

Chapter 19 – Aldehydes and Ketones: Nucleophilic Addition Reactions

Chapter Outline

- I. General information about aldehydes and ketones (Sections 19.1 – 19.3).
 - A. Naming aldehydes and ketones (Section 19.1).
 1. Naming aldehydes.
 - a. Aldehydes are named by replacing the *-e* of the corresponding alkane with *-al*.
 - b. The parent chain must contain the -CHO group.
 - c. The aldehyde carbon is always carbon 1.
 - d. When the -CHO group is attached to a ring, the suffix *-carbaldehyde* is used.
 2. Naming ketones.
 - a. Ketones are named by replacing the *-e* of the corresponding alkane with *-one*.
 - b. Numbering starts at the end of the carbon chain nearer to the carbonyl carbon.
 - c. The word *acyl* is used when a RCO- group is a substituent.
 - B. Preparation of aldehydes and ketones (Section 19.2).
 1. Preparation of aldehydes.
 - a. Oxidation of primary alcohols with PCC.
 - b. Oxidative cleavage of alkenes with at least one vinylic hydrogen.
 - c. Partial reduction of carboxylic acid derivatives.
 2. Preparation of ketones.
 - a. Oxidation of secondary alcohols.
 - b. Ozonolysis of alkenes with at least one disubstituted unsaturated carbon.
 - c. Friedel–Crafts acylation of aromatic compounds.
 - d. Hydration of terminal alkynes to produce methyl ketones.
 - e. Preparation from carboxylic acid derivatives.
 - C. Oxidation of aldehydes and ketones (Section 19.3).
 1. Aldehydes can be oxidized to carboxylic acids by many reagents.
 - a. CrO_3 is used for normal aldehydes.
 - b. Tollens reagent is used for sensitive aldehydes.
 - c. Oxidation occurs through intermediate 1,1-diols.
 2. Ketones are generally inert to oxidation, but can be oxidized to carboxylic acids with strong oxidizing agents.

The usefulness of this reaction is limited to symmetrical ketones.
- II. Nucleophilic addition reactions of aldehydes and ketones (Sections 19.4 – 19.13).
 - A. Characteristics of nucleophilic addition reactions (Section 19.4).
 1. Mechanism of nucleophilic addition reactions.
 - a. A nucleophile attacks the electrophilic carbonyl carbon from a direction 45° from the plane of the carbonyl group.
 - b. The carbonyl group rehybridizes from sp^2 to sp^3 , and a tetrahedral alkoxide intermediate is produced.
 - c. The attacking nucleophile may be neutral or negatively charged.

Neutral nucleophiles usually have a hydrogen atom that can be eliminated.
 - d. The tetrahedral intermediate has two fates:
 - i. The intermediate can be protonated to give an alcohol.
 - ii. The carbonyl oxygen can be eliminated as -OH to give a product with a C=Nu double bond.
 - e. Possible reversibility and acid/base catalysis are important features of nucleophilic addition reactions.

2. Relative reactivity of aldehydes and ketones.
 - a. Aldehydes are usually more reactive than ketones in nucleophilic addition reactions for two reasons:
 - i. A nucleophile can approach the carbonyl group of an aldehyde with more ease because only one alkyl group is in the way.
 - ii. Aldehyde carbonyl groups are more strongly polarized and electrophilic because they are less stabilized by the inductive effect of alkyl groups.
 - b. Aromatic aldehydes are less reactive than aliphatic aldehydes because the electron-donating aromatic ring makes the carbonyl carbon less electrophilic.
- B. Nucleophilic addition reactions (Section 19.5 – 19.13).
 1. Hydration (Section 19.5).
 - a. Water adds to aldehydes and ketones to give 1,1-diols (often referred to as gem-diols or hydrates).
 - b. The reaction is reversible, but generally, the equilibrium favors the carbonyl compound.
 - c. Reaction is slow in pure water, but is catalyzed by both aqueous acid and base.
 - i. The base-catalyzed reaction is an addition of OH^- , followed by protonation of the tetrahedral intermediate by water.
 - ii. In the acid-catalyzed reaction, the carbonyl oxygen is protonated, and neutral water adds to the carbonyl carbon.
 - d. The catalysts have different effects.
 - i. Base catalysis makes water a better nucleophile.
 - ii. Acid catalysis makes the carbonyl carbon a better electrophile.
 - e. Reactions of carbonyl groups with H-X , where X is electronegative, are reversible; the equilibrium favors the aldehyde or ketone.
 2. Cyanohydrin formation (Section 19.6).
 - a. HCN adds to aldehydes and ketones to give cyanohydrins.
 - i. The reaction is base-catalyzed and proceeds through a tetrahedral intermediate.
 - ii. Equilibrium favors the cyanohydrin adduct.
 - b. Cyanohydrin formation is useful for the transformations that the -CN group can undergo.
 - i. The -CN group can be reduced, to form an amine.
 - ii. The -CN group can be hydrolyzed, to produce a carboxylic acid.
 3. Addition of Grignard and hydride reagents (Section 19.7).
 - a. Addition of Grignard reagents.
 - i. Mg^{2+} complexes with oxygen, making the carbonyl group more electrophilic.
 - ii. R^- adds to the carbonyl carbon to form a tetrahedral intermediate.
 - iii. Water is added in a separate step to protonate the intermediate, yielding an alcohol.
 - iv. Grignard reactions are irreversible because R^- is not a leaving group.
 - b. Hydride addition.
 - i. LiAlH_4 and NaBH_4 act as if they are H^- donors and add to carbonyl compounds to form tetrahedral alkoxide intermediates.
 - ii. In a separate step, water is added to protonate the intermediate, yielding an alcohol.
 4. Addition of amines (Section 19.8).
 - a. Amines add to aldehydes and ketones to form imines and enamines.
 - b. Imines are formed when a primary amine adds to an aldehyde or ketone.
 - i. The process is acid-catalyzed.
 - ii. A proton transfer converts the initial adduct to a carbinolamine.
 - iii. Acid-catalyzed elimination of water yields an imine.

- iv. The reaction rate maximum occurs at $\text{pH} = 4.5$. At this pH , $[\text{H}^+]$ is high enough to catalyze elimination of water, but low enough so that the amine is nucleophilic.
- v. Some imine derivatives are useful for characterizing aldehydes and ketones.
- c. Enamines are produced when aldehydes and ketones react with secondary amines.
The mechanism is similar to that of imine formation, except a proton from the α carbon is lost in the dehydration step.
- 5. Addition of hydrazine: the Wolff–Kishner reaction (Section 19.9).
 - a. Hydrazine reacts with aldehydes and ketones in the presence of KOH to form alkanes.
The intermediate hydrazone undergoes base-catalyzed bond migration, loss of N_2 and protonation to form the alkane.
 - b. The Wolff–Kishner reduction can also be used to convert an acylbenzene to an alkylbenzene.
- 6. Addition of alcohols: acetal formation (Section 19.10).
 - a. In the presence of an acid catalyst, two equivalents of an alcohol can add to an aldehyde or ketone to produce an acetal.
 - i. The initial intermediate is a hemiacetal (a hydroxy ether).
 - ii. Protonation of $-\text{OH}$, loss of water, with formation of an oxonium ion, and addition of a second molecule of ROH yields the acetal.
 - b. The reaction is reversible, so changing the reaction conditions can drive the reaction in either direction.
 - c. Because acetals are inert to many reagents, they can be used as protecting groups in syntheses.
Diols are often used as protecting groups, forming cyclic acetals.
- 7. The Wittig reaction (Section 19.11).
 - a. The Wittig reaction converts an aldehyde or ketone to an alkene.
 - b. Steps in the Wittig reaction:
 - i. An alkyl halide reacts with triphenylphosphine to form an alkyltriphenylphosphonium salt.
 - ii. Butyllithium converts the salt to an ylide.
 - iii. The ylide adds to an aldehyde or ketone to form a dipolar betaine.
 - iv. The betaine forms a four-membered ring intermediate, which decomposes to form the alkene and triphenylphosphine oxide.
 - c. Uses of the Wittig reaction.
 - i. The Wittig reaction can be used to produce mono-, di-, and trisubstituted alkenes, but steric hindrance keeps tetrasubstituted alkenes from forming.
 - ii. The Wittig reaction produces pure alkenes of known stereochemistry (excluding *E,Z* isomers).
- 8. Biological reductions (Section 19.12).
 - a. The Cannizzaro reaction is unique in that the tetrahedral intermediate of addition of a nucleophile to an aldehyde can expel a leaving group.
 - b. Steps in the Cannizzaro reaction.
 - i. HO^- adds to an aldehyde with no α hydrogens to form a tetrahedral intermediate.
 - ii. H^- is expelled and adds to another molecule of aldehyde.
 - iii. The result is a disproportionation reaction, in which one molecule of aldehyde is oxidized and a second molecule is reduced.
 - c. The Cannizzaro reaction isn't synthetically useful, but it resembles the mode of action of the enzyme cofactor NADH .

9. Conjugate addition to α,β -unsaturated aldehydes and ketones (Section 19.13).
 - a. Steps in conjugate addition.
 - i. Because the double bond of an α,β -unsaturated aldehyde/ketone is conjugated with the carbonyl group, addition can occur at the β position, which is an electrophilic site.
 - ii. Protonation of the α carbon of the enolate intermediate results in a product having a carbonyl group and a nucleophile with a 1,3 relationship.
 - b. Conjugate addition of amines.
 - i. Primary and secondary amines add to α,β -unsaturated aldehydes and ketones.
 - ii. The conjugate addition product is often formed exclusively.
 - c. Conjugate addition of water.
 - i. Water can add to yield β -hydroxy aldehydes and ketones.
 - ii. Conjugate addition of water also occurs in living systems.
 - d. Conjugate addition of organocopper reagents.
 - i. Conjugate addition of organocopper reagents alkylates the double bond of α,β -unsaturated aldehydes and ketones.
 - ii. This type of addition doesn't occur with other organometallic reagents.
 - iii. The mechanism may involve addition of the diorganocopper anion, followed by transfer of an R group.

III. Spectroscopy of aldehydes and ketones (Section 19.14).

A. IR spectroscopy.

1. The C=O absorption of aldehydes and ketones occurs in the range 1660–1770 cm^{-1} .
 - a. The exact position of absorption can be used to distinguish between an aldehyde and a ketone.
 - b. The position of absorption also gives information about other structural features, such as unsaturation and angle strain.
 - c. The absorption values are constant from one compound to another.
2. Aldehydes also show absorptions in the range 2720–2820 cm^{-1} .

B. NMR spectroscopy.

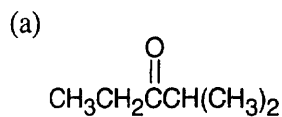
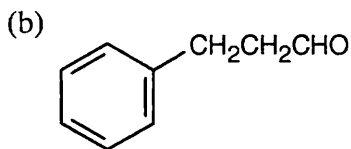
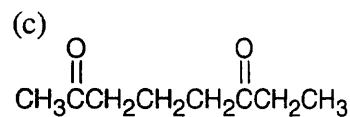
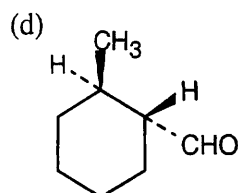
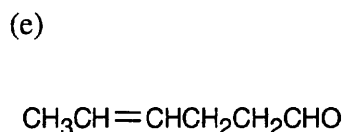
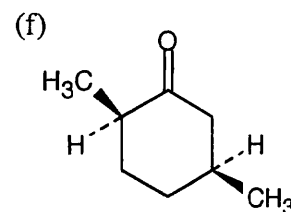
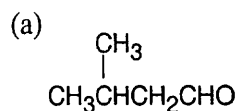
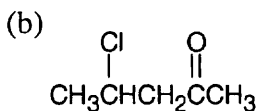
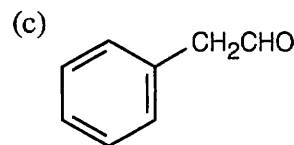
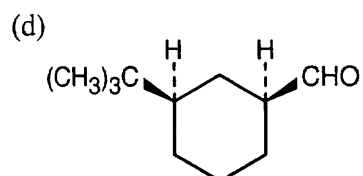
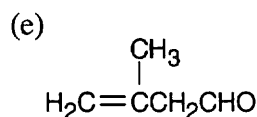
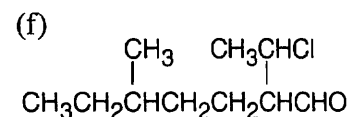
1. ^1H NMR spectroscopy.
 - a. Aldehyde protons absorb near 10 δ , and show spin–spin coupling with protons on the adjacent carbon.
 - b. Hydrogens on the carbon next to a carbonyl group absorb near 2.0–2.3 δ .
Methyl ketone protons absorb at 2.1 δ .
2. ^{13}C NMR spectroscopy.
 - a. The carbonyl-group carbons absorb in the range 190–215 δ .
 - b. These absorptions characterize aldehydes and ketones.
 - c. Unsaturation lowers the value of δ .

C. Mass spectrometry.

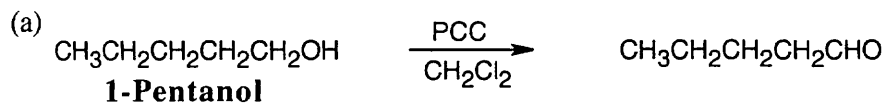
1. Some aliphatic aldehydes and ketones undergo McLafferty rearrangement.
 - a. A hydrogen on the γ carbon is transferred to the carbonyl oxygen, the bond between the α carbon and the β carbon is broken, and a neutral alkene fragment is produced.
 - b. The remaining cation radical is detected.
2. Alpha cleavage.
 - a. The bond between the carbonyl group and the α carbon is cleaved.
 - b. The products are a neutral radical and an acyl cation, which is detected.

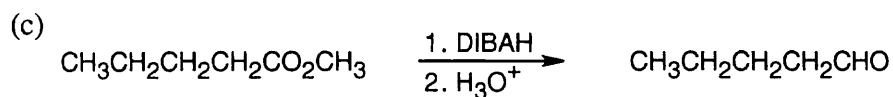
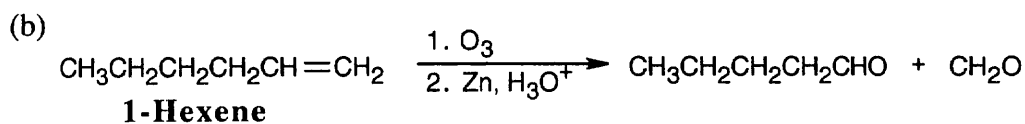
Solutions to Problems

19.1 Remember that the principal chain must contain the aldehyde or ketone group and that an aldehyde group occurs only at the end of a chain. The aldehyde carbon is carbon 1 in an acyclic compound, and the suffix *-carbaldehyde* is used when the aldehyde group is attached to a ring.

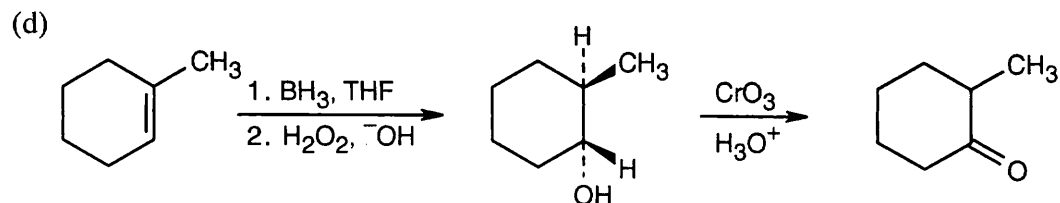
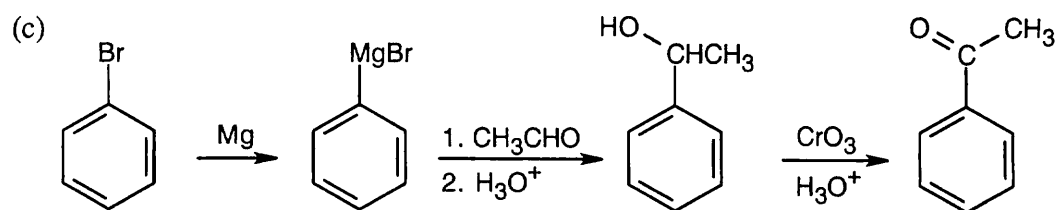
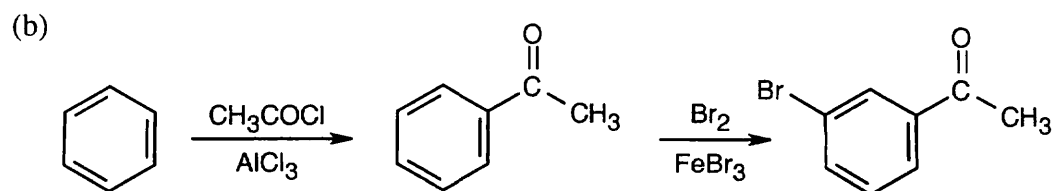
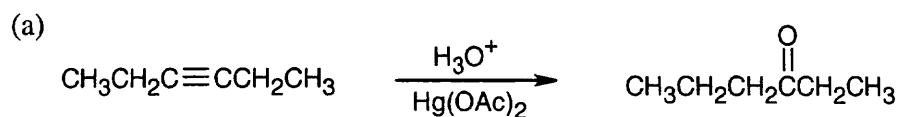
**2-Methyl-3-pentanone****3-Phenylpropanal****2,6-Octanedione*****trans*-2-Methylcyclohexanecarbaldehyde****4-Hexenal*****cis*-2,5-Dimethylcyclohexanone****19.2****3-Methylbutanal****4-Chloro-2-pentanone****Phenylacetaldehyde*****cis*-3-*tert*-Butylcyclohexanecarbaldehyde****3-Methyl-3-butenal****2-(1-Chloroethyl)-5-methylheptanal**

19.3 We have seen the first two methods of aldehyde preparation in earlier chapters.

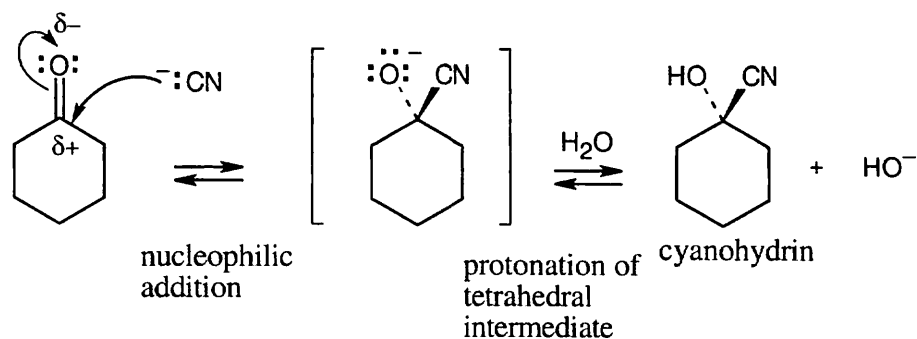




19.4 All of these methods are familiar.

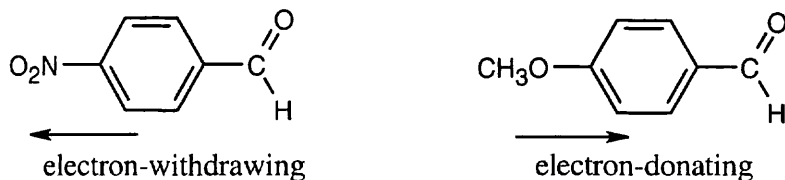


19.5



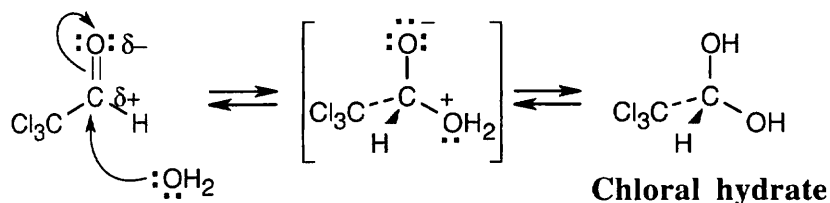
Cyanide anion adds to the positively polarized carbonyl carbon to form a tetrahedral intermediate. This intermediate is protonated to yield the cyanohydrin.

19.6

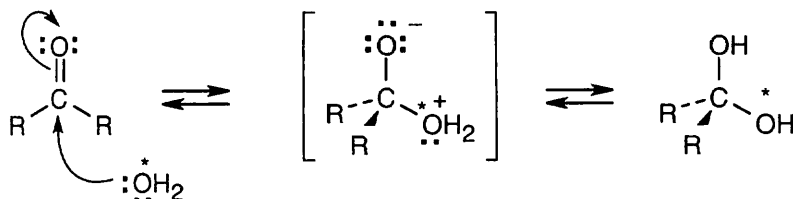


The electron-withdrawing nitro group makes the aldehyde carbon of *p*-nitrobenzaldehyde more electron-poor (more electrophilic) and more reactive toward nucleophiles than the aldehyde carbon of *p*-methoxybenzaldehyde.

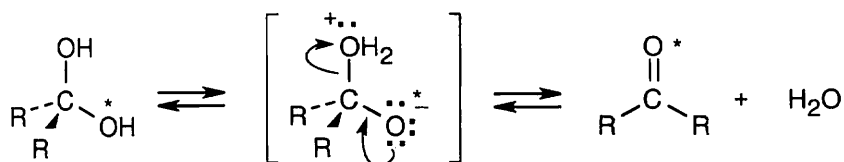
19.7



19.8

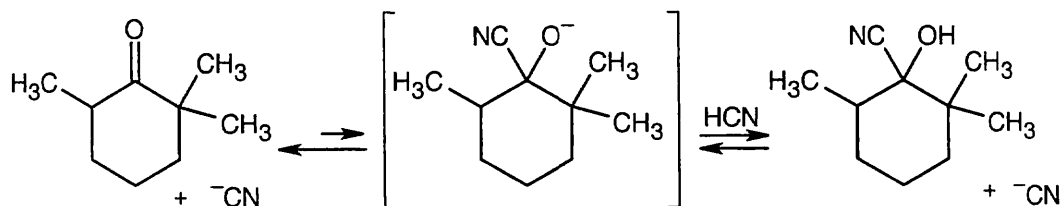


The above mechanism is similar to other nucleophilic addition mechanisms we have studied. Since all steps are reversible, we can write the above mechanism in reverse to show how labeled oxygen is incorporated into an aldehyde or ketone.



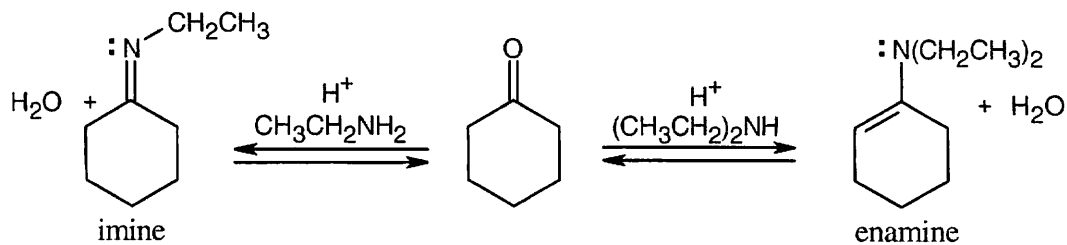
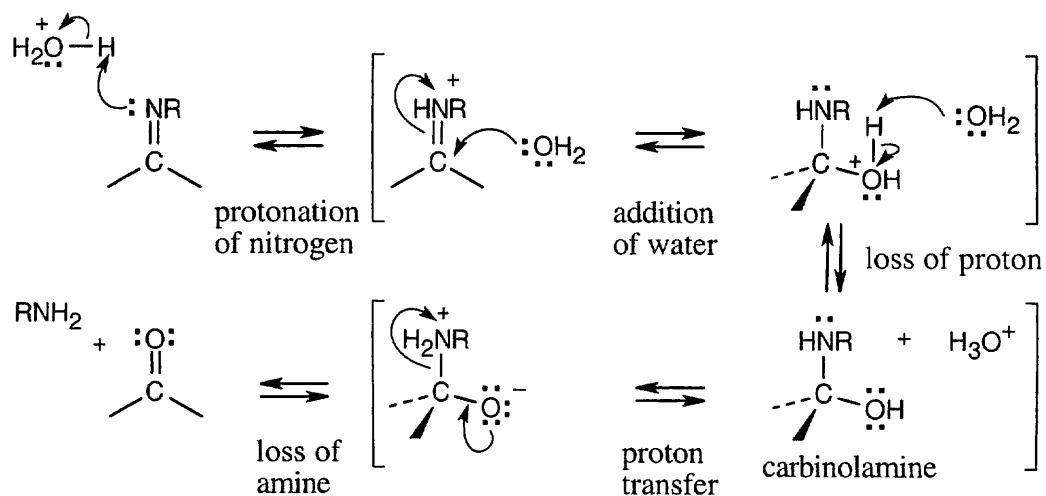
This exchange is very slow in water but proceeds more rapidly when either acid or base is present.

19.9

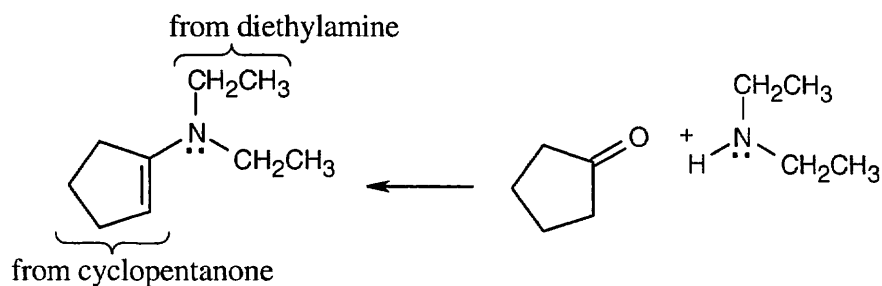
**2,2,6-Trimethylcyclohexanone**

Cyanohydrin formation is an equilibrium process. Because formation of the product of addition of HCN to 2,2,6-trimethylcyclohexanone is sterically hindered by the three methyl groups, the equilibrium lies toward the side of the unreacted ketone.

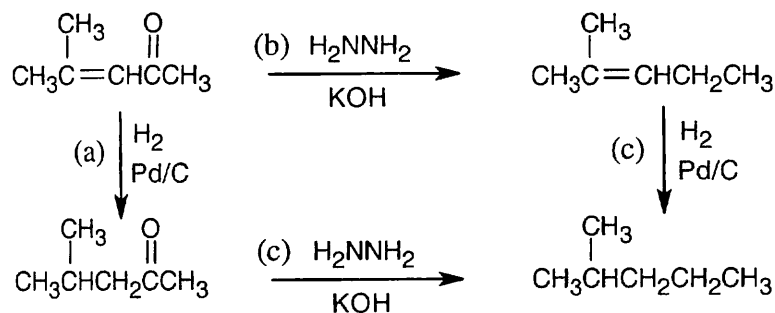
- 19.10** Reaction of a ketone or aldehyde with a primary amine yields an imine, in which $C=O$ has been replaced by $C=NR$. Reaction of a ketone or aldehyde with a secondary amine yields an enamine, in which $C=O$ has been replaced by $C-NR_2$, and the double bond has moved.

**19.11**

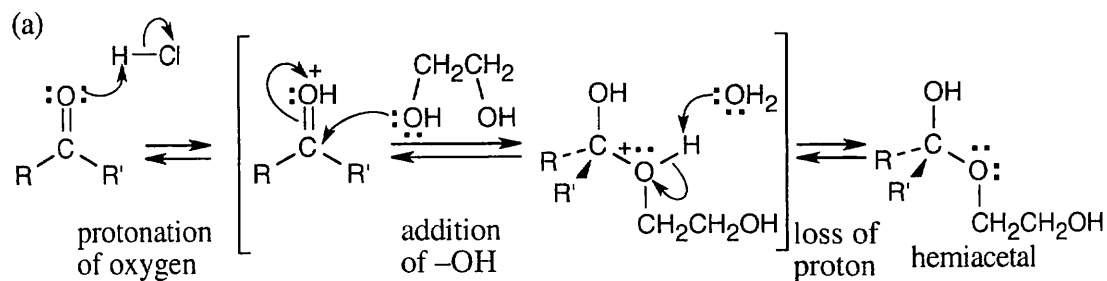
- 19.12** The structure is an enamine, which is prepared from a ketone and a secondary amine. Find the components and draw the reaction.



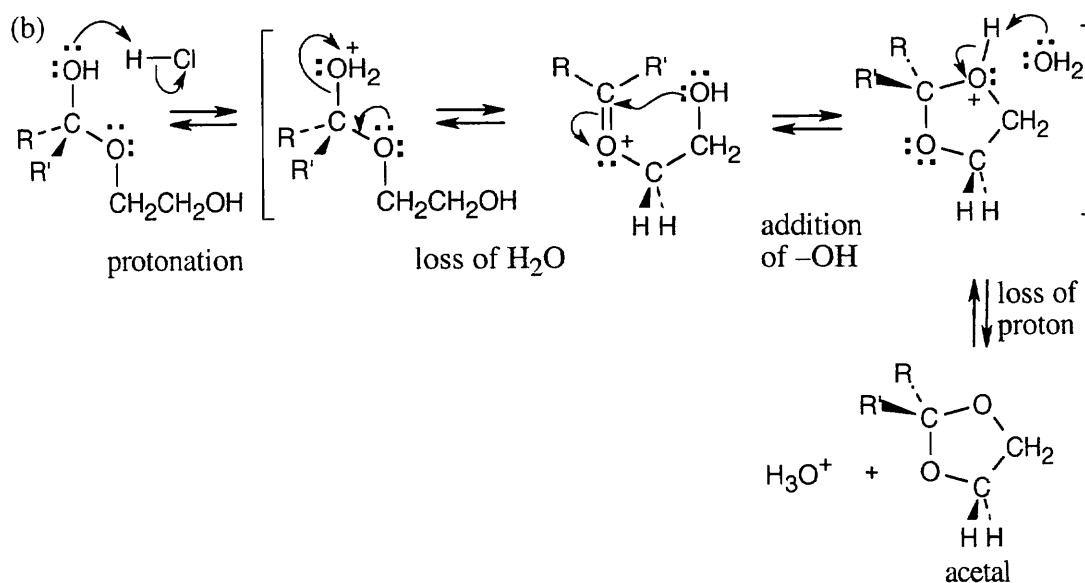
19.13



19.14



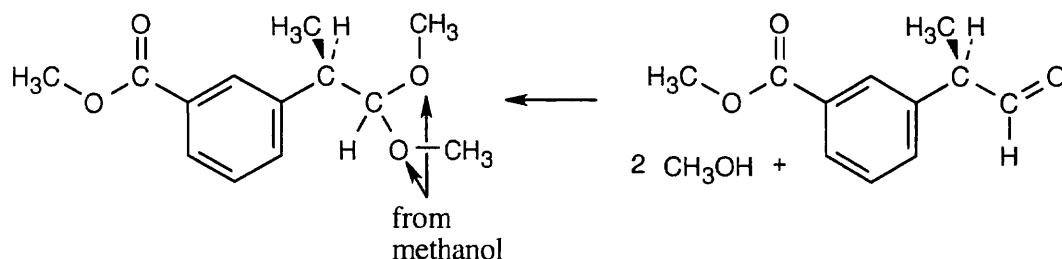
Formation of the hemiacetal is the first step.



Protonation of the hemiacetal hydroxyl group is followed by loss of water. Attack by the second hydroxyl group of ethylene glycol forms the cyclic acetal ring.

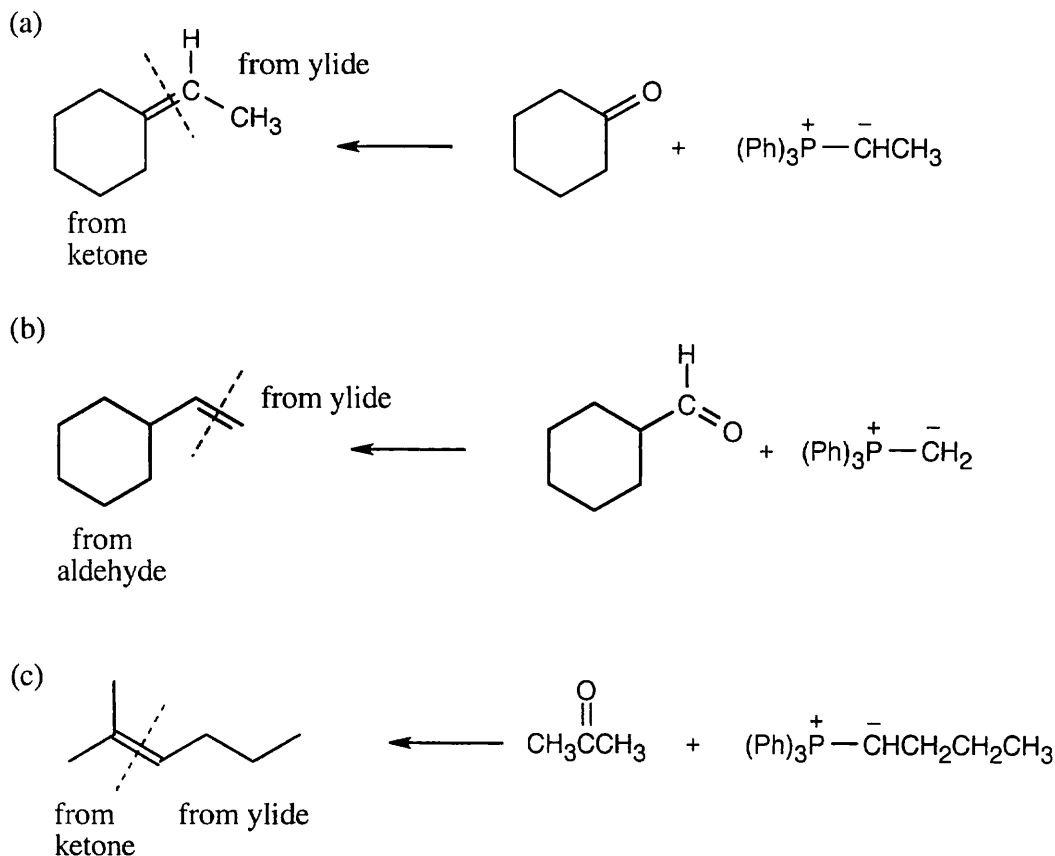
19.15 Strategy: Locate the two identical $-\text{OR}$ groups to identify the alcohol that was used to form the acetal. (The illustrated acetal was formed from methanol.) Replace these two $-\text{OR}$ groups by $=\text{O}$ to find the carbonyl compound.

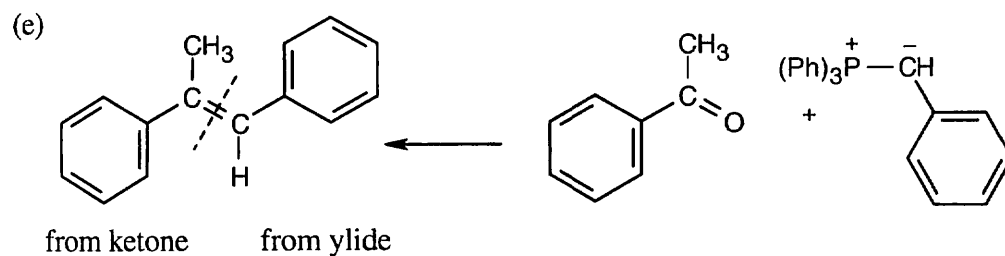
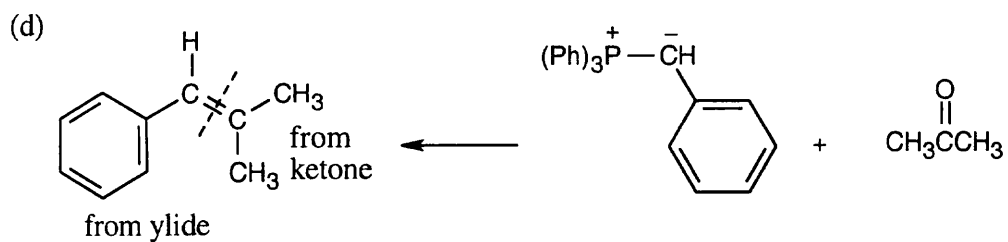
Solution:



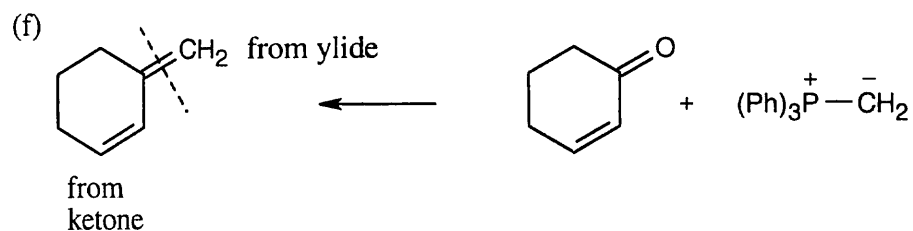
19.16 Strategy: Locate the double bond that is formed by the Wittig reaction. The simpler or less substituted component comes from the ylide, and the more substituted component comes from the aldehyde or ketone. Triphenylphosphine oxide is a byproduct of all these reactions.

Solution:

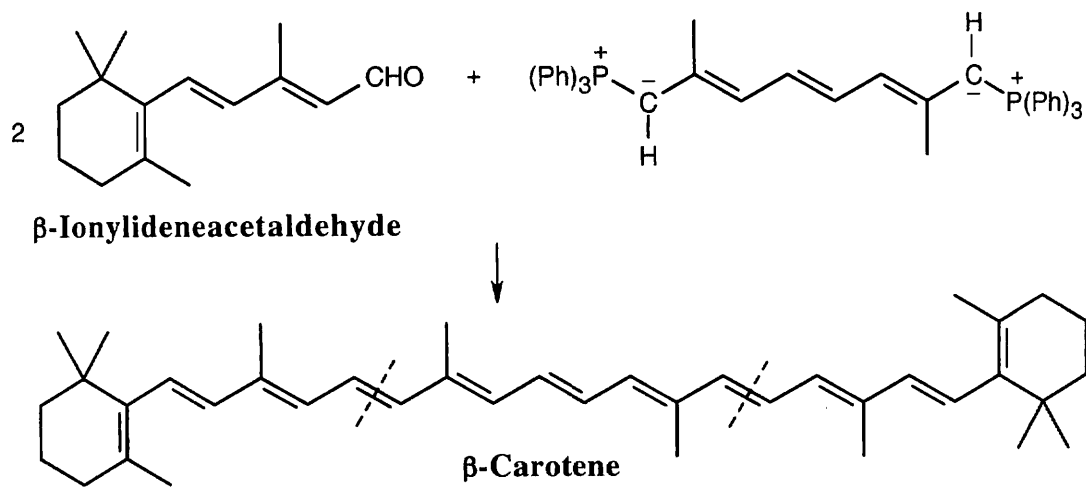




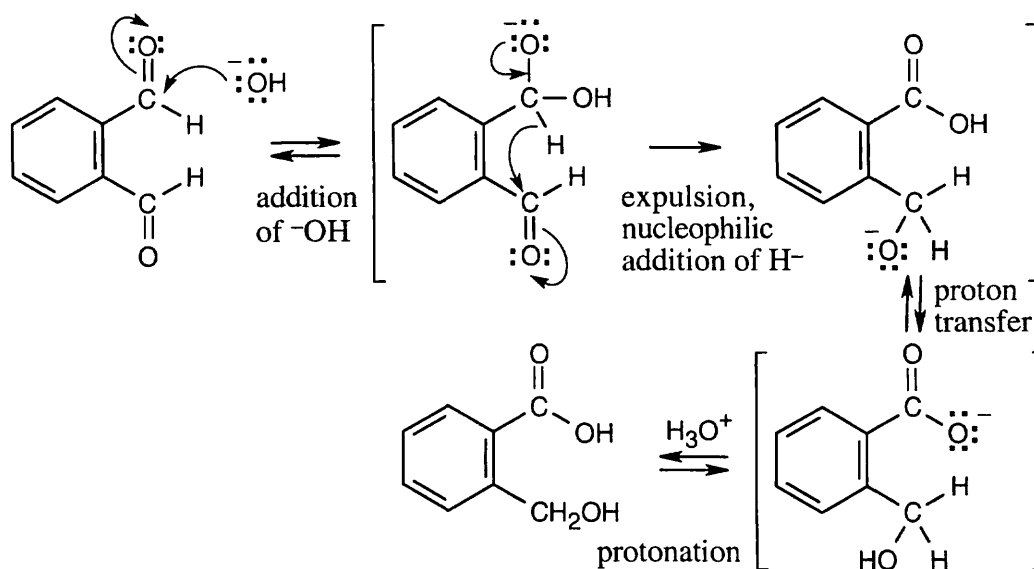
The Z isomer is also produced.



19.17

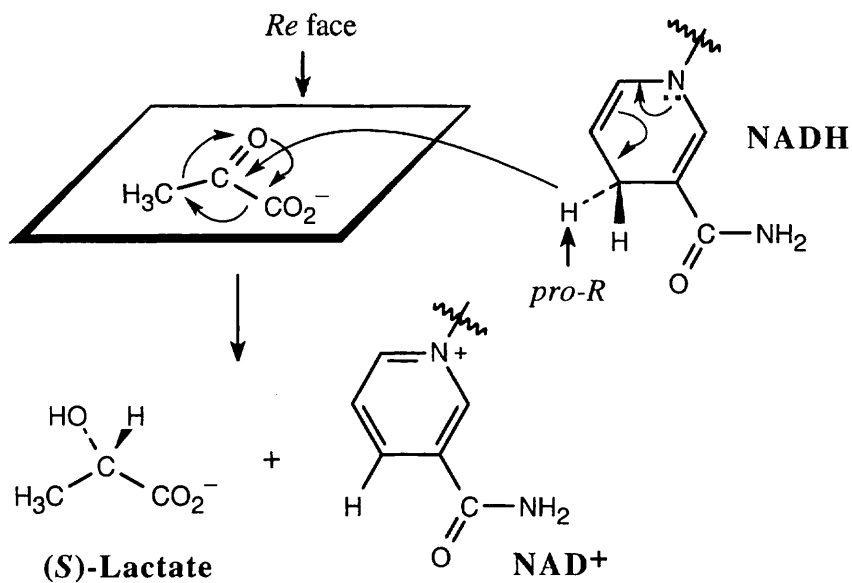


19.18

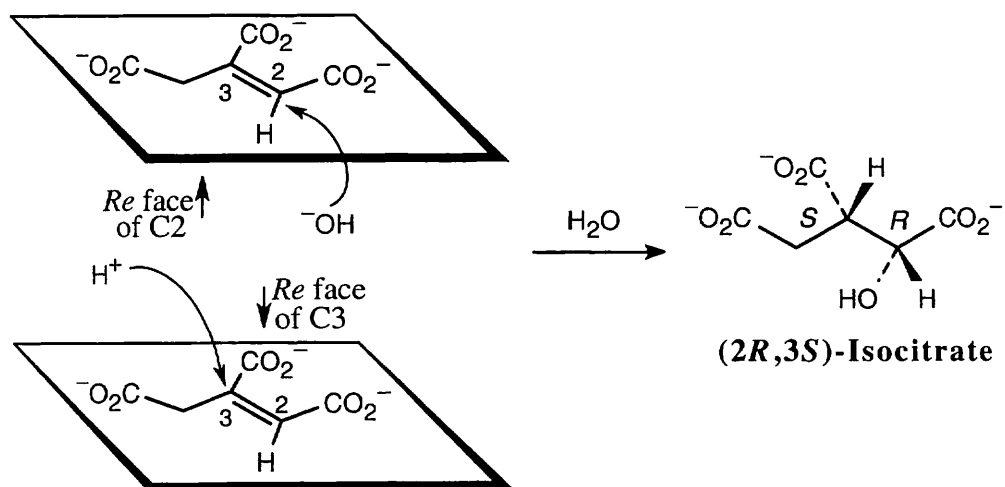


This is an intramolecular Cannizzaro reaction.

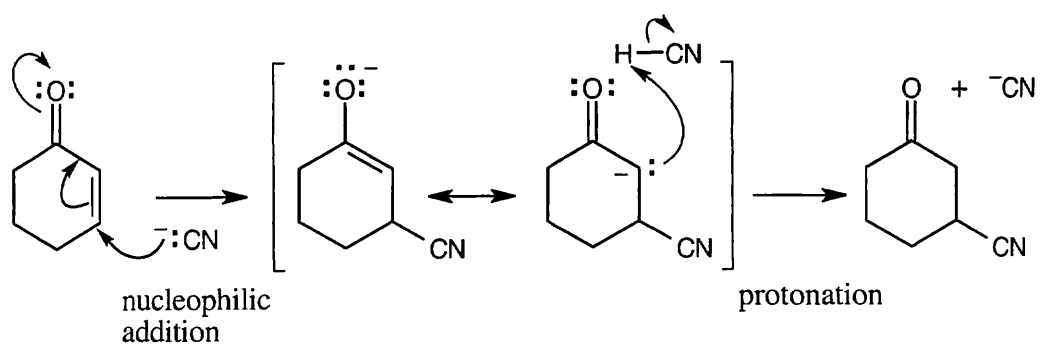
19.19 Addition of the *pro-R* hydrogen of NADH takes place at the *Re* face of pyruvate.



19.20 The -OH group adds to the *Re* face at carbon 2, and -H^+ adds to the *Re* face at carbon 3, to yield (2*R*,3*S*)-isocitrate.



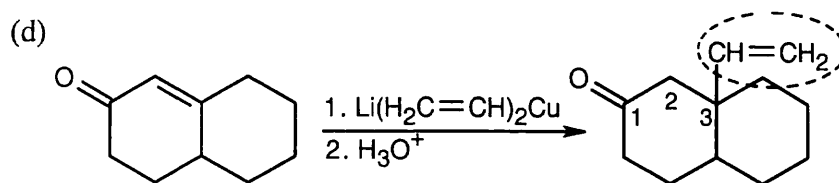
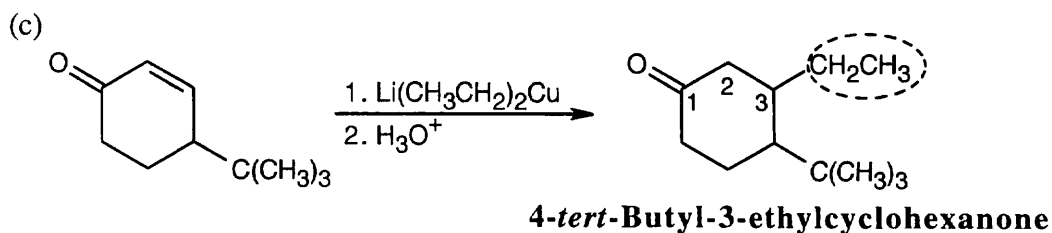
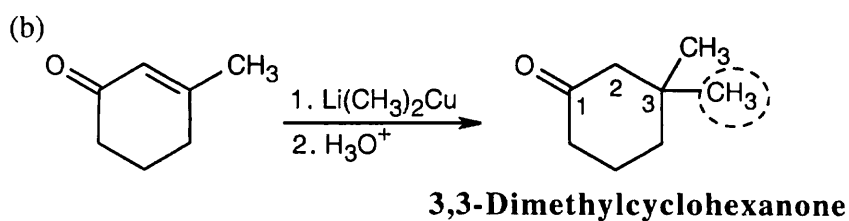
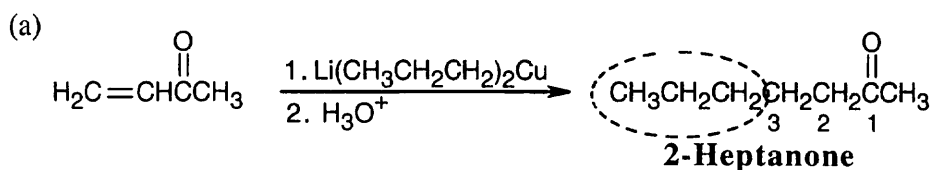
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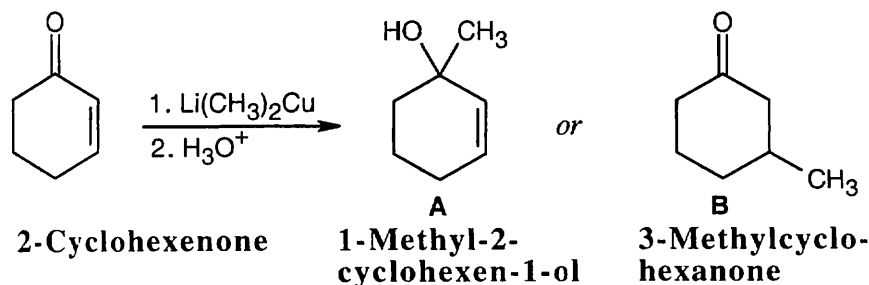
19.22 Strategy: To choose the reactants that form a conjugate addition product, follow these steps:

- (1) Give to the aldehyde or ketone carbon the number "1", and count two carbons away from the carbonyl carbon. The double bond in the α, β -unsaturated starting material connected the carbons numbered "2" and "3".
- (2) The grouping bonded to the "3" carbon (circled here) came from the alkyllithium reagent.

Solution:



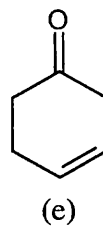
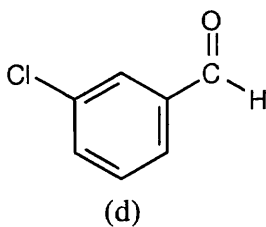
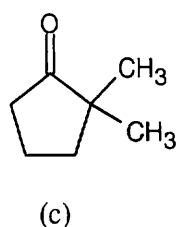
19.23



2-Cyclohexenone is a cyclic α,β -unsaturated ketone whose carbonyl IR absorption occurs at 1685 cm^{-1} . If direct addition product **A** is formed, the carbonyl absorption will vanish and a hydroxyl absorption will appear at 3300 cm^{-1} . If conjugate addition produces **B**, the carbonyl absorption will shift to 1715 cm^{-1} , where 6-membered-ring saturated ketones absorb.

19.24 (a) $\text{H}_2\text{C}=\text{CHCH}_2\text{COCH}_3$ absorbs at 1715 cm^{-1} . (4-Penten-2-one is not an α,β -unsaturated ketone.)

(b) $\text{CH}_3\text{CH}=\text{CHCOCH}_3$ is an α,β -unsaturated ketone and absorbs at 1685 cm^{-1} .



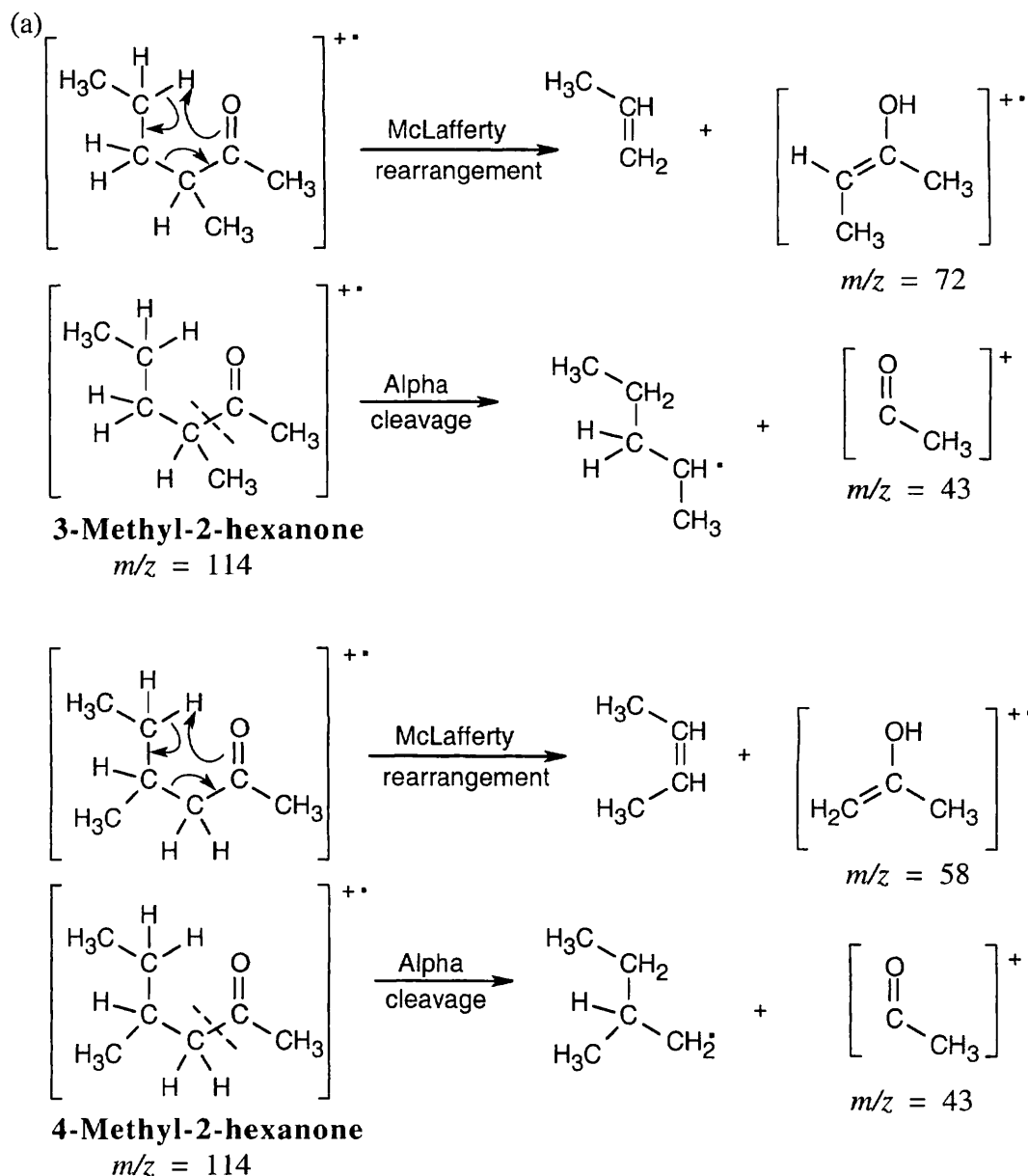
(c) 2,2-Dimethylcyclopentanone, a five-membered-ring ketone, absorbs at 1750 cm^{-1} .

(d) *m*-Chlorobenzaldehyde shows an absorption at 1705 cm^{-1} and two absorptions at 2720 cm^{-1} and 2820 cm^{-1} .

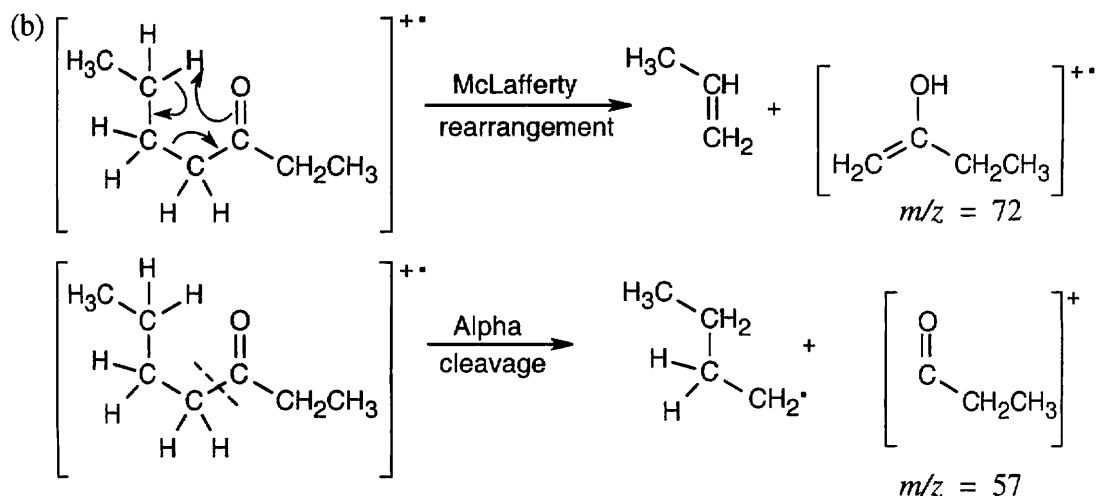
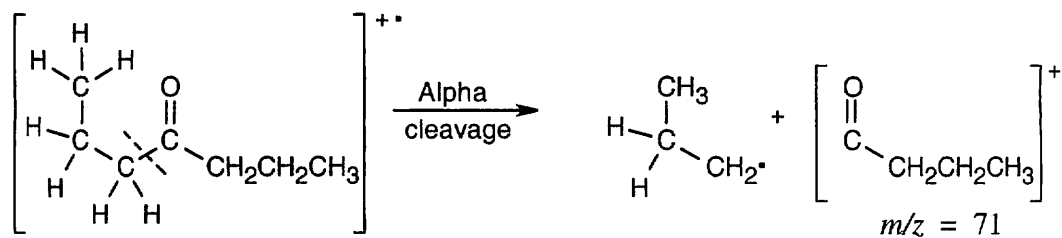
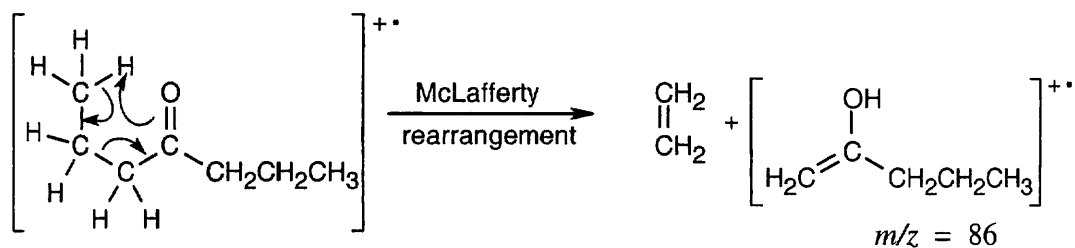
(e) 3-Cyclohexenone absorbs at 1715 cm^{-1} .

(f) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}=\text{CHCHO}$ is an α,β -unsaturated aldehyde and absorbs at 1705 cm^{-1} .

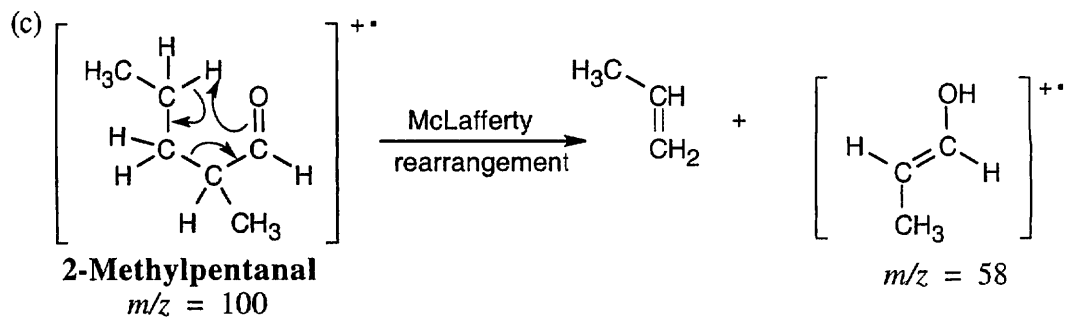
19.25 In mass spectra, only charged particles are detected. The McLafferty rearrangement produces an uncharged alkene (not detected) and an oxygen-containing fragment, which is a cation radical and is detected. Alpha cleavage produces a neutral radical (not detected) and an oxygen-containing cation, which is detected. Since alpha cleavage occurs primarily on the more substituted side of the aldehyde or ketone, only this cleavage is shown.

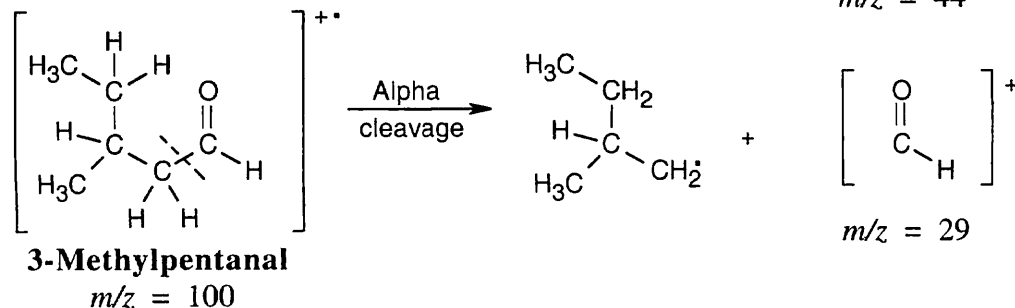
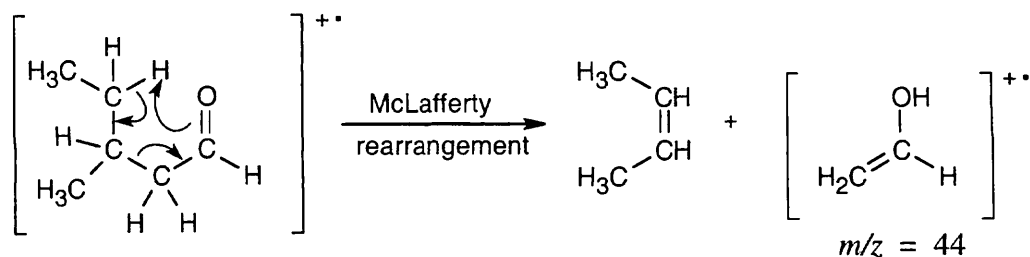
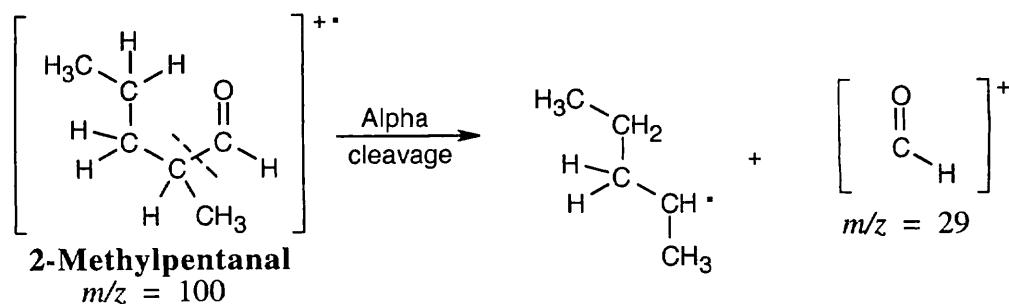


Both isomers exhibit peaks at $m/z = 43$ due to α -cleavage. The products of McLafferty rearrangement, however, occur at different values of m/z and can be used to identify each isomer.

**3-Heptanone** $m/z = 114$ **4-Heptanone** $m/z = 114$

The isomers can be distinguished on the basis of both α -cleavage products ($m/z = 57$ vs $m/z = 71$) and McLafferty rearrangement products ($m/z = 72$ vs $m/z = 86$).

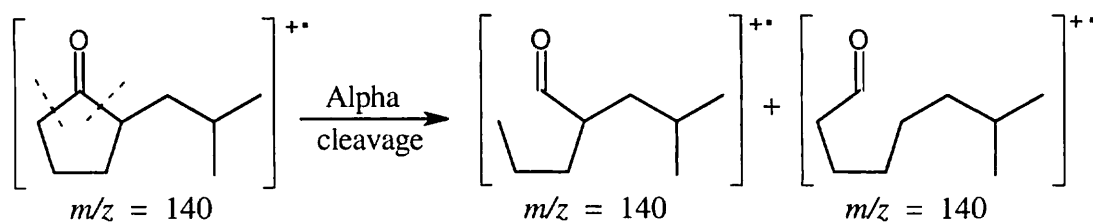




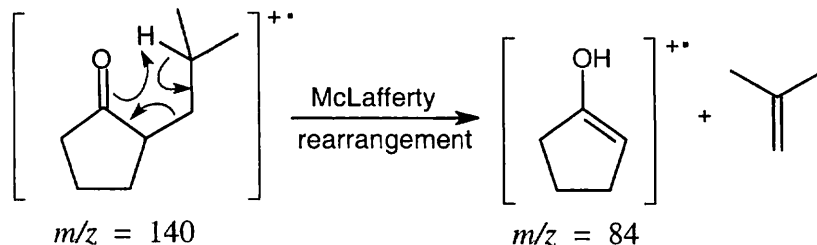
The fragments from McLafferty rearrangement, which occur at different values of m/z , serve to distinguish the two isomers.

19.26 IR: The only important IR absorption for the compound is seen at 1750 cm^{-1} , where 5-membered ring ketones absorb.

Mass spectrum: The products of alpha cleavage, which occurs in the ring, have the same mass as the molecular ion.



The charged fragment resulting from the McLafferty rearrangement appears at $m/z = 84$.

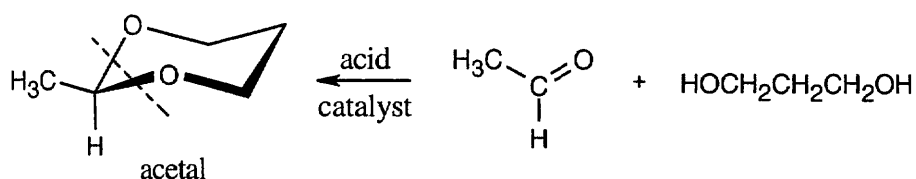


Visualizing Chemistry

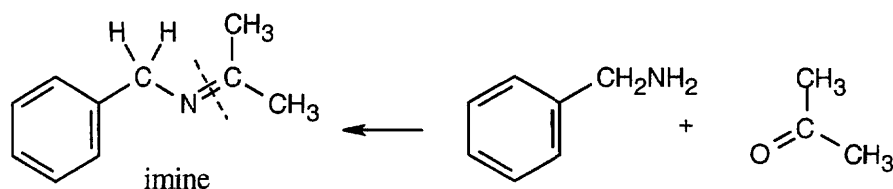
19.27 Strategy: It helps to know that all of these substances were prepared from aldehydes or ketones. Look for familiar groupings of atoms to identify the starting materials.

Solution:

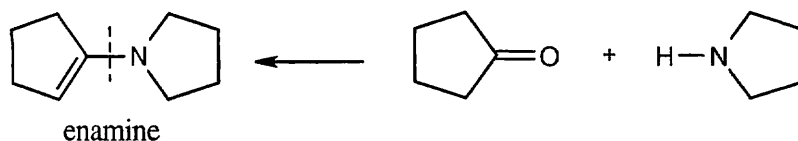
(a) Notice that the substance pictured is a cyclic acetal. The starting materials were a diol (because cyclic acetals are prepared from diols) and an aldehyde (because an $-H$ is bonded to the acetal carbon). Replace the two $-OR$ groups with $=O$ to identify the aldehyde starting material.



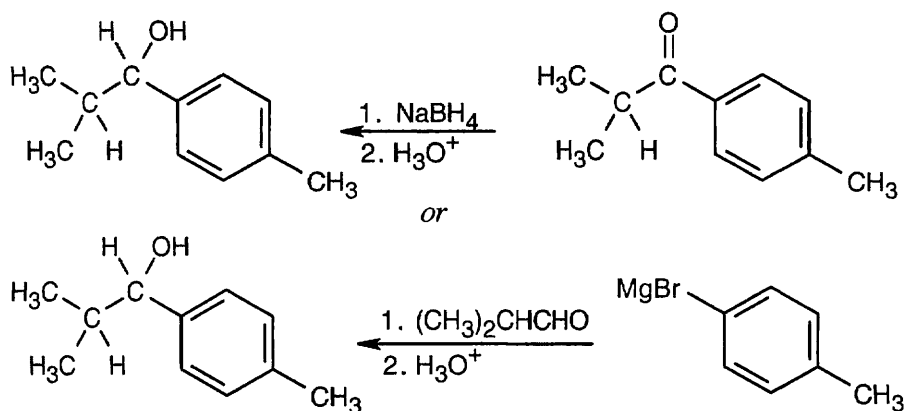
(b) We know that the product is an imine because it contains a carbon-nitrogen double bond. The carbon that is part of the $C=N$ bond came from a ketone, and the nitrogen came from a primary amine.



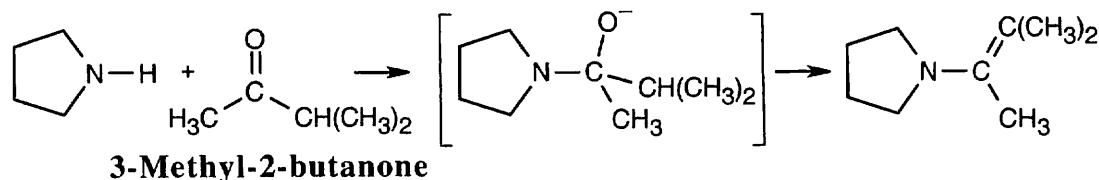
(c) The product is an enamine, formed from a ketone and a secondary amine. Nitrogen is bonded to the carbon that once bore the carbonyl oxygen.



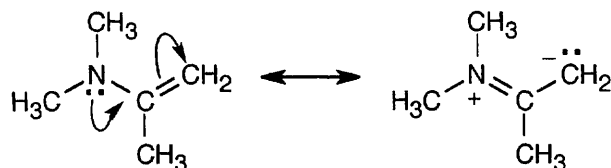
(d) The secondary alcohol product might have been formed by either of two routes – by reduction of a ketone or by Grignard addition to an aldehyde.



- 19.28** The intermediate results from the addition of an amine to a ketone. The product is an enamine because the amine nitrogen in the carbinolamine intermediate comes from a secondary amine.

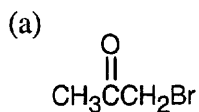


- 19.29** (a) The nitrogen atom is sp^2 -hybridized, and the geometry is trigonal planar.
 (b) A p orbital holds the lone-pair electrons of nitrogen.
 (c) The p orbital holding the lone-pair electrons of nitrogen is aligned for overlap with the π electrons of the enamine double bond. With this geometry, the nitrogen lone-pair electrons can be conjugated with the double bond.

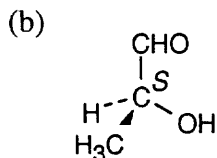


Additional Problems

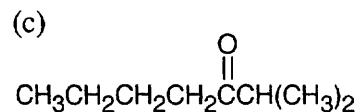
19.30



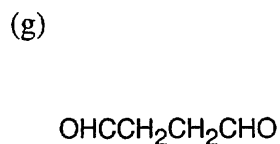
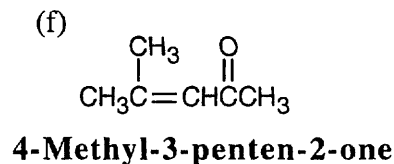
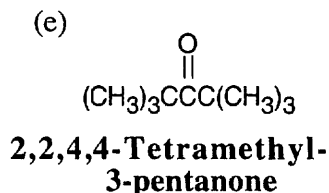
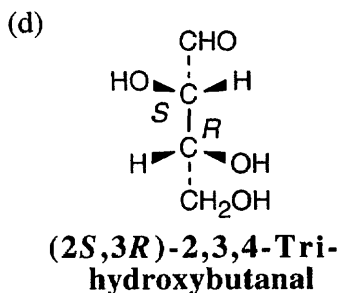
Bromoacetone



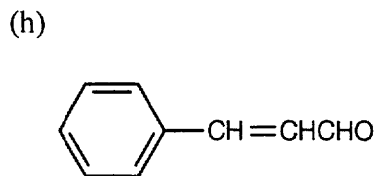
(S)-2-Hydroxypropanal



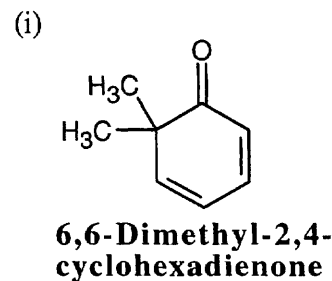
2-Methyl-3-heptanone

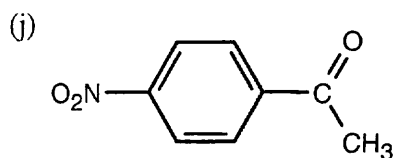


Butanedial

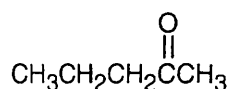
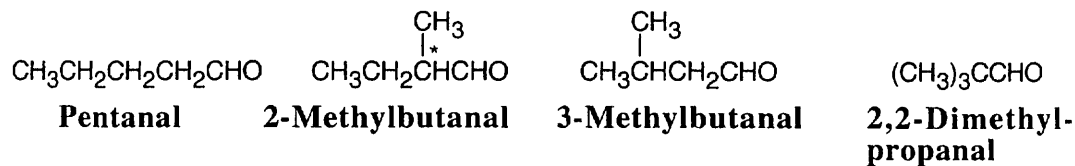
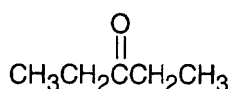
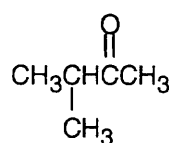


3-Phenyl-2-propenal

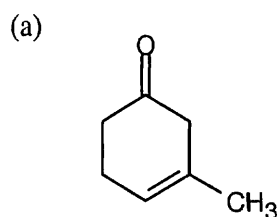
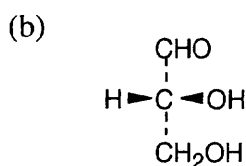
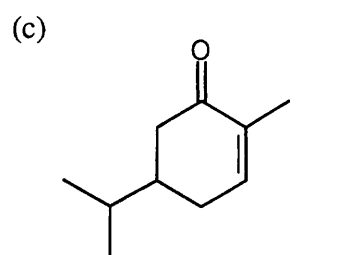
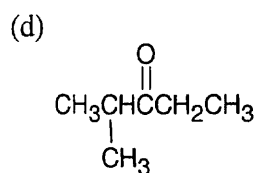
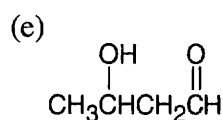
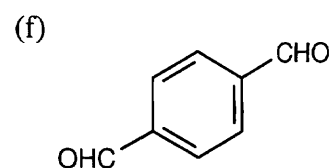


***p*-Nitroacetophenone**

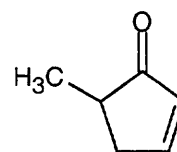
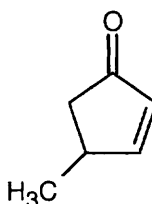
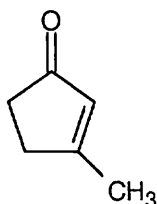
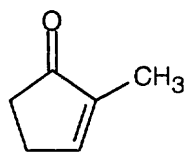
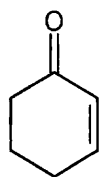
19.31 Only 2-methylbutanal is chiral.

**2-Pentanone****3-Pentanone****3-Methyl-2-butanone**

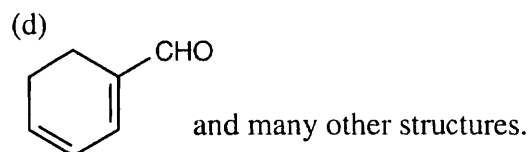
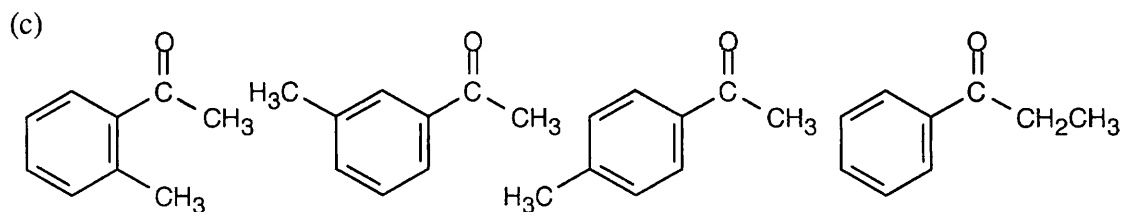
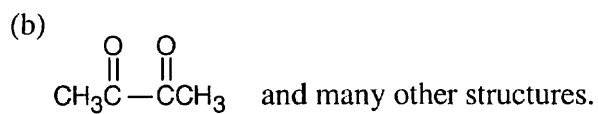
19.32

**3-Methyl-3-cyclohexenone****(*R*)-2,3-Dihydroxypropanal (D-Glyceraldehyde)****5-Isopropyl-2-methyl-2-cyclohexenone****2-Methyl-3-pentanone****3-Hydroxybutanal*****p*-Benzenedicarbaldehyde**

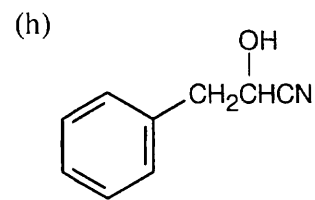
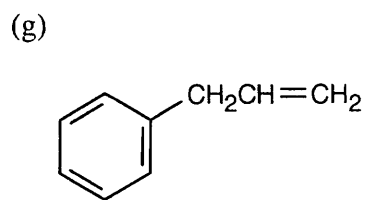
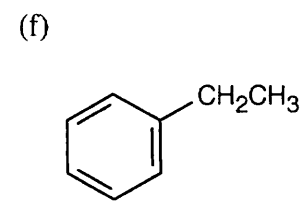
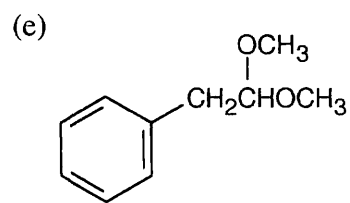
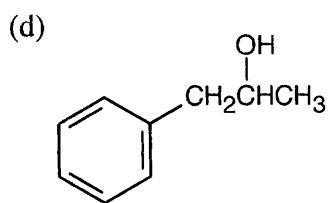
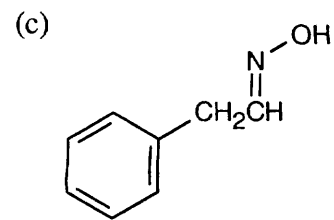
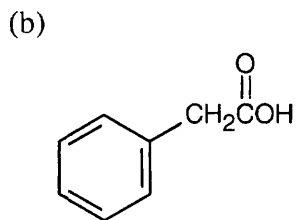
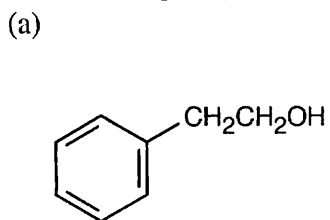
19.33 (a) The α,β -unsaturated ketone $\text{C}_6\text{H}_8\text{O}$ contains one ring. Possible structures include:



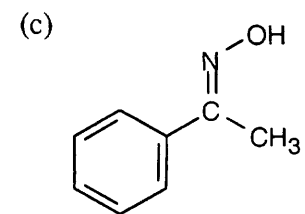
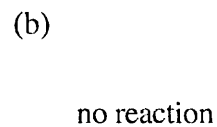
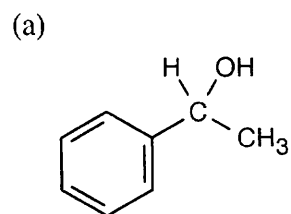
Cyclobutenones and cyclopropanones are also possible.

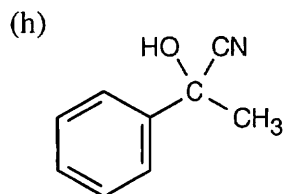
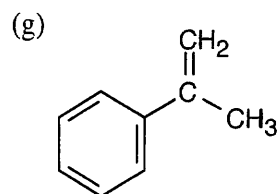
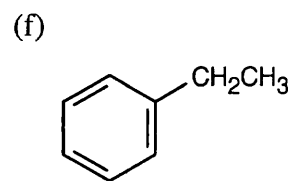
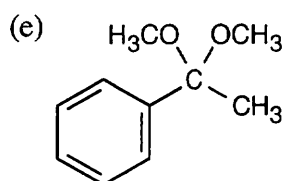
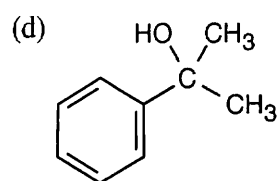


19.34 Reactions of phenylacetaldehyde:

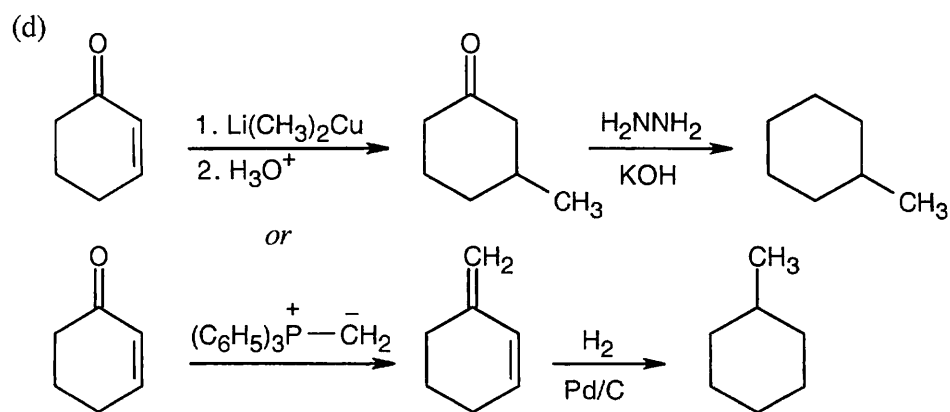
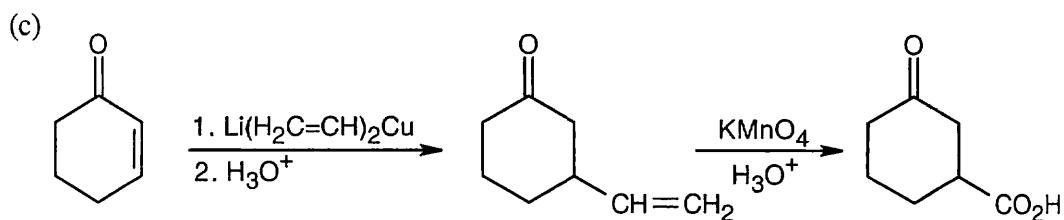
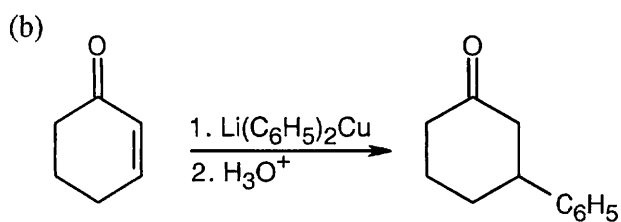
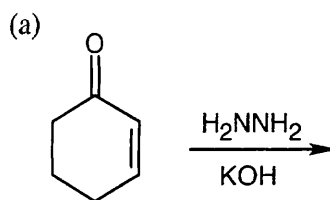


Reactions of acetophenone:

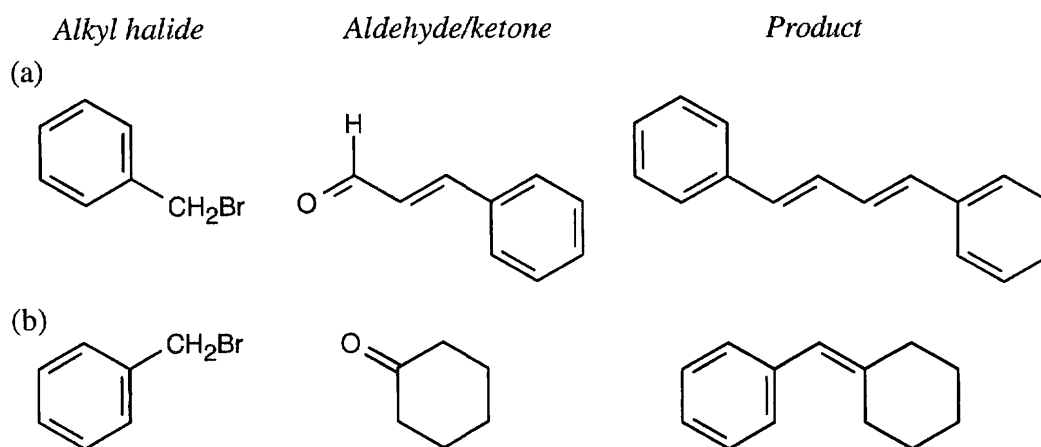
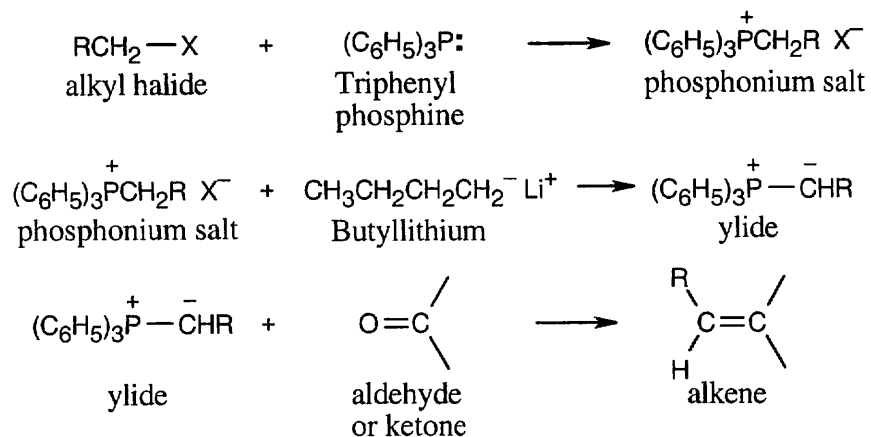




19.35



19.36 Remember:

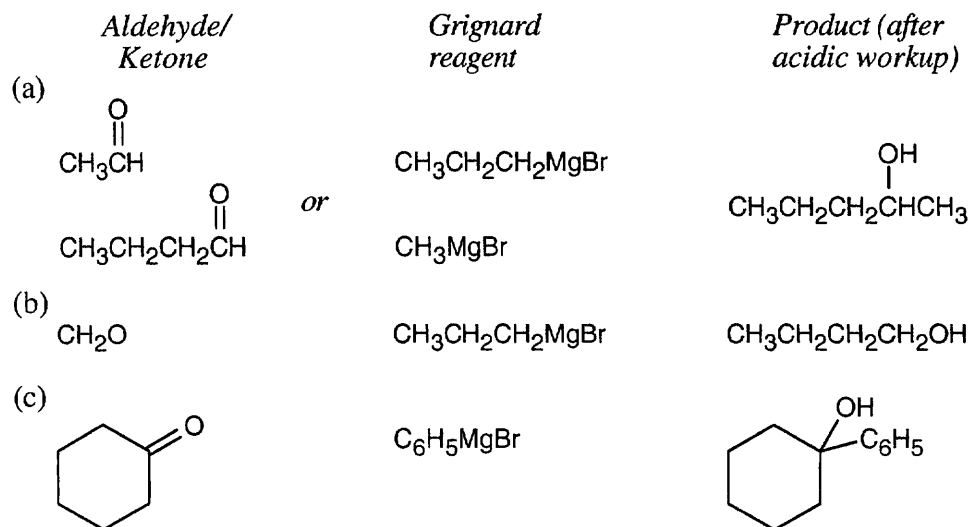


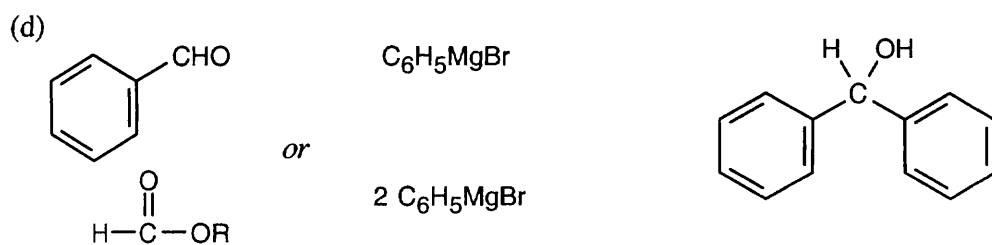
19.37 Remember from Chapter 17:

Primary alcohols are formed from formaldehyde + Grignard reagent.

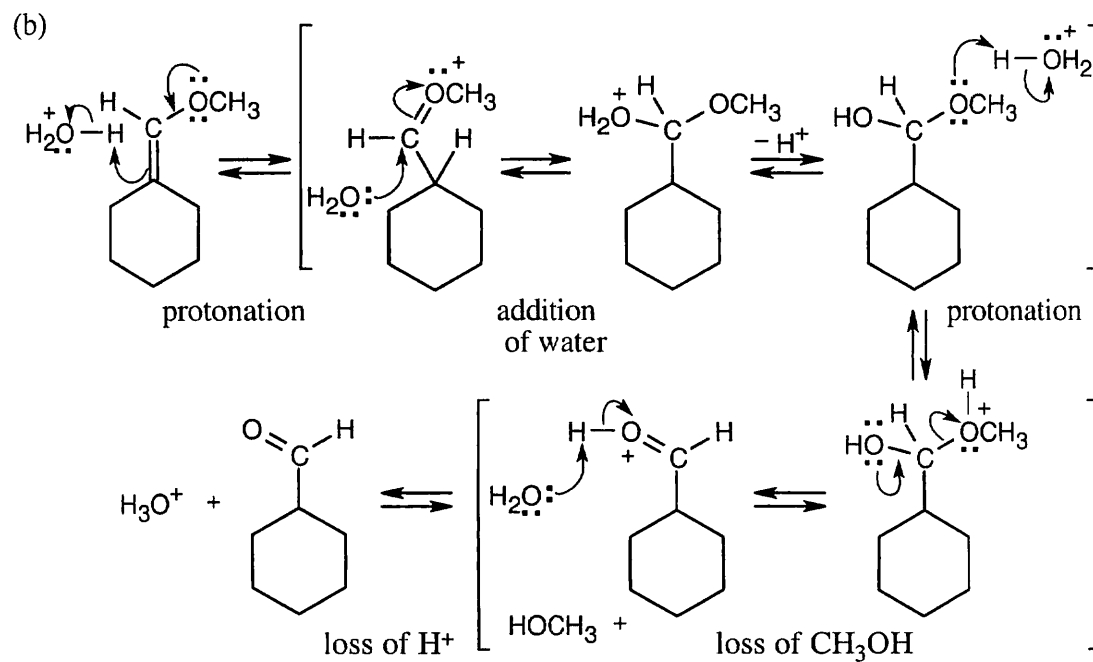
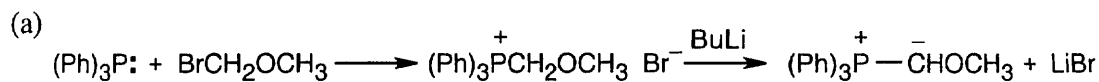
Secondary alcohols are formed from an aldehyde + Grignard reagent.

Tertiary alcohols are formed from a ketone (or an ester) + Grignard reagent.

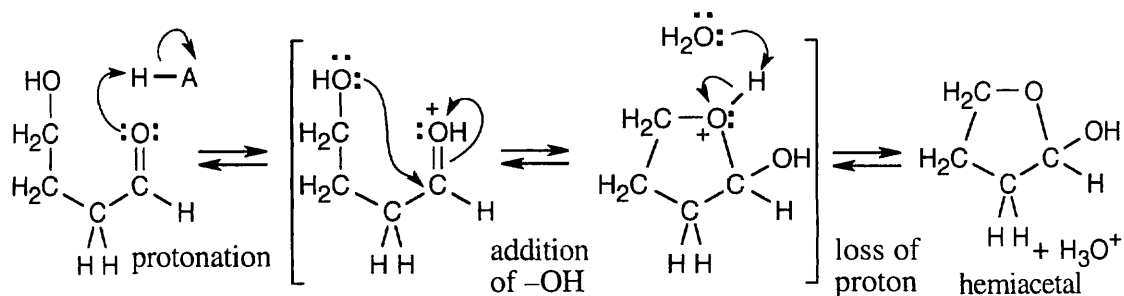




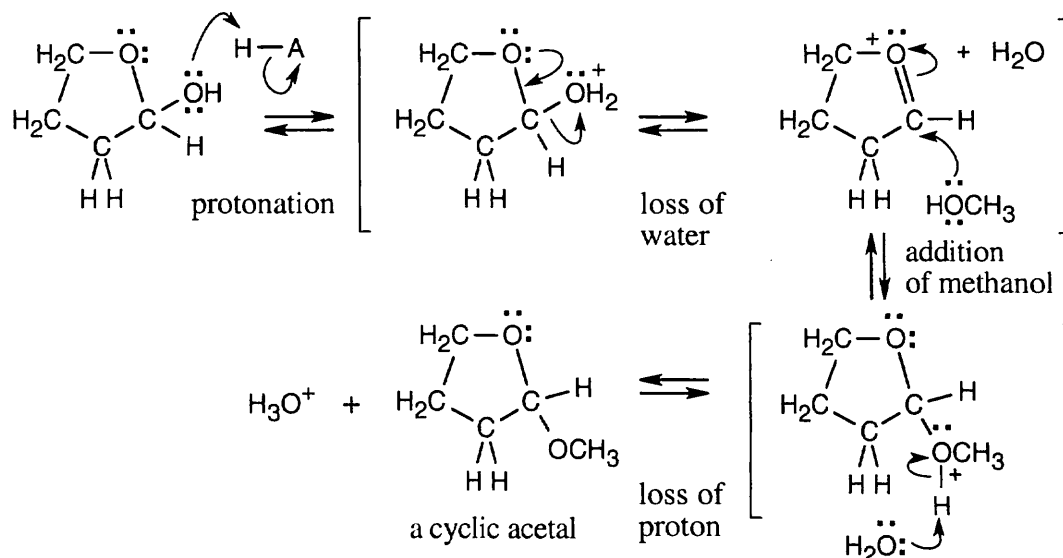
19.38



19.39 4-Hydroxybutanal forms a cyclic hemiacetal when the hydroxyl oxygen adds to the aldehyde group.



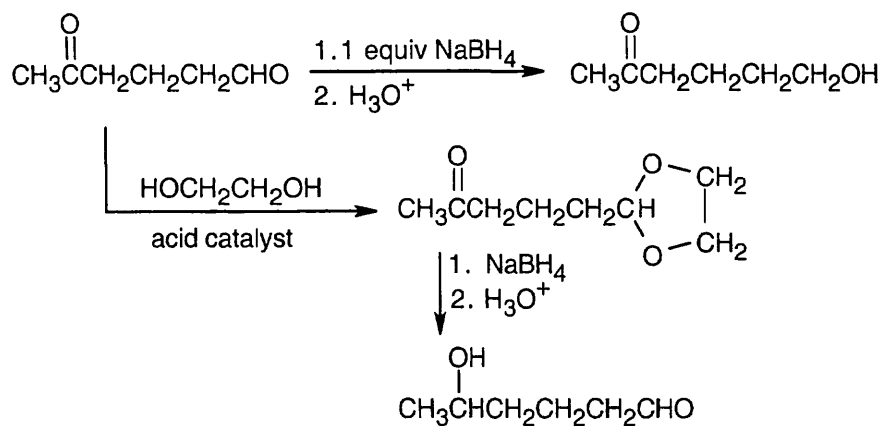
Methanol reacts with the cyclic hemiacetal to form 2-methoxytetrahydrofuran.



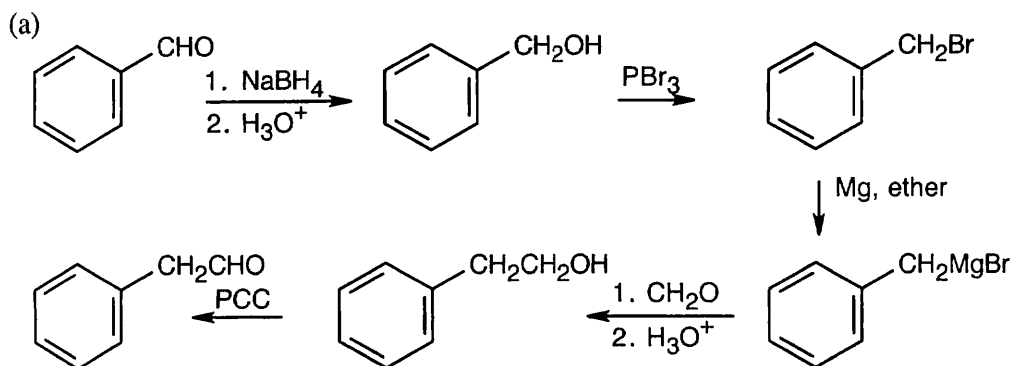
2-Methoxytetrahydrofuran is a cyclic acetal. The hydroxyl oxygen of 4-hydroxybutanal reacts with the aldehyde to form the cyclic ether linkage.

19.40 In general, ketones are less reactive than aldehydes for both steric (excess crowding) and electronic reasons. If the keto aldehyde in this problem were reduced with one equivalent of NaBH₄, the aldehyde functional group would be reduced in preference to the ketone.

For the same reason, reaction of the keto aldehyde with one equivalent of ethylene glycol selectively forms the acetal of the aldehyde functional group. The ketone can then be reduced with NaBH₄ and the acetal protecting group can be removed.

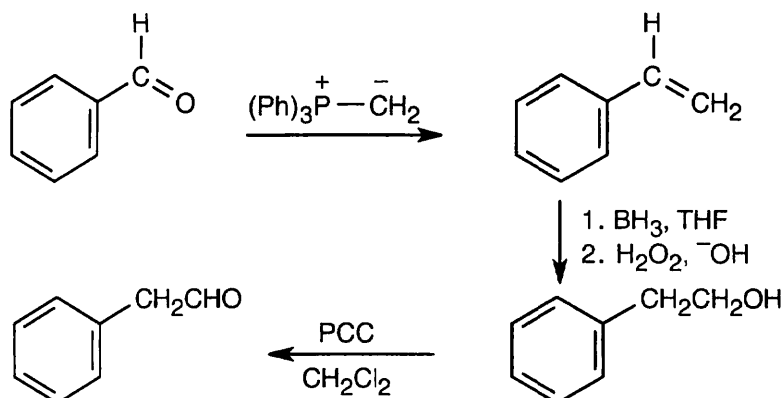


19.41

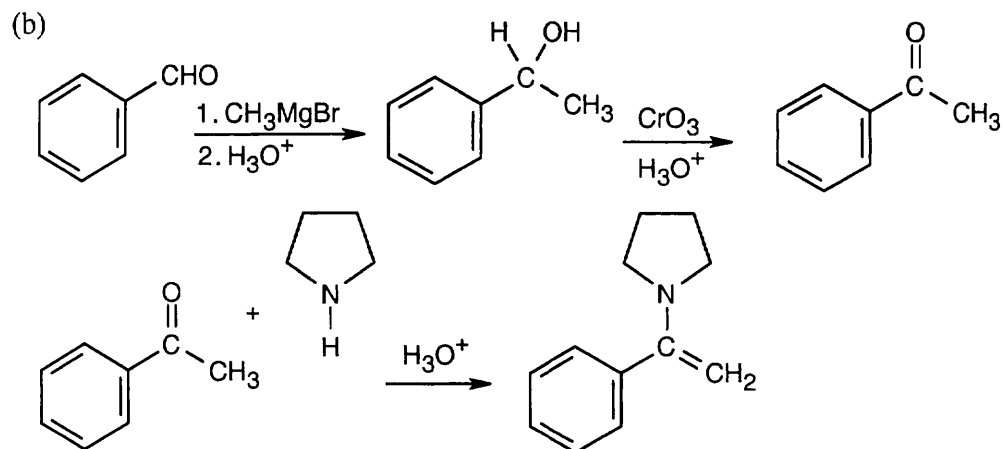


The product resembles the starting material in having an aldehyde group, but a $-\text{CH}_2-$ group lies between the aldehyde and the aromatic ring. The product aldehyde results from oxidation of an alcohol that is the product of a Grignard reaction between formaldehyde and benzylmagnesium bromide. The Grignard reagent is formed from benzyl bromide, which results from treatment of benzyl alcohol with PBr_3 . Reduction of benzaldehyde yields the alcohol.

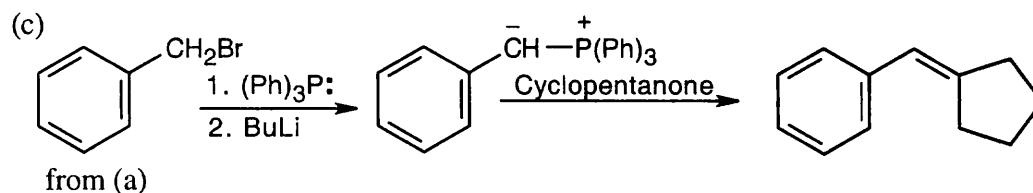
An alternate route:



In this scheme, the intermediate alcohol results from hydroboration of a double bond that is introduced by a Wittig reaction between benzaldehyde and methylenetriphenylphosphorane.

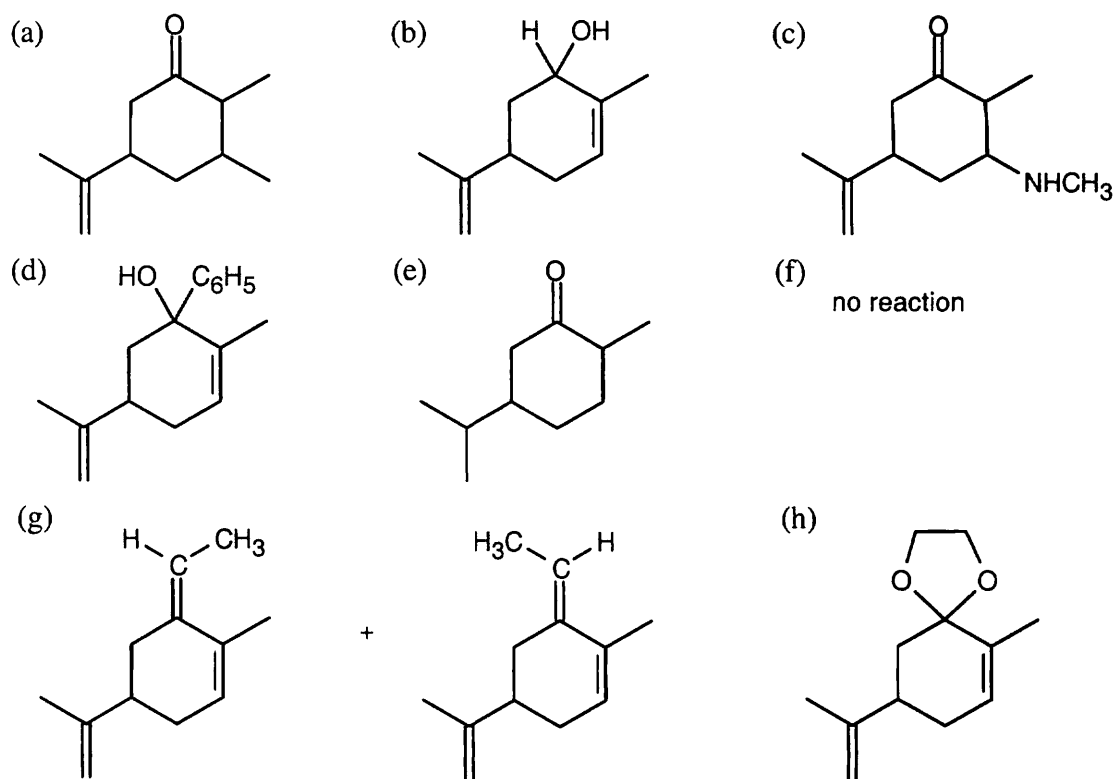


When you see a secondary amine and a double bond, you should recognize an enamine. The enamine is formed from the amine and acetophenone. Acetophenone, in turn, results from reaction of benzaldehyde with methylmagnesium bromide, followed by oxidation.

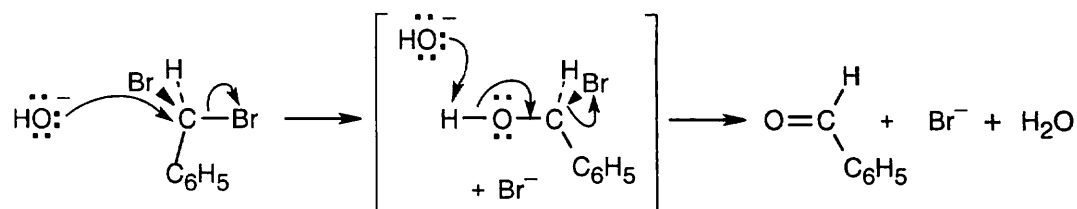


The trisubstituted double bond suggests a Wittig reaction. Reaction of cyclopentanone with the Wittig reagent formed from benzyl bromide (formed from benzaldehyde in (a)) yields the desired product.

19.42

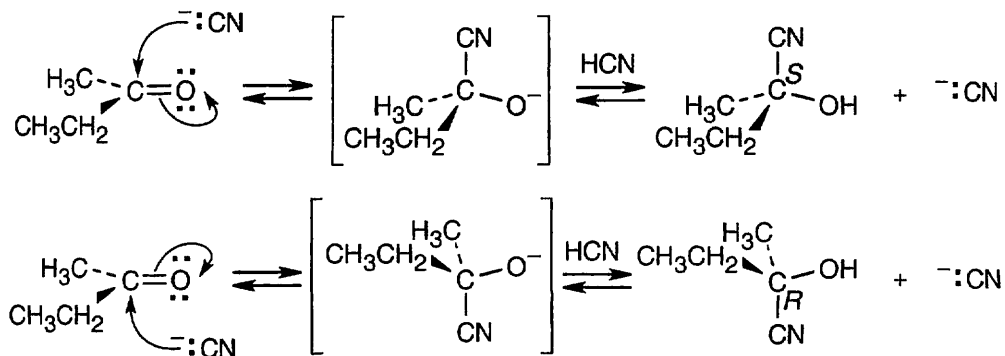


19.43



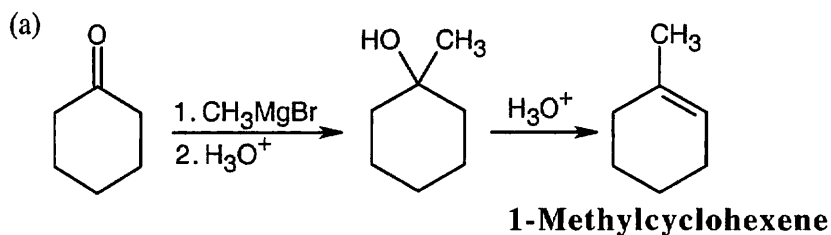
S_N2 substitution of hydroxide ion on $C_6H_5CHBr_2$ yields an unstable bromoalcohol intermediate, which loses Br^- to give benzaldehyde.

19.44

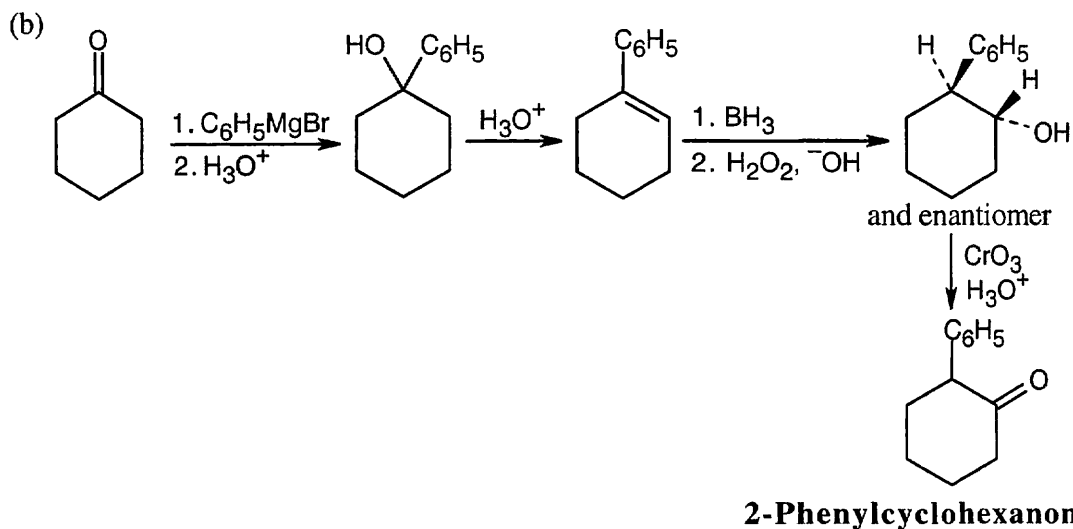


Attack can occur with equal probability on either side of the planar carbonyl group to yield a racemic product mixture that is optically inactive.

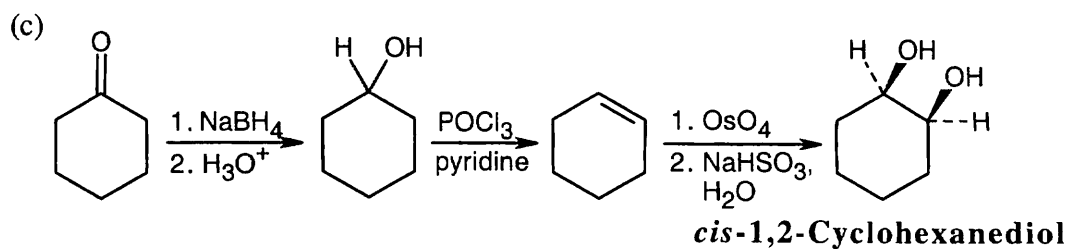
19.45



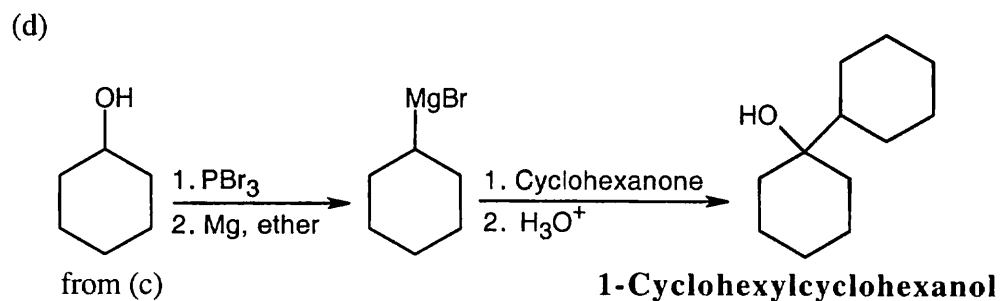
The methyl group is introduced by a Grignard reaction with methylmagnesium bromide. Dehydration of the resulting tertiary alcohol produces 1-methylcyclohexene.



Reaction with phenylmagnesium bromide yields a tertiary alcohol that can be dehydrated. The resulting double bond can be treated with BH_3 to give an alcohol that can be oxidized to produce the desired ketone.

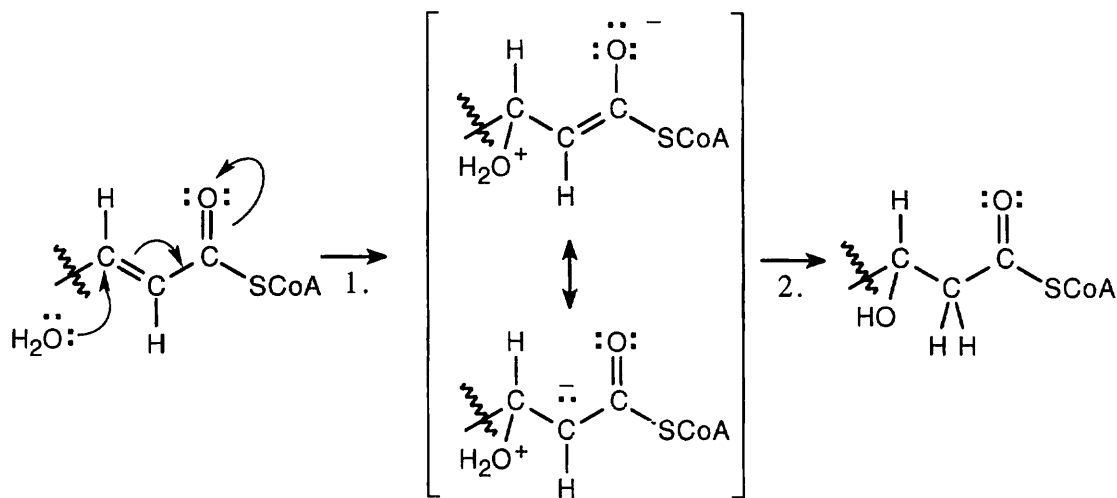


Reduction, dehydration and hydroxylation yield the desired product.



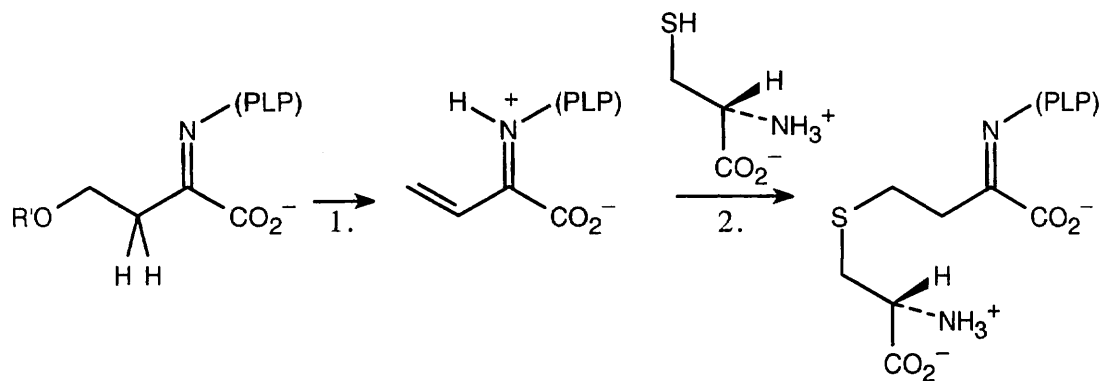
A Grignard reaction forms 1-cyclohexylcyclohexanol.

19.46



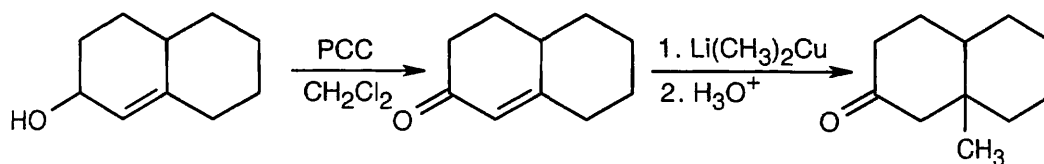
Conjugate addition of water (1) is followed by a proton shift (2) to give the β -hydroxyacyl CoA product.

19.47

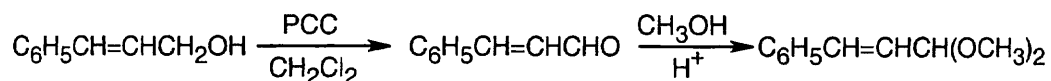


Step 1 is an elimination to form the unsaturated imine, which undergoes conjugate addition with cysteine (Step 2) to yield the observed product.

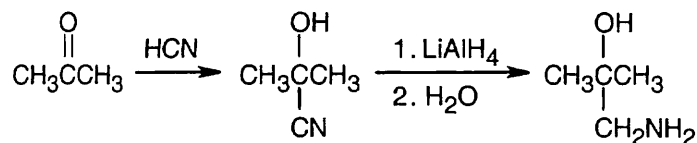
- 19.48** (a) Basic silver ion does not oxidize secondary alcohols to ketones. Grignard addition to a conjugated ketone yields the 1,2 product, not the 1,4 product. The correct scheme:



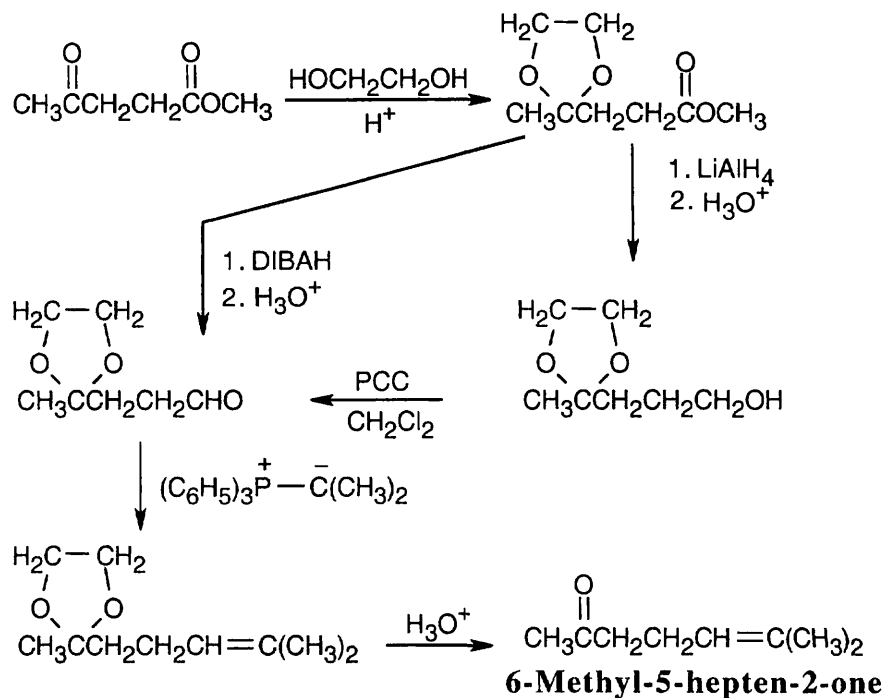
- (b) Reaction of an alcohol with acidic CrO₃ converts primary alcohols to carboxylic acids, not to aldehydes. The correct scheme:



- (c) Treatment of a cyanohydrin with H₃O⁺ produces a carboxylic acid, not an amine. The correct scheme:

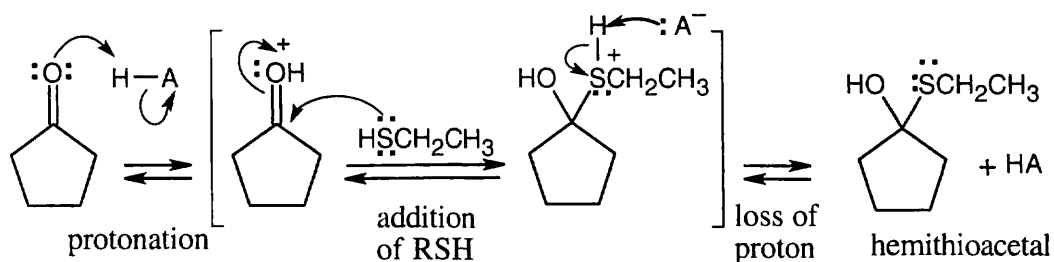


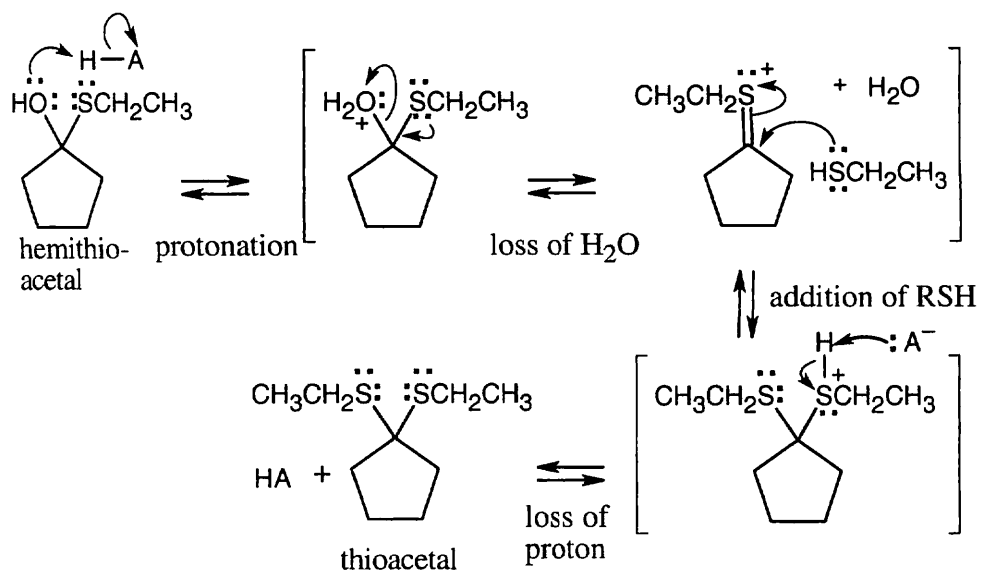
19.49



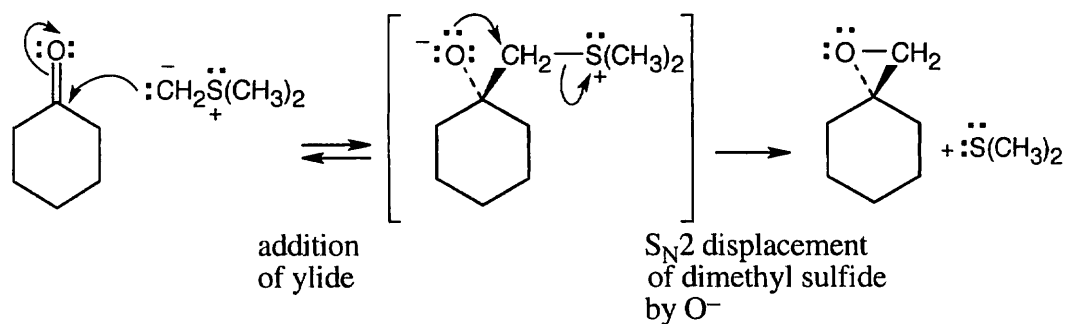
The reaction sequence involves protecting the ketone, converting the ester to an aldehyde, using a Wittig reaction to introduce a substituted double bond, and deprotecting the ketone.

19.50 The same series of steps used to form an acetal is followed in this mechanism.

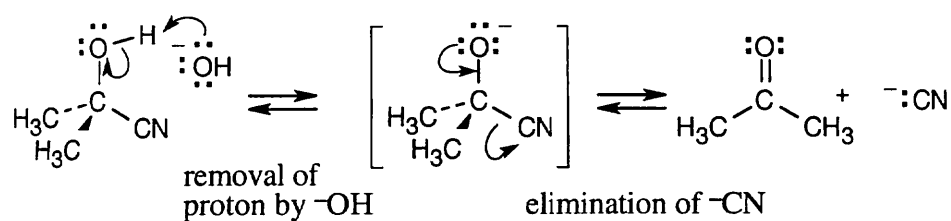




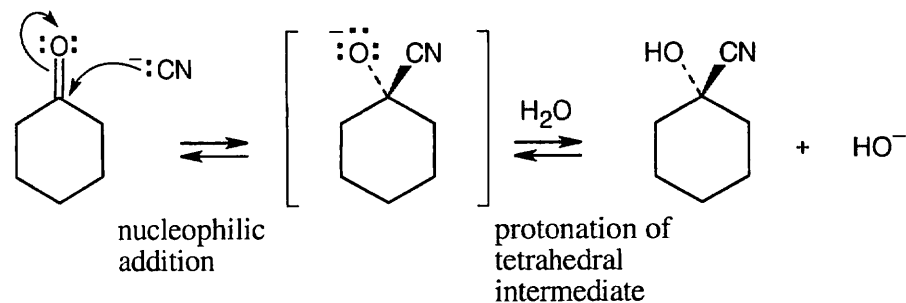
19.51 Even though the product looks unusual, this reaction is made up of steps with which you are familiar.



19.52

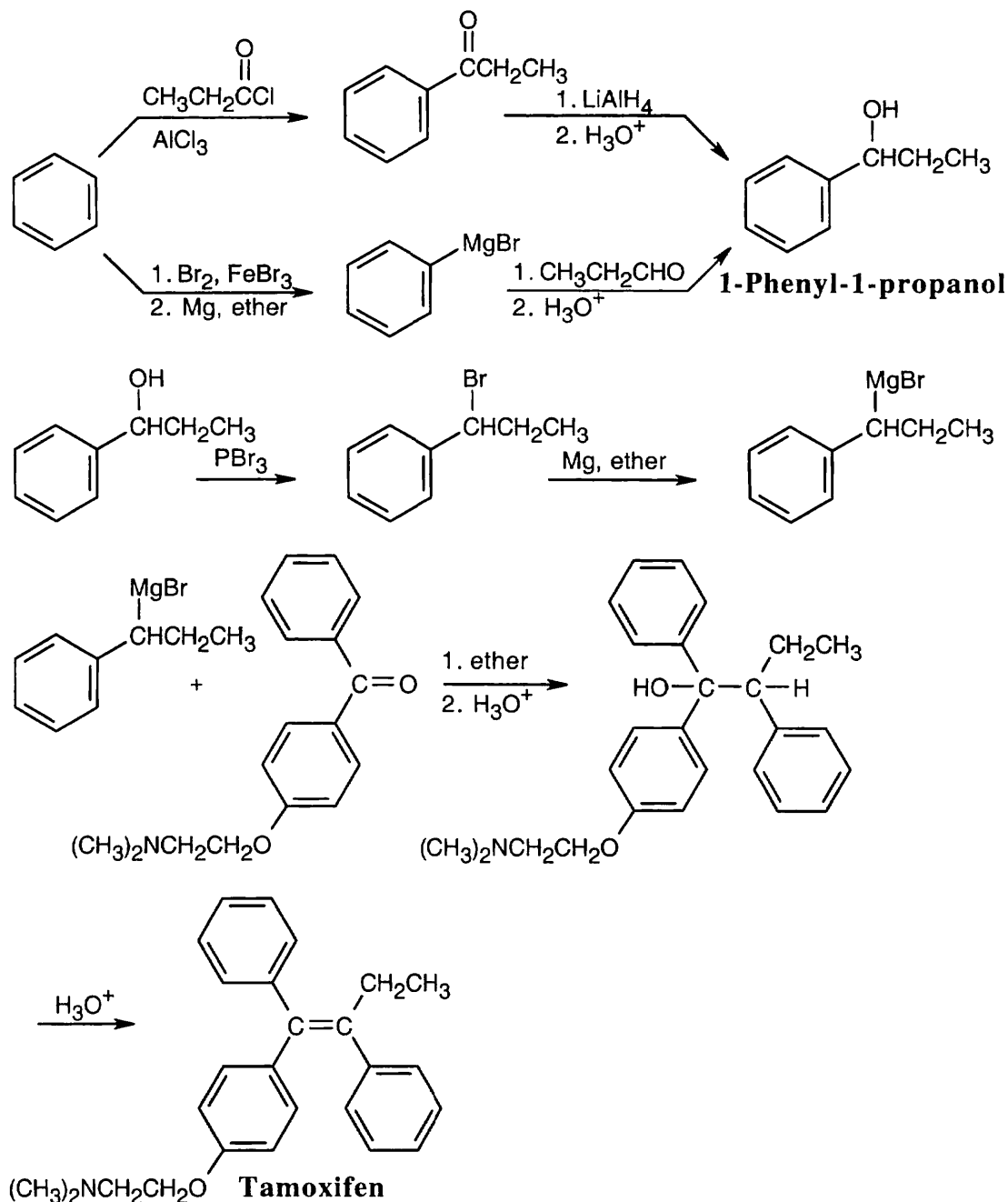


This sequence is the reverse of the mechanism shown in Section 19.6.



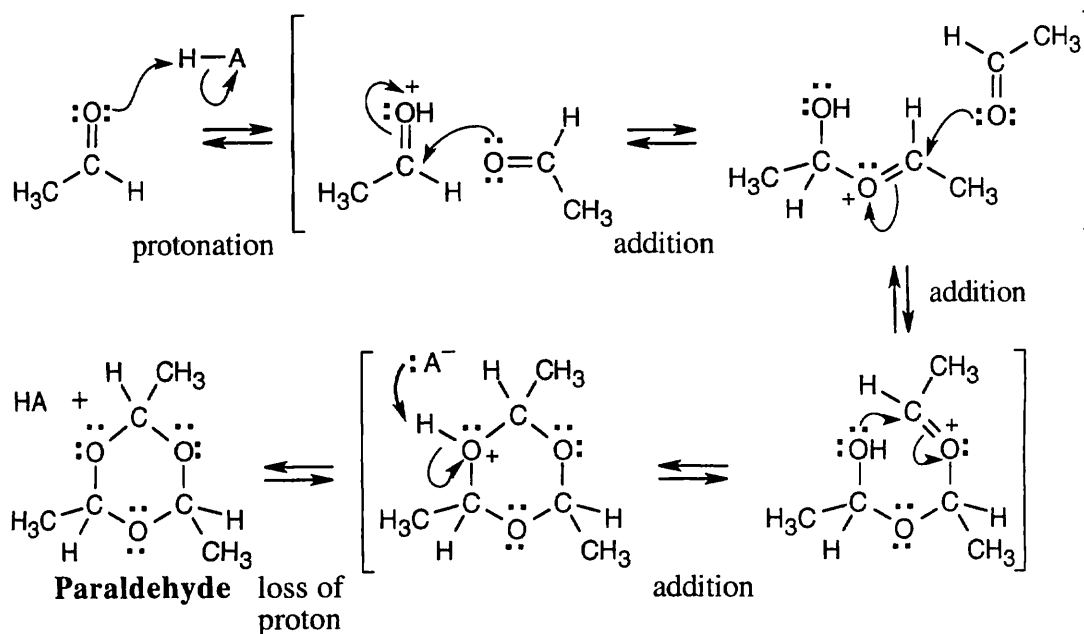
This step is a nucleophilic addition of cyanide.

19.53



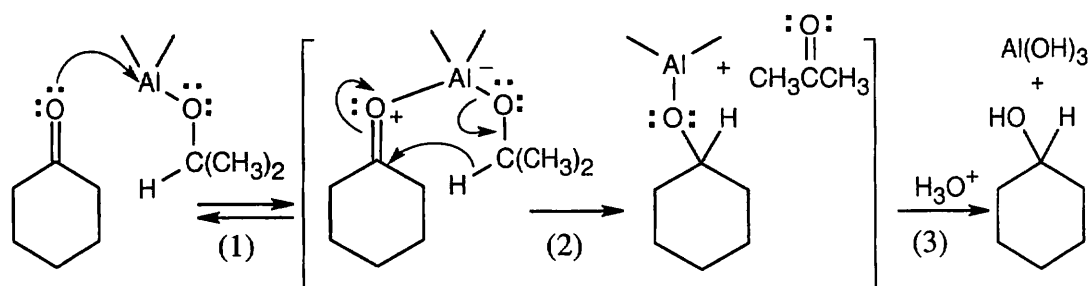
When you see a product that contains a double bond, and you also know that one of the starting materials is a ketone, it is tempting to use a Wittig reaction for synthesis. In this case, however, the tetrasubstituted double bond can't be formed by a Wittig reaction because of steric hindrance. The coupling step is achieved by a Grignard reaction between the illustrated ketone and a Grignard reagent, followed by dehydration. The Grignard reagent is synthesized from 1-phenyl-1-propanol, which can be prepared from benzene by either of two routes.

19.54



Protonation makes the carbonyl carbon more electrophilic. Three successive additions of the carbonyl oxygen of acetaldehyde to the electrophilic carbonyl carbon, followed by loss of a proton, give the cyclic product.

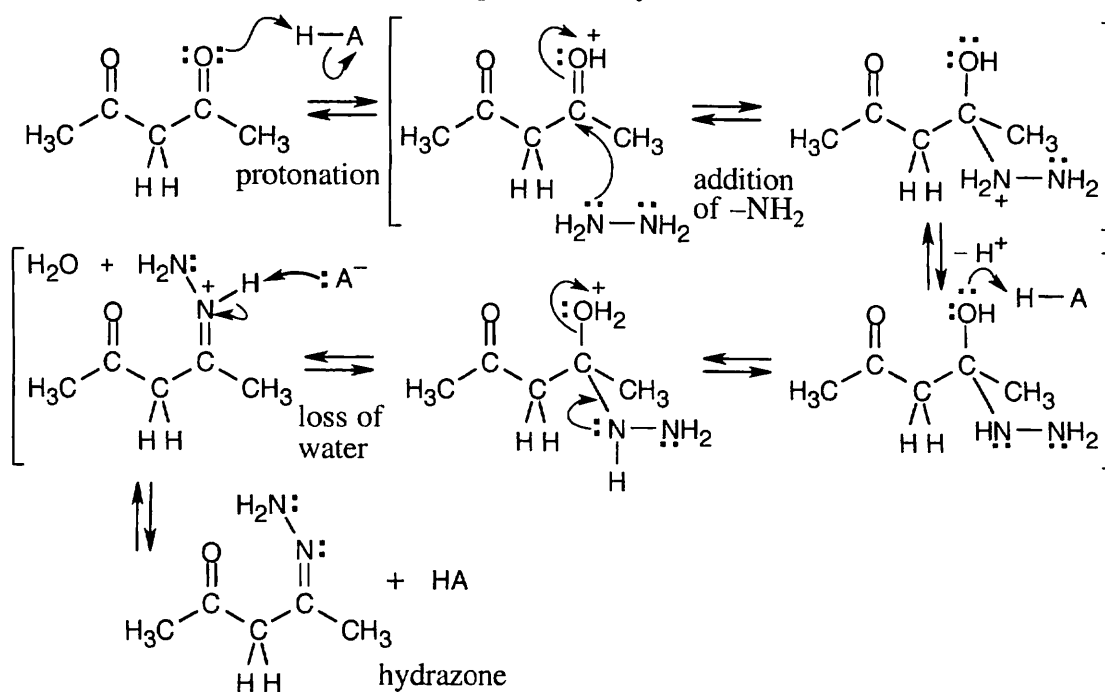
19.55



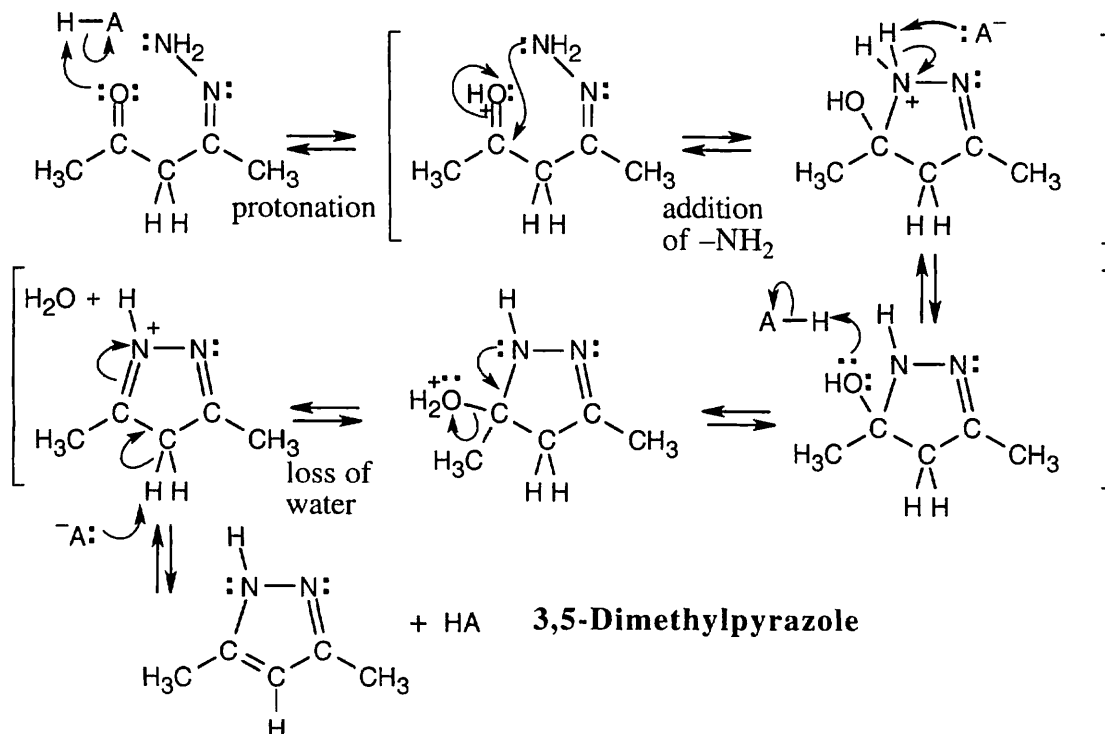
- (1) Aluminum, a Lewis acid, complexes with the carbonyl oxygen.
- (2) Complexation with aluminum makes the carbonyl group more electrophilic and facilitates hydride transfer from isopropoxide.
- (3) Treatment of the reaction mixture with aqueous acid cleaves the aluminum-oxygen bond and produces cyclohexanol.

Both the Meerwein-Ponndorf-Verley reaction and the Cannizzaro reaction are hydride transfers in which a carbonyl group is reduced by an alkoxide group, which is oxidized. Note that each aluminum triisopropoxide molecule is capable of reducing three ketone molecules.

- 19.56** (a) Nucleophilic addition of one nitrogen of hydrazine to one of the carbonyl groups, followed by elimination of water, produces a hydrazone.

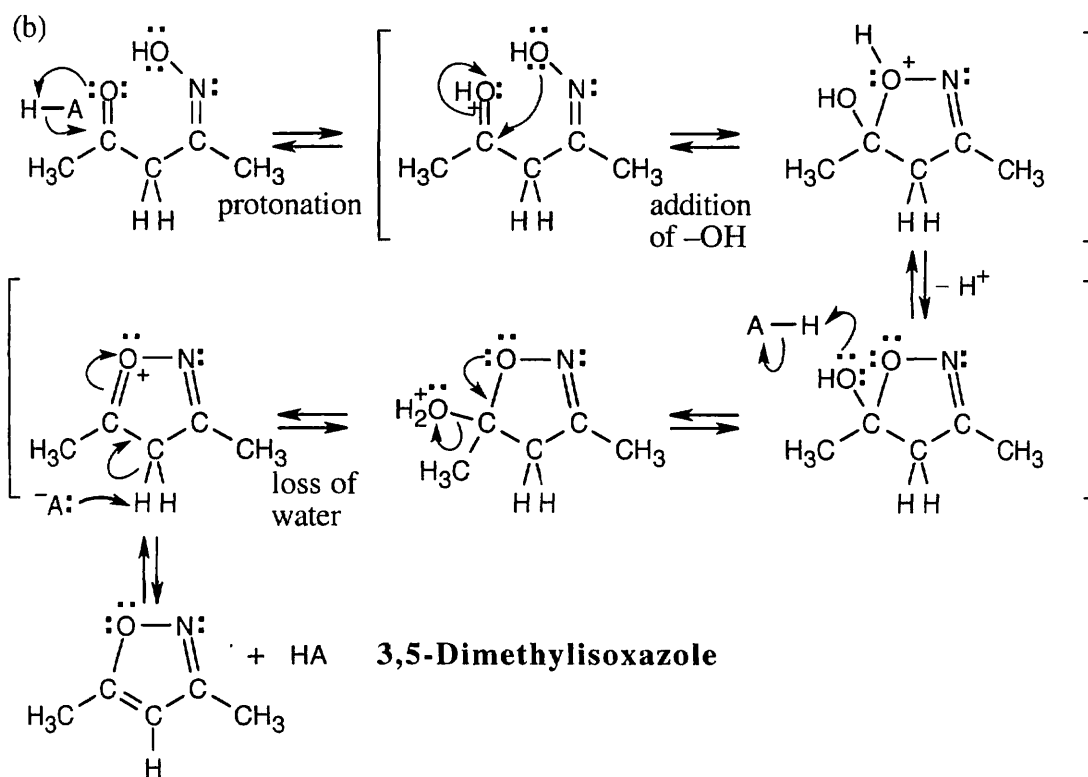
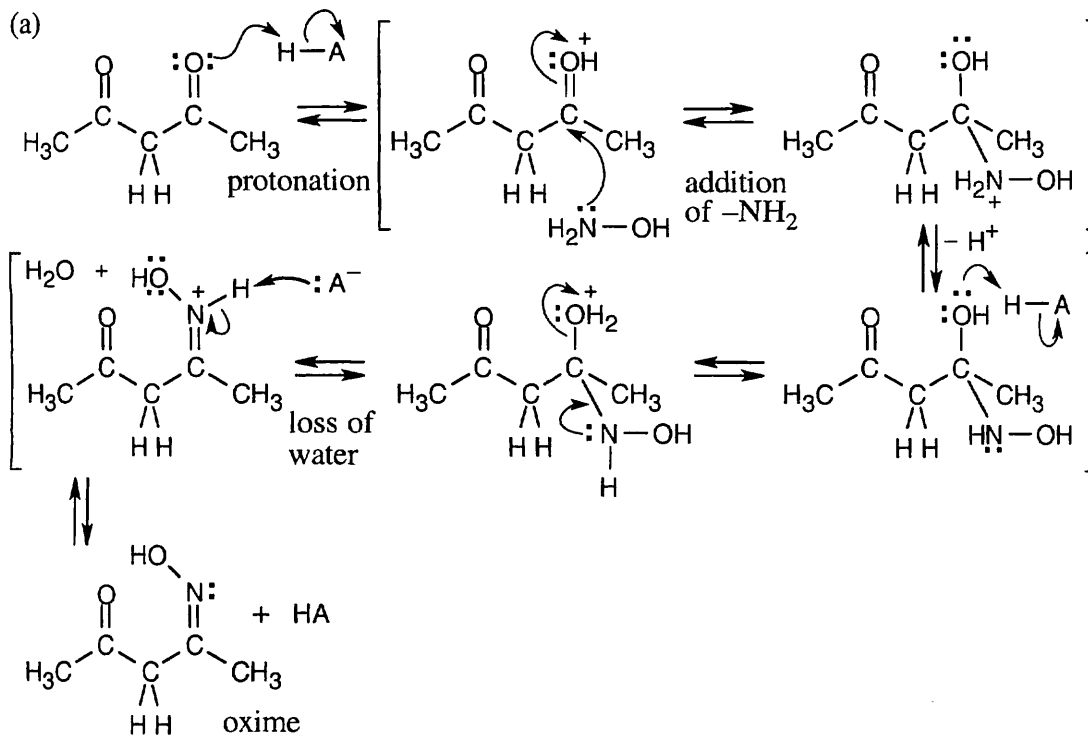


- (b) In a similar manner, the *other* nitrogen of hydrazine can add to the *other* carbonyl group of 2,4-pentanedione to form the pyrazole.

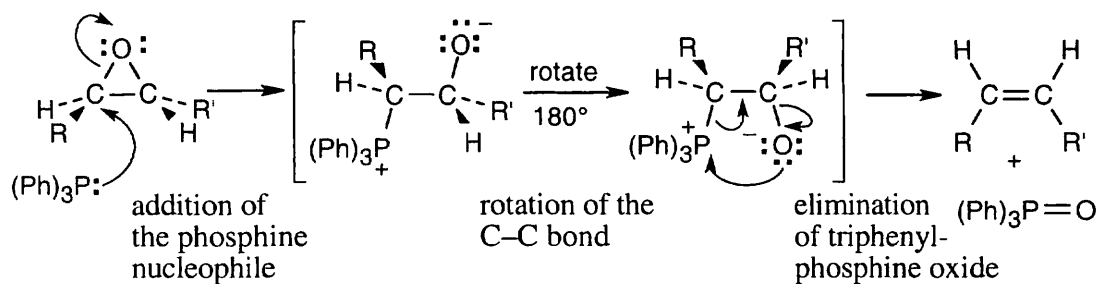


The driving force behind this reaction is the formation of an aromatic ring. The reactions in this problem are nucleophilic addition of a primary amine, followed by elimination of water to yield an imine or enamine. All of the other steps are protonations and deprotonations.

19.57 The same sequence of steps used in the previous problem leads to the formation of 3,5-dimethylisoxazole when hydroxylamine is the reagent. Loss of a proton in the last step of (b) results in a ring that is aromatic.

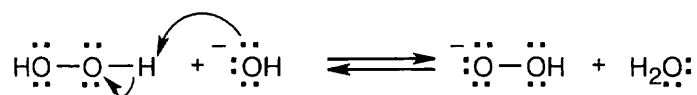


19.58

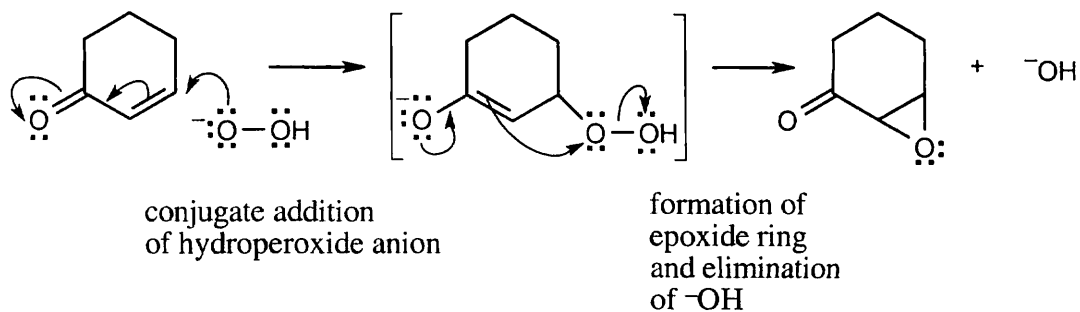


The final step is the same as the last step in a Wittig reaction.

19.59

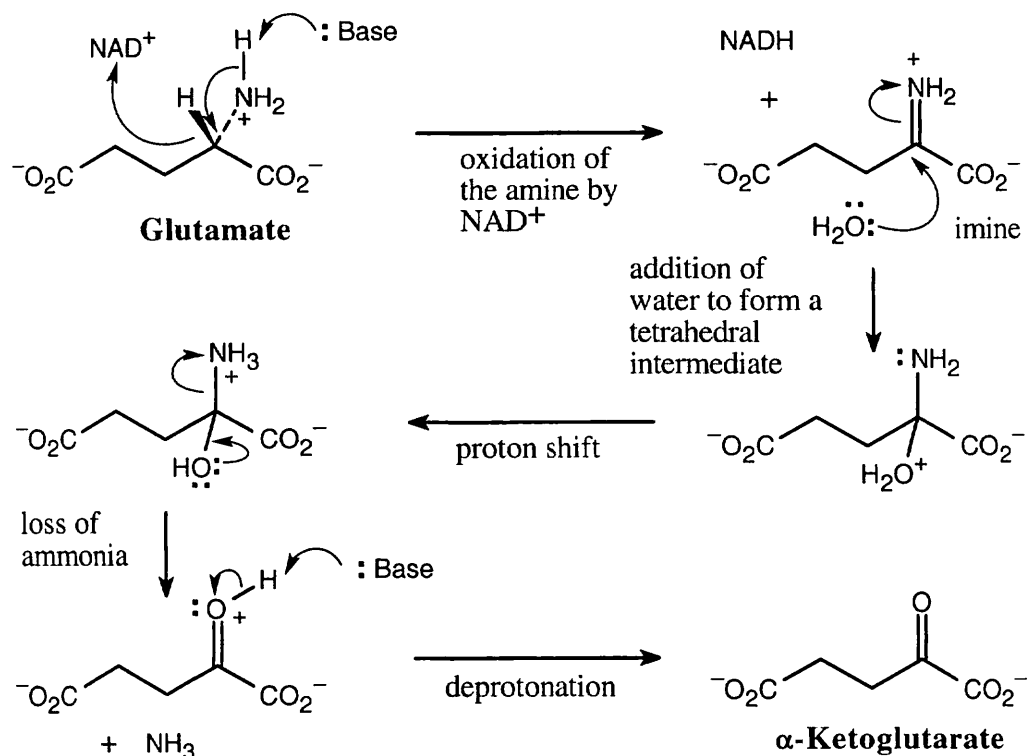


Hydrogen peroxide and hydroxide react to form water and hydroperoxide anion.



Conjugate addition of hydroperoxide anion is followed by elimination of hydroxide ion, with formation of the epoxide ring.

19.60



19.61 Use Table 19.2 if you need help.

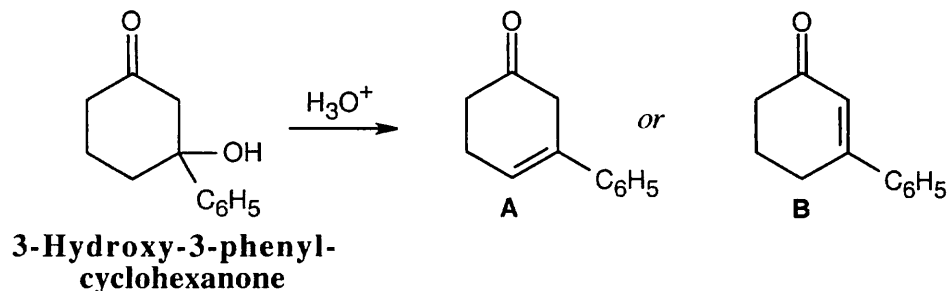
Absorption:(a) 1750 cm^{-1}
 1685 cm^{-1} (b) 1720 cm^{-1} (c) 1750 cm^{-1} (d) 1705 cm^{-1} , 2720 cm^{-1} , 2820 cm^{-1}
 1715 cm^{-1} *Due to:*5-membered ring ketone
 α,β -unsaturated ketone5-membered ring *and*
aromatic ketone

5-membered ring ketone

aromatic aldehyde
aliphatic ketone

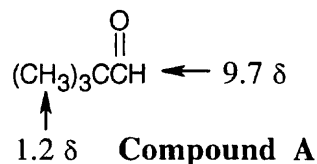
Compounds in parts (b)–(d) also show aromatic ring IR absorptions in the range 1450 cm^{-1} – 1600 cm^{-1} and in the range 690 cm^{-1} – 900 cm^{-1} .

19.62

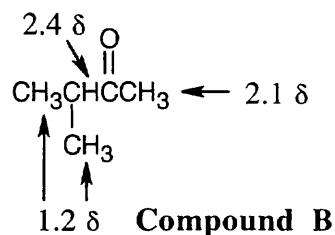


Compound **A** is a cyclic, nonconjugated keto alkene whose carbonyl infrared absorption should occur at 1715 cm^{-1} . Compound **B** is an α,β -unsaturated, cyclic ketone; additional conjugation with the phenyl ring should lower its IR absorption below 1685 cm^{-1} . Because the actual IR absorption occurs at 1670 cm^{-1} , **B** is the correct structure.

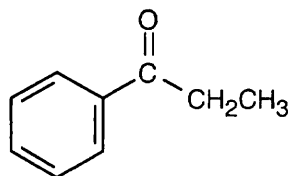
19.63 The molecular weight of Compound A shows that the molecular formula of A is $\text{C}_5\text{H}_{10}\text{O}$ (one degree of unsaturation), and the IR absorption shows that A is an aldehyde. The uncomplicated ^1H NMR is that of 2,2-dimethylpropanal.



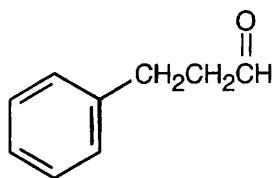
19.64 The IR of Compound B shows a ketone absorption. The splitting pattern of the ^1H NMR spectrum indicates an isopropyl group and indicates that the compound is a methyl ketone.



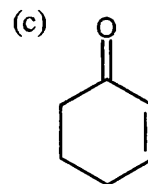
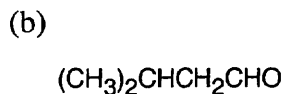
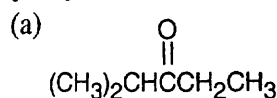
19.65 Before looking at the ^1H NMR spectrum, we know that the compound of formula $\text{C}_9\text{H}_{10}\text{O}$ has 5 degrees of unsaturation, and we know from the IR spectrum that the unknown is an aromatic ketone. The splitting pattern in the ^1H NMR spectrum shows an ethyl group next to a ketone, according to chemical shift values.



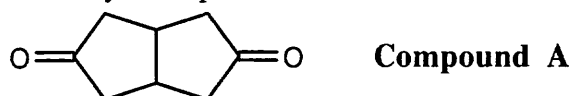
- 19.66** The IR absorption is that of an aldehyde that isn't conjugated with the aromatic ring. The two triplets in the ^1H NMR spectrum are due to two adjacent methylene groups.



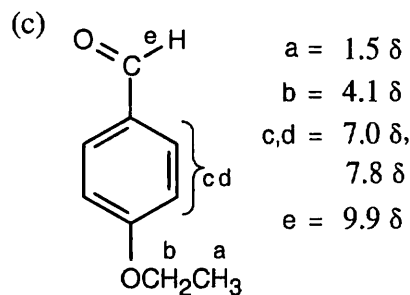
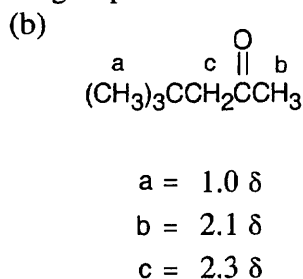
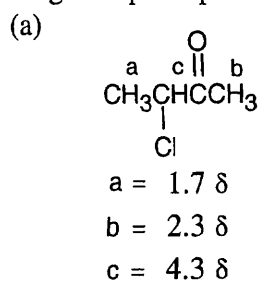
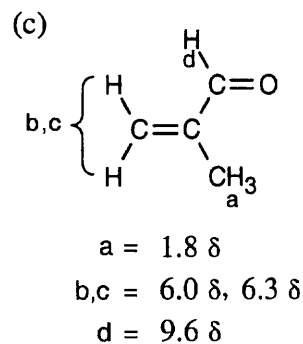
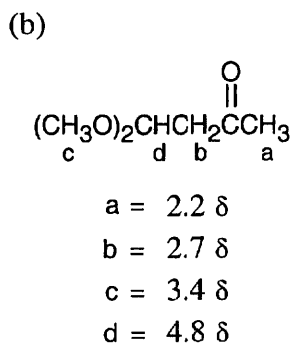
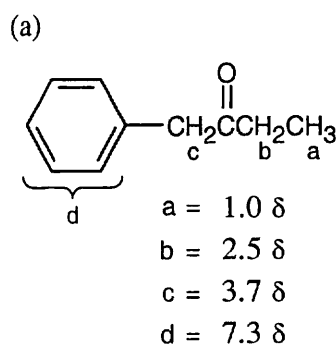
- 19.67** (a) IR shows that the unknown is a ketone, and ^{13}C NMR indicates that the carbonyl group is flanked by a secondary carbon and a tertiary carbon.
 (b) The unknown is an aldehyde and contains an isopropyl group.
 (c) The IR absorption shows that this compound is an α,β -unsaturated ketone, and the molecular formula shows 3 degrees of unsaturation. The ^{13}C NMR spectrum indicates 3 sp^2 -hybridized carbons and 3 secondary carbons.



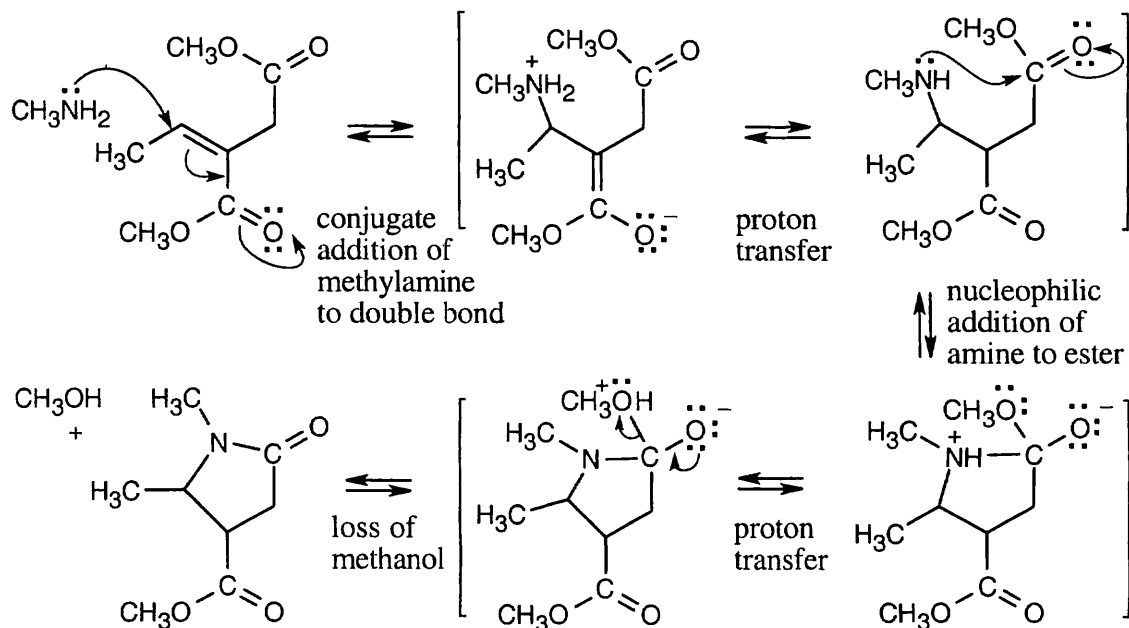
- 19.68** Compound A has 4 degrees of unsaturation and is a five-membered ring ketone. The ^{13}C NMR spectrum has only three peaks and indicates that A is very symmetrical.



- 19.69** As always, calculate the degree of unsaturation first, then use the available IR data to assign the principal functional groups.

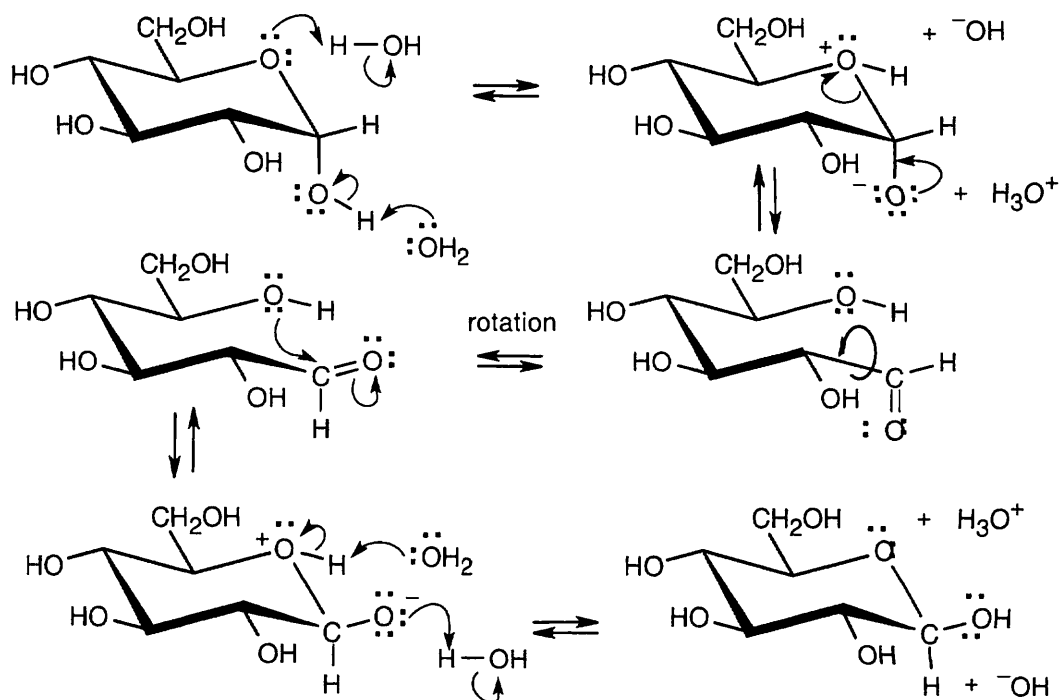
**19.70**

19.71



In this series of reactions, conjugate addition of an amine to an α,β -unsaturated ester is followed by nucleophilic addition of the amine to a second ester, with loss of methanol.

19.72 Some hydrogens have been omitted to make the drawing less cluttered.



In this series of equilibrium steps, the hemiacetal ring of α -glucose opens to yield the free aldehyde. Bond rotation is followed by formation of the cyclic hemiacetal of β -glucose. The reaction is catalyzed by both acid and base.

19.73 The free aldehyde form of glucose (Problem 19.72) is reduced in the same manner described in the text for other aldehydes to produce the polyalcohol sorbitol.

