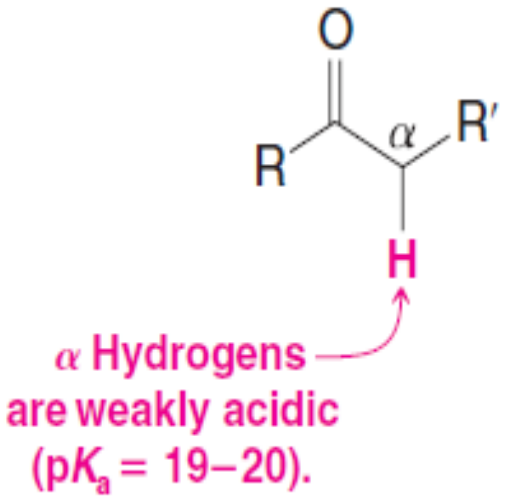
Reactions at the α Carbon of Carbonyl Compounds

In this chapter we shall discuss reactions that derive from the weak acidity of hydrogen atoms on carbon atoms adjacent to α carbonyl group. These hydrogen atoms are called the **α hydrogens**, and the carbon to which they are attached is called the **α carbon**.



The Acidity of the α Hydrogens of Carbonyl Compounds: Enolate Anions

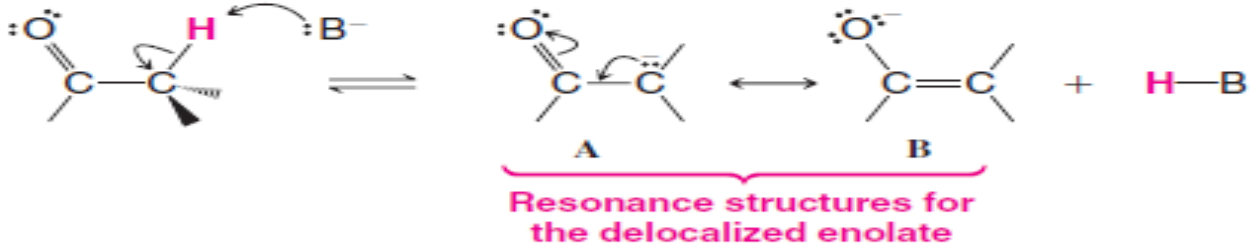
When we say that the α hydrogens of carbonyl compounds are acidic, *we mean that they are unusually acidic for hydrogen atoms attached to carbon.*

- The pK_a values for the α hydrogens of most simple aldehydes or ketones are of the order of 19–20.

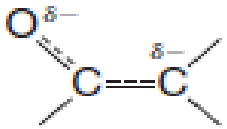
This means that they are more acidic than hydrogen atoms of ethyne, pK_a = 25, and are far more acidic than the hydrogens of ethene (pK_a = 44) or of ethane (pK_a = 50).

The reasons for the unusual acidity of the α hydrogens of carbonyl compounds are straightforward.

- The carbonyl group is strongly electron withdrawing, and when a carbonyl compound loses an α proton, the anion that is produced, called an **enolate**, is stabilized by delocalization.



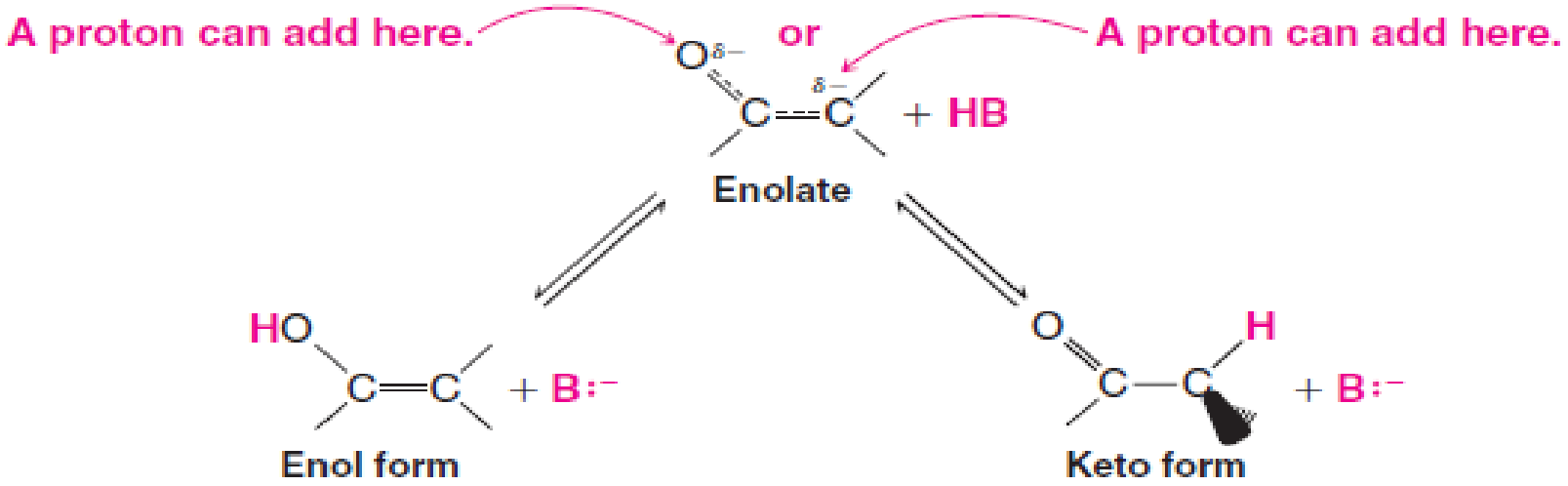
Two resonance structures, **A** and **B**, can be written for the enolate. In structure **A** the negative charge is on carbon, and in structure **B** the negative charge is on oxygen. Both structures contribute to the hybrid. Although structure **A** is favored by the strength of its carbon–oxygen π bond relative to the weaker carbon–carbon π bond of **B**, structure **B** makes a greater contribution to the hybrid because oxygen, being highly electronegative, is better able to accommodate the negative charge. We can depict the enolate hybrid in the following way:



Hybrid resonance structure
for an enolate

When this resonance-stabilized enolate accepts a proton, it can do so in either of two ways: It can accept the proton at carbon to form the original carbonyl compound in what is called the **keto form** or it may accept the proton at oxygen to form an **enol** (alkene alcohol).

- The enolate is the conjugate base of both the enol and keto forms.

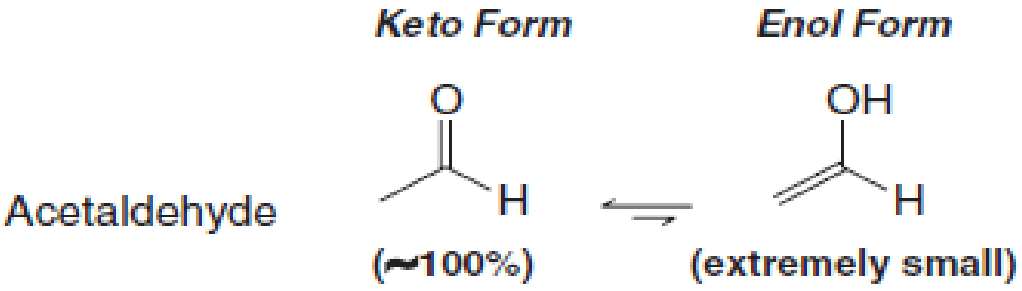


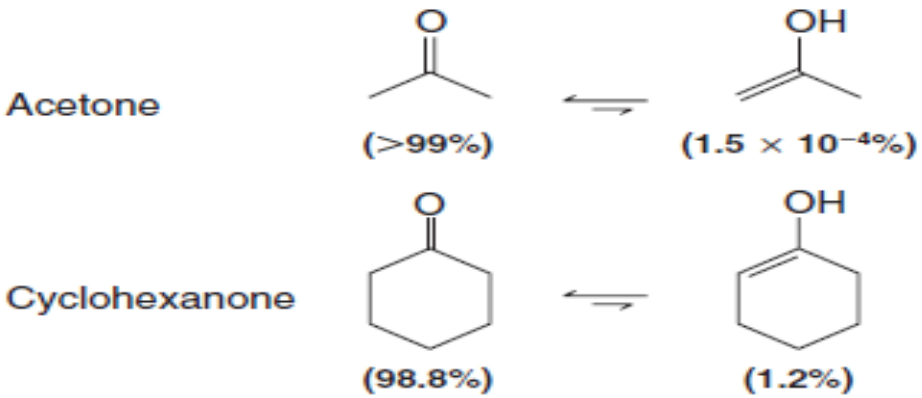
Keto and Enol Tautomers

The keto and enol forms of carbonyl compounds are constitutional isomers, but of a special type. Because they are easily interconverted in the presence of traces of acids and bases, chemists use a special term to describe this type of constitutional isomerism.

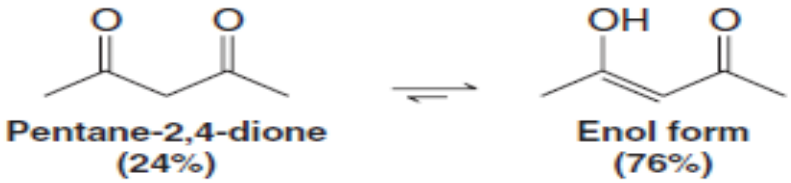
- Interconvertible keto and enol forms are called **tautomers**, and their interconversion is called **tautomerization**.

Under most circumstances, we encounter keto–enol tautomers in a state of equilibrium. (The surfaces of ordinary laboratory glassware are able to catalyze the interconversion and establish the equilibrium.) For simple monocarbonyl compounds such as acetone and acetaldehyde, the amount of the enol form present at equilibrium is *very small*. In acetone it is much less than 1%; in acetaldehyde the enol concentration is too small to be detected. The greater stability of the following keto forms of monocarbonyl compounds can be related to the greater strength of the carbon–oxygen π bond compared to the carbon–carbon π bond (~364 versus ~250 kJ mol^{-1}):

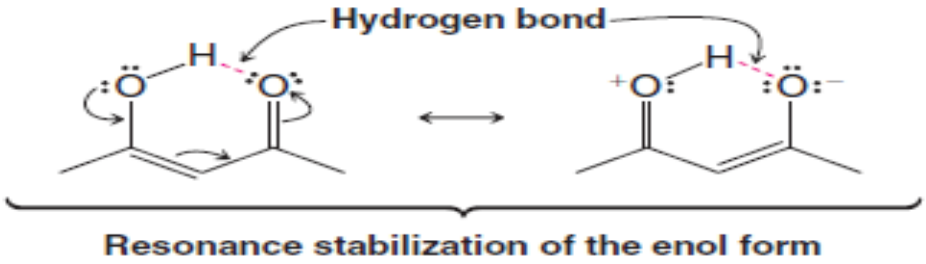




In compounds whose molecules have two carbonyl groups separated by one carbon atom (called β-dicarbonyl compounds), the amount of enol present at equilibrium is far higher. For example, pentane-2,4-dione exists in the enol form to an extent of 76%:

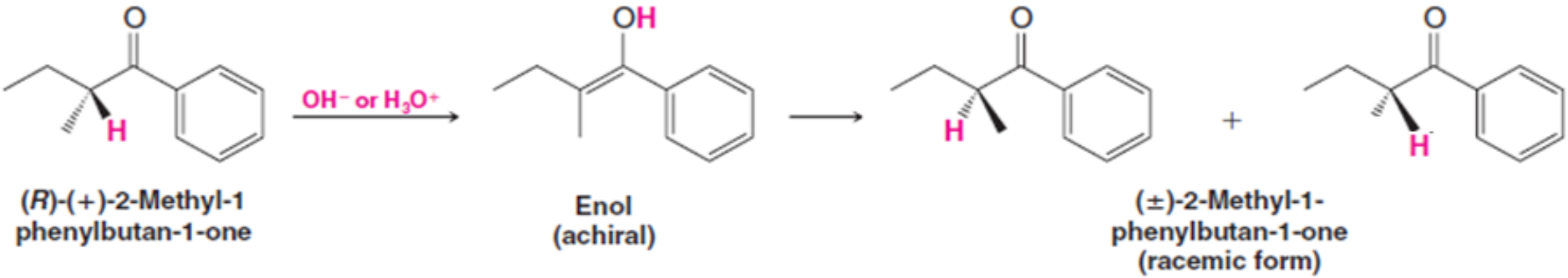


- The greater stability of the enol form of β-dicarbonyl compounds can be attributed to resonance stabilization of the conjugated double bonds and (in a cyclic form) through hydrogen bonding.



Racemization

When a solution of (*R*)-(+)-2-methyl-1-phenylbutan-1-one (see the following reaction) in aqueous ethanol is treated with either acids or bases, the solution gradually loses its optical activity. After a time, isolation of the ketone shows that it has been completely racemized. The (+) form of the ketone has been converted to an equimolar mixture of its enantiomers through its enol form.

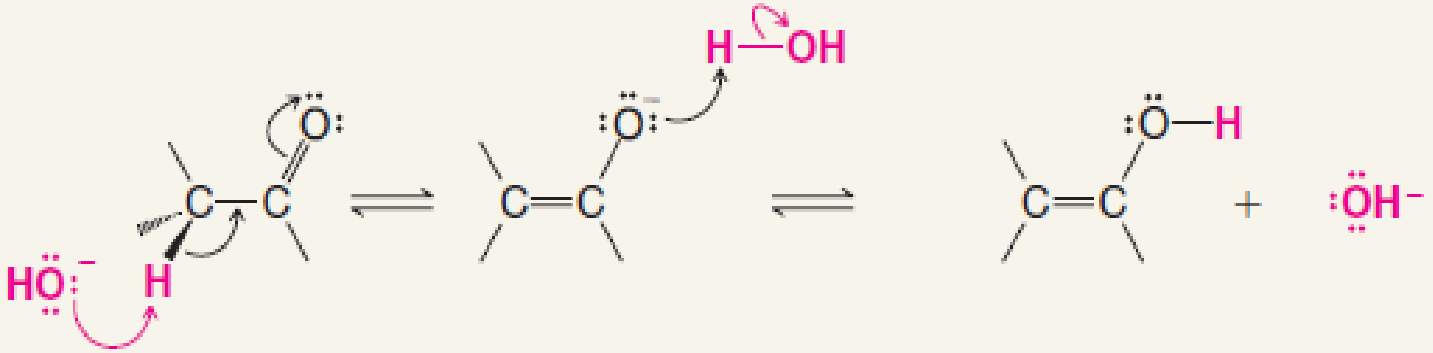


(*R*)-(+)-2-Methyl-1-phenylbutan-1-one → **Enol (achiral)** → **(±)-2-Methyl-1-phenylbutan-1-one (racemic form)**

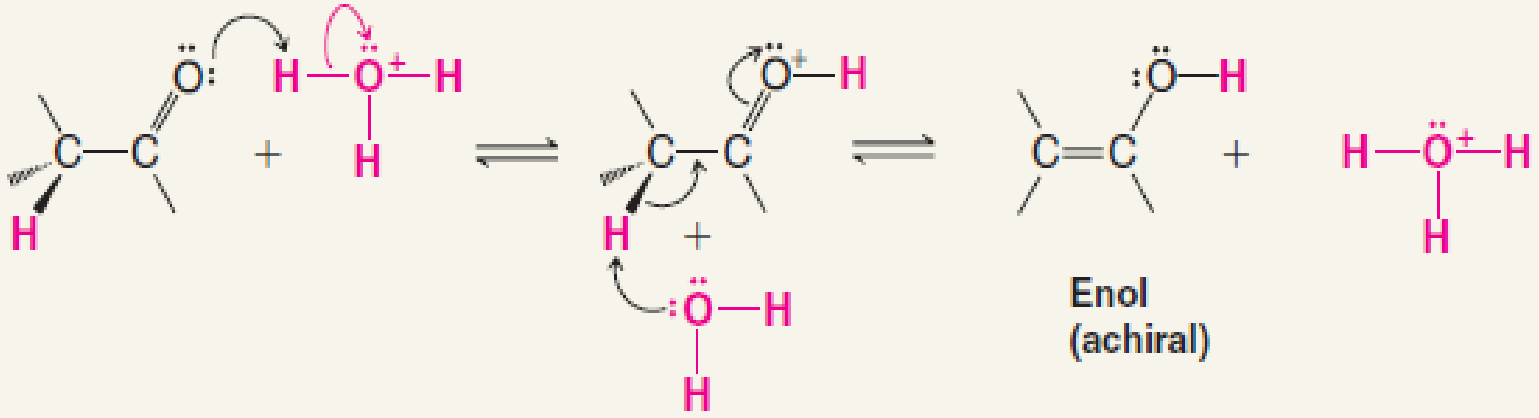
- Racemization at an α carbon takes place in the presence of acids or bases because the keto form slowly but reversibly changes to its enol *and the enol is achiral*. When the enol reverts to the keto form, it can produce equal amounts of the two enantiomers.

A base catalyzes the formation of an enol through the intermediate formation of an enolate anion.

Base-Catalyzed Enolization

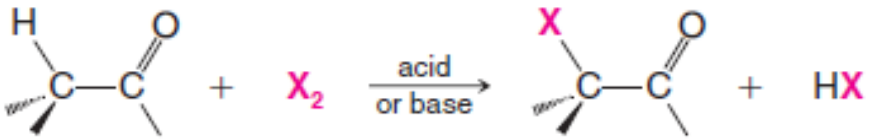


Acid-Catalyzed Enolization



Halogenation at the α Carbon

- Carbonyl compounds bearing an α hydrogen can undergo halogen substitution at the α carbon in the presence of acid or base.

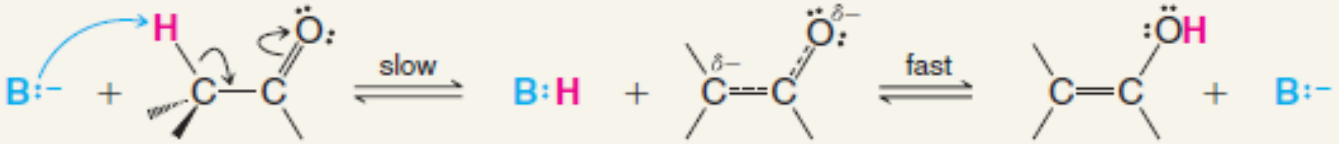


(Racemic)

Base-Promoted Halogenation In the presence of bases, halogenation takes place through the slow formation of an enolate anion or an enol followed by a rapid reaction of the enolate or enol with halogen.

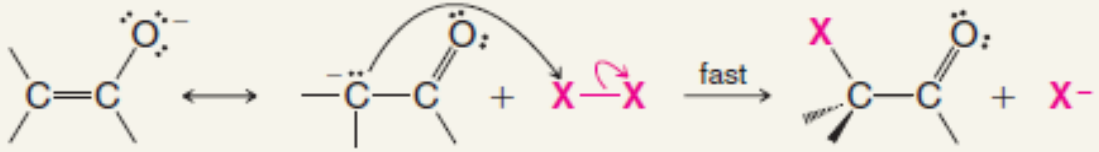
Base-Promoted Halogenation of Aldehydes and Ketones

Step 1



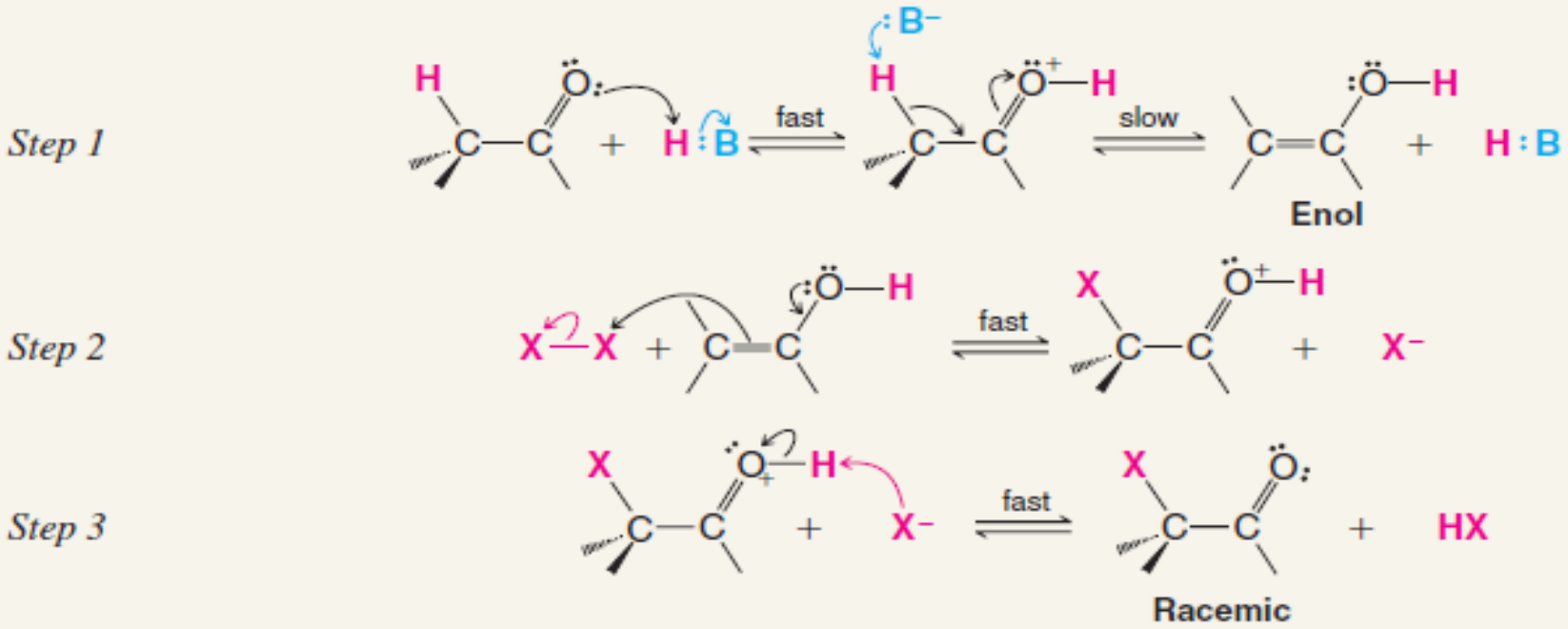
Enolate (resonance hybrid) Enol

Step 2



Enolate (contributing resonance structures) (Racemic)

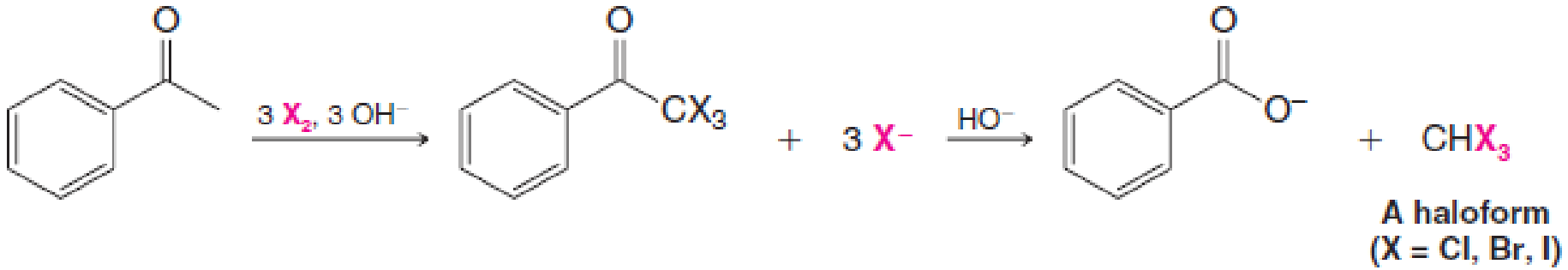
Acid-Catalyzed Halogenation of Aldehydes and Ketones



Part of the evidence that supports these mechanisms comes from studies of reaction kinetics. Both base-promoted and acid-catalyzed halogenations of ketones *show initial rates that are independent of the halogen concentration*. The mechanisms that we have written are in accord with this observation: In both instances the slow step of the mechanism occurs before the intervention of the halogen. (The initial rates are also independent of the nature of the halogen

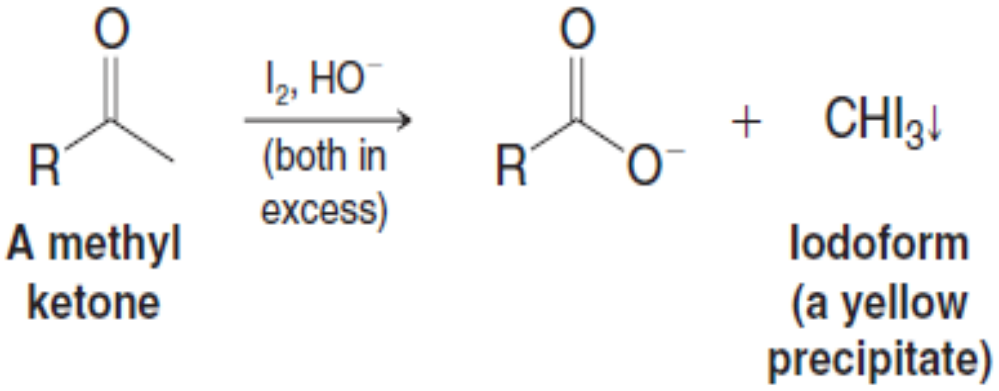
The Haloform Reaction

When methyl ketones react with halogens in the presence of excess base, multiple halogenations always occur at the carbon of the methyl group. Multiple halogenations occur because introduction of the first halogen (owing to its electronegativity) makes the remaining α hydrogens on the methyl carbon more acidic. The resulting CX_3 group bonded to the carbonyl can be a leaving group, however. Thus, when hydroxide is the base, an acyl substitution reaction follows, leading to a carboxylate salt and a haloform (CHX_3, e.g., chloroform, bromoform, or iodoform). The following is an example.



The haloform reaction is one of the rare instances in which a carbanion acts as a leaving group. This occurs because the trihalomethyl anion is unusually stable; its negative charge is dispersed by the three electronegative halogen atoms (when X = Cl, the conjugate acid, $CHCl_3$, has $pK_a = 13.6$). In the last step, a proton transfer takes place between the carboxylic acid and the trihalomethyl anion.

The **haloform reaction** is synthetically useful as a means of converting methyl ketones to carboxylic acids. When the haloform reaction is used in synthesis, chlorine and bromine are most commonly used as the halogen component. Chloroform ($CHCl_3$) and bromoform ($CHBr_3$) are both liquids which are immiscible with water and are easily separated from the aqueous solution containing the carboxylate anion. When iodine is the halogen component, the bright yellow solid iodoform (CHI_3) results. This version is the basis of the iodoform classification test for methyl ketones and methyl secondary alcohols (which are oxidized to methyl ketones first under the reaction conditions):

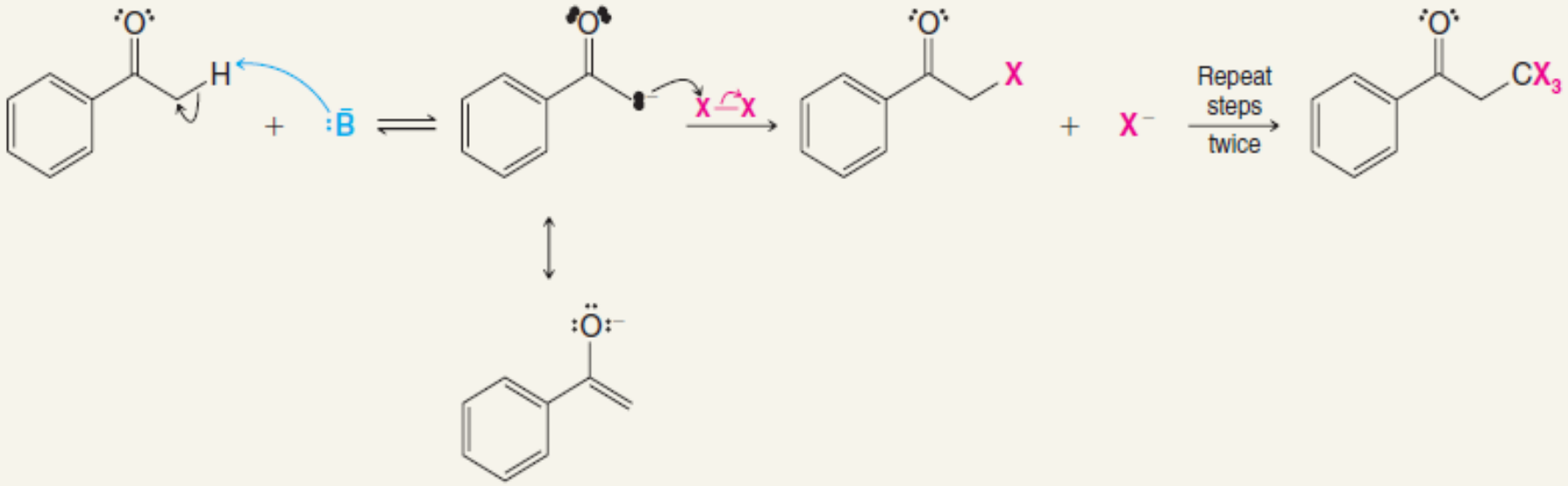


A methyl ketone

Iodoform (a yellow precipitate)

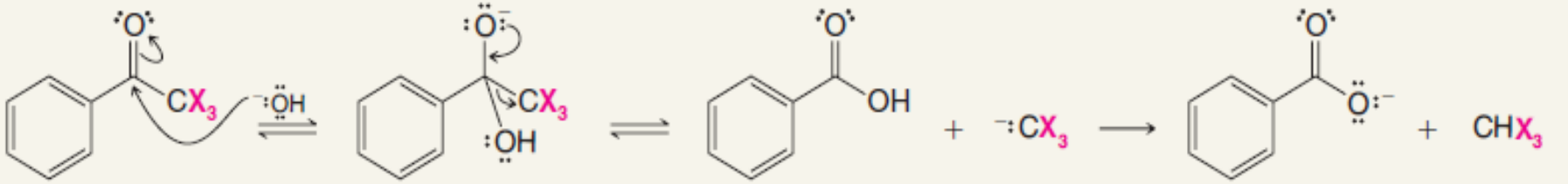
The Haloform Reaction

Halogenation Step



Enolate

Acyl substitution step



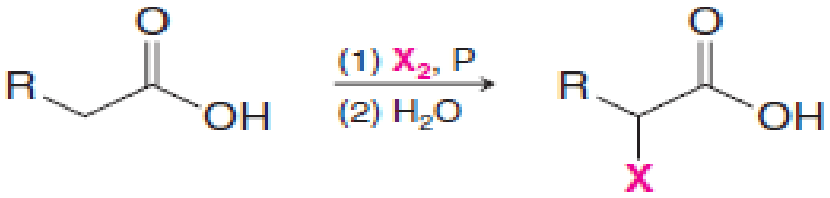
Carboxylate anion

A haloform

α- Halo Carboxylic Acids: The Hell–Volhard–Zelinski Reaction

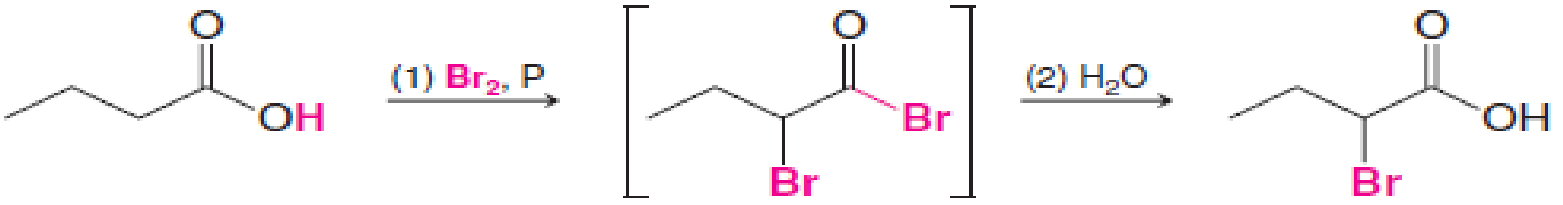
Carboxylic acids bearing α hydrogen atoms react with bromine or chlorine in the presence of phosphorus (or a phosphorus halide) to give α-halo carboxylic acids through a reaction known as the Hell–Volhard–Zelinski (or HVZ) reaction.

General Reaction



α-Halo acid

Specific Example

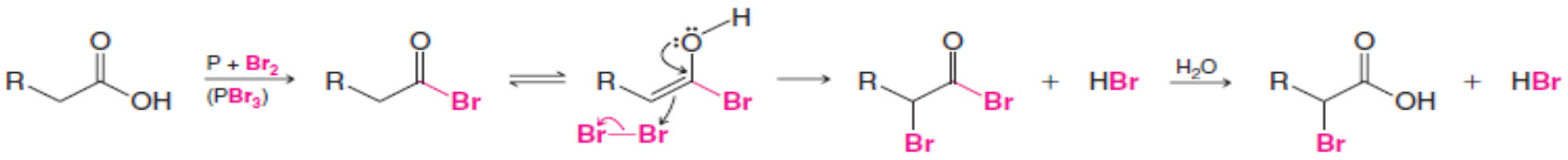


Butanoic acid

2-Bromobutanoic acid (77%)

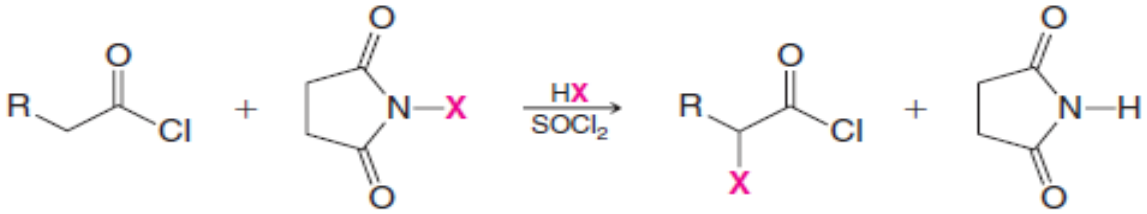
If more than one molar equivalent of bromine or chlorine is used in the reaction, the products obtained are α,α-dihalo acids or α,α,α-trihalo acids.

Important steps in the reaction are formation of an acyl halide and the enol derived from the acyl halide. The acyl halide is key because carboxylic acids do not form enols readily since the carboxylic acid proton is removed before the α hydrogen. Acyl halides lack the carboxylic acid hydrogen.



Acyl bromide **Enol form**

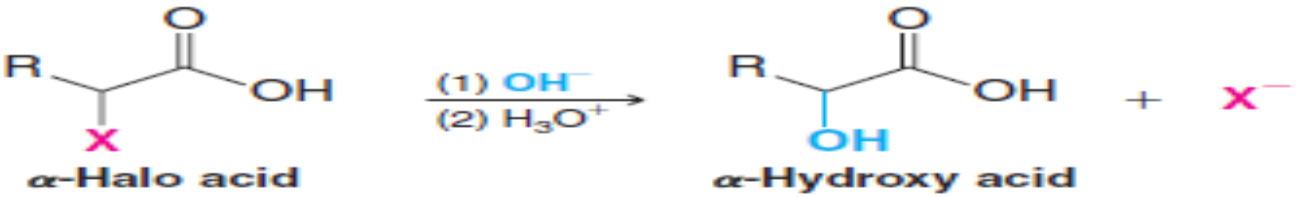
An alternative method for α-halogenation has been developed by D. N. Harpp (McGill University). Acyl chlorides, formed *in situ* by the reaction of the carboxylic acid with $SOCl_2$, are treated with the appropriate *N*-halosuccinimide and a trace of HX to produce α-chloro and α-bromo acyl chlorides.



α-Iodo acyl chlorides can be obtained by using molecular iodine in a similar reaction.

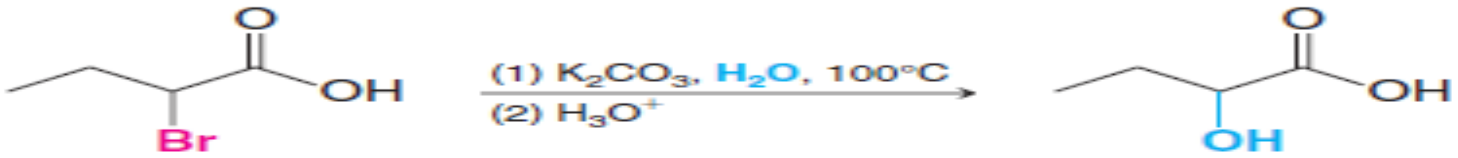
α-Halo acids are important synthetic intermediates because they are capable of reacting with a variety of nucleophiles:

Conversion to α-Hydroxy Acids



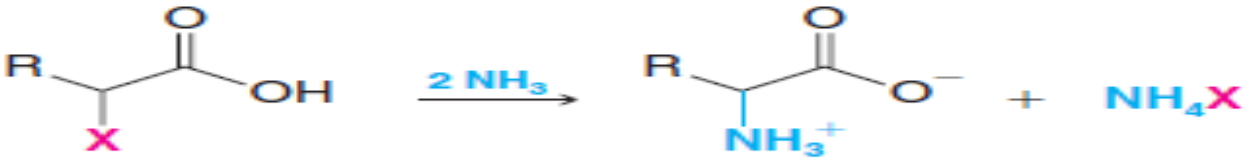
α-Halo acid → α-Hydroxy acid

Specific Example



2-Hydroxybutanoic acid (69%)

Conversion to α-Amino Acids



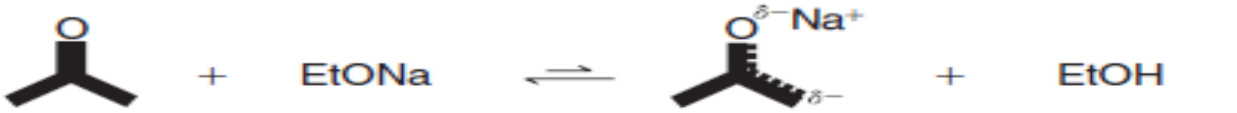
α-Halo acid → α-Amino acid

Specific Example

Aminoacetic acid (glycine) (60-64%)

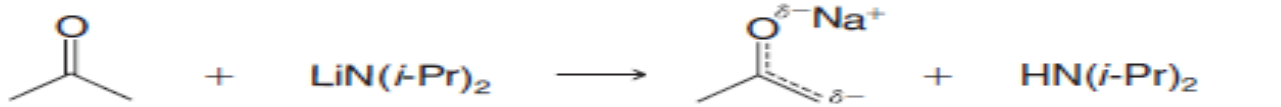
Lithium Enolates

The position of the equilibrium by which an enolate forms depends on the strength of the base used. If the base employed is a weaker base than the enolate, then the equilibrium lies to the left. This is the case, for example, when a ketone is treated with sodium ethoxide in ethanol.



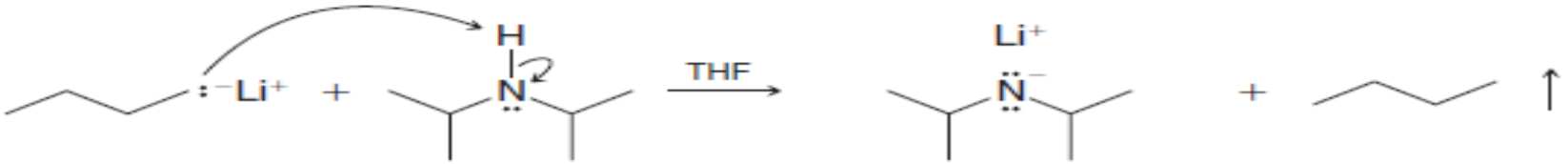
Weaker acid ($pK_a = 19$) **Weaker base** **Stronger base** **Stronger acid ($pK_a = 16$)**

On the other hand, if a very strong base is employed, the equilibrium lies far to the right. One very useful strong base for converting carbonyl compounds to enolates is **lithium diisopropylamide (LDA)** or LiN(i-Pr)2:



Ketone (stronger acid) ($pK_a = 19$) **LDA (stronger base)** **Enolate (weaker base)** **Diisopropylamine (weaker acid) ($pK_a = 38$)**

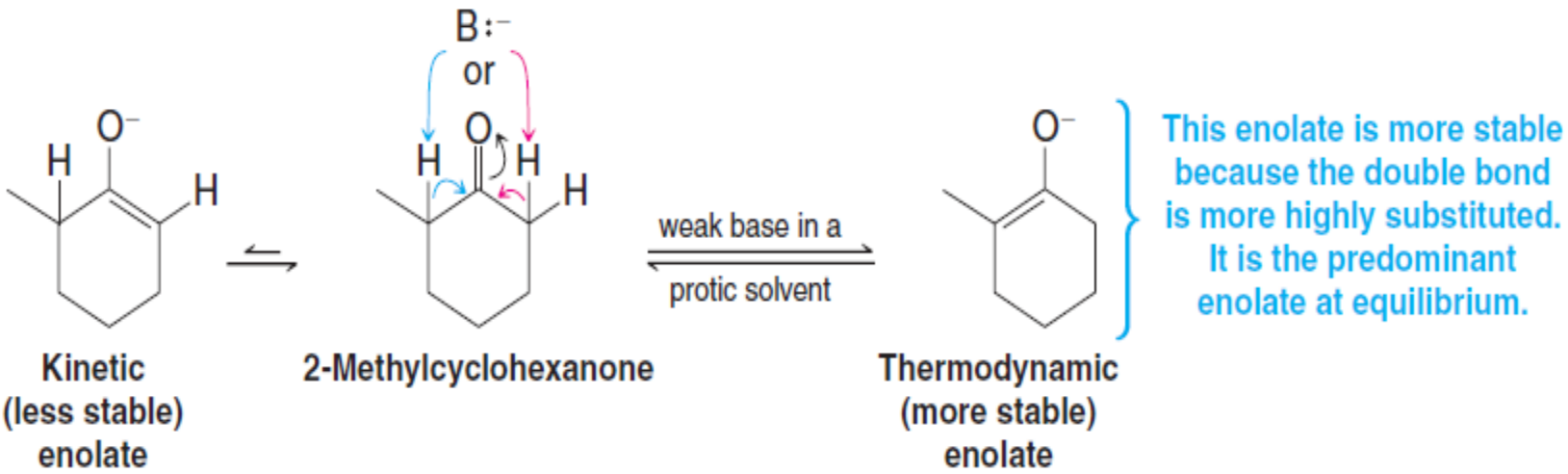
- Lithium diisopropylamide (LDA) can be prepared by dissolving diisopropylamine in a solvent such as diethyl ether or THF and treating it with an alkyllithium:



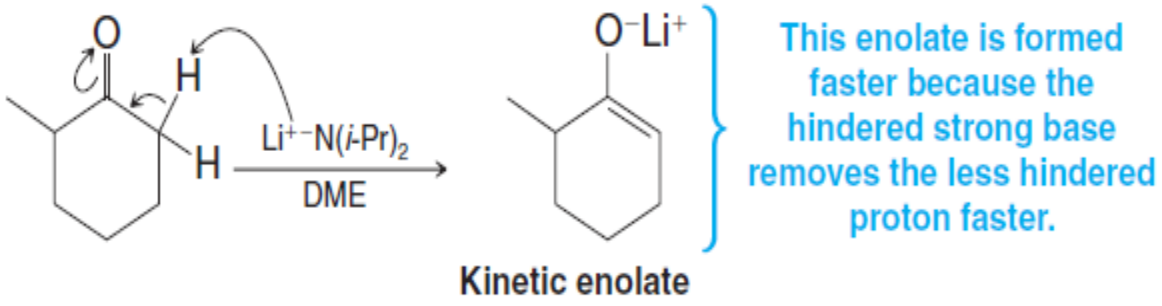
Butyllithium (BuLi) **Diisopropylamine ($pK_a = 38$)** **Lithium diisopropylamide [LDA or LiN(i-Pr)2]** **Butane ($pK_a = 50$)**

Regioselective Formation of Enolates

Formation of a Thermodynamic Enolate

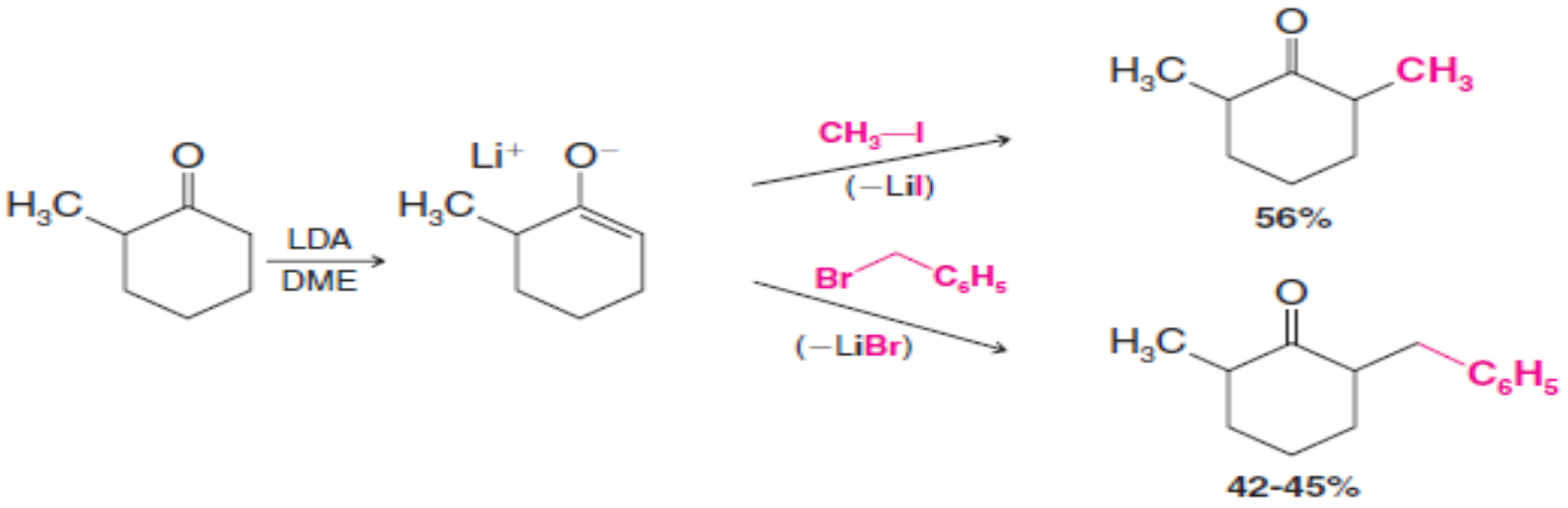


Formation of a Kinetic Enolate



Direct Alkylation of Ketones via Lithium Enolates

The formation of lithium enolates using lithium diisopropylamide furnishes a useful way of alkylating ketones in a regioselective way. For example, the lithium enolate formed from 2-methylcyclohexanone can be methylated or benzylated at the less hindered α carbon by allowing it to react with LDA followed by methyl iodide or benzyl bromide, respectively:

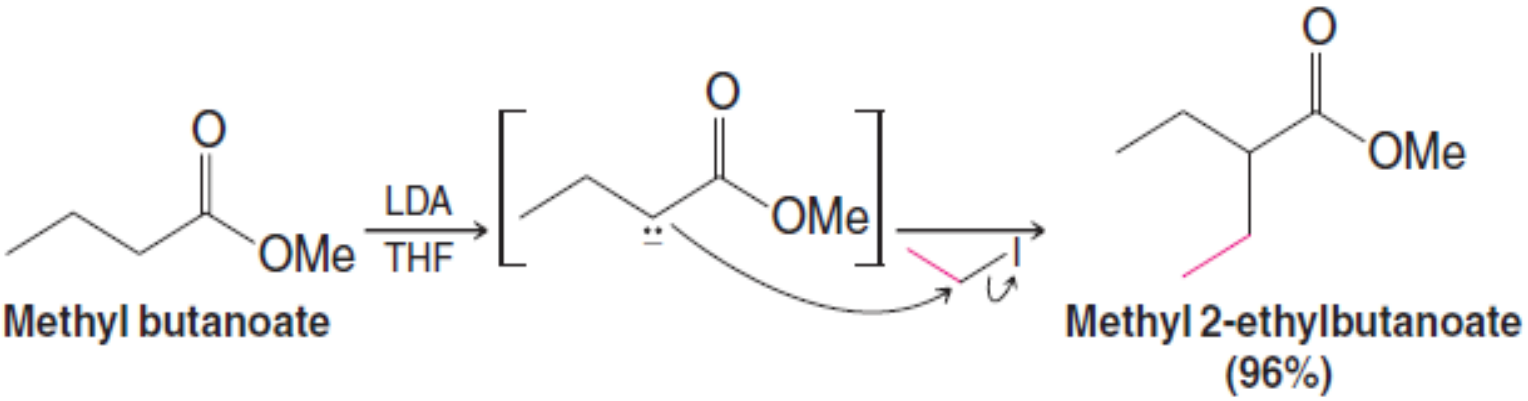


Alkylation reactions like these have an important limitation, however, because the reactions are S_N2 reactions, and also because enolates are strong bases.

- Successful alkylations occur only when primary alkyl, primary benzylic, and primary allylic halides are used. With secondary and tertiary halides, elimination becomes the main course of the reaction.

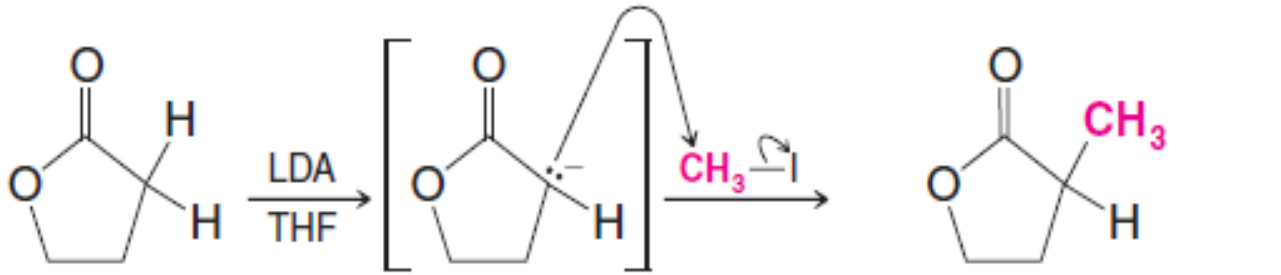
Direct Alkylation of Esters

Examples of the direct alkylation of esters are shown below. In the second example the ester is a lactone



Methyl butanoate

Methyl 2-ethylbutanoate
(96%)

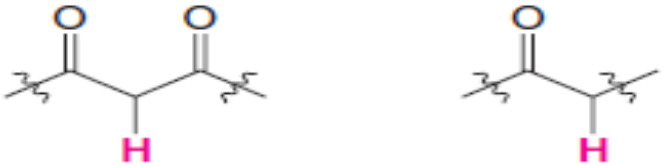


Butyrolactone

2-Methylbutyrolactone
(88%)

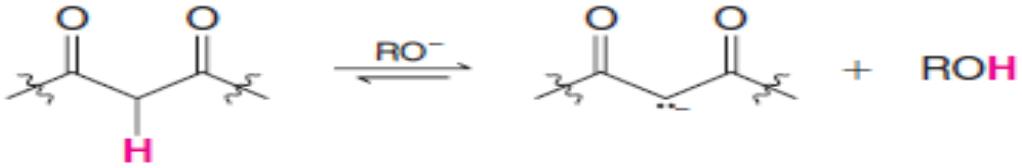
Enolates of β-Dicarbonyl Compounds

- Hydrogen atoms that are between two carbonyl groups, as in a **β-dicarbonyl compound**, have pK_a values in the range of 9–11. Such α-hydrogen atoms are much more acidic than α hydrogens adjacent to only one carbonyl group, which have pK_a values of 18–20.

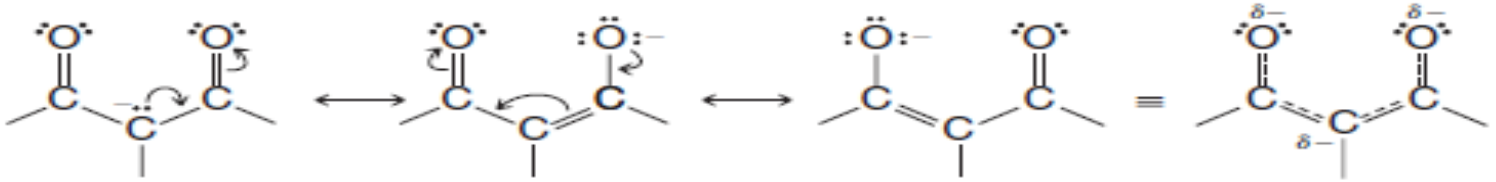


pK_a 9-11 pK_a 18-20

- A much weaker base than LDA, such as an alkoxide, can be used to form an enolate from a β-dicarbonyl compound.



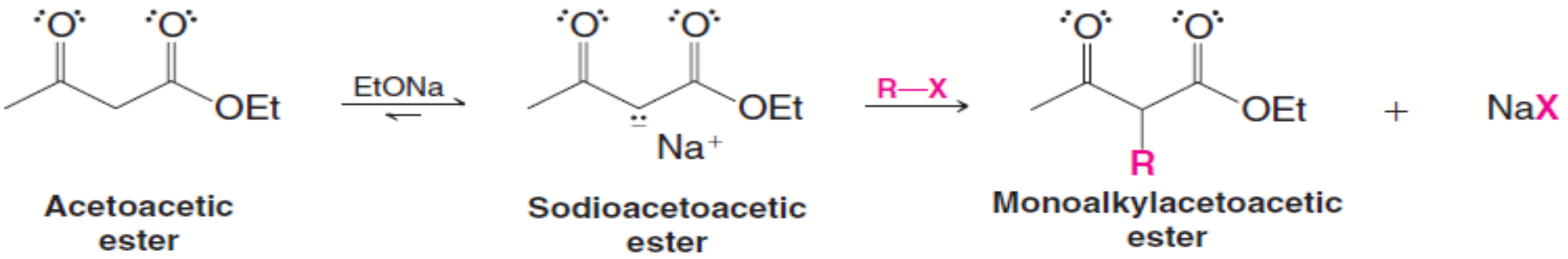
We can account for the greater acidity of β-dicarbonyl systems, as compared to single carbonyl systems, by delocalization of the negative charge to two oxygen atoms instead of one. We can represent this delocalization by drawing contributing resonance structures for a β-dicarbonyl enolate and its resonance hybrid:



Contributing resonance structures Resonance hybrid

Synthesis of Methyl Ketones: The Acetoacetic Ester Synthesis

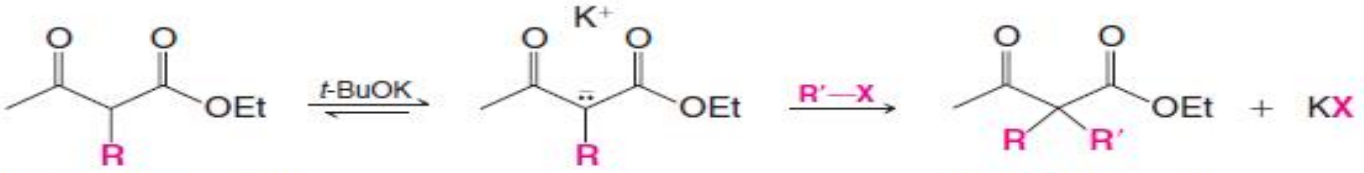
Acetoacetic ester, because it is a β-dicarbonyl compound, can easily be converted to an enolate using sodium ethoxide. We can then alkylate the resulting enolate (called sodioacetoacetic ester) with an alkyl halide. This process is called an **acetoacetic ester synthesis**.



Acetoacetic ester | **Sodioacetoacetic ester** | **Monoalkylacetoacetic ester**

- Since the alkylation in the reaction above is an S_N2 reaction, the best yields are obtained from the use of primary alkyl halides (including primary allylic and benzylic halides) or methyl halides. Secondary halides give lower yields, and tertiary halides give only elimination.

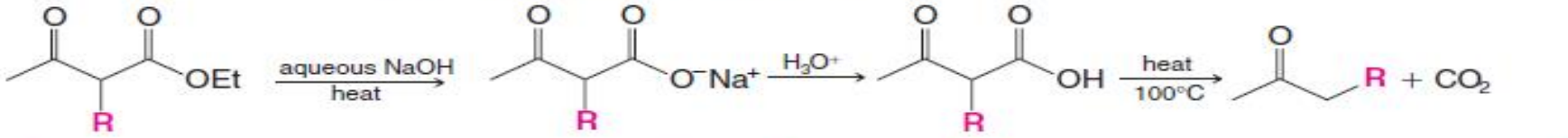
Dialkylation The monoalkylacetoacetic ester shown above still has one appreciably acidic hydrogen, and, if we desire, we can carry out a second alkylation. Because a monoalkylacetoacetic ester is somewhat less acidic than acetoacetic ester itself due to the electron-donating effect of the added alkyl group, it is usually helpful to use a stronger base than ethoxide ion for the second alkylation. Use of potassium *tert*-butoxide is common because it is a stronger base than sodium ethoxide. Potassium *tert*-butoxide, because of its steric bulk, is also not likely to cause transesterification.



Monoalkylacetoacetic ester

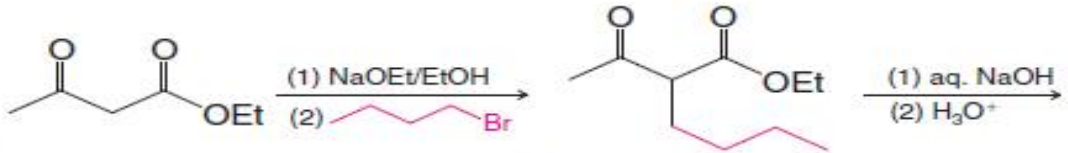
Dialkylacetoacetic ester

Substituted Methyl Ketones To synthesize a monosubstituted methyl ketone (monosubstituted acetone), we carry out only one alkylation. Then we hydrolyze the monoalkylacetoacetic ester using aqueous sodium or potassium hydroxide. Subsequent acidification of the mixture gives an alkyl-acetoacetic acid, and heating this β-keto acid to 100°C brings about decarboxylation (Section 17.10):



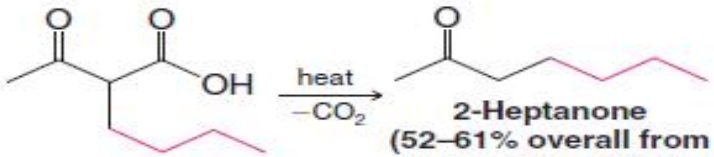
Basic hydrolysis of the ester group | Acidification | Decarboxylation of the β-keto acid

A specific example is the following synthesis of 2-heptanone:



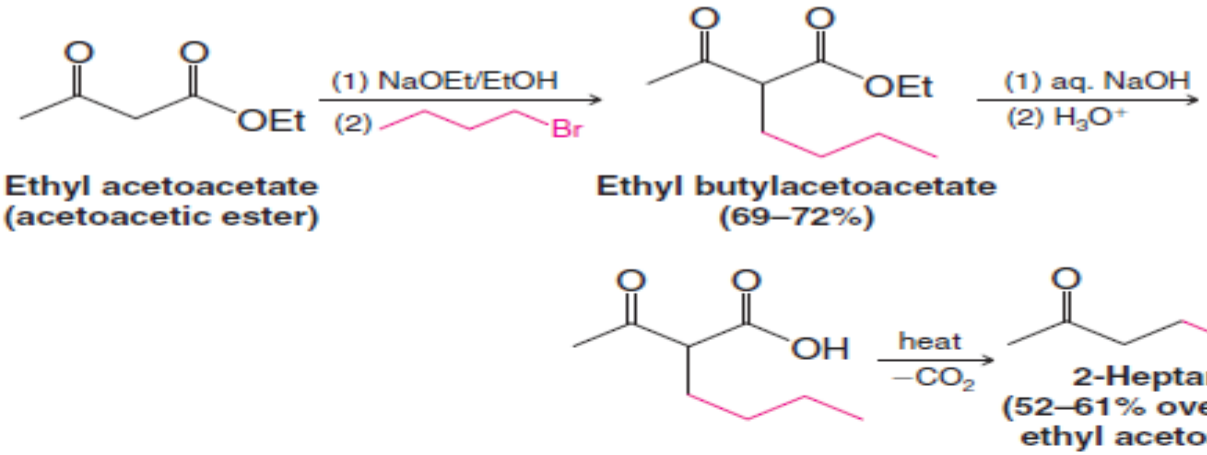
Ethyl acetoacetate (acetoacetic ester)

Ethyl butylacetoacetate (69–72%)



2-Heptanone (52–61% overall from ethyl acetoacetate)

A specific example is the following synthesis of 2-heptanone:

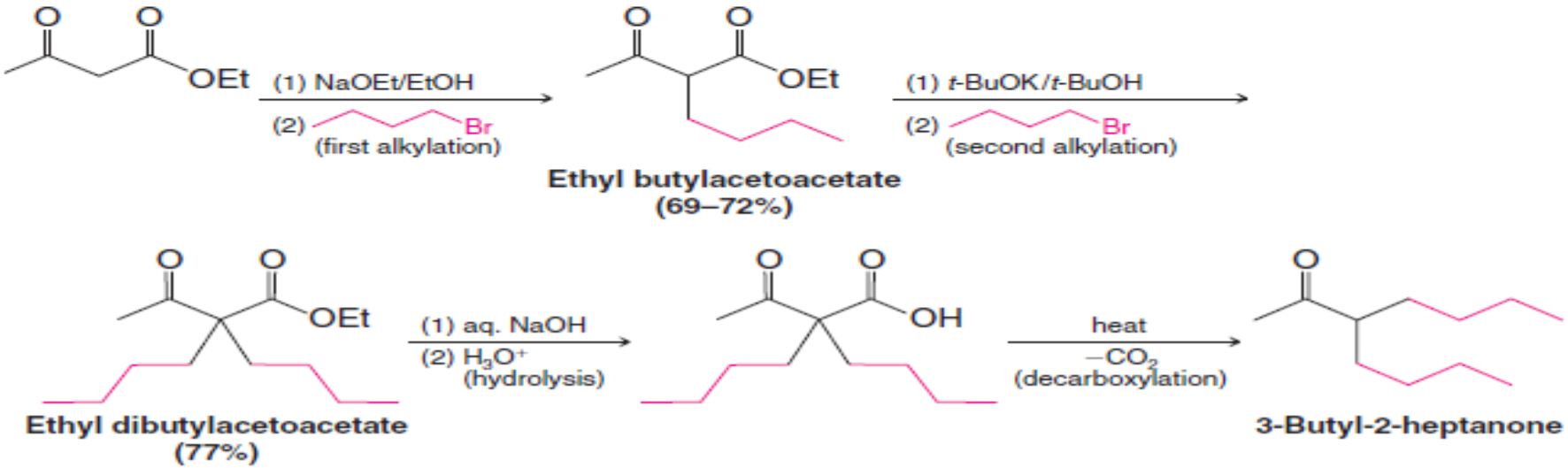


Ethyl acetoacetate (acetoacetic ester)

Ethyl butylacetoacetate (69–72%)

2-Heptanone (52–61% overall from ethyl acetoacetate)

If our goal is the preparation of a disubstituted acetone, we carry out two successive alkylations, we hydrolyze the dialkylacetoacetic ester that is produced, and then we decarboxylate the dialkylacetoacetic acid. An example of this procedure is the synthesis of 3-butyl-2-heptanone.

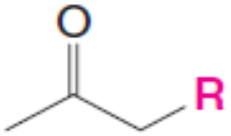


Ethyl butylacetoacetate (69–72%)

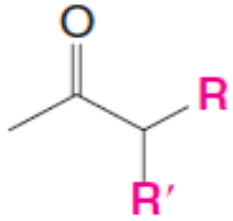
Ethyl dibutylacetoacetate (77%)

3-Butyl-2-heptanone

- As we have seen, ethyl acetoacetate is a useful reagent for the preparation of substituted acetones (methyl ketones) of the types shown below.



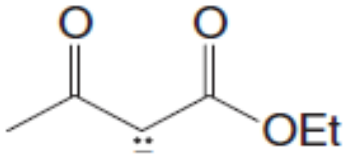
A monosubstituted acetone



A disubstituted acetone

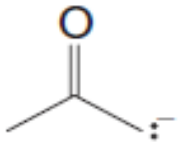
- Ethyl acetoacetate therefore serves as the synthetic equivalent of the enolate from acetone shown below.

A **synthetic equivalent** is a reagent whose structure, when incorporated into a product, gives the appearance of having come from one type of precursor when as a reactant it actually had a different structural origin. Although it is possible to form the enolate of acetone, use of ethyl acetoacetate as a synthetic equivalent is often more convenient because its α hydrogens are so much more acidic (pK_a = 9–11) than those of acetone itself (pK_a = 19–20). If we had wanted to use the acetone enolate directly, we would have had to use a much stronger base and other special conditions (see Section 18.4).



Ethyl acetoacetate ion

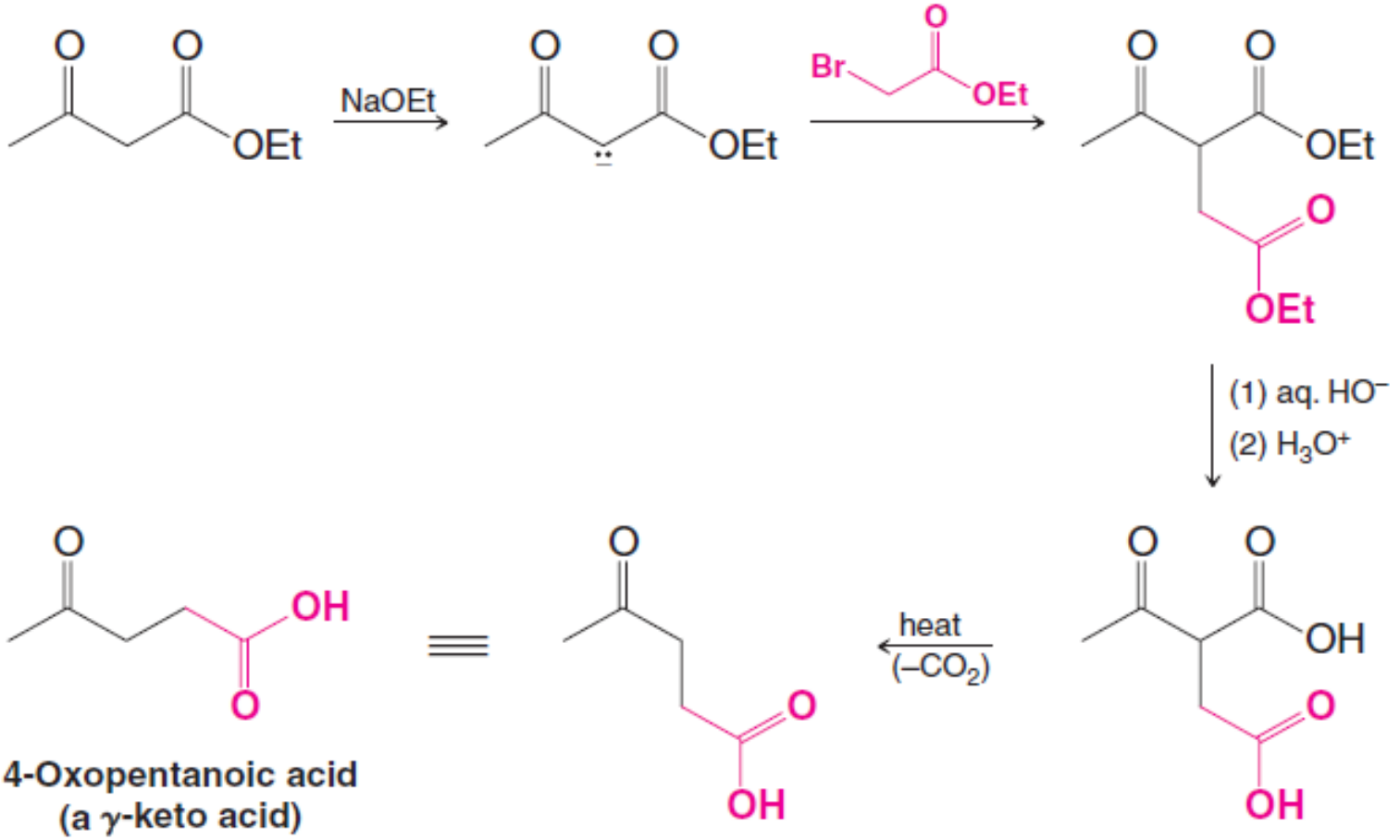
is the synthetic equivalent of



Acetone enolate

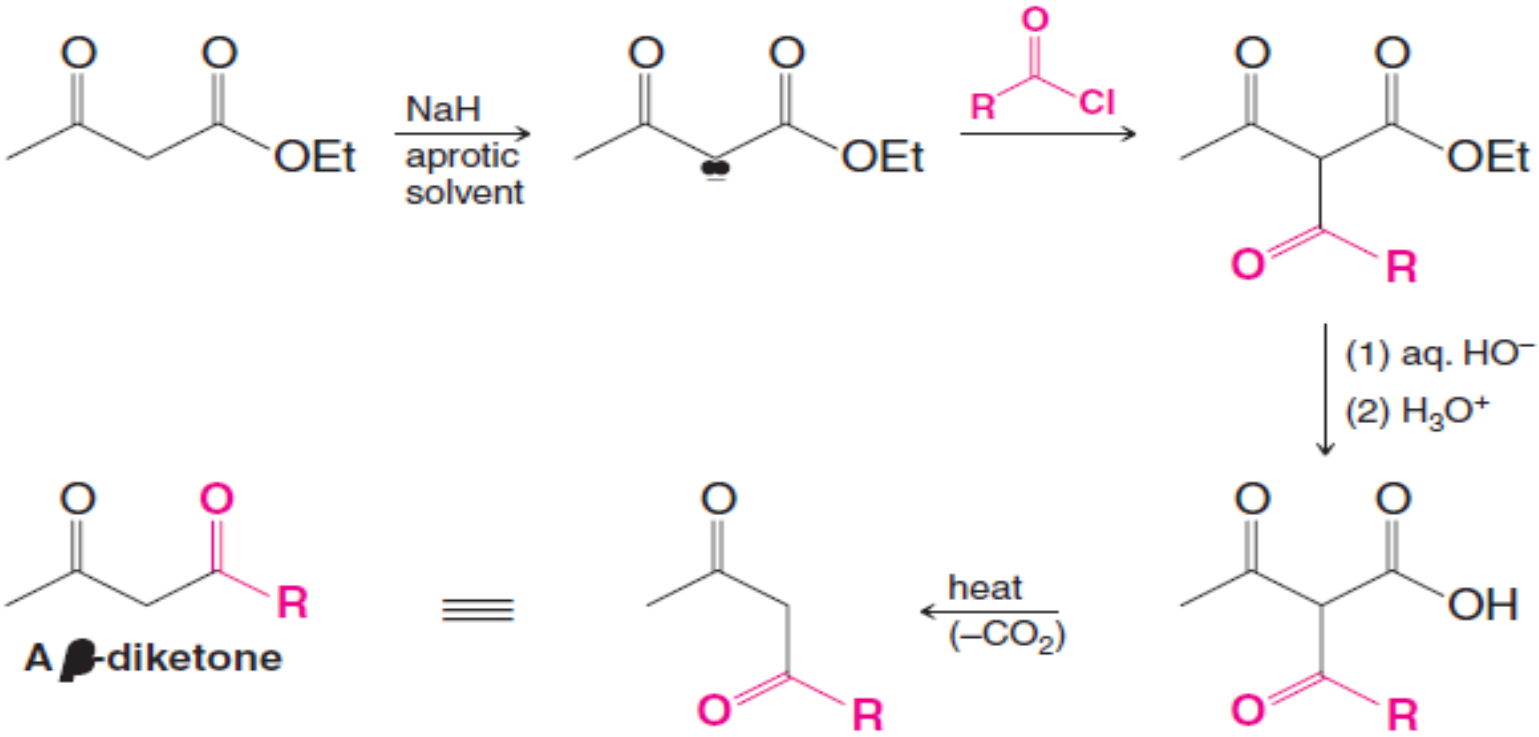
❖ Synthesis of γ-keto acids and γ-diketones:

The acetoacetic ester synthesis can also be carried out using halo esters and halo ketones
The use of an α-halo ester provides a convenient synthesis of γ-keto acids:



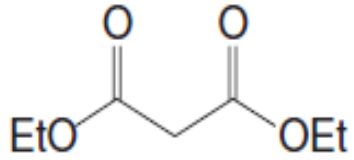
Acylation

Anions obtained from acetoacetic esters undergo acylation when they are treated with acyl chlorides or acid anhydrides. Because both of these acylating agents react with alcohols, acylation reactions cannot be carried out in ethanol and must be carried out in aprotic solvents such as DMF or DMSO (If the reaction were to be carried out in ethanol, using sodium ethoxide, for example, then the acyl chloride would be rapidly converted to an ethyl ester and the ethoxide ion would be neutralized.) Sodium hydride can be used to generate the enolate ion in an aprotic solvent:



Synthesis of Substituted Acetic Acids: The Malonic Ester Synthesis

A useful counterpart of the acetoacetic ester synthesis—one that allows the synthesis of *mono-* and *disubstituted acetic acids*—is called the **malonic ester synthesis.** The starting compound is the diester of a β-dicarboxylic acid, called a malonic ester. The most commonly used malonic ester is diethyl malonate.

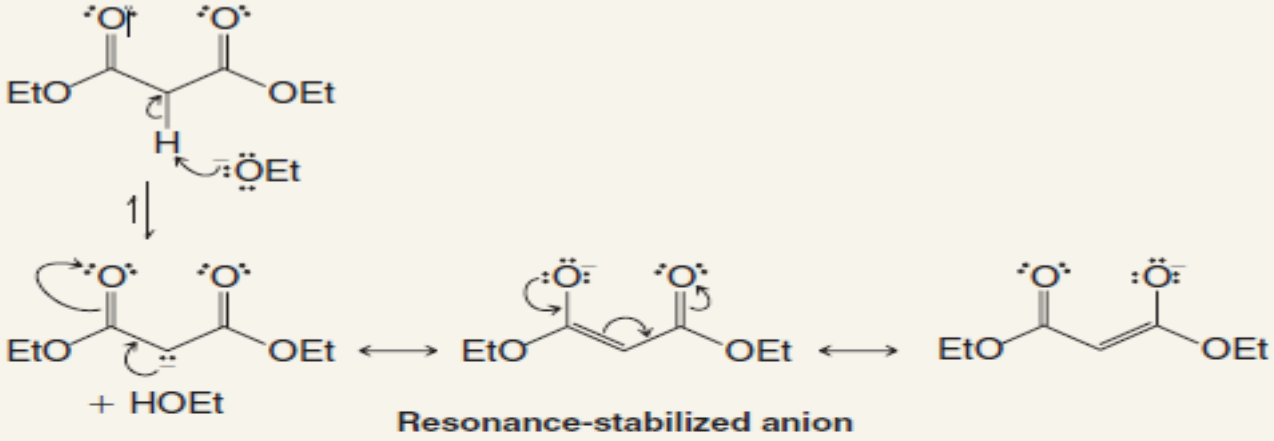


Diethyl malonate (a β-dicarboxylic acid ester)

We shall see by examining the following mechanism that the malonic ester synthesis resembles the acetoacetic ester synthesis in several respects.

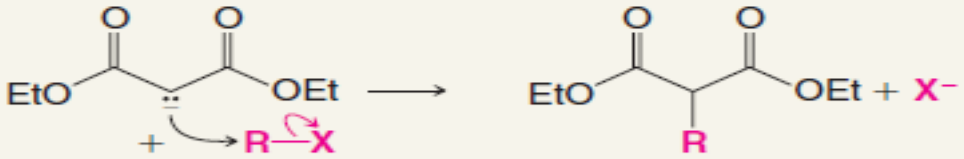
The Malonic Ester Synthesis of Substituted Acetic Acids

Step 1 *Diethyl malonate, the starting compound, forms a relatively stable enolate:*



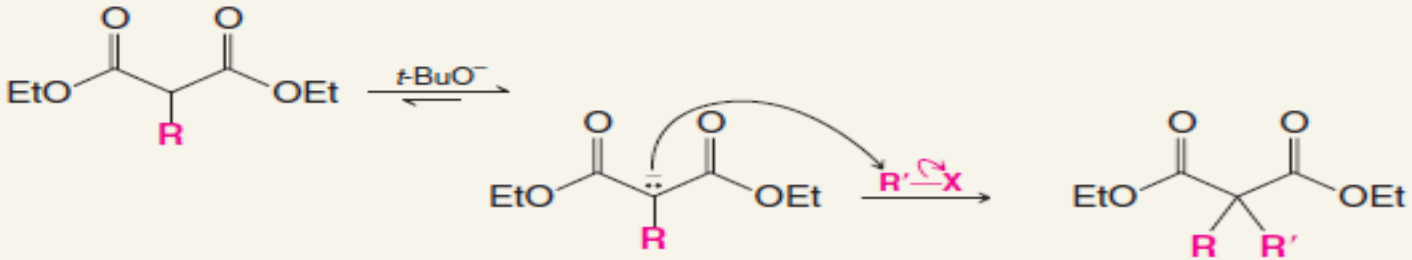
Resonance-stabilized anion

Step 2 *This enolate can be alkylated in an S_N2 reaction,*



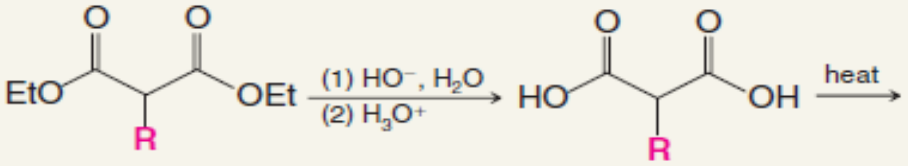
Enolate **Monoalkylmalonic ester**

and the product can be alkylated again if our synthesis requires it:

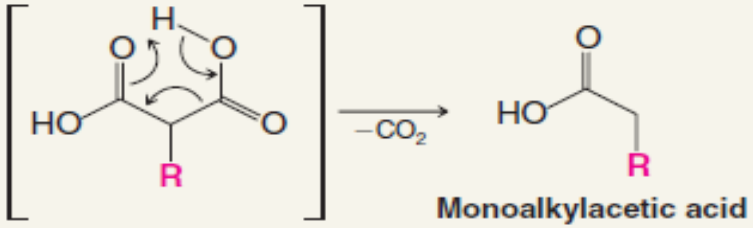


Dialkylmalonic ester

Step 3 *The mono- or dialkylmalonic ester can then be hydrolyzed to a mono- or dialkylmalonic acid, and substituted malonic acids decarboxylate readily. Decarboxylation gives a mono- or disubstituted acetic acid:*

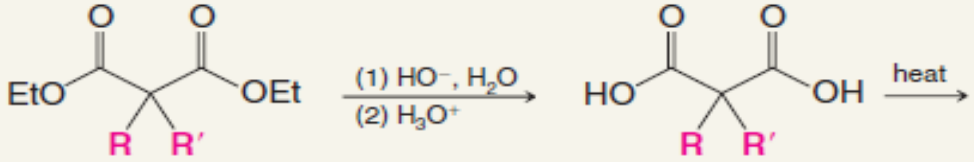


Monoalkylmalonic ester

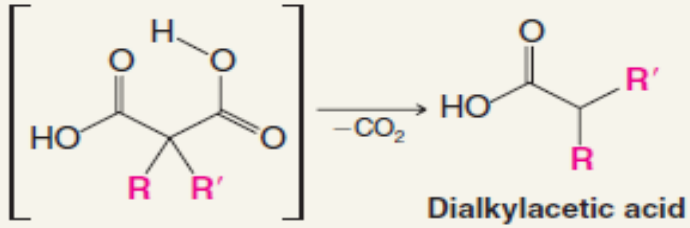


Monoalkylacetic acid

or after dialkylation,



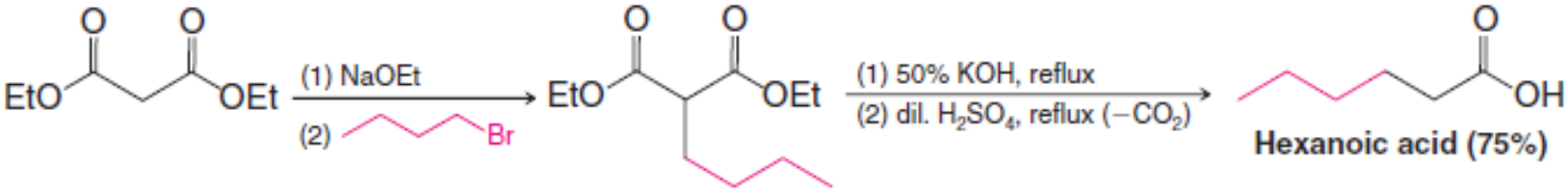
Dialkylmalonic ester



Dialkylacetic acid

Two specific examples of the malonic ester synthesis are the syntheses of hexanoic acid and 2-ethylpentanoic acid that follow.

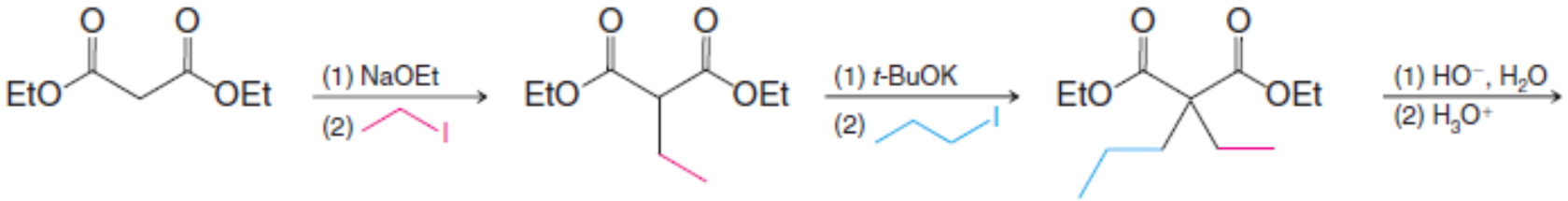
A Malonic Ester Synthesis of Hexanoic Acid



Diethyl butylmalonate (80–90%)

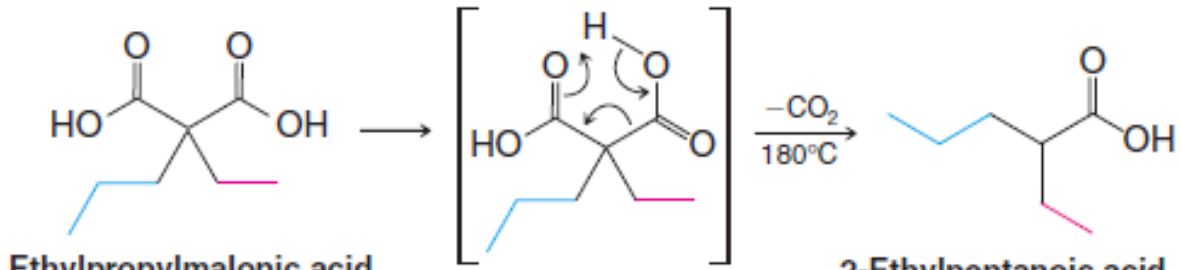
Hexanoic acid (75%)

A Malonic Ester Synthesis of 2-Ethylpentanoic Acid



Diethyl ethylmalonate

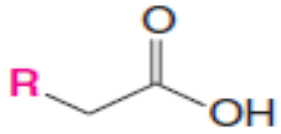
Diethyl ethylpropylmalonate



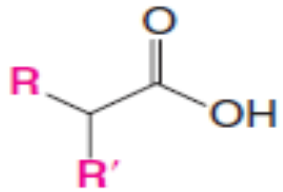
Ethylpropylmalonic acid

2-Ethylpentanoic acid

- As we have seen, the malonic ester synthesis is a useful method for preparing mono- and dialkylacetic acids:

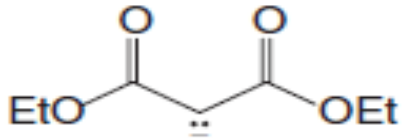


A monoalkylacetic acid



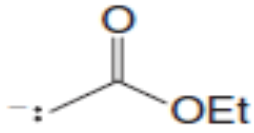
A dialkylacetic acid

- Thus, the malonic ester synthesis provides us with a synthetic equivalent of an ester enolate of acetic acid or acetic acid dianion.

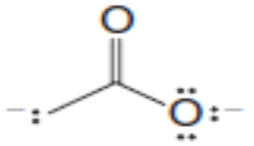


Diethyl malonate anion

is the synthetic equivalent of



and



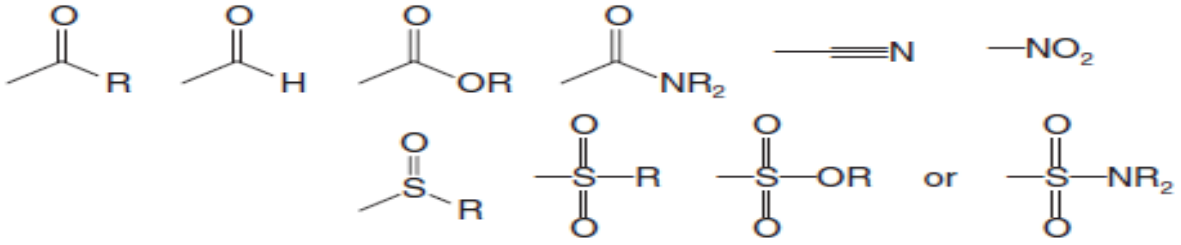
Direct formation of such anions is possible (Section 18.4), but it is often more convenient to use diethyl malonate as a synthetic equivalent because its α hydrogens are more easily removed.

Further Reactions of Active Hydrogen Compounds

Because of the acidity of their methylene hydrogens malonic esters, acetoacetic esters, and similar compounds are often called **active hydrogen compounds** or **active methylene compounds**. Generally speaking, active hydrogen compounds have two electron-withdrawing groups attached to the same carbon atom:

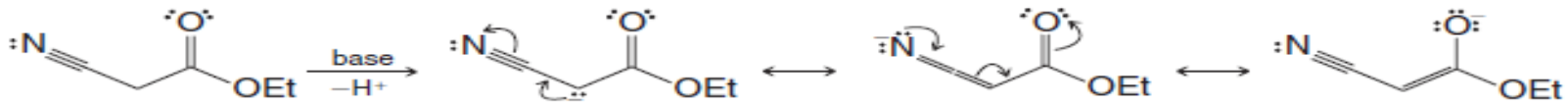
Active hydrogen compound
(Z and Z′ are electron-withdrawing groups.)

The electron-withdrawing groups can be a variety of substituents, including



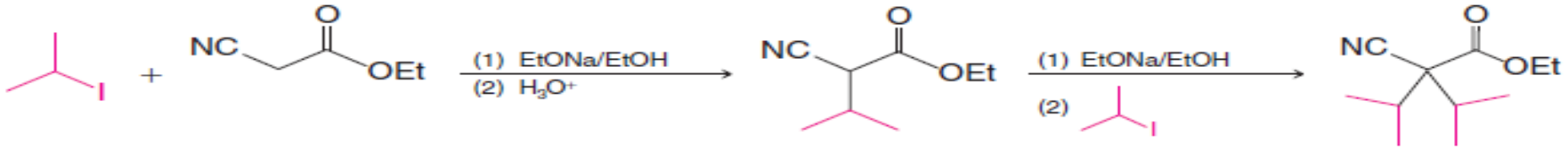
The range of pK_a values for such active methylene compounds is 3–13.

Ethyl cyanoacetate, for example, reacts with a base to yield a resonance-stabilized anion:



Ethyl cyanoacetate **Resonance structures for ethyl cyanoacetate anion**

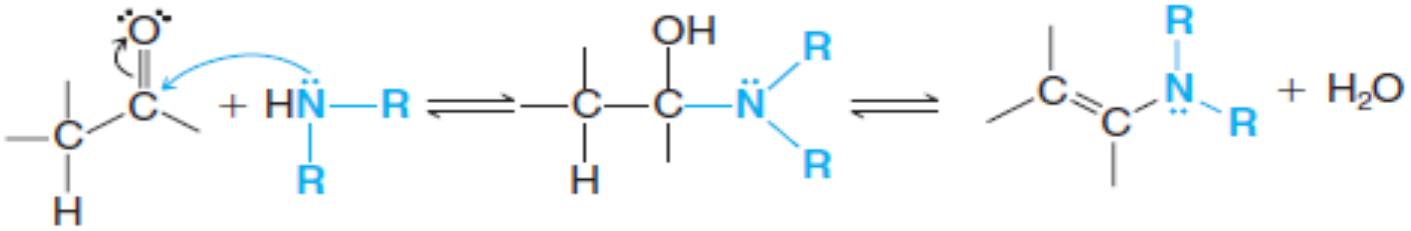
Ethyl cyanoacetate anions also undergo alkylations. They can be dialkylated with isopropyl iodide, for example:



63% 95%

Synthesis of Enamines: Stork Enamine Reactions

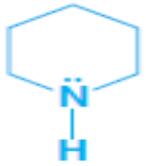
Aldehydes and ketones react with secondary amines to form compounds called **enamines.** The general reaction for enamine formation can be written as follows:



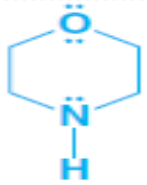
Aldehyde or ketone **2° Amine** **Enamine**

Since enamine formation requires the loss of a molecule of water, enamine preparations are usually carried out in a way that allows water to be removed as an azeotrope or by a drying agent. This removal of water drives the reversible reaction to completion. Enamine formation is also catalyzed by the presence of a trace of an acid. The secondary amines most commonly used to prepare enamines are cyclic amines such as pyrrolidine, piperidine, and morpholine:

Pyrrolidine

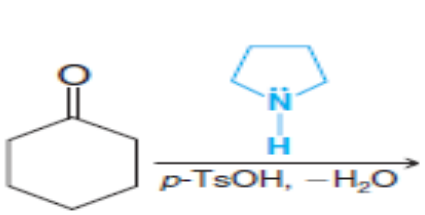


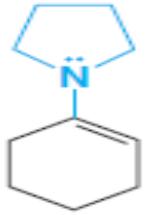
Piperidine



Morpholine

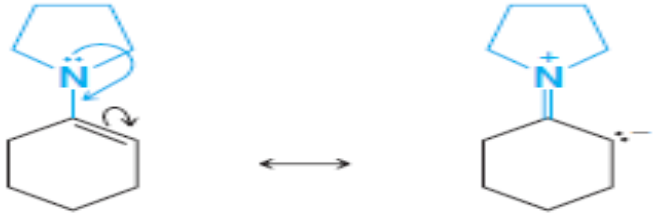
Cyclohexanone, for example, reacts with pyrrolidine in the following way:





N-(1-Cyclohexenyl)pyrrolidine
(an enamine)

Enamines are good nucleophiles. Examination of the resonance structures that follow show that we should expect enamines to have both a nucleophilic nitrogen and a *nucleophilic carbon*. A map of electrostatic potential highlights the nucleophilic region of an enamine.

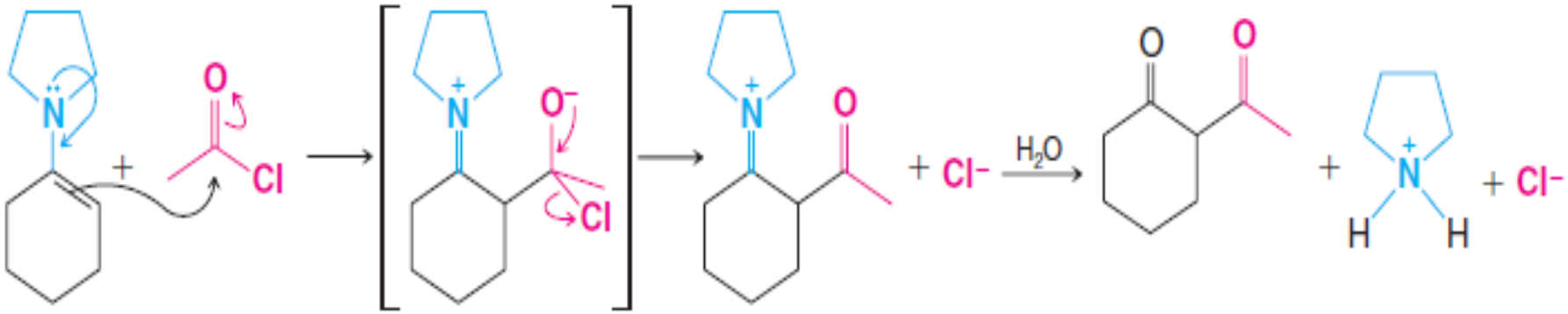


Contribution to the hybrid made by this structure confers nucleophilicity on nitrogen.

Contribution to the hybrid made by this structure confers nucleophilicity on carbon and decreases the nucleophilicity of nitrogen.

The nucleophilicity of the carbon of enamines makes them particularly useful reagents in organic synthesis because they can be **acylated, alkylated,** and used in Michael additions Enamines can be used as synthetic equivalents of aldehyde or ketone enolates because the alkene carbon of an enamine reacts the same way as does the α carbon of an aldehyde or ketone enolate and, after hydrolysis, the products are the same. Development of these techniques originated with the work of Gilbert Stork of Columbia University, and in his honor they have come to be known as **Stork enamine reactions.**

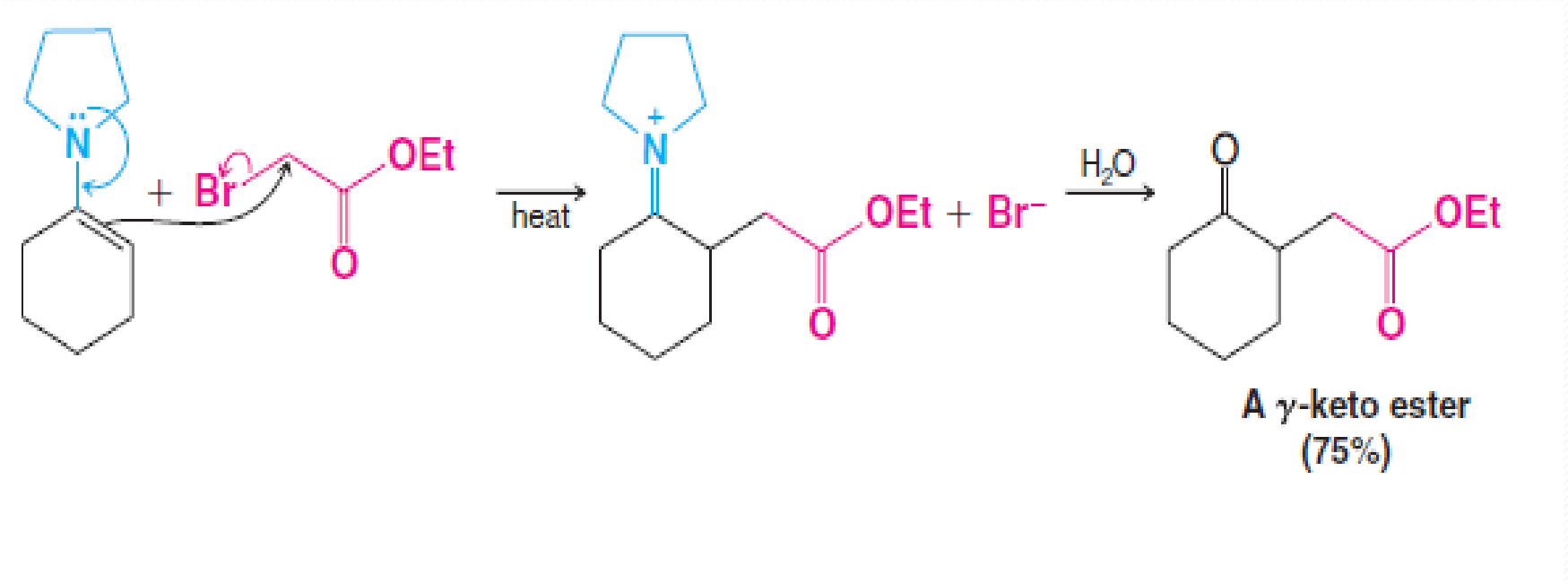
When an enamine reacts with an acyl halide or an acid anhydride, the product is the *C*-acylated compound. The iminium ion that forms hydrolyzes when water is added, and the overall reaction provides a synthesis of β-diketones:



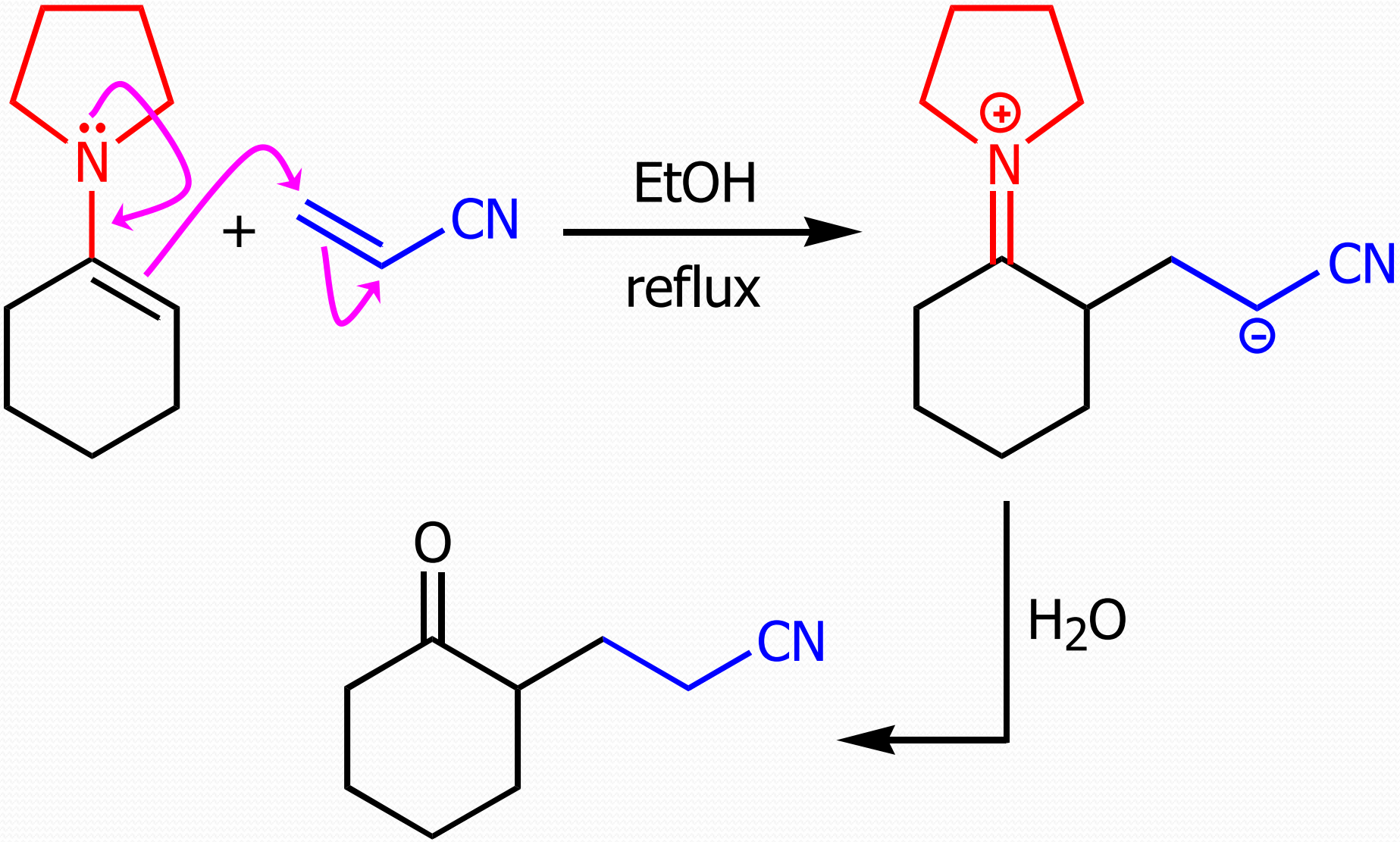
Iminium salt

2-Acetylcyclohexanone
(a β-diketone)

Synthesis of γ-keto esters: ❖

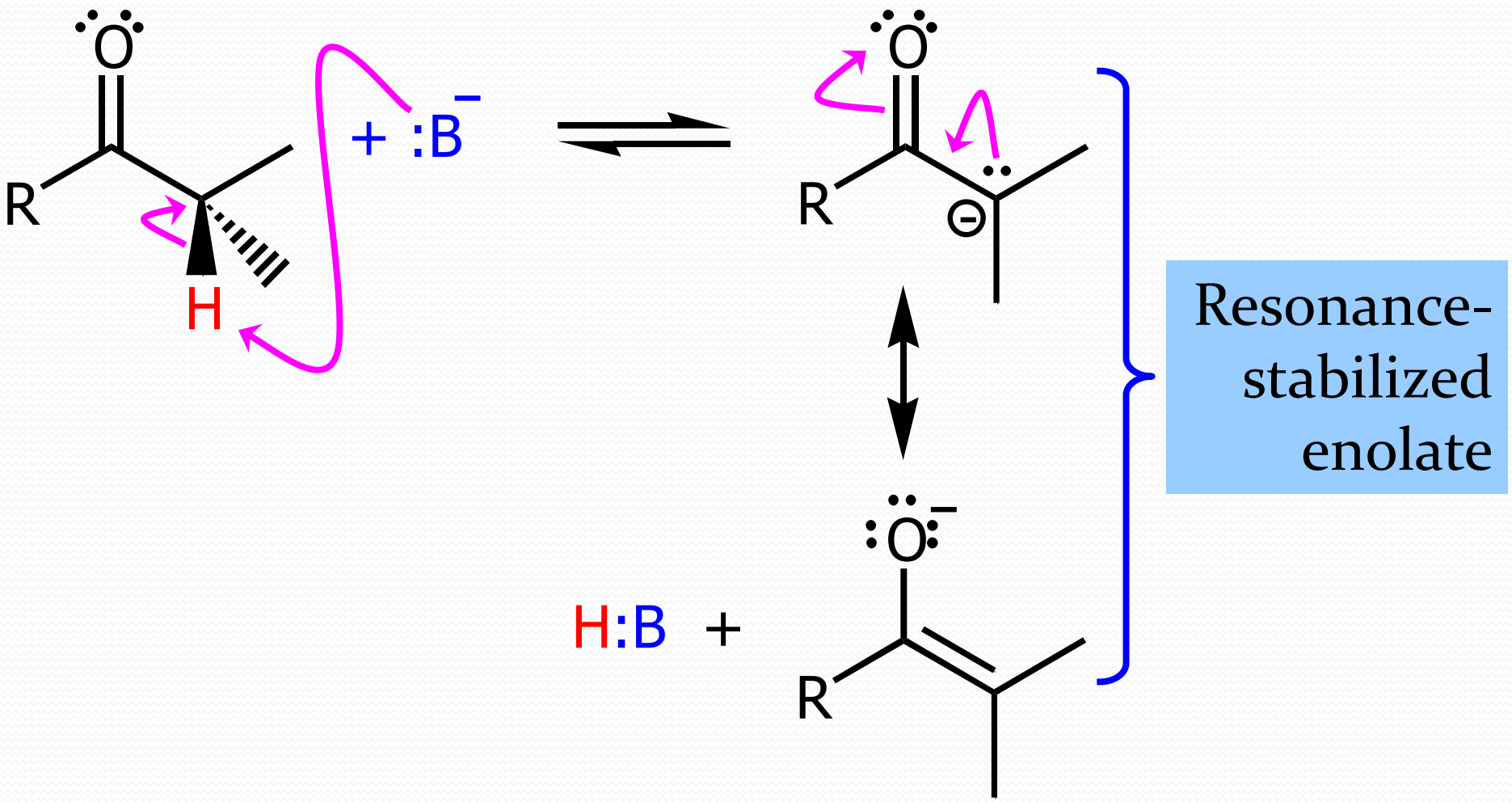


Enamines can also be used in Michael additions:

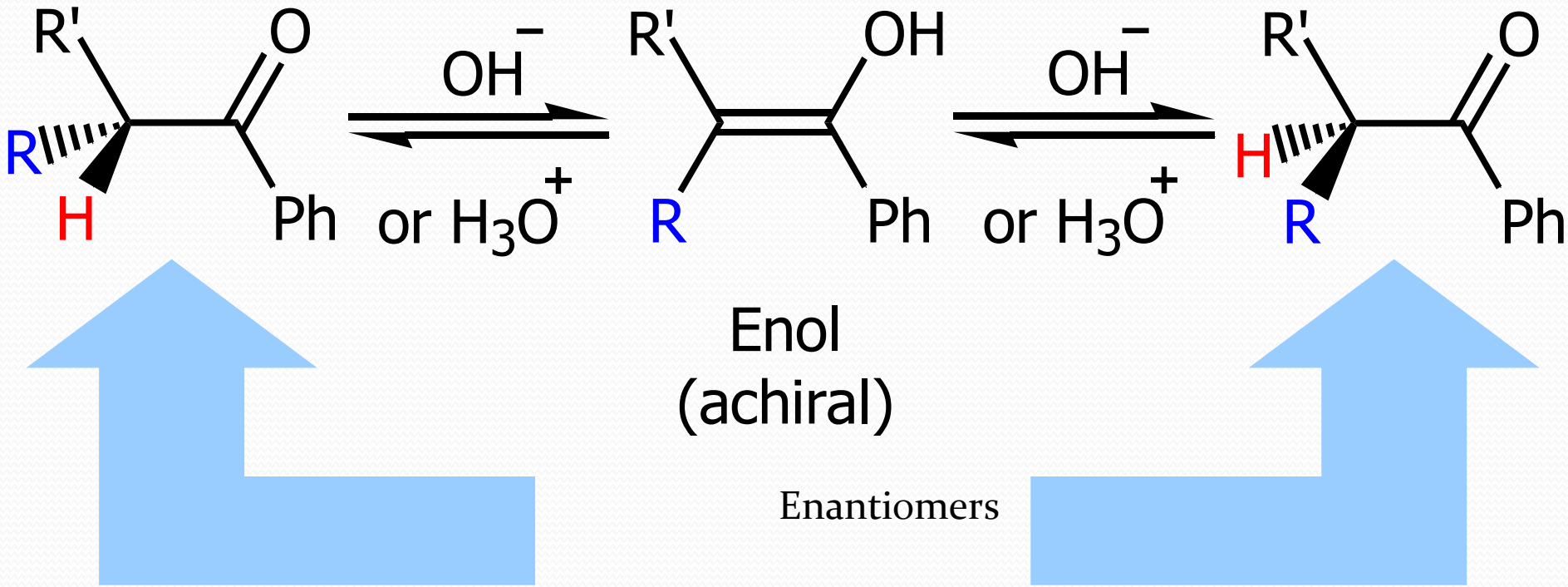


Summary of Enolate Chemistry

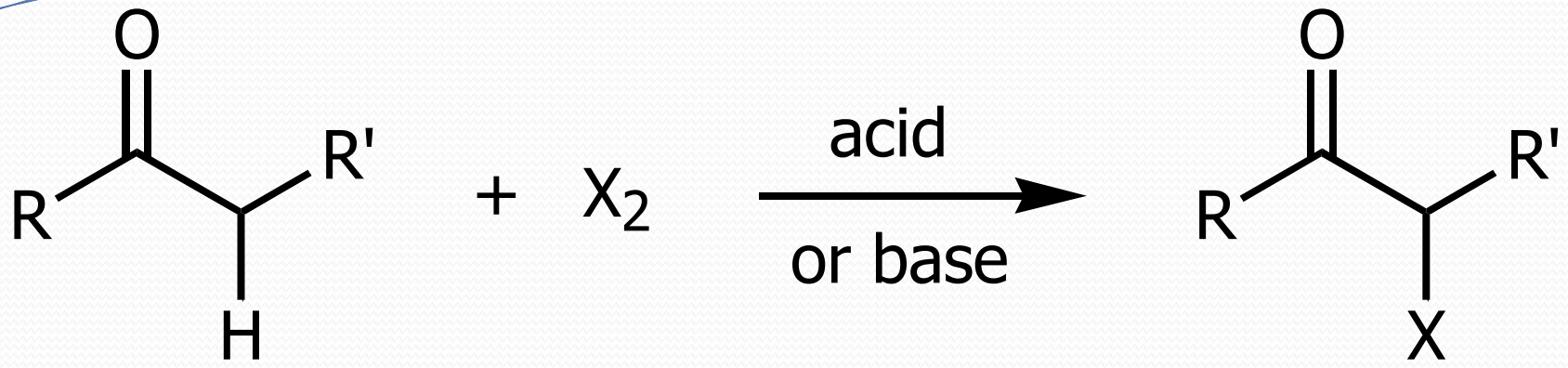
Formation of an Enolate:



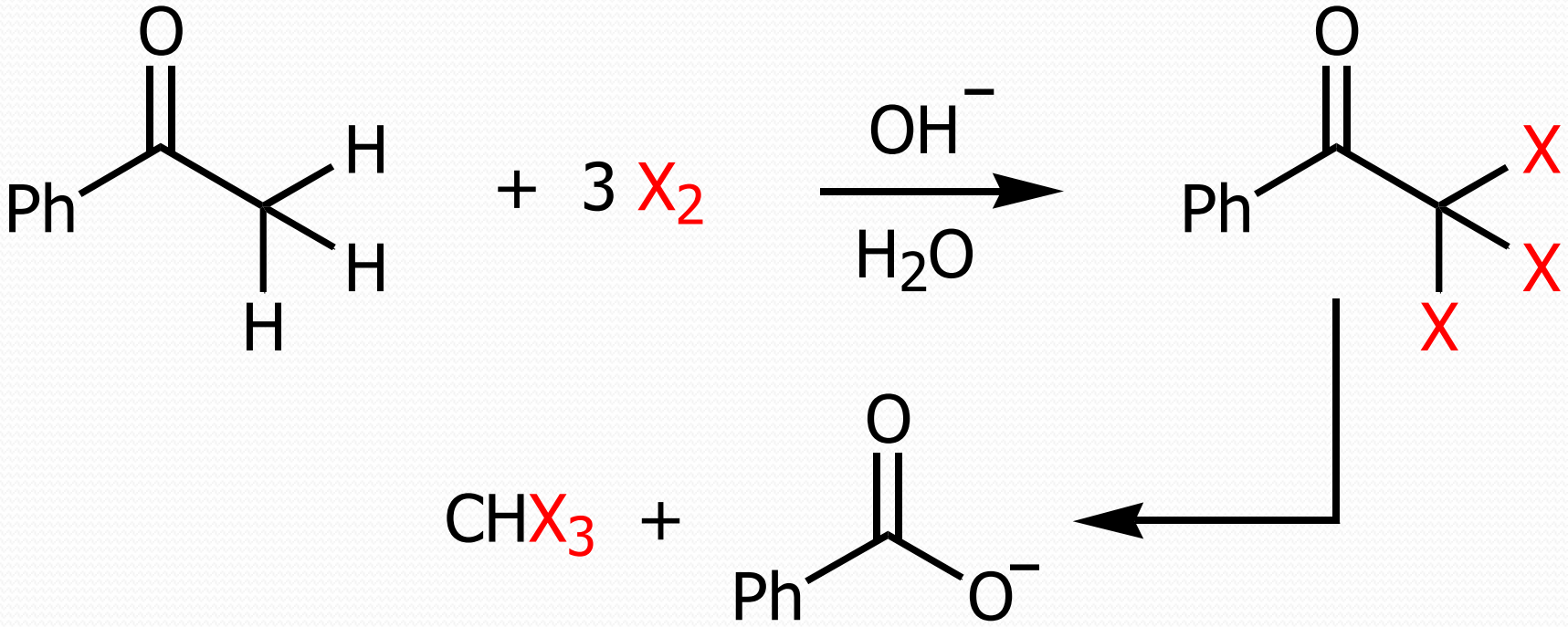
Racemization:



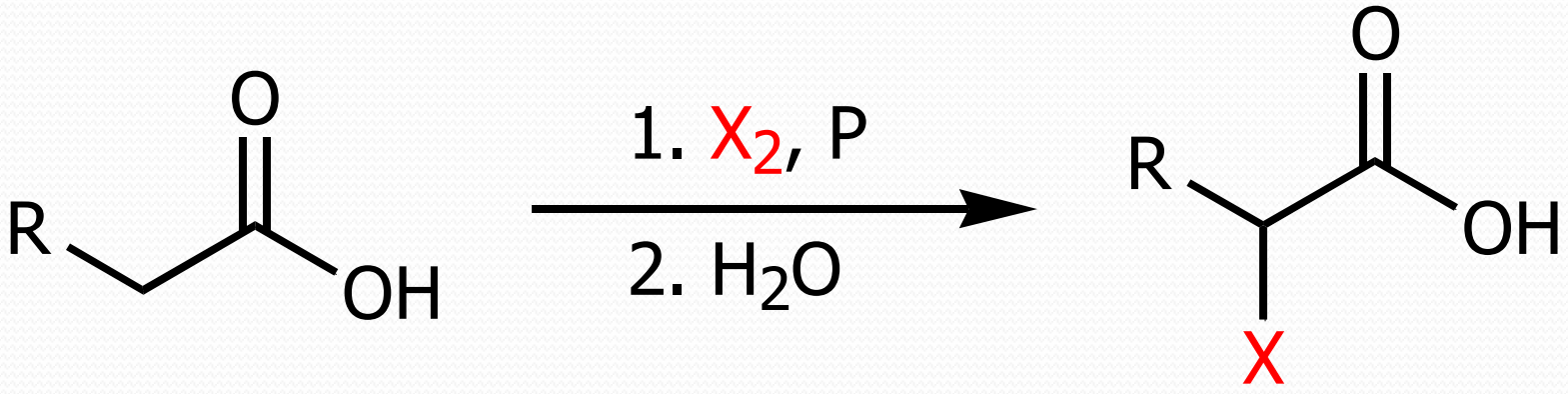
Halogenation of Aldehydes & Ketones:



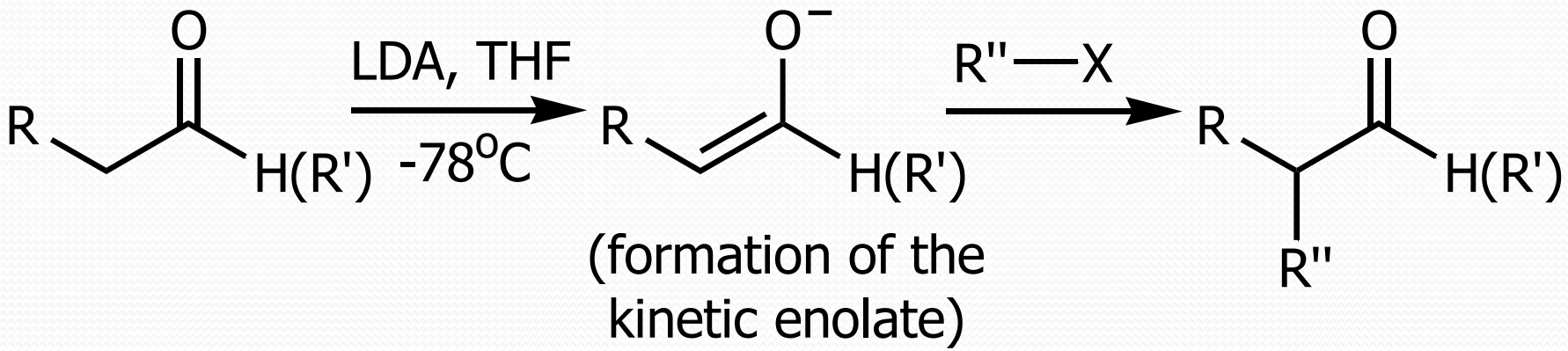
Specific example: haloform reaction:



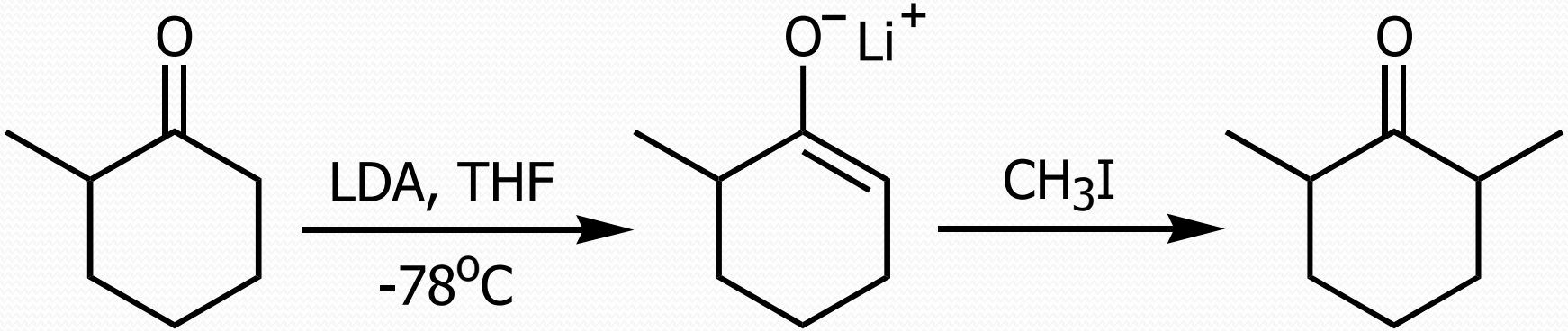
Halogenation of Carboxylic Acids: The HVZ Reaction:



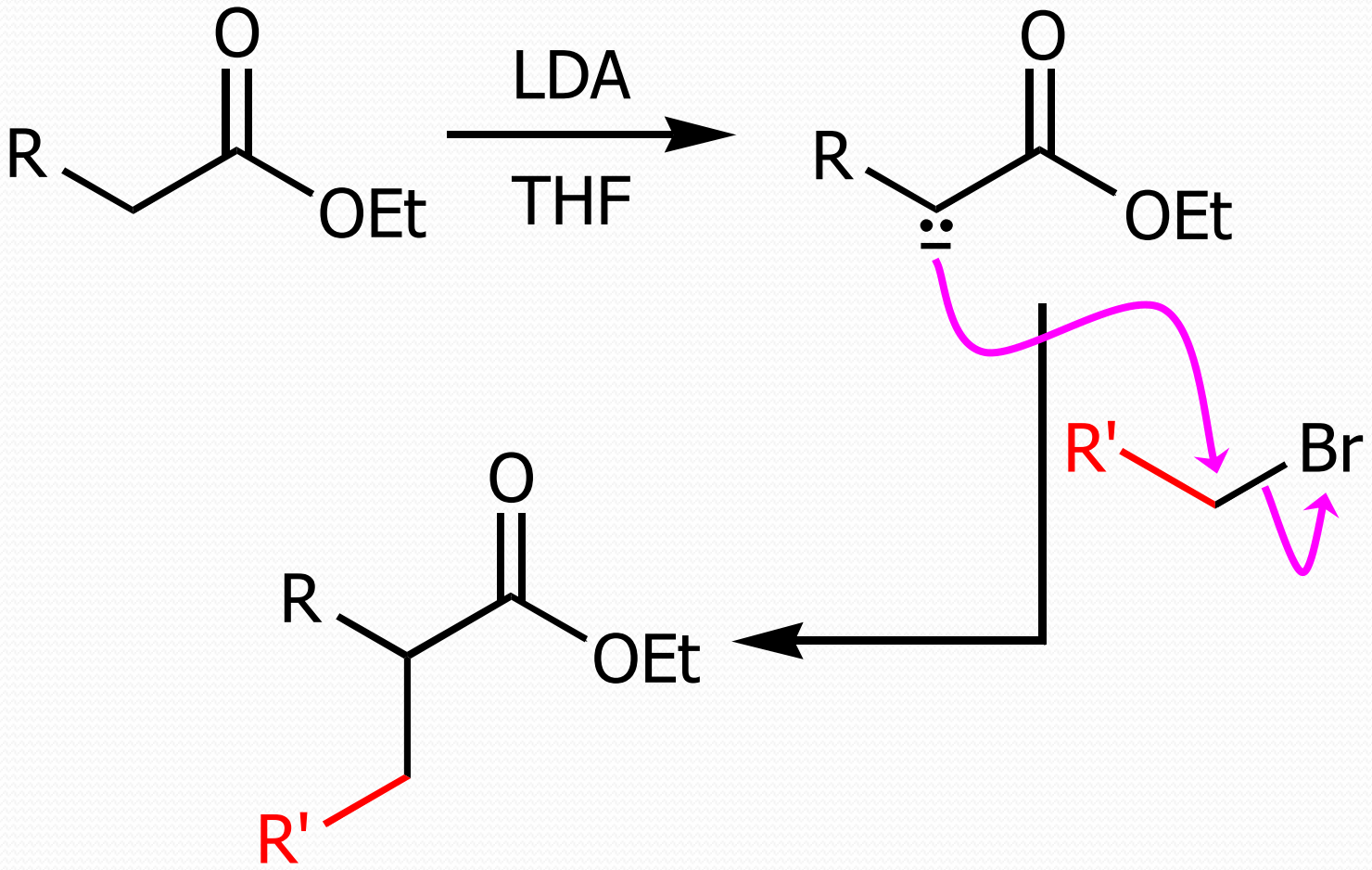
Direct Alkylation via Lithium Enolates:



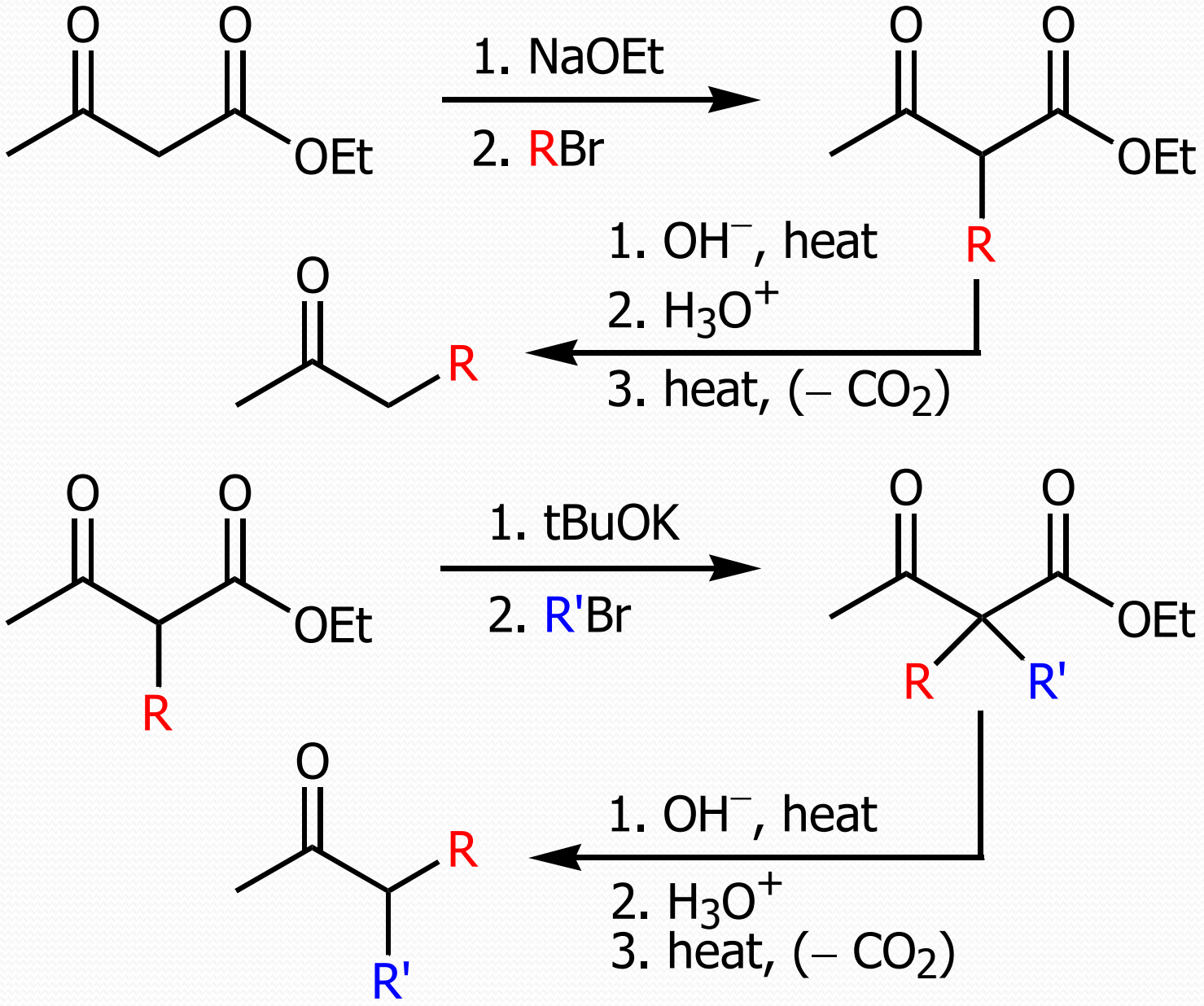
Specific example:



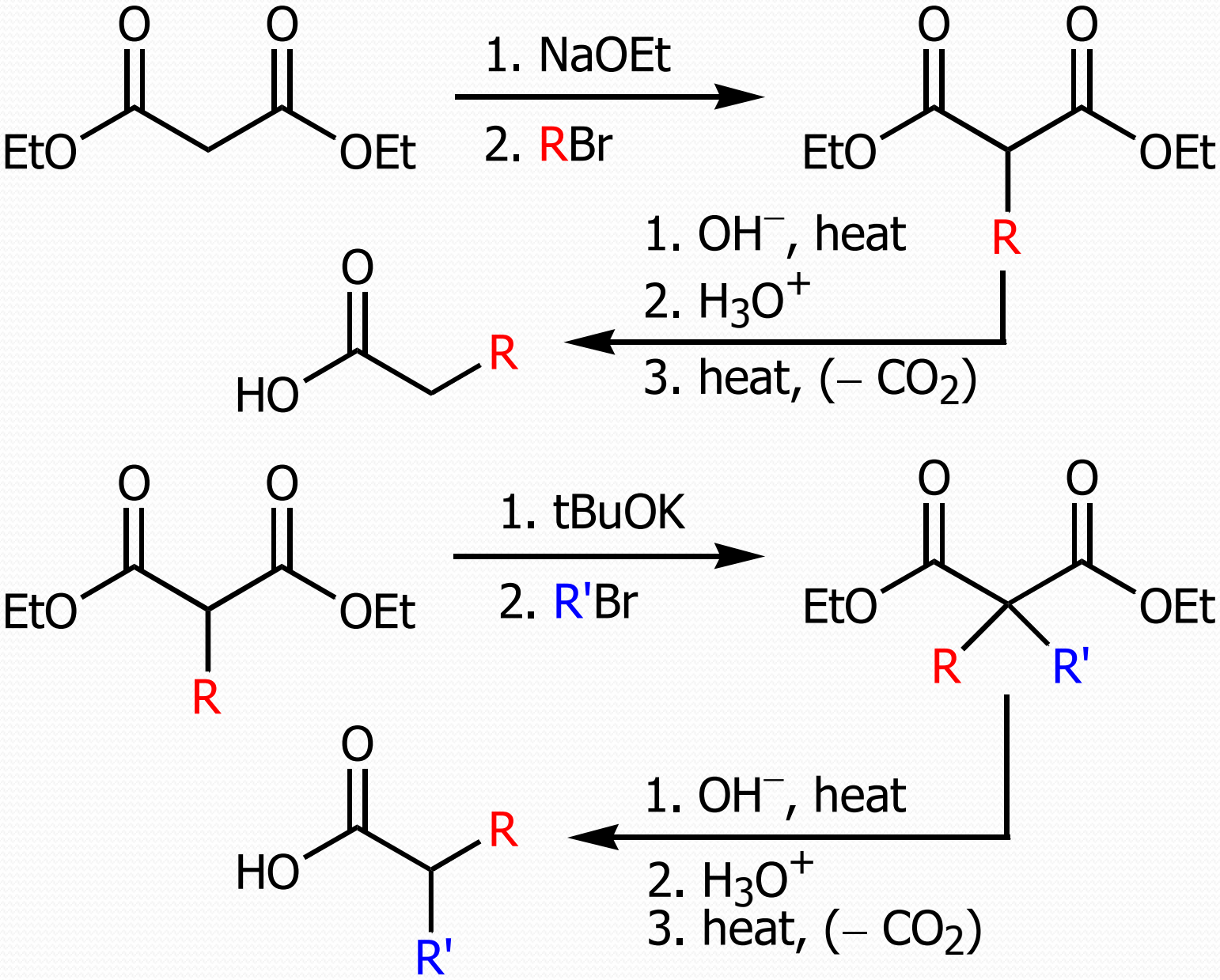
Direct Alkylation of Esters:



Acetoacetic Ester Synthesis:



Malonic Ester Synthesis:



Stork Enamine Reaction: