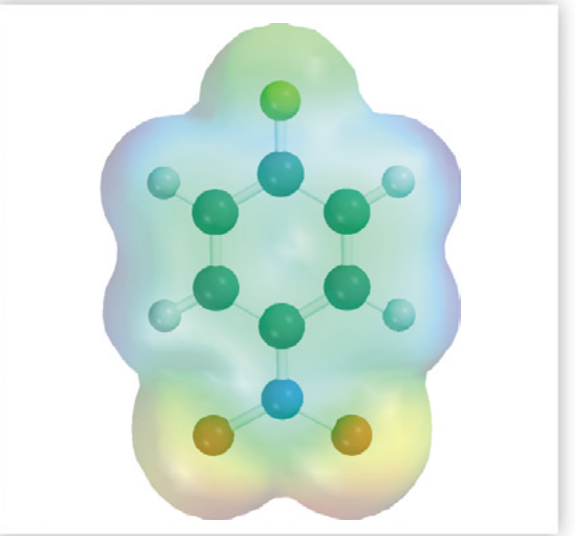


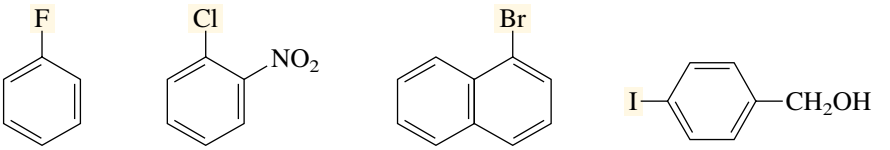
CHAPTER 23

ARYL HALIDES

The value of *alkyl halides* as starting materials for the preparation of a variety of organic functional groups has been stressed many times. In our earlier discussions, we noted that *aryl halides* are normally much less reactive than alkyl halides in reactions that involve carbon–halogen bond cleavage. In the present chapter you will see that aryl halides can exhibit their own patterns of chemical reactivity, and that these reactions are novel, useful, and mechanistically interesting.

23.1 BONDING IN ARYL HALIDES

Aryl halides are compounds in which a halogen substituent is attached directly to an aromatic ring. Representative aryl halides include

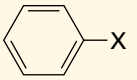


Fluorobenzene | 1-Chloro-2-nitrobenzene | 1-Bromonaphthalene | *p*-Iodobenzyl alcohol

Halogen-containing organic compounds in which the halogen substituent is not directly bonded to an aromatic ring, even though an aromatic ring may be present, are not aryl halides. Benzyl chloride ($C_6H_5CH_2Cl$), for example, is not an aryl halide.

The carbon–halogen bonds of aryl halides are both shorter and stronger than the carbon–halogen bonds of alkyl halides, and in this respect as well as in their chemical behavior, they resemble vinyl halides more than alkyl halides. A hybridization effect

TABLE 23.1 Carbon–Hydrogen and Carbon–Chlorine Bond Dissociation Energies of Selected Compounds

Compound	Hybridization of carbon to which X is attached	Bond energy, kJ/mol (kcal/mol)	
		X = H	X = Cl
CH_3CH_2X	sp^3	410 (98)	339 (81)
$CH_2{=}CHX$	sp^2	452 (108)	368 (88)
	sp^2	469 (112)	406 (97)

seems to be responsible because, as the data in Table 23.1 indicate, similar patterns are seen for both carbon–hydrogen bonds and carbon–halogen bonds. An increase in *s* character from 25% (sp^3 hybridization) to 33.3% *s* character (sp^2 hybridization) increases the tendency of carbon to attract electrons and strengthens the bond.

PROBLEM 23.1 Consider all the isomers of C_7H_7Cl containing a benzene ring and write the structure of the one that has the weakest carbon–chlorine bond as measured by its bond dissociation energy.

The strength of their carbon–halogen bonds causes aryl halides to react very slowly in reactions in which carbon–halogen bond cleavage is rate-determining, as in nucleophilic substitution, for example. Later in this chapter we will see examples of such reactions that do take place at reasonable rates but proceed by mechanisms distinctly different from the classical S_N1 and S_N2 pathways.

23.2 SOURCES OF ARYL HALIDES

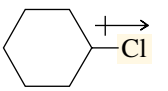
The two main methods for the preparation of aryl halides—halogenation of arenes by electrophilic aromatic substitution and preparation by way of aryl diazonium salts—were described earlier and are reviewed in Table 23.2. A number of aryl halides occur naturally, some of which are shown in Figure 23.1 on page 920.

23.3 PHYSICAL PROPERTIES OF ARYL HALIDES

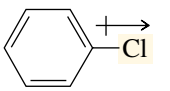
Melting points and boiling points for some representative aryl halides are listed in Appendix 1.

Aryl halides resemble alkyl halides in many of their physical properties. All are practically insoluble in water and most are denser than water.

Aryl halides are polar molecules but are less polar than alkyl halides.



Chlorocyclohexane
μ 2.2 D

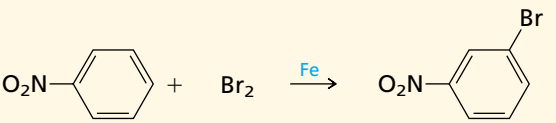
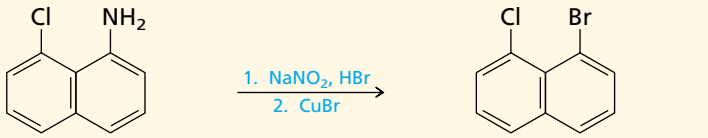


Chlorobenzene
μ 1.7 D

Compare the electronic charges at chlorine in chlorocyclohexane and chlorobenzene on *Learning By Modeling* to verify that the C—Cl bond is more polar in chlorocyclohexane.

Since carbon is sp^2-hybridized in chlorobenzene, it is more electronegative than the sp^3-hybridized carbon of chlorocyclohexane. Consequently, the withdrawal of electron density away from carbon by chlorine is less pronounced in aryl halides than in alkyl halides, and the molecular dipole moment is smaller.

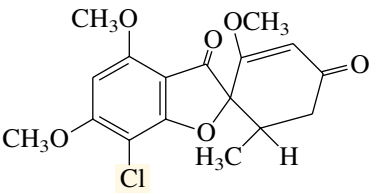
TABLE 23.2 Summary of Reactions Discussed in Earlier Chapters That Yield Aryl Halides

Reaction (section) and comments	General equation and specific example
Halogenation of arenes (Section 12.5) Aryl chlorides and bromides are conveniently prepared by electrophilic aromatic substitution. The reaction is limited to chlorination and bromination. Fluorination is difficult to control; iodination is too slow to be useful.	$ArH + X_2 \xrightarrow[\text{or } FeX_3]{Fe} ArX + HX$ Arene — Halogen — Aryl halide — Hydrogen halide  Nitrobenzene — Bromine — *m*-Bromonitrobenzene (85%)
The Sandmeyer reaction (Section 22.18) Diazotization of a primary arylamine followed by treatment of the diazonium salt with copper(I) bromide or copper(I) chloride yields the corresponding aryl bromide or aryl chloride.	$ArNH_2 \xrightarrow[2.\ CuX]{1.\ NaNO_2,\ H_3O^+} ArX$ Primary arylamine — Aryl halide  1-Amino-8-chloronaphthalene — 1-Bromo-8-chloronaphthalene (62%)
The Schiemann reaction (Section 22.18) Diazotization of an arylamine followed by treatment with fluoroboric acid gives an aryl diazonium fluoroborate salt. Heating this salt converts it to an aryl fluoride.	$ArNH_2 \xrightarrow[2.\ HBF_4]{1.\ NaNO_2,\ H_3O^+} ArN{\equiv}N{:}\ \bar{B}F_4 \xrightarrow{heat} ArF$ Primary arylamine — Aryl diazonium fluoroborate — Aryl fluoride $C_6H_5NH_2 \xrightarrow[2.\ HBF_4\ 3.\ heat]{1.\ NaNO_2,\ H_2O,\ HCl} C_6H_5F$ Aniline — Fluorobenzene (51–57%)
Reaction of aryl diazonium salts with iodide ion (Section 22.18) Adding potassium iodide to a solution of an aryl diazonium ion leads to the formation of an aryl iodide.	$ArNH_2 \xrightarrow[2.\ KI]{1.\ NaNO_2,\ H_3O^+} ArI$ Primary arylamine — Aryl iodide $C_6H_5NH_2 \xrightarrow[2.\ KI]{1.\ NaNO_2,\ HCl,\ H_2O} C_6H_5I$ Aniline — Iodobenzene (74–76%)

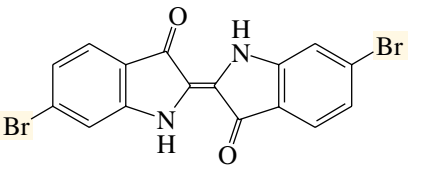
23.4 REACTIONS OF ARYL HALIDES: A REVIEW AND A PREVIEW

Table 23.3 summarizes the reactions of aryl halides that we have encountered to this point.

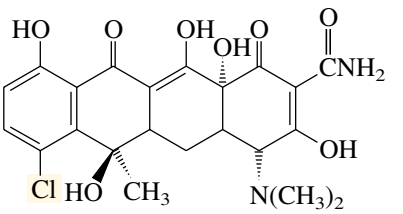
Noticeably absent from Table 23.3 are nucleophilic substitutions. We have, to this point, seen no nucleophilic substitution reactions of aryl halides in this text. Chlorobenzene, for example, is essentially inert to aqueous sodium hydroxide at room temperature. Reaction temperatures over 300°C are required for nucleophilic substitution to proceed at a reasonable rate.



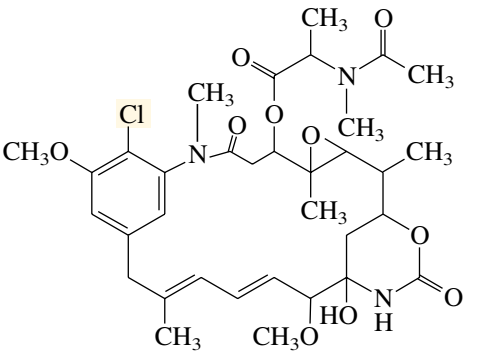
Griseofulvin: biosynthetic product of a particular microorganism, used as an orally administered antifungal agent.



Dibromoindigo: principal constituent of a dye known as Tyrian purple, which is isolated from a species of Mediterranean sea snail and was much prized by the ancients for its vivid color.



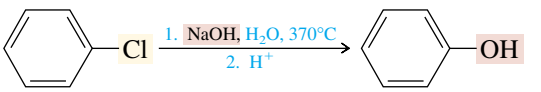
Chlortetracycline: an antibiotic.



Maytansine: a potent antitumor agent isolated from a bush native to Kenya; 10 tons of plant yielded 6 g of maytansine.

FIGURE 23.1 Some naturally occurring aryl halides.

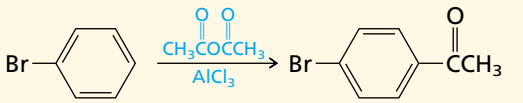
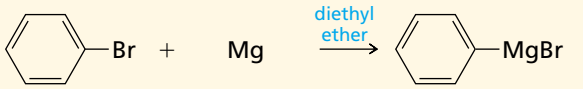
The mechanism of this reaction is discussed in Section 23.8.



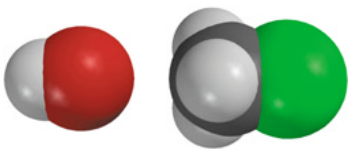
Chlorobenzene Phenol (97%)

Aryl halides are much less reactive than alkyl halides in nucleophilic substitution reactions. The carbon–halogen bonds of aryl halides are too strong, and aryl cations are too high in energy, to permit aryl halides to ionize readily in S_N1-type processes. Furthermore, as Figure 23.2 depicts, the optimal transition-state geometry required for S_N2 processes cannot be achieved. Nucleophilic attack from the side opposite the carbon–halogen bond is blocked by the aromatic ring.

TABLE 23.3 Summary of Reactions of Aryl Halides Discussed in Earlier Chapters

Reaction (section) and comments	General equation and specific example
Electrophilic aromatic substitution (Section 12.14) Halogen substituents are slightly deactivating and ortho, para-directing.	 Bromobenzene — *p*-Bromoacetophenone (69–79%)
Formation of aryl Grignard reagents (Section 14.4) Aryl halides react with magnesium to form the corresponding arylmagnesium halide. Aryl iodides are the most reactive, aryl fluorides the least. A similar reaction occurs with lithium to give aryllithium reagents (Section 14.3).	ArX + Mg $\xrightarrow{\text{diethyl ether}}$ ArMgX Aryl halide — Magnesium — Arylmagnesium halide  Bromobenzene — Magnesium — Phenylmagnesium bromide (95%)

(*a*) Hydroxide ion + chloromethane



(*b*) Hydroxide ion + chlorobenzene

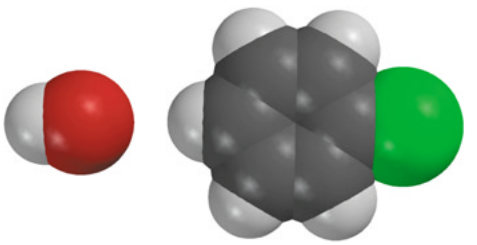
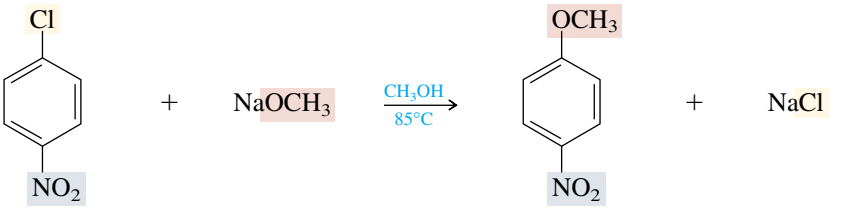


FIGURE 23.2 Nucleophilic substitution, with inversion of configuration, is blocked by the benzene ring of an aryl halide. (*a*) *Alkyl halide:* The new bond is formed by attack of the nucleophile at carbon from the side opposite the bond to the leaving group. Inversion of configuration is observed. (*b*) *Aryl halide:* The aromatic ring blocks the approach of the nucleophile to carbon at the side opposite the bond to the leaving group. Inversion of configuration is impossible.

23.5 NUCLEOPHILIC SUBSTITUTION IN NITRO-SUBSTITUTED ARYL HALIDES

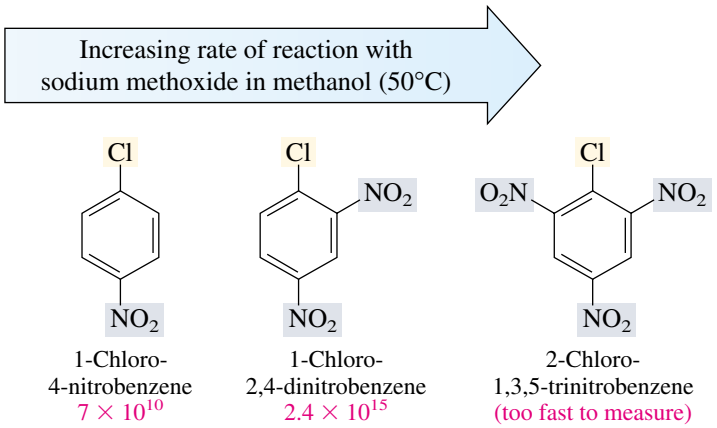
One group of aryl halides that do undergo nucleophilic substitution readily consists of those that bear a nitro group ortho or para to the halogen.



p-Chloronitrobenzene | Sodium methoxide | *p*-Nitroanisole (92%) | Sodium chloride

An *ortho*-nitro group exerts a comparable rate-enhancing effect. *m*-Chloronitrobenzene, although much more reactive than chlorobenzene itself, is thousands of times less reactive than either *o*- or *p*-chloronitrobenzene.

The effect of *o*- and *p*-nitro substituents is cumulative, as the following rate data demonstrate:



Chlorobenzene — Relative rate: 1.0

1-Chloro-4-nitrobenzene — 7×10^{10}

1-Chloro-2,4-dinitrobenzene — 2.4×10^{15}

2-Chloro-1,3,5-trinitrobenzene — (too fast to measure)

PROBLEM 23.2 Write the structure of the expected product from the reaction of 1-chloro-2,4-dinitrobenzene with each of the following reagents:

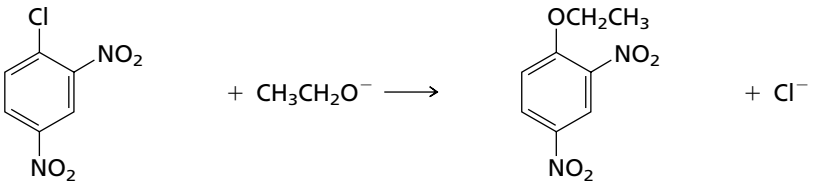
(a) CH_3CH_2ONa

(b) $C_6H_5CH_2SNa$

(c) NH_3

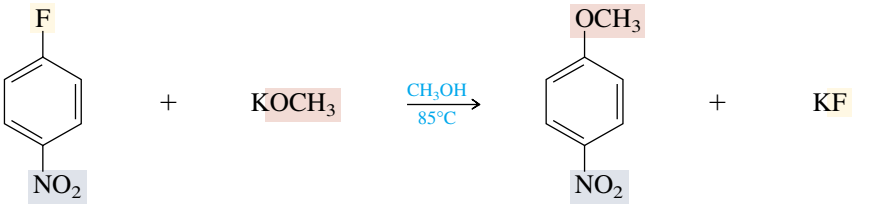
(d) CH_3NH_2

SAMPLE SOLUTION (a) Sodium ethoxide is a source of the nucleophile $CH_3CH_2O^-$, which displaces chloride from 1-chloro-2,4-dinitrobenzene.



1-Chloro-2,4-dinitrobenzene | Ethoxide anion | 1-Ethoxy-2,4-dinitrobenzene

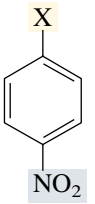
In contrast to nucleophilic substitution in alkyl halides, where *alkyl fluorides* are exceedingly unreactive, *aryl fluorides* undergo nucleophilic substitution readily when the ring bears an *o*- or a *p*-nitro group.



p-Fluoronitrobenzene Potassium methoxide *p*-Nitroanisole (93%) Potassium fluoride

The compound 1-fluoro-2,4-dinitrobenzene is exceedingly reactive toward nucleophilic aromatic substitution and was used in an imaginative way by Frederick Sanger (Section 27.10) in his determination of the structure of insulin.

Indeed, the order of leaving-group reactivity in nucleophilic aromatic substitution is the opposite of that seen in aliphatic substitution. *Fluoride is the most reactive leaving group in nucleophilic aromatic substitution, iodide the least reactive.*



Relative reactivity toward sodium methoxide in methanol (50°C):

X = F	312
X = Cl	1.0
X = Br	0.8
X = I	0.4

Kinetic studies of these reactions reveal that they follow a second-order rate law:

$$\text{Rate} = k[\text{Aryl halide}]\,[\text{Nucleophile}]$$

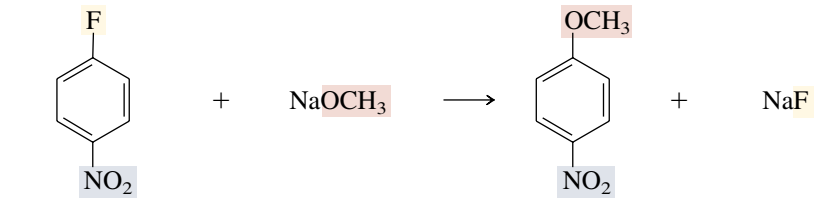
Second-order kinetics is usually interpreted in terms of a bimolecular rate-determining step. In this case, then, we look for a mechanism in which both the aryl halide and the nucleophile are involved in the slowest step. Such a mechanism is described in the following section.

23.6 THE ADDITION–ELIMINATION MECHANISM OF NUCLEOPHILIC AROMATIC SUBSTITUTION

The generally accepted mechanism for nucleophilic aromatic substitution in nitro-substituted aryl halides, illustrated for the reaction of *p*-fluoronitrobenzene with sodium methoxide, is outlined in Figure 23.3. It is a two-step **addition–elimination mechanism,** in which addition of the nucleophile to the aryl halide is followed by elimination of the halide leaving group. Figure 23.4 shows the structure of the key intermediate. The mechanism is consistent with the following experimental observations:

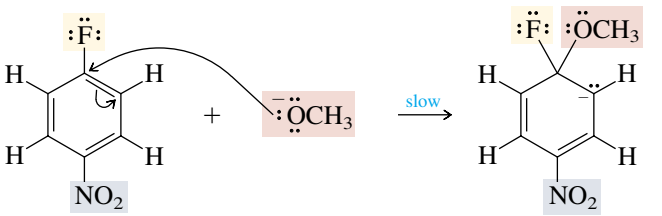
1. *Kinetics:* As the observation of second-order kinetics requires, the rate-determining step (step 1) involves both the aryl halide and the nucleophile.
2. *Rate-enhancing effect of the nitro group:* The nucleophilic addition step is rate-determining because the aromatic character of the ring must be sacrificed to form the cyclohexadienyl anion intermediate. Only when the anionic intermediate is stabilized by the presence of a strong electron-withdrawing substituent ortho or para to the leaving group will the activation energy for its formation be low enough to provide a reasonable reaction rate. We can illustrate the stabilization that a *p*-nitro group provides by examining the resonance structures for the cyclohexadienyl anion formed from methoxide and *p*-fluoronitrobenzene:

Overall reaction:



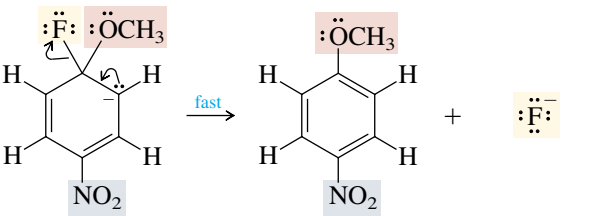
p-Fluoronitrobenzene | Sodium methoxide | *p*-Nitroanisole | Sodium fluoride

Step 1: Addition stage. The nucleophile, in this case methoxide ion, adds to the carbon atom that bears the leaving group to give a cyclohexadienyl anion intermediate.



p-Fluoronitrobenzene | Methoxide ion | Cyclohexadienyl anion intermediate

Step 2: Elimination stage. Loss of halide from the cyclohexadienyl intermediate restores the aromaticity of the ring and gives the product of nucleophilic aromatic substitution.



Cyclohexadienyl anion intermediate | *p*-Nitroanisole | Fluoride ion

FIGURE 23.3 The addition–elimination mechanism of nucleophilic aromatic substitution.

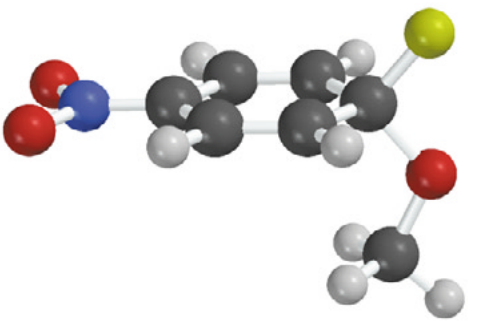
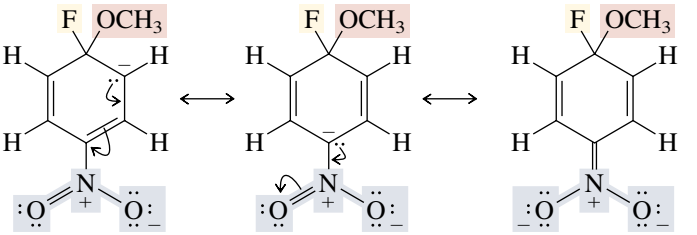


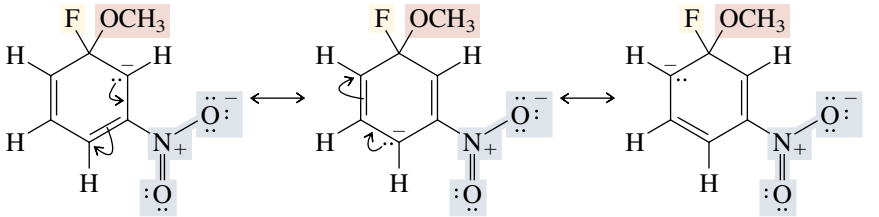
FIGURE 23.4 Structure of the rate-determining intermediate in the reaction of 1-fluoro-4-nitrobenzene with methoxide ion.



Most stable resonance structure; negative charge is on oxygen

PROBLEM 23.3 Write the most stable resonance structure for the cyclohexadienyl anion formed by reaction of methoxide ion with *o*-fluoronitrobenzene.

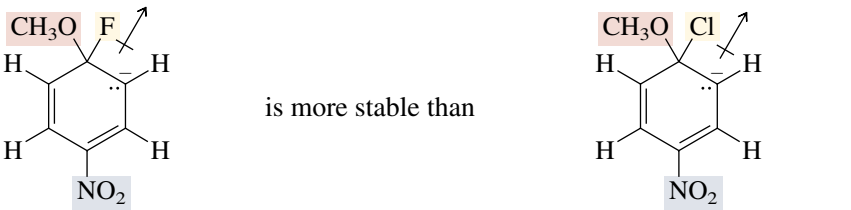
m-Fluoronitrobenzene reacts with sodium methoxide 10^5 times more slowly than its ortho and para isomers. According to the resonance description, direct conjugation of the negatively charged carbon with the nitro group is not possible in the cyclohexadienyl anion intermediate from *m*-fluoronitrobenzene, and the decreased reaction rate reflects the decreased stabilization afforded this intermediate.



(Negative charge is restricted to carbon in all resonance forms)

PROBLEM 23.4 Reaction of 1,2,3-tribromo-5-nitrobenzene with sodium ethoxide in ethanol gave a single product, $C_8H_7Br_2NO_3$, in quantitative yield. Suggest a reasonable structure for this compound.

3. *Leaving-group effects:* Since aryl fluorides have the strongest carbon–halogen bond and react fastest, the rate-determining step cannot involve carbon–halogen bond cleavage. According to the mechanism in Figure 23.3 the carbon–halogen bond breaks in the rapid elimination step that follows the rate-determining addition step. The unusually high reactivity of aryl fluorides arises because fluorine is the most electronegative of the halogens, and its greater ability to attract electrons increases the rate of formation of the cyclohexadienyl anion intermediate in the first step of the mechanism.

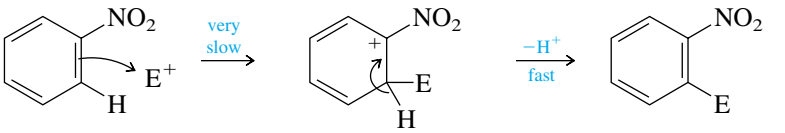


Fluorine stabilizes cyclohexadienyl anion by withdrawing electrons.

is more stable than

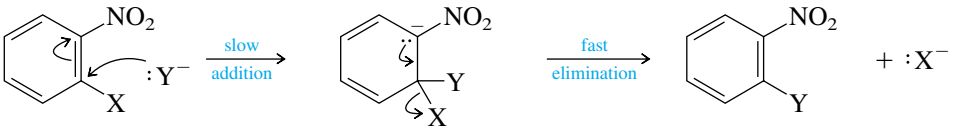
Chlorine is less electronegative than fluorine and does not stabilize cyclohexadienyl anion to as great an extent.

Before leaving this mechanistic discussion, we should mention that the addition–elimination mechanism for nucleophilic aromatic substitution illustrates a principle worth remembering. The words "activating" and "deactivating" as applied to substituent effects in organic chemistry are without meaning when they stand alone. When we say that a group is activating or deactivating, we need to specify the reaction type that is being considered. A nitro group is a strongly *deactivating* substituent in *electrophilic* aromatic substitution, where it markedly destabilizes the key cyclohexadienyl cation intermediate:



Nitrobenzene and an electrophile | Cyclohexadienyl cation intermediate; nitro group is destabilizing | Product of electrophilic aromatic substitution

A nitro group is a strongly *activating* substituent in *nucleophilic* aromatic substitution, where it stabilizes the key cyclohexadienyl anion intermediate:

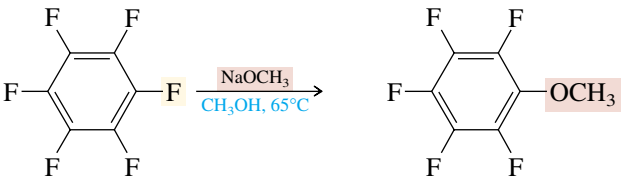


o-Halonitrobenzene (X = F, Cl, Br, or I) and a nucleophile | Cyclohexadienyl anion intermediate; nitro group is stabilizing | Product of nucleophilic aromatic substitution

A nitro group behaves the same way in both reactions: it attracts electrons. Reaction is retarded when electrons flow from the aromatic ring to the attacking species (electrophilic aromatic substitution). Reaction is facilitated when electrons flow from the attacking species to the aromatic ring (nucleophilic aromatic substitution). By being aware of the connection between reactivity and substituent effects, you will sharpen your appreciation of how chemical reactions occur.

23.7 RELATED NUCLEOPHILIC AROMATIC SUBSTITUTION REACTIONS

The most common types of aryl halides in nucleophilic aromatic substitutions are those that bear *o*- or *p*-nitro substituents. Among other classes of reactive aryl halides, a few merit special consideration. One class includes highly fluorinated aromatic compounds such as hexafluorobenzene, which undergoes substitution of one of its fluorines on reaction with nucleophiles such as sodium methoxide.

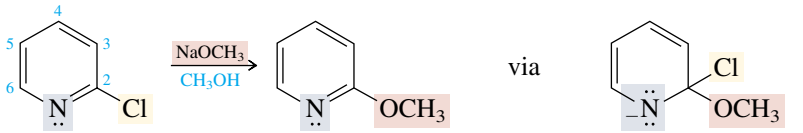


Hexafluorobenzene | 2,3,4,5,6-Pentafluoroanisole (72%)

Here it is the combined electron-attracting effects of the six fluorine substituents that stabilize the cyclohexadienyl anion intermediate and permit the reaction to proceed so readily.

PROBLEM 23.5 Write equations describing the addition–elimination mechanism for the reaction of hexafluorobenzene with sodium methoxide, clearly showing the structure of the rate-determining intermediate.

Halides derived from certain heterocyclic aromatic compounds are often quite reactive toward nucleophiles. 2-Chloropyridine, for example, reacts with sodium methoxide some 230 million times faster than chlorobenzene at 50°C.



2-Chloropyridine 2-Methoxypyridine Anionic intermediate

Again, rapid reaction is attributed to the stability of the intermediate formed in the addition step. In contrast to chlorobenzene, where the negative charge of the intermediate must be borne by carbon, the anionic intermediate in the case of 2-chloropyridine has its negative charge on nitrogen. Since nitrogen is more electronegative than carbon, the intermediate is more stable and is formed faster than the one from chlorobenzene.

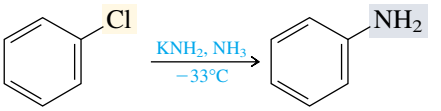
PROBLEM 23.6 Offer an explanation for the observation that 4-chloropyridine is more reactive toward nucleophiles than 3-chloropyridine.

Another type of nucleophilic aromatic substitution occurs under quite different reaction conditions from those discussed to this point and proceeds by a different and rather surprising mechanism. It is described in the following section.

23.8 THE ELIMINATION–ADDITION MECHANISM OF NUCLEOPHILIC AROMATIC SUBSTITUTION: BENZYNE

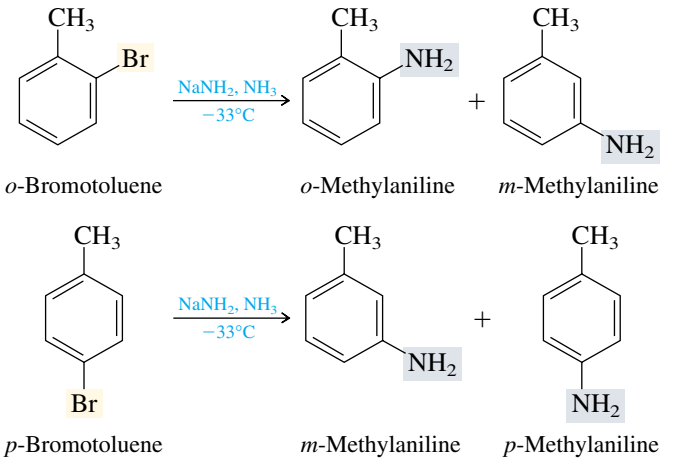
Very strong bases such as sodium or potassium amide react readily with aryl halides, even those without electron-withdrawing substituents, to give products corresponding to nucleophilic substitution of halide by the base.

Comparing the pK_a of ammonia (36) and water (16) tells us that NH_2^- is 10^{20} times more basic than OH^-.

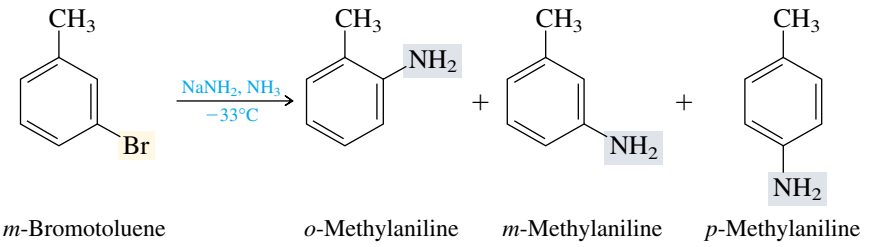


Chlorobenzene Aniline (52%)

For a long time, observations concerning the regiochemistry of these reactions presented organic chemists with a puzzle. Substitution did not occur exclusively at the carbon from which the halide leaving group departed. Rather, a mixture of regioisomers was obtained in which the amine group was either on the carbon that originally bore the leaving group or on one of the carbons adjacent to it. Thus *o*-bromotoluene gave a mixture of *o*-methylaniline and *m*-methylaniline; *p*-bromotoluene gave *m*-methylaniline and *p*-methylaniline.



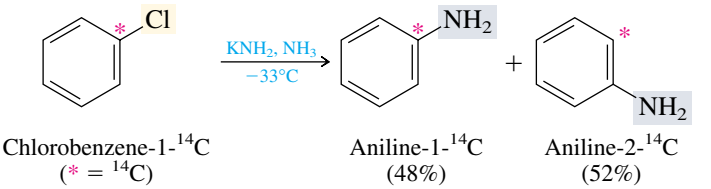
Three regioisomers (*o*-, *m*-, and *p*-methylaniline) were formed from *m*-bromotoluene.



These results rule out substitution by addition–elimination since that mechanism requires the nucleophile to attach itself to the carbon from which the leaving group departs.

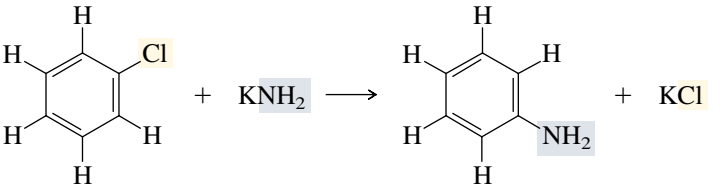
A solution to the question of the mechanism of these reactions was provided by John D. Roberts in 1953 on the basis of an imaginative experiment. Roberts prepared a sample of chlorobenzene in which one of the carbons, the one bearing the chlorine, was the radioactive mass-14 isotope of carbon. Reaction with potassium amide in liquid ammonia yielded aniline containing almost exactly half of its ^{14}C label at C-1 and half at C-2:

This work was done while Roberts was at MIT. He later moved to the California Institute of Technology, where he became a leader in applying NMR spectroscopy to nuclei other than protons, especially ^{13}C and ^{15}N.



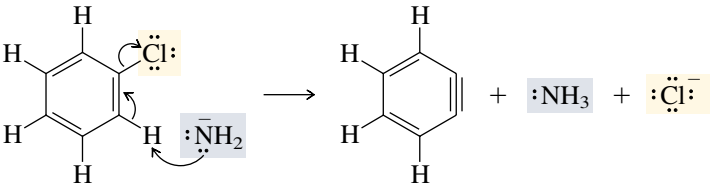
The mechanism most consistent with the observations of this isotopic labeling experiment is the **elimination–addition mechanism** outlined in Figure 23.5. The first stage in this mechanism is a base-promoted dehydrohalogenation of chlorobenzene. The intermediate formed in this step contains a triple bond in an aromatic ring and is called **benzyne.** Aromatic compounds related to benzyne are known as **arynes.** The triple bond in benzyne is somewhat different from the usual triple bond of an alkyne, however. In benzyne one of the π components of the triple bond is part of the delocalized π system of the aromatic ring. The second π component results from overlapping sp^2-hybridized orbitals (*not p-p* overlap), lies in the plane of the ring, and does not interact with the

Overall reaction:



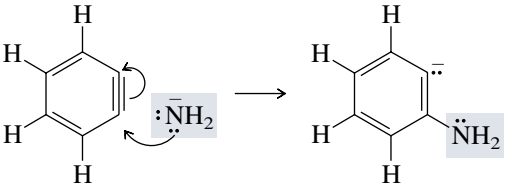
Chlorobenzene Aniline

Step 1: Elimination stage. Amide ion is a very strong base and brings about the dehydrohalogenation of chlorobenzene by abstracting a proton from the carbon adjacent to the one that bears the leaving group. The product of this step is an unstable intermediate called *benzyne*.



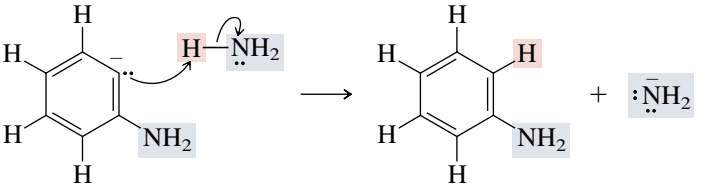
Chlorobenzene Benzyne

Step 2: Beginning of addition phase. Amide ion acts as a nucleophile and adds to one of the carbons of the triple bond. The product of this step is a carbanion.



Benzyne Aryl anion

Step 3: Completion of addition phase. The aryl anion abstracts a proton from the ammonia used as the solvent in the reaction.



Aryl anion Aniline

FIGURE 23.5 The elimination–addition mechanism of nucleophilic aromatic substitution.

aromatic π system. This π bond is relatively weak, since, as illustrated in Figure 23.6, its contributing sp^2 orbitals are not oriented properly for effective overlap.

Because the ring prevents linearity of the C—C≡C—C unit and π bonding in that unit is weak, benzyne is strained and highly reactive. This enhanced reactivity is evident in the second stage of the elimination–addition mechanism as shown in steps 2

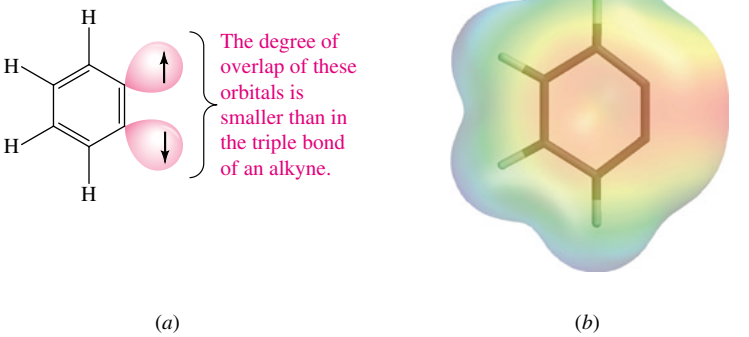


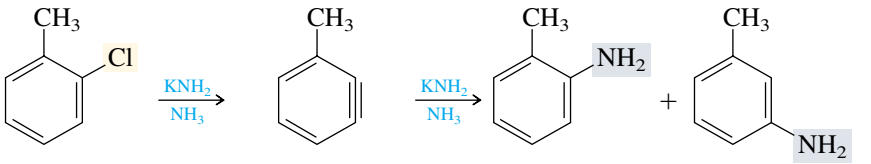
FIGURE 23.6 (*a*) The sp^2 orbitals in the plane of the ring in benzyne are not properly aligned for good overlap, and π bonding is weak. (*b*) The electrostatic potential map shows a region of high electron density associated with the "triple bond."

and 3 of Figure 23.5. In this stage the base acts as a nucleophile and adds to the strained bond of benzyne to form a carbanion. The carbanion, an *aryl anion,* then abstracts a proton from ammonia to yield the observed product.

The carbon that bears the leaving group and a carbon ortho to it become equivalent in the benzyne intermediate. Thus when chlorobenzene-1-^{14}C is the substrate, the amino group may be introduced with equal likelihood at either position.

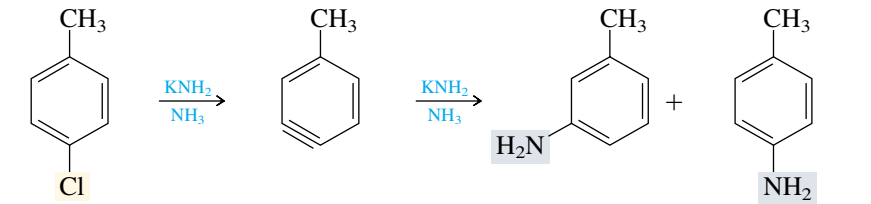
PROBLEM 23.7 2-Bromo-1,3-dimethylbenzene is inert to nucleophilic aromatic substitution on treatment with sodium amide in liquid ammonia. It is recovered unchanged even after extended contact with the reagent. Suggest an explanation for this lack of reactivity.

Once the intermediacy of an aryne intermediate was established, the reason for the observed regioselectivity of substitution in *o*-, *m*-, and *p*-chlorotoluene became evident. Only a single aryne intermediate may be formed from *o*-chlorotoluene, but this aryne yields a mixture containing comparable amounts of *o*- and *m*-methylaniline.



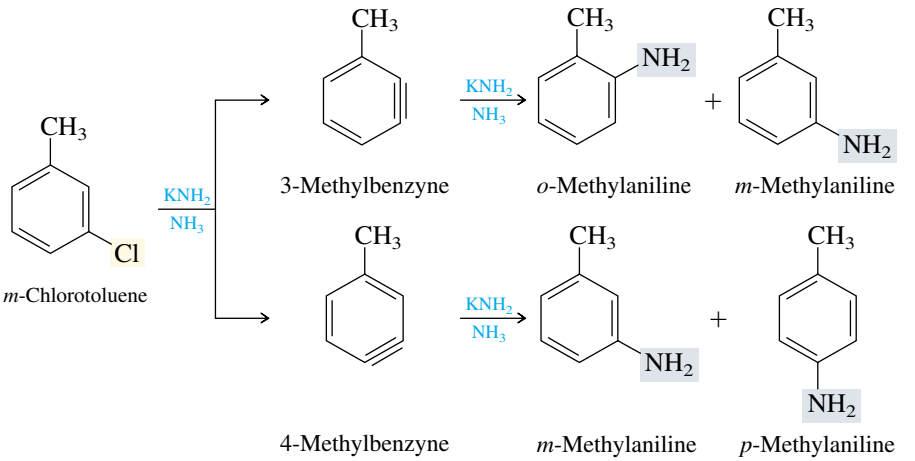
o-Chlorotoluene 3-Methylbenzyne *o*-Methylaniline *m*-Methylaniline

Similarly, *p*-chlorotoluene gives a single aryne, and this aryne gives a mixture of *m*- and *p*-methylaniline.



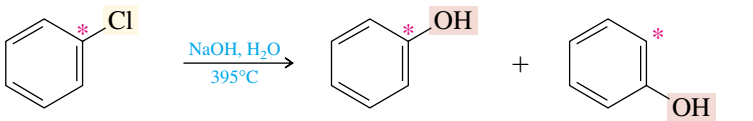
p-Chlorotoluene 4-Methylbenzyne *m*-Methylaniline *p*-Methylaniline

Two isomeric arynes give the three isomeric substitution products formed from *m*-chlorotoluene:



m-Chlorotoluene

Although nucleophilic aromatic substitution by the elimination–addition mechanism is most commonly seen with very strong amide bases, it also occurs with bases such as hydroxide ion at high temperatures. A ^{14}C-labeling study revealed that hydrolysis of chlorobenzene proceeds by way of a benzyne intermediate.

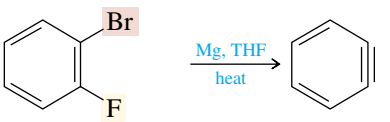


Chlorobenzene-1-^{14}C Phenol-1-^{14}C (54%) Phenol-2-^{14}C (43%)

PROBLEM 23.8 Two isomeric phenols are obtained in comparable amounts on hydrolysis of *p*-iodotoluene with 1 M sodium hydroxide at 300°C. Suggest reasonable structures for these two products.

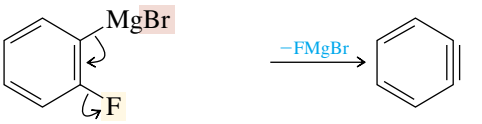
23.9 DIELS–ALDER REACTIONS OF BENZYNE

Alternative methods for its generation have made it possible to use benzyne as an intermediate in a number of synthetic applications. One such method involves treating *o*-bromofluorobenzene with magnesium, usually in tetrahydrofuran as the solvent.



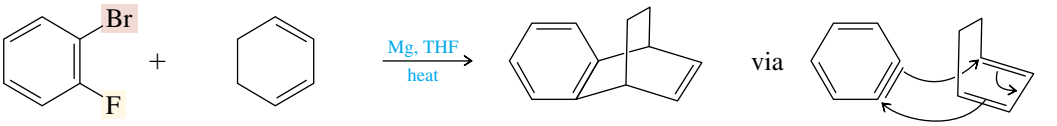
o-Bromofluorobenzene Benzyne

The reaction proceeds by formation of the Grignard reagent from *o*-bromofluorobenzene. Since the order of reactivity of magnesium with aryl halides is ArI > ArBr > ArCl > ArF, the Grignard reagent has the structure shown and forms benzyne by loss of the salt FMgBr:



o-Fluorophenylmagnesium bromide Benzyne

Its strained triple bond makes benzyne a relatively good dienophile, and when benzyne is generated in the presence of a conjugated diene, Diels–Alder cycloaddition occurs.



o-Bromofluorobenzene 1,3-Cyclohexadiene 5,6-Benzobicyclo[2.2.2]-octa-2,5-diene (46%)

PROBLEM 23.9 Give the structure of the cycloaddition product formed when benzyne is generated in the presence of furan. (See Section 11.21, if necessary, to remind yourself of the structure of furan.)

Benzyne may also be generated by treating *o*-bromofluorobenzene with lithium. In this case, *o*-fluorophenyllithium is formed, which then loses lithium fluoride to form benzyne.

23.10 SUMMARY

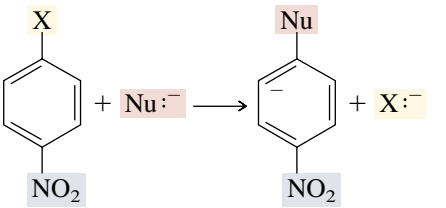
Section 23.1 Aryl halides are compounds of the type Ar—X where X = F, Cl, Br, or I. The carbon–halogen bond is stronger in ArX than in an alkyl halide (RX).

Section 23.2 Some aryl halides occur naturally, but most are the products of organic synthesis. The methods by which aryl halides are prepared were recalled in Table 23.2

Section 23.3 Aryl halides are less polar than alkyl halides.

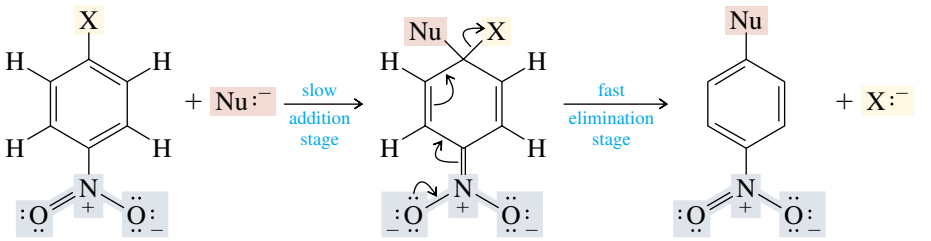
Section 23.4 Aryl halides are less reactive than alkyl halides in reactions in which C—X bond breaking is rate-determining, especially in nucleophilic substitution reactions.

Section 23.5 Nucleophilic substitution in ArX is facilitated by the presence of a strong electron-withdrawing group, such as NO_2, ortho or para to the halogen.



In reactions of this type, fluoride is the best leaving group of the halogens and iodide the poorest.

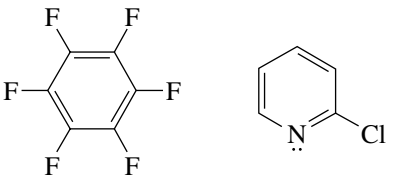
Section 23.6 Nucleophilic aromatic substitutions of the type just shown follow an **addition–elimination mechanism.**



Nitro-substituted aryl halide | Cyclohexadienyl anion intermediate | Product of nucleophilic aromatic substitution

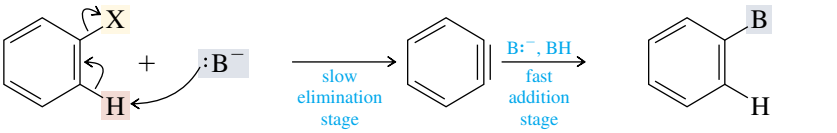
The rate-determining intermediate is a cyclohexadienyl anion and is stabilized by electron-withdrawing substituents.

Section 23.7 Other aryl halides that give stabilized anions can undergo nucleophilic aromatic substitution by the addition–elimination mechanism. Two examples are hexafluorobenzene and 2-chloropyridine.



Hexafluorobenzene | 2-Chloropyridine

Section 23.8 Nucleophilic aromatic substitution can also occur by an **elimination–addition mechanism.** This pathway is followed when the nucleophile is an exceptionally strong base such as amide ion in the form of sodium amide ($NaNH_2$) or potassium amide (KNH_2). **Benzyne** and related **arynes** are intermediates in nucleophilic aromatic substitutions that proceed by the elimination–addition mechanism.



Aryl halide | Strong base | Benzyne | Product of nucleophilic aromatic substitution

Nucleophilic aromatic substitution by the elimination–addition mechanism can lead to substitution on the same carbon that bore the leaving group or on an adjacent carbon.

Section 23.9 Benzyne is a reactive dienophile and gives Diels–Alder products when generated in the presence of dienes. In these cases it is convenient to form benzyne by dissociation of the Grignard reagent of *o*-bromofluorobenzene.

PROBLEMS

23.10 Write a structural formula for each of the following:

(a) *m*-Chlorotoluene
(b) 2,6-Dibromoanisole
(c) *p*-Fluorostyrene
(d) 4,4′-Diiodobiphenyl
(e) 2-Bromo-1-chloro-4-nitrobenzene
(f) 1-Chloro-1-phenylethane
(g) *p*-Bromobenzyl chloride
(h) 2-Chloronaphthalene
(i) 1,8-Dichloronaphthalene
(j) 9-Fluorophenanthrene

23.11 Identify the major organic product of each of the following reactions. If two regioisomers are formed in appreciable amounts, show them both.

(a) Chlorobenzene + acetyl chloride $\xrightarrow{AlCl_3}$

(b) Bromobenzene + magnesium $\xrightarrow{\text{diethyl ether}}$

(c) Product of part (b) + dilute hydrochloric acid $\longrightarrow$

(d) Iodobenzene + lithium $\xrightarrow{\text{diethyl ether}}$

(e) Bromobenzene + sodium amide $\xrightarrow{\text{liquid ammonia, } -33^\circ C}$

(f) *p*-Bromotoluene + sodium amide $\xrightarrow{\text{liquid ammonia, } -33^\circ C}$

(g) 1-Bromo-4-nitrobenzene + ammonia $\longrightarrow$

(h) *p*-Bromobenzyl bromide + sodium cyanide $\longrightarrow$

(i) *p*-Chlorobenzenediazonium chloride + *N,N*-dimethylaniline $\longrightarrow$

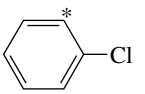
(j) Hexafluorobenzene + sodium hydrogen sulfide $\longrightarrow$

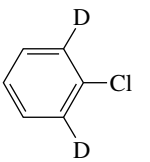
23.12 Potassium *tert*-butoxide reacts with halobenzenes on heating in dimethyl sulfoxide to give *tert*-butyl phenyl ether.

(a) *o*-Fluorotoluene yields *tert*-butyl *o*-methylphenyl ether almost exclusively under these conditions. By which mechanism (addition–elimination or elimination–addition) do aryl fluorides react with potassium *tert*-butoxide in dimethyl sulfoxide?

(b) At 100°C, bromobenzene reacts over 20 times faster than fluorobenzene. By which mechanism do aryl bromides react?

23.13 Predict the products formed when each of the following isotopically substituted derivatives of chlorobenzene is treated with sodium amide in liquid ammonia. Estimate as quantitatively as possible the composition of the product mixture. The asterisk (*) in part (a) designates ^{14}C, and D in part (b) is ^{2}H.

(a) 

(b) 

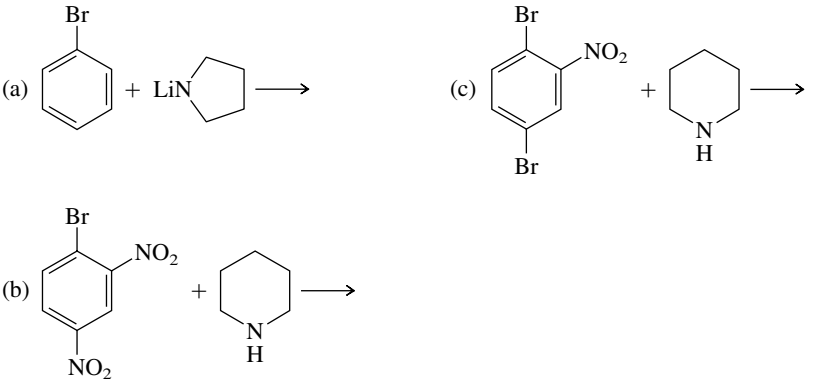
23.14 Choose the compound in each of the following pairs that reacts faster with sodium methoxide in methanol at 50°C:

(a) Chlorobenzene or *o*-chloronitrobenzene
(b) *o*-Chloronitrobenzene or *m*-chloronitrobenzene
(c) 4-Chloro-3-nitroacetophenone or 4-chloro-3-nitrotoluene

(d) 2-Fluoro-1,3-dinitrobenzene or 1-fluoro-3,5-dinitrobenzene

(e) 1,4-Dibromo-2-nitrobenzene or 1-bromo-2,4-dinitrobenzene

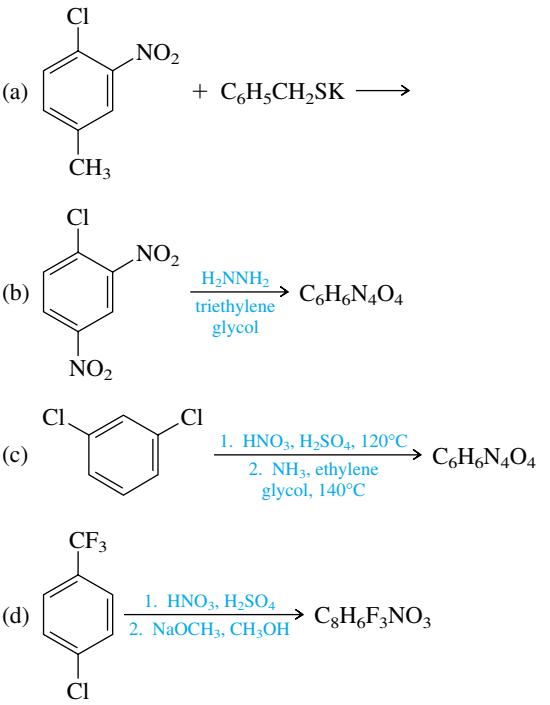
23.15 In each of the following reactions, an amine or a lithium amide derivative reacts with an aryl halide. Give the structure of the expected product, and specify the mechanism by which it is formed.

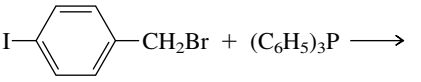


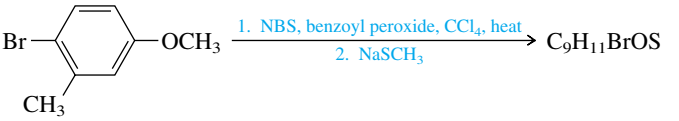
23.16 Piperidine, the amine reactant in parts (b) and (c) of the preceding problem, reacts with 1-bromonaphthalene on heating at 230°C to give a single product, compound A ($C_{15}H_{17}N$), as a noncrystallizable liquid. The same reaction using 2-bromonaphthalene yielded an isomeric product, compound B, a solid melting at 50–53°C. Mixtures of A and B were formed when either 1- or 2-bromonaphthalene was allowed to react with sodium piperidide in piperidine. Suggest reasonable structures for compounds A and B and offer an explanation for their formation under each set of reaction conditions.

23.17 1,2,3,4,5-Pentafluoro-6-nitrobenzene reacts readily with sodium methoxide in methanol at room temperature to yield two major products, each having the molecular formula $C_7H_3F_4NO_3$. Suggest reasonable structures for these two compounds.

23.18 Predict the major organic product in each of the following reactions:

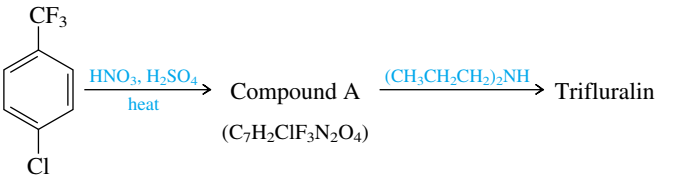


(e) 

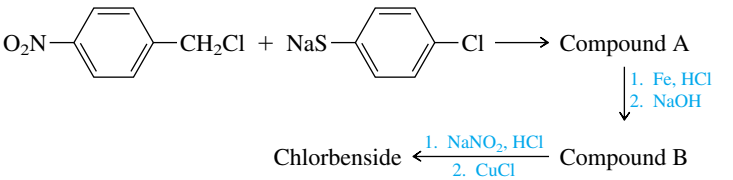
(f) 

23.19 The hydrolysis of *p*-bromotoluene with aqueous sodium hydroxide at 300°C yields *m*-methylphenol and *p*-methylphenol in a 5:4 ratio. What is the meta–para ratio for the same reaction carried out on *p*-chlorotoluene?

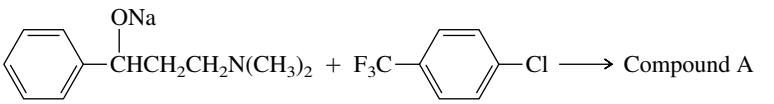
23.20 The herbicide *trifluralin* is prepared by the following sequence of reactions. Identify compound A and deduce the structure of trifluralin.



23.21 *Chlorbenside* is a pesticide used to control red spider mites. It is prepared by the sequence shown. Identify compounds A and B in this sequence. What is the structure of chlorbenside?

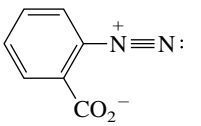


23.22 An article in the October 1998 issue of the *Journal of Chemical Education* (p. 1266) describes the following reaction.



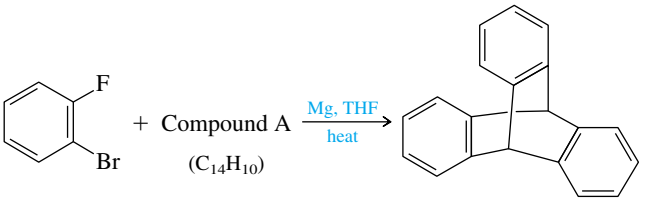
Fluoxetine hydrochloride (Prozac) is a widely prescribed antidepressant drug introduced by Eli Lilly & Co. in 1986. It differs from Compound A in having an $—NHCH_3$ group in place of $—N(CH_3)_2$. What is the structure of Prozac?

23.23 A method for the generation of benzyne involves heating the diazonium salt from *o*-aminobenzoic acid (benzenediazonium-2-carboxylate). Using curved arrows, show how this substance forms benzyne. What two inorganic compounds are formed in this reaction?



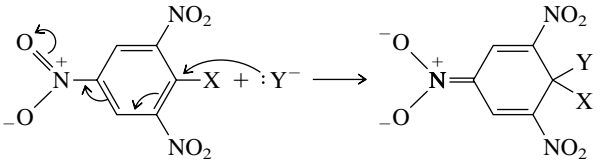
Benzenediazonium-2-carboxylate

23.24 The compound *triptycene* may be prepared as shown. What is compound A?



Triptycene

23.25 Nitro-substituted aromatic compounds that do not bear halide leaving groups react with nucleophiles according to the equation



The product of this reaction, as its sodium salt, is called a *Meisenheimer complex* after the German chemist Jacob Meisenheimer, who reported on their formation and reactions in 1902. A Meisenheimer complex corresponds to the product of the nucleophilic addition stage in the addition–elimination mechanism for nucleophilic aromatic substitution.

(a) Give the structure of the Meisenheimer complex formed by addition of sodium ethoxide to 2,4,6-trinitroanisole.

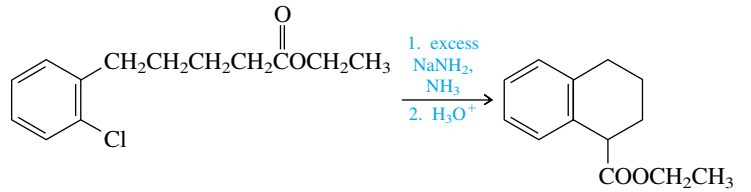
(b) What other combination of reactants yields the same Meisenheimer complex as that of part (a)?

23.26 A careful study of the reaction of 2,4,6-trinitroanisole with sodium methoxide revealed that two different Meisenheimer complexes were present. Suggest reasonable structures for these two complexes.

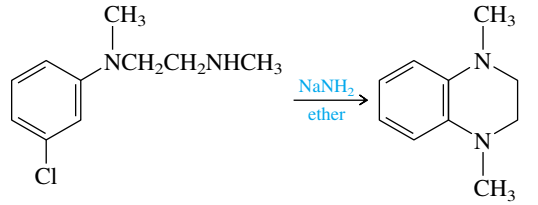
23.27 Suggest a reasonable mechanism for each of the following reactions:

(a) $C_6H_5Br + CH_2(COOCH_2CH_3)_2 \xrightarrow[2.\ H_3O^+]{1.\ \text{excess } NaNH_2,\ NH_3} C_6H_5CH(COOCH_2CH_3)_2$

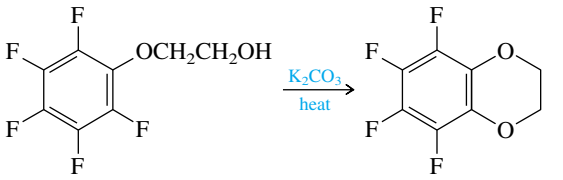
(b)



(c)



(d)



23.28 Mixtures of chlorinated derivatives of biphenyl, called *polychlorinated biphenyls,* or *PCBs,* were once prepared industrially on a large scale as insulating materials in electrical equipment. As equipment containing PCBs was discarded, the PCBs entered the environment at a rate that reached an estimated 25,000 lb/year. PCBs are very stable and accumulate in the fatty tissue of fish, birds, and mammals. They have been shown to be *teratogenic,* meaning that they induce mutations in the offspring of affected individuals. Some countries have banned the use of PCBs. A large number of chlorinated biphenyls are possible, and the commercially produced material is a mixture of many compounds.

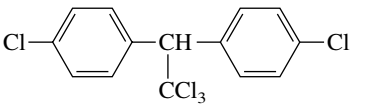
(a) How many monochloro derivatives of biphenyl are possible?

(b) How many dichloro derivatives are possible?

(c) How many octachloro derivatives are possible?

(d) How many nonachloro derivatives are possible?

23.29 DDT-resistant insects have the ability to convert DDT to a less toxic substance called DDE. The mass spectrum of DDE shows a cluster of peaks for the molecular ion at *m/z* 316, 318, 320, 322, and 324. Suggest a reasonable structure for DDE.



DDT (*d*ichloro*d*iphenyl*t*richloroethane)