Chemistry of Benzene:
Electrophilic Aromatic Substitution

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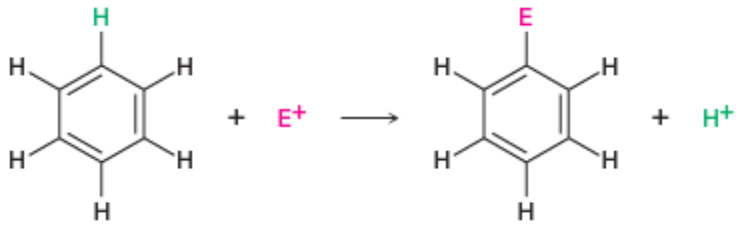
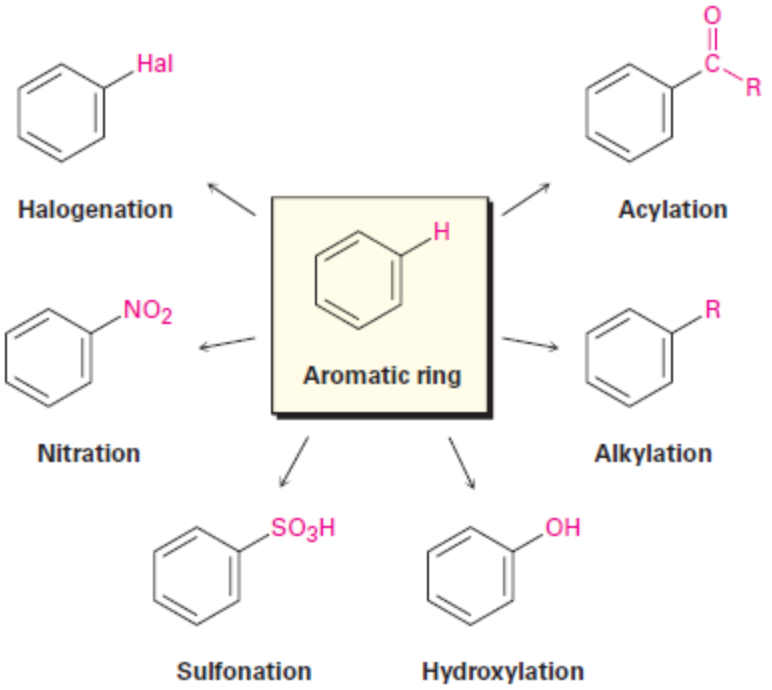
Reference Text Book:

- John McMurry "Organic Chemistry" 9th Edition, Cengage Learning, USA **(2016).**

The most common reaction of aromatic compounds is **electrophilic aromatic substitution**, in which an electrophile (E+) reacts with an aromatic ring and substitutes for one of the hydrogens. The reaction is characteristic of all aromatic rings, not just benzene and substituted benzenes. In fact, the ability of a compound to undergo electrophilic substitution is a good test of aromaticity.

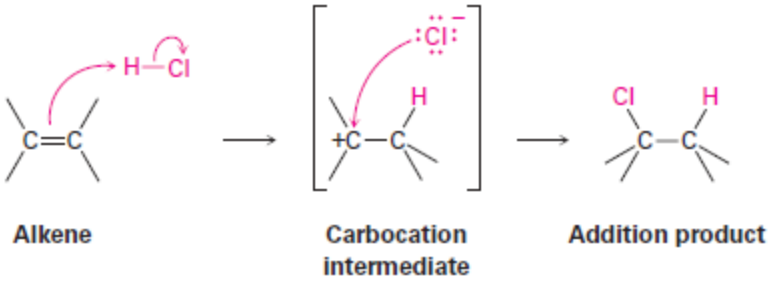


Many different substituents can be introduced onto an aromatic ring through electrophilic substitution. To list some possibilities, an aromatic ring can be substituted by a halogen (-Cl, -Br, -I), a nitro group (-NO_2), a sulfonic acid group (-SO_3H), a hydroxyl group (-OH), an alkyl group (-R), or an acyl group (-COR). Starting from only a few simple materials, it's possible to prepare many thousands of substituted aromatic compounds.

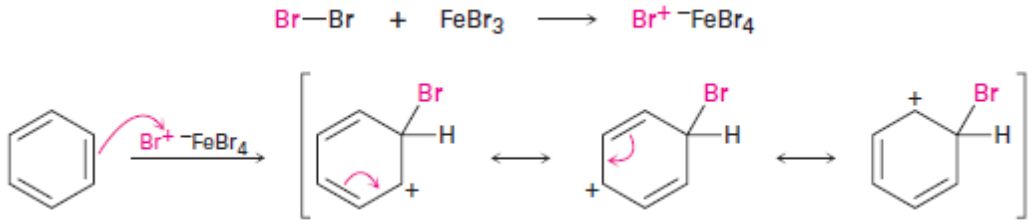


Electrophilic Aromatic Substitution Reactions: Bromination

Before seeing how electrophilic aromatic substitutions occur, let's briefly recall about electrophilic alkene additions. When a reagent such as HCl adds to an alkene, the electrophilic hydrogen approaches the *Π* electrons of the double bond and forms a bond to one carbon, leaving a positive charge at the other carbon. This carbocation intermediate then reacts with the nucleophilic Cl_2 ion to yield the addition product.



An electrophilic aromatic substitution reaction begins in a similar way, but there are a number of differences. One difference is that aromatic rings are less reactive toward electrophiles than alkenes. For example, Br_2 in CH_2Cl_2 solution reacts instantly with most alkenes but does not react with benzene at room temperature. For bromination of benzene to take place, a catalyst such as $FeBr_3$ is needed. The catalyst makes the Br_2 molecule more electrophilic by polarizing it to give an $FeBr_4^-Br^+$ species that reacts as if it were Br^+ The polarized Br_2 molecule then reacts with the nucleophilic benzene ring to yield a nonaromatic carbocation intermediate that is doubly allylic and has three resonance forms.



Another difference between alkene addition and aromatic substitution occurs after the carbocation intermediate has formed. Instead of adding Br^- to give an addition product, the carbocation intermediate loses H^+ from the bromine-bearing carbon to give a substitution product. Note that this loss of H^+ is similar to what occurs in the second step of an E1 reaction. The net effect of reaction of Br_2 with benzene is the substitution of H^+ by Br^+ by the overall mechanism shown in **Figure-1**.

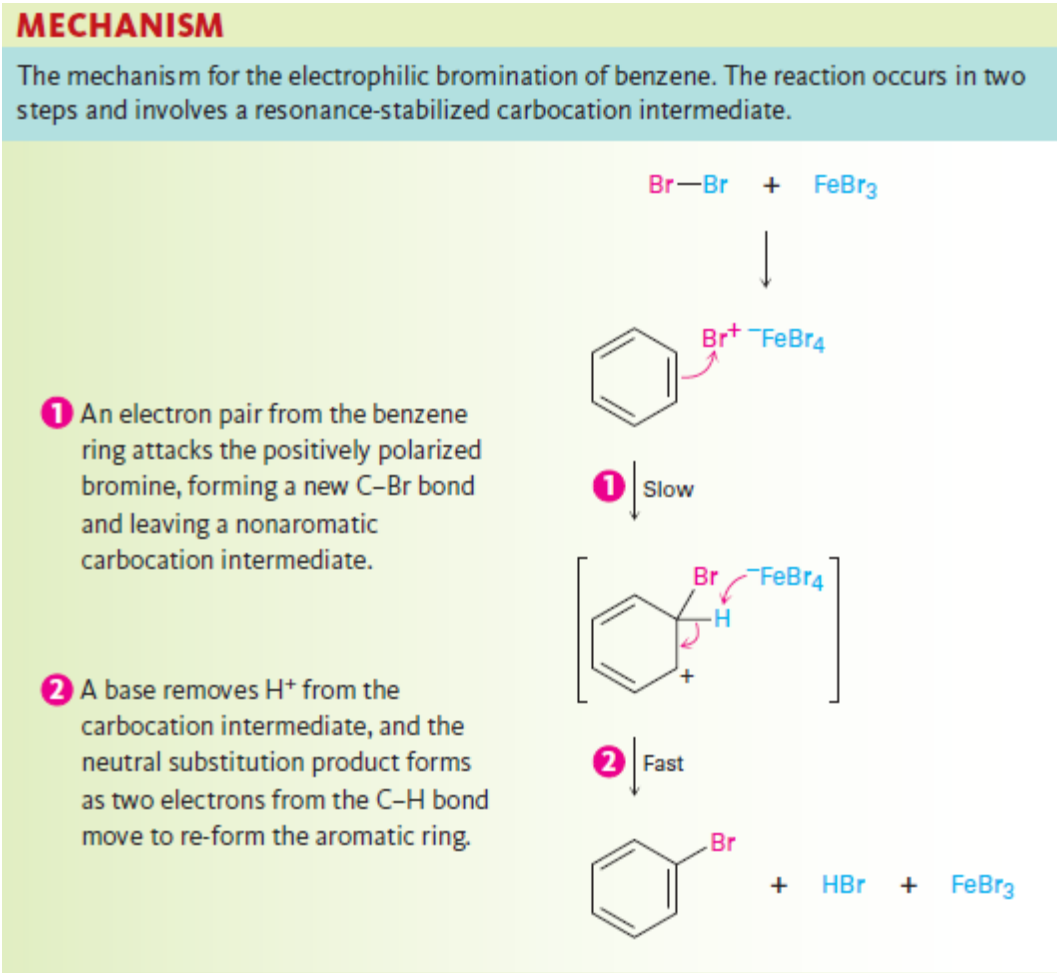


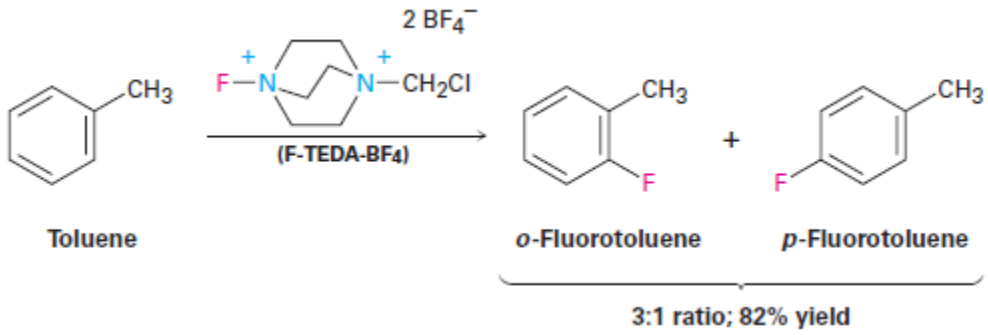
Figure-1 The mechanism for the electrophilic bromination of benzene.

Other Aromatic Substitutions

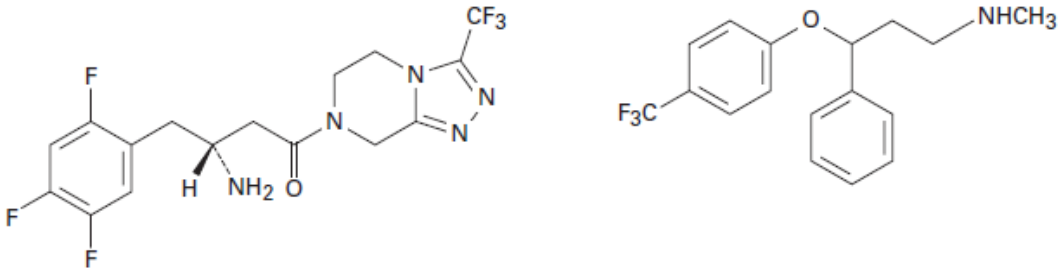
There are many other kinds of electrophilic aromatic substitutions besides bromination, and all occur by the same general mechanism. Let's look at some of these other reactions briefly.

Aromatic Halogenation

Chlorine, bromine, and iodine can be introduced into aromatic rings by electrophilic substitution reactions, but fluorine is too reactive and only poor yields of monofluoroaromatic products are obtained by direct fluorination. Instead, other sources of "F^+" are used, in which a fluorine atom is bonded to a positively charged nitrogen. One of the most common such reagents goes by the acronym F-TEDA-BF_4 and is sold under the name Selectfluor.



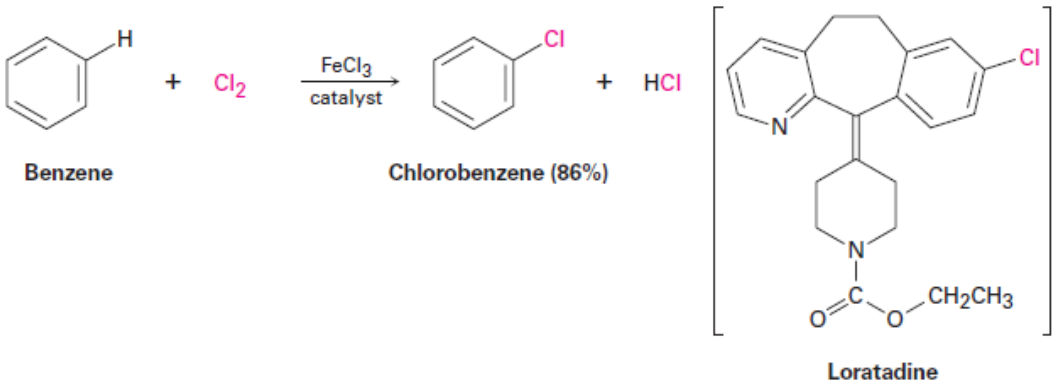
Many fluorine-containing aromatic compounds are particularly valuable as pharmaceutical agents. Approximately 80 pharmaceuticals now on the market, including 18 of the top 100 sellers, contain fluorine. Sitagliptin (Januvia), used to treat type 2 diabetes, and fluoxetine (Prozac), an antidepressant, are examples.



Sitagliptin (Januvia)

Fluoxetine (Prozac)

Aromatic rings react with Cl_2 in the presence of $FeCl_3$ catalyst to yield chlorobenzenes, just as they react with Br_2 and $FeBr_3$. This kind of reaction is used in the synthesis of numerous pharmaceutical agents, including the antiallergy medication loratadine, marketed as Claritin.

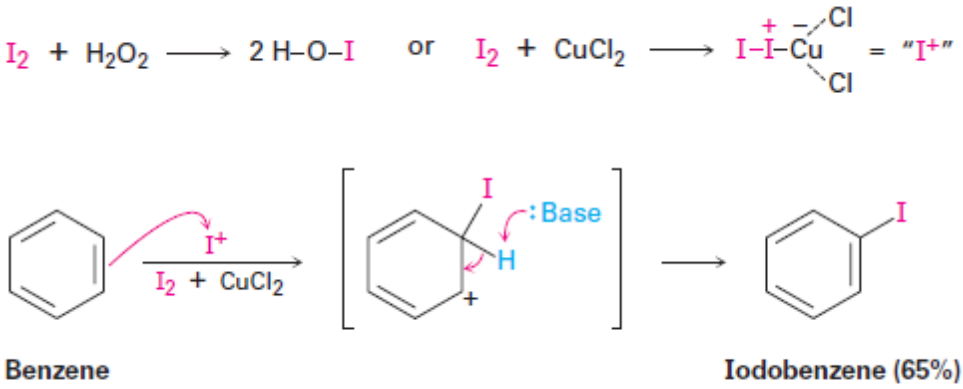


Benzene

Chlorobenzene (86%)

Loratadine

Iodine itself is unreactive toward aromatic rings, so an oxidizing agent such as hydrogen peroxide or a copper salt such as $CuCl_2$ must be added to the reaction. These substances accelerate the iodination reaction by oxidizing I_2 to a more powerful electrophilic species that reacts as if it were I^+. The aromatic ring then reacts with I^+ in the typical way, yielding a substitution product.



Benzene

Iodobenzene (65%)

Aromatic Nitration

Aromatic rings are nitrated by reaction with a mixture of concentrated nitric and sulfuric acids. The electrophile is the nitronium ion, NO_2+, which is formed from HNO_3 by protonation and loss of water. The nitronium ion reacts with benzene to yield a carbocation intermediate, and loss of H+ from this intermediate gives the neutral substitution product, nitrobenzene **(Figure-2)**.

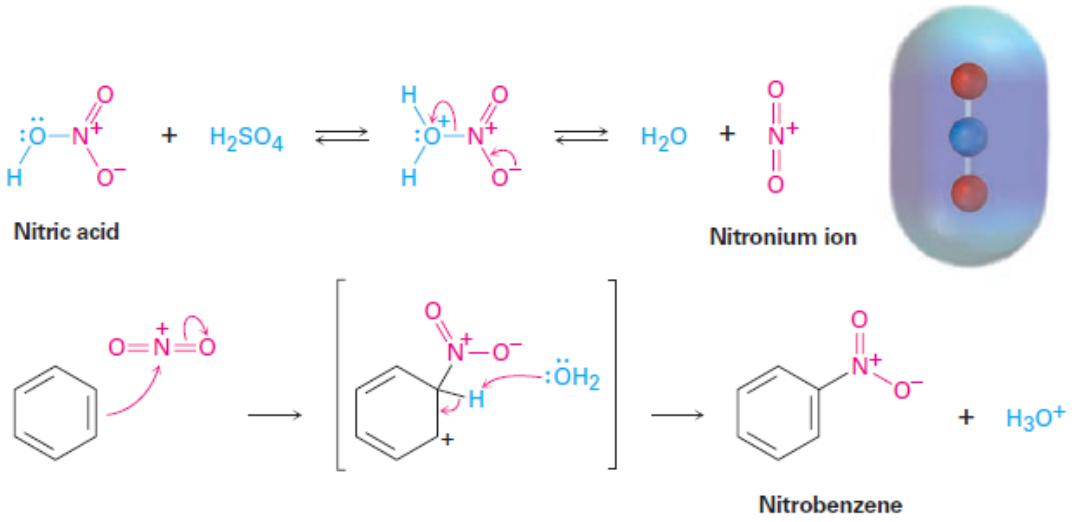
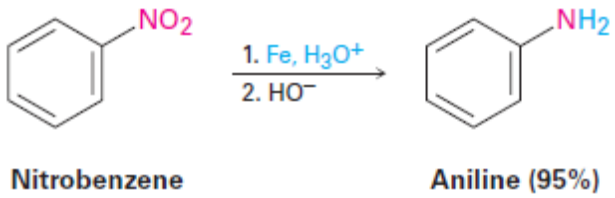


Figure-2 The mechanism for electrophilic nitration of an aromatic ring. An electrostatic potential map of the reactive electrophile NO_2 + shows that the nitrogen atom is most positive.

Electrophilic nitration of an aromatic ring does not occur in nature but is particularly important in the laboratory because the nitro-substituted productcan be reduced by reagents such as iron, tin, or $SnCl_2$ to yield an *arylamine*, $ArNH_2$. Attachment of an amino group to an aromatic ring by the two-step nitration/reduction sequence is a key part of the industrial synthesis of many dyes and pharmaceutical agents.



Aromatic Sulfonation

Aromatic rings can be sulfonated by reaction with fuming sulfuric acid, a mixture of H_2SO_4 and SO_3. The reactive electrophile is either HSO_3+ or neutral SO_3, depending on reaction conditions, and substitution occurs by the same two-step mechanism seen previously for bromination and nitration **(Figure-3)**. Note, however, that the *sulfonation* reaction is readily reversible; it can occur either forward or backward, depending on the reaction conditions. Sulfonation is favored in strong acid, but desulfonation is favored in hot, dilute aqueous acid.

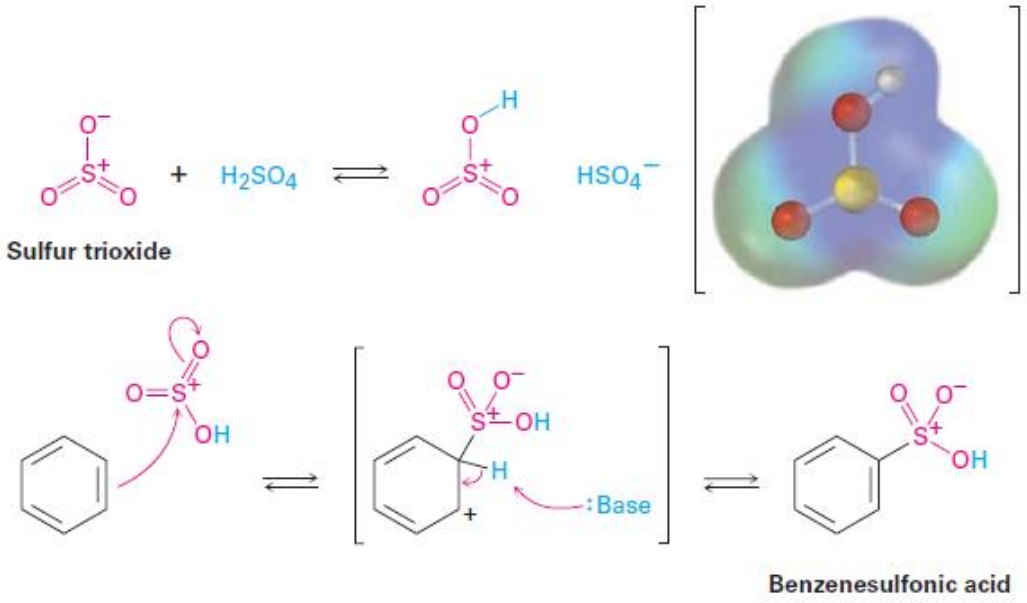
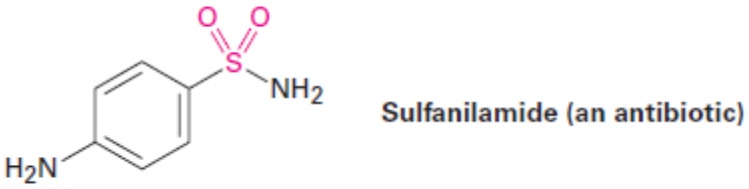


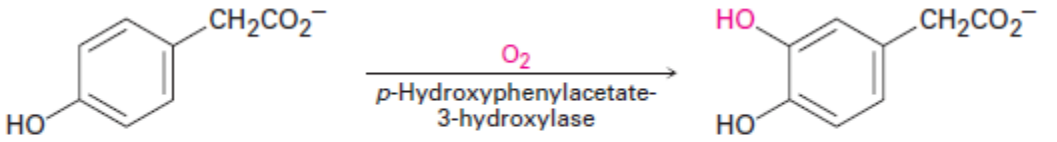
Figure-3 The mechanism for electrophilic sulfonation of an aromatic ring. An electrostatic potential map of the reactive electrophile $HOSO_2^+$ shows that sulfur and hydrogen are the most positive atoms.

Aromatic sulfonation does not occur naturally but is widely used in the preparation of dyes and pharmaceutical agents. For example, the sulfa drugs, such as sulfanilamide, were among the first clinically useful antibiotics. Although largely replaced today by more effective agents, sulfa drugs are still used in the treatment of meningitis and urinary tract infections. These drugs are prepared commercially by a process that involves aromatic sulfonation as its key step.



Aromatic Hydroxylation

Direct hydroxylation of an aromatic ring to yield a hydroxybenzene (a *phenol*) is difficult and rarely done in the laboratory but occurs much more frequently in biological pathways. An example is the hydroxylation of *p*-hydroxyphenylacetate to give 3,4-dihydroxyphenylacetate. The reaction is catalyzed by *p*-hydroxyphenylacetate-3-hydroxylase and requires molecular oxygen plus the coenzyme reduced flavin adenine dinucleotide, abbreviated $FADH_2$.



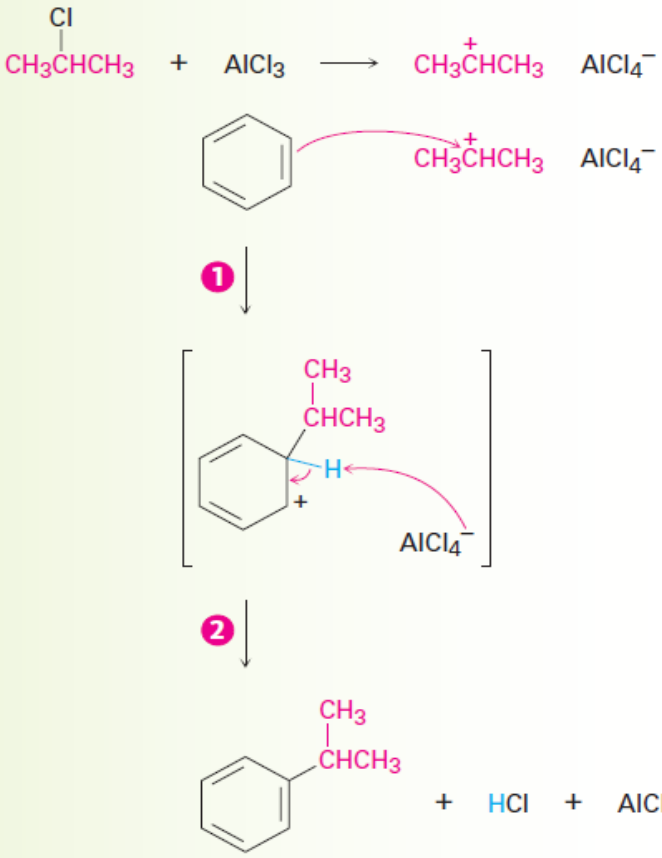
p-Hydroxyphenylacetate 3,4-Dihydroxyphenylacetate

Alkylation and Acylation of Aromatic Rings: The Friedel–Crafts Reaction

Among the most useful electrophilic aromatic substitution reactions in the laboratory is **alkylation**—the introduction of an alkyl group onto the benzene ring. Called the **Friedel–Crafts reaction** after its discoverers, the reaction is carried out by treating an aromatic compound with an alkyl chloride, RCl, in the presence of $AlCl_3$ to generate a carbocation electrophile, R+. Aluminum chloride catalyzes the reaction by helping the alkyl halide to dissociate in much the same way that $FeBr_3$ catalyzes aromatic brominations by polarizing Br_2. Loss of H+ then completes the reaction **(Figure-4)**.

MECHANISM

Mechanism for the Friedel–Crafts alkylation reaction of benzene with 2-chloropropane to yield isopropylbenzene (cumene). The electrophile is a carbocation, generated by $AlCl_3$-assisted dissociation of an alkyl halide.

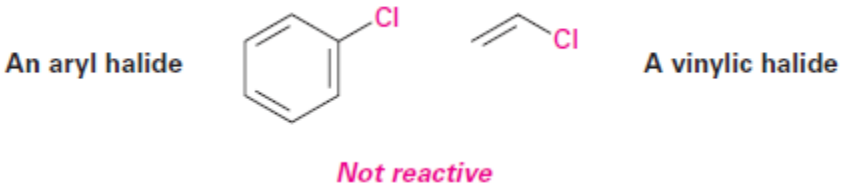


1 An electron pair from the aromatic ring attacks the carbocation, forming a C–C bond and yielding a new carbocation intermediate.

2 Loss of a proton then gives the neutral alkylated substitution product.

Figure-4 Mechanism for the Friedel–Crafts alkylation reaction of benzene

Despite its utility, the Friedel–Crafts alkylation has several limitations. For one thing, only *alkyl* halides can be used. Aromatic (aryl) halides and vinylic halides don't react because aryl and vinylic carbocations are too high in energy to form under Friedel–Crafts conditions.



Another limitation is that Friedel–Crafts reactions don't succeed on aromatic rings that are substituted either by a strongly electron-withdrawing group such as carbonyl (C=O) or by a basic amino group that can be protonated. We'll see in the next section that the presence of a substituent group already on a ring can have a dramatic effect on that ring's reactivity toward further electrophilic substitution. Rings that contain any of the substituents listed in **Figure-5** do not undergo Friedel–Crafts alkylation.

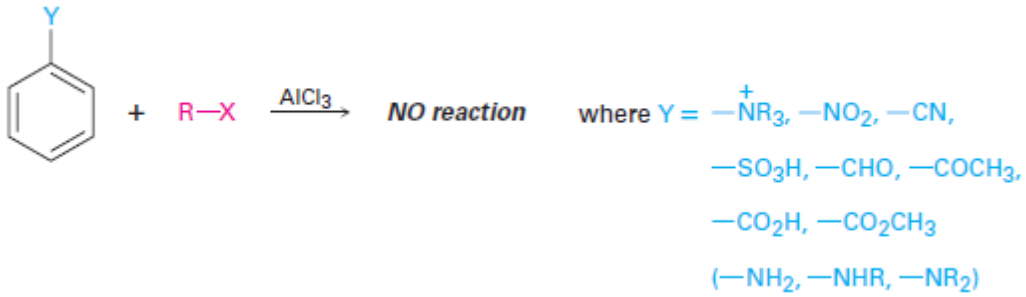
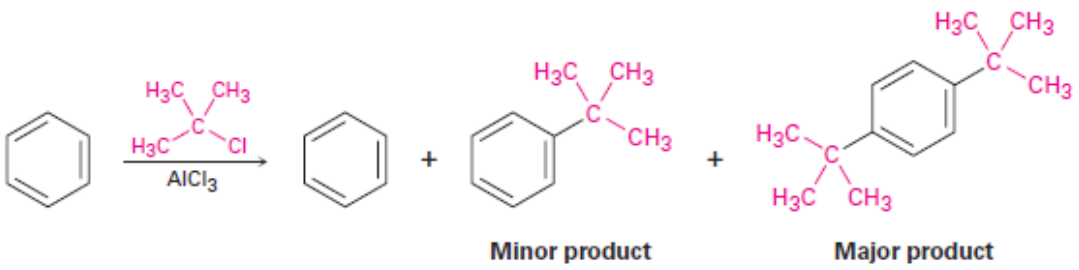


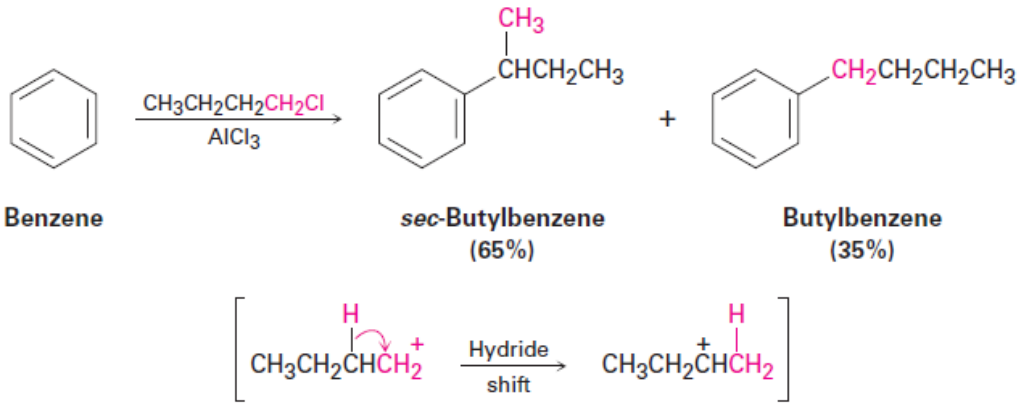
Figure-5 Limitations on the aromatic substrate in Friedel–Crafts reactions. No reaction occurs if the substrate has either an electron-withdrawing substituent or a basic amino group.

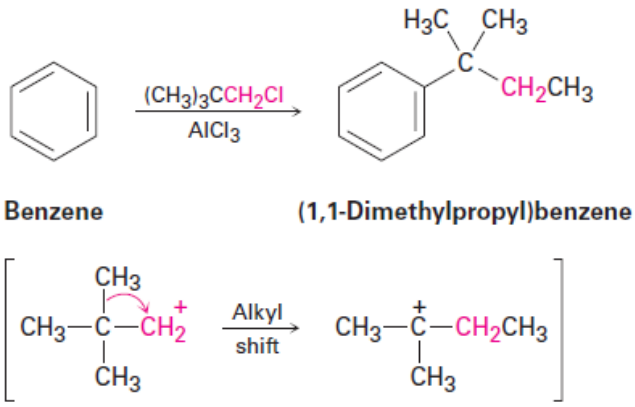
A third limitation to the Friedel–Crafts alkylation is that it's often difficult to stop the reaction after a single substitution. Once the first alkyl group is on the ring, a second substitution reaction is facilitated for reasons we'll discuss in the next section. Thus, we often observe *polyalkylation.* Reaction of benzene with 1 mol equivalent of 2-chloro-2-methylpropane, for example, yields *p*-di-*tert*-butylbenzene as the major product, along with small amounts of *tert*butylbenzene and unreacted benzene. A high yield of monoalkylation product is obtained only when a large excess of benzene is used.



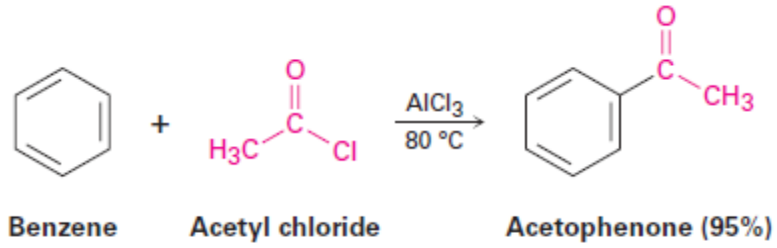
A final limitation to the Friedel–Crafts reaction is that a skeletal rearrangement of the alkyl carbocation electrophile sometimes occurs during reaction, particularly when a primary alkyl halide is used. Treatment of benzene with 1-chlorobutane at 0 °C, for instance, gives an approximately 2;1 ratio of rearranged (*sec*-butyl) to unrearranged (butyl) products.

The carbocation rearrangements that accompany Friedel–Crafts reactions are like those that accompany electrophilic additions to alkenes and occur either by hydride shift or alkyl shift. For example, the relatively unstable primary butyl carbocation produced by reaction of 1-chlorobutane with $AlCl_3$ rearranges to the more stable secondary butyl carbocation by the shift of a hydrogen atom and its electron pair (a hydride ion, H**:**-) from C2 to C1. Similarly, alkylation of benzene with 1-chloro-2,2-dimethylpropane yields (1,1-dimethylpropyl)benzene. The initially formed primary carbocation rearranges to a tertiary carbocation by shift of a methyl group and its electron pair from C2 to C1.





Just as an aromatic ring is alkylated by reaction with an alkyl chloride, it is **acylated** by reaction with a carboxylic acid chloride, RCOCl, in the presence of $AlCl_3$. That is, an **acyl group** (-COR; pronounced **a**-sil) is substituted onto the aromatic ring. For example, reaction of benzene with acetyl chloride yields the ketone acetophenone.



The mechanism of Friedel–Crafts acylation is similar to that of Friedel–Crafts alkylation, and the same limitations on the aromatic substrate noted previously in Figure-8 for alkylation also apply to acylation. The reactive electrophile is a resonance-stabilized acyl cation, generated by reaction between the acyl chloride and $AlCl_3$ **(Figure-6)**. As the resonance structures in the figure indicate, an acyl cation is stabilized by interaction of the vacant orbital on carbon with lone-pair electrons on the neighboring oxygen. Because of this stabilization, no carbocation rearrangement occurs during acylation.

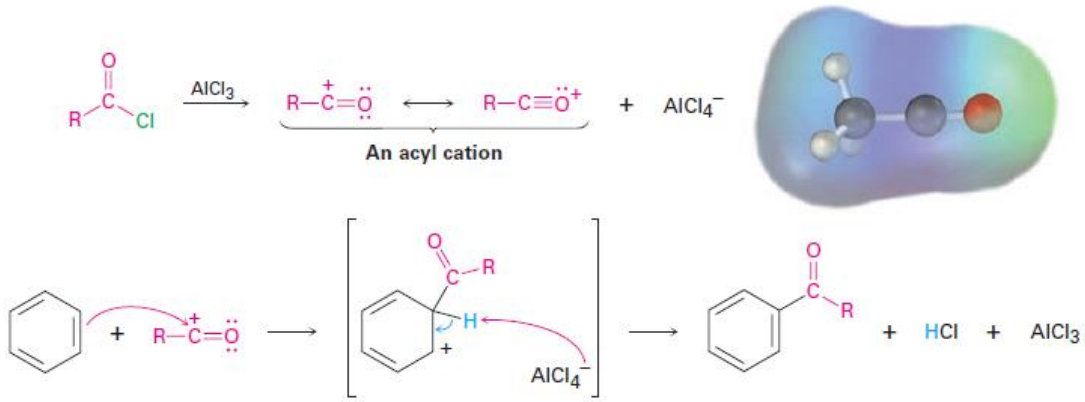


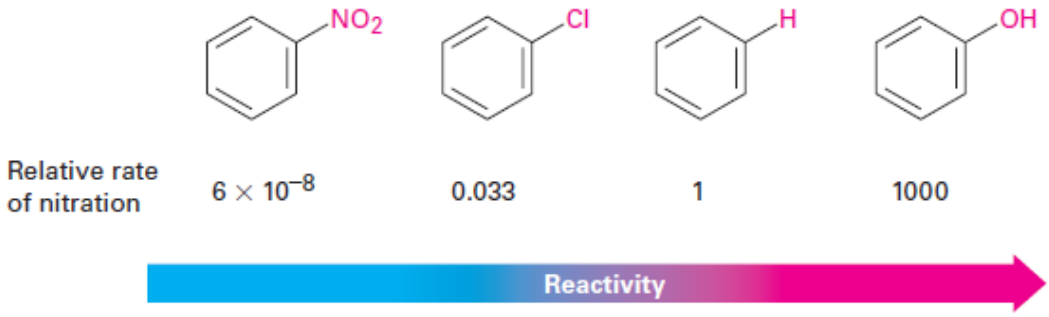
Figure -6 Mechanism of the Friedel–Crafts acylation reaction. The electrophile is a resonance-stabilized acyl cation, whose electrostatic potential map indicates that carbon is the most positive atom.

Unlike the multiple substitutions that often occur in Friedel–Crafts alkylations, acylations never occur more than once on a ring because the product acylbenzene is less reactive than the nonacylated starting material.

Substituent Effects in Electrophilic Substitutions

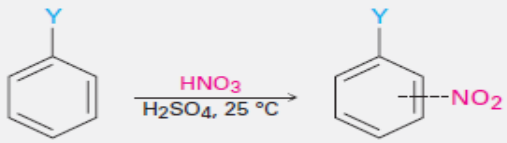
Only one product can form when an electrophilic substitution occurs on benzene, but what would happen if we were to carry out a reaction on an aromatic ring that already has a substituent? The initial presence of a substituent on the ring has two effects.

Substituents affect the *reactivity* of the aromatic ring. Some substituents activate the ring, making it more reactive than benzene, and some deactivate the ring, making it less reactive than benzene. In aromatic nitration, for instance, an -OH substituent makes the ring 1000 times more reactive than benzene, while an $-NO_2$ substituent makes the ring more than 10 million times less reactive.



Substituents affect the *orientation* of the reaction. The three possible disubstituted products—ortho, meta, and para—are usually not formed in equal amounts. Instead, the nature of the substituent initially present on the benzene ring determines the position of the second substitution. An -OH group directs substitution toward the ortho and para positions, for instance, while a carbonyl group such as -CHO directs substitution primarily toward the meta position. **Table-1** lists experimental results for the nitration of some substituted benzenes.

Table-1 Orientation of Nitration in Substituted Benzenes



	Product (%)				Product (%)		
	Ortho	Meta	Para		Ortho	Meta	Para
Meta-directing deactivators				**Ortho- and para-directing deactivators**			
$-\overset{+}{N}(CH_3)_3$	2	87	11	−F	13	1	86
$-NO_2$	7	91	2	−Cl	35	1	64
$-CO_2H$	22	76	2	−Br	43	1	56
−CN	17	81	2	−I	45	1	54
$-CO_2CH_3$	28	66	6	**Ortho- and para-directing activators**			
$-COCH_3$	26	72	2	$-CH_3$	63	3	34
−CHO	19	72	9	−OH	50	0	50
				$-NHCOCH_3$	19	2	79

Substituents can be classified into three groups, as shown in **Figure-7**: *ortho- and para-directing activators, ortho- and para-directing deactivators,*and *meta-directing deactivators.* There are no meta-directing activators. Notice how the directing effect of a group correlates with its reactivity. All metadirecting groups are strongly deactivating, and most ortho- and para-directing groups are activating. The halogens are unique in being ortho- and paradirecting but weakly deactivating.

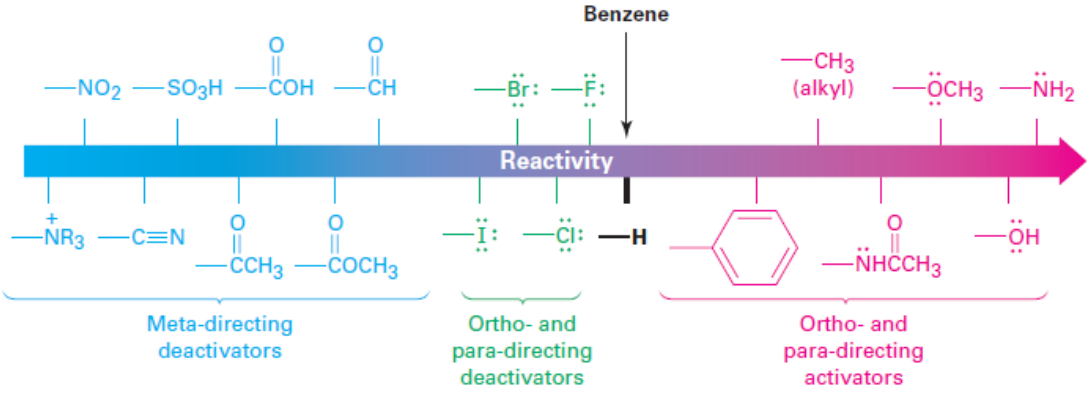
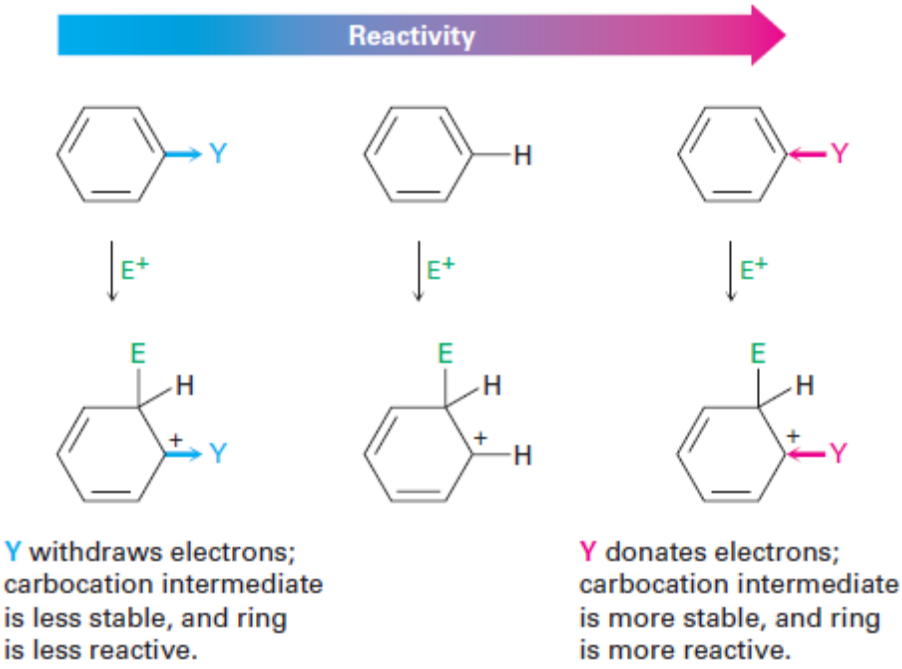


Figure-7 Classification of substituent effects in electrophilic aromatic substitution. All activating groups are ortho- and para-directing, and all deactivating groups other than halogen are meta-directing. The halogens are unique in being deactivating but ortho- and para-directing.

Activating and Deactivating Effects

What makes a group either activating or deactivating? The common characteristic of all activating groups is that they donate electrons to the ring, thereby making the ring more electron-rich, stabilizing the carbocation intermediate, and lowering the activation energy for its formation. Conversely, the common characteristic of all deactivating groups is that they withdraw electrons from the ring, thereby making the ring more electron-poor, destabilizing the carbocation intermediate, and raising the activation energy for its formation.



Compare the electrostatic potential maps of benzaldehyde (deactivated), chlorobenzene (weakly deactivated), and phenol (activated) with that of benzene.
As shown in **Figure-8**, the ring is more positive (yellow-green) when an electron-withdrawing group such as -CHO or -Cl is present and more negative (red) when an electron-donating group such as -OH is present.

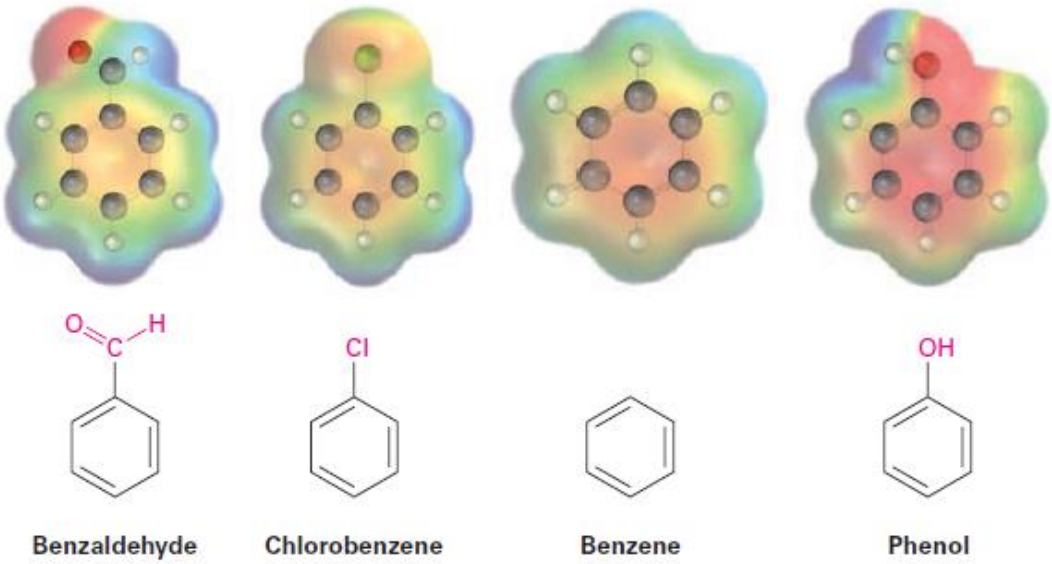
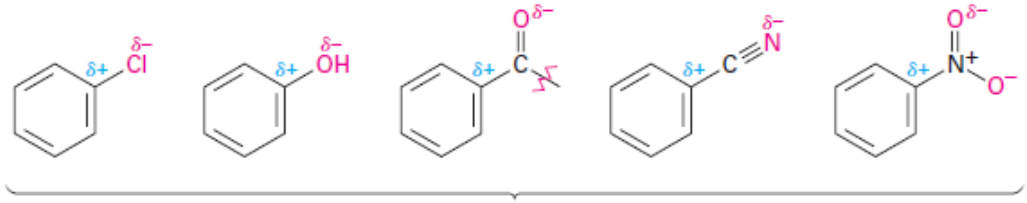
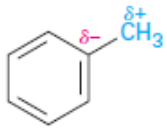


Figure-8 Electrostatic potential maps of benzene and several substituted benzenes show that an electron-withdrawing group (-CHO or -Cl) makes the ring more electron-poor,while an electron-donating group (-OH) makes the ring more electron-rich.

The withdrawal or donation of electrons by a substituent group is controlled by an interplay of *inductive effects* and *resonance effects.* As we saw, an **inductive effect** is the withdrawal or donation of electrons through a *s* bond due to electronegativity. Halogens, hydroxyl groups, carbonyl groups, cyano groups, and nitro groups inductively withdraw electrons through the *s* bond linking the substituent to a benzene ring. This effect is most pronounced in halobenzenes and phenols, in which the electronegative atom is directly attached to the ring, but is also significant in carbonyl compounds, nitriles, and nitro compounds, in which the electronegative atom is farther removed. Alkyl groups, on the other hand, inductively donate electrons. This is the same hyperconjugative donating effect that causes alkyl substituents to stabilize alkenes and carbocations.



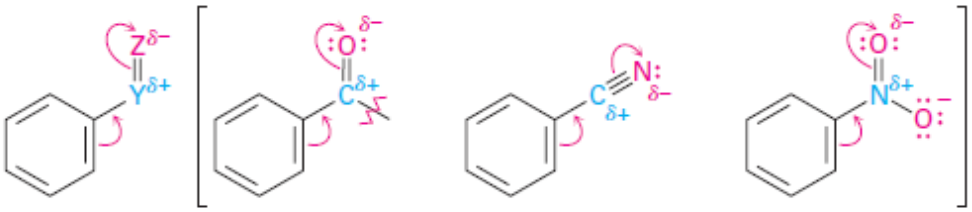
Inductive electron withdrawal



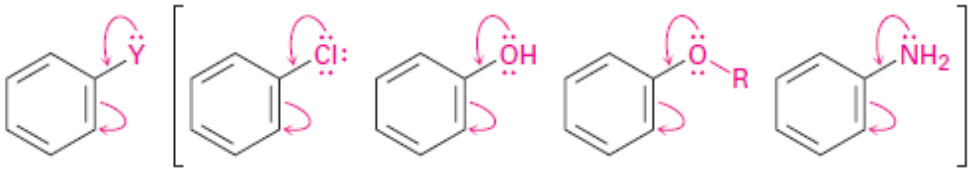
Inductive electron donation

A **resonance effect** is the withdrawal or donation of electrons through a *Π* bond due to the overlap of a *p* orbital on the substituent with a *p* orbital on the aromatic ring. Carbonyl, cyano, and nitro substituents, for example, withdraw electrons from the aromatic ring by resonance. The *Π* electrons flow from the ring to the substituent, leaving a positive charge in the ring. Note that substituents with an electron-withdrawing resonance effect have the general structure –Y=Z, where the Z atom is more electronegative than Y.

Conversely, halogen, hydroxyl, alkoxyl (-OR), and amino substituents donate electrons to the aromatic ring by resonance. Lone-pair electrons flow from the substituents to the ring, placing a negative charge on the ring. Substituents with an electron-donating resonance effect have the general structure -Y:,where the Y atom has a lone pair of electrons available for donation to the ring.



Resonance electron-withdrawing groups



Resonance electron-donating groups

One further point: inductive effects and resonance effects don't necessarily act in the same direction. Halogen, hydroxyl, alkoxyl, and amino substituents, for instance, have electron-withdrawing inductive effects because of the electronegativity of the -X, -O, or -N atom bonded to the aromatic ring but have electron-donating resonance effects because of the lone-pair electrons on those -X, -O, or -N atoms. When the two effects act in opposite directions, the stronger one dominates. Thus, hydroxyl, alkoxyl, and amino substituents are activators because their stronger electron-donating resonance effect outweighs their weaker electron-withdrawing inductive effect. Halogens, however, are deactivators because their stronger electronwithdrawing inductive effect outweighs their weaker electron-donating resonance
effect.

Ortho- and Para-Directing Activators: Alkyl Groups

Inductive and resonance effects account not only for reactivity but also for the orientation of electrophilic aromatic substitutions. Take alkyl groups, for instance, which have an electron-donating inductive effect and are ortho and para directors. The results of toluene nitration are shown in **Figure-9**.

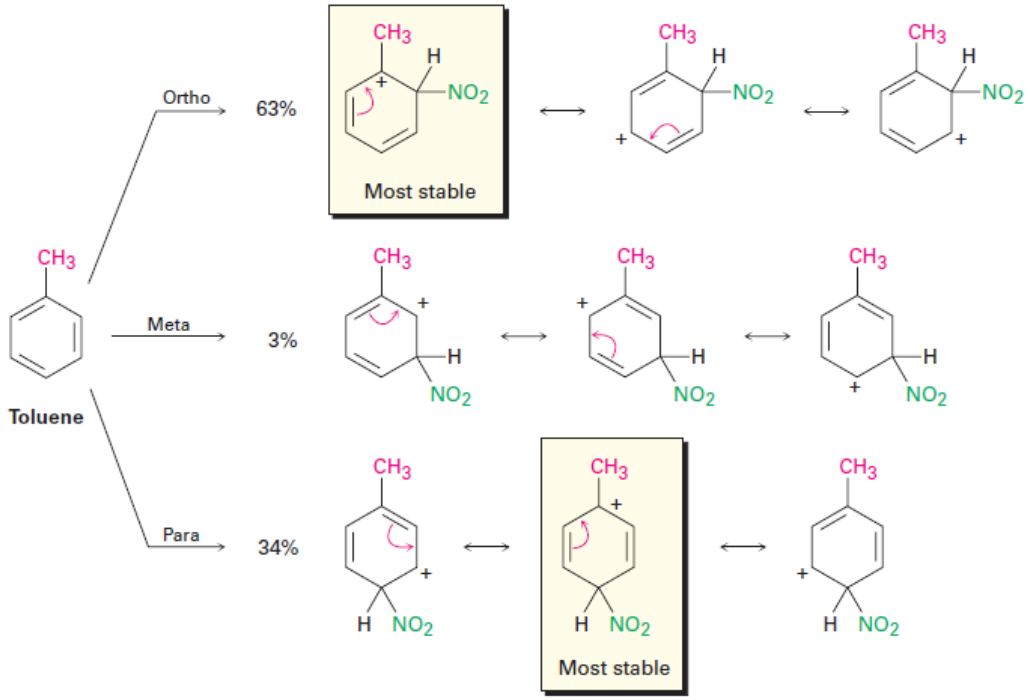


Figure-9 Carbocation intermediates in the nitration of toluene. Ortho and para intermediates are more stable than the meta intermediate because the positive charge is on a tertiary carbon rather than a secondary carbon.

Nitration of toluene might occur either ortho, meta, or para to the methyl group, giving the three carbocation intermediates shown in Figure-13. Although all three intermediates are resonance-stabilized, the ortho and para intermediates are more stabilized than the meta intermediate. For both the ortho and para reactions, but not for the meta reaction, a resonance form places the positive charge directly on the methyl-substituted carbon, where it is in a tertiary position and can be stabilized by the electron-donating inductive effect of the methyl group. The ortho and para intermediates are thus lower in energy than the meta intermediate and form faster.

Ortho- and Para-Directing Activators: OH and NH_2

Hydroxyl, alkoxyl, and amino groups are also ortho–para activators, but for a different reason than for alkyl groups. As described earlier in this section, hydroxyl, alkoxyl, and amino groups have a strong, electron-donating resonance effect that outweighs a weaker electron-withdrawing inductive effect. When phenol is nitrated, for instance, reaction can occur either ortho, meta, or para to the -OH group, giving the carbocation intermediates shown in **Figure-10**. The ortho and para intermediates are more stable than the meta intermediate because they have more resonance forms, including one particularly favorable form that allows the positive charge to be stabilized by electron donation from the substituent oxygen atom. The intermediate from the meta reaction has no such stabilization.

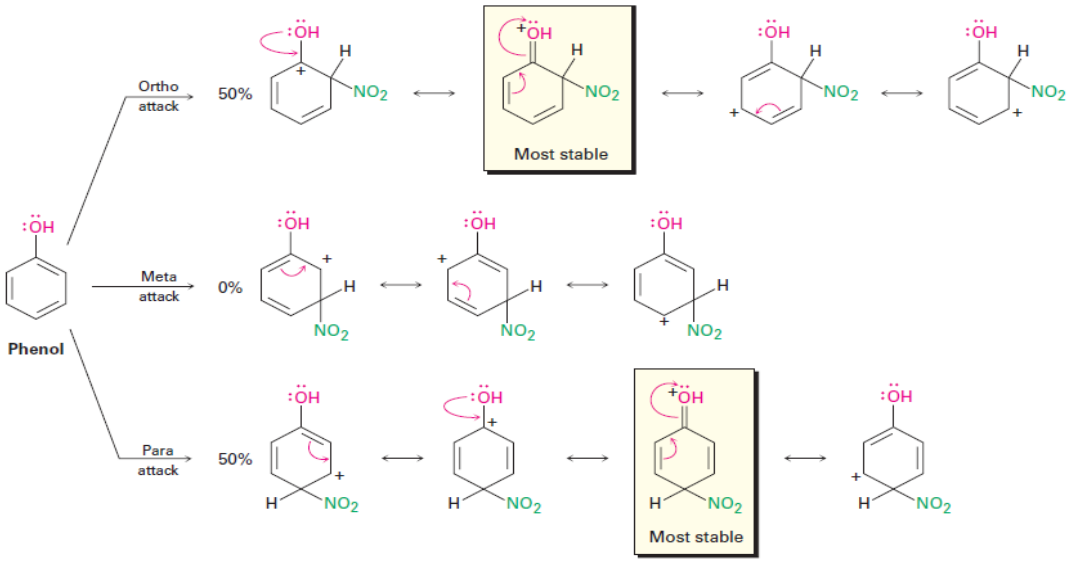


Figure-10 Carbocation intermediates in the nitration of phenol. The ortho and para intermediates are more stable than the meta intermediate because they have more resonance forms, including one particularly favorable form that involves electron donation from the oxygen atom.

Ortho- and Para-Directing Deactivators: Halogens

Halogens are deactivating because their stronger electron-withdrawing inductive effect outweighs their weaker electron-donating resonance effect. Although weak, that electron-donating resonance effect is nevertheless felt only at the ortho and para positions and not at the meta position **(Figure-11)**.Thus, a halogen substituent can stabilize the positive charge of the carbocation intermediates from ortho and para reaction in the same way that hydroxyl and amino substituents can. The meta intermediate, however, has no such stabilization and is therefore formed more slowly.

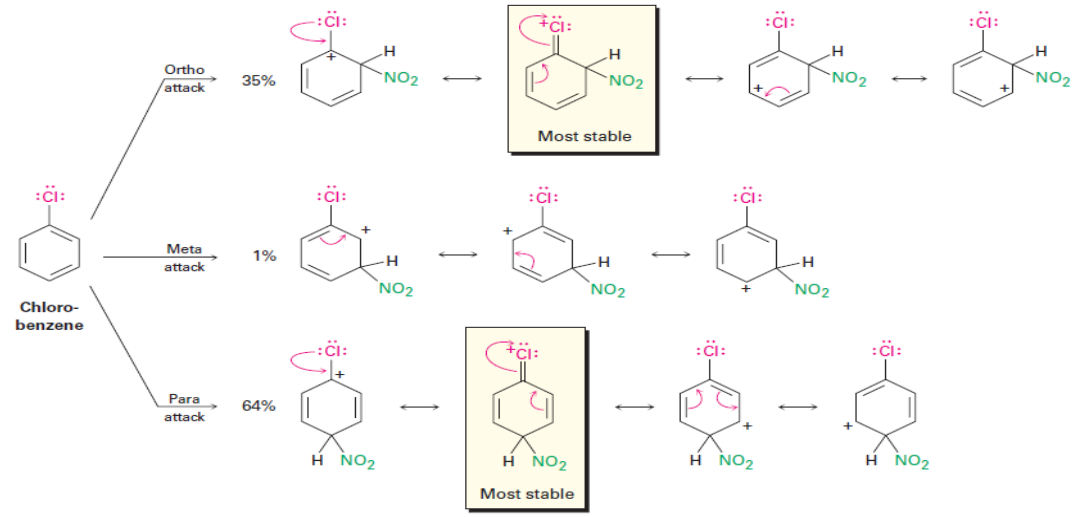


Figure-11 Carbocation intermediates in the nitration of chlorobenzene. The ortho and para intermediates are more stable than the meta intermediate because of electron donation of the halogen lone-pair electrons.

Note again that halogens, hydroxyl, alkoxyl, and amino groups all withdraw electrons inductively but donate electrons by resonance. Halogens have a stronger electron-withdrawing inductive effect but a weaker electrondonating resonance effect and are thus deactivators. Hydroxyl, alkoxyl, and amino groups have a weaker electron-withdrawing inductive effect but a stronger electron-donating resonance effect and are thus activators. All are ortho and para directors, however, because of the lone pair of electrons on the atom bonded to the aromatic ring.

Meta-Directing Deactivators

The influence of meta-directing substituents can be explained using the same kinds of arguments used for ortho and para directors. Look at the nitration of benzaldehyde, for instance **(Figure-12)**. Of the three possible carbocation intermediates, the meta intermediate has three favorable resonance forms, whereas the ortho and para intermediates have only two. In both ortho and para intermediates, the third resonance form is unfavorable because it places the positive charge directly on the carbon that bears the aldehyde group, where it is disfavored by a repulsive interaction with the positively polarized carbon atom of the C=O group. Hence, the meta intermediate is more favored and is formed faster than the ortho and para intermediates.

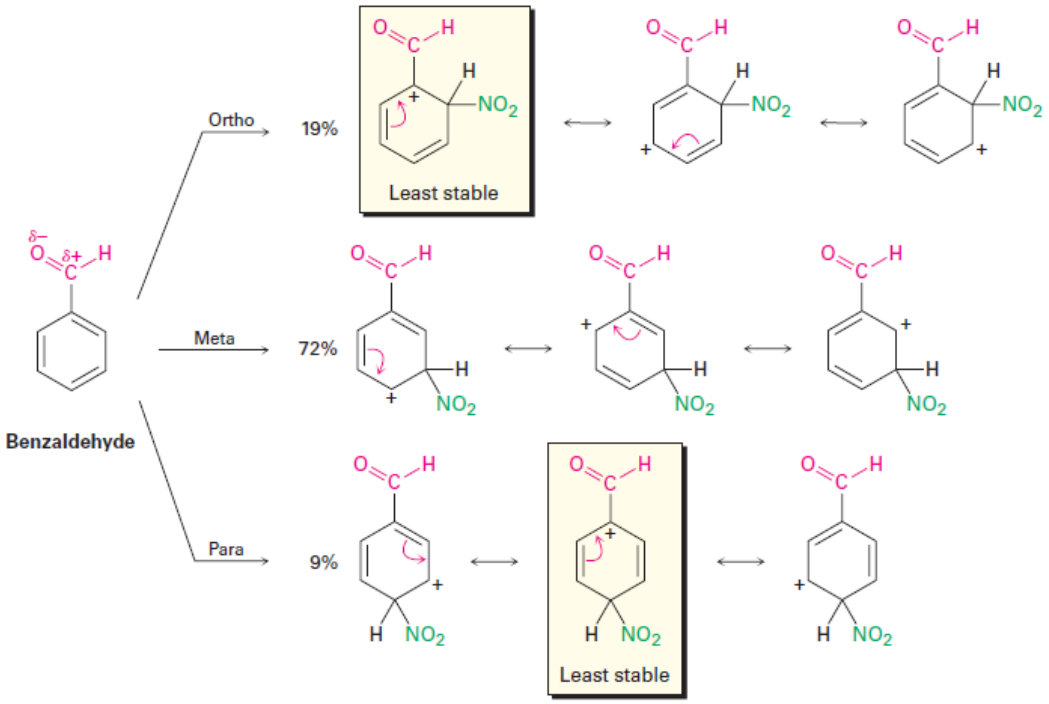


Figure-12 Carbocation intermediates in the nitration of benzaldehyde. The ortho and para intermediates are less stable than the meta intermediate. The meta intermediate is more favorable than ortho and para intermediates because it has three favorable resonance forms rather than two.

In general, any substituent that has a positively polarized atom (δ+) directly attached to the ring will make one of the resonance forms of the ortho and para intermediates unfavorable and will thus act as a meta director.

A Summary of Substituent Effects in Electrophilic Aromatic Substitution

A summary of the activating and directing effects of substituents in electrophilic aromatic substitution is shown in **Table-2**.

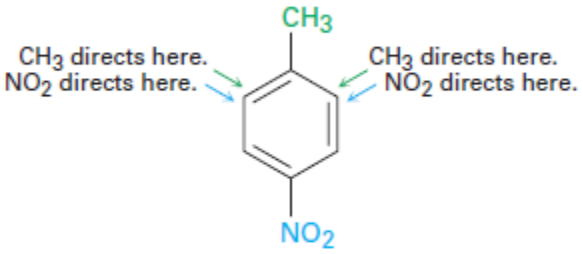
Table-2 Substituent Effects in Electrophilic Aromatic Substitution

Substituent	Reactivity	Orienting effect	Inductive effect	Resonance effect
$-CH_3$	Activating	Ortho, para	Weak donating	—
$-OH$, $-NH_2$	Activating	Ortho, para	Weak withdrawing	Strong donating
$-F$, $-Cl$ $-Br$, $-I$	Deactivating	Ortho, para	Strong withdrawing	Weak donating
$-NO_2$, $-CN$, $-CHO$, $-CO_2R$ $-COR$, $-CO_2H$	Deactivating	Meta	Strong withdrawing	Strong withdrawing

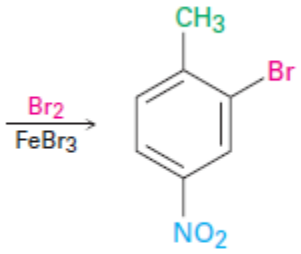
Trisubstituted Benzenes: Additivity of Effects

Electrophilic substitution of a disubstituted benzene ring is governed by the same resonance and inductive effects that influence monosubstituted rings. The only difference is that it's necessary to consider the additive effects of two different groups. In practice, this isn't as difficult as it sounds; three rules are usually sufficient.

- If the directing effects of the two groups reinforce each other, the situation is straightforward. In *p*-nitrotoluene, for example, both the methyl and the nitro group direct further substitution to the same position (ortho to the methyl = meta to the nitro). A single product is thus formed on electrophilic substitution.

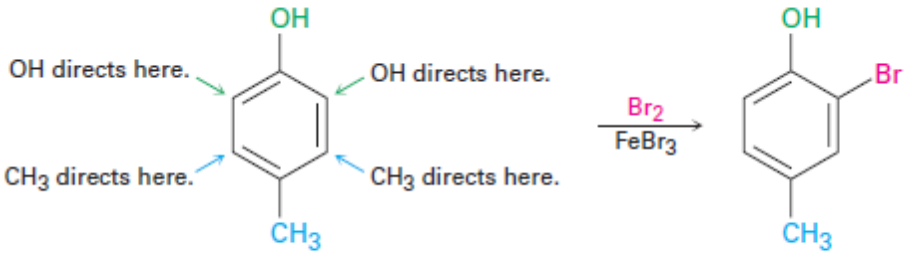


p-Nitrotoluene



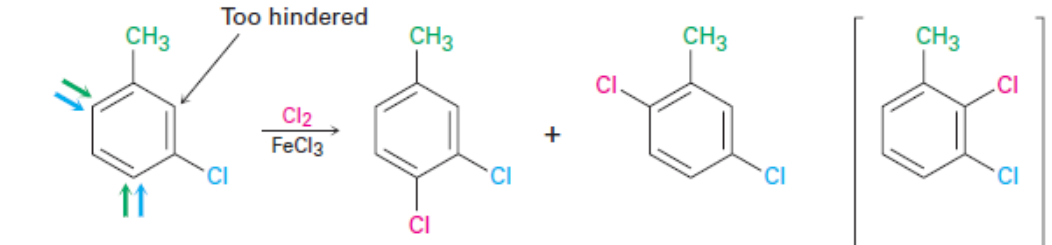
2-Bromo-4-nitrotoluene

- If the directing effects of the two groups oppose each other, the more powerful activating group has the dominant influence, but mixtures of products are often formed. For example, bromination of *p*-methylphenol yields primarily 2-bromo-4-methylphenol because -OH is a more powerful activator than $-CH_3$.



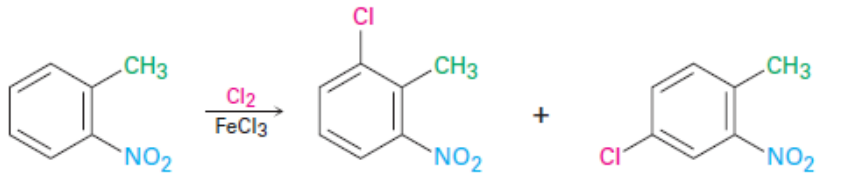
p-Methylphenol 2-Bromo-4-methylphenol

- Further substitution rarely occurs between the two groups in a metadisubstituted compound because this site is too hindered. Aromatic rings with three adjacent substituents must therefore be prepared by some other route, such as by substitution of an ortho-disubstituted compound.



m-Chlorotoluene 3,4-Dichlorotoluene 2,5-Dichlorotoluene *Not* formed

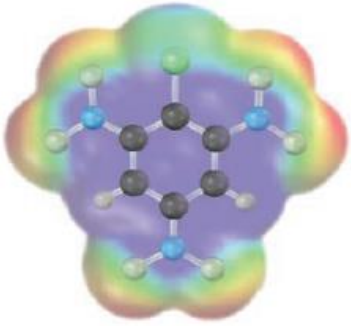
But:

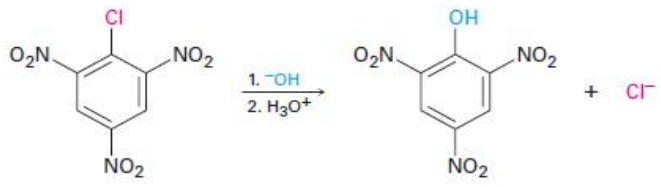


o-Nitrotoluene 2-Chloro-6-nitrotoluene 4-Chloro-2-nitrotoluene

Nucleophilic Aromatic Substitution

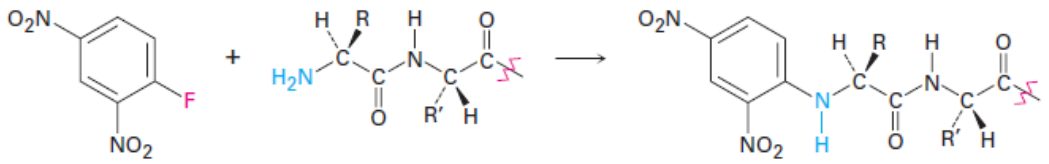
Although aromatic substitution reactions usually occur by an *electrophilic* mechanism, aryl halides that have electron-withdrawing substituents can also undergo a *nucleophilic* substitution reaction. For example, 2,4,6-trinitrochlorobenzene reacts with aqueous NaOH at room temperature to give 2,4,6-trinitrophenol. Here, the nucleophile OH- substitutes for Cl-.



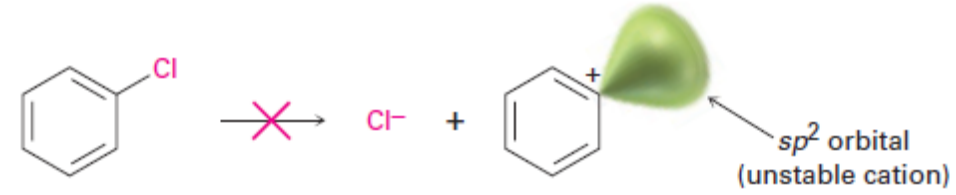


2,4,6-Trinitrochlorobenzene 2,4,6-Trinitrophenol (100%)

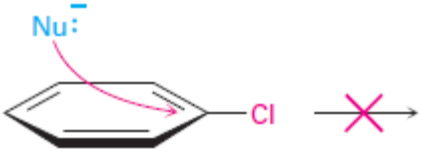
Nucleophilic aromatic substitution is much less common than electrophilic substitution but nevertheless does have certain uses. One such use is the reaction of proteins with 2,4-dinitrofluorobenzene, known as *Sanger's reagent*, to attach a "label" to the terminal NH_2 group of the amino acid at one end of the protein chain.



Although the reaction appears superficially similar to the S_N1 and S_N2 nucleophilic substitutions of alkyl halides, it must be different because aryl halides are inert to both S_N1 and S_N2 conditions. S_N1 reactions don't occur with aryl halides because dissociation of the halide is energetically unfavorable, due to the instability of the potential aryl cation product. S_N2 reactions don't occur with aryl halides because the halo-substituted carbon of the aromatic ring is sterically shielded from a backside approach. For a nucleophile to react with an aryl halide, it would have to approach directly through the aromatic ring and invert the stereochemistry of the aromatic ring carbon—a geometric impossibility.



Dissociation reaction does not occur because the aryl cation is unstable; therefore, no S_N1 reaction.



Backside displacement is sterically blocked; therefore, no S_N2 reaction.

Nucleophilic substitutions on an aromatic ring proceed by the mechanism shown in **Figure-13**. The nucleophile first adds to the electrondeficient aryl halide, forming a resonance-stabilized, negatively charged intermediate called a *Meisenheimer complex* after its discoverer. Halide ion is then eliminated.

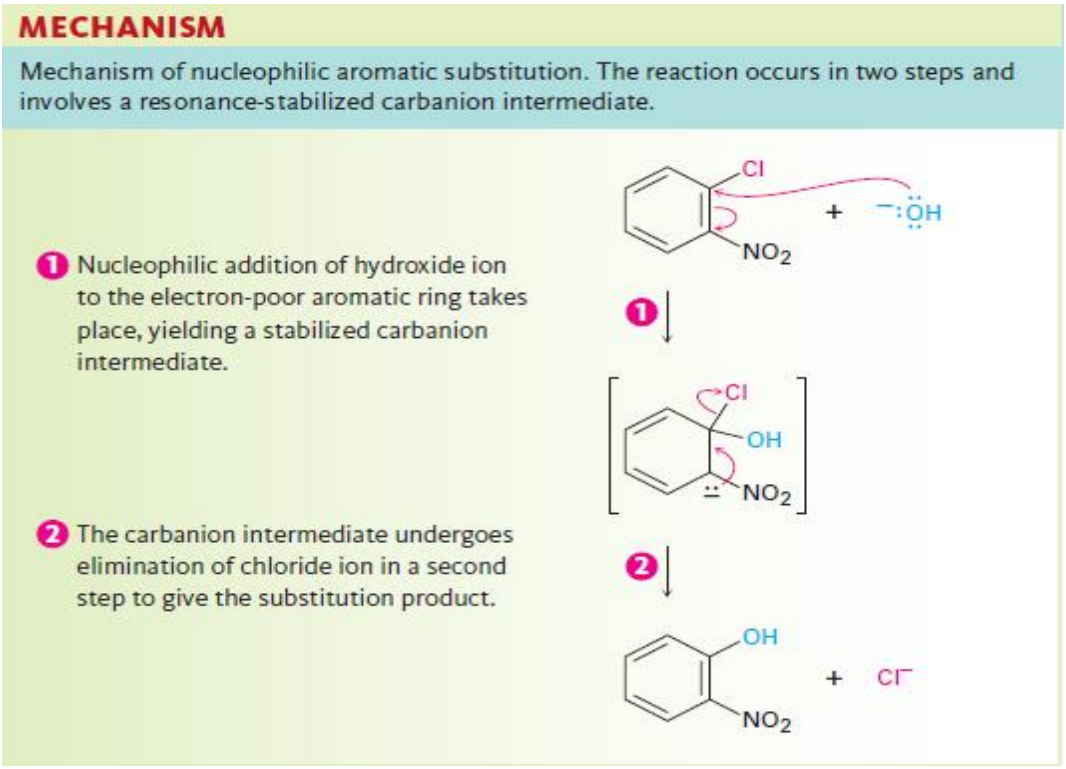


Figure-13 Mechanism of nucleophilic aromatic substitution.

Nucleophilic aromatic substitution occurs only if the aromatic ring has an electron-withdrawing substituent in a position ortho or para to the leaving group to stabilize the anion intermediate through resonance **(Fig ure-14)**. A meta substituent offers no such resonance stabilization. Thus, *p*-chloronitrobenzene and *o*-chloronitrobenzene react with hydroxide ion at 130 °C to yield substitution products, but *m*-chloronitrobenzene is inert to OH-.

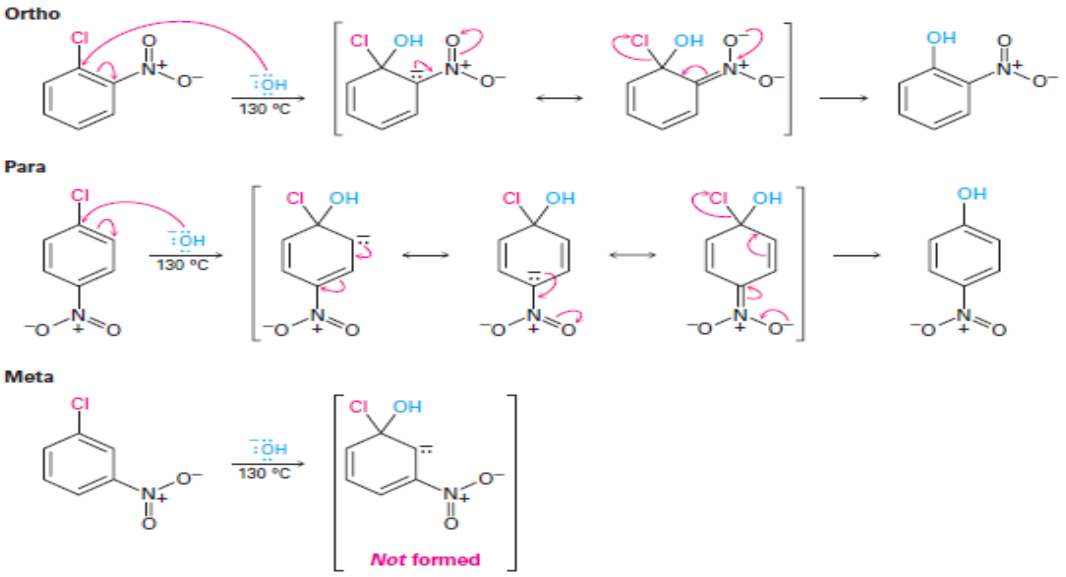
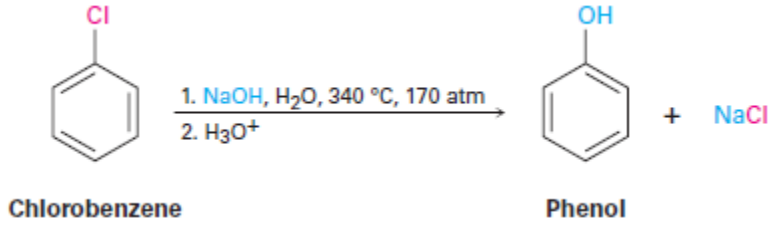


Figure-14 Nucleophilic aromatic substitution on nitrochlorobenzenes. Only in the ortho and para intermediates is the negative charge stabilized by a resonance interaction with the nitro group, so only the ortho and para isomers undergo reaction.

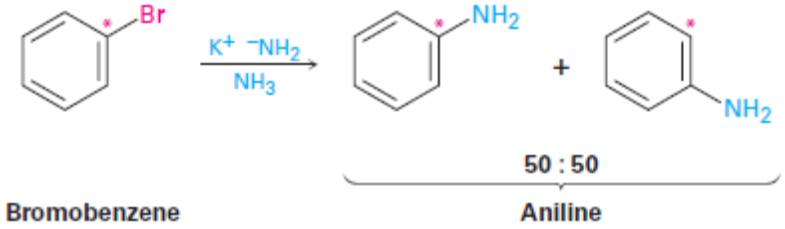
Note the differences between electrophilic and nucleophilic aromatic substitutions. Electrophilic substitutions are favored by electron-*donating* substituents, which stabilize a carbocation intermediate, while nucleophilic substitutions are favored by electron-*withdrawing* substituents, which stabilize a carbanion intermediate. Thus, the electron-withdrawing groups that *deactivate* rings for electrophilic substitution (nitro, carbonyl, cyano, and so forth) *activate* them for nucleophilic substitution. What's more, these groups are meta directors in electrophilic substitution but are ortho–para directors in nucleophilic substitution. And finally, electrophilic substitutions replace hydrogen on the ring, while nucleophilic substitutions replace a leaving group, usually halide ion.

Benzyne

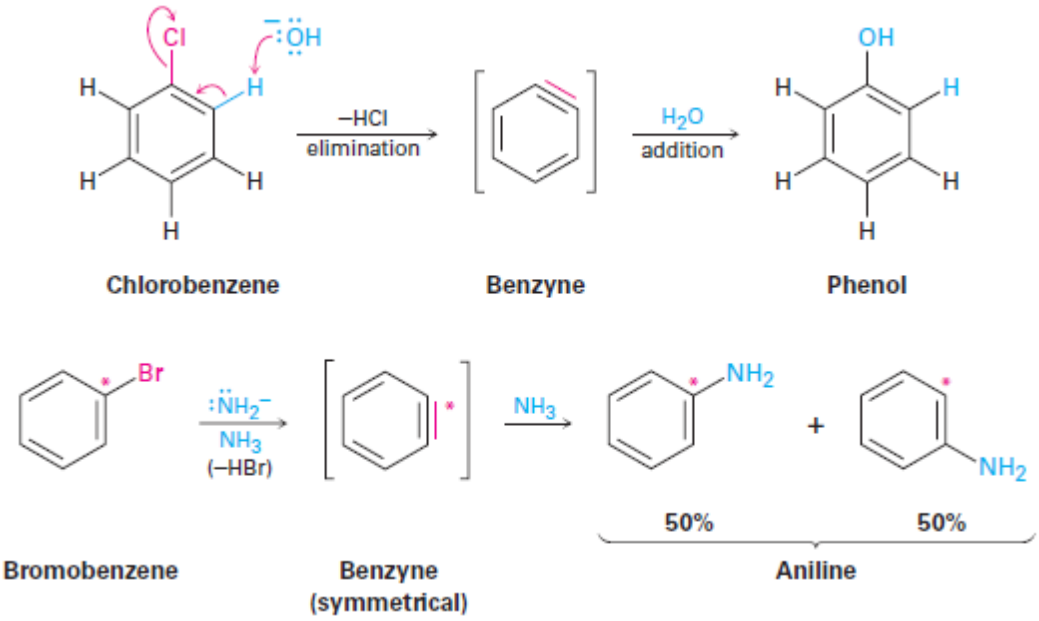
Halobenzenes without electron-withdrawing substituents don't react with nucleophiles under most conditions. At high temperature and pressure, however, even chlorobenzene can be forced to react. Phenol could be prepared on an industrial scale by treatment of chlorobenzene with dilute aqueous NaOH at 340 °C under 170 atm pressure.



A similar substitution reaction occurs with other strong bases. Treatment of bromobenzene with potassium amide (KNH_2) in liquid NH_3 solvent, for instance, gives aniline. Curiously, though, when using bromobenzene labeled with radioactive ^{14}C at the C1 position, the substitution product has equal amounts of the label at both C1 and C2, implying the presence of a symmetrical reaction intermediate in which C1 and C2 are equivalent.



Further mechanistic evidence comes from trapping experiments. When Bromobenzene is treated with KNH_2 in the presence of a conjugated diene, such as furan, a Diels–Alder reaction occurs, implying that the symmetrical intermediate is a **benzyne**, formed by elimination of HBr from bromobenzene. Benzyne is too reactive to be isolated as a pure compound but, in the presence of water, addition occurs to give phenol. In the presence of a diene, Diels–Alder cycloaddition takes place.



The electronic structure of benzyne, shown in **Figure-15**, is that of a highly distorted alkyne. Although a typical alkyne triple bond uses *sp*-hybridized carbon atoms, the benzyne triple bond uses sp^2-hybridized carbons. Furthermore, a typical alkyne triple bond has two mutually perpendicular *p* bonds formed by *p*–*p* overlap, but the benzyne triple bond has one *p* bond formed by *p*–*p* overlap and one *p* bond formed by sp^2–sp^2 overlap. The latter *p* bond is in the plane of the ring and is very weak.

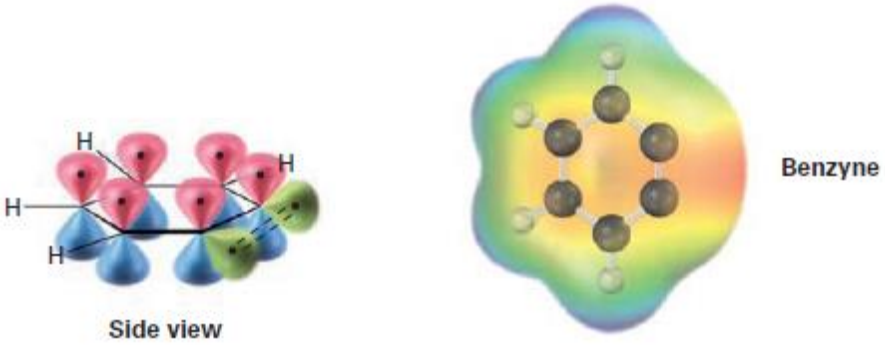
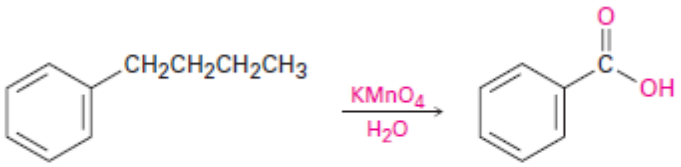


Figure-15 An orbital picture and electrostatic potential map of benzyne. The benzyne carbons are sp^2-hybridized, and the "third" bond results from weak overlap of two adjacent sp^2 orbitals.

Oxidation of Aromatic Compounds

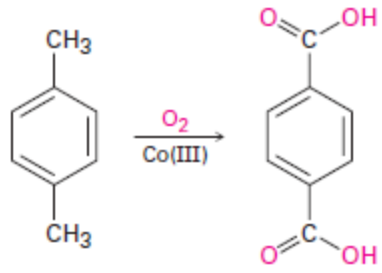
Oxidation of Alkyl Side Chains

Despite its unsaturation, the benzene ring is inert to strong oxidizing agents such as $KMnO_4$ and $Na_2Cr_2O_7$, reagents that will cleave alkene carbon–carbon bonds. It turns out, however, that the presence of the aromatic ring has a dramatic effect on alkyl side chains. These side chains react rapidly with oxidizing agents and are converted into carboxyl groups, $-CO_2H$.The net effect is conversion of an alkylbenzene into a benzoic acid, Ar-R $\longrightarrow$ Ar-CO_2H. Butylbenzene is oxidized by aqueous $KMnO_4$ to give benzoic acid, for instance.



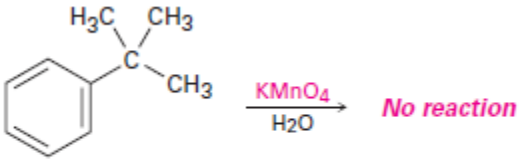
Butylbenzene **Benzoic acid (85%)**

A similar oxidation is employed industrially for the preparation of the terephthalic acid used in the production of polyester fibers. Worldwide, approximately 40 million tons per year of terephthalic acid is produced by oxidation of *p*-xylene, using air as the oxidant and Co(III) salts as catalyst.



***p*-Xylene** **Terephthalic acid**

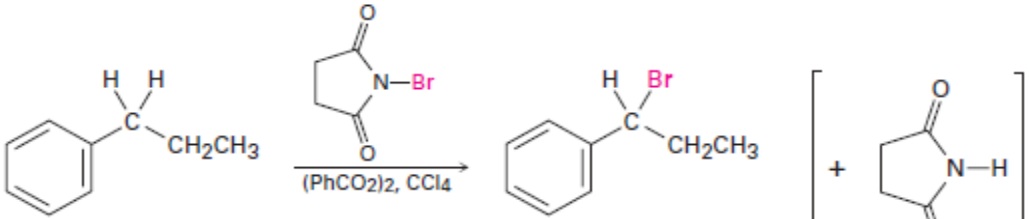
The mechanism of side-chain oxidation is complex and involves reaction of C-H bonds at the position next to the aromatic ring to form intermediate benzylic radicals. *tert*-Butylbenzene has no benzylic hydrogens, however, and is therefore inert.



***tert*-Butylbenzene**

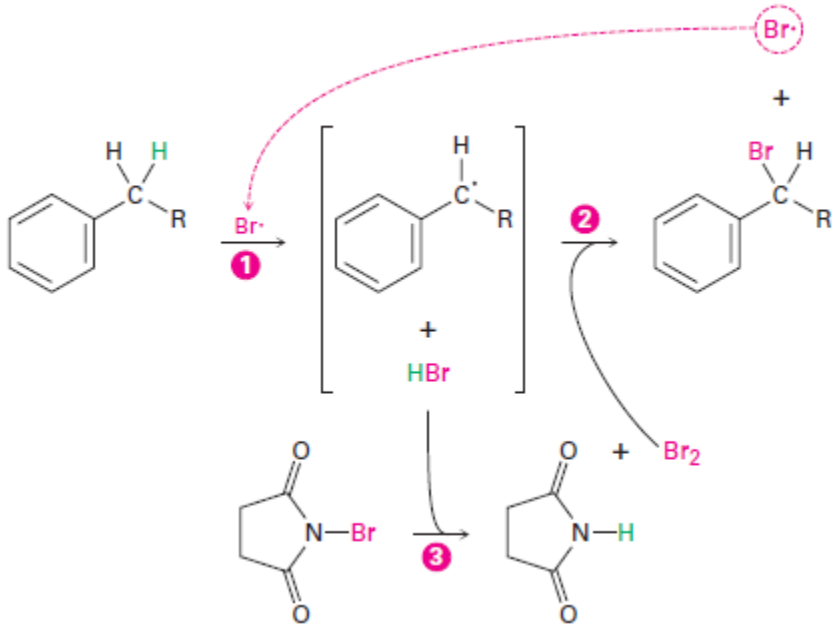
Bromination of Alkylbenzene Side Chains

Side-chain bromination at the benzylic position occurs when an alkylbenzene is treated with *N*-bromosuccinimide (NBS). For example, propylbenzene gives (1-bromopropyl)benzene in 97% yield on reaction with NBS in the presence of benzoyl peroxide, $(PhCO_2)_2$, as a radical initiator. Bromination occurs exclusively in the benzylic position next to the aromatic ring and does not give a mixture of products.



Propylbenzene **(1-Bromopropyl)benzene (97%)**

The mechanism of benzylic bromination is similar to allylic bromination of alkenes. Abstraction of a benzylic hydrogen atom first generates an intermediate benzylic radical, which then reacts with Br_2 in step 2 to yield product and a Br· radical, which cycles back into the reaction to carry on the chain. The Br_2 needed for reaction with the benzylic radical is produced in step 3 by a concurrent reaction of HBr with NBS.



Reaction occurs exclusively at the benzylic position because the benzylic radical intermediate is stabilized by resonance. **Figure-16** shows how the benzyl radical is stabilized by overlap of its *p* orbital with the ringed *Π* electron system.

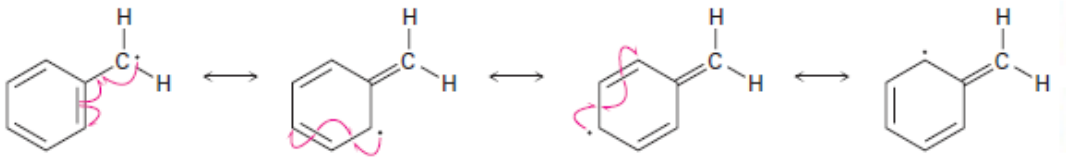
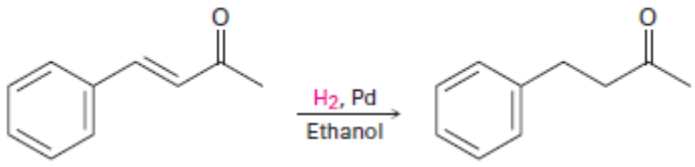


Figure-16 A resonance-stabilized benzylic radical. The spin-density surface shows that the unpaired electron is shared by the ortho and para carbons of the ring.

Reduction of Aromatic Compounds

Catalytic Hydrogenation of Aromatic Rings

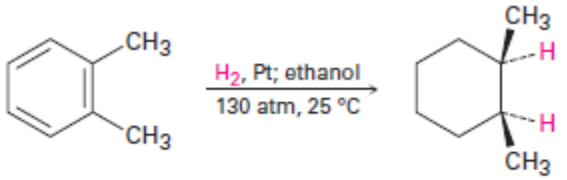
Just as aromatic rings are generally inert to oxidation, they're also inert to catalytic hydrogenation under conditions that reduce typical alkene double bonds. As a result, it's possible to reduce an alkene double bond selectively in the presence of an aromatic ring. For example, 4-phenyl-3-buten-2-one is reduced to 4-phenyl-2-butanone using a palladium catalyst at room temperature and atmospheric pressure. Neither the benzene ring nor the ketone carbonyl group is affected.



4-Phenyl-3-buten-2-one

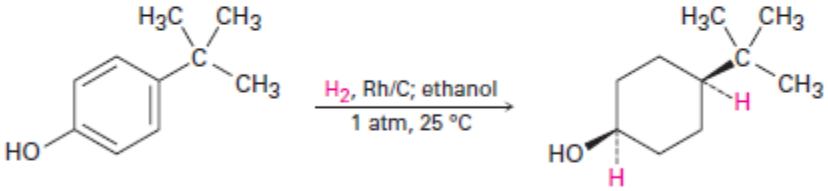
4-Phenyl-2-butanone
(100%)

To hydrogenate an aromatic ring, it's necessary either to use a platinum catalyst with hydrogen gas at a pressure of several hundred atmospheres or to use a more effective catalyst such as rhodium on carbon. Under these conditions, aromatic rings are converted into cyclohexanes. For example, *o*-xylene yields 1,2-dimethylcyclohexane, and 4-*tert*-butylphenol gives 4-*tert*-butylcyclohexanol.



o-Xylene

cis-1,2-Dimethyl-
cyclohexane

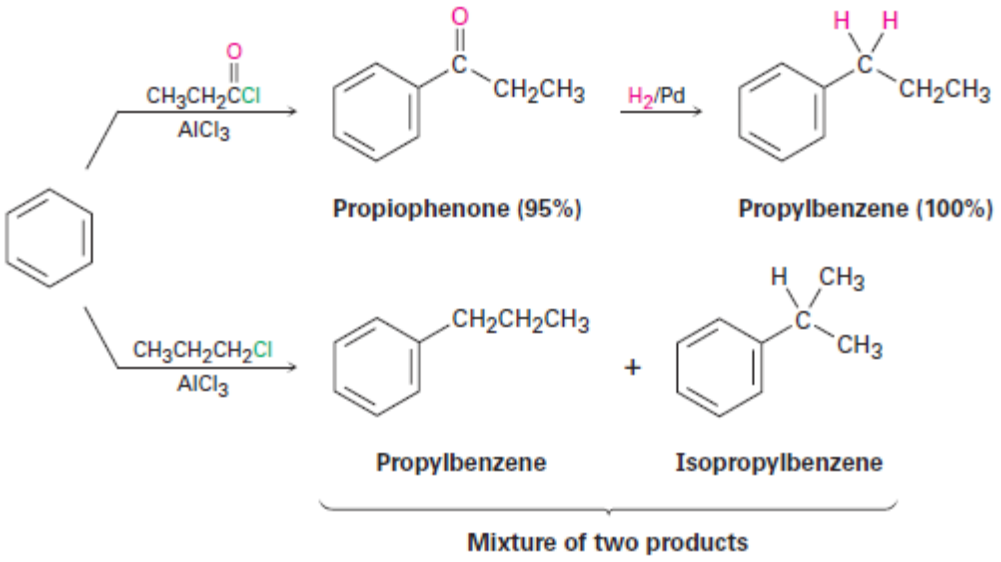


4-*tert*-Butylphenol

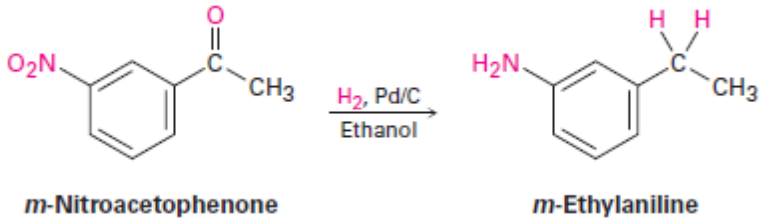
cis-4-*tert*-Butyl-
cyclohexanol

Reduction of Aryl Alkyl Ketones

In the same way that an aromatic ring activates a neighboring (benzylic) C-H toward oxidation, it also activates a benzylic carbonyl group toward reduction. Thus, an aryl alkyl ketone prepared by Friedel–Crafts acylation of an aromatic ring can be converted into an alkylbenzene by catalytic hydrogenation over a palladium catalyst. Propiophenone, for instance, is reduced to propylbenzene by catalytic hydrogenation. Since the net effect of Friedel–Crafts acylation followed by reduction is the preparation of a primary alkylbenzene, this two-step sequence of reactions makes it possible to circumvent the carbocation rearrangement problems associated with direct Friedel–Crafts alkylation using a primary alkyl halide.



The conversion of a carbonyl group into a methylene group (C=O $\longrightarrow$ CH_2) by catalytic hydrogenation is limited to *aryl* alkyl ketones; dialkyl ketones are not reduced under these conditions. Furthermore, the catalytic reduction of aryl alkyl ketones is not compatible with the presence of a nitro substituent on the aromatic ring because a nitro group is reduced to an amino group under reaction conditions.



Synthesis of Polysubstituted Benzenes

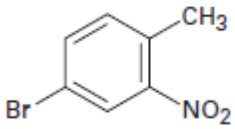
One of the surest ways to learn organic chemistry is to work synthesis problems. The ability to plan a successful multistep synthesis of a complex molecule requires a working knowledge of the uses and limitations of a great many organic reactions. Not only must you know *which* reactions to use, you must also know *when* to use them because the order in which reactions are carried out is often critical to the success of the overall scheme. The ability to plan a sequence of reactions in the right order is particularly important in the synthesis of substituted aromatic rings, where the introduction of a new substituent is strongly affected by the directing effects of other substituents. Planning syntheses of substituted aromatic compounds is therefore a good way to gain confidence in using the many reactions.

Example:

Synthesize 4-bromo-2-nitrotoluene from benzene.

Strategy:

Draw the target molecule, identify the substituents, and recall how each group can be introduced separately. Then plan retrosynthetically.

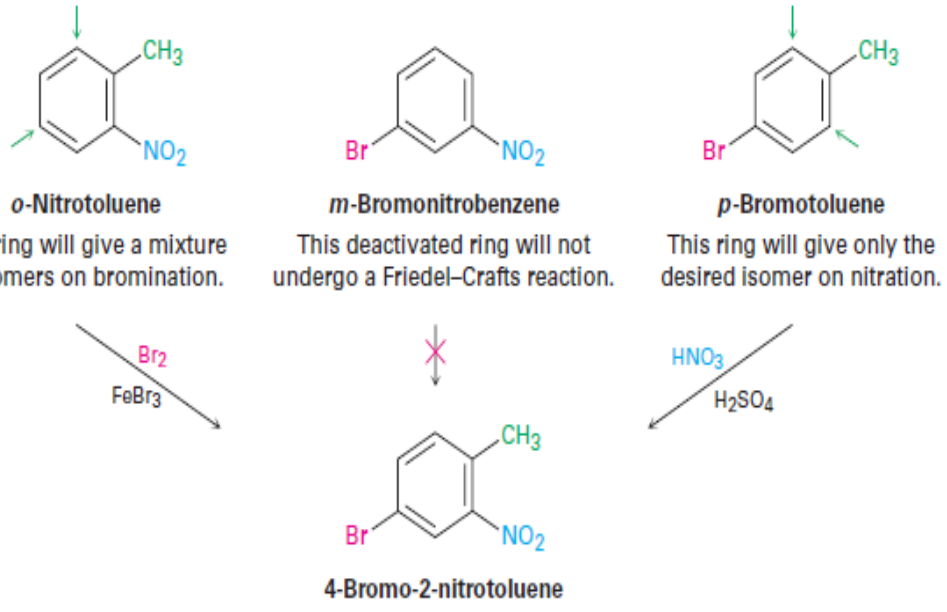


4-Bromo-2-nitrotoluene

The three substituents on the ring are a bromine, a methyl group, and a nitro group. A bromine can be introduced by bromination with $Br_2/FeBr_3$, a methyl group can be introduced by Friedel–Crafts alkylation with $CH_3Cl/AlCl_3$, and a nitro group can be introduced by nitration with HNO_3/H_2SO_4.

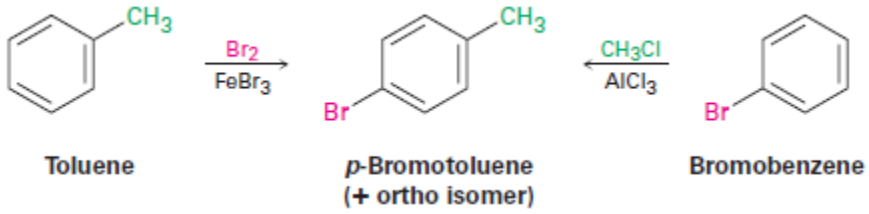
Solution:

What is an immediate precursor of the target? The final step will involve introduction of one of three groups—bromine, methyl, or nitro—so we have to consider three possibilities. Of the three, the bromination of *o*-nitrotoluene could be used because the activating methyl group would dominate the deactivating nitro group and direct bromination to the correct position. Unfortunately, a mixture of product isomers would be formed. A Friedel–Crafts reaction can't be used as the final step because this reaction doesn't work on a nitro-substituted (strongly deactivated) benzene. The best precursor of the desired product is probably *p*-bromotoluene, which can be nitrated ortho to the activating methyl group to give a single product.



What is an immediate precursor of *p*-bromotoluene? Perhaps toluene is an immediate precursor because the methyl group would direct bromination to the ortho and para positions.

Alternatively, bromobenzene might be an immediate precursor because we could carry out a Friedel–Crafts methylation and obtain a mixture of ortho and para products. Both answers are satisfactory, although both would also lead unavoidably to a product mixture that would have to be separated.



What is an immediate precursor of toluene? Benzene, which could be methylated in a Friedel–Crafts reaction. Alternatively, What is an immediate precursor of bromobenzene? Benzene, which could be brominated.The retrosynthetic analysis has provided two valid routes from benzene to 4-bromo-2-nitrotoluene.