# 13

AROMATIC NUCLEOPHILIC SUBSTITUTION

On p. 341 it was pointed out that nucleophilic substitutions proceed so slowly at an aromatic carbon that the reactions of Chapter 10 are not feasible for aromatic substrates. There are, however, exceptions to this statement, and it is these exceptions that form the subject of this chapter.[1] Reactions that *are* successful at an aromatic substrate are largely of four kinds: (1) reactions activated by electron-withdrawing groups ortho and para to the leaving group; (2) reactions catalyzed by very strong bases and proceeding through aryne intermediates; (3) reactions initiated by electron donors; and (4) reactions in which the nitrogen of a diazonium salt is replaced by a nucleophile. However, not all the reactions discussed in this chapter fit into these categories.

MECHANISMS

There are four principal mechanisms for aromatic nucleophilic substitution.[2] Each of the four is similar to one of the aliphatic nucleophilic substitution mechanisms discussed in Chapter 10.

The SNAr Mechanism

By far the most important mechanism for aromatic nucleophilic substitution consists of two steps:

Step 1

Step 2

1
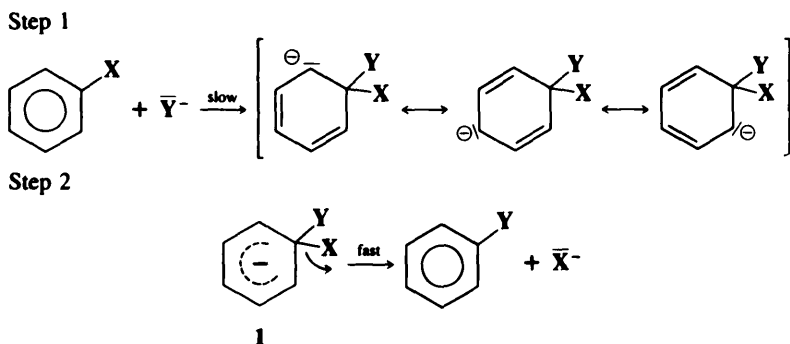
[1]For a review of aromatic nucleophilic substitution, see Zoltewicz *Top. Curr. Chem.* **1975,** *59,* 33-64.

[2]For a monograph on aromatic nucleophilic substitution mechanisms, see Miller *Aromatic Nucleophilic Substitution;* Elsevier: New York, 1968. For reviews, see Bernasconi *Chimia* **1980,** *34,* 1-11, *Acc. Chem. Res.* **1978,** *11,* 147-152; Bunnett *J. Chem. Educ.* **1974,** *51,* 312-315; Ross, in Bamford; Tipper *Comprehensive Chemical Kinetics,* vol. 13; Elsevier: New York, 1972, pp. 407-431; Buck *Angew. Chem. Int. Ed. Engl.* **1969,** *8,* 120-131 [*Angew. Chem. 81,* 136-148]; Buncel; Norris; Russell *Q. Rev., Chem. Soc.* **1968,** *22,* 123-146; Ref. 1.

The first step is usually, but not always, rate-determining. It can be seen that this mechanism greatly resembles the tetrahedral mechanism discussed in Chapter 10 and, in another way, the arenium ion mechanism of electrophilic aromatic substitution. In all three cases, the attacking species forms a bond with the substrate, giving an intermediate, and then the leaving group departs. We refer to this mechanism as the SNAr mechanism.[3] The IUPAC designation is $A_N + D_N$ (the same as for the tetrahedral mechanism; compare the designation $A_E + D_E$ for the arenium ion mechanism). This mechanism is generally found where activating groups are present on the ring (see p. 649).

There is a great deal of evidence for the mechanism; we shall discuss only some of it.[2] Probably the most convincing evidence was the isolation, as long ago as 1902, of the intermediate **2** in the reaction between ethyl picrate and methoxide ion.[4] Intermediates of this
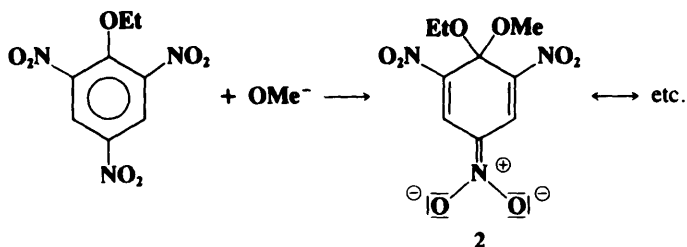
type are stable salts, called *Meisenheimer* or *Meisenheimer–Jackson salts*, and many more have been isolated since 1902.[5] The structures of several of these intermediates have been proved by nmr[6] and by x-ray crystallography.[7] Further evidence comes from studies of the effect of the leaving group on the reaction. If the mechanism were similar to either the SN1 or SN2 mechanisms described in Chapter 10, the Ar—X bond would be broken in the rate-determining step. In the SNAr mechanism this bond is not broken until after the rate-determining step (that is, if step 1 is rate-determining). We would predict from this that if the SNAr mechanism is operating, a change in leaving group should not have much effect on the reaction rate. In the reaction
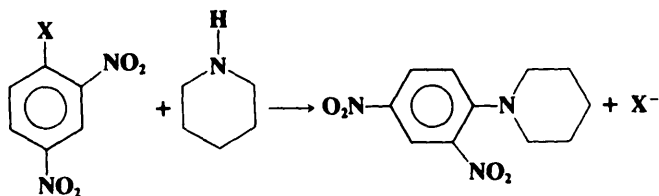
[3]The mechanism has also been called by other names, including the SN2Ar, the addition-elimination, and the intermediate complex mechanism.

[4]Meisenheimer *Liebigs Ann. Chem.* **1902,** *323,* 205. Similar salts were isolated even earlier by Jackson; see Jackson; Gazzolo *Am. Chem. J.* **1900,** *23,* 376; Jackson; Earle *Am. Chem. J.* **1903,** *29,* 89.

[5]For a monograph on Meisenheimer salts and on this mechanism, see Buncel; Crampton; Strauss; Terrier *Electron Deficient Aromatic- and Heteroaromatic-Base Interactions*; Elsevier: New York, 1984. For reviews of structural and other studies, see Illuminati; Stegel *Adv. Heterocycl. Chem.* **1983,** *34,* 305-444; Artamkina; Egorov; Beletskaya *Chem. Rev.* **1982,** *82,* 427-459; Terrier *Chem. Rev.* **1982,** *82,* 77-152; Strauss *Chem. Rev.* **1970,** *70,* 667-712, *Acc. Chem. Res.* **1974,** *7,* 181-188; Hall; Poranski, in Feuer *The Chemistry of the Nitro and Nitroso Groups,* pt. 2; Wiley: New York, 1970, pp. 329-384; Crampton, *Adv. Phys. Org. Chem.* **1969,** *7,* 211-257; Foster; Fyfe *Rev. Pure Appl. Chem.* **1966,** *16,* 61-82.

[6]First done by Crampton; Gold *J. Chem. Soc.* **1964,** 4293, *J. Chem. Soc. B* **1966,** 893. A good review of spectral studies is found in Buncel et al., Ref. 5, pp. 15-133.

[7]Destro; Gramaccioli; Simonetta *Acta Crystallogr.* **1968,** *24,* 1369; Ueda; Sakabe; Tanaka; Furusaki *Bull. Chem. Soc. Jpn.* **1968,** *41,* 2866; Messmer; Palenik *Chem. Commun.* **1969,** 470.

when X was Cl, Br, I, SOPh, SO_2Ph, or *p*-nitrophenoxy, the rates differed only by a factor of about 5.[8] This behavior would not be expected in a reaction in which the Ar—X bond is broken in the rate-determining step. We do not expect the rates to be *identical*, because the nature of X affects the rate at which Y attacks. An increase in the electronegativity of X causes a decrease in the electron density at the site of attack, resulting in a faster attack by a nucleophile. Thus, in the reaction just mentioned, when X = F, the relative rate was 3300 (compared with I = 1). The very fact that fluoro is the best leaving group among the halogens in most aromatic nucleophilic substitutions is good evidence that the mechanism is different from the S_N1 and S_N2 mechanisms, where fluoro is by far the poorest leaving group of the halogens. This is an example of the element effect (p. 336).

The pattern of base catalysis of reactions with amine nucleophiles provides additional evidence. These reactions are catalyzed by bases only when a relatively poor leaving group (such as OR) is present (not Cl or Br) and only when relatively bulky amines are nucleophiles.[9] Bases could not catalyze step 1, but if amines are nucleophiles, bases can catalyze step 2. Base catalysis is found precisely in those cases where the amine moiety cleaves easily

3
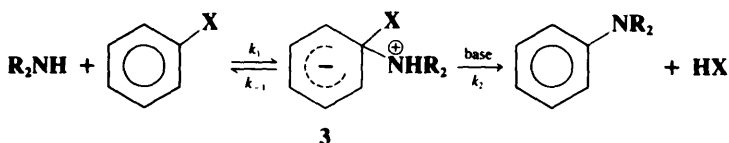
but X does not, so that k_{-1} is large and step 2 is rate-determining. This is evidence for the S_NAr mechanism because it implies two steps. Furthermore, in cases where bases *are* catalysts, they catalyze only at low base concentrations: a plot of the rate against the base concentration shows that small increments of base rapidly increase the rate until a certain concentration of base is reached, after which further base addition no longer greatly affects the rate. This behavior, based on a partitioning effect (see p. 503), is also evidence for the S_NAr mechanism. At low base concentration, each increment of base, by increasing the rate of step 2, increases the fraction of intermediate that goes to product rather than reverting to reactants. At high base concentration the process is virtually complete: there is very little reversion to reactants and the rate becomes dependent on step 1. Just how bases catalyze step 2 has been investigated. For protic solvents two proposals have been presented. One is that step 2 consists of two steps: rate-determining deprotonation of **3** followed by rapid loss of X, and that bases catalyze the reaction by increasing the rate of the deprotonation

3
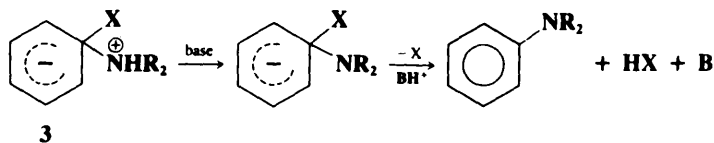
step.[10] According to the other proposal, loss of X assisted by BH^+ is rate-determining.[11] Two mechanisms, both based on kinetic evidence, have been proposed for aprotic solvents

[8]Bunnett; Garbisch; Pruitt *J. Am. Chem. Soc.* **1957**, *79*, 385.
[9]Kirby; Jencks *J. Am. Chem. Soc.* **1965**, *87*, 3217; Bunnett; Garst *J. Am. Chem. Soc.* **1965**, *87*, 3875, 3879, *J. Org. Chem.* **1968**, *33*, 2320; Bunnett; Bernasconi *J. Org. Chem.* **1970**, *35*, 70; Bernasconi; Schmid *J. Org. Chem.* **1967**, *32*, 2953; Bernasconi; Zollinger *Helv. Chim. Acta* **1966**, *49*, 103, **1967**, *50*, 1; Pietra; Vitali *J. Chem. Soc. B* **1968**, 1200; Chiacchiera; Singh; Anunziata; Silber *J. Chem. Soc., Perkin Trans. 2* **1987**, 987.
[10]Bernasconi; de Rossi; Schmid *J. Am. Chem. Soc.* **1977**, *99*, 4090, and references cited therein.
[11]Bunnett; Sekiguchi; Smith *J. Am. Chem. Soc.* **1981**, *103*, 4865, and references cited therein.

such as benzene. In both proposals the ordinary SNAr mechanism operates, but in one the attacking species involves two molecules of the amine (the *dimer mechanism*),[12] while in the other there is a cyclic transition state.[13] Further evidence for the SNAr mechanism has been obtained from $^{18}O/^{16}O$ and $^{15}N/^{14}N$ isotope effects.[14]

Step 1 of the SNAr mechanism has been studied for the reaction between picryl chloride (as well as other substrates) and OH⁻ ions (**3-1**), and spectral evidence has been reported[15] for two intermediates, one a π complex (p. 505), and the other a radical ion–radical pair:

Picryl chloride	π complex	radical ion–radical pair
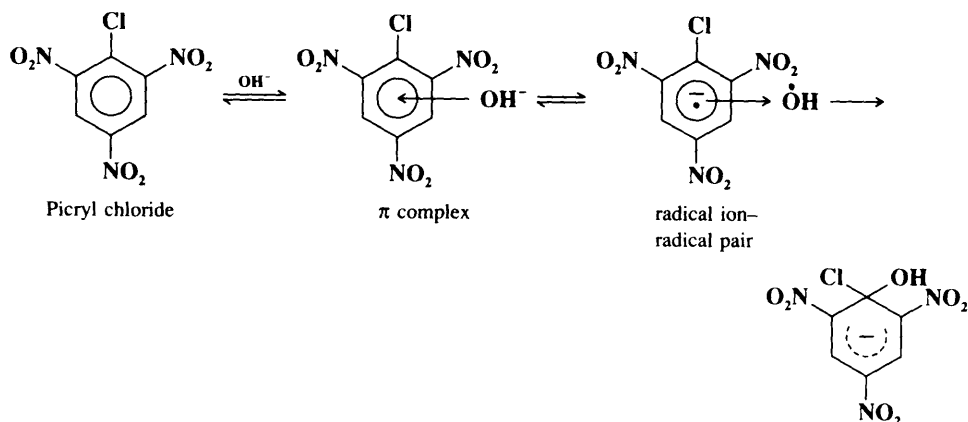
As with the tetrahedral mechanism at an acyl carbon, nucleophilic catalysis (p. 334) has been demonstrated with an aryl substrate, in certain cases.[16]

The SN1 Mechanism

For aryl halides and sulfonates, even active ones, a unimolecular SN1 mechanism (IUPAC: $D_N + A_N$) is very rare; it has only been observed for aryl triflates in which both ortho positions contain bulky groups (t-butyl or SiR_3).[17] It is in reactions with diazonium salts that this mechanism is important:[18]

Step 1

Step 2

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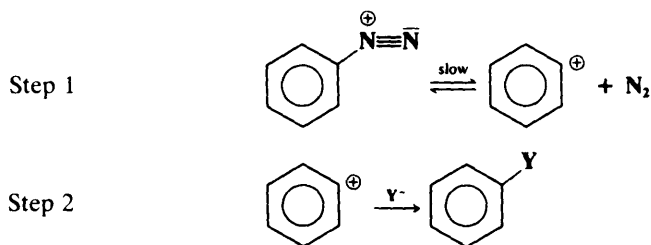
[12]For a review of this mechanism, see Nudelman *J. Phys. Org. Chem.* **1989**, *2*, 1-14. See also Nudelman; Montserrat *J. Chem. Soc., Perkin Trans. 2* **1990**, 1073.

[13]Banjoko; Ezeani *J. Chem. Soc., Perkin Trans. 2* **1986**, 531; Banjoko; Baycroju *J. Chem. Soc., Perkin Trans. 2* **1988**, 1853; Jain; Gupta; Kumar *J. Chem. Soc., Perkin Trans. 2* **1990**, 11.

[14]Hart; Bourns *Tetrahedron Lett.* **1966**, 2995; Ayrey; Wylie *J. Chem. Soc.* B **1970**, 738.

[15]Bacaloglu; Blaskó; Bunton; Dorwin; Ortega; Zucco *J. Am. Chem. Soc.* **1991**, *113*, 238, and references cited therein. For earlier reports, based on kinetic data, of complexes with amine nucleophiles, see Forlani *J. Chem. Res. (S)* **1984**, 260; Hayami; Otani; Yamaguchi; Nishikawa *Chem. Lett.* **1987**, 739; Crampton; Davis; Greenhalgh; Stevens *J. Chem. Soc., Perkin Trans. 2* **1989**, 675.

[16]See Muscio; Rutherford *J. Org. Chem.* **1987**, *52*, 5194.

[17]Himeshima; Kobayashi; Sonoda *J. Am. Chem. Soc.* **1985**, *107*, 5286.

[18]Aryl iodonium salts Ar_2I^+ also undergo substitutions by this mechanism (and by a free-radical mechanism).

Among the evidence for the S_N1 mechanism[19] with aryl cations as intermediates,[20] is the following:[21]

1. The reaction rate is first order in diazonium salt and independent of the concentration of Y.

2. When high concentrations of halide salts are added, the product is an aryl halide but the rate is independent of the concentration of the added salts.

3. The effects of ring substituents on the rate are consistent with a unimolecular rate-determining cleavage.[22]

4. When reactions were run with substrate deuterated in the ortho position, isotope effects of about 1.22 were obtained.[23] It is difficult to account for such high secondary isotope effects in any other way except that an incipient phenyl cation is stabilized by hyperconjugation,[24] which is reduced when hydrogen is replaced by deuterium.

5. That the first step is reversible cleavage[25] was demonstrated by the observation that when $Ar^{15}\overset{\oplus}{N}{\equiv}N$ was the reaction species, recovered starting material contained not only $Ar^{15}\overset{\oplus}{N}{\equiv}N$ but also $Ar\overset{\oplus}{N}{\equiv}^{15}N$.[26] This could arise only if the nitrogen breaks away from the ring and then returns. Additional evidence was obtained by treating $PhN\overset{\oplus}{\equiv}^{15}N$ with unlabeled N_2 at various pressures. At 300 atm the recovered product had lost about 3% of the labeled nitrogen, indicating that $PhN_2{}^+$ was exchanging with atmospheric N_2.[27]

There is kinetic and other evidence[28] that step 1 is more complicated and involves two steps, both reversible:

$$ArN_2{}^+ \rightleftharpoons [Ar^+ \ N_2] \rightleftharpoons Ar^+ + N_2$$
$$\textbf{4}$$

4, which is probably some kind of tight ion–molecule pair, has been trapped with carbon monoxide.[29]

[19]For additional evidence, see Lorand *Tetrahedron Lett.* **1989**, *30*, 7337.

[20]For a review of aryl cations, see Ambroz; Kemp *Chem. Soc. Rev.* **1979**, *8*, 353-365. Also see Ref. 51 in Chapter 5.

[21]For a review, see Zollinger *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 141-150 [*Angew. Chem. 90*, 151-160]. For discussions, see Swain; Sheats; Harbison *J. Am. Chem. Soc.* **1975**, *97*, 783, 796; Burri; Wahl; Zollinger *Helv. Chim. Acta* **1974**, *57*, 2099; Richey; Richey, in Olah; Schleyer *Carbonium Ions*, vol. 2; Wiley: New York, 1970, pp. 922-931; Zollinger *Azo and Diazo Chemistry*; Wiley: New York, 1961, pp. 138-142; Miller, Ref. 2, pp. 29-40.

[22]Lewis; Miller *J. Am. Chem. Soc.* **1953**, *75*, 429.

[23]Swain; Sheats; Gorenstein; Harbison *J. Am. Chem. Soc.* **1975**, *97*, 791.

[24]See Apeloig; Arad *J. Am. Chem. Soc.* **1985**, *107*, 5285.

[25]For discussions, see Williams; Buncel *Isot. Org. Chem.* **1980**, 147-230, pp. 212-221; Zollinger *Pure Appl. Chem.* **1983**, *55*, 401-408.

[26]Lewis; Insole *J. Am. Chem. Soc.* **1964**, *86*, 32; Lewis; Kotcher *Tetrahedron* **1969**, *25*, 4873; Lewis; Holliday *J. Am. Chem. Soc.* **1969**, *91*, 426; Ref. 27; Tröndlin; Medina; Rüchardt *Chem. Ber.* **1979**, *112*, 1835.

[27]Bergstrom; Landells; Wahl; Zollinger *J. Am. Chem. Soc.* **1976**, *98*, 3301.

[28]Maurer; Szele; Zollinger *Helv. Chim. Acta* **1979**, *62*, 1079; Szele; Zollinger *Helv. Chim. Acta* **1981**, *64*, 2728.

[29]Ravenscroft; Skrabal; Weiss; Zollinger *Helv. Chim. Acta* **1988**, *71*, 515.

The Benzyne Mechanism[30]

Some aromatic nucleophilic substitutions are clearly different in character from those that occur by the SnAr mechanism (or the Sn1 mechanism). These substitutions occur on aryl halides that have no activating groups; bases are required that are stronger than those normally used; and most interesting of all, the incoming group does not always take the position vacated by the leaving group. That the latter statement is true was elegantly demonstrated by the reaction of 1-^{14}C-chlorobenzene with potassium amide:
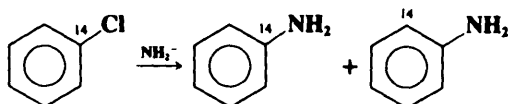
The product consisted of almost equal amounts of aniline labeled in the 1 position and in the 2 position.[31]

A mechanism that can explain all these facts involves elimination followed by addition:

Step 1

Step 2
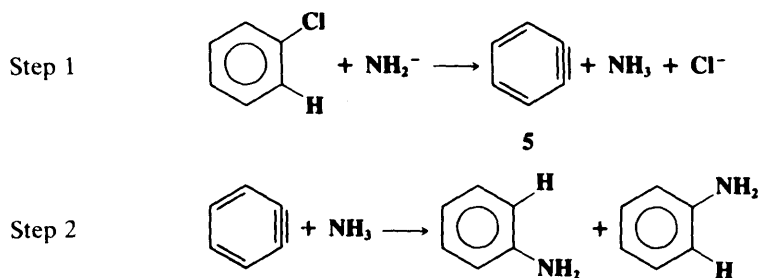
The symmetrical intermediate **5** can be attacked by the NH_3 at either of two positions, which explains why about half of the aniline produced from the radioactive chlorobenzene was labeled at the 2 position. The fact that the 1 and 2 positions were not labeled equally is the result of a small isotope effect. Other evidence for this mechanism is the following:

1. If the aryl halide contains two ortho substituents, the reaction should not be able to occur. This is indeed the case.[31]

2. It had been known many years earlier that aromatic nucleophilic substitution occasionally results in substitution at a different position. This is called *cine substitution* and can
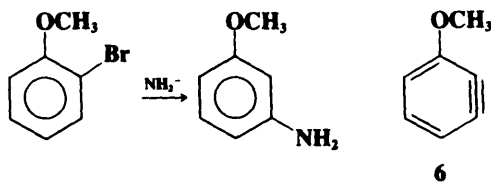
[30]For a monograph, see Hoffmann *Dehydrobenzene and Cycloalkynes*; Academic Press: New York, 1967. For reviews, see Gilchrist, in Patai; Rappoport *The Chemistry of Functional Groups, Supplement C*, pt. 1; Wiley: New York, 1983, pp. 383-419; Bryce; Vernon *Adv. Heterocycl. Chem.* **1981**, *28*, 183-229; Levin *React. Intermed.* (*Wiley*) **1985**, *3*, 1-18, **1981**, *2*, 1-14, **1978**, *1*, 1-26; Nefedov; D'yachenko; Prokof'ev *Russ. Chem. Rev.* **1977**, *46*, 941-966; Fields, in McManus *Organic Reactive Intermediates*; Academic Press: New York, 1973, pp. 449-508; Heaney *Fortschr. Chem. Forsch.* **1970**, *16*, 35-74, *Essays Chem.* **1970**, *1*, 95-115; Hoffmann, in Viehe *Acetylenes*; Marcel Dekker: New York, 1969, pp. 1063-1148; Fields; Meyerson *Adv. Phys. Org. Chem.* **1968**, *6*, 1-61; Wittig *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 731-737 [*Angew. Chem. 77*, 752-759].
[31]Roberts; Semenow; Simmons; Carlsmith *J. Am. Chem. Soc.* **1965**, *78*, 601.

be illustrated by the conversion of *o*-bromoanisole to *m*-aminoanisole.[32] In this particular case, only the meta isomer is formed. The reason a 1:1 mixture is not formed is that the intermediate **6** is not symmetrical and the methoxy group directs the incoming group meta but not ortho (see p. 651). However, not all cine substitutions proceed by this kind of mechanism (see **3-25**).

    3. The fact that the order of halide reactivity is Br > I > Cl > F (when the reaction is performed with KNH_2 in liquid NH_3) shows that the SNAr mechanism is not operating here.[31]

    In the conversion of the substrate to **6,** either proton removal or subsequent loss of halide ion can be rate-determining. In fact, the unusual leaving-group order just mentioned (Br > I > Cl) stems from a change in the rate-determining step. When the leaving group is Br or I, proton removal is rate-determining and the rate order for this step is F > Cl > Br > I. When Cl or F is the leaving group, cleavage of the C—X bond is rate-determining and the order for this step is I > Br > Cl > F. Confirmation of the latter order was found in a direct competitive study. *meta*-Dihalobenzenes in which the two halogens are different were treated with NH_2^-.[33] In such compounds, the most acidic hydrogen is the one between the two halogens; when it leaves, the remaining anion can lose either halogen. Therefore a study of which halogen is preferentially lost provides a direct measure of leaving-group ability. The order was found to be I > Br > Cl.[33]

    Species such as **5** and **6** are called *benzynes* (sometimes *dehydrobenzenes*), or more generally, *arynes*, and the mechanism is known as the *benzyne mechanism*. Benzynes are very reactive. Neither benzyne nor any other aryne has yet been isolated under ordinary conditions,[34] but benzyne has been isolated in an argon matrix at 8 K,[35] where its ir spectrum could be observed. In addition, benzynes can be trapped; e.g., they undergo the Diels–Alder reaction (see **5-47**). It should be noted that the extra pair of electrons does not affect the aromaticity. The original sextet still functions as a closed ring, and the two additional electrons are merely located in a π orbital that covers only two carbons. Benzynes do not have a formal triple bond, since two canonical forms (**A** and **B**) contribute to the hybrid.

        A   **B**
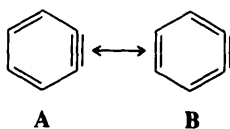
The ir spectrum, mentioned above, indicates that **A** contributes more than **B.** Not only benzene rings but other aromatic rings[36] and even nonaromatic rings (p. 338) can react through this kind of intermediate. Of course, the nonaromatic rings do have a formal triple bond.

   [32]This example is from Gilman; Avakian *J. Am. Chem. Soc.* **1945,** *67,* 349. For a table of many such examples, see Bunnett; Zahler *Chem. Rev.* **1951,** *49,* 273-412, pp. 385-386.

   [33]Bunnett; Kearley *J. Org. Chem.* **1971,** *36,* 184.

   [34]For the measurement of aryne lifetimes in solution, see Gaviña; Luis; Costero; Gil *Tetrahedron* **1986,** *42,* 155.

   [35]Chapman; Mattes; McIntosh; Pacansky; Calder; Orr *J. Am. Chem. Soc.* **1973,** *95,* 6134. For the ir spectrum of pyridyne trapped in a matrix, see Nam; Leroi *J. Am. Chem. Soc.* **1988,** *110,* 4096. For spectra of transient arynes, see Berry; Spokes; Stiles *J. Am. Chem. Soc.* **1962,** *84,* 3570; Brown; Godfrey; Rodler *J. Am. Chem. Soc.* **1986,** *108,* 1296.

   [36]For reviews of *hetarynes* (benzyne intermediates in heterocyclic rings), see van der Plas; Roeterdink, in Patai; Rappoport, Ref. 30, pt. 1, pp. 421-511; Reinecke, *React. Intermed.* (*Plenum*) **1982,** *2,* 367-526. *Tetrahedron* **1982,** *38,* 427-498; den Hertog; van der Plas, in Viehe, Ref. 30, pp. 1149-1197, *Adv. Heterocycl. Chem.* **1971,** *40,* 121-144; Kauffmann; Wirthwein *Angew. Chem. Int. Ed. Engl.* **1971,** *10,* 20-33 [*Angew. Chem. 83,* 21-34]; Kauffmann *Angew. Chem. Int. Ed. Engl.* **1965,** *4,* 543-557 [*Angew. Chem. 77,* 557-571]; Hoffmann, *Dehydrobenzene and Cycloalkynes* Ref. 30, pp. 275-309.
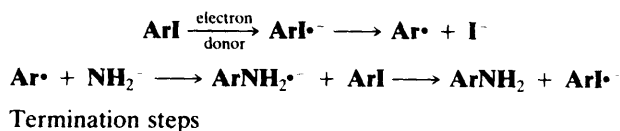
The SRN1 Mechanism

When 5-iodo-1,2,4-trimethylbenzene **7** was treated with KNH_2 in NH_3, **8** and **9** were formed in the ratio 0.63:1. From what we have already seen, the presence of an unactivated substrate,
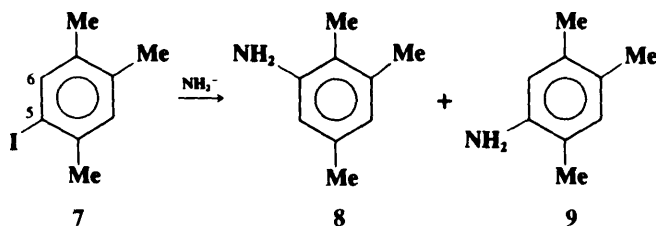
a strong base, and the occurrence of cine along with normal substitution would be strong indications of a benzyne mechanism. Yet if that were so, the 6-iodo isomer of **7** should have given **8** and **9** in the same ratio (because the same aryne intermediate would be formed in both cases), but in this case the ratio of **8** to **9** was 5.9:1 (the chloro and bromo analogs did give the same ratio, 1.46:1, showing that the benzyne mechanism may be taking place there).

To explain the iodo result, it has been proposed[37] that besides the benzyne mechanism, this free-radical mechanism is also operating here:

$$\text{ArI} \xrightarrow[\text{donor}]{\text{electron}} \text{ArI}\cdot^- \longrightarrow \text{Ar}\cdot + \text{I}^-$$

$$\text{Ar}\cdot + \text{NH}_2^- \longrightarrow \text{ArNH}_2\cdot^- + \text{ArI} \longrightarrow \text{ArNH}_2 + \text{ArI}\cdot^-$$

Termination steps

This is called the SRN1 mechanism,[38] and many other examples are known (see **3-4, 3-5, 3-7, 3-14**). The IUPAC designation is $T + D_N + A_N$.[39] Note that the last step of the mechanism produces $\text{ArI}\cdot^-$ radical ions, so the process is a chain mechanism[40] (see p. 678). An electron donor is required to initiate the reaction. In the case above it was solvated electrons from KNH_2 in NH_3. Evidence was that the addition of potassium metal (a good producer of solvated electrons in ammonia) completely suppresssed the cine substitution. Further evidence for the SRN1 mechanism was that addition of radical scavengers (which would suppress a free-radical mechanism) led to **8:9** ratios much closer to 1.46:1. Numerous other observations of SRN1 mechanisms that were stimulated by solvated electrons and inhibited by radical scavengers have also been recorded.[41] Further evidence for the SRN1 mechanism in the case above was that some 1,2,4-trimethylbenzene was found among the products. This could easily be formed by abstraction by Ar• of H from the solvent NH_3. Besides initiation

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[37]Kim; Bunnett *J. Am. Chem. Soc.* **1970**, *92*, 7463, 7464. For an alternative proposal, in which the first step is the same, but the radical ion reacts directly with the nucleophile, see Denney; Denney *Tetrahedron* **1991**, *47*, 6577.

[38]For a monograph, see Rossi; de Rossi *Aromatic Substitution by the SRN1 Mechanism*; American Chemical Society: Washington, 1983. For reviews, see Savéant *Adv. Phys. Org. Chem.* **1990**, *26*, 1-130; Russell *Adv. Phys. Org. Chem.* **1987**, *23*, 271-322; Norris, in Patai; Rappoport *The Chemistry of Functional Groups, Supplement D*, pt. 1; Wiley: New York, 1983, pp. 681-701; Chanon; Tobe *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 1-23 [*Angew. Chem. 94*, 27-49]; Rossi *Acc. Chem. Res.* **1982**, *15*, 164-170; Beletskaya; Drozd *Russ. Chem. Rev.* **1979**, *48*, 431-448; Bunnett; *Acc. Chem. Res.* **1978**, *11*, 413-420; Wolfe; Carver *Org. Prep. Proced. Int.* **1978**, *10*, 225-253. For a review of this mechanism with aliphatic substrates, see Rossi; Pierini; Palacios *Adv. Free Radical Chem. (Greenwich, Conn.)* **1990**, *1*, 193-252.

[39]The symbol T is used for electron transfer.

[40]For a discussion, see Amatore, Pinson; Savéant; Thiébault *J. Am. Chem. Soc.* **1981**, *103*, 6930.

[41]Bunnett, Ref. 38.

by solvated electrons, SRN1 reactions have been initiated photochemically,[42] electrochemically,[43] and even thermally.[44]

SRN1 reactions have a fairly wide scope. There is no requirement for activating groups or strong bases. Alkyl, alkoxy, aryl, and COO$^-$ groups do not interfere, although Me$_2$N, O$^-$, and NO$_2$ groups do interfere. Cine substitution is not found.

Other Mechanisms

There is no clear-cut proof that a one-step SN2 mechanism, so important at a saturated carbon, ever actually occurs with an aromatic substrate. The hypothetical aromatic SN2 process is sometimes called the *one-stage* mechanism to distinguish it from the *two-stage* SNAr mechanism. Some of the reactions in this chapter operate by still other mechanisms, among them an addition–elimination mechanism (see **3-17**).

REACTIVITY

The Effect of Substrate Structure

In the discussion of electrophilic aromatic substitution (Chapter 11) equal attention was paid to the effect of substrate structure on reactivity (activation or deactivation) and on orientation. The question of orientation was important because in a typical substitution there are four or five hydrogens that could serve as leaving groups. This type of question is much less important for aromatic nucleophilic substitution, since in most cases there is only one potential leaving group in a molecule. Therefore attention is largely focused on the reactivity of one molecule compared with another and not on the comparison of the reactivity of different positions within the same molecule.

SNAr mechanism   These substitutions are accelerated by electron-withdrawing groups, especially in positions ortho and para to the leaving group[45] and hindered by electron-donating groups. This is, of course, opposite to the effects of these groups on electrophilic substitutions, and the reasons are similar to those discussed in Chapter 11 (p. 507). Table 13.1 contains a list of groups arranged approximately in order of activating or deactivating ability.[46] Hetero nitrogen atoms are also strongly activating (especially to the α and γ positions) and are even more so when quaternized.[47] Thus 2- and 4-chloropyridine, for example, are often used as substrates. Heterocyclic N-oxides are readily attacked by nucleophiles in the 2 and 4 positions, but the oxygen is generally lost in these reactions.[48] The most highly activating group, N$_2$$^+$, is seldom deliberately used to activate a reaction, but it

[42]For reviews of photochemical aromatic nucleophilic substitutions, see Cornelisse, de Gunst, Havinga *Adv. Phys. Org. Chem.* **1975**, *11*, 225-266; Cornelisse *Pure Appl. Chem.* **1975**, *41*, 433-453; Pietra *Q. Rev. Chem. Soc.* **1969**, *23*, 504-521, pp. 519-521.

[43]For a review, see Savéant *Acc. Chem. Res.* **1980**, *13* 323-329. See also Alam; Amatore; Combellas; Thiébault; Verpeaux *J. Org. Chem.* **1990**, *55*, 6347.
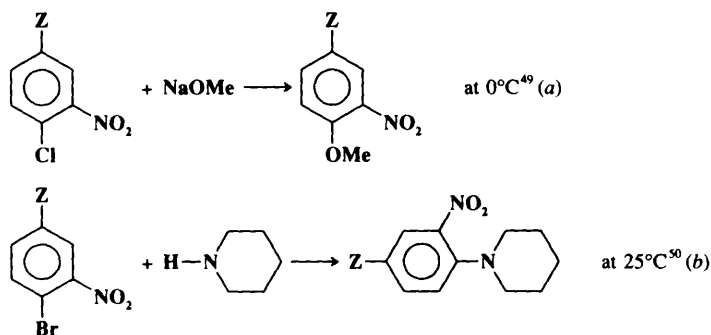
[44]Swartz; Bunnett *J. Org. Chem.* **1979**, *44*, 340, and references cited therein.

[45]The effect of meta substituents has been studied much less, but it has been reported that here too, electron-withdrawing groups increase the rate: See Nurgatin; Sharnin; Ginzburg *J. Org. Chem. USSR* **1983**, *19*, 343.

[46]For additional tables of this kind, see Miller, Ref. 2, pp. 61-136.

[47]For reviews of reactivity of nitrogen-containing heterocycles, see Illuminati *Adv. Heterocycl. Chem.* **1964**, *3*, 285-371; Shepherd; Fedrick *Adv. Heterocycl. Chem.* **1965**, *4*, 145-423.

[48]For reviews, see Albini; Pietra *Heterocyclic N-Oxides*; CRC Press: Boca Raton, FL, 1991, pp. 142-180; Katritzky; Lagowski *Chemistry of the Heterocyclic N-Oxides*; Academic Press: New York, 1971, pp. 258-319, 550-553.

TABLE 13.1 Groups listed in approximate descending order of activating ability in the S$_N$Ar mechanism[46]

For reaction (a) the rates are relative to **H**; for (b) they are relative to **NH$_2$**

	Group Z	Relative rate of reaction	
		(a) H = 1[49]	(b) NH$_2$ = 1[50]
Activates halide exchange at room temperature	N$_2$$^+$		
Activates reaction with strong nucleophiles at room temperature	⟩N$^+$—R (heterocyclic)		
Activate reactions with strong nucleophiles at 80–100°C	NO	5.22×10^6	
	NO$_2$	6.73×10^5	Very fast
	⟩N (heterocyclic)		
With nitro also present, activate reactions with strong nucleophiles at room temperature	SO$_2$Me		
	NMe$_3$$^+$		
	CF$_3$		
	CN	3.81×10^4	
	CHO	2.02×10^4	
With nitro also present, activate reactions with strong nucleophiles at 40–60°C	COR		
	COOH		
	SO$_3$$^-$		
	Br		6.31×10^4
	Cl		4.50×10^4
	I		4.36×10^4
	COO$^-$		2.02×10^4
	H		8.06×10^3
	F		2.10×10^3
	CMe$_3$		1.37×10^3
	Me		1.17×10^3
	OMe		145
	NMe$_2$		9.77
	OH		4.70
	NH$_2$		1

The comments on the left are from Bunnett and Zahler, Ref. 31, p. 308.

[49]Miller; Parker *Aust. J. Chem.* **1958**, *11*, 302.
[50]Berliner; Monack *J. Am. Chem. Soc.* **1952**, *74*, 1574.

sometimes happens that in the diazotization of a compound such as *p*-nitroaniline or *p*-chloroaniline the group para to the diazonium group is replaced by OH from the solvent or by X from ArN_2^+ X^-, to the surprise and chagrin of the investigator, who was trying only to replace the diazonium group and to leave the para group untouched. By far the most common activating group is the nitro group and the most common substrates are 2,4-dinitrophenyl halides and 2,4,6-trinitrophenyl halides (also called picryl halides).[51] Polyfluorobenzenes,[52] e.g., C_6F_6, also undergo aromatic nucleophilic substitution quite well.[53] Benzene rings that lack activating substituents are generally not useful substrates for the SNAr mechanism, because the two extra electrons in **1** are in an antibonding orbital (p. 27). Activating groups, by withrawing electron density, are able to stabilize the intermediates and the transition states leading to them. Reactions taking place by the SNAr mechanism are also accelerated when the aromatic ring is coordinated with a transition metal (e.g., **7** in Chapter 3).[54]

Just as electrophilic aromatic substitutions were found more or less to follow the Hammett relationship (with σ^+ instead of σ; see p. 518), so do nucleophilic substitutions, with σ^- instead of σ for electron-withdrawing groups.[55]

Benzyne mechanism   Two factors affect the positions of the incoming group, the first being the direction in which the aryne forms.[56] When there are groups ortho or para to the leaving group, there is no choice:
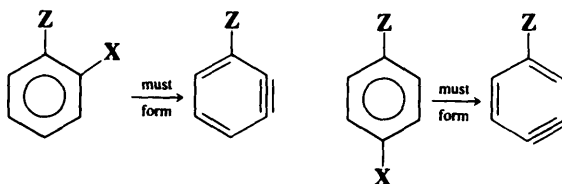
but when a meta group is present, the aryne can form in two different ways:
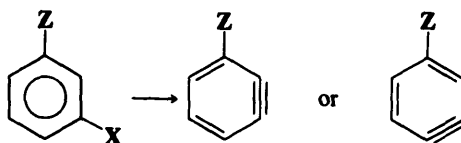
In such cases, the more acidic hydrogen is removed. Since acidity is related to the field effect of Z, it can be stated that an electron-attracting Z favors removal of the ortho hydrogen while an electron-donating Z favors removal of the para hydrogen. The second factor is that the aryne, once formed, can be attacked at two positions. The favored position for nucleophilic attack is the one that leads to the more stable carbanion intermediate, and this

[51]For a review of the activating effect of nitro groups, see de Boer; Dirkx, in Feuer, Ref. 5, pt. 1, pp. 487-612.

[52]Fluorine significantly activates ortho and meta positions, and slightly deactivates (see Table 13.1) para positions: Chambers; Seabury; Williams; Hughes *J. Chem. Soc., Perkin Trans. 1* **1988**, 255.

[53]For reviews, see Yakobson; Vlasov *Synthesis* **1976**, 652-672; Kobrina *Fluorine Chem. Rev.* **1974**, 7, 1-114.

[54]For a review, see Balas; Jhurry; Latxague; Grelier; Morel; Hamdani; Ardoin; Astruc *Bull. Soc. Chim. Fr.* **1990**, 401-426.

[55]For a discussion of linear free-energy relationships in this reaction, see Bartoli; Todesco *Acc. Chem. Res.* **1977**, *10*, 125-132. For a list of σ^- values, see Table 9.4.

[56]This analysis is from Roberts; Vaughan; Carlsmith; Semenow *J. Am. Chem. Soc.* **1956**, 78, 611. For a discussion, see Hoffmann *Dehydrobenzene and Cycloalkynes*, Ref. 30, pp. 134-150.

in turn also depends on the field effect of Z. For $-I$ groups, the more stable carbanion is the one in which the negative charge is closer to the substituent. These principles are illustrated by the reaction of the three dichlorobenzenes with alkali-metal amides. The predicted products are
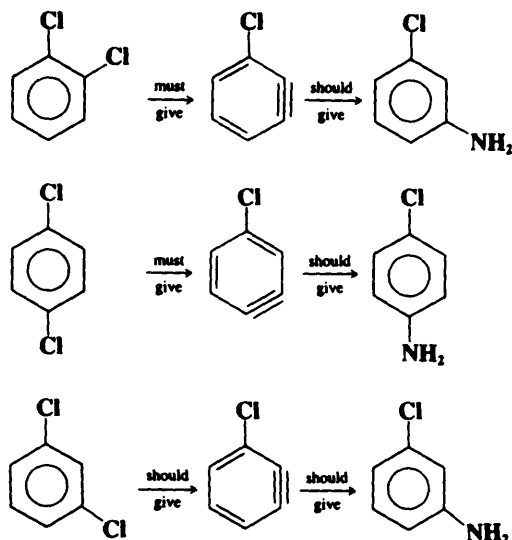
In each case the predicted product was the one chiefly formed.[57] The obtention of *m*-aminoanisole, mentioned on p. 647, is also in accord with these predictions.

The Effect of the Leaving Group[58]

The common leaving groups in aliphatic nucleophilic substitution (halide, sulfate, sulfonate, NR_3^+, etc.) are also common leaving groups in aromatic nucleophilic substitutions, but the groups NO_2, OR, OAr, SO_2R,[59] and SR, which are not generally lost in aliphatic systems, *are* leaving groups when attached to aromatic rings. Surprisingly, NO_2 is a particularly good leaving group.[60] An approximate order of leaving-group ability is[61] $F > NO_2 > OTs > SOPh > Cl, Br, I > N_3 > NR_3^+ > OAr, OR, SR, NH_2$. However, this depends greatly on the nature of the nucleophile, as illustrated by the fact that $C_6Cl_5OCH_3$ treated with NH_2 gives mostly $C_6Cl_5NH_2$; i.e., one methoxy group is replaced in preference to five chlorines.[62] As usual, OH can be a leaving group if it is converted to an inorganic ester. Among the halogens, fluoro is generally a much better leaving group than the other halogens, which have reactivities fairly close together. The order is usually $Cl > Br > I$, but not always.[63]

[57]Wotiz; Huba *J. Org. Chem.* **1959**, *24*, 595. Eighteen other reactions also gave products predicted by these principles. See also Caubere; Lalloz *Bull. Soc. Chim. Fr.* **1974**, 1983, 1989, 1996; Biehl; Razzuk; Jovanovic; Khanapure *J. Org. Chem.* **1986**, *51*, 5157.

[58]For a review, see Miller, Ref. 2, pp. 137-179.

[59]See, for example Furukawa; Ogawa; Kawai; Oae *J. Chem. Soc., Perkin Trans. 1* **1984**, 1839.

[60]For a review, see Beck *Tetrahedron* **1978**, *34*, 2057-2068. See also Effenberger; Koch; Streicher *Chem. Ber.* **1991**, *24*, 163.

[61]Loudon; Shulman *J. Chem. Soc.* **1941**, 772; Suhr *Chem. Ber.* **1963**, 97, 3268.

[62]Kobrina; Yakobson *J. Gen. Chem. USSR* **1963**, *33*, 3238.

[63]Reinheimer; Taylor; Rohrbaugh *J. Am. Chem. Soc.* **1961**, *83*, 835; Ross *J. Am. Chem. Soc.* **1959**, *81*, 2113; Bunnett; Garbisch; Pruitt *J. Am. Chem. Soc.* **1957**, *79*, 385; Parker; Read *J. Chem. Soc.* **1962**, 9, 3149; Litvinenko; Shpan'ko; Korostylev *Doklad. Chem.* **1982**, *266*, 309.

The leaving-group order is quite different from that for the S_N1 or S_N2 mechanisms. The most likely explanation is that the first step of the SNAr mechanism is usually rate determining, and this step is promoted by groups with strong $-I$ effects. This would explain why fluoro and nitro are such good leaving groups when this mechanism is operating. Fluoro is the poorest leaving group of the halogens when the second step of the SNAr mechanism is rate-determining or when the benzyne mechanism is operating. The four halogens, as well as SPh, NMe_3^+, and $OPO(OEt)_2$, have been shown to be leaving groups in the $S_{RN}1$ mechanism.[41] The only important leaving group in the S_N1 mechanism is N_2^+.

The Effect of the Attacking Nucleophile[64]

It is not possible to construct an invariant nucleophilicity order because different substrates and different conditions lead to different orders of nucleophilicity, but an overall approximate order is $NH_2^- > PH_3C^- > PhNH^-$ (aryne mechanism) $> ArS^- > RO^- > R_2NH > ArO^- > OH^- > ArNH_2 > NH_3 > I^- > Br^- > Cl^- > H_2O > ROH$.[65] As with aliphatic nucleophilic substitution, nucleophilicity is generally dependent on base strength and nucleophilicity increases as the attacking atom moves down a column of the periodic table, but there are some surprising exceptions, e.g., OH^-, a stronger base than ArO^-, is a poorer nucleophile.[66] In a series of similar nucleophiles, such as substituted anilines, nucleophilicity *is* correlated with base strength. Oddly, the cyanide ion is not a nucleophile for aromatic systems, except for sulfonic acid salts (**3-12**) and in the von Richter (**3-25**) and Rosenmund–von Braun (**3-11**) reactions, which are special cases.

REACTIONS

In the first part of this section, reactions are classified according to attacking species, with all leaving groups considered together, except for hydrogen and N_2^+, which are treated subsequently. Finally, a few rearrangement reactions are discussed.

All Leaving Groups except Hydrogen and N_2^+

A. Oxygen Nucleophiles

3-1 Hydroxy-de-halogenation

$$ArBr + OH^- \longrightarrow ArOH$$

Aryl halides can be converted to phenols only if activating groups are present or if exceedingly strenuous conditions are employed.[67] Other leaving groups, including nitro,[68] azide, NR_3^+, etc., can also be replaced by OH groups. When the reaction is carried out at high

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[64]For a review, see Miller, Ref. 2, pp. 180-233.

[65]This list is compiled from data in Bunnett; Zahler, Ref. 32, p. 340; Bunnett *Q. Rev. Chem. Soc.* **1958**, *12*, 1-16, p. 13; Sauer; Huisgen *Angew. Chem.* **1960**, *72*, 294-315, p. 311; Bunnett *Annu. Rev. Phys. Chem.* **1963**, *14*, 271-290.

[66]For studies of nucleophilicity in the $S_{RN}1$ mechanism, see Amatore; Combellas; Robveille; Savéant; Thiébault *J. Am. Chem. Soc.* **1986**, *108*, 4754, and references cited therein.

[67]For a review of OH^- and OR^- as nucleophiles in aromatic substitution, see Fyfe, in Patai *The Chemistry of the Hydroxyl Group*, pt. 1; Wiley: New York, 1971, pp. 83-124.

[68]For a convenient way of achieving this conversion, see Knudsen; Snyder *J. Org. Chem.* **1974**, *39*, 3343.

temperatures, cine substitution is observed, indicating a benzyne mechanism.[69] Phenols have been obtained from unactivated aryl halides by treatment with borane and a metal such as lithium, followed by oxidation with alkaline H_2O_2.[70]

OS **I**, 455; **II**, 451; **V**, 632. Also see OS **V**, 918.

**3-2** Replacement of an Amino Group by a Hydroxyl Group
Hydroxy-de-amination
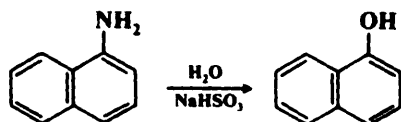
The amino group of naphthylamines can be replaced by a hydroxyl group by treatment with aqueous bisulfite.[71] The scope is greatly limited; the amino group (which may be NH_2 or NHR) must be on a naphthalene ring, with very few exceptions. The reaction is reversible (see **3-7**), and both the forward and reverse reactions are called the *Bucherer reaction*. The mechanism is completely different from any outlined in the first section of this chapter and is discussed at **3-7**.

3-3 Alkali Fusion of Sulfonate Salts
Oxido-de-sulfonato-substitution

$$ArSO_3{}^- \xrightarrow[300-320°C]{NaOH \text{ fus.}} ArO^-$$
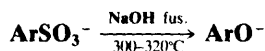
Aryl sulfonic acids can be converted, through their salts, to phenols, by alkali fusion. In spite of the extreme conditions, the reaction gives fairly good yields, except when the substrate contains other groups that are attacked by alkali at the fusion temperatures. Milder conditions can be used when the substrate contains activating groups, but the presence of deactivating groups hinders the reaction. The mechanism is obscure, but a benzyne intermediate has been ruled out by the finding that cine substitution does not occur.[72]

OS **I**, 175; **III**, 288.

3-4 Replacement by OR or OAr
Alkoxy-de-halogenation

$$ArBr + OR^- \longrightarrow ArOR$$

This reaction is similar to **3-1** and, like that one, generally requires activated substrates.[67] With unactivated substrates, side reactions predominate, though aryl methyl ethers have been prepared from unactivated chlorides by treatment with MeO^- in HMPA.[73] This reaction gives better yields than **3-1** and is used more often. A good solvent is liquid ammonia. NaOMe reacted with *o*- and *p*-fluoronitrobenzenes about 10^9 times faster in NH_3 at $-70°C$

[69]The benzyne mechanism for this reaction is also supported by ^{14}C labeling experiments: Bottini; Roberts *J. Am. Chem. Soc.* **1957**, *79*, 1458; Dalman; Neumann *J. Am. Chem. Soc.* **1968**, *90*, 1601.

[70]Pickles; Thorpe *J. Organomet. Chem.* **1974**, *76*, C23.

[71]For reviews, see Seeboth *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 307-317 [*Angew. Chem. 79*, 329-340]; Gilbert *Sulfonation and Related Reactions*; Wiley: New York, 1965, pp. 166-169.

[72]Buzbee *J. Org. Chem.* **1966**, *31*, 3289; Oae; Furukawa; Kise; Kawanishi *Bull. Chem. Soc. Jpn.* **1966**, *39*, 1212.

[73]Shaw; Kunerth; Swanson *J. Org. Chem.* **1976**, *41*, 732; Testaferri; Tiecco; Tingoli; Chianelli; Montanucci *Tetrahedron* **1983**, *39*, 193.

than in MeOH.[74] Phase transfer catalysis has also been used.[75] In addition to halides, leaving groups can be nitro, NR_3^+, other OR, etc., even OH.[76] Acid salts, $RCOO^-$, are sometimes used as nucleophiles. Good yields of aryl benzoates can be obtained by the treatment of aryl halides with cuprous benzoate in diglyme or xylene at 140 to 160°C.[77] Unactivated substrates have been converted to carboxylic esters in low-to-moderate yields under oxidizing conditions.[78] The following chain mechanism, called the $SON2$ mechanism,[79] has been suggested:[78]
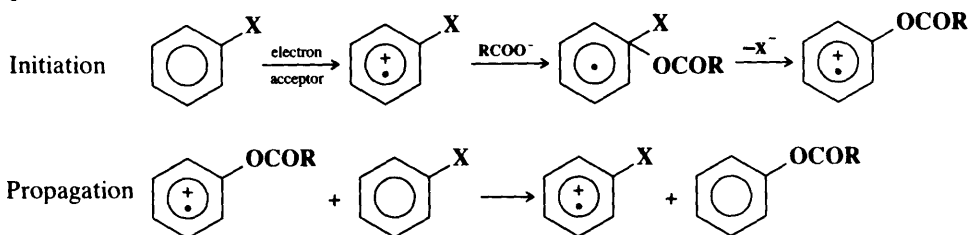
For aroxide nucleophiles, the reaction is promoted by copper salts,[80] and when these are used, activating groups need not be present. This method of preparation of diaryl ethers is called the *Ullmann ether synthesis*[81] and should not be confused with the Ullmann biaryl synthesis (3-16). The reactivity order is typical of nucleophilic substitutions, despite the presence of the copper salts.[82] Because aryloxycopper(I) reagents ArOCu react with aryl halides to give ethers, it has been suggested that they are intermediates in the Ullmann ether synthesis.[83] Indeed, high yields of ethers can be obtained by reaction of ROCu or ArOCu with aryl halides.[84] Unactivated substrates also react with phenoxide ion with electrochemical catalysis in liquid NH_3–Me_2SO, to give diaryl ethers, presumably by the $SRN1$ mechanism.[85] Diaryl ethers can be prepared from activated aryl halides by treatment with triaryl phosphate $(ArO)_3PO$.[86]

OS **I**, 219; **II**, 445; **III**, 293, 566; **V**, 926; **VI**, 150.

B. Sulfur Nucleophiles

3-5   Replacement by SH or SR

$$ArBr + SH^- \longrightarrow ArSH \qquad \textbf{Mercapto-de-halogenation}$$

$$ArBr + SR^- \longrightarrow ArSR \qquad \textbf{Alkylthio-de-halogenation}$$

Aryl thiols and thioethers can be prepared in reactions similar to **3-1** and **3-4**.[87] Activated aryl halides generally give good results, but side reactions are occasionally important. Diaryl

[74]Kizner; Shteingarts *J. Org. Chem. USSR* **1984**, *20*, 991.

[75]Artamanova; Seregina; Shner; Salov; Kokhlova; Zhdamarova *J. Org. Chem. USSR* **1989**, *25*, 554.

[76]Oae; Kiritani *Bull. Chem. Soc. Jpn.* **1964**, *37*, 770, **1966**, *39*, 611.

[77]Cohen; Lewin *J. Am. Chem. Soc.* **1966**, *88*, 4521, Cohen; Wood; Dietz *Tetrahedron Lett.* **1974**, 3555.

[78]Eberson; Jönsson; Wistrand *Tetrahedron* **1982**, *38*, 1087; Jönsson; Wistrand *J. Org. Chem.* **1984**, *49*, 3340.

[79]First proposed by Alder *J. Chem. Soc.*, *Chem. Commun.* **1980**, 1184.

[80]For a review of copper-assisted aromatic nucleophilic substitution, see Lindley *Tetrahedron* **1984**, *40*, 1433-1456.

[81]For a review of the Ullmann ether synthesis, see Moroz; Shvartsberg *Russ. Chem. Rev.* **1974**, *43*, 679-689.

[82]Weingarten *J. Org. Chem.* **1964**, *29*, 977, 3624.

[83]Kawaki; Hashimoto *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1499.

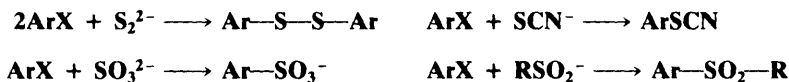[84]Whitesides; Sadowski; Lilburn *J. Am. Chem. Soc.* **1974**, *96*, 2829.

[85]Alam; Amatore; Combellas; Pinson; Savéant; Thiébault; Verpeaux *J. Org. Chem.* **1988**, *53*, 1496.

[86]Ohta; Iwasaki; Akita *Synthesis* **1982**, 828. For other procedures, see Bates; Janda *J. Org. Chem.* **1982**, *47*, 4374; Sammes; Thetford; Voyle *J. Chem. Soc.*, *Perkin Trans. 1* **1988**, 3229.

[87]For a review of sulfur nucleophiles in aromatic substitution, see Peach, in Patai *The Chemistry of the Thiol Group*, pt. 2; Wiley: New York, 1974, pp. 735-744.

sulfides can be prepared by the use of SAr$^-$. Even unactivated aryl halides react with SAr$^-$ if polar aprotic solvents, e.g., DMF,[88] Me$_2$SO,[89] tetraglyme,[90] 1-methyl-2-pyrrolidinone,[91] or HMPA,[92] are used, though the mechanisms are still mostly or entirely nucleophilic substitution. Unactivated aryl halides also give good yields of sulfides on treatment with SAr$^-$ or SR$^-$ in the presence of a catalytic amount of (Ph$_3$P)$_4$Pd.[93] Copper catalysts have also been used.[94] Diaryl sulfides can also be prepared (in high yields) by treatment of unactivated aryl iodides with ArS$^-$ in liquid ammonia under irradiation.[95] The mechanism in this case is probably S$_{RN}$1. The reaction (with unactivated halides) has also been carried out electrolytically, with a nickel complex catalyst.[96]

Other sulfur nucleophiles also react with activated aryl halides:

$$2ArX + S_2^{2-} \longrightarrow Ar\text{—}S\text{—}S\text{—}Ar \qquad ArX + SCN^- \longrightarrow ArSCN$$

$$ArX + SO_3^{2-} \longrightarrow Ar\text{—}SO_3^- \qquad ArX + RSO_2^- \longrightarrow Ar\text{—}SO_2\text{—}R$$

Unactivated thiocyanation has been accomplished with charcoal supported copper (I) thiocyanate.[97]

OS I, 220; III, 86, 239, 667; V, 107, 474; VI, 558, 824. Also see OS V, 977.

C. Nitrogen Nucleophiles

3-6 Replacement by NH$_2$, NHR, or NR$_2$
Amino-de-halogenation

$$ArBr + NH_3 \longrightarrow ArNH_2$$

$$ArBr + RNH_2 \longrightarrow ArNHR$$

$$ArBr + R_2NH \longrightarrow ArNR_2$$
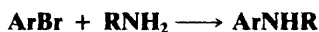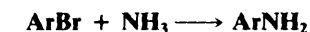
Activated aryl halides react quite well with ammonia and with primary and secondary amines to give the corresponding arylamines. Primary and secondary amines usually give better results than ammonia, with piperidine especially reactive. Picryl chloride (2,4,6-trinitrochlorobenzene) is often used to form amine derivatives. 2,4-Dinitrofluorobenzene is used to tag the amino end of a peptide or protein chain. Other leaving groups in this reaction may be NO$_2$, N$_3$, OSO$_2$R, OR, SR, N=NAr (where Ar contains electron-withdrawing groups)[98] and even NR$_2$.[99] Activated halides can be converted to diethylamino compounds ArX → ArNMe$_2$ by treatment with HMPA.[100]

[88]Campbell *J. Org. Chem.* **1964**, *29*, 1830; Testaferri; Tiecco; Tingoli; Chianelli; Montanucci *Synthesis* **1983**, 751. For the extension of this to selenides, see Tiecco; Testaferri; Tingoli; Chianelli; Montanucci *J. Org. Chem.* **1983**, *48*, 4289.

[89]Bradshaw; South; Hales *J. Org. Chem.* **1972**, *37*, 2381.

[90]Pastor; Hessell *J. Org. Chem.* **1985**, *50*, 4812; Pastor *Helv. Chim. Acta* **1988**, *71*, 859.

[91]Caruso; Colley; Bryant *J. Org. Chem.* **1991**, *56*, 862; Shaw *J. Org. Chem.* **1991**, *56*, 3728.

[92]Cogolli; Maiolo; Testaferri; Tingoli; Tiecco *J. Org. Chem.* **1979**, *44*, 2642. See also Testaferri; Tingoli; Tiecco *Tetrahedron Lett.* **1980**, *21*, 3099; Suzuki; Abe; Osuka *Chem. Lett.* **1980**, 1363.

[93]Migita; Shimizu; Asami; Shiobara; Kato; Kosugi *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1385.

[94]Bowman; Heaney; Smith *Tetrahedron Lett.* **1984**, *25*, 5821; Yamamoto; Sekine *Can. J. Chem.* **1984**, *62*, 1544. For other catalysts, see Cristau; Chabaud; Chêne; Christol *Synthesis* **1981**, 892; Takagi *Chem. Lett.* **1985**, 1307, **1986**, 1379, **1987**, 2221.

[95]Bunnett; Creary *J. Org. Chem.* **1974**, *39*, 3173, 3611.

[96]Meyer; Troupel *J. Organomet. Chem.* **1988**, *354*, 249.

[97]Clark; Jones; Duke; Miller *J. Chem. Soc., Chem. Commun.* **1989**, 81.

[98]Kazankov; Ginodman *J. Org. Chem. USSR* **1975**, *11*, 451.

[99]Sekiguchi; Horie; Suzuki *J. Chem. Soc., Chem. Commun.* **1988**, 698.

[100]See, for example, Gupton; Idoux; Baker; Colon; Crews; Jurss; Rampi *J. Org. Chem.* **1983**, *48*, 2933.

Unactivated aryl halides can be converted to amines by the use of $NaNH_2$, NaNHR, or $NaNR_2$.[101] With these reagents, the benzyne mechanism generally operates, so cine substitution is often found. Ring closure has been effected by this type of reaction,[102] e.g.,
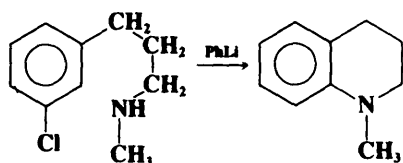

It has also proved possible to close larger rings in this manner: eight- and even twelve-membered. Triarylamines have been prepared in a similar manner from ArI and $Ar_2'NLi$, even with unactivated ArI.[103] In the *Goldberg reaction*, an aryl bromide reacts with an acetanilide in the presence of K_2CO_3 and CuI to give an N-acetyldiarylamine, which can be hydrolyzed to a diarylamine: ArBr + Ar'NHAc → ArAr'NAc.[104]

The reaction with ammonia or amines, which undoubtedly proceeds by the SnAr mechanism, is catalyzed by copper[80] and nickel[105] salts, though these are normally used only with rather unreactive halides.[106] This reaction, with phase transfer catalysis, has been used to synthesize triarylamines.[107] Copper ion catalysts (especially cuprous oxide or iodide) also permit the Gabriel synthesis (0-58) to be applied to aromatic substrates. Aryl bromides or iodides are refluxed with potassium phthalimide and Cu_2O or CuI in dimethylacetamide to give N-aryl phthalimides, which can be hydrolyzed to primary aryl amines.[108]

In certain cases the SRN1 mechanism has been found (p. 648). When the substrate is a heterocyclic aromatic nitrogen compound, still a different mechanism [the SN(ANRORC) mechanism], involving opening and reclosing of the aromatic ring, has been shown to take place.[109]

OS **I**, 544; **II**, 15, 221, 228; **III**, 53, 307, 573; **IV**, 336, 364; **V**, 816, 1067; **VII**, 15.

3-7 Replacement of a Hydroxy Group by an Amino Group
       Amino-de-hydroxylation
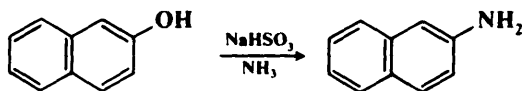
The reaction of naphthols with ammonia and sodium bisulfite is the reverse of **3-2** and has a similar scope.[71] It is also called the *Bucherer reaction*. Primary amines can be used instead

[101]For a review, see Heaney *Chem Rev.* **1962**, 62, 81-97, pp. 83-89.

[102]Huisgen; König; Lepley *Chem. Ber.* **1960**, 93, 1496; Bunnett; Hrutfiord *J. Am. Chem. Soc.* **1961**, 83, 1691. For a review of ring closures by the benzyne mechanism, see Hoffmann *Dehydrobenzene and Cycloalkynes*, Ref. 30, pp. 150-164.

[103]Neunhoeffer; Heitmann *Chem. Ber.* **1961**, 94, 2511.

[104]See Freeman; Butler; Freedman, *J. Org. Chem.* **1978**, 43, 4975; Renger *Synthesis* **1985**, 856.

[105]See Cramer; Coulson *J. Org. Chem.* **1975**, 40, 2267.

[106]For discussions of the mechanism, see Bethell; Jenkins; Quan *J. Chem. Soc., Perkin Trans. 1* **1985**, 1789; Tuong; Hida *J. Chem. Soc., Perkin Trans. 2* **1974**, 676; Kondratov; Shein *J. Org. Chem. USSR* **1979**, 15, 2160; Paine *J. Am. Chem. Soc.* **1987**, 109, 1496.

[107]Gauthier; Fréchet *Synthesis* **1987**, 383.

[108]Bacon; Karim *Chem. Commun.* **1969**, 578, *J. Chem. Soc., Perkin Trans. 1* **1973**, 272, 278; Sato; Ebine; Akabori *Synthesis* **1981**, 472. See also Yamamoto; Kurata *Can. J. Chem.* **1983**, 61, 86.

[109]For reviews, see van der Plas *Tetrahedron* **1985**, 41, 237-281, *Acc. Chem. Res.* **1978**, 11, 462-468.

of ammonia, in which case N-substituted naphthylamines are obtained. In addition, primary naphthylamines can be converted to secondary, by a transamination reaction:

$$ArNH_2 + RNH_2 \xrightarrow{NaHSO_3} ArNHR$$
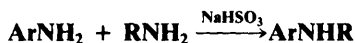
The mechanism of the Bucherer reaction amounts to a kind of overall addition–elimination:[110]
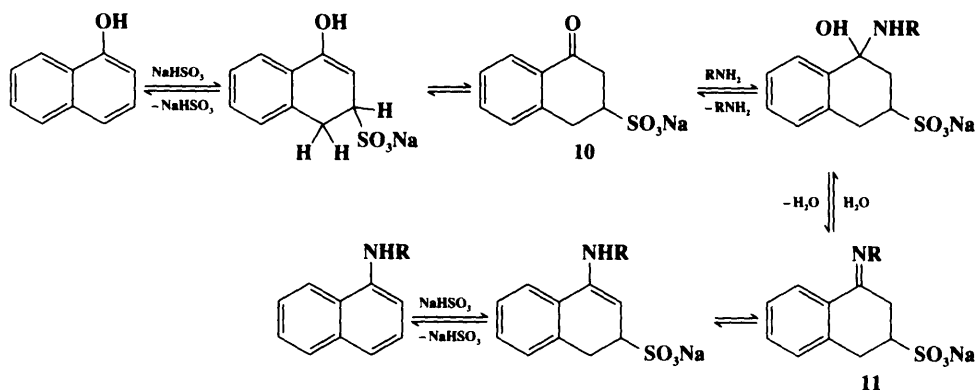
The first step in either direction consists of addition of $NaHSO_3$ to one of the double bonds of the ring, which gives an enol (or enamine) that tautomerizes to the keto (or imine) form. The conversion of **10** to **11** (or vice versa) is an example of **6-14** (or **6-2**). Evidence for this mechanism was the isolation of **10**[111] and the demonstration that for β-naphthol treated with ammonia and HSO_3^-, the rate of the reaction depends only on the substrate and on HSO_3^-, indicating that ammonia is not involved in the rate-determining step.[112] If the starting compound is a β-naphthol, the intermediate is a 2-keto-4-sulfonic acid compound, so the sulfur of the bisulfite in either case attacks meta to the OH or NH_2.[113]

Hydroxy groups on benzene rings can be replaced by NH_2 groups if they are first converted to aryl diethyl phosphates. Treatment of these with KNH_2 and potassium metal in liquid

$$ArOH \xrightarrow[(EtO)_2POCl]{NaOH} ArO\overset{\overset{O}{\|}}{P}(OEt)_2 \xrightarrow[K-NH_3]{KNH_2} ArNH_2$$

ammonia gives the corresponding primary aromatic amines.[114] The mechanism of the second step is SRN1.[115]

OS **III**, 78.

[110]Rieche; Seeboth *Liebigs Ann. Chem.* **1960**, *638*, 66.
[111]Rieche; Seeboth *Liebigs Ann. Chem.* **1960**, *638*, 43, 57.
[112]Kozlov; Veselovskaia *J. Gen. Chem. USSR* **1958**, *28*, 3359.
[113]Rieche; Seeboth *Liebigs Ann. Chem.* **1960**, *638*, 76.
[114]Rossi; Bunnett *J. Org. Chem.* **1972**, *37*, 3570.
[115]For another method of converting phenols to amines, see Scherrer; Beatty *J. Org. Chem.* **1972**, *37*, 1681.

D.   Halogen Nucleophiles

3-8   The Introduction of Halogens
Halo-de-halogenation, etc.

$$Ar—X + X'^- \longrightarrow Ar—X' + X^-$$

It is possible to replace a halogen on a ring by another halogen[116] if the ring is activated.
There is an equilibrium, but it is usually possible to shift this in the desired direction by the
use of an excess of added halide ion.[117] Another common leaving group is nitro, which can
be replaced with chloro by use of NH_4Cl, PCl_5, $SOCl_2$, HCl, Cl_2, or CCl_4. Some of these
reagents operate only at high temperatures and the mechanism is not always nucleophilic
substitution. Activated aromatic nitro compounds can be converted to fluorides with F^-.[118]

A phenolic hydroxy group can be replaced by chloro with PCl_5 or $POCl_3$, but only if
activated. Unactivated phenols give phosphates when treated with $POCl_3$: $3ArOH +
POCl_3 \rightarrow (ArO)_3PO$. Phenols, even unactivated ones, can be converted to aryl bromides
by treatment with Ph_3PBr_2[119] (see **0-66**) and to aryl chlorides by treatment with $PhPCl_4$.[120]

Halide exchange is particularly useful for putting fluorine into a ring, since there are
fewer alternate ways of doing this than for the other halogens. Activated aryl chlorides give
fluorides when treated with KF in DMF, Me_2SO, or dimethyl sulfone.[121] Halide exchange
can also be accomplished with copper halides. Since the leaving-group order in this case is
I > Br > Cl ≫ F (which means that iodides cannot normally be made by this method), the
S_NAr mechanism is probably not operating.[122] However, aryl iodides have been prepared
from bromides, by the use of Cu supported on charcoal or Al_2O_3,[123] and by treatment with
excess KI and a nickel catalyst.[124]

OS **III**, 194, 272, 475; **V**, 142, 478; **67**, 20.

E.   Hydrogen as Nucleophile

3-9   Reduction of Phenols and Phenolic Esters and Ethers[125]
Hydro-de-hydroxylation or **Dehydroxylation**, etc.

$$ArOH \xrightarrow{\text{Zn}} ArH$$
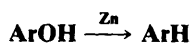
[116]For a list of reagents, with references, see Larock *Comprehensive Organic Transformations*; VCH: New York,
1989, p. 340.
[117]Sauer; Huisgen *Angew. Chem.* **1960**, *72*, 294-315, p. 297.
[118]Attiná; Cacace; Wolf *J. Chem. Soc. Chem. Commun.* **1983**, 108; Clark; Smith *Tetrahedron Lett.* **1985**, *26*, 2233;
Suzuki; Yazawa; Yoshida; Furusawa; Kimura *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2010; Effenberger; Streicher *Chem.
Ber.* **1991**, *124*, 157.
[119]Wiley; Hershkowitz; Rein; Chung *J. Am. Chem. Soc.* **1964**, *86*, 964; Wiley; Rein; Hershkowitz *Tetrahedron
Lett.* **1964**, 2509; Schaefer; Higgins *J. Org. Chem.* **1967**, *32*, 1607.
[120]Bay; Bak; Timony; Leone-Bay *J. Org. Chem.* **1990**, *55*, 3415.
[121]Starr; Finger *Chem. Ind. (London)* **1962**, 1328; Shiley; Dickerson; Finger *J. Fluorine Chem.* **1972**, *2*, 19; Kimura;
Suzuki *Tetrahedron Lett.* **1989**, *30*, 1271. For the use of phase transfer catalysis in this reaction, see Yoshida; Kimura
Chem. Lett. **1988**, 1355. For a review of the preparation of aryl fluorides by halogen exchange, see Dolby-Glover
Chem. Ind. (London) **1986**, 518-523.
[122]Bacon; Hill *J. Chem. Soc.* **1964**, 1097, 1108. See also Nefedov; Tarygina; Kryuchkova; Ryabokobylko *J. Org.
Chem. USSR* **1981**, *17*, 487; Suzuki; Kondo; Ogawa *Chem. Lett.* **1985**, 411; Liedholm; Nilsson *Acta Chem. Scand.,
Ser. B* **1988**, *42*, 289; Clark; Jones; Duke; Miller *J. Chem. Res. (S)* **1989**, 238.
[123]Clark; Jones *J. Chem. Soc., Chem. Commun.* **1987**, 1409.
[124]Yang; Li; Cheng *J. Org. Chem.* **1987**, *52*, 691.
[125]For a list of reagents, with references, see Ref. 116, pp. 27-31ff.

Phenols can be reduced by distillation over zinc dust or with HI and red phosphorus, but these methods are quite poor and are seldom feasible. Catalytic hydrogenation has also been used, but the corresponding cyclohexanol (see **5-10**) is a side product.[126]

Much better results have been obtained by conversion of phenols to certain esters or ethers and reduction of the latter:

$$ArOSO_2CF_3 \xrightarrow[\substack{Pd(OAc)_2,\ Ph_3P \\ DMF}]{HCOOH,\ Et_3N} ArH \qquad\qquad Ref.\ 127$$

$$ArOTs + NH_2NH_2 \xrightarrow{Pd} ArH \qquad\qquad Ref.\ 128$$

$$\overset{\displaystyle O}{\underset{\displaystyle \|}{}}$$
$$ArO\!-\!P(OEt)_2 \xrightarrow[THF]{Tl} ArH \qquad\qquad Ref.\ 129$$

$$Ar\!-\!O\!-\!\underset{\underset{Ph}{N}}{\overset{N-N}{\underset{N-N}{\diagdown\diagup}}} \xrightarrow[Pd\text{-}C]{H_2} ArH \qquad\qquad Ref.\ 130$$

12

12 are prepared by treatment of phenols with 1-phenyl-5-chlorotetrazole in acetone containing K_2CO_3.

OS **VI**, 150. See also OS **VII**, 476.

3-10 Reduction of Halides and Nitro Compounds

The reaction ArX → ArH is treated in Chapter 11 (reaction **1-42**), although, depending on reagent and conditions, it can be nucleophilic or free-radical substitution, as well as electrophilic.

The nitro group of aromatic nitro compounds has been removed with sodium borohydride.[131] This reaction involves an addition–elimination mechanism.

F. Carbon Nucleophiles[131a]

Some formations of new aryl–carbon bonds formed from aryl substrates have been considered in Chapter 10 (see **0-87, 0-95, 0-102, 0-103**).

3-11 The Rosenmund–von Braun Reaction
Cyano-de-halogenation

$$ArBr + \text{anhydrous } CuCN \xrightarrow{200°C} ArCN$$
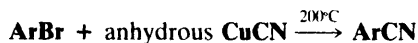
[126]Shuikin; Erivanskaya *Russ. Chem. Rev.* **1960**, *29*, 309-320, pp. 313-315. See also Bagnell; Jeffery *Aust. J. Chem.* **1981**, *34*, 697.

[127]Cacchi; Ciattini; Morera; Ortar *Tetrahedron Lett.* **1986**, *27*, 5541. See also Peterson; Kunng; McCallum; Wulff *Tetrahedron Lett.* **1987**, *28*, 1381; Chen; He *Synthesis* **1988**, 896; Cabri; De Bernardinis; Francalanci; Penco *J. Org. Chem.* **1990**, *55*, 350.

[128]Kenner; Murray *J. Chem. Soc.* **1949**, S178; Rottendorf; Sternhell *Aust. J. Chem.* **1963**, *16*, 647.

[129]Welch; Walters *J. Org. Chem.* **1978**, *43*, 4797. See also Rossi; Bunnett *J. Org. Chem.* **1973**, *38*, 2314.

[130]Musliner; Gates *J. Am. Chem. Soc.* **1966**, *88*, 4271; Hussey; Johnstone; Entwistle *Tetrahedron* **1982**, *38*, 3775; Johnstone; Price *J. Chem. Soc., Chem. Commun.* **1984**, 845. For related methods, see Pailer; Gössinger *Monatsh. Chem.* **1969**, *100*, 1613; van Muijlwijk; Kieboom; van Bekkum *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 204.

[131]Severin; Schmitz; Temme *Chem. Ber.* **1963**, *96*, 2499; Kniel *Helv. Chim. Acta* **1968**, *51*, 371. For another method, see Ono; Tamura; Kaji *J. Am. Chem. Soc.* **1983**, *105*, 4017.

[131a]For a review of many of these reactions, see Artamkina; Kovalenko; Beletskaya; Reutov *Russ. Chem. Rev.* **1990**, *59*, 750-777.

The reaction between aryl halides and cuprous cyanide is called the *Rosenmund–von Braun reaction*.[132] Reactivity is in the order I > Br > Cl > F, indicating that the SNAr mechanism does not apply.[133] Other cyanides, e.g., KCN and NaCN, do not react with aryl halides, even activated ones. However, alkali cyanides do convert aryl halides to nitriles[134] in dipolar aprotic solvents in the presence of Pd(II) salts[135] or copper[136] or nickel[137] complexes. A nickel complex also catalyzes the reaction between aryl triflates and KCN to give aryl nitriles.[138] Aromatic ethers ArOR[139] and some nitro compounds $ArNO_2$[140] have been photochemically converted to ArCN.

OS **III**, 212, 631.

3-12   Cyanide Fusion of Sulfonate Salts
Cyano-de-sulfonato-substitution

$$ArSO_3^- \xrightarrow{\text{NaCN fus.}} ArCN$$
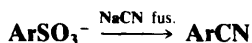
This reaction is very similar to **3-3.** Yields are usually low.

3-13   Coupling of Organometallic Compounds with Aryl Halides, Ethers, and Carboxylic Esters
Alkyl-de-halogenation, etc.

$$ArI + R_2CuLi \longrightarrow ArR$$

Aryl iodides, which need not be activated, couple with lithium dialkylcopper reagents. The reaction is discussed at **0-87.** Aryl halides, even when activated, generally do not couple with Grignard reagents, though certain transition-metal catalysts do effect this reaction in variable yields.[141] The reaction with Grignard reagents proceeds better when OR can be the leaving group, providing that activating groups are present in the ring. The oxazoline group actives *o*-methoxy and *o*-fluoro groups to reaction with Grignard reagents and organolithiums; the product can be hydrolyzed after coupling[142] (see **0-98**):
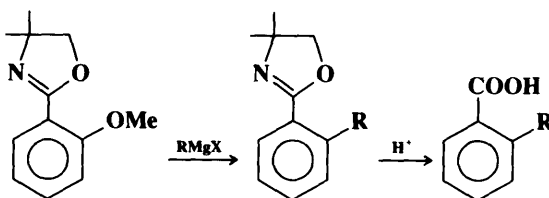
[132]For a review of cyano-de-halogenation, see Ellis; Romney-Alexander *Chem. Rev.* **1987**, *87*, 779-794.
[133]For discussions of the mechanism, see Couture; Paine *Can. J. Chem.* **1985**, *63*, 111; Connor; Leeming; Price *J. Chem. Soc.*, *Perkin Trans. 1* **1990**; 1127.
[134]For a list of reagents that convert aryl halides to cyanides, with references, see Ref. 116, pp. 861-862.
[135]Takagi; Okamoto; Sakakibara; Ohno; Oka; Hayama *Bull Chem. Soc. Jpn.* **1975**, *48*, 3298, **1976**, *49*, 3177. See also Sekiya; Ishikawa *Chem. Lett.* **1975**, 277; Takagi; Sasaki; Sakakibara *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1118.
[136]Connor; Gibson; Price *J. Chem. Soc.*, *Perkin Trans. 1* **1987**, 619.
[137]Cassar; Foà; Montanari; Marinelli *J. Organomet. Chem.* **1979**, *173*, 335; Sakakibara; Okuda; Shimobayashi; Kirino; Sakai; Uchino; Takagi *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1985.
[138]Chambers; Widdowson *J. Chem. Soc.*, *Perkin Trans. 1* **1989**, 1365; Takagi; Sakakibara *Chem. Lett.* **1989**, 1957.
[139]Letsinger; Colb *J. Am. Chem. Soc.* **1972**, *94*, 3665.
[140]See, for example, Vink; Verheijdt; Cornelisse; Havinga *Tetrahedron* **1972**, *28*, 5081.
[141]See, for example, Sekiya; Ishikawa *J. Organomet. Chem.* **1976**, *118*, 349, **1977**, *125*, 281; Negishi; Matsushita; Kobayashi; Rand *Tetrahedron Lett.* **1983**, *24*, 3823; Tiecco; Testaferri; Tingoli; Chianelli; Wenkert *Tertrahedron Lett.* **1982**, *23*, 4629; Eapen; Dua; Tamborski *J. Org. Chem.* **1984**, *49*, 478; Bell; Hu; Patel *J. Org. Chem.* **1987**, *52*, 3847; Bumagin; Andryukhova; Beletskaya *Doklad. Chem.* **1987**, *297*, 524; Ozawa; Kurihara; Fujimori; Hidaka; Toyoshima; Yamamoto *Organometallics* **1989**, *8*, 180.
[142]For a review of oxazolines in aromatic substitutions, see Reuman; Meyers *Tetrahedron* **1985**, *41*, 837-860. For the similar use of oxazoles, see Cram; Bryant; Doxsee *Chem. Lett.* **1987**, 19.

Unactivated aryl halides couple with alkyllithium reagents in THF[143] and with organotin compounds and a Pd complex catalyst[144] to give moderate-to-good yields of alkyl arenes. Unactivated aryl triflates[145] $ArOSO_2CF_3$ react to give ArR in good yields when treated with $R_2Cu(CN) Li_2$,[146] with RZnX,[147] with R_3Al,[148] or with R_3SnR and a Pd complex catalyst.[149] The coupling reaction between aryl halides and alkenes, with a Pd catalyst, is treated at **4-20**.

Unactivated aryl halides react with copper acetylides to give good yields of arylacetylenes (*Stephens–Castro coupling*).[150]

$$ArI + RC{\equiv}CCu \longrightarrow ArC{\equiv}CR$$

R many be alkyl or aryl. A wide variety of aryl iodides has been used and the reaction is of considerable synthetic importance.

Unactivated aryl iodides undergo the conversion $ArI \to ArCH_3$ when treated with tris(diethylamino)sulfonium difluorotrimethylsilicate and a palladium catalyst.[151] A number of methods, all catalyzed by palladium complexes, have been used to prepare unsymmetrical biaryls (see also **3-16**). In these methods, aryl bromides or iodides are coupled with aryl Grignard reagents,[152] with arylboronic acids $ArB(OH)_2$,[153] with aryltin compounds Ar-SnR_3,[154] and with arylmercury compounds.[155] Unsymmetrical binaphthyls were synthesized by photochemically stimulated reaction of naphthyl iodides with naphthoxide ions in an $S_{RN}1$ reaction.[156] Grignard reagents also couple with aryl halides without a palladium catalyst, by the benzyne mechanism.[157]

OS **VI**, 916; **65**, 108; **66**, 67.

3-14   Arylation at a Carbon Containing Active Hydrogen
Bis(ethoxycarbonyl)methyl-de-halogenation, etc.

$$ArBr + Z{-}\overset{\ominus}{C}H{-}Z' \longrightarrow Z{-}\underset{\underset{Ar}{|}}{C}H{-}Z'$$
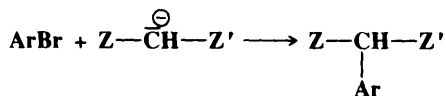
[143]Merrill; Negishi *J. Org. Chem.* **1974**, *39*, 3452. For another method, see Hallberg; Westerlund *Chem. Lett.* **1982**, 1993.

[144]Bumagin; Bumagina; Beletskaya *Doklad. Chem.* **1984**, *274*, 39; Bumagin; Ponomarev; Beletskaya *J. Org. Chem. USSR* **1987**, *23*, 1215, 1222; Kosugi; Sumiya; Ohhashi; Sano; Migita *Chem. Lett.* **1985**, 997; McKean; Parrinello; Renaldo; Stille *J. Org. Chem.* **1987**, *52*, 422.

[145]For another coupling reaction of aryl triflates, see Aoki; Fujimura; Nakamura; Kuwajima *J. Am. Chem. Soc.* **1988**, *110*, 3296.

[146]McMurry; Mohanraj *Tetrahedron Lett.* **1983**, *24*, 2723.

[147]Chen; He *Tetrahedron Lett.* **1987**, *28*, 2387.

[148]Hirota; Isobe; Maki *J. Chem. Soc., Perkin Trans. 1* **1989**, 2513.

[149]Echevarren; Stille *J. Am. Chem. Soc.* **1987**, *109*, 5478. For a similar reaction with aryl fluorosulfonates, see Roth; Fuller *J. Org. Chem.* **1991**, *56*, 3493.

[150]Castro; Stephens *J. Org. Chem.* **1963**, *28*, 2163; Stephens; Castro *J. Org. Chem.* **1963**, *28*, 3313; Sladkov; Ukhin; Korshak *Bull. Acad. Sci. USSR., Div. Chem. Sci.* **1963**, 2043. For a review, see Sladkov; Gol'ding *Russ. Chem. Rev.* **1979**, *48*, 868-896. For an improved procedure, see Bumagin; Kalinovskii; Ponomarov; Beletskaya *Doklad. Chem.* **1982**, *265*, 262.

[151]Hatanaka; Hiyama *Tetrahedron Lett.* **1988**, *29*, 97.

[152]Widdowson; Zhang *Tetrahedron* **1986**, *42*, 2111. See also Ikoma; Taya; Ozaki; Higuchi; Naoi; Fuji-i *Synthesis* **1990**, 147.

[153]Miyaura; Yanagi; Suzuki *Synth. Commun.* **1981**, *11*, 513; Miller; Dugar *Organometallics* **1984**, *3*, 1261; Sharp; Cheng; Snieckus *Tetrahedron Lett.* **1987**, *28*, 5093; Cheng; Snieckus *Tetrahedron Lett.* **1987**, *28*, 5097.

[154]Bailey *Tetrahedron Lett.* **1986**, *27*, 4407.

[155]Bumagin; More; Beletskaya *J. Organomet. Chem.* **1989**, *364*, 231.

[156]Beugelmans; Bois-Choussy; Tang *Tetrahedron Lett.* **1988**, *29*, 1705. For other preparations of biaryls via $S_{RN}1$ processes, see Alam; Amatore; Combellas; Thiébault; Verpeaux *Tetrahedron Lett.* **1987**, *28*, 6171; Picrini; Baumgartner; Rossi *Tetrahedron Lett.* **1988**, *29*, 3429.
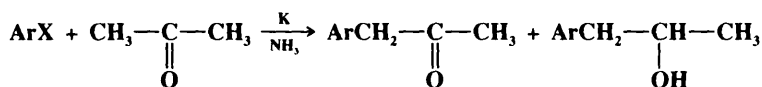
[157]Du; Hart; Ng *J. Org. Chem.* **1986**, *51*, 3162.

The arylation of compounds of the form ZCH$_2$Z' is analogous to **0-94**, and Z is as defined there. Activated aryl halides generally give good results.[158] Even unactivated aryl halides can be employed if the reaction is carried out in the presence of a strong base such as NaNH$_2$[159] or lithium diisopropylamide (LDA). Compounds of the form ZCH$_2$Z' and even simple ketones[160] and carboxylic esters have been arylated in this manner. The reaction with unactivated halides proceeds by the benzyne mechanism and represents a method for extending the malonic ester (and similar) syntheses to aromatic compounds. The base performs two functions: it removes a proton from ZCH$_2$Z' and catalyzes the benzyne mechanism. The reaction has been used for ring closure:[161]
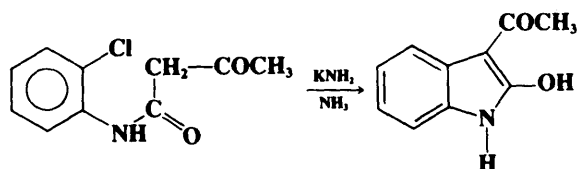
The reaction on unactivated halides can also be done with copper halide catalysts[80] (the *Hurtley reaction*),[162] and with palladium complex catalysts.[163]

Compounds of the form CH$_3$Z can be arylated by treatment with an aryl halide in liquid ammonia containing Na or K, e.g.,[164]

$$ArX + CH_3{-}\underset{\overset{\|}{O}}{C}{-}CH_3 \xrightarrow[NH_3]{K} ArCH_2{-}\underset{\overset{\|}{O}}{C}{-}CH_3 + ArCH_2{-}\underset{\overset{|}{OH}}{CH}{-}CH_3$$

The same products are obtained (though in different proportions) when Na or K is omitted but the solution is irradiated with near-uv-light.[165] In either case other leaving groups can be used instead of halogens (e.g., NR$_3$$^+$, SAr) and the mechanism is the S$_{RN}$1 mechanism. Iron(II) salts have also been used to initiate this reaction.[166] The reaction can also take place without an added initiator: Enolate ions of ketones react with PhI in the dark.[167] In this case, it has been suggested[167] that intiation takes place by

$$R_2C{=}\underset{\overset{|}{O_-}}{C}{-}R + ArI \longrightarrow R_2\overset{\bullet}{C}{-}\underset{\overset{\|}{O}}{C}{-}R + ArI\cdot^-$$

[158] There is evidence for both S$_N$Ar (see Leffek; Matinopoulos-Scordou *Can. J. Chem.* **1977**, *55*, 2656, 2664) and S$_{RN}$1 (see Zhang; Yang; Liu; Chen; Cheng *Res. Chem. Intermed.* **1989**, *11*, 281) mechanisms.

[159] Leake; Levine *J. Am. Chem. Soc.* **1959**, *81*, 1169, 1627.

[160] For example, see Caubere; Guillaumet *Bull. Soc. Chim. Fr.* **1972**, 4643, 4649.

[161] Bunnett; Hrutfiord *J. Am. Chem. Soc.* **1961**, *83*, 1691; Bunnett; Kato; Flynn; Skorcz *J. Org. Chem.* **1963**, *28*, 1. For reviews, see Biehl; Khanapure *Acc. Chem. Res.* **1989**, *22*, 275-281; Hoffmann, Ref. 102, pp. 150-164. See also Kessar, *Acc. Chem. Res.* **1978**, *11*, 283-288.

[162] For discussions and procedures, see Bruggink; McKillop, *Tetrahedron* **1975**, *31*, 2607; McKillop; Rao *Synthesis* **1977**, 759; Setsune; Matsukawa; Wakemoto; Kitao *Chem. Lett.* **1981**, 367; Osuka; Kobayashi; Suzuki *Synthesis* **1983**, 67; Suzuki; Kobayashi; Yoshida; Osuka *Chem. Lett.* **1983**, 193; Aalten; van Koten; Vrieze; van der Kerk-van Hoof *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 46.

[163] Uno; Seto; Ueda; Masuda; Takahashi *Synthesis* **1985**, 506.

[164] Rossi; Bunnett *J. Am. Chem. Soc.* **1972**, *94*, 683, *J. Org. Chem.* **1973**, *38*, 3020; Bunnett; Gloor *J. Org. Chem.* **1973**, *38*, 4156, **1974**, *39*, 382.

[165] Rossi; Bunnett *J. Org. Chem.* **1973**, *38*, 1407; Hay; Hudlicky; Wolfe *J. Am. Chem. Soc.* **1975**, *97*, 374; Bunnett; Sundberg *J. Org. Chem.* **1976**, *41*, 1702; Rajan; Muralimohan *Tetrahedron Lett.* **1978**, 483; Rossi; de Rossi; Picrini *J. Org. Chem.* **1979**, *44*, 2662; Rossi; Alonso *J. Org. Chem.* **1980**, *45*, 1239; Beugelmans *Bull. Soc. Chim. Belg.* **1984**, *93*, 547.

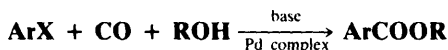[166] Galli; Bunnett *J. Org. Chem.* **1984**, *49*, 3041.

[167] Scamehorn; Bunnett *J. Org. Chem.* **1977**, *42*, 1449; Scamehorn; Hardacre; Lukanich; Sharpe *J. Org. Chem.* **1984**, *49*, 4881.

This is an SET mechanism (see p. 307). The photostimulated reaction has also been used for ring closure.[168] In certain instances of the intermolecular reaction there is evidence that the leaving group exerts an influence on the product ratios, even when it has already departed at the time that product selection takes place.[169] Malonic and β-keto esters can be arylated in high yields by treatment with aryllead tricarboxylates: RCOCHR'COOEt + ArPb(OAc)$_3$ → RCOCArR'COOEt,[170] and with triphenylbismuth carbonate[171] Ph$_3$BiCO$_3$ and other bismuth reagents.[172] In a related process, manganese(III) acetate was used to convert a mixture of ArH and ZCH$_2$Z' to ArCHZZ'.[173]

OS **V**, 12, 263; **VI**, 36, 873, 928; **VII**, 229.

3-15 Conversion of Aryl Substrates to Carboxylic Acids, Their Derivatives, Aldehydes, and Ketones[174]
Alkoxycarbonyl-de-halogenation, etc.

$$\text{ArX + CO + ROH} \xrightarrow[\text{Pd complex}]{\text{base}} \text{ArCOOR}$$

Aryl bromides and iodides, when treated with carbon monoxide, an alcohol ROH, a base, and a palladium complex catalyst, give carboxylic esters. The use of H$_2$O, RNH$_2$, or an alkali metal or calcium carboxylate[175] instead of ROH, gives the carboxylic acid,[175a] amide,[176] or mixed anhydride, respectively.[177] With certain palladium catalysts, aryl chlorides[178] and aryl triflates[179] can also be substrates. Other reagents used (instead of CO) have been nickel carbonyl Ni(CO)$_4$[180] (see **0-103**) and dicobalt octacarbonyl Co$_2$(CO)$_8$.[181] Aryl chlorides have been converted to carboxylic acids by an electrochemical synthesis,[182] and aryl iodides to aldehydes by treatment with CO, Bu$_3$SnH, and NCCMe$_2$N=NCMe$_2$CN (AIBN).[183]

Lead tetraacetate has been used to convert phenols, with a hydrazone group in the ortho position, to carboxylic esters,[184] e.g.,

[168]See Semmelhack; Bargar *J. Am. Chem. Soc.* **1980**, *102*, 7765; Bard; Bunnett *J. Org. Chem.* **1980**, *45*, 1546.
[169]Bard; Bunnett; Creary; Tremelling *J. Am. Chem. Soc.* **1980**, *102*, 2852; Tremelling; Bunnett *J. Am. Chem. Soc.* **1980**, *102*, 7375.
[170]Pinhey; Rowe *Aust. J. Chem.* **1980**, *33*, 113; Kopinski; Pinhey; Rowe *Aust. J. Chem.* **1984**, *37*, 1245; Kozyrod; Morgan, Pinhey *Aust. J. Chem.* **1991**, *44*, 369.
[171]For a review of these and related reactions, see Abramovitch; Barton; Finet *Tetrahedron* **1988**, *44*, 3039-3071.
[172]Barton; Blazejewski; Charpiot; Finet; Motherwell; Papoula; Stanforth *J. Chem. Soc., Perkin Trans. 1* **1985**, 2667; O'Donnell; Bennett; Jacobsen; Ma *Tetrahedron Lett.* **1989**, *30*, 3913.
[173]Citterio; Santi; Fiorani; Strologo *J. Org. Chem.* **1989**, *54*, 2703; Citterio; Fancelli; Finzi; Pesce; Santi *J. Org. Chem.* **1989**, *54*, 2713.
[174]For a review, see Weil; Cassar; Foà, in Wender; Pino *Organic Synthesis Via Metal Carbonyls*, vol. 2; Wiley: New York, 1977, pp. 517-543.
[175]Pri-Bar; Alper *J. Org. Chem.* **1989**, *54*, 36.
[175a]For example, see Bumagin; Nikitin; Beletskaya *Doklad. Chem.* **1990**, *312*, 149.
[176]For another reagent that also gives amides, see Bumagin; Gulevich; Beletskaya *J. Organomet. Chem.* **1985**, *285*, 415.
[177]For a review, see Heck *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985, pp. 348-358.
[178]Ben-David; Portnoy; Milstein *J. Am. Chem. Soc.* **1989**, *111*, 8742.
[179]Cacchi; Ciattini; Morera; Ortar *Tetrahedron Lett.* **1986**, *27*, 3931.
[180]Bauld *Tetrahedron Lett.* **1963**, 1841. See also Corey; Hegedus *J. Am. Chem. Soc.* **1969**, *91*, 1233; Nakayama; Mizoroki *Bull. Chem. Soc. Jpn.* **1971**, *44*, 508.
[181]Brunet; Sidot; Caubere *Tetrahedron Lett.* **1981**, *22*, 1013. *J. Org. Chem.* **1983**, *48*, 1166. See also Foà; Francalanci; Bencini; Gardano *J. Organomet. Chem.* **1985**, *285*, 293; Kudo; Shibata; Kashimura; Mori; Sugita *Chem. Lett.* **1987**, 577.
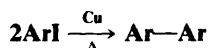[182]Heintz; Sock; Saboureau; Périchon *Tetrahedron* **1988**, *44*, 1631.
[183]Ryu; Kusano; Masumi; Yamazaki; Ogawa; Sonoda *Tetrahedron Lett.* **1990**, *31*, 6887.
[184]Katritzky; Kotali *Tetrahedron Lett.* **1990**, *31*, 6781.

The hydrazone group is hydrolyzed (6-2) during the course of the reaction. Yields are high. Aryl iodides are converted to unsymmetrical diaryl ketones on treatment with arylmercury halides and nickel carbonyl: $ArI + Ar'HgX + Ni(CO)_4 \rightarrow ArCOAr'$.[185]

3-16   The Ullmann Reaction
De-halogen-coupling

$$2ArI \xrightarrow[\Delta]{Cu} Ar—Ar$$

The coupling of aryl halides with copper is called the *Ullmann reaction*.[186] The reaction is of broad scope and has been used to prepare many symmetrical and unsymmetrical biaryls.[187] When a mixture of two different aryl halides is used, there are three possible products, but often only one is obtained. For example, picryl chloride and iodobenzene gave only 2,4,6-trinitrobiphenyl.[188] The best leaving group is iodo, and the reaction is most often done on aryl iodides, but bromides, chlorides, and even thiocyanates have been used.

The effects of other groups on the ring are ususual. The nitro group is strongly activating, but only in the ortho (not meta or para) position.[189] R and OR are active in all positions. Not only do OH, NH_2, NHR, and NHCOR inhibit the reaction, as would be expected for aromatic nucleophilic substitution, but so do COOH (but not COOR), SO_2NH_2, and similar groups for which the reaction fails completely. These groups inhibit the coupling reaction by causing side reactions.

The mechanism is not known with certainty. It seems likely that it is basically a two-step process, similar to that of the Wurtz reaction (0-86), which can be represented schematically by:

Step 1 $ArI + Cu \longrightarrow ArCu$
Step 2 $ArCu + ArI \longrightarrow ArAr$

Organocopper compounds have been trapped by coordination with organic bases.[190] In addition, arylcopper compounds (ArCu) have been independently prepared and shown to give biaryls (ArAr') when treated with aryl iodides Ar'I.[191]

A similar reaction has been used for ring closure:[192]

[185]Rhee; Ryang; Watanabe; Omura; Murai; Sonoda *Synthesis* **1977**, 776. For other acylation reactions, see Tanaka; *Synthesis* **1981**, 47. *Bull Chem. Soc. Jpn.* **1981**, *54*, 637; Bumagin; Ponomaryov; Beletskaya *Tetrahedron Lett.* **1985**, *26*, 4819; Koga; Makinouchi; Okukado *Chem. Lett.* **1988**, 1141; Echavarren; Stille *J. Am. Chem. Soc.* **1988**, *110*, 1557.
[186]For reviews, see Fanta *Synthesis* **1974**, 9-21; Goshaev; Otroshchenko; Sadykov *Russ. Chem. Rev.* **1972**, *41*, 1046-1059.
[187]For reviews of methods of aryl–aryl bond formation, see Bringmann; Walter; Weirich *Angew. Chem. Int. Ed. Engl.* **1990**, *29*. 977-991 [*Angew. Chem. 102*, 1006-1019]; Sainsbury *Tetrahedron* **1980**, *36*, 3327-3359.
[188]Rule; Smith *J. Chem. Soc.* **1937**, 1096.
[189]Forrest *J. Chem. Soc.* **1960**, 592.
[190]Lewin; Cohen *Tetrahedron Lett.* **1965**, 4531.
[191]For examples, see Nilsson *Tetrahedron Lett.* **1966**, 675; Cairncross; Sheppard *J. Am. Chem. Soc.* **1968**, *90*, 2186; Ullenius *Acta Chem. Scand.* **1972**, *26*, 3383; Mack; Suschitzky; Wakefield *J. Chem. Soc., Perkin Trans. 1* **1980**, 1682.
[192]Salfeld; Baume *Tetrahedron Lett.* **1966**, 3365; Lothrop *J. Am. Chem. Soc.* **1941**, *63*, 1187.

An important alternative to the Ullmann method is the use of certain nickel complexes.[193] This method has also been used intramolecularly.[194] Aryl halides ArX can also be converted to Ar—Ar[195] by treatment with activated Ni metal,[196] with Zn and nickel complexes,[197] with aqueous alkaline sodium formate, Pd–C, and a phase transfer catalyst,[198] and in an electrochemical process catalyzed by a nickel complex.[199]
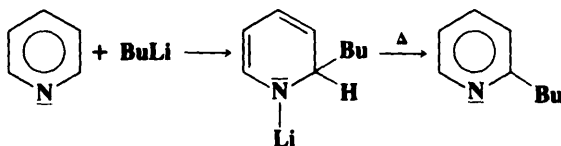
For other methods of coupling aromatic rings, see **3-13, 3-17, 4-18, 4-21,** and **4-22.**
OS III, 339; **V,** 1120.

Hydrogen as Leaving Group[200]

3-17   Alkylation and Arylation
Alkylation or **Alkyl-de-hydrogenation**, etc.

The alkylation of heterocyclic nitrogen compounds[201] with alkyllithiums is called *Ziegler alkylation*. Aryllithiums give arylation. The reaction occurs by an addition–elimination mechanism and the adduct can be isolated.[202] Upon heating of the adduct, elimination of LiH occurs (see **7-16**) and an alkylated product is obtained. With respect to the 2-carbon the first step is the same as that of the SNAr mechanism. The difference is that the unshared pair of electrons on the nitrogen combines with the lithium, so the extra pair of ring electrons has a place to go: it becomes the new unshared pair on the nitrogen.

The reaction has been applied to nonheterocyclic aromatic compounds: Benzene, naphthalene, and phenanthrene have been alkylated with alkyllithiums, though the usual reaction with these reagents is **2-21,**[203] and Grignard reagents have been used to alkylate naphthalene.[204] The addition–elimination mechanism apparently applies in these cases too.

Aromatic nitro compounds can be methylated with dimethyloxosulfonium methylide[205] or the methylsulfinyl carbanion (obtained by treatment of dimethyl sulfoxide with a strong base):[206]

[193]See. for example Semmelhack; Helquist; Jones *J. Am. Chem. Soc.* **1971,** *93,* 5908; Clark; Norman; Thomas *J. Chem. Soc., Perkin Trans. 1* **1975,** 121; Tsou; Kochi *J. Am. Chem. Soc.* **1979,** *101,* 7547; Colon; Kelsey *J. Org. Chem.* **1986,** *51,* 2627; Lourak; Vanderesse; Fort; Caubere *J. Org. Chem.* **1989,** *54,* 4840. 4844; Iyoda; Otsuka; Sato; Nisato; Oda *Bull. Chem. Soc. Jpn.* **1990,** *63,* 80. For a review of the mechanism. see Amatore; Jutand *Acta Chem. Scand.* **1990,** *44,* 755-764.
[194]See for example, Karimipour; Semones; Asleson; Heldrich *Synlett* **1990,** 525.
[195]For a list of reagents, with references, see Ref. 116, pp. 46-47.
[196]Inaba; Matsumoto; Rieke *Tetrahedron Lett.* **1982,** *23,* 4215; Matsumoto; Inaba; Rieke *J. Org. Chem.* **1983,** *48,* 840; Chao; Cheng; Chang *J. Org. Chem.* **1983,** *48,* 4904.
[197]Takagi; Hayama; Sasaki *Bull. Chem. Soc. Jpn.* **1984,** *57,* 1887.
[198]Bamfield; Quan *Synthesis* **1978,** 537.
[199]Meyer; Rollin; Perichon *J. Organomet. Chem.* **1987,** *333,* 263.
[200]For a review. see Chupakhin; Postovskii *Russ. Chem. Rev.* **1976,** *45,* 454-468. For a review of reactivity and mechanism in these cases. see Chupakhin; Charushin; van der Plas *Tetrahedron* **1988,** *44,* 1-34.
[201]For a review of substitution by carbon groups on a nitrogen heterocycle, see Vorbrüggen; Maas *Heterocycles* **1988,** *27,* 2659-2776. For a related review, see Comins; O'Connor *Adv. Heterocycl. Chem.* **1988,** *44,* 199-267.
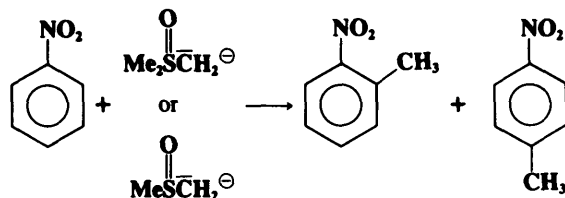[202]See. for example, Armstrong; Mulvey; Barr; Snaith; Reed *J. Organomet. Chem.* **1988,** *350,* 191.
[203]Dixon; Fishman *J. Am. Chem. Soc.* **1963,** *85,* 1356; Eppley; Dixon *J. Am. Chem. Soc.* **1968,** *90,*1606.
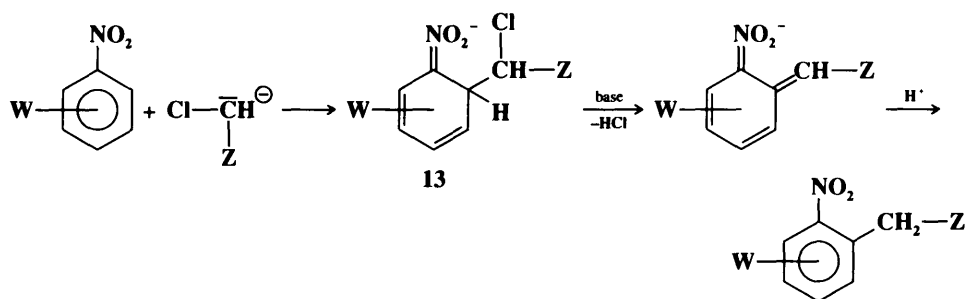[204]Bryce-Smith; Wakefield *Tetrahedron Lett.* **1964,** 3295.
[205]Traynelis; McSweeney *J. Org. Chem.* **1966,** *31,* 243.
[206]Russell; Weiner *J. Org. Chem.* **1966,** *31,* 248.

The latter reagent also methylates certain heterocyclic compounds, e.g., quinoline, and certain fused aromatic compounds, e.g., anthracene, phenanthrene.[207] The reactions with the sulfur carbanions are especially useful, since none of these substrates can be methylated by the Friedel–Crafts procedure (1-12). It has been reported[208] that aromatic nitro compounds can also be alkylated, not only with methyl but with other alkyl and substituted alkyl groups as well, in ortho and para positions, by treatment with an alkyllithium compound (or, with lower yields, a Grignard reagent), followed by an oxidizing agent such as Br_2 or DDQ (p. 1163). Trinitrobenzene was alkylated (ArH → ArR) by treatment with a silane $RSiMe_3$ in the presence of KF and a crown ether.[209] In this reaction, R was not a simple alkyl group, but a group such as CH_2COOMe, $COMe$, CH_2Ph, $CH_2CH=CH_2$, etc.

A different kind of alkylation of nitro compounds uses carbanion nucleophiles that have a chlorine at the carbanionic carbon. The following process takes place:[210]

13

This type of process is called *vicarious nucleophilic substitution of hydrogen*.[211] Z is an electron-withdrawing group such as SO_2R, SO_2OR, SO_2NR_2, $COOR$, or CN; it stabilizes the negative charge. The carbanion attacks the activated ring ortho or para to the nitro group. Hydride ion H^- is not normally a leaving group, but in this case the presence of the adjacent Cl allows the hydrogen to be replaced. Hence, Cl is a "vicarious" leaving group. Other leaving groups have been used, e.g., OMe, SPh, but Cl is generally the best. Many groups W in ortho, meta, or para positions do not interfere. The reaction is also successful for di- and trinitro compounds, for nitronaphthalenes,[212] and for many nitro heterocycles.

$Z—\overset{\ominus}{C}R—Cl$ may also be used.[213] When Br_3C^- or Cl_3C^- is the nucleophile the product is $ArCHX_2$, which can easily be hydrolyzed to ArCHO.[214] This is therefore an indirect way

[207]Ref. 206; Argabright; Hofmann; Schriesheim *J. Org. Chem.* **1965**, *30*, 3233; Trost *Tetrahedron Lett.* **1966**, 5761; Yamamoto; Nisimura; Nozaki *Bull. Chem. Soc. Jpn.* **1971**, *44*, 541.

[208]Kienzle *Helv. Chim. Acta* **1978**, *61*, 449.

[209]Artamkina; Kovalenko; Beletskaya; Reutov *J. Organomet. Chem.* **1987**, *329*, 139, *J. Org. Chem. USSR* **1990**, *26*, 801. See also RajanBabu; Reddy; Fukunaga *J. Am. Chem. Soc.* **1985**, *107*, 5473.

[210]In some cases intermediate **13** has been isolated: Stahly; Stahly; Maloney *J. Org. Chem.* **1988**, *53*, 690.

[211]Goliński; Mąkosza *Tetrahedron Lett.* **1978**, 3495. For reviews, see Mąkosza *Synthesis* **1991**, 103-111, *Russ. Chem. Rev.* **1989**, *58*, 747-757; Mąkosza; Winiarski *Acc. Chem. Res.* **1987**, *20*, 282-289.

[212]Mąkosza; Danikiewicz; Wojciechowski *Liebigs Ann. Chem.* **1987**, 711.
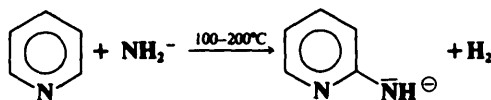
[213]See Mudryk; Mąkosza *Tetrahedron* **1988**, *44*, 209.

[214]Mąkosza; Owczarczyk *J. Org. Chem.* **1989**, *54*, 5094. See also Mąkosza; Winiarski *Chem. Lett.* **1984**, 1623.
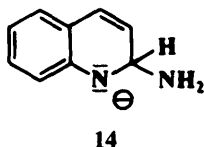
of formylating an aromatic ring containing one or more NO_2 groups, which cannot be done by any of the formylations mentioned in Chapter 11 (**1-16** to **1-18**).

For the introduction of CH_2SR groups into phenols, see **1-26**. See also **4-23**.

OS **II**, 517.

3-18 Amination of Nitrogen Heterocycles
Amination or Amino-de-hydrogenation

Pyridine and other heterocyclic nitrogen compounds can be aminated with alkali-metal amides in a process called the *Chichibabin reaction*.[215] The attack is always in the 2 position unless both such positions are filled, in which case the 4 position is attacked. Substituted alkali-metal amides, e.g., RNH^- and R_2N^-, have also been used. The mechanism is probably similar to that of **3-17**. The existence of intermediate ions such as **14**

14

(from quinoline) has been demonstrated by nmr spectra.[216] A pyridyne type of intermediate was ruled out by several observations including the facts that 3-ethylpyridine gave 2-amino-3-ethylpyridine[217] and that certain heterocycles that cannot form an aryne could nevertheless be successfully aminated. Nitro compounds do not give this reaction,[218] but they have been aminated (ArH → $ArNH_2$ or ArNHR) via the vicarious substitution principle (see **3-17**), using 4-amino- or 4-alkylamino-1,2,4-triazoles as nucleophiles.[219] The vicarious leaving group in this case is the triazole ring.

Analogous reactions have been carried out with hydrazide ions, R_2NNH^-.[220] For other methods of aminating aromatic rings, see **1-6** and **3-19**.

There are no *Organic Syntheses* references, but see OS **V**, 977, for a related reaction.

3-19 Amination by Hydroxylamine
Amination or Amino-de-hydrogenation

[215]For reviews, see Vorbrüggen *Adv. Heterocycl. Chem.* **1990**, *49*, 117-192; McGill; Rappa *Adv. Heterocycl. Chem.* **1988**, *44*, 1-79; Pozharskii; Simonov; Doron'kin *Russ. Chem. Rev.* **1978**, *47*, 1042-1060.

[216]Zoltewicz; Helmick; Oestreich; King; Kandetzki *J. Org. Chem.* **1973**, *38*, 1947; Woźniak; Baránski; Nowak; van der Plas *J. Org. Chem.* **1987**, *52*, 5643.
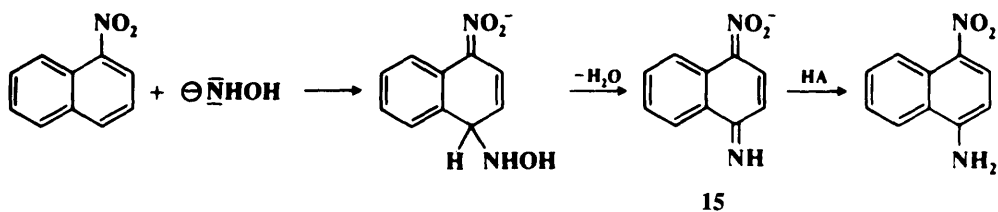
[217]Ban; Wakamatsu *Chem. Ind. (London)* **1964**, 710.

[218]See, for example, Levitt; Levitt *Chem. Ind. (London)* **1975**, 520.

[219]Katritzky; Laurenzo *J. Org. Chem.* **1986**, *51*, 5039, **1988**, *53*, 3978.

[220]Kauffmann; Hansen; Kosel; Schoeneck *Liebigs Ann. Chem.* **1962**, *656*, 103.

Activated aromatic compounds can be directly aminated with hydroxylamine in the presence of strong bases.[221] Conditions are mild and yields are high. Ions of the type **15** are intermediates:
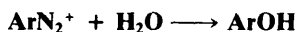

OS **III**, 664.

N_2^+ as Leaving Group

The diazonium group can be replaced by a number of groups.[222] Some of these are nucleophilic substitutions, with SN1 mechanisms (p. 644), but others are free-radical reactions and are treated in Chapter 14. The solvent in all these reactions is usually water. With other solvents it has beeen shown that the SN1 mechanism is favored by solvents of low nucleophilicity, while those of high nucleophilicity favor free-radical mechanisms.[223] (For *formation* of diazonium ions, see **2-49.**) The N_2^+ group can be replaced by Cl⁻, Br⁻, and CN⁻, by a nucleophilic mechanism (see OS **IV**, 182), but the Sandmeyer reaction is much more useful (**4-25** and **4-28**). As mentioned on p. 651 it must be kept in mind that the N_2^+ group can activate the removal of another group on the ring.

3-20   Hydroxy-de-diazoniation

$$ArN_2^+ + H_2O \longrightarrow ArOH$$

Water is usually present whenever diazonium salts are made, but at these temperatures (0 to 5°C) the reaction proceeds very slowly. When it is *desired* to have OH replace the diazonium group, the excess nitrous acid is destroyed and the solution is usually boiled. Some diazonium salts require even more vigorous treatment, e.g., boiling with aqueous sulfuric acid or with trifluoroacetic acid containing potassium trifluoroacetate.[224] The reaction can be performed on solutions of any diazonium salts, but hydrogen sulfates are preferred to chlorides or nitrates, since in these cases there is competition from the nucleophiles Cl⁻ or NO_3^-. A better method, which is faster, avoids side reactions, takes place at room temperature, and gives higher yields consists of adding Cu_2O to a dilute solution of the diazonium salt dissolved in a solution containing a large excess of $Cu(NO_3)_2$.[225] Aryl radicals are intermediates when this method is used. It has been shown that aryl radicals are at least partly involved when ordinary hydroxy-de-diazoniation is carried out in weakly alkaline

[221]See Chupakhin; Postovskii, Ref. 200, p. 456.
[222]For a review of such reactions, see Wulfman, in Patai *The Chemistry of Diazonium and Diazo Groups*, pt. 1; Wiley: New York, 1978, pp. 286-297.
[223]Szele; Zollinger *Helv. Chim. Acta* **1978**, *61*, 1721.
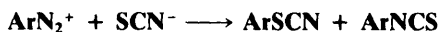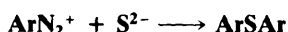[224]Horning; Ross; Muchowski *Can. J. Chem.* **1973**, *51*, 2347.
[225]Cohen; Dietz; Miser *J. Org. Chem.* **1977**, *42*, 2053.

aqueous solution.[226] Decomposition of arenediazonium tetrafluoroborates in F_3CSO_2OH gives aryl triflates directly, in high yields.[226a]

OS **I**, 404; **III**, 130, 453, 564; **V**, 1130.
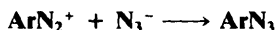
3-21   Replacement by Sulfur-Containing Groups
Mercapto-de-diazoniation, etc.

$$ArN_2^+ + HS^- \longrightarrow ArSH$$

$$ArN_2^+ + S^{2-} \longrightarrow ArSAr$$

$$ArN_2^+ + RS^- \longrightarrow ArSR$$

$$ArN_2^+ + SCN^- \longrightarrow ArSCN + ArNCS$$

These reactions are convenient methods for putting sulfur-containing groups onto an aromatic ring. With Ar'S⁻, diazosulfides Ar—N=N—S—Ar' are intermediates,[227] which can in some cases be isolated.[228] Thiophenols can be made as shown above, but more often the diazonium ion is treated with EtO—CSS⁻ or S_2^{2-}, which give the expected products, and these are easily convertible to thiophenols. See also **4-27**.

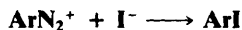OS **II**, 580; **III**, 809 (but see OS **V**, 1050). Also see OS **II**, 238.

3-22   Azido-de-diazoniation

$$ArN_2^+ + N_3^- \longrightarrow ArN_3$$

Diazonium salts can be converted to aryl azides by the addition of sodium azide to the acidic diazonium salt solution.[229]

OS **IV**, 75; **V**, 829.

3-23   Iodo-de-diazoniation

$$ArN_2^+ + I^- \longrightarrow ArI$$

One of the best methods for the introduction of iodine into aromatic rings is the reaction of diazonium salts with iodide ions. Analogous reactions with chloride, bromide, and fluoride ions give poorer results, and **4-25** and **3-24** are preferred for the preparation of aryl chlorides, bromides, and fluorides. However, when other diazonium reactions are carried out in the presence of these ions, halides are usually side products.

The actual attacking species is probably not only I⁻, if it is I⁻ at all. The iodide ion is oxidized (by the diazonium ion, nitrous acid, or some other oxidizing agent) to iodine, which in a solution containing iodide ions is converted to I_3^-; this is the actual attacking species, at least partly. This was shown by isolation of $ArN_2^+ \ I_3^-$ salts, which, on standing, gave ArI.[230] From this, it can be inferred that the reason the other halide ions give poor results

[226]Dreher; Niederer; Rieker; Schwarz; Zollinger *Helv. Chim. Acta* **1981**, *64*, 488.

[226a]Yoneda; Fukuhara; Mizokami; Suzuki *Chem. Lett.* **1991**, 459.

[227]Abeywickrema; Beckwith *J. Am. Chem. Soc.* **1986**, *108*, 8227, and references cited therein.

[228]See, for example Price; Tsunawaki *J. Org. Chem.* **1963**, *28*, 1867.

[229]Smith; Brown *J. Am. Chem. Soc.* **1951**, *73*, 2438. For a review, see Biffin; Miller; Paul, in Patai *The Chemistry of the Azido Group*; Wiley: New York, 1971, pp. 147-176.
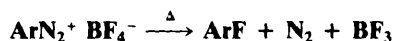
[230]Carey; Millar *Chem. Ind. (London)* **1960**, 97.

is not that they are poor nucleophiles but that they are poor reducing agents (compared with iodide). There is also evidence for a free radical mechanism.[231]

OS II, 351, 355, 604; V, 1120.

3-24 The Schiemann Reaction
Fluoro-de-diazoniation (overall tranformation)

$$ArN_2^+ \ BF_4^- \xrightarrow{\Delta} ArF + N_2 + BF_3$$

Heating of diazonium fluoroborates (the *Schiemann* or *Balz–Schiemann reaction*) is by far the best way of introducing fluorine into an aromatic ring.[232] In the most common procedure, the fluoroborate salts are prepared by diazotizing as usual with nitrous acid and HCl and then adding a cold aqueous solution of $NaBF_4$, HBF_4, or NH_4BF_4. A precipitate forms, which is dried, and the salt is heated in the dry state. These salts are unusually stable for diazonium salts, and the reaction is usually successsful. In general, any aromatic amine that can be diazotized will form a BF_4^- salt, usually with high yields. The diazonium fluoroborates can be formed directly from primary aromatic amines with *t*-butyl nitrate and BF_3–etherate.[233] The reaction has also been carried out on $ArN_2^+ \ PF_6^-$, $ArN_2^+ \ SbF_6^-$, and $ArN_2^+ \ AsF_6^-$ salts, in many cases with better yields.[234] The reaction has been extended to $ArN_2^+ \ BCl_4^-$ and $ArN_2^+ \ BBr_4^-$,[235] but aryl chlorides and bromides are more commonly prepared by the Sandmeyer reaction (**4-25**). In an alternative procedure, aryl fluorides have been prepared by treatment of aryltriazenes Ar—N=N—NR₂ with 70% HF in pyridine.[236]

The mechanism is of the SN1 type. That aryl cations are intermediates was shown by the following experiments:[237] aryl diazonium chlorides are known to arylate other aromatic rings by a free-radical mechanism (see **4-18**). In radical arylation it does not matter whether the other ring contains electron-withdrawing or electron-donating groups; in either case a mixture of isomers is obtained, since the attack is not by a charged species. If an aryl radical were an intermediate in the Schiemann reaction and the reaction were run in the presence of other rings, it should not matter what kinds of groups were on these other rings: mixtures of biaryls should be obtained in all cases. But if an aryl cation is an intermediate in the Schiemann reaction, compounds containing meta-directing groups, i.e., meta-directing for *electrophilic* substitutions, should be meta-arylated and those containing ortho-para-directing groups should be ortho- and para-arylated, since an aryl cation should behave in this respect like any electrophile (see Chapter 11). Experiments are shown[238] that such orientation is observed, demonstrating that the Schiemann reaction has a positively charged intermediate. The attacking species, in at least some instances, is not F^- but BF_4^-.[239]

OS II, 188, 295, 299; V, 133.

[231]Singh; Kumar *Aust. J. Chem.* **1972**, *25*, 2133; Kumar; Singh *Tetrahedron Lett.* **1972**, 613; Meyer; Rössler; Stöcklin *J. Am. Chem. Soc.* **1979**, *101*, 3121; Packer; Taylor *Aust. J. Chem.* **1985**, *38*, 991; Abeywickrema; Beckwith *J. Org. Chem.* **1987**, *52*, 2568.

[232]For a review, see Suschitzky *Adv. Fluorine Chem.* **1965**, *4*, 1-30.

[233]Doyle; Bryker *J. Org. Chem.* **1979**, *44*, 1572.

[234]Rutherford, Redmond; Rigamonti *J. Org. Chem.* **1961**, *26*, 5149; Sellers; Suschitzky *J. Chem. Soc. C* **1968**, 2317.

[235]Olah; Tolgyesi *J. Org. Chem.* **1961**, *26*, 2053.

[236]Rosenfeld; Widdowson *J. Chem. Soc., Chem. Commun.* **1979**, 914. For another alternative procedure, see Yoneda; Fukuhara; Kikuchi; Suzuki *Synth. Commun.* **1989**, *19*, 865.

[237]See also Swain; Sheats; Harbison, Ref. 21; Becker; Israel *J. Prakt. Chem.* **1979**, *321*, 579.

[238]Makarova; Matveeva *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1958**, 548; Makarova; Matveeva; Gribchenko *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1958**, 1399.

[239]Swain; Rogers *J. Am. Chem. Soc.* **1975**, *97*, 799.

Rearrangements

3-25 The von Richter Rearrangement
Hydro-de-nitro-cine-substitution
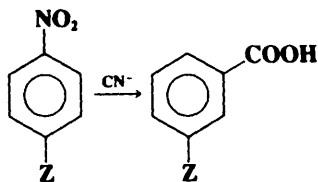
When aromatic nitro compounds are treated with cyanide ion, the nitro group is displaced and a carboxyl group enters with cine substitution (p. 646), always ortho to the displaced group, never meta or para. The scope of this reaction, called the *von Richter rearrangement*, is variable.[240] As with other nucleophilic aromatic substitutions, the reaction gives best results when electron-withdrawing groups are in ortho and para positions, but yields are low, usually less than 20% and never more than 50%.

At one time it was believed that a nitrile, ArCN, was an intermediate, since cyanide is the reagent and nitriles are hydrolyzable to carboxylic acids under the reaction conditions (6-5). However, a remarkable series of results proved this belief to be in error. Bunnett and Rauhut demonstrated[241] that α-naphthyl cyanide is *not* hydrolyzable to α-naphthoic acid under conditions at which β-nitronaphthalene undergoes the von Richter rearrangement to give α-naphthoic acid. This proved that the nitrile cannot be intermediate. It was subsequently demonstrated that N_2 is a major product of the reaction.[242] It had previously been assumed that all the nitrogen in the reaction was converted to ammonia, which would be compatible with a nitrile intermediate, since ammonia is a hydrolysis product of nitriles. At the same time it was shown that NO_2^- is not a major product. The discovery of nitrogen indicated that a nitrogen–nitrogen bond must be formed during the course of the reaction. A mechanism in accord with all the facts was proposed by Rosenblum:[242]
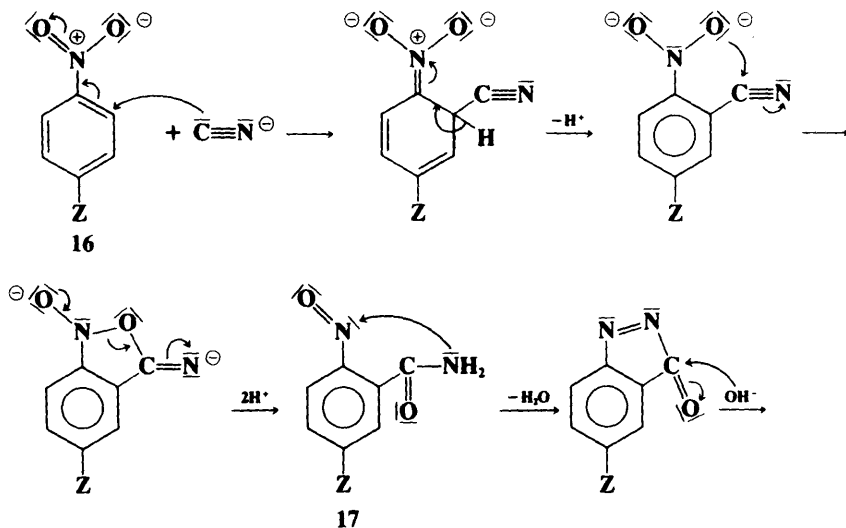
[240]For a review, see Shine *Aromatic Rearrangements*; Elsevier: New York, 1967, pp. 326-335.
[241]Bunnett; Rauhut *J. Org. Chem.* **1956**, *21*, 934, 944.
[242]Rosenblum *J. Am. Chem. Soc.* **1960**, *82*, 3796.
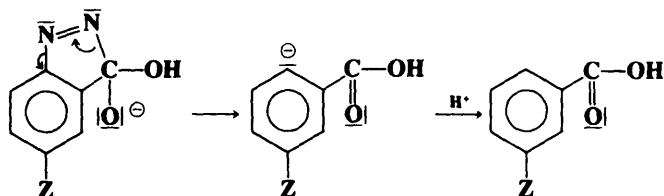
It may be noted that **17** are stable compounds; hence it should be possible to prepare them independently and to subject them to the conditions of the von Richter rearrangement. This was done and the correct products are obtained.[243] Further evidence is that when **16** (Z = Cl or Br) was treated with cyanide in $H_2^{18}O$, half the oxygen in the product was labeled, showing that one of the oxygens of the carboxyl group came from the nitro group and one from the solvent, as required by this mechanism.[244]

3-26   The Sommelet–Hauser Rearrangement
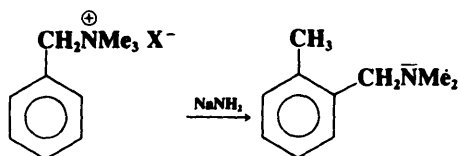
Benzylic quaternary ammonium salts, when treated with alkali-metal amides, undergo a rearrangement called the *Sommelet–Hauser rearrangement*.[245] Since the product is a benzylic tertiary amine, it can be further alkylated and the product again subjected to the rearrangement. This process can be continued around the ring until an ortho position is blocked.[246]

The rearrangement occurs with high yields and can be performed with various groups present in the ring.[247] The reaction is most often carried out with three methyl groups on the nitrogen, but other groups can also be used, though if a β hydrogen is present, Hofmann elimination (**7-6**) often competes. The Stevens rearrangement (**8-22**) is also a competing process.[248] When both rearrangements are possible, the Stevens is favored at high temperatures and the Sommelet–Hauser at low temperatures.[249] The mechanism is
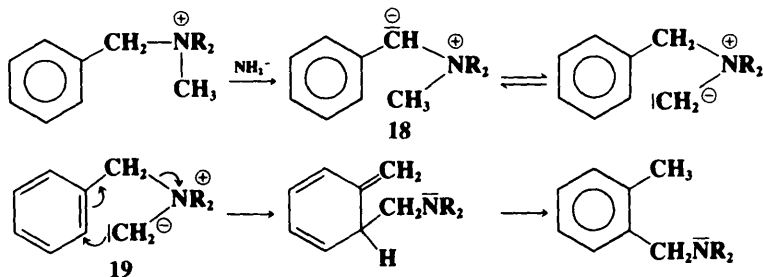
[243]Ibne-Rasa; Koubek *J. Org. Chem.* **1963**, *28*, 3240.

[244]Samuel *J. Chem. Soc.* **1960**, 1318. For other evidence, see Cullen; L'Ecuyer *Can. J. Chem.* **1961**, *39*, 144, 155, 382; Ullman; Bartkus *Chem. Ind. (London)* **1962**, 93.

[245]For reviews, see Pine, *Org. React.* **1970**, *18*, 403-464; Lepley; Giumanini *Mech. Mol. Migr.* **1971**, *3*, 297-440; Wittig *Bull. Soc. Chim. Fr.* **1971**, 1921-1924; Stevens; Watts *Selected Molecular Rearrangements*; Van Nostrand-Reinhold: Princeton, 1973, pp. 81-88; Shine, Ref. 240, pp. 316-326.

[246]Beard; Hauser *J. Org. Chem.* **1960**, *25*, 334.

[247]Beard; Hauser *J. Org. Chem.* **1961**, *26*, 371; Jones; Beard; Hauser *J. Org. Chem.* **1963**, *28*, 199.

[248]For a method that uses nonbasic conditions, and gives high yields of the Sommelet–Hauser product, with little or no Stevens rearrangement, see Nakano; Sato *J. Org. Chem.* **1987**, *52*, 1844; Shirai; Sato *J. Org. Chem.* **1988**, *53*, 194.

[249]Wittig; Streib *Liebigs Ann. Chem.* **1953**, *584*, 1.

The benzylic hydrogen is most acidic and is the one that first loses a proton to give the ylide **18.** However, **19,** which is present in smaller amount, is the species that undergoes the rearrangement, shifting the equilibrium in its favor. This mechanism is an example of a [2,3] sigmatropic rearrangment (see **8-37**). Another mechanism that might be proposed is one in which a methyl group actually breaks away (in some form) from the nitrogen and then attaches itself to the ring. That this is not so was shown by a product study.[250] If the second mechanism were true, **20** should give **21,** but the first mechanism predicts the formation of **22,** which is what was actually obtained.[251]
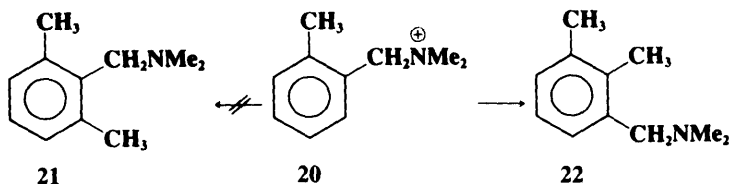
The mechanism as we have pictured it can lead only to an ortho product. However, a small amount of para product has been obtained in some cases.[252] A mechanism[253] in which there is a dissociation of the ArC—N bond (similar to the ion-pair mechanism of the Stevens rearrangement, p. 1101) has been invoked to explain the obtention of the para products.

Sulfur ylides containing a benzylic group (analogous to **19**) undergo an analogous rearrangement.[254]

OS **IV,** 585.

3-27 Rearrangement of Aryl Hydroxylamines
1/C-Hydro-5/N-hydroxy-interchange
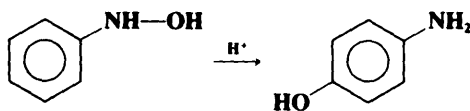
Aryl hydroxylamines treated with acids rearrange to aminophenols.[255] Although this reaction (known as the *Bamberger rearrangement*) is similar in appearance to **1-32** to **1-36,** the attack on the ring is not electrophilic but nucleophilic. The rearrangement is intermolecular, with the following mechanism:
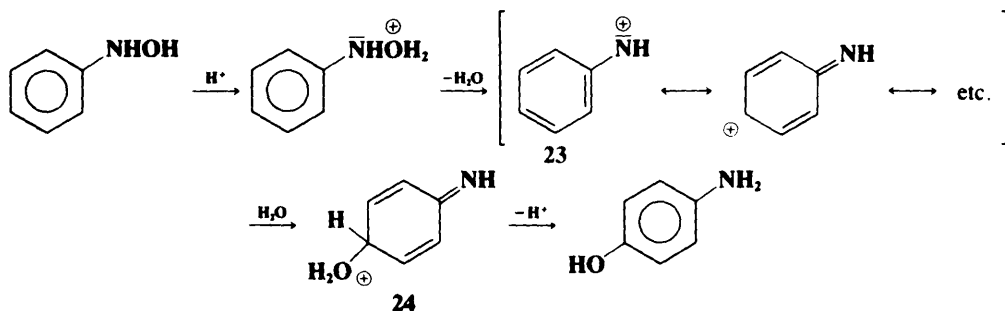
[250]For other evidence for the mechanism given, see Hauser; Van Eenam *J. Am. Chem. Soc.* **1957,** *79,* 5512; Jones; Hauser *J. Org. Chem.* **1961,** *26,* 2979; Puterbaugh; Hauser *J. Am. Chem. Soc.* **1964,** *86,* 1105; Pine; Sanchez *Tetrahedron Lett.* **1969,** 1319; Shirai; Watanabe; Sato *J. Org. Chem.* **1990,** *55,* 2767.
[251]Kantor; Hauser *J. Am. Chem. Soc.* **1951,** *73,* 4122.
[252]Pine *Tetrahedron Lett.* **1967,** 3393; Pine, Ref. 245. p. 418.
[253]Bumgardner *J. Am. Chem. Soc.* **1963,** *85,* 73.
[254]See Block *Reactions of Organosulfur Compounds;* Academic Press: New York, 1978. pp. 118-124.
[255]For a review, see Ref. 240. pp. 182-190.

Among the evidence[256] for this mechanism are the facts that other products are obtained when the reaction is run in the presence of competing nucleophiles, e.g., p-ethoxyaniline when ethanol is present, and that when the para position is blocked, compounds similar to **24** are isolated. In the case of 2,6-dimethylphenylhydroxylamine, the intermediate nitrenium ion **23** was trapped, and its lifetime in solution was measured.[257] The reaction of **23** with water was found to be diffusion controlled.[257]

OS **IV**, 148.

3-28   The Smiles Rearrangement
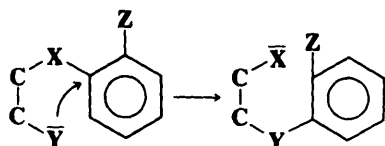
The *Smiles rearrangement* actually comprises a group of rearrangements that follow the pattern given above.[258] A specific example is

25
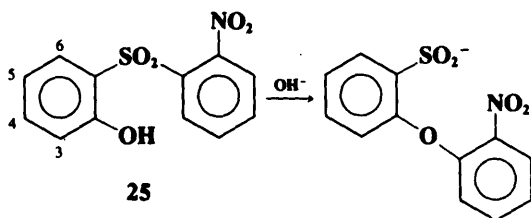
Smiles rearrangements are simply intramolecular nucleophilic substitutions. In the example given, SO_2Ar is the leaving group and ArO^- the nucleophile, and the nitro group serves to activate its ortho position. The ring at which the substitution takes place is nearly always activated, usually by ortho or para nitro groups. X is usually S, SO, SO_2,[259] O, or COO. Y is usually the conjugate base of OH, NH_2, NHR, or SH. The reaction has even been carried out with Y = CH_2^- (phenyllithium was the base here).[260]

The reaction rate is greatly enhanced by substitution in the 6 position of the attacking ring, for steric reasons. For example, a methyl, chloro, or bromo group in the 6 position of **25** caused the rate to be about 10^5 times faster than when the same groups were in the 4 position,[261] though electrical effects should be similar at these positions. The enhanced rate comes about because the most favorable conformation the molecule can adopt to suit the bulk of the 6-substituent is also the conformation required for the rearrangement. Thus, less entropy of activation is required.

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[256]For additional evidence, see Sone; Hamamoto; Seiji; Shinkai; Manabe *J. Chem. Soc., Perkin Trans. 2* **1981**, 1596; Kohnstam; Petch; Williams *J. Chem. Soc., Perkin Trans. 2* **1984**, 423; Sternson; Chandrasakar *J. Org. Chem.* **1984**, *49*, 4295, and references cited in these papers.

[257]Fishbein; McClelland *J. Am. Chem. Soc.* **1987**, *109*, 2824.

[258]For reviews, see Truce; Kreider; Brand *Org. React.* **1971**, *18*, 99-215; Shine, Ref. 240, pp. 307-316; Stevens; Watts, Ref. 245, pp. 120-126.

[259]For a review for the case of X = SO_2, see Cerfontain *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*; Wiley: New York, 1968, pp. 262-274.

[260]Truce; Ray *J. Am. Chem. Soc.* **1959**, *81*, 481; Truce; Robbins; Kreider **1966**, *88*, 4027; Drozd; Nikonova *J. Org. Chem. USSR* **1969**, *5*, 313.

[261]Bunnett; Okamoto *J. Am. Chem. Soc.* **1956**, *78*, 5363.

Although the Smiles rearrangement is usually carried out on compounds containing two rings, this need not be the case; e.g.,[262]

26
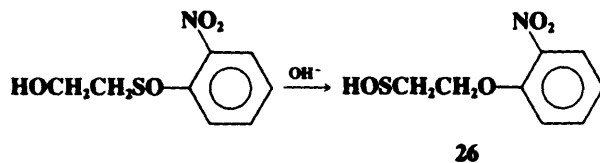
In this case the sulfenic acid (**26**) is unstable[263] and the actual products isolated were the corresponding sulfinic acid (RSO_2H) and disulfide (R_2S_2).

[262]Kent; Smiles *J. Chem. Soc.* **1934**, 422.
[263]For a stable sulfenic acid, see Nakamura *J. Am. Chem. Soc.* **1983**, *105*, 7172.