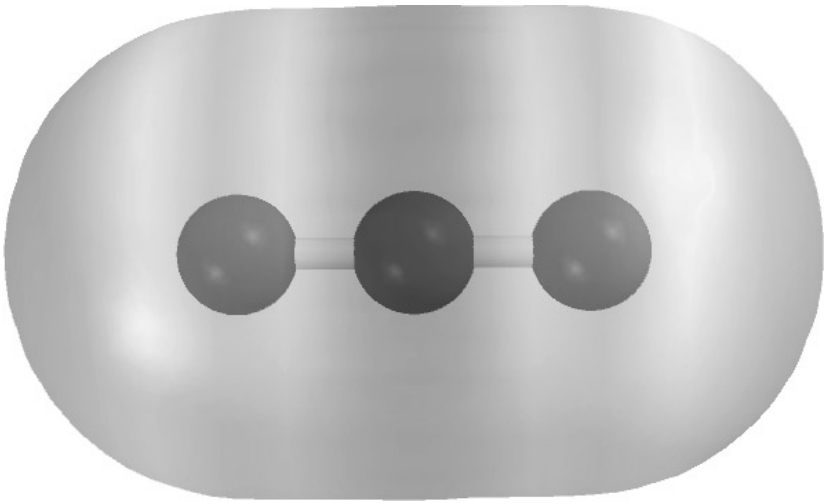
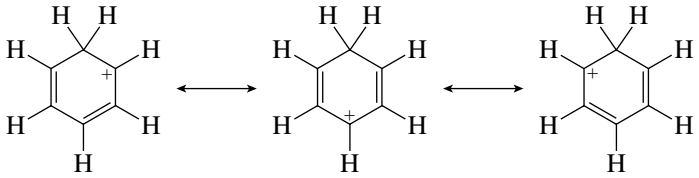


CHAPTER 12

REACTIONS OF ARENES: ELECTROPHILIC AROMATIC SUBSTITUTION

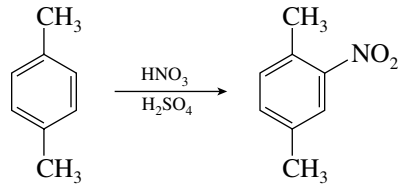
SOLUTIONS TO TEXT PROBLEMS

12.1 The three most stable resonance structures for cyclohexadienyl cation are



The positive charge is shared equally by the three carbons indicated. Thus the two carbons ortho to the sp^3-hybridized carbon and the one para to it each bear one third of a positive charge (+0.33). None of the other carbons is charged. The resonance picture and the simple MO treatment agree with respect to the distribution of charge in cyclohexadienyl cation.

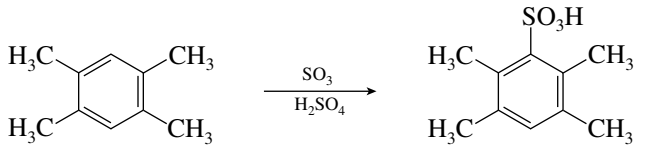
12.2 Electrophilic aromatic substitution leads to replacement of one of the hydrogens directly attached to the ring by the electrophile. All four of the ring hydrogens of *p*-xylene are equivalent; so it does not matter which one is replaced by the nitro group.



p-Xylene

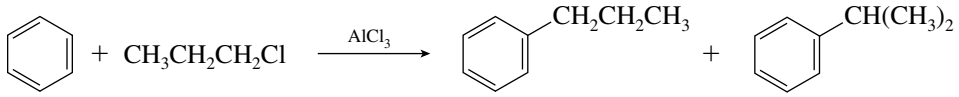
1,4-Dimethyl-2-nitrobenzene

12.3 The aromatic ring of 1,2,4,5-tetramethylbenzene has two equivalent hydrogen substituents. Sulfonation of the ring leads to replacement of one of them by $—SO_3H$.



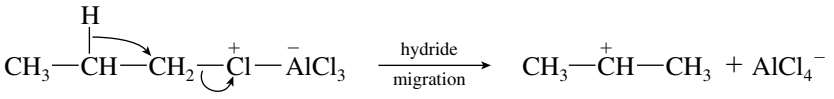
1,2,4,5-Tetramethylbenzene — 2,3,5,6-Tetramethylbenzenesulfonic acid

12.4 The major product is isopropylbenzene.



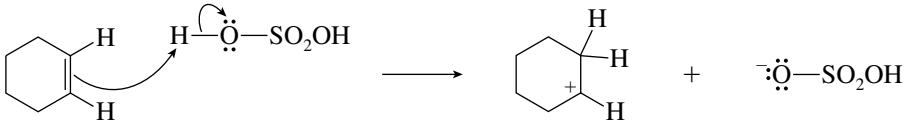
Benzene — 1-Chloropropane — Propylbenzene (20% yield) + Isopropylbenzene (40% yield)

Aluminum chloride coordinates with 1-chloropropane to give a Lewis acid/Lewis base complex, which can be attacked by benzene to yield propylbenzene or can undergo an intramolecular hydride shift to produce isopropyl cation. Isopropylbenzene arises by reaction of isopropyl cation with benzene.



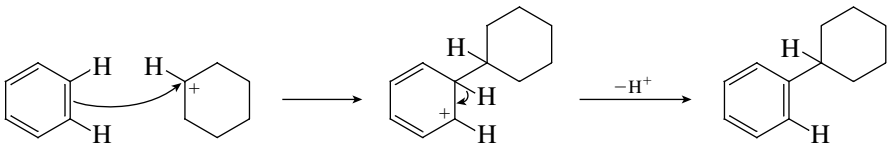
Isopropyl cation

12.5 The species that attacks the benzene ring is cyclohexyl cation, formed by protonation of cyclohexene.



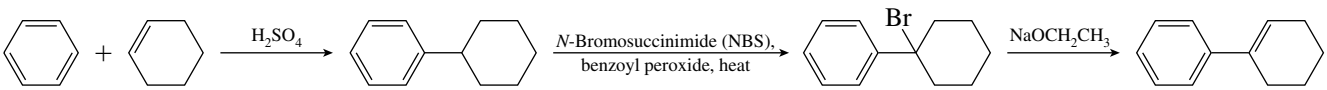
Cyclohexene — Sulfuric acid — Cyclohexyl cation — Hydrogen sulfate ion

The mechanism for the reaction of cyclohexyl cation with benzene is analogous to the general mechanism for electrophilic aromatic substitution.



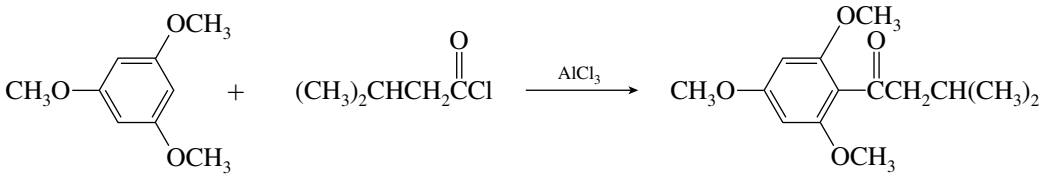
Benzene — Cyclohexyl cation — Cyclohexadienyl cation intermediate — Cyclohexylbenzene

12.6 The preparation of cyclohexylbenzene from cyclohexene and benzene was described in text Section 12.6. Cyclohexylbenzene is converted to 1-phenylcyclohexene by benzylic bromination, followed by dehydrohalogenation.



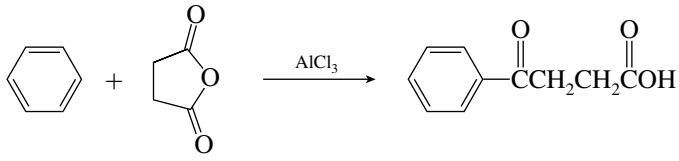
Benzene — Cyclohexene — Cyclohexylbenzene — 1-Bromo-1-phenylcyclohexane — 1-Phenylcyclohexene

12.7 Treatment of 1,3,5-trimethoxybenzene with an acyl chloride and aluminum chloride brings about Friedel–Crafts acylation at one of the three equivalent positions available on the ring.



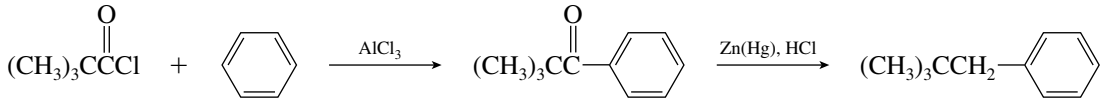
1,3,5-Trimethoxybenzene | 3-Methylbutanoyl chloride | Isobutyl 1,3,5-trimethoxyphenyl ketone

12.8 Because the anhydride is cyclic, its structural units are not incorporated into a ketone and a carboxylic acid as two separate product molecules. Rather, they become part of a four-carbon unit attached to benzene by a ketone carbonyl. The acyl substituent terminates in a carboxylic acid functional group.



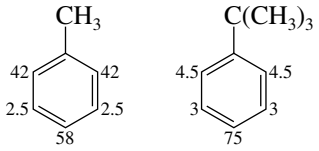
Benzene | Succinic anhydride | 4-Oxo-4-phenylbutanoic acid

12.9 (*b*) A Friedel–Crafts alkylation of benzene using 1-chloro-2,2-dimethylpropane would not be a satisfactory method to prepare neopentylbenzene because of the likelihood of a carbocation rearrangement. The best way to prepare this compound is by Friedel–Crafts acylation followed by Clemmensen reduction.



2,2-Dimethylpropanoyl chloride | Benzene | 2,2-Dimethyl-1-phenyl-1-propanone | Neopentylbenzene

12.10 (*b*) Partial rate factors for nitration of toluene and *tert*-butylbenzene, relative to a single position of benzene, are as shown:



The sum of these partial rate factors is 147 for toluene, 90 for *tert*-butylbenzene. Toluene is 147/90, or 1.7, times more reactive than *tert*-butylbenzene.

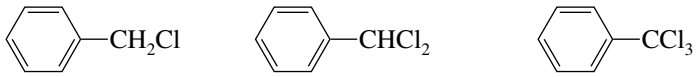
(*c*) The product distribution for nitration of *tert*-butylbenzene is determined from the partial rate factors.

$$\text{Ortho:} \quad \frac{2(4.5)}{90} = 10\%$$

$$\text{Meta:} \quad \frac{2(3)}{90} = 6.7\%$$

$$\text{Para:} \quad \frac{75}{90} = 83.3\%$$

12.11 The compounds shown all undergo electrophilic aromatic substitution more slowly than benzene. Therefore, —CH_2Cl, —$CHCl_2$, and —CCl_3 are *deactivating* substituents.

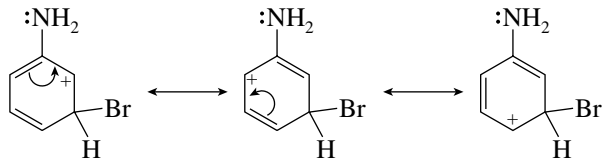


Benzyl chloride (Dichloromethyl)benzene (Trichloromethyl)benzene

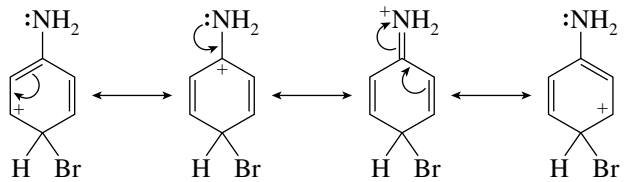
The electron-withdrawing power of these substituents, and their tendency to direct incoming electrophiles meta to themselves, will increase with the number of chlorines each contains. Thus, the substituent that gives 4% meta nitration (96% ortho + para) contains the fewest chlorine atoms (—CH_2Cl), and the one that gives 64% meta nitration contains the most (—CCl_3).

—CH_2Cl	—$CHCl_2$	—CCl_3
Deactivating, ortho, para-directing	Deactivating, ortho, para-directing	Deactivating, meta-directing

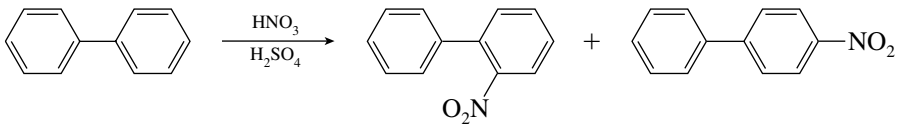
12.12 (*b*) Attack by bromine at the position meta to the amino group gives a cyclohexadienyl cation intermediate in which delocalization of the nitrogen lone pair cannot participate in dispersal of the positive charge.



(*c*) Attack at the position para to the amino group yields a cyclohexadienyl cation intermediate that is stabilized by delocalization of the electron pair of the amino group.

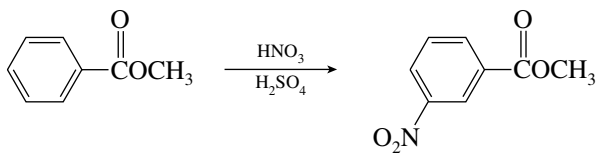


12.13 Electrophilic aromatic substitution in biphenyl is best understood by considering one ring as the functional group and the other as a substituent. An aryl substituent is ortho, para-directing. Nitration of biphenyl gives a mixture of *o*-nitrobiphenyl and *p*-nitrobiphenyl.



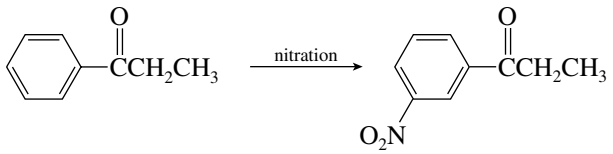
Biphenyl *o*-Nitrobiphenyl (37%) *p*-Nitrobiphenyl (63%)

12.14 (*b*) The carbonyl group attached directly to the ring is a signal that the substituent is a meta-directing group. Nitration of methyl benzoate yields methyl *m*-nitrobenzoate.



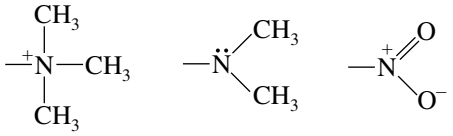
Methyl benzoate Methyl *m*-nitrobenzoate (isolated in 81–85% yield)

(*c*) The acyl group in 1-phenyl-1-propanone is meta-directing; the carbonyl is attached directly to the ring. The product is 1-(*m*-nitrophenyl)-1-propanone.



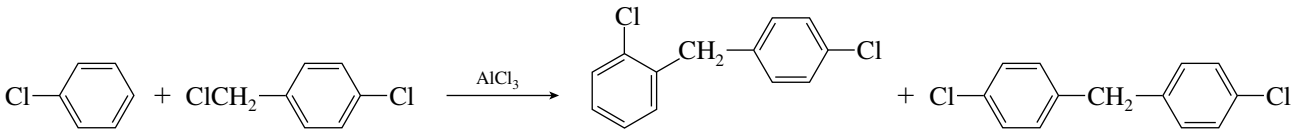
1-Phenyl-1-propanone — 1-(*m*-Nitrophenyl)-1-propanone (isolated in 60% yield)

12.15 Writing the structures out in more detail reveals that the substituent $-\overset{+}{\text{N}}(CH_3)_3$ lacks the unshared electron pair of $-\ddot{\text{N}}(CH_3)_2$.



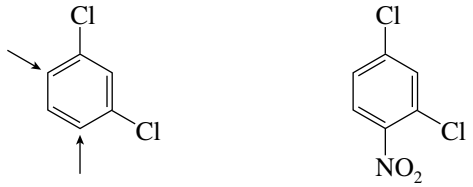
This unshared pair is responsible for the powerful activating effect of an $-\ddot{\text{N}}(CH_3)_2$ group. On the other hand, the nitrogen in $-\overset{+}{\text{N}}(CH_3)_3$ is positively charged and in that respect resembles the nitrogen of a nitro group. We expect the substituent $-\overset{+}{\text{N}}(CH_3)_3$ to be deactivating and meta-directing.

12.16 The reaction is a Friedel–Crafts alkylation in which 4-chlorobenzyl chloride serves as the carbocation source and chlorobenzene is the aromatic substrate. Alkylation occurs at the positions ortho and para to the chlorine substituent of chlorobenzene.



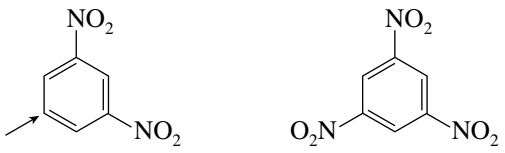
Chlorobenzene — 4-Chlorobenzyl chloride — 1-Chloro-2-(4′-chlorobenzyl)-benzene — 1-Chloro-4-(4′-chlorobenzyl)-benzene

12.17 (*b*) Halogen substituents are ortho, para-directing, and the disposition in *m*-dichlorobenzene is such that their effects reinforce each other. The major product is 2,4-dichloro-1-nitrobenzene. Substitution at the position between the two chlorines is slow because it is a sterically hindered position.



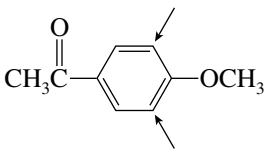
Most reactive positions in electrophilic aromatic substitution of *m*-dichlorobenzene — 2,4-Dichloro-1-nitrobenzene (major product of nitration)

(*c*) Nitro groups are meta-directing. Both nitro groups of *m*-dinitrobenzene direct an incoming substituent to the same position in an electrophilic aromatic substitution reaction. Nitration of *m*-nitrobenzene yields 1,3,5-trinitrobenzene.

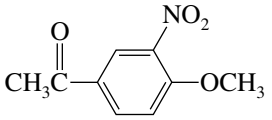


Both nitro groups of *m*-dinitrobenzene direct electrophile to same position. — 1,3,5-Trinitrobenzene (principal product of nitration of *m*-dinitrobenzene)

(*d*) A methoxy group is ortho, para-directing, and a carbonyl group is meta-directing. The open positions of the ring that are activated by the methoxy group in *p*-methoxyacetophenone are also those that are meta to the carbonyl, so the directing effects of the two substituents reinforce each other. Nitration of *p*-methoxyacetophenone yields 4-methoxy-3-nitroacetophenone.

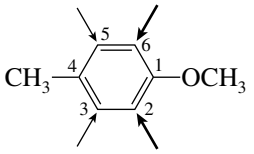


Positions ortho to the methoxy group are meta to the carbonyl.

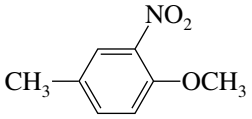


4-Methoxy-3-nitroacetophenone

(*e*) The methoxy group of *p*-methylanisole activates the positions that are ortho to it; the methyl activates those ortho to itself. Methoxy is a more powerful activating substituent than methyl, so nitration occurs ortho to the methoxy group.

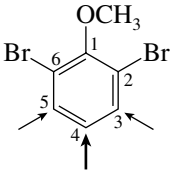


Methyl activates C-3 and C-5; methoxy activates C-2 and C-6.

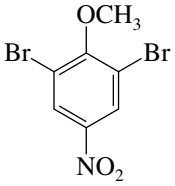


4-Methyl-2-nitroanisole (principal product of nitration)

(*f*) All the substituents in 2,6-dibromoanisole are ortho, para-directing, and their effects are felt at different positions. The methoxy group, however, is a far more powerful activating substituent than bromine, so it controls the regioselectivity of nitration.

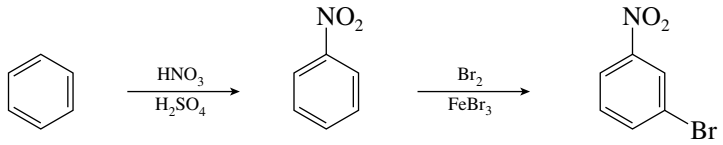


Methoxy directs toward C-4; bromines direct toward C-3 and C-5.



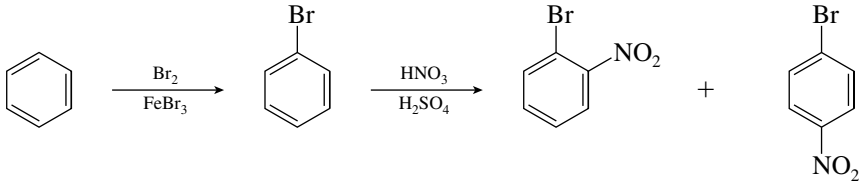
2,6-Dibromo-4-nitroanisole (principal product of nitration)

12.18 The product that is obtained when benzene is subjected to bromination and nitration depends on the order in which the reactions are carried out. A nitro group is meta-directing, and so if it is introduced prior to the bromination step, *m*-bromonitrobenzene is obtained.



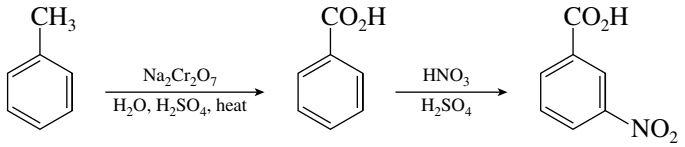
Benzene Nitrobenzene *m*-Bromonitrobenzene

Bromine is an ortho, para-directing group. If it is introduced first, nitration of the resulting bromobenzene yields a mixture of *o*-bromonitrobenzene and *p*-bromonitrobenzene.



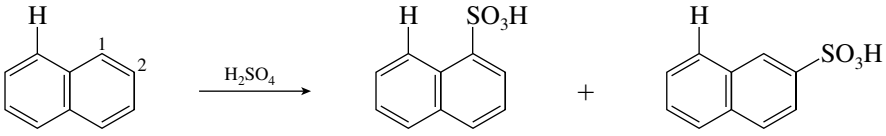
Benzene Bromobenzene *o*-Bromonitrobenzene *p*-Bromonitrobenzene

12.19 A straightforward approach to the synthesis of *m*-nitrobenzoic acid involves preparation of benzoic acid by oxidation of toluene, followed by nitration. The carboxyl group of benzoic acid is meta-directing. Nitration of toluene prior to oxidation would lead to a mixture of ortho and para products.



Toluene Benzoic acid *m*-Nitrobenzoic acid

12.20 The text points out that C-1 of naphthalene is more reactive than C-2 toward electrophilic aromatic substitution. Thus, of the two possible products of sulfonation, naphthalene-1-sulfonic acid should be formed faster and should be the major product under conditions of kinetic control. Since the problem states that the product under conditions of thermodynamic control is the other isomer, naphthalene-2-sulfonic acid is the major product at elevated temperature.



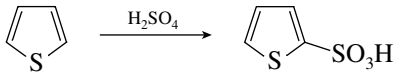
Naphthalene

Naphthalene-1-sulfonic acid
major product at 0°C;
formed faster

Naphthalene-2-sulfonic acid
major product at 160°C;
more stable

Naphthalene-2-sulfonic acid is the more stable isomer for steric reasons. The hydrogen at C-8 (the one shown in the equation) crowds the $-SO_3H$ group in naphthalene-1-sulfonic acid.

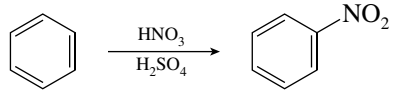
12.21 The text states that electrophilic aromatic substitution in furan, thiophene, and pyrrole occurs at C-2. The sulfonation of thiophene gives thiophene-2-sulfonic acid.



Thiophene

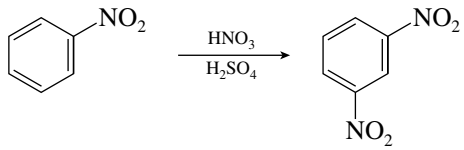
Thiophene-2-
sulfonic acid

12.22 (*a*) Nitration of benzene is the archetypical electrophilic aromatic substitution reaction.



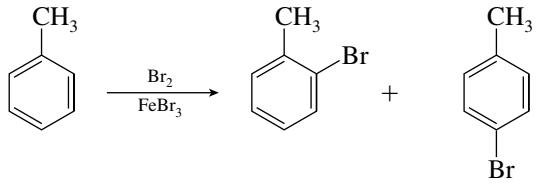
Benzene Nitrobenzene

(*b*) Nitrobenzene is much less reactive than benzene toward electrophilic aromatic substitution. The nitro group on the ring is a meta director.



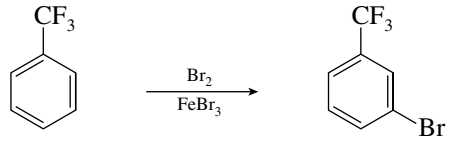
Nitrobenzene *m*-Dinitrobenzene

(*c*) Toluene is more reactive than benzene in electrophilic aromatic substitution. A methyl substituent is an ortho, para director.



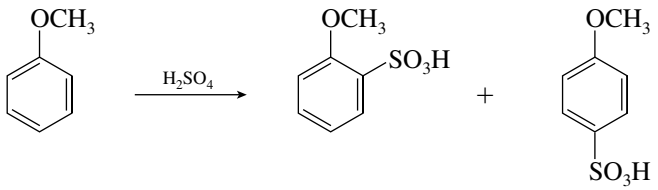
Toluene | *o*-Bromotoluene | *p*-Bromotoluene

(*d*) Trifluoromethyl is deactivating and meta-directing.



(Trifluoromethyl)-benzene | *m*-Bromo(trifluoromethyl)-benzene

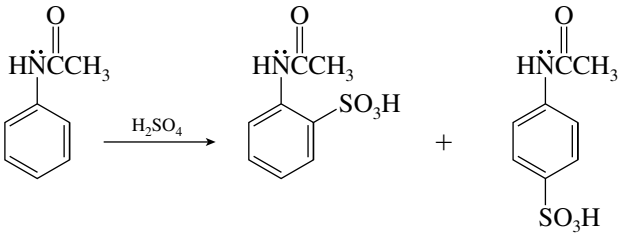
(*e*) Anisole is ortho, para-directing, strongly activated toward electrophilic aromatic substitution, and readily sulfonated in sulfuric acid.



Anisole | *o*-Methoxybenzene-sulfonic acid | *p*-Methoxybenzene-sulfonic acid

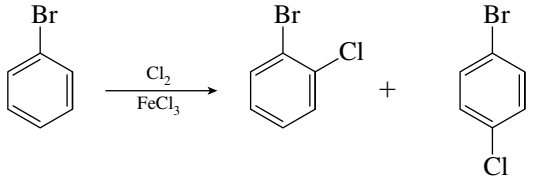
Sulfur trioxide could be added to the sulfuric acid to facilitate reaction. The para isomer is the predominant product.

(*f*) Acetanilide is quite similar to anisole in its behavior toward electrophilic aromatic substitution.



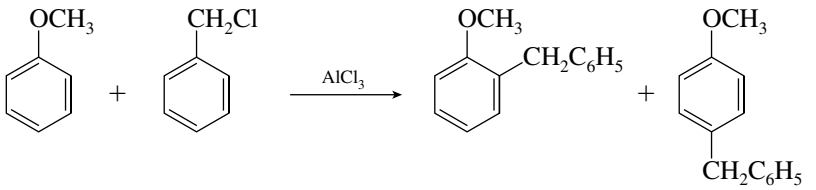
Acetanilide | *o*-Acetamidobenzene-sulfonic acid | *p*-Acetamidobenzene-sulfonic acid

(*g*) Bromobenzene is less reactive than benzene. A bromine substituent is ortho, para-directing.



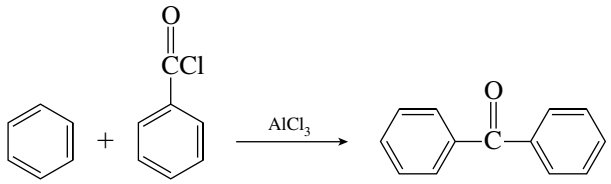
Bromobenzene | *o*-Bromochloro-benzene | *p*-Bromochloro-benzene

(*h*) Anisole is a reactive substrate toward Friedel–Crafts alkylation and yields a mixture of *o*- and *p*-benzylated products when treated with benzyl chloride and aluminum chloride.



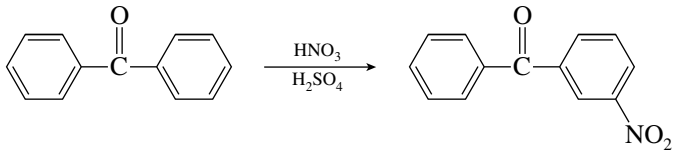
Anisole Benzyl chloride *o*-Benzylanisole *p*-Benzylanisole

(*i*) Benzene will undergo acylation with benzoyl chloride and aluminum chloride.



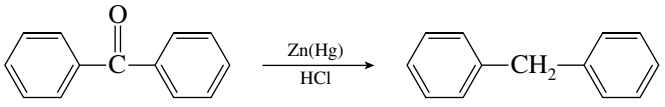
Benzene Benzoyl chloride Benzophenone

(*j*) A benzoyl substituent is meta-directing and deactivating.



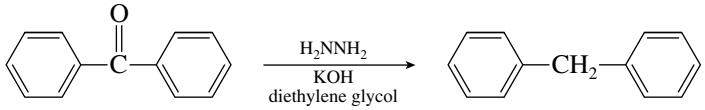
Benzophenone *m*-Nitrobenzophenone

(*k*) Clemmensen reduction conditions involve treating a ketone with zinc amalgam and concentrated hydrochloric acid.



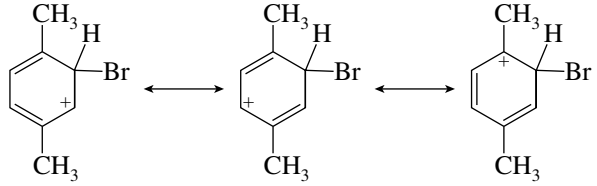
Benzophenone Diphenylmethane

(*l*) Wolff–Kishner reduction utilizes hydrazine, a base, and a high-boiling alcohol solvent to reduce ketone functions to methylene groups.



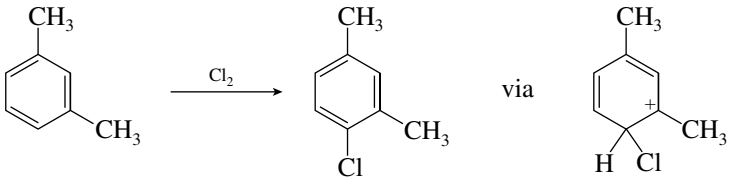
Benzophenone Diphenylmethane

12.23 (*a*) There are three principal resonance forms of the cyclohexadienyl cation intermediate formed by attack of bromine on *p*-xylene.



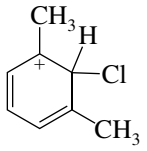
Any one of these resonance forms is a satisfactory answer to the question. Because of its tertiary carbocation character, this carbocation is more stable than the corresponding intermediate formed from benzene.

(*b*) Chlorination of *m*-xylene will give predominantly 4-chloro-1,3-dimethylbenzene.



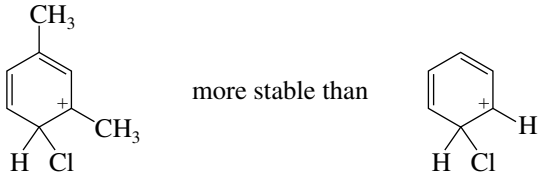
m-Xylene | 4-Chloro-1,3-dimethylbenzene | More stable cyclohexadienyl cation

The intermediate shown (or any of its resonance forms) is more stable for steric reasons than

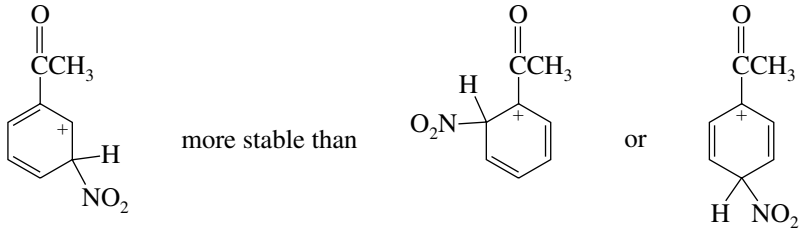


Less stable cyclohexadienyl cation

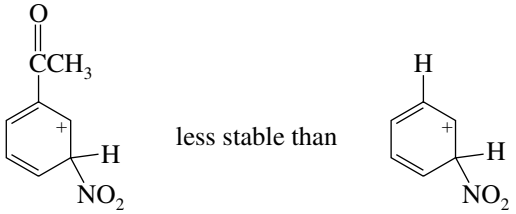
The cyclohexadienyl cation intermediate leading to 4-chloro-1,3-dimethylbenzene is more stable and is formed faster than the intermediate leading to chlorobenzene because of its tertiary carbocation character.



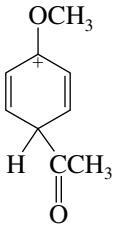
(*c*) The most stable carbocation intermediate formed during nitration of acetophenone is the one corresponding to meta attack.



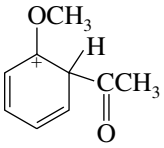
An acyl group is electron-withdrawing and destabilizes a carbocation to which it is attached. The most stable carbocation intermediate in the nitration of acetophenone is less stable and is formed more slowly than is the corresponding carbocation formed during nitration of benzene.



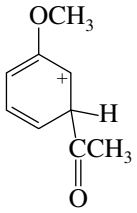
(*d*) The methoxy group in anisole is strongly activating and ortho, para-directing. For steric reasons and because of inductive electron withdrawal by oxygen, the intermediate leading to para substitution is the most stable.



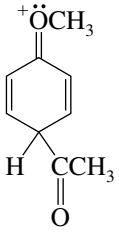
slightly more stable than



more stable than



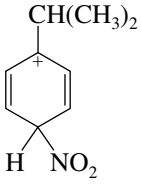
Of the various resonance forms for the most stable intermediate, the most stable one has eight electrons around each oxygen and carbon atom.



Most stable resonance form

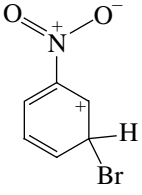
This intermediate is much more stable than the corresponding intermediate from acylation of benzene.

(*e*) An isopropyl group is an activating substituent and is ortho, para-directing. Attack at the ortho position is sterically hindered. The most stable intermediate is



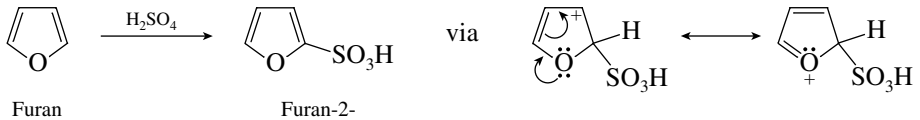
or any of its resonance forms. Because of its tertiary carbocation character, this cation is more stable than the corresponding cyclohexadienyl cation intermediate from benzene.

(*f*) A nitro substituent is deactivating and meta-directing. The most stable cyclohexadienyl cation formed in the bromination of nitrobenzene is



This ion is less stable than the cyclohexadienyl cation formed during bromination of benzene.

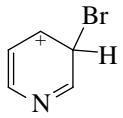
(*g*) Sulfonation of furan takes place at C-2. The cationic intermediate is more stable than the cyclohexadienyl cation formed from benzene because it is stabilized by electron release from oxygen.



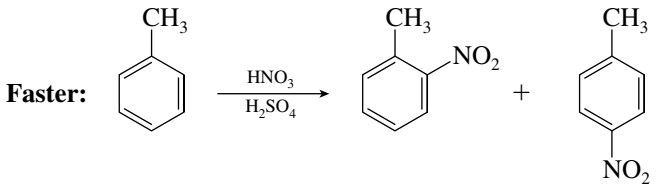
Furan

Furan-2-sulfonic acid

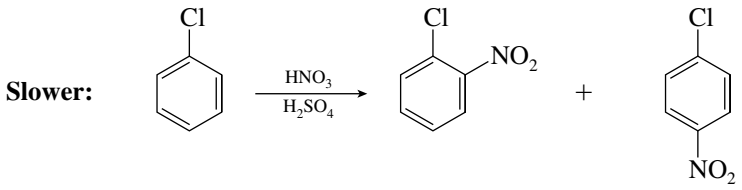
(*h*) Pyridine reacts with electrophiles at C-3. It is less reactive than benzene, and the carbocation intermediate is less stable than the corresponding intermediate formed from benzene.



12.24 (*a*) Toluene is more reactive than chlorobenzene in electrophilic aromatic substitution reactions because a methyl substituent is activating but a halogen substituent is deactivating. Both are ortho, para-directing, however. Nitration of toluene is faster than nitration of chlorobenzene.

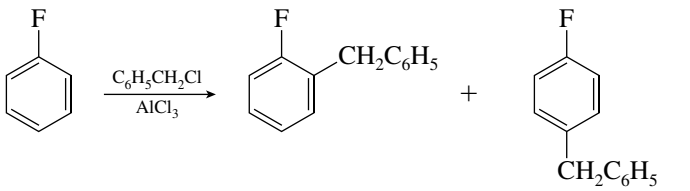


Toluene *o*-Nitrotoluene *p*-Nitrotoluene



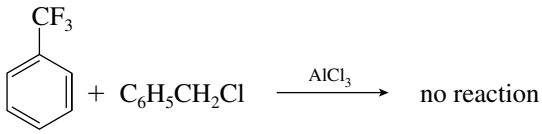
Chlorobenzene *o*-Chloronitrobenzene *p*-Chloronitrobenzene

(*b*) A fluorine substituent is not nearly as strongly deactivating as a trifluoromethyl group. The reaction that takes place is Friedel–Crafts alkylation of fluorobenzene.

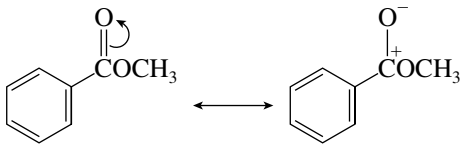


o-Benzylfluorobenzene (15%) *p*-Benzylfluorobenzene (85%)

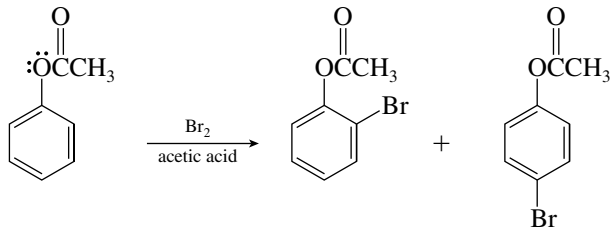
Strongly deactivated aromatic compounds do not undergo Friedel–Crafts reactions.



(*c*) A carbonyl group directly bonded to a benzene ring strongly **deactivates** it toward electrophilic aromatic substitution. Methyl benzoate is much less reactive than benzene.



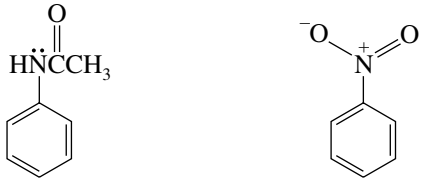
An oxygen substituent directly attached to the ring strongly **activates** it toward electrophilic aromatic substitution. Phenyl acetate is much more reactive than benzene or methyl benzoate.



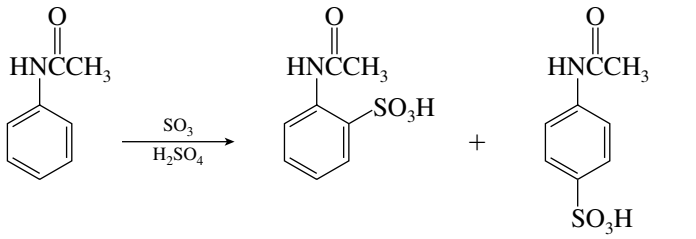
Phenyl acetate | *o*-Bromophenyl acetate | *p*-Bromophenyl acetate

Bromination of methyl benzoate requires more vigorous conditions; catalysis by iron(III) bromide is required for bromination of deactivated aromatic rings.

(*d*) Acetanilide is strongly activated toward electrophilic aromatic substitution and reacts faster than nitrobenzene, which is strongly deactivated.

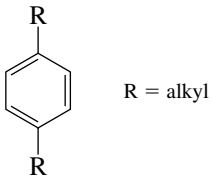


Acetanilide (Lone pair on nitrogen can stabilize cyclohexadienyl cation intermediate.) | Nitrobenzene (Nitrogen is positively charged and is electron-withdrawing.)

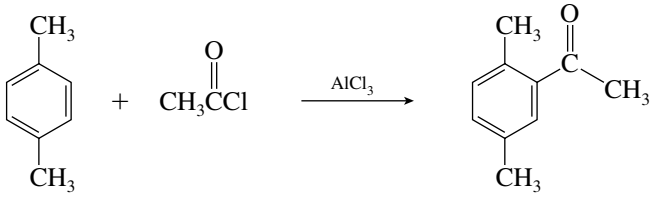


Acetanilide | *o*-Acetamidobenzenesulfonic acid | *p*-Acetamidobenzenesulfonic acid

(*e*) Both substrates are of the type

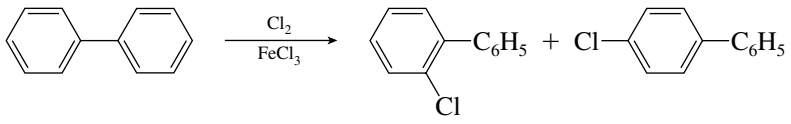


and are activated toward Friedel–Crafts acylation. Since electronic effects are comparable, we look to differences in steric factors and conclude that reaction will be faster for R = CH_3 than for R = $(CH_3)_3C$—.



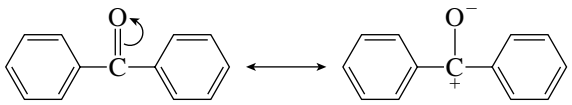
p-Xylene | Acetyl chloride | 2,5-Dimethylacetophenone

(*f*) A phenyl substituent is activating and ortho, para-directing. Biphenyl will undergo chlorination readily.



Biphenyl *o*-Chlorobiphenyl *p*-Chlorobiphenyl

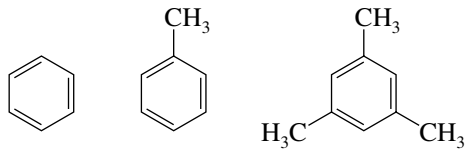
Each benzene ring of benzophenone is deactivated by the carbonyl group.



Benzophenone

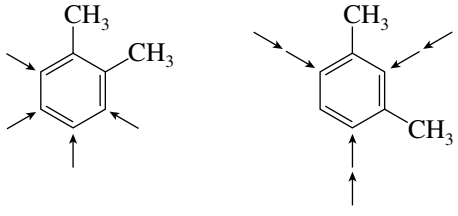
Benzophenone is much less reactive than biphenyl in electrophilic aromatic substitution reactions.

12.25 Reactivity toward electrophilic aromatic substitution increases with increasing number of electron-releasing substituents. Benzene, with no methyl substituents, is the least reactive, followed by toluene, with one methyl group. 1,3,5-Trimethylbenzene, with three methyl substituents, is the most reactive.



Benzene	Toluene	1,3,5-Trimethylbenzene
Relative reactivity: 1	60	2×10^7

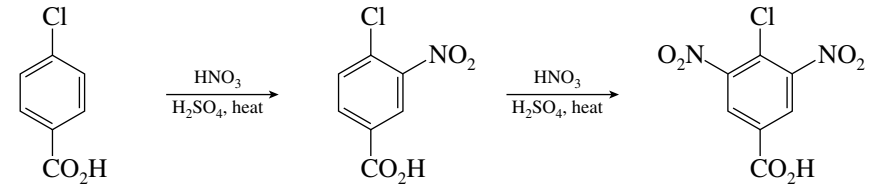
o-Xylene and *m*-xylene are intermediate in reactivity between toluene and 1,3,5-trimethylbenzene. Of the two, *m*-xylene is more reactive than *o*-xylene because the activating effects of the two methyl groups reinforce each other.



o-Xylene (all positions somewhat activated)	*m*-Xylene (activating effects reinforce each other)
Relative reactivity: 5×10^2	5×10^4

12.26 (*a*) Chlorine is ortho, para-directing, carboxyl is meta-directing. The positions that are ortho to the chlorine are meta to the carboxyl, so that both substituents direct an incoming electrophile to the same position. Introduction of the second nitro group at the remaining

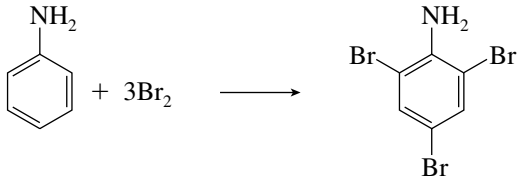
position that is ortho to the chlorine puts it meta to the carboxyl and meta to the first nitro group.



p-Chlorobenzoic acid

4-Chloro-3,5-dinitrobenzoic acid (90%)

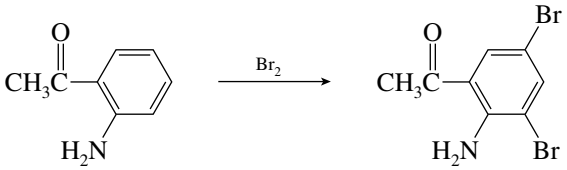
(*b*) An amino group is one of the strongest activating substituents. The para and both ortho positions are readily substituted in aniline. When aniline is treated with excess bromine, 2,4,6-tribromoaniline is formed in quantitative yield.



Aniline

2,4,6-Tribromoaniline (100%)

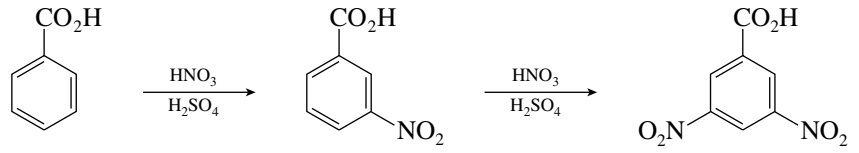
(*c*) The positions ortho and para to the amino group in *o*-aminoacetophenone are the ones most activated toward electrophilic aromatic substitution.



o-Aminoacetophenone

2-Amino-3,5-dibromoacetophenone (65%)

(*d*) The carboxyl group in benzoic acid is meta-directing, and so nitration gives *m*-nitrobenzoic acid. The second nitration step introduces a nitro group meta to both the carboxyl group and the first nitro group.

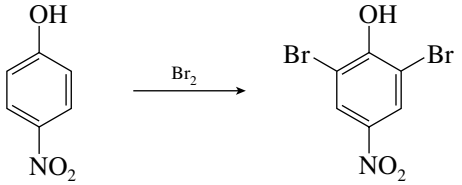


Benzoic acid

m-Nitrobenzoic acid

3,5-Dinitrobenzoic acid (54–58%)

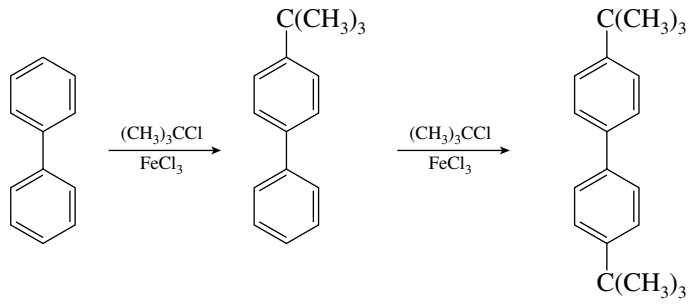
(*e*) Both bromine substituents are introduced ortho to the strongly activating hydroxyl group in *p*-nitrophenol.



p-Nitrophenol

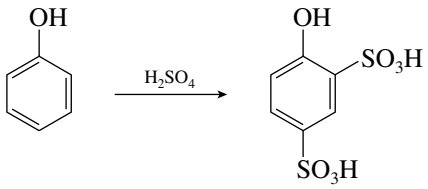
2,6-Dibromo-4-nitrophenol (96–98%)

(*f*) Friedel–Crafts alkylation occurs when biphenyl is treated with *tert*-butyl chloride and iron (III) chloride (a Lewis acid catalyst); the product of monosubstitution is *p*-*tert*-butylbiphenyl. All the positions of the ring that bears the *tert*-butyl group are sterically hindered, so the second alkylation step introduces a *tert*-butyl group at the para position of the second ring.



Biphenyl — 4,4′-Di-*tert*-butylbiphenyl (70%)

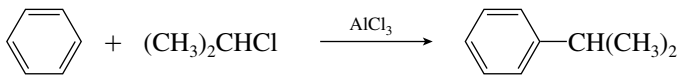
(*g*) Disulfonation of phenol occurs at positions ortho and para to the hydroxyl group. The ortho, para product predominates over the ortho, ortho one.



Phenol — 2-Hydroxy-1,5-benzenedisulfonic acid

12.27 When carrying out each of the following syntheses, evaluate how the structure of the product differs from that of benzene or toluene; that is, determine which groups have been substituted on the benzene ring or altered in some way. The sequence of reaction steps when multiple substitution is desired is important; recall that some groups direct ortho, para and others meta.

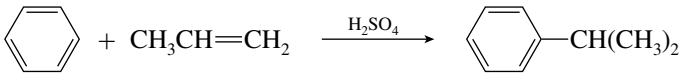
(*a*) Isopropylbenzene may be prepared by a Friedel–Crafts alkylation of benzene with isopropyl chloride (or bromide, or iodide).



Benzene — Isopropyl chloride — Isopropylbenzene

It would not be appropriate to use propyl chloride and trust that a rearrangement would lead to isopropylbenzene, because a mixture of propylbenzene and isopropylbenzene would be obtained.

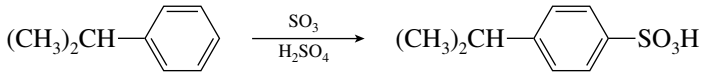
Isopropylbenzene may also be prepared by alkylation of benzene with propene in the presence of sulfuric acid.



Benzene — Propene — Isopropylbenzene

(*b*) Since the isopropyl and sulfonic acid groups are para to each other, the first group introduced on the ring must be the ortho, para director, that is, the isopropyl group. We may therefore use the product of part (*a*), isopropylbenzene, in this synthesis. An isopropyl group is a fairly

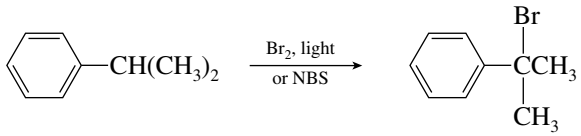
bulky ortho, para director, and so sulfonation of isopropylbenzene gives mainly *p*-isopropylbenzenesulfonic acid.



Isopropylbenzene — *p*-Isopropylbenzenesulfonic acid

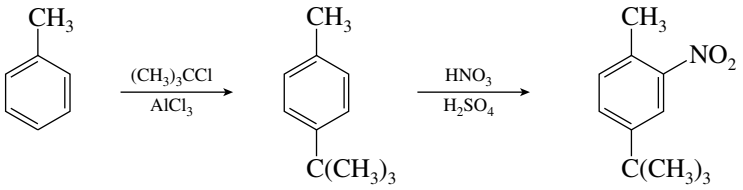
A sulfonic acid group is meta-directing, so that the order of steps must be alkylation followed by sulfonation rather than the reverse.

(*c*) Free-radical halogenation of isopropylbenzene occurs with high regioselectivity at the benzylic position. *N*-Bromosuccinimide (NBS) is a good reagent to use for benzylic bromination reactions.



Isopropylbenzene — 2-Bromo-2-phenylpropane

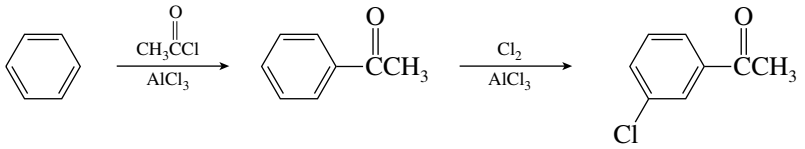
(*d*) Toluene is an obvious starting material for the preparation of 4-*tert*-butyl-2-nitrotoluene. Two possibilities, both involving nitration and alkylation of toluene, present themselves; the problem to be addressed is in what order to carry out the two steps. Friedel–Crafts alkylation must precede nitration.



Toluene — *p*-*tert*-Butyltoluene — 4-*tert*-Butyl-2-nitrotoluene

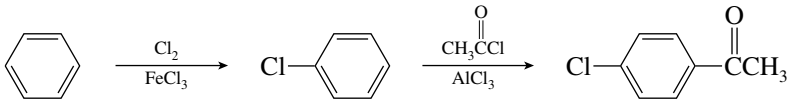
Introduction of the nitro group as the first step is an unsatisfactory approach since Friedel–Crafts reactions cannot be carried out on nitro-substituted aromatic compounds.

(*e*) Two electrophilic aromatic substitution reactions need to be performed: chlorination and Friedel–Crafts acylation. The order in which the reactions are carried out is important; chlorine is an ortho, para director, and the acetyl group is a meta director. Since the groups are meta in the desired compound, introduce the acetyl group first.



Benzene — Acetophenone — *m*-Chloroacetophenone

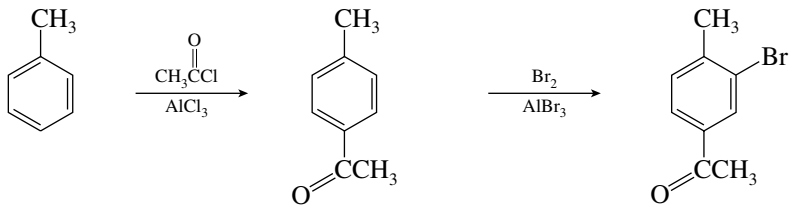
(*f*) Reverse the order of steps in part (*e*) to prepare *p*-chloroacetophenone.



Benzene — Chlorobenzene — *p*-Chloroacetophenone

Friedel–Crafts reactions can be carried out on halobenzenes but not on arenes that are more strongly deactivated.

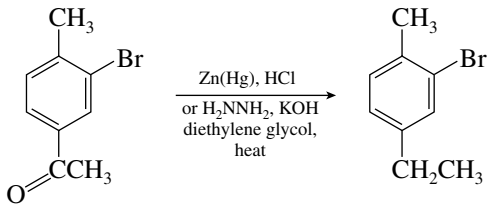
(*g*) Here again the problem involves two successive electrophilic aromatic substitution reactions, in this case using toluene as the initial substrate. The proper sequence is Friedel–Crafts acylation first, followed by bromination of the ring.



Toluene — *p*-Methylacetophenone — 3-Bromo-4-methylacetophenone

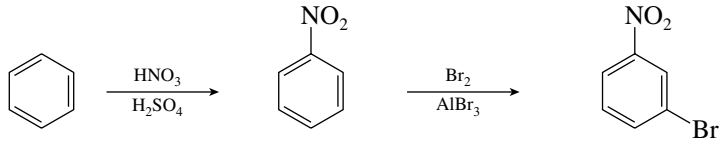
If the sequence of steps had been reversed, with halogenation preceding acylation, the first intermediate would be *o*-bromotoluene, Friedel–Crafts acylation of which would give a complex mixture of products because both groups are ortho, para-directing. On the other hand, the orienting effects of the two groups in *p*-methylacetophenone reinforce each other, so that its bromination is highly regioselective and in the desired direction.

(*h*) Recalling that alkyl groups attached to the benzene ring by CH_2 may be prepared by reduction of the appropriate ketone, we may reduce 3-bromo-4-methylacetophenone, as prepared in part (*g*), by the Clemmensen on Wolff–Kishner procedure to give 2-bromo-4-ethyltoluene.



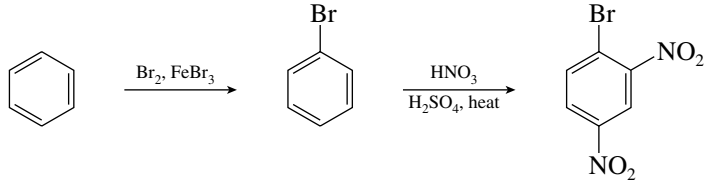
3-Bromo-4-methylacetophenone — 2-Bromo-4-ethyltoluene

(*i*) This is a relatively straightforward synthetic problem. Bromine is an ortho, para-directing substituent; nitro is meta-directing. Nitrate first, and then brominate to give 1-bromo-3-nitrobenzene.



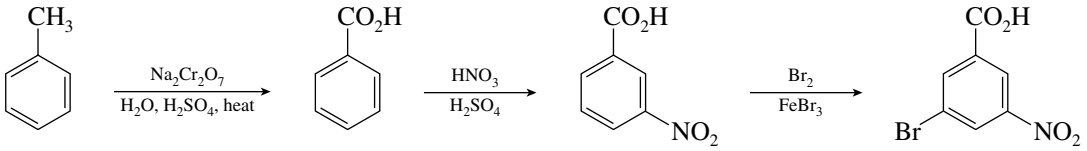
Benzene — Nitrobenzene — 1-Bromo-3-nitrobenzene

(*j*) Take advantage of the ortho, para-directing properties of bromine to prepare 1-bromo-2,4-dinitrobenzene. Brominate first, and then nitrate under conditions that lead to disubstitution. The nitro groups are introduced at positions ortho and para to the bromine and meta to each other.



Benzene — Bromobenzene — 1-Bromo-2,4-dinitrobenzene

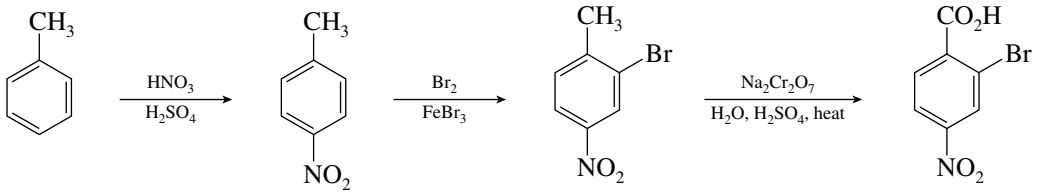
(*k*) Although bromo and nitro substituents are readily introduced by electrophilic aromatic substitution, the only methods we have available so far to prepare carboxylic acids is by oxidation of alkyl side chains. Thus, use toluene as a starting material, planning to convert the methyl group to a carboxyl group by oxidation. Nitrate next; nitro and carboxyl are both meta-directing groups, so that the bromination in the last step occurs with the proper regioselectivity.



Toluene — Benzoic acid — 3-Nitrobenzoic acid — 3-Bromo-5-nitrobenzoic acid

If bromination is performed prior to nitration, the bromine substituent will direct an incoming electrophile to positions ortho and para to itself, giving the wrong orientation of substituents in the product.

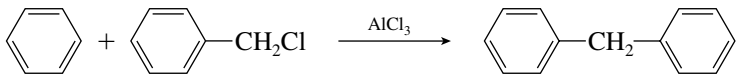
(*l*) Again toluene is a suitable starting material, with its methyl group serving as the source of the carboxyl substituent. The orientation of the substituents in the final product requires that the methyl group be retained until the final step.



Toluene — *p*-Nitrotoluene — 2-Bromo-4-nitrotoluene — 2-Bromo-4-nitrobenzoic acid

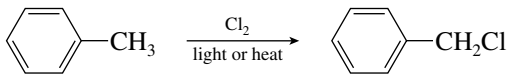
Nitration must precede bromination, as in the previous part, in order to prevent formation of an undesired mixture of isomers.

(*m*) Friedel–Crafts alkylation of benzene with benzyl chloride (or benzyl bromide) is a satisfactory route to diphenylmethane.



Benzene — Benzyl chloride — Diphenylmethane

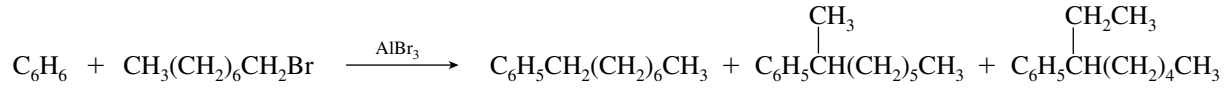
Benzyl chloride is prepared by free-radical chlorination of toluene.



Toluene — Benzyl chloride

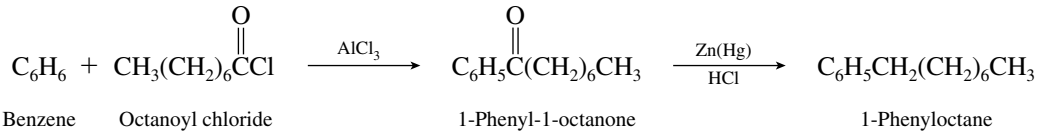
Alternatively, benzene could have been subjected to Friedel–Crafts acylation with benzoyl chloride to give benzophenone. Clemmensen or Wolff–Kishner reduction of benzophenone would then furnish diphenylmethane.

(*n*) 1-Phenyloctane cannot be prepared efficiently by direct alkylation of benzene, because of the probability that rearrangement will occur. Indeed, a mixture of 1-phenyloctane and 2-phenyloctane is formed under the usual Friedel–Crafts conditions, along with 3-phenyloctane.



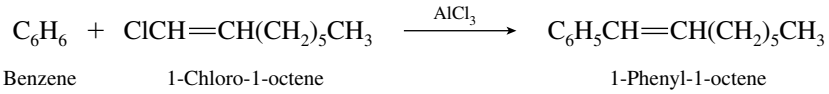
Benzene — 1-Bromooctane — 1-Phenyloctane (40%) — 2-Phenyloctane (30%) — 3-Phenyloctane (30%)

A method that permits the synthesis of 1-phenyloctane free of isomeric compounds is acylation followed by reduction.



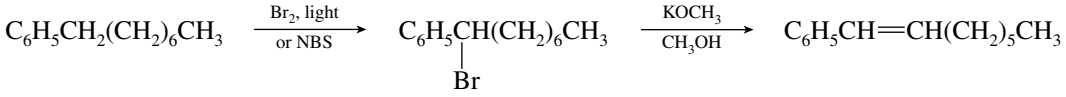
Alternatively, Wolff–Kishner conditions (hydrazine, potassium hydroxide, diethylene glycol) could be used in the reduction step.

(*o*) Direct alkenylation of benzene under Friedel–Crafts reaction conditions does not take place, and so 1-phenyl-1-octene cannot be prepared by the reaction

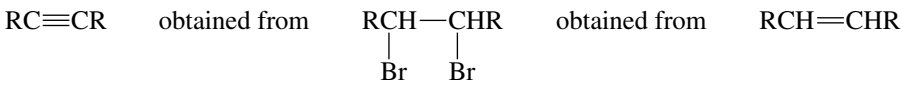


No! Reaction effective only with *alkyl* halides, not 1-haloalkenes.

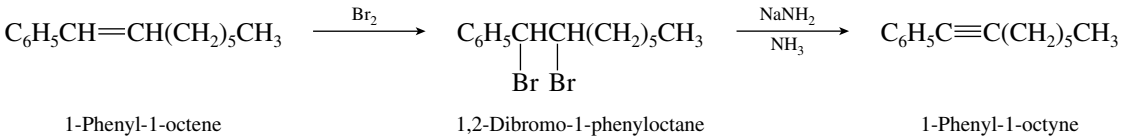
Having already prepared 1-phenyloctane in part (*n*), however, we can functionalize the benzylic position by bromination and then carry out a dehydrohalogenation to obtain the target compound.



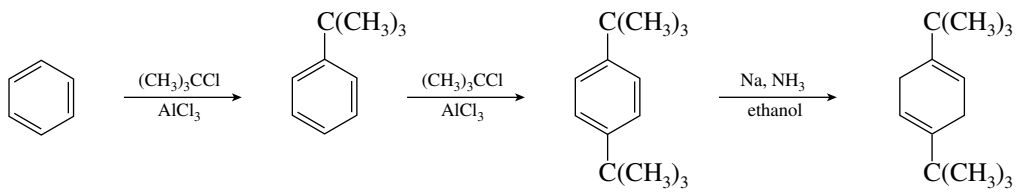
(*p*) 1-Phenyl-1-octyne cannot be prepared in one step from benzene; 1-haloalkynes are unsuitable reactants for a Friedel–Crafts process. In Chapter 9, however, we learned that alkynes may be prepared from the corresponding alkene:



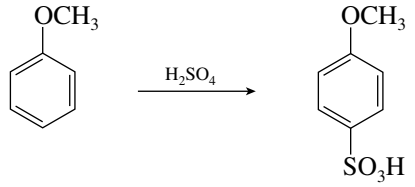
Using the alkene prepared in part (*o*),



(*q*) Nonconjugated cyclohexadienes are prepared by Birch reduction of arenes. Thus the last step in the synthesis of 1,4-di-*tert*-butyl-1,4-cyclohexadiene is the Birch reduction of 1,4-di-*tert*-butylbenzene.

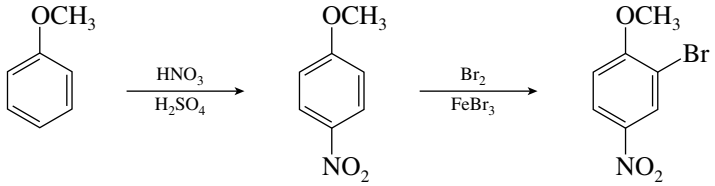


12.28 (*a*) Methoxy is an ortho, para-directing substituent. All that is required to prepare *p*-methoxybenzenesulfonic acid is to sulfonate anisole.



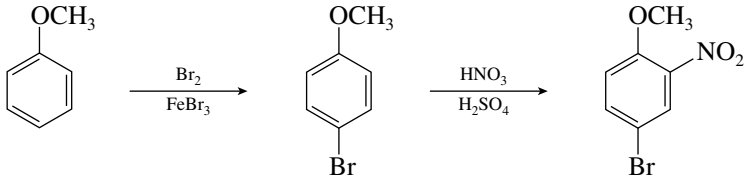
Anisole — *p*-Methoxybenzenesulfonic acid

(*b*) In reactions involving disubstitution of anisole, the better strategy is to introduce the para substituent first. The methoxy group is ortho, para-directing, but para substitution predominates.



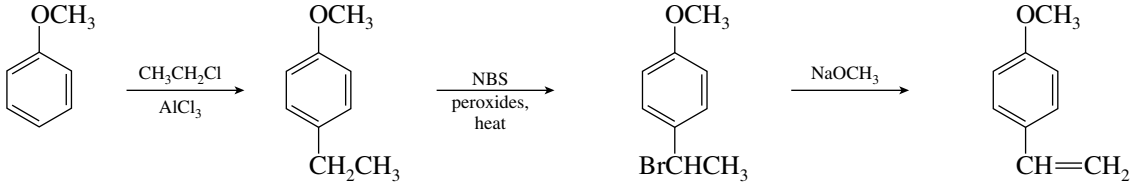
Anisole — *p*-Nitroanisole — 2-Bromo-4-nitroanisole

(*c*) Reversing the order of the steps used in part (*b*) yields 4-bromo-2-nitroanisole.



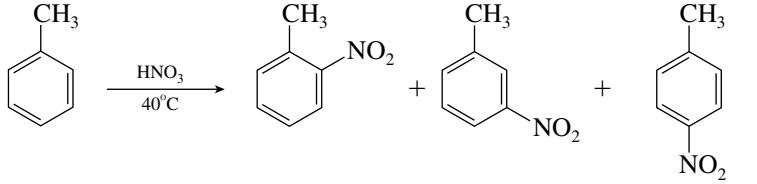
Anisole — *p*-Bromoanisole — 4-Bromo-2-nitroanisole

(*d*) Direct introduction of a vinyl substituent onto an aromatic ring is not a feasible reaction. *p*-Methoxystyrene must be prepared in an indirect way by adding an ethyl side chain and then taking advantage of the reactivity of the benzylic position by bromination (e.g., with *N*-bromosuccinimide) and dehydrohalogenation.



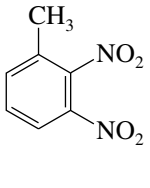
Anisole — *p*-Ethylanisole — *p*-(1-Bromoethyl)anisole — *p*-Methoxystyrene

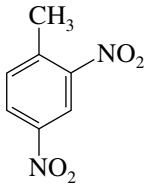
12.29 (*a*) Methyl is an ortho, para-directing substituent, and toluene yields mainly *o*-nitrotoluene and *p*-nitrotoluene on mononitration. Some *m*-nitrotoluene is also formed.

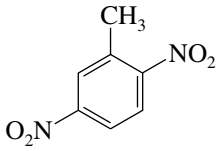


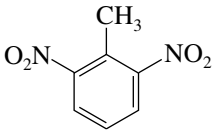
Toluene — *o*-Nitrotoluene — *m*-Nitrotoluene — *p*-Nitrotoluene

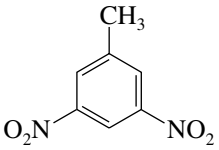
(*b*) There are six isomeric dinitrotoluenes:

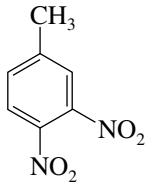

2,3-Dinitrotoluene


2,4-Dinitrotoluene


2,5-Dinitrotoluene

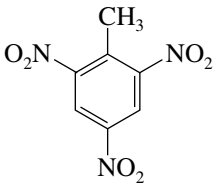

2,6-Dinitrotoluene

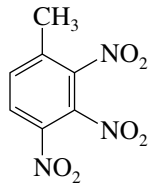

3,5-Dinitrotoluene

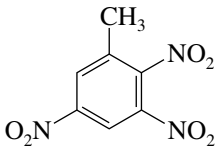

3,4-Dinitrotoluene

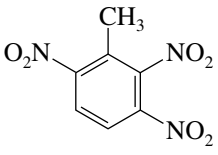
The least likely product is 3,5-dinitrotoluene because neither of its nitro groups is ortho or para to the methyl group.

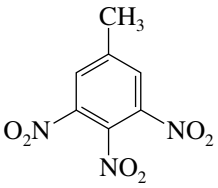
(*c*) There are six trinitrotoluene isomers:

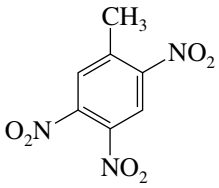

2,4,6-Trinitrotoluene


2,3,4-Trinitrotoluene


2,3,5-Trinitrotoluene

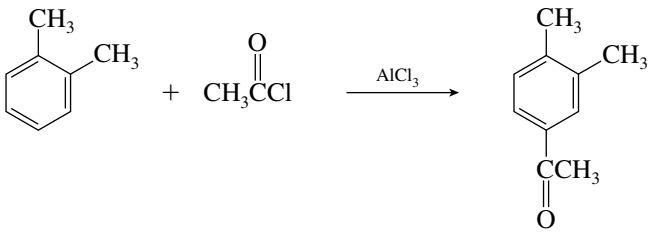

2,3,6-Trinitrotoluene


3,4,5-Trinitrotoluene


2,4,5-Trinitrotoluene

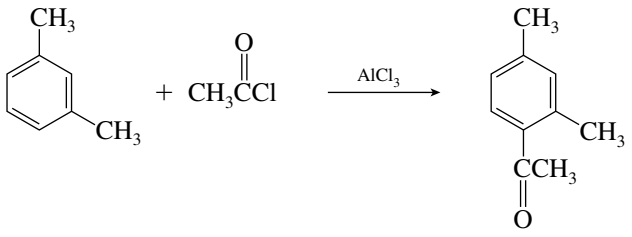
The most likely major product is 2,4,6-trinitrotoluene because all the positions activated by the methyl group are substituted. This is, in fact, the compound commonly known as TNT.

12.30 From *o*-xylene:



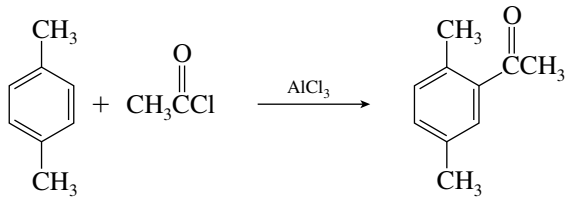
o-Xylene Acetyl chloride 3,4-Dimethyl-acetophenone (94%)

From *m*-xylene:



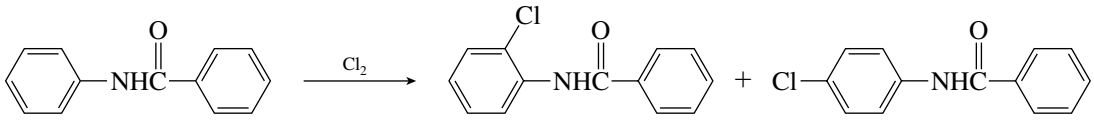
m-Xylene — 2,4-Dimethylacetophenone (86%)

From *p*-xylene:



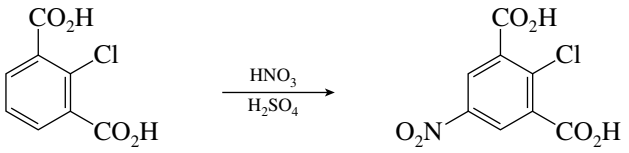
p-Xylene — 2,5-Dimethylacetophenone (99%)

12.31 The ring that bears the nitrogen in benzanilide is activated toward electrophilic aromatic substitution. The ring that bears the C═O is strongly deactivated.



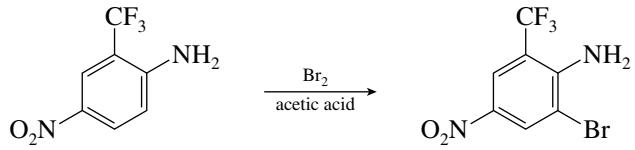
Benzanilide — *N*-(*o*-Chlorophenyl)benzamide — *N*-(*p*-Chlorophenyl)benzamide

12.32 (*a*) Nitration of the ring takes place para to the ortho, para-directing chlorine substituent; this position is also meta to the meta-directing carboxyl groups.



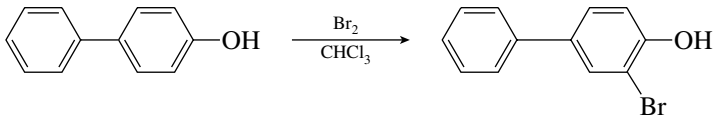
2-Chloro-1,3-benzenedicarboxylic acid — 2-Chloro-5-nitro-1,3-benzenedicarboxylic acid (86%)

(*b*) Bromination of the ring occurs at the only available position activated by the amino group, a powerful activating substituent and an ortho, para director. This position is meta to the meta-directing trifluoromethyl group and to the meta-directing nitro group.



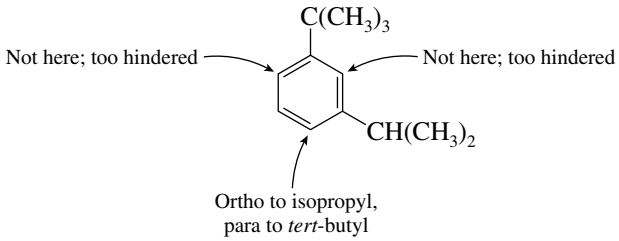
4-Nitro-2-(trifluoromethyl)aniline — 2-Bromo-4-nitro-6-(trifluoromethyl)aniline (81%)

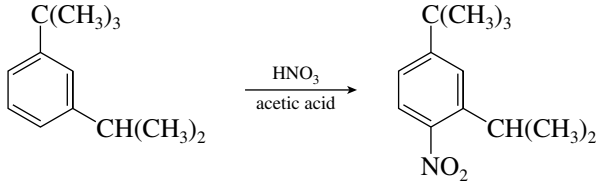
(*c*) This may be approached as a problem in which there are two aromatic rings. One of them bears two activating substituents and so is more reactive than the other, which bears only one activating substituent. Of the two activating substituents (—OH and C_6H_5—), the hydroxyl substituent is the more powerful and controls the regioselectivity of substitution.



p-Phenylphenol — 2-Bromo-4-phenylphenol

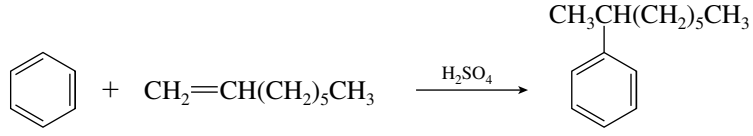
(*d*) Both substituents are activating, nitration occurring readily even in the absence of sulfuric acid; both are ortho, para-directing and comparable in activating power. The position at which substitution takes place is therefore





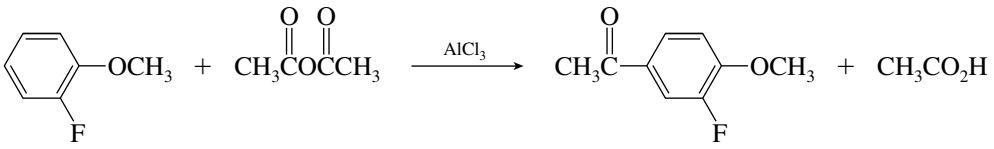
1-*tert*-Butyl-3-isopropylbenzene — 4-*tert*-Butyl-2-isopropyl-1-nitrobenzene (78%)

(*e*) Protonation of 1-octene yields a secondary carbocation, which attacks benzene.



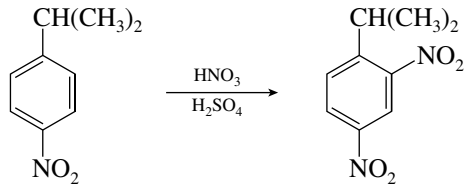
Benzene — 1-Octene — 2-Phenyloctane (84%)

(*f*) The reaction that occurs with arenes and acid anhydrides in the presence of aluminum chloride is Friedel–Crafts acylation. The methoxy group is the more powerful activating substituent, so acylation occurs para to it.



o-Fluoroanisole — Acetic anhydride — 3-Fluoro-4-methoxyacetophenone (70–80%)

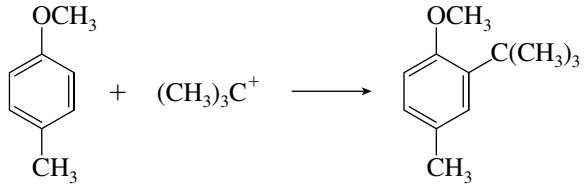
(*g*) The isopropyl group is ortho, para-directing, and the nitro group is meta-directing. In this case their orientation effects reinforce each other. Electrophilic aromatic substitution takes place ortho to isopropyl and meta to nitro.



p-Nitroisopropylbenzene

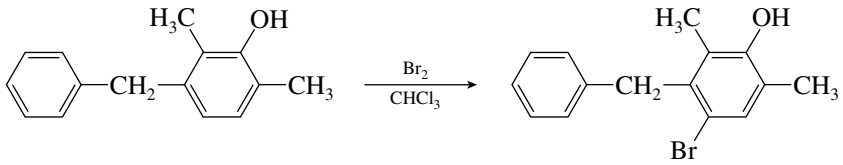
2,4-Dinitroisopropylbenzene (96%)

(*h*) In the presence of an acid catalyst (H_2SO_4), 2-methylpropene is converted to *tert*-butyl cation, which then attacks the aromatic ring ortho to the strongly activating methoxy group.



In this particular example, 2-*tert*-butyl-4-methylanisole was isolated in 98% yield.

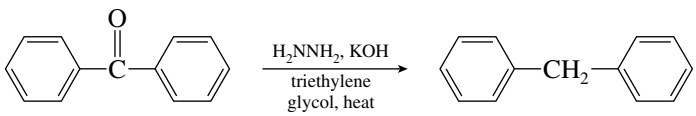
(*i*) There are two things to consider in this problem: (1) In which ring does bromination occur, and (2) what is the orientation of substitution in that ring? All the substituents are activating groups, so substitution will take place in the ring that bears the greater number of substituents. Orientation is governed by the most powerful activating substituent, the hydroxyl group. Both positions ortho to the hydroxyl group are already substituted, so that bromination takes place para to it. The product shown was isolated from the bromination reaction in 100% yield.



3-Benzyl-2,6-dimethylphenol

3-Benzyl-4-bromo-2,6-dimethylphenol (100%)

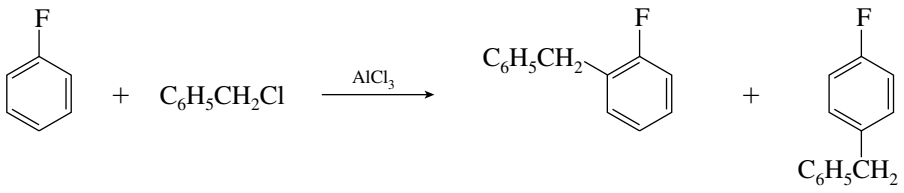
(*j*) Wolff–Kishner reduction converts benzophenone to diphenylmethane.



Benzophenone

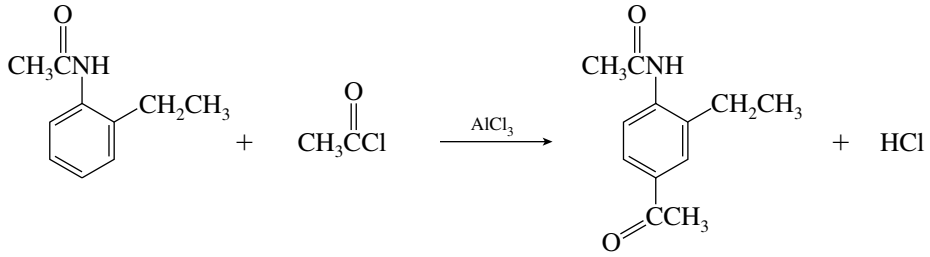
Diphenylmethane (83%)

(*k*) Fluorine is an ortho, para-directing substituent. It undergoes Friedel–Crafts alkylation on being treated with benzyl chloride and aluminum chloride to give a mixture of *o*-fluorodiphenylmethane and *p*-fluorodiphenylmethane.



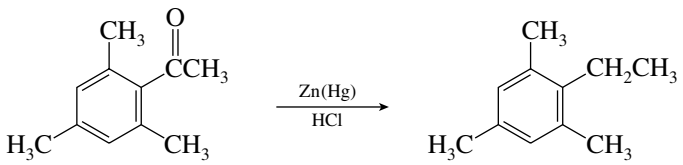
Fluorobenzene — Benzyl chloride — *o*-Fluorodiphenylmethane (15%) — *p*-Fluorodiphenylmethane (85%)

(*l*) The $-\ddot{N}HCCH_3$ substituent is a more powerful activator than the ethyl group. It directs Friedel–Crafts acylation primarily to the position para to itself.



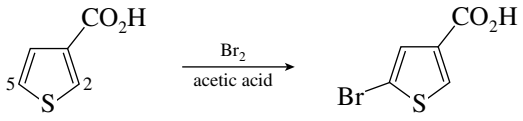
o-Ethylacetanilide — Acetyl chloride — 4-Acetamido-3-ethylacetophenone (57%)

(*m*) Clemmensen reduction converts the carbonyl group to a CH_2 unit.



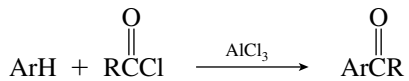
2,4,6-Trimethylacetophenone — 2-Ethyl-1,3,5-trimethylbenzene (74%)

(*n*) Bromination occurs at C-5 on thiophene-3-carboxylic acid. Reaction does not occur at C-2 since substitution at this position would place a carbocation adjacent to the electron-withdrawing carboxyl group.

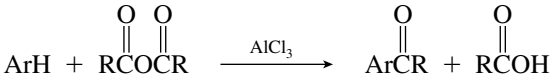


Thiophene-3-carboxylic acid — 2-Bromo-thiophene-4-carboxylic acid (69%)

12.33 In a Friedel–Crafts acylation reaction an acyl chloride or acid anhydride reacts with an arene to yield an aryl ketone.

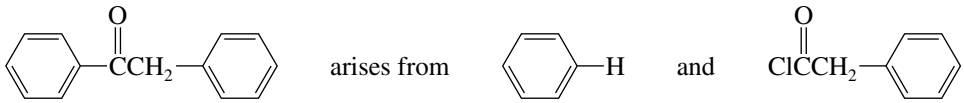


or

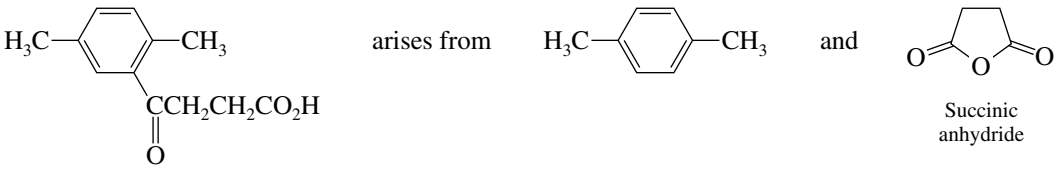


The ketone carbonyl is bonded directly to the ring. In each of these problems, therefore, you should identify the bond between the aromatic ring and the carbonyl group and realize that it arises as shown in this general reaction.

(*a*) The compound is derived from benzene and $C_6H_5CH_2\overset{\overset{O}{\|}}{C}Cl$. The observed yield in this reaction is 82%.

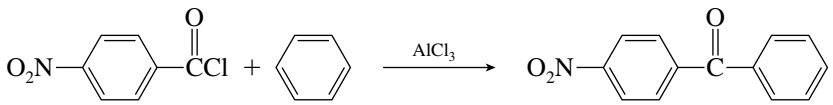


(*b*) The presence of the $Ar\overset{\overset{O}{\|}}{C}CH_2CH_2CO_2H$ unit suggests an acylation reaction using succinic anhydride.



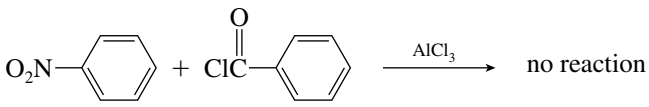
In practice, this reaction has been carried out in 55% yield.

(*c*) Two methods seem possible here but only one actually works. The only effective combination is



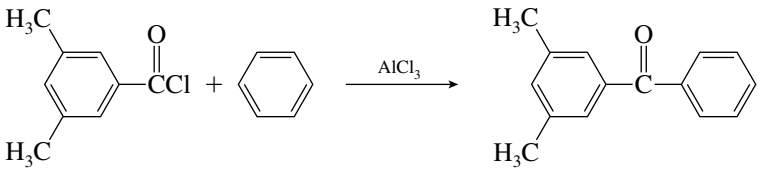
p-Nitrobenzoyl chloride | Benzene | *p*-Nitrobenzophenone (87%)

The alternative combination



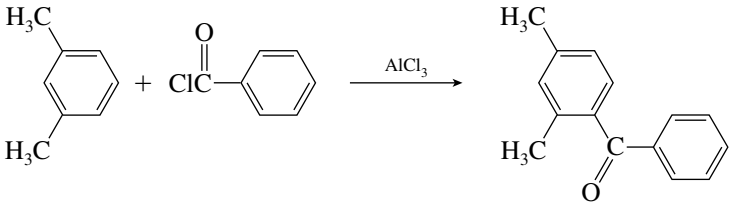
fails because it requires a Friedel–Crafts reaction on a strongly deactivated aromatic ring (nitrobenzene).

(*d*) Here also two methods seem possible, but only one is successful in practice. The valid synthesis is



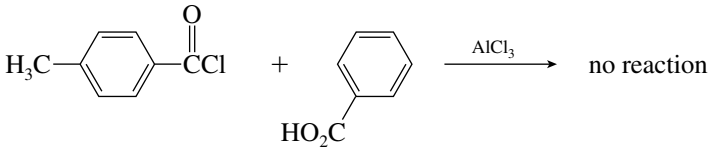
3,5-Dimethylbenzoyl chloride | Benzene | 3,5-Dimethylbenzophenone (89%)

The alternative combination will not give 3,5-dimethylbenzophenone, because of the ortho, para-directing properties of the methyl substituents in *m*-xylene. The product will be 2,4-dimethylbenzophenone.



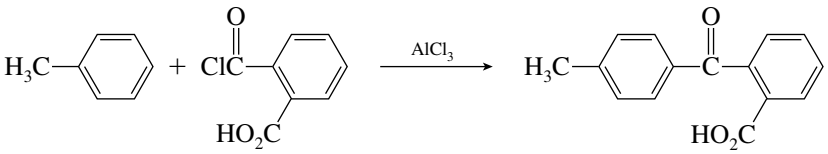
m-Xylene Benzoyl chloride 2,4-Dimethylbenzophenone

(*e*) The combination that follows is not effective, because it involves a Friedel–Crafts reaction on a deactivated aromatic ring.

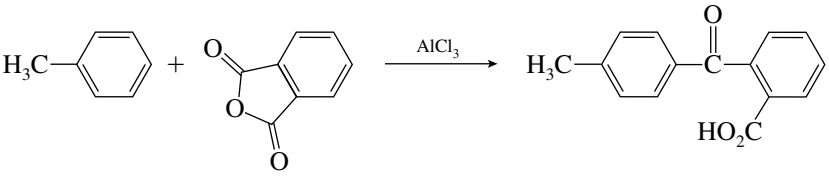


p-Methylbenzoyl chloride Benzoic acid

The following combination, utilizing toluene, therefore seems appropriate:

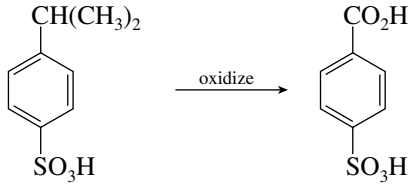


The actual sequence used a cyclic anhydride, phthalic anhydride, in a reaction analogous to that seen in part (*b*).



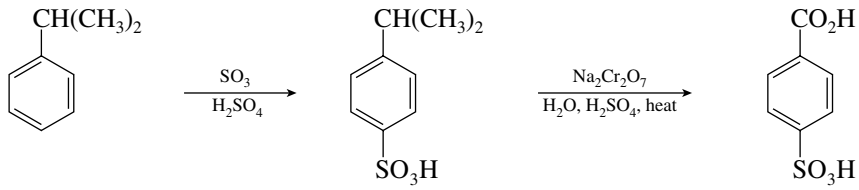
Toluene Phthalic anhydride *o*-(4-Methylbenzoyl)benzoic acid (96%)

12.34 (*a*) The problem to be confronted here is that two meta-directing groups are para to each other in the product. However, by recognizing that the carboxylic acid function can be prepared by oxidation of the isopropyl group



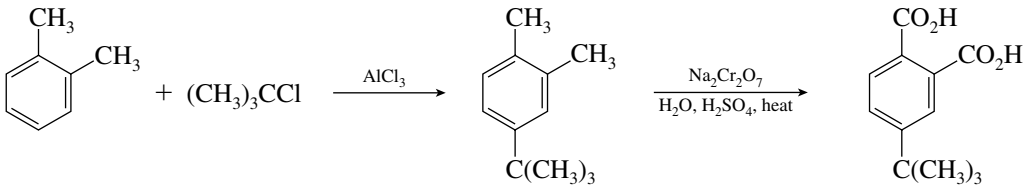
we have a reasonable last step in the synthesis. The key intermediate has its sulfonic acid group para to the ortho, para-directing isopropyl group, which suggests the following

approach:



Isopropylbenzene — *p*-Isopropylbenzenesulfonic acid — *p*-Carboxylbenzenesulfonic acid

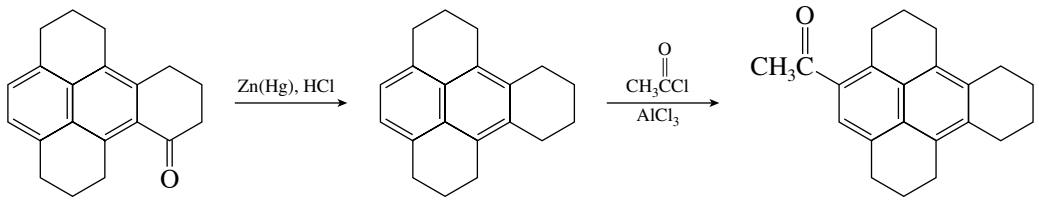
(*b*) In this problem two methyl groups must be oxidized to carboxylic acid functions, and a *tert*-butyl group must be introduced, most likely by a Friedel–Crafts reaction. Since Friedel–Crafts alkylations cannot be performed on deactivated aromatic rings, oxidation must *follow,* not precede, alkylation. The following reaction sequence therefore seems appropriate:



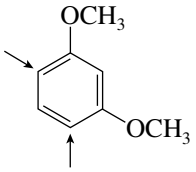
o-Xylene — 4-*tert*-Butyl-1,2-dimethylbenzene — 4-*tert*-Butylbenzene-1,2-dicarboxylic acid

In practice, zinc chloride was used as the Lewis acid to catalyze the Friedel–Crafts reaction (64% yield). Oxidation of the methyl groups occurs preferentially because the *tert*-butyl group has no benzylic hydrogens.

(*c*) The carbonyl group is directly attached to the naphthalene unit in the starting material. Reduce it in the first step so that a Friedel–Crafts acylation can be accomplished on the naphthalene ring. An aromatic ring that bears a strongly electron-withdrawing group such as C═O does not undergo Friedel–Crafts reactions.

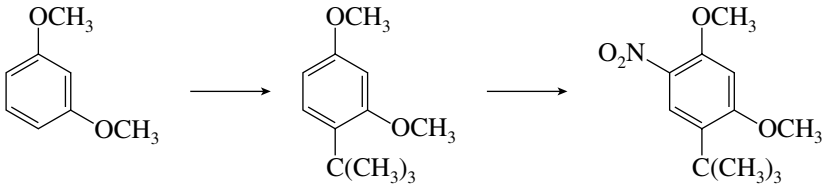


(*d*) *m*-Dimethoxybenzene is a strongly activated aromatic compound and so will undergo electrophilic aromatic substitution readily. The ring position between the two methoxy groups is sterically hindered and less reactive than the other activated positions.

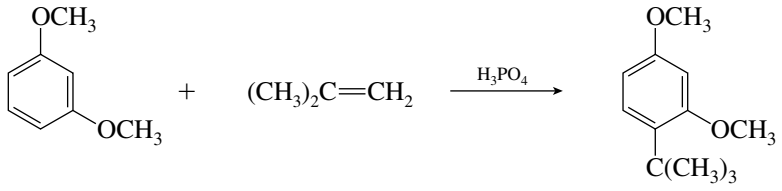


Arrows indicate equivalent ring positions strongly activated by methoxy groups.

Because Friedel–Crafts reactions may not be performed on deactivated aromatic rings, the *tert*-butyl group must be introduced before the nitro group. The correct sequence is therefore

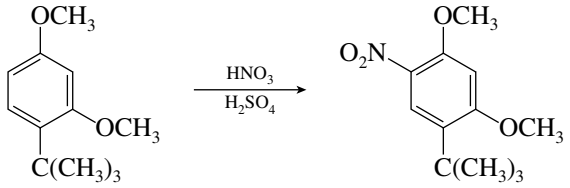


This is essentially the procedure actually followed. Alkylation was effected, however, not with *tert*-butyl chloride and aluminum chloride but with 2-methylpropene and phosphoric acid.



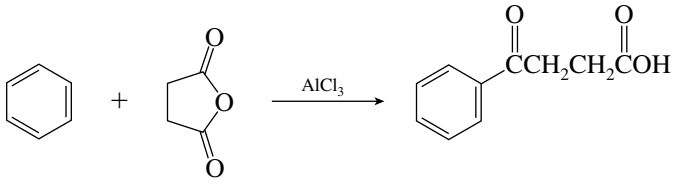
m-Dimethoxybenzene — 2-Methylpropene — 1-*tert*-Butyl-2,4-dimethoxybenzene (75%)

Nitration was carried out in the usual way. the orientation of nitration is controlled by the more powerfully activating methoxy groups rather than by the weakly activating *tert*-butyl.



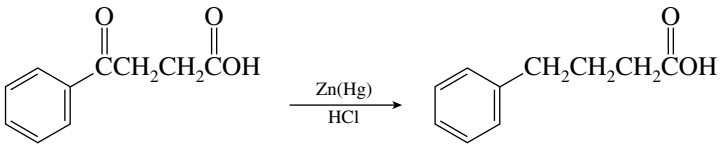
1-*tert*-Butyl-2,4-dimethoxy-5-nitrobenzene

12.35 The first step is a Friedel–Crafts acylation reaction. The use of a cyclic anhydride introduces both the acyl and carboxyl groups into the molecule.



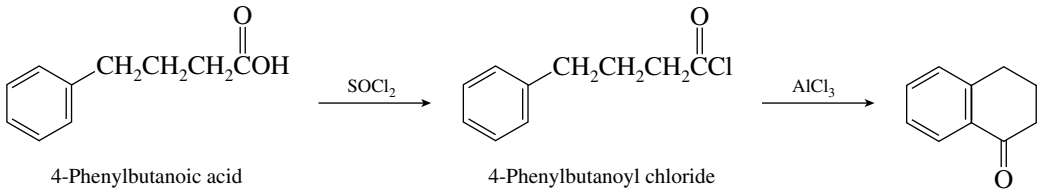
Benzene — Succinic anhydride — 4-Oxo-4-phenylbutanoic acid

The second step is a reduction of the ketone carbonyl to a methylene group. A Clemmensen reduction is normally used for this step.



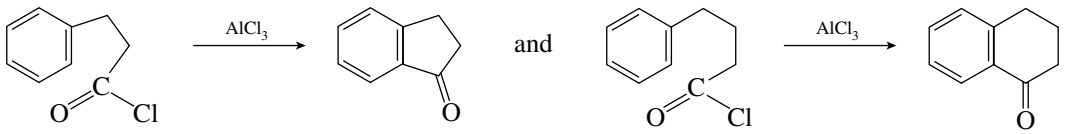
4-Oxo-4-phenylbutanoic acid — 4-Phenylbutanoic acid

The cyclization phase of the process is an intramolecular Friedel–Crafts acylation reaction. It requires conversion of the carboxylic acid to the acyl chloride (thionyl chloride is a suitable reagent) followed by treatment with aluminum chloride.

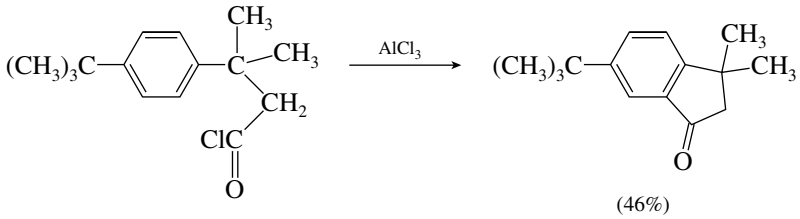


4-Phenylbutanoic acid 4-Phenylbutanoyl chloride

12.36 Intramolecular Friedel–Crafts acylation reactions that produce five-membered or six-membered rings occur readily. Cyclization must take place at the position ortho to the reacting side chain.

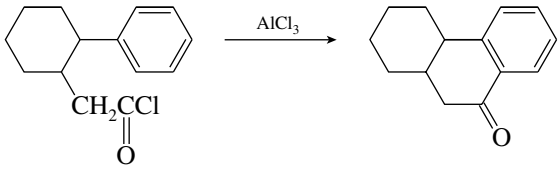


(*a*) A five-membered cyclic ketone is formed here.



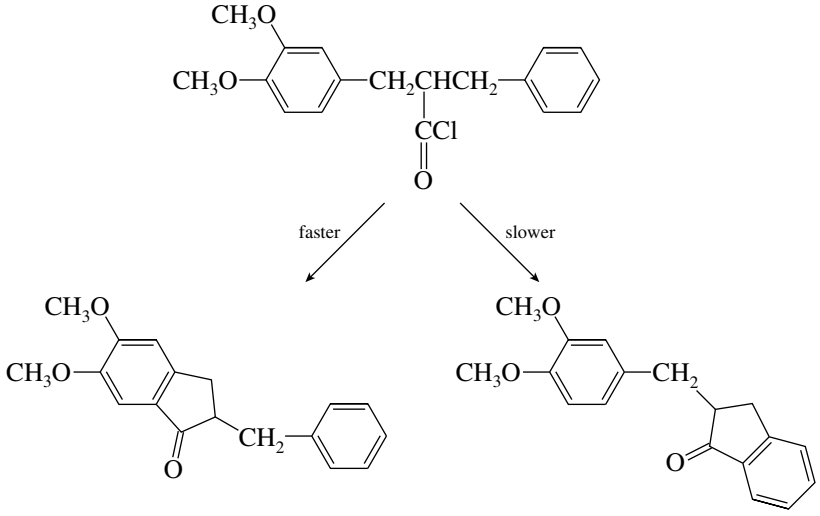
(46%)

(*b*) This intramolecular Friedel–Crafts acylation takes place to form a six-membered cyclic ketone in excellent yield.



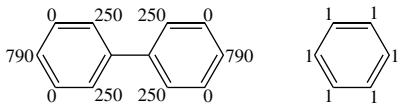
93%

(*c*) In this case two aromatic rings are available for attack in the acylation reaction. The more reactive ring is the one that bears the two activating methoxy groups, and cyclization occurs on it.



Only product (78% yield) (Not observed)

12.37 (*a*) To determine the total rate of chlorination of biphenyl relative to that of benzene, we add up the partial rate factors for all the positions in each substrate and compare them.



Biphenyl (sum = 2580) Benzene (sum = 6)

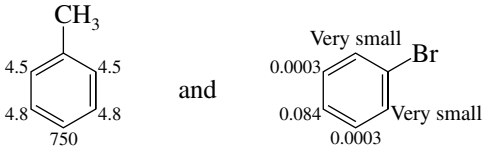
$$\text{Relative rate of chlorination: } \frac{\text{Biphenyl}}{\text{Benzene}} = \frac{2580}{6} = \frac{430}{1}$$

(*b*) The relative rate of attack at the para position compared with the ortho positions is given by the ratio of their partial rate factors.

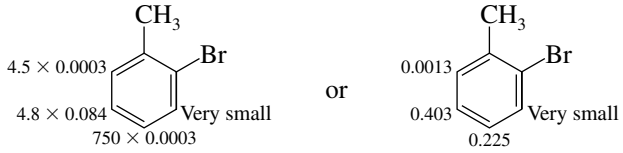
$$\frac{\text{Para}}{\text{Ortho}} = \frac{1580}{1000} = \frac{1.58}{1}$$

Therefore, 15.8 g of *p*-chlorobiphenyl is formed for every 10 g of *o*-chlorobiphenyl.

12.38 The problem stipulates that the reactivity of various positions in *o*-bromotoluene can be estimated by multiplying the partial rate factors for the corresponding positions in toluene and bromobenzene. Therefore, given the partial rate factors:



the two are multiplied together to give the combined effects of the two substituents at the various ring positions.

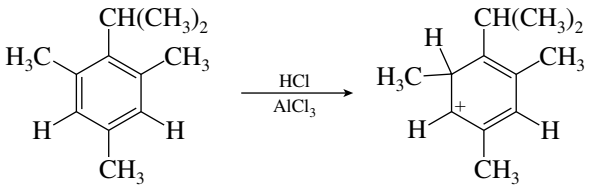


The most reactive position is the one that is para to bromine. The predicted product is therefore 4-bromo-3-methylacetophenone. Indeed, this is what is observed experimentally.

o-Bromotoluene Acetyl chloride 4-Bromo-3-methyl-acetophenone

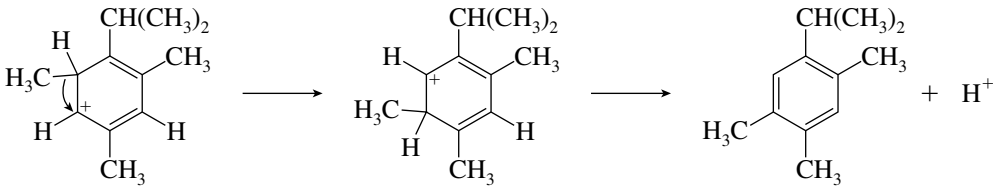
This was first considered to be "anomalous" behavior on the part of *o*-bromotoluene, but, as can be seen, it is consistent with the individual directing properties of the two substituents.

12.39 The isomerization is triggered by protonation of the aromatic ring, an electrophilic attack by HCl catalyzed by $AlCl_3$.



2-Isopropyl-1,3,5-trimethylbenzene

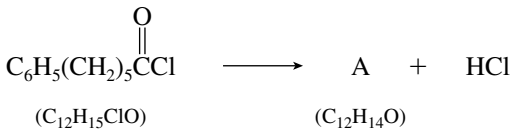
The carbocation then rearranges by a methyl shift, and the rearranged cyclohexadienyl cation loses a proton to form the isomeric product



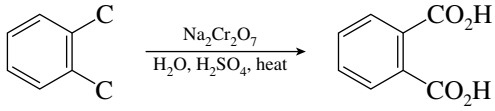
1-Isopropyl-2,4,5-trimethylbenzene

The driving force for rearrangement is relief of steric strain between the isopropyl group and one of its adjacent methyl groups. Isomerization is acid-catalyzed. Protonation of the ring generates the necessary carbocation intermediate and rearomatization occurs by loss of a proton.

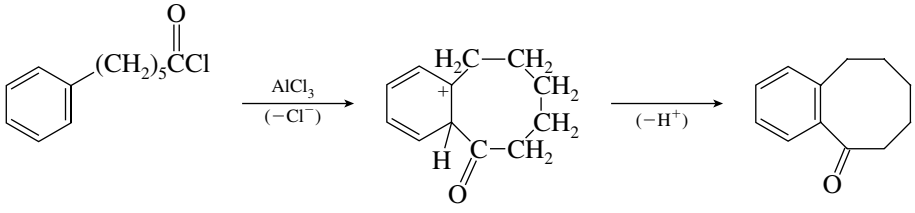
12.40 The relation of compound A to the starting material is



The starting acyl chloride has lost the elements of HCl in the formation of A. Because A forms benzene-1,2-dicarboxylic acid on oxidation, it must have two carbon substituents ortho to each other.



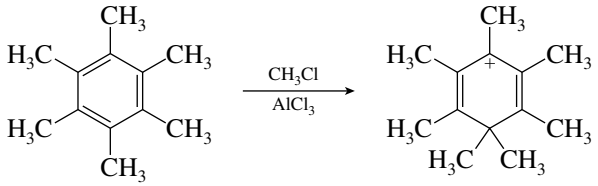
These facts suggest the following process:



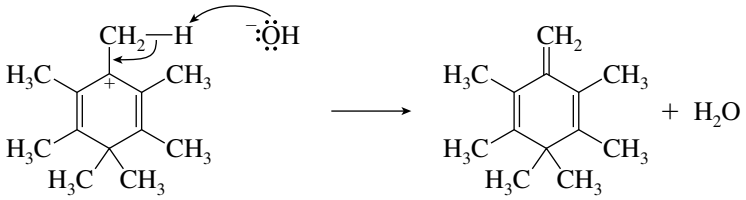
A

The reaction leading to compound A is an intramolecular Friedel–Crafts acylation. Since cyclization to form an eight-membered ring is difficult, it must be carried out in dilute solution to minimize competition with intermolecular acylation.

12.41 Although hexamethylbenzene has no positions available at which ordinary electrophilic aromatic *substitution* might occur, electrophilic *attack* on the ring can still take place to form a cyclohexadienyl cation.

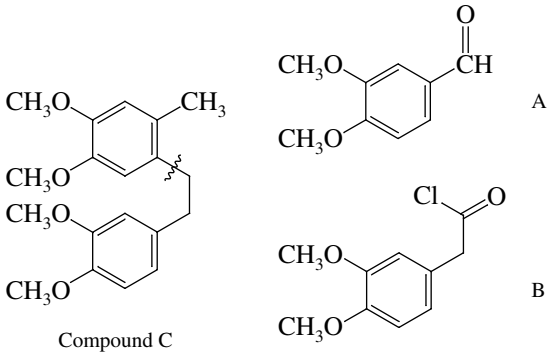


Compound A is the tetrachloroaluminate ($AlCl_4^-$) salt of the carbocation shown. It undergoes deprotonation on being treated with aqueous sodium bicarbonate.



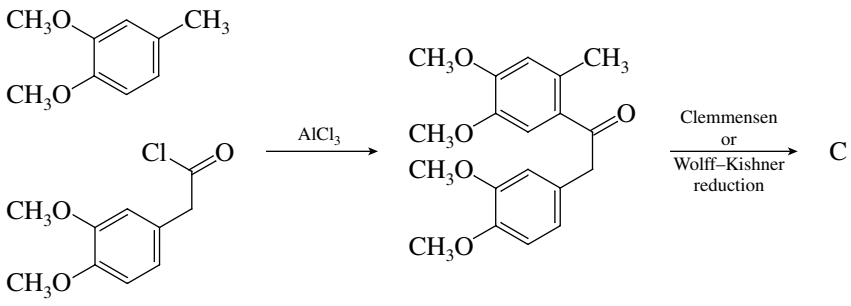
B

12.42 By examining the structure of the target molecule, compound C, we see that the bond indicated in the following structure joins two fragments that are related to the given starting materials A and B:



Compound C

The bond connecting the two fragments can be made by a Friedel–Crafts acylation-reduction sequence using the acyl chloride B.



The orientation is right; attack is para to one of the methoxy groups and ortho to the methyl. The substrate for the Friedel–Crafts acylation reaction, 3,4-dimethoxytoluene, is prepared from compound A by a Clemmensen or Wolff–Kishner reduction. Compound A cannot be acylated directly because it bears a strongly deactivating —CH(=O) substituent.

12.43 In the presence of aqueous sulfuric acid, the side-chain double bond of styrene undergoes protonation to form a benzylic carbocation.

$$C_6H_5CH{=}CH_2 + H^+ \longrightarrow C_6H_5\overset{+}{C}HCH_3$$

Styrene — 1-Phenylethyl cation

This carbocation then reacts with a molecule of styrene in the manner we have seen earlier (Chapter 6) for alkene dimerization.

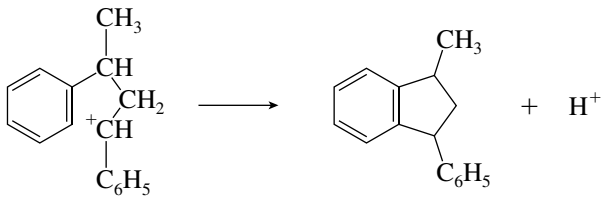
$$C_6H_5\overset{+}{C}HCH_3 + C_6H_5CH{=}CH_2 \longrightarrow C_6H_5\overset{+}{C}HCH_2CHC_6H_5$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad CH_3$$

The carbocation produced in this step can lose a proton to form 1,3-diphenyl-1-butene

$$C_6H_5\overset{+}{C}HCH_2CHC_6H_5 \longrightarrow C_6H_5CH{=}CHCHC_6H_5 + H^+$$
$$\qquad\qquad\qquad\quad |\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad CH_3\qquad\qquad\qquad\qquad\quad CH_3$$

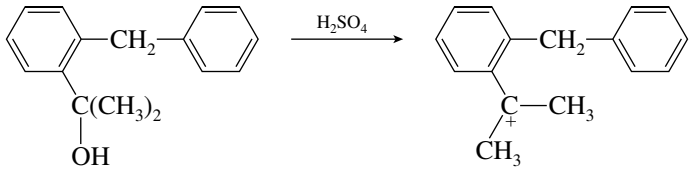
1,3-Diphenyl-1-butene

or it can undergo a cyclization reaction in what amounts to an intramolecular Friedel–Crafts alkylation

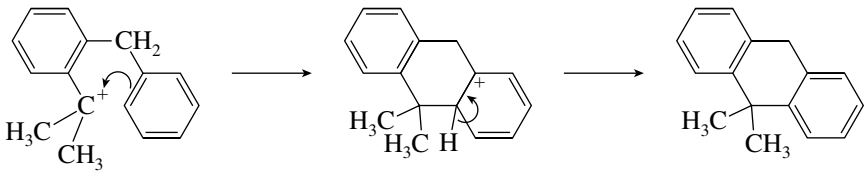


1-Methyl-3-phenylindan

12.44 The alcohol is tertiary and benzylic. In the presence of sulfuric acid a carbocation is formed.



An intramolecular Friedel–Crafts alkylation reaction follows, in which the carbocation attacks the adjacent aromatic ring.



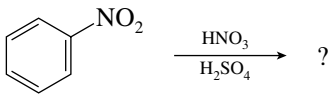
$C_{16}H_{16}$

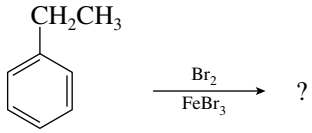
SELF-TEST

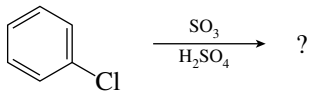
PART A

A-1. Write the three most stable resonance contributors to the cyclohexadienyl cation found in the ortho bromination of toluene.

A-2. Give the major product(s) for each of the following reactions. Indicate whether the reaction proceeds faster or slower than the corresponding reaction of benzene.

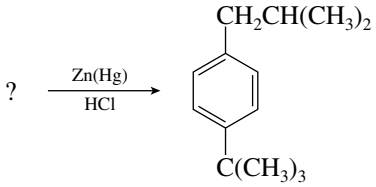
(*a*) 

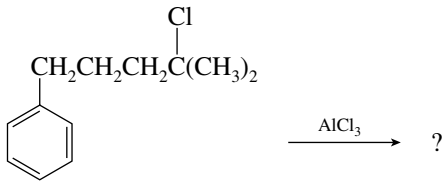
(*b*) 

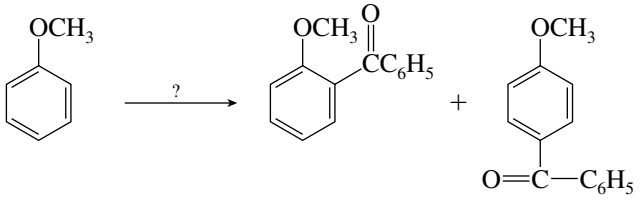
(*c*) 

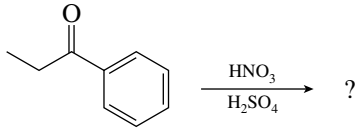
A-3. Write the formula of the electrophilic reagent species present in each reaction of the preceding problem.

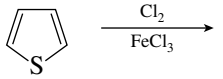
A-4. Provide the reactant, reagent, or product omitted from each of the following:

(*a*) 

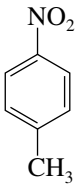
(*b*) 

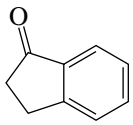
(*c*) 

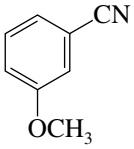
(*d*) 

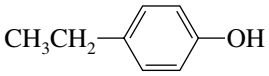
(*e*) 

A-5. Draw the structure(s) of the major product(s) formed by reaction of each of the following compounds with Cl_2 and $FeCl_3$. If two products are formed in significant amounts, draw them both.

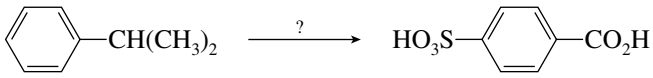
(*a*) 

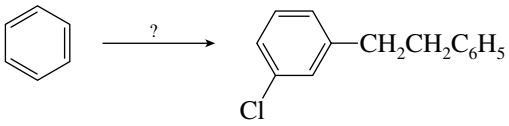
(*c*) 

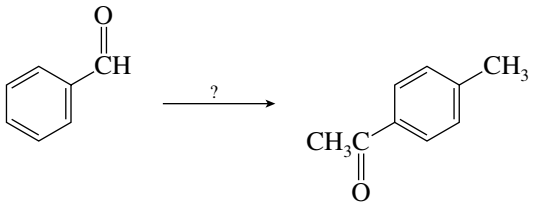
(*b*) 

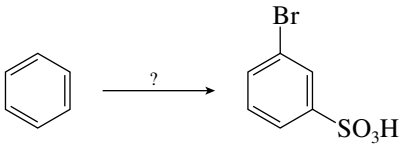
(*d*) 

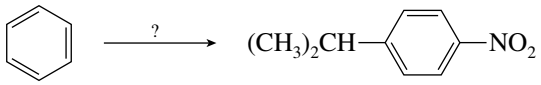
A-6. Provide the necessary reagents for each of the following transformations. More than one step may be necessary.

(*a*) 

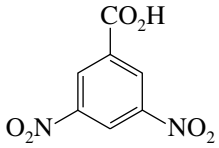
(*b*) 

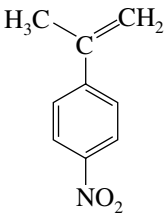
(*c*) 

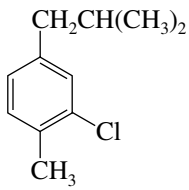
(*d*) 

(*e*) 

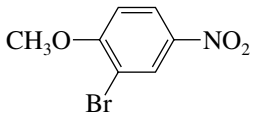
A-7. Outline a reasonable synthesis of each of the following from either benzene or toluene and any necessary organic or inorganic reagents.

(a) 

(b) 

(c) 

A-8. Outline a reasonable synthesis of the compound shown using anisole ($C_6H_5OCH_3$) and any necessary inorganic reagents.



PART B

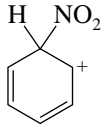
B-1. Consider the following statements concerning the effect of a trifluoromethyl group, $-CF_3$, on an electrophilic aromatic substitution.

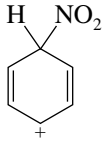
1. The CF_3 group will activate the ring.
2. The CF_3 group will deactivate the ring.
3. The CF_3 group will be a meta director.
4. The CF_3 group will be an ortho, para director.

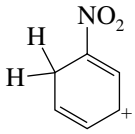
Which of these statements are correct?

(*a*) 1, 3 (*b*) 1, 4 (*c*) 2, 3 (*d*) 2, 4

B-2. Which of the following resonance structures is **not** a contributor to the cyclohexadienyl cation intermediate in the nitration of benzene?

(*a*) 

(*c*) 

(*b*) 

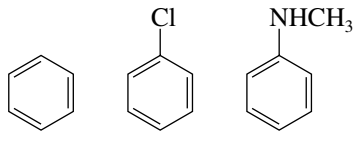
(*d*) None of these (all are contributors)

B-3. All the following groups are activating ortho, para directors when attached to a benzene ring *except*

(*a*) $-OCH_3$ (*c*) $-Cl$

(*b*) $-NHCCH_3$ (with O) (*d*) $-N(CH_3)_2$

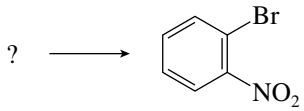
B-4. Rank the following in terms of increasing reactivity toward nitration with HNO_3, H_2SO_4 (least → most):



(*a*) $1 < 2 < 3$ (*c*) $3 < 1 < 2$

(*b*) $2 < 1 < 3$ (*d*) $3 < 2 < 1$

B-5. For the reaction

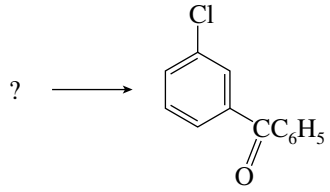


the best reactants are:

(*a*) $C_6H_5Br + HNO_3, H_2SO_4$ (*c*) $C_6H_5Br + H_2SO_4$, heat

(*b*) $C_6H_5NO_2 + Br_2, FeBr_3$ (*d*) $C_6H_5NO_2 + HBr$

B-6. For the reaction



the best reactants are

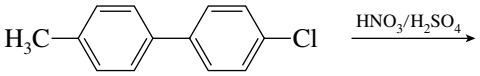
(*a*) $C_6H_5Cl + C_6H_5\overset{\overset{O}{\|}}{C}Cl, AlCl_3$

(*b*) $C_6H_5\overset{\overset{O}{\|}}{C}C_6H_5 + Cl_2, FeCl_3$

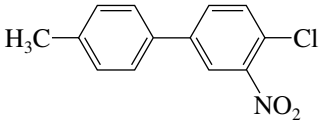
(*c*) $C_6H_5CH_2C_6H_5 + Cl_2, FeCl_3$, followed by oxidation with chromic acid

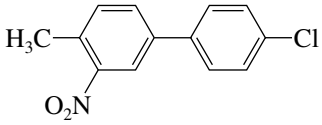
(*d*) None of these yields the desired product.

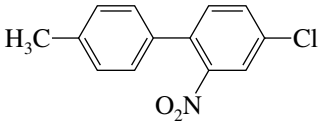
B-7. The reaction

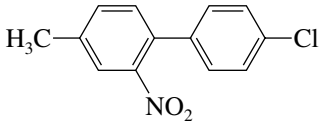


gives as the major product:

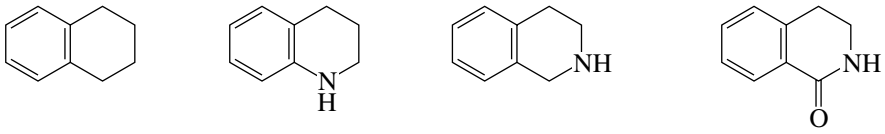
(*a*) 

(*c*) 

(*b*) 

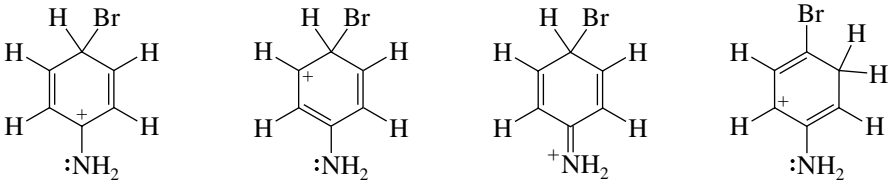
(*d*) 

B-8. Which one of the following compounds undergoes bromination of its aromatic ring (electrophilic aromatic substitution) at the **fastest** rate?



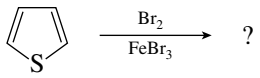
(*a*) (*b*) (*c*) (*d*)

B-9. Which one of the following is the **most stable**?

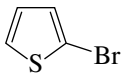


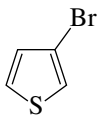
(*a*) (*b*) (*c*) (*d*)

B-10. The major product of the reaction



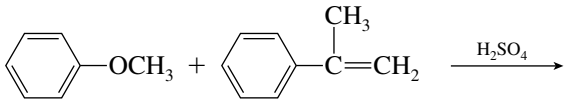
is

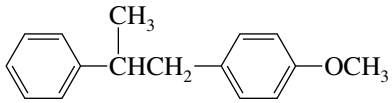
(*a*) 

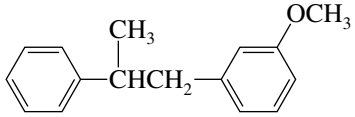
(*b*) 

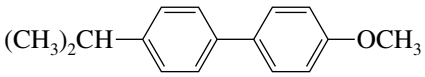
(*c*) An **equal** mixture of compound (*a*) and (*b*) would form.
(*d*) None of these; substitution would not occur.

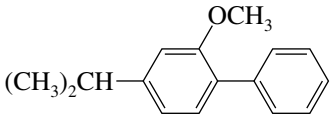
B-11. What is the product of the following reaction?

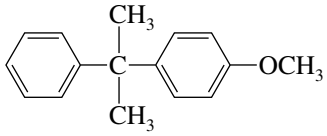


(*a*) 

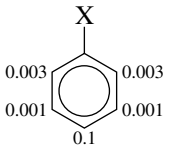
(*b*) 

(*c*) 

(*d*) 

(*e*) 

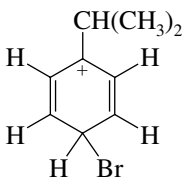
B-12. Partial rate factors are shown for nitration of a particular aromatic compound. Based on these data, the most reasonable choice for substituent X is:



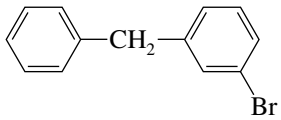
(*a*) $-N(CH_3)_2$
(*b*) $-SO_3H$
(*c*) —Br
(*d*) $-CH(CH_3)_2$
(*e*) —CH═O

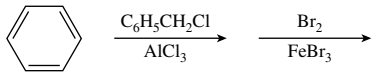
B-13. Which reactants combine to give the species shown at the right as a reactive intermediate?

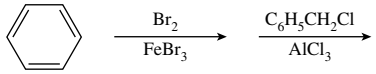
(*a*) Benzene, isopropyl bromide, and HBr
(*b*) Bromobenzene, isopropyl chloride, and $AlCl_3$
(*c*) Isopropylbenzene, Br_2, and $FeBr_3$
(*d*) Isopropylbenzene, Br_2, light, and heat
(*e*) Isopropylbenzene, *N*-bromosuccinimide, benzoyl peroxide, and heat

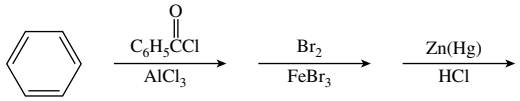


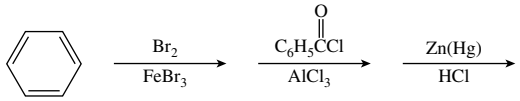
B-14. Which sequence of steps describes the best synthesis of the compound shown?



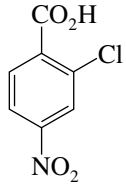
(*a*) 

(*b*) 

(*c*) 

(*d*) 

B-15. Which one of the following is the best synthesis of 2-chloro-4-nitrobenzoic acid?



2-Chloro-4-nitrobenzoic acid

(*a*) 1. Heat benzoic acid with HNO_3, H_2SO_4
2. Cl_2, $FeCl_3$, heat

(*b*) 1. Treat toluene with HNO_3, H_2SO_4
2. $K_2Cr_2O_7$, H_2O, H_2SO_4, heat
3. Cl_2, $FeCl_3$, heat

(*c*) 1. Treat toluene with HNO_3, H_2SO_4
2. Cl_2, $FeCl_3$, heat
3. $K_2Cr_2O_7$, H_2O, H_2SO_4, heat

(*d*) 1. Treat nitrobenzene with Cl_2, $FeCl_3$, heat
2. CH_3Cl, $AlCl_3$
3. $K_2Cr_2O_7$, H_2O, H_2SO_4, heat

(*e*) 1. Treat chlorobenzene with HNO_3, H_2SO_4
2. CH_3Cl, $AlCl_3$
3. $K_2Cr_2O_7$, H_2O, H_2SO_4, heat