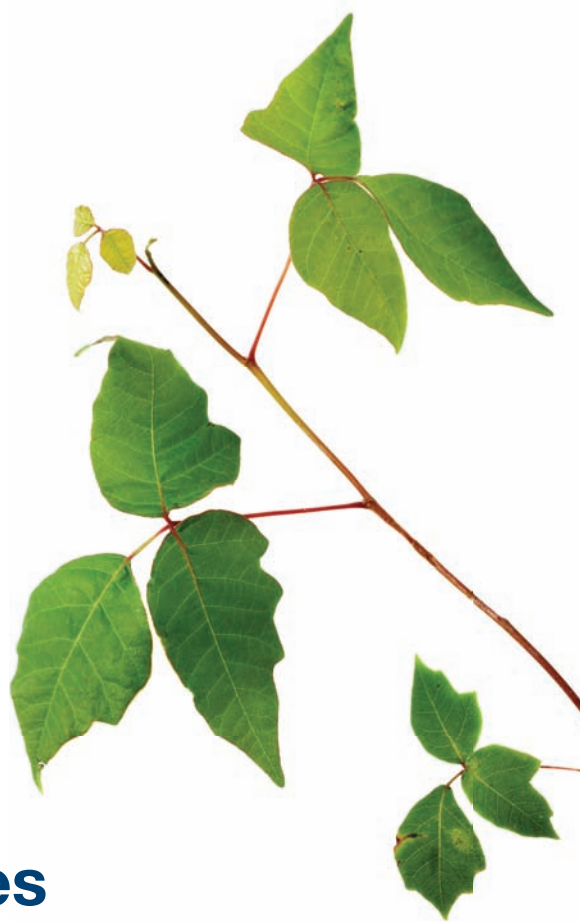
CHAPTER

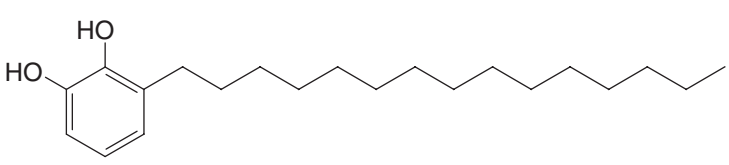
21



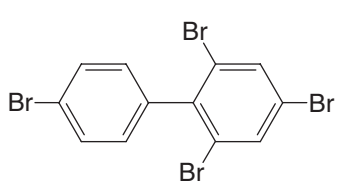
Phenols and Aryl Halides

NUCLEOPHILIC AROMATIC SUBSTITUTION

Although we have already studied the chemistry of both alcohols and halides, when these functional groups are attached to benzene rings to make phenols and aryl halides, some unique chemical reactivity results. For instance, phenols take part in a powerful bond-forming process known as the Claisen rearrangement, while certain aryl halides can participate in *nucleophilic* aromatic substitution reactions. Phenols and aryl halides also have unique physical and biochemical properties. Some phenols act as hormones and play a role in chemical signaling, others are antioxidants and antibiotics, and still others are the blistering agents found in poison ivy (shown below). Aryl halides are also quite useful, although several, such as polychlorinated and polybrominated biphenyls, have been shown to be harmful to the environment.



A poison ivy blistering agent



A polybrominated biphenyl

PHOTO CREDIT: © NoDerog/iStockphoto

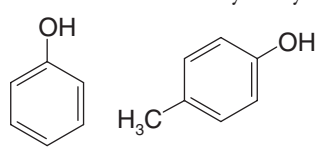
IN THIS CHAPTER WE WILL CONSIDER:

- the synthesis and properties of phenols
- the synthesis and properties of aryl halides
- powerful transformations using the functionality of phenols and aryl halides, such as the Claisen rearrangement and nucleophilic aromatic substitution

[WHY DO THESE TOPICS MATTER?] At the end of this chapter, we will show how subtle alterations in the structures of one specific group of phenols can turn compounds with a pleasant odor and taste profile into molecules that can both lead to the perception of pain as well as serve as analgesics.

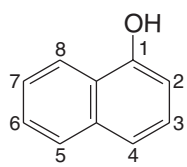
21.1 STRUCTURE AND NOMENCLATURE OF PHENOLS

Compounds that have a hydroxyl group directly attached to a benzene ring are called **phenols**. Thus, **phenol** is the specific name for hydroxybenzene, and it is the general name for the family of compounds derived from hydroxybenzene:

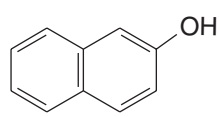


Phenol **4-Methylphenol (a phenol)**

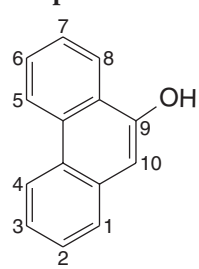
Compounds that have a hydroxyl group attached to a polycyclic benzenoid ring are chemically similar to phenols, but they are called **naphthols** and **phenanthrols**. For example:



1-Naphthol (α-naphthol)



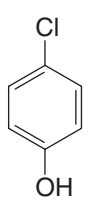
2-Naphthol (β-naphthol)



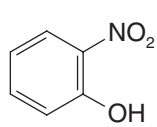
9-Phenanthrol

21.1A Nomenclature of Phenols

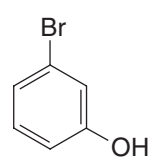
We studied the nomenclature of some phenols in Chapter 14. In many compounds *phenol* is the base name:



4-Chlorophenol (*p*-chlorophenol)

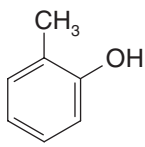


2-Nitrophenol (*o*-nitrophenol)

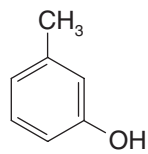


3-Bromophenol (*m*-bromophenol)

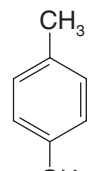
The methylphenols are commonly called *cresols*:



2-Methylphenol (*o*-cresol)

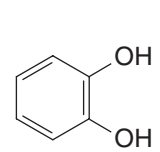


3-Methylphenol (*m*-cresol)

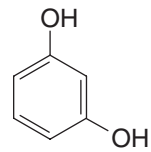


4-Methylphenol (*p*-cresol)

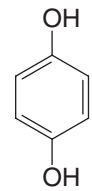
The benzenediols also have common names:



1,2-Benzenediol (catechol)



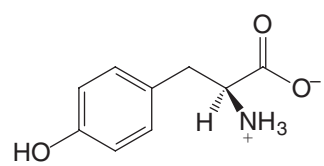
1,3-Benzenediol (resorcinol)



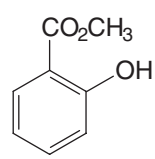
1,4-Benzenediol (hydroquinone)

21.2 NATURALLY OCCURRING PHENOLS

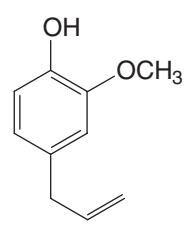
Phenols and related compounds occur widely in nature. Tyrosine is an amino acid that occurs in proteins. Methyl salicylate is found in oil of wintergreen, eugenol is found in oil of cloves, and thymol is found in thyme.



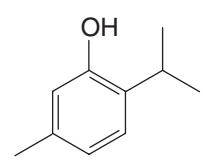
L-Tyrosine



Methyl salicylate (oil of wintergreen)

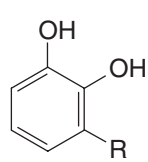


Eugenol (oil of cloves)



Thymol (thyme)

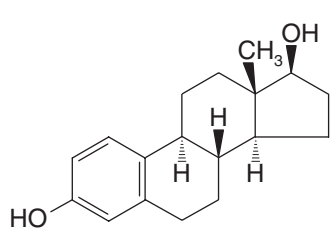
The urushiols are blistering agents (vesicants) found in poison ivy.



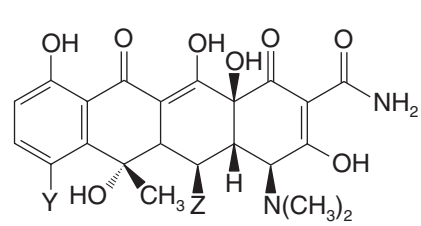
Urushiols

R = $-(CH_2)_{14}CH_3$,
$-(CH_2)_7CH{=}CH(CH_2)_5CH_3$, or
$-(CH_2)_7CH{=}CHCH_2CH{=}CH(CH_2)_2CH_3$, or
$-(CH_2)_7CH{=}CHCH_2CH{=}CHCH{=}CHCH_3$ or
$-(CH_2)_7CH{=}CHCH_2CH{=}CHCH_2CH{=}CH_2$

Estradiol is a female sex hormone, and the tetracyclines are important antibiotics.



Estradiol



Tetracyclines
(Y = Cl, Z = H; Aureomycin)
(Y = H, Z = OH; Terramycin)

21.3 PHYSICAL PROPERTIES OF PHENOLS

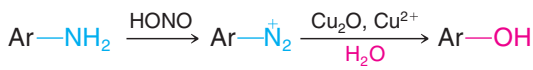
The presence of hydroxyl groups in phenols means that phenols are like alcohols (Section 11.2) in some respects. For example, they are able to form strong intermolecular hydrogen bonds, and therefore have higher boiling points than hydrocarbons of the same molecular weight. Phenol (bp 182 °C) has a boiling point more than 70 °C higher than toluene (bp 110.6 °C), even though the two compounds have almost the same molecular weight. Phenols are also modestly soluble in water because of their ability to form strong hydrogen bonds with water molecules.

21.4 SYNTHESIS OF PHENOLS

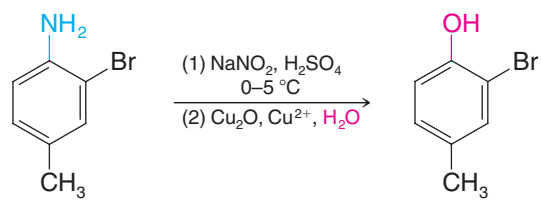
21.4A Laboratory Synthesis

The most important laboratory synthesis of phenols is by hydrolysis of arenediazonium salts (Section 20.7E). This method is highly versatile, and the conditions required for the diazotization step and the hydrolysis step are mild. This means that other groups present on the ring are unlikely to be affected.

General Reaction



Specific Example

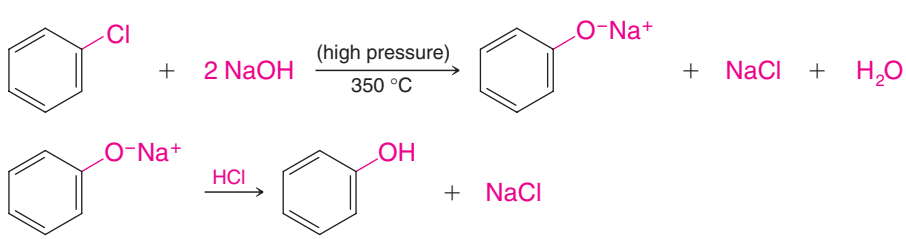


2-Bromo-4-methylphenol (80–92%)

21.4B Industrial Syntheses

Phenol is a highly important industrial chemical; it serves as the raw material for a large number of commercial products ranging from aspirin to a variety of plastics. Worldwide production of phenol (which in industry is sometimes called carbolic acid) is more than 3 million tons per year. Several methods have been used to synthesize phenol commercially.

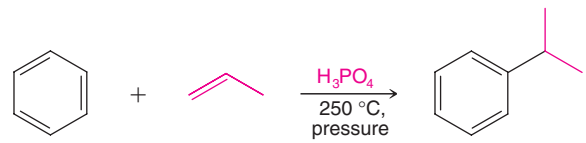
1. **Hydrolysis of Chlorobenzene (Dow Process).** In this process chlorobenzene is heated at 350 °C (under high pressure) with aqueous sodium hydroxide. The reaction produces sodium phenoxide, which, on acidification, yields phenol. The mechanism for the reaction probably involves the formation of benzyne (Section 21.11B).



2. **From Cumene Hydroperoxide.** This process illustrates industrial chemistry at its best. Overall, it is a method for converting two relatively inexpensive organic compounds—benzene and propene—into two more valuable ones—phenol and acetone. The only other substance consumed in the process is oxygen from air. Most of the worldwide production of phenol is now based on this method. The synthesis

begins with the Friedel–Crafts alkylation of benzene with propene to produce cumene (isopropylbenzene):

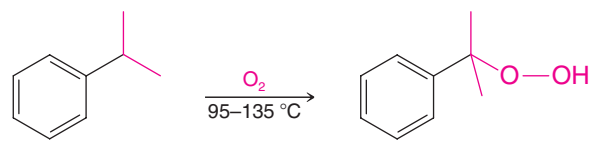
Reaction 1



Cumene

Then cumene is oxidized to cumene hydroperoxide:

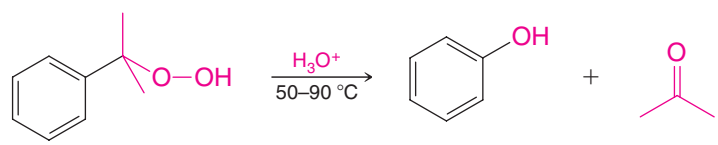
Reaction 2



Cumene hydroperoxide

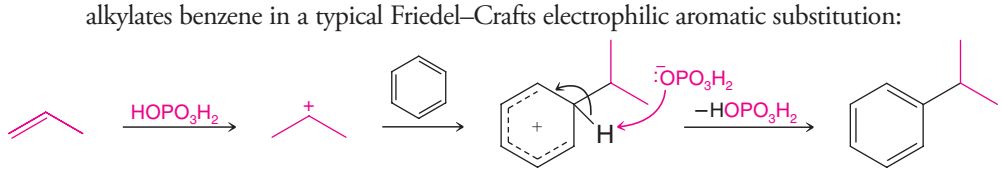
Finally, when treated with 10% sulfuric acid, cumene hydroperoxide undergoes a hydrolytic rearrangement that yields phenol and acetone:

Reaction 3



Phenol **Acetone**

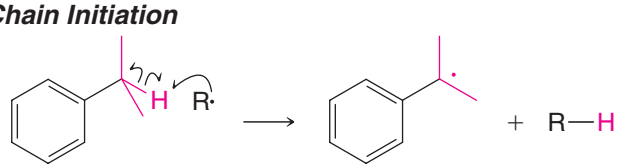
The mechanism of each of the reactions in the synthesis of phenol from benzene and propene via cumene hydroperoxide requires some comment. The first reaction is a familiar one. The isopropyl cation generated by the reaction of propene with the acid (H_3PO_4) alkylates benzene in a typical Friedel–Crafts electrophilic aromatic substitution:



The second reaction is a radical chain reaction. A radical initiator abstracts the benzylic hydrogen atom of cumene, producing a 3° benzylic radical. Then a chain reaction with oxygen, which exists as a paramagnetic diradical in the ground state, produces cumene hydroperoxide:

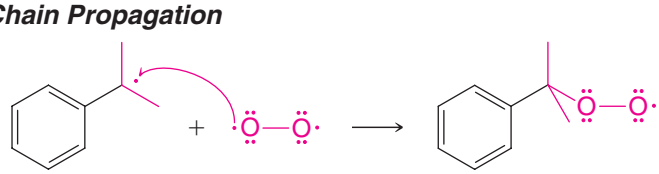
Chain Initiation

Step 1

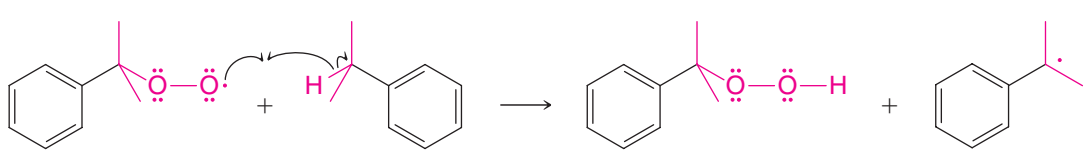


Chain Propagation

Step 2

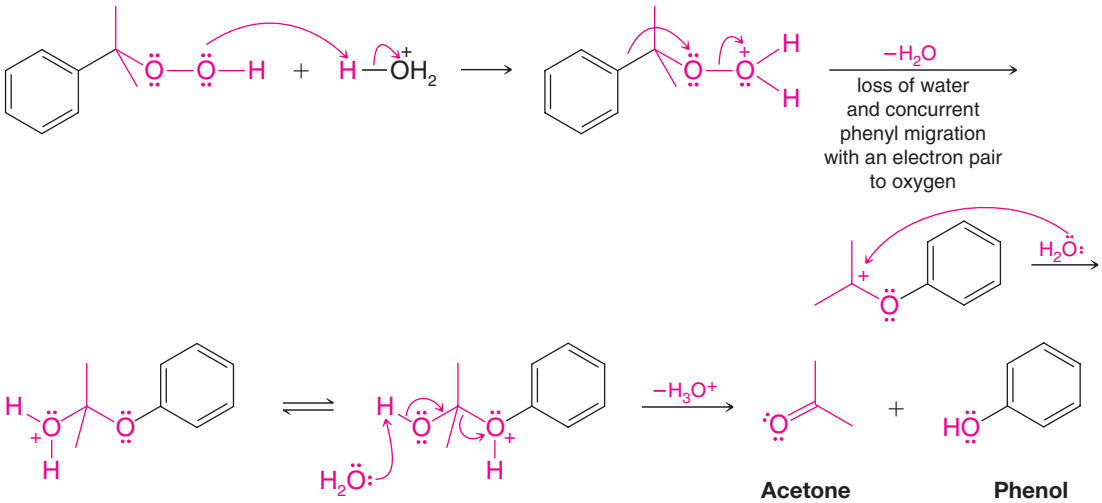


Step 3



The reaction continues with steps 2, 3, 2, 3, and so on.

The third reaction—the hydrolytic rearrangement—resembles the carbocation rearrangements that we have studied before. In this instance, however, the rearrangement involves the migration of a phenyl group to *a cationic oxygen atom*. Phenyl groups have a much greater tendency to migrate to a cationic center than do methyl groups. The following equations show all the steps of the mechanism.



The second and third steps of the mechanism may actually take place at the same time; that is, the loss of H_2O and the migration of C_6H_5— may be concerted.

21.5 REACTIONS OF PHENOLS AS ACIDS

21.5A Strength of Phenols as Acids

Although phenols are structurally similar to alcohols, they are much stronger acids. The pK_a values of most alcohols are of the order of 18. However, as we see in Table 21.1, the pK_a values of phenols are smaller than 11.

TABLE 21.1 ACIDITY CONSTANTS OF PHENOLS

Name	pK_a (in H_2O at 25 °C)	Name	pK_a (in H_2O at 25 °C)
Phenol	9.89	3-Nitrophenol	8.28
2-Methylphenol	10.20	4-Nitrophenol	7.15
3-Methylphenol	10.01	2,4-Dinitrophenol	3.96
4-Methylphenol	10.17	2,4,6-Trinitrophenol (picric acid)	0.38
2-Chlorophenol	8.11		
3-Chlorophenol	8.80	1-Naphthol	9.31
4-Chlorophenol	9.20	2-Naphthol	9.55
2-Nitrophenol	7.17		

Let us compare two *superficially* similar compounds, cyclohexanol and phenol:

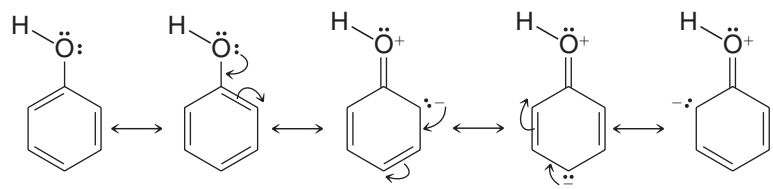
Cyclohexanol pK_a = 18 **Phenol** pK_a = 9.89

Although phenol is a weak acid when compared with a carboxylic acid such as acetic acid ($pK_a = 4.76$), phenol is a much stronger acid than cyclohexanol (by a factor of eight pK_a units).

Experimental and theoretical results have shown that the greater acidity of phenol owes itself primarily to an electrical charge distribution in phenol that causes the —OH oxygen to be more positive; therefore, the proton is held less strongly. In effect, the benzene ring of phenol acts as if it were an electron-withdrawing group when compared with the cyclohexane ring of cyclohexanol.

We can understand this effect by noting that the carbon atom which bears the hydroxyl group in phenol is sp^2 hybridized, whereas in cyclohexane it is sp^3 hybridized. Because of their greater *s* character, sp^2-hybridized carbon atoms are more electronegative than sp^3-hybridized carbon atoms (Section 3.8A).

Another factor influencing the electron distribution may be the contributions to the overall resonance hybrid of phenol made by structures **2**–**4**. Notice that the effect of these structures is to withdraw electrons from the hydroxyl group and to make the oxygen positive:

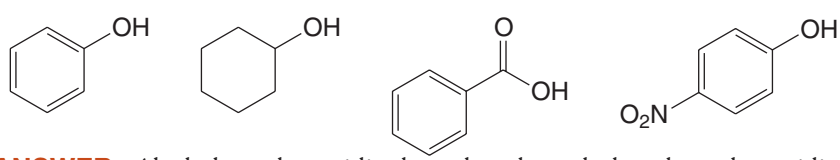


Resonance structures for phenol

An alternative explanation for the greater acidity of phenol relative to cyclohexanol can be based on similar resonance structures for the phenoxide ion. Unlike the structures for phenol, **2**–**4**, resonance structures for the phenoxide ion do not involve charge separation. According to resonance theory, such structures should stabilize the phenoxide ion more than structures **2**–**4** stabilize phenol. (No resonance structures can be written for cyclohexanol or its anion, of course.) Greater stabilization of the phenoxide ion (the conjugate base) than of phenol (the acid) has an acid-strengthening effect.

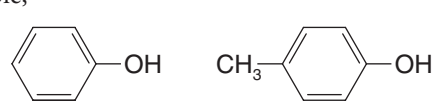
SOLVED PROBLEM 21.1

Rank the following compounds in order of increasing acidity.



STRATEGY AND ANSWER: Alcohols are less acidic than phenols, and phenols are less acidic than carboxylic acids. An electron-withdrawing group increases the acidity of a phenol relative to phenol itself. Thus the order of increasing acidity among these examples is cyclohexanol < phenol < 4-nitrophenol < benzoic acid.

PRACTICE PROBLEM 21.1 If we examine Table 21.1, we find that the methylphenols (cresols) are less acidic than phenol itself. For example,



Phenol $pK_a = 9.89$ **4-Methylphenol** $pK_a = 10.17$

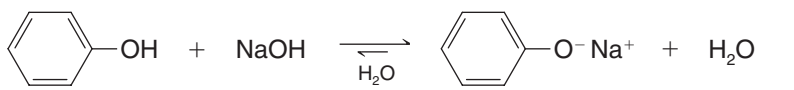
This behavior is characteristic of phenols bearing electron-releasing groups. Provide an explanation.

PRACTICE PROBLEM 21.2

If we examine Table 21.1, we see that phenols having electron-withdrawing groups (Cl— or O_2N—) attached to the benzene ring are more acidic than phenol itself. Account for this trend on the basis of resonance and inductive effects. Your answer should also explain the large acid-strengthening effect of nitro groups, an effect that makes 2,4,6-trinitrophenol (also called *picric acid*) so exceptionally acidic ($pK_a = 0.38$) that it is more acidic than acetic acid ($pK_a = 4.76$).

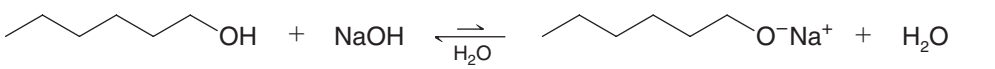
21.5B Distinguishing and Separating Phenols from Alcohols and Carboxylic Acids

Because phenols are more acidic than water, the following reaction goes essentially to completion and produces water-soluble sodium phenoxide:



Stronger acid $pK_a \cong 10$ **(slightly soluble)** + **Stronger base** ⇌ H_2O → **Weaker base (soluble)** + **Weaker acid** $pK_a \cong 16$

The corresponding reaction of 1-hexanol with aqueous sodium hydroxide does not occur to a significant extent because 1-hexanol is a weaker acid than water:



Weaker acid $pK_a \cong 18$ **(very slightly soluble)** + **Weaker base** ⇌ H_2O → **Stronger base** + **Stronger acid** $pK_a \cong 16$

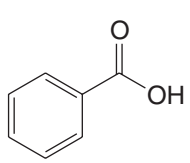
The fact that phenols dissolve in aqueous sodium hydroxide, whereas most alcohols with six carbon atoms or more do not, gives us a convenient means for distinguishing and separating phenols from most alcohols. (Alcohols with five carbon atoms or fewer are quite soluble in water—some are infinitely so—and so they dissolve in aqueous sodium hydroxide even though they are not converted to sodium alkoxides in appreciable amounts.)

Most phenols, however, are not soluble in aqueous sodium bicarbonate ($NaHCO_3$), but carboxylic acids are soluble. Thus, aqueous $NaHCO_3$ provides a method for distinguishing and separating most phenols from carboxylic acids.

SOLVED PROBLEM 21.2

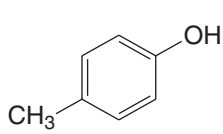
Assume that each of the following mixtures was added to a flask or a separatory funnel that contained diethyl ether (as an organic solvent) and mixed well. In which layer (diethyl ether or water) would the organic compound predominate in each case, and in what form would it exist (in its neutral form or as its conjugate base)?

(a)



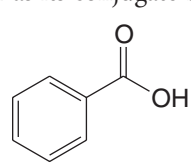
+ aqueous $NaHCO_3$

(b)



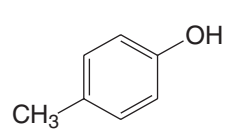
+ aqueous $NaHCO_3$

(c)



+ aqueous NaOH

(d)



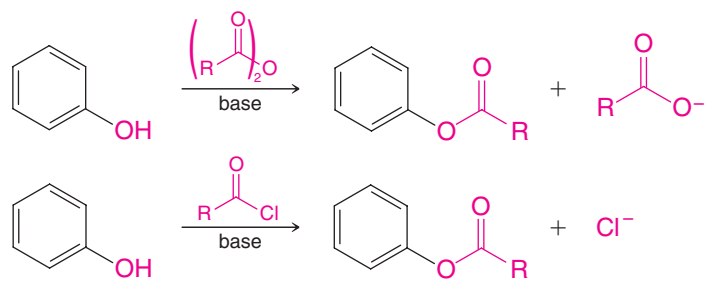
+ aqueous NaOH

STRATEGY AND ANSWER: Sodium bicarbonate will remove a proton from a carboxylic acid to form a water-soluble carboxylate salt, but sodium bicarbonate will not remove a proton from a typical phenol. Sodium hydroxide will remove a proton from both a carboxylic acid and a phenol to form salts in each case. Thus, in **(a)** benzoic acid will be found in the water layer as its sodium salt, whereas in **(b)** 4-methylphenol will remain in its neutral form and be found predominantly in the ether layer. In **(c)** and **(d)** both benzoic acid and 4-methylphenol will be found in the aqueous layer as their corresponding salts.

PRACTICE PROBLEM 21.3 Your laboratory instructor gives you a mixture of 4-methylphenol, benzoic acid, and toluene. Assume that you have available common laboratory acids, bases, and solvents and explain how you would proceed to separate this mixture by making use of the solubility differences of its components.

21.6 OTHER REACTIONS OF THE O—H GROUP OF PHENOLS

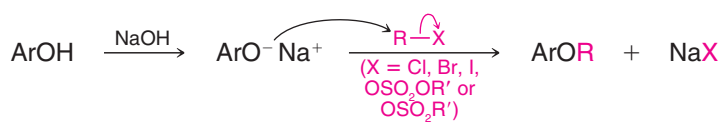
Phenols react with carboxylic acid anhydrides and acid chlorides to form esters. These reactions are quite similar to those of alcohols (Section 17.7).



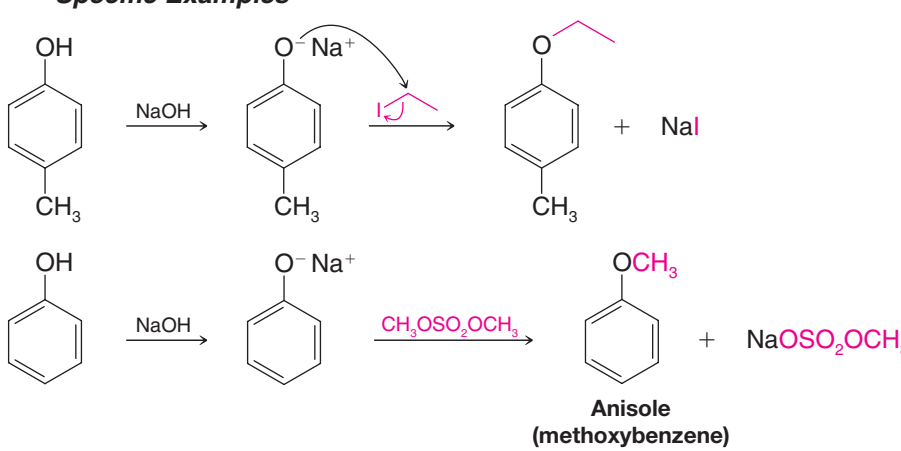
21.6A Phenols in the Williamson Synthesis

Phenols can be converted to ethers through the Williamson synthesis (Section 11.11B). Because phenols are more acidic than alcohols, they can be converted to sodium phenoxides through the use of sodium hydroxide (rather than sodium hydride or metallic sodium, the reagents used to convert alcohols to alkoxide ions).

General Reaction



Specific Examples



21.7 CLEAVAGE OF ALKYL ARYL ETHERS

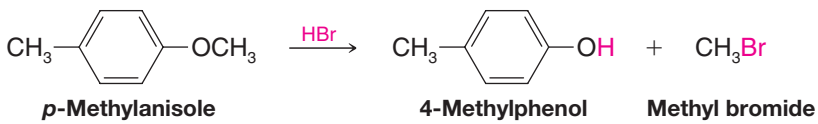
We learned in Section 11.12A that when dialkyl ethers are heated with excess concentrated HBr or HI, the ethers are cleaved and alkyl halides are produced from both alkyl groups:

When alkyl aryl ethers react with strong acids such as HI and HBr, the reaction produces an alkyl halide and a phenol. The phenol does not react further to produce an aryl halide because the phenol carbon–oxygen bond is very strong and because phenyl cations do not form readily.

General Reaction

$$\text{Ar—O—R} \xrightarrow[\text{heat}]{\text{concd HX}} \text{Ar—OH} + \text{R—X}$$

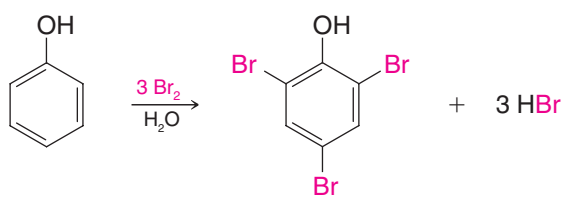
Specific Example



***p*-Methylanisole** **4-Methylphenol** **Methyl bromide**

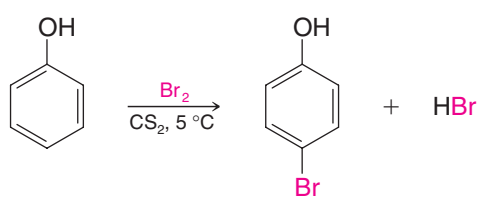
21.8 REACTIONS OF THE BENZENE RING OF PHENOLS

Bromination The hydroxyl group is a powerful activating group—and an ortho–para director—in **electrophilic aromatic substitutions**. Phenol itself reacts with bromine in aqueous solution to yield 2,4,6-tribromophenol in nearly quantitative yield. Note that a Lewis acid is not required for the bromination of this highly activated ring:



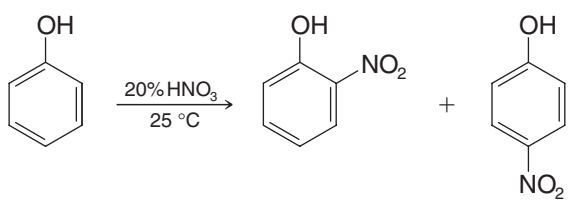
2,4,6-Tribromophenol (~100%)

Monobromination of phenol can be achieved by carrying out the reaction in carbon disulfide at a low temperature, conditions that reduce the electrophilic reactivity of bromine. The major product is the para isomer:



***p*-Bromophenol (80–84%)**

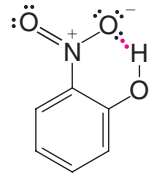
Nitration Phenol reacts with dilute nitric acid to yield a mixture of *o*- and *p*-nitrophenol:



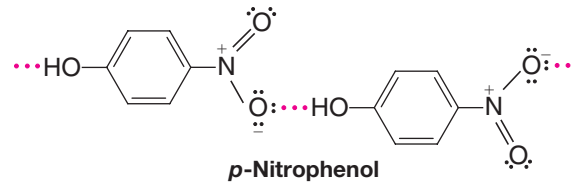
30–40% **15%**

Although the yield is relatively low (because of oxidation of the ring), the ortho and para isomers can be separated by steam distillation. *o*-Nitrophenol is the more volatile isomer because its hydrogen bonding (see the following structures) is *intramolecular*. *p*-Nitrophenol is less volatile because *intermolecular* hydrogen bonding causes association

among its molecules. Thus, *o*-nitrophenol passes over with the steam, and *p*-nitrophenol remains in the distillation flask.

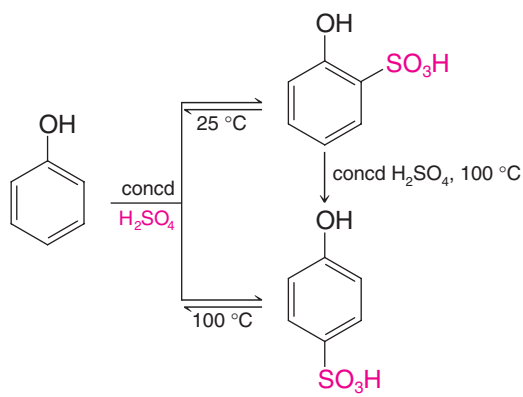


***o*-Nitrophenol**
(more volatile because of intramolecular hydrogen bonding)



***p*-Nitrophenol**
(less volatile because of intermolecular hydrogen bonding)

Sulfonation Phenol reacts with concentrated sulfuric acid to yield mainly the orthosulfonated product if the reaction is carried out at 25 °C and mainly the para-sulfonated product at 100 °C. This is another example of thermodynamic versus kinetic control of a reaction (Section 13.10A):



Major product under kinetic control

Major product under thermodynamic control

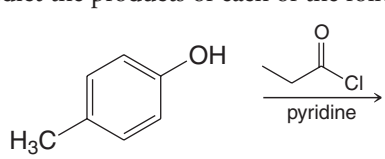
SOLVED PROBLEM 21.3

Consider the sulfonation reactions of phenol shown above. **(a)** Which sulfonation product is more stable, ortho or para? **(b)** For which sulfonation product is the free energy of activation lower?

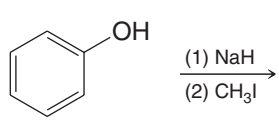
ANSWER: **(a)** The para-sulfonated phenol is more stable. We know this because at the higher temperature, where the reaction is under equilibrium control, it is the major product. **(b)** The free energy of activation is lower for ortho substitution. We know this because at the lower temperature, where the reaction is under kinetic control, it is formed faster.

PRACTICE PROBLEM 21.4 Predict the products of each of the following reactions.

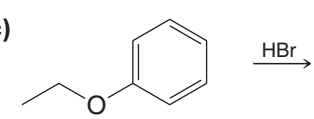
(a)



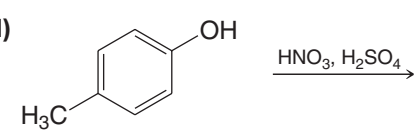
(b)



(c)



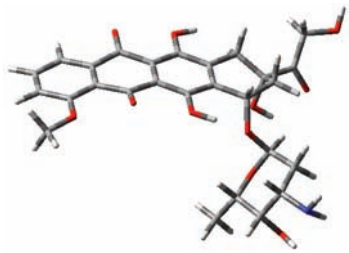
(d)



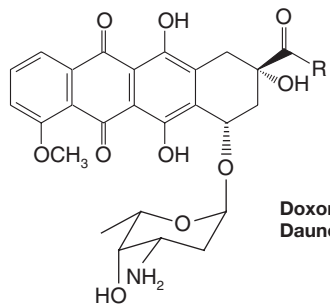
THE CHEMISTRY OF... Polyketide Anticancer Antibiotic Biosynthesis

Doxorubicin (also known as adriamycin) is a highly potent anticancer drug that contains phenol functional groups. It is effective against many forms of cancer, including tumors of the ovaries, breast, bladder, and lung, as well as against Hodgkin's disease and other acute leukemias. Doxorubicin is a member of the anthracycline family of antibiotics.

Another member of the family is daunomycin. Both of these antibiotics are produced in strains of *Streptomyces* bacteria by a pathway called polyketide biosynthesis.

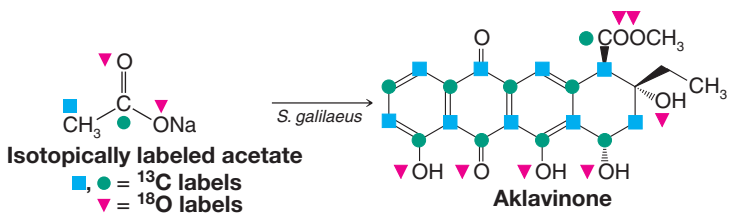


A molecular model of doxorubicin.



Doxorubicin (R = CH_2OH)
Daunomycin (R = CH_3)

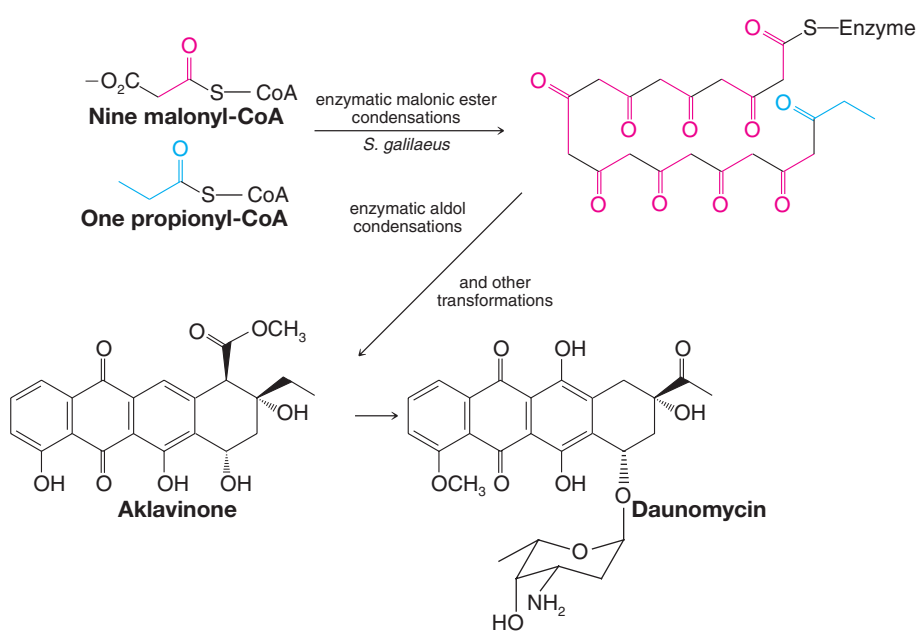
Isotopic labeling experiments have shown that daunomycin is synthesized in *Streptomyces galilaeus* from a tetracyclic precursor called aklavinone. Aklavinone, in turn, is synthesized from acetate. When *S. galilaeus* is grown in a medium containing acetate labeled with carbon-13 and oxygen-18, the aklavinone produced has isotopic labels in the positions indicated below. Notice that oxygen atoms occur at alternate carbons in several places around the structure, consistent with the linking of acetate units in head-to-tail fashion. This is typical of aromatic polyketide biosynthesis.



Isotopically labeled acetate
■, ● = ^{13}C labels
▼ = ^{18}O labels

Aklavinone

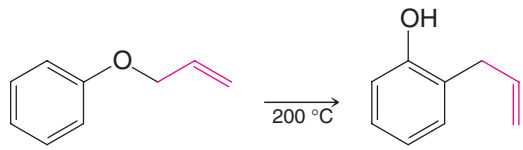
This and other information show that nine C_2 units from malonyl-coenzyme A and one C_3 unit from propionyl-coenzyme A condense to form the linear polyketide intermediate shown below. These units are joined by acylation reactions that are the biosynthetic equivalent of the *malonic ester synthesis* we studied in Section 18.7. These reactions are also similar to the acylation steps we saw in fatty acid biosynthesis (Special Topic E in *WileyPLUS*). Once formed, the linear polyketide cyclizes by enzymatic reactions akin to intramolecular *aldol additions and dehydrations* (Section 19.6). These steps form the tetracyclic core of aklavinone. Phenolic hydroxyl groups in aklavinone arise by enolization of ketone carbonyl groups present after the aldol condensation steps. Several other transformations ultimately lead to daunomycin:



There are many examples of important biologically active molecules formed by polyketide biosynthesis. Aureomycin and terramycin (Section 21.2) are examples of other aromatic polyketide antibiotics. Erythromycin (Section 17.7C) and aflatoxin, a carcinogen (see "Why do these topics matter?" in Chapter 14), are polyketides from other pathways.

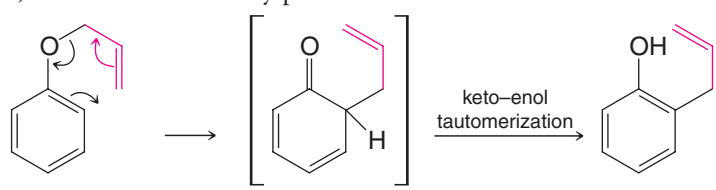
21.9 THE CLAISEN REARRANGEMENT

Heating allyl phenyl ether to 200 °C effects an intramolecular reaction called a **Claisen rearrangement**. The product of the rearrangement is *o*-allylphenol:



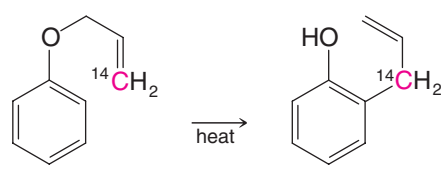
Allyl phenyl ether **o-Allylphenol**

The reaction takes place through a **concerted rearrangement** in which the bond between C3 of the allyl group and the ortho position of the benzene ring forms at the same time that the carbon–oxygen bond of the allyl phenyl ether breaks. The product of this rearrangement is an unstable intermediate that, like the unstable intermediate in the Kolbe reaction (Section 21.8), undergoes a proton shift (a keto–enol tautomerization, see Section 18.2) that leads to the *o*-allylphenol:



Unstable intermediate

That only C3 of the allyl group becomes bonded to the benzene ring was demonstrated by carrying out the rearrangement with allyl phenyl ether containing ^{14}C at C3. All of the product of this reaction had the labeled carbon atom bonded to the ring:



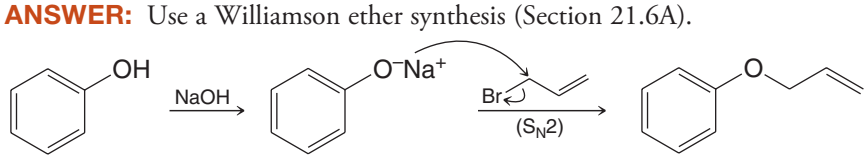
Only product

PRACTICE PROBLEM 21.5 The labeling experiment just described eliminates from consideration a mechanism in which the allyl phenyl ether dissociates to produce an allyl cation (Section 13.4) and a phenoxide ion, which then subsequently undergo a Friedel–Crafts alkylation (Section 15.6) to produce the *o*-allylphenol. Explain how this alternative mechanism can be discounted by showing the product (or products) that would result from it.

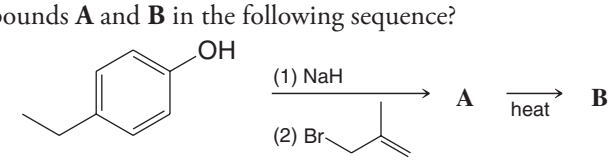
SOLVED PROBLEM 21.4

Show how you could synthesize allyl phenyl ether from phenol and allyl bromide.

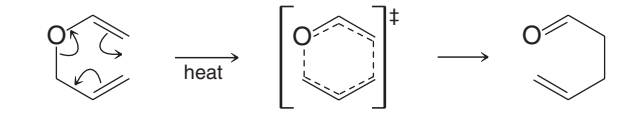
STRATEGY AND ANSWER: Use a Williamson ether synthesis (Section 21.6A).



PRACTICE PROBLEM 21.6 What are compounds **A** and **B** in the following sequence?

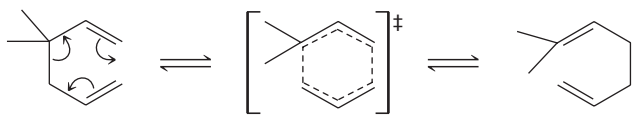


A Claisen rearrangement also takes place when allyl vinyl ethers are heated. For example,



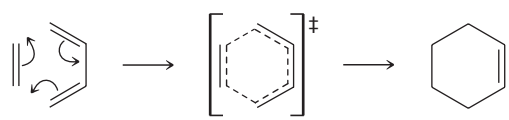
Allyl vinyl ether — **Aromatic transition state** — **4-Pentenal**

The transition state for the Claisen rearrangement involves a cycle of six electrons. Having six electrons suggests that the transition state has aromatic character (Section 14.7). Other reactions of this general type are known, and they are called **pericyclic reactions**. Another similar pericyclic reaction is the **Cope rearrangement** shown here:



3,3-Dimethyl-1,5-hexadiene — **Aromatic transition state** — **2-Methyl-2,6-heptadiene**

The Diels–Alder reaction (Section 13.11) is also a pericyclic reaction. The transition state for the Diels–Alder reaction also involves six electrons:

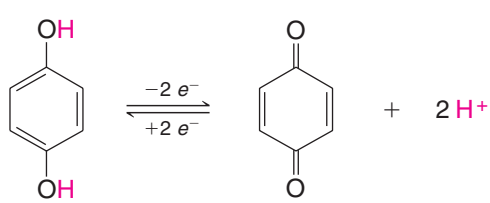


Aromatic transition state

The mechanism of the Diels–Alder reaction is discussed further in Special Topic H in *WileyPLUS*.

21.10 QUINONES

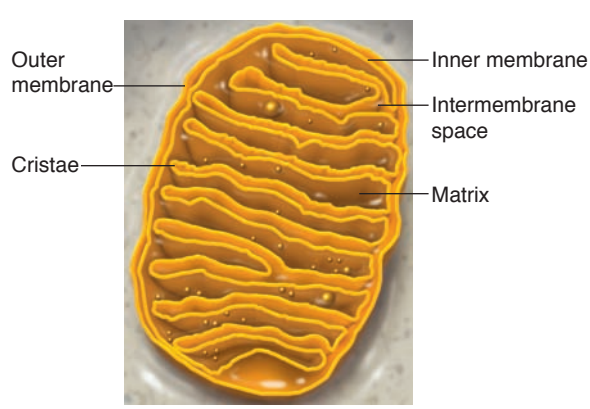
Oxidation of hydroquinone (1,4-benzenediol) produces a compound known as *p*-benzoquinone. The oxidation can be brought about by mild oxidizing agents, and, overall, the oxidation amounts to the removal of a pair of electrons (2 e^-) and two protons from hydroquinone. (Another way of visualizing the oxidation is as the loss of a hydrogen molecule, H:H, making it a dehydrogenation.)



Hydroquinone — ***p*-Benzoquinone**

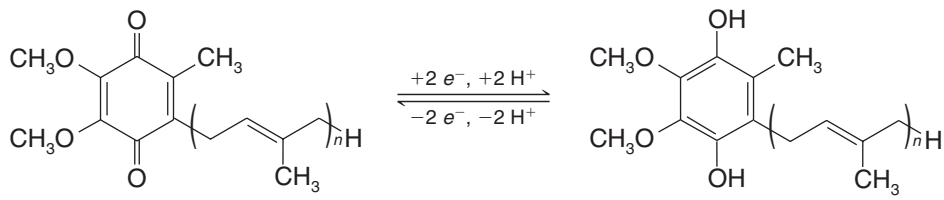
This reaction is reversible; *p*-benzoquinone is easily reduced by mild reducing agents to hydroquinone.

Nature makes much use of this type of reversible oxidation–reduction to transport a pair of electrons from one substance to another in enzyme-catalyzed reactions. Important compounds in this respect are the compounds called **ubiquinones** (from *ubiquitous* + quinone—these quinones are found within the inner mitochondrial membrane of every living cell). Ubiquinones are also called coenzymes Q (CoQ).



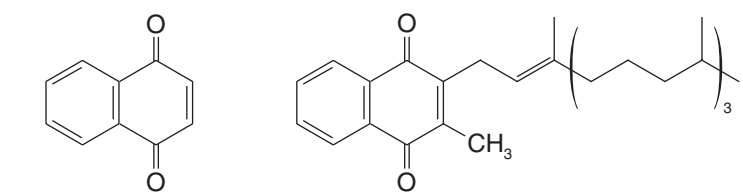
Cross section of a mitochondrion.

Ubiquinones have a long, isoprene-derived side chain (see Special Topic E in *WileyPLUS* and Section 23.3). Ten isoprene units are present in the side chain of human ubiquinones. This part of their structure is highly nonpolar, and it serves to solubilize the ubiquinones within the hydrophobic bilayer of the mitochondrial inner membrane. Solubility in the membrane environment facilitates their lateral diffusion from one component of the electron transport chain to another. In the electron transport chain, ubiquinones function by accepting two electrons and two hydrogen atoms to become a hydroquinone. The hydroquinone form carries the two electrons to the next acceptor in the chain:



Ubiquinones (n = 6–10) (coenzymes Q) **Ubiquinol (hydroquinone form)**

Vitamin K_1, the important dietary factor that is instrumental in maintaining the coagulant properties of blood, contains a 1,4-naphthoquinone structure:



1,4-Naphthoquinone **Vitamin K_1**

THE CHEMISTRY OF... The Bombardier Beetle's Noxious Spray

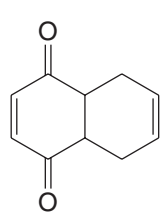
The bombardier beetle defends itself by spraying a jet stream of hot (100 °C), noxious *p*-benzoquinones at an attacker. The beetle mixes *p*-hydroquinones and hydrogen peroxide from one abdominal reservoir with enzymes from another reservoir. The enzymes convert hydrogen peroxide to oxygen, which in turn oxidizes the *p*-hydroquinones to *p*-benzoquinones and explosively propels the irritating spray at the attacker. Photos by T. Eisner and D. Aneshansley (Cornell University) have shown that the amazing bombardier beetle can direct its spray in virtually any direction, even parallel over its back, to ward off a predator.

Thomas Eisner and Daniel Aneshansley, Cornell University

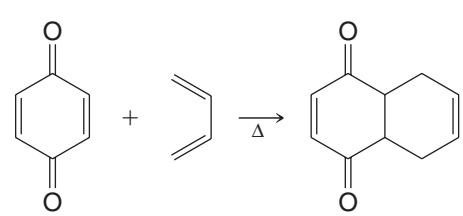
Bombardier beetle in the process of spraying.

SOLVED PROBLEM 21.5

Outline a synthesis of the following compound.



STRATEGY AND ANSWER: The presence of a cyclohexane ring with a double bond in it suggests that the compound could be made by a Diels–Alder reaction. Suitable reactants here would be *p*-benzoquinone as the dienophile and 1,3-butadiene as the diene.



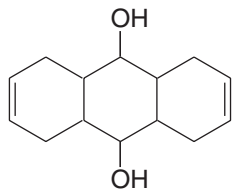
PRACTICE PROBLEM 21.7

p-Benzoquinone and 1,4-naphthoquinone act as dienophiles in Diels–Alder reactions. Give the structures of the products of the following reactions:

(a) 1,4-Naphthoquinone + butadiene **(b)** *p*-Benzoquinone + cyclopentadiene

PRACTICE PROBLEM 21.8

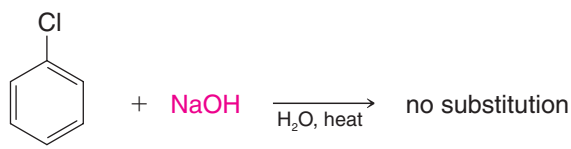
Outline a possible synthesis of the following compound.

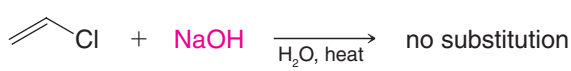


21.11 ARYL HALIDES AND NUCLEOPHILIC AROMATIC SUBSTITUTION

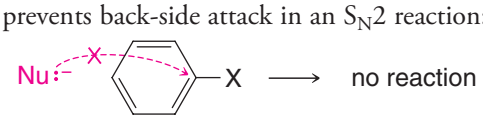
- Simple aryl halides, like vinylic halides (Section 6.14A), are relatively unreactive toward nucleophilic substitution under conditions that would give rapid nucleophilic substitution with alkyl halides.

Chlorobenzene, for example, can be boiled with sodium hydroxide for days without producing a detectable amount of phenol (or sodium phenoxide).* Similarly, when vinyl chloride is heated with sodium hydroxide, no substitution occurs:



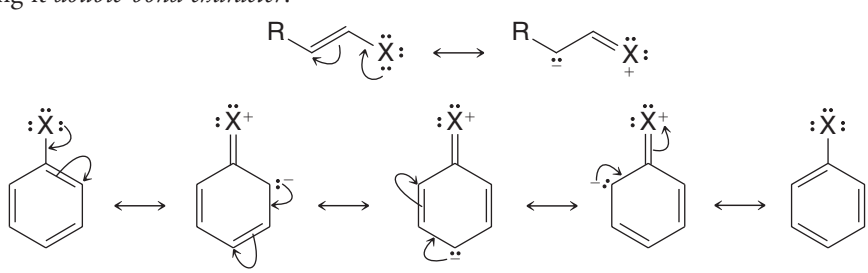


We can understand this lack of reactivity on the basis of several factors. The benzene ring of an aryl halide prevents back-side attack in an S_N2 reaction:



Phenyl cations are very unstable; thus S_N1 reactions do not occur. The carbon–halogen bonds of aryl (and vinylic) halides are shorter and stronger than those of alkyl, allylic, and benzylic halides. Stronger carbon–halogen bonds mean that bond breaking by either an S_N1 or S_N2 mechanism will require more energy.

Two effects make the carbon–halogen bonds of aryl and vinylic halides shorter and stronger: (1) The carbon of either type of halide is sp^2 hybridized, and therefore the electrons of the carbon orbital are closer to the nucleus than those of an sp^3-hybridized carbon. (2) Resonance of the type shown here strengthens the carbon–halogen bond by giving it *double-bond character*:



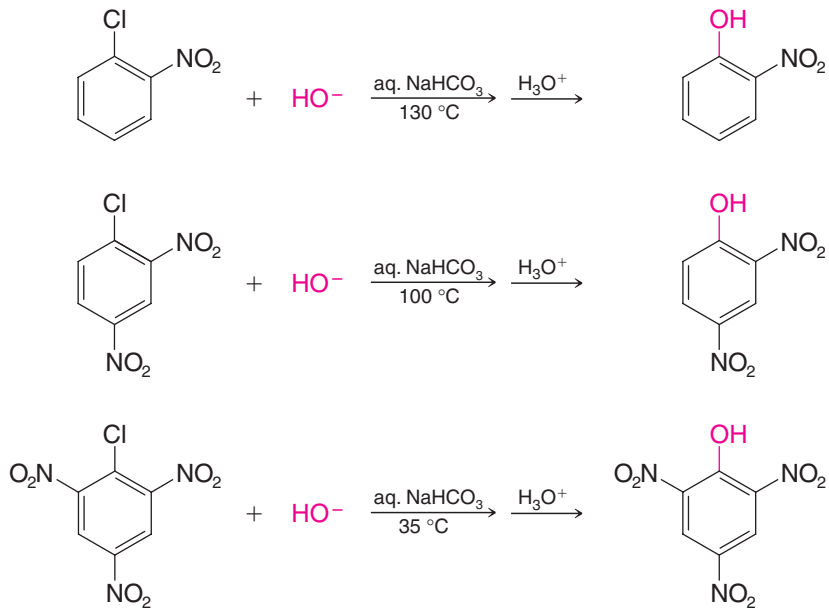
*The Dow process for making phenol by substitution (Section 21.4B) requires extremely high temperature and pressure to effect the reaction. These conditions are not practical in the laboratory.

Having said all this, we shall find in the next two subsections that *aryl halides can be remarkably reactive toward nucleophiles* if they bear certain substituents or when we allow them to react under the proper conditions.

21.11A Nucleophilic Aromatic Substitution by Addition–Elimination: The S_NAr Mechanism

Nucleophilic substitution reactions of aryl halides *do* occur readily when an electronic factor makes the aryl carbon bonded to the halogen susceptible to nucleophilic attack.

- Nucleophilic aromatic substitution can occur when strong electron-withdrawing groups are ortho or para to the halogen atom:



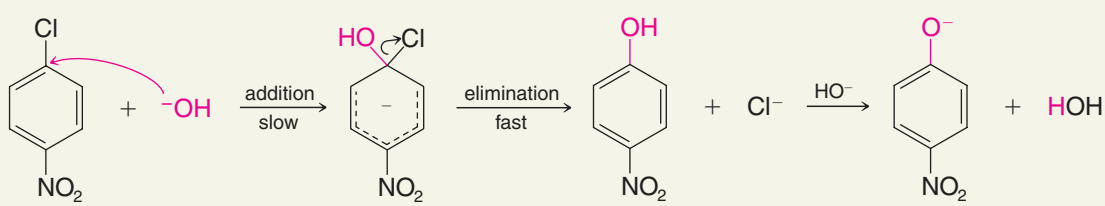
We also see in these examples that the temperature required to bring about the reaction is related to the number of ortho or para nitro groups. Of the three compounds, *o*-nitrochlorobenzene requires the highest temperature (*p*-nitrochlorobenzene reacts at 130 °C as well) and 2,4,6-trinitrochlorobenzene requires the lowest temperature.

A meta-nitro group does not produce a similar activating effect. For example, *m*-nitrochlorobenzene gives no corresponding reaction.

- The mechanism that operates in these reactions is an *addition–elimination* mechanism involving the formation of a *carbanion* with delocalized electrons, called a **Meisenheimer intermediate**. The process is called **nucleophilic aromatic substitution (S_NAr)**.

In the first step of the following example, addition of a hydroxide ion to *p*-nitrochlorobenzene produces the carbanion; then elimination of a chloride ion yields the substitution product as the aromaticity of the ring is recovered.

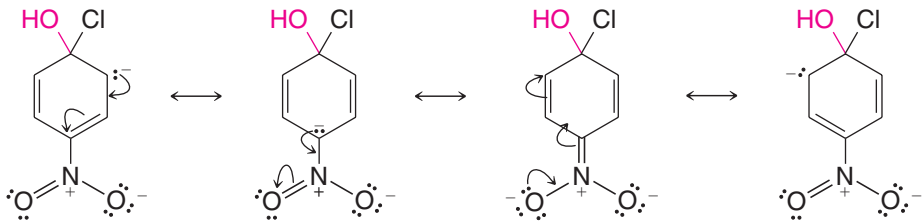
A MECHANISM FOR THE REACTION — The S_NAr Mechanism



Carbanion (Meisenheimer intermediate)

Structures of the contributing resonance forms are shown further below.

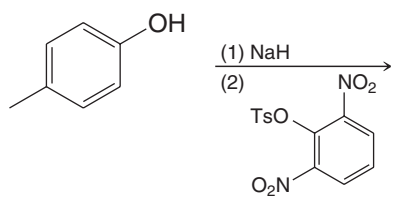
The carbanion is stabilized by *electron-withdrawing groups* in the positions ortho and para to the halogen atom. If we examine the following resonance structures for a Meisenheimer intermediate, we can see how:



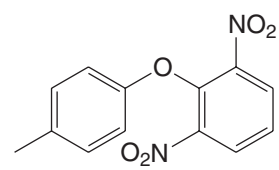
Especially stable (Negative charges are both on oxygen atoms.)

SOLVED PROBLEM 21.6

What is the product of the following reaction?



STRATEGY AND ANSWER: NaH is a strong base that will convert 4-methylphenol to its phenoxide salt. 1-(*p*-Toluenesulfonyl)-2,6-dinitrobenzene contains both a good leaving group and two strong electron-withdrawing groups. Thus the likely reaction is a nucleophilic aromatic substitution (S_NAr), leading to the following diaryl ether.



PRACTICE PROBLEM 21.9

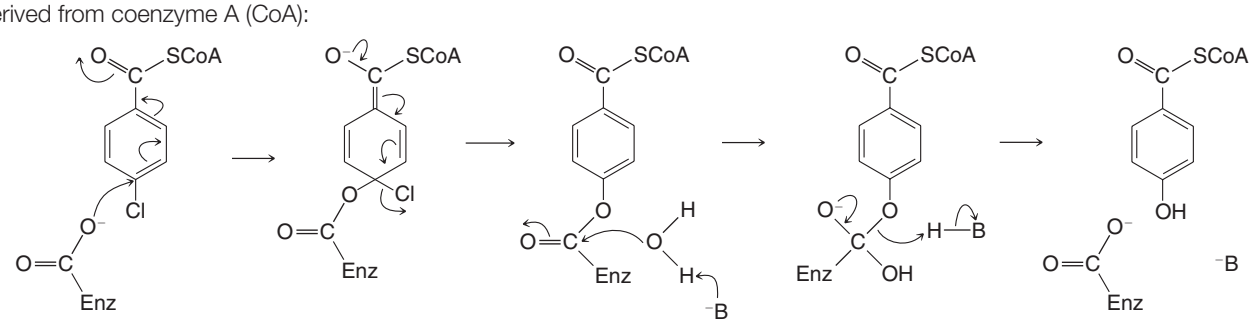
1-Fluoro-2,4-dinitrobenzene is highly reactive toward nucleophilic substitution through an S_NAr mechanism. (In Section 24.5B we shall see how this reagent is used in the Sanger method for determining the structures of proteins.) What product would be formed when 1-fluoro-2,4-dinitrobenzene reacts with each of the following reagents?

(a) EtONa **(b)** NH_3 **(c)** $C_6H_5NH_2$ **(d)** EtSNa

THE CHEMISTRY OF... Bacterial Dehalogenation of a PCB Derivative

Polychlorinated biphenyls (PCBs) are compounds that were once used in a variety of electrical devices, industrial applications, and polymers. Their use and production were banned in 1979, however, owing to the toxicity of PCBs and their tendency to accumulate in the food chain.

4-Chlorobenzoic acid is a degradation product of some PCBs. It is now known that certain bacteria are able to dehalogenate 4-chlorobenzoic acid by an enzymatic nucleophilic aromatic substitution reaction. The product is 4-hydroxybenzoic acid, and a mechanism for this enzyme-catalyzed process is shown here. The sequence begins with the thioester of 4-chlorobenzoic acid derived from coenzyme A (CoA):

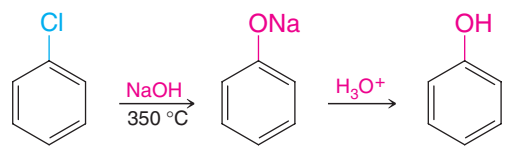


(continues on next page)

Some key features of this enzymatic S_NAr mechanism are the following. The nucleophile that attacks the chlorinated benzene ring is a carboxylate anion of the enzyme. When the carboxylate attacks, positively charged groups within the enzyme stabilize the additional electron density that develops in the thioester carbonyl group of the Meisenheimer intermediate. Collapse of the Meisenheimer intermediate, with rearomatization of the ring and loss of the chloride ion, results in an intermediate where the substrate is covalently bonded to the enzyme as an ester. Hydrolysis of this ester linkage involves a water molecule whose nucleophilicity has been enhanced by a basic site within the enzyme. Hydrolysis of the ester releases 4-hydroxybenzoic acid and leaves the enzyme ready to catalyze another reaction cycle.

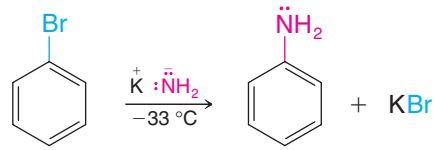
21.11B Nucleophilic Aromatic Substitution through an Elimination–Addition Mechanism: Benzyne

Although aryl halides such as chlorobenzene and bromobenzene do not react with most nucleophiles under ordinary circumstances, they do react under highly forcing conditions. Chlorobenzene can be converted to phenol by heating it with aqueous sodium hydroxide in a pressurized reactor at 350 °C (Section 21.4B):



Phenol

Bromobenzene reacts with the very powerful base, $^-NH_2$, in liquid ammonia:

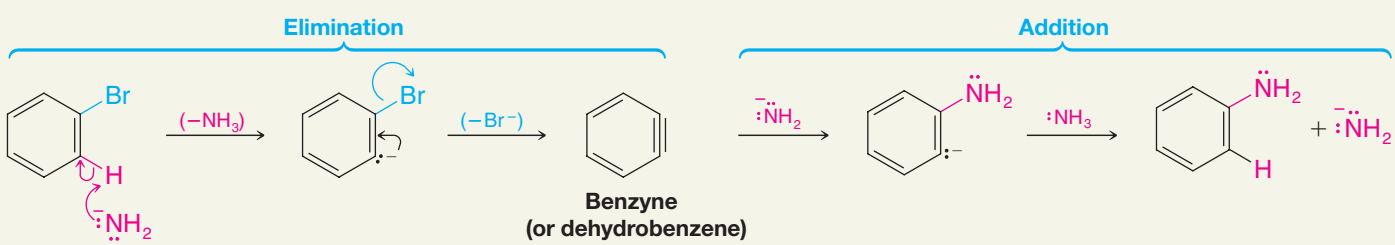


Aniline

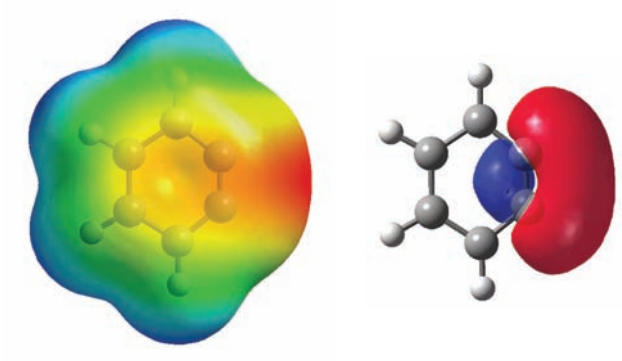
- These reactions take place through an **elimination–addition mechanism** that involves the formation of a highly unstable intermediate called *benzyne* (or *dehydrobenzene*).

We can illustrate this mechanism with the reaction of bromobenzene and amide ion. In the first step (see the following mechanism), the amide ion initiates an elimination by abstracting one of the ortho protons because they are the most acidic. The negative charge that develops on the ortho carbon is stabilized by the inductive effect of the bromine. The anion then loses a bromide ion. This elimination produces the highly unstable, and thus highly reactive, **benzyne**. Benzyne then reacts with any available nucleophile (in this case, an amide ion) by a two-step addition reaction to produce aniline.

A MECHANISM FOR THE REACTION — The Benzyne Elimination–Addition Mechanism



We can better understand the reactive and unstable nature of benzyne if we consider aspects of its electronic structure.



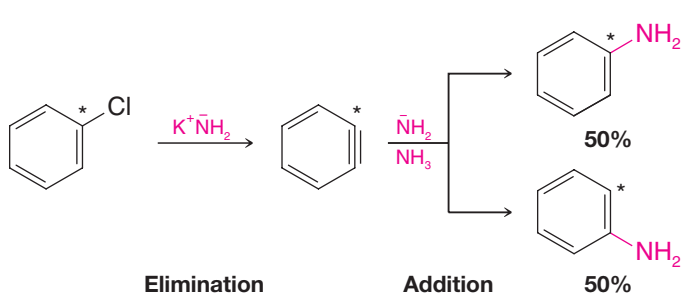
(*a*) (*b*)

FIGURE 21.1 (*a*) A calculated electrostatic potential map for benzyne shows the relatively greater negative charge (in red) at the edge of the ring, corresponding to electron density from the additional π bond in benzyne. (*b*) A schematic representation of the molecular orbital associated with the additional π bond in benzyne. (Red and blue indicate orbital phase, not charge distribution.) Note that the orientation of this orbital is in the same plane as the ring and perpendicular to the axis of the aromatic π system.

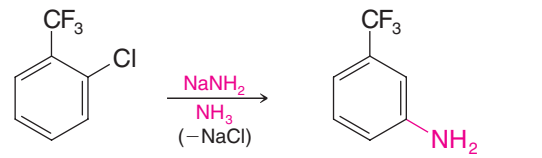
The calculated electrostatic potential map for benzyne, shown in Fig. 21.1*a*, shows the relatively greater negative charge at the edge of the ring, corresponding to the electron density from the additional π bond in benzyne. Figure 21.1*b* shows a schematic representation of the orbital associated with the additional π bond. We can see from these models that the orbitals of the additional π bond in benzyne lie in the same plane as the ring, perpendicular to the axis of the aromatic π system. We can also see in Fig. 21.1 that, because the carbon ring is not a perfect hexagon as in benzene, there is angle strain in the structure of benzyne. The distance between the carbons of the additional π bond in benzyne is shorter than between the other carbons, and the bond angles of the ring are therefore distorted from their ideal values. The result is that benzyne is highly unstable and highly reactive. Consequently, benzyne has never been isolated as a pure substance, but it has been detected and trapped in various ways.

What, then, is some of the evidence for an elimination–addition mechanism involving benzyne in some nucleophilic aromatic substitutions?

The first piece of clear-cut evidence was an experiment done by J. D. Roberts (Section 9.10) in 1953—one that marked the beginning of benzyne chemistry. Roberts showed that when ^{14}C-labeled (C*) chlorobenzene is treated with amide ion in liquid ammonia, the aniline that is produced has the label equally divided between the 1 and 2 positions. This result is consistent with the following elimination–addition mechanism but is, of course, not at all consistent with a direct displacement or with an addition–elimination mechanism. (Why?)

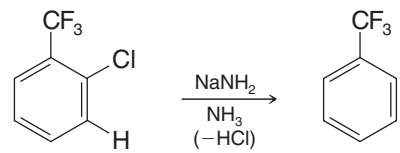


An even more striking illustration can be seen in the following reaction. When the ortho derivative **1** is treated with sodium amide, the only organic product obtained is *m*-(trifluoromethyl)aniline:



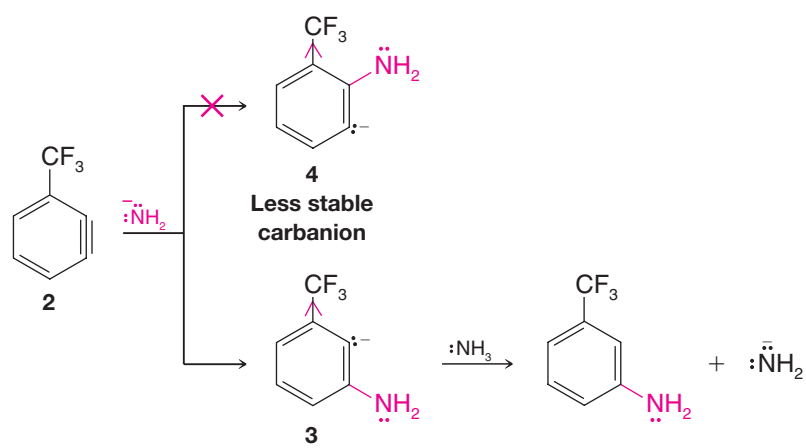
1 ***m*-(Trifluoromethyl)aniline**

This result can also be explained by an elimination–addition mechanism. The first step produces the benzyne **2**:



1 **2**

This benzyne then adds an amide ion in the way that produces the more stable carbanion **3** rather than the less stable carbanion **4**:

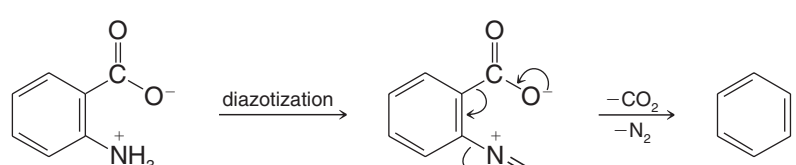


More stable carbanion (The negative charge is closer to the electronegative trifluoromethyl group.)

Carbanion **3** then accepts a proton from ammonia to form *m*-(trifluoromethyl)aniline.

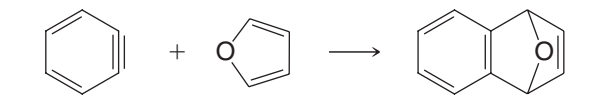
Carbanion **3** is more stable than **4** because the carbon atom bearing the negative charge is closer to the highly electronegative trifluoromethyl group. The trifluoromethyl group stabilizes the negative charge through its inductive effect. (Resonance effects are not important here because the sp^2 orbital that contains the electron pair does not overlap with the π orbitals of the aromatic system.)

Benzyne intermediates have been "trapped" through the use of Diels–Alder reactions. One convenient method for generating benzyne is the diazotization of anthranilic acid (2-aminobenzoic acid) followed by elimination of CO_2 and N_2:



Anthranilic acid **Benzyne (trapped in situ)**

When benzyne is generated in the presence of the diene *furan*, the product is a Diels–Alder adduct:



Benzyne (generated by an elimination reaction) **Furan** **Diels–Alder adduct**

In a fascinating application of host–guest chemistry (an area founded by the late D. Cram, and for which he shared the Nobel Prize in Chemistry in 1987), benzyne itself has been trapped at very low temperature inside a molecular container called a hemicarcerand. Under these conditions, R. Warmuth and D. Cram found that the incarcerated benzyne was sufficiently stabilized for its ^{1}H and ^{13}C NMR spectra to be recorded (see Fig. 21.2), before it ultimately underwent a Diels–Alder reaction with the container molecule.

DONALD CRAM shared the 1987 Nobel Prize for his work on host–guest chemistry.

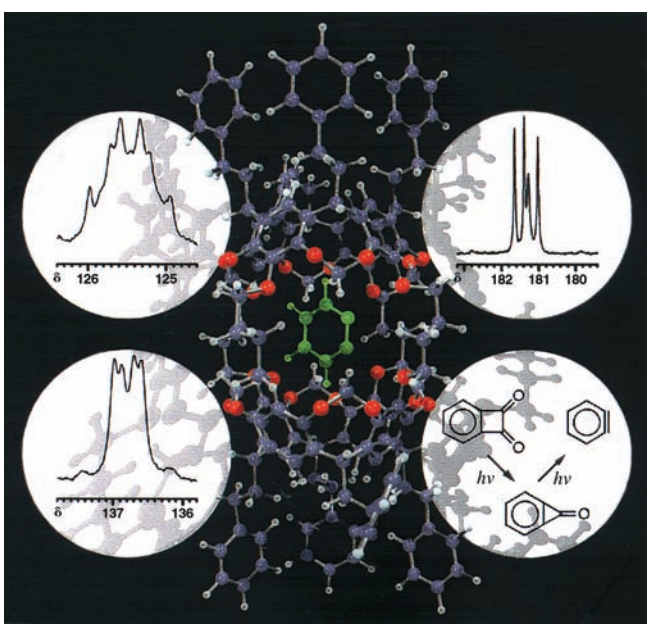
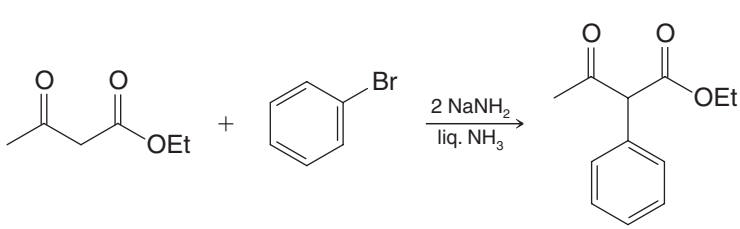


Image courtesy of Jan Haller; Reprinted with permission of Ralf Warmuth

FIGURE 21.2 A molecular graphic of benzyne (green) trapped in a hemicarcerand. Images of ^{13}C NMR data from benzyne and a reaction used to synthesize it are shown in the white circles.

21.11C Phenylation

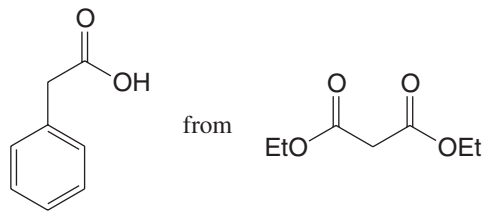
Reactions involving benzyne can be useful for formation of a carbon–carbon bond to a phenyl group (a process called phenylation). For example, if acetoacetic ester is treated with bromobenzene and two molar equivalents of sodium amide, phenylation of ethyl acetoacetate occurs. The overall reaction is as follows:



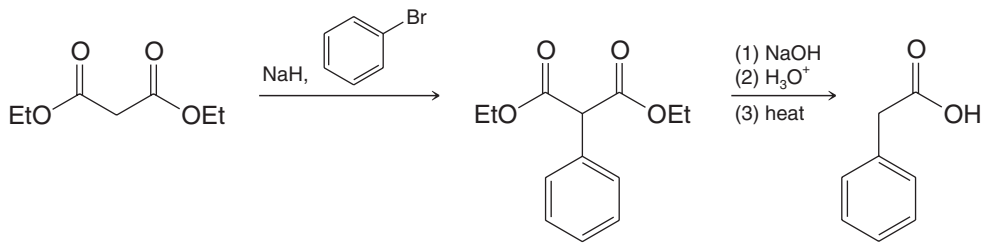
Malonic esters can be phenylated in an analogous way. This process is a useful complement to the alkylation reactions of acetoacetic and malonic esters that we studied in Chapter 18 because, as you may recall, substrates like bromobenzene are not susceptible to S_N2 reactions [see Section 6.14A and Practice Problem 18.8(c)].

SOLVED PROBLEM 21.7

Outline a synthesis of phenylacetic acid from diethyl malonate.



STRATEGY AND ANSWER: Diethyl malonate must first be substituted at the α carbon by a phenyl group, and then hydrolyzed and decarboxylated. Introduction of the phenyl group requires involvement of a benzyne intermediate.



PRACTICE PROBLEM 21.10 When *o*-chlorotoluene is subjected to the conditions used in the Dow process (i.e., aqueous NaOH at 350 °C at high pressure), the products of the reaction are *o*-cresol and *m*-cresol. What does this result suggest about the mechanism of the Dow process?

PRACTICE PROBLEM 21.11 When 2-bromo-1,3-dimethylbenzene is treated with sodium amide in liquid ammonia, no substitution takes place. This result can be interpreted as providing evidence for the elimination–addition mechanism. Explain how this interpretation can be given.

PRACTICE PROBLEM 21.12 **(a)** Outline a step-by-step mechanism for the phenylation of acetoacetic ester by bromobenzene and two molar equivalents of sodium amide. (Why are two molar equivalents of $NaNH_2$ necessary?) **(b)** What product would be obtained by hydrolysis and decarboxylation of the phenylated acetoacetic ester? **(c)** How would you prepare 2-phenylpropanoic acid from malonic ester?

21.12 SPECTROSCOPIC ANALYSIS OF PHENOLS AND ARYL HALIDES

Infrared Spectra Phenols show a characteristic absorption band (usually broad) arising from O—H stretching in the 3400–3600-cm^{-1} region. Phenols and aryl halides also show the characteristic absorptions that arise from their benzene rings (see Section 14.11C).

^{1}H NMR Spectra The hydroxylic proton of a phenol is more deshielded than that of an alcohol due to proximity of the benzene π electron ring current. The exact position of the O—H signal depends on the extent of hydrogen bonding and on whether

the hydrogen bonding is *intermolecular* or *intramolecular*. The extent of intermolecular hydrogen bonding depends on the concentration of the phenol, and this strongly affects the position of the O—H signal. In phenol, itself, for example, the position of the O—H signal varies from δ 2.55 for pure phenol to δ 5.63 at 1% concentration in CCl_4. Phenols with strong intramolecular hydrogen bonding, such as salicylaldehyde, show O—H signals between δ 0.5 and δ 1.0, and the position of the signal varies only slightly with concentration. As with other protons that undergo exchange (Section 9.10), the identity of the O—H proton of a phenol can be determined by adding D_2O to the sample. The O—H proton undergoes rapid exchange with deuterium and the proton signal disappears. The aromatic protons of phenols and aryl halides give signals in the δ 7–9 region.

^{13}C NMR Spectra The carbon atoms of the aromatic ring of phenols and aryl halides appear in the region δ 135–170.

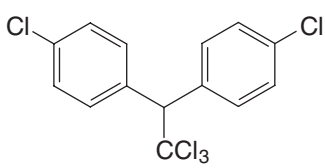
Mass Spectra Mass spectra of phenols often display a prominent molecular ion peak, $M^{+\cdot}$. Phenols that have a benzylic hydrogen produce an $M^{+\cdot} - 1$ peak that can be larger than the $M^{+\cdot}$ peak.

THE CHEMISTRY OF... Aryl Halides: Their Uses and Environmental Concerns

Aryl Halides as Insecticides

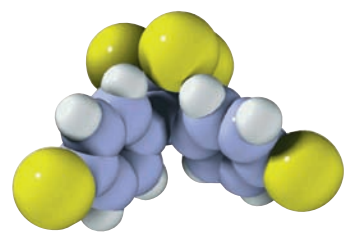
Insects, especially mosquitoes, fleas, and lice, have been responsible for innumerable human deaths throughout history. The bubonic plague or "black death" of medieval times that killed nearly one-third of Europe's population was borne by fleas. Malaria and yellow fever, diseases that were responsible for the loss of millions of lives in the twentieth century alone, are mosquito-borne diseases.

One compound widely known for its insecticidal properties and environmental effects is DDT [1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane].



DDT
[1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane]

From the early 1940s through the early 1970s, when its use was banned in the United States, vast quantities of DDT were sprayed over many parts of the world in an effort to destroy insects. These efforts rid large areas of the world of disease-carrying insects, especially those responsible for malaria, yellow fever, sleeping sickness (caused by tsetse flies), and typhus. Though it has since resurged, by 1970, malaria had been largely eliminated from the developed world. According to estimates by the National Academy of Sciences, the use of DDT during that time had prevented more that 500 million deaths from malaria alone.

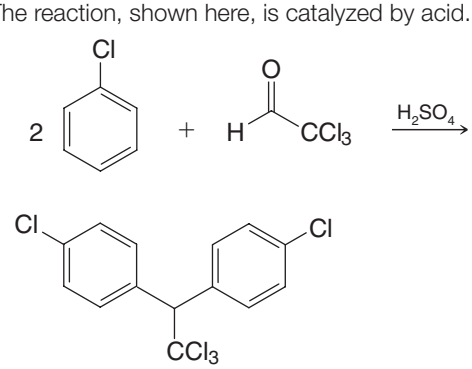


DDT

Eventually it began to become clear that the prodigious use of DDT had harmful side effects. Aryl halides are usually highly stable compounds that are only slowly destroyed by natural processes. As a result they remain in the environment for years; they are what we now call "persistent insecticides" or "hard insecticides." The U.S. Environmental Protection Agency banned the use of DDT beginning in 1973.

Aryl halides are also fat soluble and tend to accumulate in the fatty tissues of most animals. The food chain that runs from plankton to small fish to birds and to larger animals, including humans, tends to magnify the concentrations of aryl halides at each step.

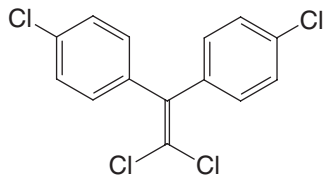
The chlorohydrocarbon DDT is prepared from inexpensive starting materials, chlorobenzene and trichloroacetaldehyde. The reaction, shown here, is catalyzed by acid.



DDT
[1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane]

(continues on next page)

In nature the principal decomposition product of DDT is DDE.



DDE
[1,1-dichloro-2,2-bis(4-chlorophenyl)ethene]

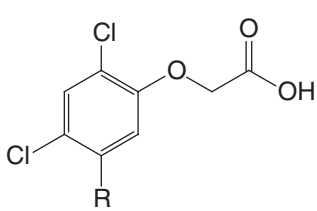
Estimates indicate that nearly 1 billion pounds of DDT were spread throughout the world ecosystem. One pronounced environmental effect of DDE, after conversion from DDT, has been in its action on eggshell formation in many birds. DDE inhibits the enzyme *carbonic anhydrase* that controls the calcium supply for shell formation. As a consequence, the shells are often very fragile and do not survive to the time of hatching. During the late 1940s the populations of eagles, falcons, and hawks dropped dramatically. There can be little doubt that DDT was primarily responsible. DDE also accumulates in the fatty tissues of humans. Although humans appear to have a short-range tolerance to moderate DDE levels, the long-range effects are uncertain.

Study Problem 1 The mechanism for the formation of DDT from chlorobenzene and trichloroacetaldehyde in sulfuric acid involves two electrophilic aromatic substitution reactions. In the first electrophilic substitution reaction, the electrophile is protonated trichloroacetaldehyde. In the second, the electrophile is a carbocation. Propose a mechanism for the formation of DDT.

Study Problem 2 What kind of reaction is involved in the conversion of DDT to DDE?

Organic Halides as Herbicides

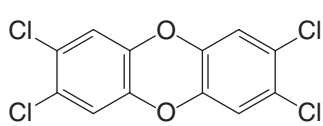
Other chlorinated organic compounds have been used extensively as herbicides. The following two examples are 2,4-D and 2,4,5-T.



R = H; 2,4-D (2,4-dichlorophenoxyacetic acid)

R = Cl; 2,4,5-T (2,4,5-trichlorophenoxyacetic acid)

Enormous quantities of these two compounds were used in an approximately 1:1 mixture as the defoliant Agent Orange during the Vietnam War. Some samples of 2,4,5-T were shown to be teratogenic (a fetus-deforming agent), and its use has been banned in the United States.

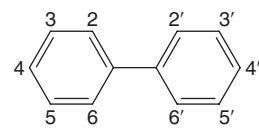


2,3,7,8-Tetrachlorodibenzodioxin (also called TCDD)

This dioxin is also highly stable; it persists in the environment and because of its fat solubility can be passed up the food chain. In sublethal amounts it can cause a disfiguring skin disease called chloracne.

Polychlorinated Biphenyls (PCBs)

Mixtures of polychlorinated biphenyls have been produced and used commercially since 1929. In these mixtures, biphenyls with chlorine atoms at any of the numbered positions (see the following structure) may be present. In all, there are 210 possible compounds. A typical commercial mixture may contain as many as 50 different PCBs. Mixtures are usually classified on the basis of their chlorine content, and most industrial mixtures contain from 40 to 60% chlorine.



Biphenyl

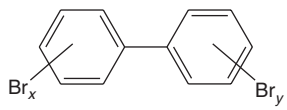
Polychlorinated biphenyls have had a multitude of uses: as heat-exchange agents in transformers; in capacitors, thermostats, and hydraulic systems; as plasticizers in polystyrene coffee cups, frozen food bags, bread wrappers, and plastic liners for baby bottles. They have been used in printing inks, in carbonless carbon paper, and as waxes for making molds for metal castings. Between 1929 and 1972, about 500,000 metric tons of PCBs were manufactured.

Polychlorinated biphenyls are highly persistent in the environment, and, being fat soluble, tend to accumulate in the food chain. PCBs have been found in rainwater, in many species of fish, birds, and other animals (including polar bears) all over the globe, and in human tissue. Fish that feed in PCB-contaminated waters, for example, have PCB levels 1000–100,000 times the level of the surrounding water, and this amount is further magnified in birds that feed on the fish. The toxicity of PCBs depends on the composition of the individual mixture.

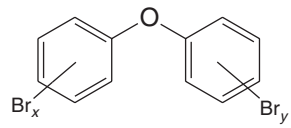
As late as 1975, industrial concerns were legally discharging PCBs into the Hudson River. In 1977, the EPA banned the direct discharge into waterways, and since 1979 their manufacture, processing, and distribution have been prohibited. In 2000 the EPA specified certain sections of the Hudson River for cleanup of PCBs. In 2009, a plan to decontaminate parts of the Hudson River by dredging was finally implemented. See "The Chemistry of…Bacterial Dehalogenation of a PCB Derivative" (Section 21.11A) for a potential method of PCB remediation.

Polybrominated Biphenyls and Biphenyl Ethers (PBBs and PBDEs)

As with polychlorinated biphenyls (PCBs), polybrominated aromatic compounds have been used in industry since the early twentieth century. The fire retardant properties of polybrominated and polychlorinated biphenyls and biphenyl ethers, for example, led to their use in building materials, furniture, clothing, and other consumer items. However, the 1970s discovery in Michigan of polybrominated biphenyls (PBBs) in feed for livestock, and subsequently in meat and dairy products, led to suspension of the use of PBBs in 1979.



***x* + *y* = 1-10**
Polybrominated biphenyls (PBBs)



***x* + *y* = 1-10**
Polybrominated diphenyl ethers (PBDEs)

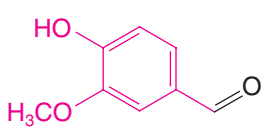
(*x* and *y* indicate the possibility of multiple bromine substitution sites on each ring.)

Meanwhile, there is mounting concern about polybromodiphenyl ethers (PBDEs). Although use of PBDEs could potentially save lives and property in their roles as flame retardants, these compounds are now widespread in the environment, and studies have led to significant concern about their toxicity to humans and other animals. As with PCBs, polybrominated biphenyls and polybrominated diphenyl ethers persist in the environment and accumulate in fatty biological tissues. PBDEs have been found in birds, fish, and breast milk. They are now banned in a number of areas.

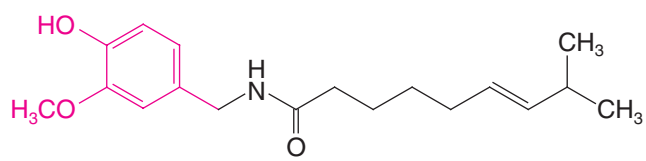
[WHY Do These Topics Matter?

RELATIONSHIPS BETWEEN CHEMICAL STRUCTURE AND ACTIVITY

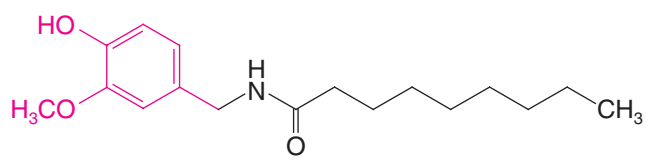
Knowing what we do about functional groups, it is not surprising that changing the structure of a molecule can lead to changes in activity. However, it is sometimes surprising how very small structural changes can lead to extreme alterations in activity, like the proverbial Dr. Jekyll turning into Mr. Hyde. There is at least one group of phenols found in nature that beautifully illustrates this idea. Drawn below is the molecule vanillin, the compound responsible for the wonderful smell and taste of vanilla. This compound is used in large quantities in the food and fragrance industries.



Vanillin



Capsaicin



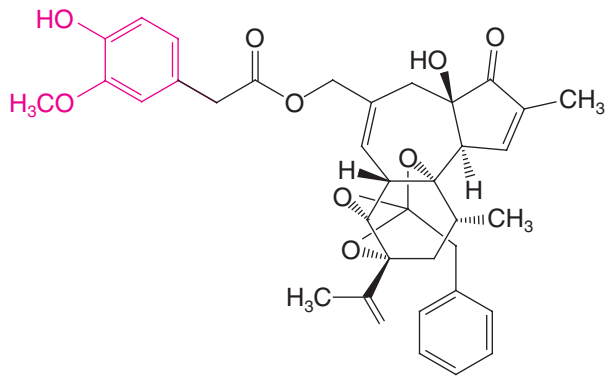
Nonivamide

If the aldehyde group of vanillin is changed to the amide-linked alkyl fragment of capsaicin, we then obtain a natural product found in many peppers. Instead of having a pleasant taste, this compound activates pain receptors in our mouths, sending signals to the brain that register as a sensation of heat. You have likely had this experience if you have ever eaten a jalapeño pepper. If you activate these pain receptors enough times, you can eventually destroy their efficacy, training your mouth to be able to tolerate more and more "heat." Capsaicin, though, is not all bad. In fact, applied to your skin (as the active ingredient in the medicine Capzacin), it can help to modulate pain by activating the pain receptors and preventing them from firing further, thus serving as an analgesic. Interestingly, subtle changes to the structure of capsaicin can diminish its impact. For instance, the natural product nonivamide, which is also found in peppers, is missing one of the terminal methyl groups and the double bond of capsaicin. These changes are small, but they are sufficient to decrease the "hotness" of the compound by nearly half. Nonivamide is still hot enough, though, that it has been used commercially as the active ingredient in some pepper sprays.

The key structural component that is consistent between all these molecules is the aryl ring, the phenol, and the methyl ether, which collectively is termed a vanilloid group (highlighted in magenta in each) and is recognized by a number of critical receptors throughout our bodies. Key to our perception of the resultant activity, be it a pleasant smell or pain, are the remaining atoms attached to the other side of the benzene ring.

(continues on next page)

As a final example of this concept, consider the natural product resiniferatoxin shown below. This compound comes from the latex of several flowering cactus species. Although it contains the same vanilloid group, it has a far more complex right-hand half. These structural changes yield a compound that is over 1000 times more potent than capsaicin and has been used as a natural analgesic for over two thousand years.



Resiniferatoxin

To learn more about these topics, see:

1. Walpole, C. S. J. et al. *Similarities and Differences in the Structure-Activity Relationships of Capsaicin and Resiniferatoxin Analogues*. J. Med. Chem. **1996**, 39, 2939-2952.

2. Nicolaou, K. C.; Montagnon, T. *Molecules that Changed the World*. Wiley-VCH: Weinheim, **2008**, p. 262.

SUMMARY AND REVIEW TOOLS

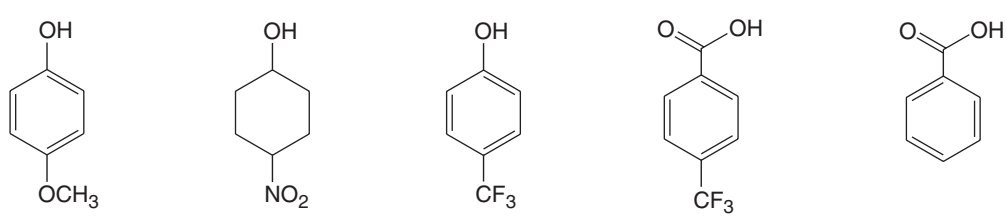
The study aids for this chapter include key terms and concepts (which are highlighted in bold, blue text within the chapter and defined in the Glossary (at the back of the book) and have hyperlinked definitions in the accompanying *WileyPLUS* course (www.wileyplus.com), and a Synthetic Connections scheme of reaction pathways.

PROBLEMS

Note to Instructors: Many of the homework problems are available for assignment via *WileyPLUS*, an online teaching and learning solution.

PHYSICAL PROPERTIES

21.13 Rank the following in order of increasing acidity.



21.14 Without consulting tables, select the stronger acid from each of the following pairs:

(a) 4-Methylphenol and 4-fluorophenol
(b) 4-Methylphenol and 4-nitrophenol
(c) 4-Nitrophenol and 3-nitrophenol
(d) 4-Methylphenol and benzyl alcohol
(e) 4-Fluorophenol and 4-bromophenol

21.15 What products would be obtained from each of the following acid–base reactions?

(a) Sodium ethoxide in ethanol + phenol →
(b) Phenol + aqueous sodium hydroxide →
(c) Sodium phenoxide + aqueous hydrochloric acid →
(d) Sodium phenoxide + H_2O + CO_2 →

21.16 Describe a simple chemical test that could be used to distinguish between members of each of the following pairs of compounds:

(a) 4-Chlorophenol and 4-chloro-1-methylbenzene
(b) 4-Methylphenol and 4-methylbenzoic acid
(c) 4-Methylphenol and 2,4,6-trinitrophenol
(d) Ethyl phenyl ether and 4-ethylphenol

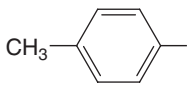
GENERAL REACTIONS

21.17 Complete the following equations:

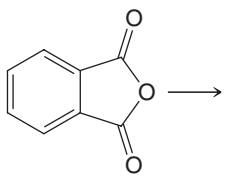
(a) Phenol + Br_2 $\xrightarrow[5\ °C,\ CS_2]{}$

(b) Phenol + concd H_2SO_4 $\xrightarrow[25\ °C]{}$

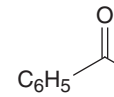
(c) Phenol + concd H_2SO_4 $\xrightarrow[100\ °C]{}$

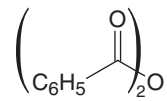
(d)  + *p*-toluenesulfonyl chloride $\xrightarrow{HO^-}$

(e) Phenol + Br_2 $\xrightarrow[H_2O]{}$

(f) Phenol + 

(g) *p*-Cresol + Br_2 $\xrightarrow[H_2O]{}$

(h) Phenol +  $\xrightarrow{base}$

(i) Phenol +  $\xrightarrow{base}$

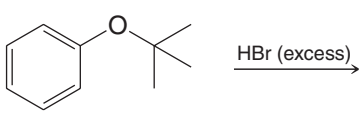
(j) Phenol + NaH $\longrightarrow$

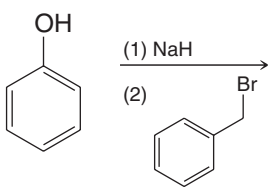
(k) Product of (j) + $CH_3OSO_2OCH_3$ $\longrightarrow$

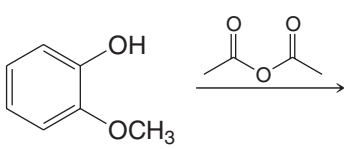
(l) Product of (j) + CH_3I $\longrightarrow$

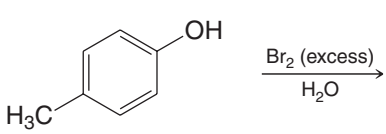
(m) Product of (j) + $C_6H_5CH_2Cl$ $\longrightarrow$

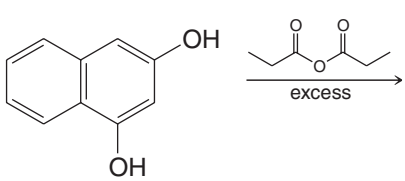
21.18 Predict the product of the following reactions.

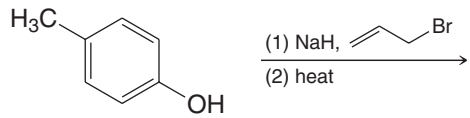
(a) 

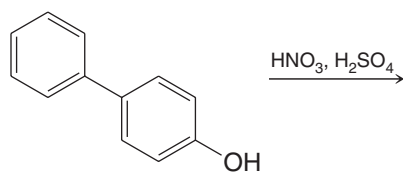
(b) 

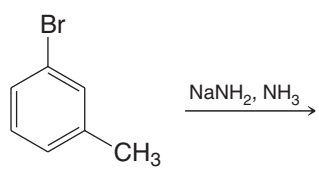
(c) 

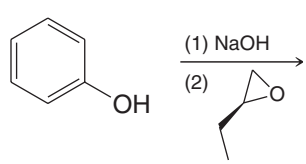
(d) 

(e) 

(f) 

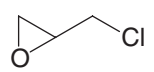
(g) 

(h) 

(i) 

MECHANISMS AND SYNTHESIS

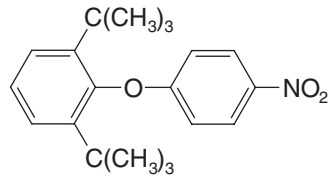
21.19 A synthesis of the β-receptor blocker called toliprolol begins with a reaction between 3-methylphenol and epichlorohydrin. The synthesis is outlined below. Give the structures of the intermediates and of toliprolol.

3-Methylphenol +  $\longrightarrow$ $C_{10}H_{13}O_2Cl$ $\xrightarrow{HO^-}$

Epichlorohydrin

$C_{10}H_{12}O_2$ $\xrightarrow{(CH_3)_2CHNH_2}$ toliprolol, $C_{13}H_{21}NO_2$

21.20 *p*-Chloronitrobenzene was allowed to react with sodium 2,6-di-*tert*-butylphenoxide with the intention of preparing the diphenyl ether **1**. The product was not **1**, but rather was an isomer of **1** that still possessed a phenolic hydroxyl group.

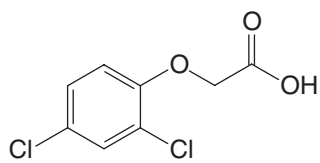


1

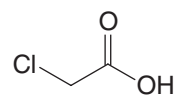
What was this product, and how can one account for its formation?

21.21 When *m*-chlorotoluene is treated with sodium amide in liquid ammonia, the products of the reaction are *o*-, *m*-, and *p*-toluidine (i.e., *o*-$CH_3C_6H_4NH_2$, *m*-$CH_3C_6H_4NH_2$, and *p*-$CH_3C_6H_4NH_2$). Propose plausible mechanisms that account for the formation of each product.

21.22 The herbicide **2,4-D** can be synthesized from phenol and chloroacetic acid. Outline the steps involved.



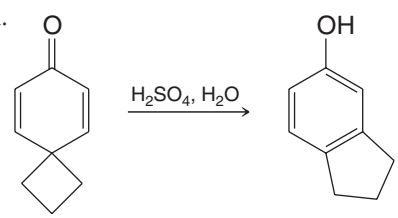
2,4-D
(2,4-dichlorophenoxyacetic acid)



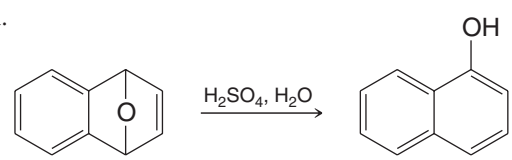
Chloroacetic acid

21.23 The first synthesis of a crown ether (Section 11.16) by C. J. Pedersen (of the DuPont Company) involved treating 1,2-benzenediol with di(2-chloroethyl) ether, $(ClCH_2CH_2)_2O$, in the presence of NaOH. The product was a compound called dibenzo-18-crown-6. Give the structure of dibenzo-18-crown-6 and provide a plausible mechanism for its formation.

21.24 Provide a mechanism for the following reaction.

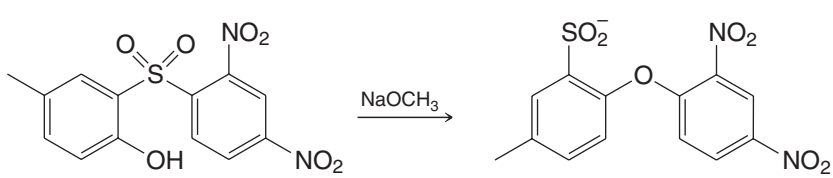


21.25 Provide a mechanism for the following reaction.

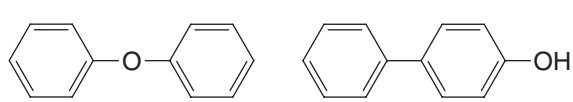


21.26 The widely used antioxidant and food preservative called **BHA (b**utylated **h**ydroxy**a**nisole) is actually a mixture of 2-*tert*-butyl-4-methoxyphenol and 3-*tert*-butyl-4-methoxyphenol. BHA is synthesized from *p*-methoxyphenol and 2-methylpropene. **(a)** Suggest how this is done. **(b)** Another widely used antioxidant is BHT **(b**utylated **h**ydroxy**t**oluene). BHT is actually 2,6-di-*tert*-butyl-4-methylphenol, and the raw materials used in its production are *p*-cresol and 2-methylpropene. What reaction is used here?

21.27 Provide a mechanism for the following reaction.

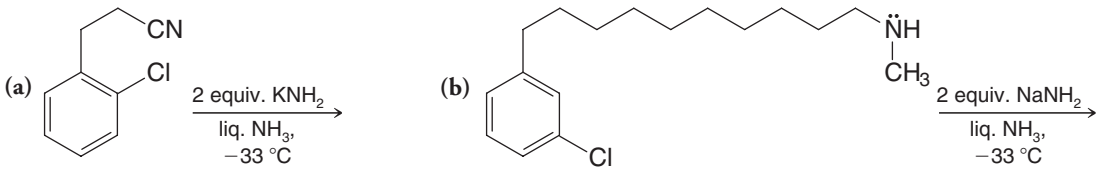


21.28 Account for the fact that the Dow process for the production of phenol produces both diphenyl ether **(1)** and 4-hydroxybiphenyl **(2)** as by-products:

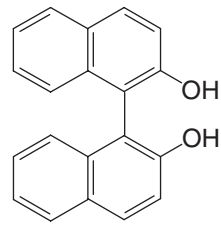


1 **2**

21.29 Predict the outcome of the following reactions:



21.30 Explain how it is possible for 2,2′-dihydroxy-1,1′-binaphthyl (shown at right) to exist in enantiomeric forms.



21.31 Phenols are often effective antioxidants (see Problem 21.26 and "The Chemistry of…Antioxidants" in Section 10.11) because they are said to "trap" radicals. The trapping occurs when phenols react with highly reactive radicals to produce less reactive (more stable) phenolic radicals. **(a)** Show how phenol itself might react with an alkoxyl radical (RO·) in a hydrogen abstraction reaction involving the phenolic —OH. **(b)** Write resonance structures for the resulting radical that account for its being relatively unreactive.

SPECTROSCOPY

21.32 A compound **X** ($C_{10}H_{14}O$) dissolves in aqueous sodium hydroxide but is insoluble in aqueous sodium bicarbonate. Compound **X** reacts with bromine in water to yield a dibromo derivative, $C_{10}H_{12}Br_2O$. The 3000–4000-cm^{-1} region of the IR spectrum of **X** shows a broad peak centered at 3250 cm^{-1}; the 680–840-cm^{-1} region shows a strong peak at 830-cm^{-1}. The ^{1}H NMR spectrum of **X** gives the following: singlet at δ 1.3 (9H), singlet at δ 4.9 (1H), and multiplet at δ 7.0 (4H). What is the structure of **X**?

21.33 Compound **Z** ($C_5H_{10}O$) decolorizes bromine in carbon tetrachloride. The IR spectrum of **Z** shows a broad peak in the 3200–3600-cm^{-1} region. The 300-MHz ^{1}H NMR spectrum of **Z** is given in Fig. 21.3. Propose a structure for **Z**.

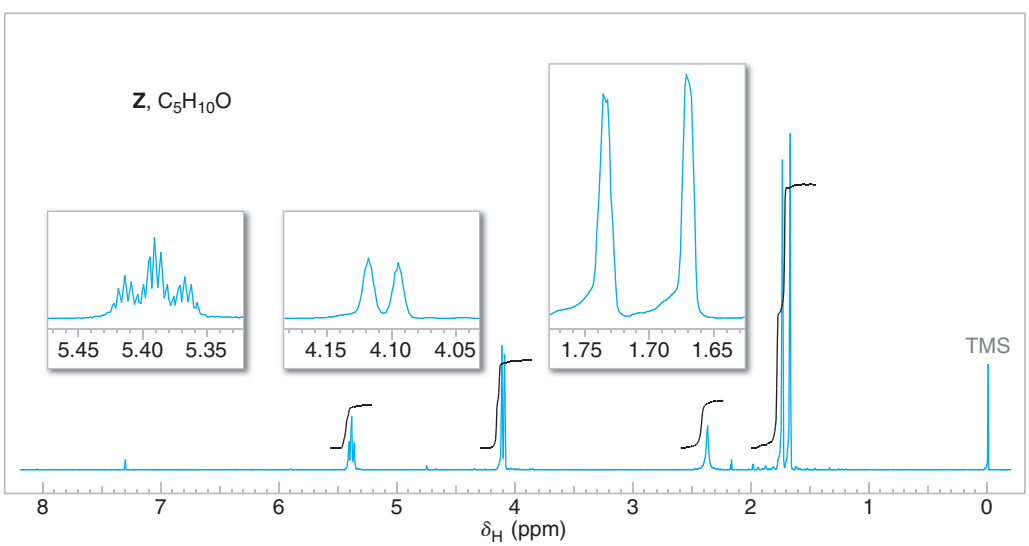
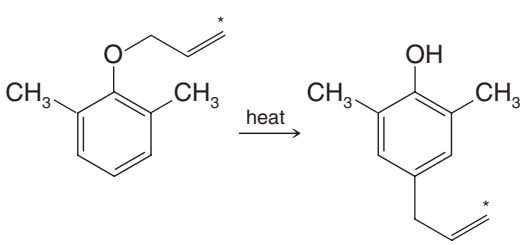


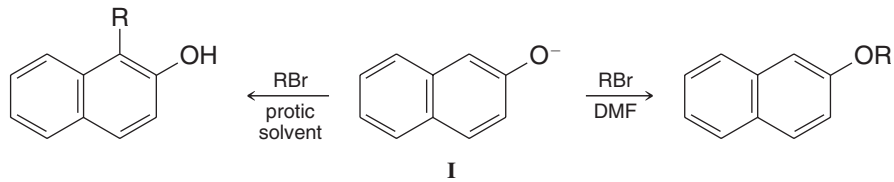
FIGURE 21.3 The 300-MHz ^{1}H NMR spectrum of compound Z (Problem 21.33). Expansions of the signals are shown in the offset plots.

CHALLENGE PROBLEMS

21.34 Explain why, in the case shown, the allyl group has migrated with no change having occurred in the position of the labeled carbon atom within the allyl group:



21.35 In protic solvents the naphthoxide ion **(I)** is alkylated primarily at position 1 (*C*-alkylation) whereas in polar aprotic solvents, such as DMF, the product is almost exclusively the result of a conventional Williamson ether synthesis (*O*-alkylation):

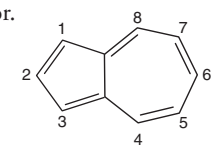


I

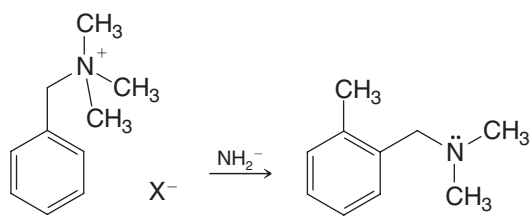
Why does the change in solvent make a difference?

21.36 In comparing nucleophilic aromatic substitution reactions that differ only in the identity of the halogen that is the leaving group in the substrate, it is found that the fluorinated substrate reacts faster than either of the cases where bromine or chlorine is the leaving group. Explain this behavior, which is contrary to the trend among the halogens as leaving groups in S_N1 and S_N2 reactions (in protic solvents).

21.37 In the case of halogen-substituted azulenes, a halogen atom on C6 can be displaced by nucleophiles while one on C1 is unreactive toward nucleophiles. Rationalize this difference in behavior.

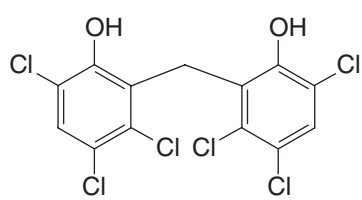


21.38 In the Sommelet–Hauser rearrangement, a benzyl quaternary ammonium salt reacts with a strong base to give a benzyl tertiary amine, as exemplified below:

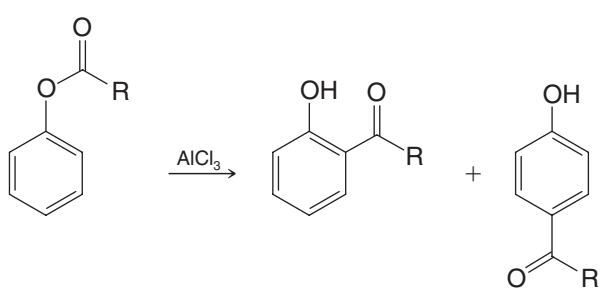


Suggest a mechanism for this rearrangement.

21.39 Hexachlorophene was a widely used germicide until it was banned in 1972 after tests showed that it caused brain damage in test animals. Suggest how this compound might be synthesized, starting with benzene.



21.40 The Fries rearrangement occurs when a phenolic ester is heated with a Friedel–Crafts catalyst such as $AlCl_3$:



The reaction may produce both ortho and para acylated phenols, the former generally favored by high temperatures and the latter by low temperatures. **(a)** Suggest an experiment that might indicate whether the reaction is inter- or intramolecular. **(b)** Explain the temperature effect on product formation.

21.41 Compound **W** was isolated from a marine annelid commonly used in Japan as a fish bait, and it was shown to be the substance that gives this organism its observed toxicity to some insects that contact it.

MS (*m/z*): 151 (relative abundance 0.09), 149 ($M^{+\cdot}$, rel. abund. 1.00), 148

IR (cm^{-1}): 2960, 2850, 2775

^{1}H NMR (δ): 2.3 (s, 6H), 2.6 (d, 4H), and 3.2 (pentet, 1H)

^{13}C NMR (δ): 38 (CH_3), 43 (CH_2), and 75 (CH)

These reactions were used to obtain further information about the structure of **W**:

$$\mathbf{W} \xrightarrow{NaBH_4} \mathbf{X} \xrightarrow{C_6H_5COCl} \mathbf{Y} \xrightarrow{\text{Raney Ni}} \mathbf{Z}$$

Compound **X** had a new infrared band at 2570 cm^{-1} and these NMR data:

^{1}H NMR (δ): 1.6 (t, 2H), 2.3 (s, 6H), 2.6 (m, 4H), and 3.2 (pentet, 1H)

^{13}C NMR (δ): 28 (CH_2), 38 (CH_3), and 70 (CH)

Compound **Y** had these data:

IR (cm^{-1}): 3050, 2960, 2850, 1700, 1610, 1500, 760, 690

^{1}H NMR (δ): 2.3 (s, 6H), 2.9 (d, 4H), 3.0 (pentet, 1H), 7.4 (m, 4H), 7.6 (m, 2H), and 8.0 (m, 4H)

^{13}C NMR (δ): 34 (CH_2), 39 (CH_3), 61 (CH), 128 (CH), 129 (CH), 134 (CH), 135 (C), and 187 (C)

Compound **Z** had

MS (*m/z*): 87 ($M^{+\cdot}$), 86, 72

IR (cm^{-1}): 2960, 2850, 1385, 1370, 1170

^{1}H NMR (δ): 1.0 (d, 6H), 2.3 (s, 6H), and 3.0 (heptet, 1H)

^{13}C NMR (δ): 21 (CH_3), 39 (CH_3), and 55 (CH)

What are the structures of **W** and of each of its reaction products **X**, **Y**, and **Z**?

21.42 Phenols generally are not changed on treatment with sodium borohydride followed by acidification to destroy the excess, unreacted hydride. For example, the 1,2-, 1,3-, and 1,4-benzenediols and 1,2,3-benzenetriol are unchanged under these conditions. However, 1,3,5-benzenetriol (phloroglucinol) gives a high yield of a product **A** that has these properties:

MS (*m/z*): 110

IR (cm^{-1}): 3250 (broad), 1613, 1485

^{1}H NMR (δ in DMSO): 6.15 (m, 3H), 6.89 (t, 1H), and 9.12 (s, 2H)

(a) What is the structure of **A**?

(b) Suggest a mechanism by which the above reaction occurred. (1,3,5-Benzenetriol is known to have more tendency to exist in a keto tautomeric form than do simpler phenols.)

21.43 Open the molecular model file for benzyne and examine the following molecular orbitals: the LUMO (lowest unoccupied molecular orbital), the HOMO (highest occupied molecular orbital), the HOMO-1 (next lower energy orbital), the HOMO-2 (next lower in energy), and the HOMO-3 (next lower in energy). **(a)** Which orbital best represents the region where electrons of the additional π bond in benzyne would be found? **(b)** Which orbital would accept electrons from a Lewis base on nucleophilic addition to benzyne? **(c)** Which orbitals are associated with the six π electrons of the aromatic system? Recall that each molecular orbital can hold a maximum of two electrons.

LEARNING GROUP PROBLEMS

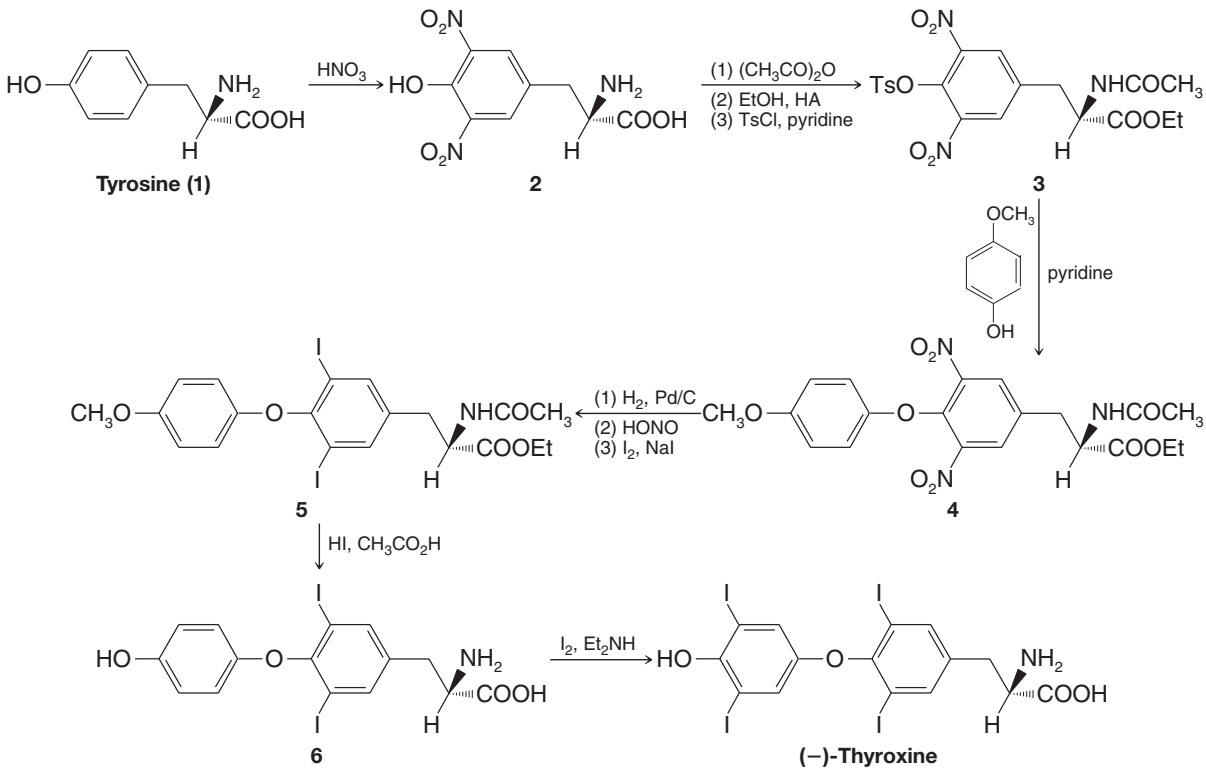
1. Thyroxine is a hormone produced by the thyroid gland that is involved in regulating metabolic activity. In a previous Learning Group Problem (Chapter 15) we considered reactions involved in a chemical synthesis of thyroxine. The following is a synthesis of optically pure thyroxine from the amino acid tyrosine (also see Problem 2, below). This synthesis proved to be useful on an industrial scale. (Scheme adapted from Fleming, I., *Selected Organic Syntheses*, pp. 31–33. © 1973 John Wiley & Sons, Limited. Reproduced with permission.)

(a) 1 to 2 What type of reaction is involved in the conversion of **1** to **2**? Write a detailed mechanism for this transformation. Explain why the nitro groups appear where they do in **2**.

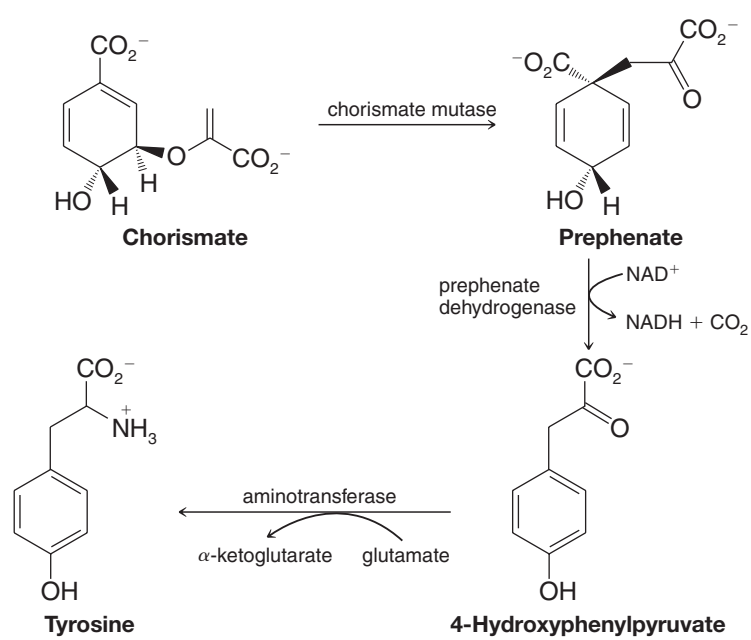
(b) 2 to 3 (i) Write a detailed mechanism for step (1) in the conversion of **2** to **3**.
(ii) Write a detailed mechanism for step (2) in the conversion of **2** to **3**.
(iii) Write a detailed mechanism for step (3) in the conversion of **2** to **3**.

(c) 3 to 4 (i) What type of reaction mechanism is involved in the conversion of **3** to **4**?
(ii) Write a detailed mechanism for the reaction from **3** to **4**. What key intermediate is involved?

(d) 5 to 6 Write a detailed mechanism for conversion of the methoxyl group of **5** to the phenolic hydroxyl of **6**.

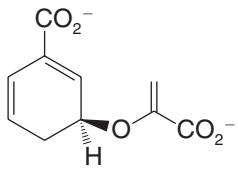


2. Tyrosine is an amino acid with a phenolic side chain. Biosynthesis in plants and microbes of tyrosine involves enzymatic conversion of chorismate to prephenate, below. Prephenate is then processed further to form tyrosine. These steps are shown here:



(a) There has been substantial research and debate about the enzymatic conversion of chorismate to prephenate by chorismate mutase. Although the enzymatic mechanism may not be precisely analogous, what laboratory reaction have we studied in this chapter that resembles the biochemical conversion of chorismate to prephenate? Draw arrows to show the movement of electrons involved in such a reaction from chorismate to prephenate.

(b) When the type of reaction you proposed above is applied in laboratory syntheses, it is generally the case that the reaction proceeds by a concerted chair conformation transition state. Five of the atoms of the chair are carbon and one is oxygen. In both the reactant and product, the chair has one bond missing, but at the point of the bond reorganization there is roughly concerted flow of electron density throughout the atoms involved in the chair. For the reactant shown below, draw the structure of the product and the associated chair conformation transition state for this type of reaction:

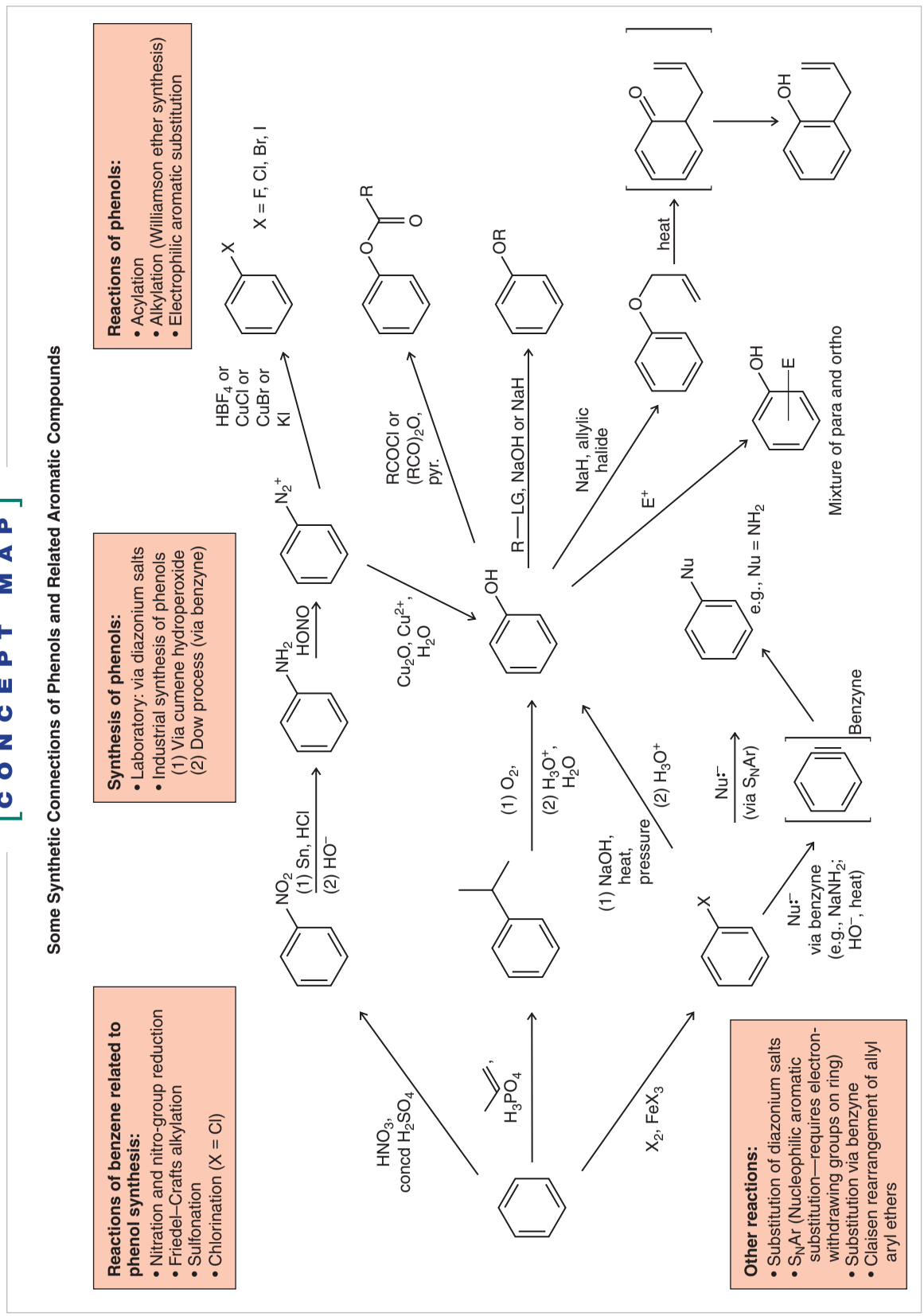


(c) Draw the structure of the nicotinamide ring of NAD^+ and draw mechanism arrows to show the decarboxylation of prephenate to 4-hydroxyphenylpyruvate with transfer of the hydride to NAD^+ (this is the type of process involved in the mechanism of prephenate dehydrogenase).

(d) Look up the structures of glutamate (glutamic acid) and α-ketoglutarate and consider the process of transamination involved in conversion of 4-hydroxyphenylpyruvate to tyrosine. Identify the source of the amino group in this transamination (i.e., what is the amino group "donor"?). What functional group is left after the amino group has been transferred from its donor? Propose a mechanism for this transamination. Note that the mechanism you propose will likely involve formation and hydrolysis of several imine intermediates—reactions similar to others we studied in Section 16.8.

[CONCEPT MAP]

Some Synthetic Connections of Phenols and Related Aromatic Compounds

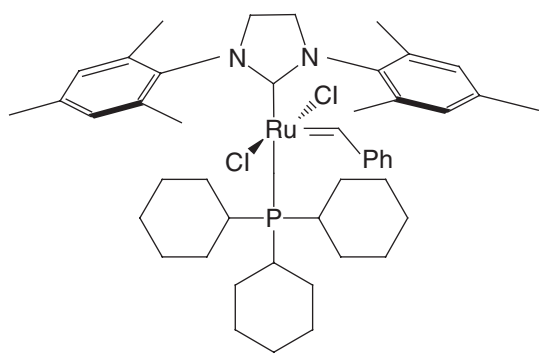


See Second Review Problem Set in *WileyPLUS*

SPECIAL TOPIC

G

Carbon–Carbon Bond–Forming and Other Reactions of Transition Metal Organometallic Compounds



Second generation Grubbs olefin metathesis catalyst

A number of transition metal–catalyzed carbon–carbon bond-forming reactions have been developed into highly useful tools for organic synthesis. The great power of many transition metal–catalyzed reactions is that they provide ways to form bonds between groups for which there are very limited or perhaps no other carbon–carbon bond-forming reactions available. For example, using certain **transition metal catalysts** we can form bonds between alkenyl (vinyl) or aryl substrates and sp^2- or *sp*-hybridized carbons of other reactants. We shall provide examples of a few of these methods here, including the **Heck–Mizoroki reaction**, the **Suzuki–Miyaura coupling**, the **Stille coupling**, and the **Sonogashira coupling**. These reactions are types of **cross-coupling reactions**, whereby two reactants of appropriate structure are coupled by a new carbon–carbon σ bond.

Olefin metathesis is another reaction type, whereby the groups of two alkene reactants exchange position with each other. We shall discuss olefin metathesis reactions that are promoted by **Grubbs' catalyst**.

Another transition metal–catalyzed carbon–carbon bond-forming reaction we shall discuss is the **Corey–Posner, Whitesides–House reaction**. Using this reaction an alkyl halide can be coupled with the alkyl group from a **lithium dialkyl cuprate** reagent (often called a **Gilman reagent**). This reaction does not have a catalytic mechanism.

All of these reactions involve transition metals such as palladium, copper, and ruthenium, usually in complex with certain types of ligands. After we see the practical applications of these reactions for carbon–carbon bond formation, we shall consider some general aspects of transition metal complex structure and representative steps in the mechanisms of transition metal–catalyzed reactions. We shall consider as specific examples the mechanism for a transition metal–catalyzed hydrogenation using a rhodium complex called Wilkinson's catalyst, and the mechanism for the Heck–Mizoroki reaction.

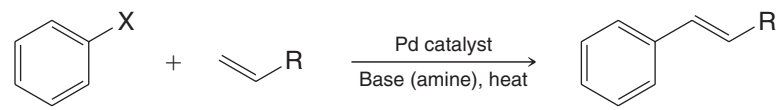
G.1 CROSS-COUPLING REACTIONS CATALYZED BY TRANSITION METALS

G.1A The Heck–Mizoroki Reaction

ROBERT F. HECK shared the 2010 Nobel Prize in Chemistry with Ei-ichi Negishi and Akira Suzuki for development of palladium-catalyzed cross coupling reactions.

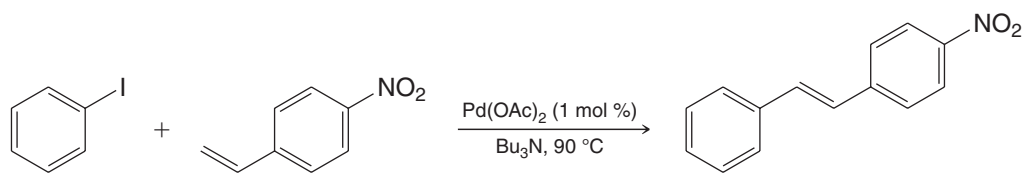
The Heck–Mizoroki reaction involves palladium-catalyzed coupling of an alkene with an alkenyl or aryl halide, leading to a substituted alkene. The alkene product is generally trans due to a 1,2-elimination step in the mechanism.

General Reaction



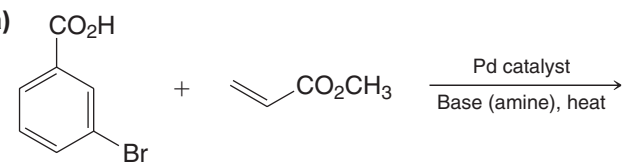
X = I, Br, Cl
(in order of relative reactivity)

Specific Example

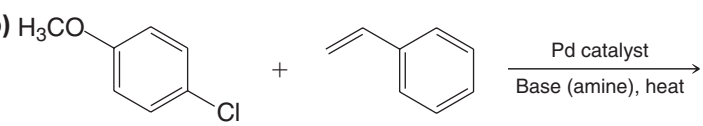


PRACTICE PROBLEM G.1 What product would you expect from each of the following reactions?

(a)

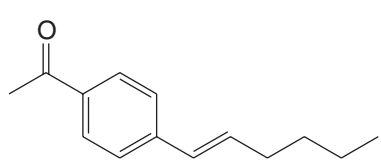


(b)

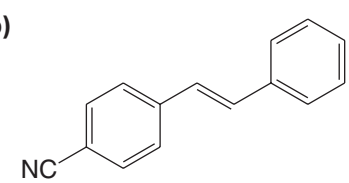


PRACTICE PROBLEM G.2 What starting materials could be used to synthesize each of the following compounds by a Heck–Mizoroki reaction?

(a)



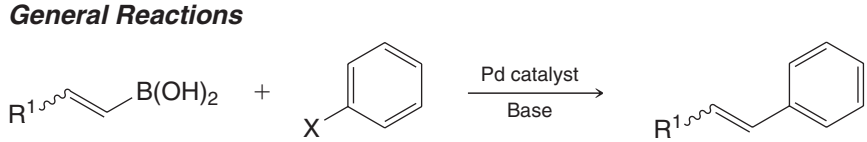
(b)



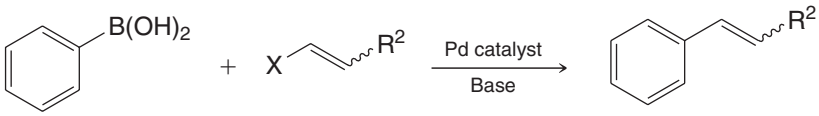
G.1B The Suzuki–Miyaura Coupling

The Suzuki–Miyaura coupling joins an alkenyl or aryl borate with an alkenyl or aryl halide in the presence of a palladium catalyst. The stereochemistry of alkenyl reactants is preserved in the coupling.

General Reactions

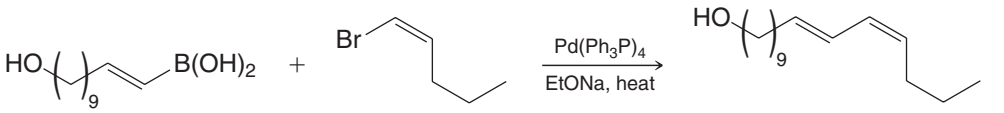


Alkenyl borate **Aryl halide (or alkenyl halide)**



Aryl borate **Alkenyl halide (or aryl halide)**

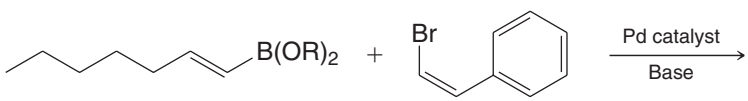
Specific Example



Bombykol (a sex hormone released by the female silkworm)

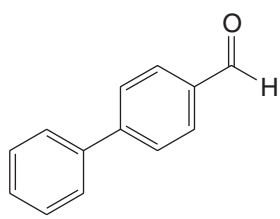
PRACTICE PROBLEM G.3

What is the product of the following Suzuki–Miyaura coupling?



PRACTICE PROBLEM G.4

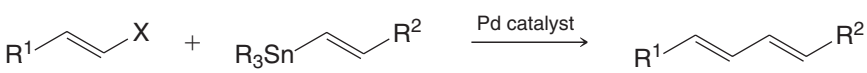
What starting materials could be used to synthesize the following compound by a Suzuki–Miyaura coupling?



G.1C The Stille Coupling and Carbonylation

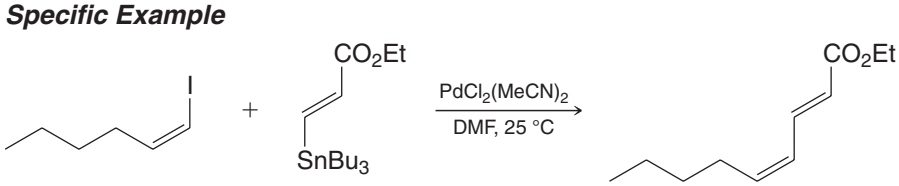
The Stille coupling is a cross-coupling reaction that involves an organotin reagent as one reactant. In the presence of appropriate palladium catalysts, alkenyl and aryl tin reactants can be coupled with alkenyl triflates, iodides, and bromides, as well as allylic chlorides and acid chlorides.

General Reaction

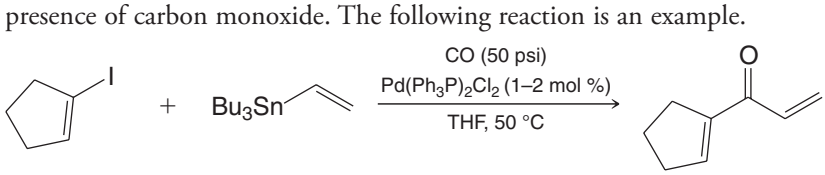


X = triflate, I, or Br

Specific Example

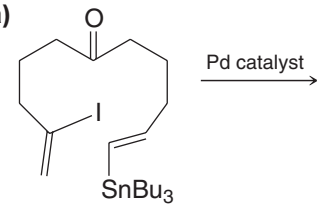


Ketones can be synthesized by a variation of the Stille coupling that involves coupling in the presence of carbon monoxide. The following reaction is an example.

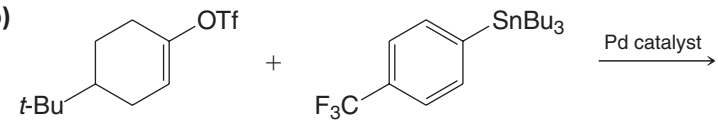


PRACTICE PROBLEM G.5 What is the product of each of the following reactions?

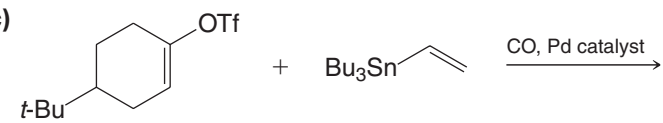
(a)



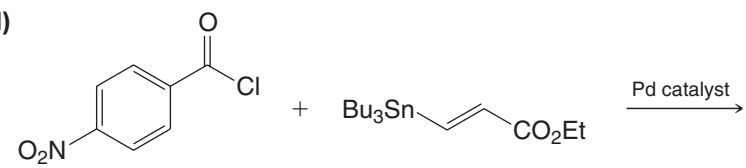
(b)



(c)

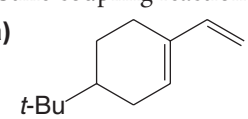


(d)

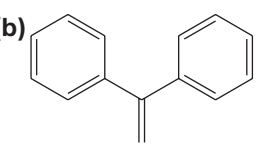


PRACTICE PROBLEM G.6 What starting materials could be used to synthesize each of the following compounds by a Stille coupling reaction?

(a)



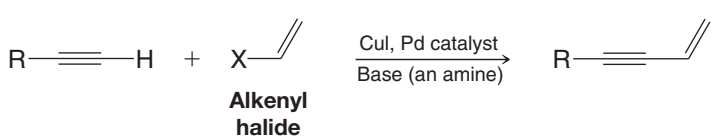
(b)



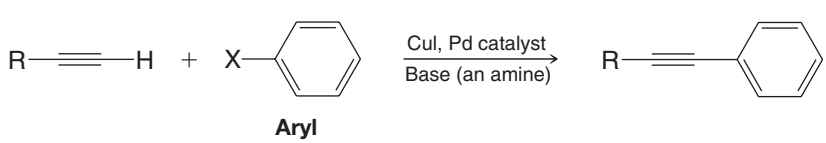
G.1D The Sonogashira Coupling

The Sonogashira coupling joins an alkyne with an alkenyl or aryl halide in the presence of catalytic palladium and copper. A copper alkynide is formed as an intermediate in the reaction. (When palladium is not used, the reaction is called the Stephens–Castro coupling, and it is not catalytic.) In addition to providing a method for joining an alkyne directly to an aromatic ring, the Sonogashira coupling provides a way to synthesize enynes.

General Reactions

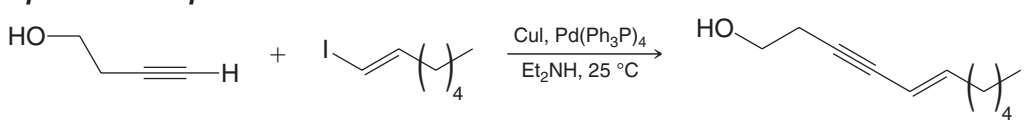


Alkenyl halide



Aryl halide

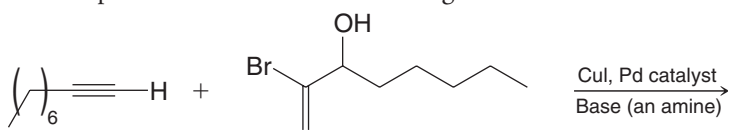
Specific Example



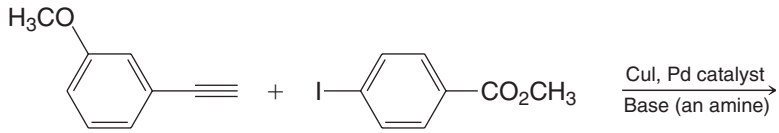
PRACTICE PROBLEM G.7

Provide the products of each of the following reactions.

(a)



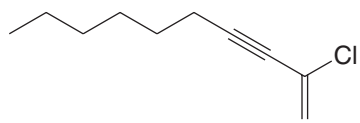
(b)



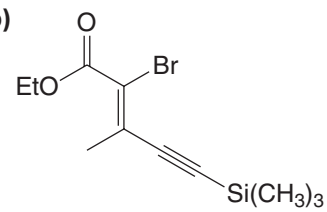
PRACTICE PROBLEM G.8

What starting materials could be used to synthesize each of the following compounds by a Sonogashira coupling reaction?

(a)



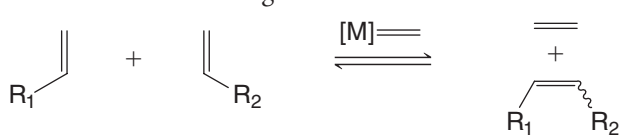
(b)



G.2 OLEFIN METATHESIS: RUTHENIUM CARBENE COMPLEXES AND GRUBBS' CATALYSTS

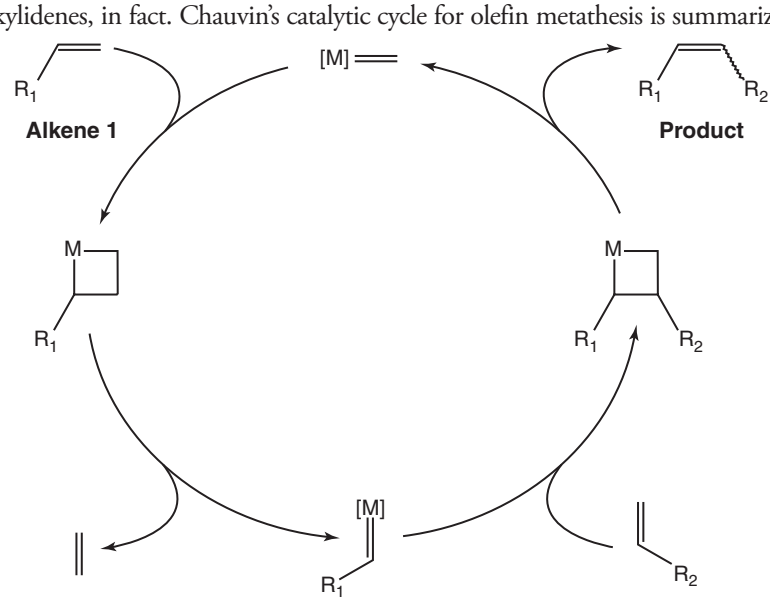
Pairs of alkene double bonds can trade ends with each other in a remarkable molecular "dance" called olefin metathesis (*meta*, Greek: to change; *thesis*, Greek: position).

The overall reaction is the following.

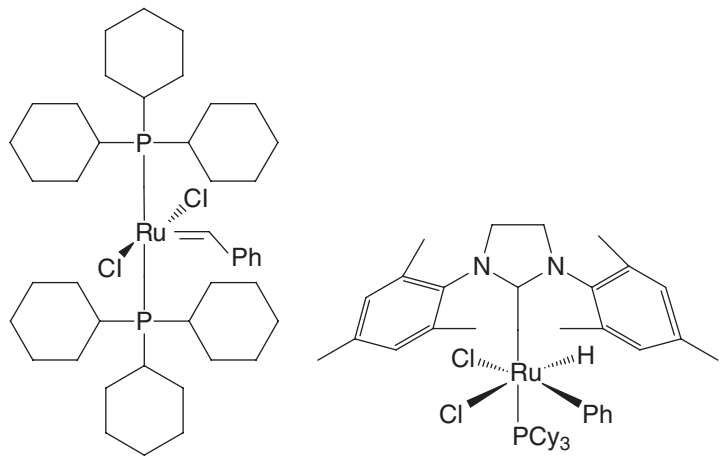


[M]═ represents a ruthenium alkylidene complex

The generally accepted catalytic cycle for this "change partners" dance was proposed by Yves Chauvin and is believed to involve metallocyclobutane intermediates that result from reaction of metal alkylidenes (also called metal carbenes) with alkenes. The catalysts themselves are metal alkylidenes, in fact. Chauvin's catalytic cycle for olefin metathesis is summarized here.



Richard Schrock investigated the properties of some of the first catalysts for olefin metathesis. His work included catalysts prepared from tantalum, titanium, and molybdenum. The catalysts predominantly in use today, however, are ruthenium catalysts developed by Robert Grubbs. His so-called first generation and second generation catalysts are shown here.



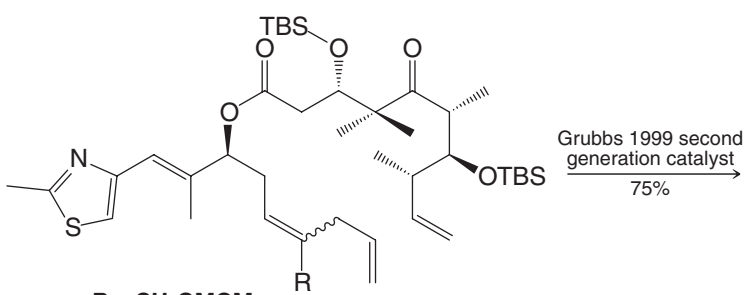
Cy = cyclohexyl

Grubbs, 1995
First generation Grubbs catalyst
(commercially available)

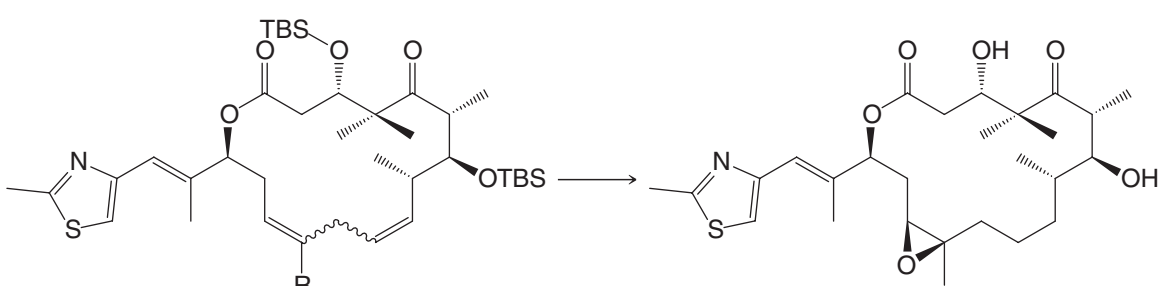
Grubbs, 1999
Second generation Grubbs catalyst
(commercially available)

2005 Nobel Prize: Chauvin, Grubbs, and Schrock

Olefin metathesis has proved to be such a powerful tool for synthesis that the 2005 Nobel Prize in Chemistry was awarded to Chauvin, Grubbs, and Shrock for their work in this area. Uses include its application to several syntheses of anticancer agents in the epothilone family by Danishefsky, Nicolaou, Shinzer, Sinha, and others, as in the example shown here.



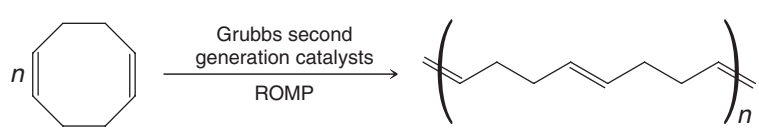
R = CH_2OMOM



R = CH_2OMOM
[mixture of (*Z*) and (*E, Z*) dienes]

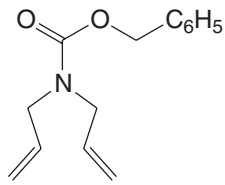
Epothilone B

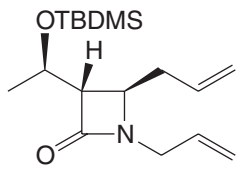
Another example is ring-opening olefin metathesis polymerization (ROMP), as can be used for synthesis of polybutadiene from 1,5-cyclooctadiene.

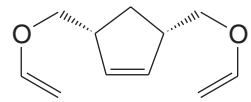


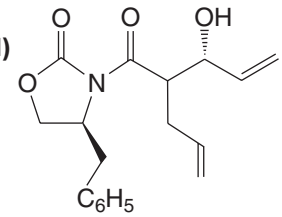
PRACTICE PROBLEM G.9

What products would form when each of the following compounds is treated with $(PCy_3)_2Cl_2Ru{=}CHPh$, one of Grubbs' catalysts?

(a) 

(b) 

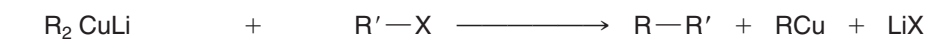
(c) 

(d) 

G.3 THE COREY–POSNER, WHITESIDES–HOUSE REACTION: USE OF LITHIUM DIALKYL CUPRATES (GILMAN REAGENTS) IN COUPLING REACTIONS

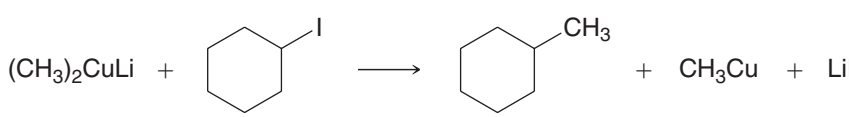
The Corey–Posner, Whitesides–House reaction involves the coupling of a lithium dialkylcuprate (called a Gilman reagent) with an alkyl, alkenyl, or aryl halide. The alkyl group of the lithium dialkylcuprate reagent may be primary, secondary, or tertiary. However, the halide with which the Gilman reagent couples must be a primary or cyclic secondary alkyl halide if it is not alkenyl or aryl.

General Reaction



A lithium dialkyl cuprate (a Gilman reagent) — **Alkenyl, aryl, or 1° or cyclic 2° alkyl halide**

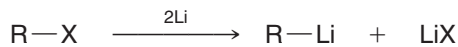
Specific Example



Lithium dimethylcuprate — **75%**

The required lithium dimethylcuprate (Gilman) reagent must be synthesized by a two-step process from the corresponding alkyl halide, as follows.

Synthesis of an Organolithium Compound

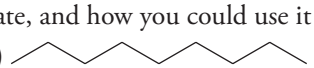


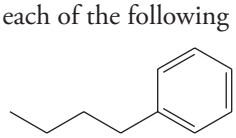
Synthesis of the Lithium Dialkylcuprate (Gilman) Reagent

All of the reagents in a Corey–Posner, Whitesides–House reaction are consumed stoichiometrically. The mechanism does not involve a catalyst, as in the other reactions of transition metals that we have studied.

PRACTICE PROBLEM G.10

Show how 1-bromobutane could be converted to the Gilman reagent lithium dibutylcuprate, and how you could use it to synthesize each of the following compounds.

(a) 

(b) 

G.4 SOME BACKGROUND ON TRANSITION METAL ELEMENTS AND COMPLEXES

Now that we have seen examples of some important reactions involving transition metals, we consider aspects of the electronic structure of the metals and their complexes.

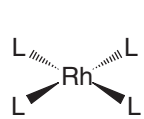
Transition metals are defined as those elements that have partly filled *d* (or *f*) shells, either in the elemental state or in their important compounds. The transition metals that are of most concern to organic chemists are those shown in the green and yellow portion of the periodic table given in Fig. G.1, which include those whose reactions we have just discussed.

Periods	1/IA	2/IIA	3/IIIB	4/IVB	5/VB	6/VIB	7/VIIB	8/VIIIB	9/VIIIB	10/VIIIB	11/IB	12/IIB
1	1 H 1.00797											
2	3 Li 6.941	4 Be 9.01218										
3	11 Na 22.98977	12 Mg 24.305										
4	19 K 39.098	20 Ca 40.08	21 Sc 44.9559	22 Ti 47.90	23 V 50.9414	24 Cr 51.996	25 Mn 54.9380	26 Fe 55.847	27 Co 58.9332	28 Ni 58.71	29 Cu 63.546	30 Zn 65.38
5	37 Rb 85.4678	38 Sr 87.62	39 Y 89.9059	40 Zr 91.22	41 Nb 92.9064	42 Mo 95.94	43 Tc 98.9062	44 Ru 101.07	45 Rh 102.9055	46 Pd 106.4	47 Ag 107.868	48 Cd 112.40
6	55 Cs 132.9054	56 Ba 137.34	57 La 138.9055	72 Hf 178.49	73 Ta 180.9479	74 W 183.85	75 Re 186.2	76 Os 190.2	77 Ir 192.22	78 Pt 195.09	79 Au 196.9665	80 Hg 200.59
Valence electrons	1	2	3	4	5	6	7	8	9	10	11	12

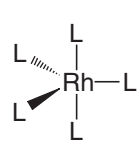
FIGURE G.1 Important transition elements are shown in the green and yellow portion of the periodic table. Given across the bottom is the total number of valence electrons (*s* and *d*) of each element.

Transition metals react with a variety of molecules or groups, called *ligands*, to form *transition metal complexes*. In forming a complex, the ligands donate electrons to vacant orbitals of the metal. The bonds between the ligand and the metal range from very weak to very strong. The bonds are covalent but often have considerable polar character.

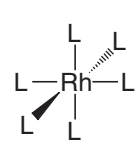
Transition metal complexes can assume a variety of geometries depending on the metal and on the number of ligands around it. Rhodium, for example, can form complexes with four ligands in a configuration called *square planar*. On the other hand, rhodium can also form complexes with five or six ligands that are trigonal bipyramidal or octahedral. These typical shapes are shown below, with the letter L used to indicate a ligand.



Square planar rhodium complex



Trigonal bipyramidal rhodium complex



Octahedral rhodium complex

G.5 ELECTRON COUNTING IN METAL COMPLEXES

Transition metals are like the elements that we have studied earlier in that they are most stable when they have the electronic configuration of a noble gas. In addition to *s* and *p* orbitals, transition metals have five *d* orbitals (which can hold a total of 10 electrons). Therefore, the noble gas configuration for a transition metal is *18 electrons*, not 8 as with carbon, nitrogen, oxygen, and so on.

- When the metal of a transition metal complex has 18 valence electrons, it is said to be **coordinatively saturated**.*

To determine the valence electron count of a transition metal in a complex, we take the total number of valence electrons of the metal in the elemental state (see Fig. G.1) and subtract from this number the oxidation state of the metal in the complex. This gives us what is called the *d* electron count, d^n. The oxidation state of the metal is the charge that would be left on the metal if all the ligands (Table G.1) were removed.

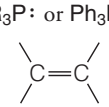
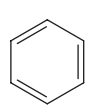
$$d^n = \begin{array}{c}\text{total number of valence electrons}\\ \text{of the elemental metal}\end{array} - \begin{array}{c}\text{oxidation state of}\\ \text{the metal in the complex}\end{array}$$

Then to get the total valence electron count of the metal *in the complex*, we add to d^n the number of electrons donated by all of the ligands. Table G.1 gives the number of electrons donated by several of the most common ligands.

$$\begin{array}{c}\text{total number of valence electrons}\\ \text{of the metal in the complex}\end{array} = d^n + \begin{array}{c}\text{electrons donated}\\ \text{by ligands}\end{array}$$

Let us now work out the valence electron count of two examples.

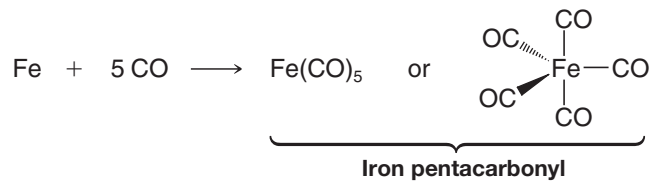
TABLE G.1 COMMON LIGANDS IN TRANSITION METAL COMPLEXES[a]

Ligand	Count as	Number of Electrons Donated
Negatively charged ligands		
Hydride, H	H:$^-$	2
Alkanide, R	R:$^-$	2
Halide, X	X:$^-$	2
Allyl anion		4
Cyclopentadienyl anion, Cp		6
Electrically neutral ligands		
Carbonyl (carbon monoxide)	:C≡O:	2
Phosphine	R_3P: or Ph_3P:	2
Alkene		2
Diene		4
Benzene		6

[a]Based on data obtained from the *Journal of Chemical Education*, Vol. 57, No. 1, 1980, pp. 170–175, copyright ©1980, Division of Chemical Education.

*We do not usually show the unshared electron pairs of a metal complex in our structures, because to do so would make the structure unnecessarily complicated.

Example A Consider iron pentacarbonyl, $Fe(CO)_5$, a toxic liquid that forms when finely divided iron reacts with carbon monoxide.



From Fig. G.1 we find that an iron atom in the elemental state has 8 valence electrons. We arrive at the oxidation state of iron in iron pentacarbonyl by noting that the charge on the complex as a whole is zero (it is not an ion), and that the charge on each CO ligand is also zero. Therefore, the iron is in the zero oxidation state.

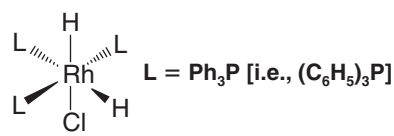
Using these numbers, we can now calculate d^n and, from it, the total number of valence electrons of the iron in the complex.

$$d^n = 8 - 0 = 8$$

$$\text{total number of valence electrons} = d^n + 5(CO) = 8 + 5(2) = 18$$

We find that the iron of $Fe(CO)_5$ has 18 valence electrons and is, therefore, coordinatively saturated.

Example B Consider the rhodium complex $Rh[(C_6H_5)_3P]_3H_2Cl$, a complex that, as we shall see later, is an intermediate in certain alkene hydrogenations.



The oxidation state of rhodium in the complex is +3. [The two hydrogen atoms and the chlorine are each counted as −1 (hydride and chloride, respectively), and the charge on each of the triphenylphosphine ligands is zero. Removing all the ligands would leave a Rh^{3+} ion.] From Fig. G.1 we find that, in the elemental state, rhodium has 9 valence electrons. We can now calculate d^n for the rhodium of the complex.

$$d^n = 9 - 3 = 6$$

Each of the six ligands of the complex donates two electrons to the rhodium in the complex, and, therefore, the total number of valence electrons of the rhodium is 18. The rhodium of $Rh[(C_6H_5)_3P]_3H_2Cl$ is coordinatively saturated.

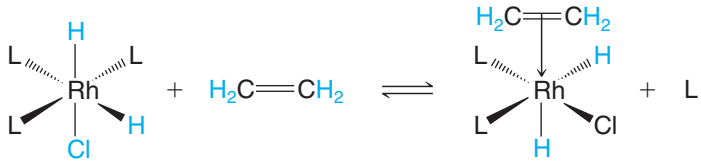
$$\text{total number of valence electrons rhodium} = d^n + 6(2) = 6 + 12 = 18$$

G.6 MECHANISTIC STEPS IN THE REACTIONS OF SOME TRANSITION METAL COMPLEXES

Much of the chemistry of organic transition metal compounds becomes more understandable if we are able to follow the mechanisms of the reactions that occur. These mechanisms, in most cases, amount to nothing more than a sequence of reactions, each of which represents *a fundamental reaction type that is characteristic of a transition metal complex*. Let us examine three of the fundamental reaction types now. In each instance we shall use steps that occur when an alkene is hydrogenated using a catalyst called Wilkinson's catalyst. In Section G.7 we shall examine the entire hydrogenation mechanism. In Section G.8 we shall see how similar types of steps are involved in the Heck–Mizoroki reaction.

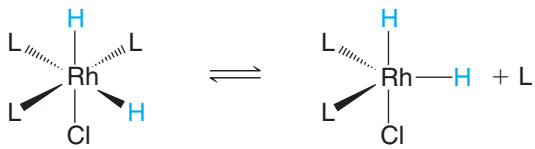
1. **Ligand Dissociation–Association (Ligand Exchange).** A transition metal complex can lose a ligand (by dissociation) and combine with another ligand (by association). In the process it undergoes *ligand exchange*. For example, the rhodium complex that

we encountered in Example B above can react with an alkene (in this example, with ethene) as follows:



L = Ph_3P [i.e., $(C_6H_5)_3P$]

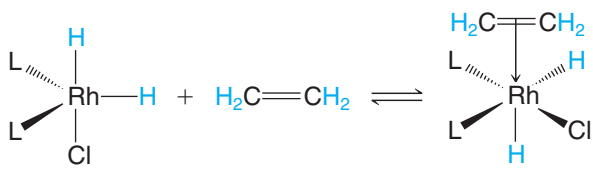
Two steps are actually involved. In the first step, one of the triphenylphosphine ligands dissociates. This leads to a complex in which the rhodium has only 16 electrons and is, therefore, coordinatively *unsaturated*.



(18 electrons) **(16 electrons)**

L = Ph_3P

In the second step, the rhodium associates with the alkene to become coordinatively saturated again.



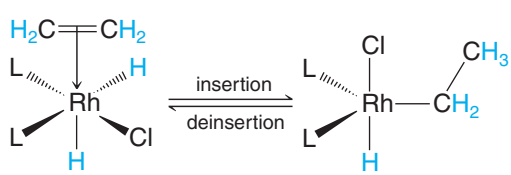
(16 electrons) **(18 electrons)**

The complex between the rhodium and the alkene is called a π *complex*. In it, two electrons are donated by the alkene to the rhodium. Alkenes are often called π donors to distinguish them from σ donors such as Ph_3P:, Cl^-, and so on.

In a π complex such as the one just given, there is also a donation of electrons from a populated *d* orbital of the metal back to the vacant π^* orbital of the alkene. This kind of donation is called "back-bonding."

2. Insertion–Deinsertion. An unsaturated ligand such as an alkene can undergo *insertion* into a bond between the metal of a complex and a hydrogen or a carbon. These reactions are reversible, and the reverse reaction is called *deinsertion*.

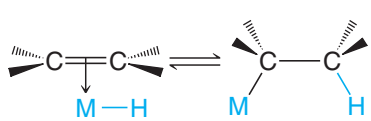
The following is an example of insertion–deinsertion.



(18 electrons) **(16 electrons)**

In this process, a π bond (between the rhodium and the alkene) and a σ bond (between the rhodium and the hydrogen) are exchanged for two new σ bonds (between rhodium and carbon, and between carbon and hydrogen). The valence electron count of the rhodium decreases from 18 to 16.

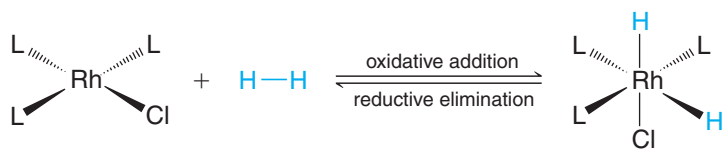
This insertion–deinsertion occurs in a stereospecific way, as a *syn addition* of the M—H unit to the alkene.



3. Oxidative Addition–Reductive Elimination. Coordinatively unsaturated metal complexes can undergo oxidative addition of a variety of substrates in the following way.*

The substrate, A—B, can be H—H, H—X, R—X, RCO—H, RCO—X, and a number of other compounds.

In this type of oxidative addition, the metal of the complex undergoes an increase in the number of its valence electrons *and in its oxidation state*. Consider, as an example, the oxidative addition of hydrogen to the rhodium complex that follows (L = Ph_3P).



(16 electrons) Rh is in +1 oxidation state. **(18 electrons) Rh is in +3 oxidation state.**

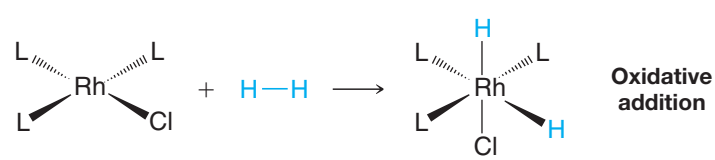
Reductive elimination is the reverse of oxidative addition. With this background, we are now in a position to examine the mechanisms of two applications of transition metal complexes in organic synthesis.

G.7 THE MECHANISM FOR A HOMOGENEOUS HYDROGENATION: WILKINSON'S CATALYST

The catalytic hydrogenations that we have examined in prior chapters have been heterogeneous processes. Two phases were involved: the solid phase of the catalyst (Pt, Pd, Ni, etc.), containing the adsorbed hydrogen, and the liquid phase of the solution, containing the unsaturated compound. In homogeneous hydrogenation using a transition metal complex such as $Rh[(C_6H_5)_3P]_3Cl$ (Wilkinson's catalyst), hydrogenation takes place *in a single phase*, i.e., in solution.

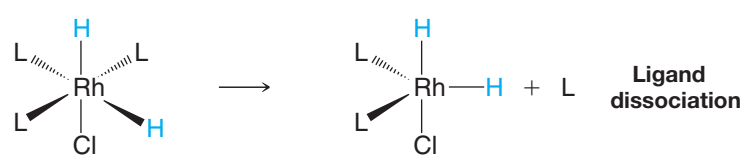
When Wilkinson's catalyst is used to carry out the hydrogenation of an alkene, the following steps take place (L = Ph_3P).

Step 1



16 valence electrons **18 valence electrons**

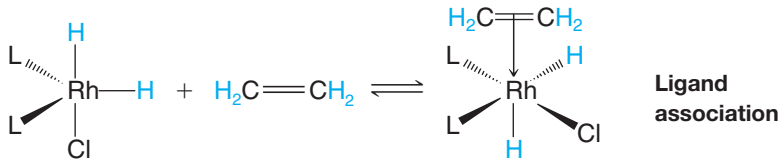
Step 2



18 valence electrons **16 valence electrons**

*Coordinatively saturated complexes also undergo oxidative addition.

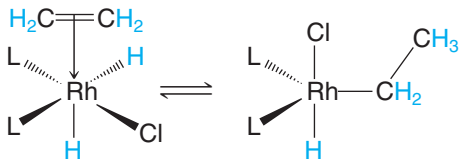
Step 3



Ligand association

16 valence electrons **18 valence electrons**

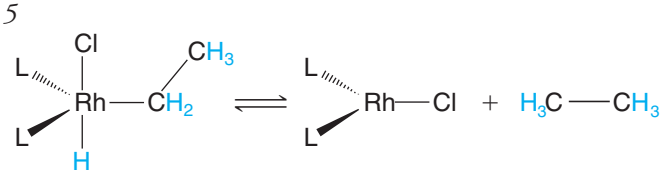
Step 4



Insertion

18 valence electrons **16 valence electrons**

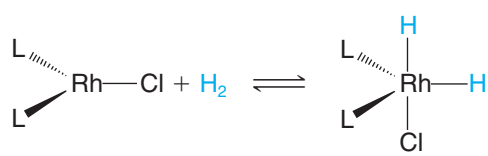
Step 5



Reductive elimination

16 valence electrons **14 valence electrons**

Step 6



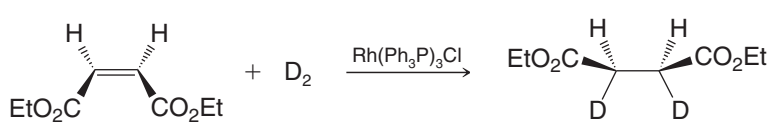
Oxidative addition

14 valence electrons **16 valence electrons**

(Cycle repeats from step 3.)

Step 6 regenerates the hydrogen-bearing rhodium complex and reaction with another molecule of the alkene begins at step 3.

Because the insertion step 4 and the reductive elimination step 5 are stereospecific, the net result of the hydrogenation using Wilkinson's catalyst is a *syn addition* of hydrogen to the alkene. The following example (with D_2 in place of H_2) illustrates this aspect.



A *cis*-alkene (diethyl maleate) **A meso compound**

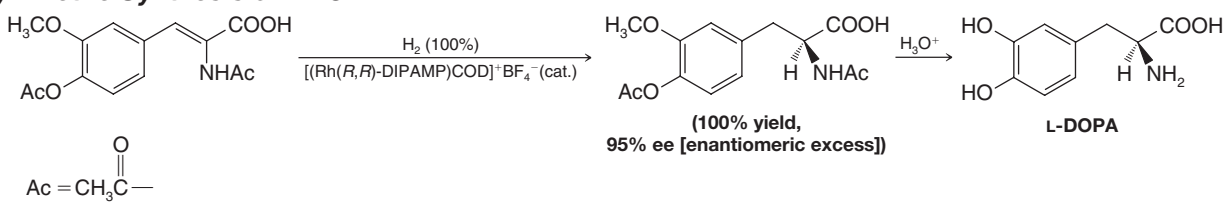
PRACTICE PROBLEM G.11

What product (or products) would be formed if the *trans*-alkene corresponding to the *cis*-alkene (see the previous reaction) had been hydrogenated with D_2 and Wilkinson's catalyst?

THE CHEMISTRY OF... Homogeneous Asymmetric Catalytic Hydrogenation: Examples Involving L-DOPA, (S)-Naproxen, and Aspartame

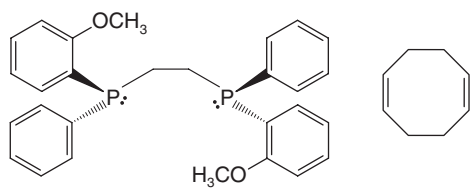
Development by Geoffrey Wilkinson of a soluble catalyst for hydrogenation [tris(triphenylphosphine)rhodium chloride, Section 7.13 and Special Topic G] led to Wilkinson's earning a share of the 1973 Nobel Prize in Chemistry. His initial discovery, while at Imperial College, University of London, inspired many other researchers to create novel catalysts based on the Wilkinson catalyst. Some of these researchers were themselves recognized by the 2001 Nobel Prize in Chemistry, 50% of which was awarded to William S. Knowles (Monsanto Corporation, retired) and Ryoji Noyori (Nagoya University). (The other half of the 2001 prize was awarded to K. B. Sharpless, Scripps Research Institute, for asymmetric oxidation reactions. See Chapter 8.) Knowles, Noyori, and others developed chiral catalysts for homogeneous hydrogenation that have proved extraordinarily useful for enantioselective syntheses ranging from small laboratory-scale reactions to industrial- (ton-) scale reactions. An important example is the method developed by Knowles and co-workers at Monsanto Corporation for synthesis of L-DOPA, a compound used in the treatment of Parkinson's disease:

Asymmetric Synthesis of L-DOPA



(100% yield, 95% ee [enantiomeric excess])

L-DOPA

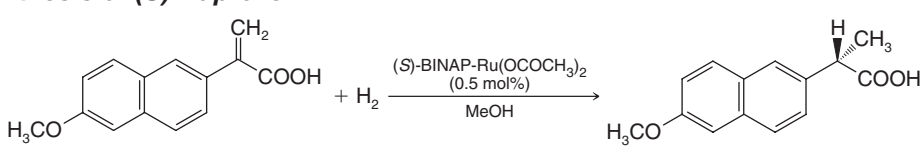


(*R*,*R*)-DIPAMP (Chiral ligand for rhodium)

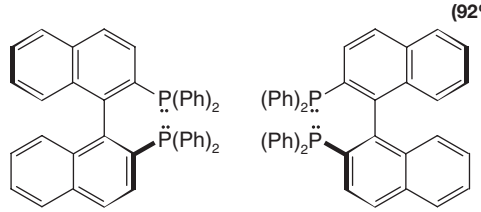
COD = 1,5-Cyclooctadiene

Another example is synthesis of the over-the-counter analgesic (*S*)-naproxen using a BINAP rhodium catalyst developed by Noyori (Sections 5.11 and 5.18).

Asymmetric Synthesis of (S)-Naproxen



(*S*)-Naproxen (an anti-inflammatory agent) (92% yield, 97% ee)

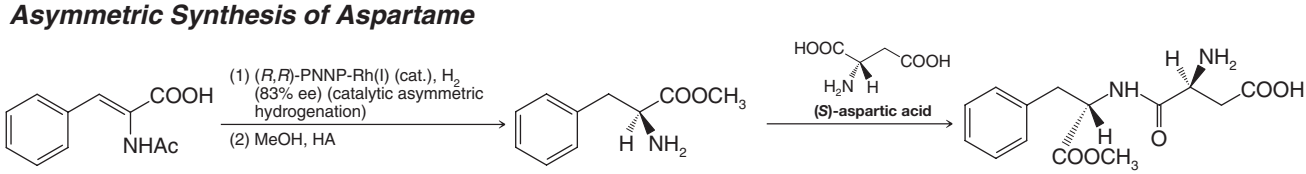


(*S*)-BINAP **(*R*)-BINAP**

(*S*)-BINAP and (*R*)-BINAP are chiral atropisomers (see Section 5.18).

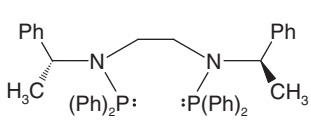
Catalysts like these are important for asymmetric chemical synthesis of amino acids (Section 24.3D), as well. A final example is the synthesis of (*S*)-phenylalanine methyl ester, a compound used in the synthesis of the artificial sweetener aspartame. This preparation employs yet a different chiral ligand for the rhodium catalyst.

Asymmetric Synthesis of Aspartame



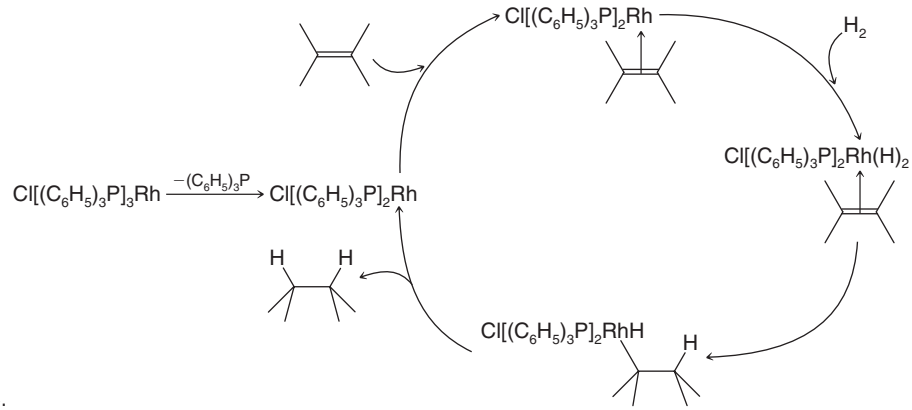
(*S*)-phenylalanine methyl ester (97% ee after recrystallization)

Aspartame



(*R*,*R*)-PNNP (Chiral ligand for rhodium)

The mechanism of homogeneous catalytic hydrogenation involves reactions characteristic of transition metal organometallic compounds. A general scheme for hydrogenation using Wilkinson's catalyst is shown here. We have seen structural details of the mechanism in Section G.7.



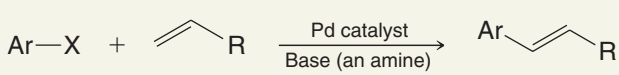
A general mechanism for the Wilkinson catalytic hydrogenation method, adapted with permission of John Wiley & Sons, Inc. from Noyori, *Asymmetric Catalysis in Organic Synthesis*, p. 17. Copyright 1994.

G.8 THE MECHANISM FOR AN EXAMPLE OF CROSS-COUPLING: THE HECK–MIZOROKI REACTION

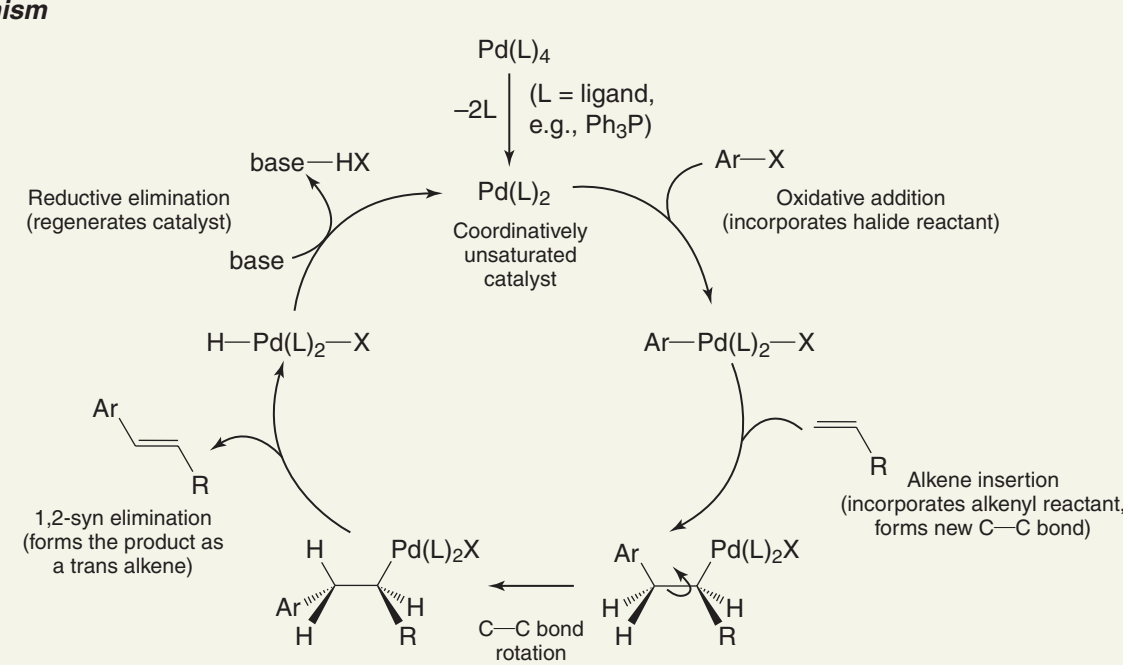
Having seen steps such as oxidative addition, insertion, and reductive elimination in the context of transition metal–catalyzed hydrogenation using Wilkinson's catalyst, we can now see how these same types of mechanistic steps are involved in a mechanism proposed for the Heck–Mizoroki reaction. Aspects of the Heck–Mizoroki mechanism are similar to steps proposed for other cross-coupling reactions as well, although there are variations and certain steps that are specific to each, and not all of the steps below are involved or serve the same purpose in other cross-coupling reactions.

A MECHANISM FOR THE REACTION — The Heck–Mizoroki Reaction Using an Aryl Halide Substrate

General Reaction



Mechanism



G.9 VITAMIN B_{12}: A TRANSITION METAL BIOMOLECULE

The discovery (in 1926) that pernicious anemia can be overcome by the ingestion of large amounts of liver led ultimately to the isolation (in 1948) of the curative factor, called vitamin B_{12}. The complete three-dimensional structure of vitamin B_{12} [Fig. G.2(*a*)] was elucidated in 1956 through the X-ray studies of Dorothy Hodgkin (Nobel Prize, 1964), and in 1972 the synthesis of this complicated molecule was announced by R. B. Woodward (Harvard University) and A. Eschenmoser (Swiss Federal Institute of Technology). The synthesis took 11 years and involved more than 90 separate reactions. One hundred coworkers took part in the project.

Vitamin B_{12} is the only known biomolecule that possesses a carbon–metal bond. In the stable commercial form of the vitamin, a cyano group is bonded to the cobalt, and the cobalt is in the +3 oxidation state. The core of the vitamin B_{12} molecule is a *corrin ring* [Fig. G.2(*b*)] with various attached side groups. The corrin ring consists of four pyrrole subunits, the nitrogen of each of which is coordinated to the central cobalt. The sixth ligand [(below the corrin ring in Fig. G.2(*a*)] is a nitrogen of a heterocyclic group derived from 5,6-dimethylbenzimidazole.

The cobalt of vitamin B_{12} can be reduced to a +2 or a +1 oxidation state. When the cobalt is in the +1 oxidation state, vitamin B_{12} (called B_{12s}) becomes one of the most powerful nucleophiles known, being more nucleophilic than methanol by a factor of 10^{14}.

Acting as a nucleophile, vitamin B_{12s} reacts with adenosine triphosphate (Fig. 22.2) to yield the biologically active form of the vitamin [Fig. G.2(*c*)].

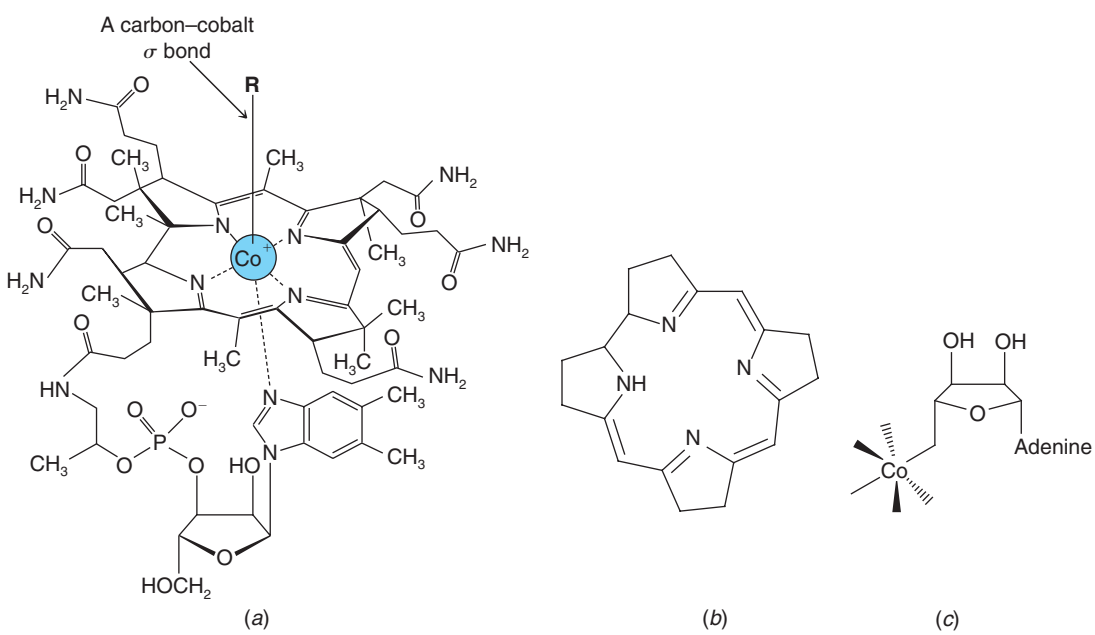


FIGURE G.2 (*a*) The structure of vitamin B_{12}. In the commercial form of the vitamin (cyanocobalamin), R = CN. (*b*) The corrin ring system. (*c*) In the biologically active form of the vitamin (5′-deoxyadenosylcobalamin), the 5′ carbon atom of 5′-deoxyadenosine is coordinated to the cobalt atom. For the structure of adenine, see Section 25.2.

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