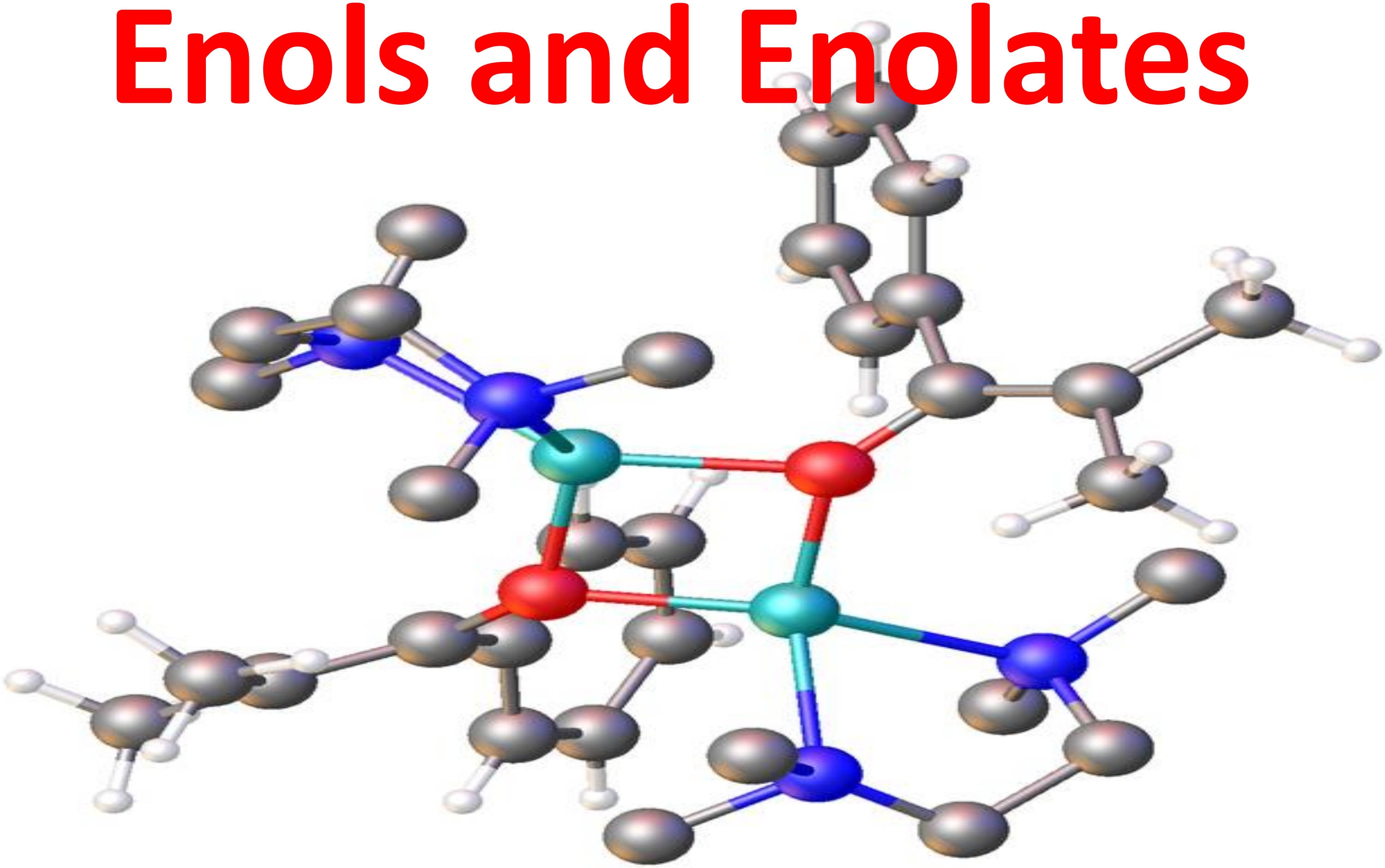
Enols and Enolates



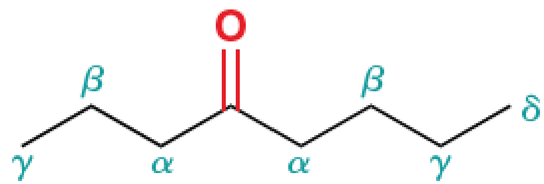
Organic Chemistry

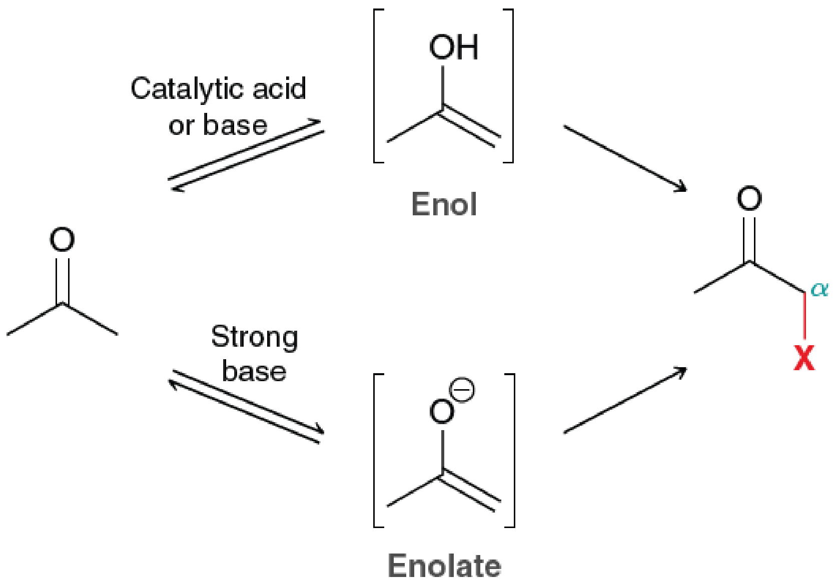
Pharmacy College/ 2nd Stage

Dr.Sham Wali Qurban

21.1 Introduction to Alpha Carbon Chemistry: Enols and Enolates

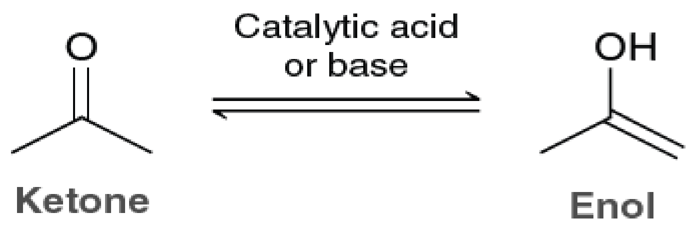
- **The Alpha Carbon**





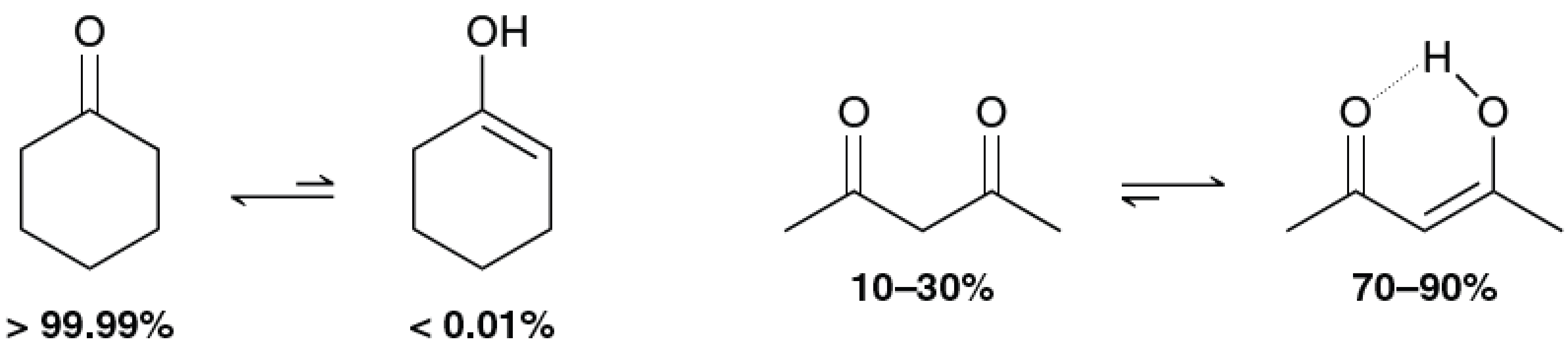
Enols

In the presence of catalytic acid or base, a ketone will exist in equilibrium with an enol.



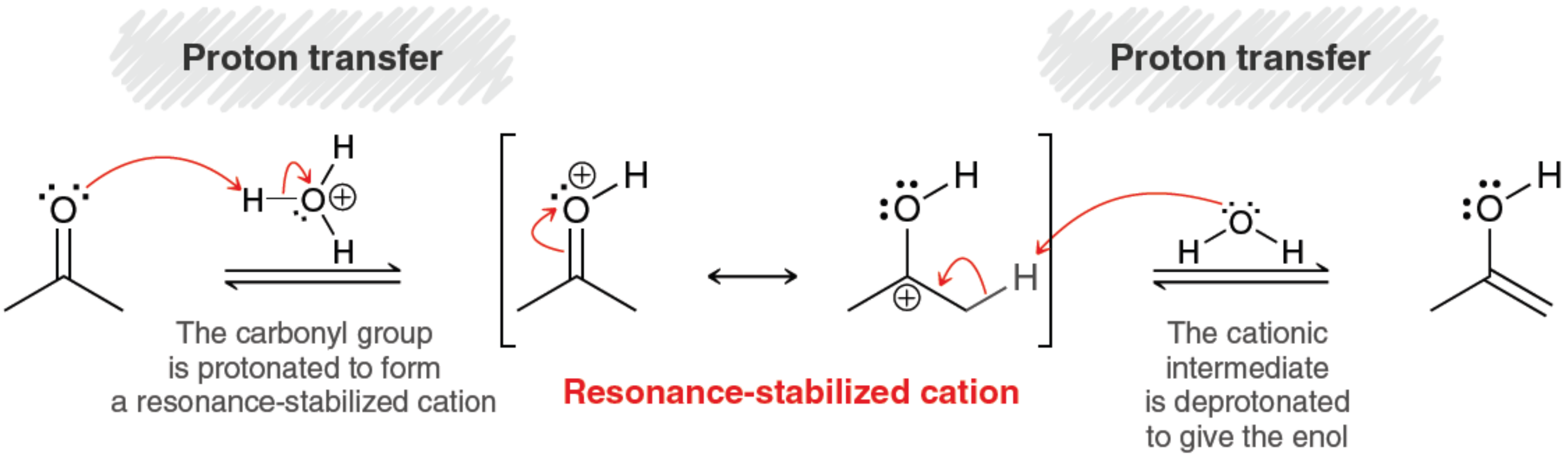
ketone and enol shown are **tautomers**—rapidly interconverting constitutional isomers that differ from each other in the placement of a proton and the position of a double bond.

Do not confuse tautomers with resonance structures.

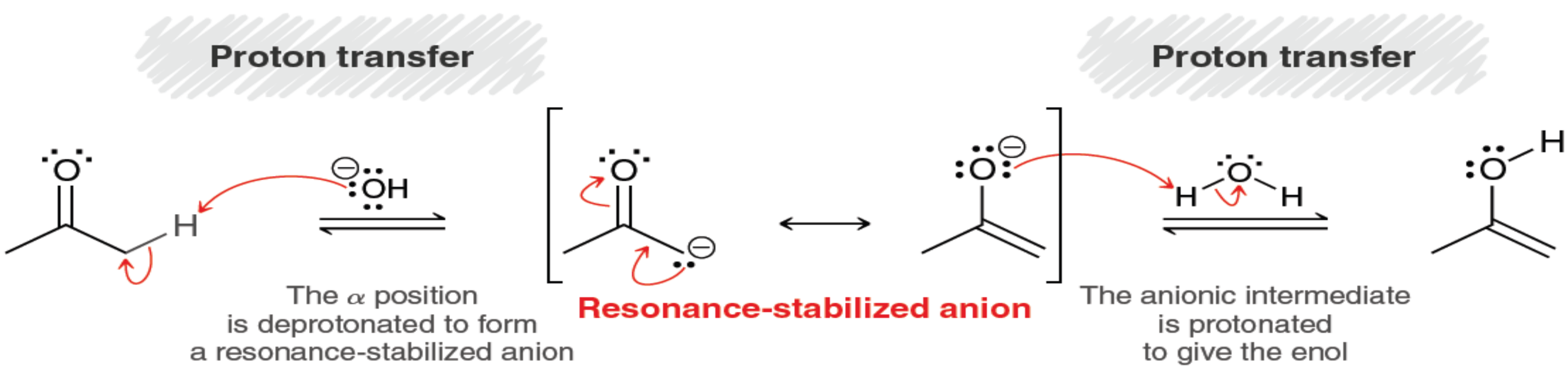


Tautomerization is catalyzed by trace amounts of either acid or base.

MECHANISM 21.1 ACID-CATALYZED TAUTOMERIZATION

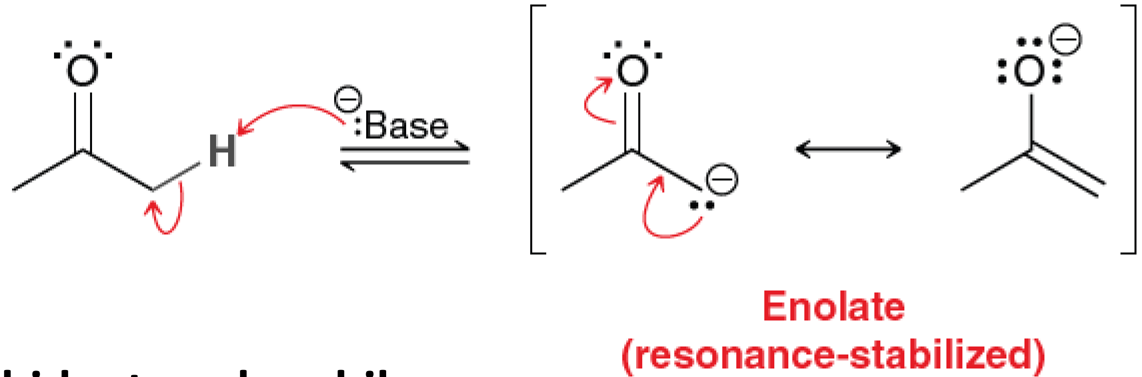


MECHANISM 21.2 BASE-CATALYZED TAUTOMERIZATION

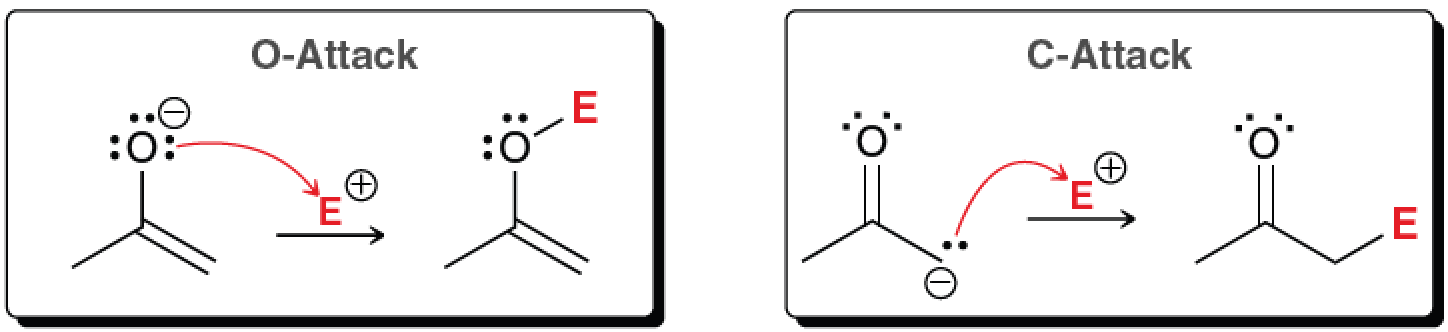


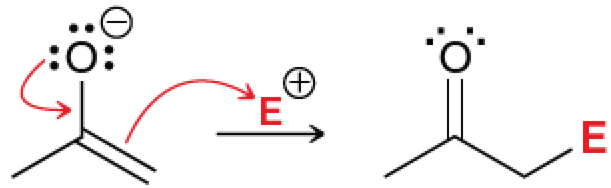
Enolates

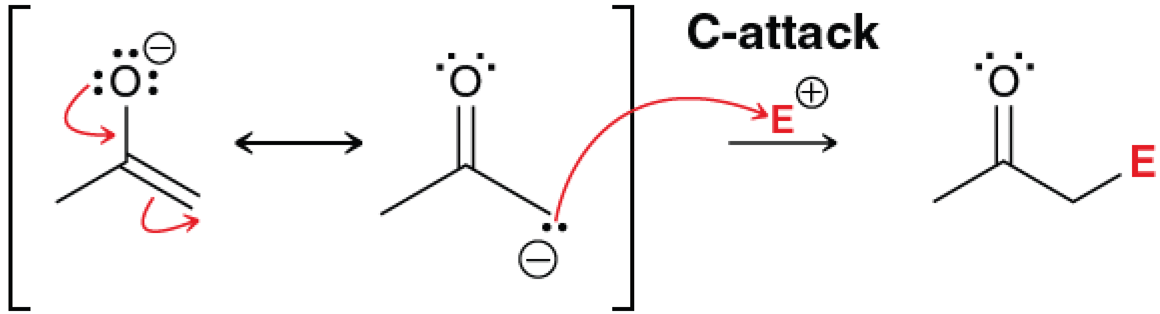
When treated with a strong base, the α position of a ketone is deprotonated to give a resonance-stabilized intermediate called an **enolate**.



Enolates are ambident nucleophiles

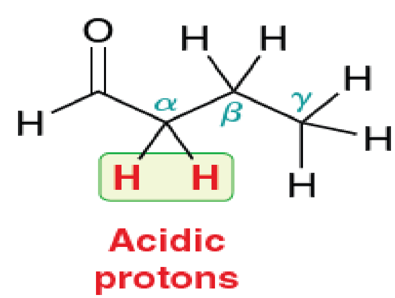






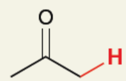
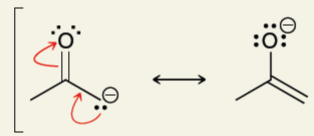
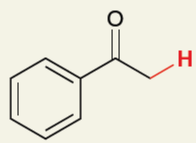
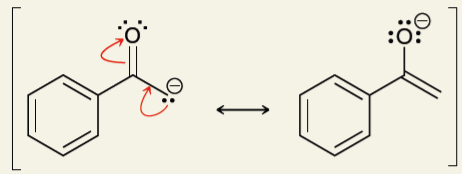
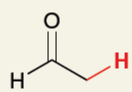
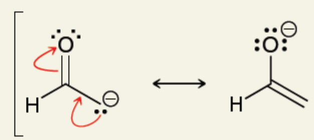
Enolates are more useful than enols because

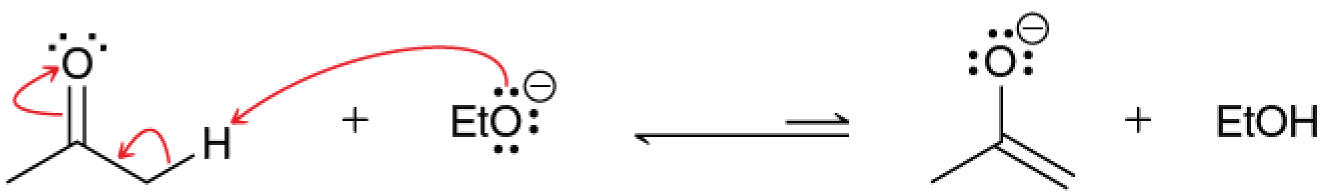
1. Enolates possess a full negative charge and are therefore more reactive than enols.
2. Enolates can be isolated and stored for short periods of time, unlike enols, which cannot be isolated or stored.



Choosing a Base for Enolate Formation

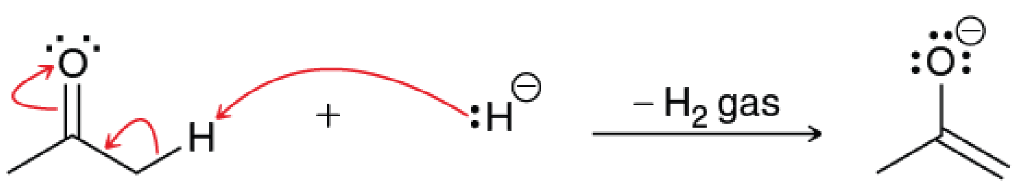
TABLE 21.1 pK_a VALUES OF SOME COMMON KETONES AND ALDEHYDES

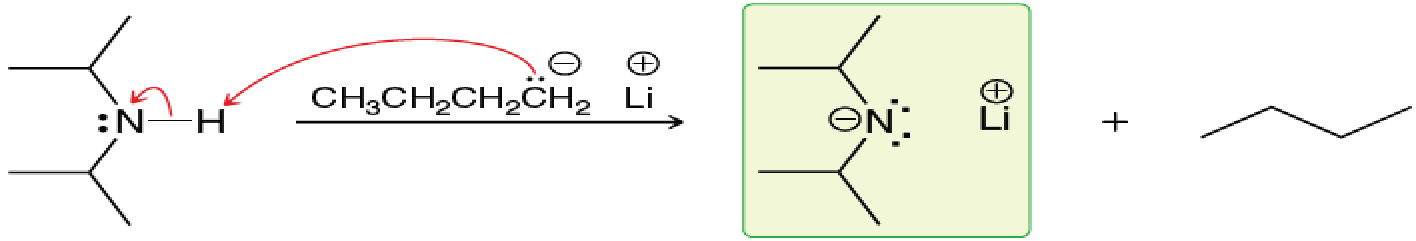
Compound	pK_a	Enolate
 Acetone	19.2	
 Acetophenone	18.3	
 Acetaldehyde	16.7	



pK_a = 19.2

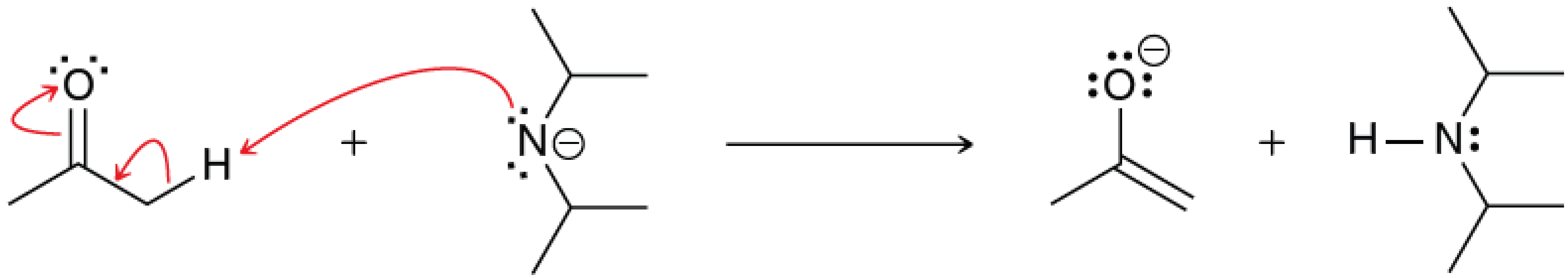
pK_a = 15.9





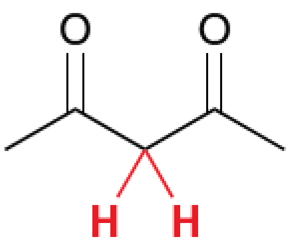
Diisopropylamine

Lithium diisopropylamide

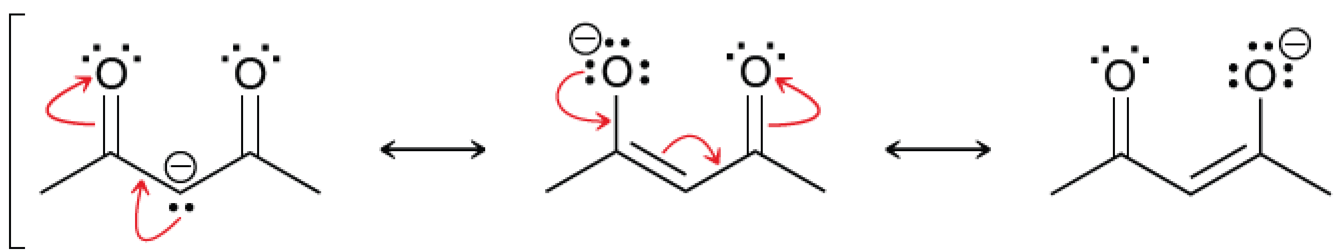


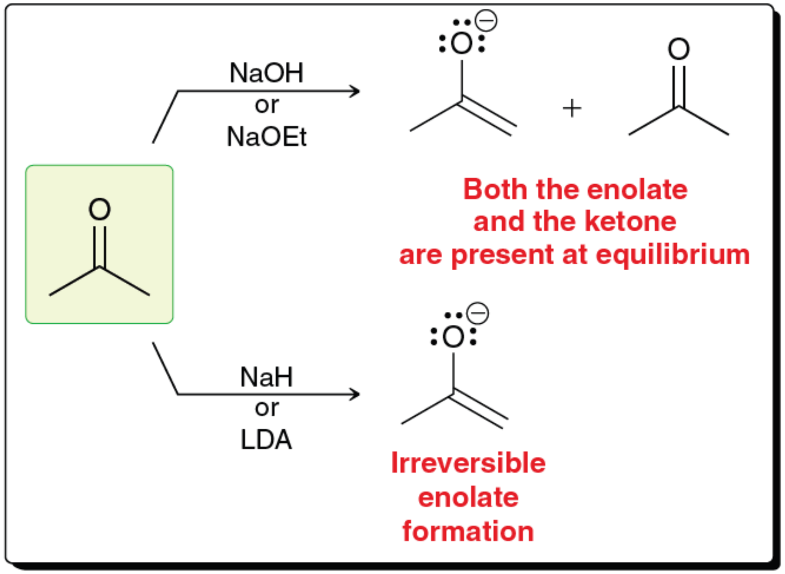
pK_a = 19.2

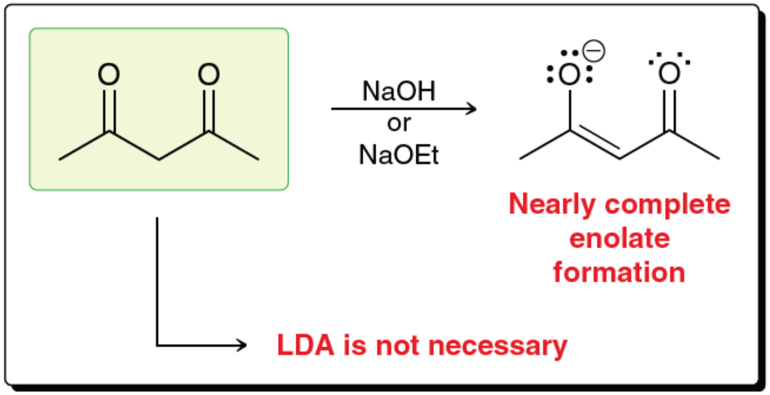
pK_a = 36



pK_a = 9



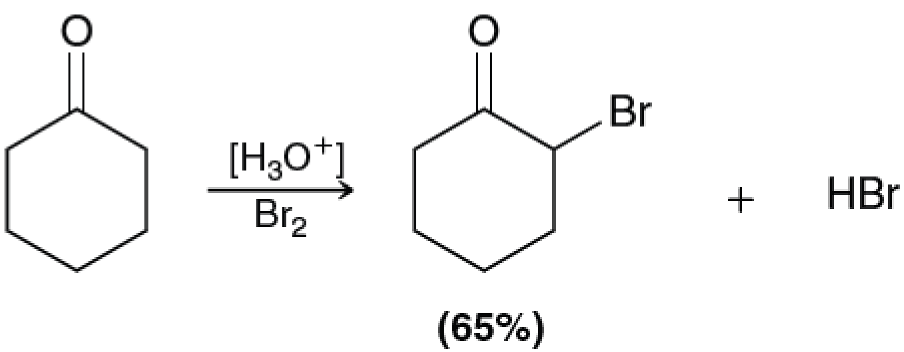


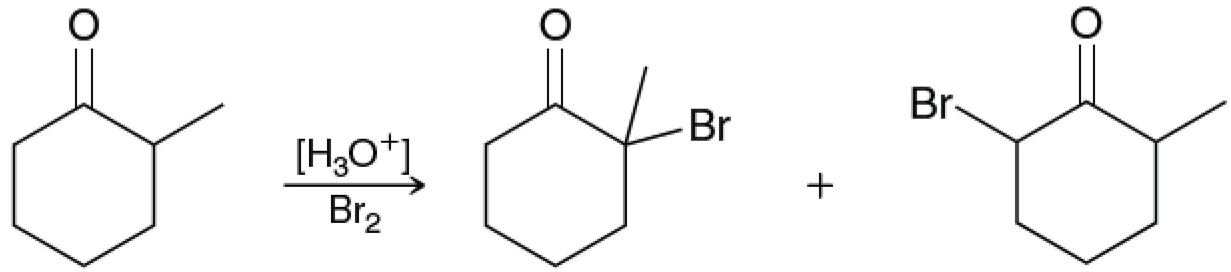


21.2 Alpha Halogenation of Enols and Enolates

- **Alpha Halogenation in Acidic Conditions**

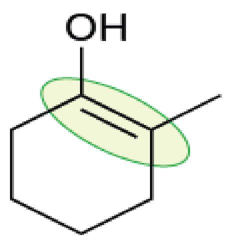
Under acid-catalyzed conditions, ketones and aldehydes will undergo halogenation at the α position.



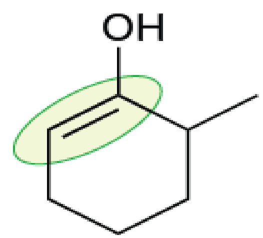


Major

Minor

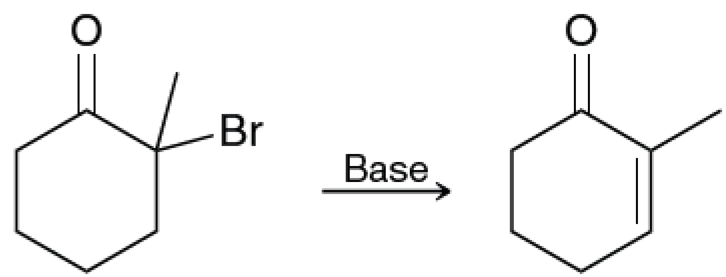


More substituted
(more stable)

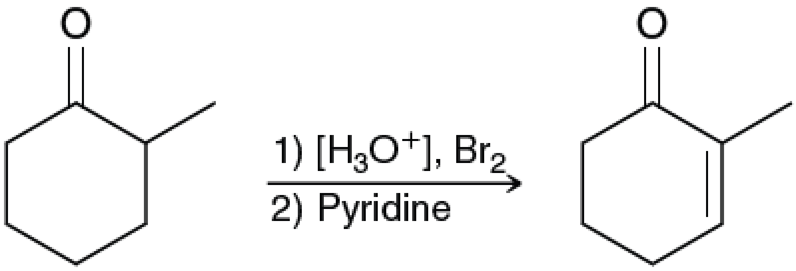


Less substituted
(less stable)

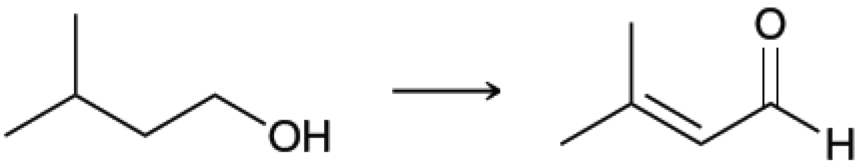
The halogenated product can undergo elimination when treated with a base.



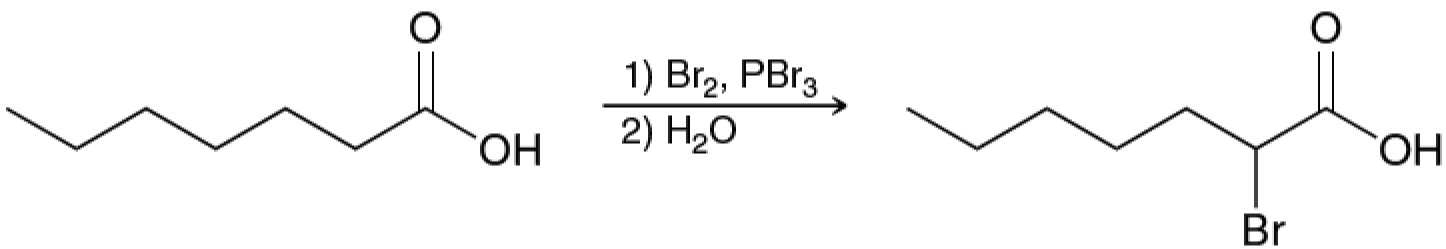
A variety of bases can be used, including **pyridine**, **lithium carbonate (Li_2CO_3), or potassium *tert*-butoxide**. This provides a two-step method for introducing **α,β**-unsaturation in a ketone. This procedure is only practical in some cases, and yields are often low.



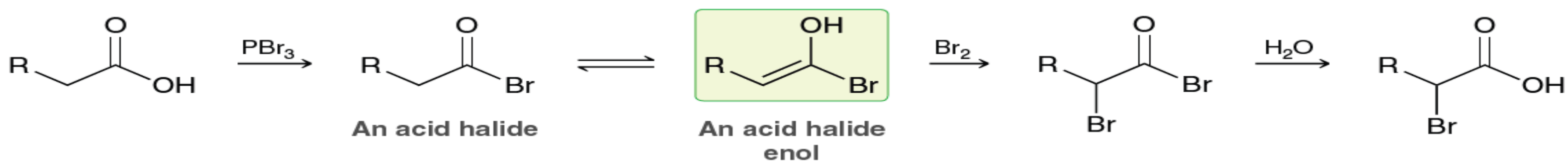
21.9 Identify reagents that can be used to accomplish each of the following transformations



Alpha Bromination of Carboxylic Acids: The Hell–Volhard–Zelinsky Reaction

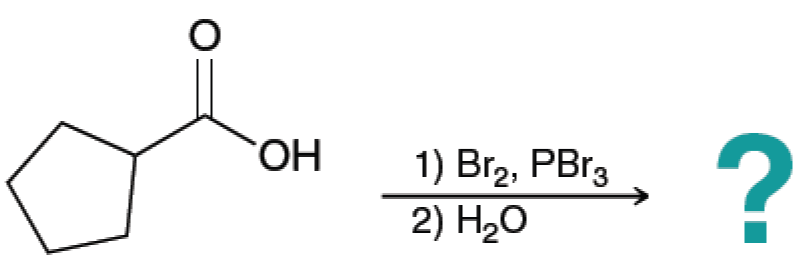


This process, called the **Hell–Volhard–Zelinsky reaction**, is believed to occur via the following sequence of events:

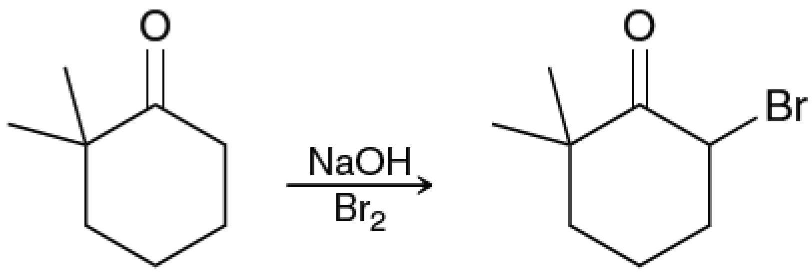


21.10 Predict the major product for each of the following reaction sequences:

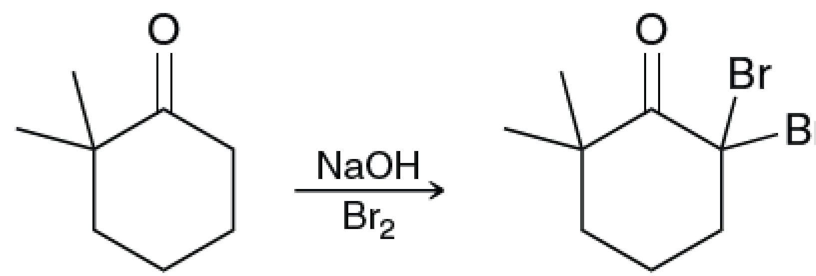
(a)

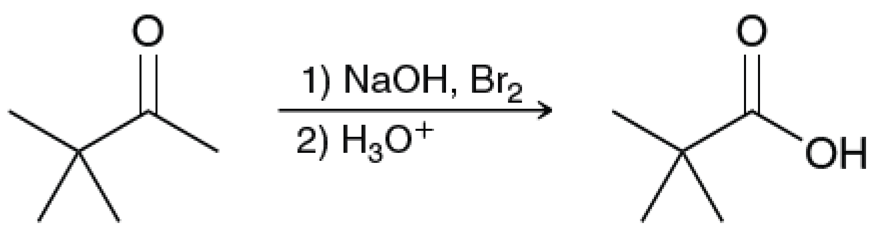


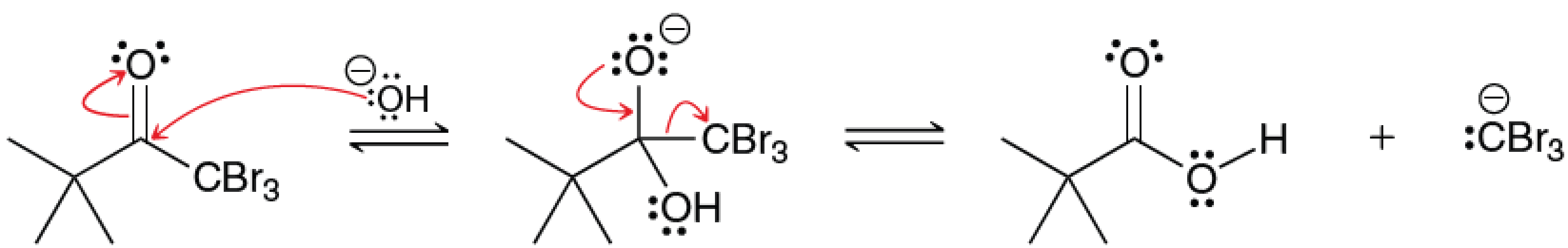
Alpha Halogenation in Basic Conditions: The Haloform Reaction



When more than one α proton is present, it is difficult to achieve monobromination in basic conditions, because the brominated product is more reactive and rapidly undergoes further bromination.

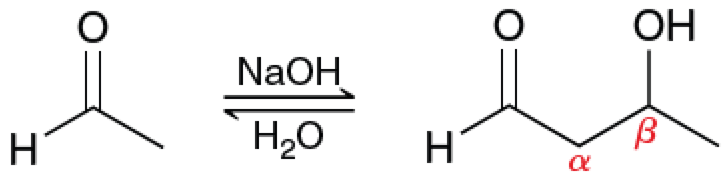






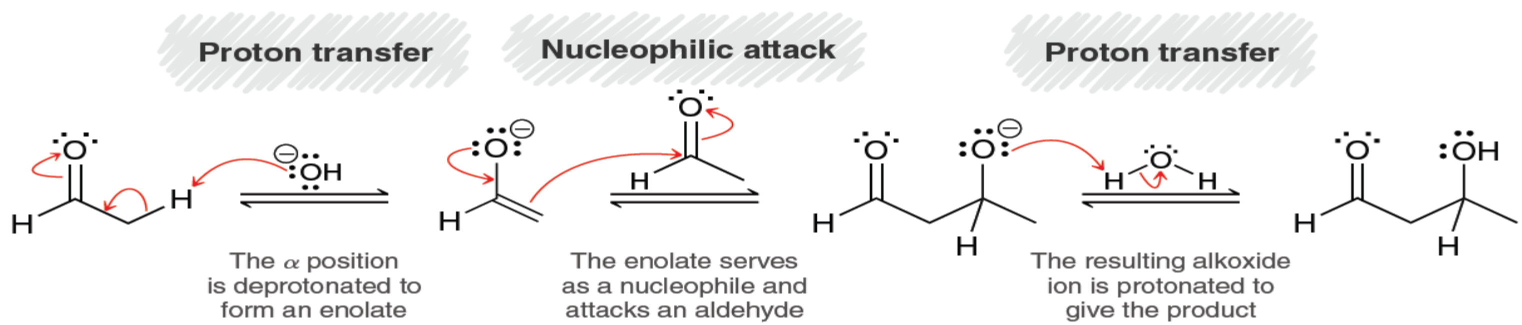
21.3 Aldol Reactions

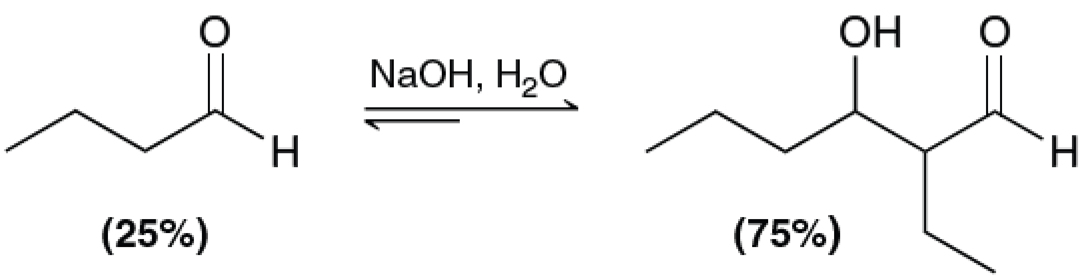
- **Aldol Additions**



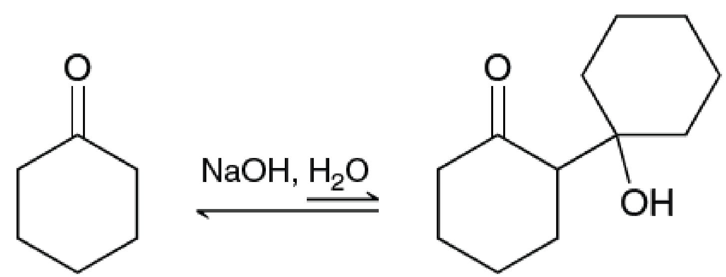
aldol addition reaction

MECHANISM 21.4 ALDOL ADDITION





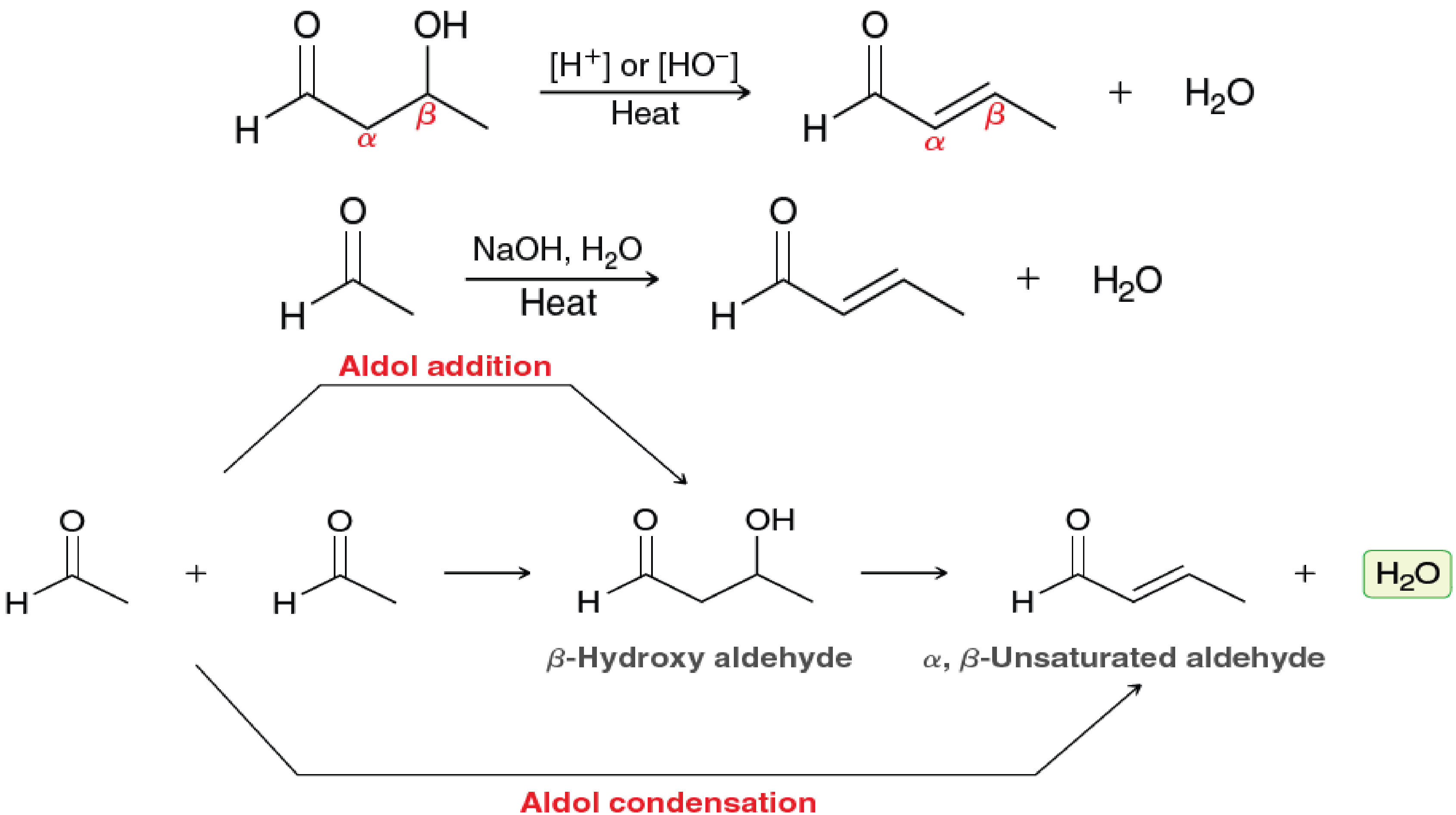
(25%) (75%)



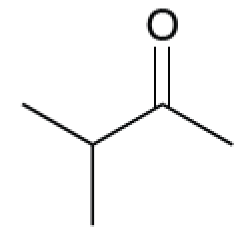
(80%) (20%)

- **Aldol Condensations**

When heated in acidic or basic conditions, the product of an aldol addition reaction will undergo elimination to produce unsaturation between the α and β positions:

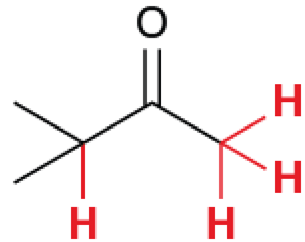


21.3 drawing the product of an aldol condensation



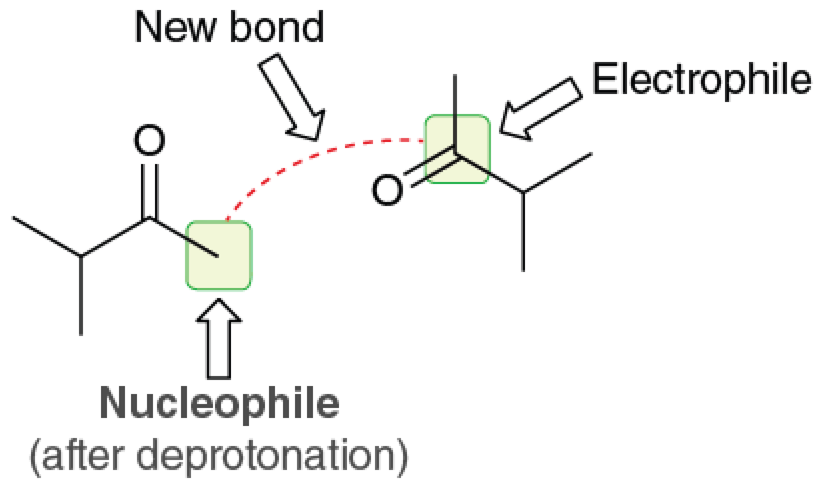
STEP 1

Identify an α position that bears at least two protons.



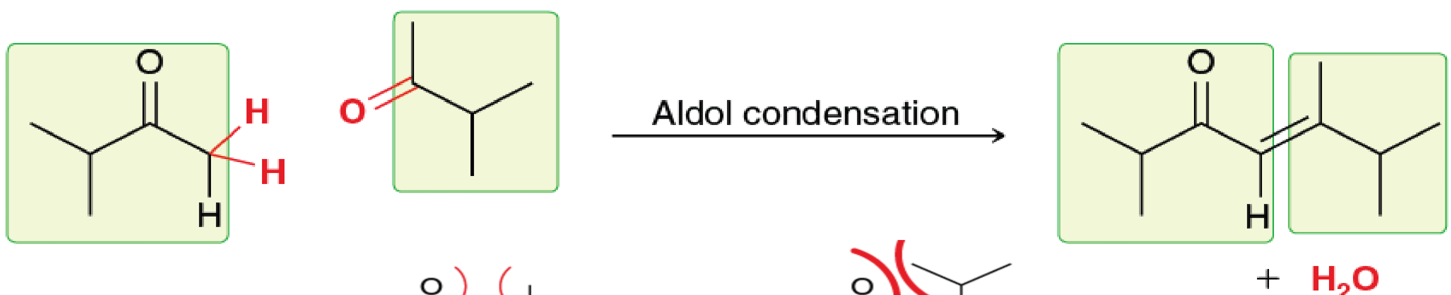
STEP 2

Redraw two molecules of the ketone, oriented such that the two α protons of one molecule are directly facing the carbonyl group of the other molecule.



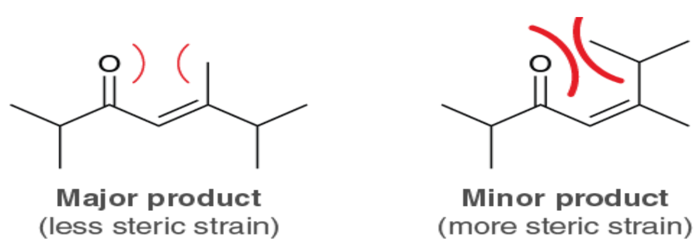
STEP 3

Remove H_2O and replace with a C=C bond.

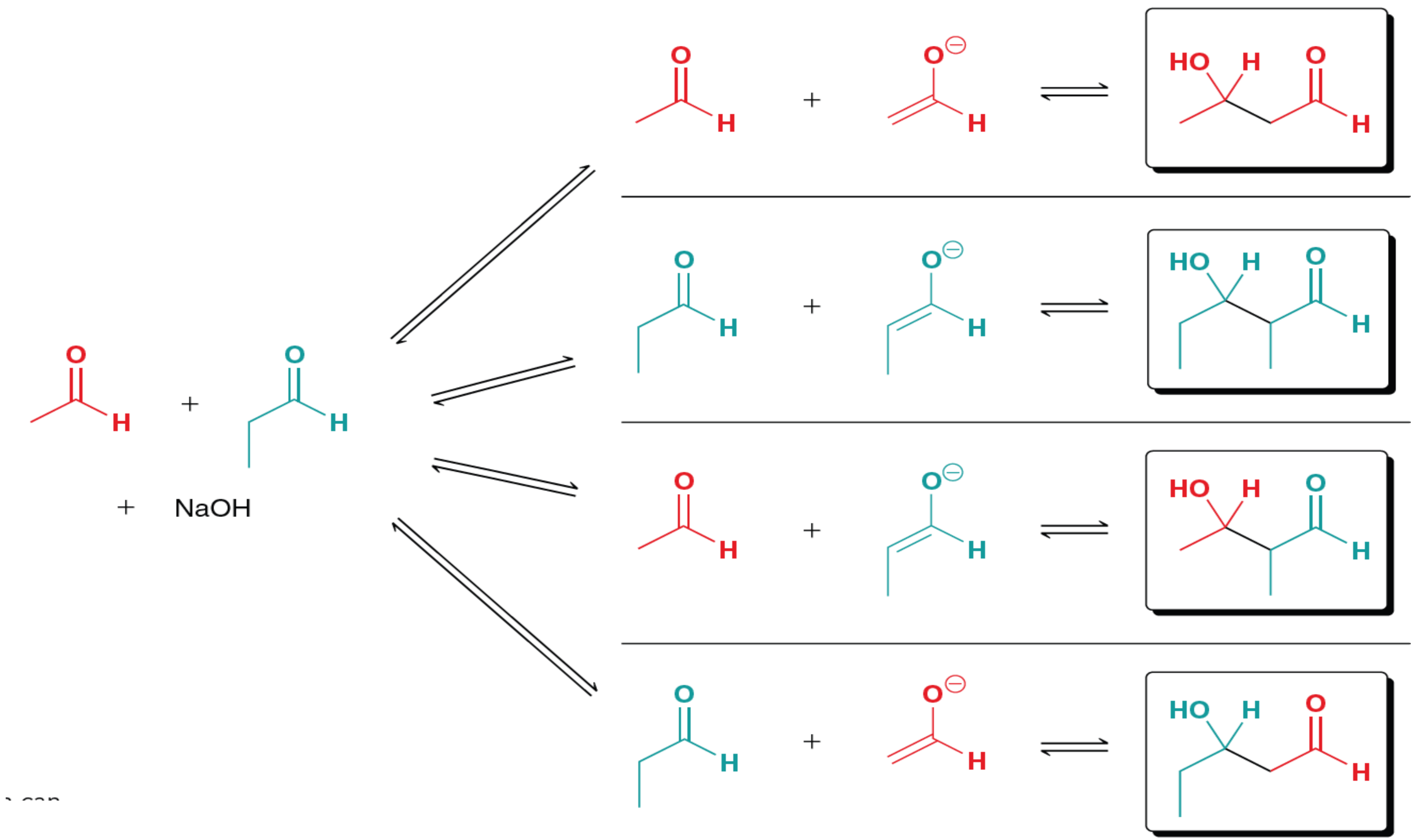


STEP 4

Draw the isomer with less steric strain.

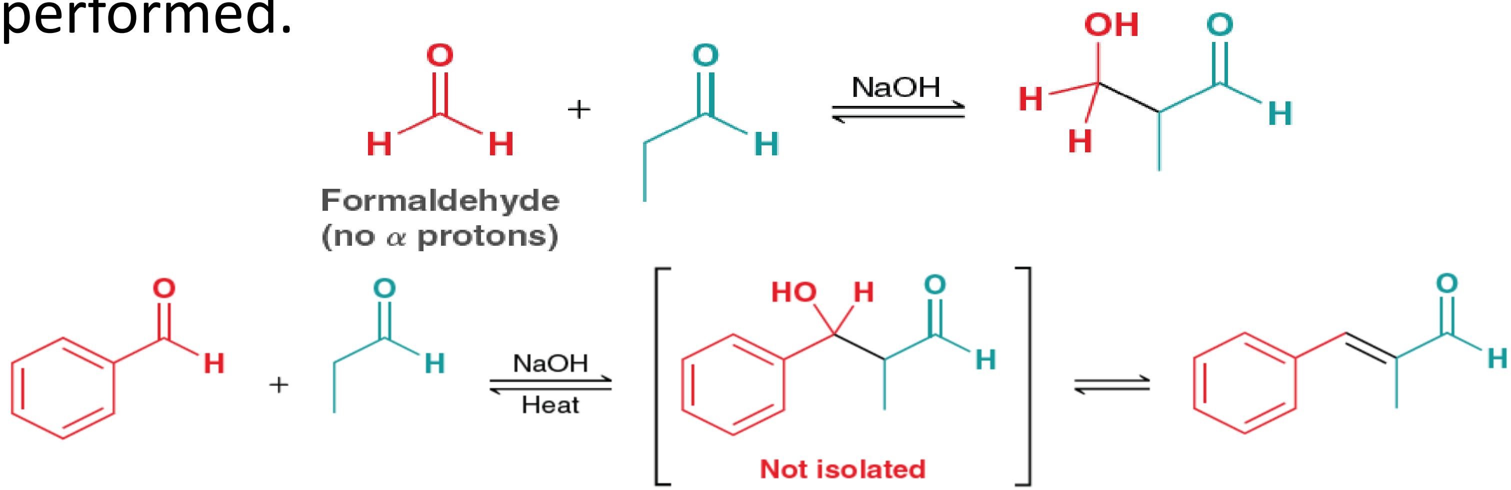


Crossed Aldol Reactions

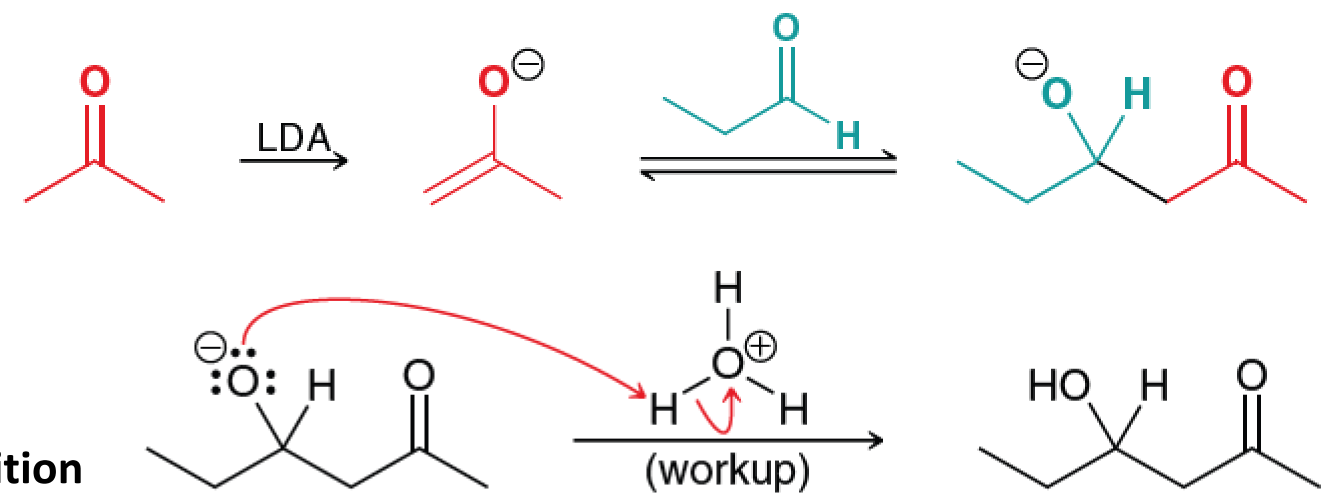


Crossed aldol reactions are only efficient if they can be performed in a way that minimizes the number of possible products. This is best accomplished in either of the following ways:

1. If one of the aldehydes lacks α protons and possesses an unhindered carbonyl group, then a crossed aldol can be performed.

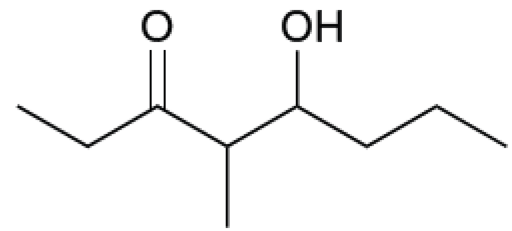


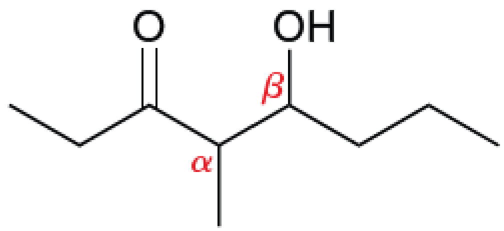
1. Crossed aldol reactions can also be performed using LDA as a base.

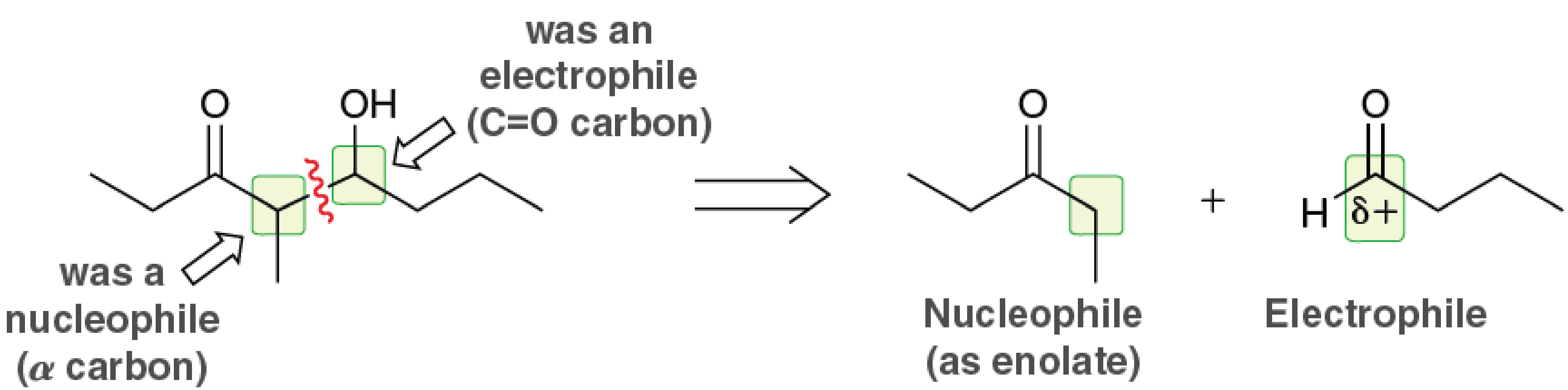


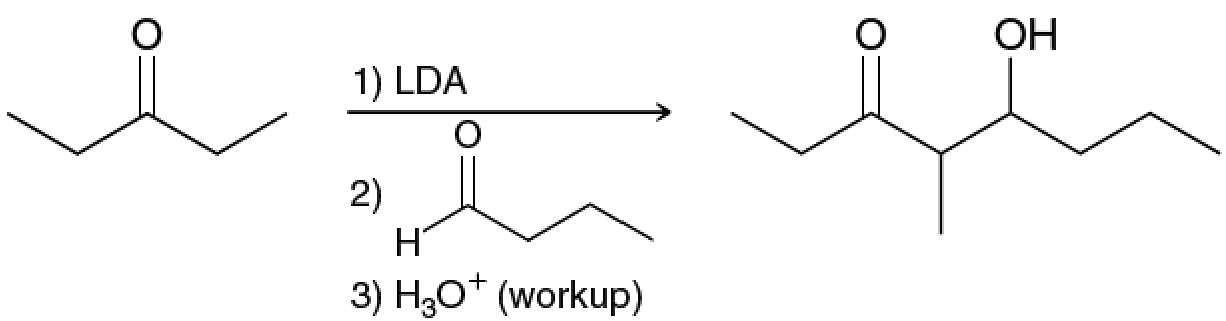
directed aldol addition

21.4 Identify reagents that can be used to produce the following compound via an aldol reaction:





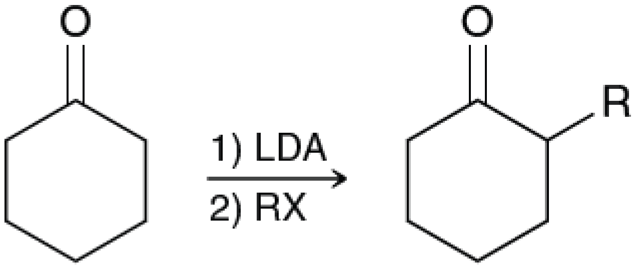




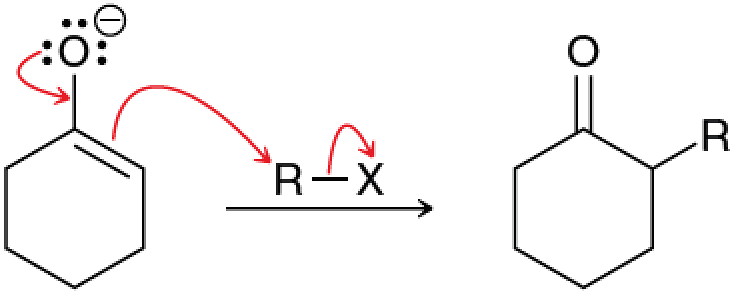
21.5 Alkylation of the Alpha Position

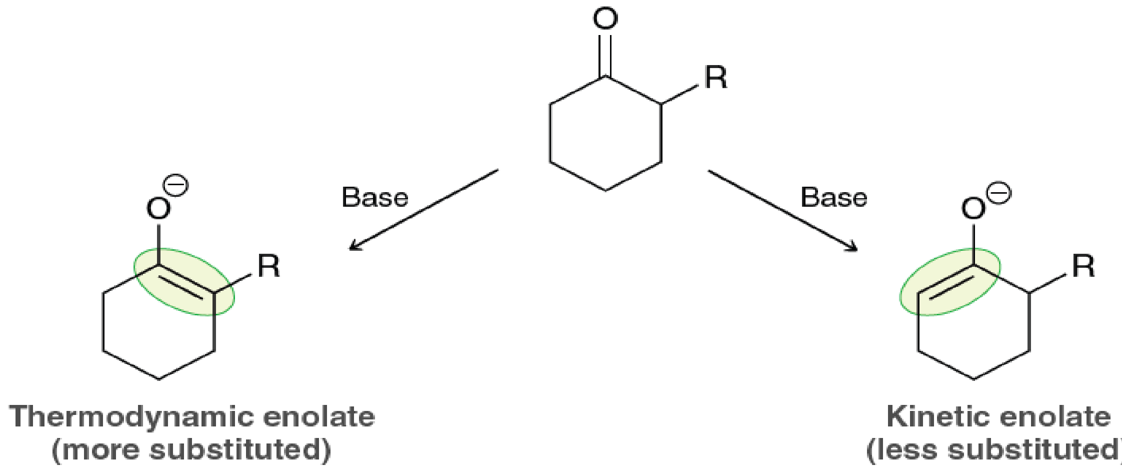
- **Alkylation via Enolate Ions**

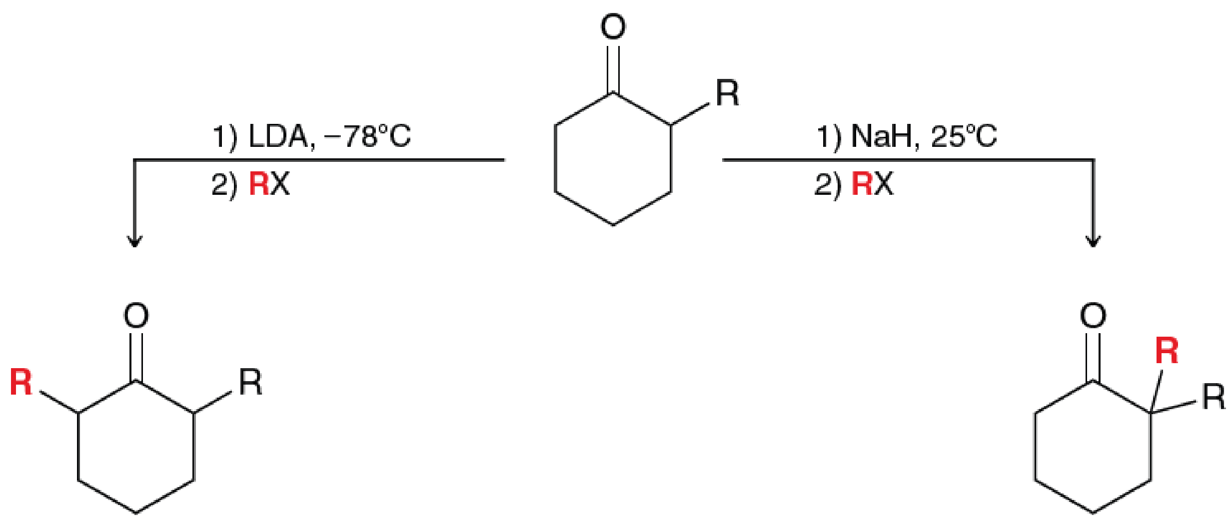
The α position of a ketone or an aldehyde can be alkylated via a two-step process: (1) formation of an enolate followed by (2) treating the enolate with an alkyl halide.



In this process, the enolate ion functions as a nucleophile and attacks the alkyl halide in an S_N2 reaction.



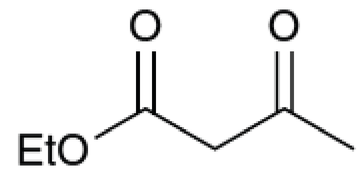




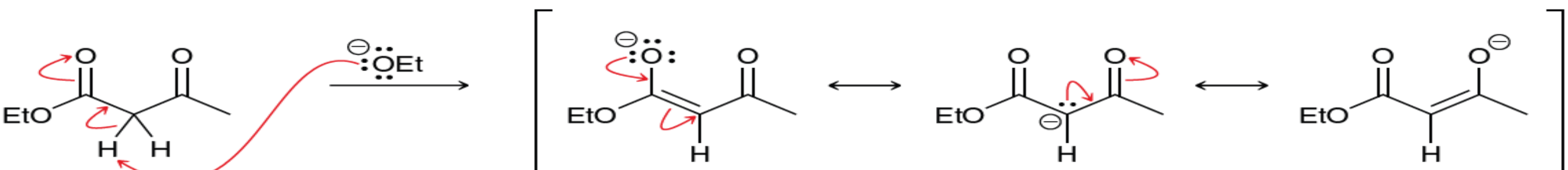
When the base is LDA (at low temperature), alkylation occurs at the **less-substituted** α position. When the base is NaH (at room temperature), alkylation occurs at the **more-substituted** α position.

The Acetoacetic Ester Synthesis

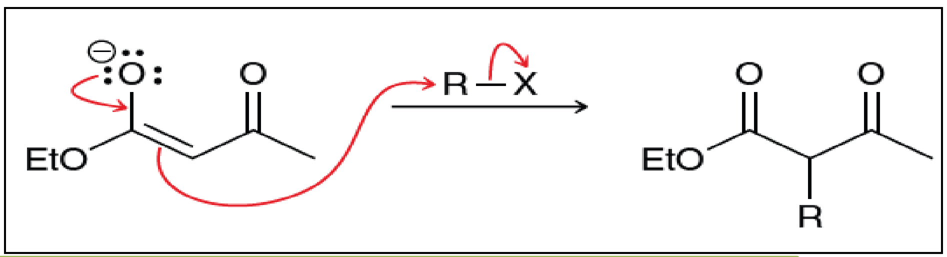
The alternative method begins with a compound called ethyl acetoacetate:

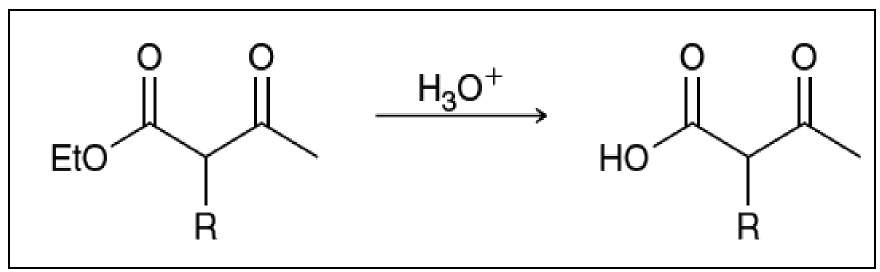


Ethyl acetoacetate

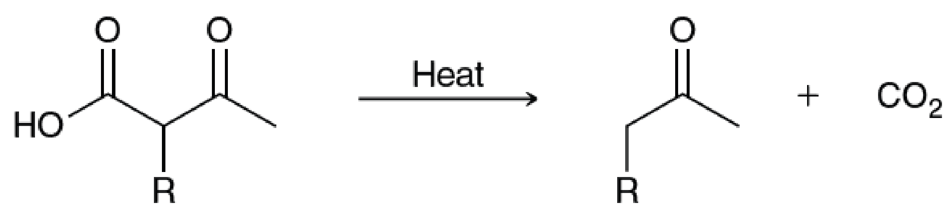


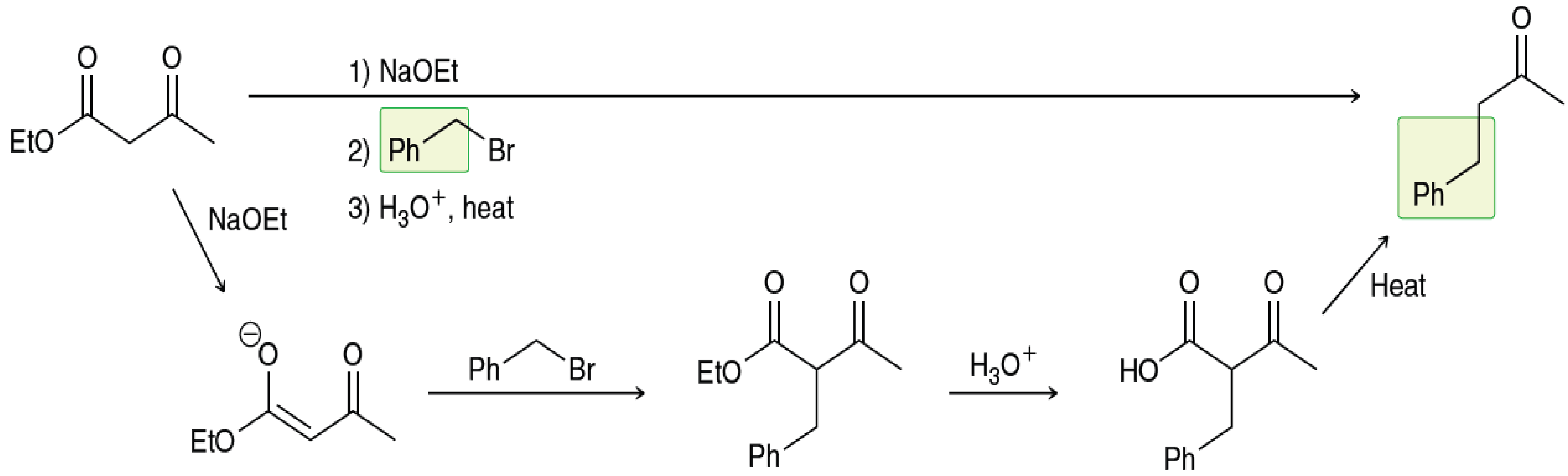
A highly stabilized enolate

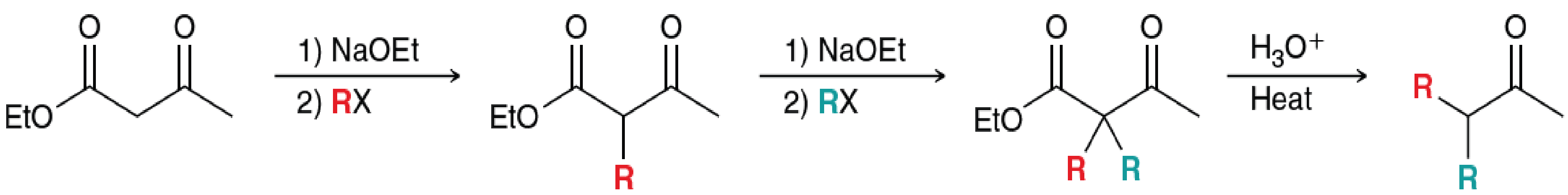




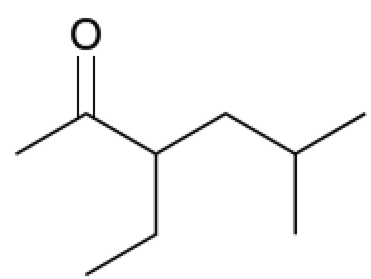
If hydrolysis is performed at an elevated temperature, the resulting carboxylic acid will undergo a reaction, called **decarboxylation**, to produce a monosubstituted derivative of acetone, as well as carbon dioxide:





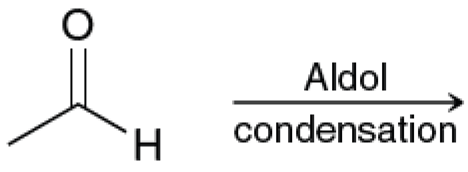


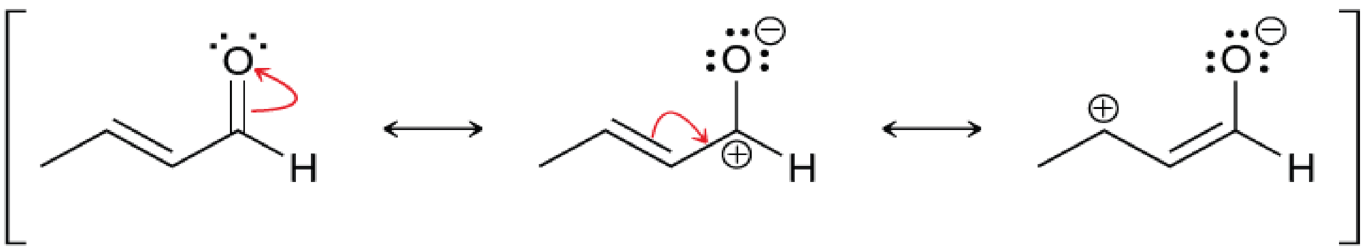
21.5 Show how you would use an acetoacetic ester synthesis to prepare the following compound:

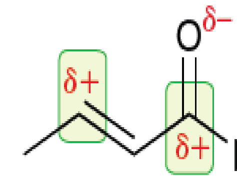


21.6 Conjugate Addition Reactions

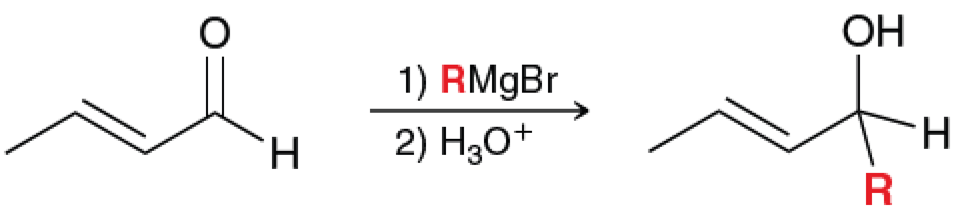
- **Michael Reactions**

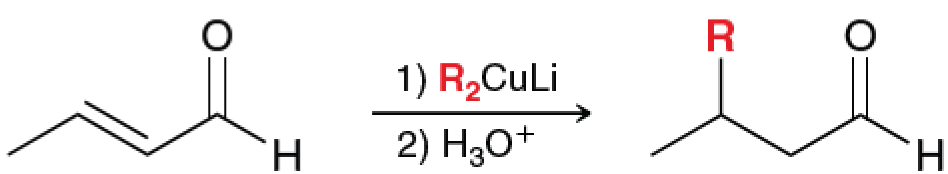


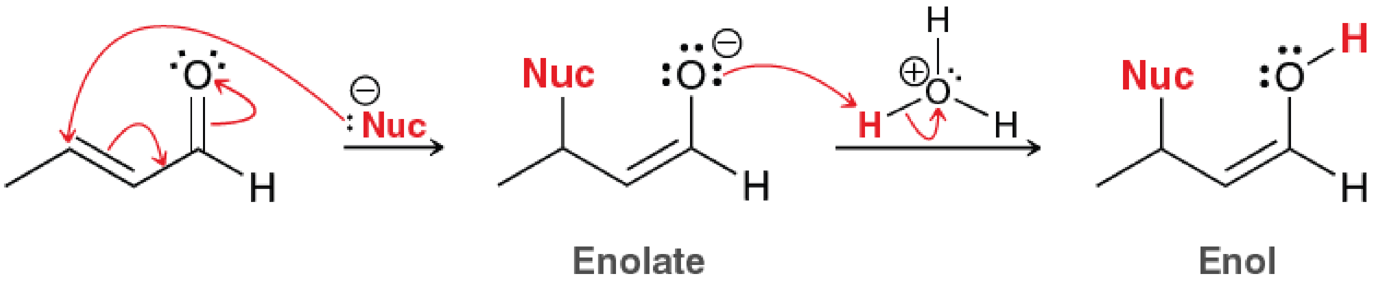




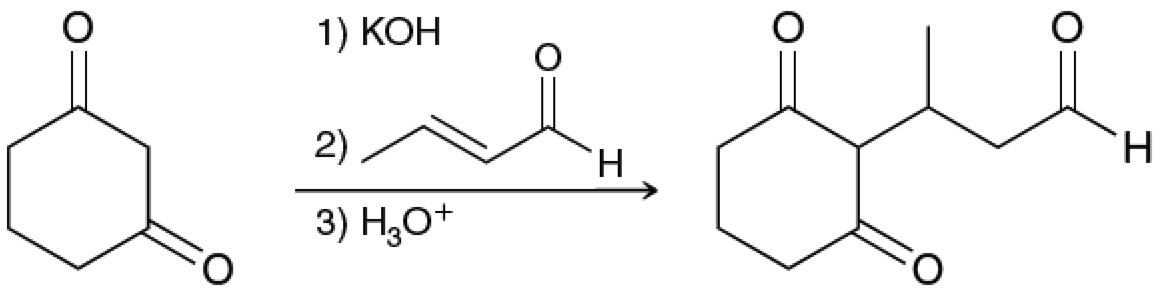
Two electrophilic positions





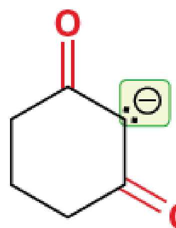


This type of reaction is called a **conjugate addition**, or a *1,4-addition*

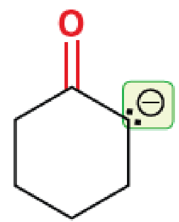


The starting diketone is deprotonated to form a highly stabilized enolate ion, which then serves as a nucleophile in a 1,4-conjugate addition.

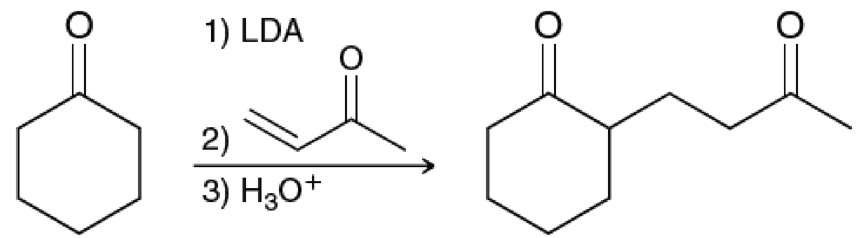
- **The Stork Enamine Synthesis**



A Michael donor

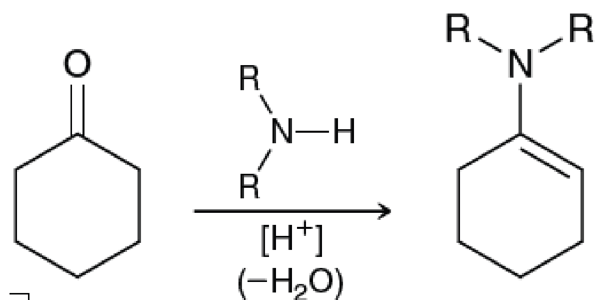


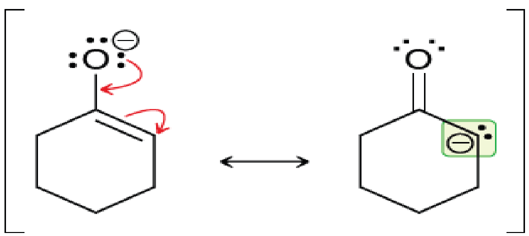
Not a Michael donor



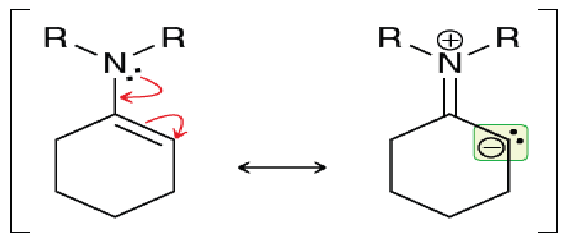
Not obtained in good yields

Gilbert Stork (Columbia University) developed a method for such a transformation in which the ketone is converted into an enamine by treatment with a secondary amine.

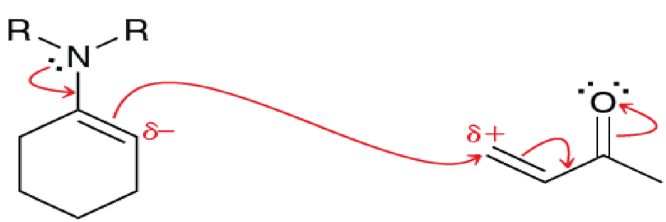




An enolate ion

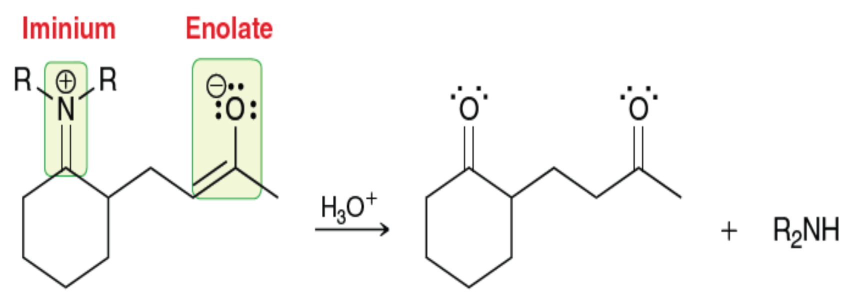


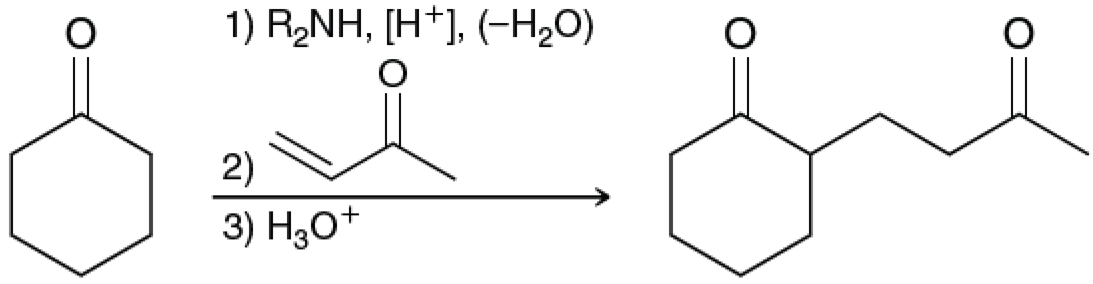
An enamine



Michael donor

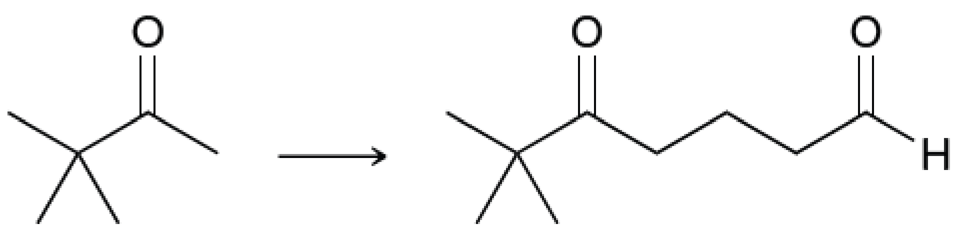
Michael acceptor

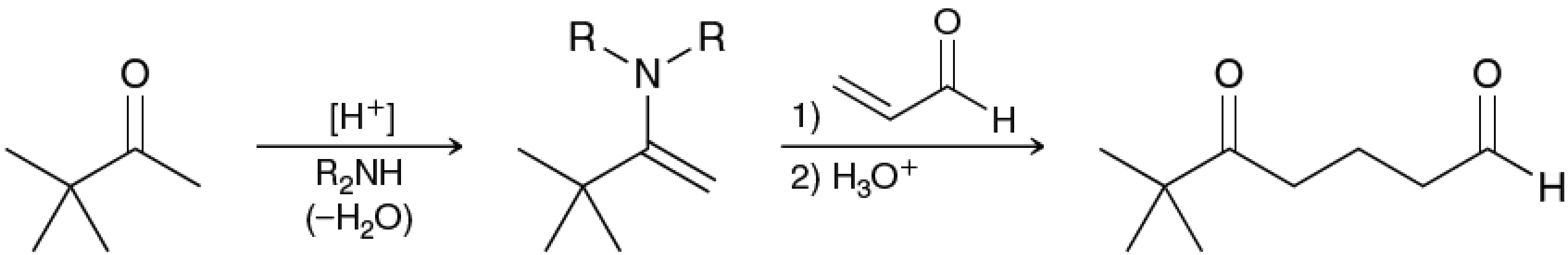




This process is called a **Stork enamine synthesis**, and it has three steps: (1) formation of an enamine, (2) a Michael addition, and (3) hydrolysis.

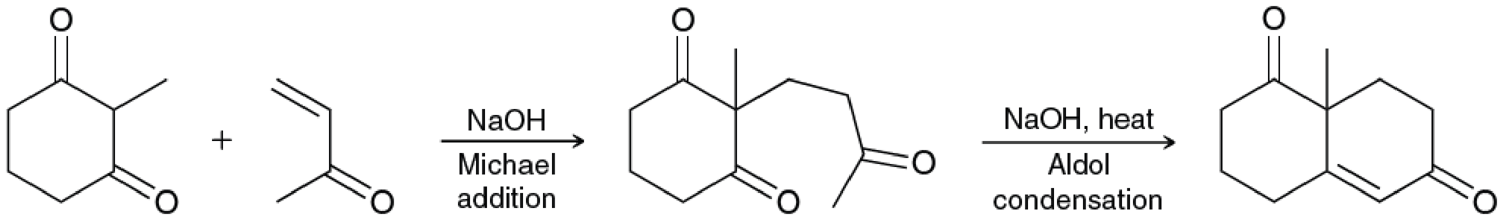
21.7 Using any reagents of your choosing, show how you might accomplish the following transformation:





- **The Robinson Annulation Reaction**

One such example is a two-step method for forming a ring, in which a Michael addition is followed by an intramolecular aldol condensation.



This two-step method is called a **Robinson annulation**, and is often used for the synthesis of polycyclic compounds. The term *annulation* is derived from the Latin word for ring (*annulus*).