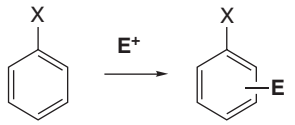
11

Aromatic Substitution Reactions

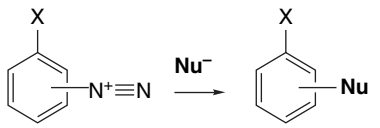
Introduction

This chapter is concerned with reactions that introduce or replace substituent groups on aromatic rings. The synthetic methods for aromatic substitution were among the first to be developed. The basic mechanistic concepts for electrophilic aromatic substitution and some of the fundamental reactions are discussed in Chapter 9 of Part A. These reactions provide methods for introduction of nitro groups, the halogens, sulfonic acids, and alkyl and acyl groups. The regioselectivity of these reactions depends upon the nature of the existing substituent and can be *ortho*, *meta*, or *para* selective.



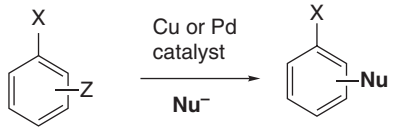
E = NO_2, F, Cl, Br. I, SO_3H, SO_2Cl, R, RC = O

A second group of aromatic substitution reactions involves aryl diazonium ions. As for electrophilic aromatic substitution, many of the reactions of aromatic diazonium ions date to the nineteenth century. There have continued to be methodological developments for substitution reactions of diazonium intermediates. These reactions provide routes to aryl halides, cyanides, and azides, phenols, and in some cases to alkenyl derivatives.



Nu = F, Cl, Br, I, CN, N_3, OH, CH = CHR

Direct nucleophilic displacement of halide and sulfonate groups from aromatic rings is difficult, although the reaction can be useful in specific cases. These reactions can occur by either addition-elimination (Section 11.2.2) or elimination-addition (Section 11.2.3). Recently, there has been rapid development of metal ion catalysis, and old methods involving copper salts have been greatly improved. Palladium catalysts for nucleophilic substitutions have been developed and have led to better procedures. These reactions are discussed in Section 11.3.



Z = I, Br, Cl, O_3SAr **Nu** = CN, R_2N, RO

Several radical reaction have some synthetic application, including radical substitution (Section 11.4.1) and the $S_{RN}1$ reaction (Section 11.4.2).

11.1. Electrophilic Aromatic Substitution

The basic mechanistic concepts and typical electrophilic aromatic substitution reactions are discussed in Sections 9.1 and 9.4 of Part A. In the present section, we expand on that material, with particular emphasis on synthetic methodology.

11.1.1. Nitration

Nitration is the most important method for introduction of nitrogen functionality on aromatic rings. Nitro compounds can be reduced easily to the corresponding amino derivatives, which can provide access to diazonium ions. There are several reagent systems that are useful for nitration. A major factor in the choice of reagent is the reactivity of the ring to be nitrated. Nitration is a very general reaction and satisfactory conditions can normally be developed for both activated and deactivated aromatic compounds. Since each successive nitro group reduces the reactivity of the ring, it is easy to control conditions to obtain a mononitration product. If polynitration is desired, more vigorous conditions are used.

Concentrated nitric acid can effect nitration but it is not as reactive as a mixture of nitric acid with sulfuric acid. The active nitrating species in both media is the nitronium ion, NO_2^+, which is formed by protonation and dissociation of nitric acid. The concentration of NO_2^+ is higher in the more strongly acidic sulfuric acid than in nitric acid.

$$HNO_3 + 2\,H^+ \rightleftharpoons H_3O^+ + NO_2^+$$

Nitration can also be carried out in organic solvents, with acetic acid and nitromethane being common examples. In these solvents the formation of the NO_2^+ is often the rate-controlling step.[1]

[1] E. D. Hughes, C. K. Ingold, and R. I. Reed, *J. Chem. Soc.*, 2400 (1950); J. G. Hoggett, R. B. Moodie, and K. Schofield, *J. Chem. Soc. B*, 1 (1969); K. Schofield, *Aromatic Nitration*, Cambridge University Press, Cambridge, 1980, Chap. 2.

$$2\ HNO_3 \rightleftharpoons H_2NO_3^+ + NO_3^-$$
$$H_2NO_3^+ \xrightarrow{slow} NO_2^+ + H_2O$$
$$ArH + NO_2^+ \xrightarrow{fast} ArNO_2 + H^+$$

Another useful medium for nitration is a solution prepared by dissolving nitric acid in acetic anhydride, which generates acetyl nitrate. This reagent tends to give high *ortho*:*para* ratios for some nitrations.[2]

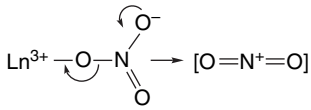
$$HNO_3 + (CH_3CO)_2O \rightleftharpoons CH_3C(=O)ONO_2 + CH_3CO_2H$$

A convenient procedure involves reaction of the aromatic in chloroform or dichloromethane with a nitrate salt and trifluoroacetic anhydride.[3] Presumably trifluoroacetyl nitrate is generated under these conditions.

$$NO_3^- + (CF_3CO)_2O \longrightarrow CF_3C(=O)ONO_2 + CF_3CO_2^-$$

Acetic anhydride and trifluoroacetic anhydride have both been used in conjunction with nitric acid and zeolite β. This system gives excellent *para* selectivity in many cases.[4] The improved selectivity is thought to occur as a result of nitration within the zeolite pores, which may restrict access to the *ortho* position; see, e.g., Entry 7 in Scheme 11.1.

Nitration can be catalyzed by lanthanide salts. For example, the nitration of benzene, toluene, and naphthalene by aqueous nitric acid proceeds in good yield in the presence of $Yb(O_3SCF_3)_3$.[5] The catalysis presumably results from an oxyphilic interaction of nitrate ion with the cation, which generates or transfers the NO_2^+ ion.[6] This catalytic procedure uses a stoichiometric amount of nitric acid and avoids the excess strong acidity associated with conventional nitration conditions.



A variety of aromatic compounds can be nitrated using $Sc(O_3SCF_3)_3$, with $LiNO_3$ or $Al(NO_3)_3$ and acetic anhydride (see Scheme 11.1, Entry 9).[7]

Salts containing the nitronium ion can be prepared and are reactive nitrating agents. The tetrafluoroborate salt has been used most frequently,[8] but the

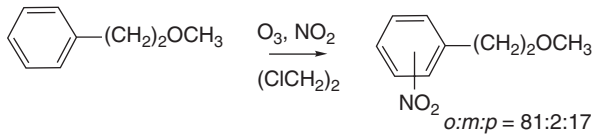
2. A. K. Sparks, *J. Org. Chem.*, **31**, 2299 (1966).
3. J. V. Crivello, *J. Org. Chem.*, **46**, 3056 (1981).
4. K. Smith, T. Gibbins, R. W. Millar, and R. P. Claridge, *J. Chem. Soc., Perkin Trans. 1*, 2753 (2000); K. Smith, A. Musson, and G. A. DeBoos, *J. Org. Chem.*, **63**, 8448 (1998).
5. F. J. Walker, A. G. M. Barrett, D. C. Braddock, and D. Ramprasad, *J. Chem. Soc., Chem. Commun.*, 613 (1997).
6. F. J. Walker, A. G. M. Barrett, D. C. Braddock, R. M. McKinnell, and D. Ramprasad, *J. Chem. Soc., Perkin Trans. 1*, 867 (1999).
7. A. Kawada, S. Takeda, K. Yamashita, H. Abe, and T. Harayama, *Chem. Pharm. Bull.*, **50**, 1060 (2002).
8. S. J. Kuhn and G. A. Olah, *J. Am. Chem. Soc.,* **83**, 4564 (1961); G. A. Olah and S. J. Kuhn, *J. Am. Chem. Soc.*, **84**, 3684 (1962); G. A. Olah, S. C. Narang, J. A. Olah, and K. Lammertsma, *Proc. Natl. Acad. Sci., USA*, **79**, 4487 (1982); C. L. Dwyer and C. W. Holzapfel, *Tetrahedron*, **54**, 7843 (1998).

trifluoromethansulfonate can also be prepared readily.[9] Nitrogen heterocycles such as pyridine and quinoline form *N*-nitro salts on reaction with NO_2BF_4.[10] These *N*-nitro heterocycles in turn can act as nitrating reagents, in a reaction called *transfer nitration* (see Scheme 11.1, Entry 10).

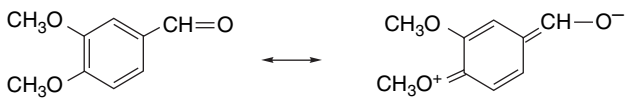
Another nitration procedure uses ozone and nitrogen dioxide.[11] With aromatic hydrocarbons and activated derivatives, this nitration is believed to involve the radical cation of the aromatic reactant.

$$NO_2 + O_3 \longrightarrow NO_3 + O_2$$
$$ArH + NO_3 \longrightarrow [ArH]^{+\cdot} + NO_3^-$$
$$[ArH]^{+\cdot} + NO_2 \longrightarrow [Ar(H)(NO_2)]^+ \longrightarrow ArNO_2 + H^+$$

Compounds such as phenylacetate esters and phenylethyl ethers, which have oxygen substituents that can serve as directing groups, show high *ortho*:*para* ratios under these conditions.[12] These reactions are believed to involve coordination of the NO_2^+ at the substituent oxygen, followed by intramolecular transfer.



Scheme 11.1 gives some examples of nitration reactions. Entries 1 to 3 are cases involving mixed nitric and sulfuric acids. Entry 2 illustrates the *meta*-directing effect of the protonated amino substituent. Entry 3 is an example of dinitration. Entry 4 involves an activated ring, and nitric acid suffices for nitration. At first glance, the position of substitution might seem surprising, but it may be that the direct resonance interaction of the 4-methoxy group with the formyl group attenuates its donor effect, leading to dominance of the 3-methoxy group.

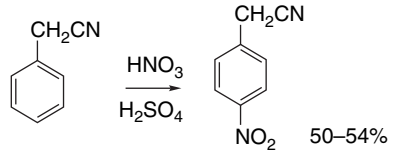


Entry 5 is an example of nitration in acetic anhydride. An interesting aspect of this reaction is its high selectivity for the *ortho* position. Entry 6 is an example of the use of trifluoroacetic anhydride. Entry 7 illustrates the use of a zeolite catalyst with improved *para* selectivity. With mixed sulfuric and nitric acids, this reaction gives a 1.8:1 *para*:*ortho* ratio. Entry 8 involves nitration using a lanthanide catalyst, whereas Entry 9 illustrates catalysis by $Sc(O_3SCF_3)_3$. Entry 10 shows nitration done directly with $NO_2^+BF_4^-$, and Entry 11 is also a transfer nitration. Entry 12 is an example of the use of the $NO_2{-}O_3$ nitration method.

9. C. L. Coon, W. G. Blucher, and M. E. Hill, *J. Org. Chem.*, **38**, 4243 (1973).
10. G. A. Olah, S. C. Narang, J. A. Olah, R. L. Pearson, and C. A. Cupas, *J. Am. Chem. Soc.*, **102**, 3507 (1980).
11. H. Suzuki and T. Mori, *J. Chem. Soc., Perkin Trans. 2*, 677 (1996); N. Noryama, T. Mori, and H. Suzuki, *Russ. J. Org. Chem.*, **34**, 1521 (1998).
12. H. Suzuki, T. Takeuchi, and T. Mori, *J. Org. Chem.*, **61**, 5944 (1996).

Scheme 11.1. Aromatic Nitration

1[a]



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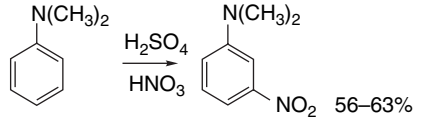
2 [b]



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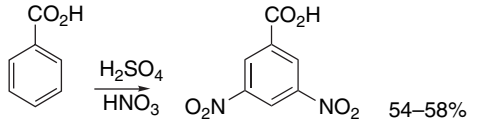
3[c]



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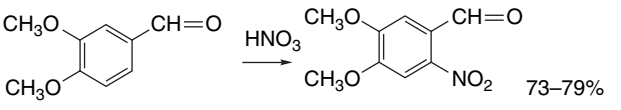
4[d]



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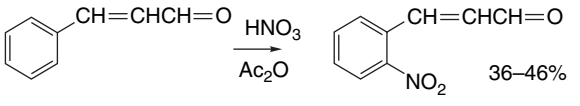
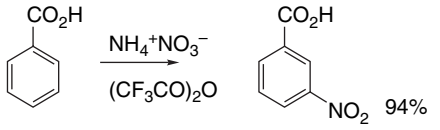
5[e]



36–46%

6[f]



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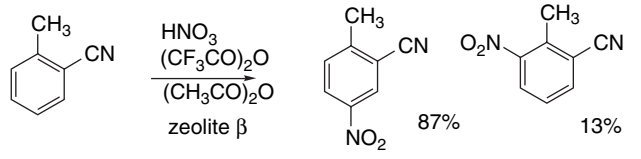
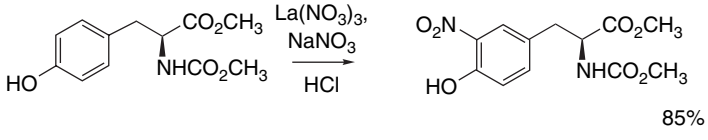
7[g]



87%

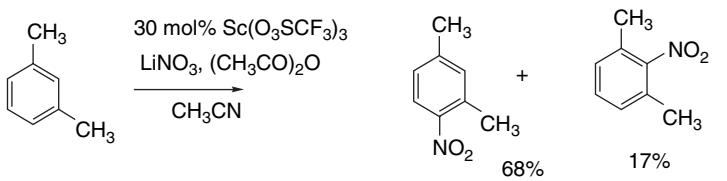
13%

8[h]



85%

9[i]



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17%

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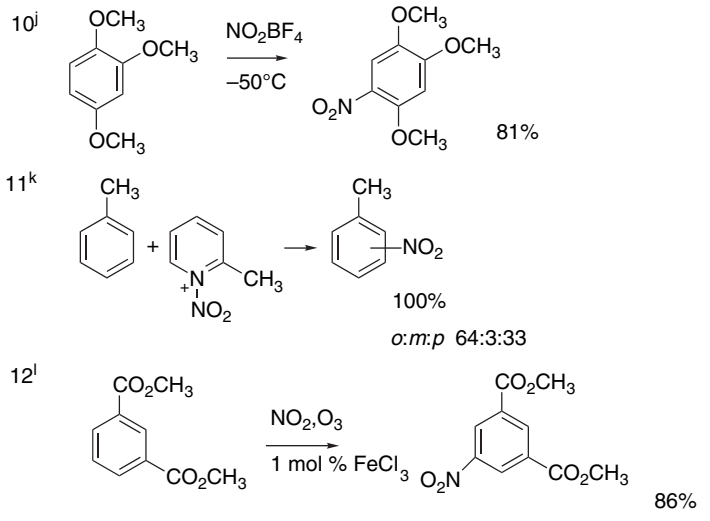
Scheme 11.1. (*Continued*)

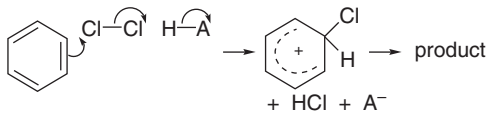


a. G. R. Robertson, *Org. Synth.*, **I**, 389 (1932).
b. H. M. Fitch, *Org. Synth.*, **III**, 658 (1955).
c. R. Q. Brewster, B. Williams, and R. Phillips, *Org. Synth.*, **III**, 337 (1955).
d. C. A. Fetscher, *Org. Synth.*, **IV**, 735 (1963).
e. R. E. Buckles and M. P. Bellis, *Org. Synth.*, **IV**, 722 (1963).
f. J. V. Crievello, *J. Org. Chem.*, **46**, 3056 (1981).
g. K. Smith, T. Gibbins, R. W. Millar, and R. P. Claridge, *J. Chem. Soc., Perkin Trans. 1*, 2753 (2000).
h. D. Ma and W. Tang, *Tetrahedron Lett.*, **39**, 7369 (1998).
i. A. Kawada, S. Takeda, K. Yamashita, H. Abe, and T. Harayama, *Chem. Pharm. Bull.*, **50**, 1060 (2002).
j. C. L. Dwyer and C. W. Holzapel, *Tetrahedron*, **54**, 7843 (1998).
k. C. A. Cupas and R. L. Pearson, *J. Am. Chem. Soc.*, **90**, 4742 (1968).
l. M. Nose, H. Suzuki, and H. Suzuki, *J. Org. Chem.*, **66**, 4356 (2001).

11.1.2. Halogenation

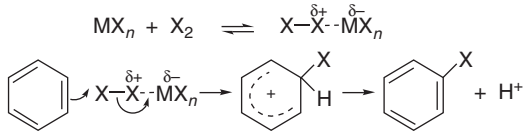
The introduction of the halogens onto aromatic rings by electrophilic substitution is an important synthetic procedure. Chlorine and bromine are reactive toward aromatic hydrocarbons, but Lewis acid catalysts are normally needed to achieve desirable rates. Elemental fluorine reacts very exothermically and careful control of conditions is required. Molecular iodine can effect substitution only on very reactive aromatics, but a number of more reactive iodination reagents have been developed.

Rate studies show that chlorination is subject to acid catalysis, although the kinetics are frequently complex.[13] The proton is believed to assist Cl–Cl bond breaking in a reactant-Cl_2 complex. Chlorination is much more rapid in polar than in nonpolar solvents.[14] Bromination exhibits similar mechanistic features.



13. L. M. Stock and F. W. Baker, *J. Am. Chem. Soc.*, **84**, 1661 (1962); L. J. Andrews and R. M. Keefer, *J. Am. Chem. Soc.*, **81**, 1063 (1959); R. M. Keefer and L. J. Andrews, *J. Am. Chem. Soc.*, **82**, 4547 (1960); L. J. Andrews and R. M. Keefer, *J. Am. Chem. Soc.*, **79**, 5169 (1957).
14. L. M. Stock and A. Himoe, *J. Am. Chem. Soc.*, **83**, 4605 (1961).

For preparative reactions, Lewis acid catalysts are used. Zinc chloride or ferric chloride can be used in chlorination, and metallic iron, which generates ferric bromide, is often used in bromination. The Lewis acid facilitates cleavage of the halogen-halogen bond.



N-Bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS) are alternative halogenating agents. Activated aromatics, such as 1,2,4-trimethoxybenzene, are brominated by NBS at room temperature.[15] Both NCS and NBS can halogenate moderately active aromatics in nonpolar solvents by using HCl[16] or $HClO_4$[17] as a catalyst. Many other "positive halogen" compounds can act as halogenating agents. (See Table 4.2 for examples of such reagents.)

A wide variety of aromatic compounds can be brominated. Highly reactive ones, such as anilines and phenols, may undergo bromination at all activated positions. More selective reagents such as pyridinium bromide perbromide or tetraalkylammonium tribromides can be used in such cases.[18] Moderately reactive compounds such as anilides, haloaromatics, and hydrocarbons can be readily brominated and the usual directing effects control the regiochemistry. Use of Lewis acid catalysts permits bromination of rings with deactivating substituents, such as nitro and cyano.

Halogenations are strongly catalyzed by mercuric acetate or trifluoroacetate. These conditions generate acyl hypohalites, which are the active halogenating agents. The trifluoroacetyl hypohalites are very reactive reagents. Even nitrobenzene, for example, is readily brominated by trifluoroacetyl hypobromite.[19]

$$Hg(O_2CR)_2 + X_2 \rightleftharpoons HgX(O_2CR) + RCO_2X$$

A solution of bromine in CCl_4 containing sulfuric acid and mercuric oxide is also a reactive brominating agent.[20]

Fluorination can be carried out using fluorine diluted with an inert gas. However, great care is necessary to avoid uncontrolled reaction.[21] Several other reagents have been devised that are capable of aromatic fluorination.[22] Acetyl hypofluorite can be prepared in situ from fluorine and sodium acetate.[23] This reagent effects fluorination

15. M. C. Carreno, J. L. Garcia Ruano, G. Sanz, M. A. Toledo, and A. Urbano, *J. Org. Chem.*, **60**, 5328 (1995).
16. B. Andersh, D. L. Murphy, and R. J. Olson, *Synth. Commun.*, **30**, 2091 (2000).
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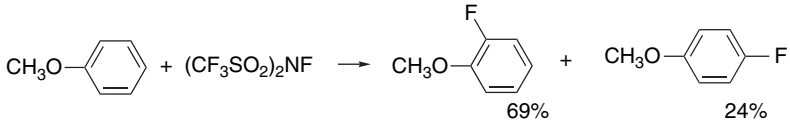
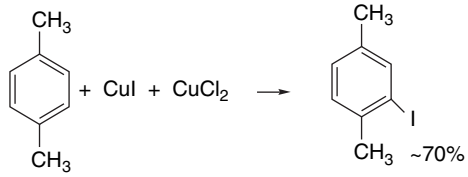
18. W. P. Reeves and R. M. King, II, *Synth. Commun.*, **23**, 855 (1993); J. Berthelot, C. Guette, P. L. Desbene, and J. J. Basselier, *Can. J. Chem.*, **67**, 2061 (1989); S. Kajgaeshi, T. Kakinami, T. Inoue, M. Kondo, H. Nakamura, M. Fujikawa, and T. Okamoto, *Bull. Chem. Soc. Jpn.*, **61**, 597 (1988); S. Kajigaeshi, T. Kakinami, T. Yamasaki, S. Fujisaki, M. Fujikawa, and T. Okamoto, *Bull. Chem. Soc. Jpn.*, **61**, 2681 (1988); S. Gervat, E. Leonel, J.-Y. Barraud, and V. Ratovelomanana, *Tetrahedron Lett.*, **34**, 2115 (1993). M. K. Chaudahuri, A. J. Khan, B. K. Patel, D. Dey, W. Kharmawophlang, T. R. Lakshimprabha, and G. C. Mandal, *Tetrahedron Lett.*, **39**, 8163 (1998).
19. J. R. Barnett, L. J. Andrews, and R. M. Keefer, *J. Am. Chem. Soc.*, **94**, 6129 (1972).
20. S. A. Khan, M. A. Munawar, and M. Siddiq, *J. Org. Chem.*, **53**, 1799 (1988).
21. F. Cacace, P. Giacomello, and A. P. Wolf, *J. Am. Chem. Soc.*, **102**, 3511 (1980).
22. S. T. Purrington, B. S. Kagan, and T. B. Patrick, *Chem. Rev.*, **86**, 997 (1986).
23. O. Lerman, Y. Tor, and S. Rozen, *J. Org. Chem.*, **46**, 4629 (1981); O. Lerman, Y. Tor, D. Hebel, and S. Rozen, *J. Org. Chem.*, **49**, 806 (1984); G. W. M. Visser, C. N. M. Bakker, B. W. v. Halteren, J. D. M. Herscheid, G. A. Brinkman, and A. Hoekstra, *J. Org. Chem.*, **51**, 1886 (1986).

of activated aromatics. Although this procedure does not avoid the special precautions necessary for manipulation of elemental fluorine, it does provide a system with much greater selectivity. Acetyl hypofluorite shows a strong preference for *o*-fluorination of alkoxy and acetamido-substituted rings. *N*-Fluoro-*bis*-(trifluoromethansulfonyl)amine (*N*-fluorotriflimide) displays similar reactivity and can fluorinate benzene and activated aromatics.[24]



Several *N*-fluoro derivatives of 1,4-diazabicyclo[2.2.2]octane are useful for aromatic fluorination.[25]

Iodinations can be carried out by mixtures of iodine and various oxidants such as periodic acid,[26] I_2O_5,[27] NO_2,[28] and $Ce(NH_3)_2(NO_3)_6$.[29] A mixture of cuprous iodide and a cupric salt can also effect iodination.[30]



Iodination of moderately reactive aromatics can be effected by mixtures of iodine and silver or mercuric salts.[31] Hypoiodites are presumably the active iodinating species. *Bis*-(pyridine)iodonium salts can iodinate benzene and activated derivatives in the presence of strong acids such as HBF_4 or CF_3SO_3H.[32]

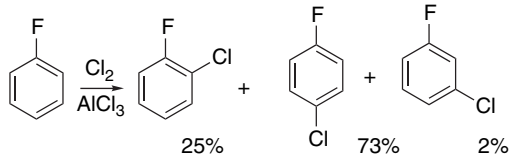
Scheme 11.2 shows some representative halogenation reactions. Entries 1 and 2 involve Lewis acid–catalyzed chlorination. Entry 3 is an acid-catalyzed chlorination using NCS as the reagent. Entry 4 shows a high-yield chlorination of acetanilide by *t*-butyl hypochlorite. This seems to be an especially facile reaction, since anisole is not chlorinated under these conditions, and may involve the *N*-chloroamide as an intermediate. Entry 5 describes a large-scale chlorination done with NCS. The product was used for the synthesis of sulamserod, a drug candidate.

24. S. Singh, D. D. DesMarteau, S. S. Zuberi, M. Whitz, and H.-N. Huang, *J. Am. Chem. Soc.*, **109**, 7194 (1987).
25. T. Shamma, H. Buchholz, G. K. S. Prakash, and G. A. Olahn, *Israel J. Chem.*, **39**, 207 (1999); A. J. Poss and G. A. Shia, *Tetrahedron Lett.*, **40**, 2673 (1999); T. Umemoto and M. Nagayoshi, *Bull. Chem. Soc. Jpn.*, **69**, 2287 (1996).
26. H. Suzuki, *Org. Synth.*, **VI**, 700, (1988).
27. L. C. Brazdil and C. J. Cutler, *J. Org. Chem.*, **61**, 9621 (1996).
28. Y. Noda and M. Kashima, *Tetrahedron Lett.*, **38**, 6225 (1997).
29. T. Sugiyama, *Bull. Chem. Soc. Jpn.*, **54**, 2847 (1981).
30. W. C. Baird, Jr., and J. H. Surridge, *J. Org. Chem.*, **35**, 3436 (1970).
31. Y. Kobayashi, I. Kumadaki, and T. Yoshida, *J. Chem. Res.* (Synopses), 215 (1977); R. N. Hazeldine and A. G. Sharpe, *J. Chem. Soc.*, 993 (1952); W. Minnis, *Org. Synth.*, **II**, 357 (1943); D. E. Janssen and C. V. Wilson, *Org. Synth.*, **IV**, 547 (1963); N.-W. Sy and B. A. Lodge, *Tetrahedron Lett.*, **30**, 3769 (1989).
32. J. Barluenga, J. M. Gonzalez, M. A. Garcia-Martin, P. J. Campos, and G. Asensio, *J. Org. Chem.*, **58**, 2058 (1993).

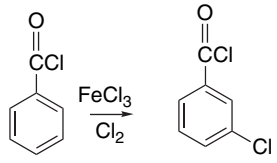
Scheme 11.2. Aromatic Halogenation

A. Chlorination

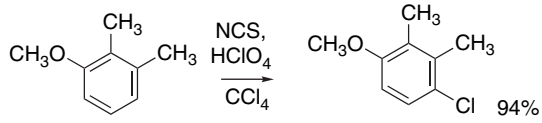
1[a]



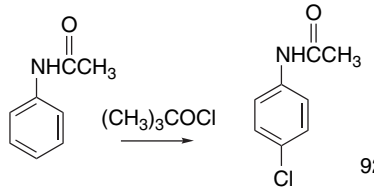
2[b]



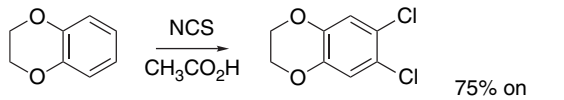
3[c]



4[d]

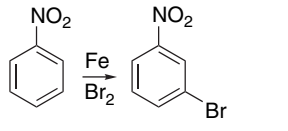


5[e]

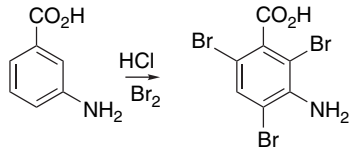


B. Bromination

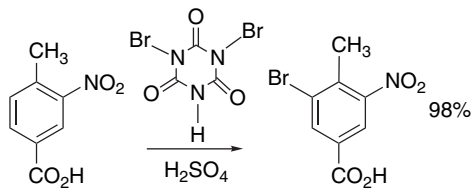
6[f]



7[g]



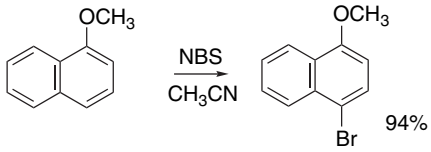
8[h]



(*Continued*)

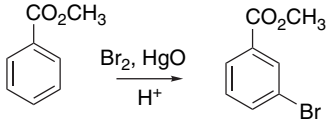
Scheme 11.2. (*Continued*)

9[i]



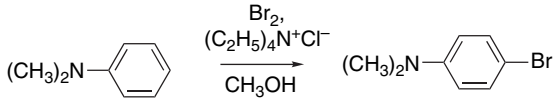
94%

10[j]



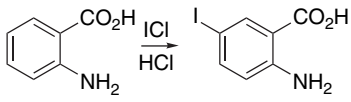
80%

11[k]



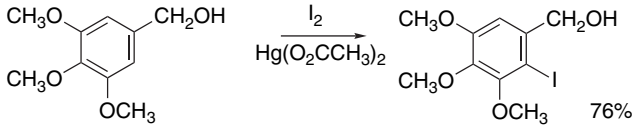
C. Iodination

12[l]



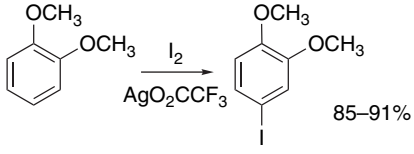
76–84%

13[m]



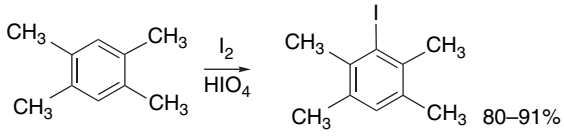
76%

14[n]



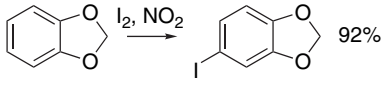
85–91%

15[o]



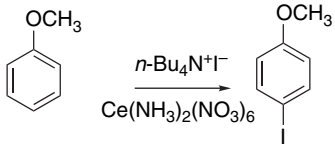
80–91%

16[p]



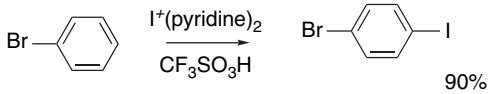
92%

17[q]



84%

18[r]

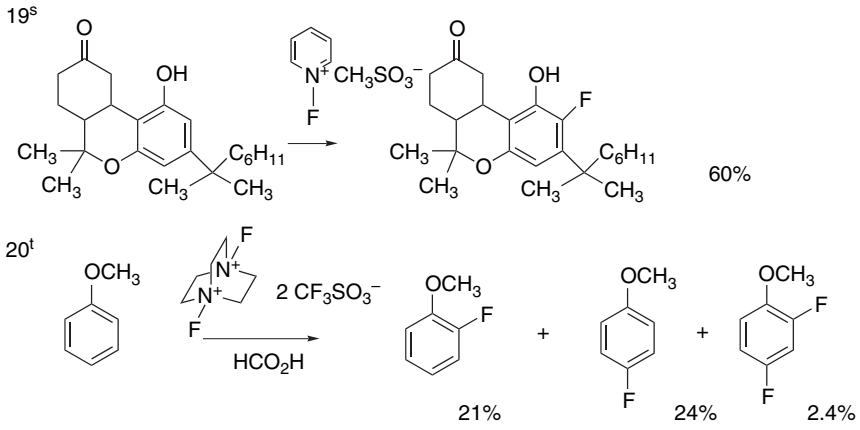


90%

(*Continued*)

Scheme 11.2. (*Continued*)

D. Fluorination



a. G. A. Olah, S. J. Kuhn, and B. A. Hardi, *J. Am. Chem. Soc.*, **86**, 1055 (1964).
b. E. Hope and G. F. Riley, *J. Chem. Soc.*, **121**, 2510 (1922).
c. V. Goldberg and H. Alper, *J. Org. Chem.*, **58**, 3072 (1993).
d. I. Lengyel, V. Cesare, and R. Stephani, *Synth. Commun.*, **28**, 1891 (1998).
e. B. A. Kowalczyk, J. Robinson, III, and J. O. Gardner, *Org. Proc. Res. Dev.*, **5**, 116 (2001).
f. J. R. Johnson and C. G. Gauerke, *Org. Synth.*, **I**, 123 (1941).
g. M. M. Robison and B. L. Robison, *Org. Synth.*, **IV**, 947 (1963).
h. A. R. Leed, S. D. Boettger, and B. Ganem, *J. Org. Chem.*, **45**, 1098 (1980).
i. M. C. Carreno, J. L. Garcia Russo, G. Sanz, M. A. Toledo, and A Urbano, *J. Org. Chem.*, **60**, 5328 (1995).
j. S. A. Khan, M. A. Munawar, and M. Siddiq, *J. Org. Chem.*, **53**, 1799 (1988).
k. S. Gervat, E. Leonel, J.-Y. Barraud, and V. Ratovelomanana, *Tetrahedron Lett.*, **34**, 2115 (1993).
l. V. H. Wallingford and P. A. Krueger, *Org. Synth.*, **II**, 349 (1943).
m. F. E. Ziegler and J. A. Schwartz, *J. Org. Chem.*, **43**, 985 (1978).
n. D. E. Janssen and C. V. Wilson, *Org. Synth.*, **IV**, 547 (1963).
o. H. Suzuki, *Org. Synth.*, **51**, 94 (1971).
p. Y. Noda and M. Kashima, *Tetrahedron Lett.*, **38**, 6225 (1997).
q. T. Sugiyama, *Bull. Chem. Soc. Jpn.*, **54**, 2847 (1981).
r. J. Barluenga, J. M. Gonzalez, M. A. Garcia-Martin, P. J. Campos, and G. Asensio, *J. Org. Chem.*, **58**, 2058 (1993).
s. M. A. Tius, J. K. Kawakami, W. A. G. Hill, and A. Makriyannis, *J. Chem. Soc., Chem. Commun.*, 2085 (1996).
t. T. Umemoto and M. Nagayoshi, *Bull. Chem. Soc. Jpn.*, **69**, 2287 (1996).

Entry 6 is a case of *meta* bromination of a deactivated aromatic. Entry 7 is a case in which all activated positions are brominated. It is interesting that the reaction occurs in acidic solution. It may be that each successive bromine addition accelerates the reaction by decreasing the basicity of the aniline and increasing the amount that is present in the neutral form. Entry 8 employs dibromoisocyanuric acid in concentrated H_2SO_4 as a brominating reagent. These conditions have been found useful for unreactive aromatics. Entry 9 is an example of bromination using NBS. Entry 10 uses bromine and mercuric oxide under conditions that were found effective for deactivated aromatics. Entry 11 describes conditions that are applicable for bromination of anilines. It is suggested that the reaction may involve formation of methyl hypobromite as the active bromination reagent.

Entries 12 to 18 show iodinations under various conditions. The reaction in Entry 12, using iodine monochloride, is done in concentrated HCl, but presumably occurs through the neutral form of the reactant ($pK_1 = 2.17$). Entries 13 and 14 involve reactions activated by mercuric and silver salts, respectively, and probably involve the

hypoiodites as the active reagents. Entry 15 uses iodine and periodic acid, a reagent combination that was found effective for moderately activated aromatics. The I_2-NO_2 combination illustrated in Entry 16 is also applicable to activated species. Entry 17 illustrates an oxidative procedure that can be used with moderately activated aromatics such as the methyl and methoxy derivatives of benzene. The *bis*-pyridine-iodonium reagent shown in Entry 18 was used with two equivalents of a strong acid, either HBF_4 or CF_3SO_3H, in dichloromethane. These conditions were applicable even to deactivated aromatics, such as methyl benzoate and nitrobenzene.

Entries 19 and 20 are fluorinations. In Entry 19, the fluorination is on an activated ring in the antinausea drug nabilone. Entry 20 illustrates the use *N*,*N*′-difluoro-1,4-diazabicyclo[2.2.2]octane ditriflate.

11.1.3. Friedel-Crafts Alkylation

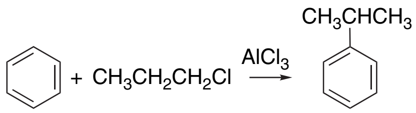
Friedel-Crafts alkylation reactions are an important method for introducing carbon substituents on aromatic rings. The reactive electrophiles can be either discrete carbocations or polarized complexes that contain a reactive leaving group. Various combinations of reagents can be used to generate alkylating species. Alkylations usually involve alkyl halides and Lewis acids or reactions of alcohols or alkenes with strong acids.

$$\mathrm{R{-}X + AlCl_3 \rightleftharpoons R{-}\overset{+}{X}{-}\overset{-}{Al}Cl_3 \rightleftharpoons R^+ + X\overset{-}{Al}Cl_3}$$

$$\mathrm{R{-}OH + H^+ \rightleftharpoons R{-}\overset{+}{O}H(H) \rightleftharpoons R^+ + H_2O}$$

$$\mathrm{RCH{=}CH_2 + H^+ \rightleftharpoons R\overset{+}{C}HCH_3}$$

Owing to the involvement of carbocations, Friedel-Crafts alkylations can be accompanied by rearrangement of the alkylating group. For example, isopropyl groups are often introduced when *n*-propyl reactants are used.[33]



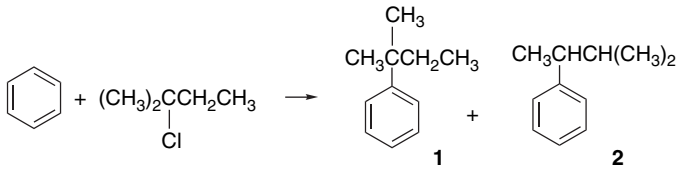
Similarly, under a variety of reaction conditions, alkylation of benzene with either 2-chloro or 3-chloropentane gives rise to a mixture of both 2-pentyl- and 3-pentylbenzene.[34]

Rearrangement can also occur after the initial alkylation. The reaction of 2-chloro-2-methylbutane with benzene is an example of this behavior.[35] With relatively mild Friedel-Crafts catalysts such as BF_3 or $FeCl_3$, the main product is **1**. With $AlCl_3$, equilibration of **1** and **2** occurs and the equilibrium favors **2**. The rearrangement is the result of product equilibration via reversibly formed carbocations.

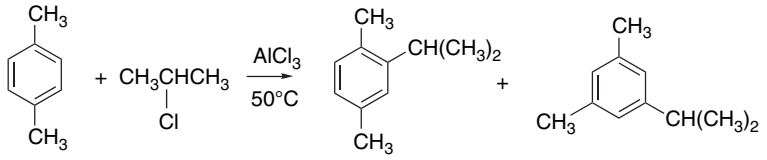
[33] S. H. Sharman, *J. Am. Chem. Soc.*, **84**, 2945 (1962).

[34] R. M. Roberts, S. E. McGuire, and J. R. Baker, *J. Org. Chem.*, **41**, 659 (1976).

[35] A. A. Khalaf and R. M. Roberts, *J. Org. Chem.*, **35**, 3717 (1970); R. M. Roberts and S. E. McGuire, *J. Org. Chem.*, **35**, 102 (1970).



Alkyl groups can also migrate from one position to another on the ring.[36] Such migrations are also thermodynamically controlled and proceed in the direction of minimizing steric interactions between substituents.



The relative reactivity of Friedel-Crafts catalysts has not been described in a quantitative way, but comparative studies using a series of benzyl halides has resulted in the qualitative groupings shown in Table 11.1. Proper choice of catalyst can minimize subsequent product equilibrations.

The Friedel-Crafts alkylation reaction does not proceed successfully with aromatic reactants having EWG substituents. Another limitation is that each alkyl group that is introduced *increases the reactivity of the ring toward further substitution*, so polyalkylation can be a problem. Polyalkylation can be minimized by using the aromatic reactant in excess.

Apart from the alkyl halide–Lewis acid combination, two other sources of carbocations are often used in Friedel-Crafts reactions. Alcohols can serve as carbocation precursors in strong acids such as sulfuric or phosphoric acid. Alkylation can also be effected by alcohols in combination with BF_3 or $AlCl_3$.[37] Alkenes can serve as alkylating agents when a protic acid, especially H_2SO_4, H_3PO_4, and HF, or a Lewis acid, such as BF_3 and $AlCl_3$, is used as a catalyst.[38]

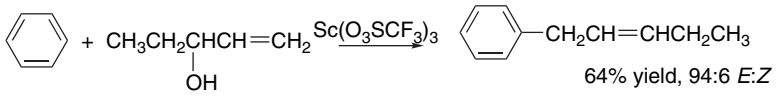
Stabilized carbocations can be generated from allylic and benzylic alcohols by reaction with $Sc(O_3SCF_3)_3$ and results in formation of alkylation products from benzene and activated derivatives.[39]

Table 11.1. Relative Activity of Friedel-Crafts Catalysts[a]

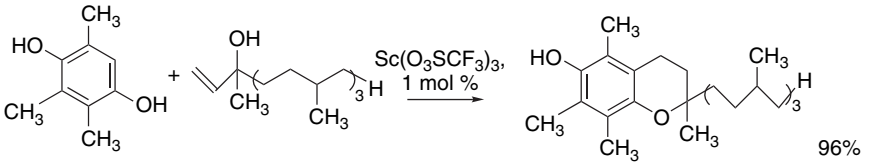
Very active	Moderately active	Mild
$AlCl_3$, $AlBr_3$,	$InCl_3$, $InBr_3$, $SbCl_4$,	BCl_3, $SnCl_4$,
$GaCl_3$, $GaCl_2$,	$FeCl_3$, $AlCl_3-CH_3NO_2$,	$TiCl_4$, $TiBr_4$,
SbF_5, $MoCl_5$,	$SbF_5-CH_3NO_2$	$FeCl_2$

a. G. A. Olah, S. Kobayashi, and M. Tashiro, *J. Am. Chem. Soc.*, **94**, 7448 (1972).

36. R. M. Roberts and D. Shiengthong, *J. Am. Chem. Soc.*, **86**, 2851 (1964).
37. A. Schriesheim, in *Friedel-Crafts and Related Reactions*, Vol. II, G. Olah, ed., Interscience, New York, 1964, Chap. XVIII.
38. S. H. Patinkin and B. S. Friedman, in *Friedel-Crafts and Related Reactions*, Vol. II, G. Olah, ed., Interscience, New York, 1964, Chap. XIV.
39. T. Tsuchimoto, K. Tobita, T. Hiyama, and S. Fukuzawa, *Synlett*, 557 (1996); T. Tsuchimoto, K. Tobita, T. Hiyama, and S. Fukuzawa, *J. Org. Chem.*, **62**, 6997 (1997).

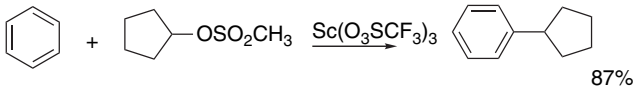


This kind of reaction has been used to synthesize α-tocopherol, in a reaction that involves alkylation, followed by cyclization involving the phenyl hydroxy group.

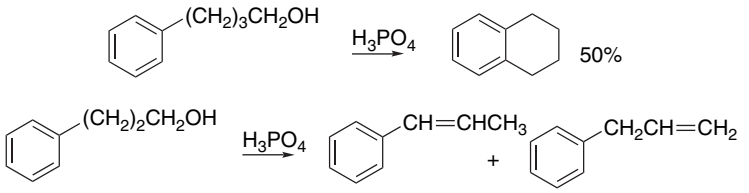


Ref. 40

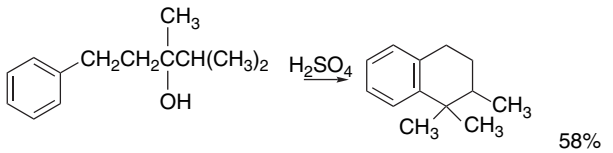
Methanesulfonate esters of secondary alcohols also give Friedel-Crafts products in the presence of $Sc(O_3SCF_3)_3$[41] or $Cu(O_3SCF_3)_2$.[42]



Friedel-Crafts alkylation can occur intramolecularly to form a fused ring. Intramolecular Friedel-Crafts reactions provide an important method for constructing polycyclic hydrocarbon frameworks. It is somewhat easier to form six-membered than five-membered rings in such reactions. Thus, whereas 4-phenyl-1-butanol gives a 50% yield of a cyclized product in phosphoric acid, 3-phenyl-1-propanol is mainly dehydrated to alkenes.[43]



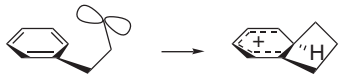
If a potential carbocation intermediate can undergo a hydride or alkyl shift, this shift occurs in preference to closure of the five-membered ring.



Ref. 44

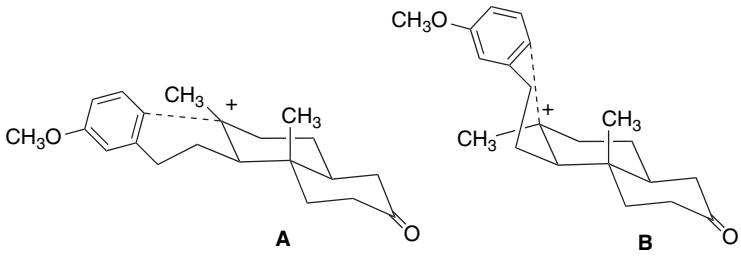
[40] M. Matsui, N. Karibe, K. Hayashi, and H. Yamamoto, *Bull. Chem. Soc. Jpn.*, **68**, 3569 (1995).
[41] H. Kotsuki, T. Ohishi, and M. Inoue, *Synlett*, 255 (1998); H. Kotsuki, T. Ohishi, M. Inoue, and T. Kojima, *Synthesis*, 603 (1999).
[42] R. P. Singh, R. M. Kamble, K. L. Chandra, P. Saravaran, and V. K. Singh, *Tetrahedron*, **57**, 241 (2001).
[43] A. A. Khalaf and R. M. Roberts, *J. Org. Chem.*, **34**, 3571 (1969).
[44] A. A. Khalaf and R. M. Roberts, *J. Org. Chem.*, **37**, 4227 (1972).

These results reflect a rather general tendency for 6 > 5, 7 in ring closure by intramolecular Friedel-Crafts reactions.[44,45] The difficulty in forming five-membered rings may derive from steric and electronic factors. Some strain must develop because of the sp^2 carbons included in the ring. Perhaps more important is the need for approach perpendicular to the ring. With three of the five carbons coplanar, it is difficult to align the empty *p* orbital of the carbocation with the π system.



Scheme 11.3 gives some examples of both inter- and intramolecular Friedel-Crafts alkylations. Entry 1 is carried out using $AlCl_3$ in an excess of refluxing benzene. Entry 2 was also done using benzene as the solvent, but this reaction is done at 0°C. A tertiary carbocation is generated by protonation of the double bond. Entry 3 involves alkylation by both bromo substituents in the reactant. The reaction is carried out in excess benzene, using $AlBr_3$. Entry 4 demonstrates the ability of a typical aromatic sulfonic acid to generate a reactive carbocation by alkene protonation. The reaction was carried out in excess toluene at 105°C. Note the relatively weak position selectivity (see also Part A, Section 9.4.4). Secondary alkyl tosylates are also sources of reactive carbocations under these conditions.

Entries 5 to 7 show intramolecular reactions. Entry 5 is an example of formation of a polycyclic ring system. The product is a 3:1 mixture of β:α methyl isomers at the new ring junction, and reflects a preference for TS **A** over TS **B**.



Entry 6 involves formation of a stabilized benzylic carbocation and results in a very efficient closure of a six-membered ring. Entry 7 involves an activated ring. The reaction was done using enantiomerically pure alcohol, but, as expected for a carbocation intermediate, the product was nearly racemic (6% e.e.). This cyclization was done enantiospecifically by first forming the $Cr(CO)_3$ complex (see Section 8.5).

11.1.4. Friedel-Crafts Acylation

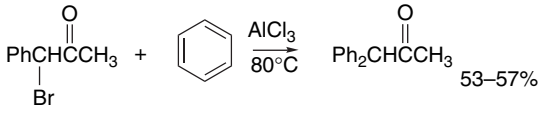
Friedel-Crafts acylation generally involves reaction of an acyl halide and Lewis acid such as $AlCl_3$, SbF_5, or BF_3. Bismuth(III) triflate is also a very active acylation catalyst.[46] Acid anhydrides can also be used in some cases. For example, a combination

45. R. J. Sundberg and J. P. Laurino, *J. Org. Chem.*, **49**, 249 (1984); S. R. Angle and M. S. Louie, *J. Org. Chem.*, **56**, 2853 (1991).
46. C. Le Roux and J. Dubac, *Synlett*, 181 (2002); J. R. Desmurs, M. Labrouillere, C. Le Roux, H. Gaspard, A. Laporterie, and J. Dubac, *Tetrahedron Lett.*, **38**, 8871 (1997); S. Repichet, C. LeRoux, J. Dubac, and J.-R. Desmurs, *Eur. J. Org. Chem.*, 2743 (1998).

Scheme 11.3. Friedel-Crafts Alkylation Reactions

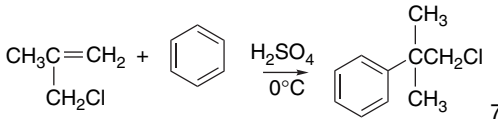
A. Intermolecular reactions

1[a]



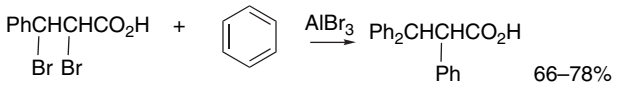
53–57%

2[b]



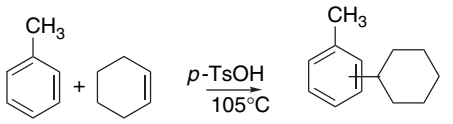
70–73%

3[c]



66–78%

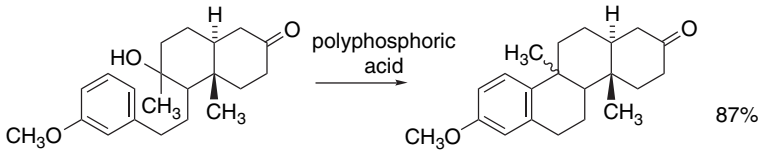
4[d]



98% yield, *o:m:p* = 29:18:53

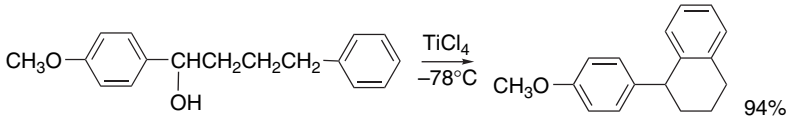
B. Intramolecular Friedel–Crafts cyclizations

5[e]



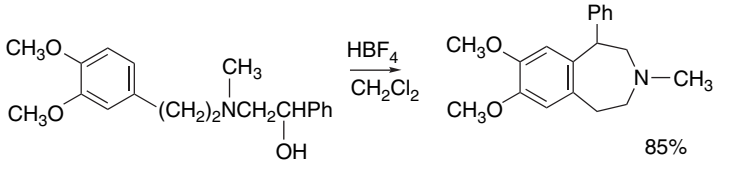
87%

6[f]



94%

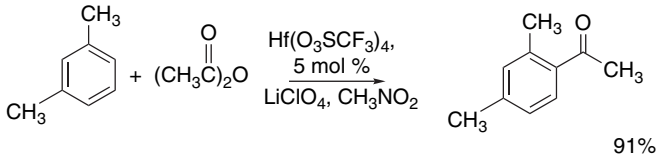
7[g]



85%

a. E. M. Shultz and S. Mickey, *Org. Synth.*, **III**, 343 (1955).
b. W. T. Smith, Jr., and J. T. Sellas, *Org. Synth.*, **IV,** 702 (1963).
c. C. P. Krimmol, L. E. Thielen, E. A. Brown, and W. J. Heidtke, *Org. Synth.*, **IV**, 960 (1963).
d. M. P. D. Mahindaratne and K. Wimalasena, *J. Org. Chem.*, **63**, 2858 (1998).
e. R. E. Ireland, S. W. Baldwin, and S. C. Welch, *J. Am. Chem. Soc.*, **94**, 2056 (1972).
f. S. R. Angle and M. S. Louie, *J. Org. Chem.*, **56**, 2853 (1991).
g. S. J. Coote, S. G. Davies, D. Middlemiss, and A. Naylor, *Tetrahedron Lett.*, **30**, 3581 (1989).

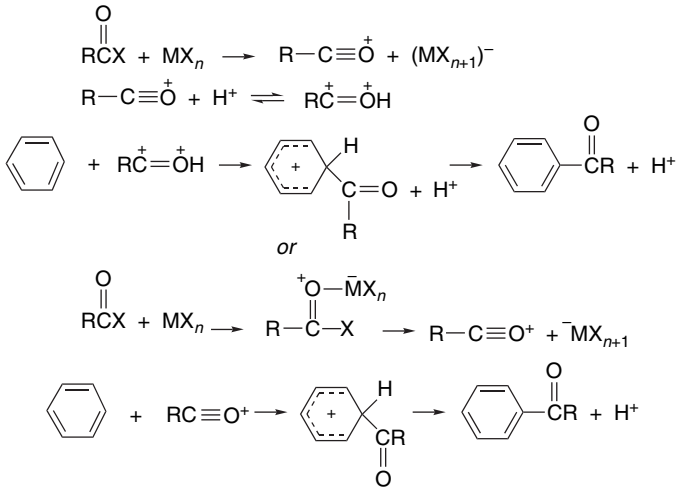
of hafnium(IV) triflate and $LiClO_4$ in nitromethane catalyzes acylation of moderately reactive aromatics by acetic anhydride.



Ref. 47

Mixed anhydrides with trifluoroacetic acid are particularly reactive acylating agents.[48] For example, Entry 5 in Scheme 11.4 shows the use of a mixed anhydride in the course of synthesis of the anticancer agent tamoxifen.

As in the alkylation reaction, the reactive intermediate in Friedel-Crafts acylation can be a dissociated acylium ion or a complex of the acyl chloride and Lewis acid.[49] Recent mechanistic studies have indicated that with benzene and slightly deactivated derivatives, it is the *protonated acylium ion* that is the kinetically dominant electrophile.[50]

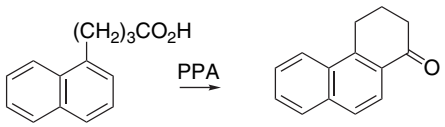


Regioselectivity in Friedel-Crafts acylations can be quite sensitive to the reaction solvent and other procedural variables.[51] In general, *para* attack predominates for

47. I. Hachiya, M. Moriwaki, and S. Kobayashi, *Tetrahedron Lett.*, **36**, 409 (1995); A. Kawada, S. Mitamura, and S. Kobabyashi, *J. Chem. Soc., Chem. Commun.*, 183 (1996); I. Hachiya, M. Moriwaki, and S. Kobayashi, *Bull. Chem. Soc. Jpn.*, **68**, 2053 (1995).
48. E. J. Bourne, M. Stacey, J. C. Tatlow, and J. M. Teddar, *J. Chem. Soc.*, 719 (1951); C. Galli, *Synthesis*, 303 (1979); B. C. Ranu, K. Ghosh, and U. Jana, *J. Org. Chem.*, **61**, 9546 (1996).
49. F. R. Jensen and G. Goldman, in *Friedel-Crafts and Related Reactions*, Vol. III, G. Olah, ed., Interscience, New York, 1964, Chap. XXXVI.
50. Y. Sato, M. Yato, T. Ohwada, S. Saito, and K. Shudo, *J. Am. Chem. Soc.*, **117**, 3037 (1995).
51. For example, see L. Friedman and R. J. Honour, *J. Am. Chem. Soc.*, **91**, 6344 (1969).

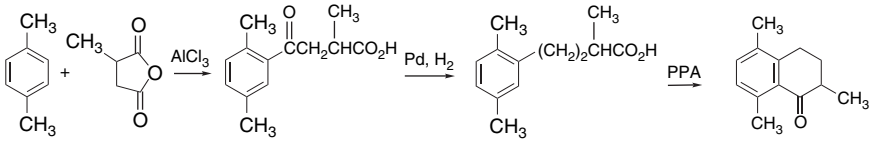
alkylbenzenes.[52] The percentage of *ortho* attack increases with the electrophilicity of the acylium ion and as much as 50% *ortho* product is observed with the formylium and 2,4-dinitrobenzoylium ions.[53] Rearrangement of the acyl group is not a problem in Friedel-Craft acylation. Neither is polyacylation, because the first acyl group serves to deactivate the ring to further attack. For these reasons, it is often preferable to introduce primary alkyl groups by a sequence of acylation followed by reduction of the acyl group (see Section 5.7.1).

Intramolecular acylations are very common, and the normal conditions involving an acyl halide and Lewis acid can be utilized. One useful alternative is to dissolve the carboxylic acid in polyphosphoric acid (PPA) and heat to effect cyclization. This procedure probably involves formation of a mixed phosphoric-carboxylic anhydride.[54]



Cyclizations can also be carried out with an esterified oligomer of phosphoric acid called "polyphosphate ester," which is chloroform soluble.[55] Another reagent of this type is trimethylsilyl polyphosphate (Scheme 11.4, Entry 13).[56] Neat methanesulfonic acid is also an effective reagent for intramolecular Friedel-Crafts acylation (Scheme 11.4, Entry 14).[57]

A classical procedure for fusing a six-membered ring to an aromatic ring uses succinic anhydride or a derivative. An intermolecular acylation is followed by reduction and an intramolecular acylation. The reduction step is necessary to provide a more reactive ring for the second acylation.



Ref. 58

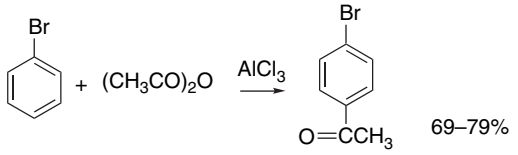
Scheme 11.4 shows some other representative Friedel-Crafts acylation reactions. Entries 1 and 2 show typical Friedel-Crafts acylation reactions using $AlCl_3$. Entries 3 and 4 are similar, but include some functionality in the acylating reagents. Entry 5 involves formation of a mixed trifluoroacetic anhydride, followed by acylation in 85% H_3PO_4. The reaction was conducted on a kilogram scale and provides a starting material for the synthesis of tamoxifen. Entry 6 illustrates the use of bismuth triflate as

52. H. C. Brown, G. Marino, and L. M. Stock, *J. Am. Chem. Soc.*, **81**, 3310 (1959); H. C. Brown and G. Marino, *J. Am. Chem. Soc.*, **81**, 5611 (1959); G. A. Olah, M. E. Moffatt, S. J. Kuhn, and B. A. Hardie, *J. Am. Chem. Soc.*, **86**, 2198 (1964).
53. G. A. Olah and S. Kobayashi, *J. Am. Chem. Soc.*, **93**, 6964 (1971).
54. W. E. Bachmann and W. J. Horton, *J. Am. Chem. Soc.*, **69**, 58 (1947).
55. Y. Kanaoka, O. Yonemitsu, K. Tanizawa, and Y. Ban, *Chem. Pharm. Bull.*, **12**, 773 (1964); T. Kametani, S. Takano, S. Hibino, and T. Terui, *J. Heterocycl. Chem.*, **6**, 49 (1969).
56. E. M. Berman and H. D. H. Showalter, *J. Org. Chem.*, **54**, 5642 (1989).
57. V. Premasagar, V. A. Palaniswamy, and E. J. Eisenbraun, *J. Org. Chem.*, **46**, 2974 (1981).
58. E. J. Eisenbraun, C. W. Hinman, J. M. Springer, J. W. Burnham, T. S. Chou, P. W. Flanagan, and M. C. Hamming, *J. Org. Chem.*, **36**, 2480 (1971).

Scheme 11.4. Friedel-Crafts Acylation Reactions

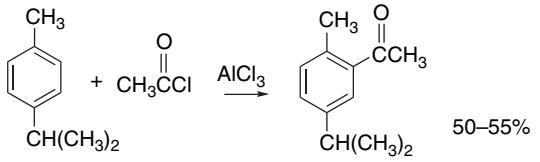
A. Intermolecular reactions

1[a]



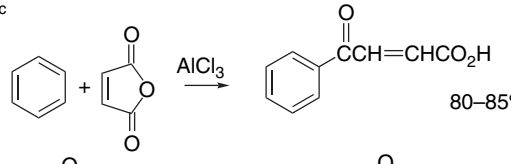
69–79%

2[b]



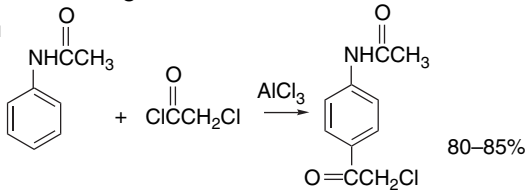
50–55%

3[c]



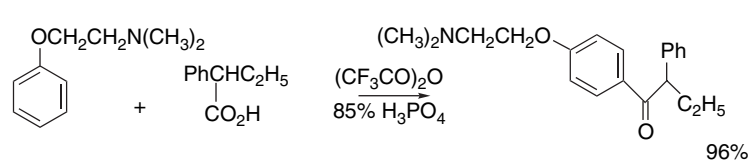
80–85%

4[d]



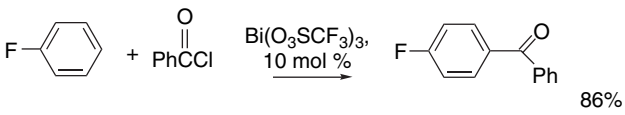
80–85%

5[e]



96%

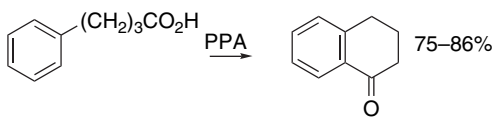
6[f]



86%

B. Intramolecular friedel–crafts acylations

7[g]

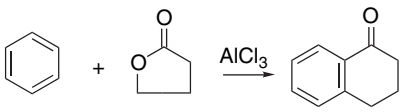


75–86%

8[h]

74–91%

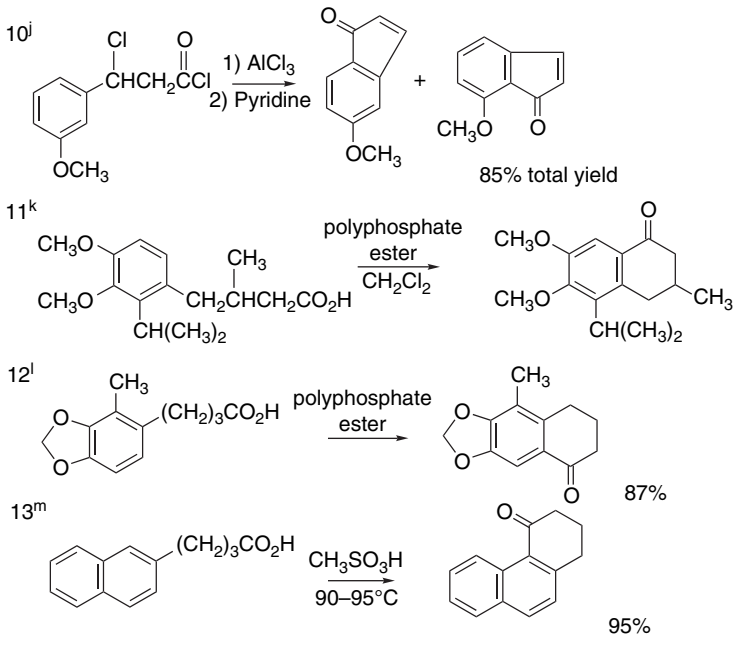
9[i]



91–96%

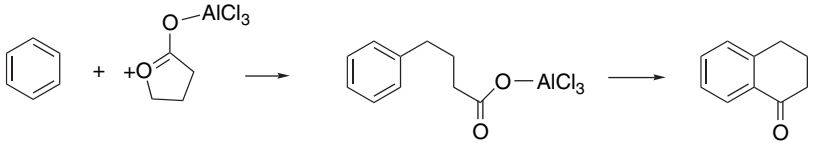
(*Continued*)

Scheme 11.4. (***Continued***)



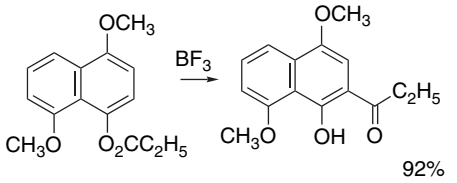
a. R. Adams and C. R. Noller, *Org. Synth.*, **I**, 109 (1941).
b. C. F. H. Allen, *Org. Synth.*, **II**, 3 (1943).
c. O. Grummitt, E. I. Becker, and C. Miesse, *Org. Synth.*, **III**, 109 (1955).
d. J. L. Leiserson and A. Weissberger, *Org. Synth.*, **III**, 183 (1955).
e. T. P. Smythe and B. W. Corby, *Org. Process Res. Dev.*, **1**, 264 (1997).
f. J. R. Desmurs, M. Labrouillere, C. Le Roux, H. Gaspard, A. Laporterie, and J. Dubac, *Tetrahedron Lett.*, **38**, 8871 (1997).
g. L. Arsnijevic, V. Arsenijevic, A. Horeua, and J. Jaques, *Org. Synth.*, **53**, 5 (1973).
h. E. L. Martin and L. F. Fieser, *Org. Synth.*, **II**, 569 (1943).
i. C. E. Olson and A. F. Bader, *Org. Synth.*, **IV**, 898 (1963).
j. M. B. Floyd and G. R. Allen, Jr., *J. Org. Chem.*, **35**, 2647 (1970).
k. M. C. Venuti, *J. Org. Chem.*, **46**, 3124 (1981).
l. G. Esteban, M. A. Lopez-Sanchez, E. Martinez, and J. Plumet, *Tetrahedron*, **54**, 197 (1998).
m. V. Premasagar, V. A. Palaniswamy, and E. J. Eisenbraun, *J. Org. Chem.*, **46**, 2974 (1981).

a Lewis acid. Entries 7 and 8 exemplify typical conditions for intramolecular Friedel-Crafts reactions. In Entry 9, both alkylation and acylation occur, presumably in that order.

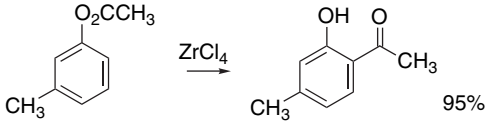


In Entry 10, intramolecular acylation is followed by dehydrohalogenation. Entries 11 and 12 illustrate the use of polyphosphate ester. The cyclization in Entry 13 is done in neat methanesulfonic acid.

A special case of aromatic acylation is the *Fries rearrangement*, which is the conversion of an ester of a phenol to an *o*-acyl phenol by a Lewis acid.



Ref. 59

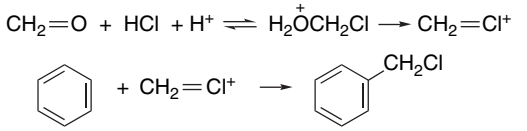


Ref. 60

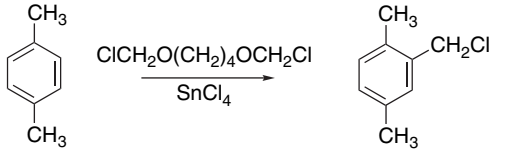
Lanthanide triflates are also good catalysts for Fries rearrangements.[61]

11.1.5. Related Alkylation and Acylation Reactions

There are a number of variations of the Friedel-Crafts reactions that are useful in synthesis. The introduction of chloromethyl substituents is brought about by reaction with formaldehyde in concentrated hydrochloric acid and halide salts, especially zinc chloride.[62] The reaction proceeds with benzene and activated derivatives. The reactive electrophile is probably the chloromethylium ion.



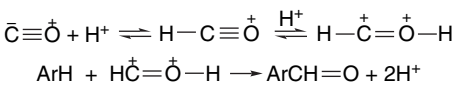
Chloromethylation can also be carried out using various chloromethyl ethers and $SnCl_4$.[63]



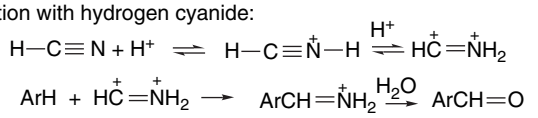
Carbon monoxide, hydrogen cyanide, and nitriles also react with aromatic compounds in the presence of strong acids or Friedel-Crafts catalysts to introduce formyl or acyl substituents. The active electrophiles are believed to be *dications* resulting from diprotonation of CO, HCN, or the nitrile.[64] The general outlines of the mechanisms of these reactions are given below.

59. Y. Naruta, Y. Nishgaichi, and K. Maruyama, *J. Org. Chem.*, **53**, 1192 (1988).
60. D. C. Harrowven and R. F. Dainty, *Tetrahedron Lett.*, **37**, 7659 (1996).
61. S. Kobayahis, M. Moriwaki, and J. Hachiya, *Bull. Chem. Soc. Jpn.*, **70**, 267 (1997).
62. R. C. Fuson and C. H. McKeever, *Org. React.*, **1**, 63 (1942); G. A. Olah and S. H. Yu, *J. Am. Chem. Soc.*, **97**, 2293 (1975).
63. G. A. Olah, D. A. Beal, and J. A. Olah, *J. Org. Chem.*, **41**, 1627 (1976); G. A. Olah, D. A. Bell, S. H. Yu, and J. A. Olah, *Synthesis*, 560 (1974).
64. M. Yato, T. Ohwada, and K. Shudo, *J. Am. Chem. Soc.*, **113**, 691 (1991); Y. Sato, M. Yato, T. Ohwada, S. Saito, and K. Shudo, *J. Am. Chem. Soc.*, **117**, 3037 (1995).

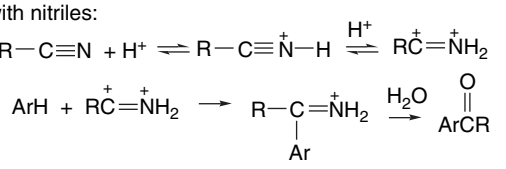
a. Formylation with carbon monoxide:



b. Formylation with hydrogen cyanide:

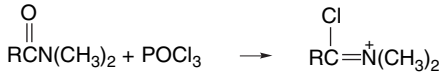


c. Acylation with nitriles:



Many specific examples of these reactions can be found in reviews in the *Organic Reactions* series.[65] Dichloromethyl ethers are also precursors of the formyl group via alkylation catalyzed by $SnCl_4$ or $TiCl_4$.[66] The dichloromethyl group is hydrolyzed to a formyl group.

Another useful method for introducing formyl and acyl groups is the *Vilsmeier-Haack reaction*.[67] *N*,*N*-dialkylamides react with phosphorus oxychloride or oxalyl chloride[68] to give a chloroiminium ion, which is the reactive electrophile.



This species acts as an electrophile in the absence of any added Lewis acid, but only rings with ERG substituents are reactive.

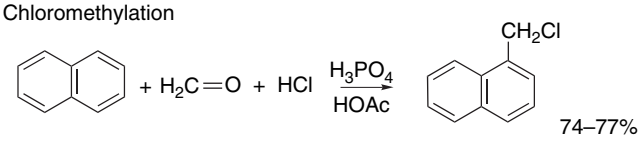
Scheme 11.5 gives some examples of these acylation reactions. Entry 1 is an example of a chloromethylation reaction. Entry 2 is a formylation using carbon monoxide. Entry 3 is an example of formylation via *bis*-chloromethyl ether. A cautionary note on this procedure is the potent carcinogenicity of this reagent. Entries 4 and 5 are examples of formylation and acetylation, using HCN and acetonitrile, respectively. Entries 6 to 8 are examples of Vilsmeier-Haack reactions, all of which are conducted on strongly activated aromatics.

65. N. N. Crounse, *Org. React.*, **5**, 290 (1949); W. E. Truce, *Org. React.*, **9**, 37 (1957); P. E. Spoerri and A. S. DuBois, *Org. React.*, **5**, 387 (1949); see also G. A. Olah, L. Ohannesian, and M. Arvanaghi, *Chem. Rev.*, **87**, 671 (1987).
66. P. E. Sonnet, *J. Med. Chem.*, **15**, 97 (1972); C. H. Hassall and B. A. Morgan, *J. Chem. Soc.*, *Perkin Trans. 1*, 2853 (1973); R. Halterman and S.-T. Jan, *J. Org. Chem.*, **56**, 5253 (1991).
67. G. Martin and M. Martin, *Bull. Soc. Chim. Fr.*, 1637 (1963); S. Seshadri, *J. Sci. Ind. Res.*, **32**, 128 (1973); C. Just, in *Iminium Salts in Organic Chemistry*, H. Bohme and H. G. Viehe, eds., Vol. 9 in *Advances in Organic Chemistry: Methods and Results*, Wiley-Interscience, 1976, pp. 225–342.
68. J. N. Frekos, G. W. Morrow, and J. S. Swenton, *J. Org. Chem.*, **50**, 805 (1985).

Scheme 11.5. Other Electrophilic Aromatic Substitutions Related to Friedel-Crafts Reactions

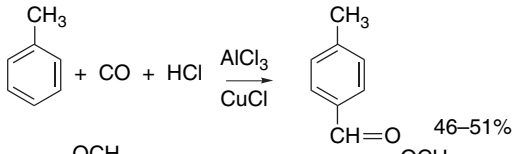
A. Chloromethylation

1[a]

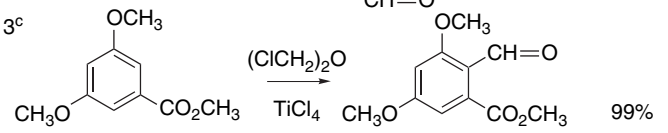


B. Formylation

2[b]

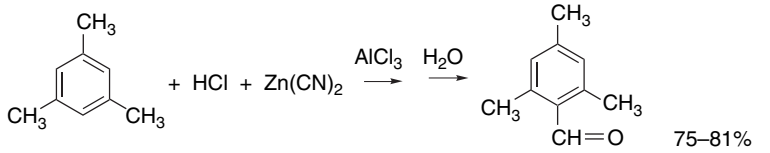


3[c]

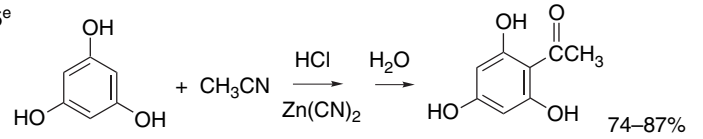


C. Acylation with cyanide and nitriles

4[d]

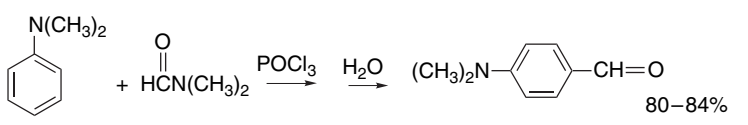


5[e]

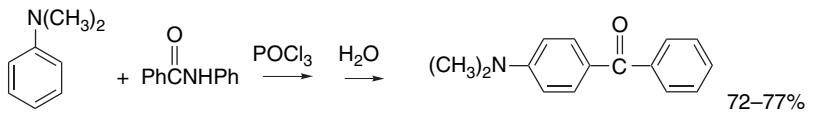


D. Vilsmeier–Haack acylation

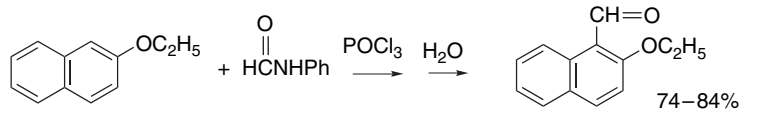
6[f]



7[g]



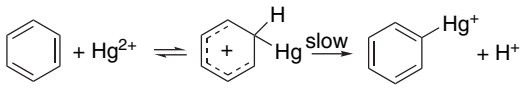
8[h]



a. C. Grummitt and A. Buck, *Org. Synth.*, **III**, 195 (1955).
b. G. H. Coleman and D. Craig, *Org. Synth.*, **II**, 583 (1943).
c. C. H. Hassall and B. A. Morgan, *J. Chem. Soc., Perkin Trans. 1*, 2853 (1973).
d. R. C. Fuson, E. C. Horning, S. P. Rowland, and M. L. Ward, *Org. Synth.*, **III**, 549 (1955).
e. K. C. Gulati, S. R. Seth, and K. Venksataraman, *Org. Synth.*, **II**, 522 (1943).
f. E. Campaigne and W. L. Archer, *Org. Synth.*, **IV**, 331 (1963).
g. C. D. Hurd and C. N. Webb, *Org. Synth.*, **I**, 217 (1941).
h. J. H. Wood and R. W. Bost, *Org. Synth.*, **III**, 98 (1955).

11.1.6. Electrophilic Metallation

Aromatic compounds react with mercuric salts to give arylmercury compounds.[69] Mercuric acetate or mercuric trifluoroacetate are the usual reagents.[70] The reaction shows substituent effects that are characteristic of electrophilic aromatic substitution.[71] Mercuration is one of the few electrophilic aromatic substitutions in which proton loss from the σ complex is rate determining. Mercuration of benzene shows an isotope effect $k_H/k_D = 6$,[72] which indicates that the σ complex must be formed reversibly.



The synthetic utility of the mercuration reaction derives from subsequent transformations of the arylmercury compounds. As indicated in Section 7.3.3, these compounds are only weakly nucleophilic, but the carbon-mercury bond is reactive to various electrophiles. They are particularly useful for synthesis of nitroso compounds. The nitroso group can be introduced by reaction with nitrosyl chloride[73] or nitrosonium tetrafluoroborate[74] as the electrophile. Arylmercury compounds are also useful in certain palladium-catalyzed reactions, as discussed in Section 8.2.

Thallium(III), particularly as the trifluoroacetate salt, is also a reactive electrophilic metallating species, and a variety of synthetic schemes based on arylthallium intermediates have been devised.[75] Arylthallium compounds are converted to chlorides or bromides by reaction with the appropriate cupric halide.[76] Reaction with potassium iodide gives aryl iodides.[77] Fluorides are prepared by successive treatment with potassium fluoride and boron trifluoride.[78] Procedures for converting arylthallium compounds to nitriles and phenols have also been described.[79]

The thallium intermediates can be useful in directing substitution to specific positions when the site of thallation can be controlled in an advantageous way. The two principal means of control are chelation and the ability to effect thermal equilibration of arylthallium intermediates. Oxygen-containing groups normally direct thallation to the *ortho* position by a chelation effect. The thermodynamically favored position is

69. W. Kitching, *Organomet. Chem. Rev.*, **3**, 35 (1968).
70. A. J. Kresge, M. Dubeck, and H. C. Brown, *J. Org. Chem.*, **32**, 745 (1967); H. C. Brown and R. A. Wirkkala, *J. Am. Chem. Soc.*, **88**, 1447, 1453, 1456 (1966).
71. H. C. Brown and C. W. McGary, Jr., *J. Am. Chem. Soc.*, **77**, 2300, 2310 (1955); A. J. Kresge and H. C. Brown, *J. Org. Chem.*, **32**, 756 (1967); G. A. Olah, I. Hashimoto, and H. C. Lin, *Proc. Natl. Acad. Sci., USA*, **74**, 4121 (1977).
72. C. Perrin and F. H. Westheimer, *J. Am. Chem. Soc.*, **85**, 2773 (1963); A. J. Kresge and J. F. Brennan, *J. Org. Chem.*, **32**, 752 (1967); C. W. Fung, M. Khorramdel-Vahad, R. J. Ranson, and R. M. G. Roberts, *J. Chem. Soc., Perkin Trans. 2*, 267 (1980).
73. L. I. Smith and F. L. Taylor, *J. Am. Chem. Soc.*, **57**, 2460 (1935); S. Terabe, S. Kuruma, and R. Konaka, *J. Chem. Soc., Perkin Trans. 2*, 1252 (1973).
74. L. M. Stock and T. L. Wright, *J. Org. Chem.*, **44**, 3467 (1979).
75. E. C. Taylor and A. McKillop, *Acc. Chem. Res.*, **3**, 338 (1970).
76. S. Uemura, Y. Ikeda, and K. Ichikawa, *Tetrahedron*, **28**, 5499 (1972).
77. A. McKillop, J. D. Hunt, M. J. Zelesko, J. S. Fowler, E. C. Taylor, G. McGillivray, and F. Kienzle, *J. Am. Chem. Soc.*, **93**, 4841 (1971); M. L. dos Santos, G. C. de Magalhaes, and R. Braz Filhe, *J. Organomet. Chem.*, **526**, 15 (1996).
78. E. C. Taylor, E. C. Bigham, and D. K. Johnson, *J. Org. Chem.*, **42**, 362 (1977).
79. S. Uemura, Y. Ikeda, and K. Ichikawa, *Tetrahedron*, **28**, 3025 (1972); E. C. Taylor, H. W. Altland, R. H. Danforth, G. McGillivray, and A. McKillop, *J. Am. Chem. Soc.*, **92**, 3520 (1970).

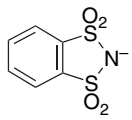
normally the *meta* position, and heating the thallium derivatives of alkylbenzenes gives a predominance of the *meta* isomer.[80] Both mercury and thallium compounds are very toxic, so special care is needed in their manipulation.

11.2. Nucleophilic Aromatic Substitution

Synthetically important substitutions of aromatic compounds can also be done by nucleophilic reagents. There are several general mechanism for substitution by nucleophiles. Unlike nucleophilic substitution at saturated carbon, aromatic nucleophilic substitution does not occur by a single-step mechanism. The broad mechanistic classes that can be recognized include addition-elimination, elimination-addition, and metal-catalyzed processes. (See Section 9.5 of Part A to review these mechanisms.) We first discuss diazonium ions, which can react by several mechanisms. Depending on the substitution pattern, aryl halides can react by either addition-elimination or elimination-addition. Aryl halides and sulfonates also react with nucleophiles by metal-catalyzed mechanisms and these are discussed in Section 11.3.

11.2.1. Aryl Diazonium Ions as Synthetic Intermediates

The first widely used intermediates for nucleophilic aromatic substitution were the aryl diazonium salts. Aryl diazonium ions are usually prepared by reaction of an aniline with nitrous acid, which is generated in situ from a nitrite salt.[81] Unlike aliphatic diazonium ions, which decompose very rapidly to molecular nitrogen and a carbocation (see Part A, Section 4.1.5), aryl diazonium ions are stable enough to exist in solution at room temperature and below. They can also be isolated as salts with nonnucleophilic anions, such as tetrafluoroborate or trifluoroacetate.[82] Salts prepared with *o*-benzenedisulfonimidate also appear to have potential for synthetic application.[83]



benzenedisulfonimidate anion

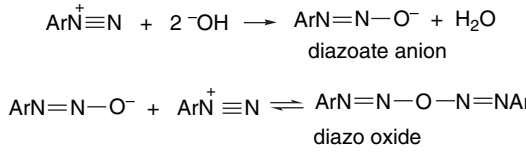
The steps in forming a diazonium ion are addition of the nitrosonium ion, ^{+}NO, to the amino group, followed by elimination of water.

$$ArNH_2 + HONO \xrightarrow{H^+} ArN(H)-N=O + H_2O$$

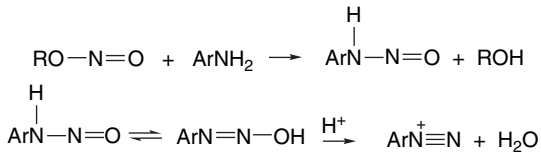
$$ArN(H)-N=O \longrightarrow ArN=N-OH \xrightarrow{H^+} Ar\overset{+}{N}\equiv N + H_2O$$

80. A. McKillop, J. D. Hunt, M. J. Zelesko, J. S. Fowler, E. C. Taylor, G. McGillivray, and F. Kienzle, *J. Am. Chem. Soc.*, **93**, 4841 (1971); M. L. dos Santas, G. C. de Mangalhaes, and R. Braz Filho, *J. Organomet. Chem.*, **526**, 15 (1996).
81. H. Zollinger, *Azo and Diazo Chemistry*, Interscience, New York, 1961; S. Patai, ed., *The Chemistry of Diazonium and Diazo Groups*, Wiley, New York, 1978, Chaps. 8, 11, and 14; H. Saunders and R. L. M. Allen, *Aromatic Diazo Compounds*, 3rd Edition, Edward Arnold, London, 1985.
82. C. Colas and M. Goeldner, *Eur. J. Org. Chem.*, 1357 (1999).
83. M. Barbero, M. Crisma, I. Degani, R. Fochi, and P. Perracino, *Synthesis*, 1171 (1998); M. Babero, I. Degani, S. Dughera, and R. Fochi, *J. Org. Chem.*, **64**, 3448 (1999).

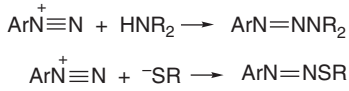
In alkaline solution, diazonium ions are converted to diazoate anions, which are in equilibrium with diazo oxides.[84]



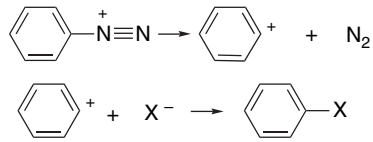
In addition to the aqueous method for diazotization, diazonium ions can be generated in organic solvents by reaction with alkyl nitrites.



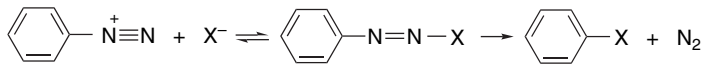
Diazonium ions form stable adducts with certain nucleophiles such as secondary amines and sulfide anions.[85] These compounds can be used as precursors of diazonium ion intermediates.



The wide utility of aryl diazonium ions as synthetic intermediates results from the excellence of N_2 as a leaving group. There are several general mechanisms by which substitution can occur. One involves unimolecular thermal decomposition of the diazonium ion, followed by capture of the resulting aryl cation by a nucleophile. The phenyl cation is very unstable (see Part A, Section 3.4.1.1) and therefore highly unselective.[86] Either the solvent or an anion can act as the nucleophile.



Another general mechanism for substitution is adduct formation followed by collapse of the adduct with loss of nitrogen.



84. E. S. Lewis and M. P. Hanson, *J. Am. Chem. Soc.*, **89**, 6268 (1967).
85. M. L. Gross, D. H. Blank, and W. M. Welch, *J. Org. Chem.*, **58**, 2104 (1993); S. A. Haroutounian, J. P. DiZio, and J. A. Katzenellenbogen, *J. Org. Chem.*, **56**, 4993 (1991).
86. C. G. Swain, J. E. Sheats, and K. G. Harbison, *J. Am. Chem. Soc.*, **97**, 783 (1975).

A third mechanism involves redox processes,[87] and is particularly likely to operate in reactions in which copper salts are used as catalysts.[88]

$$ArN^{+}\equiv N + [Cu(I)X_2]^- \longrightarrow Ar{-}Cu(III)X_2 + N_2$$

$$Ar{-}Cu(III)X_2 \longrightarrow ArX + Cu(I)X$$

Examples of the three mechanistic types are, respectively: (a) hydrolysis of diazonium salts to phenols[89]; (b) reaction with azide ion to form aryl azides[90]; and (c) reaction with cuprous halides to form aryl chlorides or bromides.[91] In the paragraphs that follow, these and other synthetically useful reactions of diazonium intermediates are considered. The reactions are organized on the basis of the group that is introduced, rather than on the mechanism involved. It will be seen that the reactions that are discussed fall into one of the three general mechanistic types.

11.2.1.1. Reductive Dediazonization. Replacement of a nitro or amino group by hydrogen is sometimes required as a sequel to a synthetic operation in which the substituent was used to control the position selectivity of a prior transformation. The best reagents for reductive dediazonation are hypophosphorous acid, H_3PO_2,[92] and $NaBH_4$.[93] The reduction by H_3PO_2 is substantially improved by catalysis with cuprous oxide.[94] The reduction by H_3PO_2 proceeds by one-electron reduction followed by loss of nitrogen and formation of the phenyl radical.[95] The hypophosphorous acid then serves as a hydrogen atom donor.

$$\text{initiation} \quad ArN^{+}\equiv N + e^- \longrightarrow Ar\cdot + N_2$$

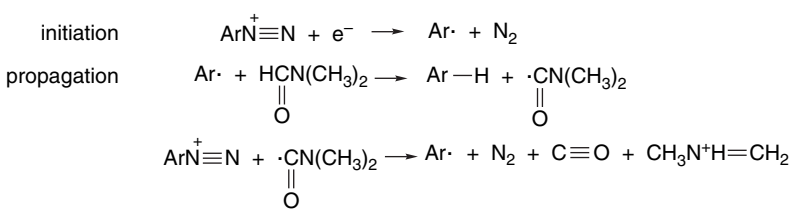
$$\text{propagation} \quad Ar\cdot + H_3PO_2 \longrightarrow Ar{-}H + [H_2PO_2\cdot]$$

$$ArN^{+}\equiv N + [H_2PO_2\cdot] \longrightarrow Ar\cdot + N_2 + [H_2PO_2^{+}]$$

$$[H_2PO_2^{+}] + H_2O \longrightarrow H_3PO_3 + H^{+}$$

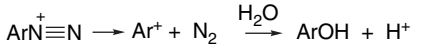
An alternative method for reductive dediazonation involves in situ diazotization by an alkyl nitrite in dimethylformamide.[96] This reduction is a chain reaction with the solvent acting as the hydrogen atom donor.

87. C. Galli, *Chem. Rev.*, **88**, 765 (1988).
88. T. Cohen, R. J. Lewarchik, and J. Z. Tarino, *J. Am. Chem. Soc.*, **97**, 783 (1975).
89. E. S. Lewis, L. D. Hartung, and B. M. McKay, *J. Am. Chem. Soc.*, **91**, 419 (1969).
90. C. D. Ritchie and D. J. Wright, *J. Am. Chem. Soc.*, **93**, 2429 (1971); C. D. Ritchie and P. O. I. Virtanen, *J. Am. Chem. Soc.*, **94**, 4966 (1972).
91. J. K. Kochi, *J. Am. Chem. Soc.*, **79**, 2942 (1957); S. C. Dickerman, K. Weiss, and A. K. Ingberman, *J. Am. Chem. Soc.*, **80**, 1904 (1958).
92. N. Kornblum, *Org. React.*, **2**, 262 (1944).
93. J. B. Hendrickson, *J. Am. Chem. Soc.*, **83**, 1251 (1961).
94. S. Korzeniowski, L. Blum, and G. W. Gokel, *J. Org. Chem.*, **42**, 1469 (1977).
95. N. Kornblum, G. D. Cooper, and J. E. Taylor, *J. Am. Chem. Soc.*, **72**, 3013 (1950).
96. M. P. Doyle, J. F. Dellaria, Jr., B. Siegfried, and S. W. Bishop, *J. Org. Chem.*, **42**, 3494 (1977); J. H. Markgraf, R. Chang, J. R. Cort, J. L. Durant, Jr., M. Finkelstein, A. W. Gross, M. H. Lavyne, W. M. Moore, R. C. Peterson, and S. D. Ross, *Tetrahedron*, **53**, 10009 (1997).

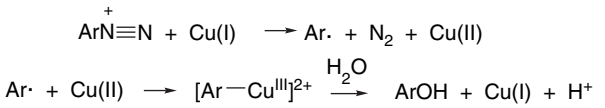


This reaction can be catalyzed by $FeSO_4$.[97]

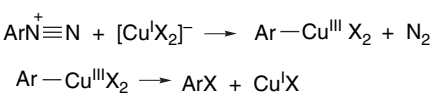
11.2.1.2. Phenols from Diazonium Ion Intermediates. Aryl diazonium ions can be converted to phenols by heating in water. Under these conditions, there is probably formation of a phenyl cation.



By-products from capture of nucleophilic anions may be observed.[53] Phenols can be formed under milder conditions by an alternative redox mechanism.[98] The reaction is initiated by cuprous oxide, which effects reduction and decomposition to an aryl radical, and is run in the presence of Cu(II) salts. The radical is captured by Cu(II) and converted to the phenol by reductive elimination. This procedure is very rapid and gives good yields of phenols over a range of structural types.



11.2.1.3. Aryl Halides from Diazonium Ion Intermediates. Replacement of diazonium groups by halides is a valuable alternative to direct halogenation for the preparation of aryl halides. Aryl bromides and chlorides are usually prepared by a reaction using the appropriate Cu(I) salt, which is known as the *Sandmeyer reaction*. Under the classic conditions, the diazonium salt is added to a hot acidic solution of the cuprous halide.[99] The Sandmeyer reaction occurs by an oxidative addition reaction of the diazonium ion with Cu(I) and halide transfer from a Cu(III) intermediate.



Good yields of chlorides have also been obtained for reaction of isolated diazonium tetrafluoroborates with $FeCl_2$-$FeCl_3$ mixtures.[100] It is also possible to convert anilines to aryl halides by generating the diazonium ion in situ. Reaction of anilines with alkyl nitrites and Cu(II) halides in acetonitrile gives good yields of aryl chlorides and bromides.[101]

97. F. W. Wassmundt and W. F. Kiesman, *J. Org. Chem.*, **60**, 1713 (1995).
98. T. Cohen, A. G. Dietz, Jr., and J. R. Miser, *J. Org. Chem.*, **42**, 2053 (1977).
99. W. A. Cowdrey and D. S. Davies, *Q. Rev. Chem. Soc.*, **6**, 358 (1952); H. H. Hodgson, *Chem. Rev.*, **40**, 251 (1947).
100. K. Daasbjerg and H. Lund, *Acta Chem. Scand.*, **46**, 157 (1992).
101. M. P. Doyle, B. Sigfried, and J. F. Dellaria, Jr., *J. Org. Chem.*, **42**, 2426 (1977).

Diazonium salts can also be converted to halides by processes involving aryl free radicals. In basic solutions, aryl diazonium ions are converted to radicals via the diazo oxide.[102]

$$2\ ArN^{+}{\equiv}N\ +\ 2\ ^{-}OH\ \longrightarrow\ ArN{=}N{-}O{-}N{=}NAr\ +\ H_2O$$

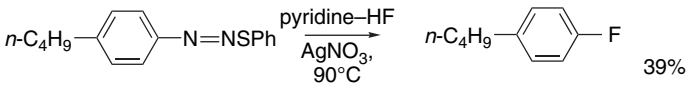
$$ArN{=}N{-}O{-}N{=}NAr \longrightarrow ArN{=}N{-}O\cdot\ +\ Ar\cdot\ +\ N_2$$

The reaction can be carried out efficiently using aryl diazonium tetrafluoroborates with crown ethers, polyethers, or phase transfer catalysts.[103] In solvents that can act as halogen atom donors, the radicals react to give aryl halides. Bromotrichloromethane gives aryl bromides, whereas methyl iodide and diiodomethane give iodides.[104] The diazonium ions can also be generated by in situ methods. Under these conditions bromoform and bromotrichloromethane have been used as bromine donors and carbon tetrachloride is the best chlorine donor.[105] This method was used successfully for a challenging chlorodeamination in the vancomycin system (Entry 6, Scheme 11.6).

Fluorine substituents can also be introduced via diazonium ions. One procedure is to isolate aryl diazonium tetrafluoroborates. These decompose thermally to give aryl fluorides.[106] Called the *Schiemann reaction*, it probably involves formation of an aryl cation that abstracts fluoride ion from the tetrafluoroborate anion.[107]

$$ArN^{+}{\equiv}N\ +\ BF_4^{-} \longrightarrow ArF\ +\ N_2\ +\ BF_3$$

Hexfluorophosphate salts behave similarly.[108] The diazonium tetrafluoroborates can be prepared either by precipitation from an aqueous solution by fluoroboric acid[109] or by anhydrous diazotization in ether, THF, or acetonitrile using *t*-butyl nitrite and boron trifluoride.[110] Somewhat milder reaction conditions can be achieved by reaction of aryl diazo sulfide adducts with pyridine-HF in the presence of AgF or $AgNO_3$.

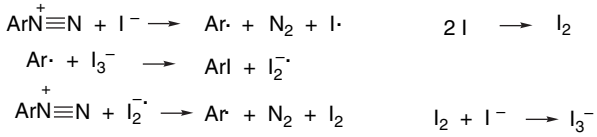


Ref. 111

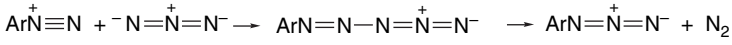
Aryl diazonium ions are converted to iodides in high yield by reaction with iodide salts. This reaction is initiated by reduction of the diazonium ion by iodide. The aryl radical then abstracts iodine from either I_2 or I_3^{-}. A chain mechanism then proceeds

102. C. Rüchardt and B. Freudenberg, *Tetrahedron Lett.*, 3623 (1964); C. Rüchardt and E. Merz, *Tetrahedron Lett.*, 2431 (1964).
103. S. H. Korzeniowski and G. W. Gokel, *Tetrahedron Lett.*, 1637 (1977).
104. S. H. Korzeniowski and G. W. Gokel, *Tetrahedron Lett.*, 3519 (1977); R. A. Bartsch and I. W. Wang, *Tetrahedron Lett.*, 2503 (1979); W. C. Smith and O. C. Ho, *J. Org. Chem.*, **55**, 2543 (1990).
105. J. I. G. Cadogan, D. A. Roy, and D. M. Smith, *J. Chem. Soc. C*, 1249 (1966).
106. A. Roe, *Org. React.*, **5**, 193 (1949).
107. C. G. Swain and R. J. Rogers, *J. Am. Chem. Soc.*, **97**, 799 (1975).
108. M. S. Newman and R. H. B. Galt, *J. Org. Chem.*, **25**, 214 (1960).
109. E. B. Starkey, *Org. Synth.*, **II**, 225 (1943); G. Schiemann and W. Winkelmuller, *Org. Synth.*, **II**, 299 (1943).
110. M. P. Doyle and W. J. Bryker, *J. Org. Chem.*, **44**, 1572 (1979).
111. S. A. Haroutounian, J. P. DiZio, and J. A. Katzenellenbogen, *J. Org. Chem.*, **56**, 4993 (1991).

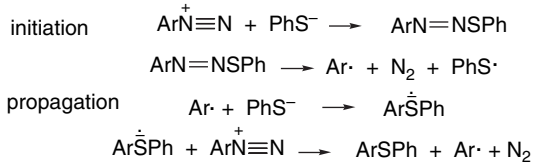
and consumes I^- and ArN_2^+.[112] Evidence for the involvement of radicals includes the isolation of cyclized products from *o*-allyl derivatives.



11.2.1.4. Introduction of Other Nucleophiles Using Diazonium Ion Intermediates. Cyano and azido groups are also readily introduced via diazonium intermediates. The former involves a copper-catalyzed reaction analogous to the Sandmeyer reaction. Reaction of diazonium salts with azide ion gives adducts that smoothly decompose to nitrogen and the aryl azide.[56]



Aryl thiolates react with aryl diazonium ions to give diaryl sulfides. This reaction is believed to be a radical chain process, similar to the mechanism for reaction of diazonium ions with iodide ion.[113]



Scheme 11.6 gives some examples of the various substitution reactions of aryl diazonium ions. Entries 1 to 6 are examples of reductive dediazonization. Entry 1 is an older procedure that uses hydrogen abstraction from ethanol for reduction. Entry 2 involves reduction by hypophosphorous acid. Entry 3 illustrates use of copper catalysis in conjunction with hypophosphorous acid. Entries 4 and 5 are DMF-mediated reductions, with ferrous catalysis in the latter case. Entry 6 involves reduction by $NaBH_4$.

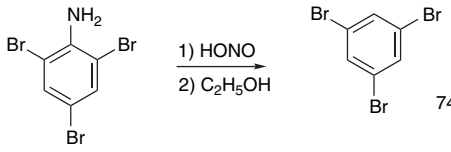
Entries 7 and 8 illustrate conversion of diazonium salts to phenols. Entries 9 and 10 use the traditional conditions for the Sandmeyer reaction. Entry 11 is a Sandmeyer reaction under in situ diazotization conditions, whereas Entry 12 involves halogen atom transfer from solvent. Entry 13 is an example of formation of an aryl iodide. Entries 14 and 15 are Schiemann reactions. The reaction in Entry 16 was used to introduce a chlorine substituent on vancomycin. Of several procedures investigated, the CuCl-$CuCl_2$ catalysis of chlorine atom transfer form CCl_4 proved to be the best. The diazonium salt was isolated as the tetrafluoroborate after in situ diazotization. Entries 17 and 18 show procedures for introducing cyano and azido groups, respectively.

112. P. R. Singh and R. Kumar, *Aust. J. Chem.*, **25**, 2133 (1972); A. Abeywickrema and A. L. J. Beckwith, *J. Org. Chem.*, **52**, 2568 (1987).
113. A. N. Abeywickrema and A. L. J. Beckwith, *J. Am. Chem. Soc.*, **108**, 8227 (1986).

Scheme 11.6. Aromatic Substitution via Diazonium Ions

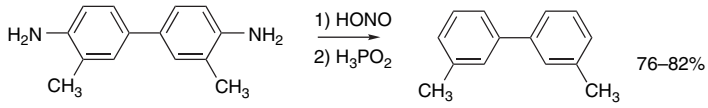
A. Replacement by hydrogen

1[a]



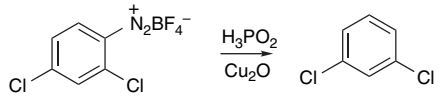
74–77%

2[b]



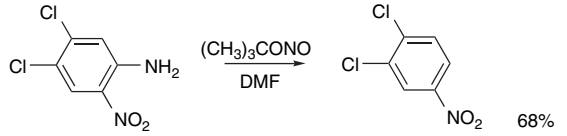
76–82%

3[c]



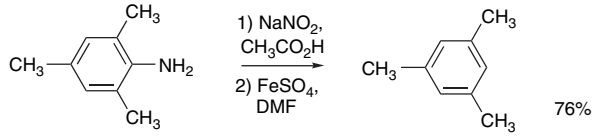
97%

4[d]



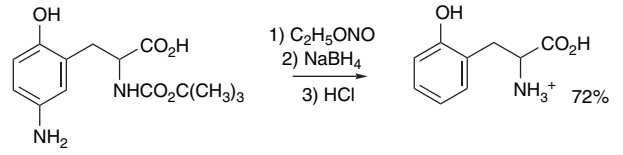
68%

5[e]



76%

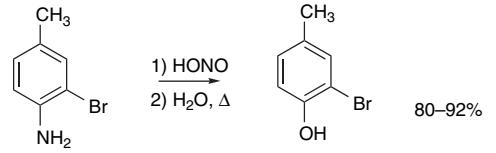
6[f]



72%

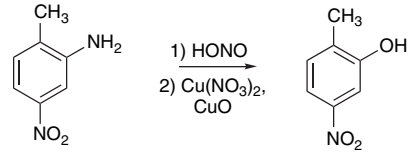
B. Replacement by hydroxy

7[g]



80–92%

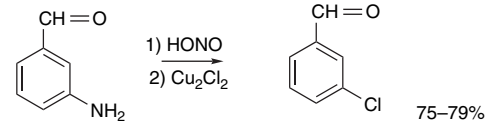
8[h]



95%

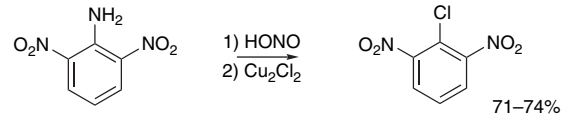
C. Replacement by halogen

9[i]



75–79%

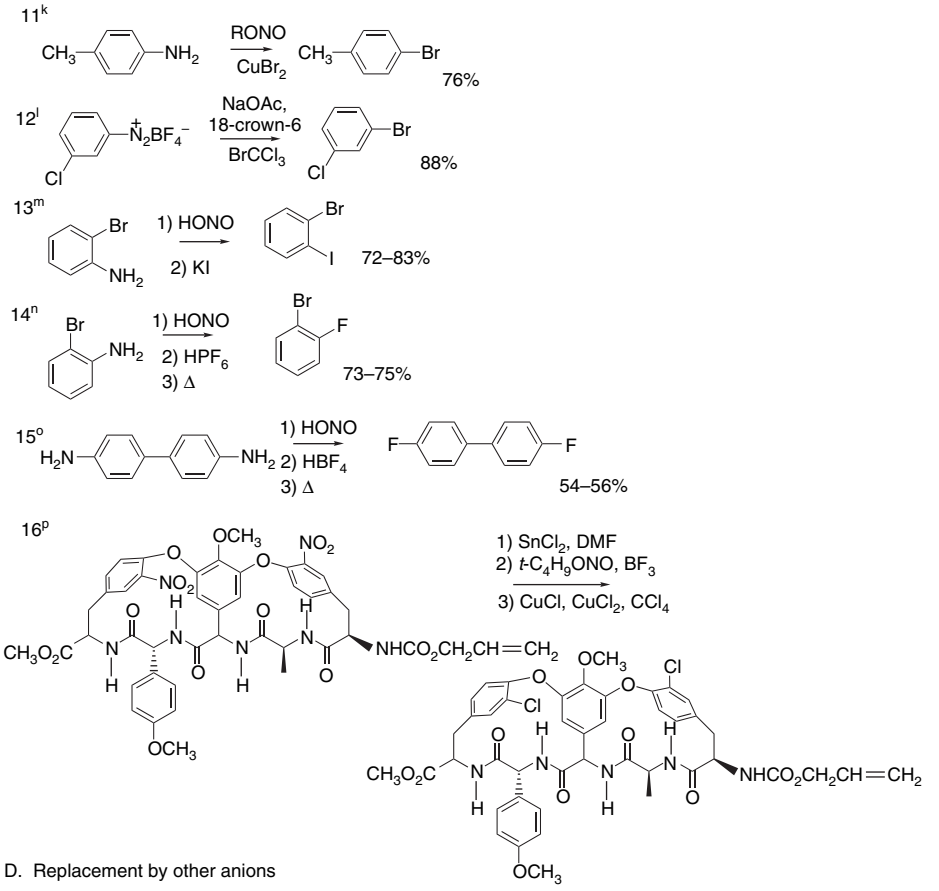
10[j]



71–74%

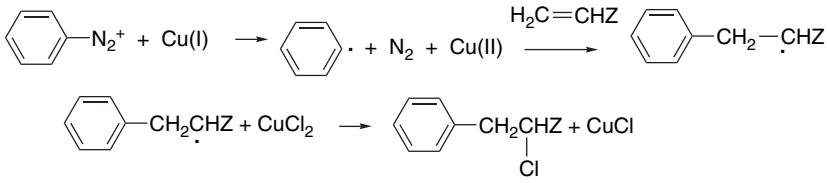
(*Continued*)

Scheme 11.6. (*Continued*)



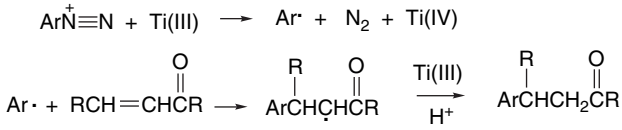
a. G. H. Coleman and W. F. Talbot, *Org. Synth.*, **II**, 592 (1943).
b. N. Kornblum, *Org. Synth.*, **III**, 295 (1955).
c. S. H. Korzeniowski, L. Blum, and G. W. Gokel, *J. Org. Chem.*, **42**, 1469 (1977).
d. M. P. Doyle, J. F. Dellaria, Jr., B. Siegfried, and S. W. Bishop, *J. Org. Chem.*, **42**, 3494 (1977).
e. F. W. Wassmundt and W. F. Kiesman, *J. Org. Chem.*, **60**, 1713 (1995).
f. C. Dugave, *J. Org. Chem.*, **60**, 601 (1995).
g. H. E. Ungnade and E. F. Orwoll, *Org. Synth.*, **III**, 130 (1943).
h. T. Cohen, A. G. Dietz, Jr., and J. R. Miser, *J. Org. Chem.*, **42**, 2053 (1977).
i. J. S. Buck and W. S. Ide, *Org. Synth.*, **II**, 130 (1943).
j. F. D. Gunstone and S. H. Tucker, *Org. Synth.*, **1V**, 160 (1963).
k. M. P. Doyle, B. Siegfried, and J. F. Dellaria, Jr., *J. Org. Chem.*, **42**, 2426 (1977).
l. S. H. Korzeniowsky and G. W. Gokel, *Tetrahedron Lett.*, 3519 (1977).
m. H. Heaney and I. T. Millar, *Org. Synth.*, **40**, 105 (1960).
n. K. G. Rutherford and W. Redmond, *Org. Synth.*, **43**, 12 (1963).
o. G. Schiemann and W. Winkelmuller, *Org. Synth.*, **II**, 188 (1943).
p. C. Vergne, M. Bois-Choussy, and J. Zhu, *Synlett*, 1159 (1998).
q. H. T. Clarke and R. R. Read, *Org. Synth.*, **I**, 514 (1941).
r. P. A. S. Smith and B. B. Brown, *J. Am. Chem. Soc.*, **73**, 2438 (1951).

11.2.1.5. Meerwein Arylation Reactions. Aryl diazonium ions can also be used to form certain types of carbon-carbon bonds. The copper-catalyzed reaction of diazonium ions with conjugated alkenes results in arylation of the alkene, known as the *Meerwein arylation reaction*.[114] The reaction sequence is initiated by reduction of the diazonium ion by Cu(I). The aryl radical adds to the alkene to give a new β-aryl radical. The final step is a ligand transfer that takes place in the copper coordination sphere. An alternative course is oxidation-deprotonation, which gives a styrene derivative.



The reaction gives better yield with dienes, styrenes, or alkenes substituted with EWGs than with simple alkenes. These groups increase the rate of capture of the aryl radical. The standard conditions for the Meerwein arylation employ aqueous solutions of diazonium ions. Conditions for in situ diazotization by *t*-butyl nitrite in the presence of $CuCl_2$ and acrylonitrile or styrene are also effective.[115]

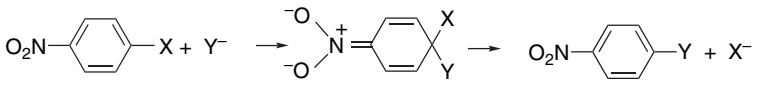
Reduction of aryl diazonium ions by Ti(III) in the presence of α,β-unsaturated ketones and aldehydes leads to β-arylation and formation of the saturated ketone or aldehyde. The early steps in this reaction parallel the copper-catalyzed reaction. However, rather than being oxidized, the radical formed by the addition step is reduced by Ti(III).[116]



Scheme 11.7 illustrates some arylation of alkenes by diazonium ions. Entries 1 to 4 are typical conditions. Entry 5 illustrates generation of the diazonium ion under in situ conditions. Entry 6 is an example of the reductive conditions using Ti(III).

11.2.2. Substitution by the Addition-Elimination Mechanism

The addition of a nucleophile to an aromatic ring, followed by elimination of a substituent, results in nucleophilic substitution. The major energetic requirement for this mechanism is formation of the addition intermediate. The addition step is greatly facilitated by strongly electron-attracting substituents, and nitroaromatics are the best reactants for nucleophilic aromatic substitution. Other EWGs such as cyano, acetyl, and trifluoromethyl also enhance reactivity.

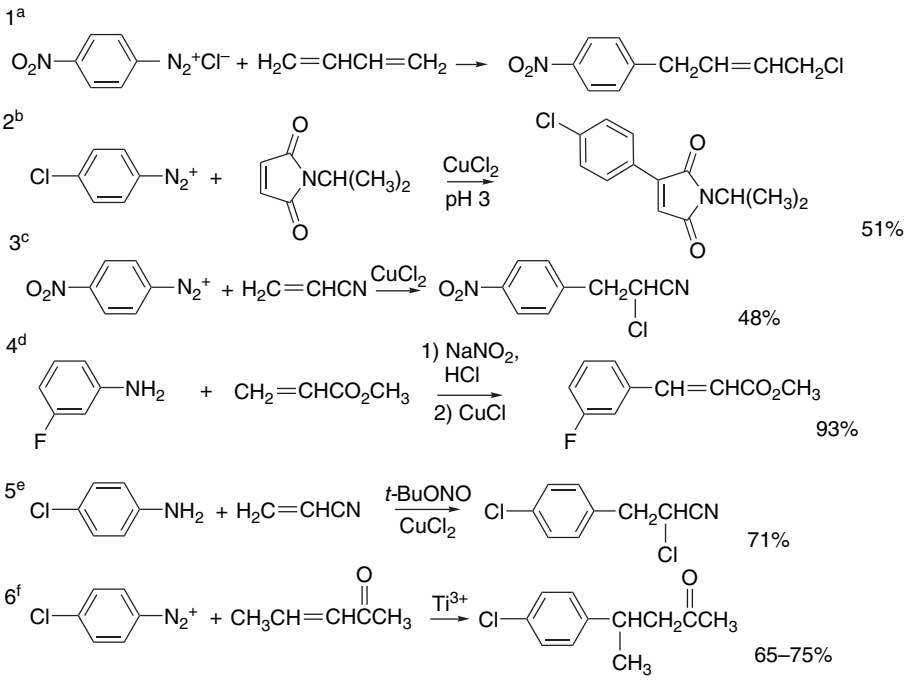


[114] C. S. Rondestvedt, Jr., *Org. React.*, **11**, 189 (1960); C. S. Rondestvedt, *Org. React.*, **24**, 225 (1976); A. V. Dombrovskii, *Russ. Chem. Rev.* (Engl. Transl.), **53**, 943 (1984).

[115] M. P. Doyle, B. Siegfried, R. C. Elliot, and J. F. Dellaria, Jr., *J. Org. Chem.*, **42**, 2431 (1977).

[116] A. Citterio and E. Vismara, *Synthesis*, 191 (1980); A. Citterio, A. Cominelli, and F. Bonavoglia, *Synthesis*, 308 (1986).

Scheme 11.7. Meerwein Arylation Reactions



a. G. A. Ropp and E. C. Coyner, *Org. Synth.*, **IV**, 727 (1963).
b. C. S. Rondestvedt, Jr., and O. Vogel, *J. Am. Chem. Soc.*, **77**, 2313 (1955).
c. C. F. Koelsch, *J. Am. Chem. Soc.*, **65**, 57 (1943).
d. G. Theodoridis and P. Malamus, *J. Heterocycl. Chem.*, **28**, 849 (1991).
e. M. P. Doyle, B. Siegfried, R. C. Elliott, and J. F. Dellaria, Jr., *J. Org. Chem.*, **42**, 2431 (1977).
f. A. Citterio and E. Vismara, *Synthesis*, 191 (1980); A. Citterio, *Org. Synth.*, **62**, 67 (1984).

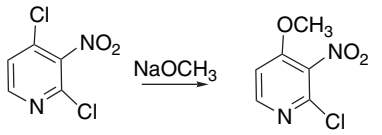
Nucleophilic substitution occurs when there is a potential leaving group present at the carbon at which addition occurs. Although halides are the most common leaving groups, alkoxy, cyano, nitro, and sulfonyl groups can also be displaced. The leaving group ability does not necessarily parallel that found for nucleophilic substitution at saturated carbon. As a particularly striking example, fluoride is often a better leaving group than the other halogens in nucleophilic aromatic substitution. The relative reactivity of the *p*-halonitrobenzenes toward sodium methoxide at 50°C is F(312) >> Cl(1) > Br (0.74) > I (0.36).[117] A principal reason for the order I > Br > Cl > F in S_N2 reactions is the carbon-halogen bond strength, which increases from I to F. The carbon-halogen bond strength is not so important a factor in nucleophilic aromatic substitution because bond breaking is not ordinarily part of the rate-determining step. Furthermore, the highly electronegative fluorine favors the addition step more than the other halogens.

The addition-elimination mechanism has been used primarily for arylation of oxygen and nitrogen nucleophiles. There are not many successful examples of arylation of carbanions by this mechanism. A major limitation is the fact that aromatic nitro

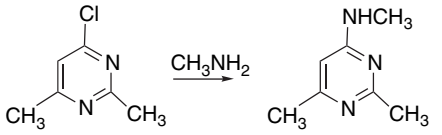
117. G. P. Briner, J. Mille, M. Liveris, and P. G. Lutz, *J. Chem. Soc.*, 1265 (1954).

compounds often react with carbanions by electron transfer processes.[118] However, substitution by carbanions can be carried out under the conditions of the $S_{RN}1$ reaction (see Section 11.4).

The pyridine family of heteroaromatic nitrogen compounds is reactive toward nucleophilic substitution at the C(2) and C(4) positions. The nitrogen atom serves to activate the ring toward nucleophilic attack by stabilizing the addition intermediate. This kind of substitution reaction is especially important in the chemistry of pyrimidines.

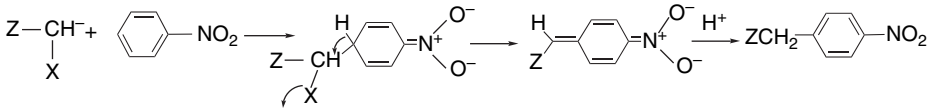


Ref. 119



Ref. 120

A variation of the aromatic nucleophilic substitution process in which the leaving group is part of the entering nucleophile has been developed and is known as *vicarious nucleophilic aromatic substitution.* These reactions require a strong EWG substituent such as a nitro group but require no halide or other leaving group. The reactions proceed through addition intermediates.[121]

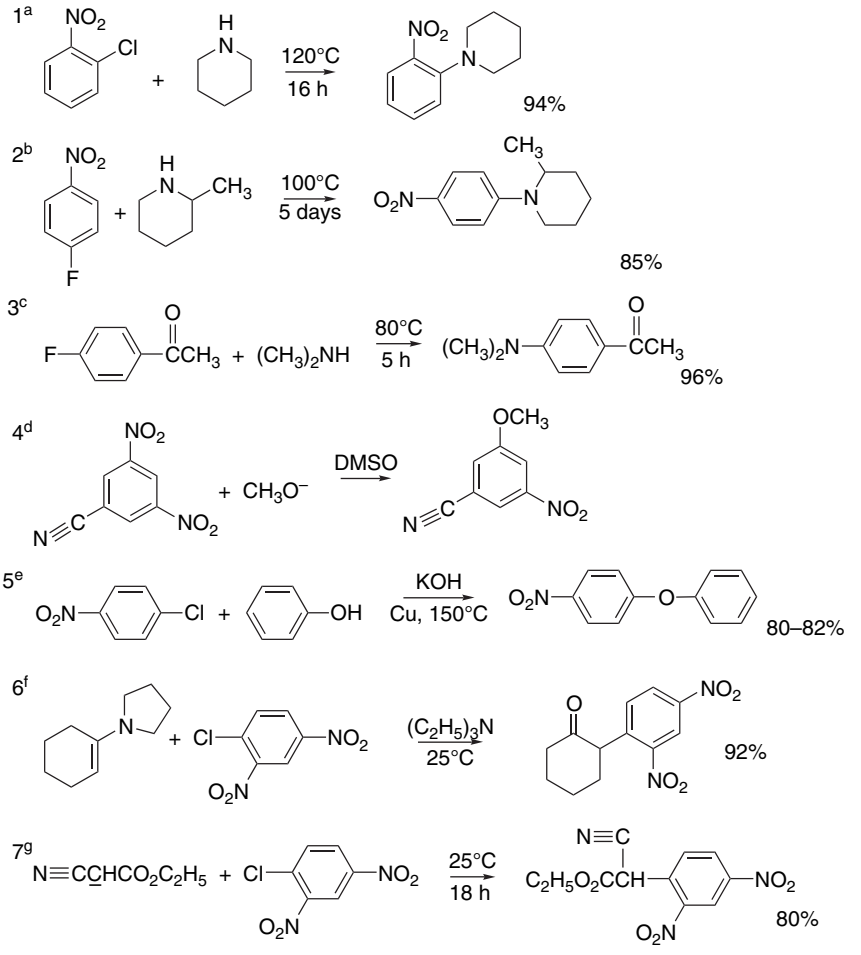


The combinations Z = CN, RSO_2, CO_2R, and SR and X = F, Cl, Br, I, ArO, ArS, and $(CH_3)_2NCS_2$ are among those that have been demonstrated.[122]

Scheme 11.8 gives some examples of addition-elimination reactions. Entries 1 and 2 illustrate typical *o*- and *p*-nitrophenylations of amines. Note the rather vigorous conditions that are required. Entry 3 shows a rather unusual case in which an acetyl group is the activating substituent. Good yields were obtained for a number of amines in polar aprotic solvents. The corresponding chloro and bromo derivative were much less reactive. Entry 4 represents a case of a very electrophilic aromatic ring, but

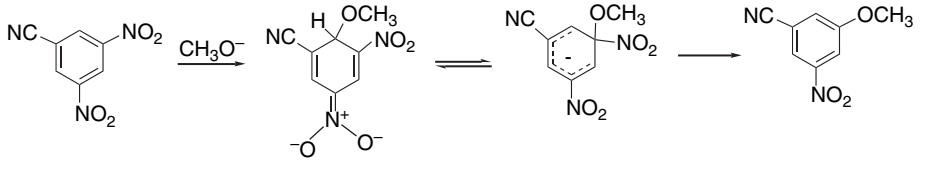
118. R. D. Guthrie, in *Comprehensive Carbanion Chemistry*, Part A, E. Buncel and T. Durst, eds., Elsevier, Amsterdam, 1980, Chap. 5.
119. J. A. Montgomery and K. Hewson, *J. Med. Chem.*, **9**, 354 (1966).
120. D. J. Brown, B. T. England, and J. M. Lyall, *J. Chem. Soc. C*, 226 (1966).
121. M. Makosza, T. Lemek, A. Kwast, and F. Terrier, *J. Org. Chem.*, **67**, 394 (2002); M. Makosza and A. Kwast, *J. Phys. Org. Chem.*, **11**, 341 (1998).
122. M. Makosza and J. Winiarski, *J. Org. Chem.*, **45**, 1534 (1980); M. Makosza, J. Golinski, and J. Baran, *J. Org. Chem.*, **49**, 1488 (1984); M. Makosza and J. Winiarski, *J. Org. Chem.*, **49**, 1494 (1984); M. Makosza and J. Winiarski, *J. Org. Chem.*, **49**, 5272 (1984); M. Makosza and J. Winiarski, *Acc. Chem. Res.*, **20**, 282 (1987); M. Makosza and K. Wojciechowski, *Liebigs Ann. Chem./Recueil*, 1805 (1997).

Scheme 11.8. Nucleophilic Aromatic Substitution



a. S. D. Ross and M. Finkelstein, *J. Am. Chem. Soc.*, **85**, 2603 (1963).
b. F. Pietra and F. Del Cima, *J. Org. Chem.*, **33**, 1411 (1968).
c. H. Bader, A. R. Hansen, and F. J. McCarty, *J. Org. Chem.*, **31**, 2319 (1966).
d. E. J. Fendler, J. H. Fendler, N. I. Arthur, and C. E. Griffin, *J. Org. Chem.*, **37**, 812 (1972).
e. R. O. Brewster and T. Groening, *Org. Synth.*, **II**, 445 (1943).
f. M. E. Kuehne, *J. Am. Chem. Soc.*, **84**, 837 (1962).
g. H. R. Snyder, E. P. Merica, C. G. Force, and E. G. White, *J. Am. Chem. Soc.*, **80**, 4622 (1958).

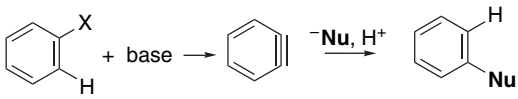
the favored addition intermediate does not have a potential leaving group. Reaction evidently occurs through a minor adduct.



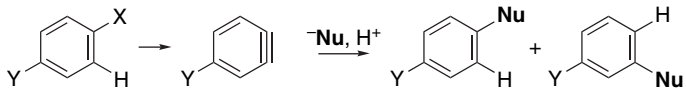
Entry 5 involves metallic copper as a catalyst and is probably a metal-catalyzed reaction (see Section 11.3). The reaction is carried out with excess phenol without solvent. Entries 6 and 7 are cases of C-arylation, both using 2,4-dinitrochlorobenzene.

11.2.3. Substitution by the Elimination-Addition Mechanism

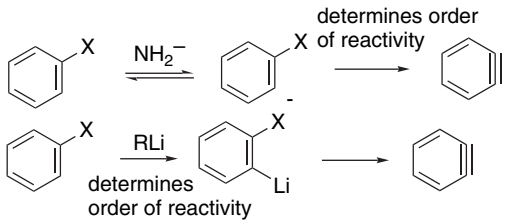
The elimination-addition mechanism involves a highly unstable intermediate called *dehydrobenzene or benzyne*.[123] (See Section 10.6 of Part A for a discussion of the structure of benzyne.)



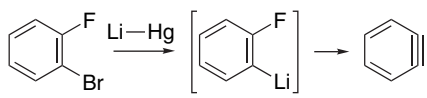
A unique feature of this mechanism is that the entering nucleophile does not necessarily become bound to the carbon to which the leaving group was attached.



The elimination-addition mechanism is facilitated by electronic effects that favor removal of a hydrogen from the ring as a proton. Relative reactivity also depends on the halide. The order Br > I > Cl >> F has been established in the reaction of aryl halides with KNH_2 in liquid ammonia[124] and has been interpreted as representing a balance of two effects. The polar order favoring proton removal would be F > Cl > Br > I, but this is largely overwhelmed by the ease of bond breaking, which is I > Br > Cl > F. With organolithium reagents in ether solvents, the order of reactivity is F > Cl > Br > I, which indicates that the acidity of the ring hydrogen is the dominant factor governing reactivity.[125]

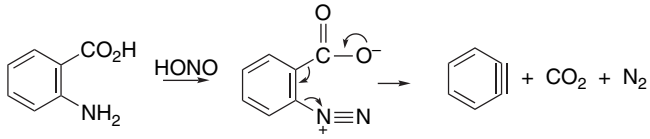


Benzyne can also be generated from *o*-dihaloaromatics. Reaction with lithium amalgam or magnesium results in the formation of transient organometallic compounds that decompose with elimination of lithium halide. *o*-Fluorobromobenzene is the usual starting material in this procedure.[126]

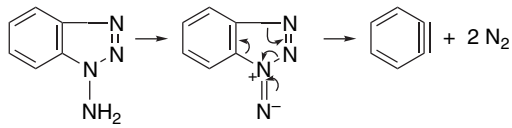


123. R. W. Hoffmann, *Dehydrobenzene and Cycloalkynes*, Academic Press, New York, 1967.
124. F. W. Bergstrom, R. E. Wright, C. Chandler, and W. A. Gilkey, *J. Org. Chem.*, **1**, 170 (1936).
125. R. Huisgen and J. Sauer, *Angew. Chem.*, **72**, 91 (1960).
126. G. Wittig and L. Pohmer, *Chem. Ber.*, **89**, 1334 (1956); G. Wittig, *Org. Synth.*, **IV**, 964 (1963).

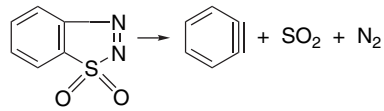
There are several methods for generation of benzyne in addition to base-catalyzed elimination of hydrogen halide from a halobenzene and some of these are more generally applicable for preparative work. Probably the most useful method is diazotization of *o*-aminobenzoic acids.[127] Loss of nitrogen and carbon dioxide follows diazotization and generates benzyne. This method permits generation of benzyne in the presence of a number of molecules with which it can react.



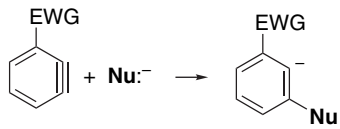
Oxidation of 1-aminobenzotriazole also serves as a source of benzyne under mild conditions. An oxidized intermediate decomposes with loss of two molecules of nitrogen.[128]



Another heterocyclic molecule that can serve as a benzyne precursor is benzothiadiazole-1,1-dioxide, which decomposes with elimination of nitrogen and sulfur dioxide.[129]

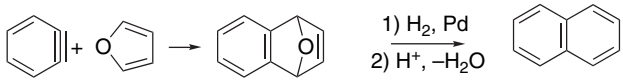


Addition of nucleophiles such as ammonia or alcohols, or their conjugate bases, to benzynes takes place very rapidly. The addition is believed to involve capture of the nucleophile by benzyne, followed by protonation to give the substitution product.[130] Electronegative groups tend to favor addition of the nucleophile at the more distant end of the "triple bond," since this permits stabilization of the developing negative charge. Selectivity is usually not high, however, and formation of both possible products from monosubstituted benzynes is common.[131]

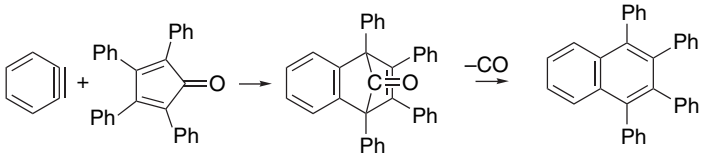


127. M. Stiles, R. G. Miller, and U. Burckhardt, *J. Am. Chem. Soc.*, **85**, 1792 (1963); L. Friedman and F. M. Longullo, *J. Org. Chem.*, **34**, 3089 (1969).
128. C. D. Campbell and C. W. Rees, *J. Chem. Soc. C*, 742, 752 (1969); S. E. Whitney and B. Rickborn, *J. Org. Chem.*, **53**, 5595 (1988); H. Hart and D. Ok, *J. Org. Chem.*, **52**, 3835 (1987).
129. G. Wittig and R. W. Hoffmann, *Org. Synth.*, **47**, 4 (1967); G. Wittig and R. W. Hoffmann, *Chem. Ber.*, **95**, 2718, 2729 (1962).
130. J. F. Bunnett, D. A. R. Happer, M. Patsch, C. Pyun, and H. Takayama, *J. Am. Chem. Soc.*, **88**, 5250 (1966); J. F. Bunnett and J. K. Kim, *J. Am. Chem. Soc.*, **95**, 2254 (1973).
131. E. R. Biehl, E. Nieh, and K. C. Hsu, *J. Org. Chem.*, **34**, 3595 (1969).

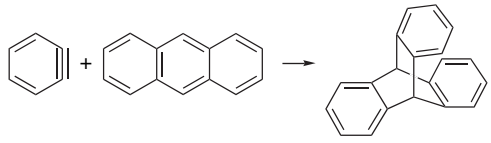
When benzyne is generated in the absence of another reactive molecule it dimerizes to biphenylene.[132] In the presence of dienes, benzyne is a very reactive dienophile and [4 + 2] cycloaddition products are formed. The adducts with furans can be converted to polycyclic aromatic compounds by elimination of water. Similarly, cyclopentadienones can give a new aromatic ring by loss of carbon monoxide. Pyrones give adducts that can aromatize by loss of CO_2, as illustrated by Entry 7 in Scheme 11.9.



Ref. 133

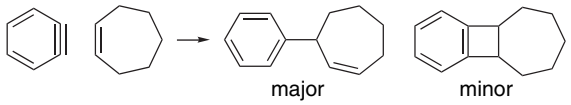


Ref. 134

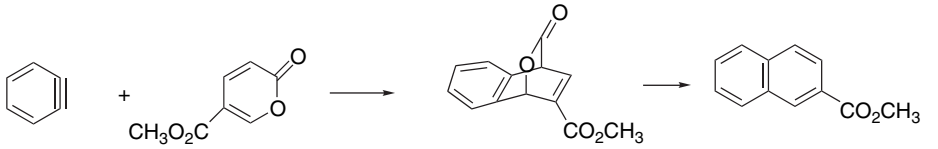


Ref. 135

Benzyne gives both [2 + 2] cycloaddition and ene reaction products with simple alkenes.[136]

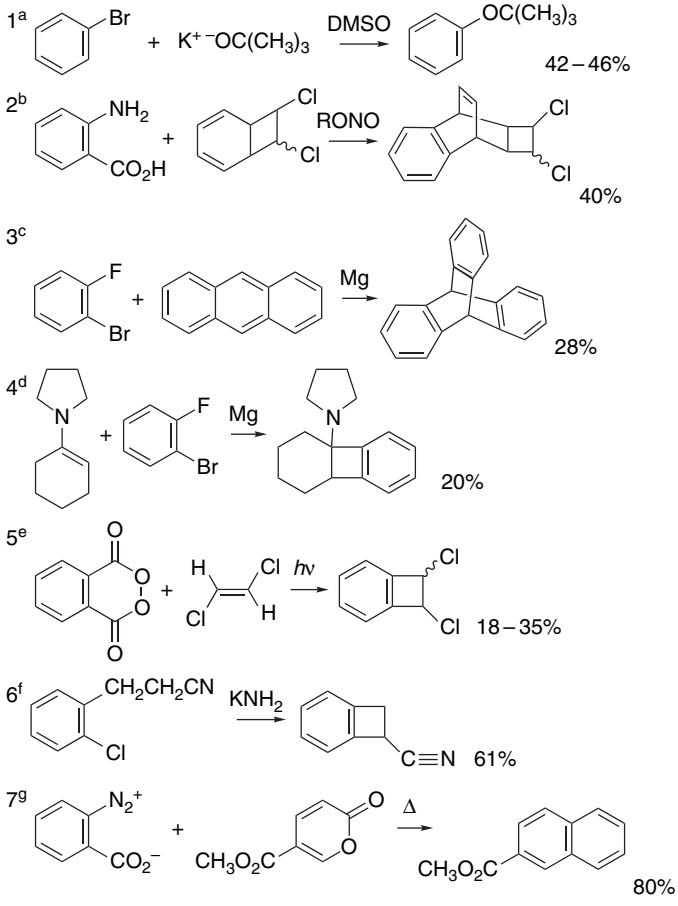


Scheme 11.9 illustrates some of the types of compounds that can be prepared via benzyne intermediates. Entry 1 is an example of the generation of benzyne in a strongly basic DMSO solution. Entry 2 is a Diels-Alder reaction involving in situ generation of benzyne. The adduct was used to synthesize several polycyclic strained-ring systems having fused benzene rings. Entry 3 illustrates the formation of benzyne from *o*-bromofluorobenzene by reaction with magnesium. The benzyne undergoes a Diels-Alder reaction with anthracene. Entry 4 also uses this method of benzyne generation and results in a [2 + 2] cycloaddition with an enamine. Entry 5 is photolytic generation of benzyne employing phthaloyl peroxide. This method seems to have been used only rarely. Entry 6 shows a case of intramolecular trapping of benzyne by a nitrile-stabilized carbanion. Entry 7 is a Diels-Alder reaction with a pyrone, in which the adduct undergoes decarboxylation under the reaction conditions.



132. F. M. Logullo, A. H. Seitz, and L. Friedman, *Org. Synth.*, **V**, 54 (1973).
133. G. Wittig and L. Pohmer, *Angew. Chem.*, **67**, 348 (1955).
134. L. F. Fieser and M. J. Haddadin, *Org. Synth.*, **V**, 1037 (1973).
135. L. Friedman and F. M. Logullo, *J. Org. Chem.*, **34**, 3089 (1969).
136. P. Crews and J. Beard, *J. Org. Chem.*, **38**, 522 (1973).

Scheme 11.9. Syntheses via Benzyne Intermediates



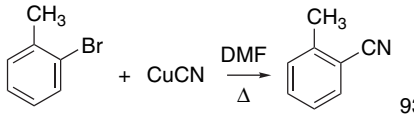
a. M. R. V. Sahyun and D. J. Cram, *Org. Synth.*, **45**, 89 (1965).
b. L. A. Paquette, M. J. Kukla, and J. C. Stowell, *J. Am. Chem. Soc.*, **94**, 4920 (1972).
c. G. Wittig, *Org. Synth.*, **IV**, 964 (1963).
d. M. E. Kuehne, *J. Am. Chem. Soc.*, **84**, 837 (1962).
e. M. Jones, Jr., and M. R. DeCamp, *J. Org. Chem.*, **36**, 1536 (1971).
f. J. F. Bunnett and J. A. Skorcz, *J. Org. Chem.*, **27**, 3836 (1962).
g. S. Escudero, D. Perez, E. Guitan, and L. Castedo, *Tetrahedron Lett.*, **38**, 5375 (1997).

11.3. Transition Metal–Catalyzed Aromatic Substitution Reactions

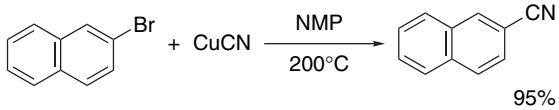
11.3.1. Copper-Catalyzed Reactions

As noted in Section 11.2.2, nucleophilic substitution of aromatic halides lacking activating substituents is generally difficult. It has been known for a long time that the nucleophilic substitution of aromatic halides can be catalyzed by the presence of copper metal or copper salts.[137] Synthetic procedures based on this observation are used to prepare aryl nitriles by reaction of aryl bromides with Cu(I)CN. The reactions are usually carried out at elevated temperature in DMF or a similar solvent.

137. J. Lindley, *Tetrahedron*, **40**, 1433 (1984).

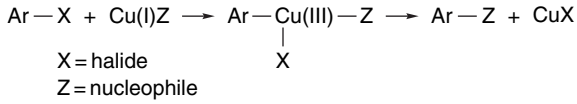


Ref. 138

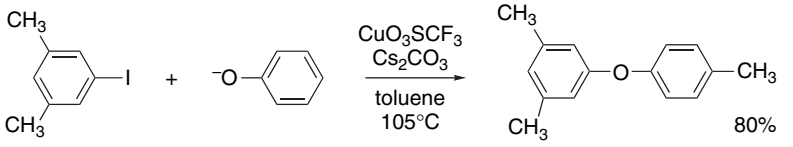


Ref. 139

A general mechanistic description of the copper-promoted nucleophilic substitution involves an oxidative addition of the aryl halide to Cu(I) followed by collapse of the arylcopper intermediate with a ligand transfer (reductive elimination).[140]



Several other kinds of nucleophiles can be arylated by copper-catalyzed substitution. Among the reactive nucleophiles are carboxylate ions,[141] alkoxide ions,[142] amines,[143] phthalimide anions,[144] thiolate anions,[145] and acetylides.[146] In some of these reactions there is competitive reduction of the aryl halide to the dehalogenated arene, which is attributed to protonolysis of the arylcopper intermediate. Most of these reactions are carried out at high temperature under heterogeneous conditions using copper powder or copper bronze as the catalyst. The general mechanism suggests that these catalysts act as sources of Cu(I) ions. Homogeneous reactions can be carried out using soluble Cu(I) salts, particularly $Cu(I)O_3SCF_3$.[147] These reactions occur under milder conditions than those using other sources of copper. The range and effectiveness of coupling aryl halides and phenolates to give diaryl ethers is improved by use of with $CsCO_3$.[148] Reaction occurs in refluxing toluene.

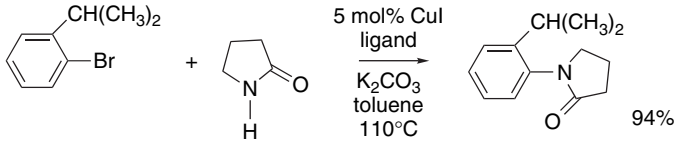


Some reactions of this type are accelerated further by use of naphthoic acid as an additive. This effect is believed to result from formation of a mixed anionic cuprate

138. L. Friedman and H. Shechter, *J. Org. Chem.*, **26**, 2522 (1961).
139. M. S. Newman and H. Bode, *J. Org. Chem.*, **26**, 2525 (1961).
140. T. Cohen, J. Wood, and A. G. Dietz, *Tetrahedron Lett.*, 3555 (1974).
141. T. Cohen and A. H. Lewin, *J. Am. Chem. Soc.*, **88**, 4521 (1966).
142. R. G. R. Bacon and S. C. Rennison, *J. Chem. Soc. C*, 312 (1969).
143. A. J. Paine, *J. Am. Chem. Soc.*, **109**, 1496 (1987).
144. R. G. R. Bacon and A. Karim, *J. Chem. Soc., Perkin Trans. 1*, 272 (1973).
145. H. Suzuki, H. Abe, and A. Osuka, *Chem. Lett.*, 1303 (1980); R. G. R. Bacon and H. A. O. Hill, *J. Chem. Soc.*, 1108 (1964).
146. C. E. Castro, R. Havlin, V. K. Honwad, A. Malte, and S. Moje, *J. Am. Chem. Soc.*, **91**, 6464 (1969).
147. T. Cohen and J. G. Tirpak, *Tetrahedron Lett.*, 143 (1975).
148. J. F. Marcoux, S. Doye, and S. L. Buchwald, *J. Am. Chem. Soc.*, **119**, 10539 (1997).

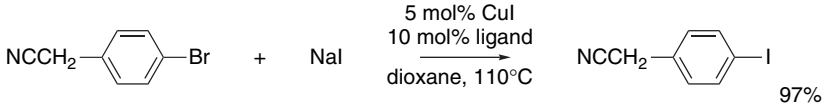
having naphthoate as one of the ligands. The Cs^+ salts are beneficial in maximizing the solubility of the phenolate and naphthoates.

It has been found that a number of bidentate ligands greatly expand the scope of copper catalysis. Copper(I) iodide used in conjunction with a chelating diamine is a good catalyst for amidation of aryl bromides. Of several diamines that were examined, *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine was among the best. These conditions are applicable to aryl bromides and iodides with either ERG or EWG substituents, as well as to relatively hindered halides. The nucleophiles that are reactive under these conditions include acyclic and cyclic amides.[149]



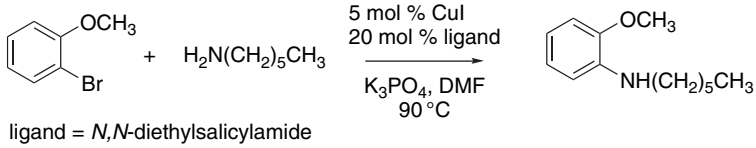
ligand = *trans-N,N'*-dimethyl-1,2-cyclohexanediamine

This catalytic system also promotes exchange of iodide for bromide on aromatic rings.[150] The reaction is an equilibrium process that is driven forward by the low solubility of NaBr in the solvent, dioxane.



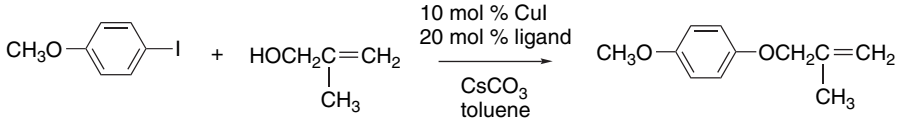
ligand = *trans-N,N'*-dimethyl-1,2-cyclohexanediamine

The *N*,*N*-diethylamide of salicylic acid is a useful ligand in conjunction with CuI and permits amination of aryl bromides by primary alkylamines.[151]



ligand = *N,N*-diethylsalicylamide

Copper(I) iodide with 1,10-phenanthroline catalyzes substitution of aryl iodides by alcohols. The reaction can be done either in excess alcohol or in toluene.[152]

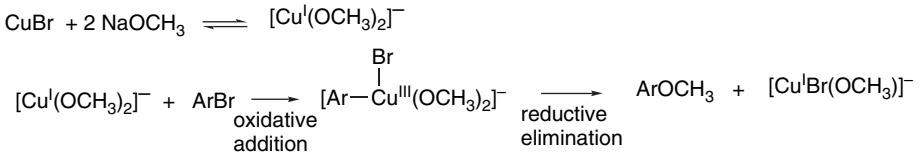


ligand = 1,10-phenanthroline

These copper-catalyzed reactions are generally applicable to aryl halides with either EWG or ERG substituents. The order of reactivity is I > Br> Cl > OSO_2R, which is consistent with an oxidative addition mechanism.

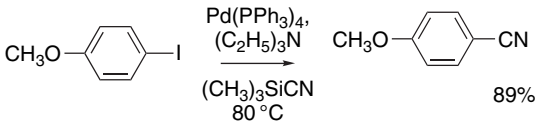
149. A. Klapars, X. Huang, and S. L. Buchwald, *J. Am. Chem. Soc.*, **124**, 7421 (2002).
150. A. Klapars and S. L. Buchwald, *J. Am. Chem. Soc.*, **124**, 14844 (2002).
151. F. Y. Kwong and S. L. Buchwald, *Org. Lett.*, **5**, 793 (2003).
152. M. Wolter, G. Nordmann, G. E. Job, and S. L. Buchwald, *Org. Lett.*, **4**, 973 (2002).

One aspect of the copper catalytic system that has received attention is the identity of the active catalytic species. In the case of displacement of aryl bromides by methoxide ion in the presence of CuBr, it has been suggested that the active species is $Cu(I)(OCH_3)_2$, an anionic cuprate.[153]



11.3.2. Palladium-Catalyzed Reactions

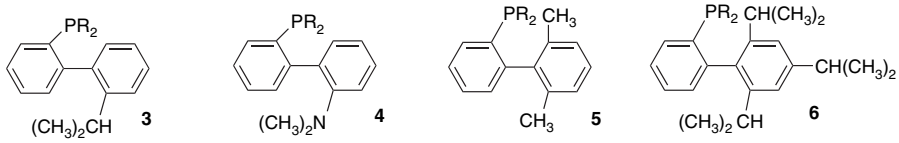
In Section 8.2.3.2, we discussed arylation of enolates and enolate equivalents using palladium catalysts. Related palladium-phosphine combinations are very effective catalysts for aromatic nucleophilic substitution reactions. For example, conversion of aryl iodides to nitriles can be done under mild conditions with $Pd(PPh_3)_4$ as a catalyst.



Ref. 154

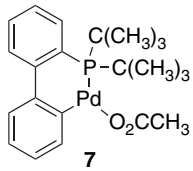
A great deal of effort has been devoted to finding efficient catalysts for substitution by oxygen and nitrogen nucleophiles.[155] These studies have led to optimization of the catalysis with ligands such as triarylphosphines,[156] *bis*-phosphines such as BINAP,[157] dppf,[158] and phosphines with additional chelating substituents.[159] Among the most effective catalysts are highly hindered trialkyl phosphines such as tri-*t*-butyl and tricyclohexylphosphine.[160] A series of 2-biphenylphosphines **3**–**6** has also been found to have excellent activity.[161]

153. H. L. Aalten, C. van Koten, D. M. Grove, T. Kuilman, O. G. Piekstra, L. A. Hulshof, and R. A. Sheldon, *Tetrahedron*, **45**, 5565 (1989).
154. N. Chatani and T. Hanafusa, *J. Org. Chem.*, **51**, 4714 (1986).
155. S. L. Buchwald, A. S. Guram, and R. A. Rennels, *Angew. Chem. Intl. Ed. Engl.*, **34**, 1348 (1995); J. F. Hartwig, *Synlett*, 329 (1997); J. F. Hartwig, *Angew. Chem. Intl. Ed. Engl.*, **37**, 2047 (1998); J. P. Wolfe, S. Wagaw, J. F. Marcoux, and S. L. Buchwald, *Acc. Chem. Res.*, **31**, 805 (1998); J. F. Hartwig, *Acc. Chem. Res.*, **31**, 852 (1998); B. H. Yang and S. L. Buchwald, *J. Organomet. Chem.*, **576**, 125 (1999).
156. J. P. Wolfe and S. L. Buchwald, *J. Org. Chem.*, **61**, 1133 (1996); J. Louie and J. F. Hartwig, *Tetrahedron Lett.*, **36**, 3609 (1995).
157. J. P. Wolfe, S. Wagaw, and S. L. Buchwald, *J. Am. Chem. Soc.*, **118**, 7215 (1996).
158. M. S. Driver and J. F. Hartwig, *J. Am. Chem. Soc.*, **118**, 7217 (1996).
159. D. W. Old, J. P. Wolfe, and S. L. Buchwald, *J. Am. Chem. Soc.*, **120**, 9722 (1998); B. C. Hamann and J. F. Hartwig, *J. Am. Chem. Soc.*, **120**, 7369 (1998); S. Vyskocil, M. Smrcina, and P. Kocovsky, *Tetrahedron Lett.*, **39**, 9289 (1998).
160. M. Nishiyama, T. Yamamoto, and Y. Koie, *Tetrahedron Lett.*, **39**, 617 (1998); N. P. Reddy and M. Tanaka, *Tetrahedron Lett.*, **38**, 4807 (1997).
161. M. C. Harris, X. Huang, and S. L. Buchwald, *Org. Lett.*, **4**, 2885 (2002); D. W. Old, J. P. Wolfe, and S. L. Buchwald, *J. Am. Chem. Soc.*, **120**, 9722 (1998); H. Tomori, J. M. Fox, and S. L. Buchwald, *J. Org. Chem.*, **65**, 5334 (2000).



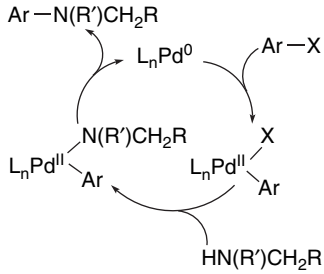
R = *t*-Bu, *c*-C_6H_{11}

A stable palladacycle **7** derived from biphenyl is also an active catalyst.[162]

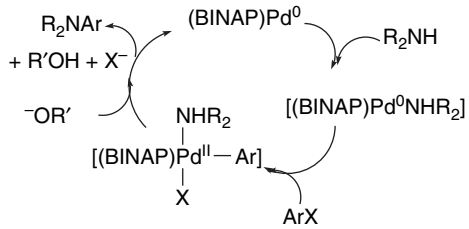


7

In addition to bromides and iodides, the reaction has been successfully extended to chlorides,[163] triflates,[164] and nonafluorobutanesulfonates (nonaflates).[165] These reaction conditions permit substitution in both electron-poor and electron-rich aryl systems by a variety of nitrogen nucleophiles, including alkyl or aryl amines and heterocycles. These reactions proceed via a catalytic cycle involving Pd(0) and Pd(II) intermediates.

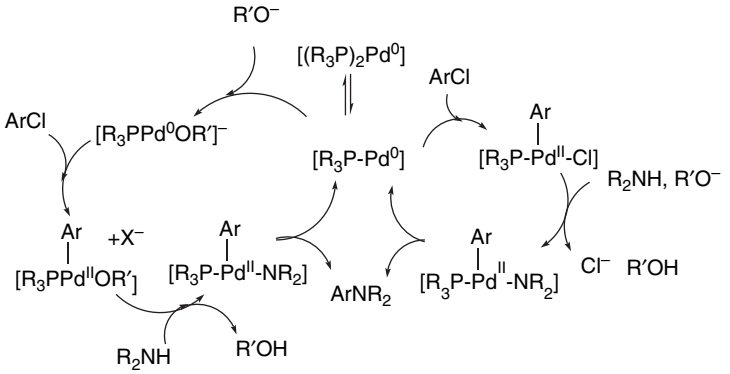


Some of the details of the mechanism may differ for various catalytic systems. There have been kinetic studies on two of the amination systems discussed here. The results of a study of the kinetics of amination of bromobenzene using $Pd_2(dba)_3$, BINAP, and sodium *t*-amyloxide in toluene were consistent with the oxidative addition occurring *after* addition of the amine at Pd. The reductive elimination is associated with *deprotonation of the aminated palladium complex*.[166]



162. D. Zim and S. L. Buchwald, *Org. Lett.*, **5**, 2413 (2003).
163. X. Bei, A. S. Guram, H. W. Turner, and W. H. Weinberg, *Tetrahedron Lett.*, **40**, 1237 (1999).
164. J. P. Wolfe and S. L. Buchwald, *J. Org. Chem.*, **62**, 1264 (1997); J. Louie, M. S. Driver, B. C. Hamann, and J. T. Hartwig, *J. Org. Chem.*, 62, 1268 (1997).
165. K. W. Anderson, M. Mendez-Perez, J. Priego, and S. L. Buchwald, *J. Org. Chem.*, **68**, 9563 (2003).
166. U. K. Singh, E. R. Strieter, D. G. Blackmond, and S. L. Buchwald, *J. Am. Chem. Soc.*, **124**, 14104 (2002).

A study of the reaction of chlorobenzene with *N*-methylaniline in the presence of $Pd[P(t\text{-}Bu)_3]_2$ and several different bases indicated that two mechanisms may occur concurrently, with their relative importance depending on the base, as indicated in the catalytic cycle below. The cycle on the right depicts oxidative addition followed by ligation by the deprotonated amine. The cycle on the left suggests that oxidative addition occurs on an anionic adduct of the catalyst and the base, followed by exchange with the amine ligand.[167]



A comparison of several of the biphenylphosphine ligands has provided some insight into the mechanism of catalyst activation.[168] The results of this study suggest that dissociation of the diphosphino to a monophosphino complex is an essential step in catalyst activation, which would explain why some of the most hindered phosphines are among the best catalyst ligands. This study also indicated that deprotonation of the amine ligand is an essential step. Finally, in catalyst systems that are based on Pd(II) salts, there must be a mechanism for reduction to the active Pd(0) species. In the case of amines, this may occur by reduction by the amine ligand.

Steps in Catalyst Activation

$$[(R_3P)_2Pd^{II}X_2] \rightleftharpoons [R_3P\text{-}Pd^{II}X_2] + R_3P \qquad \text{ligand dissociation}$$

$$[R_3P\text{-}Pd^{II}X_2] + R'CH_2NHR'' \rightleftharpoons [R_3P\text{-}Pd^{II}(X)_2NHCH_2R'] \qquad \text{amine association}$$

$$[R_3P\text{-}Pd^{II}(X)_2NHCH_2R'] \xrightleftharpoons{NaOCR_3} [R_3P\text{-}Pd^{II}(X)_2NCH_2R']^- \qquad \text{ligand deprotonation}$$

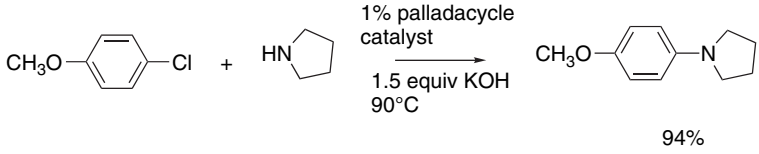
$$[R_3P\text{-}Pd^{II}(X)_2NCH_2R']^- \rightleftharpoons [R_3P\text{-}Pd^0] + R''N{=}CHR' \qquad \text{Pd reduction}$$

The various palladium species can be subject to decomposition and deposition of palladium metal, which generally leads to catalyst inactivation. Apart from their effect on the catalyst activity, the ligands and bases also affect catalyst longevity.

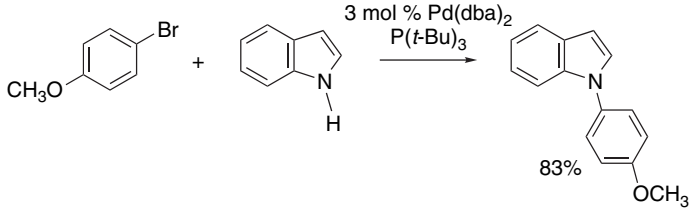
Most of the synthetic applications to date have been based on empirical screening and comparison of ligand systems for effectiveness. A number of useful procedures have been developed. Aryl chlorides are generally less reactive than iodides and

167. L. M. Alcazar-Roman and J. F. Hartwig, *J. Am. Chem. Soc.*, **123**, 12905 (2001).
168. E. R. Strieter, D. G. Blackmond, and S. L. Buchwald, *J. Am. Chem. Soc.*, **125**, 13978 (2003).

bromides. The palladacycle **7** (see p. 1046), was used successfully in the amination of aryl chlorides.[169]

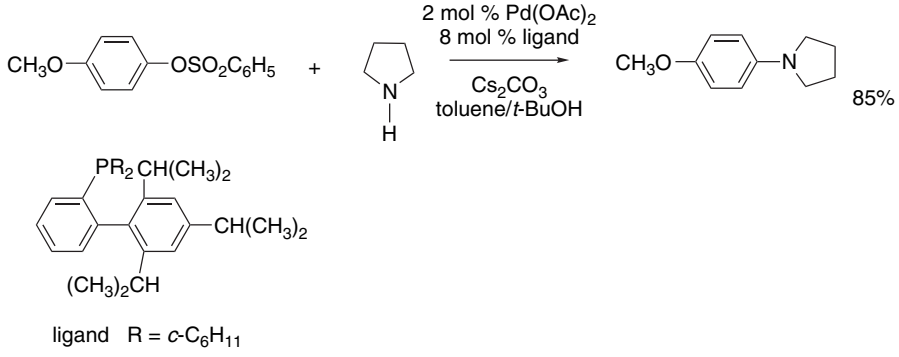


Palladium-catalyzed substitution can also be applied to nonbasic nitrogen heterocycles, such as indoles, in the absence of strong bases.



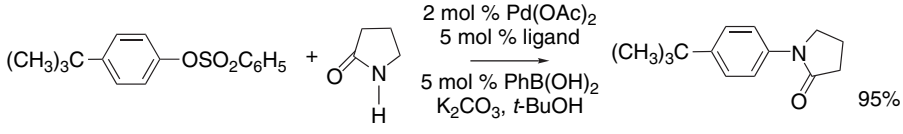
Ref. 170

Except for the perfluoro cases, aryl sulfonates are generally less reactive than the halides. However certain catalyst systems can achieve reactions with benzenesulfonates and tosylates. The hindered biphenyphosphines are the most effective ligands.



Ref. 171

These conditions were also successfully applied to arylation of amides and carbamates.

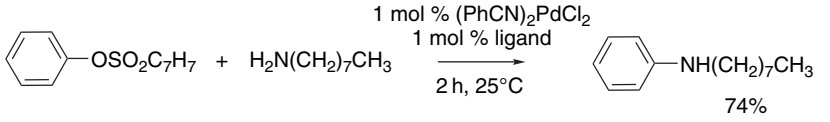


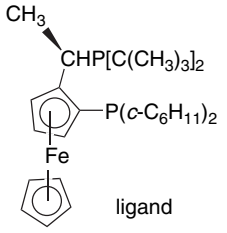
169. D. Zim and S. L. Buchwald, *Org. Lett.*, **5**, 2413 (2003).

170. J. F. Hartwig, M. Kawatsura, S. I. Hauck, K. H. Shaughnessy, and L. M. Alcazar-Roman, *J. Org. Chem.*, **64**, 5575 (1999).

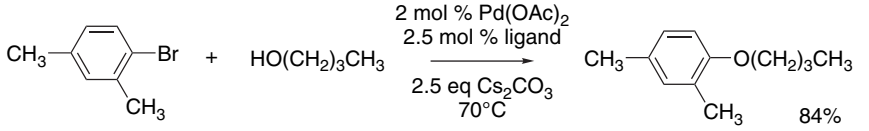
171. X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, and S. L. Buchwald, *J. Am. Chem. Soc.*, **125**, 6653 (2003).

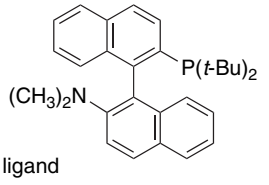
Amination of tosylates has been achieved using a hindered ferrocenyldiphosphine ligand.[172]



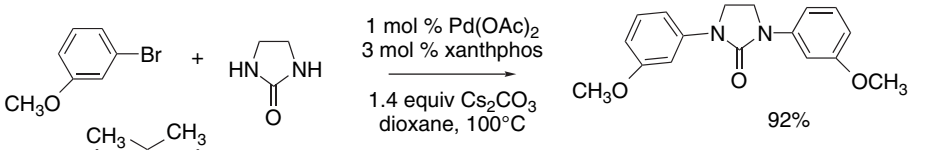


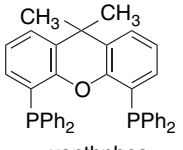
Similar reactions have been used for substitution by alkoxide and phenoxide nucleophiles. Hindered binaphthyl ligands have proven useful in substitutions by alcohols.[173]





Palladium acetate in conjunction with a diphosphine ligand, xantphos, is active for arylation of amides, ureas, oxazolidinones and sulfonamides.[174]



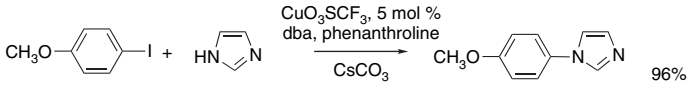


172. A. H. Roy and J. F. Hartwig, *J. Am. Chem. Soc.*, **125**, 8704 (2003).
173. K. E. Torraca, X. Huang, C. A. Parrish, and S. L. Buchwald, *J. Am. Chem. Soc.*, **123**, 10770 (2001).
174. J. Yin and S. L. Buchwald, *J. Am. Chem. Soc.*, **124**, 6043 (2002).

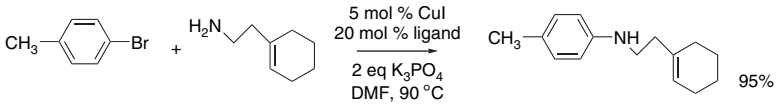
Scheme 11.10. Copper- and Palladium-Catalyzed Aromatic Substitution

A. Copper-catalyzed substitution

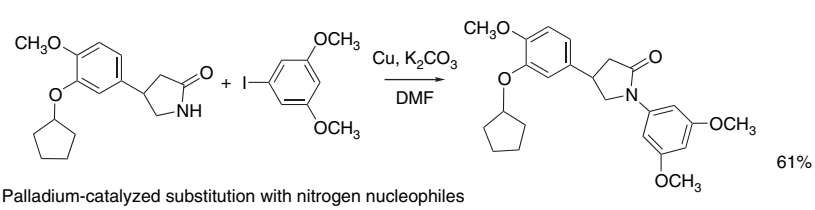
1[a]



2[b]

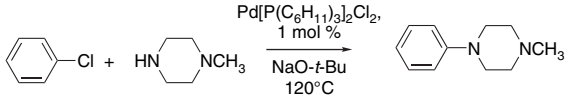


3[c]

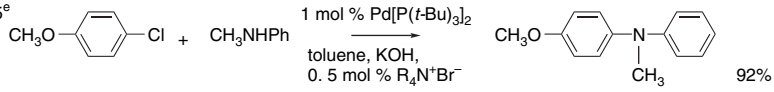


B. Palladium-catalyzed substitution with nitrogen nucleophiles

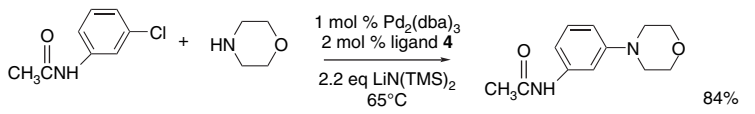
4[d]



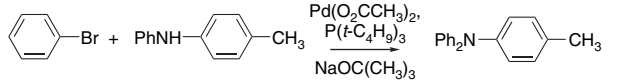
5[e]



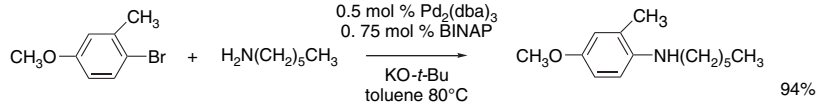
6[f]



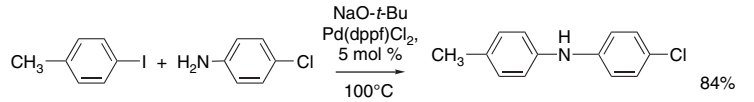
7[g]



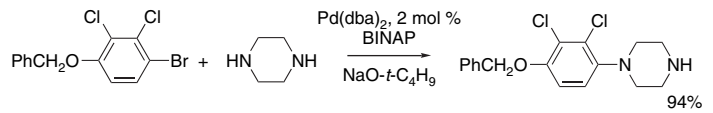
8[h]



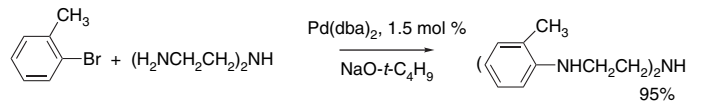
9[i]



10[j]



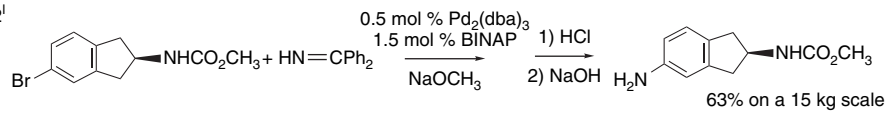
11[k]



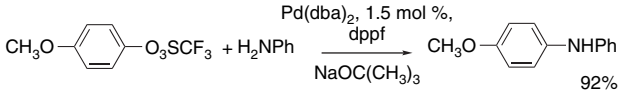
(*Continued*)

Scheme 11.10. (*Continued*)

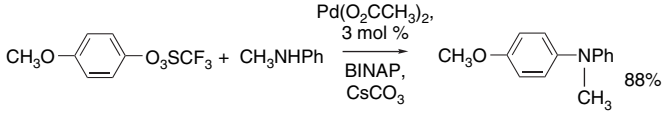
12[l]



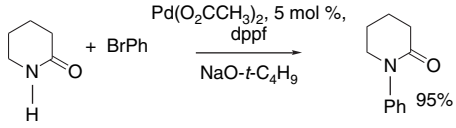
13[m]



14[n]

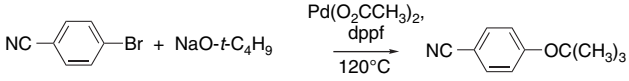


15[o]

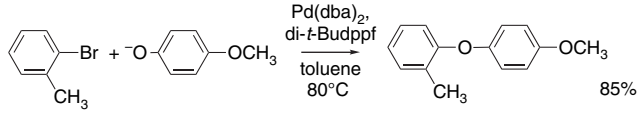


C. Palladium-catalyzed reactions with oxygen nucleophiles.

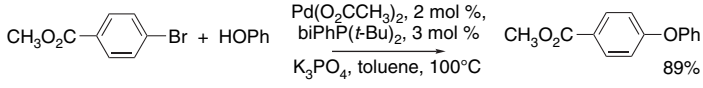
16[p]



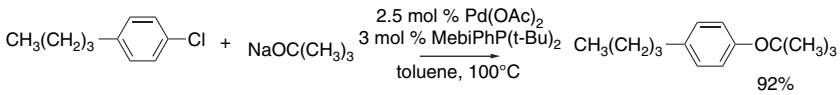
17[q]



18[r]



19[s]



a. A. Kiyomori, J.-F. Marcoux, and S. L. Buchwald, *Tetrahedron Lett.*, **40**, 2657 (1999).
b. F. Y. Kwong and S. L. Buchwald, *Org. Lett.*, **5**, 793 (2003).
c. E. Aebischer, E. Bacher, F. W. J. Demnitz, T. H. Keller, M. Kurzmeyer, M. L. Ortiz, E. Pombo-Villar, and H.-P. Weber, *Hetereocycles*, **48**, 2225 (1998).
d. N. P. Reddy and M. Tanaka, *Tetrahedron Lett.*, **38**, 4807 (1997).
e. R. Kuwano, M. Utsunomiya, and J. F. Hartwig, *J. Org. Chem.*, **67**, 6479 (2002).
f. M. C. Harris, X. Huang, and S. L. Buchwald, *Org. Lett.*, **4**, 2885 (2002).
g. T. Yamamoto, M. Nishiyama, and Y. Koie, *Tetrahedron Lett.*, **39**, 2367 (1998).
h. K. E. Torraca, X. Huang, C. A. Parrish, and S. L. Buchwald, *J. Am. Chem. Soc.*, **123**, 10770 (2001).
i. M. S. Driver and J. F. Hartwig, *J. Am. Chem. Soc.*, **118**, 7217 (1996).
j. S. Morita, K. Kitano, J. Matsubara, T. Ohtani, Y. Kawano, K. Otsubo, and M. Uchida, *Tetrahedron*, **54**, 4811 (1998).
k. Y. Hong, C. H. Senanayake, T. Xiang, C. P. Vandenbossche, G. J. Tanoury, R. P. Bakale, and S. A. Wald, *Tetrahedron Lett.*, **39**, 3121 (1998).
l. M. Prashad, B. Hu, D. Har, O. Repic, T. J. Blacklock, and M. Avemoglu, *Adv. Synth. Catal.*, **343**, 461 (2001).
m. J. Louie, M. S. Driver, B. C. Hamann, and J. F. Hartwig, *J. Org. Chem.*, **62**, 1268 (1997).
n. J. Ahman and S. L. Buchwald, *Tetrahedron Lett.*, **38**, 6363 (1997).
o. W. C. Shakespeare, *Tetrahedron Lett.*, **40**, 2035 (1999).
p. G. Mann and J. F. Hartwig, *J. Org. Chem.*, **62**, 5413 (1997).
q. G. Mann, C. Incarvito, A. L. Rheingold, and J. F. Hartwig, *J. Am. Chem. Soc.*, **121**, 3224 (1999).
r. A. Aranyos, D. W. Old, A. Kiyomori, J. P. Wolfe, J. P. Sadighi, and S. L. Buchwald, *J. Am. Chem. Soc.*, **121**, 4369 (1999).
s. C. A. Parrish and S. L. Buchwald, *J. Org. Chem.*, **66**, 2498 (2001).

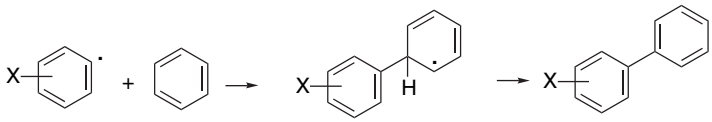
Some other examples of metal-catalyzed substitutions are given in Scheme 11.10. Entries 1 to 3 are copper-catalyzed reactions. Entry 1 is an example of arylation of imidazole. Both dibenzylideneacetone and 1,10-phenanthroline were included as ligands and Cs_2CO_3 was used as the base. Entry 2 is an example of amination by a primary amine. The ligand used in this case was *N*,*N*-diethylsalicylamide. These conditions proved effective for a variety of primary amines and aryl bromides with both ERG and EWG substituents. Entry 3 is an example of more classical conditions. The target structure is a phosphodiesterase inhibitor of a type used in treatment of asthma. Copper powder was used as the catalyst.

The remainder of the entries in Scheme 11.10 depict palladium-catalyzed reactions. Entries 4 to 6 are examples of aminations of aryl chlorides. In Entry 4, a Pd(II) salt with a hindered phosphine ligand was used as the catalyst. Entry 5 uses the Pd(0)-tri-(*t*-butyl)phosphine complex as the catalyst in conjunction with a phase transfer salt. The reaction was done in a water-toluene mixture and these conditions were applicable to chlorides with both ERG and EWG substituents. Entry 6 used the biphenyl ligand **4** (see p. 1046). LiHMDS was a particularly good base in this case. Entries 7 to 11 use bromides (or iodides) as reactants and *t*-alkoxides as bases. In cases where the catalyst source is a Pd(II) salt, catalyst activation by reduction is necessary. Entry 12 is a large-scale amination carried out using the imine of benzophenone as the nucleophile, with subsequent hydrolysis to provide the amine. Entries 13 and 14 use aryl triflates as reactants. Again, the palladium sources must be reduced as part of catalyst activation. Entry 15 is an example of arylation of an amide. The conditions are similar to those for amination, and subsequent studies have shown that many other nonbasic nitrogen compounds can be arylated (e.g. see p. 1049). Entries 16 to 19 involve alkoxide and phenoxide nucleophiles. The best ligands for these reactions seem to be highly hindered phosphines.

11.4. Aromatic Substitution Reactions Involving Radical Intermediates

11.4.1. Aromatic Radical Substitution

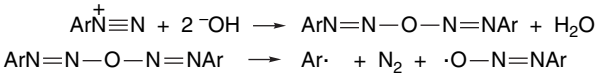
Aromatic rings are moderately reactive toward addition of free radicals (see Part A, Section 12.2) and certain synthetically useful substitution reactions involve free radical substitution. One example is the synthesis of biaryls.[175]



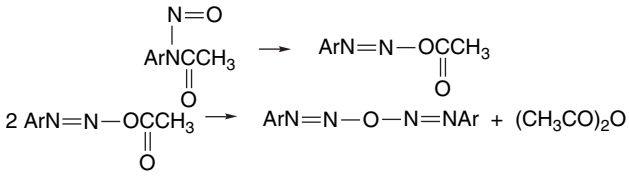
There are some inherent limits to the usefulness of such reactions. Radical substitutions are only moderately sensitive to substituent directing effects, so substituted reactants usually give a mixture of products. This means that the practical utility is limited to symmetrical reactants, such as benzene, where the position of attack

[175] W. E. Bachmann and R. A. Hoffman, *Org. React.*, **2**, 224 (1944); D. H. Hey, *Adv. Free Radical Chem.*, **2**, 47 (1966).

is immaterial. The best sources of aryl radicals are aryl diazonium ions and *N*-nitrosoacetanilides. In the presence of base, diazonium ions form diazooxides, which decompose to aryl radicals.[176]



In the classical procedure, base is added to a two-phase mixture of the aqueous diazonium salt and an excess of the aromatic that is to be substituted. Improved yields can be obtained by using polyethers or phase transfer catalysts with solid aryl diazonium tetrafluoroborate salts in an excess of the aromatic reactant.[177] Another source of aryl radicals is *N*-nitrosoacetanilides, which rearrange to diazonium acetates and give rise to aryl radicals via diazo oxides.[178]



A procedure for arylation involving in situ diazotization has also been developed.[179]

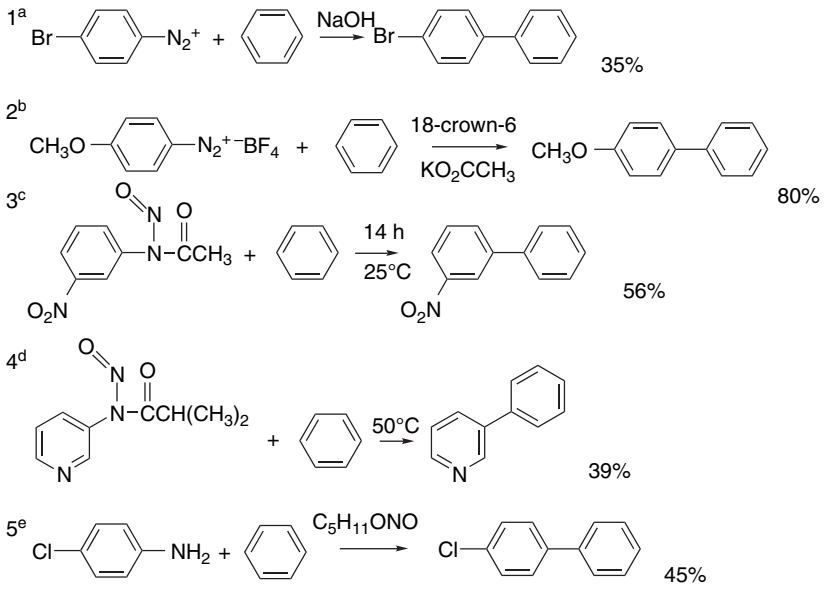
Scheme 11.11 gives some representative preparative reactions based on these methods. Entry 1 is an example of the classical procedure. Entry 2 uses crown-ether catalysis. These reactions were conducted in the aromatic reactant as the solvent. In the study cited for Entry 2, it was found that substituted aromatic reactants such as toluene, anisole, and benzonitrile tended to give more *ortho* substitution product than expected on a statistical basis.[180] The nature of this directive effect does not seem to have been studied extensively. Entries 3 and 4 involve in situ decomposition of *N*-nitrosoamides. Entry 5 is a case of in situ nitrosation.

11.4.2. Substitution by the $S_{RN}1$ Mechanism

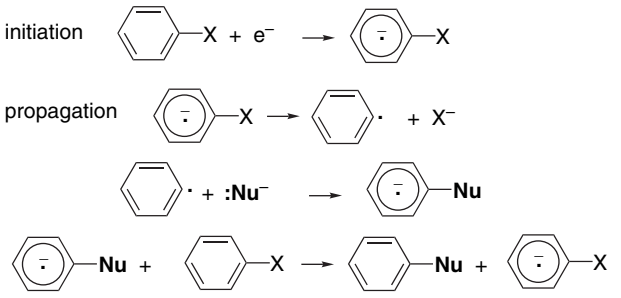
The mechanistic aspects of the $S_{RN}1$ reaction were discussed in Section 11.6 of Part A. The distinctive feature of the $S_{RN}1$ mechanism is an electron transfer between the nucleophile and the aryl halide.[181] The overall reaction is normally a chain process.

176. C. Rüchardt and B. Freudenberg, *Tetrahedron Lett.*, 3623 (1964); C. Rüchardt and E. Merz, *Tetrahedron Lett.*, 2431 (1964); C. Galli, *Chem. Rev.*, **88**, 765 (1988).
177. J. R. Beadle, S. H. Korzeniowski, D. E. Rosenberg, G. J. Garcia-Slanga, and G. W. Gokel, *J. Org. Chem.*, **49**, 1594 (1984).
178. J. I. G. Cadogan, *Acc. Chem. Res.*, **4**, 186 (1971); *Adv. Free Radical Chem.*, **6**, 185 (1980).
179. J. I. G. Cadogan, *J. Chem. Soc.*, 4257 (1962).
180. See also T. Inukai, K. Kobayashi, and O. Shinmura, *Bull. Chem. Soc. Jpn.*, **35**, 1576 (1962).
181. J. F. Bunnett, *Acc. Chem. Res.*, **11**, 413 (1978); R. A. Rossi and R. H. de Rossi, *Aromatic Substitution by the $S_{RN}1$ Mechanism*, ACS Monograph Series, No. 178, American Chemical Society, Washington, DC, 1983.

Scheme 11.11. Synthesis of Biaryls by Radical Substitution



a. M. Gomberg and W. E. Bachman, *Org. Synth.*, **I**, 113 (1941).
b. S. H. Korzeniowski, L. Blum, and G. W. Gokel, *Tetrahedron Lett.*, 1871 (1977); J. R. Beadle, S. H. Korzeniowski, D. E. Rosenberg, B. J. Garcia-Slanga, and G. W. Gokel, *J. Org. Chem.*, **49**, 1594 (1984).
c. W. E. Bachmann and R. A. Hoffman, *Org. React.*, **2**, 249 (1944).
d. H. Rapoport, M. Lick, and G. J. Kelly, *J. Am. Chem. Soc.*, **74**, 6293 (1952).
e. J. I. G. Cadogan, *J. Chem. Soc.*., 4257 (1962).



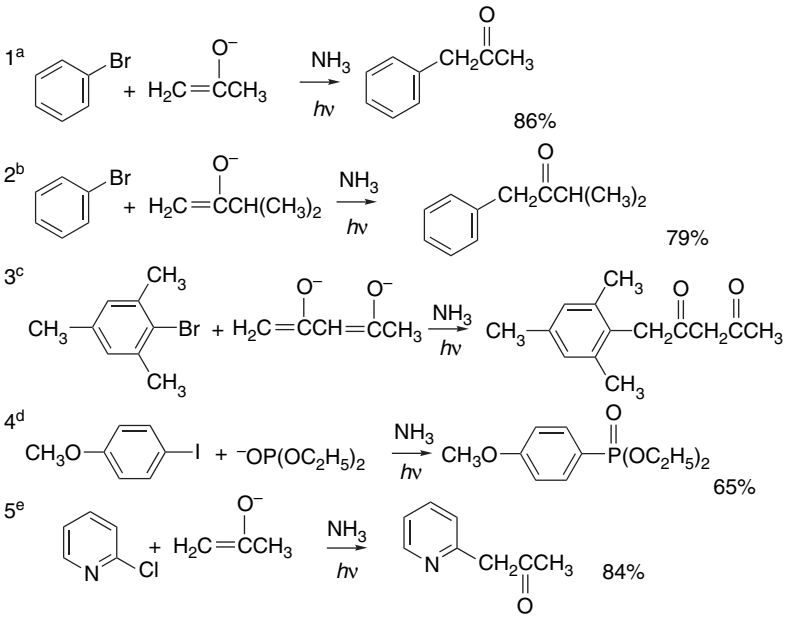
A potential advantage of the $S_{RN}1$ mechanism is that it is not particularly sensitive to the nature of other aromatic ring substituents, although EWG substituents favor the nucleophilic addition step. For example, chloropyridines and chloroquinolines are excellent reactants.[182] A variety of nucleophiles undergo the reaction, although not always in high yield. The nucleophiles that have been found to participate in

182. J. V. Hay, T. Hudlicky, and J. F. Wolfe, *J. Am. Chem. Soc.*, **97**, 374 (1975); J. V. Hay and J. F. Wolfe, *J. Am. Chem. Soc.*, **97**, 3702 (1975); A. P. Komin and J. F. Wolfe, *J. Org. Chem.*, **42**, 2481 (1977); R. Beugelmans, M. Bois-Choussy, and B. Boudet, *Tetrahedron*, **24**, 4153 (1983).

$S_{RN}1$ substitution include ketone enolates,[183] ester enolates,[184] amide enolates,[185] 2,4-pentanedione dianion,[186] pentadienyl and indenyl carbanions,[187] phenolates,[188] diethyl phosphite anion,[189] phosphides,[190] and thiolates.[191] The reactions are frequently initiated by light, which promotes the initiating electron transfer. As for other radical chain processes, the reaction is sensitive to substances that can intercept the propagation intermediates.

Scheme 11.12 provides some examples of the preparative use of the $S_{RN}1$ reaction. Entries 1 and 2 involve arylations of ketone enolates, whereas Entry 3 involves a dianion. Entry 4 is an example of a convenient preparation of arylphosphonates. Entry 5 is an example of application of the $S_{RN}1$ reaction to a chloropyridine.

Scheme 11.12. Aromatic Substitution by the $S_{RN}1$ Mechanism



a. R. A. Rossi and J. F. Bunnett, *J. Org. Chem.*, **38**, 1407 (1973).
b. M. F. Semmelhack and T. Bargar, *J. Am. Chem. Soc.*, **102**, 7765 (1980).
c. J. F. Bunnett and J. E. Sundberg, *J. Org. Chem.*, **41**, 1702 (1976).
d. J. F. Bunnett and X. Creary, *J. Org. Chem.*, **39**, 3612 (1974).
e. A. P. Komin and J. F. Wolfe, *J. Org. Chem.*, **42**, 2481 (1977).

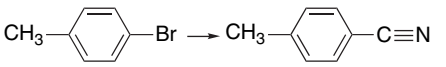
183. M. F. Semmelhack and T. Bargar, *J. Am. Chem. Soc.*, **102**, 7765 (1980).
184. J.-W. Wong, K. J. Natalie, Jr., G. C. Nwokogu, J. S. Pisipati, S. Jyothi, P. T. Flaherty, T. D. Greenwood, and J. F. Wolfe, *J. Org. Chem.*, **62**, 6152 (1997).
185. R. A. Rossi and R. A. Alonso, *J. Org. Chem.*, **45**, 1239 (1980).
186. J. F. Bunnett and J. E. Sundberg, *J. Org. Chem.*, **41**, 1702 (1976).
187. R. A. Rossi and J. F. Bunnett, *J. Org. Chem.*, **38**, 3020 (1973).
188. A. B. Pierini, M. T. Baumgartner, and R. A. Rossi, *Tetrahedron Lett.*, **29**, 3429 (1988).
189. J. F. Bunnett and X. Creary, *J. Org. Chem.*, **39**, 3612 (1974); A. Boumekouez, E. About-Jaudet, N. Collignon, and P. Savignac, *J. Organomet. Chem.*, **440**, 297 (1992).
190. E. Austin, R. A. Alonso, and R. A. Rosi, *J. Org. Chem.*, **56**, 4486 (1991).
191. J. F. Bunnett and X. Creary, *J. Org. Chem.*, **39**, 3173, 3611 (1974); J. F. Bunnett and X. Creary, *J. Org. Chem.*, **40**, 3740 (1975).

Problems

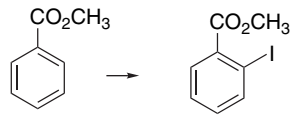
(*References for these problems will be found on page 1289.*)

11.1. Give reagents and reaction conditions that would accomplish each of the following transformations. Multistep schemes are not necessary. Be sure to choose conditions that would lead to the desired isomer as the major product.

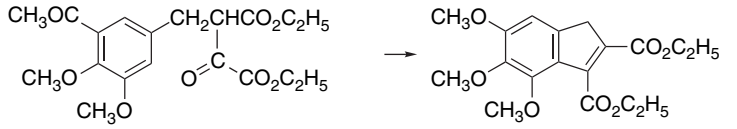
(a)



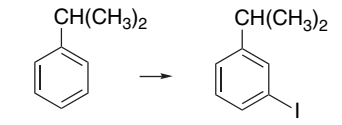
(b)



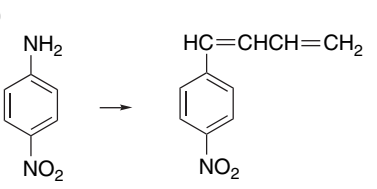
(c)



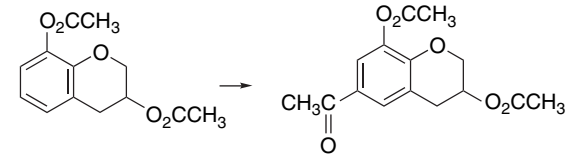
(d)



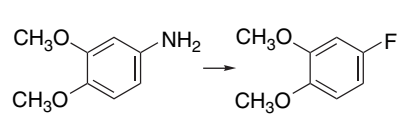
(e)



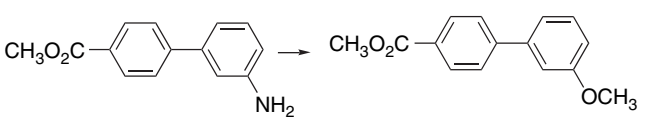
(f)



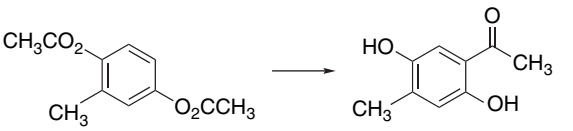
(g)



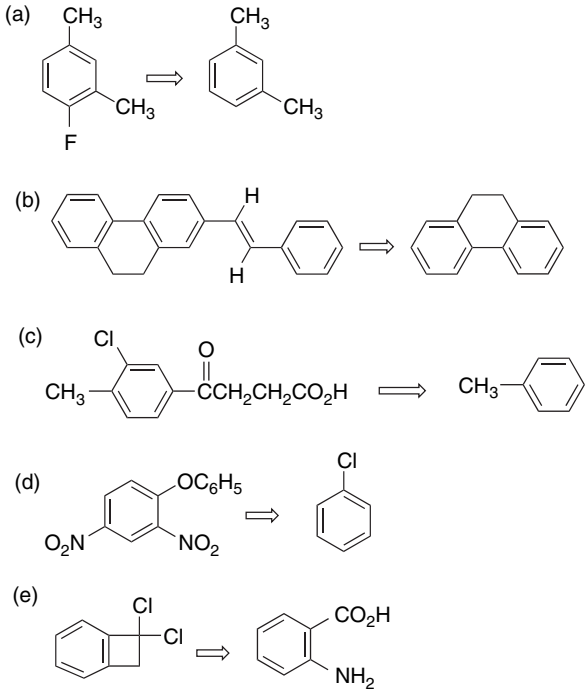
(h)



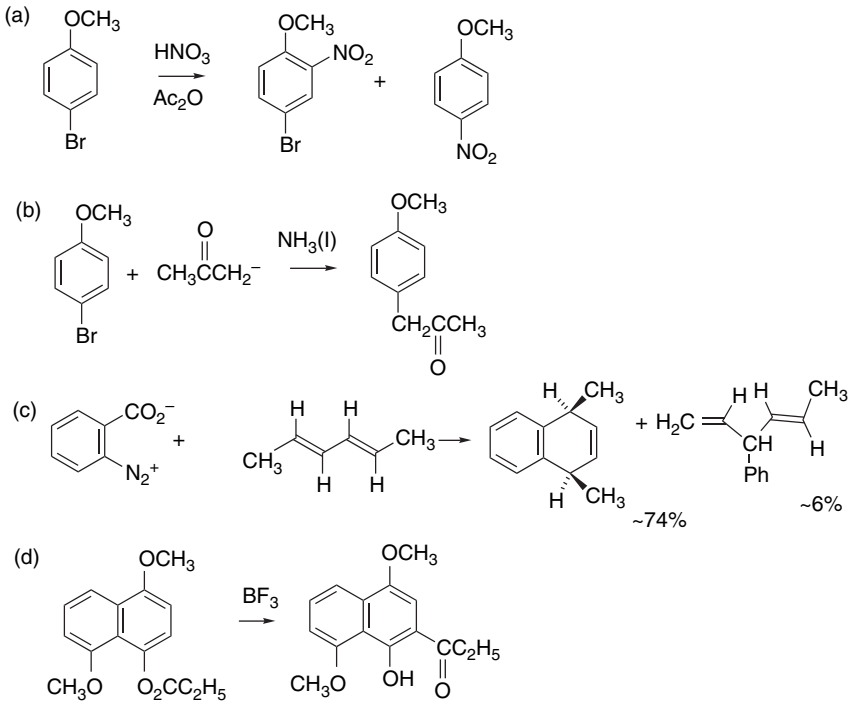
(i)

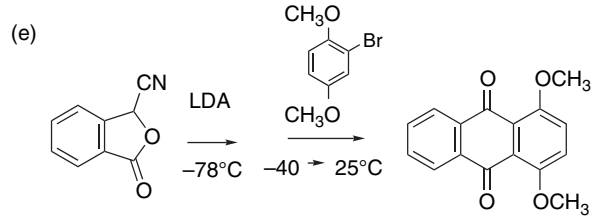


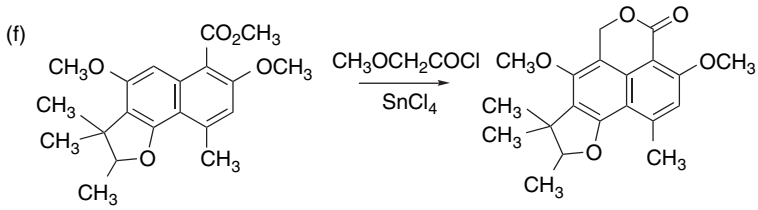
11.2. Suggest a short series of reactions that would be expected to transform the material on the right into the desired product shown on the left.



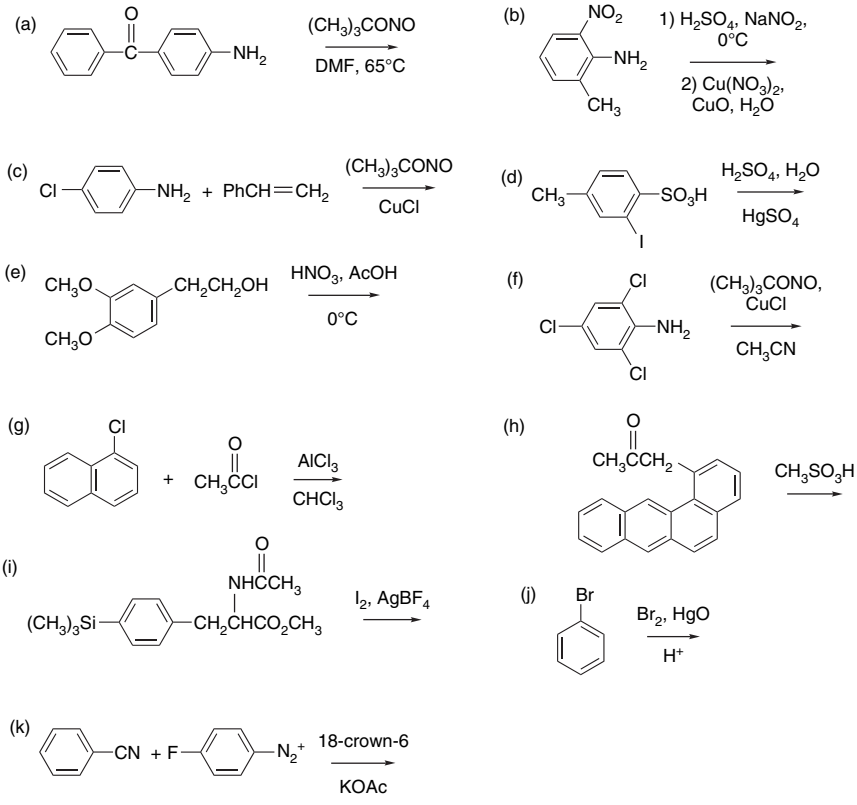
11.3. Write mechanisms that would account for the following reactions:







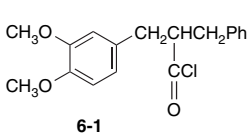
11.4. Predict the product(s) of the following reactions. If more than one product is expected, indicate which will be major and which will be minor.



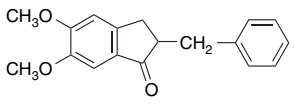
11.5. Suggest efficient syntheses of *o*-, *m*-, and *p*-fluoropropiophenone from benzene and other necessary reagents.

11.6. Treatment of compound **6-1** in dibromethane with one equivalent of aluminum bromide yields **6-2** as the only product in 78% yield. When three equivalents of

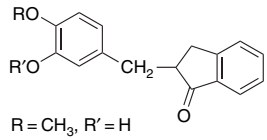
aluminum bromide are used, compounds **6-3** and **6-4** are obtained in a combined yield of 97%. Suggest an explanation for these observations.



6-1



6-2



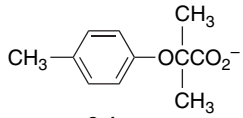
6-3 R = CH_3, R′ = H

6-4 R = H, R′ = CH_3

11.7. Some data on the alkylation of naphthalene by 2-bromopropane using $AlCl_3$ under different conditions are given below. What factors are responsible for the differing product ratios for the two solvents, and why does the product ratio change with time?

	α:β Product ratio	
	Solvent	
Time (min)	CS_2	CH_3NO_2
5	4:96	83:17
15	2.5:97.5	74:26
45	2:98	70:30

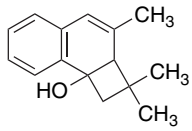
11.8. Addition of a solution of bromine and potassium bromide to a solution of the carboxylate salt **8-1** results in the precipitation of a neutral compound having the formula $C_{11}H_{13}BrO_3$. Spectroscopic data show that the compound is nonaromatic. Suggest a structure and discuss the mechanistic significance of its formation.



8-1

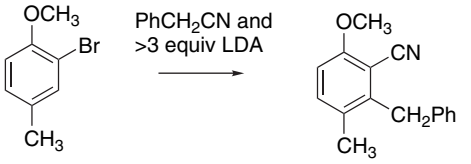
11.9. Benzaldehyde, benzyl methyl ether, benzoic acid, methyl benzoate, and phenylacetic acid all undergo thallation initially in the *ortho* position. Explain this observation.

11.10. Reaction of 3,5,5-trimethyl-2-cyclohexenone with three equivalents of $NaNH_2$ in THF generates the corresponding enolate. When bromobenzene is added and the solution stirred for 4 h, the product **10-1** is isolated in 30% yield. Formulate a mechanism for this transformation.

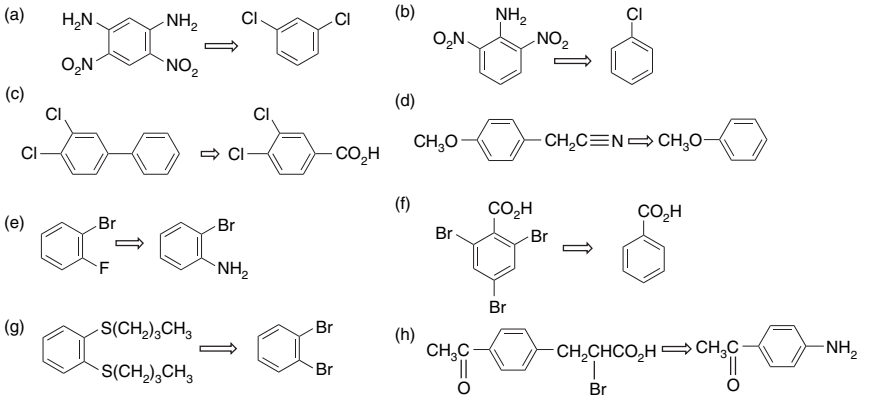


10-1

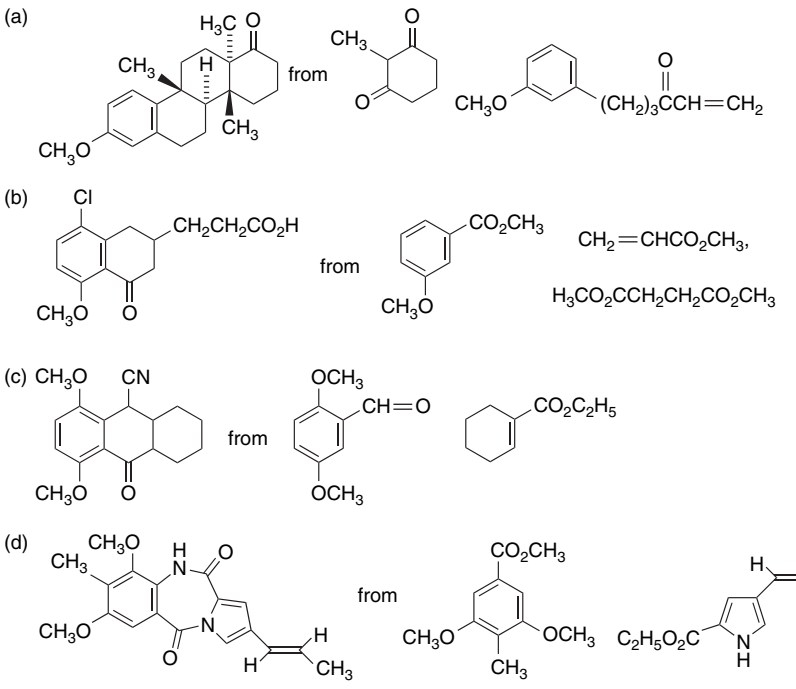
11.11. When phenylacetonitrile is converted to its anion in the presence of excess LDA and then allowed to react with 2-bromo-4-methyl-1-methoxybenzene, the product contains both a benzyl and cyano substituent. Propose a mechanism for this reaction.



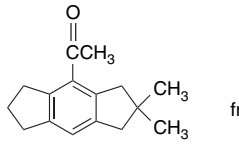
11.12. Suggest a reaction sequence that would permit synthesis of the following aromatic compounds from the starting material indicated on the right.



11.13. Aromatic substitution reactions are key steps in the multistep synthetic sequences that effect the following transformations. Suggest a sequence of reactions that could effect the desire syntheses.



(e)



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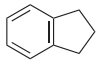
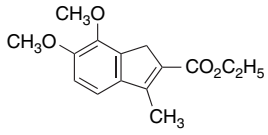


(f)



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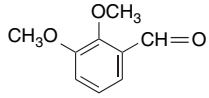
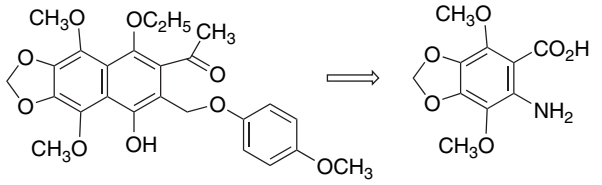
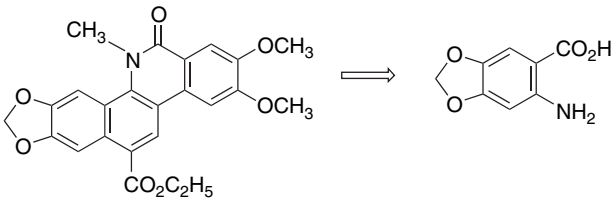


11.14. The following intermediates in the synthesis of naturally occurring materials have been synthesized by reactions based on a benzyne intermediate. The benzyne precursor is shown. By retrosynthetic analysis identify an appropriate co-reactant that would form the desired compound.

a)

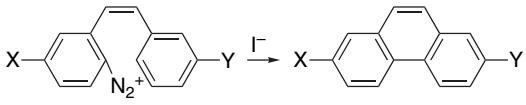


b)



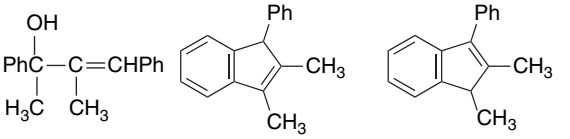
11.15. Aryltrimethylsilanes has been found to be a useful complement to direct thallation in the preparation of arylthallium(III) intermediates. The thallium(III) replaces the silyl substituent and the scope of the reaction is expanded to include some EWGs, such as trifluoromethyl. How does the silyl group function in these systems?

11.16. The Pschorr reaction is a method of synthesis of phenanthrenes from diazotized *Z*-2-aminostilbenes. A traditional procedure involves heating with a copper catalyst. Improved yields are often observed, however, if the diazonium ion is treated with iodide ion. Suggest a mechanism for the iodide-catalyzed reaction.



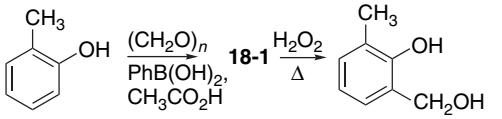
11.17. When compound **17-1** is dissolved in FSO_3H at −78°C, NMR spectroscopy shows that a carbocation is formed. If the solution is then allowed to warm to −10°C, a different ion forms. The first ion gives compound **17-2** when

quenched with base, whereas the second ion gives **17-3**. What are the structures of the two carbocations, and why do they give different products on quenching?

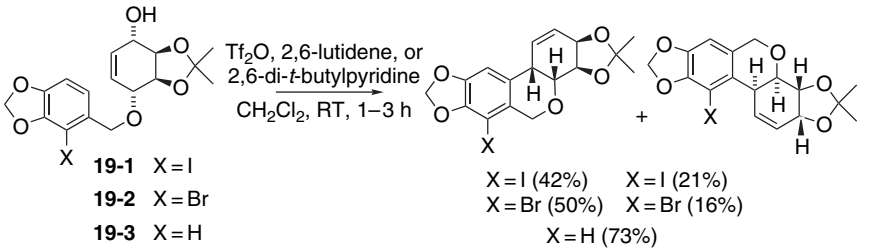


17-1 **17-2** **17-3**

11.18. Various phenols can be selectively hydroxymethylated at the *ortho* position by heating with paraformaldehyde and phenylboronic acid. An intermediate **18-1** having the formula $C_{14}H_{13}O_2B$ for the case shown can be isolated prior to the oxidation. Suggest a structure for the intermediate and comment on its role in the reaction.



11.19. The electrophilic cyclization of **19-1** and **19-2** gives two isomers, but with the unsubstituted reactant **19-3**, only a single stereoisomer is formed. Explain the origin of the isomers and the absence of isomer formation in the case of **19-3.**



19-1 X = I
19-2 X = Br
19-3 X = H

X = I (42%) X = I (21%)
X = Br (50%) X = Br (16%)
X = H (73%)

11.20. Entry 5 in Scheme 11.4 is a step in the synthesis of the anticancer drug tamoxifen. Explain why the 2-phenylbutanoyl group is introduced in preference to a trifluoroacetyl group.