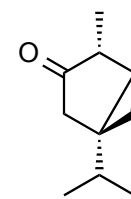


Chemistry 2600

Chapter 17

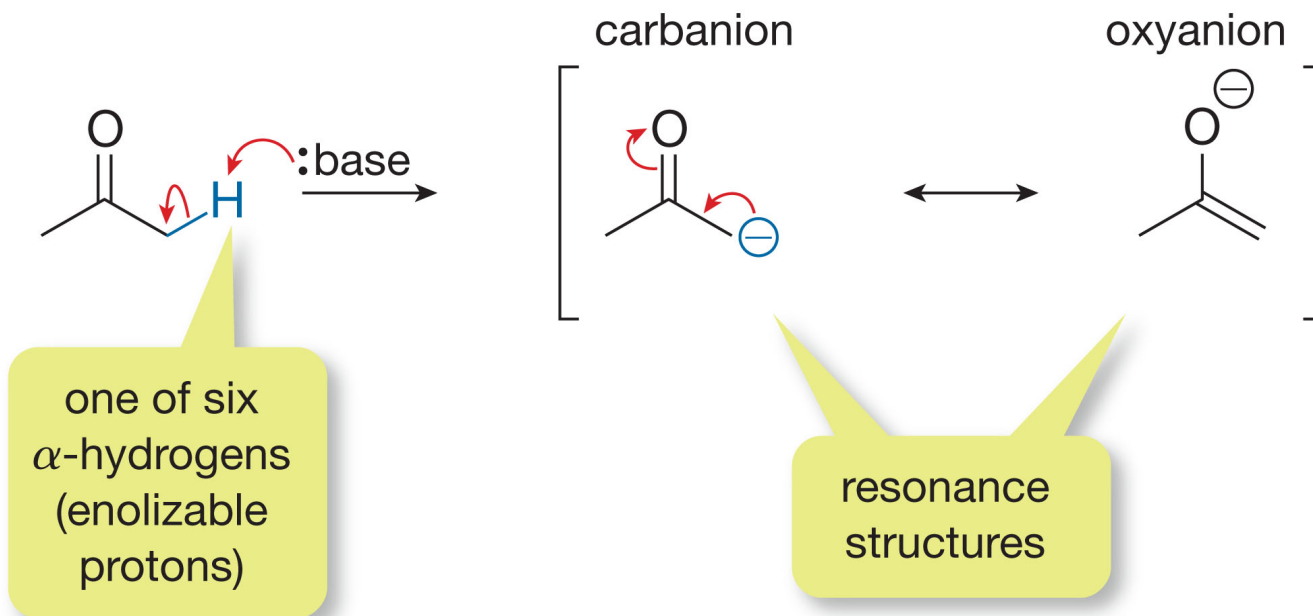
Carbonyl Based Nucleophiles

(sections 17.1-17.5 excluding 17.4.2)

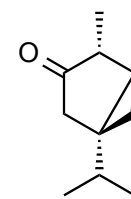


Enolates

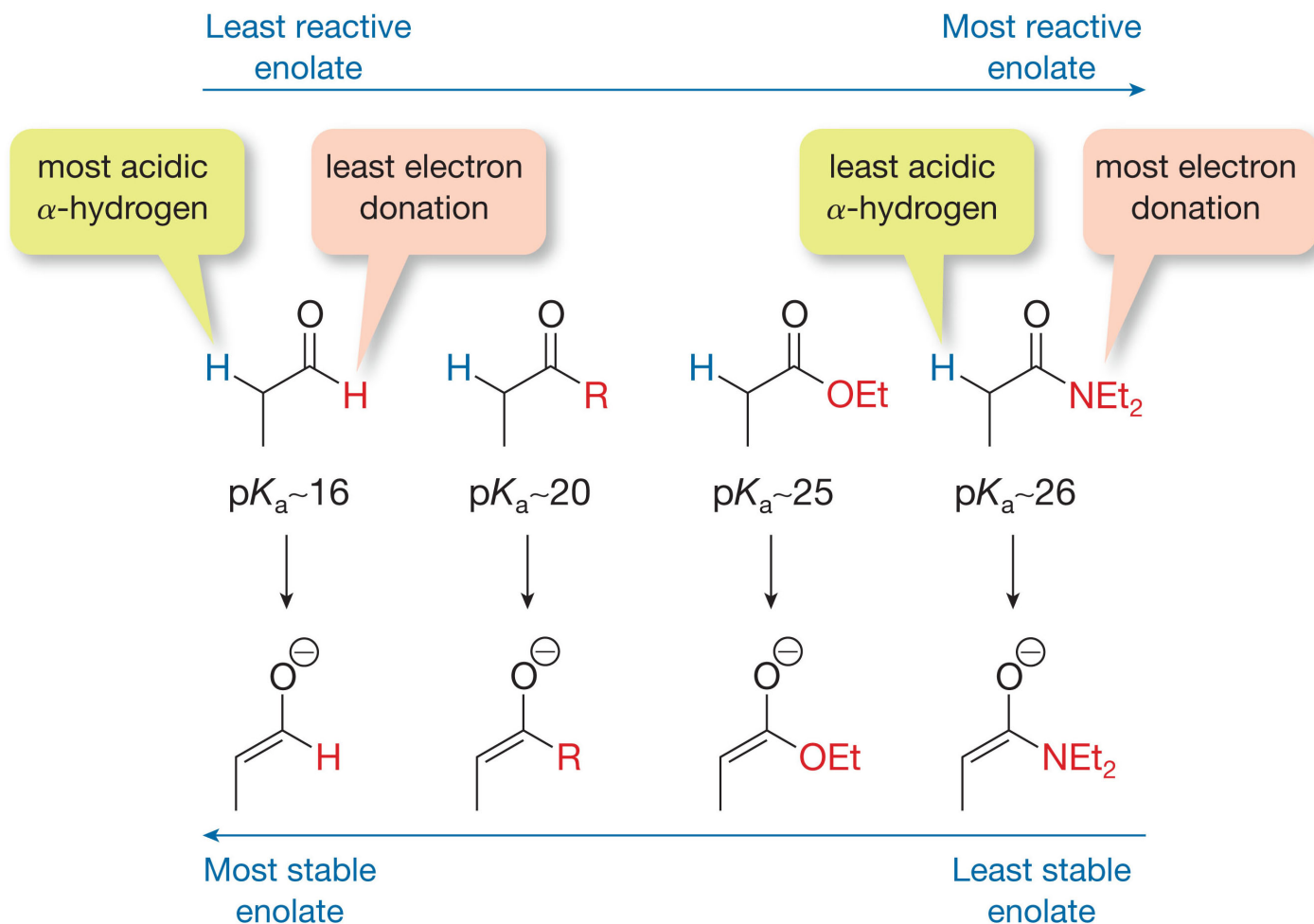
- In Chapters 7, 15, and 16, we saw how carbonyl groups are electrophiles in a variety of reactions.
- These groups can also act as nucleophiles by deprotonation of the hydrogen atoms on the α -carbon, giving a resonance stabilized **enolate**.



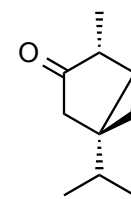
Enolates



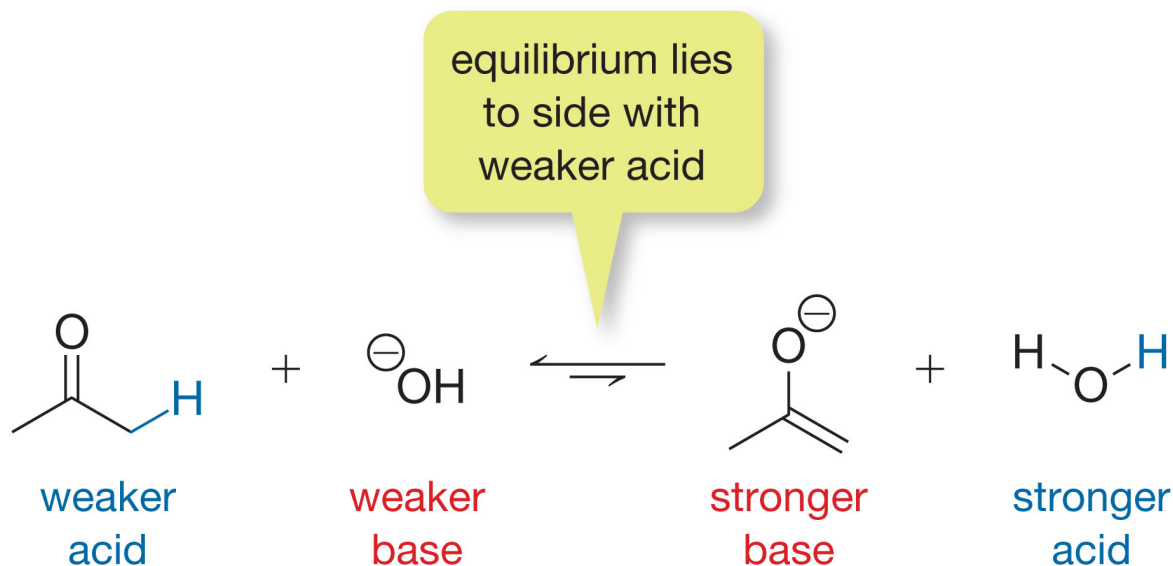
- The nature of the carbonyl group influences the acidity of the α -carbon.

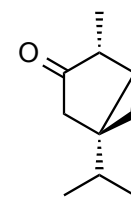


The Acidity of Carbonyl Compounds



- The choice of base used to generate an enolate is important.
- Hydroxide (OH^-) will generate only a small amount of the enolate as it is not a strong enough base.

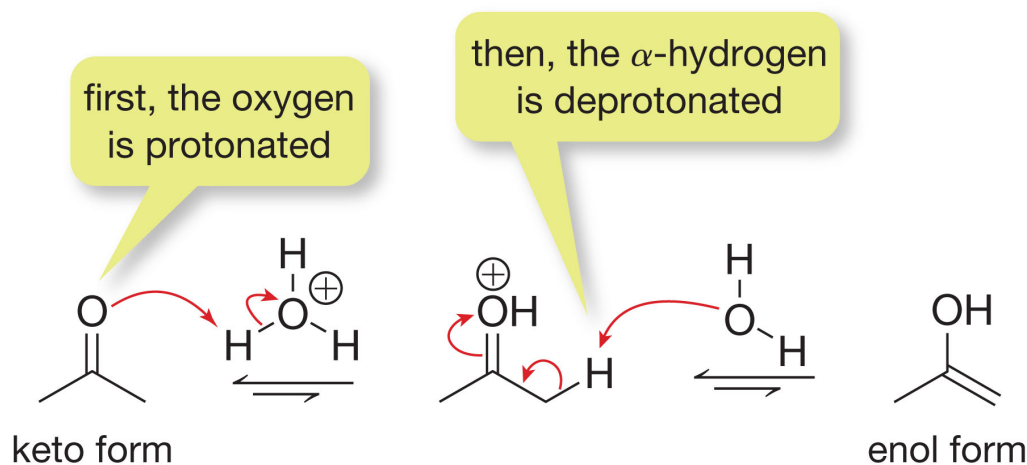




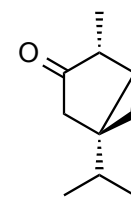
Keto-Enol Equilibria

- You have seen enolates before, in their neutral form, in Chapter 8. These are called **enols**.
- Recall that enols are in equilibrium with their much more favorable keto form.
- The keto-enol tautomerization is catalyzed in both acid and base.

Tautomerization in acid

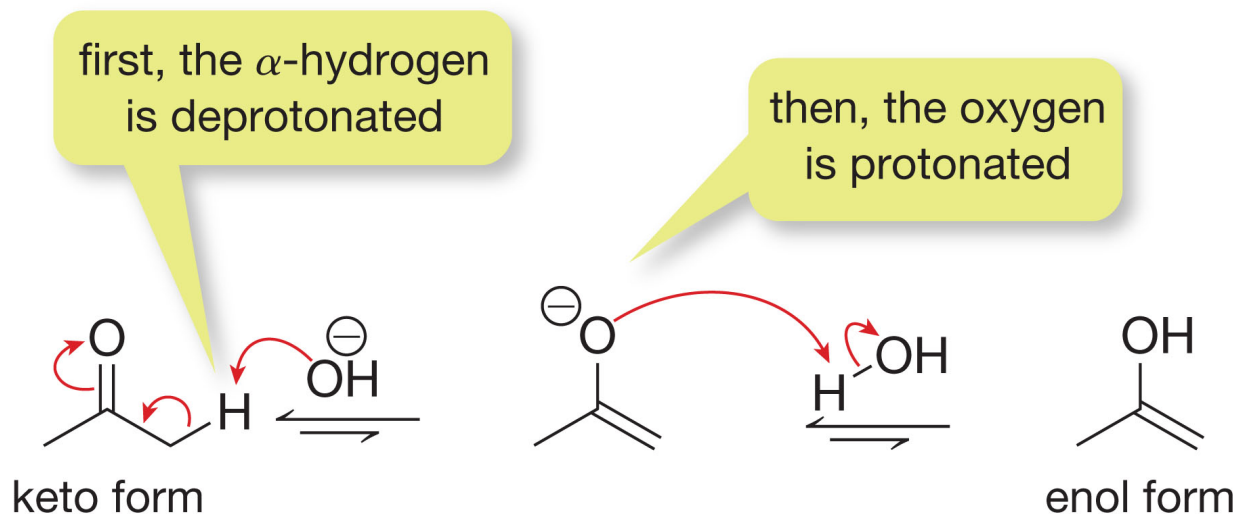


Keto-Enol Equilibria

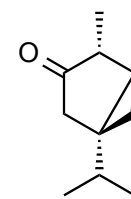


- The keto-enol tautomerization is catalyzed in both acid and base.

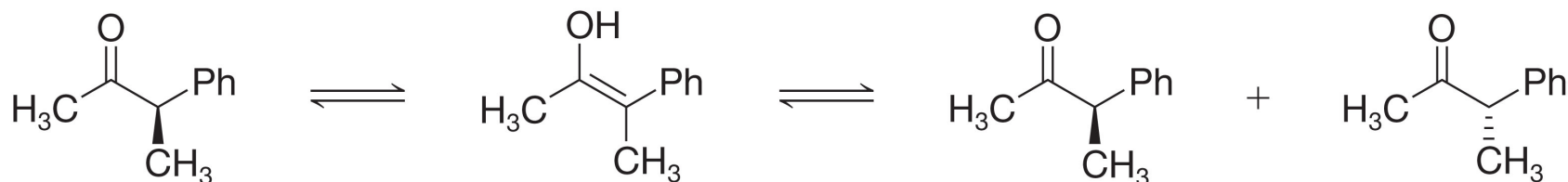
Tautomerization in base



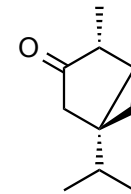
Keto-Enol Equilibria



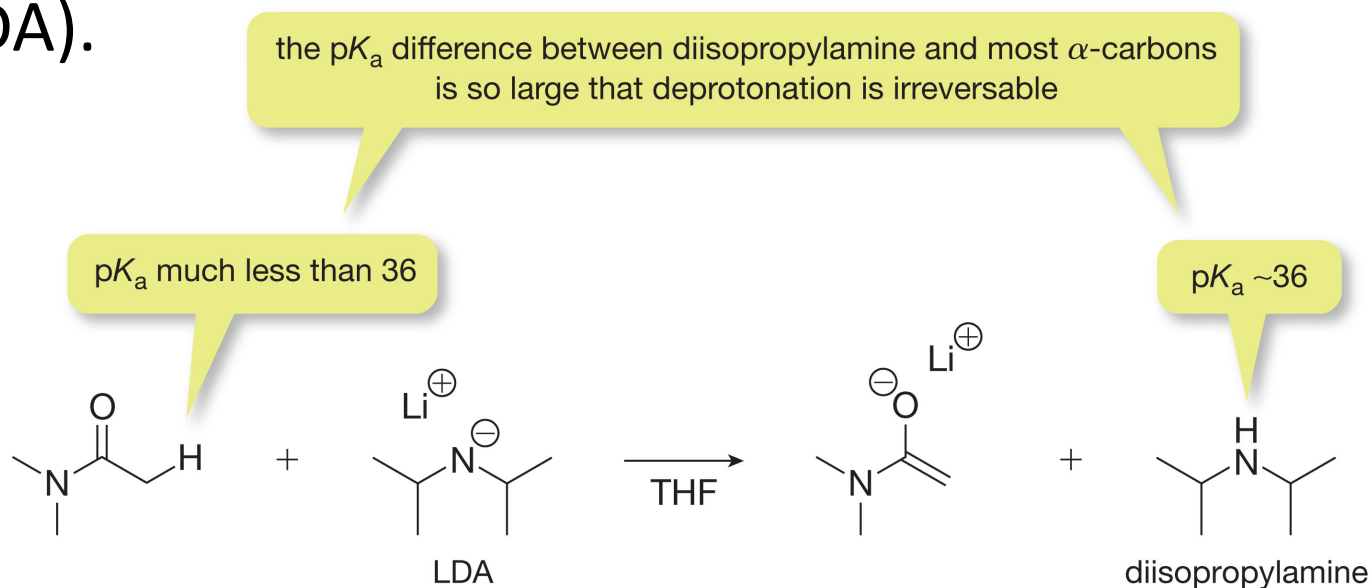
- Tautomerization is responsible for the slow racemization of carbonyl-containing compounds that form enols by deprotonation at a stereogenic centre.



Quantitative Formation of Enolates

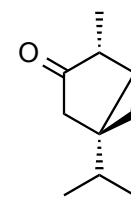


- In order to quantitatively convert a carbonyl group into its corresponding enolate, a strong base is required.
- Typically, sterically hindered nitrogen bases are used (e.g. LDA).



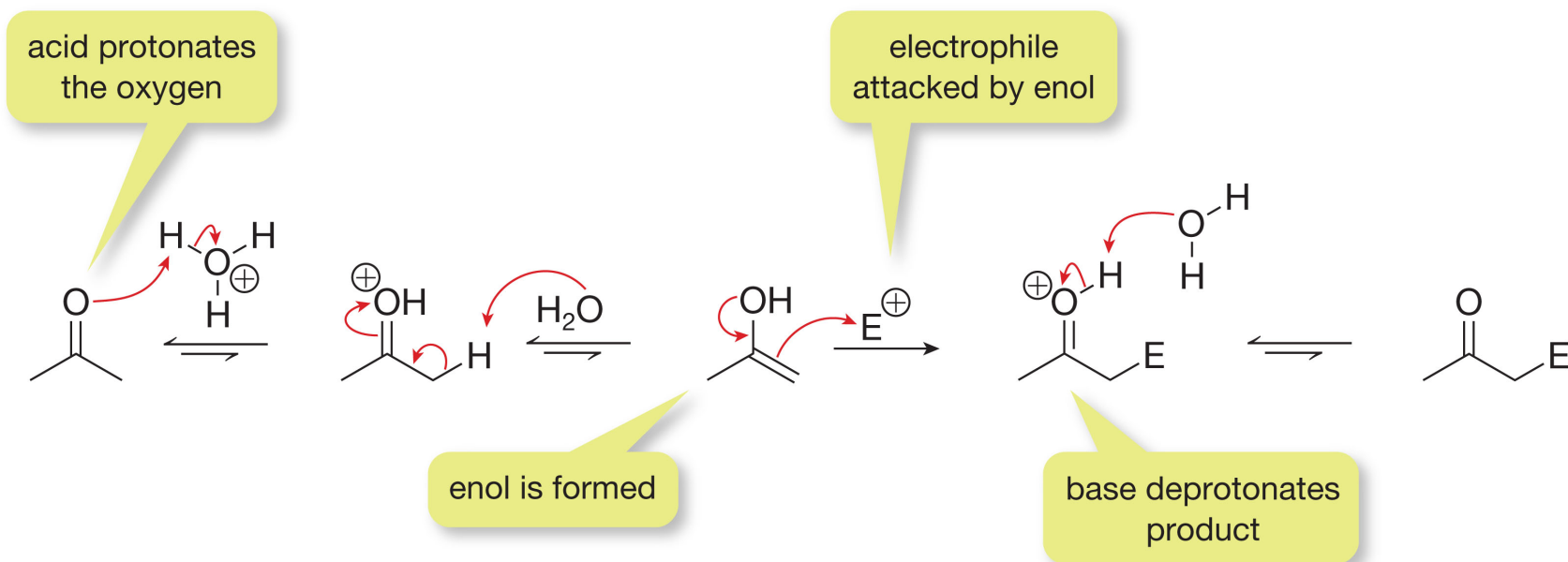
- In general, a pK_a difference of 10 or more results in quantitative deprotonation.

Reactions of Enolates with Electrophiles

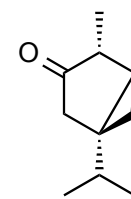


- The α -carbon of an enolate or enol is nucleophilic, and can add an electrophile and attach a new group.
- These reactions can be catalyzed by acid or base, although base catalysis is much more common.

Acid catalysis

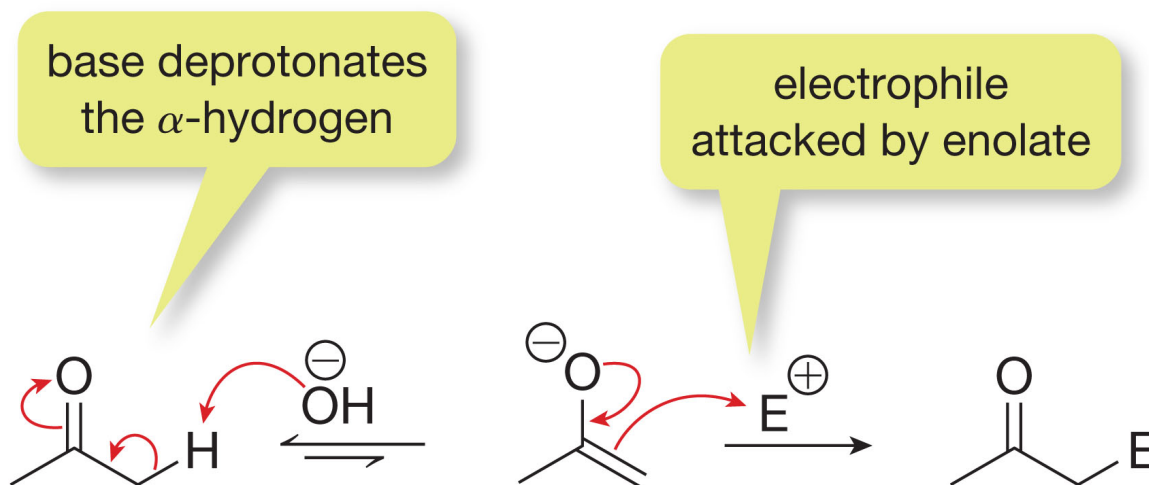


Reactions of Enolates with Electrophiles

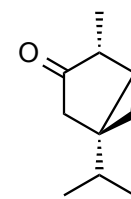


- The α -carbon of an enolate or enol is nucleophilic, and can add an electrophile and attach a new group.
- These reactions can be catalyzed by acid or base, although base catalysis is much more common.

Base catalysis

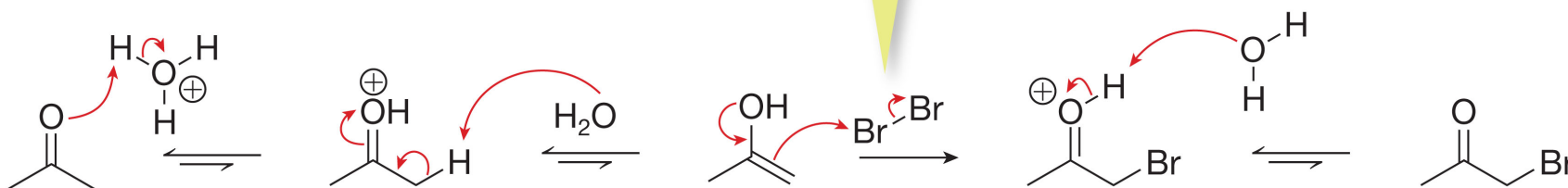


α -Halogenation of Carbonyl Compounds

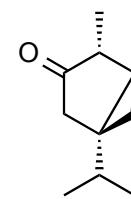


- Most carbonyl compounds can be halogenated at the α -carbon by replacing an α -hydrogen with a halogen.
- This reaction is best done under acidic conditions:

Acid catalysis

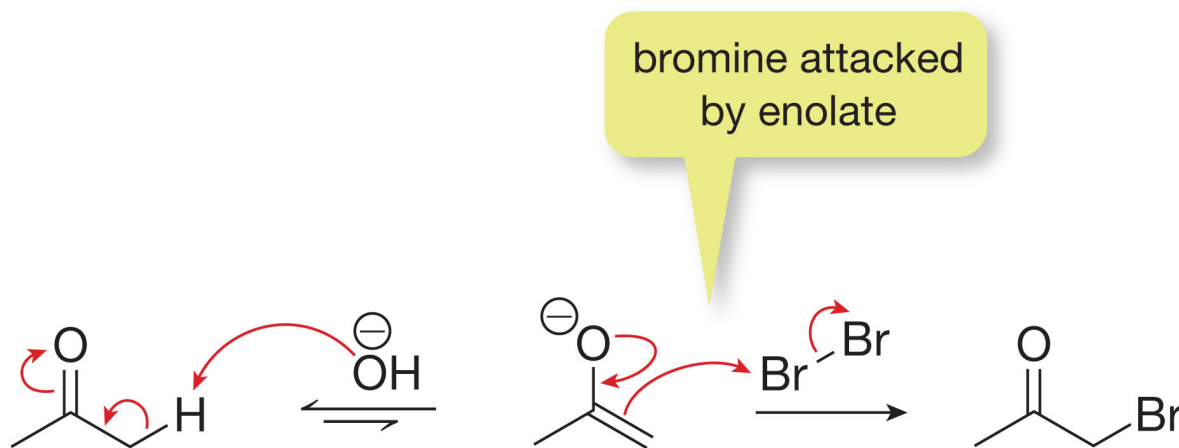


α -Halogenation of Carbonyl Compounds

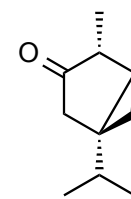


- Under basic conditions, the brominated product continues to react, producing a carboxylate.
- This reaction is known as the **haloform reaction** and is a useful method of making carboxylic acids from methyl ketones.

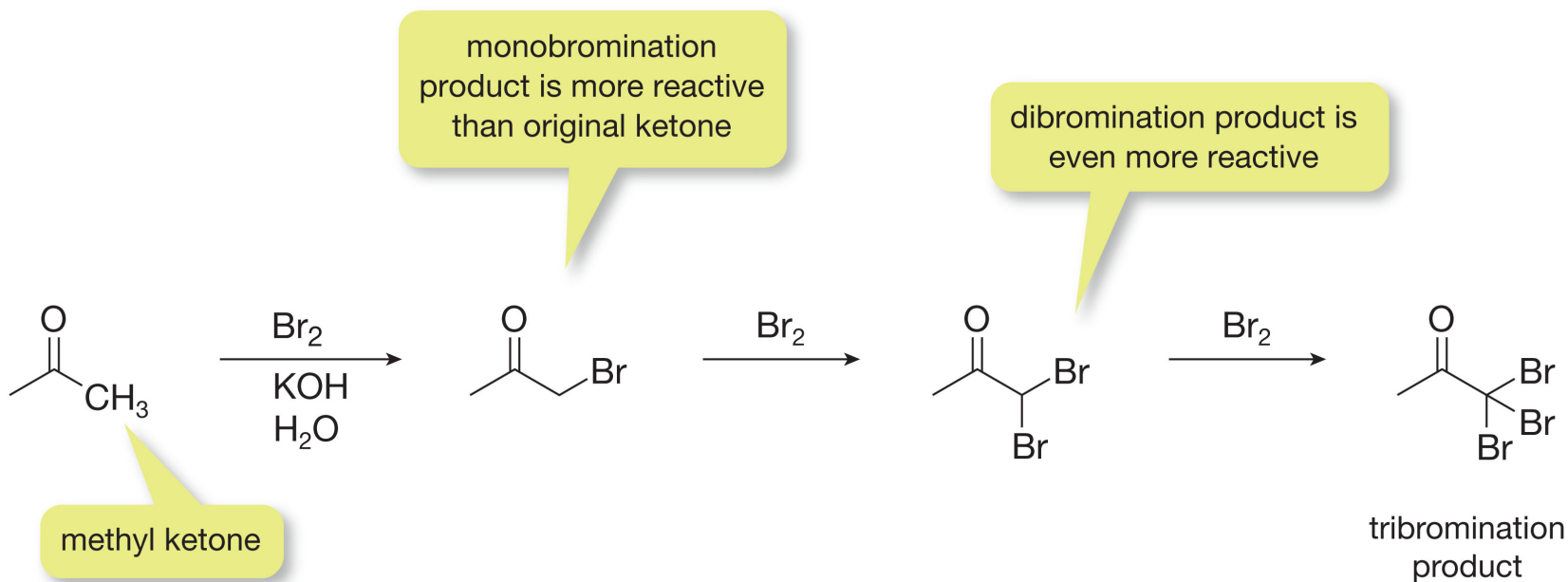
Base catalysis



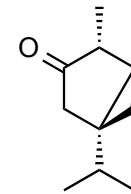
α -Halogenation of Carbonyl Compounds



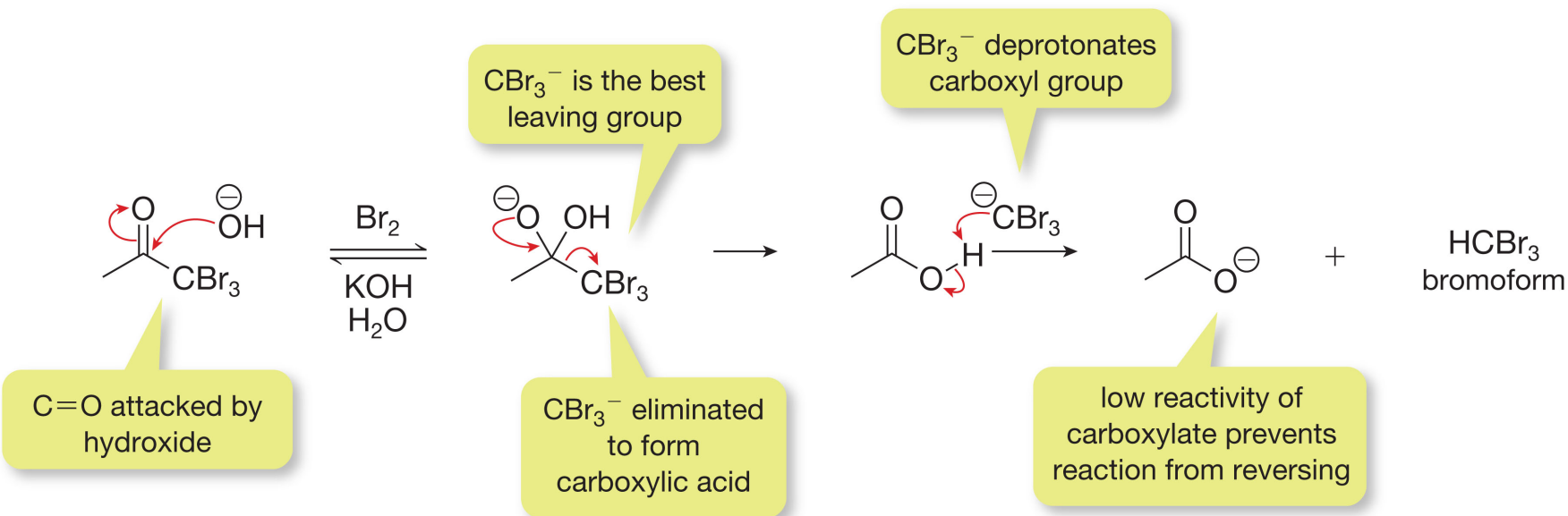
- The brominated product reacts with more base, generating another, more stable enolate.
- This continues until all α -hydrogen atoms have been replaced with halogens.



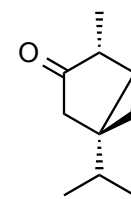
α -Halogenation of Carbonyl Compounds



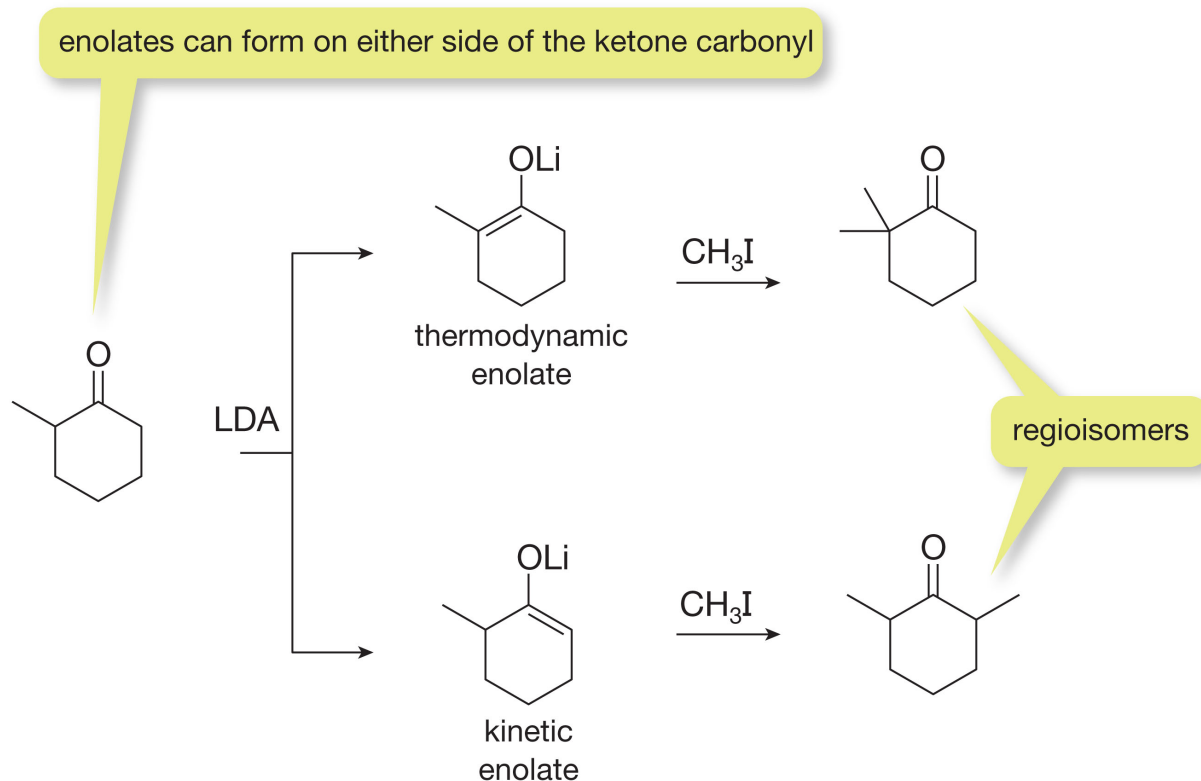
- The tribrominated product (a CAD!) undergoes an addition-elimination reaction with HO^- , giving the carboxylate.



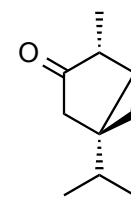
Alkylation of Enolates



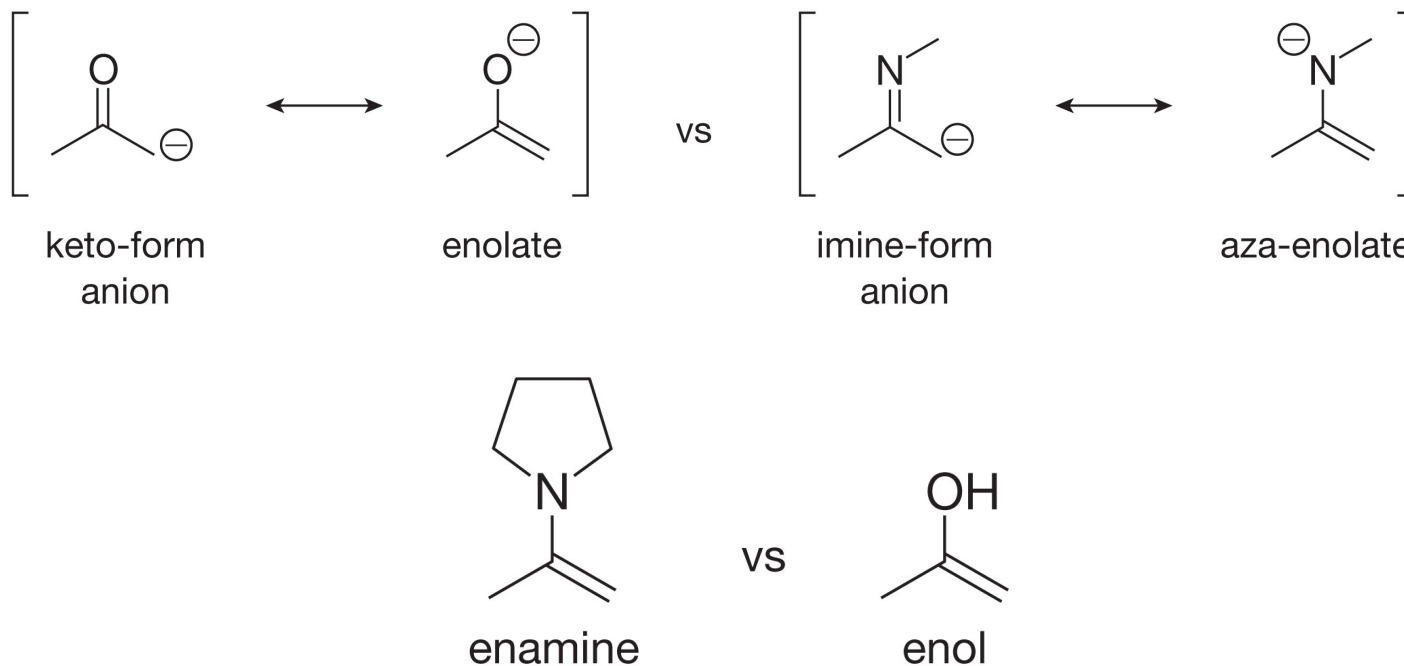
- Unsymmetrical ketones can make 2 different enolates, each leading to different alkylation products.
- Generally, conditions are chosen to form the less substituted enolate (the kinetic enolate).



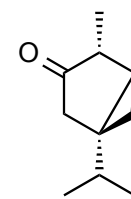
Alkylation of Enamines



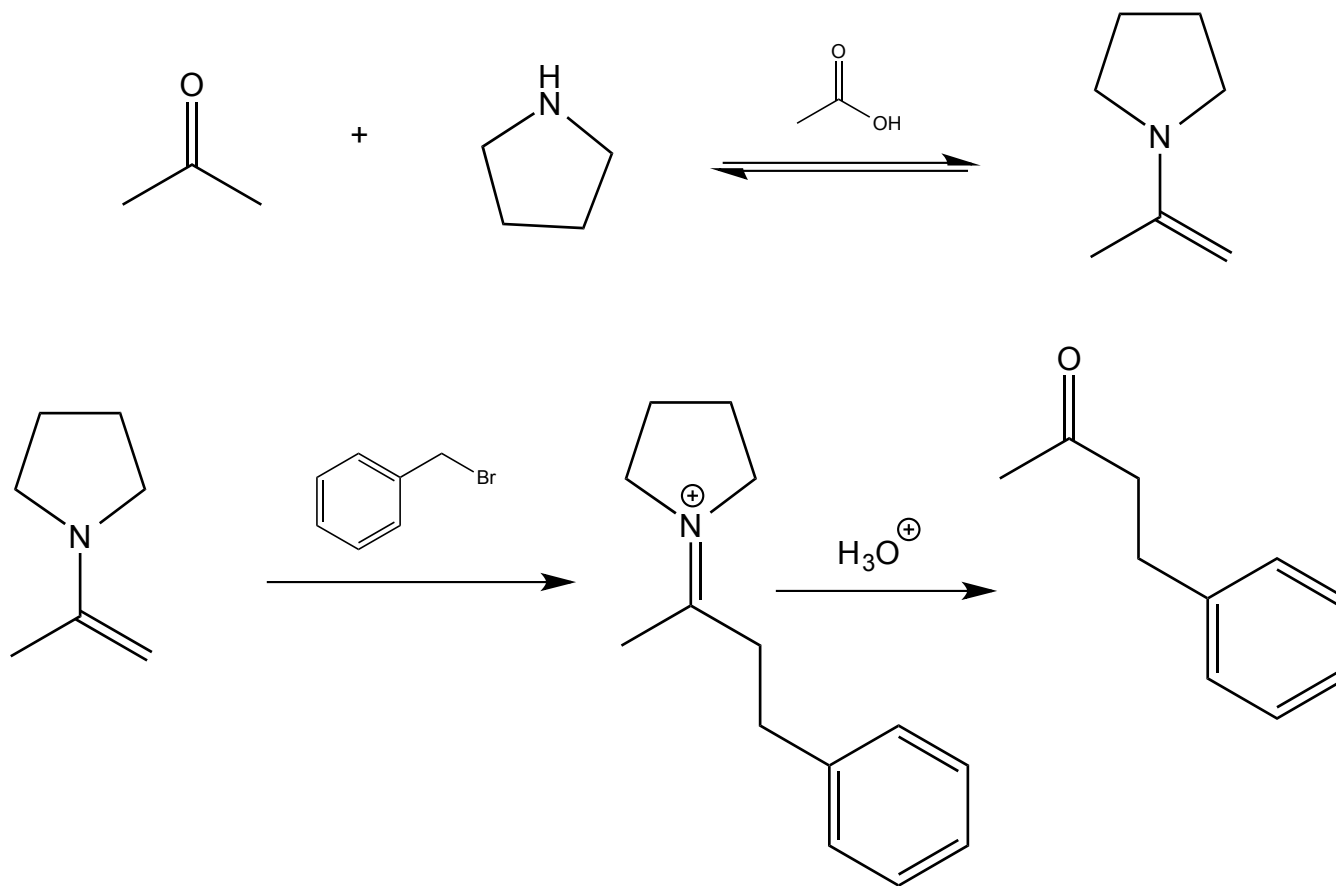
- Imines and enamines are electronically similar to ketones and enols and therefore can be used as equivalents of enols and enolates.



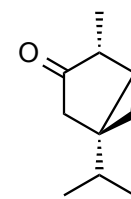
Alkylation of Enamines



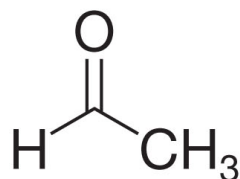
- Enamines are useful intermediates for alkylations of carbonyl compounds.



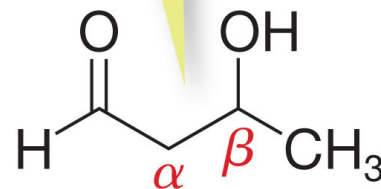
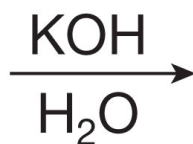
The Aldol Reaction



- An aldehyde stirred with base produces a compound that has double the molar mass of the original aldehyde.
- This product is an **aldol**, and is formed from an **aldol reaction**.

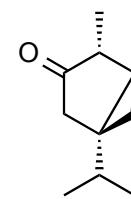


MW = 44 g/mol

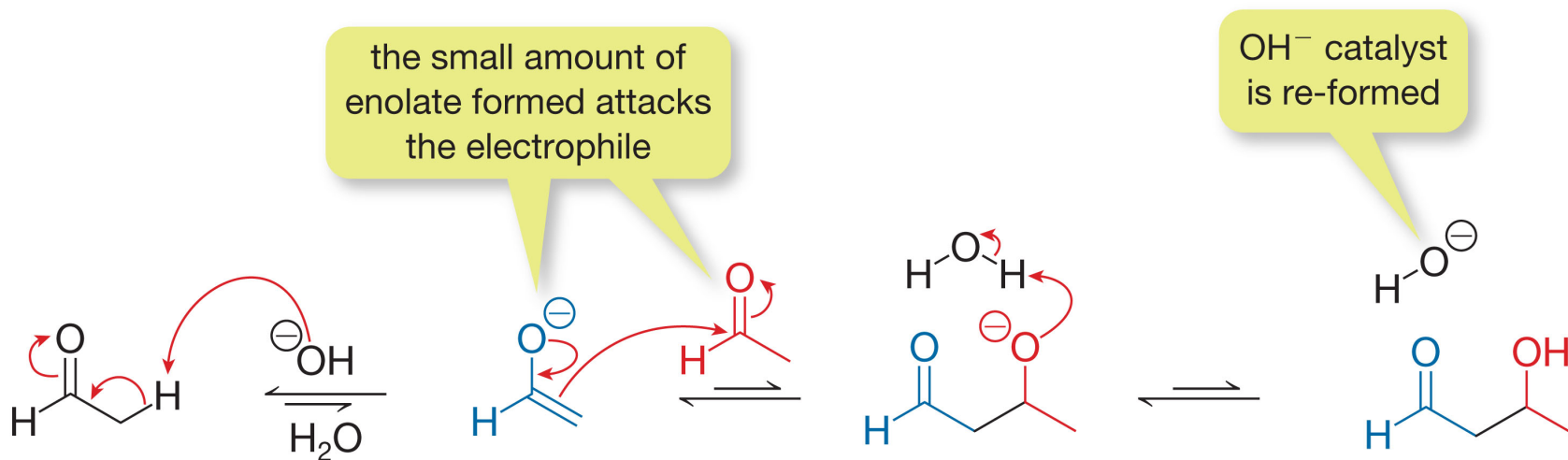


aldol
MW = 88 g/mol

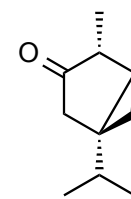
The Aldol Reaction



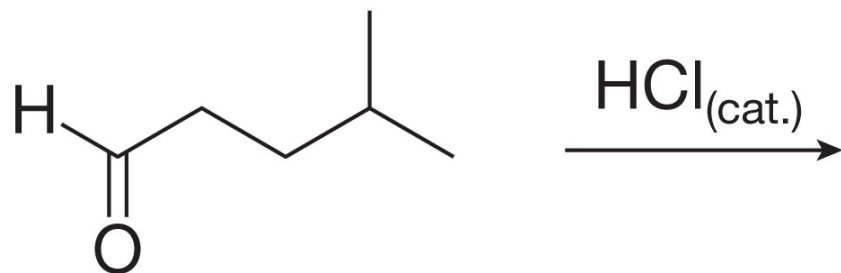
- In this reaction, two molecules of the same aldehyde acts as the nucleophile and the electrophile.
- This is known as self-addition.



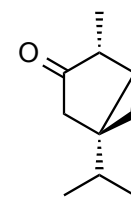
The Aldol Reaction



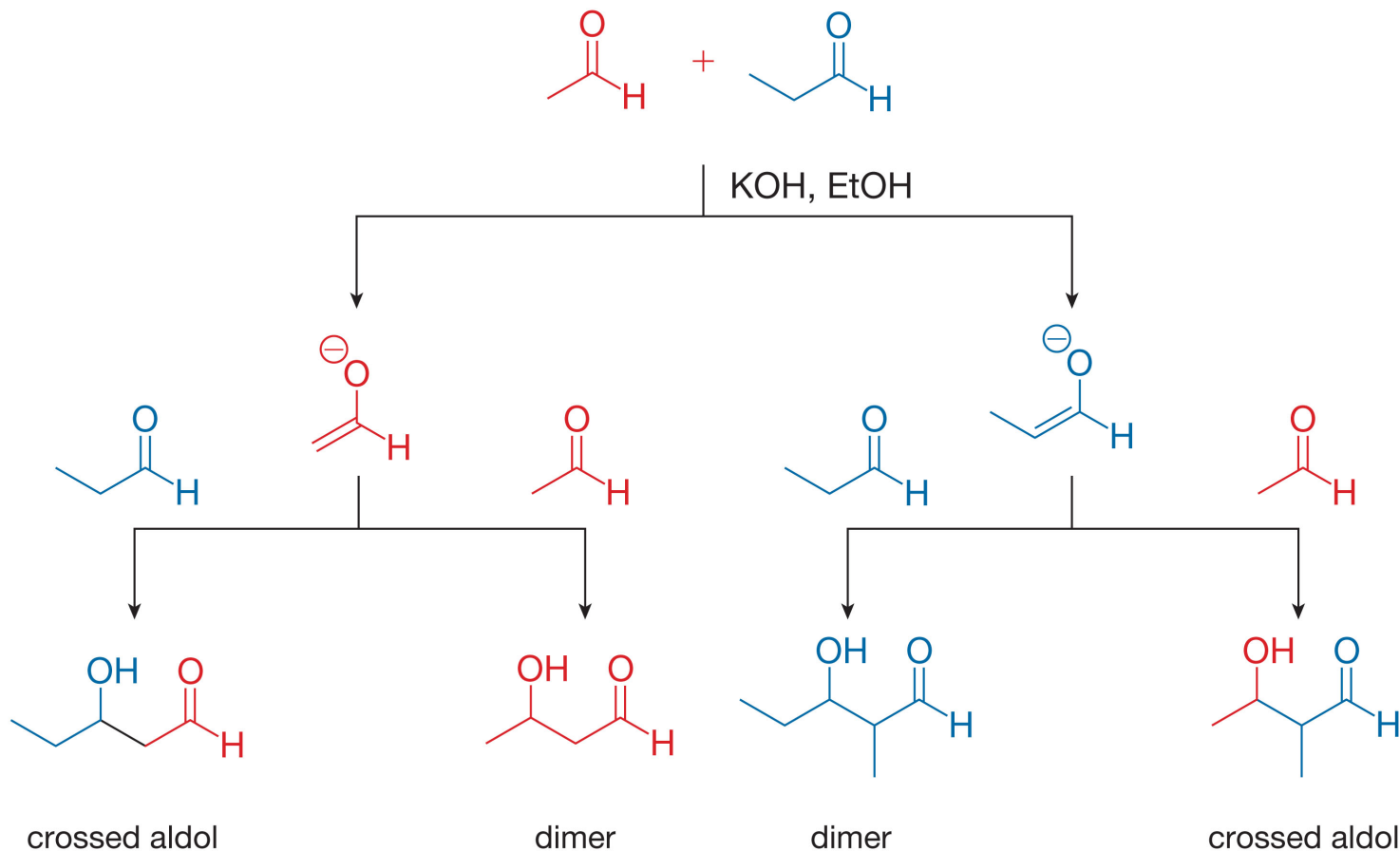
- The aldol reaction can also be performed under acidic conditions.
- Propose a mechanism for the following aldol reaction catalyzed in acid:



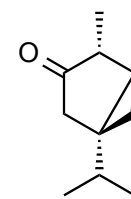
Crossed Aldol Reactions



- If two different aldehydes are combined with base, then a mixture of 4 different products can be formed.

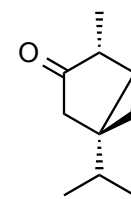


Crossed Aldol Reactions



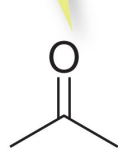
- With carefully chosen reagents, crossed aldol reactions can produce only one product.
- This is known as the **Claisen-Schmidt** reaction.
- In the Claisen-Schmidt reaction, an aldehyde with no α -hydrogen, is reacted with an enolizable ketone.
- Because aldehydes are more electrophilic than ketones, the enolate will only react with the aldehyde, giving one product.

Crossed Aldol Reactions

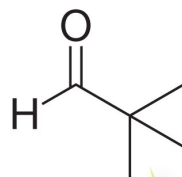


- The ***Claisen-Schmidt*** reaction.

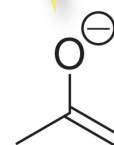
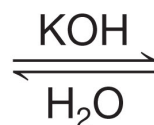
α -hydrogens are available, so can form an enolate



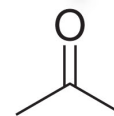
starting materials



only nucleophile present

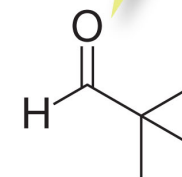


less reactive electrophile



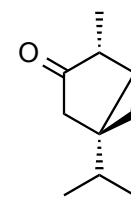
intermediate product mixture

more reactive electrophile

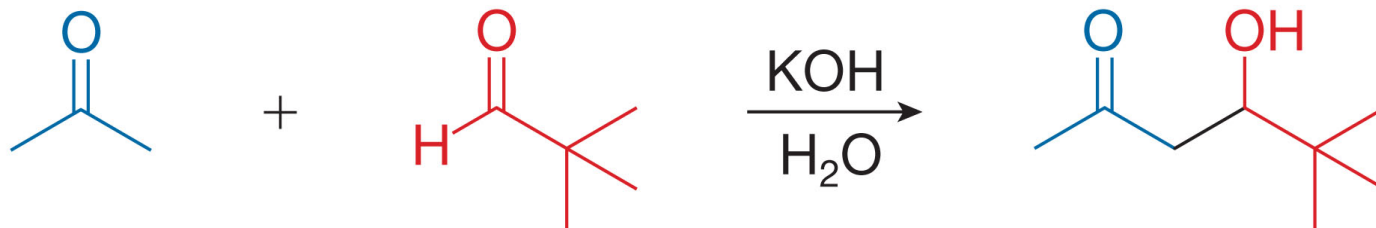
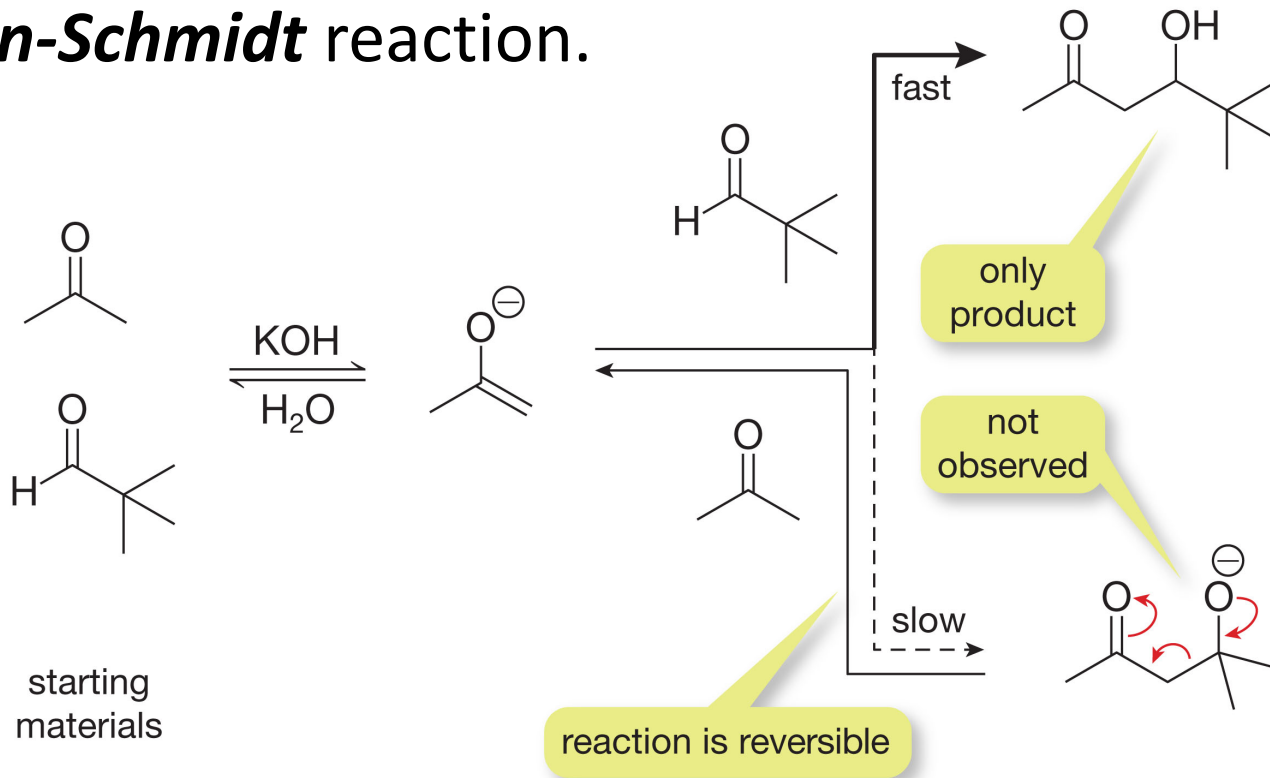


no α -hydrogens available, so cannot form an enolate

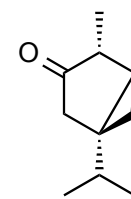
Crossed Aldol Reactions



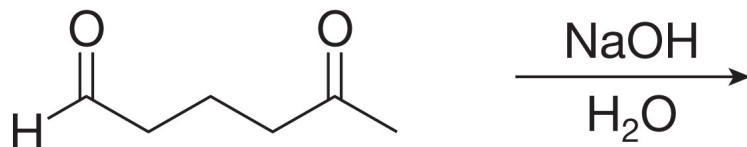
- The **Claisen-Schmidt** reaction.



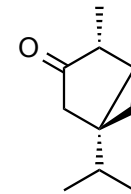
Intramolecular Aldol Reactions



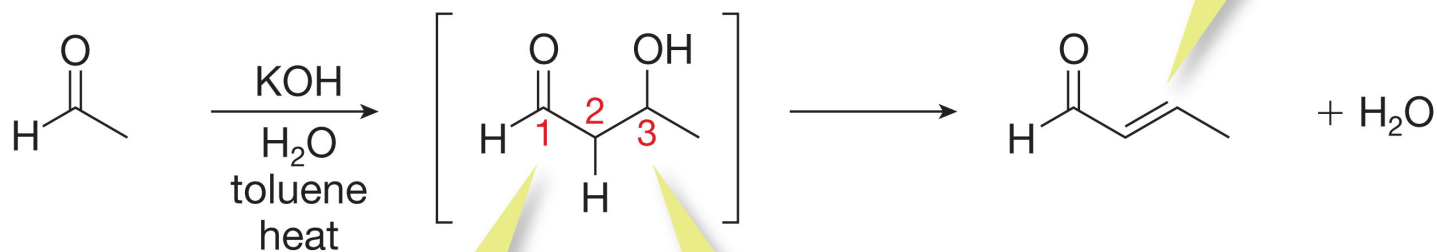
- Intramolecular aldol reactions are also possible, the products of which are cyclic molecules.
- If more than one product is possible, the reaction will favour the formation of 5- and 6-membered rings.
- Draw all possible products for the following reaction, and predict the major product(s).



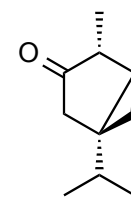
Aldol Condensation Reactions



- The aldol reaction produces a product that has a hydroxyl group in a 1,3 relationship with a carbonyl.
- Under certain conditions, this hydroxyl group (a β -hydroxy group), can act as a leaving group producing an α, β -unsaturated carbonyl in an **aldol condensation** reaction.

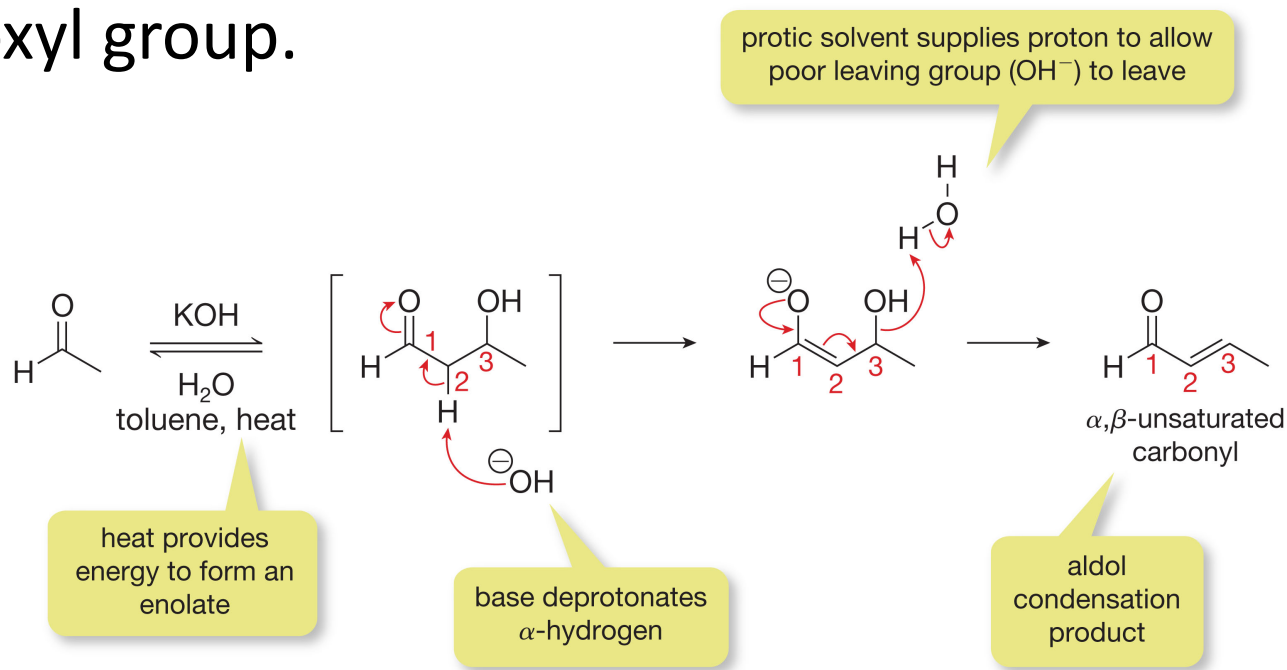


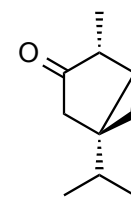
a 1,3 relationship between a heteroatom and a carbonyl group



Aldol Condensation Reactions

- Heating the reaction promotes β -elimination via a second enolate in a ***E1_{cb}* reaction** (elimination, unimolecular, conjugate base).
- In this mechanism, the enolate (conjugate base) is formed first in the RDS, then followed by loss of the hydroxyl group.



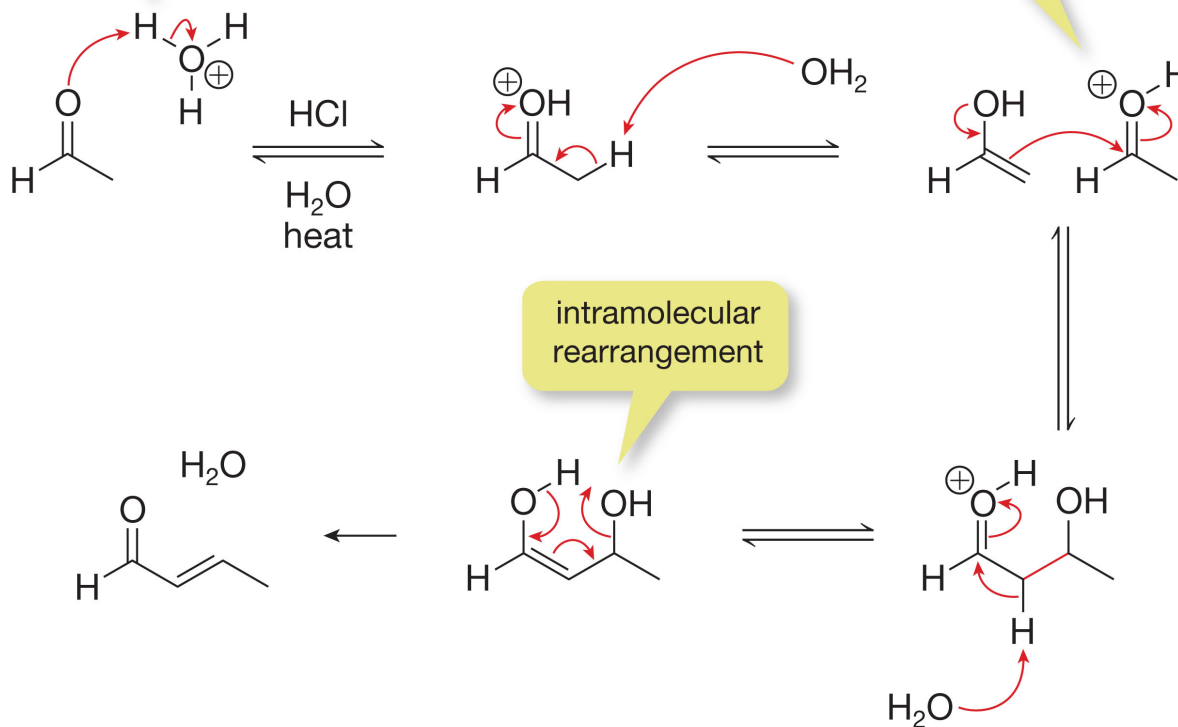


Aldol Condensation Reactions

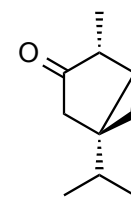
- Acid catalyzed aldols are prone to β -eliminations because good leaving groups are generated.

enol formation is assisted by acid

another molecule of the starting material is protonated and is attacked by enol



Claisen Condensation



- In a Claisen condensation reaction, an enolate generated from an ester undergoes self-addition similar to that in an aldol reaction.

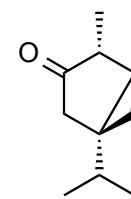
Claisen condensation



Aldol addition

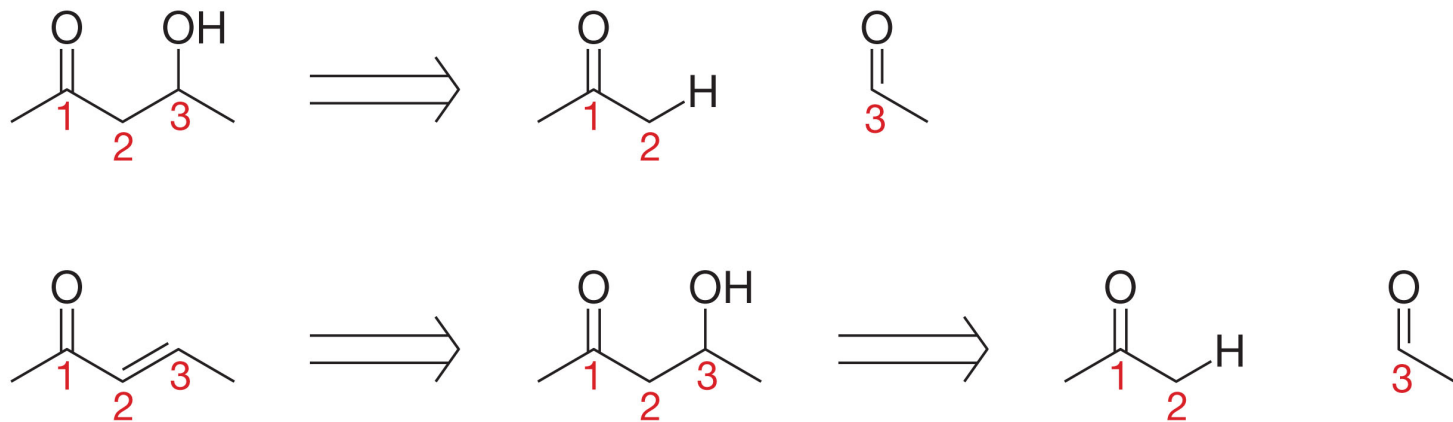


- Propose a mechanism for the above Claisen condensation reaction.

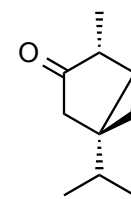


Retrosynthetic Analysis of Adols

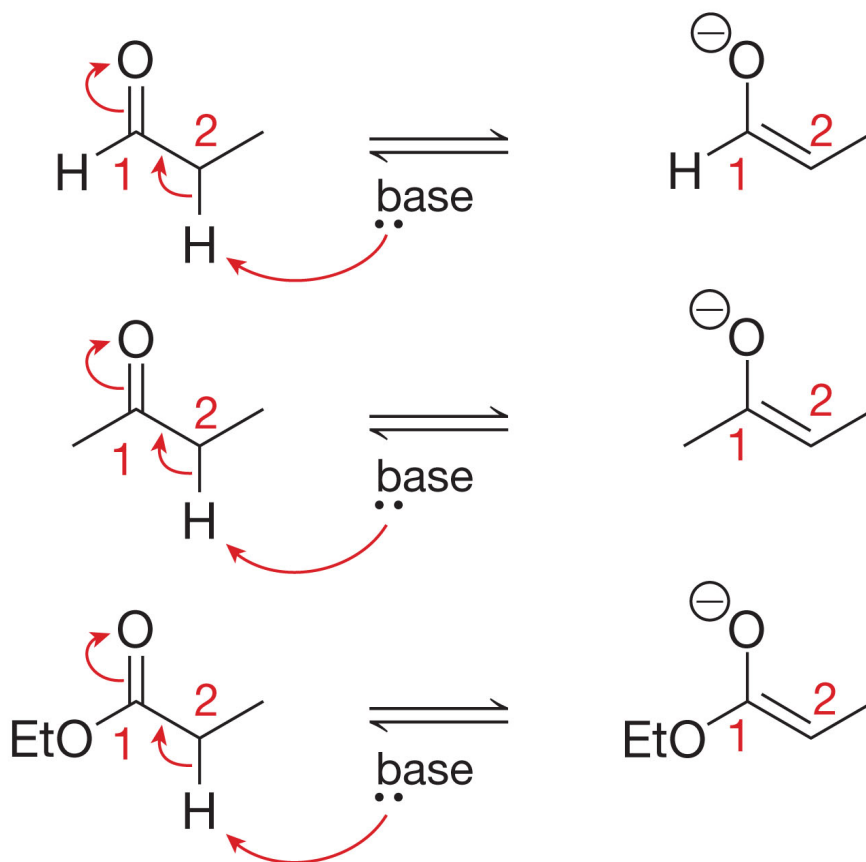
- Aldol reactions produce molecules with a hydroxy group β to a carbonyl.
- Aldol condensation reactions produce α, β -unsaturated carbonyl.
- Both are produced from an enolate and a carbonyl group.



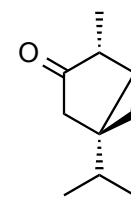
Patterns in Enolate Chemistry



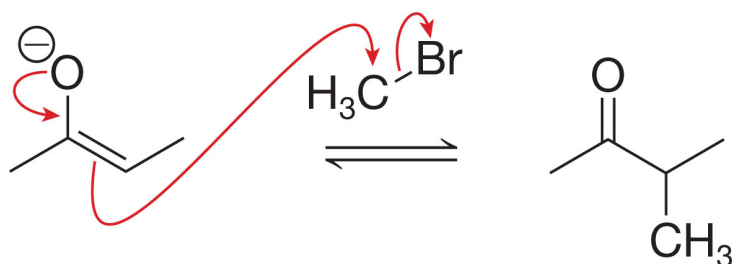
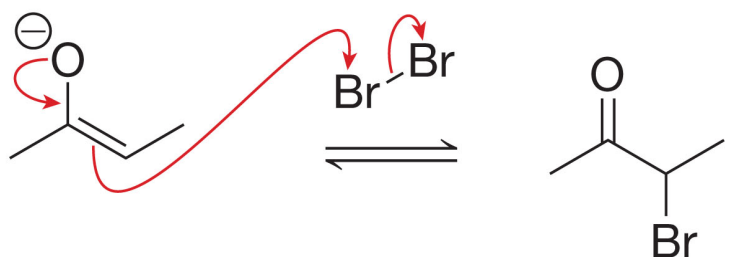
- The α -hydrogen of various carbonyl groups is relatively acidic and can be deprotonated to generate an enolate conjugate base.



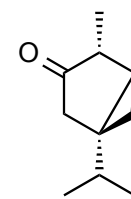
Patterns in Enolate Chemistry



- Enolates are nucleophilic and react with a variety of different electrophiles.

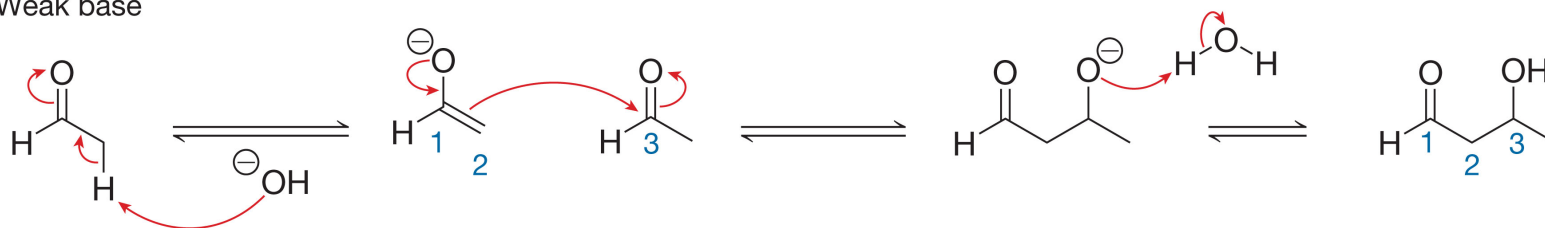


Patterns in Enolate Chemistry



- Enolates are nucleophilic and react with a variety of different electrophiles.

Weak base



Strong base

