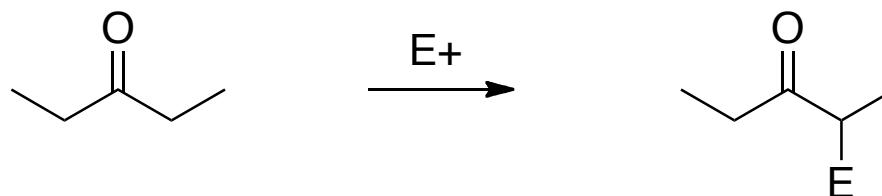
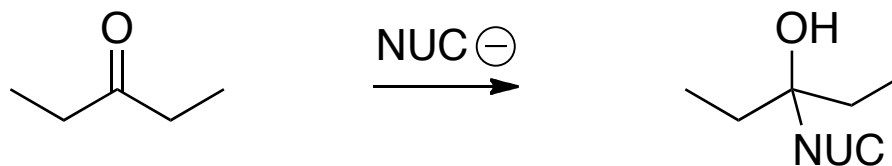


## Enols and Enolates

A type of reaction with carbonyl compounds is an  $\alpha$ -substitution  
(an electrophile adds to the  $\alpha$  carbon of a carbonyl)

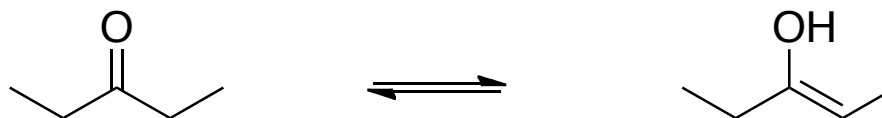


In the preceding chapters, we primarily studied nucleophiles  
reacting at the electrophilic carbonyl carbon



## Enols

Enol and a ketone are tautomers



Usually the ketone is more stable than the enol and it predominates

Under either slightly basic or acidic conditions the concentration of enol can be increased

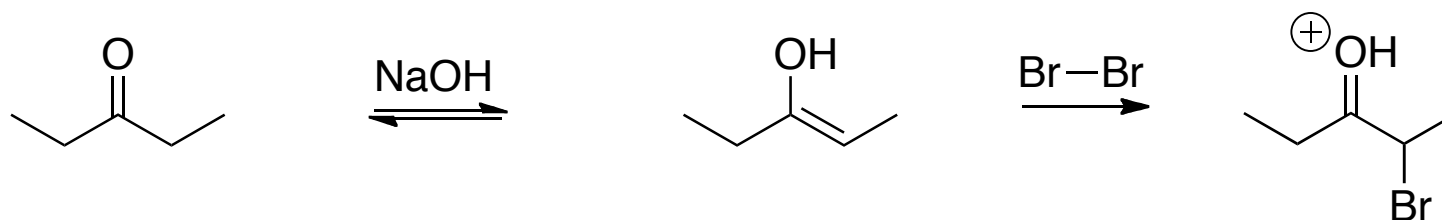
The keto form still predominates

With aldehydes there is relatively more enol form than with ketones

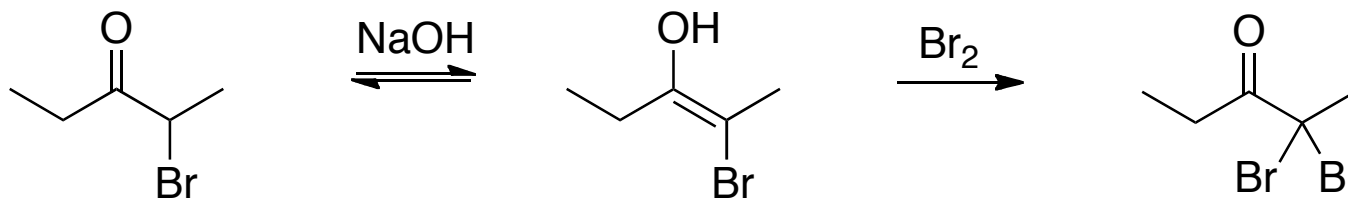
## Reactions of Enols

The enol form can react with electrophiles

A common reaction is halogenation



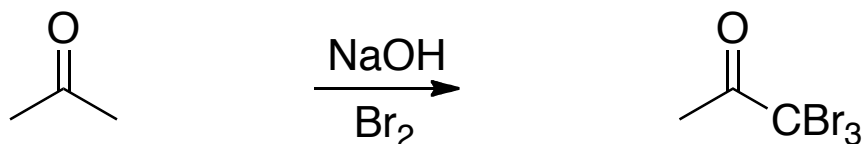
Under basic conditions it is hard to stop at one addition due to hydrogen abstraction of product is more favored than starting material



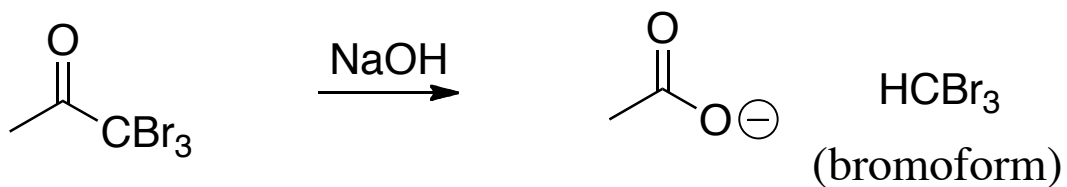
## Haloform Reaction

This polyhalogenation is exploited with a haloform reaction

A methyl ketone will react until three halogens have been substituted on the  $\alpha$ -carbon



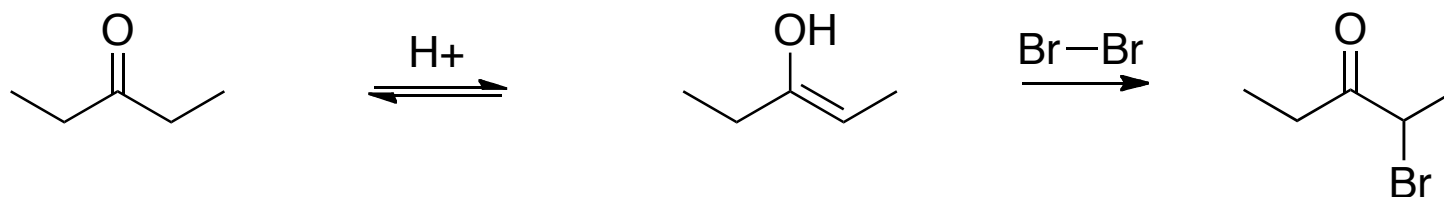
With three halogens attached to the carbon, it becomes a good leaving group



The three halogens stabilize the negative charge of the leaving group

## Acid Catalyzed Enol Formation

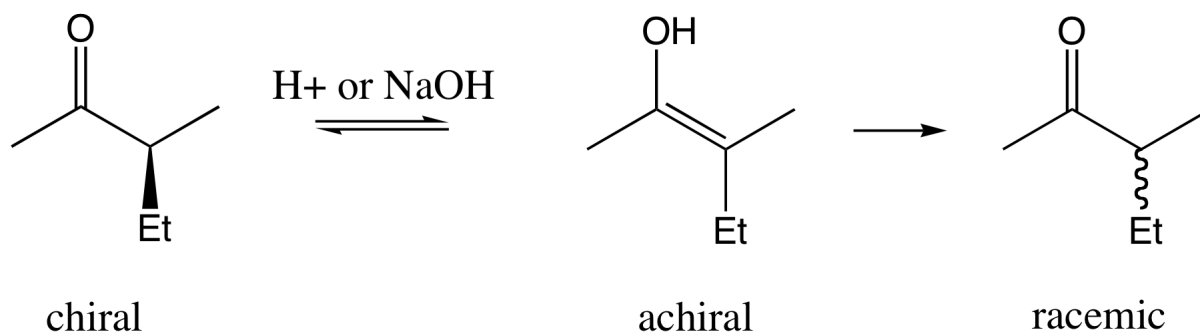
Under acidic conditions, the enol can react with halogen and stop after one addition



With acidic conditions, do not form anion adjacent to halogen as in basic mechanism, therefore the reaction can be stopped after one addition

## Enolizable Positions

A consequence of the ability to form enols is that chiral  $\alpha$ -carbons can racemize

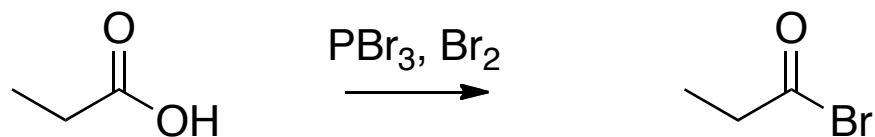


Since the  $\alpha$ -position can form an enol, and the enol is achiral, chiral atoms that are  $\alpha$  to carbonyls will lose chirality whenever enol formation is favored

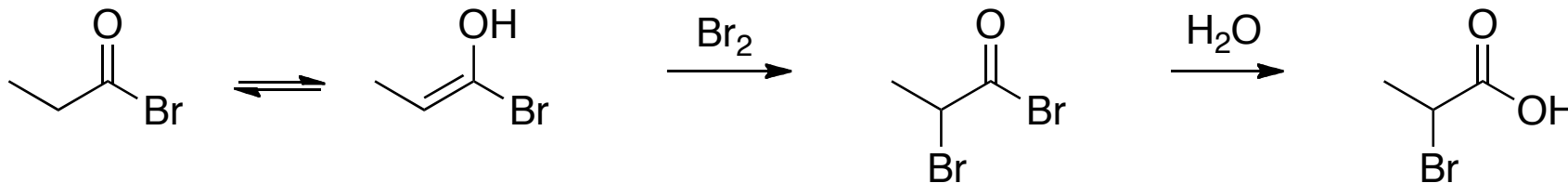
## Bromination of Acids

Carboxylic acids can also be brominated

First need to convert carboxylic acid into acid halide  
(labile H would interfere)



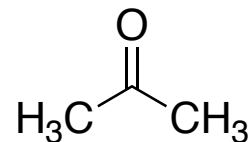
This acid bromide can form enol under these conditions, which will react with  $\text{Br}_2$



## Enolates

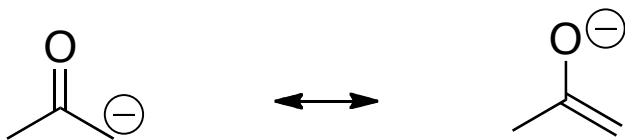
Enolates are similar to enols but they are far more nucleophilic

In order to generate an enolate, need a base to abstract an  $\alpha$ -hydrogen



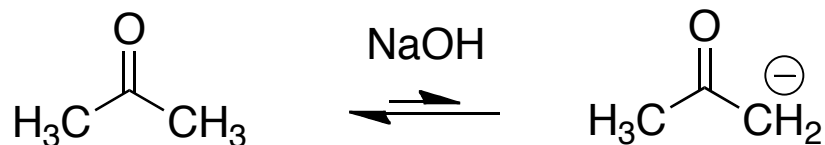
pKa of  $\alpha$ -hydrogens  $\sim$ 20

The  $\alpha$ -hydrogens are more acidic than normal alkane hydrogens due to electron withdrawing carbonyl group that can delocalize the resultant negative charge



## Base Abstraction

Since the pK<sub>a</sub> of an α-hydrogen of a ketone is ~20, the choice of base will determine the extent of enolate formation

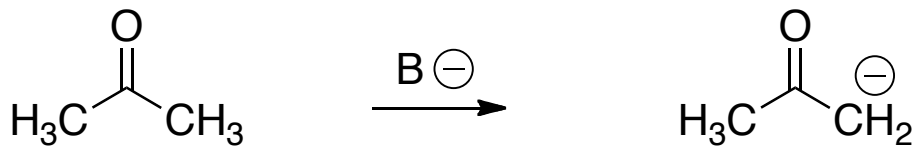
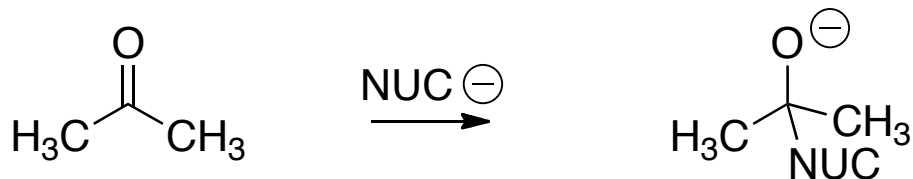


Both water (pK<sub>a</sub> ~15.7) or alcohols (pK<sub>a</sub> ~16) are less acidic, therefore with these bases the majority of the compounds will be in the keto form

## Basicity versus Nucleophilicity

Most strong bases are also strong nucleophiles  
(remember  $S_N2$  vs. E2)

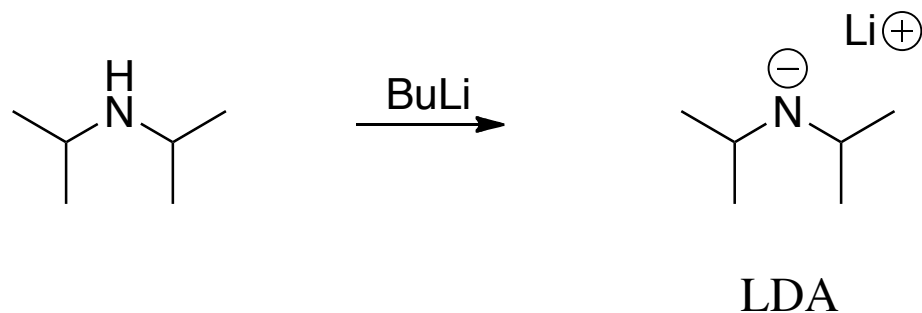
With carbonyls need to balance two different type of reactions:  
a strong nucleophile reacting with the carbonyl and a strong base abstracting  $\alpha$ -hydrogen



## Enolate

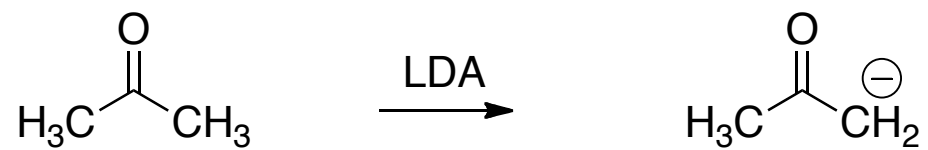
To generate enolate need to use a base that will not act as a nucleophile

Common choice is to use lithium diisopropylamide (LDA)



LDA is a strong base (pK<sub>a</sub> of conjugate is close to 40), while it is very bulky so it will not react as nucleophile on carbonyl

LDA will quantitatively form enolate

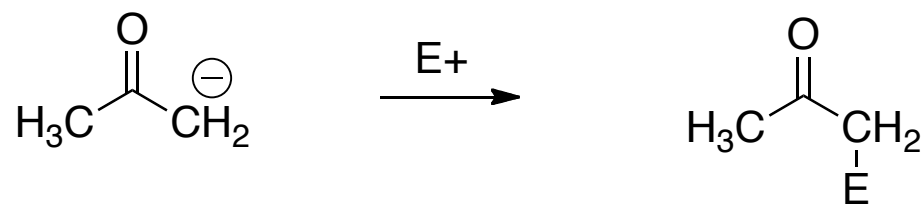


Using LDA the enolate will be formed quantitatively,  
with weaker bases will only form the enolate in a small fraction

## Enolate as a Nucleophile

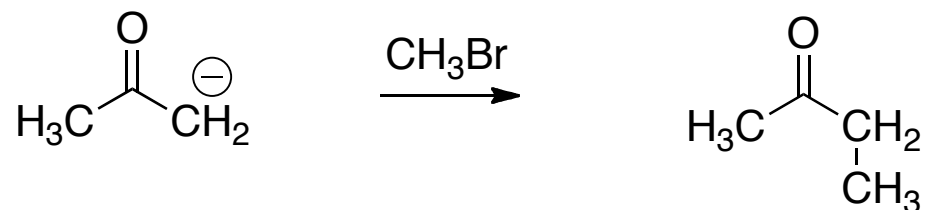
Have already observed many reactions with a negatively charged nucleophile  
(most S<sub>N</sub>2 reactions)

An enolate is simply another type of nucleophile,  
it can react in similar manner as other nucleophiles



## Alkylation of Enolates

One common reaction is to alkylate the enolate

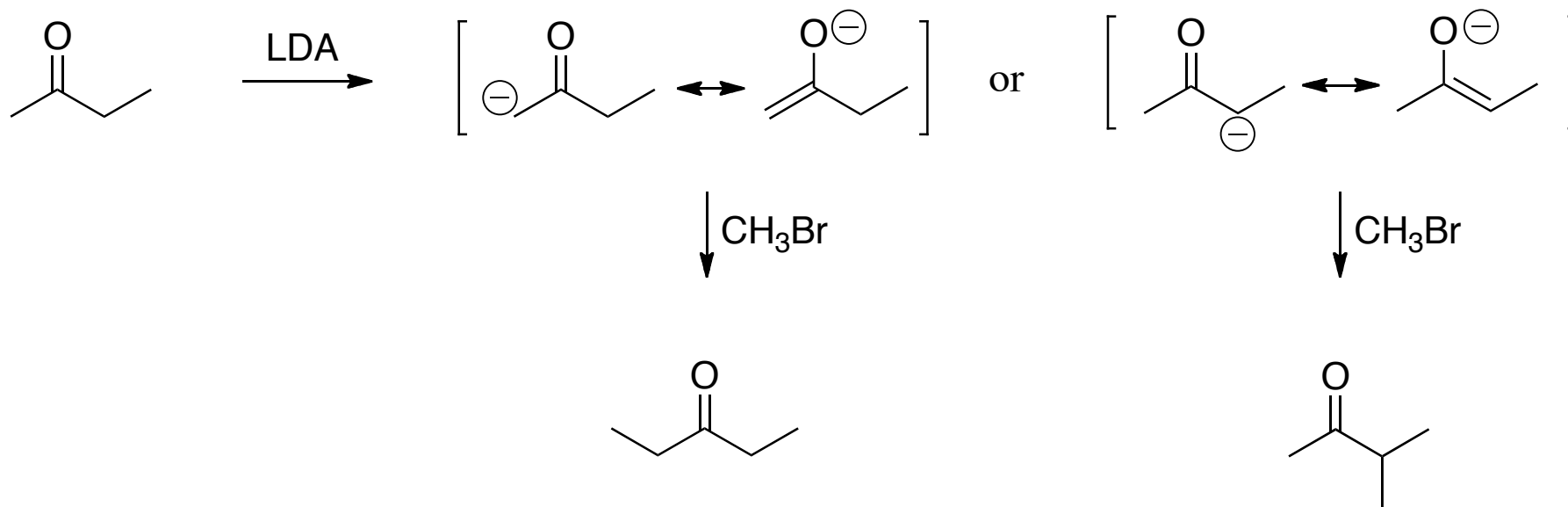


This reaction will place an alkyl substituent at the  $\alpha$ -position of a carbonyl

Any electrophile that will react in a  $\text{S}_{\text{N}}2$  reaction can be used

## Unsymmetrical Carbonyls

With an unsymmetrical carbonyl can obtain two different enolates



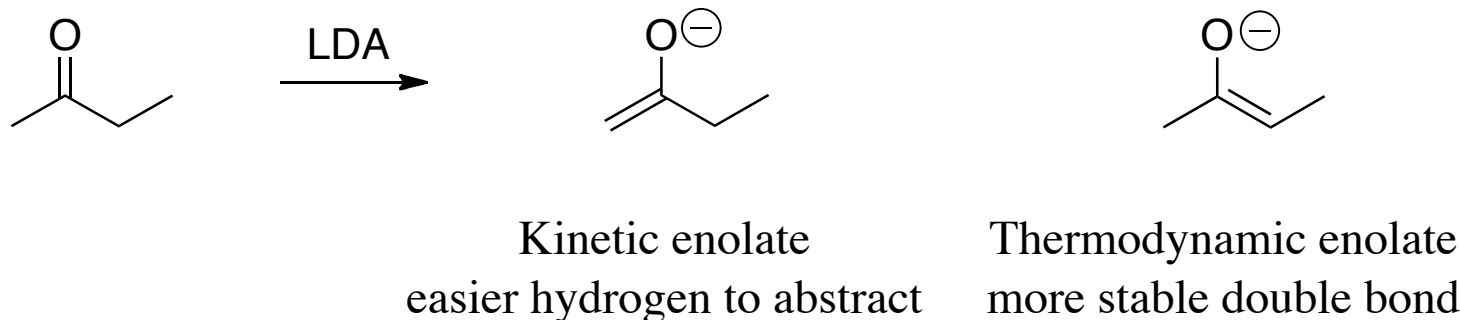
When alkylated in second step, two enolates generate different products

How to obtain one product preferentially?

## Thermodynamic vs. Kinetic Control

The key is the stability of each enolate generated

The enolate can be preferentially generated at either site depending upon conditions

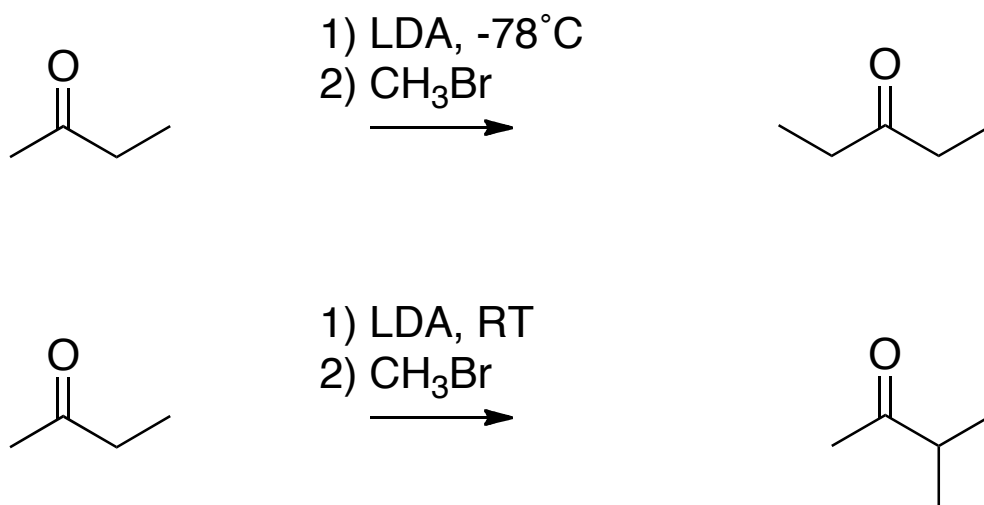


Lower temperature favors kinetic product

Higher temperatures (in this case usually room temperature and above)  
favors thermodynamic product

## Product Formation

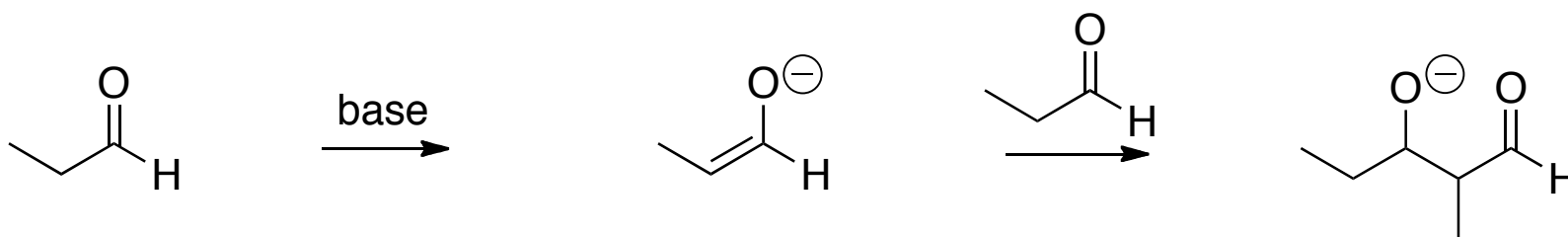
By controlling which enolate is generated, where the  $\alpha$ -substitution occurs can be controlled



## Cannot Alkylate Aldehydes with Enolates

Will not obtain  $\alpha$ -substitution with aldehydes with enolate chemistry

The aldehyde carbonyl is too reactive and it will react with the initially formed enolate

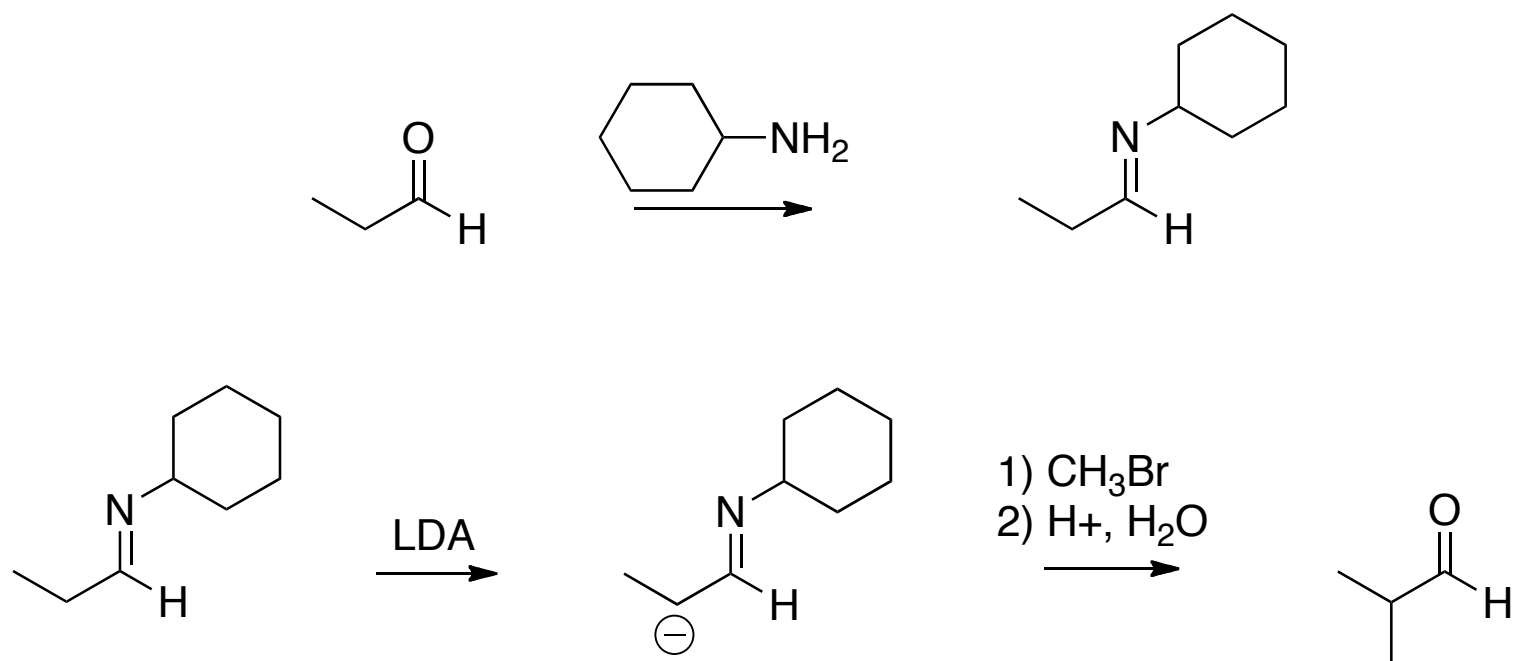


Enolate acts as nucleophile and carbonyl reacts as electrophile

## $\alpha$ -Alkylation of Aldehydes

To alkylate an aldehyde, first need to convert the aldehyde to a less reactive system

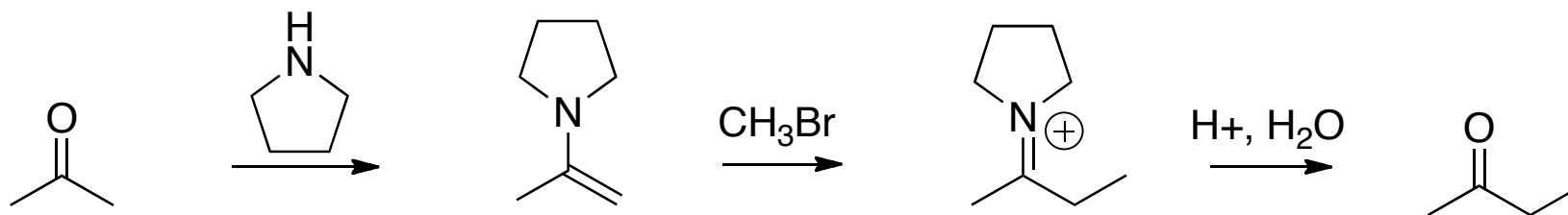
An imine or imine derivative is used most frequently



## Enamines

Another option instead of enolate formation is to form an enamine

React carbonyl with 2° amine

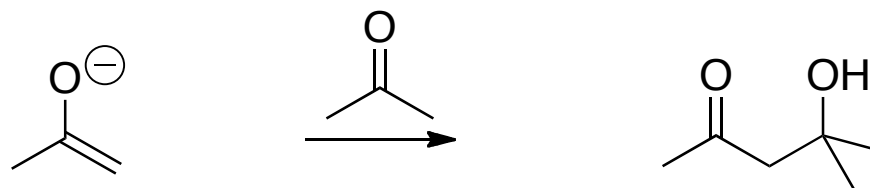


The enamine is not as reactive as an enolate, but it is more reactive than an enol

## Aldol Condensation

Instead of reacting the enolate with an alkyl halide, we can also react the enolate with a carbonyl compound

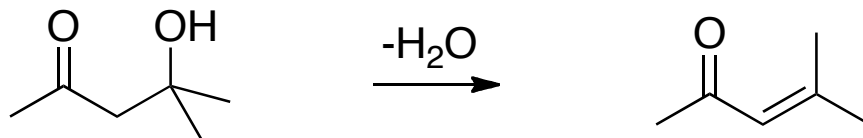
The carbonyl can react as an electrophile



Upon work-up obtain a  $\beta$ -hydroxy ketone

## Dehydration of Aldol Product

The  $\beta$ -hydroxy ketone that is formed can also lose water to form an  $\alpha,\beta$ -unsaturated ketone

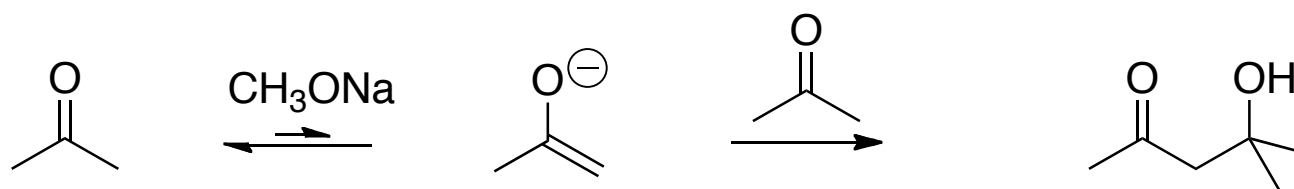


Greater the conjugation, the easier for loss of water

The loss of water can sometimes occur during work-up, it can be driven to this product through heat and either acidic or basic conditions

## Procedure for Aldol Reaction

When reacting in a self-condensation can use an alkoxide base

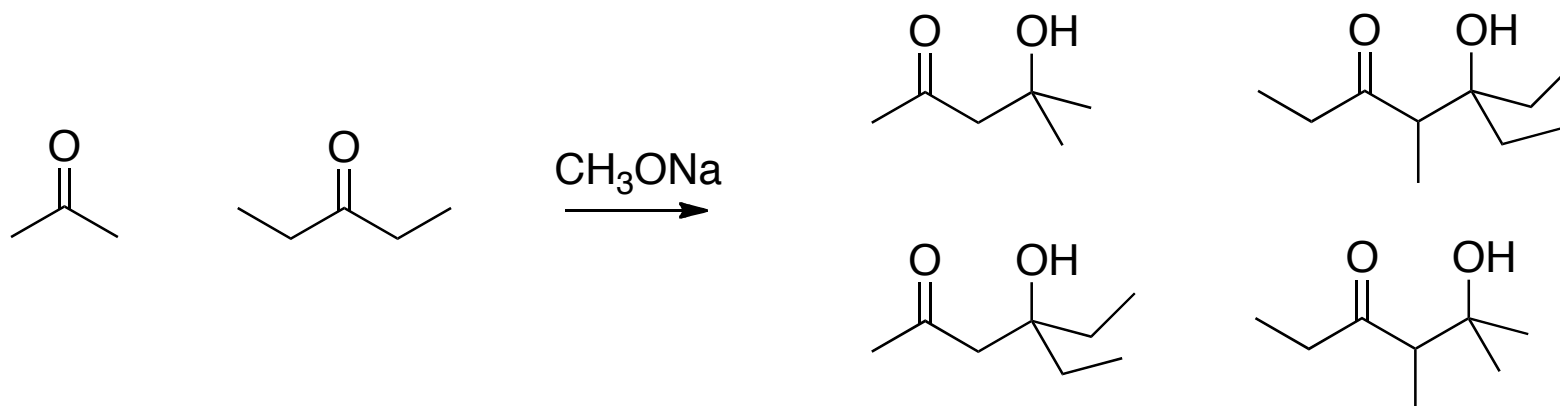


The alkoxide base will only deprotonate a small proportion of ketone, but those enolates will react quickly with keto form in an aldol reaction

Can drive the reaction to completion

## Using Different Carbonyl Compounds

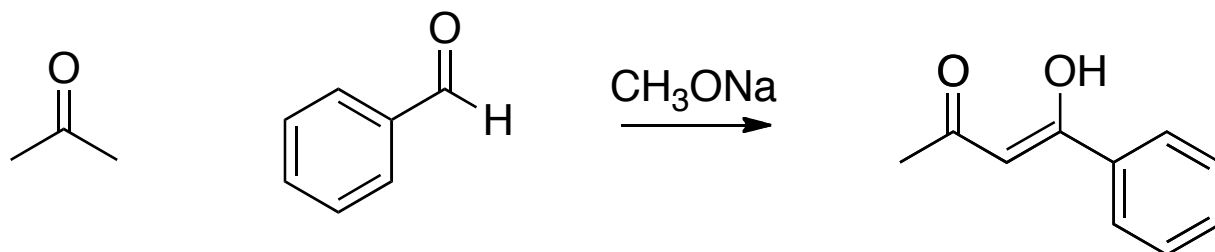
If there are different carbonyl compounds ( a mixed aldol or crossed aldol)  
then conditions need to be considered



If using two different ketones, then four different aldol products will be obtained

## Options to Control Regioproducts

One way to limit the number of products obtained is to use one carbonyl that does not have  $\alpha$ -hydrogens, therefore there are no hydrogens to abstract and can only react as electrophile



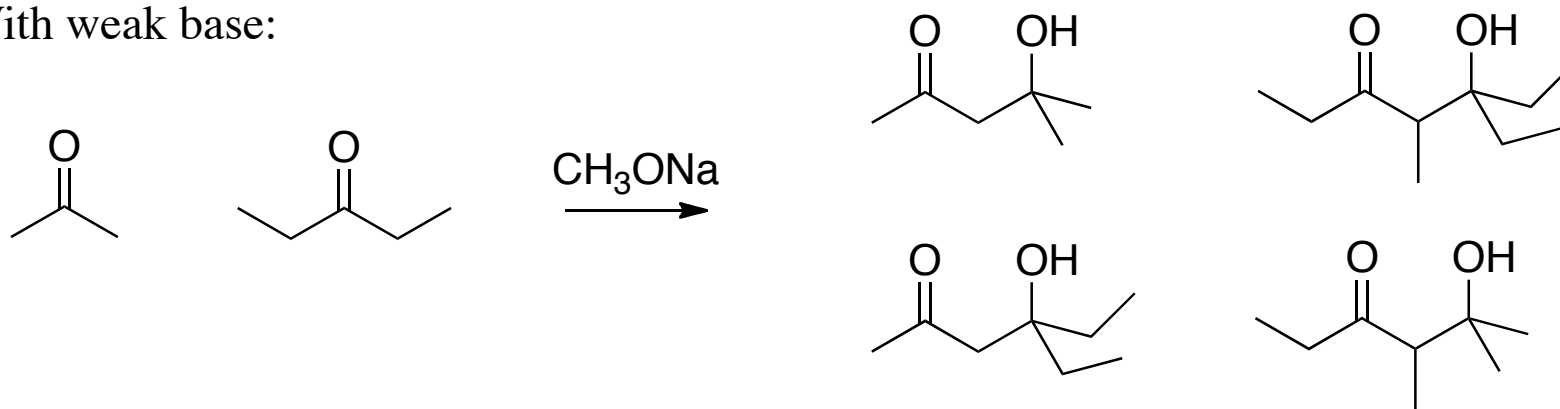
Due to conjugation,  
product will quickly dehydrate

Want to add compound with  $\alpha$ -hydrogens (acetone in example shown)  
slowly to basic benzaldehyde solution

## Options to Control Regioproducts

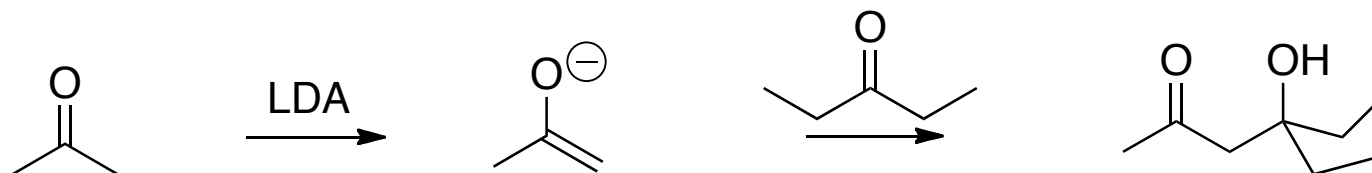
Another option: if need to use two carbonyls that both contain  $\alpha$ -hydrogens, need to first generate the enolate quantitatively (strong base) and then add the second carbonyl compound

With weak base:



Four products

With strong base:



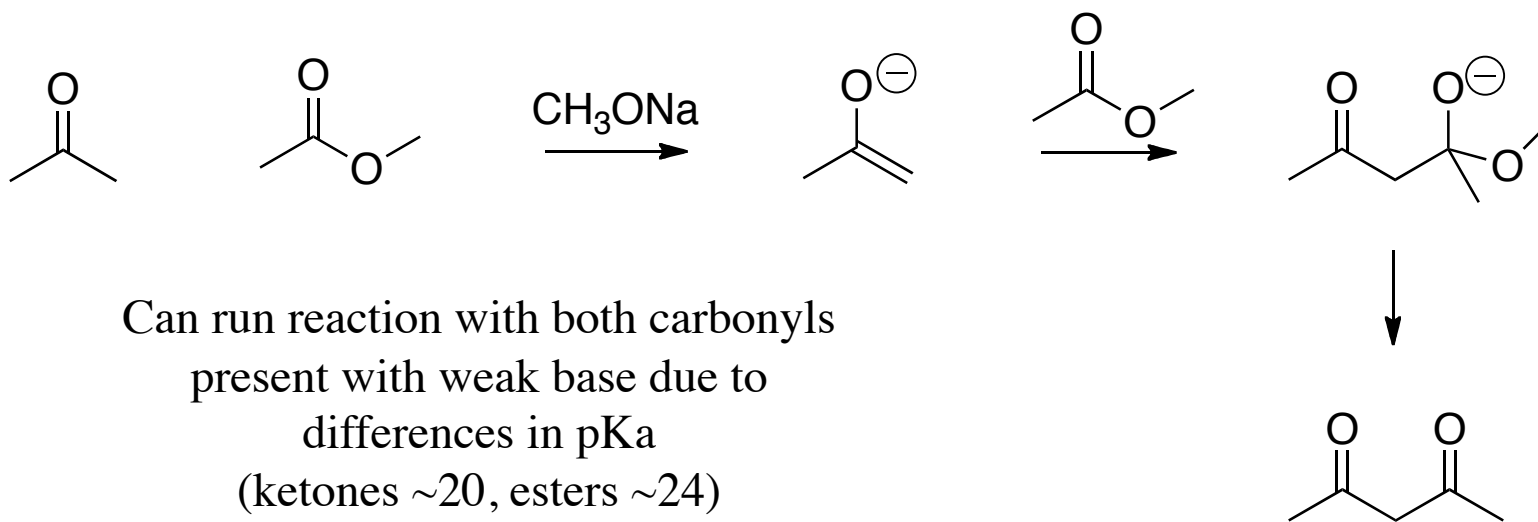
One product

Can obtain high yield of desired aldol product with this method

## Claisen Condensation

There are many “Name” reactions that are modifications of the aldol condensation,  
A Claisen condensation is an aldol where one carbonyl compound is an ester

By using an ester, the chemistry is changed due to the presence of a leaving group



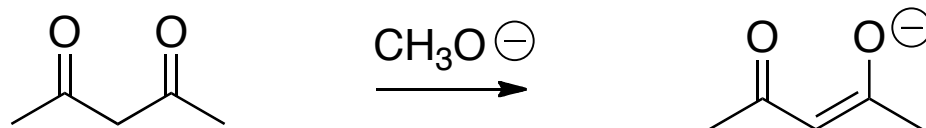
Can run reaction with both carbonyls  
present with weak base due to  
differences in pKa  
(ketones  $\sim 20$ , esters  $\sim 24$ )

With ester leaving group,  
obtain diketone product

## Reactions are Driven to Completion

Unlike other aldol reactions, which are under equilibrium control, Claisen condensations give very high yield without adjusting equilibrium conditions

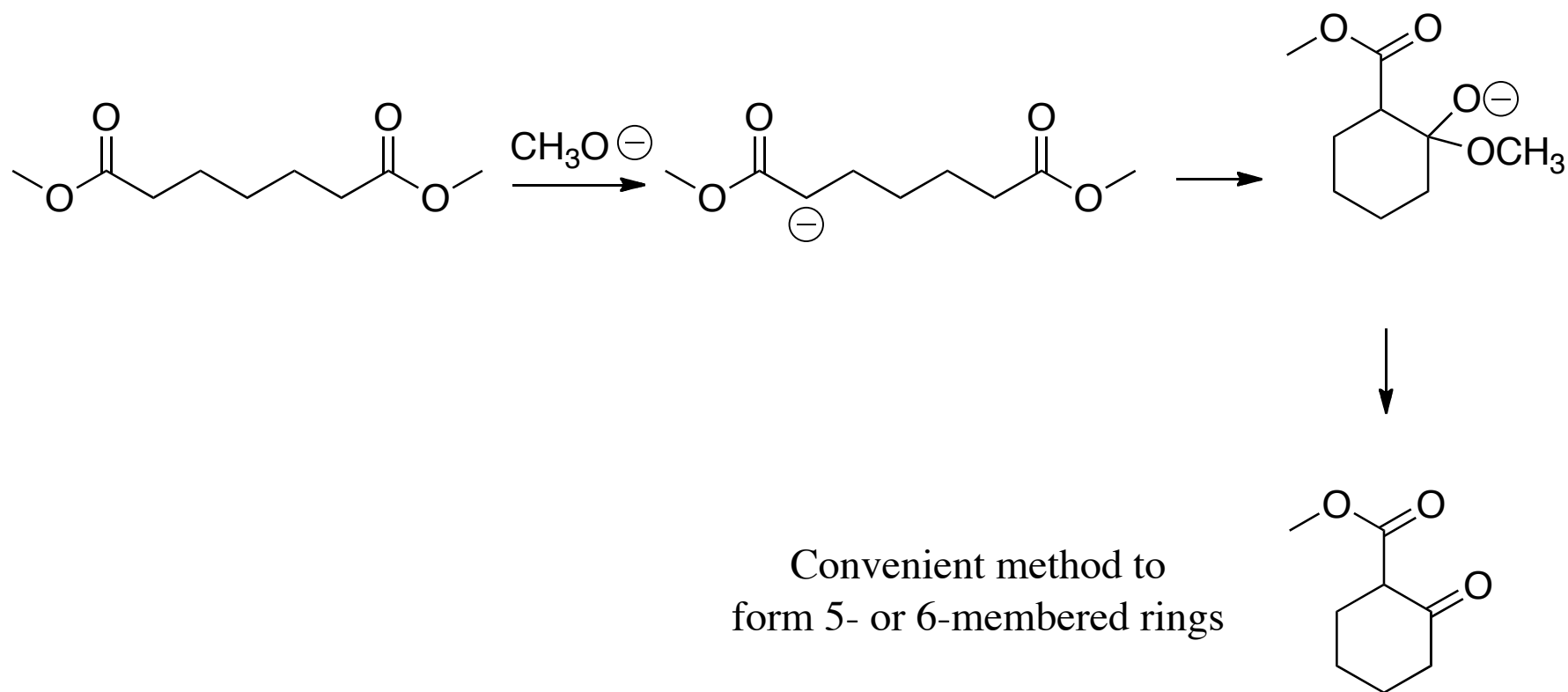
The last step generates an alkoxide with a  $\beta$ -diketone



Diketones have a pK<sub>a</sub> ~10, therefore methoxide will quantitatively abstract the hydrogen

## Dieckmann

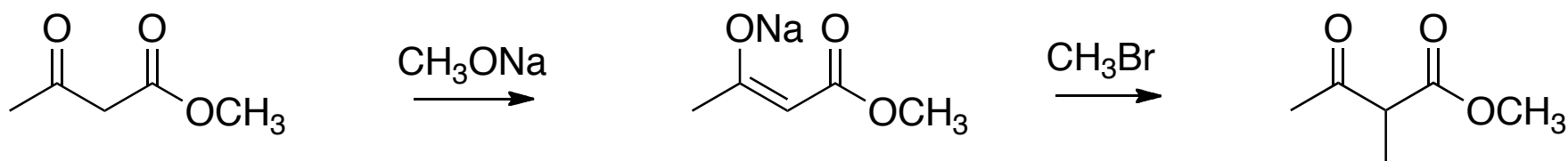
A Dieckmann condensation is an intramolecular Claisen condensation



## $\beta$ -Dicarbonyls

Both Claisen and Dieckmann condensations form  $\beta$ -dicarbonyl compounds

$\beta$ -keto esters are another type of dicarbonyl systems that are very useful synthetically  
(formed in Dieckmann if use two ester compounds)

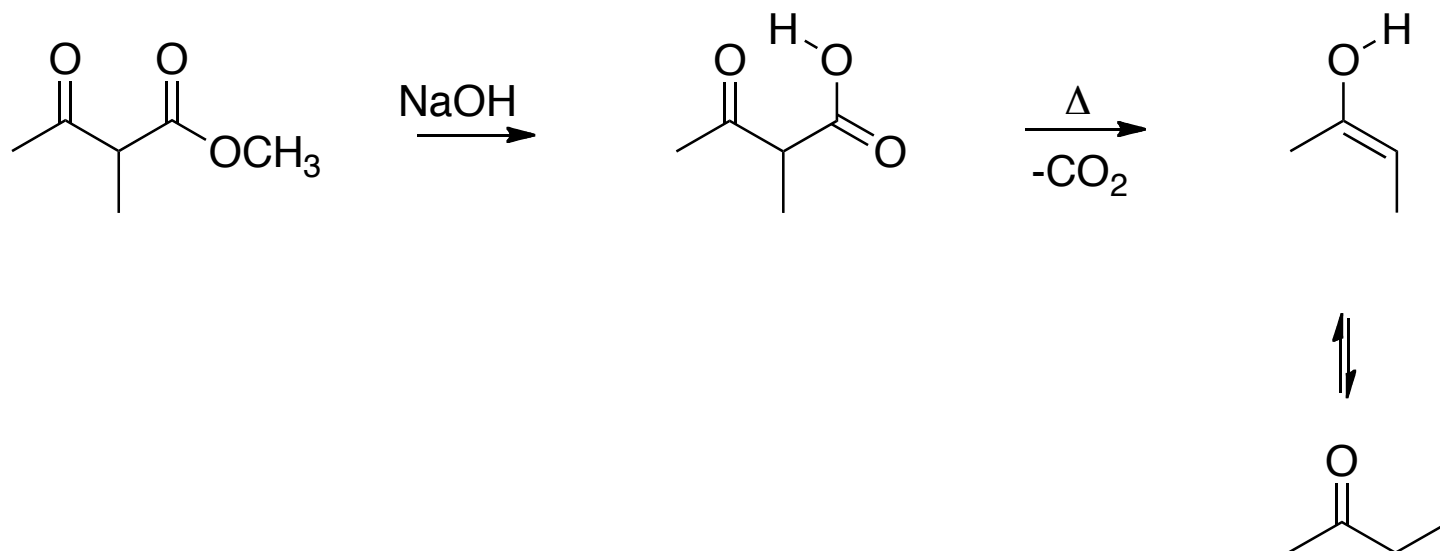


Due to the acidity of the methylene position, alkylation reactions are easy to perform quantitatively with weak base

With only one carbonyl present need to use LDA to quantitatively form enolate

## Decarboxylation

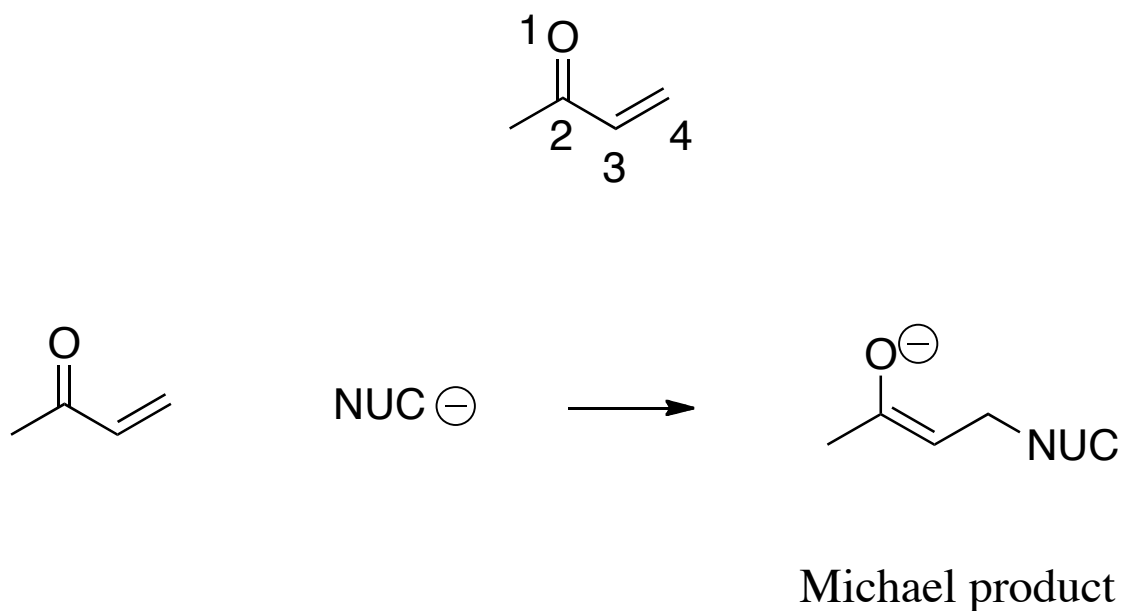
After alkylation, the ester group can be hydrolyzed to acid



Allows alkylation of ketone in much milder method than starting directly with ketone

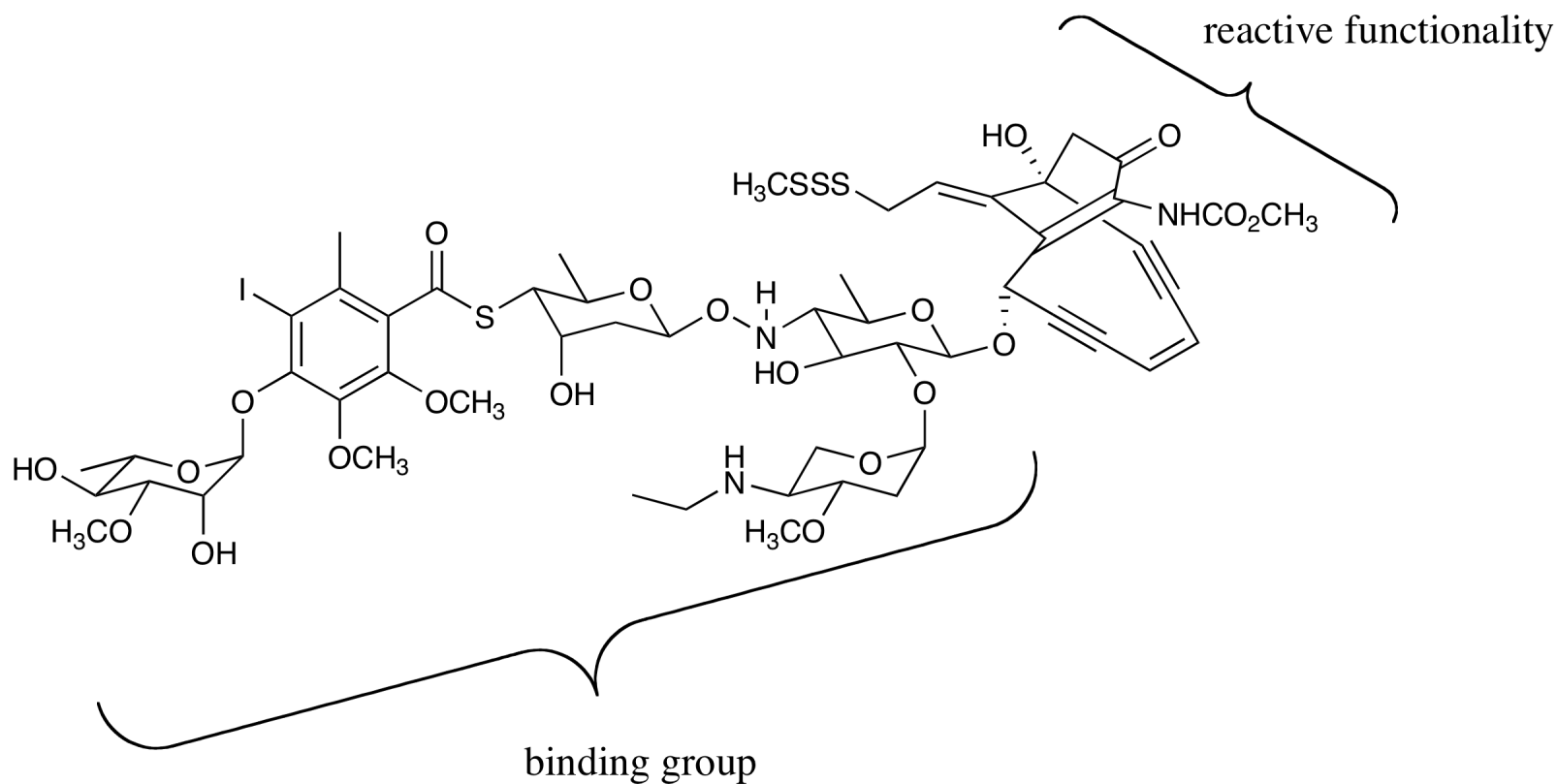
## Michael Addition

If we add enolate to  $\alpha,\beta$ -unsaturated system, the reaction often reacts with 1,4-addition  
Called Michael addition

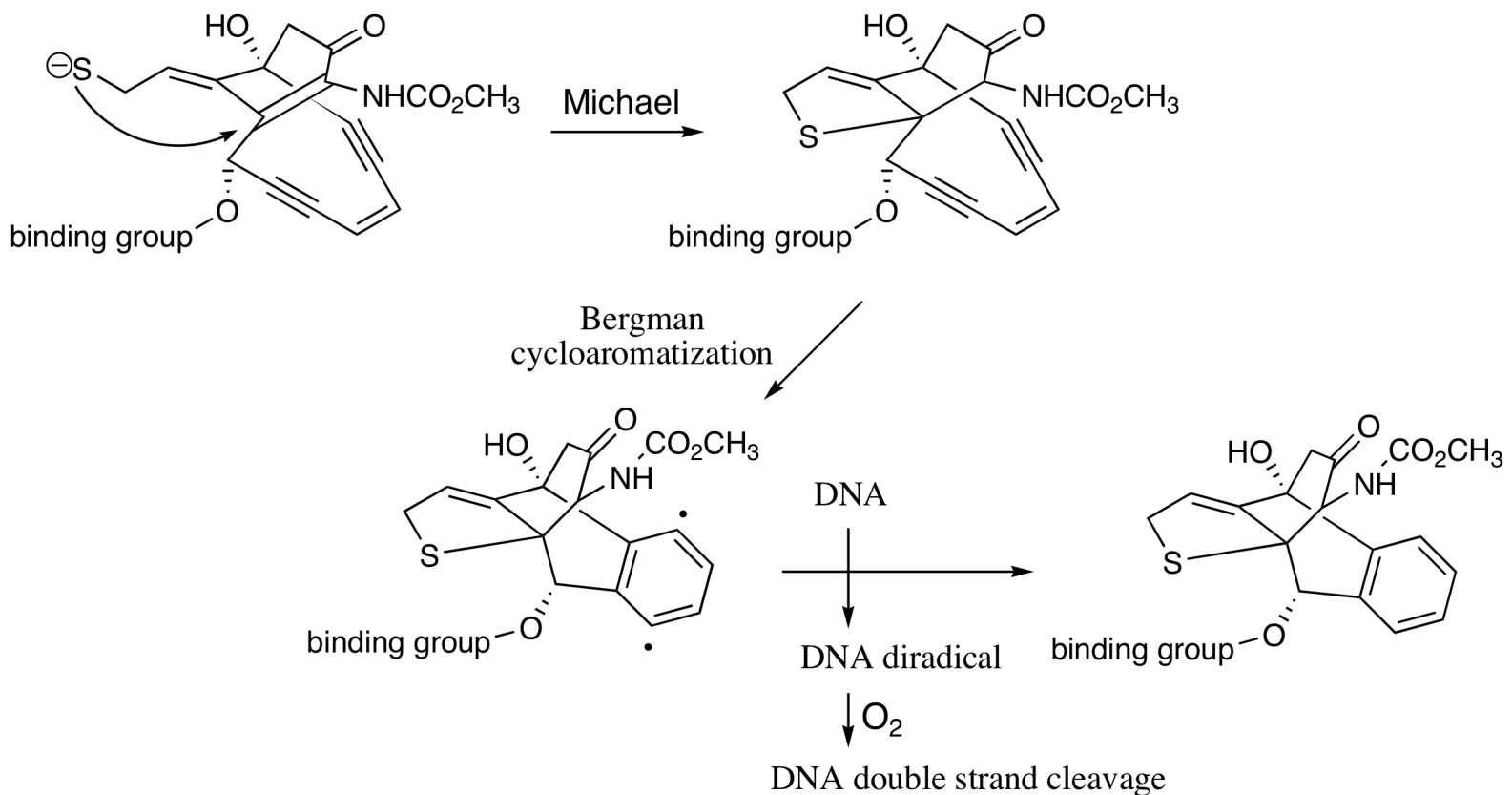


# Calicheamicin $\gamma_1^1$ : An Example of Michael Addition in Drug Action

In chapter 4 we first saw a drug that uses Michael addition



After binding group binds in the minor groove of DNA a sulfide is generated

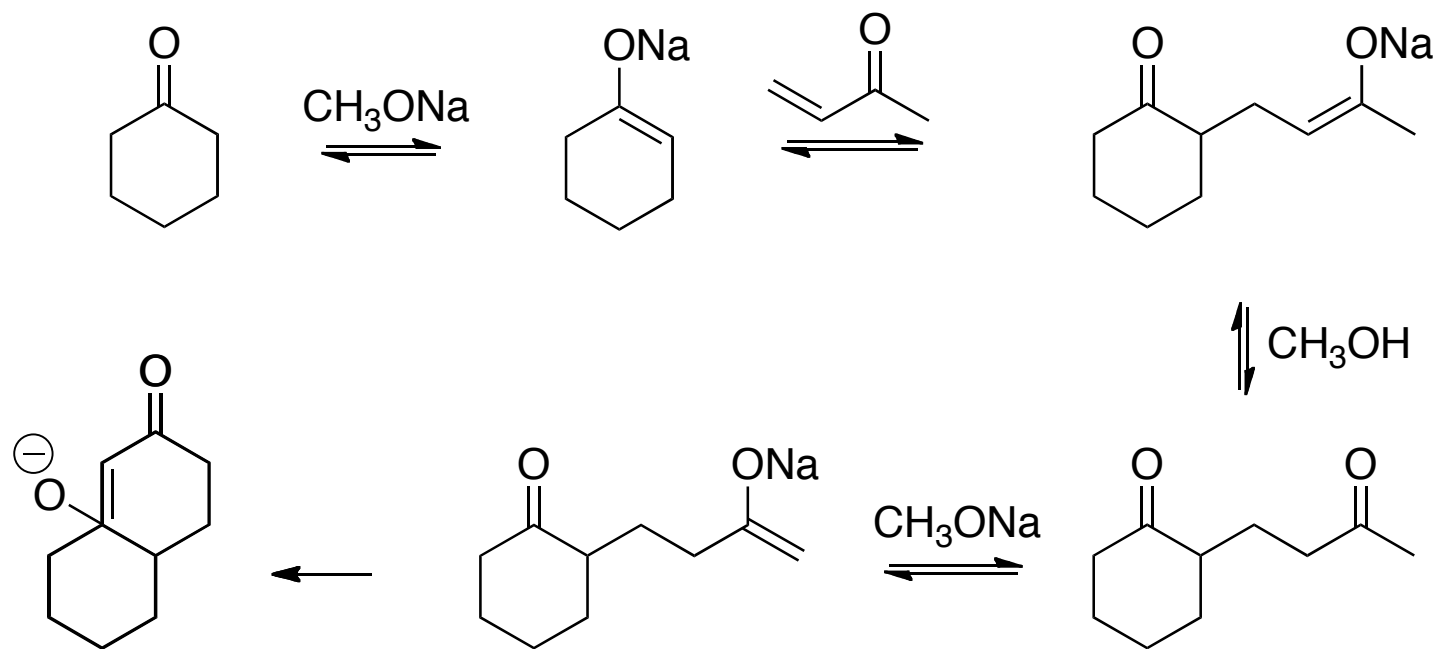


After the Michael addition occurs, the conformational change causes the Bergman cyclization to occur eventually leading to cell death after DNA cleavage

## Robinson Annulation

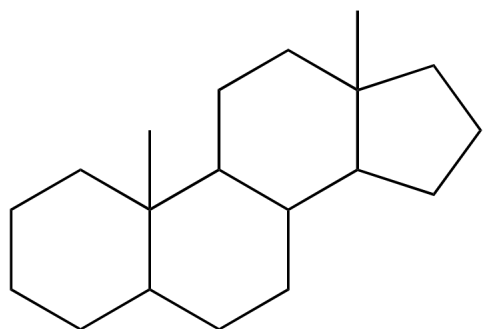
Another convenient method to form 6-membered rings

A Michael addition is followed by an aldol condensation

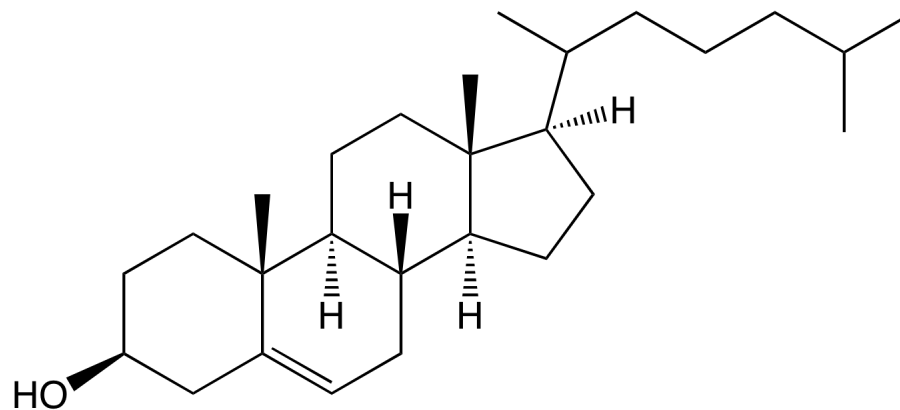


Upon work-up,  
hydroxy group readily dehydrates

## Convenient Method to Synthetically Produce Multi-Ring Systems



steroid ring system



cholesterol

Nature has more efficient ways to synthesize steroids, but a Robinson annulation can be used to prepare 6-6 and 6-5 ring junctions in a one-pot reaction