

Chapter 16 – Chemistry of Benzene: Electrophilic Aromatic Substitution

Chapter Outline

I. Electrophilic aromatic substitution reactions (Sections 16.1 – 16.3).

A. Bromination of aromatic rings (Section 16.1).

1. Characteristics of electrophilic aromatic substitution reactions.

- The accessibility of the π electrons of an aromatic ring make it a nucleophile.
- Aromatic rings are less reactive to electrophiles than are alkenes.

A catalyst is needed to make the reacting molecule more electrophilic.

2. Mechanism of bromination.

- Br_2 complexes with FeBr_3 .
- The polarized electrophile is attacked by the π electrons of the ring in a slow, rate-limiting step.
- The cation intermediate is doubly allylic but is much less stable than the starting aromatic compound.
- The carbocation intermediate loses H^+ from the bromine-bearing carbon in a fast step to regenerate an aromatic ring.

B. Other aromatic substitution reactions (Section 16.2).

1. Chlorination and iodination.

- Chlorine reacts in the presence of FeCl_3 to yield chlorinated rings.
- Iodination occurs only in the presence of an oxidizing agent.
- Fluorine is too reactive to be useful.

2. Nitration.

- A mixture of HNO_3 and H_2SO_4 is used for nitration.
- The reactive electrophile is NO_2^+ .
- Products of nitration can be reduced with Fe or SnCl_2 to yield an arylamine.

3. Sulfonation.

- Rings can be sulfonated by a mixture of SO_3 and H_2SO_4 to yield sulfonic acids.
- The reactive electrophile is either SO_3 or HSO_3^+ .
- Sulfonation is reversible.

4. Hydroxylation.

- Hydroxylation of an arylamine is rarely done in the laboratory.
- In enzyme-catalyzed biological hydroxylations, the reactive species is an " OH^+ " equivalent.

C. Alkylation of aromatic rings (Section 16.3).

- The Friedel–Crafts reaction introduces an alkyl group onto an aromatic ring.
- An alkyl chloride, plus an AlCl_3 catalyst, produces an electrophilic carbocation.
- There are several limitations to using the Friedel–Crafts reaction.
 - Only alkyl halides – not aryl or vinylic halides – can be used.
 - Friedel–Crafts reactions don't succeed on rings that have amino substituents or deactivating groups.
 - Polyalkylation is often seen.
 - Rearrangements of the alkyl carbocation often occur.

Rearrangements may occur by hydride shifts or by alkyl shifts.

D. Acylation of aromatic rings.

- Friedel–Crafts acylation occurs when an aromatic ring reacts with a carboxylic acid chloride.
- The reactive electrophile is an acyl cation, which doesn't rearrange.
- Polyacylation never occurs in acylation reactions.

II. Substituent effects in substituted aromatic rings (Sections 16.4 – 16.6).

A. Types of substituent effects (Section 16.4).

1. Substituents affect the reactivity of an aromatic ring.
2. Substituents affect the orientation of further substitution.
3. Substituents can be grouped into three groups:
 - a. Ortho- and para-directing activators.
 - b. Ortho- and para-directing deactivators.
 - c. Meta-directing deactivators.
4. Two kinds of effects are responsible for reactivity and orientation.
 - a. Inductive effects are due to differences in bond polarity.
 - b. Resonance effects are due to overlap of a *p* orbital of a substituent with a *p* orbital on an aromatic ring.
 - i. Carbonyl, cyano and nitro substituents withdraw electrons.
These substituents have the structure $-Y=Z$.
 - ii. Halogen, hydroxyl, alkoxyl and amino substituents donate electrons.
These substituents have the structure $-Y:$.
 - iii. Resonance effects are greatest at the ortho and para positions.
 - c. Resonance and inductive effects don't always act in the same direction.

B. Explanation of substituent effects (Section 16.5).

1. All activating groups donate electrons to an aromatic ring.
2. All deactivating groups withdraw electrons from a ring.
3. Alkyl groups – ortho- and para-directing activators.
 - a. Alkyl groups inductively donate electrons to a ring.
 - b. Alkyl groups are *o,p*-directors because the carbocation intermediates from attack are best stabilized when attack occurs at the ortho and para positions.
4. OH, NH₂ groups – ortho- and para-directing activators.
 - a. OH, NH₂ donate electrons by resonance involving the ring and the group.
 - b. The intermediates of ortho- and para-attack are more stabilized by resonance than are intermediates of meta attack.
5. Halogens – ortho- and para-directing deactivators.
 - a. The electron-withdrawing inductive effect of halogen outweighs its electron-donating resonance effect.
 - b. The resonance effect orients substitution to the *o,p* positions.
 - c. The inductive effect deactivates the ring.
6. Meta-directing deactivators.
 - a. Meta-directing deactivators act through both inductive and resonance effects.
 - b. Because resonance effects destabilize ortho and para positions the most, substitution ion occurs at the meta position.

C. Trisubstituted benzenes: additivity of effects (Section 16.6).

1. If the effects of both groups are additive, the product of substitution is easy to predict.
2. If the directing effects of the groups are opposed, the more powerful activating group determines the product, although mixtures sometimes result.
3. For steric reasons, substitution rarely occurs between two groups that are meta to each other.

III. Other reactions of aromatic rings (Sections 16.7 – 16.10).

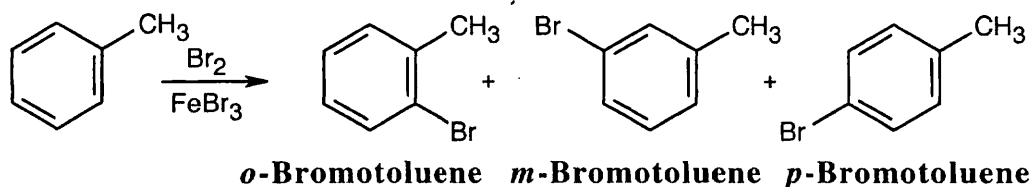
A. Nucleophilic aromatic substitution (Section 16.7).

1. An aryl halide with electron-withdrawing groups can undergo nucleophilic aromatic substitution.
2. This reaction occurs through an addition/elimination mechanism.
3. Addition of the nucleophile proceeds through an intermediate Meisenheimer complex that is stabilized by *o,p* electron-withdrawing substituents on the ring.
4. The halide is eliminated to yield product.

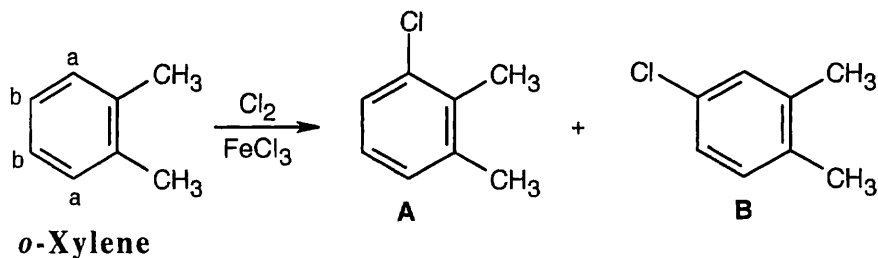
- B. Benzyne (Section 16.8).
1. At high temperatures and with strong base, aryl halides without electron-withdrawing substituents can be converted to phenols.
 2. This reaction occurs by an elimination/addition reaction that involves a benzyne intermediate.
 - a. Strong base causes elimination of HX from the aryl halide to generate benzyne.
 - b. A nucleophile adds to benzyne to give the product.
 3. The benzyne intermediate can be trapped in a Diels-Alder reaction.
 4. Benzyne has the electronic structure of a distorted alkyne and has one very weak π bond.
- C. Oxidation of aromatic compounds (Section 16.9).
1. Oxidation of alkylbenzene side chains.
 - a. Strong oxidizing agents cause the oxidation of alkyl side chains with benzylic hydrogens.
 - b. The products of side-chain oxidation are benzoic acids.
 - c. Reaction proceeds by a complex radical mechanism.
 2. Bromination of alkylbenzene side chains.
 - a. NBS brominates alkylbenzene side chains at the benzylic position.
 - b. Bromination occurs by the mechanism described for allylic bromination and requires a radical initiator.
 - c. The intermediate benzylic radical is stabilized by resonance.
- D. Reduction of aromatic compounds (Section 16.10).
1. Catalytic hydrogenation of aromatic rings.
 - a. It is possible to selectively reduce alkene bonds in the presence of aromatic rings because rings are relatively inert to catalytic hydrogenation.
 - b. With a stronger catalyst, aromatic rings can be reduced.
 2. Reduction of aryl alkyl ketones.
 - a. Aryl alkyl ketones can undergo catalytic hydrogenation to form alkylbenzenes.
 - b. Acylation plus reduction is a route to alkyl substitution without rearrangement.
 - c. This reaction only occurs with aryl alkyl ketones and also reduces nitro groups to amino groups.
- IV. Synthesis of substituted benzenes (Section 16.11).
- A. To synthesize substituted benzenes, it is important to introduce groups so that they have the proper orienting effects.
 - B. It is best to use retrosynthetic analysis to plan a synthesis.

Solutions to Problems

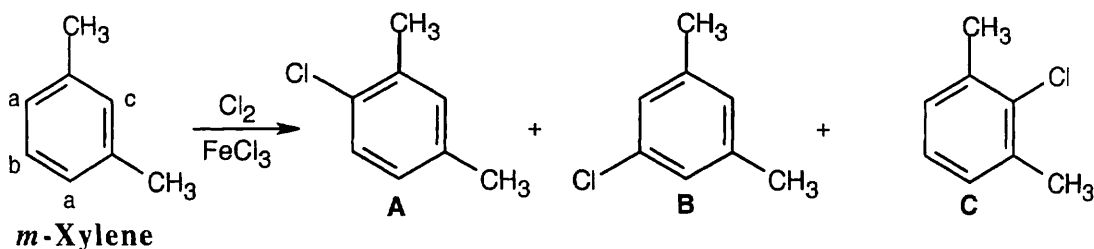
16.1



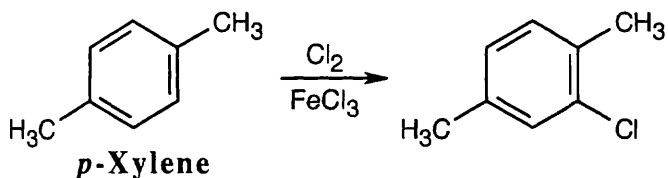
16.2



Chlorination at position "a" of *o*-xylene yields product **A**, and chlorination at position "b" yields product **B**.

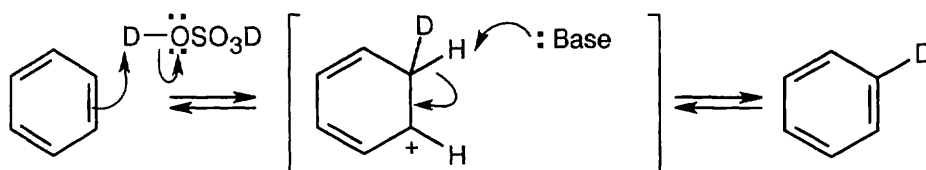


Three products might be expected to form on chlorination of *m*-xylene.



Only one product results from chlorination of *p*-xylene because all sites are equivalent.

16.3



Benzene can be protonated by strong acids. The resulting intermediate can lose either deuterium or hydrogen. If -H is lost, deuterated benzene is produced. Attack by deuterium can occur at all positions of the ring and leads to eventual replacement of all hydrogens by deuterium.

16.4 Strategy: Carbocation rearrangements of alkyl halides occur (1) if the initial carbocation is primary or secondary, and (2) if it is possible for the initial carbocation to rearrange to a more stable secondary or tertiary cation.

Solution:

(a) Although CH_3CH_2^+ is a primary carbocation, it can't rearrange to a more stable cation.

(b) $\text{CH}_3\text{CH}_2\text{CH}(\text{Cl})\text{CH}_3$ forms a secondary carbocation that doesn't rearrange.

(c) $\text{CH}_3\text{CH}_2\text{CH}_2^+$ rearranges to the more stable $\text{CH}_3\text{CH}^+\text{CH}_3$.

(d) $(\text{CH}_3)_3\text{CCH}_2^+$ (primary) undergoes an alkyl shift to yield $(\text{CH}_3)_2\text{C}^+\text{CH}_2\text{CH}_3$ (tertiary).

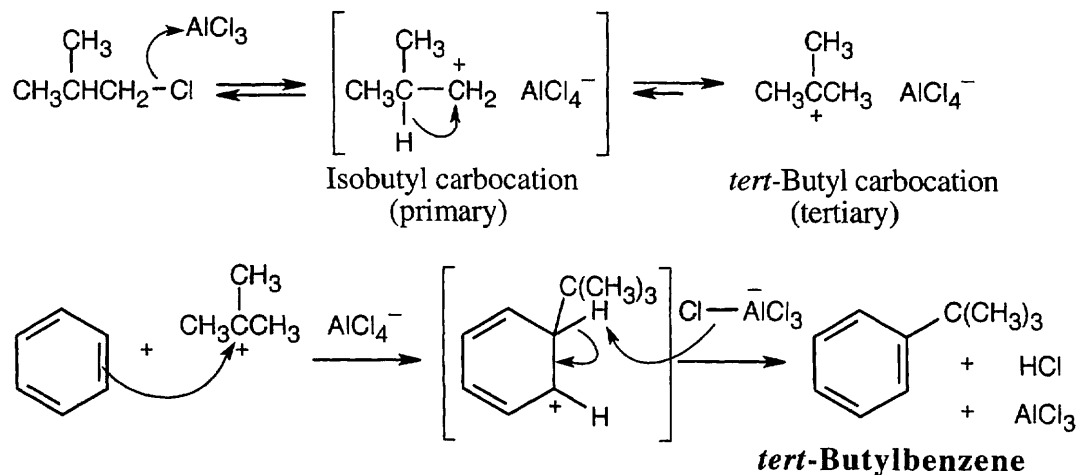
(e) The cyclohexyl carbocation doesn't rearrange.

In summary:

No rearrangement: (a) $\text{CH}_3\text{CH}_2\text{Cl}$, (b) $\text{CH}_3\text{CH}_2\text{CH}(\text{Cl})\text{CH}_3$, (e) chlorocyclohexane

Rearrangement: (c) $\text{CH}_3\text{CH}_2\text{CH}_2\text{Cl}$, (d) $(\text{CH}_3)_3\text{CCH}_2\text{Cl}$

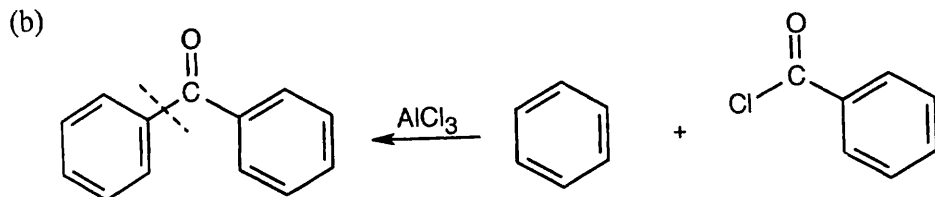
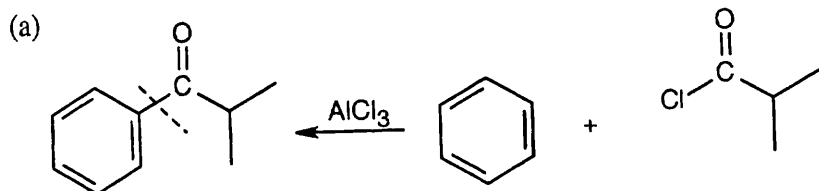
16.5



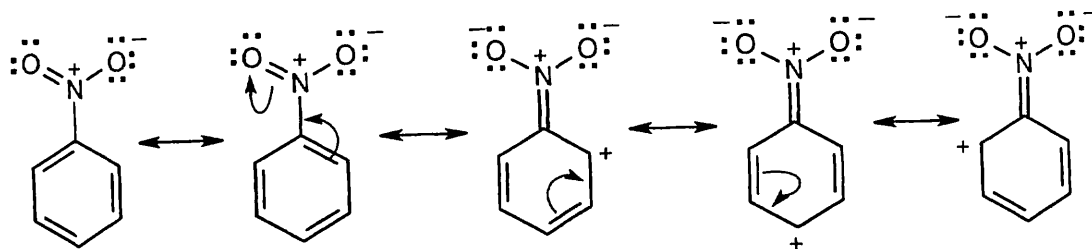
The isobutyl carbocation, initially formed when 1-chloro-2-methylpropane and AlCl_3 react, rearranges via a hydride shift to give the more stable *tert*-butyl carbocation, which can then alkylate benzene to form *tert*-butylbenzene.

16.6 Strategy: To identify the carboxylic acid chloride used in the Friedel–Crafts acylation of benzene, break the bond between benzene and the ketone carbon and replace it with a --Cl .

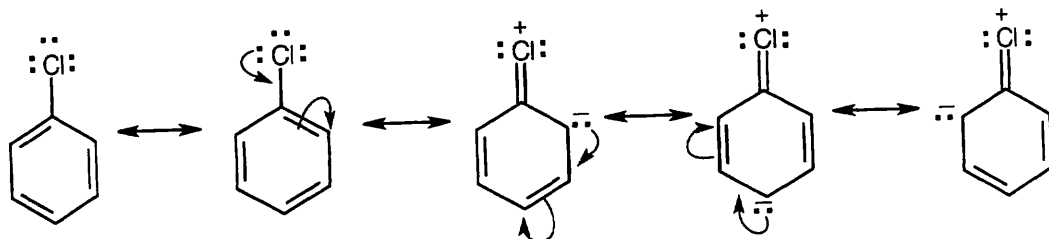
Solution:



16.7

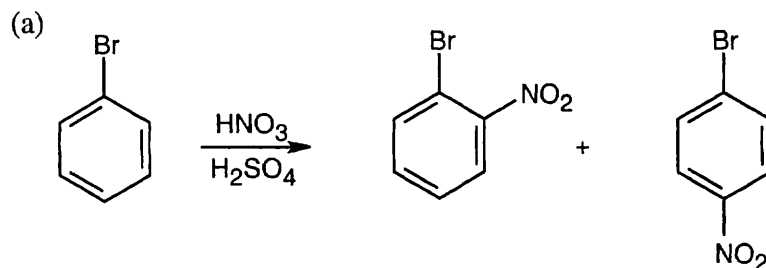


16.8

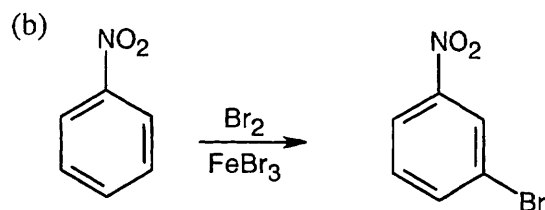


16.9 Strategy: Refer to Figure 16.11 in the text for the directing effects of substituents. You should memorize the effects of the most important groups. As in Worked Example 16.2, identify the directing effect of the substituent, and draw the product.

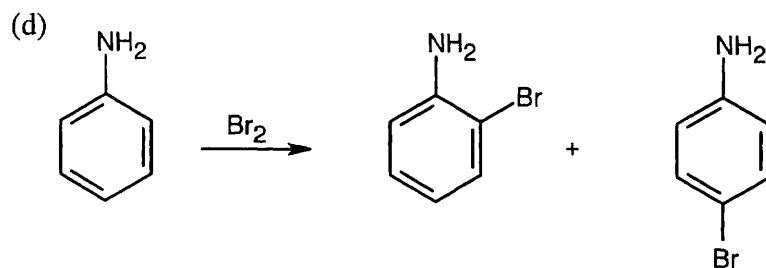
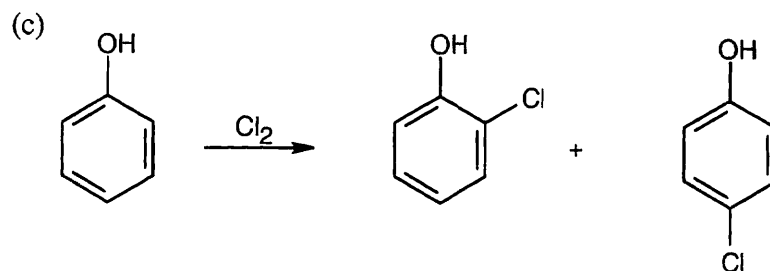
Solution:



Even though bromine is a deactivator, it is an ortho-para director.



The $-\text{NO}_2$ group is a meta-director.



No catalyst is necessary because aniline is highly activated.

16.10 Use Figure 16.11 to find the activating and deactivating effects of groups.

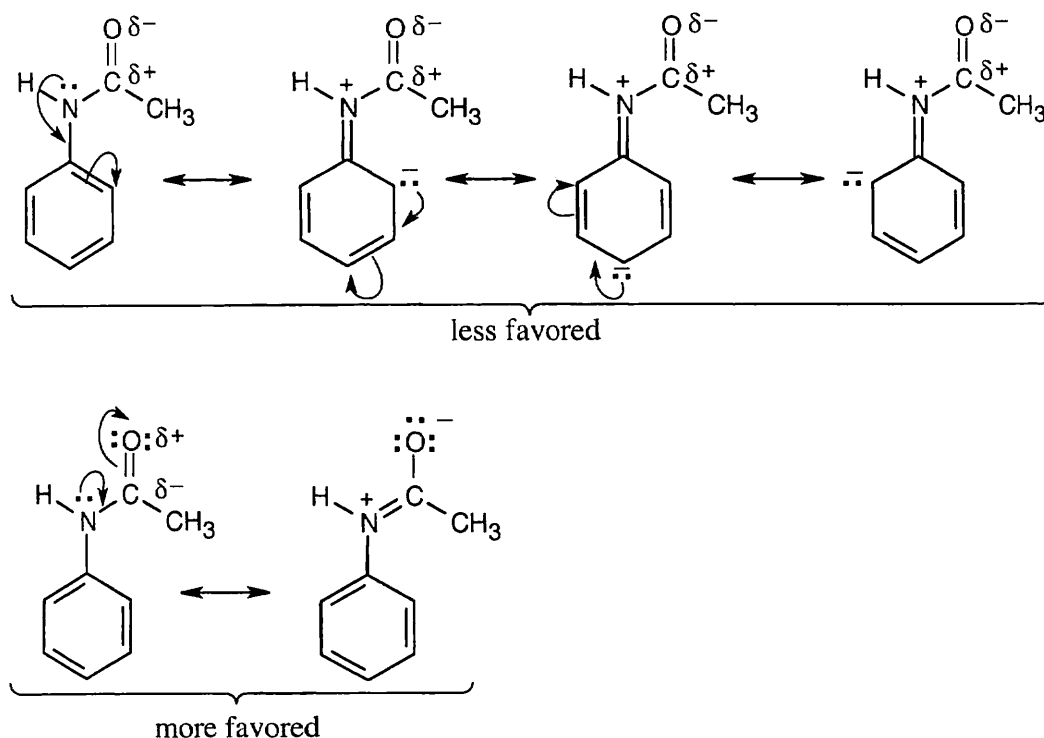
Most Reactive \longrightarrow *Least Reactive*

- (a) Phenol > toluene > benzene > nitrobenzene
- (b) Phenol > benzene > chlorobenzene > benzoic acid
- (c) Aniline > benzene > bromobenzene > benzaldehyde

16.11 An acyl substituent is deactivating. Once an aromatic ring has been acylated, it is much less reactive to further substitution. An alkyl substituent is activating, however, so an alkyl-substituted ring is more reactive than an unsubstituted ring, and polysubstitution occurs readily.

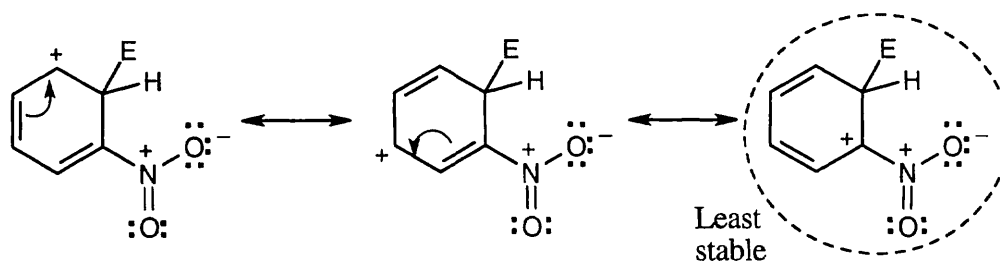
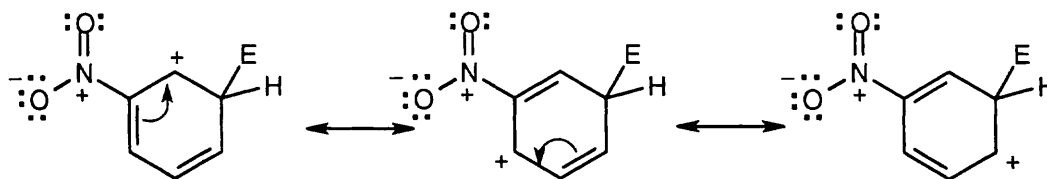
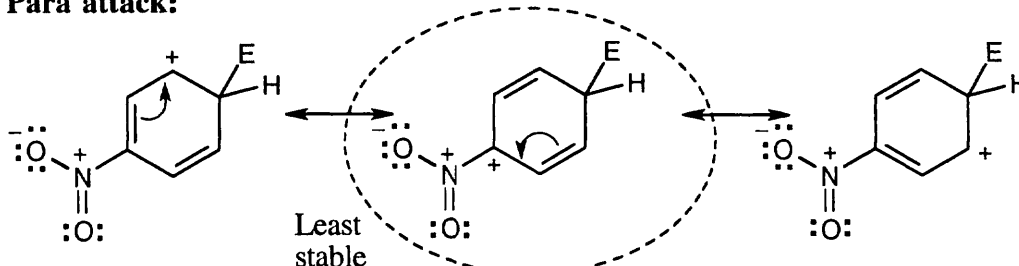
16.12 (Trifluoromethyl)benzene is less reactive toward electrophilic substitution than toluene. The electronegativity of the three fluorine atoms causes the trifluoromethyl group to be electron-withdrawing and deactivating toward electrophilic substitution. The electrostatic potential map shows that the aromatic ring of (trifluoromethyl)benzene is more electron-poor, and thus less reactive, than the ring of toluene shown in Figure 16.12.

16.13



For acetanilide, resonance delocalization of the nitrogen lone pair electrons to the aromatic ring is less favored because the positive charge on nitrogen is next to the positively polarized carbonyl group. Resonance delocalization to the carbonyl oxygen is favored because of the electronegativity of oxygen. Since the nitrogen lone pair electrons are less available to the ring, the reactivity of the ring toward electrophilic substitution is decreased, and acetanilide is less reactive than aniline toward electrophilic substitution.

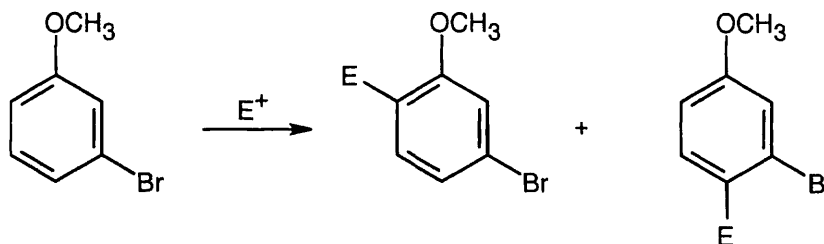
16.14

Ortho attack:**Meta attack:****Para attack:**

The circled resonance forms are unfavorable, because they place two positive charges adjacent to each other. The intermediate from meta attack is thus favored.

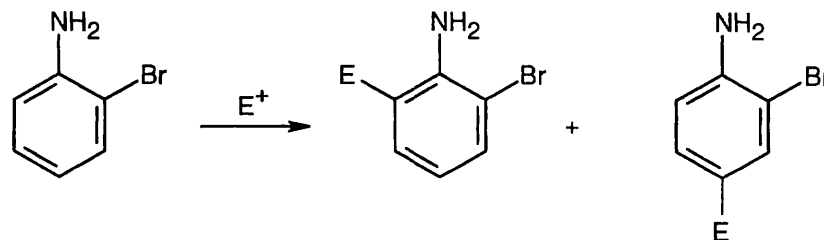
16.15

(a)

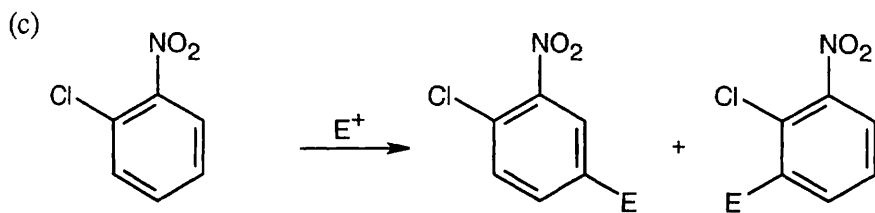


Both groups are ortho–para directors and direct substitution to the same positions. Attack doesn't occur between the two groups for steric reasons.

(b)

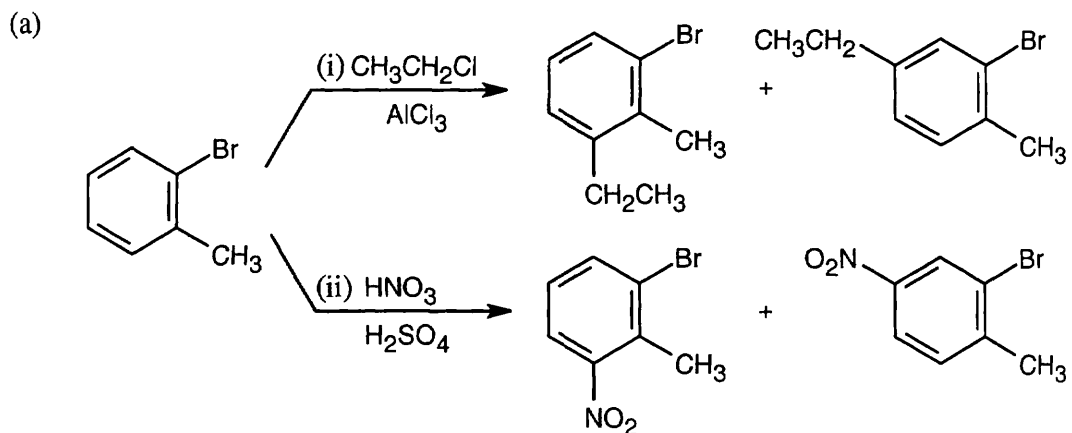


Both groups are ortho–para directors, but direct to different positions. Because -NH_2 group is a more powerful activator, substitution occurs ortho and para to it.

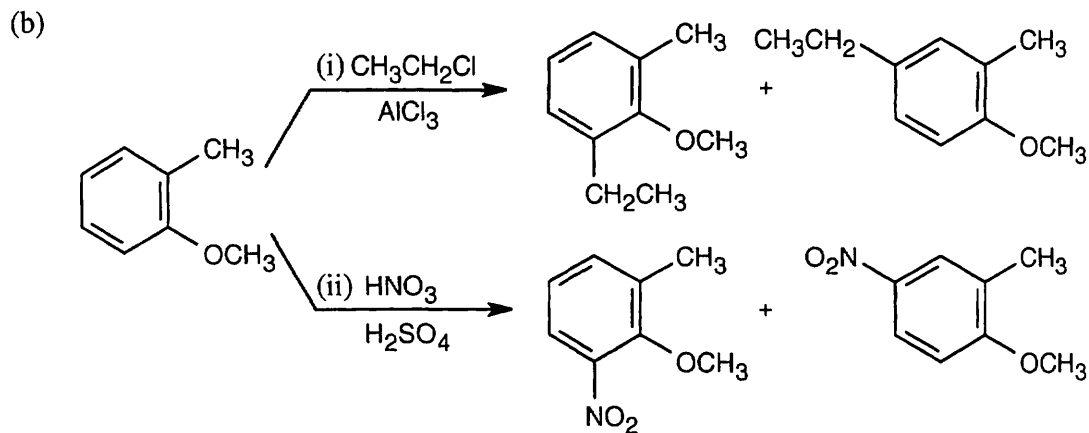


Both groups are deactivating, but they orient substitution toward the same positions.

16.16

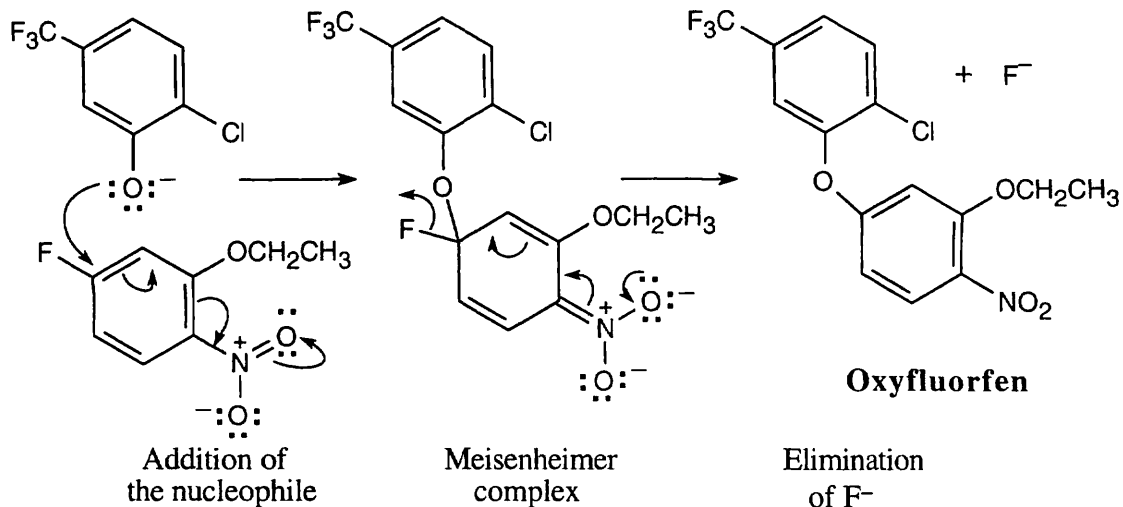


The methyl group directs the orientation of the substituents because it is a stronger activating group than bromine.



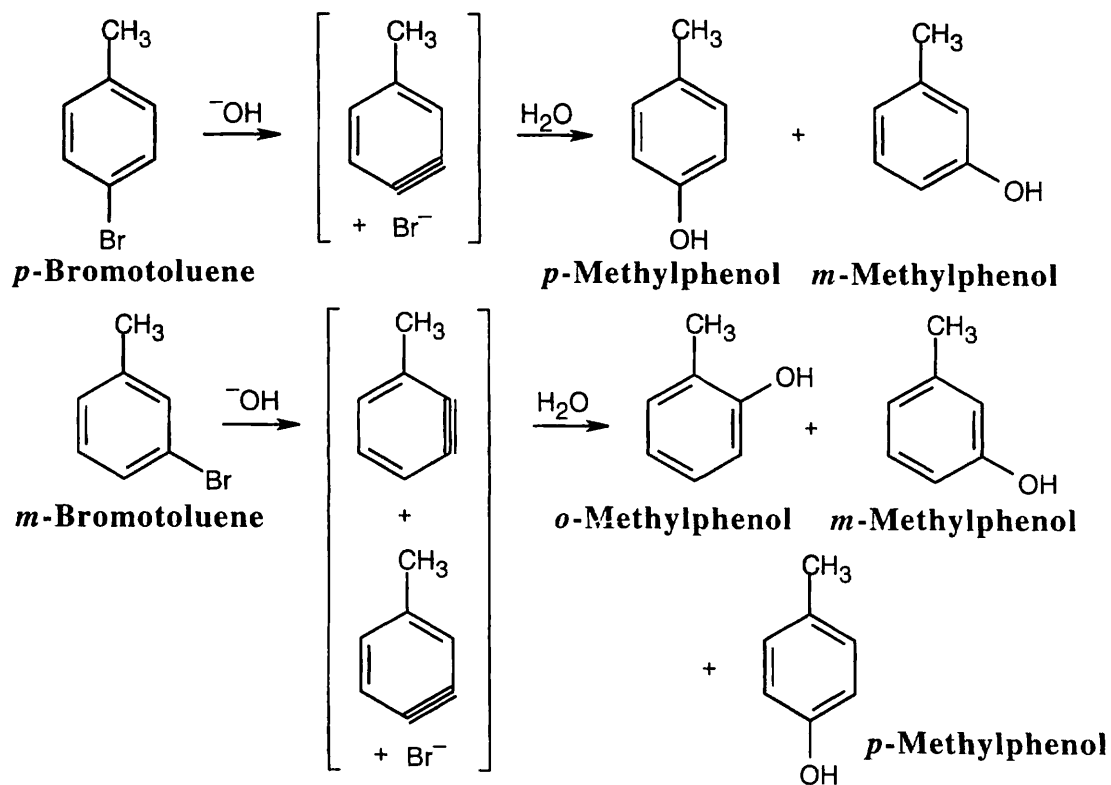
The methoxyl group directs substitution to the positions ortho and para to it.

16.17 Hydroxide is used to form the nucleophilic phenoxide anion.



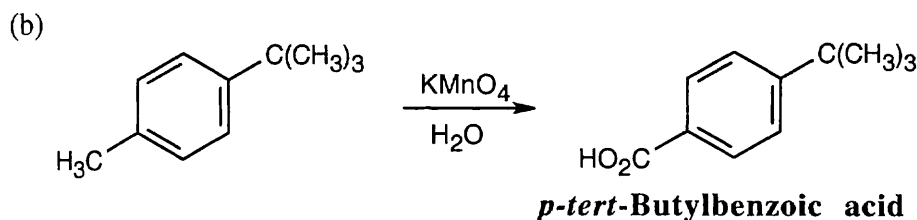
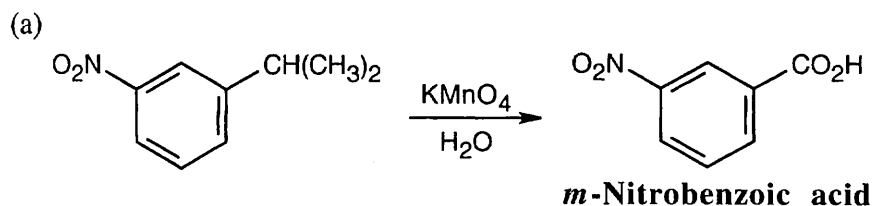
The nitro group makes the ring electron-poor and vulnerable to attack by the nucleophilic RO^- group. It also stabilizes the negatively charged Meisenheimer complex.

16.18



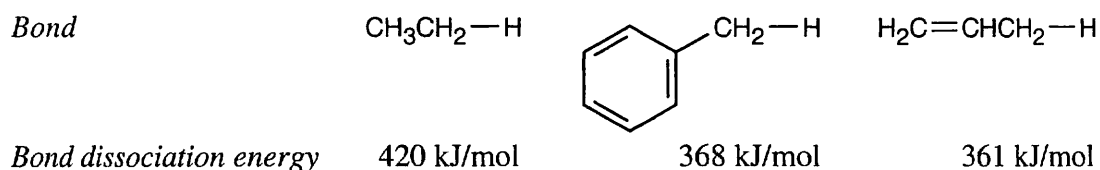
Treatment of *m*-bromotoluene with NaOH leads to two possible benzyne intermediates, which react with water to yield three methylphenol products.

16.19



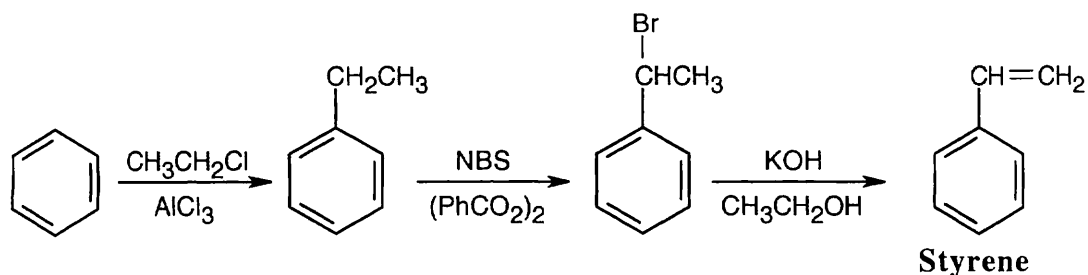
Treatment with KMnO_4 oxidizes the methyl group but leaves the *tert*-butyl group untouched.

16.20

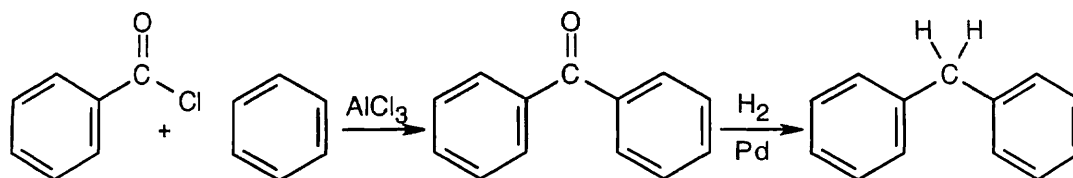


Bond dissociation energies measure the amount of energy that must be supplied to cleave a bond into two radical fragments. A radical is thus higher in energy and less stable than the compound it came from. Since the C–H bond dissociation energy is 420 kJ/mol for ethane and 368 kJ/mol for a methyl group C–H bond of toluene, less energy is required to form a benzyl radical than to form an ethyl radical. A benzyl radical is thus more stable than a primary alkyl radical by 52 kJ/mol. The bond dissociation energy of an allyl C–H bond is 361 kJ/mol, indicating that a benzyl radical is nearly as stable as an allyl radical.

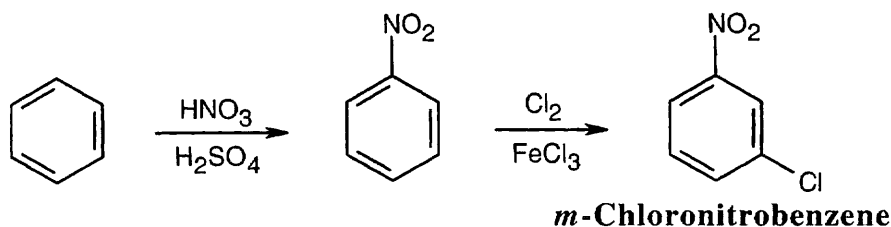
16.21



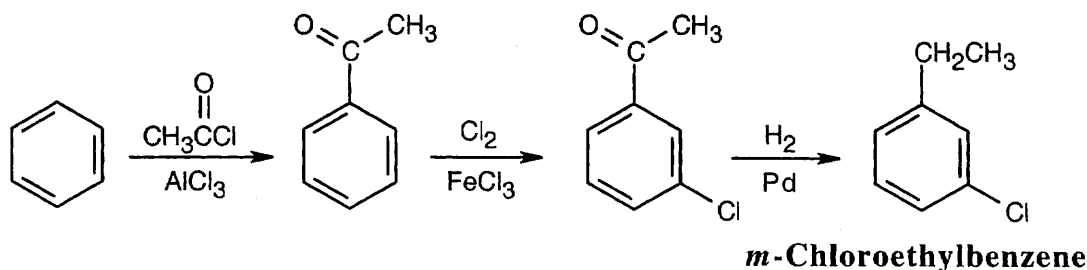
16.22



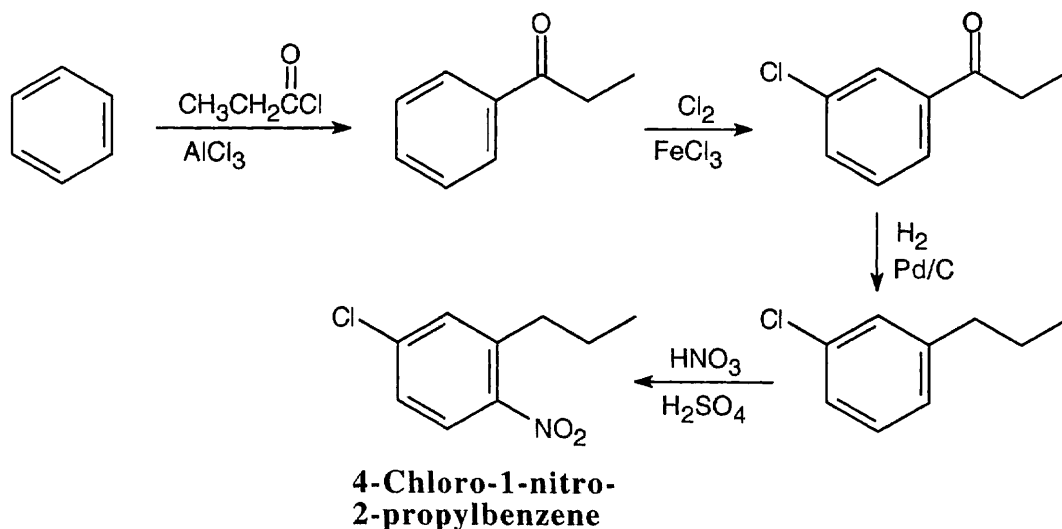
- 16.23** (a) In order to synthesize the product with the correct orientation of substituents, benzene must be nitrated before it is chlorinated.



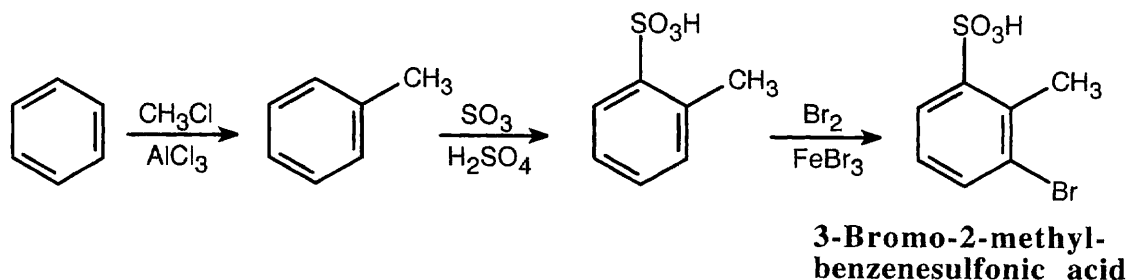
- (b) Chlorine can be introduced into the correct position if benzene is first acylated. The chlorination product can then be reduced.



- (c) Friedel–Crafts acylation, followed by chlorination, reduction, and nitration, is the only route that gives a product in which the alkyl group and chlorine have a meta relationship.



- (d) In planning this pathway, remember that the ring must be sulfonated after Friedel–Crafts alkylation because a sulfonated ring is too deactivated for alkylation to occur. Performing the reactions in this order allows the first two groups to direct bromine to the same position.

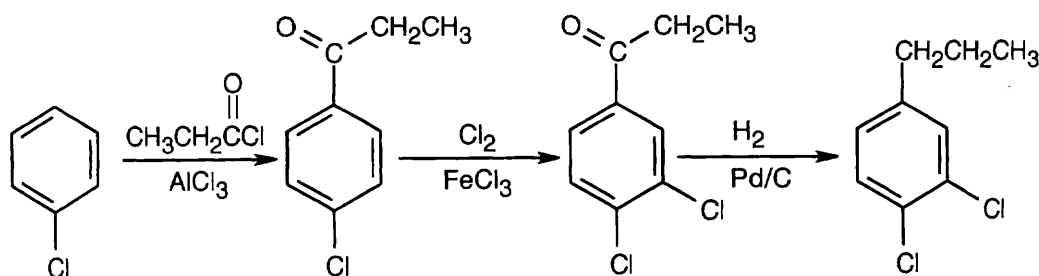


16.24 (a) Friedel–Crafts acylation, like Friedel–Crafts alkylation, does not occur at an aromatic ring carrying a strongly electron-withdrawing group.

(b) There are two problems with this synthesis as it is written:

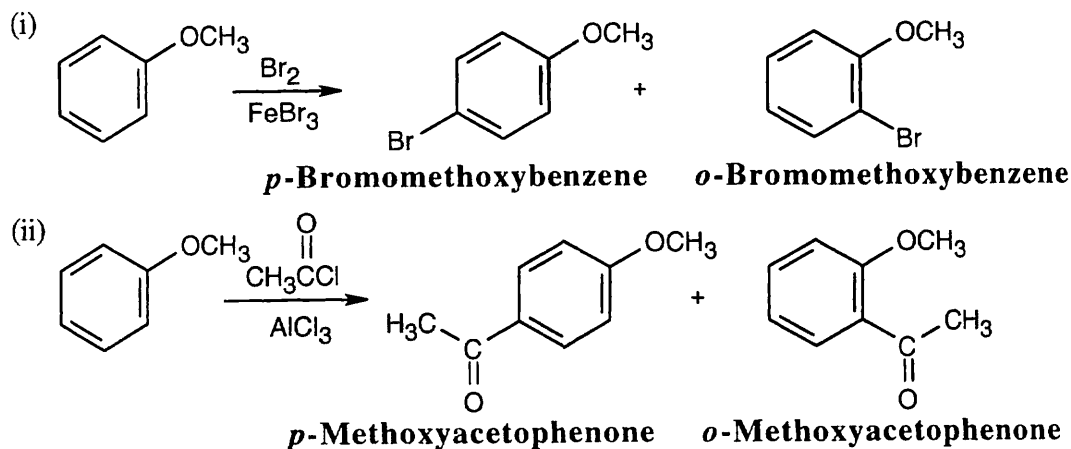
1. Rearrangement often occurs during Friedel–Crafts alkylations using primary halides.
2. Even if *p*-chloropropylbenzene could be synthesized, introduction of the second –Cl group would occur ortho to the alkyl group.

A possible route to this compound:

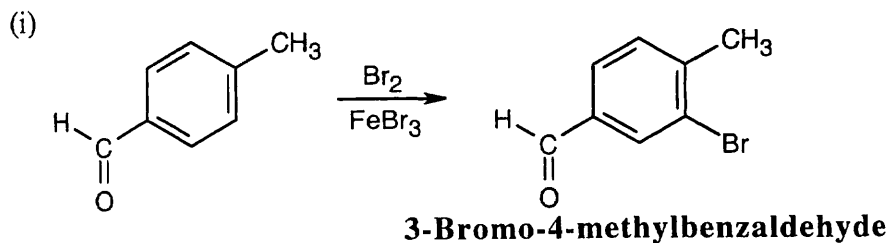


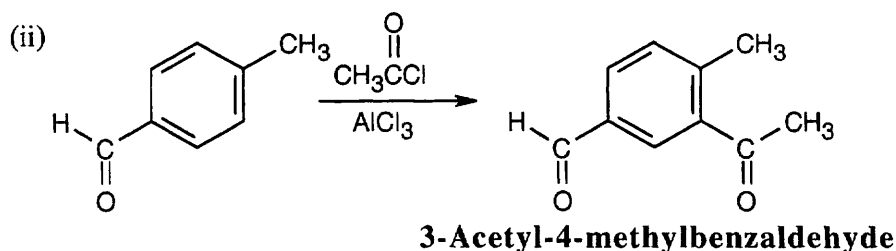
Visualizing Chemistry

16.25 (a) The methoxyl group is an ortho–para director.



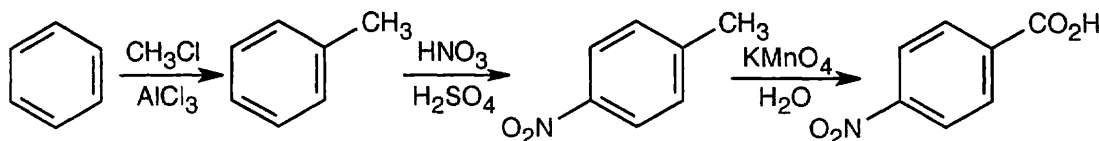
(b) Both functional groups direct substituents to the same position.





16.26 In the lowest-energy conformation of the biphenyl, the aromatic rings are tilted. If the rings had a planar relationship, steric strain between the methyl groups and the ring hydrogens on the other ring would occur. Complete rotation around the single bond doesn't take place because the repulsive interaction between the methyl groups causes a barrier to rotation.

16.27



16.28 Imagine two routes for synthesis of *m*-nitrotoluene:

(1) Alkylation of benzene, followed by nitration, doesn't succeed because an alkyl group is an *o,p*-director.

(2) Nitration of benzene, followed by alkylation, doesn't succeed because nitrobenzene is unreactive to Friedel–Crafts alkylation.

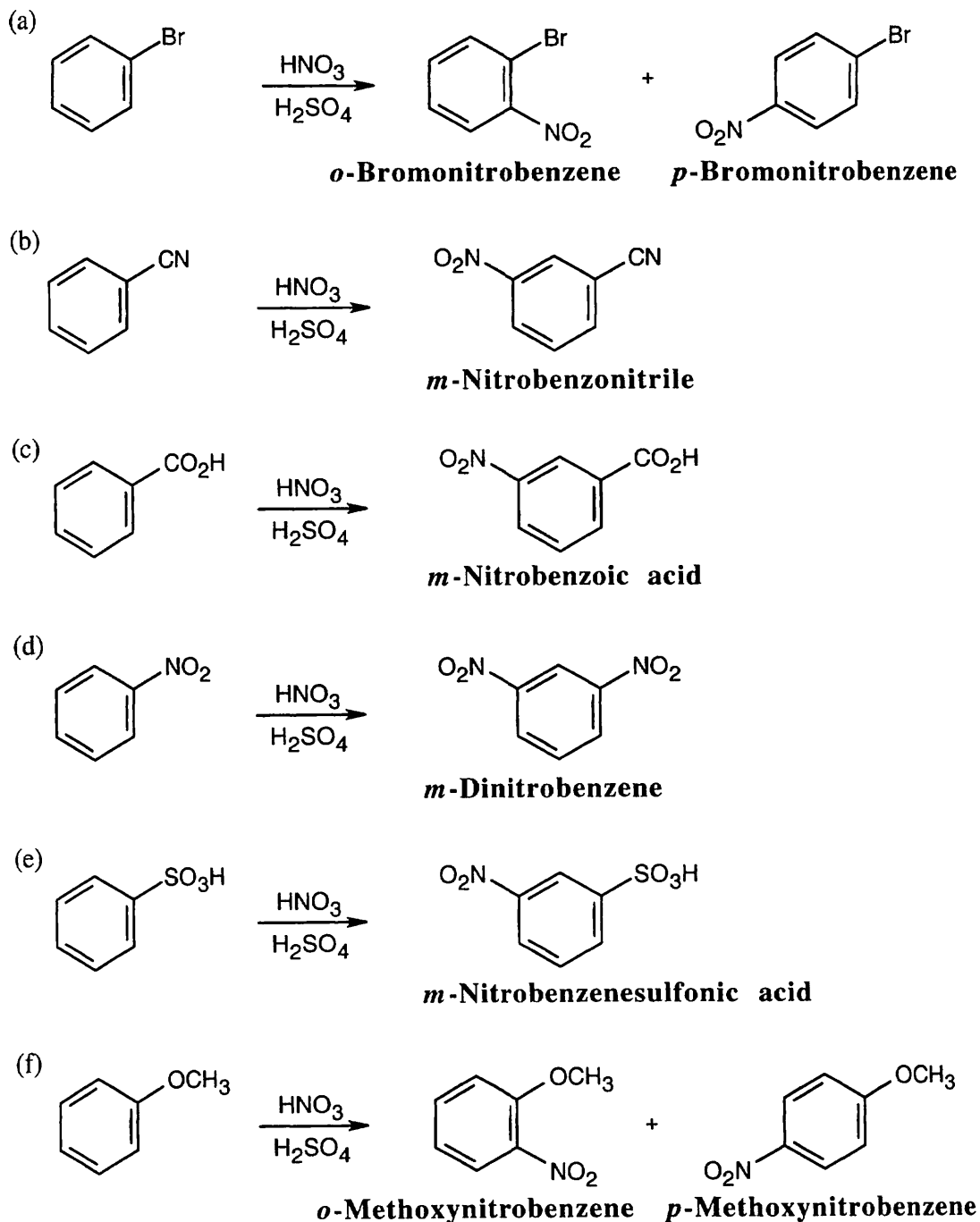
Thus, it isn't possible to synthesize *m*-nitrotoluene by any route that we have studied in this chapter.

Additional Problems

16.29

Group:	Identification:	Reason:
(a)	<i>o,p</i> -activator	Reaction intermediates are stabilized by electron donation by the amine nitrogen.
(b)	<i>o,p</i> -activator	Reaction intermediates are stabilized by the electron donating inductive effect of the alkyl group.
(c)	<i>o,p</i> -activator	Reaction intermediates are stabilized by electron donation by the ether oxygen.
(d)	<i>m</i> -deactivator	Reaction intermediates are destabilized by electron withdrawal by the carbonyl oxygen.

16.30

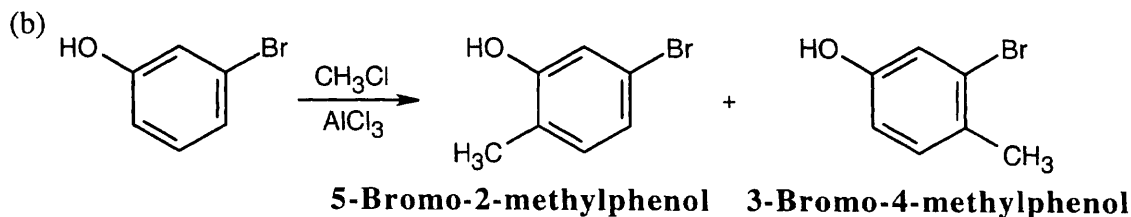
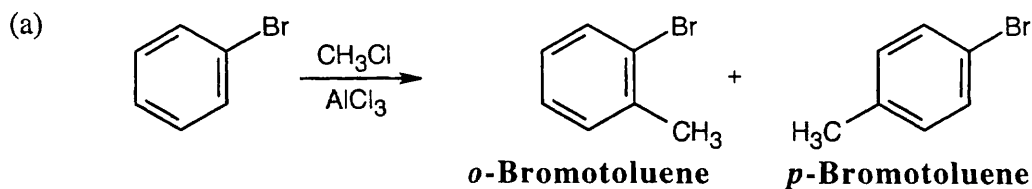


Only methoxybenzene reacts faster than benzene.

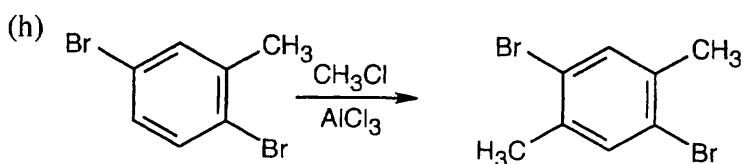
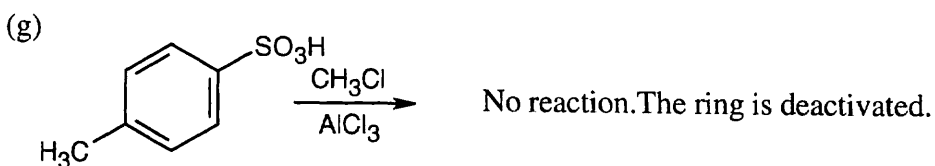
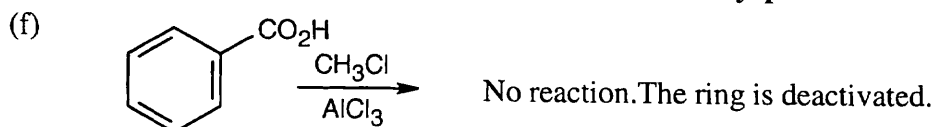
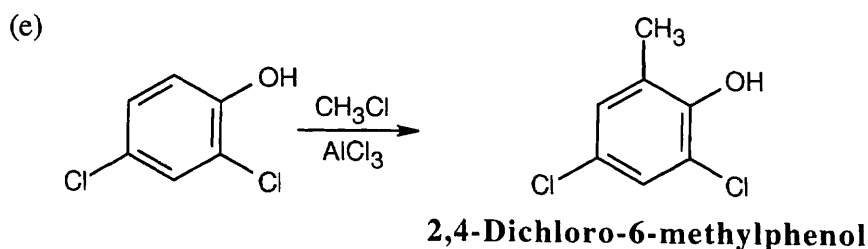
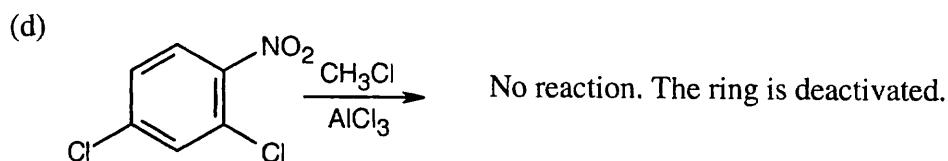
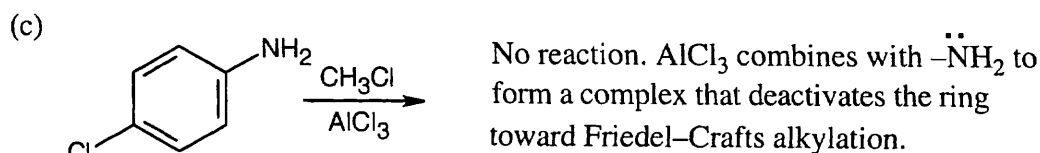
16.31 Most reactive \longrightarrow Least reactive

- (a) Benzene > Chlorobenzene > *o*-Dichlorobenzene
 (b) Phenol > Nitrobenzene > *p*-Bromonitrobenzene
 (c) *o*-Xylene > Fluorobenzene > Benzaldehyde
 (d) *p*-Methoxybenzonitrile > *p*-Methylbenzonitrile > Benzonitrile

16.32

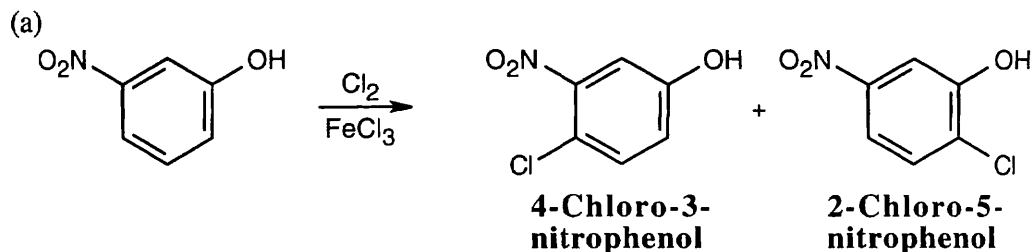


Both groups direct substitution to the same position.

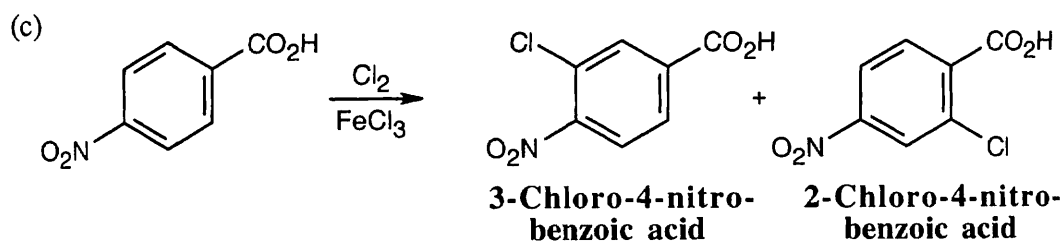
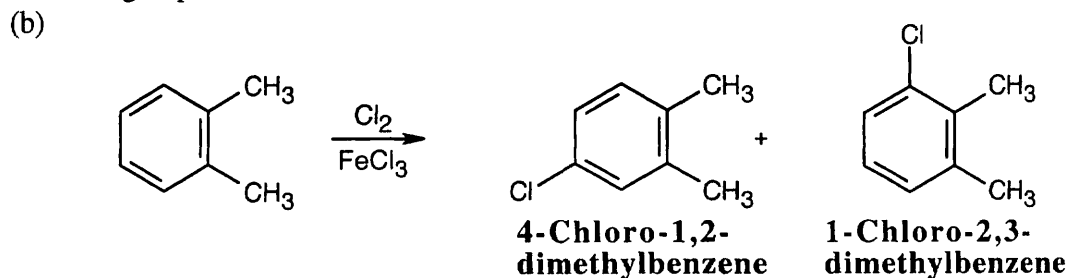


Alkylation occurs in the indicated position because the methyl group is more activating than bromine, and because substitution rarely takes place between two groups.

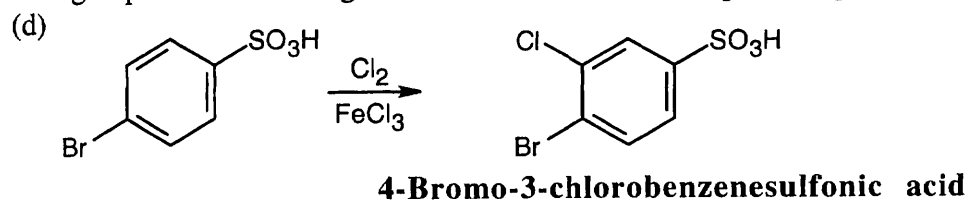
16.33



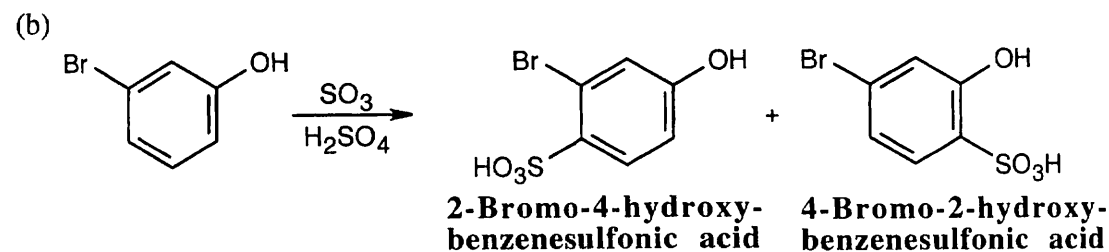
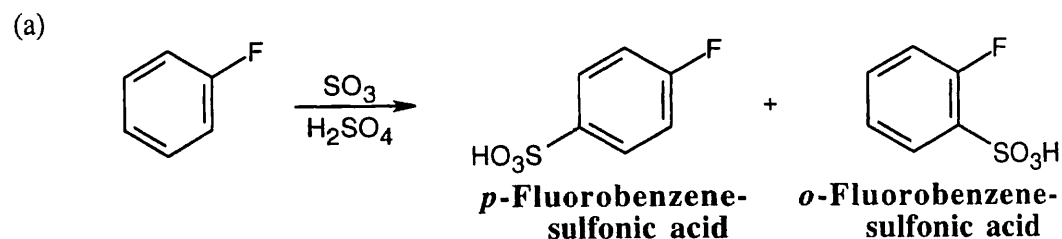
The $-\text{OH}$ group directs the orientation of substitution.

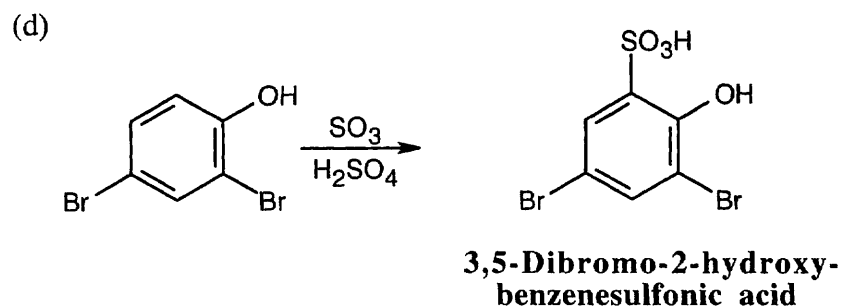
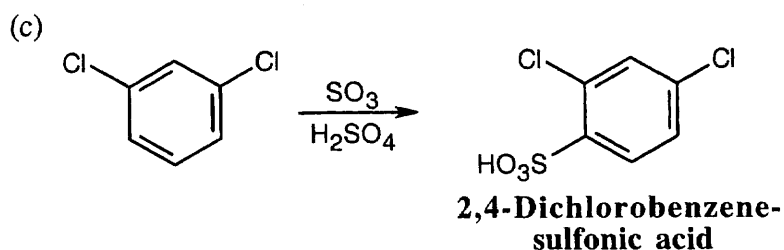


Both groups are deactivating to a similar extent, and both possible products form.



16.34

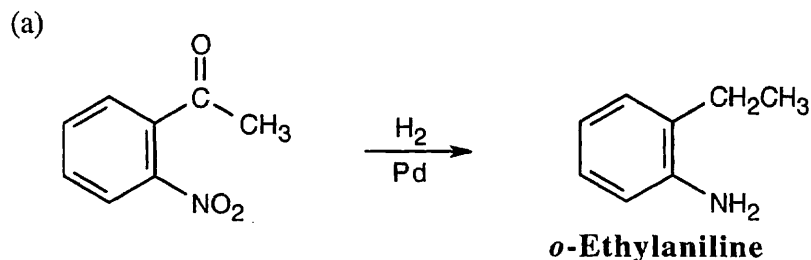




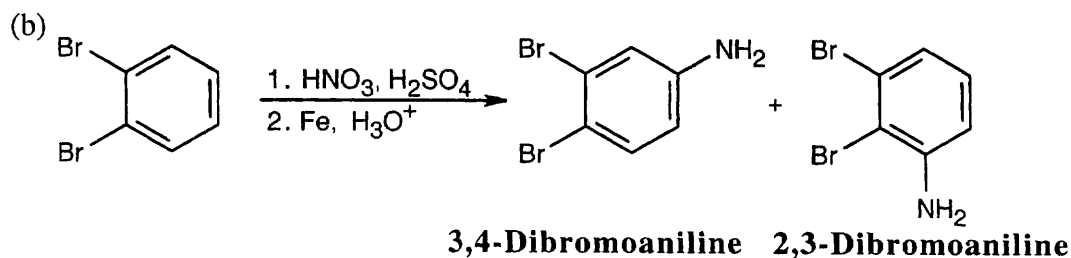
16.35 Most reactive \longrightarrow Least reactive

Phenol > Toluene > *p*-Bromotoluene > Bromobenzene
 Aniline and nitrobenzene don't undergo Friedel-Crafts alkylations.

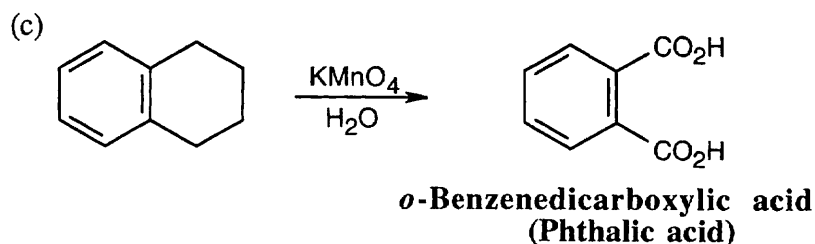
16.36



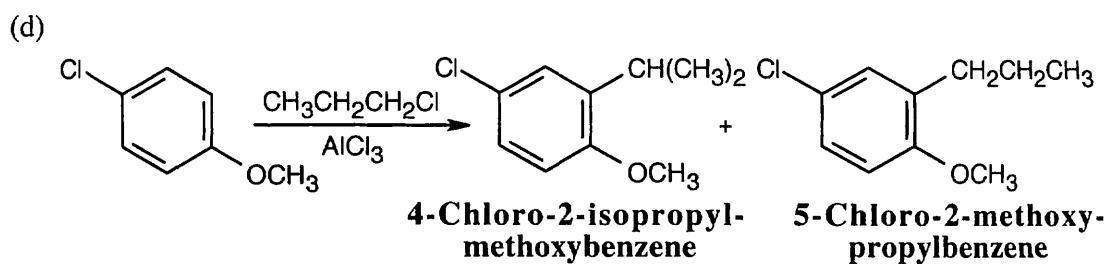
Catalytic hydrogenation reduces both the aromatic ketone and the nitro group.



Nitration, followed by reduction with Fe, produces substituted anilines.

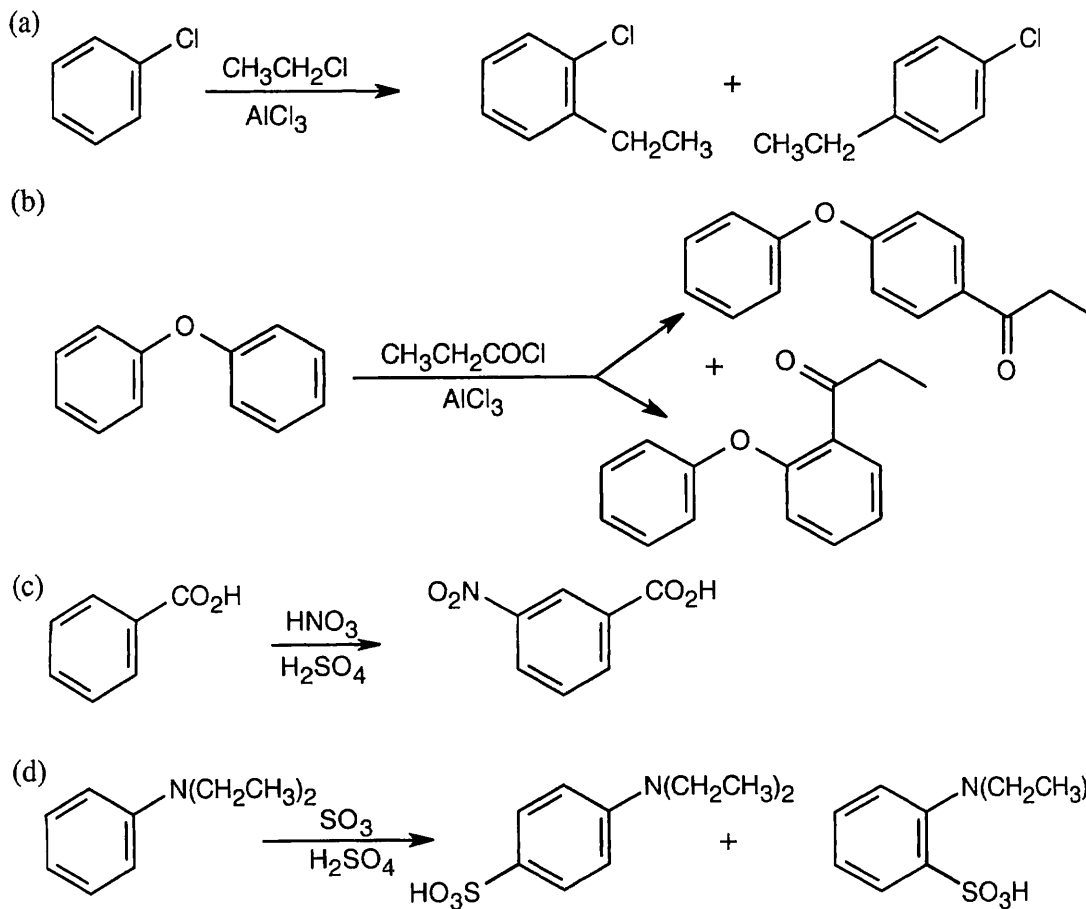


Aqueous KMnO_4 oxidizes alkyl side chains to benzoic acids.

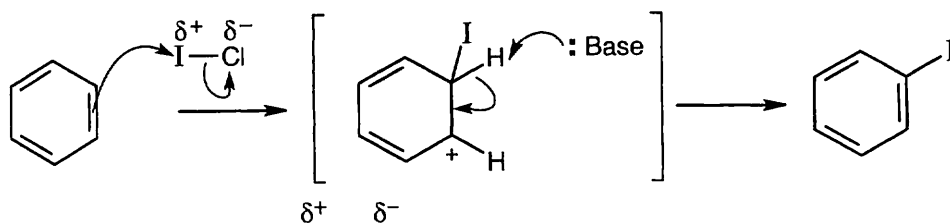


The methoxyl group directs substitution because it is a more powerful activating group. Rearranged and unrearranged products are formed.

16.37

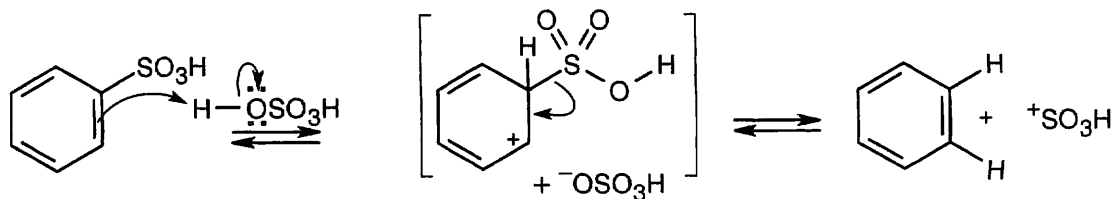


16.38



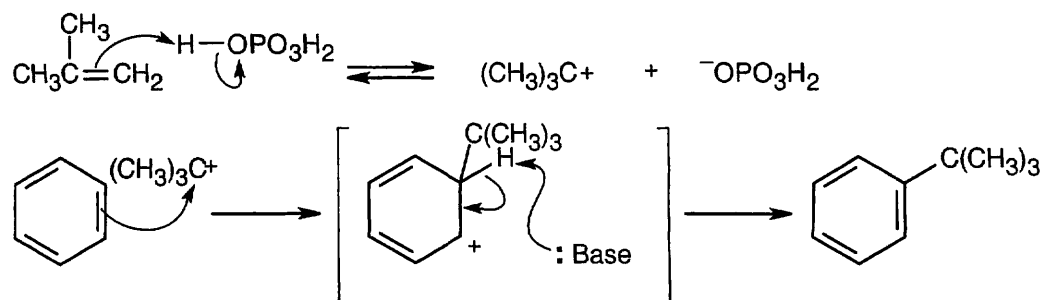
ICl can be represented as $\text{I}^{\delta+}-\text{Cl}^{\delta-}$ because chlorine is a more electronegative element than iodine. Iodine can act as an electrophile in electrophilic aromatic substitution reactions.

16.39



This mechanism is the reverse of the sulfonation mechanism illustrated in the text. H^+ is the electrophile in this reaction.

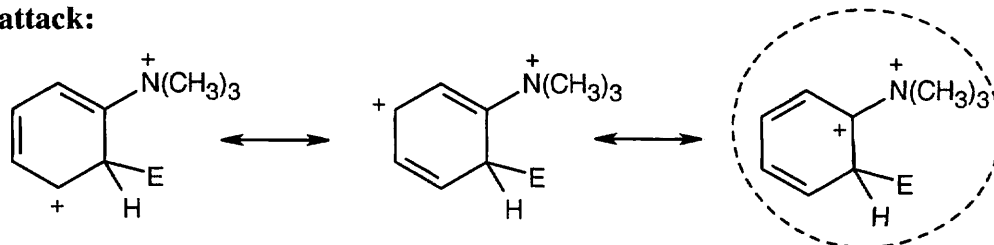
16.40



Phosphoric acid protonates 2-methylpropene, forming a *tert*-butyl carbocation. The carbocation acts as an electrophile in a Friedel-Crafts reaction to yield *tert*-butylbenzene.

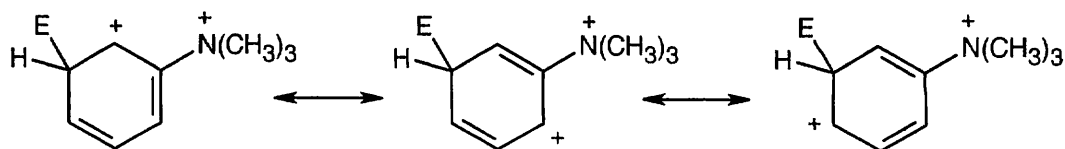
16.41 When an electrophile reacts with an aromatic ring bearing a $(\text{CH}_3)_3\text{N}^+$ group:

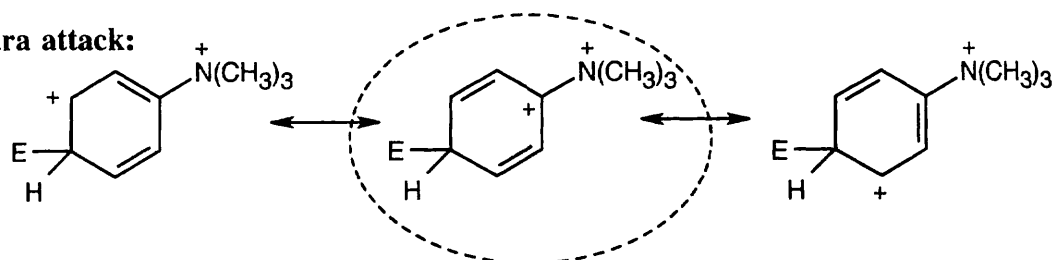
Ortho attack:



This is a destabilizing resonance form because two positive charges are next to each other.

Meta attack:

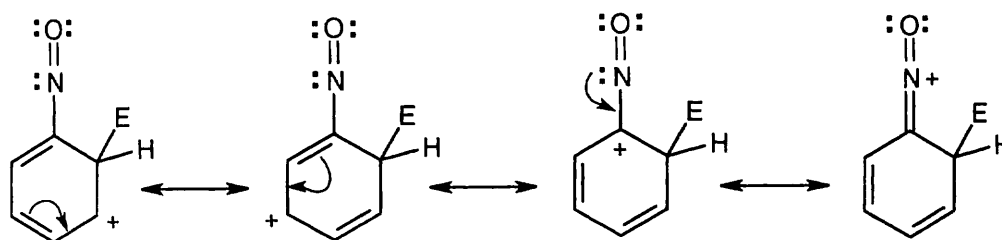
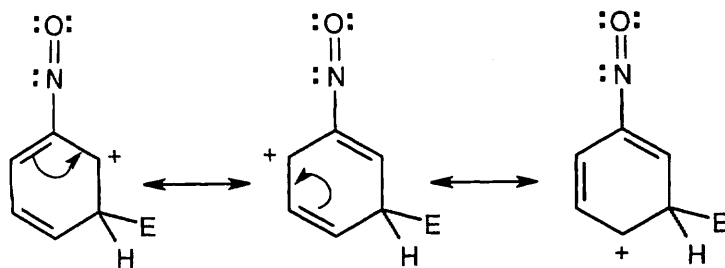
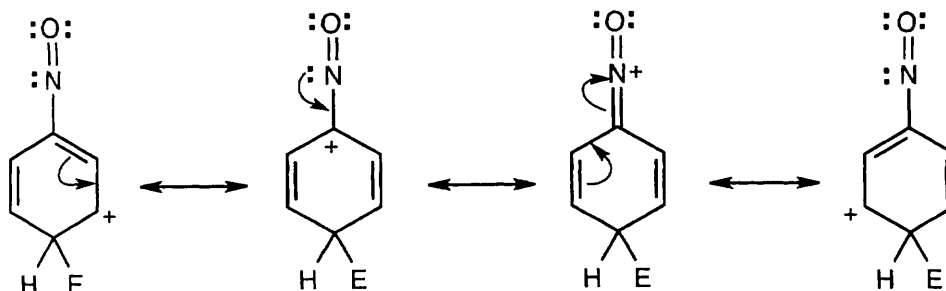


Para attack:

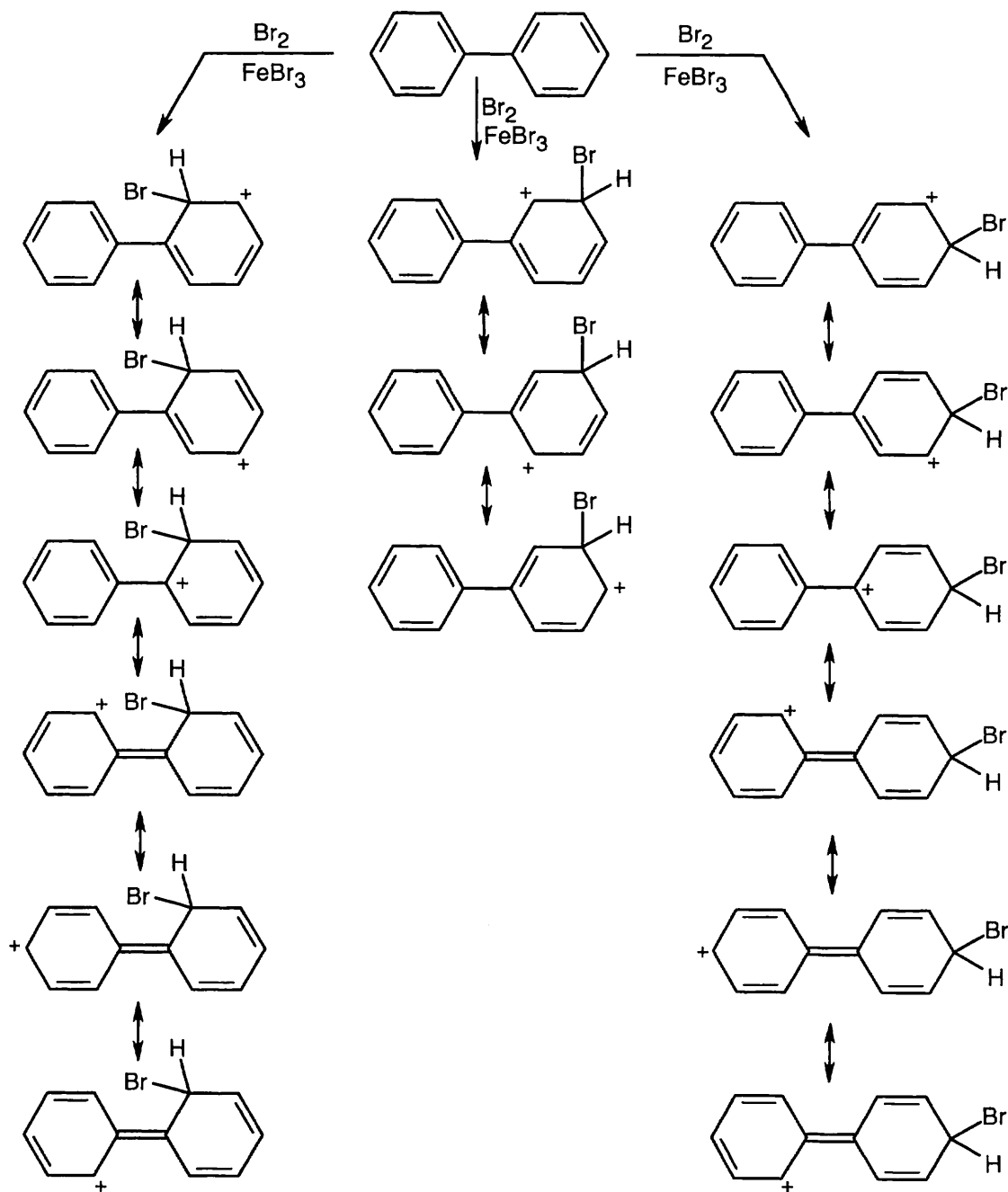
This form is destabilizing.

The *N,N,N*-trimethylammonium group has no electron-withdrawing resonance effect because it has no vacant *p* orbitals to overlap with the π orbital system of the aromatic ring. The $(\text{CH}_3)_3\text{N}^+$ group is inductively deactivating, however, because it is positively charged. It is meta-directing because the cationic intermediate resulting from meta attack is somewhat more stable than those resulting from ortho or para attack.

- 16.42** The aromatic ring is deactivated toward electrophilic aromatic substitution by the combined electron-withdrawing inductive effect of electronegative nitrogen and oxygen. The lone pair of electrons of nitrogen can, however, stabilize by resonance the ortho and para substituted intermediates but not the meta intermediate.

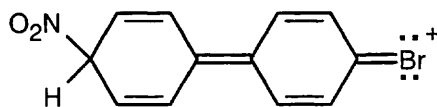
Ortho attack:**Meta attack:****Para attack:**

16.43



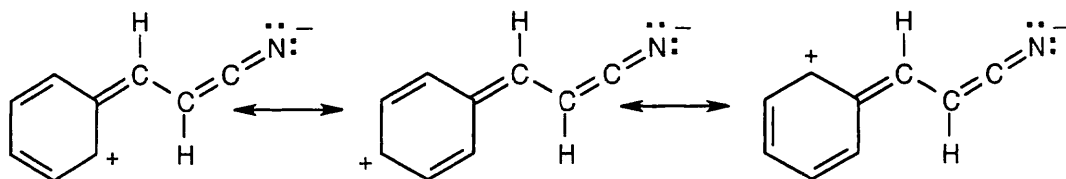
Resonance structures explain that bromination occurs in the ortho and para positions of the rings. The positively charged intermediate formed from ortho or para attack can be stabilized by resonance contributions from the second ring of biphenyl, but this stabilization is not possible for meta attack.

- 16.44** Attack occurs on the unsubstituted ring because bromine is a deactivating group. Attack occurs at the ortho and para positions of the ring because the positively charged intermediate can be stabilized by resonance contributions from bromine and from the second ring (Problem 16.43).

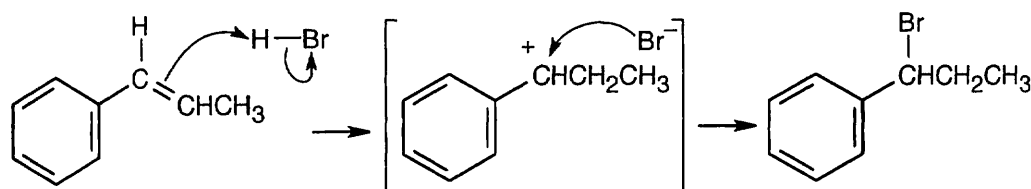


- 16.45** When directly bonded to a ring, the $-\text{CN}$ group is a meta-directing deactivator for both inductive and resonance reasons. In 3-phenylpropanenitrile, however, the saturated side chain does not allow resonance interactions of $-\text{CN}$ with the aromatic ring, and the $-\text{CN}$ group is too far from the ring for its inductive effect to be strongly felt. The side chain acts as an alkyl substituent, and ortho-para substitution is observed.

In 3-phenylpropenenitrile, the $-\text{CN}$ group interacts with the ring through the π electrons of the side chain. Resonance forms show that $-\text{CN}$ deactivates the ring toward electrophilic substitution, and substitution occurs at the meta position.

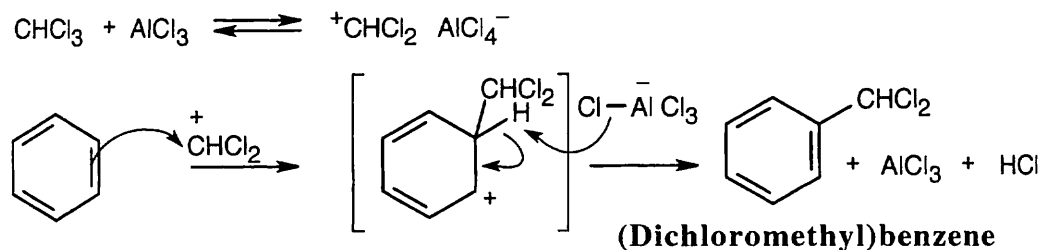


16.46

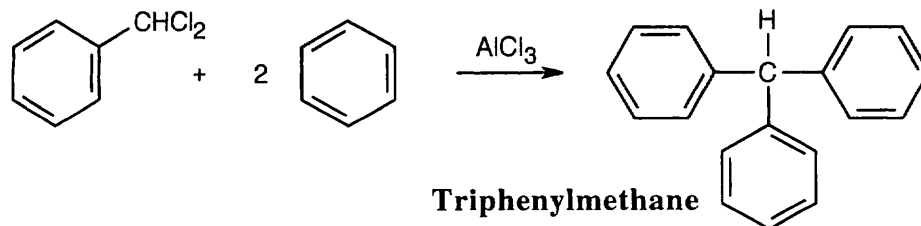


Protonation of the double bond at carbon 2 of 1-phenylpropene leads to an intermediate that can be stabilized by resonance involving the benzene ring.

16.47

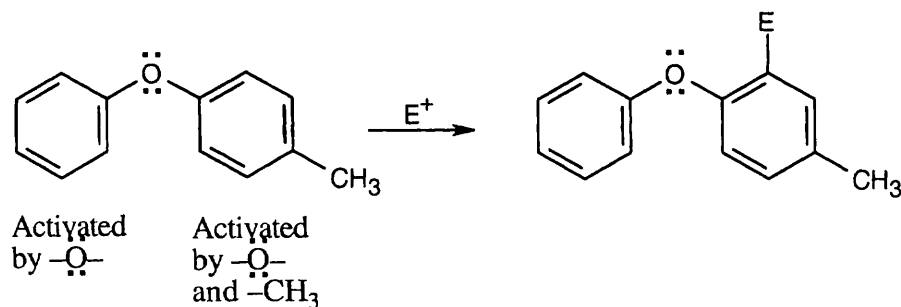


(Dichloromethyl)benzene can react with two additional equivalents of benzene by the same mechanism to produce triphenylmethane.



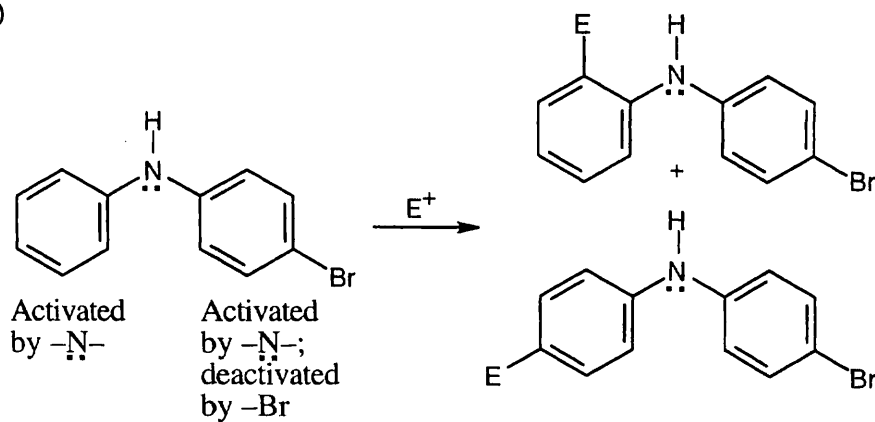
16.48

(a)



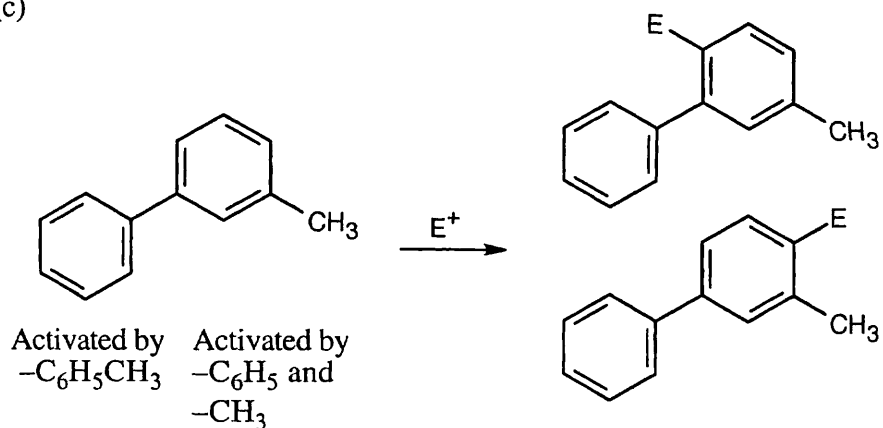
Substitution occurs in the more activated ring. The position of substitution is determined by the more powerful activating group – in this case, the ether oxygen.

(b)



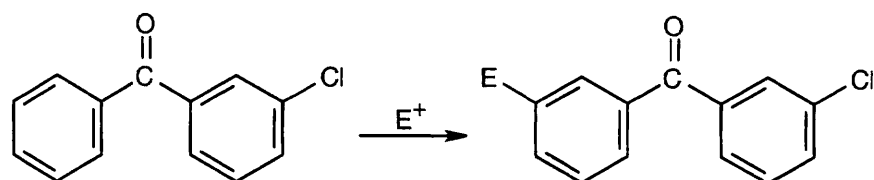
The left ring is more activated than the right ring. $-\text{NHR}$ is an ortho-para director.

(c)



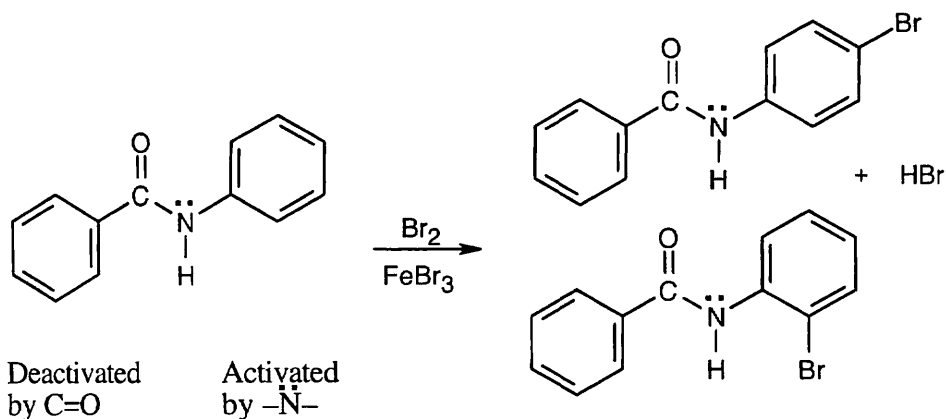
Substitution occurs at the ortho and para positions of the more activated ring. Substitution doesn't occur between $-\text{C}_6\text{H}_5$ and $-\text{CH}_3$ for steric reasons.

(d)

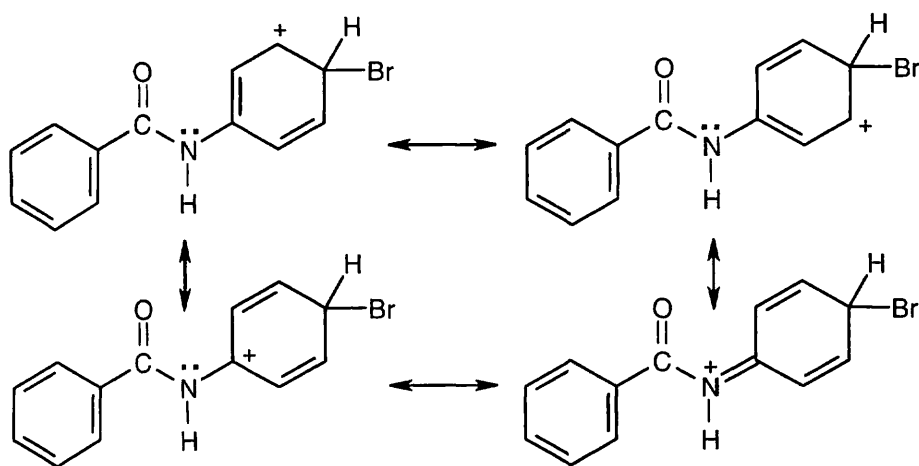
Deactivated
by -C=O Deactivated
by -C=O
and -Cl

Substitution occurs at the meta positions of the ring on the left because it is less deactivated.

16.49



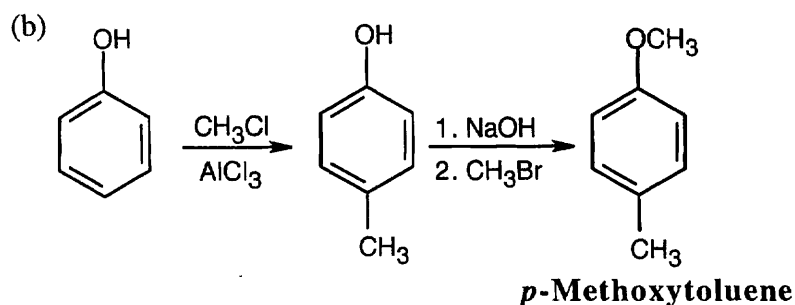
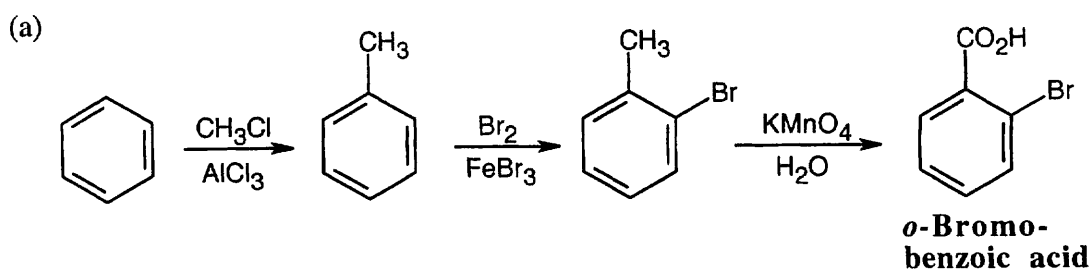
Attack occurs in the activated ring and yields ortho and para bromination products. The intermediate is resonance-stabilized by overlap of the nitrogen lone pair electrons with the π electrons of the substituted ring.



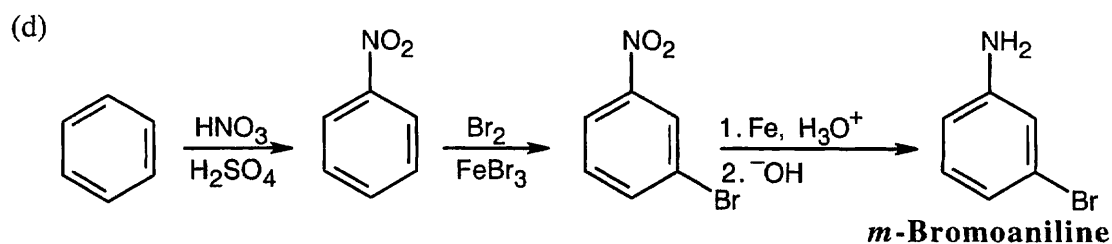
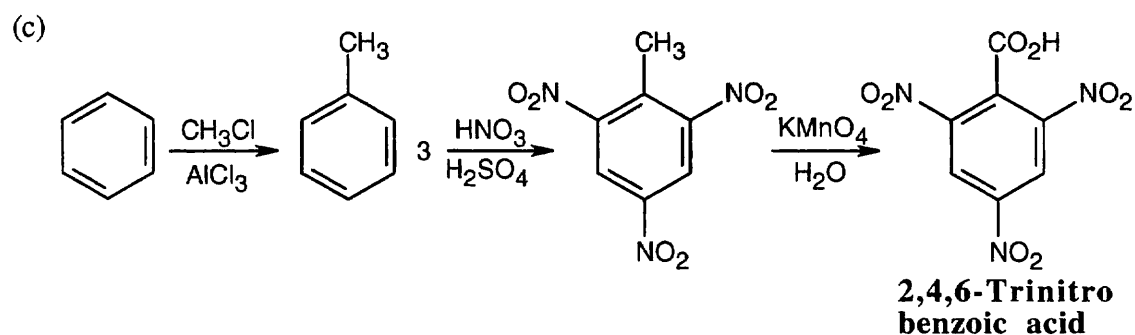
Similar drawings can be made of the resonance forms of the intermediate resulting from ortho attack. Even though the nitrogen lone-pair electrons are less available for delocalization than the lone-pair electrons of aniline (Problem 16.13), the -NH- group is nevertheless more activating than the C=O group.

16.50 Reaction of (*R*)-2-chlorobutane with AlCl_3 produces an ion pair $[\text{CH}_3^+\text{CHCH}_2\text{CH}_3 \text{ } ^-\text{AlCl}_4]$. The planar, sp^2 -hybridized carbocation is achiral, and its reaction with benzene yields racemic product.

16.51

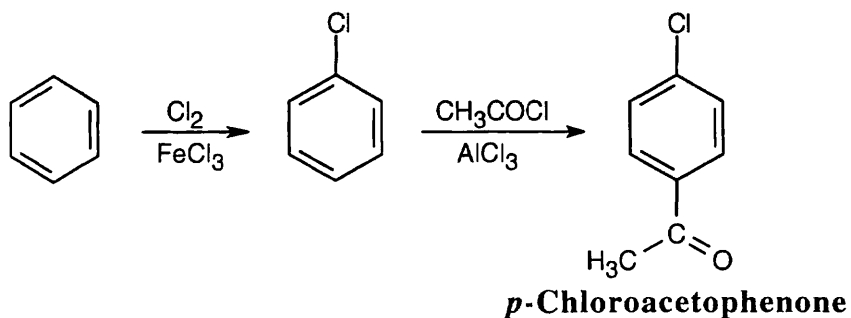


The reactions can be performed in either order.

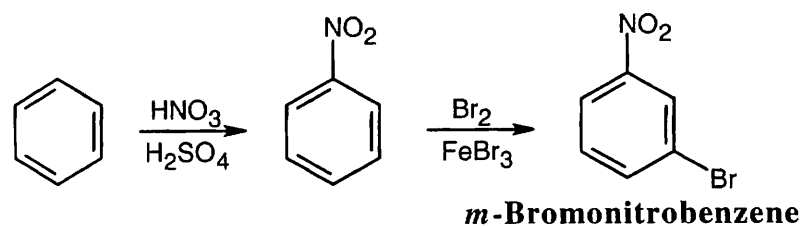


16.52 When synthesizing substituted aromatic rings, it is necessary to introduce substituents in the proper order. A group that is introduced out of order will not have the proper directing effect. Remember that in many of these reactions a mixture of ortho and para isomers may be formed.

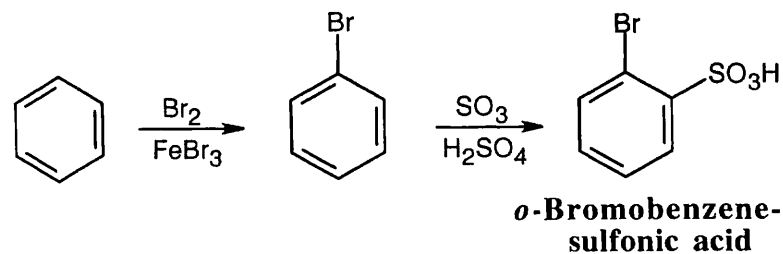
(a)



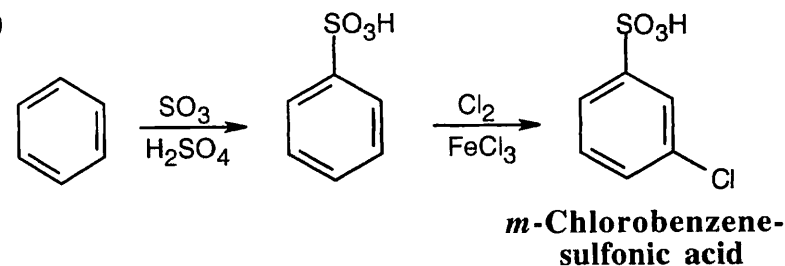
(b)



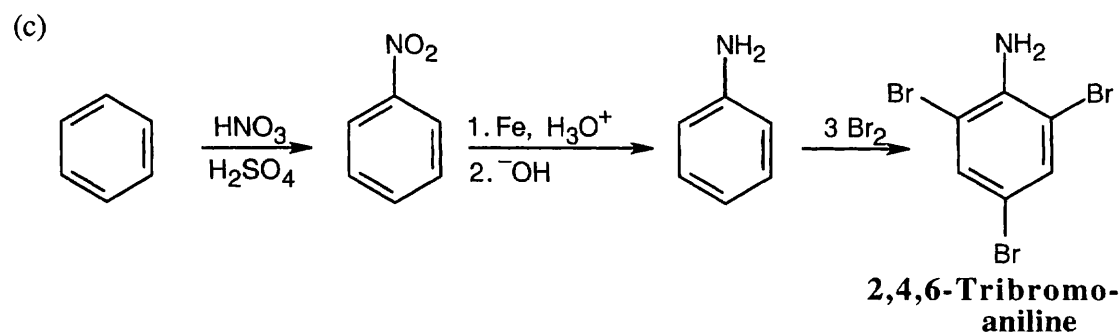
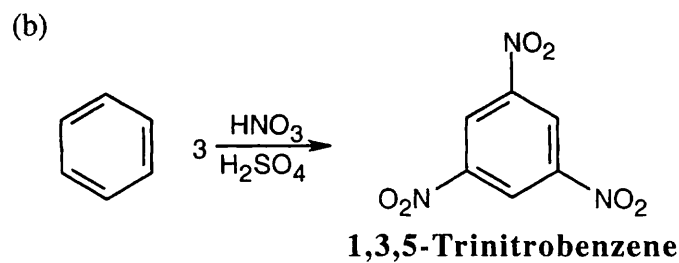
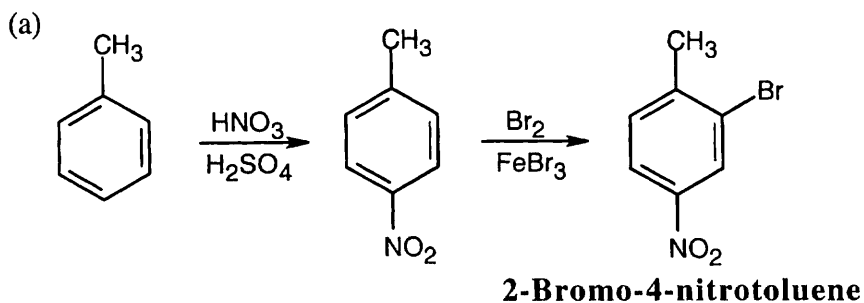
(c)



(d)



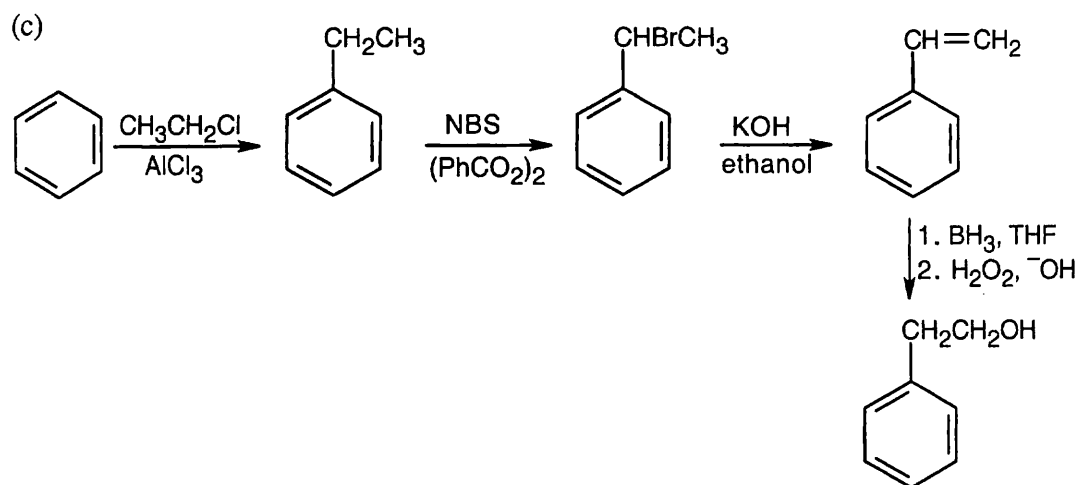
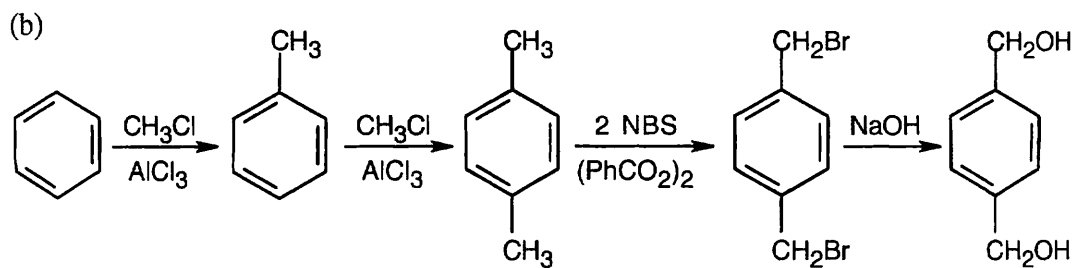
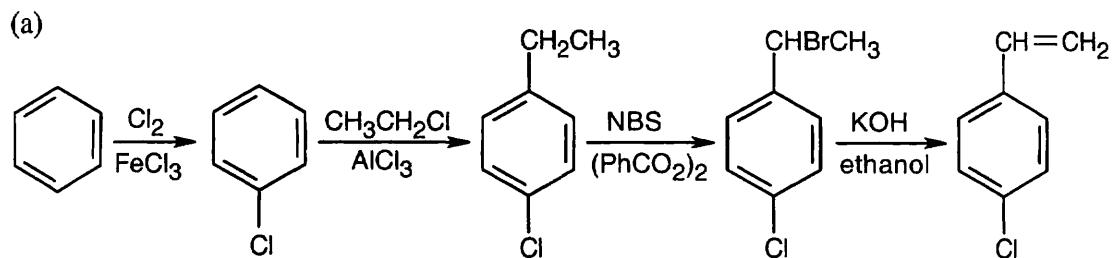
16.53



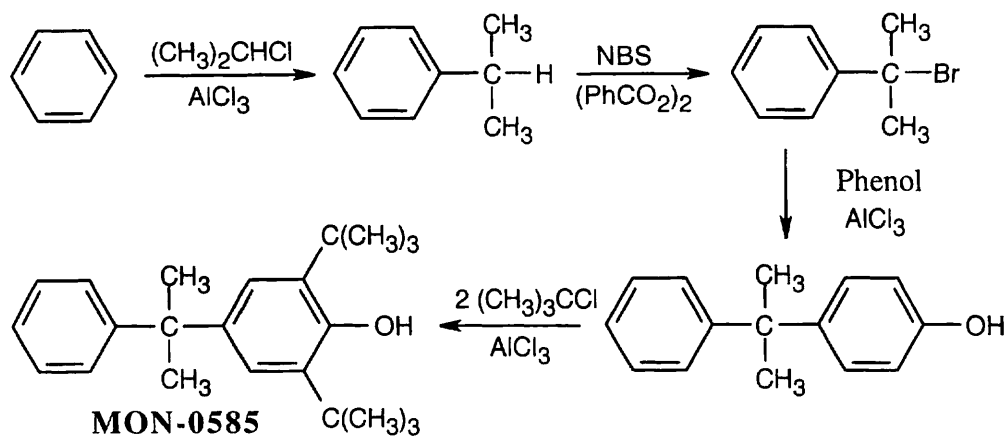
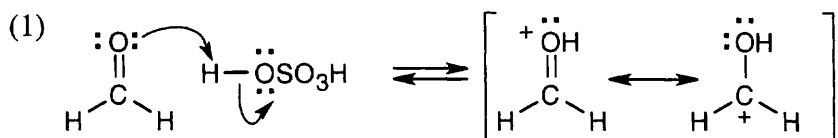
No catalyst is needed for bromination because aniline is very activated toward substitution.

- 16.54** (a) Chlorination of toluene occurs at the ortho and para positions. To synthesize the given product, first oxidize toluene to benzoic acid and then chlorinate.
(b) *p*-Chloronitrobenzene is inert to Friedel–Crafts alkylation because the ring is deactivated.
(c) The first two steps in the sequence are correct, but H_2/Pd reduces the nitro group as well as the ketone.

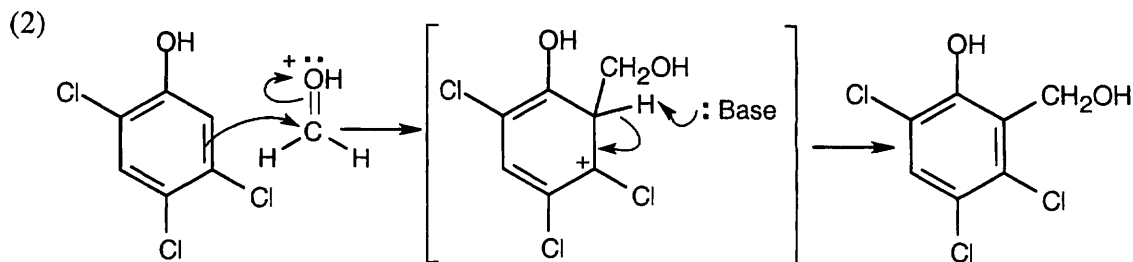
16.55 All of these syntheses involve NBS bromination of the benzylic position of a side chain.



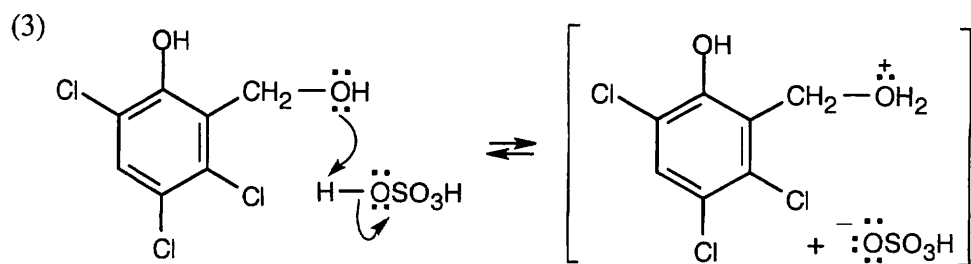
16.56 The product is a substituted phenol, whose $-\text{OH}$ group directs the orientation of the $-\text{C}(\text{CH}_3)_3$ groups. The precursor to MON-0585 is synthesized by a Friedel–Crafts alkylation of phenol by the appropriate hydrocarbon halide. This compound is synthesized by NBS bromination of the product of alkylation of benzene with 2-chloropropane.

**16.57**

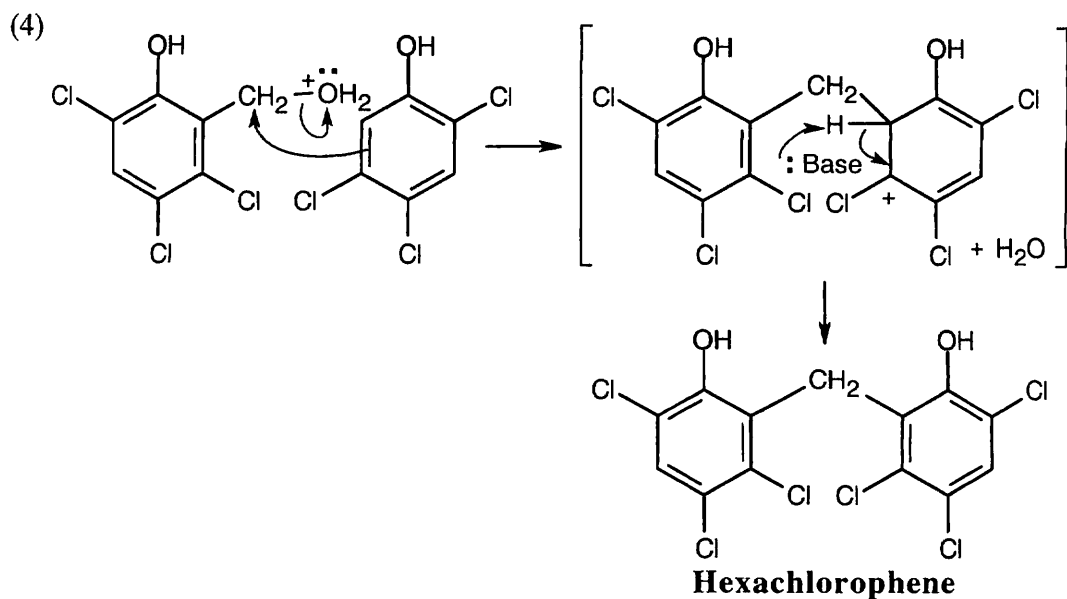
Formaldehyde is protonated to form a carbocation.



The formaldehyde cation acts as the electrophile in a substitution reaction at the “6” position of 2,4,5-trichlorophenol.

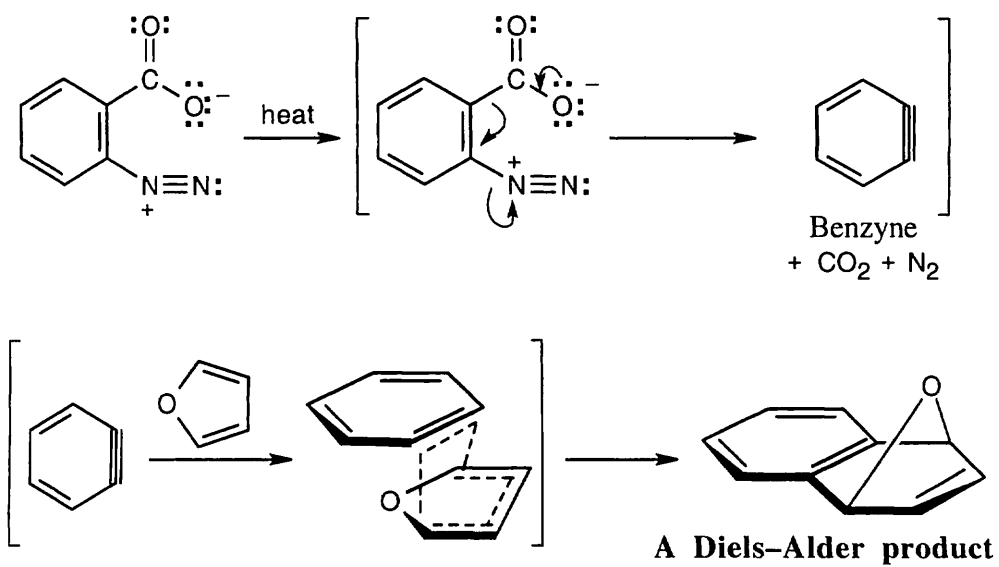


The product from step 2 is protonated by strong acid to produce a cation.

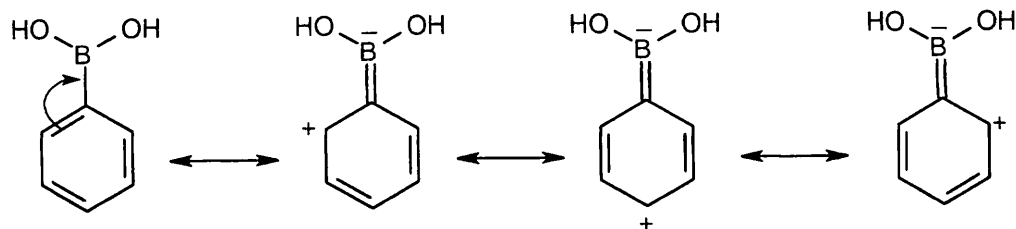


This cation is attacked by a second molecule of 2,4,5-trichlorophenol to produce hexachlorophene.

16.58

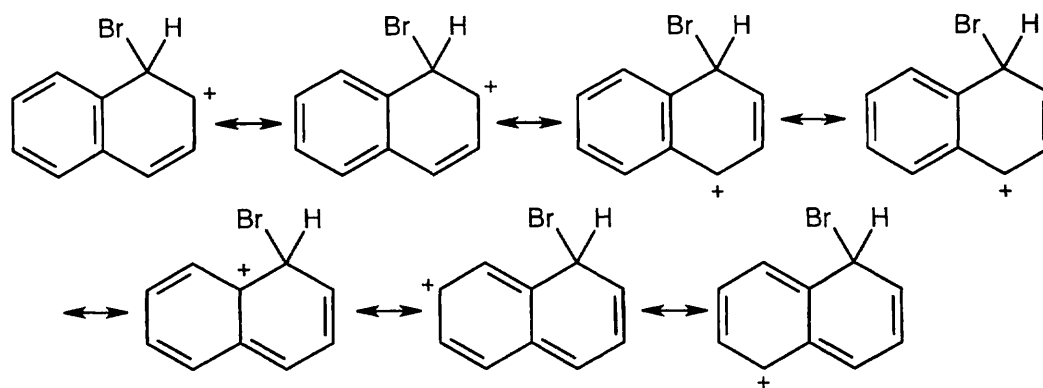


16.59

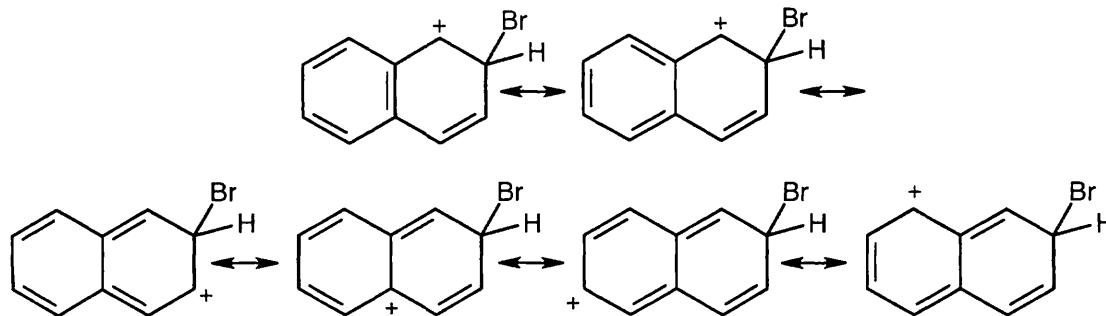


The trivalent boron atom in phenylboronic acid has only six outer-shell electrons and is a Lewis acid. It is possible to write resonance forms for phenylboronic acid in which an electron pair from the phenyl ring is delocalized onto boron. In these resonance forms, the ortho and para positions of phenylboronic acid are the most electron-deficient, and substitutions occur primarily at the meta position.

16.60 Resonance forms for the intermediate from attack at C1:

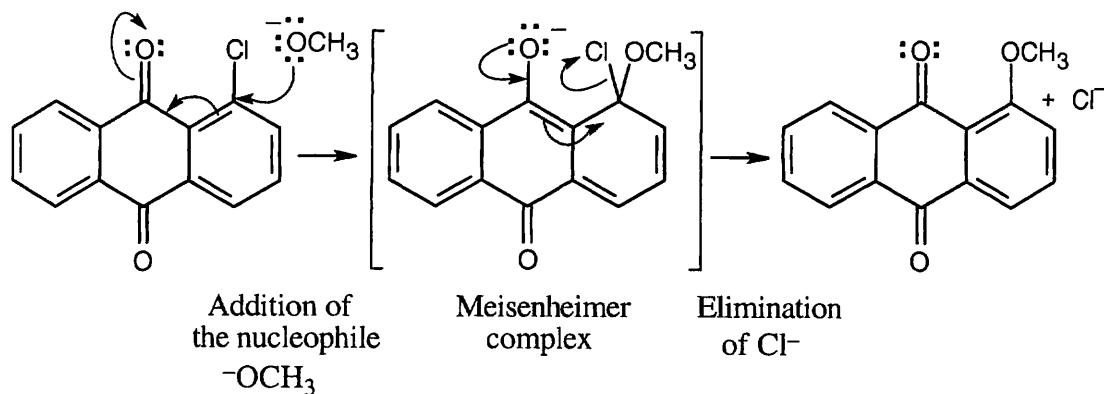


Resonance forms for the intermediate from attack at C2:



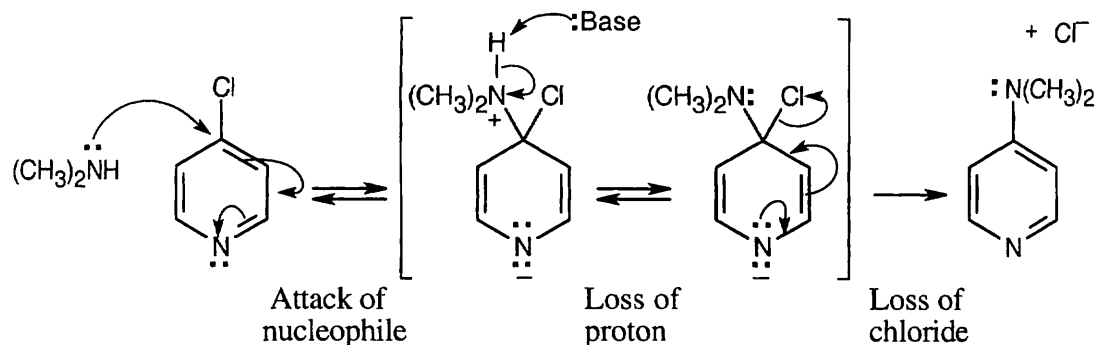
There are seven resonance forms for attack at C1 and six for attack at C2. Look carefully at the forms, however. In the first four resonance structures for C1 attack, the second ring is still fully aromatic. In the other three forms, however, the positive charge has been delocalized into the second ring, destroying the ring's aromaticity. For C2 attack, only the first two resonance structures have a fully aromatic second ring. Since stabilization is lost when aromaticity is disrupted, the intermediate from C2 attack is less stable than the intermediate from C1 attack, and C1 attack is favored.

16.61



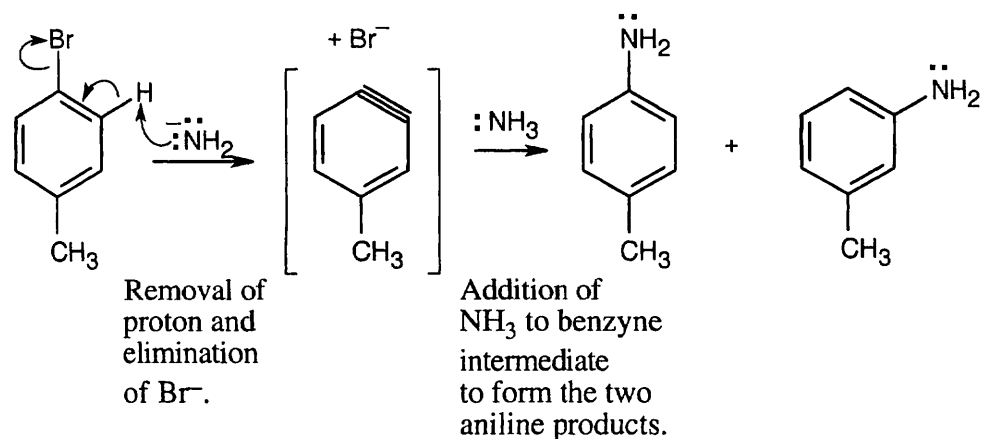
The carbonyl oxygens make the chlorine-containing ring electron-poor and open to attack by the nucleophile $^-\text{OCH}_3$. They also stabilize the negatively charged Meisenheimer complex.

16.62



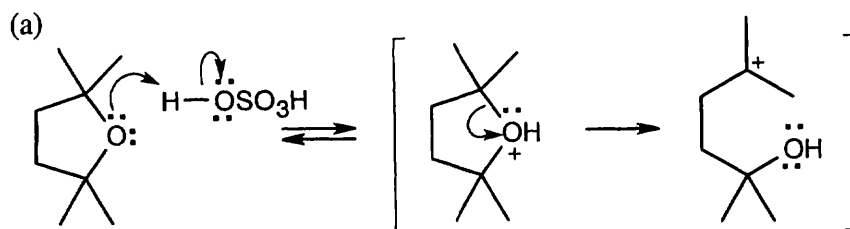
This reaction is an example of nucleophilic aromatic substitution. Dimethylamine is a nucleophile, and the pyridine nitrogen acts as an electron-withdrawing group that can stabilize the negatively-charged intermediate.

16.63

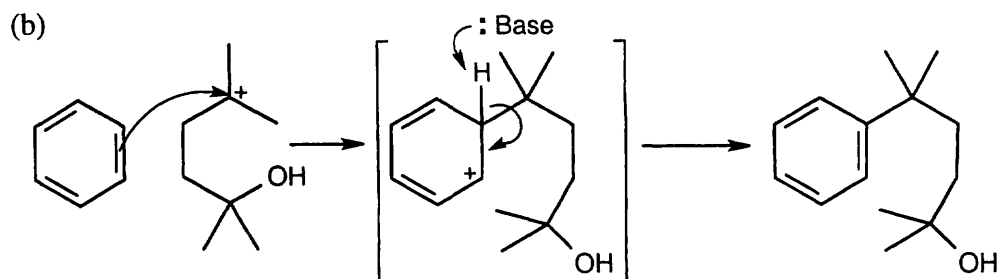


The reaction of an aryl halide with potassium amide proceeds through a benzyne intermediate. Ammonia can then add to either end of the triple bond to produce the two methylanilines observed.

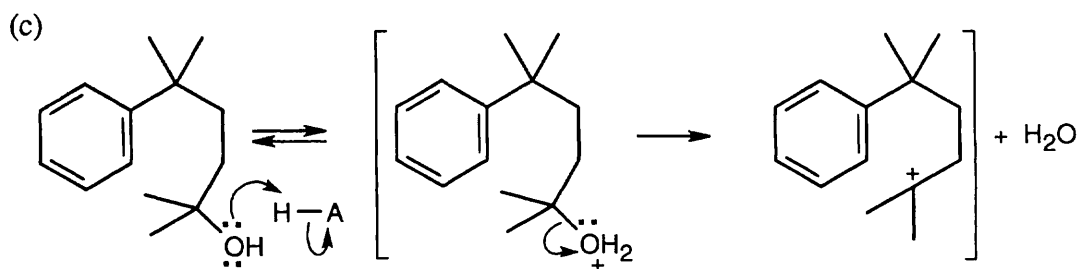
16.64



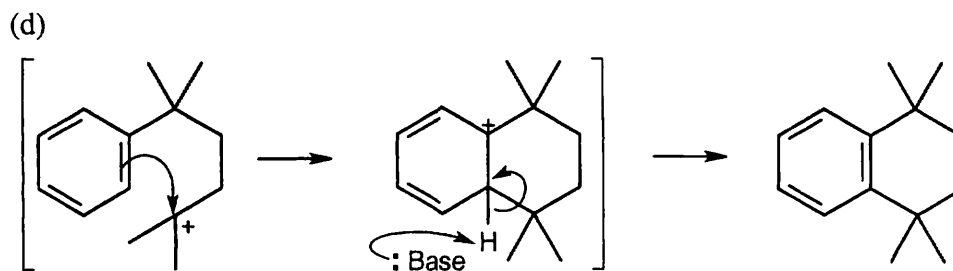
Protonation of the cyclic ether creates a carbocation intermediate that can react in a Friedel–Crafts alkylation.



The intermediate alkylates benzene, forming an alcohol product.

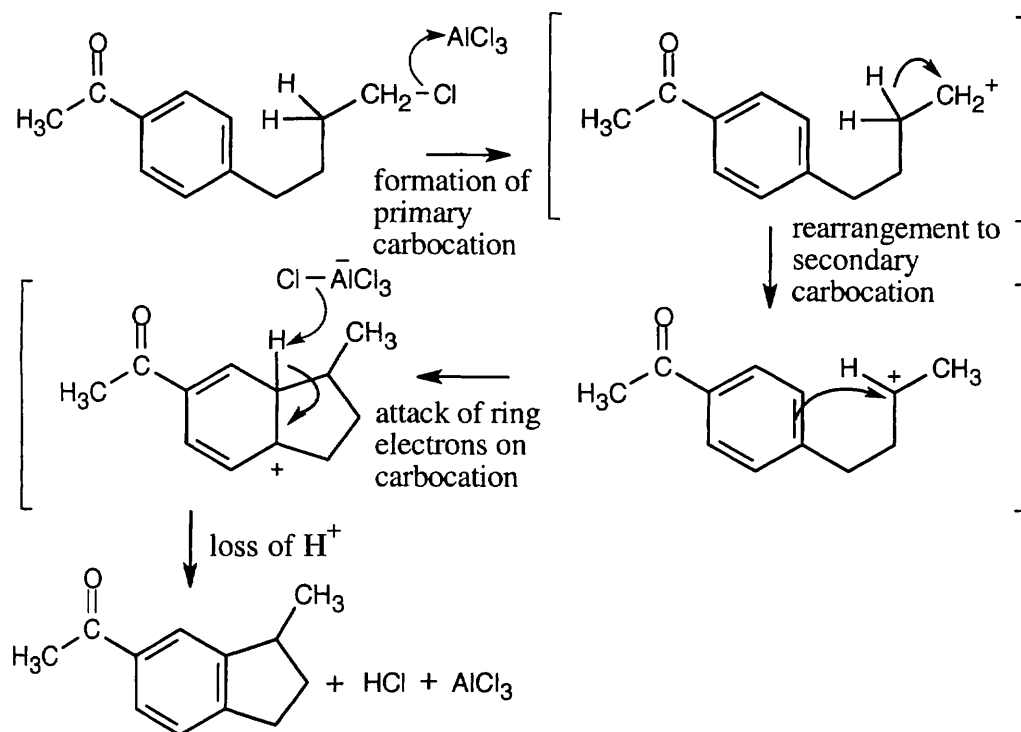


Protonation of the alcohol, followed by loss of water, generates a second carbocation.



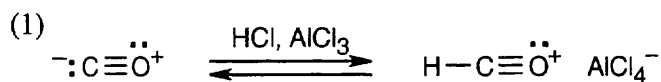
This carbocation undergoes internal alkylation to yield the observed product.

16.65

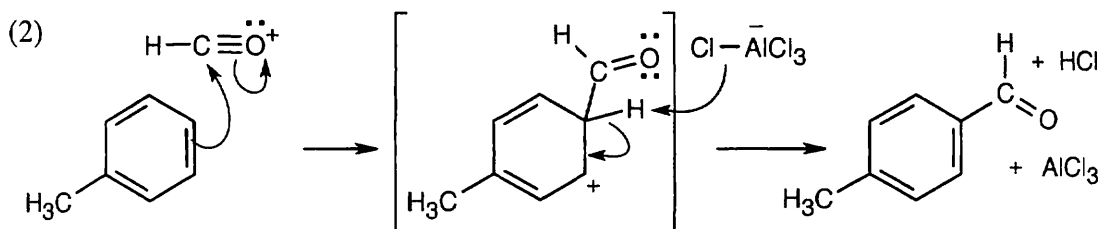


This reaction takes place despite the fact that an electron-withdrawing group is attached to the ring. Apparently, the cyclization reaction is strongly favored.

16.66

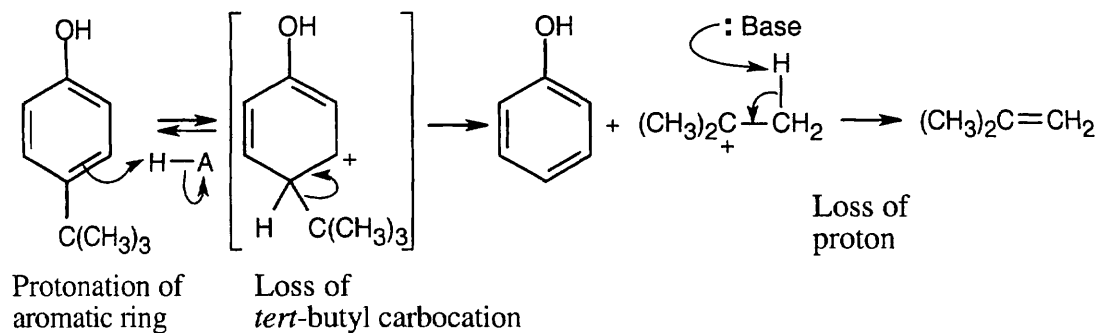


Carbon monoxide is protonated to form an acyl cation.

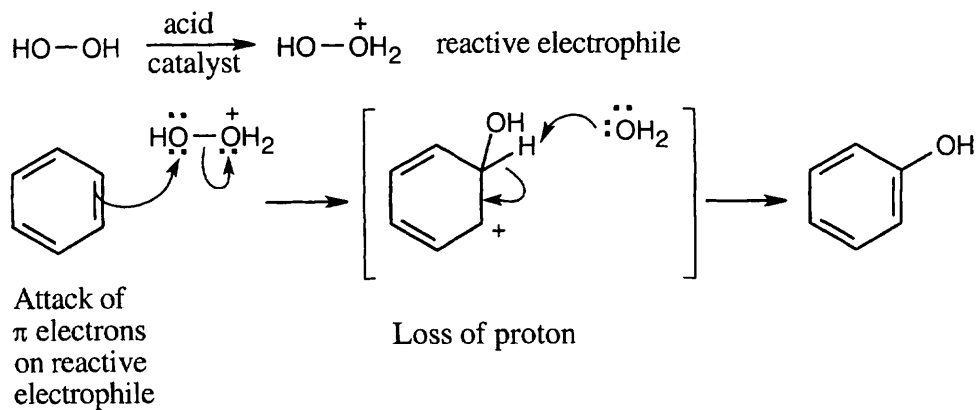


The acyl cation reacts with benzene by a Friedel-Crafts acylation mechanism.

16.67



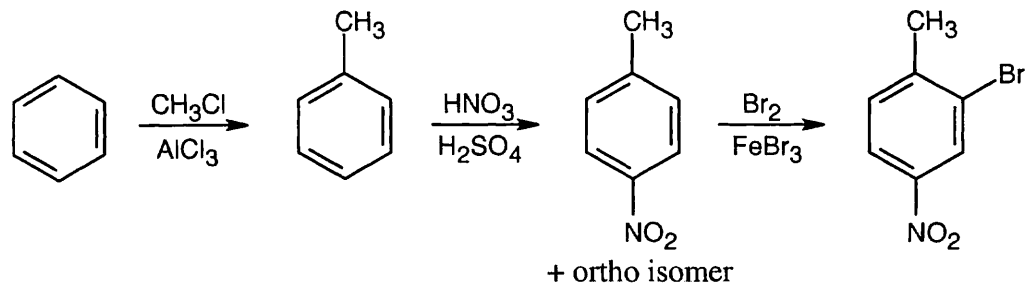
16.68



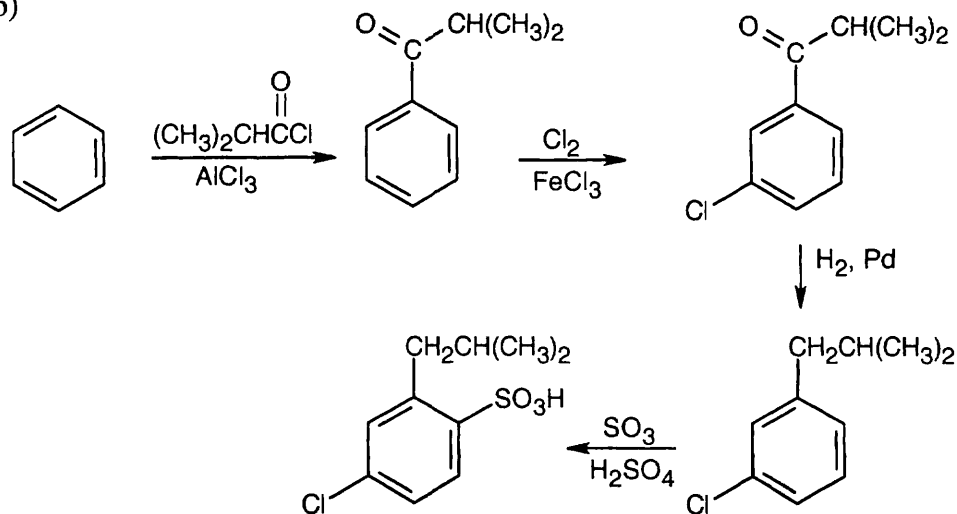
The reactive electrophile (protonated H_2O_2) is equivalent to ^+OH .

16.69 Both of these syntheses test your ability to carry out steps in the correct order.

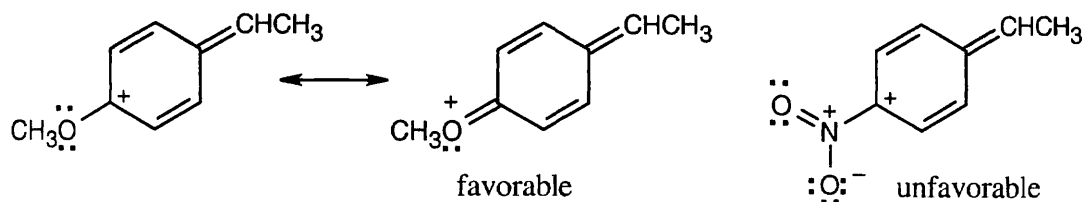
(a)



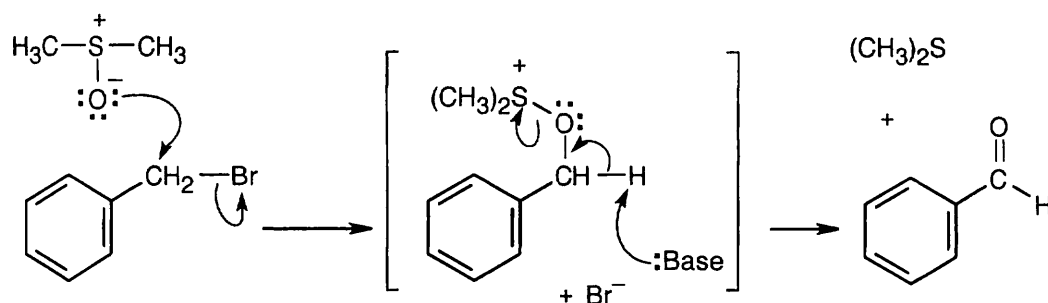
(b)



16.70 Problem 16.46 shows the mechanism of the addition of HBr to 1-phenylpropene and shows how the aromatic ring stabilizes the carbocation intermediate. For the methoxyl-substituted styrene, an additional resonance form can be drawn in which the cation is stabilized by the electron-donating resonance effect of the oxygen atom. For the nitro-substituted styrene, the cation is destabilized by the electron-withdrawing effect of the nitro group.

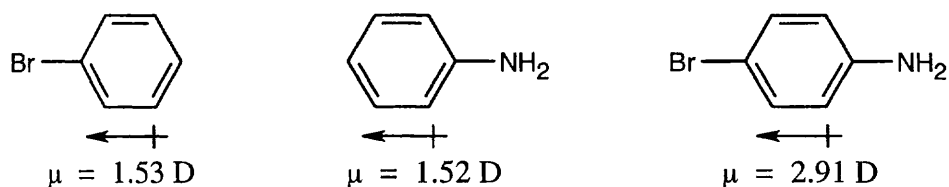


Thus, the intermediate resulting from addition of HBr to the methoxyl-substituted styrene is more stable, and reaction of *p*-methoxystyrene is faster.

16.71

$\text{S}_{\text{N}}2$ displacement occurs when the negatively charged oxygen of dimethyl sulfoxide attacks the benzylic carbon of benzyl bromide, displacing Br^-

Base removes a benzylic proton, and dimethyl sulfide is eliminated in an $\text{E}2$ reaction.

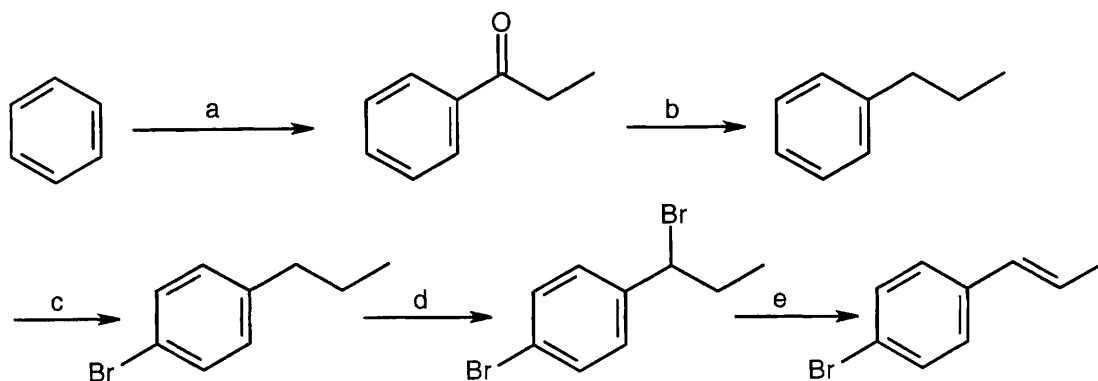
16.72

$-\text{Br}$ has a strong electron-withdrawing inductive effect.

$-\text{NH}_2$ has a strong electron-donating resonance effect.

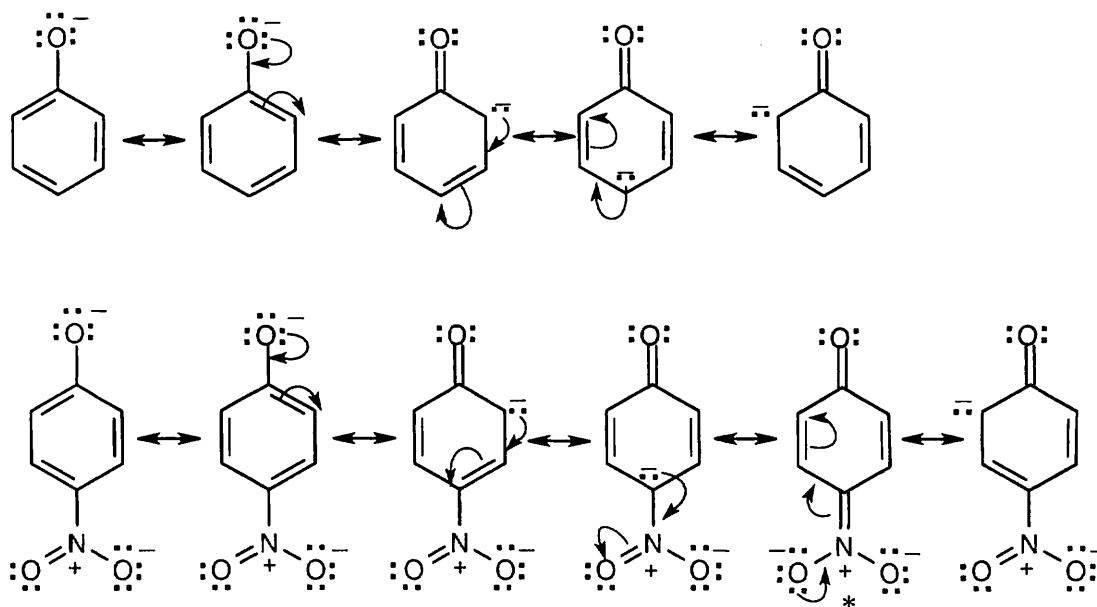
The polarities of the two groups add to produce a net dipole moment almost equal to the sum of the individual moments.

16.73



(a) $\text{CH}_3\text{CH}_2\text{COCl}$, AlCl_3 ; (b) H_2 , Pd/C ; (c) Br_2 , FeBr_3 ; (d) NBS , $(\text{PhCO}_2)_2$; (e) KOH , ethanol

16.74



An electron-withdrawing substituent *destabilizes* a positively charged intermediate (as in electrophilic aromatic substitution) but *stabilizes* a negatively charged intermediate. In the case of the dissociation of a phenol, an $-\text{NO}_2$ group stabilizes the phenoxide anion by resonance, thus lowering ΔG° and $\text{p}K_a$. In the starred resonance form for *p*-nitrophenol, the negative charge has been delocalized onto the oxygens of the nitro group.

16.75 For the same reason described in the previous problem, a methyl group destabilizes the negatively charged intermediate, thus raising ΔG° and $\text{p}K_a$.

Review Unit 6: Conjugation and Aromaticity

Major Topics Covered (with vocabulary):

Conjugated dienes:

delocalization 1,4-addition allylic position thermodynamic control kinetic control
vulcanization Diels–Alder cycloaddition dienophile *endo* product *exo* product *s-cis*
conformation

Ultraviolet spectroscopy:

highest occupied molecular orbital (HOMO) lowest unoccupied molecular orbital (LUMO) molar
absorptivity

Aromaticity:

aromatic arene phenyl group benzyl group ortho, meta, para substitution degenerate
Hückel $4n + 2$ rule antiaromatic heterocycle polycyclic aromatic compound ring current

Chemistry of aromatic compounds:

electrophilic aromatic substitution sulfonation alkali fusion Friedel–Crafts alkylation
polyalkylation Friedel–Crafts acylation ortho- and para-directing activator ortho- and para-
directing deactivator meta-directing deactivator inductive effect resonance effect nucleophilic
aromatic substitution Meisenheimer complex benzyne benzylic position

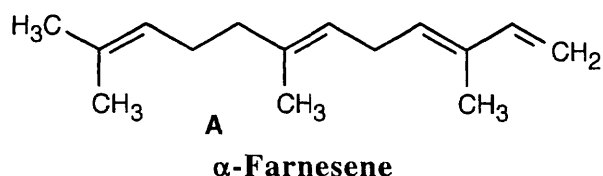
Types of Problems:

After studying these chapters, you should be able to:

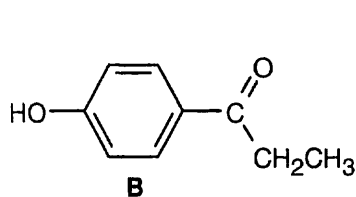
- Predict the products of electrophilic addition to conjugated molecules.
- Understand the concept of kinetic vs. thermodynamic control of reactions.
- Recognize diene polymers, and draw a representative segment of a diene polymer.
- Predict the products of Diels–Alder reactions, and identify compounds that are good dienophiles and good dienes.
- Calculate the energy required for UV absorption, and use molar absorptivity to calculate concentration.
- Predict if and where a compound absorbs in the ultraviolet region.
- Name and draw substituted benzenes.
- Draw resonance structures and molecular orbital diagrams for benzene and other cyclic conjugated molecules.
- Use Hückel's rule to predict aromaticity.
- Draw orbital pictures of cyclic conjugated molecules.
- Use NMR, IR and UV data to deduce the structures of aromatic compounds.
- Predict the products of electrophilic aromatic substitution reactions.
- Formulate the mechanisms of electrophilic aromatic substitution reactions.
- Understand the activating and directing effects of substituents on aromatic rings, and use inductive and resonance arguments to predict orientation and reactivity.
- Predict the products of other reactions of aromatic compounds.
- Synthesize substituted benzenes.

Points to Remember:

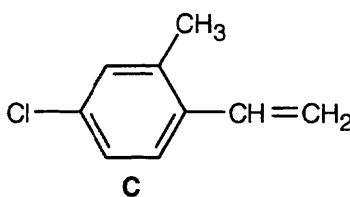
- * It's not always easy to recognize Diels–Alder products, especially if the carbon–carbon double bond of the initial product has been hydrogenated. If no hydrogenation has taken place, look for a double bond in a six-membered ring and at least one electron-withdrawing group across the ring from the double bond. When a bicyclic product has been formed, it has probably resulted from a Diels–Alder reaction in which the diene is cyclic.
- * To be aromatic, a molecule must be planar, cyclic, conjugated, and it must have $4n + 2$ electrons in its π system.
- * The carbocation intermediate of electrophilic aromatic substitution loses a proton to yield the aromatic product. In all cases, a base is involved with proton removal, but the nature of the base varies with the type of substitution reaction. Although this book shows the loss of the proton, it often doesn't show the base responsible for proton removal. This doesn't imply that the proton flies off, unassisted; it just means that the base involved has not been identified in the problem.
- * Nucleophilic aromatic substitution reactions and substitution reactions proceeding through benzyne intermediates take place by different routes. In the first reaction, the substitution takes place by an addition, followed by an elimination. In the second case, the substitution involves an elimination, followed by an addition. Virtually all substitutions are equivalent to an addition and an elimination (in either order).
- * Activating groups achieve their effects by making an aromatic ring more electron-rich and reactive toward electrophiles. Ortho and para directing groups achieve their effects by stabilizing the positive charge that results from ortho or para addition of an electrophile to the aromatic ring. The intermediate resulting from addition to a ring with an ortho or para director usually has one resonance form that is especially stable. The intermediate resulting from addition to a ring with a meta director usually has a resonance form that is especially unfavorable when addition occurs ortho or para to the functional group. Meta substitution results because it is less unfavorable than ortho or para substitution.

Self-test:

α -Farnesene (**A**), an important biological intermediate in the synthesis of many natural products, has double bonds that are both conjugated and unconjugated. Show the products you would expect from conjugate addition of HBr; of Br₂. What products would you expect from ozonolysis of **A**? Give one or more distinctive absorptions that you might see in the IR spectrum of **A** and distinguishing features of the ¹H NMR of **A**. Would you expect **A** to be UV-active?



Paroxypropione

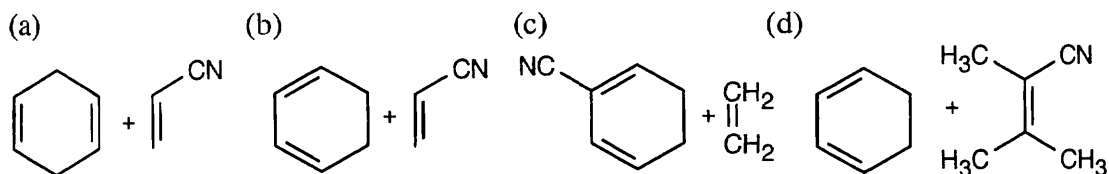


Paroxypropione (**B**) is a hormone inhibitor. Predict the products of reaction of **B** with: (a) Br_2 , FeBr_3 ; (b) CH_3Cl , AlCl_3 ; (c) KMnO_4 , H_3O^+ ; (d) H_2 , Pd/C . If the product of (d) is treated with the reagents in (a) or (b), does the orientation of substitution change? What significant information can you obtain from the IR spectrum of **B**?

Name **C**. Plan a synthesis of **C** from benzene. Describe the ^1H NMR of **C** (include spin-spin splitting). Where might **C** show an absorption in a UV spectrum?

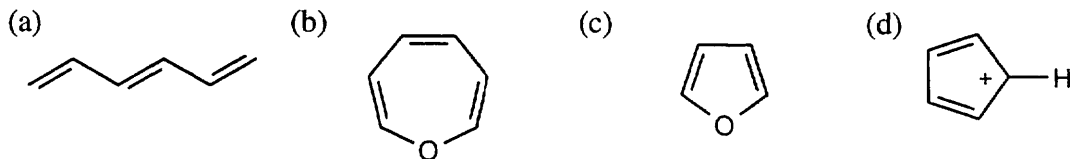
Multiple choice:

- What are the hybridizations of the carbons in 1,2-butadiene, starting with C1?
(a) sp^2 , sp^2 , sp^2 , sp^2 (b) sp^2 , sp^2 , sp^2 , sp^3 (c) sp^2 , sp , sp^2 , sp^3 (d) sp , sp , sp^2 , sp^3
- In a reaction in which the less stable (ls) product is formed at lower temperature, and the more stable product (ms) is formed at higher temperature:
(a) $\Delta G_{\text{ms}}^\circ > \Delta G_{\text{ls}}^\circ$ and $\Delta G_{\text{ms}}^\ddagger > \Delta G_{\text{ls}}^\ddagger$ (b) $\Delta G_{\text{ms}}^\circ > \Delta G_{\text{ls}}^\circ$ and $\Delta G_{\text{ls}}^\ddagger > \Delta G_{\text{ms}}^\ddagger$
(c) $\Delta G_{\text{ms}}^\circ < \Delta G_{\text{ls}}^\circ$ and $\Delta G_{\text{ms}}^\ddagger > \Delta G_{\text{ls}}^\ddagger$ (d) $\Delta G_{\text{ms}}^\circ < \Delta G_{\text{ls}}^\circ$ and $\Delta G_{\text{ls}}^\ddagger > \Delta G_{\text{ms}}^\ddagger$
Note: In this problem, a large value for ΔG° means a large negative value.
- Which of the following combinations is most likely to undergo a successful Diels–Alder reaction?



- Which of the following groups, when bonded to the terminal carbon of a conjugated π system, probably affects the value of λ_{max} the least?
(a) $-\text{NH}_2$ (b) $-\text{Cl}$ (c) $-\text{OH}$ (d) $-\text{CH}_3$
- If the value of λ_{max} for an unsubstituted diene is approximately 220 nm, and each additional double bond increases the value of λ_{max} by 30 nm, what is the minimum number of double bonds present in a compound that absorbs in the visible range of the electromagnetic spectrum?
(a) 6 (b) 7 (c) 8 (d) 9

6. Which of the following compounds is aromatic?



7. How many benzene isomers of $C_7H_6Br_2$ can be drawn?

(a) 10 (b) 11 (c) 12 (d) 14

8. Which of the following functional groups isn't a meta-directing deactivator?

(a) $-NO_2$ (b) $-N=O$ (c) $-N(CH_3)_3^+$ (d) $-NHCOCH_3$

9. Which of the following compounds can't be synthesized by an electrophilic aromatic substitution reaction that we have studied?

(a) *m*-Cresol (b) *p*-Chloroaniline (c) 2,4-Toluenedisulfonic acid (d) *m*-Bromotoluene

10. In only one of the following compounds can you reduce the aromatic ring without also reducing the side chain. Which compound is it?

(a) *p*-Bromoanisole (b) Acetophenone (methyl phenyl ketone) (c) Styrene
(d) Phenylacetylene