

# CFQ & PP: Carbonyl Chemistry: Enolates and Enols

## Reading

Brown and Foote: Sections 16.11, 16.12 and 19.1 - 5

## Optional Web Site Reading

Enolates (<http://www.colby.edu/chemistry/OChem/DEMOS/Enolates.html>)

## Suggested Text Exercises

Brown and Foote: Chapter 16: 46 – 53

Chapter 19: 1 – 6, 18 – 45, 53 - 63

## Optional Interactive Organic Chemistry CD and Workbook

Supporting Concepts: Enolate (p. 73)

Mechanisms: Acid-Catalyzed Alpha Halogenation of a Ketone (p. 18)

Base-Catalyzed Aldol Reaction (p. 21)

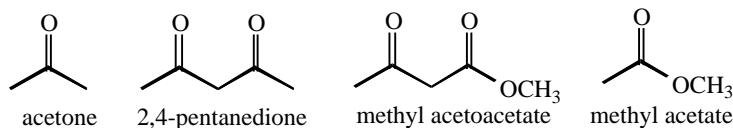
Base-Promoted Alpha Halogenation of a Ketone (p. 22)

Claisen Condensation (p. 23)

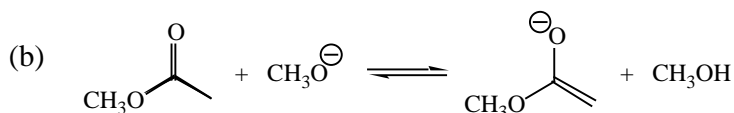
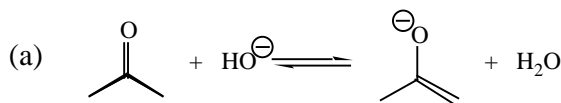
Dieckmann Condensation (p. 24)

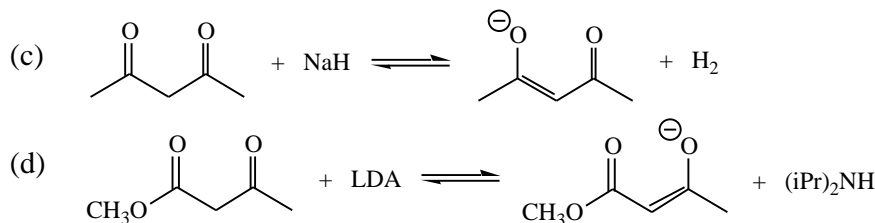
## Concept Focus Questions

1. Briefly explain why acetone ( $pK_a$  20) is more acidic than propane ( $pK_a$  ~50).
2. Draw all the significant resonance contributors as well as the resonance hybrid for the most stable enolate of 3-methyl-2-butanone (isopropyl methyl ketone).
3. Rank the following compounds in order of  $pK_a$  and briefly explain your logic.



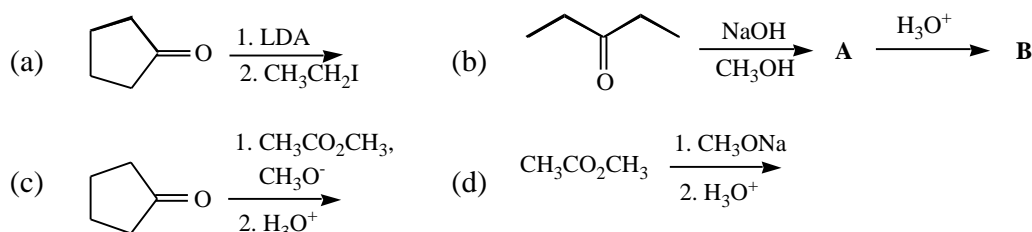
4. Draw the structure of LDA. Why is this base used in many instances instead of hydroxide or methoxide?
5. Predict the position of each equilibrium. In which cases will the enolate condense with the carbonyl compound from which it was derived?



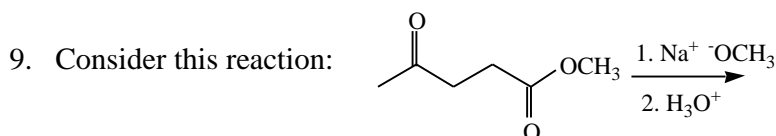


6. Hydroxide ( $\text{HO}^-$ ) and alkoxide ions ( $\text{RO}^-$ ) do not function as leaving groups, except in certain circumstances where some reaction feature results in reduction of activation energy. Give two distinctly different cases where these ions may be leaving groups. Illustrate each with a specific example that includes a mechanism.

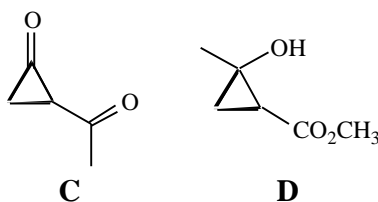
7. Give the product of each reaction. Be prepared to provide mechanisms as well.



8. What is the driving force for the conversion of product **A** into product **B** in reaction 7(b) above?



- (a) Determine the major product of this reaction and write a mechanism for its formation.
- (b) Cyclopropanes **C** and **D** may also be products of this reaction. Write mechanisms that show how they might be formed, and explain why they are, in fact, not observed as products of this reaction.

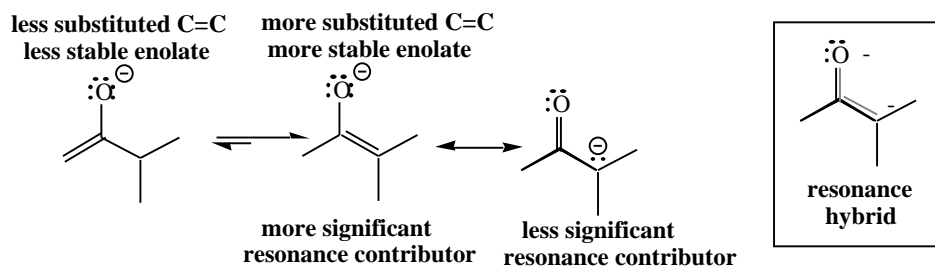


10. Briefly describe the most significant similarity and difference between enolates and enols.

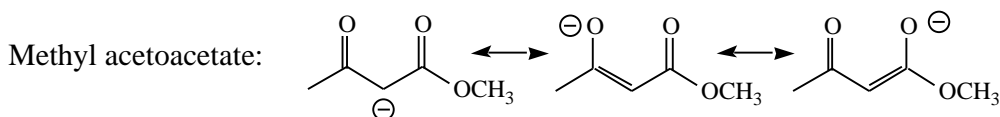
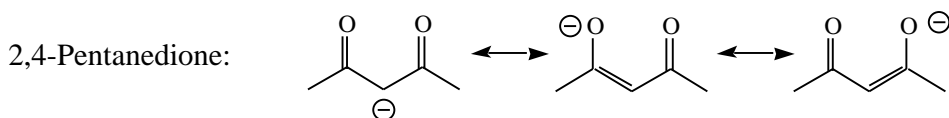
- Write mechanisms for the acid and base-catalyzed conversions of acetone into the corresponding enol.
- Draw the structure of a simple enamine and explain why it is a nucleophile. Illustrate its nucleophilicity in a reaction with  $\text{CH}_3\text{I}$ .

### Concept Focus Questions Solutions

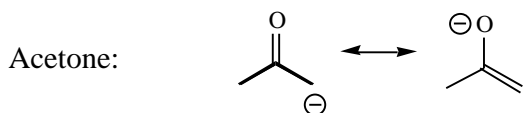
- Acetone is more acidic (lower  $\text{pK}_a$ ) than propane because the conjugate base of acetone (the enolate) has significant resonance stabilization, whereas the conjugate base of propane (the propyl carbanion) has no resonance stabilization. Bases that are more stable (weaker bases) are derived from stronger conjugate acids.
- Enolates are structurally similar to alkenes, and follow the same rules for relative stability. In this case, the most stable enolate is the more highly substituted enolate.

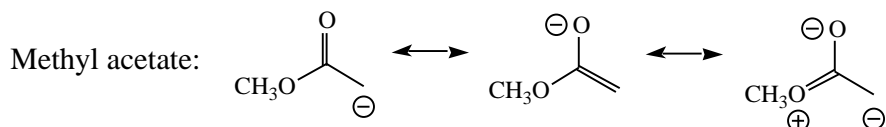


- $\text{pK}_a$  values may be ranked by considering the stability of the conjugate bases. Everything else being equal, an enolate with a greater number of significant resonance contributors will be more stable than an enolate with a lesser number of significant resonance contributors. The enolates of 2,4-pentanedione and methyl acetoacetate each have three significant resonance contributors.

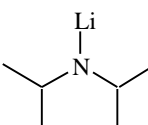


The enolates of acetone and methyl acetate each have only two resonance contributors.





The ester methoxy group donates electron density to the adjacent carbonyl group by resonance. This decreases the carbonyl's ability to accept electron density from elsewhere in the molecule, especially the neighboring negative charge. Thus, the methoxy group destabilizes the adjacent negative charge. (It is also correct to say that because the methoxy group donates electron density by resonance, it increases the magnitude of the negative charge, and thus destabilizes the enolate.) Listing the enolates in order of decreasing stability: 2,4-pentanedione enolate (most stable) > methyl acetoacetate enolate > acetone enolate > methyl acetate enolate (least stable). More stable conjugate bases have stronger conjugate acids. Therefore the  $pK_a$  order is: 2,4-pentanedione (most acidic; lowest  $pK_a$ ) < methyl acetoacetate < acetone < methyl acetate (least acidic; highest  $pK_a$ ). Actual data: 2,4-pentanedione  $pK_a$  9, methyl acetoacetate  $pK_a$  11, acetone  $pK_a$  20, methyl acetate  $pK_a$  25.

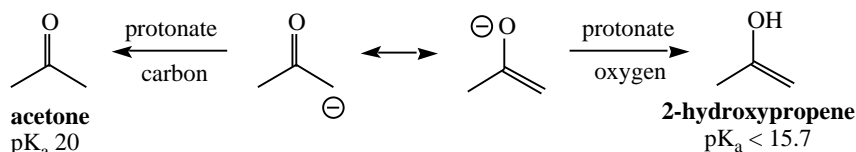
4. LDA is an abbreviation for lithium diisopropyl amide: 

Hydroxide and methoxide ions may undergo nucleophilic addition to the carbonyl group in competition with deprotonation to form an enolate. The isopropyl groups of LDA make it too sterically hindered to attack the carbonyl carbon, but not so hindered that it cannot remove a proton. Thus LDA functions as a base without also undergoing addition to the carbonyl group. In addition, LDA is a much stronger base than hydroxide or methoxide ( $iPr_2NH$   $pK_a$  36,  $H_2O$   $pK_a$  15.7,  $CH_3OH$   $pK_a$  15.5). Consider the equilibrium between the carbonyl compound, the base, and the enolate. When LDA is used as the base, the equilibrium will favor the enolate by orders of magnitude. If hydroxide or methoxide is used, the equilibrium will lie mostly to the side of the carbonyl compound; the concentration of enolate will be small. Thus, LDA is often used in reactions where it is desirable to have complete conversion of the carbonyl compound to the corresponding enolate.

5. Any equilibrium favors the most thermodynamically stable side. In the case of a proton transfer equilibrium, the most stable side is the weakest acid/base pair. Thus, we can determine the position of the equilibrium by comparing  $pK_a$  values of the acids. (The weakest acid always lies on the same side as the weakest base.) Recall that the magnitude of the equilibrium constant can be estimated as the difference in the  $pK_a$  values of the acids. (Review your general chemistry text or the Acids and Bases CFQ as needed.)

(a) Acetone (typical ketone  $pK_a$  20) is a weaker acid than water ( $pK_a$  15.7). The equilibrium lies to the left with  $K_{eq} = 10^{-4.3}$

That acetone is less acidic than water seems contrary to what we have learned about the effects of resonance on acidity. We might predict that acetone enolate is less basic than hydroxide ion because protonation of acetone enolate occurs with loss of resonance whereas protonation of hydroxide ion does not. However this is not quite a fair comparison, as formation of acetone from acetone enolate involves protonation at carbon whereas hydroxide accepts a proton at oxygen. If we consider protonation of both species on oxygen, we arrive at 2-hydroxypropene (acetone enol) and water. The measured  $pK_a$  of 2-hydroxypropene is less than 15.7, indicating our prediction about resonance effects on  $pK_a$  is still viable.

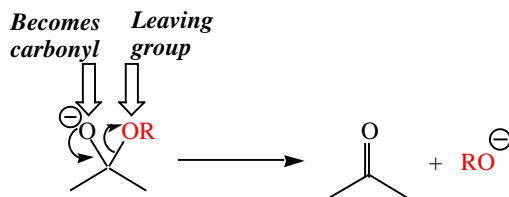


**Self-condensation:** For an enolate to condense with the carbonyl compound from which it was derived, the reaction must contain reasonable concentrations of both the enolate and the carbonyl compound. Stronger bases favor more deprotonation, increasing the concentration of enolate and decreasing the concentration of carbonyl compound. The difference in  $pK_a$  of the carbonyl compound and conjugate acid of the base used to promote condensation must be very large to prevent self-condensation. The  $pK_a$  difference must be at least 15 or more (or  $K_{eq} > 10^{15}$  or  $K_{eq} < 10^{-15}$ ) to prevent condensation. Since the  $pK_a$  of acetone is 20 and the  $pK_a$  of water is 15.7, we predict there will be sufficient concentration of both acetone and acetone enolate for self-condensation to occur.

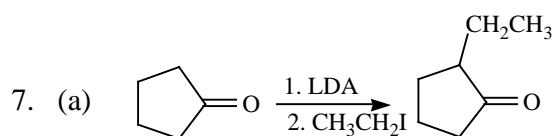
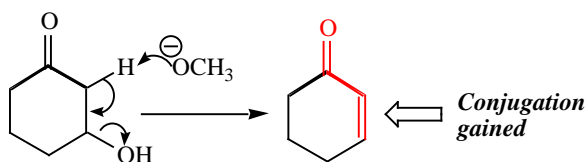
- (b) Methyl acetate (typical ester  $pK_a$  25) is a weaker acid than methanol ( $pK_a$  15.5). The equilibrium lies to the left with  $K_{eq} = 10^{-9.5}$ . Self-condensation is possible.
- (c) 2,4-Pentanedione (typical 1,3-dione  $pK_a$  9) is a stronger acid than hydrogen ( $pK_a$  35). The equilibrium lies to the right with  $K_{eq} = 10^{26}$ . At equilibrium all the dione is deprotonated, leaving none to serve as the electrophile in a self-condensation reaction.
- (d) Methyl acetoacetate (typical  $\alpha$ -ketoester  $pK_a$  11) is a stronger acid than  $(iPr)_2NH$  (typical amine  $pK_a$  36). The equilibrium lies to the right with  $K_{eq} = 10^{25}$ . At equilibrium all the acetoacetate is deprotonated, leaving none to serve as the electrophile in a self-condensation reaction.

6. Hydroxide or alkoxide ions can be leaving groups when:

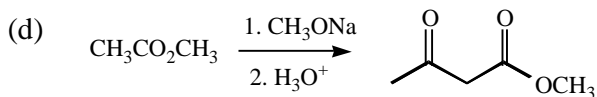
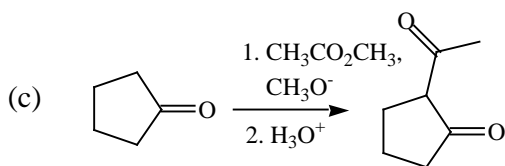
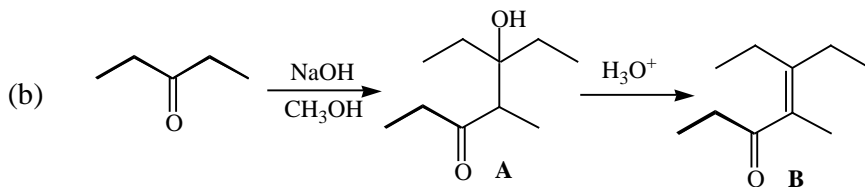
- A negatively charged tetrahedral intermediate fragments, transferring the negative charge from oxygen that becomes the carbonyl oxygen to the leaving group oxygen.



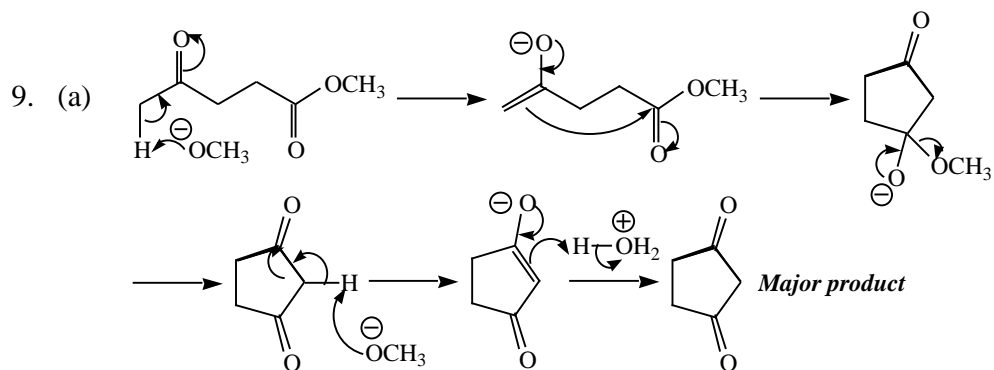
- Loss of  $\text{RO}^-$  results in conjugation or aromaticity.



**Hint:** To predict if an enolate will condense with more of the carbonyl compound from which it was derived, look for the presence of a second electrophile. In this case, there is a second electrophile ( $\text{CH}_3\text{CH}_2\text{I}$ ), so the reaction is run such that cyclopentanone enolate cannot react with cyclopentanone. Note the absence of a second electrophile in the next reaction.

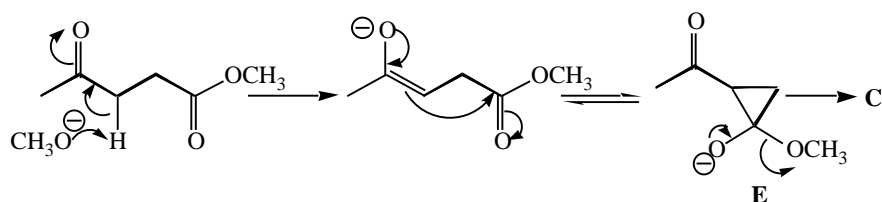


8. The driving force for the dehydration reaction is the formation of a conjugated molecule.



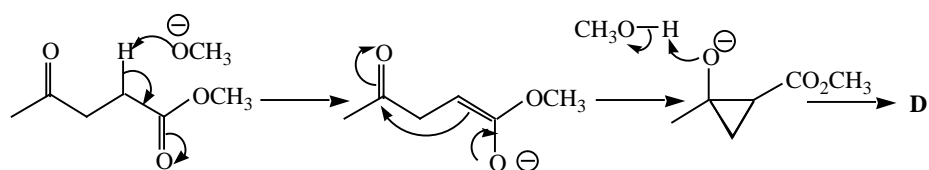
(b) Recall that every reaction and mechanism step is an equilibrium, but we are often only interested in moving the equilibrium to the right. Consider each mechanism step as an equilibrium as you write the mechanisms leading to **C** and **D**.

Product **C**:



Tetrahedral intermediate **E** can eject two different leaving groups. Ejection of  $\text{CH}_3\text{O}^-$  leads to product **C**, complete with a high level of ring strain. Ejection of the enolate moves backward in the mechanism but relieves ring strain. Ring strain and carbonyl addition reversibility prevent formation of **C**.

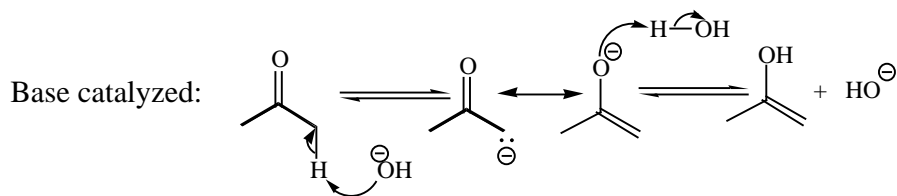
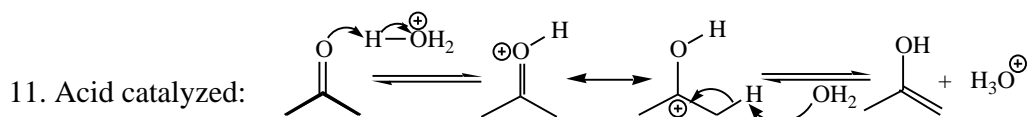
Product **D**:



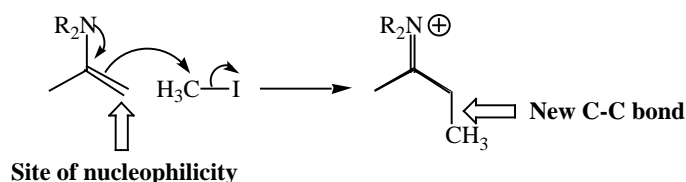
Product **D** is derived from intramolecular ester enolate attack on the ketone carbonyl. A ketone is more acidic than an ester, so formation of the ester enolate (and hence product **D**) is suppressed.

10. Most significant similarity: Both have a C-C pi bond and at least two lone pairs on the oxygen atom, so both usually react as nucleophiles.

Most significant difference: An enolate bears a negative charge whereas an enol is neutral, so an enolate is a more reactive nucleophile than an enol.



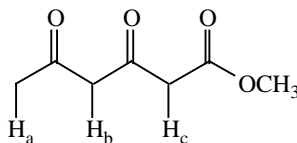
12. An enamine contains the N-C=C structure substructure. Enamines are nucleophilic at the carbon to the nitrogen.



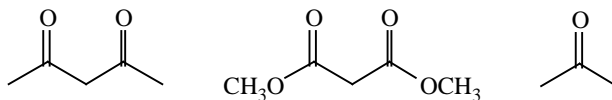
This nucleophilicity arises from the double bond pi electrons and is greatly assisted by resonance with the nitrogen lone pair.

### Practice Problems

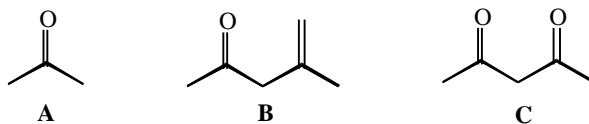
1. Assign these  $pK_a$  values to hydrogen atoms a - c: 9, 13, 20. Briefly but clearly explain your reasoning.



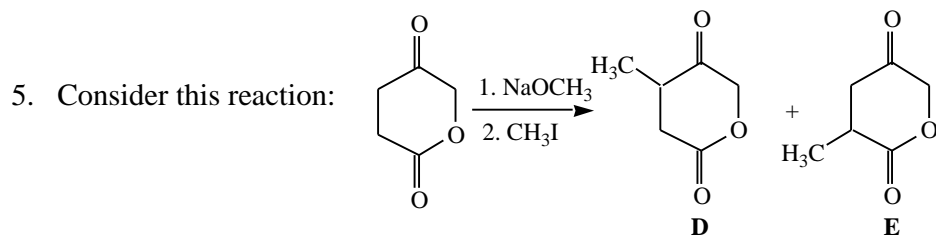
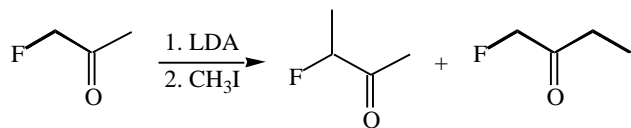
2. Assign a  $pK_a$  value to each structure. Briefly explain your reasoning.  $pK_a$  choices: 20, 13, 9.



3. Of the following structures, which has the lowest  $pK_a$ ? Briefly explain.



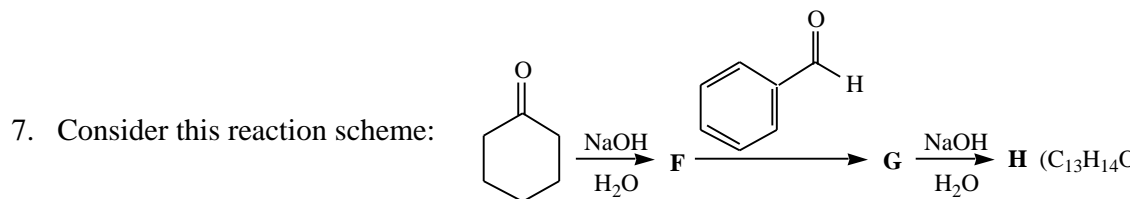
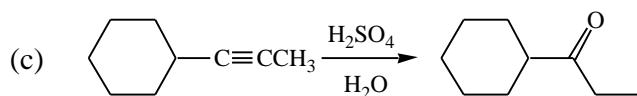
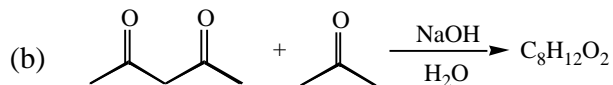
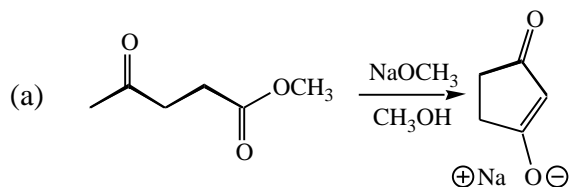
4. Select the major product of the following reaction. Briefly explain your reasoning.



(a) Provide a complete mechanism for the formation of product **D**.

(b) Select the major product and briefly explain your reasoning.

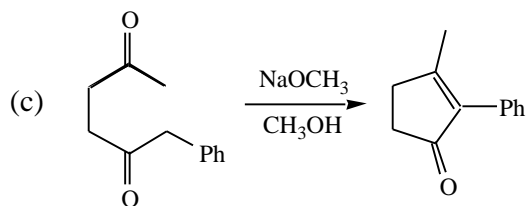
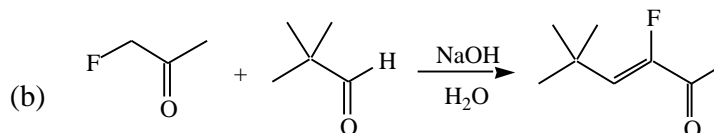
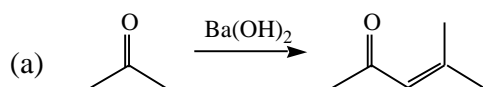
6. Provide a detailed curved arrow mechanism for each reaction.



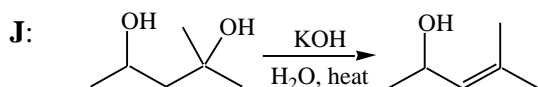
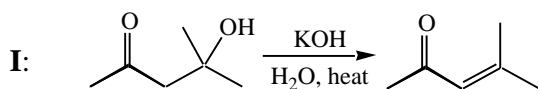
(a) Write the structures of products **F**, **G** and **H**.

(b) What is the driving force for the conversion of **G** into **H**?

8. Provide complete mechanisms.



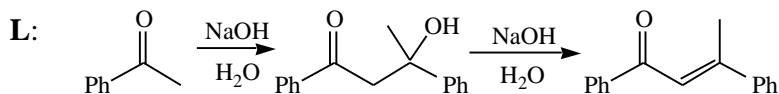
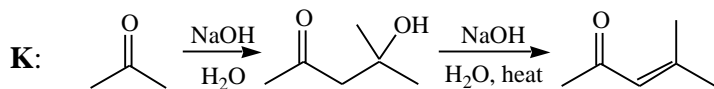
9. Consider these reactions:



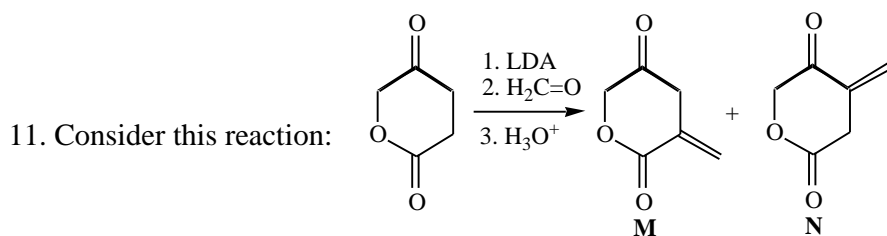
Select all the statements that apply to reactions **I** and **J**. Briefly explain your reasoning.

- (i) **I** is faster than **J**.
- (ii) **J** is faster than **I**.
- (iii) The rate of reaction **I** is zero.
- (iv) The rate of reaction **J** is zero.
- (v) Both **I** and **J** proceed at roughly the same rate.

10. Consider these reactions:

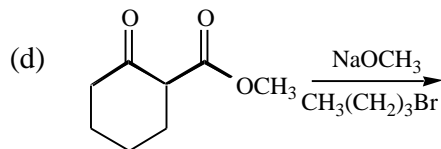
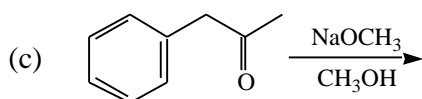
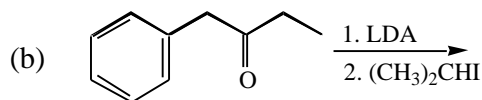
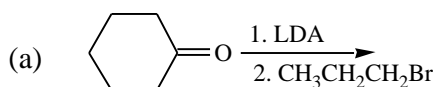


- (a) Provide a complete mechanism for the alcohol and enone products of reaction **L**.
- (b) Briefly explain why heat is needed in reaction **K** to lose a molecule of water but reaction **L** does not.

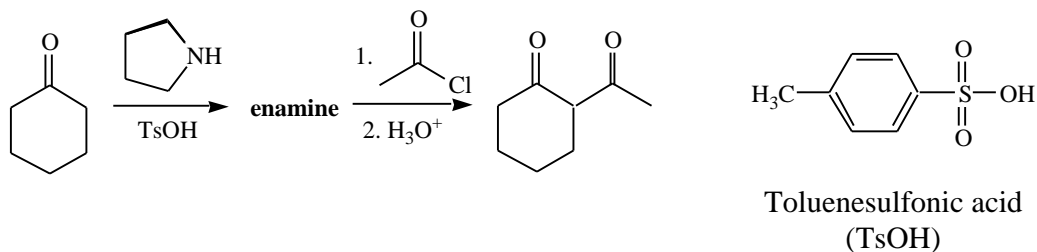


Provide detailed mechanism for the formation of the major product. Briefly explain your choice of major product.

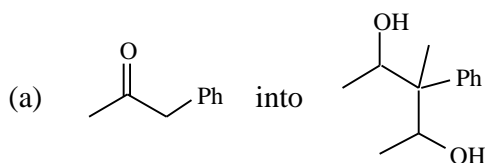
12. Provide the organic product(s) of the following reactions. Pay careful attention to stereochemistry. If more than one product is formed, indicate which product is the major one, if possible. If no reaction occurs, write "NR." Be prepared to write a complete mechanism for any of these reactions.

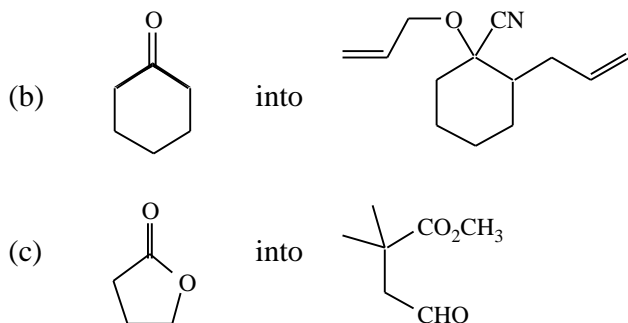


13. Provide the structure of the enamine intermediate, and mechanisms for the entire reaction scheme. (TsOH = a strong acid that is soluble organic solvents.)



14. Show how the following transformations might be carried out. Include your retrosynthetic reasoning.





### Practice Problems Solutions

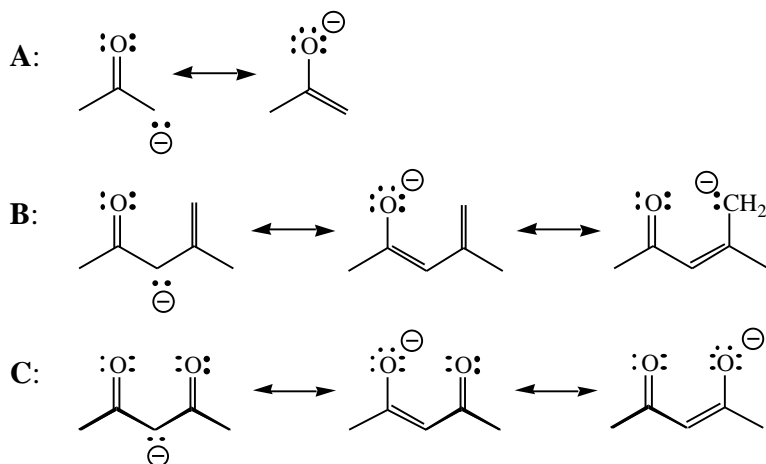
- $pK_a$  is an equilibrium constant that measures the acidity of a molecule. More acidic molecules give up protons more readily, have lower  $pK_a$  values, and more stable conjugate bases. Thus to assign these  $pK_a$  values we can rank the conjugate bases by stability. Removal of  $H_b$  or  $H_c$  affords enolates with three significant resonance contributors whereas the enolate formed from removal of  $H_a$  has only two significant resonance contributors. (See the solution to CFQ problem 3.) Everything else being equal, a structure with a greater number of resonance forms is more stable (easier to form). Thus  $H_a$  is the least acidic ( $pK_a$  20). The  $OCH_3$  oxygen of the ester group is electron donating by resonance. This increases the magnitude of the negative charge on the ester enolate, making it less stable and thus more difficult to form. Therefore  $H_c$  is harder to remove than  $H_b$ . Thus the final  $pK_a$  assignments are:  $H_a$   $pK_a = 20$ ;  $H_b$   $pK_a = 9$ ,  $H_c$   $pK_a = 13$ .
- A convenient way to consider  $pK_a$  is by examining the stability of the conjugate bases. Factors that stabilize the negative charge of the conjugate base (more resonance contributors, electron-withdrawing groups) will lower  $pK_a$ .

Comparing 2,4-pentanedione (first structure) with acetone (third structure): Removal of one of the hydrogen atoms on the  $CH_2$  between the two carbonyl groups affords an enolate with three resonance contributors. Deprotonation of acetone affords an enolate with two resonance contributors. The enolate derived from 2,4-pentanedione is more stable than the enolate derived from acetone, so the  $pK_a$  of 2,4-pentanedione is less than the  $pK_a$  of acetone.

Comparing 2,4-pentanedione with dimethyl malonate (center structure): Both afford enolates with three resonance contributors. The  $CH_3$  groups of 2,4-pentanedione are weak electron donors, so they will reduce the conjugate base stability by a small amount. The methoxy groups of dimethyl malonate are strong electron donors by resonance, so they reduce the stability of the conjugate base by a larger amount. Therefore the enolate of 2,4-pentanedione is more stable than the enolate of dimethyl malonate, so the  $pK_a$  of 2,4-pentanedione is lower than the  $pK_a$  of dimethyl malonate. The  $pK_a$  assignments are: acetone 20; dimethyl malonate 13; 2,4-pentanedione 9.

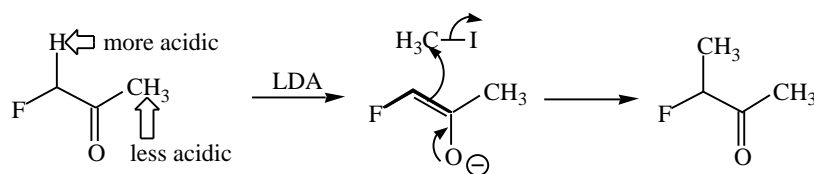
- The lowest  $pK_a$  corresponds to the compound that most readily gives up a proton to a base. A compound with more stable conjugate base is more readily deprotonated.

Thus to find the lowest  $pK_a$  in the set, we need to find the most stable conjugate base. The conjugate bases are:

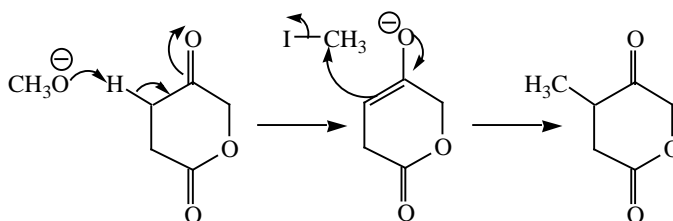


The conjugate base of **A** has two resonance contributors compared with three resonance contributors for the conjugate bases of **B** and **C**, making the conjugate base of **A** least easily formed. In only one resonance contributor of the conjugate base of **B** is the negative charge on oxygen (versus carbon, where it is less stable). Two resonance contributors for the conjugate base of **C** place the negative charge on oxygen. Thus the conjugate base of **B** is harder to form than the conjugate base of **C**. Since the conjugate base of **C** is most easily formed, **C** will be most readily deprotonated, and thus have the lowest  $pK_a$  of the group.

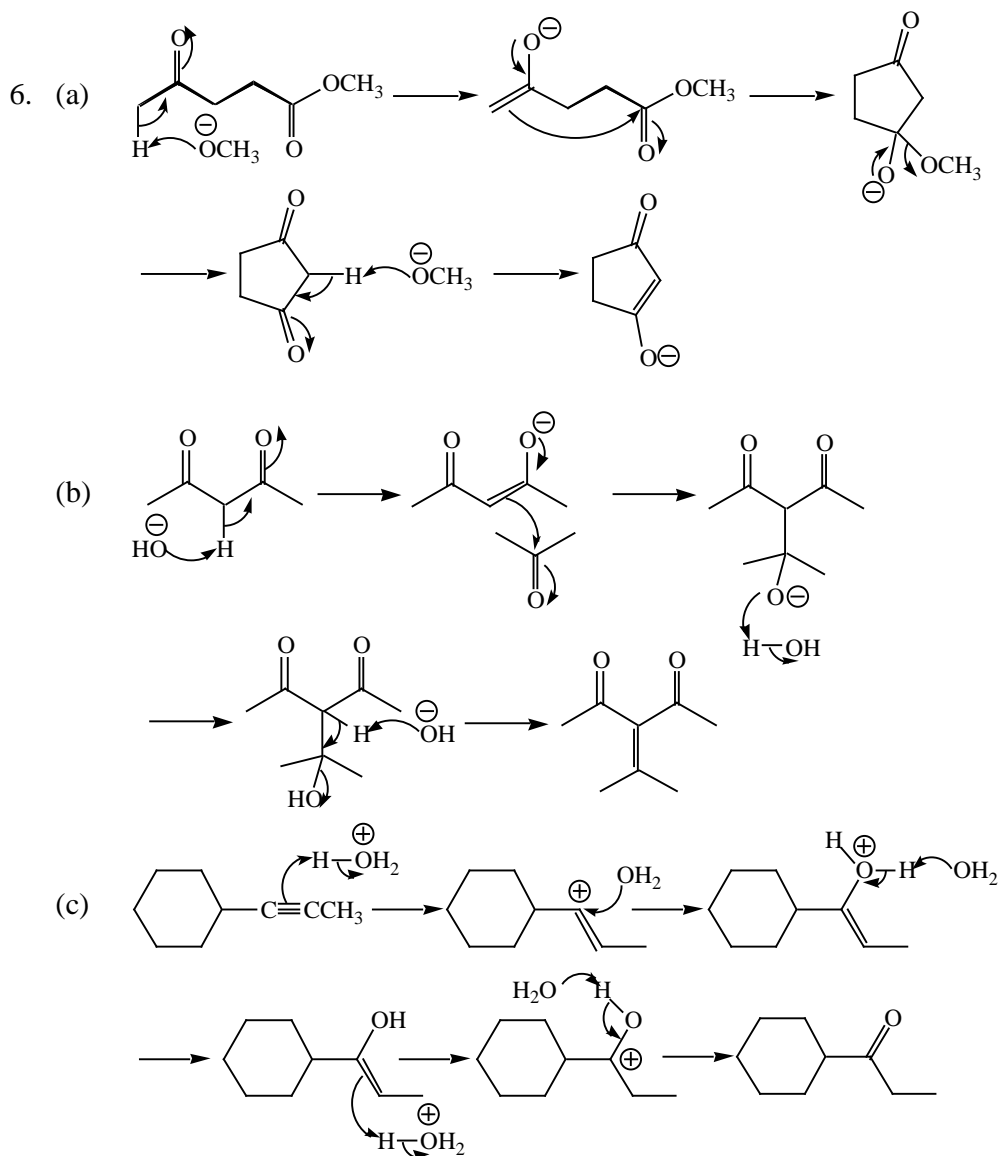
4. LDA is a strong base. It will remove the most acidic proton. In this case, the difference between the protons is the presence of a neighboring fluorine atom. Fluorine is highly electronegative, so it will make the adjacent protons more acidic by the inductive effect. Once the enolate is formed, acts as a nucleophile and undergoes an  $S_N2$  reaction with methyl iodide. The first product will therefore be the major one.

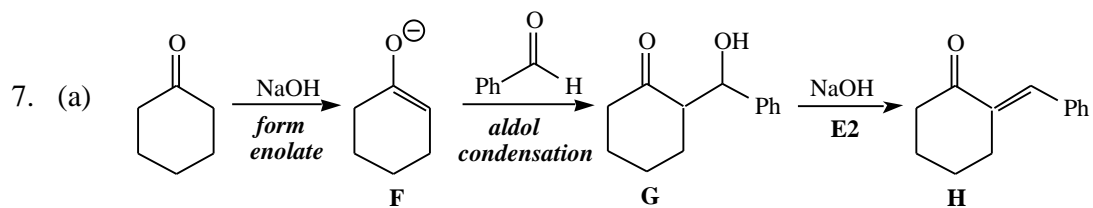


5. (a)

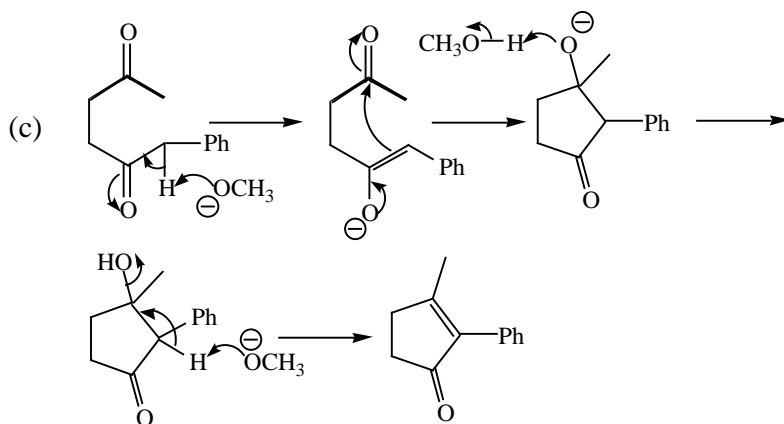
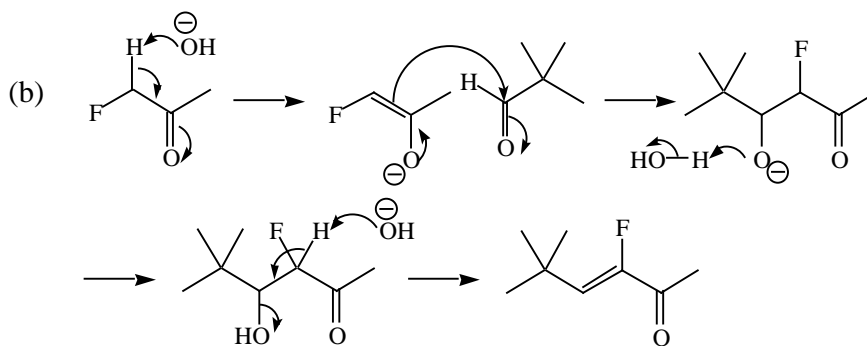
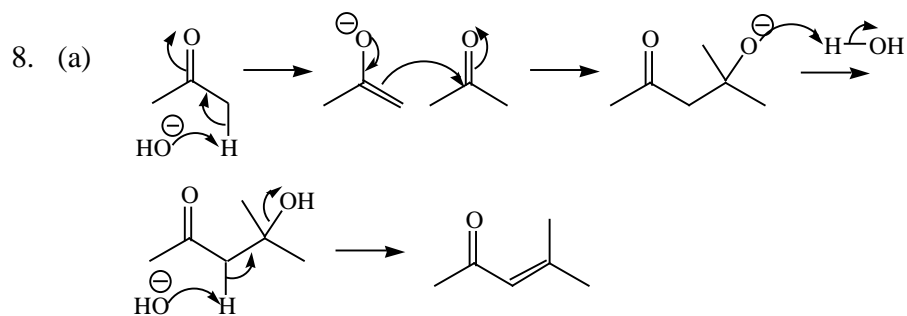


(b) The site of the new methyl group is controlled by the position of the deprotonation to form the enolate. Keeping with the idea that the more stable structure is formed more readily, we need to compare the stability of the enolates leading to **D** and **E**. Both have two significant resonance contributors. However, the ester oxygen that is not part of the carbonyl group donates electron density to the enolate by resonance. This electron donation increases the magnitude of the negative charge, thus destabilizing the enolate. Because the ketone enolate (leading to **D**) is more stable than the ester enolate (leading to **E**), compound **D** is the major product. (Steric effects are about equal for the two enolates.)





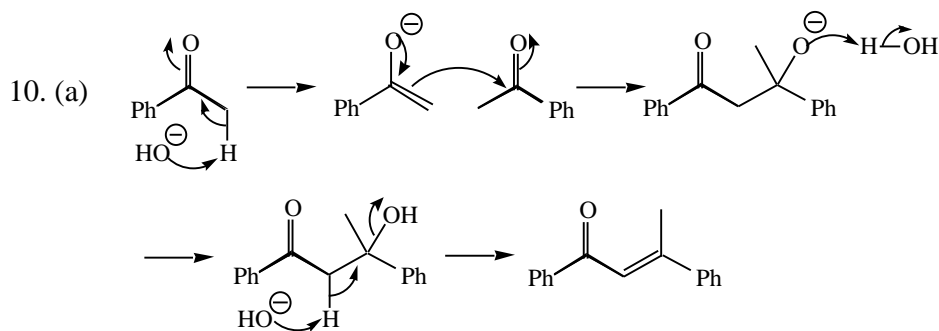
(b) This dehydration step is driven by the formation of a conjugated system.



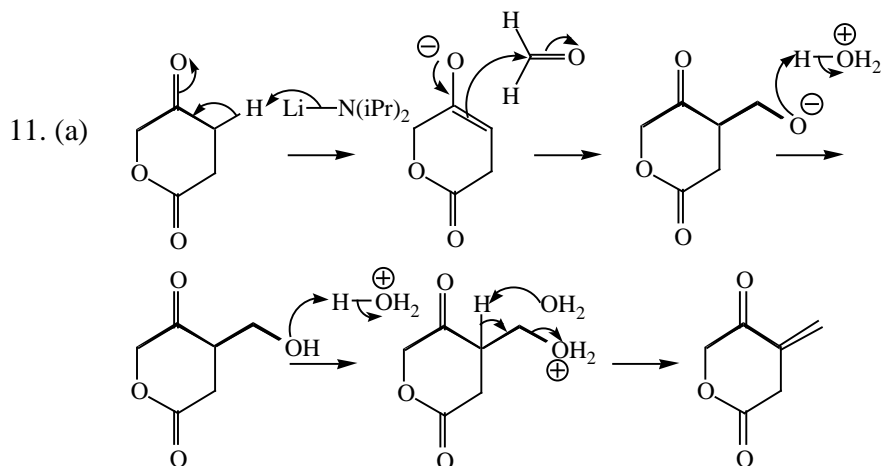
9. Correct statements: (i) **I** is faster than **J**, and (iv) the rate of reaction **J** is zero.

Explanation: Hydroxide ion is normally a poor leaving group. We have seen it leave in only two circumstances: when it was "forced out" of a tetrahedral intermediate by

another negatively charged oxygen, or when the transition state for hydroxide departure was stabilized by formation of a conjugated system. Reaction **J** has neither of these attributes, so we expect it to have a reaction rate of zero, hence (iv) is correct. In reaction **I**, hydroxide departure forms a conjugated enone, so we expect reaction **I** to proceed with a nonzero reaction rate. Therefore answer (i) is correct, and answers (ii), (iii), and (v) are incorrect.

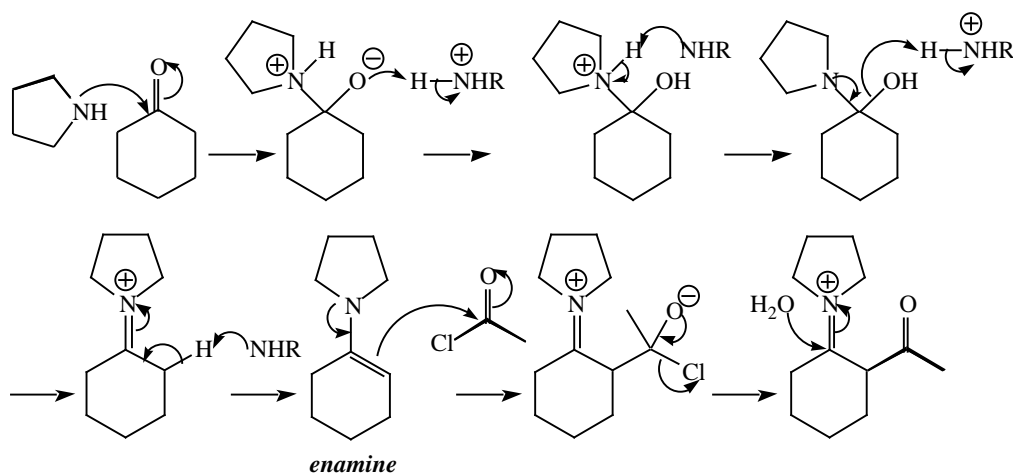
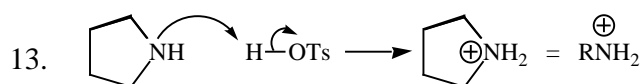
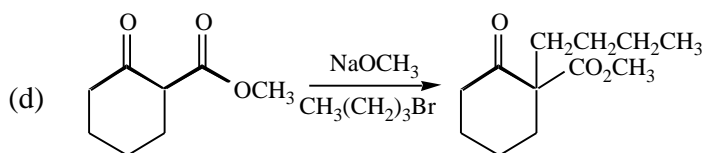
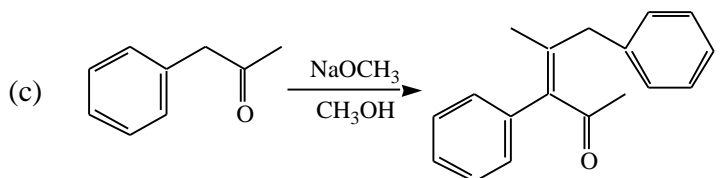
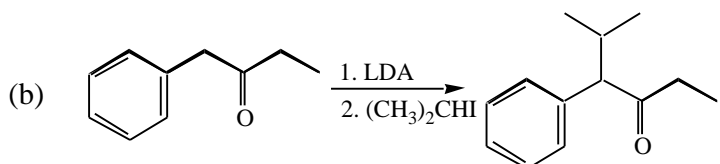
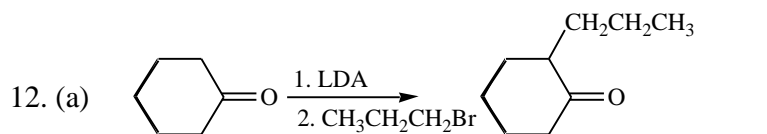


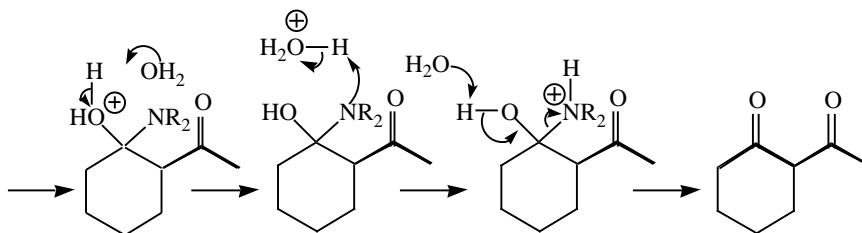
(b) The ease of dehydration is a function of the energy of activation of this step. The energy of activation is controlled by the transition state. If the transition state is more stable, the energy of activation is lower, and the step proceeds more readily. The dehydration step leads to a conjugated product. The enone of reaction **L** is more highly conjugated than the enone of reaction **K**. This conjugation is also appearing in the corresponding transition states. Thus, the activation energy for the formation of enone in reaction **L** is lower than the activation energy for the formation of the enone in reaction **K**. (Generally speaking, in most organic reactions, the more stable product is easier to form.)



(b) The position of the new carbon-carbon double bond is determined when the enolate is formed. Any time a reactive intermediate such as a carbocation, carbanion or radical is produced in a mechanism step, and the most stable intermediate is formed preferentially. Thus LDA will deprotonate so that the

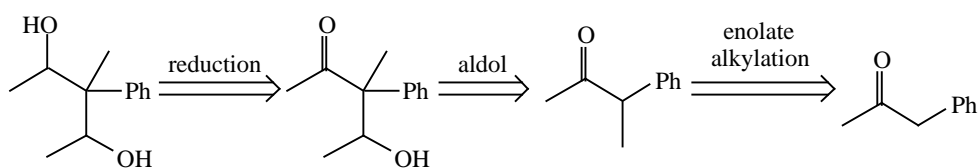
most stable enolate is formed. Each of the enolates that lead to **M** and **N** have an equal number of major resonance contributors. The ring oxygen of the ester enolate, however, can also donate electron density through resonance in a way that increases the negative charge on the enolate, destabilizing it. Because the ketone enolate is more stable than the ester enolate, the ketone enolate and subsequently product **N** are formed.



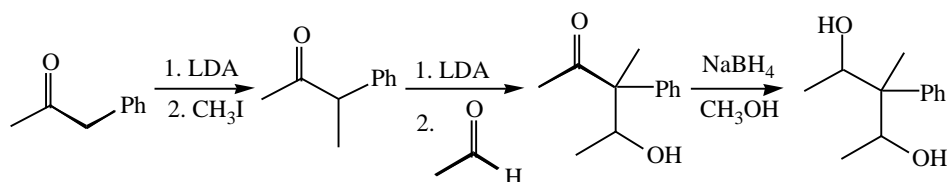


The amine is protonated first because it is the strongest base present. Note that an enamine allows formation of a new carbon-carbon bond at the  $\alpha$ -position without the need for strong base. This is an important synthetic advantage of enamines.

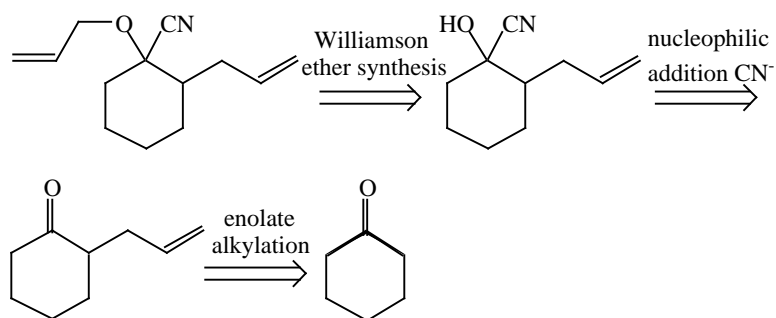
14. (a) Retrosynthesis:



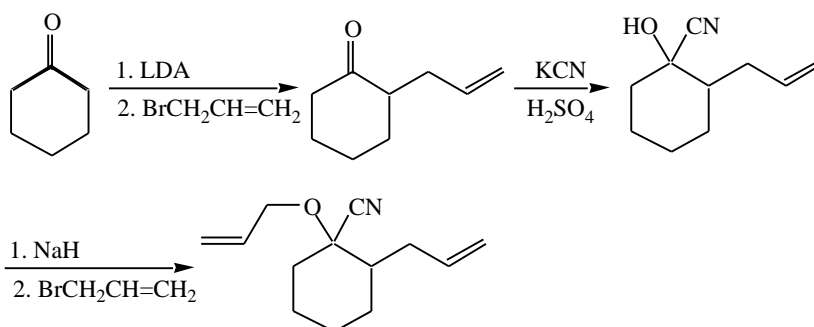
Forward direction:



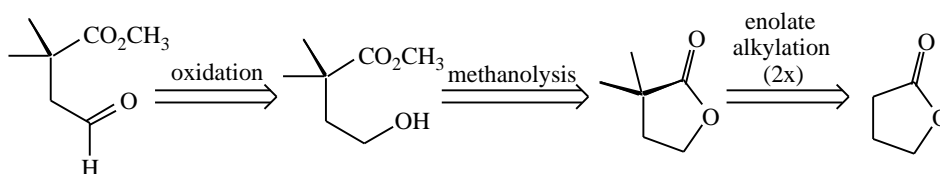
(b) Retrosynthesis:



Forward direction:



(c) Retrosynthesis:



Forward direction:

