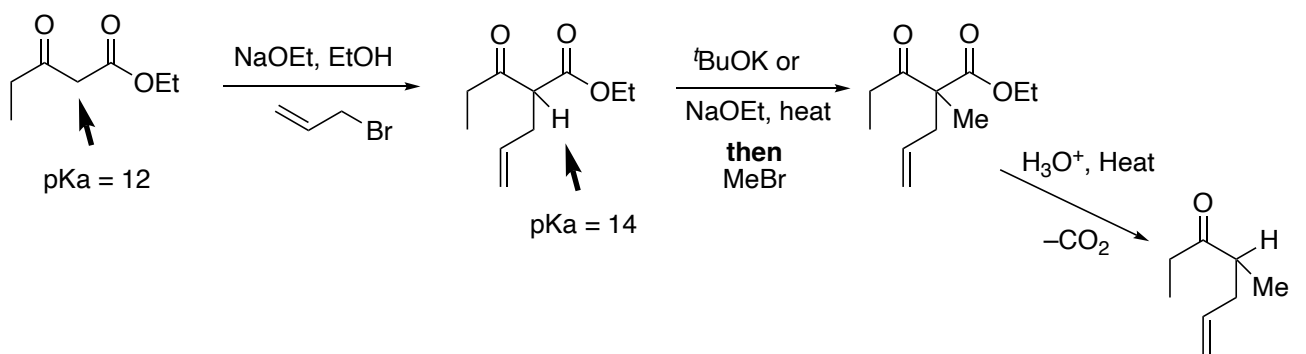
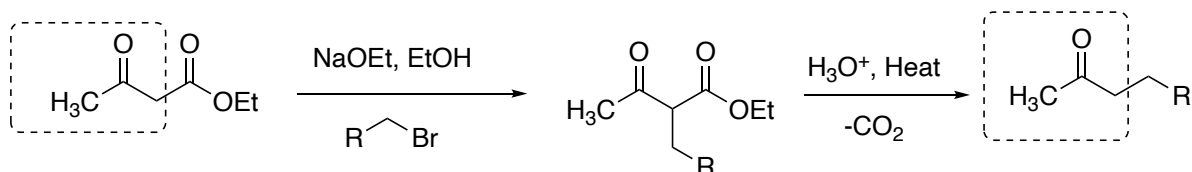
1,3-Diester compounds are useful for preparing carboxylic acids where two additional carbons have been added. If the product of the alkylation is hydrolyzed to the diacid and heated, one of the carboxylic acids cleaves and comes off as  $\text{CO}_2$ . Below is an example using this reaction with a dialkylation to make a new ring.

**Example: Intramolecular Malonic Ester Synthesis**

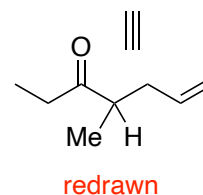
### Acetoacetic Ester Synthesis

Identical to the malonic ester synthesis, if one of the carbonyls is a methyl ketone instead of an ester, you can add the equivalent of acetone to an alkyl halide. Note that only the Carboxylic Acid part cleaves off in the end, not the Ketone part.

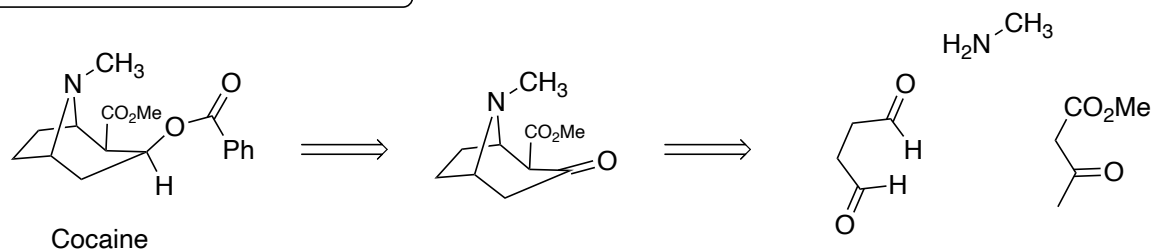
Examples:



Show mechanism of each step

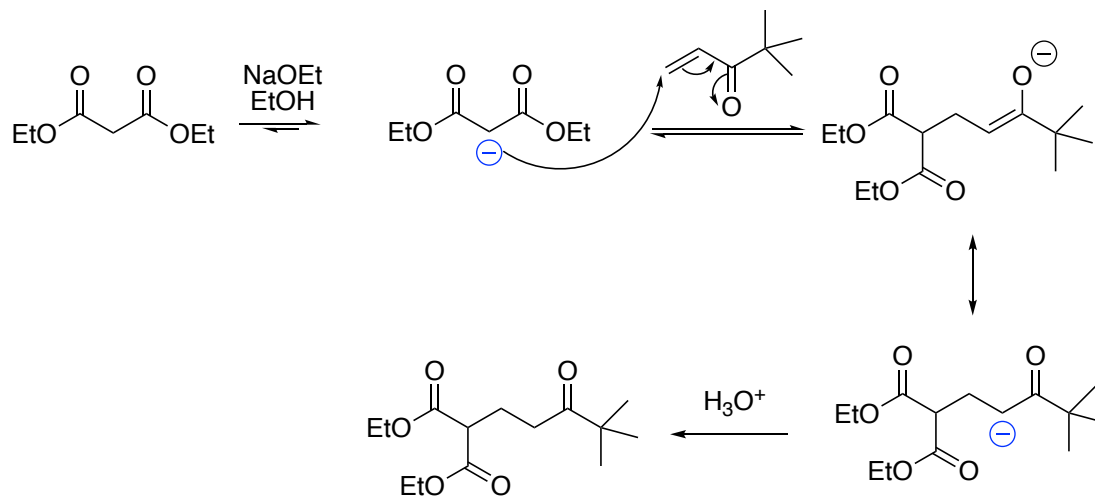


### Synthesis of a Cocaine Intermediate



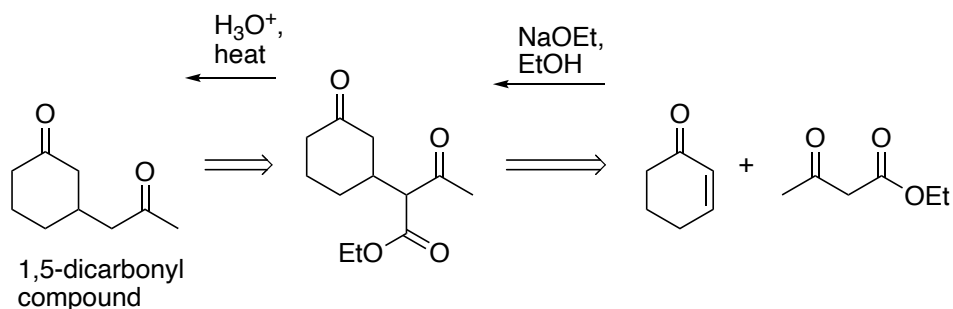
### Michael Reaction

1,3-dicarbonyl compounds can also undergo conjugate additions to  $\alpha,\beta$ -unsaturated carbonyl compounds. These reactions are called Michael additions which we covered in Ch. 21.



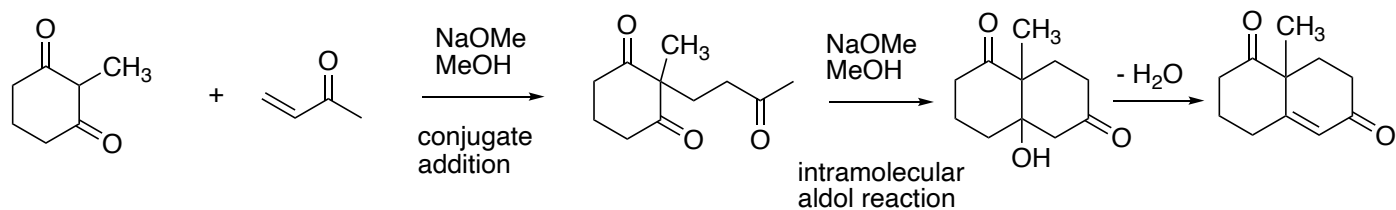
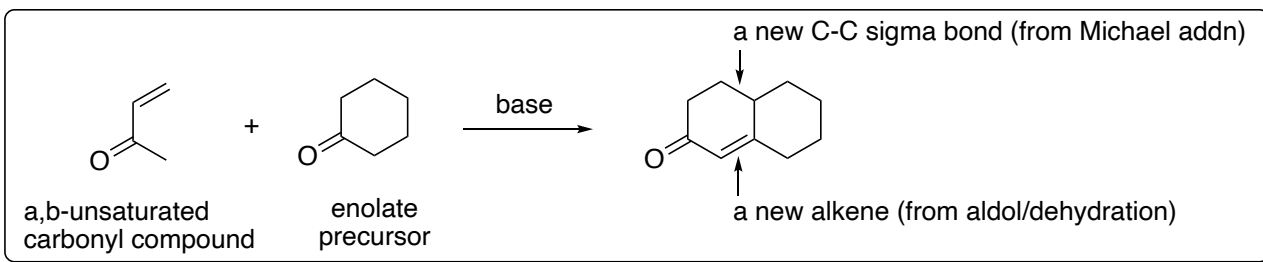
the enolate is protonated by acid during reaction workup.

### Retrosynthesis Example:



### Robinson Annulation

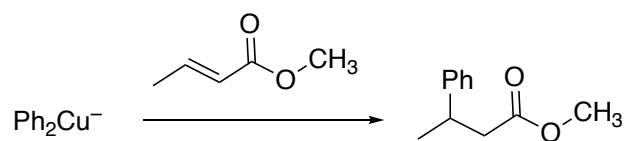
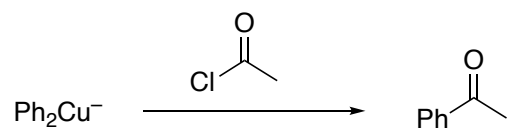
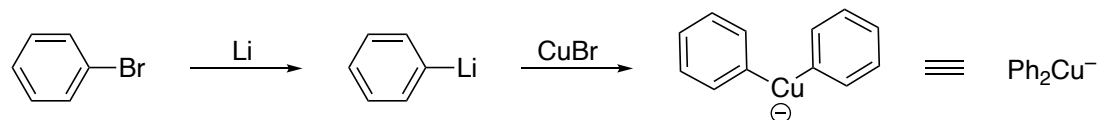
This is a reaction that combines a Michael reaction with an intramolecular aldol reaction.



## Show Mechanism

## Cuprates

Good for  $S_N2$  type chemistry (unlike Grignard and Lithium reagents)  
Adds once to acid chloride



Review

