

CFQ & PP: Carbonyl Chemistry: Survey of Reactions and Mechanisms

Reading

Brown and Foote: Sections 15.1, 16.6 – 16.11, 16.13, 16.14 17.4 – 17.8, 18.2 and 18.4 – 18.12

Lecture Supplement

Carbonyl Reaction Catalysis (page 50 of this Thinkbook)

Suggested Text Exercises

Brown and Foote: Chapter 15: 1, 2
Chapter 16: 4 – 11, 12 – 14, 19 – 45, 54 – 68
Chapter 17: 2 – 5, 18 – 43
Chapter 18: 2 – 12, 20 - 53

Optional Interactive Organic Chemistry CD and Workbook

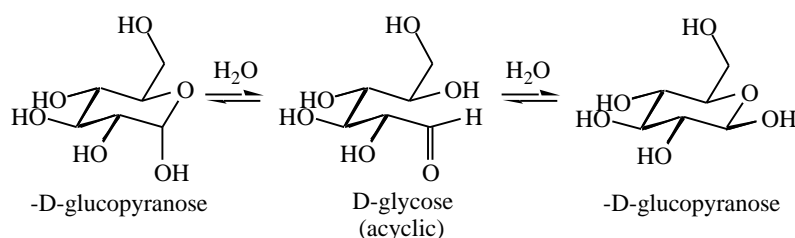
Supporting Concepts: Carbonyl Chemistry (p. 70)

Mechanisms: Acid Anhydride Hydrolysis (p. 17)
Acid-Catalyzed Formation of an Acetal (p. 18)
Acid-Catalyzed Formation of a Hemiacetal (p. 19)
Acid Chloride Hydrolysis (p. 19)
Acid Hydrolysis of an Amide (p. 20)
Base Hydrolysis of an Amide (p. 21)
Base Hydrolysis of a Nitrile (p. 21)
Ester Hydrolysis in Aqueous Base (p. 25)
Fischer Esterification (p. 25)
Formation of a Cyanohydrin (p. 26)
Formation of an Imine from a Ketone (p. 26)
Nylon Formation (p. 29)
Reaction of an Ester with a Grignard Reagent (p. 31)
Reduction of an Amide by LAH (p. 31)
Reduction of an Ester by LAH (p. 32)
Sodium Borohydride Reduction of a Ketone (p. 32)
Wittig Reaction (p. 32)
Wolff-Kishner Reduction (p. 32)

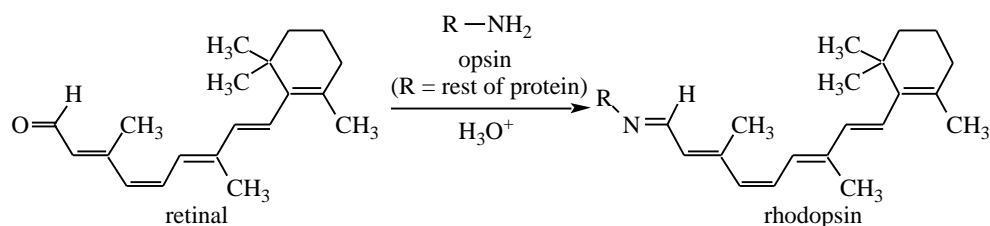
Reactivity Explorer: Acid Chlorides and Anhydrides (p. 40)
Amides (p. 43)
Carboxylic Acids (p. 44)
Esters (p. 45)
Ketones and Aldehydes (p. 46)

Concept Focus Questions

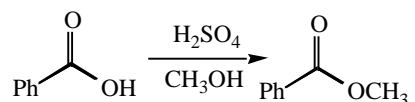
1. Shown below is the formation of cyclic glucopyranose from acyclic glucose, an example of the intramolecular formation of a hemiacetal.



- (a) Show the mechanism of the reaction.
(b) Why is the reaction faster in the presence of acid?
(c) Why is the reaction faster in the presence of base?
(d) How would the reactants be different if this reaction occurred in a living cell?
2. The reaction of retinal and opsin to form rhodopsin, a key step in the chemistry of vision, is an example of imine formation.



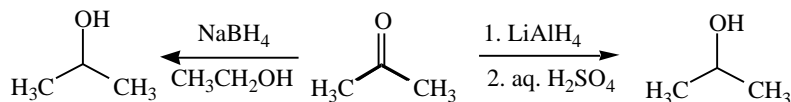
- (a) Write a mechanism for this reaction.
(b) Explain how the mechanism suggests that H_3O^+ need be present in only a catalytic quantity for this reaction.
3. Reaction of a carboxylic acid with a large excess of an alcohol in the presence of a strong acid (usually H_2SO_4) is called the Fischer esterification.



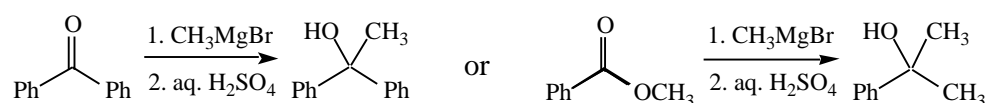
- (a) Give two specific reasons why must the carboxylic acid carbonyl be protonated prior to nucleophilic attack.
(b) The first step of the mechanism is protonation of methanol and not the carboxylic acid. Explain.
(c) In the second step of the mechanism, the carboxylic acid accepts a proton on the carbonyl oxygen instead of the hydroxyl oxygen. Explain this regioselectivity.
(d) Provide a complete mechanism for this Fischer esterification.
(e) How strong must the acid be?

(f) Suggest a general guideline concerning the necessity of carbonyl group protonation prior to nucleophilic attack.

4. Metal hydrides can be used to reduce an aldehyde or ketone into an alcohol. Write the mechanisms of the following reactions.



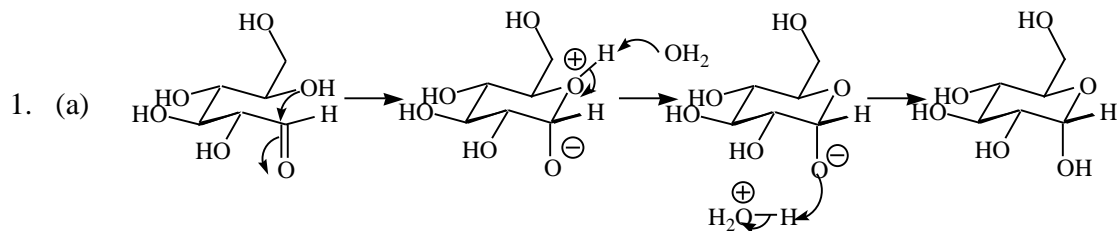
5. Grignard reactions involve the combination of a Grignard reagent of general form RMgX with a carbonyl compound. These reactions are commonly used to make carbon-carbon bonds, as shown below.



- (a) Define "organometallic compound."
 (b) Why do organometallic reagents provide a source of nucleophilic carbon groups?
 (c) Provide the mechanisms for both reactions given above.
 (d) Although carbon and magnesium are both common elements in the human body, Grignard reactions do not occur in cells. Why is this so?

6. Describe how the Wittig reaction could be used to transform benzaldehyde into styrene. Include all relevant reactions and mechanisms.

Concept Focus Questions Solutions



The other diastereomer ($-D$ -glucopyranose) is formed by an identical mechanism.

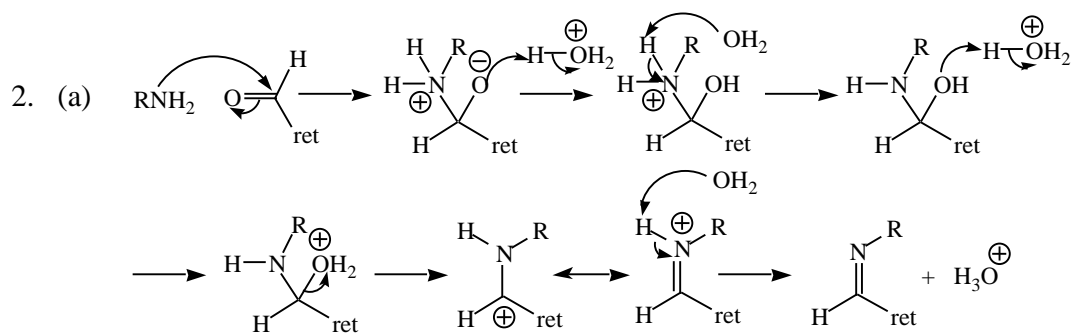
The timing of proton transfer steps in this mechanism is not crucial. The alkoxide oxygen could be protonated prior to deprotonation of the oxonium ion. Because proton transfers are common mechanism steps, this timing issue will be encountered frequently.

- (b) Protonation of the alkoxide (RO^-) of the tetrahedral intermediate bearing the negative charge in the last mechanism step shifts the last mechanism step

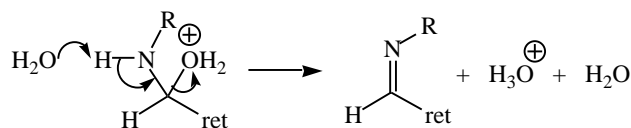
equilibrium further to the right, thus accelerating the reaction overall. Also, protonation of the carbonyl oxygen atom increases the electrophilicity of the carbonyl group.

(c) Deprotonation of the oxonium ion (R_2OH^+) of the tetrahedral intermediate at the end of the first step makes for a poorer leaving group. This disfavors return to the acyclic glucose, shifting the equilibrium to the right, and thus accelerating the reaction overall. Also, deprotonation converts the alcohol (a weak nucleophile) into an alkoxide (a stronger nucleophile).

(d) In a living cell the proton would probably be "shuttled" by an enzyme instead of by water. A sufficiently acidic proton within the enzyme would be the acid and some lone pair within the enzyme would be the base.



Dehydration may also occur by an E2-like pathway.



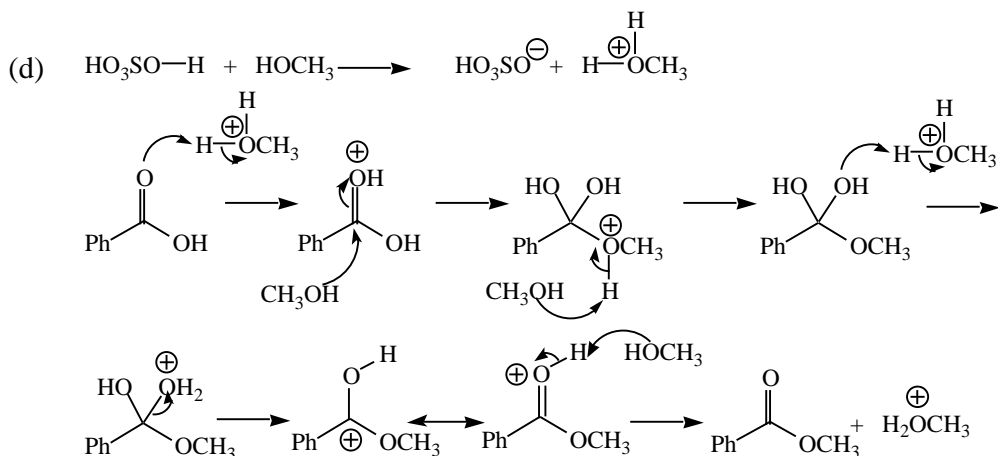
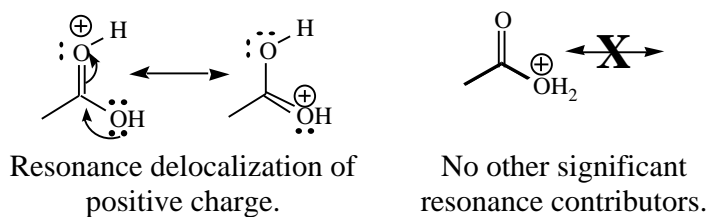
(b) A catalyst participates in the reaction, altering the mechanism and increasing the reaction rate, and returns to its original structure at the end. Hydronium ion is a catalyst for this reaction because it is regenerated in the last step.

3. (a) Reason 1: A carboxylic acid is a poor electrophile due to significant resonance between the carbonyl and hydroxyl groups. Nucleophilic attack would result in loss of this stabilizing resonance, so resonance inhibits nucleophilic attack.

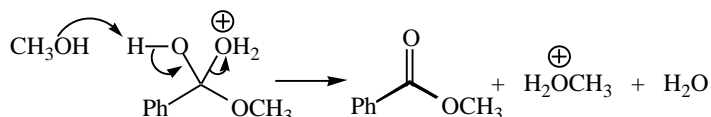
Reason 2: An alcohol is a poor nucleophile due to the high electronegativity of oxygen.

(b) Protonation of the carboxylic acid increases resonance whereas protonation of the alcohol does not. Therefore we might predict the carboxylic acid to be protonated in preference to the alcohol. However, for reasons that defy our simplistic predictions of basicity, the alcohol is more basic. (It is probably due to subtle inductive effects.)

- (c) Protonation of the carbonyl oxygen leads to an oxonium ion that can stabilize the positive charge by resonance. No such resonance is possible when the hydroxyl oxygen is protonated.



Dehydration may also occur by an E2-like pathway.

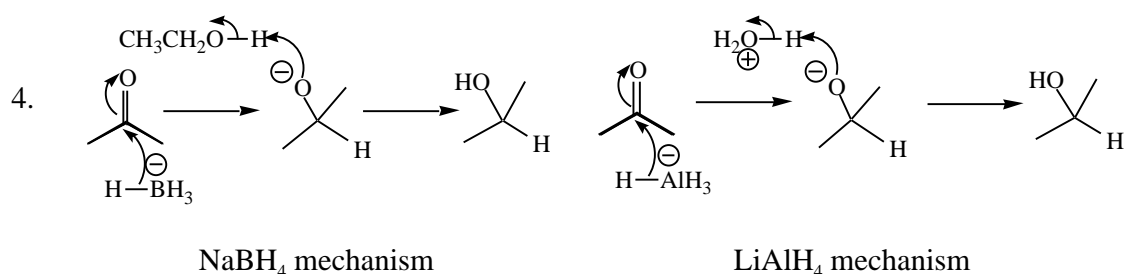


Methanol is protonated before the carbonyl because methanol is a stronger base. (While this does not agree with our simplistic predictions about basicity, it is an empirical fact, and cannot be ignored.) In addition, we use methanol as the solvent (large excess) to push the equilibrium toward the ester. There is so much more methanol than carboxylic acid that it is much more likely for H_2SO_4 to encounter CH_3OH than PhCO_2H .

- (e) For the reaction to proceed at a reasonable rate, the acid must be rather strong. Sulfuric and phosphoric acids are usually used. Weaker acids such as acetic acid are not sufficiently acidic to protonate the alcohol or carbonyl group to any useful extent.
- (f) Protonation of a carbonyl group increases its electrophilicity and hence susceptibility to nucleophilic attack. However, the carbonyl does not need to be

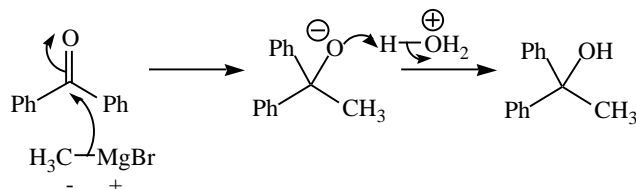
protonated in every instance in order to accept a nucleophile at a reasonable rate. In general, the more reactive carbonyls (aldehydes and ketones) need only be protonated when the nucleophile is very weak (such as water). (Even in the absence of acid, aldehydes can still add water to form hydrates, but the rate is much slower.) Less reactive carbonyls (such as ester and amides) need protonation before they can be attacked by all but the strongest nucleophiles (such as LiAlH_4 and Grignard reagents).

When considering protonation, take into account the strength of the acid and the basicity of the nucleophile. Protonation of a carbonyl requires a strong acid: H_3O^+ or stronger. Some nucleophiles such as NaBH_4 , LiAlH_4 , alkyne anions, Grignard reagents and organolithium reagents are very strong bases, and thus incompatible with the presence of an acid that is strong enough to protonate a carbonyl group.

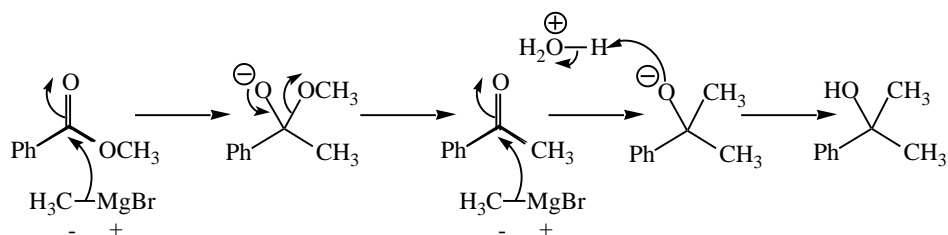


Note the great similarity between these two mechanisms. Recall that similar reagents or functional groups will have similar mechanisms.

5. (a) An organometallic compound is a compound that has a carbon-metal bond.
- (b) Carbon is more electronegative than any metal. The carbon-metal bond is therefore polar, having a $-$ on the carbon end and a $+$ on the metal end. This $-$ on the carbon end represents a slight electron surplus, thus making the carbon end nucleophilic.
- (c) Ketone addition mechanism:



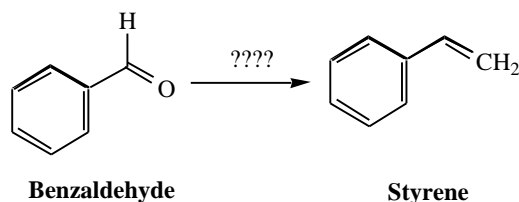
Ester substitution/addition mechanism:



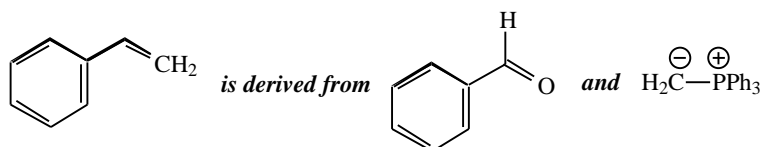
Hydroxide and alkoxide ions (RO^-) are normally not considered to be leaving groups. In this case the negative charge is being transferred from the oxygen atom of the tetrahedral intermediate to the oxygen atom of the leaving group. These negative charges are of equal stability, so there is little if any energetic price to be paid. Thus hydroxide and alkoxide can leave when expelled by the fragmentation of a negatively charged tetrahedral intermediate. (Alternate explanation: The negative charge is shared by two oxygen atoms in the transition state. This charge delocalization provides sufficient stabilization to lower the free energy of activation by enough so the step can proceed at a reasonable rate.)

- (d) Grignard reagents are strong bases, and so would be rapidly protonated by water present in any living cell. In addition, formation of a Grignard reagent usually requires Mg metal, not found in a living cell.

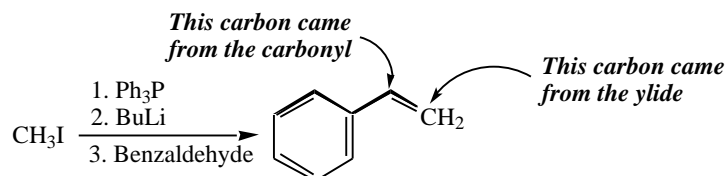
6. The desired transformation is:



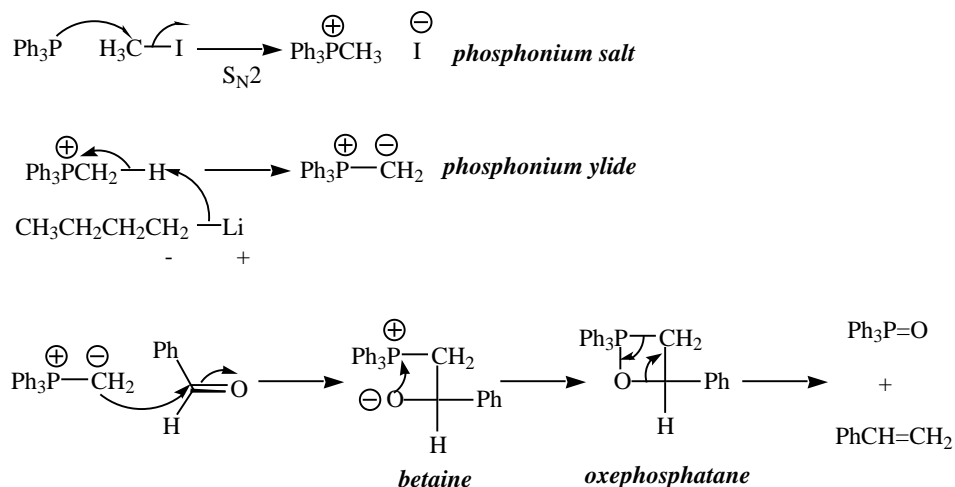
The conversion of an aldehyde or ketone into an alkene is efficiently achieved with the Wittig reaction, the reaction of a phosphonium ylide with a carbonyl compound. In this reaction, the carbon end of the phosphonium ylide replaces the carbonyl group's oxygen atom. (It looks a bit like the reverse of an ozonolysis reaction.)



The phosphonium ylide is prepared from triphenylphosphine (Ph_3P) and an alkyl halide in a two-step process. The overall reaction is:



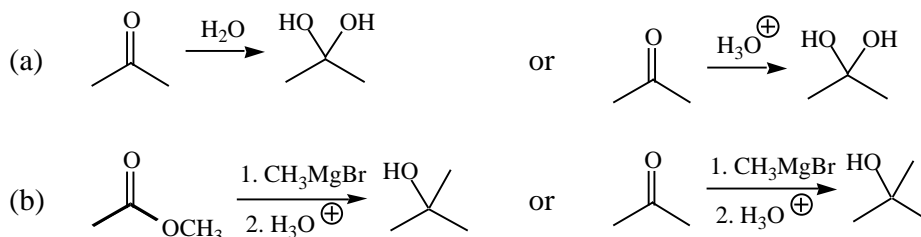
BuLi = butyllithium = Li-CH₂CH₂CH₂CH₃, a very strong base. Here are the mechanism details:

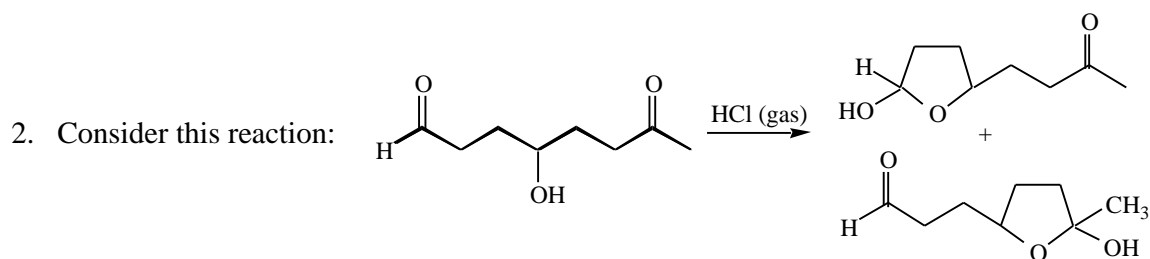


The betaine closure to the oxaphosphatane creates ring strain. The quenching of the formal positive charge on phosphorus and creation of a strong phosphorus-oxygen bond counteract this strain. Relief of this ring strain and formation of another oxygen-phosphorus bond is the driving force for the decomposition of the oxaphosphatane into triphenylphosphine oxide (Ph₃P=O) and the alkene product.

Practice Problems

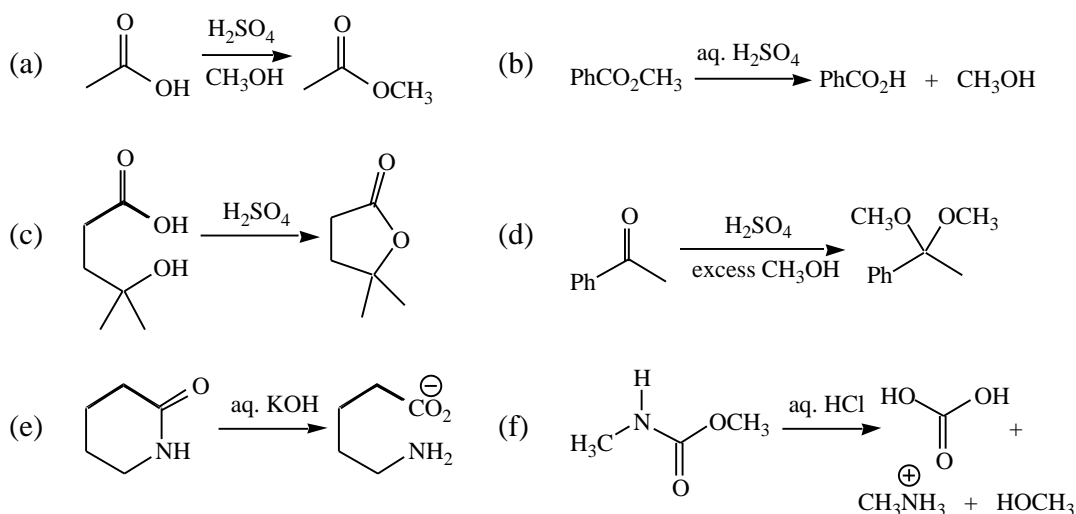
1. Select the faster reaction of each pair and briefly explain your choice.



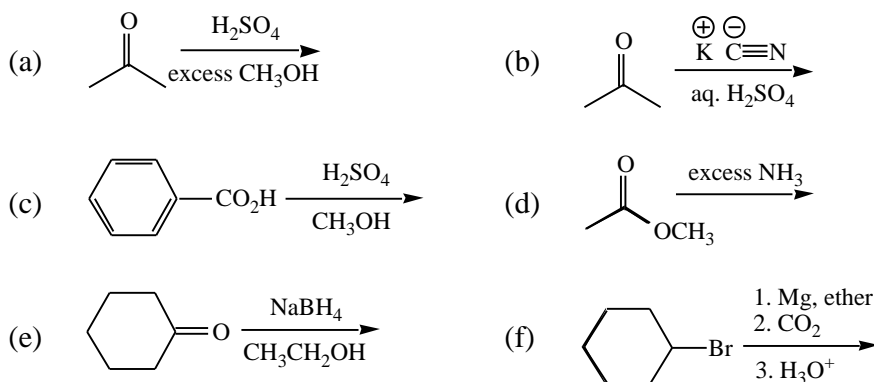


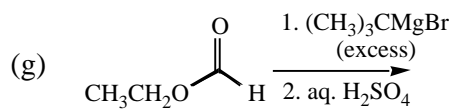
Write a complete and detailed curved arrow mechanism for the formation of the major product. Briefly explain your choice of major product.

3. Provide detailed curved arrow mechanisms.

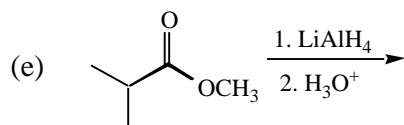
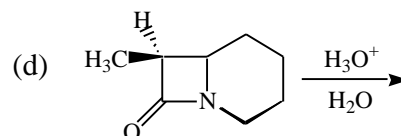
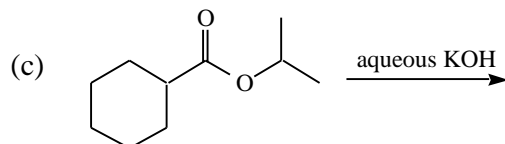
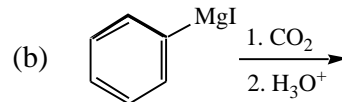
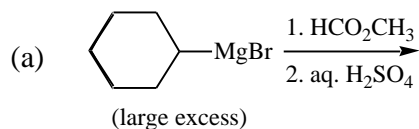


4. Provide the organic product(s) for the following reactions. If more than one product is formed, indicate which product (if any) is the major one. If no reaction occurs, write "NR." (Almost any time you are asked to provide a reaction product, you should also be able to write the mechanism for the reaction as well. If you do not know the product, then trying to figure out the mechanism will guide you in the right direction.)

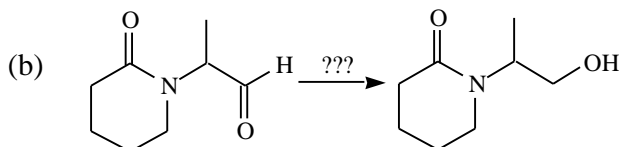
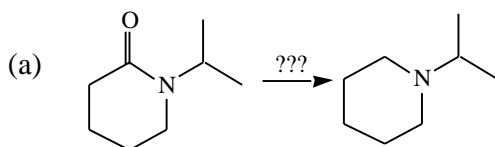




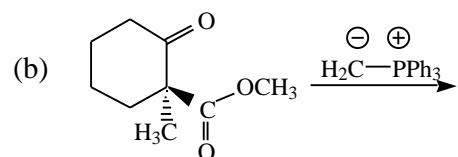
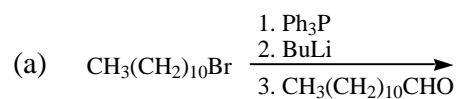
5. For each reaction give the organic product(s) and draw the reaction mechanism.



6. Suggest the appropriate reagent(s) to carry out each reaction.

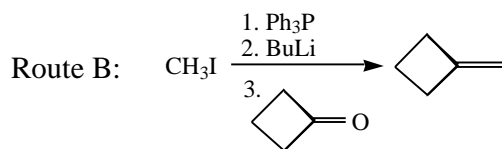
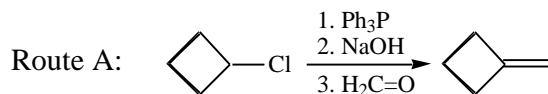


7. Provide the organic product(s) for the following reactions.

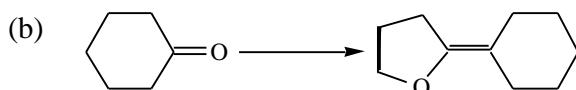
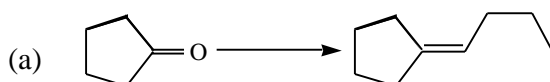


8. Provide a mechanism for part (a) of the previous question.

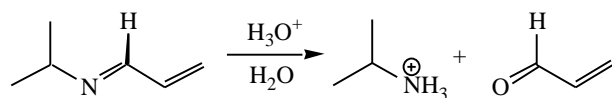
9. Consider the two Wittig reactions shown below. Select the most efficient route and provide three reasons for your choice.



10. Design Wittig reactions to carry out the following transformations.

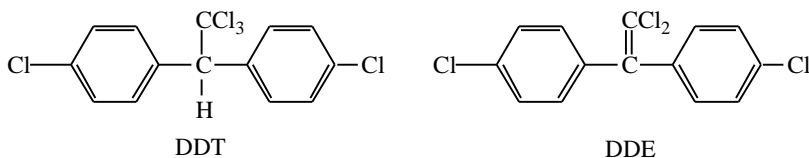


11. The imine functional group (C=N) is similar to the carbonyl group (C=O) in that each has a carbon-heteroatom double bond. The carbon has a δ^+ charge in both cases because the heteroatom is more electronegative than the carbon. The heteroatom has at least one lone pair. This similarity between the electronic structure of the imine and carbonyl bonds suggests that they will have similar reactions as well. Bearing this concept in mind, rewrite the three fundamental carbonyl mechanism steps for imines. In each case, state whether the imine mechanism step will occur more readily than the corresponding carbonyl step, and briefly explain your reasoning.
12. In an important step in the chemistry of the vision cycle, the reaction of a primary amine group of the protein opsin condenses with the aldehyde group of the chromophore 11-cis-retinal (a highly conjugated aldehyde derived from vitamin E) to form the protein conjugate called rhodopsin. A later step involves the enzymatic hydrolysis of isomerized rhodopsin into opsin and 11-trans-retinal. In this way the retinal is released for recycling back into the 11-cis isomer. Write a mechanism for the hydrolysis of the model imine shown below.

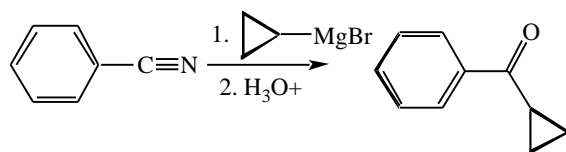


13. DDT is an insecticide that accumulates up the food chain. Predator birds can be contaminated with quite high levels of the chemical by eating much lightly contaminated prey. Metabolism of DDT affords DDE. At the cellular level, DDE inhibits the production of the enzyme carbonic anhydrase that controls calcium metabolism. It is believed that interfering with calcium metabolism causes eggshells

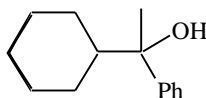
to be thinner and weaker than normal and makes the eggs more prone to breakage. (This is one of reasons why the condor was near extinction in California.) Assuming the carbonic anhydrase production inhibition involves reaction of DDE with a nucleophile, explain how this process works.



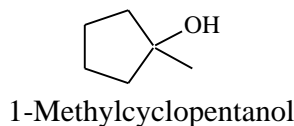
14. Nitriles undergo nucleophilic attack by Grignard reagents to afford ketones after a hydrolysis step with aqueous acid.



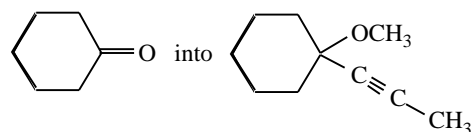
- (a) Why is the nitrile group subject to nucleophilic attack?
 (b) Draw a detailed curved arrow mechanism for this reaction.
 (c) Nucleophilic addition of a Grignard reagent to the carbonyl group results in replacement of the C-O bond by a C-C bond. A nitrile group has two C-N bonds, yet even in the presence of a large excess of the Grignard reagent, one nitrile group reacts with only one equivalent of Grignard reagent, not two. Explain.
15. Show how cyclohexanone might be transformed into the alcohol shown below. Include your retrosynthetic reasoning.



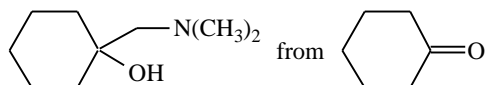
16. Design a synthesis of 1-methylcyclopentanol using alcohols with no more than five carbon atoms as the only source of carbon in the final product.



17. Suggest a sequence of reactions to carry out this transformation. The reagents that supply the new carbon atoms in the product can have only one or two carbons.



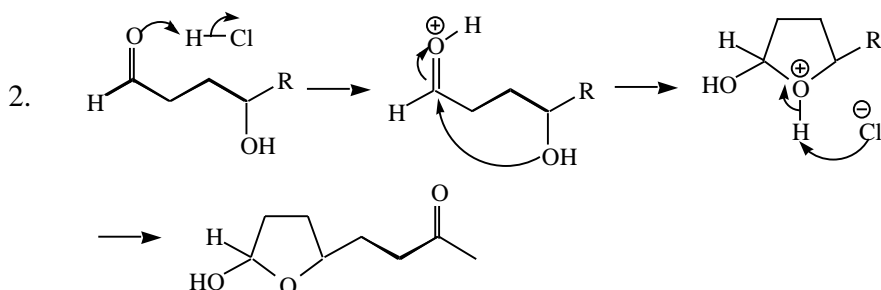
18. Suggest a series of reactions to carry out this transformation. One intermediate must be an alkene.



Practice Problems Solutions

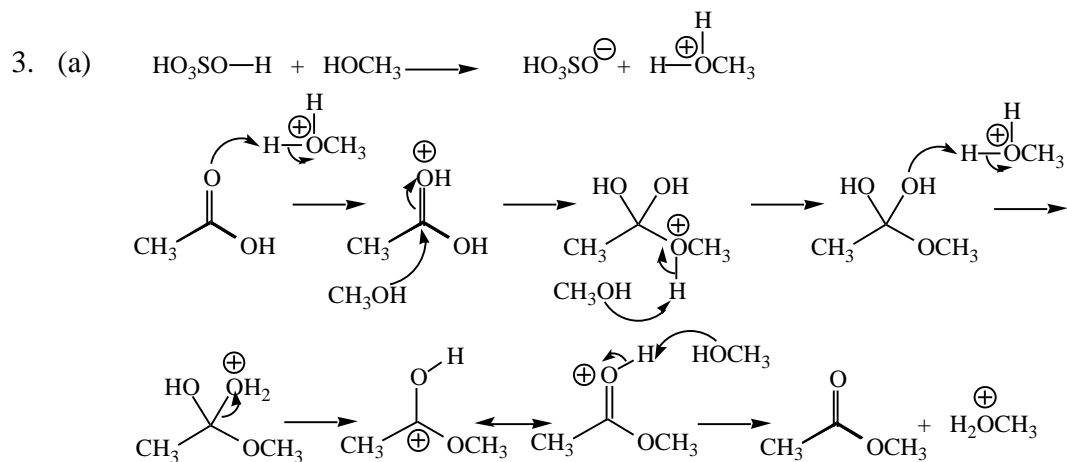
- (a) The H_3O^+ reaction is faster. Protonation of the carbonyl oxygen makes this oxygen atom even more electron-poor. This results in a greater carbonyl carbon δ^+ for the protonated carbonyl than for a carbonyl that is not protonated. Greater δ^+ allows more rapid attack by a nucleophile (water).

(b) Nucleophilic addition to an ester is slower than addition to a ketone because the carbonyl carbon of the ester is less electrophilic. This ester carbonyl is less electrophilic because it has a smaller δ^+ , due to resonance with the lone pairs of the OCH_3 oxygen atom. In addition, the ester loses resonance when attacked, but the ketone does not. Thus, nucleophilic attack on the ester is further inhibited.

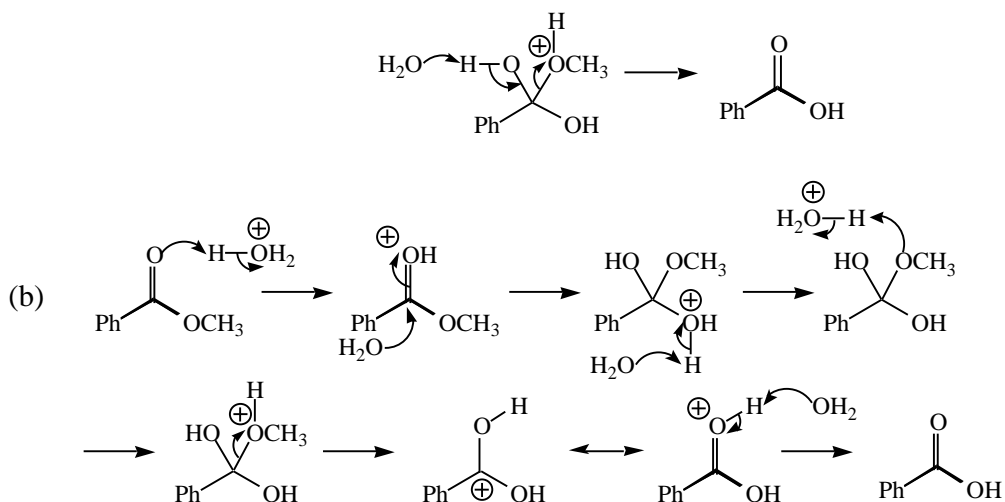


The aldehyde carbonyl is attacked for two reasons:

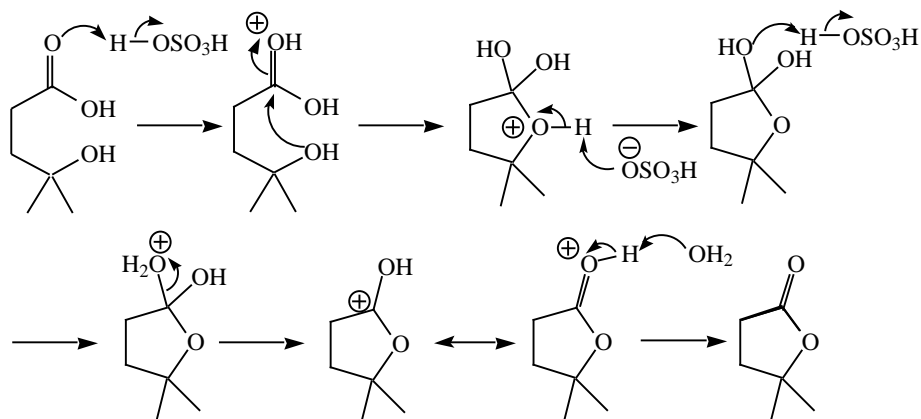
- An aldehyde carbonyl has less steric hindrance to nucleophilic attack than the ketone carbonyl.
- An aldehyde has a greater carbonyl carbon δ^+ than a ketone carbonyl carbon due to the electron donating effect of the ketone methyl group. The same reasoning applies to a protonated aldehyde carbonyl vs. a protonated ketone carbonyl.



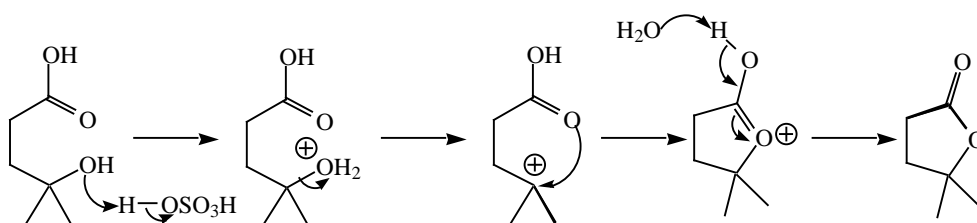
The last two steps of this mechanism show loss of water in an E1 fashion. An E2-type of dehydration is also acceptable.



(c) Two reasonable mechanisms can be written: a traditional Fischer esterification or a carbonyl carbocation capture mechanism. Both are acceptable, although the traditional Fischer esterification mechanism is probably the minor pathway as an alcohol is more basic than a carboxylic acid. Fischer esterification mechanism:

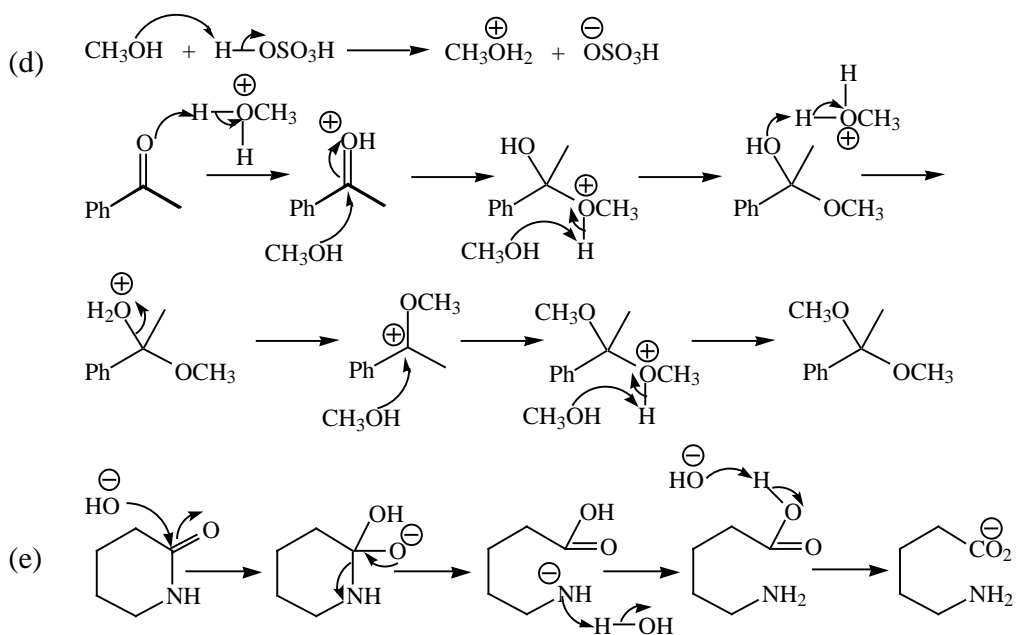


Carbocation capture of carbonyl mechanism:



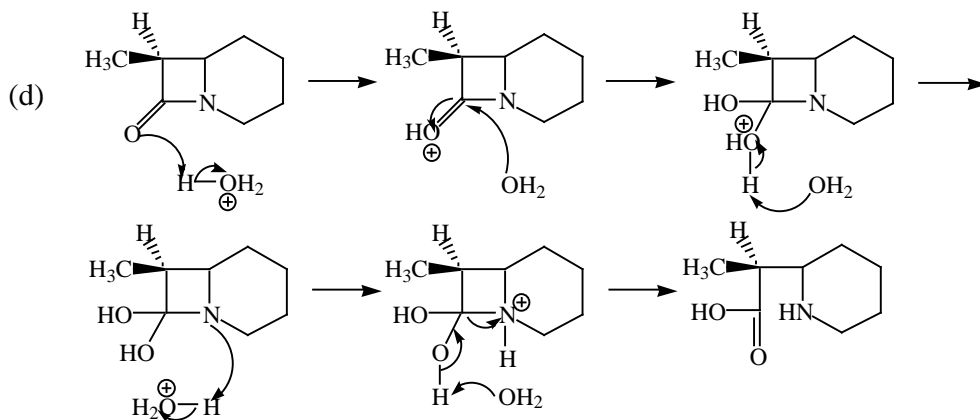
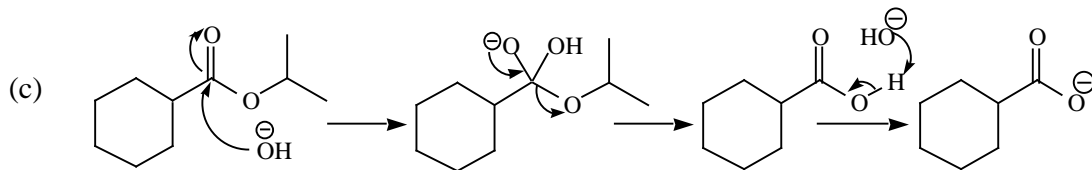
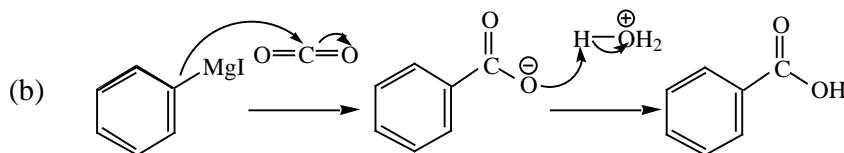
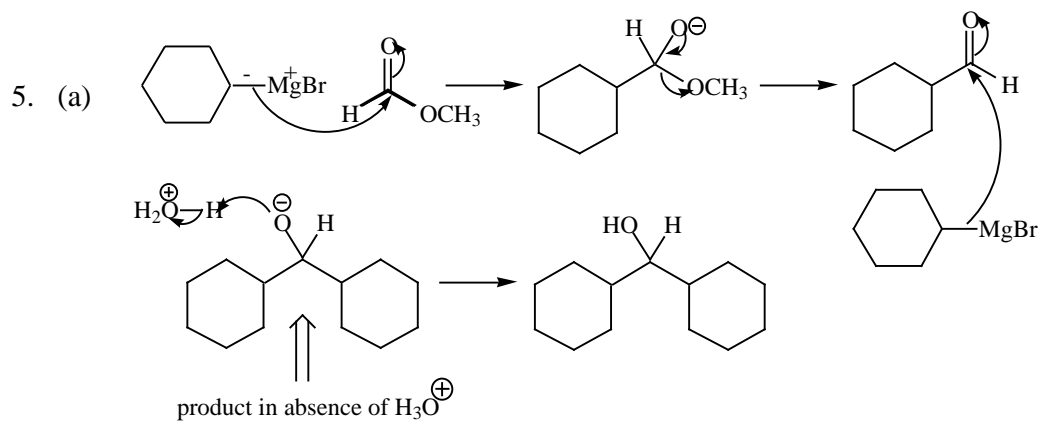
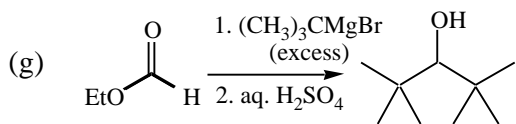
The carbocation captures the carbonyl oxygen of the CO_2H group instead of the OH oxygen, because it leads to the more stable oxonium ion intermediate. The oxonium ion shown enjoys resonance stabilization; the oxonium ion formed by OH capture does not.

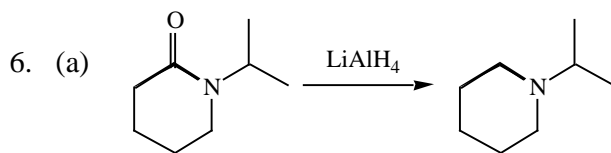
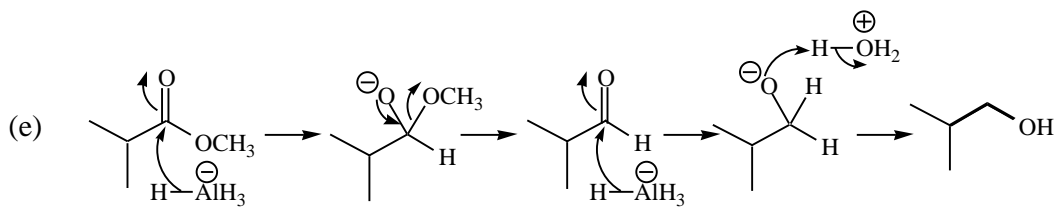
This carbocation-carbonyl capture mechanism for acid-catalyzed esterification of a carboxylic acid can only be a possibility when the carbocation derived from the alcohol is sufficiently stable (secondary or better).



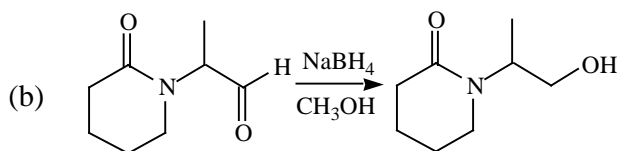
Fragmentation of the tetrahedral intermediate with an amide anion leaving group (in this case RNH^-) is the obvious rate-determining step, because an amide anion is such a poor leaving group. (An amide anion is a poorer leaving group than hydroxide ion.) One could combine this step with the nitrogen anion protonation to avoid having an amide anion leaving group. This is reasonable, as the solvent is water, and the amine will be hydrogen bonded before it departs.

The amide anion leaving group problem cannot be solved by protonation with H_3O^+ because H_3O^+ is simply not present. The reaction medium is strongly basic, so any strong acids such as hydronium ion will be immediately neutralized.

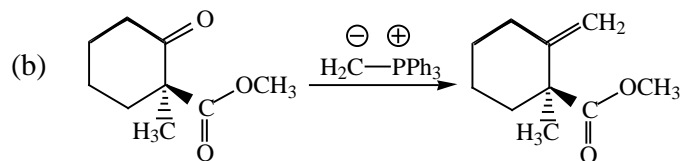
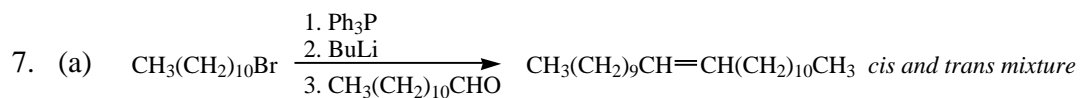




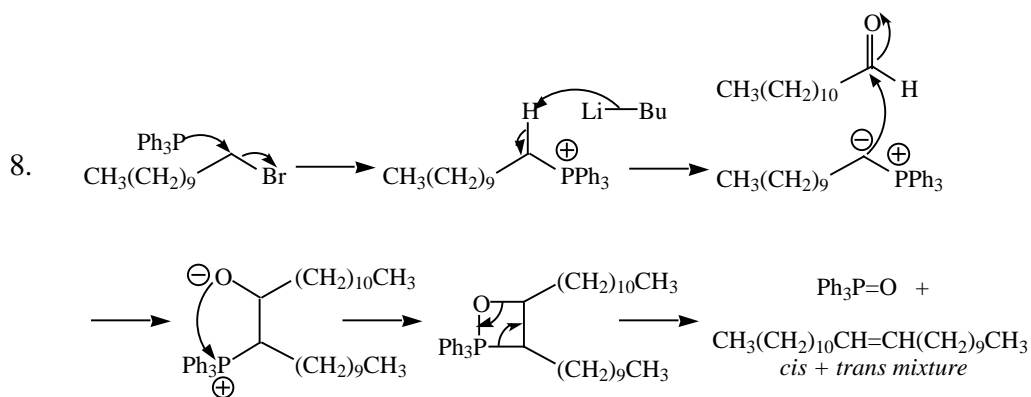
NaBH_4 is not sufficiently nucleophilic to attack an amide.



NaBH_4 reduces ketones and aldehydes but not esters, amides, or carboxylic acids.



A phosphonium ylide is sufficiently nucleophilic to attack an aldehyde or ketone but not an ester, amide or other less-reactive carbonyl functional group.



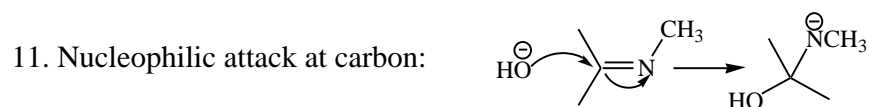
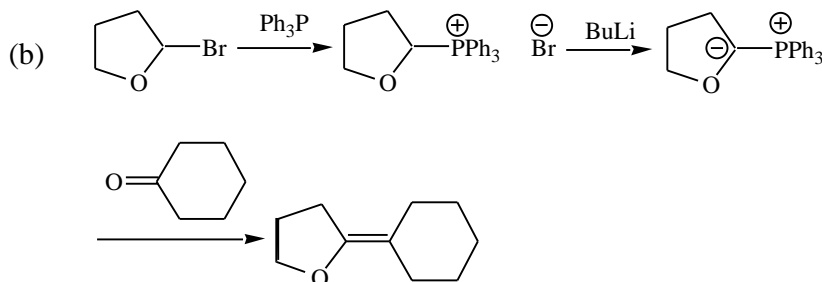
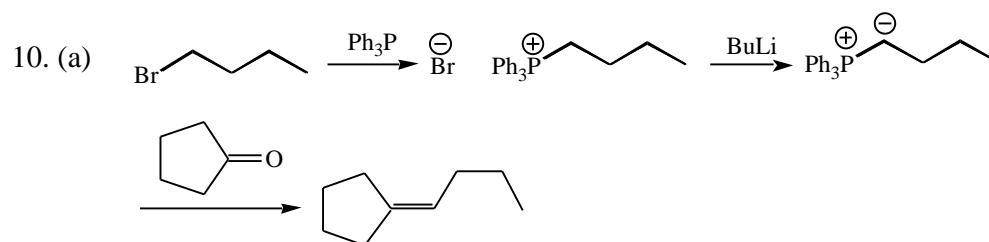
9. Route B is the most efficient route. Reasons:

Iodide (route B) is a better leaving group than chloride (route A), so the S_N2 reaction with Ph_3P in route A is expected to be less efficient. (Favors route B.)

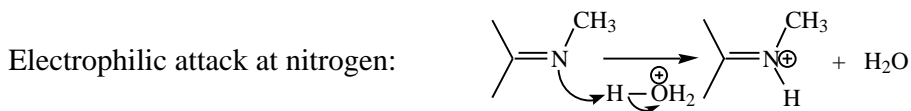
Hydroxide (route A) is not a strong enough base to deprotonate a simple phosphonium salt. BuLi (route B) is a much stronger base. (Favors Route B.)

An aldehyde such as formaldehyde (route A) is a better electrophile than a ketone such as cyclobutanone (route B). (Favors route A).

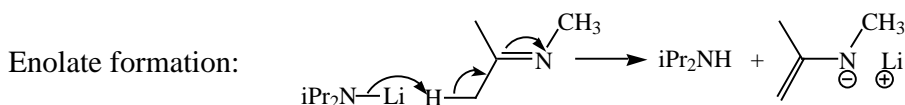
A methyl halide (route B) is less sterically hindered than a secondary halide (route A), so the PPh_3 S_N2 reaction of route B is more efficient than the S_N2 reaction of route A. (Favors route B.)



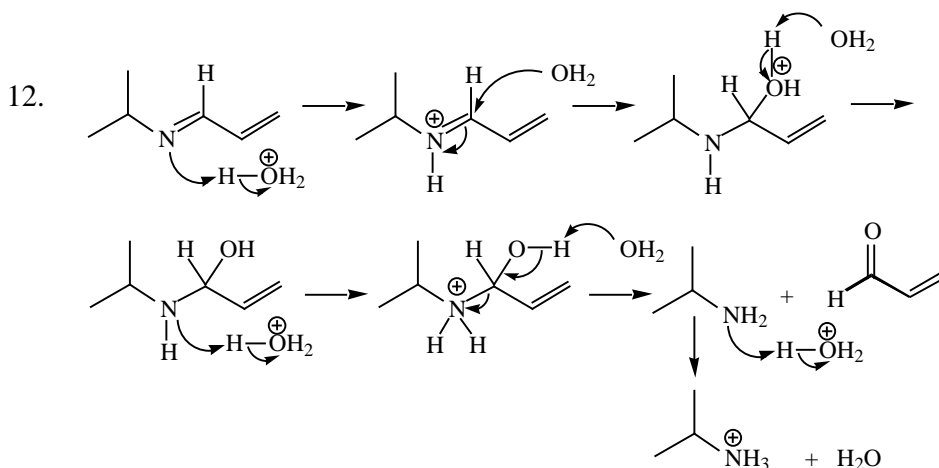
A carbonyl can react with a nucleophile because of the δ^+ charge on the carbonyl carbon, and because the oxygen can readily accept the pair of electrons that was the C-O bond. The carbon of the imine group will have a smaller δ^+ than the carbon of a carbonyl group, because nitrogen is less electronegative than oxygen. This same difference in electronegativity also implies that nitrogen cannot accept the electrons that were the C-N bond as readily as an oxygen atom can accept the same electrons from a carbonyl bond. Therefore an imine group is less readily attacked by nucleophiles than a carbonyl group.



A carbonyl can react with an electrophile because it has two lone pairs on the oxygen atom. The imine nitrogen has a lone pair, and is less electronegative than oxygen. Therefore we predict that an imine will react with electrophiles more readily than a carbonyl group.

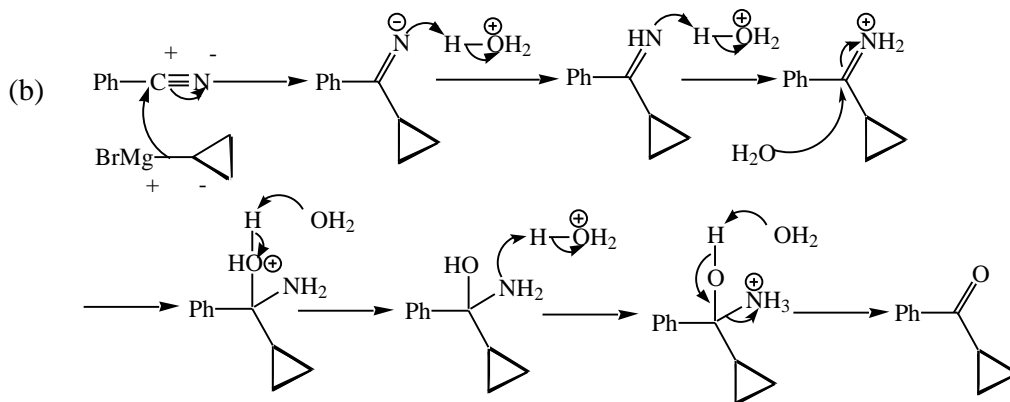


The fundamental difference between an imine and a carbonyl is the nature of the heteroatom. The number of resonance contributors for the carbonyl and imine enolates is equal. Because nitrogen is less electronegative than oxygen, it cannot stabilize the enolate negative charge as well. Thus we predict that imines will not form enolates as readily as carbonyl compounds. (Formation of an imine enolate requires a strong base such as LDA, shown above, or butyllithium. Enolates are discussed in more depth in Chem 30C.)



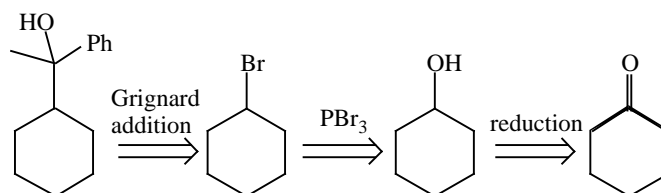
13. Reaction with a nucleophile would require DDE to function as an electrophile. The dichloroalkene unit ($C=CCl_2$) is an electrophilic bond due to the two electron-withdrawing chlorine atoms. Thus, it is reasonable to assume that carbonic anhydrase production might be inhibited because some important nucleophile reacts with the DDE $C=CCl_2$ bond, and is thus prevented from producing carbonic anhydrase.

14. (a) The nitrile group is subject to nucleophilic attack because it is a polarized bond. Nitrogen is more electronegative than carbon, so the carbon bears a $+$ charge, much in the same way as a carbonyl or imine group. A combination of this $+$ charge and the nitrogen atom's ability to accept the bond electrons allow the nitrile group to accept a nucleophile.

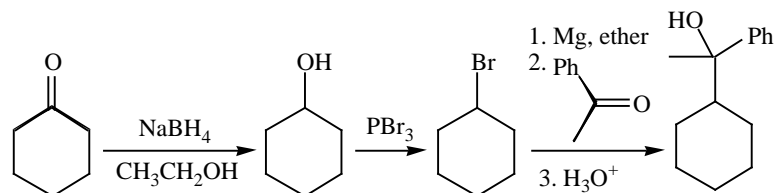


(c) Addition of the first molecule of cyclopropyl magnesium bromide to the nitrile, replacing the C-N bond with a new C-C bond, affords a negatively charged nitrogen atom. Addition of the second molecule of Grignard reagent to replace the second C-N bond would result in a nitrogen atom with a 2^- charge. This is very thermodynamically expensive, so the second addition cannot occur. Addition of acid rapidly protonates any Grignard reagent that is present, so addition to the C=NH bond formed during the hydrolysis step also cannot occur.

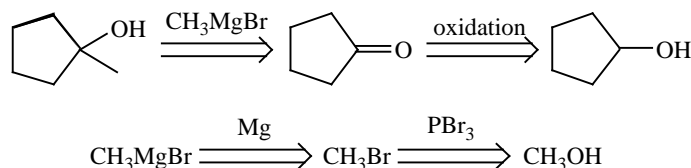
15. Retrosynthesis:



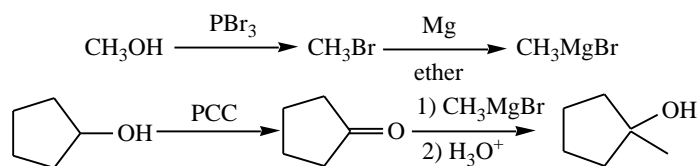
Forward direction:



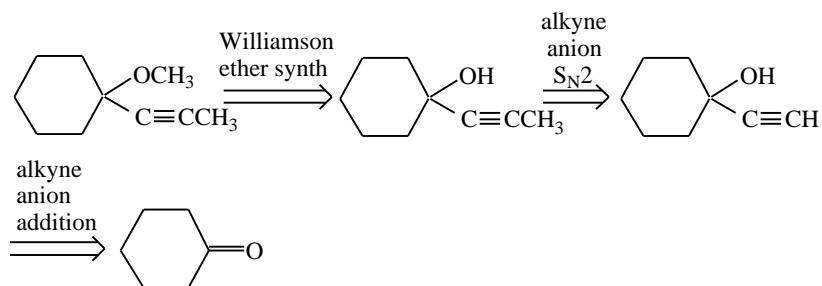
16. Retrosynthesis:



Forward direction:

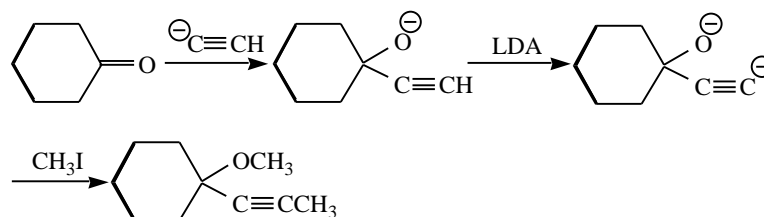


17. Retrosynthesis:



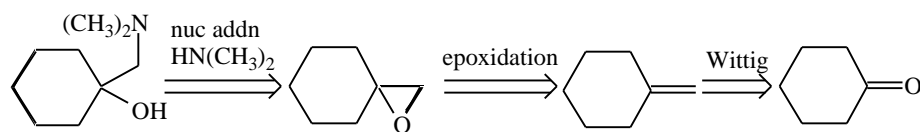
The two-carbon limitation prevents the shorter route using a three-carbon alkyne anion in place of a two-carbon anion.

Forward direction:



18. There are many alkene reactions, so this really is not a significant restriction. Starting with a ketone suggests a Wittig route might be possible.

Retrosynthesis:



Forward direction:

