Nucleophilic Substitution Reactions by Electron Transfer

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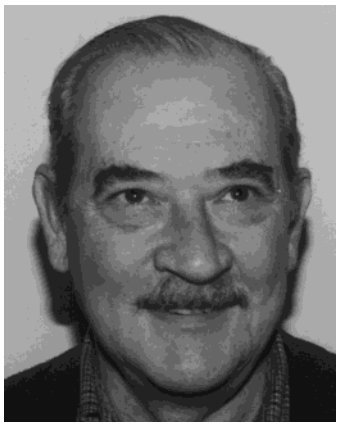

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I. Introduction

The available mechanisms to achieve nucleophilic substitution vary greatly, depending on the substrate, the nucleophile, and the reaction conditions.

In the aliphatic family the nucleophilic substitution can proceed through the classical polar bond forming−bond breaking S_N1, S_N2, and related mechanisms, which are visualized as involving the transfer of a pair of electrons.

In the aromatic family and during the past five decades organic chemists have recognized that the achievement of nucleophilic substitution is just as easy as that of electrophilic substitution. With substrates bearing an electron-withdrawing group (EWG), S_NAr is usually the accepted mechanism. Unactivated halides also react by this procedure when activated by complexation with chromium tricarbonyl. They can also react with strong bases to give substitution by the benzyne mechanism. Nucleophilic substitution can also be achieved from aromatic diazonium salts. Even hydrogen atoms can be substituted, under adequate conditions, by a vicarious nucleophilic substitution. For this reaction to proceed the presence of an EWG is also required.

Halogen metal exchange is another well-established route to account for nucleophilic substitution of halobenzenes and alkyl halides, generally with nucleophiles derived from tin, silicon, and germanium.

Besides this relatively wide polar mechanistic spectrum, many systems have been shown to react slowly or to be unreactive through any of them. Their lack of reactivity is usually due to strain (cycloalkyl and polycycloalkyl halides), steric (cycloalkyl, polycycloalkyl, and neopentyl halides), electronic factors [unactivated aromatic and heteroaromatic substrates, vinyl halides, and perfuoroalkyl halides (R_fX)], or a combination of them. For these compounds nucleophilic substitution can be accomplished by mechanisms that involve electron transfer (ET) steps.

In addition, there are families of compounds for which, although the polar and ET routes are feasible, the ET pathway is favored. An example is alkyl halides substituted by π acceptor EWGs.

For a compound to be substituted by ET, its radical has to be formed by an initial ET, which can be performed by different means. The most widely used are electrochemical initiation, thermal ET from an adequate donor, usually a charged nucleophile, and photoinitiated ET from the nucleophile. The latter two types of initiation are favored between nucleophiles that are very good electron donors and substrates that are very good electron acceptors.

Once the radicals are formed, they can react through the $S_{RN}1$ chain mechanism with radical and radical anions as intermediates. Substitution by a nonchain $S_{RN}1$ process has also been proposed, albeit in a considerably more limited number of cases.

ET followed by the collapse of radicals within a solvent cage has been proposed as a possible mechanism for some thermally initiated substitution of alkyl halides. Between these two possible pathways the $S_{RN}1$ is the one that has been most thoroughly tested with respect to its mechanistic characteristics and the one that has been shown to operate in most systems. This mechanism, known by the initials for Unimolecular Radical Nucleophilic Substitution, was first proposed independently by Kornblum[1] and Russell[2] in 1966 for the substitution of alkyl derivatives bearing EWG and a suitable leaving moiety. In 1970 Bunnett et al. applied it to rationalize the substitution of unactivated aromatic halides (ArX).[3]

The process has a considerably wide scope in relation to substrates, nucleophiles (Nu^-), and synthetic capabilities. The most important substrates that participate are alkyl halides with EWG (nitroalkyl, nitroallyl, nitro- or cyanobenzyl, and their heterocyclic analogues, as well as quinone derivatives), unactivated aromatic and heteroaromatic substrates, vinyl halides, R_fX, cycloalkyl, polycycloalkyl, and neopentyl halides. In addition to halides, other leaving groups are known [i.e., $(EtO)_2P(O)O$, RS (R = Ar, alkyl), ArSO, $ArSO_2$, PhSe, Ph_2S^+, RSN_2 (R = *t*-Bu, Ph), N_2BF_4, R_3N^+, N_2^+, N_3, NO_2, and XHg].

Many substituents are compatible with the reaction, such as alkyl groups, OR, OAr, SAr, CF_3, CO_2R, NH_2, NHCOR, NHBoc, SO_2R, CN, COAr, NR_2, and F. Even though the reaction is not inhibited by the presence of negatively charged substituents such as carboxylate ions, other charged groups such as oxyanions hinder the process. In general, substituents such as NO_2 groups are not suitable for $S_{RN}1$ substitution on aromatic substrates but are important EWG on aliphatic substrates, favoring the ET process.

Carbanions from hydrocarbons, nitriles, nitroalkanes, ketones, esters, *N*,*N*-dialkyl acetamides and thioamides, and mono- and dianions from β-dicarbonyl compounds are some of the most common Nu^- through which a new C−C bond can be formed. C−C bond formation is also achieved by reaction of aromatic alkoxides with aromatic substrates. On the other hand, O-alkylation is obtained by reaction of these anions and MeO^- ions with α-substituted nitroalkanes and *p*-nitrocumyl derivatives.

Among the nitrogen nucleophiles known to react are NH_2^- ions, anions from aromatic amines, pyrrole, diazoles, and triazoles. These anions and the aromatic alkoxides show similar behaviors. Although they react with aromatic substrates to usually afford C-arylation, N-alkylation is the main reaction with alkyl halides bearing EWG.

Anions from tin, phosphorus, arsenic, antimony, sulfur, selenium, and tellurium react through the heteroatom to form a new C−heteroatom bond.

Carbonylation to afford the acid or ester derivatives is possible by reaction with cobalt carbonyl species. In this system substitution of ArCl and vinyl and alkyl halides is achieved in excellent yields.

When the substrate has two leaving groups, disubstitution by the same Nu^- is possible. There are few examples of tri- and tetrasubstitutions. Substitution by different Nu^- can also be achieved by a sequence of separated $S_{RN}1$ reactions on appropriate ArX. Aromatic compounds substituted by three different Nu^- have been synthesized following this approach. More recently, the combination of the synthesis of stannanes by the $S_{RN}1$ mechanism followed by a cross-coupling reaction with electrophiles catalyzed by Pd(0) has shown to be an alternative synthetic approach to polyaryl compounds.

Tri- and tetrasubstituted olefins can be synthesized by reaction of nitronate anions with alkyl halides bearing EWG due to the possibility of nitrous acid elimination from the substitution product.

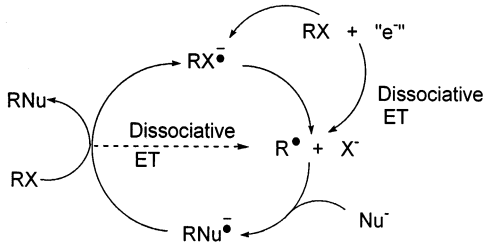
The $S_{RN}1$ mechanism has proved to be an important route to ring closure reactions, mainly in aromatic systems. The synthesis of indoles, isocarbostyrils, binaphthyls, etc., and an important number of natural products has been achieved by this process. Cyclization has also been reported in the reaction of alkyl halides with EWG.

Several reviews have been published on the subject in relation to the mechanism of bond formation and bond breaking by ET,[4] substitution at activated[5,6] and nonactivated[5b,7] sp^3 carbons, $S_{RN}1$ reactions at sp^2 carbons,[5b,8] aromatic photoinitiated substitutions,[5b,9] reactions performed under electrochemical catalysis,[10] and synthetic applications of the process.[11]

II. Mechanism

The $S_{RN}1$ mechanism is presented in Scheme 1. In the initiation step an ET from the Nu^- or from a suitable electron source to the substrate takes place. This ET can follow a concerted dissociative step to directly afford radicals and the anion of the leaving group.[4,12] A stepwise ET pathway is another possibil-

Scheme 1



ity through which the radical anion of the substrate is formed as intermediate. This radical anion cleaves in a subsequent step.

The R• can react with the Nu^- to give $RNu^{\bullet -}$, which by ET to the substrate forms the intermediates needed to continue the propagation cycle. The process affords, on the whole, a nucleophilic substitution. The mechanism has termination steps that depend on the RX, Nu^-, and experimental conditions.

The description of the two possible mechanistic pathways followed by the ET of a heterogeneous (electrochemical) or homogeneous initiation, that is, concerted dissociative versus stepwise, has been thoroughly discussed by Savéant.[4] Nowadays, it is accepted that the ET to aliphatic halides follows the concerted dissociative pathway, that is, the C−halogen bond is being broken as the electron is being transferred. According to the model proposed to describe the dynamics of the reaction, its intrinsic barrier depends on, besides the solvent reorganization energy associated with the Marcus−Hush theory, one-fourth of the BDE.[4,12] On the other hand, the stepwise mechanism can be envisaged as the preferred pathway followed by ET to a halide bearing a π acceptor of sufficiently low energy to accommodate the extra electron. This π system can be directly joined to the C−halogen bond, as in the case of an aromatic halide or through the mediation of a bridge. This nondissociative outer sphere ET is described by the Marcus−Hush[13] equation with the usual meaning for the intrinsic barrier, that is, small internal geometric modifications accompanied by solvent reorganization. The radical anion thus formed can dissociate into a radical and the halide anion in a second step through an intramolecular ET from the π system to the σ^* C−halogen bond. For both mechanisms the surface of the fragments formed by dissociation has no minimum with the exception of a possible shallow one corresponding to a loose $R^{\bullet}X^-$ complex.

Passage from a stepwise to a concerted mechanism is possible, and several factors have been identified to control this transition. (For a discussion on this matter see section IV.A.)

Because the $S_{RN}1$ mechanism is a chain reaction, the overall reactivity depends on the initiation, propagation, and termination steps. For the process to work efficiently not many initiations events are needed, but in this case, the propagation cycle must be fast and efficient to allow for long chains to build up.

Inhibition by radical traps or radical anion scavengers has been extensively used to provide mechanistic evidences. The most commonly employed are di-*tert*-butylnitroxide (DTBN), 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), galvinoxyl, and dioxygen, as well as good reversible electron acceptors such as *p*-dinitrobenzene (*p*-DNB).

Radical probes have also been used to assess the formation of radicals along the propagation cycle. Products from ring closure, ring opening, and rearrangement of the radicals were thus taken as evidence of their presence.

The relative reactivity of pairs of Nu^- toward a given radical, formed from different substrates, is further evidence in favor of the same radical as intermediate. For example, it has been demonstrated that the pair of $(EtO)_2PO^-$ and $^-CH_2COBu\text{-}t$ ions has the same relative reactivity toward PhX, PhSPh, and $PhNMe_3I$, compounds that have different steric demands but give the same Ph• radical intermediate.[14] This behavior has also been observed in the reaction of $XCMe_2NO_2$ (X = Cl, NO_2, or *p*-$MePhSO_2$) with $^-CMe_2NO_2$ and $^-CMe(CO_2Et)_2$ ions in DMSO.[15]

The process offers the possibility to afford the substitution of an unreactive substrate or Nu^- through *entrainment* conditions, which are a support for the chain nature of the mechanism. Entrainment is useful when the Nu^- (or the substrate) is rather unreactive at initiation, but quite reactive at propagation. Under these conditions the addition of tiny amounts of another Nu^- (or substrate), more reactive at initiation, increases the generation of intermediates and allows the less reactive Nu^- (or substrate) to start its own propagation.

Recently, it has been shown that excellent yields of substitution can be achieved by a nonchain $S_{RN}1$ reaction.[16] In this system, the possibility of a cage mechanism was ruled out mainly due to formation of trialkylamine, ascribed to ET from the radical anion of the substitution product to the benzyltriethylammonium counterion present in the reaction medium. These results show that the lack of inhibition by redox traps is not always a valid criterion against an $S_{RN}1$ reaction.

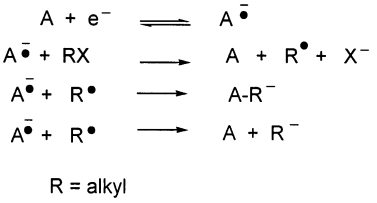
Another mechanistic possibility for ET nucleophilic substitutions of alkyl halides involves an initial dissociative ET within a solvent cage followed by coupling of the R• radicals with Nu• to give the substitution product by a geminate or cage collapse process (eq 1).

$$RX\ Nu^- \xrightarrow{ET} \left[R^{\bullet}\ X^-\ Nu^{\bullet}\right] \longrightarrow RNu\ X^- \qquad (1)$$

This alternative has been proposed for the reaction of some aliphatic systems with electrochemically generated carbanions.[17] The possibility of coupling outside the solvent cage was followed by reaction of substrates bearing a cyclizable radical probe the cyclization of which is $\geq 10^4$ times too slow to compete with a geminate coupling ($\geq 10^{10}$ s^{-1}).[17c] However, no conclusive evidence for the mechanism could be obtained under the experimental conditions used.

A cage collapse mechanism has also been proposed in the substitution of certain alkyl halides by stannyl anions.[18] The main pieces of evidence in favor of this mechanistic option are the lack of inhibition by the presence of radical or radical anion traps and the

Scheme 2



increase of reduction product by decreasing the solvent viscosity in the presence of good hydrogen donors such as dicyclohexylphosphine (DCHP), despite the fact that it can also act as an anion trap in some systems. Moreover, the role of the radical of DCHP, formed after hydrogen donation, has not been clearly established, and in some cases it has been proposed as the initiator of a propagation cycle. Thus, the mechanistic evidence presented up to now seems to be inconclusive, and the possibility of an $S_{RN}1$ mechanism cannot be excluded (see section VII.A.1).

Radical anions of aromatic compounds are other possible Nu^- through which a substitution reaction can be performed. Chemically or electrochemically generated aromatic radical anions can transfer electrons to ArX, which results in the reduction of the ArX and regeneration of the precursor of the aromatic radical anion.[19]

The mechanism for the reaction of aromatic radical anions with alkyl halides is presented in Scheme 2.[10g,17a,20,21] The rate-determining step of the reaction is the dissociative ET to the RX. The R• radicals thus formed can couple with the radical anion or can be reduced by this species in fast follow-up reactions. Although aromatic radical anions are in general considered to be strong and efficient electron donors, a nucleophilic behavior has been observed in some cases and a competition between ET and S_N2 is possible (see section IV.B.6).[20,22]

The possibility of an $S_{RN}2$ instead of an $S_{RN}1$ mechanism has been indicated for ArX.[23] In the $S_{RN}2$ process a direct coupling between the Nu^- and $ArX^{-\bullet}$ is proposed (eq 2). This possibility has been com-

$$ArX^{\bullet -} + Nu^- \longrightarrow ArNu^{\bullet -} + X^- \qquad (2)$$

pletely disregarded in the case of ArX unsubstituted by strong EWG, mainly on the basis of the extremely short lifetimes of their radical anions, which cleave with rate constants of at least 10^4 s^{-1} up to 10^{10} s^{-1}.[24,25] Stereochemical evidence, the independence between product distribution and leaving group ability in photoinitiated reactions, the same trend of relative reactivity in aromatic and aliphatic substrates, cyclization of aromatic radical probes, scrambling of substitution products, and kinetic determinations using electrochemical methods are other pieces of experimental evidence that have clearly demonstrated that all of these systems react by the $S_{RN}1$ mechanism.[25,26]

The dependence of the substitution to reduction product ratio observed by changing the leaving group in reactions promoted by alkali metals was also used as a criterion in favor of the $S_{RN}2$ proposal. However, these experimental pieces of evidence can be rationalized through the $S_{RN}1$ mechanism by the proposal according to which the reaction occurs within a thin reaction layer located inside the diffusion layer.[26,27]

Moreover, several possible transition states or intermediates examined for the direct displacement of the halide ion of a radical anion by Nu^- were considered to be unacceptable because of violation of quantum mechanical principles or by incompatibility with experimental observations, mainly related to the insensitivity of the reactions to steric hindrance.[24]

The $S_{RN}2$ mechanism seems to be more plausible for the substitution of compounds that form long-lived radical anions. Actually, it was initially proposed for the reaction between NaO_2SPh and the four p-$XC_6H_4NO_2$ derivatives.[23a] The NO_2 photosubstitution of p-$C_6H_5COC_6H_4NO_2$[23b] and p-$NCC_6H_4NO_2$,[23b] the fluorine substitution of pentafluoronitrobenzene,[28] the formation of indophenol from *N*-chlorobenzoquinone imine in the Gibbs reaction,[29a] and the substitution of 1-benzyl-2,4,6-triphenylpyridinium salt[29b,c] are other stabilized systems proposed to react with some Nu^- by the $S_{RN}2$ mechanism. However, conclusive evidence against the $S_{RN}2$ mechanism was provided for the substitution of p-$XC_6H_4NO_2$ with NaO_2SPh, which fails to give the predicted substitution product by preparative electrolysis.[30] In the pyridinium salt case, a nondissociative outer sphere ET is unlikely due to an unfavorable relationship between its reduction potential and the lower electron donor capability of the Nu^- used (nitronate and ethyl malonate ions).[29c] Besides, in some previous nitroaryl-substituted systems the S_NAr mechanism cannot be excluded.[31]

In the nitro-substituted aliphatic family the $S_{RN}2$ process has been proposed by Russell and colleagues to rationalize the substitution and enolate dimerization products formed in the reactions of 2-substituted 2-nitropropanes ($XCMe_2NO_2$, X = Cl, NO_2, or p-Me-$PhSO_2$) with the enolate anions $^-CHRCOAr$ (R = Me, Et, *i*-Pr, and *n*-Bu) and $^-CH_2COBu$-*t* ions.[32] However, the mechanistic evidence presented is not conclusive enough to disregard an $S_{RN}1$ reaction.

A. Conditions That Favor an ET Route

1. At sp² Carbons

Vinyl halides and aromatic compounds without EWG are very unreactive toward polar nucleophilic substitutions. One reason suggested for this lack of reactivity is that sp^2 carbons have a higher electronegativity than sp^3 carbons, and so the latter lose the leaving group more easily. Besides, bond distances decrease with increasing *s* character and the C−X bond is stronger for the vinylic and aromatic halides than for the aliphatic derivatives.

An S_N1 mechanism is very costly in terms of the energy of a cation center at a vinylic or aromatic carbon. S_N1 reactions at vinylic carbons can be accelerated by α substituents that stabilize the cation. Reactions by the tetrahedral mechanism can be accelerated by β substituents that stabilize the carbanion. Also, reactions at vinylic substrates can in certain cases proceed by the addition−elimination or elimination−addition sequence. With strong bases usually elimination occurs.

Thus, unactivated aryl and vinyl halides, for which the TS for a polar reaction is not favored, can react through an ET route. In the heteroaromatic family competition with an S_NAr process can occur mainly when more than one heteroatom is present.

In the case of aromatic compounds and for the same aryl moiety, there is a rough correlation between the reduction potential and their reactivity in ET reactions.[33,34] The order of reduction potential in liquid ammonia, PhI > PhBr > $PhNMe_3I$ > PhSPh > PhCl > PhF > PhOPh,[35] coincides with the reactivity order determined under photoinitiation. By competition experiments of the pair of PhX toward $^-CH_2COBu$-*t* ions the following reactivity order was found: PhCl/PhF = 29; PhBr/PhCl = 450; PhI/PhBr = 8.3 (liquid ammonia under irradiation). Therefore, the increase in reactivity from PhF to PhI is about 100000.[8c]

On the other hand, for a given halogen, the reduction potential gets more positive as the π systems gets bigger or is stabilized by electron acceptor substituents (phenyl < 2-, 3-, 4-pyridyl < naphthyl < CNC_6H_4- < $MeCOC_6H_4-$ ≅ 2- or 4-quinolyl < 1-, 2-, 9-anthracenyl < $PhCOC_6H_4-$ < $NO_2C_6H_4-$).[34b]

2. At sp^3 Carbons

Alternatives to the classical view of S_N reactions at sp^3 carbons are intimately linked to the Marcus theory[13] and its extension to dissociative ET by Savéant.[4,12] In the 1980s Shaik and Pross proposed, within the valence bond approximation, that the barrier that accompanies a polar nucleophilic substitution at a tetrahedral carbon arises mainly from the avoided crossing between the electronic state of the reactants Nu^-RX and its excited state $Nu^•RX^{•-}$, which arises by an ET.[36] On the basis of this description that includes not only the covalent but also the ionic contributions to properly describe both electronic states, the S_N2 process has been recognized as an inner-sphere ET accompanied by ligand transfer.[20,36] Thus, the distinction between an S_N2 and an ET process is related to the Nu···RX bonding interactions of their respective TSs, whereas in an ET reaction there is no substantial bond formation in the TS, in an S_N2 process the ET is accompanied by an important breaking and forming bond reorganization within the reaction complex.

The S_N2 pathway is thus favored in terms of energy ($\Delta H^{\#}$) by the bonding interactions. However, an S_N2 TS has strict requirements for the relative alignment of Nu, R, and X, which explains its relatively high negative entropy. On the other hand, the ET TS has a looser structure and thus possesses an entropy advantage over the S_N2 pathway. Steric, geometric, or electronic factors could be responsible for low Nu···RX bonding interactions in the TS, conditions under which an ET pathway could be favored.

This picture has led to the visualization of the S_N2 TS as a common TS for both the S_N2 and ET reactions. According to this view ET and S_N2 have been considered as the ends of a continuous mechanistic spectrum, implying that a single TS is to be found on the potential energy hypersurface of the reacting system.[37] Several ab initio studies have been carried out on simple systems according to which the S_N2 and ET product selection is the result of a bifurcation that occurs after the common TS.[38] As stated by Lund, Shaik, and colleagues the isostructural mechanistic *crossover* can be promoted by *electronic* or *steric* factors and by *structural constraints*.[37,38a,39]

The other conception of the passage between one mechanism (S_N2) and the other (ET) implies the existence of two different TSs on the potential energy hypersurface of the reacting system connected respectively to the S_N2 and ET products.[10f,40]

Recent ab initio investigations on the model system RCl + NO^- (R = Me, Et, *i*-Pr, or *t*-Bu) have led to a complete visualization of the whole picture.[4,40a] In these studies, besides the typical S_N2 TS, an outer sphere ET TS has been located. In the latter, the ET from NO^- to RCl occurs through an ON···Cl−R front side approach. In the absence of steric hindrance the S_N2 pathway is energetically favored over the ET pathway, the bifurcation toward ET products being negligible. On the other hand, in the presence of strong steric hindrance (R = *t*-Bu), not only is the ET TS energetically favored but also the bifurcation toward ET products is favored once the S_N2 TS has been overcome. All directions of attack are thus possible, and all lead to ET products with similar activation energies, similar reacting distances, and negligible bonded interactions in the TS.

For systems with less steric hindrance the competition will involve the formation of products following an S_N2 pathway as well as ET products coming in part from the ET TS and in part from the bifurcation followed after overcoming the S_N2 TS. This trend could explain the stereochemical outcome of the reaction of aromatic radical anions with optically active alkyl halides (see section IV.B.6).[4]

In relation to the shift from an ET to an S_N1-like pathway, the effect of the solvent has been recently investigated for the reaction of alkyl and benzyl halides with electrochemically generated electron donors.[41]

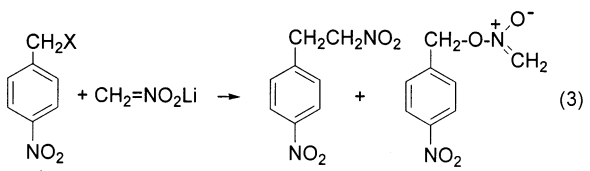
Electronic Factors. The donor−acceptor ability of the nucleophile−substrate pair is one of the factors that can favor an ET route. Given a favorable relationship between the electron affinity of the substrate and the ionization potential of the donor, it is more likely that little or no covalent Nu···RX bond formation will be present at the TS. This possibility has been theoretically investigated for the reaction between substituted formyl radical anions and methyl halides.[39a] It was found that for the poorest electron donor, cyanoformaldehyde radical anion, and CH_3X (X = Cl or Br) the TSs that afford the C-alkylated products are favored. Further increase in the acceptor ability of the alkyl halide to X = I led to an ET-like TS even with cyanoformaldehyde.[39a] The effects of this driving force on the ET polar dichotomy remain to be theoretically investigated under the views of the recent progress made in relation to the existence of two distinct TSs.

Experimentally, the competition between ET and S_N2 processes has been investigated in the reaction between the radical anions of anthracene, pyrene,

(*E*)-stilbene, *m*- and *p*-MeC_6H_4CN with different substrates such as Me, Et, *n*-Bu, *s*-Bu, neopentyl, and 1-adamantyl halides (1-XAd), and their methanesulfonate analogous.[22a,b] The mechanistic pathway was characterized in most cases using the reaction of the radical anions with the corresponding $R_3S^+I^-$ as a model for an ET reaction. In general, it was found that for a given alkyl group the ET percentage increases in the leaving group order Cl, Br, I, and Me_2S^+, a trend that is related to the electron affinity of the substrate. With regard to the electron donor, the percentage of ET increases as the standard reduction potential of the aromatic compound becomes more negative, that is, from the radical anion of anthracene to *p*-MeC_6H_4CN.[22a,b] Iodomethyldimethylsulfonium is a potent electron acceptor. Not only the iodo- ($E_{pc/MeCN} = -0.99$ V) but also the chloromethyldimethylsulfonium ($E_{pc/MeCN} = -2.25$ V) as well as the analogous iodomethyltrimethylammonium salts ($E_{pc/MeCN} = -1.39$ V) can be substituted by PhS^- ions through an ET route.[42]

The ET pathway is also favored in the reaction of alkyl halides with other EWGs such as NO_2, CN, and CF_3, which increase the electron affinity of the substrates (see section VI).

Changes in the leaving group of the *p*-nitrobenzyl system afford modifications in the distribution of products, which was attributed to an $S_N2-S_{RN}1$ competition. Whereas O-alkylation is ascribed to an S_N2 reaction, which after hydrolysis gives the aldehyde, C-alkylation is proposed to occur by the $S_{RN}1$ mechanism (eq 3).[43] The regiochemistry of the ET



reaction changes toward O-alkylation under appropriate steric constrains at the reacting centers (see section IV.B.5)

As can be seen, in this system in contrast to the behavior shown by the aromatic halides, the ET pathway is favored for X = Cl. For these compounds, the electron acceptor group is the nitrophenyl moiety. In the presence of such a good electron acceptor the ET reaction is less sensitive to the leaving group ability than the S_N2 process. ET is expected to be more sensitive to the C−halogen electron affinity in the case of simple alkyl halides for which this bond is the electron acceptor group and for aromatic halides with the same aryl moiety.

Recently, a borane effect, which increases the C/O alkylation ratio from 1.2 to 5.7, has been observed for the dark reaction of $^-CMe_2NO_2$ with *p*-$O_2NC_6H_4CH_2Br$ in the presence of Et_3B. This compound is proposed to be a source of $Et^\bullet$ radicals which, after bromine abstraction from the substrate, yield EtBr and the more stable *p*-$O_2NC_6H_4CH_2^\bullet$ radicals that propagate the chain.[44]

Changes in the mechanism with the leaving group ability have also been observed in the reaction of the *p*-nitrocumyl system. For example, although the reaction of *p*-$O_2NC_6H_4CMe_2Cl$ with $^-CR_2NO_2$ ions in dipolar aprotic solvents follows an $S_{RN}1$ process,[45] the reaction of the bromide with NO_2^- ions in DMSO[46a] and the reaction of the chloro or bromo derivatives with N_3^- [46b] show no evidence of $S_{RN}1$.

R_fI are other compounds notoriously resistant to displacement of I^- under S_N1 or S_N2 conditions due to the shielding of the carbon by the surrounding lone pair electrons on F that destabilize a carbocation and repel the backside attack of the Nu^-.[47] This fact and an increased electron affinity due to the substituent are responsible for the variety of nucleophilic substitutions that these substrates are able to undergo by the $S_{RN}1$ mechanism.

Steric and Strain Factors. These factors play an important role in favoring an ET pathway. Among the compounds that react through an ET mechanism are neopentyl halides and several cyclo and bridgehead polycyclo alkyl halides.

The S_N2 mechanism is notoriously slow for neopentyl, and it is not possible for bridgehead bicyclo and polycycloalkyl halides. The S_N1 mechanism is also precluded because generation of a carbocation at a bridgehead position is highly energetic. These are the main reasons these compounds are very good substrates for ET reactions. For a given halogen, on the other hand, an increase in strain at the bridgehead carbon is accompanied by an increase of their LUMO energy, which disfavors the ET to the compound.[48] For a given strain, the leaving group ability is as expected I > Br > Cl.

Substituted cyclopropanes react by the S_N1 mechanism through a disrotatory ring opening. This electrocyclic process has a relatively high activation energy due to the fragmentation of two bonds in a concerted process. On the other hand, halocyclopropanes do not usually suffer nucleophilic substitution by the S_N2 mechanism. Instead, an elimination−addition process occurs in the presence of strong bases. Similarly, the mechanism of substitution of other cycloalkyl halides depends on the ring size, the Nu^-, the leaving group, and the reaction conditions. Cycloalkyl halides such as halo- and *gem*-dihalocyclopropanes, *c*-C_5H_9Cl, *c*-$C_6H_{11}X$ (X = Cl or Br), *c*-$C_7H_{13}X$ (X = Cl or Br), and 2-BrAd have been found to react by ET. Competition between polar and ET reactions has been proposed for the reaction of *c*-C_4H_7Br, *c*-C_5H_9Br, and *c*-$C_7H_{13}Br$ (see VII.B.1 and VII.B.2).

Substitution at the α-carbon of *m*-$O_2NC_6H_4CH_2Cl$ by a *t*-Bu group shifts the mechanism from polar to $S_{RN}1$. Similar results were observed in the 2-halomethyl-5-nitrofuran family[49a] and in the reaction of *p*-nitrophenylallyl chlorides with different carbanions.[49b]

Theoretical studies used to test the model proposed for dissociative ET on methyl halides led to a satisfactory agreement with the activation barrier and the TSs predicted by the model.[50] The predictions also fit the experimental kinetics of the electrochemical reduction of butyl and benzyl halides.[12b] In relation

to the reduction by homogeneous electron donors, mainly aromatic radical anions, a good agreement was obtained with tertiary halides, but deviations were observed with secondary and primary derivatives. The deviations, being bigger for the latter, have been ascribed to a competition between the ET and S_N2 mechanisms.[12b,21a,51]

Activation parameters, stereochemical evidence, and kinetic tests have been used to characterize the ET versus polar nature of the reaction.[17a,37] The kinetic test compares the rate constant of substitution on an alkyl halide (k_{SUB}) with the rate constant of ET (k_{ET}) to the same alkyl halide from an outer-sphere electron donor (usually the radical anion of an aromatic compound with the same standard potential of the Nu^-); the ratio k_{SUB}/k_{ET} is a measure of the difference in the activation energy between the substitution reaction and the outer-sphere ET. If $k_{SUB}/k_{ET} \sim 1$, then the rate-limiting step for the substitution could be assumed to be the ET from the Nu^- to the alkyl halide.

This approach has been used by Lund and colleagues to elucidate the mechanism for the substitution reaction of the electrogenerated anion of 4-methoxycarbonyl-1-methyl-1,4-dihydropyridine with EtBr, *n*-BuBr, *s*-BuBr, *t*-BuCl, neopentyl bromide, *exo*-norbornyl bromide, isobornyl bromide, bornyl bromide, and 1-BrAd.[37,52] The test was also used with dianions of aromatic compounds[17a,53a,b] and the anions of 2,4,6-triphenylthiopyran, 1,4-dihydro-1-methyl-2,4,6-triphenylpyridine, and 4-benzoyl-1,4-dihydro-1-methylpyridine, which give stable radicals on oxidation.[37b,53c]

In the reaction of the 4-methoxycarbonyl-1-methyl-1,4-dihydropyridine anion with *trans*-2-bromomethoxycyclohexane the $k_{SUB}/k_{ET} \approx 1$ correlates well with the stereochemical results of nearly 100% racemization.[54a] The same anion gave $k_{SUB}/k_{ET} = 103$ with *cis*-2-bromomethoxycyclohexane and nearly complete inversion (>99.5%). Similarly, the anion reacts with *s*-BuBr ($k_{SUB}/k_{ET} = 170$) with complete inversion of configuration.[54b] Although the values of k_{SUB}/k_{ET} for these primary and secondary RX are too low because k_{ET} does not correspond to a pure outer-sphere ET and should be corrected for a possible S_N2 contribution, this will not significantly alter the conclusions achieved.[20,22b,j] The results obtained for the whole set of compounds indicate that for a given leaving group, substitution by Nu^- will take place by ET between anions with very negative redox potentials and sterically hindered alkyl halides.

The kinetic test has also been employed in the reaction of iron(I) and cobalt(I) porphyrins with BuX, yielding the σ-butyliron(III) and σ-butylcobalt(III) complexes. The rate constants determined indicate the occurrence of an inner-sphere S_N2 mechanism.[55] An increase in the steric hindrance at the carbon reacting center of the halide or at the iron center favors an ET route.[20]

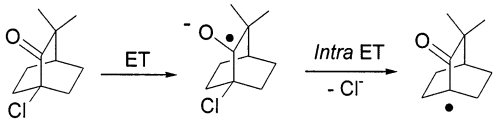
On the basis of spectroscopic evidence, in the reaction of MeI an increase in the steric hindrance of the carbanion from 9-phenylfluorenyl to 9-mesitylfluorenyl has been proposed to shift the reaction mechanism from S_N2 to ET.[56]

9-Substituted fluorenide carbanions in the series 9-Me-Fl^-, 9-MeO-Fl^-, and 9-R_2N-Fl^- [57a,b] were used to probe for ET components in reactions with alkyl halides. The test fails to reveal evidence for an ET contribution in reactions of simple alkyl halides; however, a switch to an ET mechanism is observed with halides that have more positive reduction potentials and also offer hindrance to polar S_N2 reactions, for example, $PhSO_2CH_2Cl$, Ph_2CHCl, and F_3CCH_2I.[57a] The k_{SUB}/k_{ET} ratios for the reaction of 9-R_2N-Fl^- ions with Ph_2CHCl, F_3CCH_2I, and (p-$ClC_6H_4)_2CHCl$ were nearly unity; the ratios were, with few exceptions, larger for the reactions with $PhCH_2Cl$ and c-$C_6H_{11}Br$. The k_{SUB}/k_{ET} ratio for the reaction with *n*-BuBr was 10^3-10^4, which places the mechanism in the S_N2 category.[57b] This type of work has been extended to nitranions, oxanions, thianions, and carbanions derived from β-diketones.[57c]

Electronic, Steric, and Strain Factors. Aliphatic substrates that do not react by polar mechanisms due to steric or strain factors may react slowly by ET if the electronic requirements are not favorable. For example, it has been shown that 3,3-dimethylbicyclo[2.2.2]oct-1-yl and bicyclo[2.2.1]hepta-1-yl chlorides do not react with Ph_2P^- ions under irradiation. On the other hand, the 2- and 3-oxo derivatives react under the same experimental conditions,[58] indicating that the presence of good π-electron acceptors facilitate the ET pathway.

The LUMOs of these oxobicyclic compounds belong to the carbonyl group and have an energy similar to the σ^* C−Br LUMO of 1-BrAd but lower than the σ^* C−Cl LUMO of 1-ClAd. In agreement with the LUMO predictions, 1-chloro-3,3-dimethyl-2-oxobicyclo[2.2.2]octane was found to be 700 times more reactive than 1-ClAd and only 0.40 times less reactive than 1-BrAd.[58b]

This increase in reactivity was explained by an intramolecular entrainment reaction. It is proposed that the oxo compound receives an electron in its antibonding carbonyl π^* MO, which by an intramolecular ET to the antibonding σ^* MO of the C−Cl bond forms the bridgehead radical that propagates the chain reaction (eq 4).[58a,b]

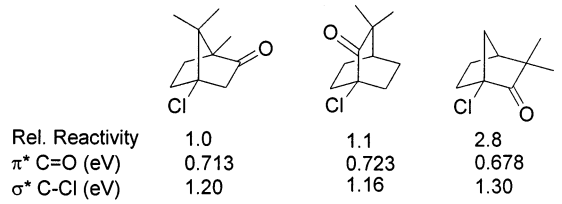


(4)

The relative reactivity for 4-chloro-1,7,7-trimethyl-2-oxobicyclo[2.2.1]heptane is similar to that of 1-chloro-2-oxo-3,3-dimethylbicyclo[2.2.2]octane and lower than that of 1-chloro-3,3-dimethyl-2-oxobicyclo[2.2.1]heptane. This reactivity order is in agreement with the energy value of the C=O π^* LUMO but not with that of the C−Cl σ^* MO of the compounds (Scheme 3).[58a]

Different mechanisms, mainly through bonds and through space, have been proposed for intramolecular ET in aliphatic systems. Not only the number of σ bonds between the groups but also their relative orientations and their spatial proximities are important factors for the reaction. For example, whereas the presence of an oxo substituent at the α or β

Scheme 3



Scheme 4

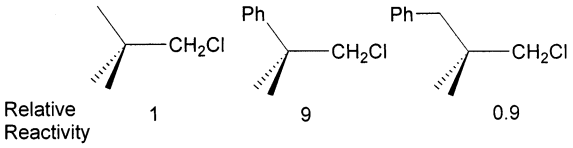
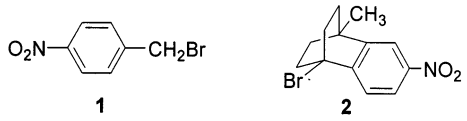


Chart 1

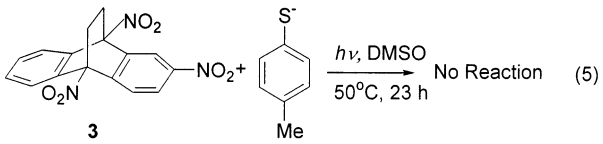


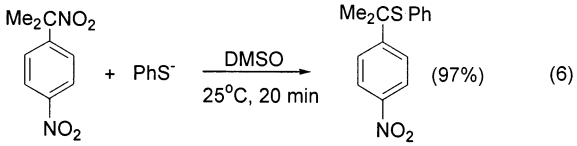
position is required to achieve the substitution of 3,3-dimethylbicyclo[2.2.2]oct-1-yl and bicyclo[2.2.1]hepta-1-yl chlorides, no redox catalysis was observed in the reaction of Me_3Sn^- and Ph_2P^- ions with 5-chloro-2-adamantanone,[59] in which the carbonyl group is at a γ position.

There are precedents that the phenyl ring in 1-chloro-2-methyl-2-phenylpropane (neophyl chloride) increases the rate of reaction with Ph_2P^- ions, compared with the parent neopentyl chloride, by an intramolecular redox catalysis. 1-Chloro-2,2-dimethyl-3-phenylpropane, with an extra bond between the phenyl ring and the C−Cl bond, reacts more slowly than neophyl chloride. Although the previous compound also has a phenyl ring, its lower reactivity is ascribed to a decrease in the rate of the intramolecular ET by elongation of the chain in one methylene unit (Scheme 4).[60]

Other examples of the importance of orbital symmetry restrictions are the radical anions of p-$O_2NC_6H_4CH_2Br$ (**1**) and the rigid bicyclooctane analogue **2**, with rate constants for cleavage of $\geq 7.9 \times 10^8$ s^{-1} (estimated) and 9.3×10^{-3} s^{-1}, respectively (Chart 1).[61] In the latter compound the rigid bicyclic structure precludes overlap between the π* MO, where the unpaired electron initially locates, and the σ* C−Br MO, to which it should be transferred concertedly with C−Br bond dissociation.[61]

Another example is the compound **3**, which does not react with p-$MeC_6H_4S^-$ [62] (eq 5) in contrast with what is observed in the benzylic derivative **4** (eq 6).[63]





III. Initiation Step

A. Spontaneous Initiation

Spontaneous or thermal ET is a possible initiation depending on the relationship between the electron affinity of the substrate and the oxidation potential of the Nu^-. For example, easily oxidizable delocalized anions derived from 4-methoxycarbonyl-1-methyl-1,4-dihydropyridine and related compounds[17a,52,53c] and Me_3Sn^- ions[18,64] can initiate the thermal ET substitution of several alkyl halides. The initiation does not need to be very efficient whenever it is accompanied by a fast and effective propagation cycle.

For example, in most cases, the $S_{RN}1$ substitution of aliphatic systems with EWG is initiated by a thermal ET that can be accelerated by light.[65] Thus, the reaction of $^-CMe_2NO_2$ ions with 2-bromo-2-nitropropane produces a nearly quantitative yield of 2,3-dinitro-2,3-dimethylbutane in the dark or under irradiation. On the other hand, the dark reaction with 2,2-dinitropropane at the same temperature (30 °C) is very slow but proceeds with good yield of substitution at 60 °C. Meanwhile, this reaction is quantitative at 30 °C under photoinitiation.[66]

The mechanism of the thermally initiated substitution of 4-nitrocumyl and 4-nitrobenzyl chlorides by $^-CMe_2NO_2$ ions has been elucidated.[67] Nitronate anions are poor electron donors, and the outer-sphere ET from the $^-CMe_2NO_2$ ion to 4-nitrocumyl chloride to form its radical anion has been determined to be too slow due to a large difference between the oxidation potential of the anion and the reduction potential of the halide (unfavorable driving force of $\approx$1.2 eV). Thus, a dissociative ET from the anion to the substrate seems to be the most probable initiation step. Despite this slow initiation, the intrinsic barrier of which depends on the C−halogen bond dissociation, the substitution reaction proceeds to a large extent in short reaction times. This fact is explained on the basis of the kinetic amplification of the chain process. Along this cycle the ET from the radical anion of the substitution product $(RNu)^{\bullet -}$ to the substrate has a high driving force and can take place through a stepwise mechanism.

Although in the aromatic family the $S_{RN}1$ mechanism was discovered for the spontaneous reaction of NH_2^- ions with iodopseudocumenes,[3a] there are few aromatic compounds that react without the need of light stimulation. Examples are ArN_2SR (R = Ph or *t*-Bu), very good electron acceptors that are able to react with different Nu^-.[68,69]

The enolate ions of aliphatic ketones can react in the dark with PhI and its derivatives in DMSO.[70] The occurrence of these spontaneous initiations is facilitated by the electron affinity of the substrates and the ~55 °C increment in temperature with respect to liquid ammonia in which no dark reaction occurs. It is known that the higher the pK_a of the ketones and related compounds, the higher the electron donor capability of its conjugated base and so the higher the probability of a spontaneous ET reaction.[71] The

main evidence that this spontaneous reaction occurs by the $S_{RN}1$ mechanism is given by the similar relative reactivities of pairs of enolates toward a given radical in competition experiments, in contrast with their reactivity measured in separated experiments.[70a] Other substrates that can react in the dark with enolate ions of ketones are halo-substituted pyrimidines,[72] pyrazines,[73] pyridazines,[73] and quinoxalines.[74] For these compounds, which are π electron deficient, competition with an S_NAr mechanism may occur.

Other spontaneous reactions in the aromatic field are the substitution of iodotoluenes by Ph_2P^- ion[75] and of 2-chloroquinoline by Me_3Sn^- ions.[76] Carbonylation of ArX by cobalt complex reducing agents is also possible in the dark.[77]

B. Photostimulated Reactions

In photostimulated induced reactions, the reactivity of the substrate−nucleophile pair can be modified by changing the solvent and the irradiation source. For instance, PhI does not react under irradiation (Pyrex-filtered flask) with the $^-CH_2COPh$ anion in liquid ammonia,[78] but it does react in DMSO.[79] However, the reaction occurs in liquid ammonia by irradiation in an immersion well.[80]

Even though photoinduction is a widely used initiation method, there are not many studies on the mechanism. This step can involve photoexcitation of a charge transfer complex (CTC) formed between the Nu^- and the substrate. The proposal is reinforced by studies of the wavelength dependence of the quantum yield. This type of initiation has been proposed for the reaction of $^-CH_2COMe$ ions with PhI and PhBr in DMSO,[81] for nitrile carbanions with ArX such as 2-bromonaphthalene or *p*-bromobiphenyl in liquid ammonia,[82] and in the reaction of PhI[83] and PhSEt[84] with $(EtO)_2PO^-$ ions in DMSO and DMF, respectively. Acceleration by KI in the substitution of ArX with $(EtO)_2PO^-$ ions or with 2-naphthoxide ions has been explained on the same basis.[85,86] Initiation by a CTC has been also suggested for the photoinduced reaction of neophyl iodide with carbanions in DMSO.[87]

ET from an excited Nu^- is another possibility for initiation. This is highly probable because they are the best candidates for absorption in the common reaction conditions used ($\lambda > 350$ nm). An example of the involvement of the anion excited state is the reaction of organic sulfides under laboratory light with Ph_2P^- ions, which absorb strongly in the visible region ($\lambda = 475$ nm).[84] Further evidence for this type of initiation is the fluorescence quenching of the diphenylindenyl anion by PhBr[88a] and of 2-naphthoxide anion by 1-IAd.[88b]

Photoejection from the Nu^- has been suggested in the reaction of ArS^- ions with 1-IAd with a quantum yield for photoejection of 0.43−0.75 at $\lambda = 308$ nm in MeCN.[16]

Initiation of the reaction of 1-chloro-2-naphthoxide anion with Na_2SO_3 has been proposed to occur by ET between the excited triplet state of the substrate and its ground state.[89] For the 1-bromo derivative, photohomolytic C−Br dissociation is proposed.[89] The substitution of 1-chloro-2-naphthoxide ions with Na_2SO_3 can be dye-photoinitiated[89] or initiated by visible light with Ru complex as sensitizer and Co complex as the intermediate electron carrier.[89]

For the photochemical initiation by an excited donor, the occurrence of a concerted ET bond-breaking reaction seems intuitively to be a situation in which the quantum yield quenching of fragmentation should be unity. This takes into account that the back-ET from the fragments associated in the solvent cage has a too high activation barrier to compete with their diffusion out of the cage.[4,90] On the other hand, quenching quantum yields are expected to be lower for a stepwise photoinduced ET due to the higher probability of back-ET from the intermediate radical anion formed.[4,90] However, it has been shown on theoretical grounds that photoinduced dissociative ET does not necessarily mean a quantum yield equal to unity. The main reason for observing a less than unity quantum yield is the possibility of partition between fragmentation and back-ET when the upper first-order potential energy surface of the system intersects the reactants and fragments zero-order surfaces. Thus, the experimental quenching quantum yields measured for the ET from the excited singlets of perylene and 2-ethyl-9,10-dimethoxyanthracene (EDA) to CCl_4 are 0.70 and 0.77, respectively.[91a] Similarly, the experimental quenching quantum yields measured for the ET from the excited singlets of perylene to 4-cyanotrifluoromethylbenzene and from EDA to dimethylphenyl sulfonium to 4-cyanobenzylmethylphenyl sulfonium and to 4-cyanobenzyl chloride are 0.25, 0.35, 0.77, and 0.55, respectively.[91b] The first two values are assigned to a stepwise ET mechanism, the last one (0.55) to a concerted mechanism, and the value of 0.77, corresponding to 4-cyanobenzylmethylphenyl sulfonium, is considered a situation in which both mechanisms are competitive.[91b]

C. Electrochemically Induced Reactions[10,12a]

Electrochemical initiation is an approach that has been successful in a considerable number of cases with aromatic and heteroaromatic substrates. The Savéant group has studied most of these reactions. This approach allows, in addition, a quantitative analysis of the mechanism as the determination of the fragmentation rate constants of radical anions and the absolute rate constant for the coupling reaction of a wide number of Nu^- with radicals.

According to the difference of the standard potentials between the $RX/RX^{\bullet -}$ and $RNu/RNu^{\bullet -}$ couples, two different situations may arise. If E^0 $(RX/RX^{\bullet -}) \gg E^0$ $(RNu/RNu^{\bullet -})$ and $RX^{-\bullet}$ fragments slowly, $R^\bullet$ and $RNu^{\bullet -}$ are formed far from the electrode surface. The $RNu^{\bullet -}$ formed can be oxidized at the electrode surface or in the solution (eq 7) to continue the propagation

$$ArNu^{\bullet} + ArX \rightleftharpoons ArNu + ArX^{\bullet} \qquad (7)$$

cycle. Under this situation complete conversion of RX into RNu can be obtained with a catalytic amount of electrons whenever the radical−nucleophile coupling is fast enough to overcome side reactions. The occur-

rence of reaction 7 as a downhill step from left to right is the basis of the chain process.

When $RX^{\bullet-}$ fragments very quickly, $R^{\bullet}$ is formed close to the electrode surface and will be reduced before reacting with the Nu^- in the solution. This situation can be reversed by the presence of a redox mediator M that is reduced to $M^{\bullet-}$ at a more positive potential than RX. $M^{\bullet-}$ lives long enough to reduce RX away from the electrode to form $R^{\bullet}$. Properties and selection of adequate redox mediators have been proposed.[92] Under these conditions, the yields of substitution can be increased at lower current.[93]

In the case of dissociative heterogeneous ET as in the electrochemically induced reaction of 1-IAd with ArS^- ions, reduction to AdH is the main reaction pathway, which could not be avoided by the use of redox mediators.[16]

For the opposite order of the potentials, E^0 (RX/$RX^{\bullet-}$) $\ll E^0$ (RNu/$RNu^{\bullet-}$), the $RNu^{\bullet-}$ formed is electrochemically stable at the potential at which it is generated, that is, the reduction potential of RX. Therefore, $RNu^{\bullet-}$ does not tend to be oxidized at the electrode surface or by ET to the substrate. For this reason the situation is termed noncatalytic and eq 7 is uphill from left to right. The corresponding consumption of electrons is one per molecule whenever the coupling reaction is fast enough to compete successfully with the side reactions. An example of a noncatalytic system is the reaction of $Ph^{\bullet}$ radicals with CN^- ions.[94]

D. Solvated Electrons and Sodium Amalgam in Liquid Ammonia

The solvated electron-stimulated reaction of aromatic substrates with $^-CH_2COMe$ ions was studied in liquid ammonia. Substitution was found with PhX (X = F, Cl, Br, or I), Ph_2O, Ph_2S, Ph_2Se, Ph_2I^+, $PhNMe_3^+$, $(PhO)_3PO$, and $PhOPO(OEt)_2$. Substitution was not obtained with the compounds Ph_3Z (Z = P, As, Sb, or Bi), Ph_2SO, Ph_2SO_2, $PhSO_2Me$, and $PhSO_3^-$.[95]

This initiation can be of importance whenever the products coming from a benzyne mechanism are to be avoided, as in the reaction of *o*-$MeOC_6H_4Br$ with NH_2^- ions.[3] Another example is the reaction of ArX bearing an EWG with the $^-CH_2CONMe_2$ ion, in which a benzyne mechanism prevails over the photoinitiated $S_{RN}1$ reaction, yielding substituted anilines. In the reaction of *p*-NCC_6H_4X (X = Cl, Br, or I) with the latter anion and K metal, high yields of the substitution compound, uncontaminated by the benzyne products, were obtained.[96]

The main disadvantages of this type of initiation can be the formation of dehalogenated reduction compounds and the reduction of the substitution product.[27,97,98] The distribution of both types of products can be predicted on the basis of the mixing model proposed to describe this type of reaction.[26,27]

Sodium amalgam has been used to induce $S_{RN}1$ reactions of those substrates with redox potentials close to or more positive than the redox potential of Na(Hg). The reaction of $^-CH_2COMe$,[99] $^-CH_2COPh$,[99] and Ph_2P^- ions[100] can be initiated with this reagent. When the radical anion of the substrate fragments quickly and consequently close to the Na(Hg) surface, such as with PhBr and *p*-$MeOC_6H_4Br$, substitution is obtained only in the presence of a redox mediator.[99,100]

E. Reactions Induced by Inorganic Salts

Although several inorganic salts were tested,[101] the most used is the ferrous ion. Initiation by ferrous ions ($FeSO_4$ in liquid ammonia; $FeCl_2$ or $FeBr_2$ in DMSO) is growing in importance due to its possible synthetic advantages.

Three possible initiation mechanisms have been suggested: ET from Fe^{2+} to ArI; iron-mediated ET from the Nu^- to ArI; or direct capture of iodine from ArI, with formation of Ar· radicals.[102] The role of the Fe^{2+} ion in the reaction remains intriguing. Its presence is required from catalytic to equimolecular amounts, which depends on the leaving group and the Nu^- used.

Inducement by $FeSO_4$ has been possible for the reaction, in liquid ammonia, of $^-CH_2COMe$,[101] $^-CH_2CO_2Bu$-*t*,[103] *N*-acetylmorpholine,[103] and a number of higher *N*-acylmorpholine ions[103] with ArX and in the substitution of PhI with the enolate ions of 2-acetylfuran, 2-acetylthiophene,[104] and 2-acetyl-1-methylpyrrole.[105] The substitution of 1-IAd, neopentyl iodide, and 7-iodobicyclo[4.1.0]heptane with carbanions from ketones,[106] and of 1-IAd with the anion from *N*-acetylthiomorpholine,[107a] has been successfully achieved in the presence of $FeBr_2$ in DMSO. In a detailed kinetic study, it has been shown that the reaction of 1-iodonaphthalene and 1-IAd with *N*-thioacetylmorpholine anion gave good yield of substitution products (86%) with as low as 0.6−1.6 mol % of $FeBr_2$ in DMSO.[107b]

SmI_2 has been used to induce $S_{RN}1$ reactions of ArX with $^-CH_2COPh$ ions in DMSO. PhCl and PhBr do not react under these experimental conditions, but good yields of substitution are obtained with PhI, 2-bromopyridine, and 1-chloro- and 2-bromonaphthalenes.[108] Substitution of ArX and 1-BrAd with PhZ^- ions (Z = S, Se, or Te) can be also be achieved in moderate to good yields by SmI_2 initiation.[109]

F. Miscellaneous

Reactions that are not spontaneous can take place in liquid ammonia under pressure and sonication as in the case of *p*-$MeOC_6H_4I$ and 1-halonaphthalene (X = Cl, Br, or I) with Ph_2P^- ion in liquid ammonia at room temperature.[110] The reaction of *p*-$O_2NC_6H_4CH_2Br$ with the $^-CMe_2NO_2$ ion can also be initiated by sonication. Under optimal conditions the ratio C/O alkylation is practically reversed with respect to that of the silent reaction, indicating a direct intervention of sonic waves in the ET.[111]

Microwave irradiation has been shown to be very effective in initiating $S_{RN}1$ reactions in activated systems. Thus, by a simple and rapid method involving the use of wet silica gel and an opened Erlenmeyer flask, good yields of substitution products were isolated, under microwave irradiation, in the reactions of *p*-$O_2NC_6H_4CH_2Cl$,[112] 2-chloromethyl-3-nitroimidazo[1,2-*a*]pyridine,[112] 2-methyl-4-chloromethyl-

5-nitrothiazole,[112] and 2-chloromethylnaphthoimidazoledione[113] with the $^{-}CMe_2NO_2$ ion.

Radical anions and dianions of aromatic compounds have been used as initiators and Nu^{-} in ET substitution reactions of RX.[114] Radical anions have been also used to catalyze the reactions of 2,2-dinitropropane with $^{-}CMe_2NO_2$ ions and $^{-}CEt(CO_2Et)_2$ ions.[66]

Nucleophilic substitution of α,*p*-dinitrocumene by the N_3^{-} ion can be induced by radiolysis with ^{60}Co in deaerated alkaline methanol.[115]

IV. Propagation Steps

Any of the intermediates can initiate the chain. By far the most commonly used is the radical anion of the substrate or its radical, if the substrate is involved in a dissociative ET reaction.

If the radical anion of the substrate is an intermediate, it has to fragment at a considerable rate. The importance of this reaction is shown in the following system in which the relative reactivity of various ArBr versus PhBr toward the $^{-}CH_2COBu$-*t* ion has been determined.[116] The reactivity, which correlates with the standard reduction potential of the substrate, increases from Ar = Ph to Ar = anthracenyl, despite the fact that the fragmentation rate of the radical anion decreases from approximately 10^{10} s^{-1} (Ar = Ph) to 3×10^5 s^{-1} (Ar = anthracenyl). However, an inversion in the reactivity trend was observed for the pair PhBr−*p*-$C_6H_5COC_6H_4Br$. This was attributed to the fact that, even though *p*-$C_6H_5COC_6H_4Br$ is the better acceptor, its radical anion has the slower fragmentation rate (6×10^2 s^{-1} in liquid ammonia) in relation to PhBr.[116]

Furthermore, the fragmentation rate of the radical anion of the substrate has been proposed as the rate-determining step in the reaction of RX bearing EWG with a number of Nu^{-}.[117,118]

Whenever the radical anion of the substrate has an efficient fragmentation rate, the coupling reaction between the radical and the Nu^{-} and the ET from the radical anion of the substitution compound to the substrate are crucial steps. If these reactions are not efficient, the chain will be short or even nonexistent and the achievement of substitution will fail in the absence of an efficient initiation.

Even though ET from the radical anion of the product to the substrate is usually exergonic, NO_2^{-} and CN^{-} ions are not good nucleophiles in their photoinduced reaction with ArX, probably due to the stability of the $(ArNu)^{\bullet -}$ formed, which does not transfer the electron to the substrate and thus avoids chain propagation. However, photoinduced substitution by CN^{-} ions can be achieved with good electron acceptors such as ArN_2SPh[119,120] and *p*-$O_2NC_6H_4CMe_2Cl$[121] or under noncatalytic electrochemical conditions.[94]

The quantum yields of the photoinitiated reactions have been used as a qualitative measure of the chain length. The quantum yields for the substitution of *p*-$O_2NC_6H_4CMe_2Cl$ with N_3^{-} ions and quinuclidine have been determined to be 6000 and 3.5, respectively.[122] For the reaction of α,*p*-dinitrocumene with N_3^{-} ions the quantum yield was intermediate (570),[122] and it has a value of 220 for the displacement of the NO_2^{-} ion from ethyl α-nitroisobutyrate by the $^{-}CMe_2NO_2$ ion.[122]

The quantum yields for substitution of ArX with nitrile-stabilized carbanions range from 7 to 31 in liquid ammonia.[82] Quantum yields from 50 to 20 have been determined for the substitution of halonaphthoxides and PhI by $(EtO)_2PO^{-}$.[83] On the other hand, a nonchain $S_{RN}1$ reaction with excellent yields of substitution, after prolonged irradiation times, has been proposed for the substitution of 1-IAd by ArS^{-} ions.[16]

In the case of Nu^{-} reactive at the initiation and propagation pathways, the quantum yields for substitution (Φ_{global}) depend on the efficiency of both initiation and the turnover in the propagation steps. Thus, the magnitude of the chain length of any $S_{RN}1$ reaction can easily be derived from the overall quantum yield by knowing the quantum yield of initiation. The latter could be obtained provided that the propagation cycle is eliminated or reduced significantly in comparison with the initiation step. The chain length can then be obtained from eq 8.

$$\text{Chain Length} = \Phi_{propagation} = \Phi_{global} / \Phi_{initiation} \qquad (8)$$

The quantum yield for substitution of neophyl iodide by the $^{-}CH_2COPh$ ion was determined to be 0.127.[87] The quantum yield of initiation, evaluated by suppressing the propagation steps with the presence of the radical trap DTBN, has a value of 10^{-3}. On the basis of both quantum yields, the chain length or $\Phi_{propagation}$ obtained for the reaction is ∼127. This is the first report of $\Phi_{propagation}$ for an $S_{RN}1$ process, demonstrating that overall quantum yields below 1 cannot be taken as a criterion against a chain. Following a similar procedure a chain length of ∼2 was evaluated for the reaction of neophyl iodide with $^{-}CH_2NO_2$ in the presence of 3-cyclohexenone enolate ion as entrainment reagent. Although the coupling reaction with the $^{-}CH_2NO_2$ ion is faster than with the $^{-}CH_2COPh$ ion, the ET from the stable radical anion of the product to the substrate is slower, and a competitive ET to other acceptors precludes continuation of the cycle. This fact accounts for the short chain length, that is, 2.[87] However, good percentages of substitution can be obtained under these conditions, due to a more efficient initiation from the enolate anion of an aliphatic than an aromatic ketone (quantum yield of initiation to neophyl iodide from 3-cyclohexenone enolate 0.2 versus 10^{-3} from the $^{-}CH_2COPh$ ion).

A. Intermediates Formed by ET to the Substrates

As previously stated the ET to aliphatic halides proceeds through a concerted dissociative path. On the other hand, most of the evidence points to the conclusion that radical anions are intermediates in the reductive cleavage of aromatic and aliphatic halides with π acceptors. The dissociation of these intermediates occurs through an intramolecular ET from the π system to the σ C−halogen bond, and the activation-driving force that describes the dynamics of this intramolecular dissociative ET has been

explained by an extension of the Savéant model for concerted dissociative ETs (eqs 9−10).

$$\Delta G^{\ddagger}_{RX^{-\cdot}/R^{\cdot}+X^{-}} = \Delta G^{\ddagger}_{o\,RX^{-\cdot}/R^{\cdot}+X^{-}} \times (1 + \Delta G^{\circ}_{RX^{-\cdot}/R^{\cdot}+X^{-}}/4\,\Delta G^{\ddagger}_{o\,RX^{-\cdot}/R^{\cdot}+X^{-}})^2 \quad (9)$$

$$\Delta G^{\ddagger}_{o\,RX^{-\cdot}/R^{\cdot}+X^{-}} = (D_{RX^{-\cdot}} + \lambda_0)/4$$

$$\Delta G^{\circ}_{RX^{-\cdot}/R^{\cdot}+X^{-}} = D_{RX} + E^{\circ}_{RX/RX^{-\cdot}} - E^{\circ}_{X^{\cdot}/X^{-}} \quad (10)$$

However, the existence of radical anions on the anionic potential surface does not necessarily mean that the reaction will proceed through this pathway. The main molecular factors that control the transition between a stepwise and a concerted sequence are the BDE (D), $E^0_{RX/RX^{-\cdot}}$ and $E^0_{X^{\cdot}/X^-}$ (eq 10).[4,123] The transition between mechanisms can be determined on an electrochemical basis or by a change in the slope of the rate constant (log *k*) with the reduction potential of the donor under homogeneous conditions.

For the reduction of benzyl halides, the energy of the π^* LUMO, which accommodates the incoming electron, and the C−X bond dissociation energy are the most important factors. Thus, nitro-substituted benzyl halides (X = Cl or Br) with a low-lying π^* LUMO react stepwisely, because reduction to the radical anion proceeds easily (not very negative formal potential $E^0_{RX/RX^{-\cdot}}$).[51]

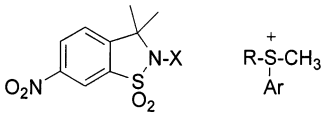
The radical anions of these compounds are usually too unstable to be detected by ordinary ESR techniques.[66,124] However, radical anions derived from 2-chloro- and 2-iodo-2-nitropropane,[117,125] *p*-nitrobenzyl,[126a,b] *p*-nitrocumyl,[126b] *m*-nitrobenzyl,[126c] substituted-2-methyl-5-nitrofurans,[127a] 4-nitroimidazoles derivatives[127b] and 5-X-2*H*,3*H*-benzo[*b*]thiophene-2,3-diones (X = F, Cl, Br, or I)[128] have been observed with this technique, and in some cases their loss of X^- ions has been followed.[125,117] The structures of these radical anions reveal a significant overlap between the nitro or nitroaromatic π^* MO and the C−X σ^* MO. Similar results have been proposed on a theoretical basis.[129]

The fragmentation rates were determined to be 80 s^{-1} for *m*-$O_2NC_6H_4CH_2Cl$,[51] 5.7 × 10^6 s^{-1} for *p*-$O_2NC_6H_4CH_2Cl$,[67a] and 4.0 × 10^7 s^{-1} for *p*-$O_2NC_6H_4CMe_2Cl$[67b] in MeCN. The rate constants determined by pulse radiolysis in aqueous alcoholic solutions are $<5.4 \times 10^3$ and 1.0 × 10^4 s^{-1} for *m*-, *p*-, and *o*-$O_2NC_6H_4CMe_2Cl$, respectively.[130] α-Substitution with a methyl group increases the rate constant of dehalogenation by a factor of ∼20, whereas α-substitution by a *tert*-butyl group decreases the rate by a factor of ∼3−10.[130]

The cleavage rate constants for the radical anions of the following nitrocumyl derivatives have been determined to be 3 × 10^6 s^{-1} for $C_6H_5CMe_2NO_2$, 5 × 10^6 s^{-1} for *p*-$NCC_6H_4CMe_2NO_2$, and 240 s^{-1} for *p*-$O_2NC_6H_4CMe_2NO_2$.[131a]

The electrochemical rate constant for the fragmentation of the radical anion from 1,1-dinitrocyclohexane is 1.6 × 10^6 s^{-1} in DMF (in aqueous solution 1.1 × 10^6 s^{-1} obtained by pulse radiolysis); meanwhile, for the 1,1′-dinitrobicyclohexyl it is 6 × 10^3 s^{-1}.[131b]

Chart 2



The association of the fragments formed in the cleavage into a charge−dipole complex within the solvent cage can decrease the activation energy of both the dissociative and the stepwise fragmentation. For example, the classical dissociative ET theory predicts that the reaction of the $^-CMe_2NO_2$ ion with *p*-nitrobenzyl chloride is significantly slower than observed experimentally. This can be explained on the basis of a stabilized caged interaction, which is negligible in the 4-nitrocumyl case in which the interaction is prevented by steric and electronic factors.[67] On the basis of the model proposed to interpret this effect, a 20% decrease in the intrinsic barrier is predicted when the dissociation of the caged fragments accounts for 4% of the BDE.[4]

Cyano- or unsubstituted benzyl halides (R = CN or H; X = Cl or Br) with a higher energy π^* LUMO undergo a concerted electrochemical cleavage in DMF.[51] An increased driving force is expected for an ET induced by pulse radiolysis. For example, the reaction of 3-cyanobenzyl bromide in water is stepwise under radiolysis, whereas its electrochemical reduction in MeCN is concerted.

N-Halosultams (2-halo-3,3-dimethyl-6-nitro-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide, X = Cl, Br, or F) and sulfonium cations (Chart 2) are other examples of compounds for which the energy of the π^* LUMO and the C−X BDE play an important role. The sultams (X = Cl or Br), although characterized by LUMO energies similar to those found for the benzyl halides, react concertedly because the N−X bond is weaker than the C−X nitrobenzyl counterpart. Only the fluorosultam (X = F), which has a high N−F bond dissociation energy, returns to a stepwise cleavage.[132a] In the electrochemical reduction of the aryldialkyl sulfonium cations, when Ar = Ph or 1-naphthyl, the mechanism is stepwise for R = Me (π LUMO control), borderline for R = $PhCH_2$, and concerted for remaining Rs (BDE control). The process is stepwise for Ar = 9-anthracenyl, R = Me, and *p*-$CNC_6H_4CH_2$ (π LUMO control).[132b]

A transition between mechanisms is also possible by changing the driving force of the experimental conditions,[4,133] for example, by increasing the scan rate of a cyclic voltametry[132b] or by modifying the temperature.[134a] Transition from one mechanism to the other can also take place by reduction with homogeneous electron donors.[134b,c]

In the radical anions of bicyclic or polycyclic alkyl halides bearing EWG, the rate of fragmentation depends on the relative disposition of the π and σ (C−X) systems that participate in the intramolecular ET required for dissociation of the radical anions into radicals and the leaving group anion (see section II.A.2). The effect of the electronic and distance factors on the efficiency of the intramolecular ET has been determined in a series of 4-benzoyloxy-1-methylcyclohexyl bromides bearing substituents with dif-

ferent electron acceptor abilities at the benzoyloxy moiety.[135]

Both theoretical and experimental evidence proposed the formation of π radical anions in the outer-sphere ET to ArX.[136] In this family, the π and σ systems are adjacent and orthogonal. The main reaction coordinates for the intramolecular ET from the π to the σ state, which dissociates into Ar$^{\bullet}$ radicals and X^- ions, are the C−X bond elongation and bending with respect to the aryl plane. Both types of anionic potential energy surfaces have been located by means of semiempirical and DFT calculations for PhX, haloacetophenones, and halonitrobenzenes.[129,137] The theoretical behavior predicted for PhX is in agreement with the electrochemical evidence according to which the fragmentation rate constants for X = Br and I are too high to be measured by this technique, that for X = Cl has been determined to be 4×10^7 s^{-1} (liquid ammonia, − 38 °C),[33b] and the radical anion of PhF is the most stable of the series.[137f,c] The haloaromatic family is another example of modification of the ET mechanism with the scan rate under electrochemical initiation. Whereas a change from concerted to stepwise was observed by changing the scan rate for PhI, PhBr and 1-iodonaphthalene follow a stepwise mechanism over the whole range of scan rate.[138a] On the other hand, despite the lower driving force exerted under homogeneous relative to that under electrochemical reduction, a stepwise mechanism has been proposed for the reduction of PhI by different radical anions.[138b]

The cleavage rate constants of some ArX (X = Cl, Br, or I) in DMSO,[33c] MeCN,[33c] and liquid ammonia[34a,35] have been measured. For a given halogen (X = Cl), the rate constants for dissociation vary in the following order (DMF, 25 °C): *p*-$CNC_6H_4^-$ (1.6×10^8 s^{-1}); 1- or 2-naphthyl (10^7−10^8 s^{-1}); 2- or 4-quinolyl (6.3×10^5 s^{-1}); *p*-$MeCOC_6H_4^-$ (3×10^5 s^{-1}); 9-anthracenyl (1.6×10^2 s^{-1}); and *p*-$PhCOC_6H_4^-$ (40 s^{-1}).[34b]

The rate constant for fragmentation of substituted haloaromatic radical anions is usually ortho > para > meta.[139a−c] This experimental order was theoretically explained for the haloacetophenones and halobenzonitriles series on the basis of the destabilization of the ortho-π radical anion with respect to the σ intermediate. This behavior, due mainly to steric factors, is not observed in the para intermediates.[137a] Within this trend, a low regioselectivity for the dissociation of the more crowded C−I bond of 1,4-diiodo-2,6-dimethylbenzene was determined in its reaction with the $^-CH_2COBu$-*t* ion.[139d]

On the other hand, the lower fragmentation rate order of the meta- derivatives was ascribed to differences in the adiabaticity of the intramolecular ET from the π to the σ system due to the nodal properties of the π SOMOs.[137c]

Fragmentation rates of nitro-substituted aryl halides, determined electrochemically[140] or by pulse radiolysis,[141] range from 10^{-3} to 10^2 s^{-1}. These low fragmentation rates could be explained due to the good electron acceptor ability of the π $PhNO_2$ system and its orthogonality with respect to the C−X σ* MO,[137b] in contrast with the nitrobenzyl halides in which a π−σ overlap exits. For this reason and contrary to what is found in the aliphatic family, nitrophenyl derivatives are not suitable substrates for $S_{RN}1$ reactions. Exceptions are found for *o*-$O_2NC_6H_4I$,[142] nitroaryldiazo phenyl, or *tert*-butyl sulfides[143] and for *p*-$O_2NC_6H_4I$.[144]

The radical anions of (*Z*)-4-NO_2, (*Z*)-3-NO_2, and (*Z*)-4-$NCC_6H_4N_2SBu$-*t* isomerize to the (*E*)-radical anions at very fast rate (≈6.3×10^6 s^{-1}). A cleavage recombination mechanism with aryldiazenyl radicals as intermediates has been proposed to explain this behavior.[145a,b] The rate constant for cleavage of (*Z*)-4-NO_2 and (*Z*)-4-$NCC_6H_4N_2SBu$-*t* is 10^6 s^{-1}, whereas those of the E isomers are on the order of 10^{-2} and 10^2 s^{-1} respectively. On the other hand, on the basis of electrochemical studies and gas phase mass spectrometric determinations the fragmentation of the radical anions of (*Z*)-4-F, 3-F, 4-*t*-Bu-, 4-$MeC_6H_4N_2SBu$-*t*, 2,4,6-$Me_3C_6H_2N_2SBu$-*t*, and $C_6H_5N_2SBu$-*t* can be envisaged to follow a cleave path without isomerization to probably afford aryl radicals. The rate constants for cleavage of the E and Z isomers of these intermediates are on the order of 10^3 and 10^5 s^{-1} respectively. The rate constants for dissociation of (*E*)-4-$NCC_6H_4N_2Ph$ and (*E*)-4-$O_2NC_6H_4N_2Ph$ have been determined to be 2.7×10^4 and 75 s^{-1}, respectively, in MeCN. The isomerization of the radical anions of (*Z*)-4-NO_2, (*Z*)-3-NO_2, and (*Z*)-4-$NCC_6H_4N_2SBu$-*t* bears consequences on the mechanism of the $S_{RN}1$ reaction of these compounds. It has been proposed that the attack of the nucleophile could take place on the 4-$O_2NC_6H_4N_2^{\bullet}$ radical and not on the 4-$O_2NC_6H_4^{\bullet}$ radical as previously proposed.[145]

Dissociation of stable radical anions, as those of 1-bromo- and 1-iodoanthraquinone,[146a] *p*-Cl and *p*-$BrC_6H_4NO_2$,[140a,b] *m*-Cl, and *m*-$BrC_6H_4NO_2$,[140c] is facilitated from their photoexcited states. The rate constant for the reverse reaction of 1-anthraquinolyl radicals with I^- ions[146a] and of *p*-nitrophenyl radicals with I^-, Br^-, and Cl^- ions[146b] has been determined.

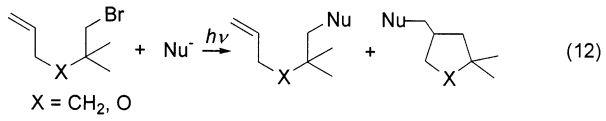
With other leaving groups, as in the case of unsymmetrical ArSAr′, fragmentation of the radical anions is possible at either of the C−S bonds. For example, in their reaction with the $^-CH_2COMe$ ion the formation of phenylacetone and arylacetone provides a measure of the relative tendencies of the diaryl sulfide radical anion to split in the two possible ways (eq 11).[147]

$$\underset{\text{Ar = } m\text{-, } p\text{-}MeC_6H_4 \quad m\text{-, } p\text{-}MeOC_6H_4}{ArSPh + {}^-CH_2COMe} \xrightarrow[NH_3]{h\nu} \underset{38\text{-}50\%}{ArCH_2COMe} + \underset{16\text{-}39\%}{PhCH_2COMe} \qquad (11)$$

B. Reactions of the Radicals Intermediates

1. Radical Rearrangement versus Coupling

Cyclized and straightforward substitution products, taken as evidence of the presence of radical intermediates, were formed in the reaction of neopentyl halide derivatives containing a cyclizable probe of the 5-hexenyl type (eq 12), and in the reaction of ArX bearing a cyclizable probe in ortho position (eq 13). In these reactions, performed with



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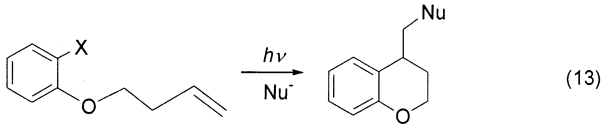
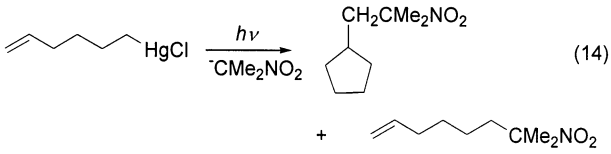


(13)

PhS^- and Ph_2P^- ions, the product distribution was dependent on the solvent and the Nu^- used.[148,149]

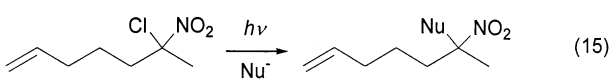
Similar experimental evidence was obtained in the reaction of secondary halides (6-halo-1-heptenes) with Me_3Sn^- [64a,b] and R_3Ge^- (R = Me or Ph)[64c] ions and in the reaction of cyclohexyl-type bromides, substituted by a cyclizable radical probe, with Ph_2P^- ions.[150] In the photoinitiated reaction of Ph_2P^- ions with 2-chloro-2-methyl-6-heptene, a tertiary chloride, only the cyclized substitution product was obtained, indicating that ring closure is faster than the coupling of the tertiary radical with Ph_2P^- ions.[151] In the reaction of the probe 6-bromo-1-hexene with the anthracene radical anion, the ratio of cyclized to uncyclized products was found to decrease with the concentration of the anthracene radical anion as a result of the competition between cyclization of the hexenyl radical and its coupling with the anthracene radical anion.[17c]

These systems offer the possibility to determine the rate constant for the Nu^-—radical coupling by knowing the rate constant for cyclization of the probe. This approach has been followed, for example, to determine the rate constant for the reaction of 5-hexenyl radicals, generated by ET to 5-hexenylmercury chloride, with the $^-CMe_2NO_2$ anion (eq 14).[152]



(14)

On the other hand, ring closure products were not observed in the $S_{RN}1$ reaction of 2-chloro-2-nitro-6-heptene[153] and 2-bromo-2-nitro-5-hexene[154] with different Nu^- (eq 15).

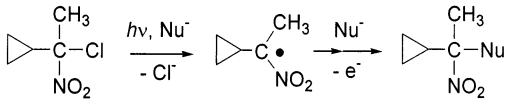


(15)

Bowman et al. proposed that the lack of cyclization of the 2-nitrohex-5-enyl radical is due to a faster rate for $^-CMe_2NO_2$ addition than for cyclization. Nitroalkyl radicals are also intermediates in the oxidative addition to nitronate anions, a reaction in which no cyclization was detected.[155] Nevertheless, they add readily when the alkene is strongly nucleophilic as in the alkylation of enamines.[156] According to these results, cyclization of α-nitroalkyl radicals is possible whenever the unsaturated bond is more nucleophilic than that of a simple alkene.

Another evidence in favor of the presence of radicals is the formation of products from ring opening when the cyclopropylcarbinyl radicals are proposed as intermediates. The Me_3Sn^- ion yielded straightforward and rearrangement substitution products in its reaction with cyclopropylcarbinyl bromide[64c,e] and iodide,[64e] but only straightforward substitution with the chloride.[64e] Both products are also formed in the alkylation of cyclopentadienyldicarbonyl iron anion by cyclopropylcarbinyl iodide.[64e] Rearranged substitution products have also been observed, in low yield, in the reaction of the radical anion and dianion of *p*-dicyanobenzene with cyclopropylcarbinyl bromide.[157]

Ring opening was not observed in the substitution of 1-chloro-1-cyclopropyl-1-nitroethane by different nitronate, malonate, and ketone enolate anions, which reflects the ability of a nitro group to stabilize a radical center (eq 16).[153,158] Assuming that $^-CMe_2$-

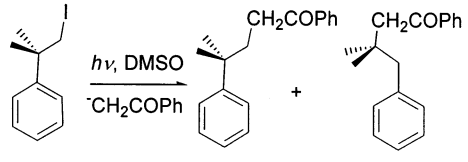


(16)

NO_2 couples with the *c*-$C_3H_5C(Me)(NO_2)^\bullet$ radical with a rate constant of 10^5 M^{-1} s^{-1},[153] and considering that the ring opening of the cyclopropylcarbinyl radical occurs with a rate constant of 1.3×10^8 M^{-1} s^{-1},[158] an α-nitro substituent has been estimated to retard the rate of ring opening of the cyclopropylcarbinyl radical by a factor of at least 10^4.

As can be seen from the above observations both radical rearrangement (cyclization or ring opening) and coupling between $^-CR_2NO_2$ ions and α-nitroalkyl or α-nitrocycloalkyl radicals are affected by the presence of the nitro group; that is, the rearrangements are slower and the coupling faster than the corresponding rates for unsubstituted alkyl radicals. This can probably be explained by the presence of two nitro groups, which considerably stabilize the radical anion formed in the coupling reaction.

Another rearrangement reaction is that shown by the neophyl radicals. In the reaction of neophyl iodide with the $^-CH_2COPh$ ion, straightforward and rearrangement substitution products are formed (50 and 16%, respectively) (eq 17). On the basis of this



(17)

rearrangement reaction, the rate constant for the coupling of the anion with the neophyl radical has been obtained.[87]

When a bridgehead radical has alkyl hydrogens at the 5-position, rearrangement of the radicals by 1,5-hydrogen migration has been observed to give a primary alkyl radical that can followed the chain propagation of the $S_{RN}1$ reaction (see section VII.C.4, eq 88).

2. Coupling with the Nucleophile

Aromatic Radicals. The absolute value of rate constants for the reaction of $Ar^{\bullet}$ radicals with Nu^- has been determined electrochemically. A large number of these values are close to the diffusion limit. For instance, the rate constants for the coupling of 2-, 3-, and 4-cyanophenyl, 1-naphthyl, 3-pyridyl, and 3- and 4-quinolyl radicals with PhS^-, $(EtO)_2PO^-$, and $^-CH_2COMe$ ions range from 10^9 to 10^{10} M^{-1} s^{-1} in liquid ammonia.[34a,35]

$Ph^{\bullet}$ radicals appear to be less reactive than the other $Ar^{\bullet}$ radicals, with rate constants for nucleophilic attack that are below the diffusion limit. The rate constants for its reaction with the previously mentioned Nu^- are in the range of 10^7-10^8 M^{-1} s^{-1}.[33b] Other examples with low rate constants are the reactions with 2-quinolyl and 2-pyridyl radicals.[34a] This effect has been rationalized by the existence of an electronic repulsion between the lone pair electrons on the nitrogen and the pair of electrons of the incoming nucleophile and also by the increase in energy of the extra electron of the C−Nu bond being formed.

One of the less reactive nucleophiles is the CN^- ion, with rate constants, determined electrochemically, below the diffusion limit. Thus, $Ph^{\bullet}$ radicals react with a rate constant of $\leq 4 \times 10^5$ M^{-1} s^{-1}; 1-naphthyl radicals, 10^6 M^{-1} s^{-1}; *o*-, 9.5×10^8 M^{-1} s^{-1}, *m*-, 5×10^7 M^{-1} s^{-1}, and *p*-$CNC_6H_5^{\bullet}$ radicals, $\sim 3 \times 10^7$ M^{-1} s^{-1}; 2-, $\leq 2 \times 10^6$ M^{-1} s^{-1} and 4-quinolyl radicals, 3×10^8 M^{-1} s^{-1}; and 4-benzoyl radicals, 4.5×10^7.[94]

The rate constants for the coupling of the *o*-(*ω*-alkenyl)phenyl cyclizable radical probe with PhS^- and $(EtO)_2PO^-$ ions were found to be $\sim 3 \times 10^8$ M^{-1} s^{-1} [148,159] and 2.5×10^9 M^{-1} s^{-1} in DMSO at 25 °C, respectively.[159] The coupling rate constants of the $^-CH_2COBu$-*t* ion with 9-anthracenyl (4.4×10^8 M^{-1} s^{-1}) and 1-naphthyl (2.9×10^9 M^{-1} s^{-1}) radicals were determined in DMSO using hydrogen abstraction from the solvent as competitive reaction.[159]

Relative reactivities for pairs of Nu^- toward the same radical can be obtained from the ratio of the two substitution products in competition reactions. The following relative reactivity order toward the $Ph^{\bullet}$ radical was found in liquid ammonia with the $^-CH_2COBu$-*t* ion (1.00) as reference: PhS^- (0.08), $(EtO)_2PO^-$ (1.4), Ph_2PO^- (2.7), and Ph_2P^- (5.9).[14] Ph_2As^- (0.44) has a lower reactivity than Ph_2P^- (1.00), which was ascribed to its reversible coupling with the $Ph^{\bullet}$ radical in liquid ammonia. When the competition was performed with 2-quinolyl radicals (irreversible coupling with Ph_2As^-), the reactive order found was NH_2^- (1.00), Ph_2P^- (6.4), and Ph_2As^- (6.4).[160] On the basis of their same reactivity, it was proposed that Ph_2P^- and Ph_2As^- react at a diffusion-controlled rate. Similar reactivities were observed, and thus diffusion-controlled rate constants were also estimated for the reactions of Ph_2P^-, Ph_3Sn^-, and Me_3Sn^- toward *p*-anisyl radicals in liquid ammonia.[76] The relative reactivity found for the chalcogenide family PhS^- (1.00), $PhSe^-$ (5.8), and $PhTe^-$ (28) toward 2-quinolyl radicals[161] seems to indicate that, as $Ar^{\bullet}$ radicals are soft electrophiles, they react more quickly as the Nu^- becomes softer along a row of the periodic table.

On the basis of these previous studies and taking PhS^- as reference, the following reactivity order can be obtained in liquid ammonia: PhS^- (1.00), $PhSe^-$ (5.8), NH_2^- (11.5), $^-CH_2COBu$-*t* ion (13), $(EtO)_2PO^-$ (18), $PhTe^-$ (28), Ph_2PO^- (34), Ph_2P^-, Ph_2As^-, Me_3Sn^-, and Ph_3Sn^- (74). As can be seen, from the less reactive to the more reactive Nu^-, the span in reactivity is <2 orders of magnitude.

The relative reactivity determined for carbanions of aliphatic ketones toward the $Ph^{\bullet}$ radical in DMSO is in the order phenyl acetone (0.39),[70a] cyclohexanone (0.67,[70a] 0.5[162a]), pinacolone (1.00), acetone (1.09), 2-butanone (1.10), and 3-pentanone (1.40,[70a] 1.50[162a]). The span in reactivity is higher for aromatic ketones with the following reactivity order: $^-CH_2COMe$ (1.00), $^-CH_2COPh$ (7.5), and anthrone anion (16.5).[79] Besides, the reactivity order of enolate anions of other aromatic ketones versus $^-CH_2COPh$ was determined to be: carbanions from 2-acetylthiophene (0.49),[104] 3-acetyl-*N*-methylpyrrole (0.73),[105] 2-acetylfuran (0.83),[104] methyl 2-naphthyl ketone (1.1,[104] 1.35[162b]), and 2-acetyl-*N*-methylpyrrole (2.6).[105] With the $^-CH_2COBu$-*t* ion as reference, the following reactivity order can be obtained toward $Ph^{\bullet}$ radicals, in DMSO, for the carbanions derived from phenyl acetone (0.39), cyclohexanone (0.67), pinacolone (1.00), acetone (1.09), 2-butanone (1.10), 3-pentanone (1.40), 2-acetylthiophene (4.0), 3-acetyl-*N*-methylpyrrole (6.0), 2-acetylfuran (6.8), acetophenone (8.2), methyl 2-naphthyl ketone (9.0), anthrone (18), and 2-acetyl-*N*-methylpyrrole (21).

All of these results are consistent with the notion that the reaction of Nu^- with $Ar^{\bullet}$ radicals occurs at or near the encounter-controlled limit. This can be rationalized considering that, for the substitution to be effective, the coupling of the radicals with the Nu^- has to compete with quite fast side reactions.

The coupling reaction with $Ar^{\bullet}$ radicals is quite insensitive to steric hindrance; thus, ArX bearing OMe or Me groups in the ortho position react quite well with many Nu^- even when they have an important steric demand. However, a small but detectable preference for hydrogen abstraction versus coupling has been observed with the radical formed by dissociation of the more crowded C−I bond of 1,4-diiodo-2,6-dimethylbenzene.[139d] An *i*-Pr group in the ortho position does not inhibit the reaction. Only when two *i*-Pr or one *t*-Bu groups are in the ortho position are the yields low.[11b,c] Another substrate, such as *p-tert*-butyl-calyx[4]arene diethyl phosphate ester, reacts to yield the reduction product quantitatively, a result that is explained on the basis of steric problems and the proximity of hydrogens to the aromatic radical center.[163]

Aliphatic Radicals. In contrast with the $Ar^{\bullet}$ radicals, not much is known about the absolute rate constants for the coupling reaction or the relative reactivities of Nu^- toward aliphatic radicals.

The rate constants for the reaction of nitronate ions with $Me^{\bullet}$ radicals in DMSO decrease as the steric hindrance at the carbon nucleophilic center increases: $^-CH_2NO_2$ (1.35×10^8 M^{-1} s^{-1}), $^-CHMeNO_2$

(1.6×10^7 M^{-1} s^{-1}), $^-CHEtNO_2$ (1.35×10^7 M^{-1} s^{-1}), and $^-CMe_2NO_2$ (2.35×10^6 M^{-1} s^{-1}).[164] The same order (10^6 M^{-1} s^{-1}) has been determined for the reaction of the $^-CMe_2NO_2$ anion with 5-hexenyl radicals[152] and for the reaction of the less sterically hindered $^-CH_2NO_2$ ion with the more hindered neophyl radicals.[87] This latter effect is also shown for the coupling of $^-CMe_2NO_2$ with p-$O_2NC_6H_4CH_2^\bullet$ and p-$O_2NC_6H_4CMe_2^\bullet$ radicals with rate constants of $\sim 0.63-1.1 \times 10^8$ and 1.2×10^6 M^{-1} s^{-1} respectively.[67]

A marked solvent effect was observed on the rate constant of the coupling between the 1-nitrocyclohexyl radical and the anion of nitrocyclohexane. Thus, the value obtained in water by pulse radiolysis was 2.6×10^6 M^{-1} s^{-1} and that in DMF, 5×10^8 M^{-1} s^{-1}, the latter calculated by the fitting of a fast-scan cyclic voltagram by digital simulation.[131]

Absolute values have also been obtained, by the radical rearrangement approach, for the reaction of neophyl radicals with the $^-CH_2COPh$ ion (1.2×10^5 M^{-1} s^{-1}),[87] and for 2,2-dimethyl-5-hexenyl radicals with PhS^- ions (1.2×10^8 M^{-1} s^{-1}) in DMSO.[148] It has been proposed that, in the same solvent, the coupling of ArS^- ions with 1-Ad$^\bullet$ is not higher than 10^7 M^{-1} s^{-1}.[16]

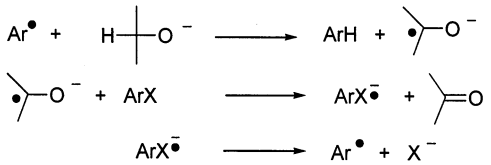
In those systems in which the substitution arises from the coupling of alkyl radicals with aromatic radical anions, the rate constant for the reaction has been estimated to be close to 10^9 M^{-1} s^{-1} in DMF.[165]

The relative reactivities of a series of anions relative to the $^-CMe_2NO_2$ ion toward the radicals $^\bullet CMe_2NO_2$, p-$O_2NC_6H_4CH_2^\bullet$, and p-$O_2NC_6H_4CMe_2^\bullet$ are known. Both the change of the counterions (by ion paring) and the change in solvent have a strong effect on the relative reactivities.[15] Consistent values were obtained with different leaving groups (X = Cl, p-$MeC_6H_4SO_2$, or NO_2). By changing the counterion the relative reactivities of the $^-CMe(CO_2Et)_2$ ion versus the $^-CMe_2NO_2$ ion can be dramatically reversed from 10 with K^+ [2.2.2]-cryptand to 0.24 in the presence of 2 M Li^+. Also, $(EtO)_2PO^-$ ion is not reactive with Li^+ as counterion, whereas with K^+ [2.2.2]-cryptand it is half as reactive as the $^-CMe_2NO_2$ ion. This was ascribed to a preferential ion pairing of $(EtO)_2PO^-$ and $^-CMe(CO_2Et)_2$ with Li^+. A change in solvent from HMPA, DMSO, or DMF to the less polar THF has an important effect on the relative reactivity of the Li^+ salts of $^-CMe(CO_2Et)_2$ versus $^-CMe_2NO_2$. Thus, the ratio increases from 0.22 in HMPA to 70 in THF, which is associated with an increase in ion pairing and a decrease in reactivity of $^-CMe_2NO_2$ ions as the polarity of the solvent decreases.

With the p-$O_2NC_6H_4CH_2^\bullet$ radical with Na^+ in EtOH or Li^+ in DMF as counterions, the following reactivity series, $(EtO)_2PS^- > {}^-CMe_2NO_2 \gg (EtO)_2PO^-$, was observed.[166] The $(EtO)_2PS^-$ ion is considerably more reactive than $^-CMe_2NO_2$, $^-CMe(CO_2Et)_2$, and $(EtO)_2PO^-$ toward p-$O_2NC_6H_4CMe_2^\bullet$ radicals. All of the results are consistent with $(EtO)_2PS^-$ being a better trap than $(EtO)_2PO^-$ for α-nitroalkyl radicals, particularly when ion pairing is important.[166]

Steric effects on the rate and product distribution of the reaction between p-nitrobenzyl substrates and nitronate anions are known. With tertiary carbanions increasing the size of the alkyl groups attached to the benzylic or the anionic carbons causes substantial decrease in the proportions of substitution. In this case formation of reduced products is observed.[167] Besides these steric limitations, most of the C-alkylated products obtained in the reaction of alkyl halides with EWG are sterically crowded molecules.

Scheme 5



By competition experiments, 1-Ad$^\bullet$ radicals are more selective than Ph$^\bullet$ radicals toward Nu^-. Thus, the relative reactivity of Ph_2P^- and PhS^- toward the 1-Ad$^\bullet$ radical is 830 but only 8.4 toward p-anisyl radicals.[168] The following relative reactivity order has been determined for the reaction of 1-Ad$^\bullet$ radical with the carbanions from anthrone (80) > CH_3NO_2 (32) > CH_3COPh (11) > N-acetylthiomorpholine (3.3)[107a] > CH_3COCH_3 (1.0).[169]

The bicyclo[4.1.0]hept-7-yl radical is slightly more selective; thus, the relative reactivity of the $^-CH_2NO_2$ ion versus the $^-CH_2COPh$ ion is 6.4 for this radical, whereas it is 3.0 with respect to the 1-Ad$^\bullet$ radical.[170] The enolate anion of methyl 2-naphthyl ketone is 1.7 times more reactive than $^-CH_2COPh$ toward 7-norcaranyl radicals.[106]

The following relative reactivity of a series of Nu^- toward the t-Bu$^\bullet$ radical from RHgX was found: $^-CH_2NO_2$ (35), $^-CHPhNO_2$ (7.4), $^-CPh_2CN$ (6.5), $^-CHMeNO_2$ (6.1), $^-CPh_2COPh$ (2.2), $^-CHPhCOPh$ (1.1), $^-CMe_2NO_2$ (1.00), NO_2^- (0.4), $^-CHMeCOPh$ (0.2), and $^-CMe_2COPh$ (0.03).[171]

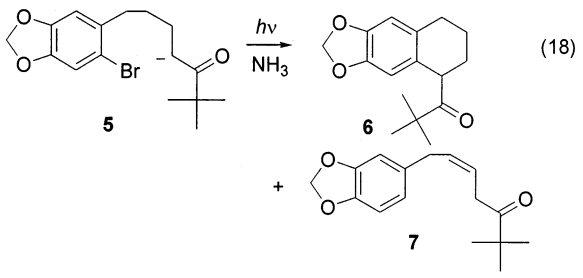
3. Coupling versus Reduction by the Nucleophile

Primary and secondary alkoxide ions do not afford the expected substitution product from their coupling reaction with Ar$^\bullet$ radicals along the $S_{RN}1$ cycle. Instead, they react with ArX by an ET-catalyzed chain process leading, through hydrogen atom abstraction, to the oxidation of the alkoxide into the radical anion of the corresponding carbonyl compound and the reductive dehalogenation of the aromatic halide.[172] Electrochemical[172d] and kinetic determinations lead to the proposal of the following reaction mechanism (Scheme 5). In this system the alkoxide acts as both hydrogen and electron donor and is responsible for the reduction of ArX and the continuation of the propagation cycle.

Although reductive dehalogenation has been observed with neopentyl iodide, MeBr, and MeI,[172a] MeO^- ions react with α-nitro-substituted alkyl radicals to afford the O-coupling product (see section VI.A.3). Substitution has also been observed with nitroperfluorobenzene probably through an $S_{RN}2$-type mechanism.[28]

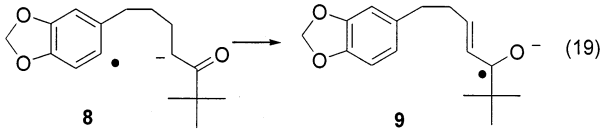
Hydrogen atom transfer from the Nu^- can compete with the coupling in reactions that involve Ar$^\bullet$ radicals as intermediates and enolate ions bearing

hydrogen at the β carbon. For example, in the reaction of the aryl halo ketone **5**, the cyclic compound **6**, obtained through an intramolecular $S_{RN}1$ reaction, is formed in low yields (11%); the major product (67%) is the β,γ-unsaturated ketone **7** (eq 18)



(18)

(presumably from isomerization of its α,β isomer).[173] Formation of this product suggests the possibility of hydrogen atom transfer from the β position of the enolate to the $Ar^{\bullet}$ radical **8** to produce the enone radical anion **9**, which continues to propagate the radical-chain (eq 19).[173]



(19)

Hydrogen atom abstraction from Nu^- has been reported for the reaction of ArX with the enolates of tertiary esters[173] and of ketones, such as diisopropyl ketone.[174] Similarly, AdH (52%) is the main compound formed by reaction of the enolate ion of isobutyrophenone with 1-IAd.[175]

4. Energetic Factors of the Coupling

The model proposed to rationalize the main experimental observations of the cleavage of radical anions (eqs 9 and 10) applies, taking the opposite sign, to the reverse reaction and so to the coupling of radicals with Nu^-.[176a] The model reproduces reasonably well the quantitative rate data available for some systems.

In terms of driving force, the factors governing the coupling are the strength of the bond being formed in the oxidized product (D_{RNu}), the standard potential for its reduction ($E^0_{RNu/RNu^{-\bullet}}$), and the standard potential for oxidation of the Nu^- (eq 10, X = Nu).

The first two factors also play an important role in determining the height of the intrinsic barrier, making the reaction less sensitive to their variations than simple driving force considerations would predict (eq 10).

The approach predicts, by estimation of $\Delta G°$ and the rate constants at zero driving force, the ~10 times faster coupling of the $^-CH_2COMe$ ion (~10^8 M^{-1} s^{-1})[33b] versus the PhS^- ion (~10^7 M^{-1} s^{-1})[33b] toward the $Ph^{\bullet}$ radical and the low reactivity of CN^- ions toward the same radical (rate constant below 4×10^5 M^{-1} s^{-1}),[94b] despite the latter being thermodynamically more favored reaction due mainly to the strength of the bond being formed (D_{PhSPh} = 3.38 eV; D_{PhCH_2COMe} = 4.18 eV; D_{PhCN} = 5.68 eV).[176] The low reactivity of CN^- toward $Ph^{\bullet}$ radicals is thus attributed to the very positive oxidation standard potential of CN^-, which is a hard nucleophile, and to a large reorganization energy precisely due to the strength of the bond being formed.[176a] The higher reactivity of the latter ion toward $Ar^{\bullet}$ radicals with EWG such as p-C_6H_5-$COC_6H_4^{\bullet}$ (4.5×10^7 M^{-1} s^{-1}),[35,94] o-$CNC_6H_4^{\bullet}$ (9.5×10^8 M^{-1} s^{-1}),[94b] and polycyclic aryl radicals is ascribed to the less negative reduction potentials of RNu/$RNu^{\bullet-}$, or equivalently to the lower energy of the π^* orbital that accommodates the unpaired electron in the course of the reaction. This factor is responsible for the higher reactivity of the anion at approximately similar strength of the bond being formed.[176a]

The coupling rate constant of NH_2^- ions with $Ph^{\bullet}$ is estimated as practically at the diffusion limit, whereas with OH^- ions, which do not react with $Ar^{\bullet}$ radicals, the predicted reactivity is very low. The main factor responsible for the difference in reactivity between NH_2^- and OH^- is attributed, according to this model, to the large difference between their oxidizabilities ($-E^0_{NH_2^{\bullet}/NH_2^-}$ = 0.03 versus −1.47 eV for OH^-).[176a]

The coupling of Nu^- with benzyl radicals proceeds if strong EWGs are present, whereas unsubstituted $Ph^{\bullet}$ radicals react with many Nu^-. The main reason for this difference in behavior is the strength of the bond being formed, which is more than 1 eV larger with $Ph^{\bullet}$ than with $PhCH_2^{\bullet}$ radicals. Substitution by a nitro group shifts the reduction potential of RNu toward more positive values and compensates the bond strength disadvantage causing acceleration in the rate constant of the coupling with the latter radicals. Similar accelerations can be obtained by substitution with two CN groups.[176a]

The difference in energy between the SOMO of the radical anion formed and the HOMO of the Nu^- ($\Delta E\pi$ or π destabilization) has been proposed to be a measurement of the difference between $E^0_{RNu/RNu^{\bullet-}}$ and $E^0_{Nu^{\bullet}/Nu^-}$, and so the $\Delta E\pi$ of the reaction can be taken as an indication of its driving force for a given bond strength. On this basis, the relative reactivity of a given radical toward a series of anions, mainly enolate ions of ketones, has been explained by assuming similar intrinsic barriers for the reaction.[79,162a,169] It has been theoretically evaluated that the HOMO energy of enolate anions decreases as the pK_a of the conjugate acid decreases, and the same tendency is followed by the SOMO energy of the radical anions formed when the anion couples with a radical. Thus, it is proposed that for a given family of carbanions their reactivity toward the same radical increases as the pK_a of the conjugate acid decreases whenever the $\Delta E\pi$ of the reaction follows a similar tendency. The higher reactivity of enolates of aromatic ketones versus aliphatic ones has been explained on these bases.[79,169]

On pK_a considerations the monoanion of acetylacetone is expected to be highly reactive; however, an important loss in π energy occurs in its coupling with $Ph^{\bullet}$ radicals[79] or 1-$Ad^{\bullet}$ radicals.[169] This high loss in π energy is attributed to an important decrease in stabilization in going from a five-center π-stabilized system of the anion (low HOMO) to a low-stabilized

π system in the radical anion formed [two carbonyl groups separated by an sp^3 carbon (high-energy SOMO)]. This situation can be reversed by reaction of monoanions of β-dicarbonyl compounds with Ar$^\bullet$ radicals stabilized by EWG. In fact, these anions are known to react with cyanophenyl,[177a] cyanopyridyl,[177a] trifluoropyridyl,[177b] $R_f^\bullet$, and other aliphatic radicals stabilized by EWG. Their behavior can thus be explained on a basis similar to that applied for the coupling of CN^-, PhS^-, and $(RO)_2PO^-$ ions with stabilized Ar$^\bullet$ radicals. For example, *o*-, *m*-, and *p*-CN, *o*-carbonyl, *o*-MeO, or *o*-NH_2 substituents have an important activating effect on the reaction of PhX with PhO^- ions, the enolate ions of aldehydes, and the enolates of β-dicarbonyl compounds.[177a,178,179] A similar effect has been observed in the reaction of ArS^- ions with chloropyridines bearing a CF_3 substituent.[180]

5. Regiochemistry of the Coupling

An ambident behavior is possible in unsaturated systems such as ketone enolates and ArO^- ions. Ketone enolate ions invariably react at the α-carbon rather than at oxygen. There is a strong driving force advantage for the C−C over the C−O bond formation with 4.18 and 3.05 eV bond strengths, respectively. In addition to this, the reduction potential of the product formed by C−O coupling is more negative than the one formed by C−C coupling.[176a] In the photostimulated reaction of 1-IAd with crowded ketone enolate ions, such as isobutyrophenone anion, C−C coupling at the para position of the phenyl ring is also observed.[175]

In the reaction of *p*-nitrobenzyl substrates with ambident nitronate anions, branching at the position adjacent to both reaction sites (C_β) causes a shift in the product distribution toward O-alkylation and away from C-alkylation. Both compounds are formed by the $S_{RN}1$ mechanism.[181,182]

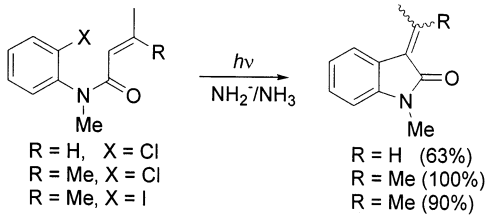
Among the aryloxide ions, PhO^- ions have a low reactivity toward Ph$^\bullet$ or *p*-anisyl radicals, but they react with Ar$^\bullet$ radicals that have a lower π^* MO due mainly to the driving force factors previously explained. The coupling occurs at the *p*- and *o*-carbons of the anion. Thermochemical estimations do not show a definite advantage of one route over the other in terms of bond strengths. On the other hand, the reduction potential of the C−C coupling product with the Ph$^\bullet$ radical is expected to be positive with respect of the C−O product.[176a] On these bases, the C−O route is expected to be slower than the C−C route. MO calculations of the driving force of the reaction are in agreement with these facts.[183]

On the other hand, an efficient O-alkylation occurs in the $S_{RN}1$ reaction of 1-methyl-2-naphthoxide ions with α,*p*-dinitrocumene and α-chloro-*p*-nitrocumene[121] and of PhO^- ions with α,*p*-dinitrocumene.[63] This difference in reactivity was explained by considering that an aryloxy substituent attached to the α-benzylic carbon has less influence on the π^* orbital of the system than when it is directly attached to a Ph$^\bullet$ radical. Therefore, the effect of the positive shift of $E^0_{RNu/RNu^{-\bullet}}$, favoring the C−C coupling in the phenyl case, becomes negligible in the benzyl case.[176a] More studies on the subject to clarify this dichotomy need to be done.

Another system in which C−C and C−heteroatom couplings occur involves the reaction of ambident $ArNH^-$ ions and heteroaryl nitrogen nucleophiles, which have a preference for *N*-alkylation (with alkyl radicals substituted by EWG)[184−188] and C-arylation with Ar$^\bullet$ radicals[189−192] and perfluoralkyl radicals.[193−195]

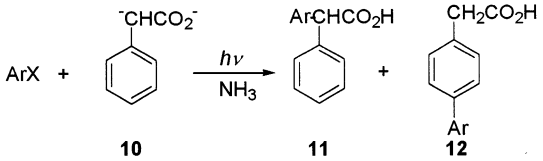
Most ArS^- ions give S-substitution, but low yield of C-arylation has been observed in the reaction of 2-naphthalenethiolate ions with Ar$^\bullet$ radicals.[183] Selective S-coupling is observed with RSO_2^- and heterocyclic S−N ambident anions and P-coupling with $(RO)_2PO^-$ and $(RO)_2PS^-$ ions.[5]

In the reaction of an Ar$^\bullet$ radical with a conjugate carbanion, such as pentadienyl anion, the lower loss in π energy for the reaction occurs by coupling at the terminal site of the π system of the anion in order to form the most stable radical anion.[196] Ar$^\bullet$ radicals also couple at the terminal site of carbanions derived from α,β-unsaturated nitriles,[197] but the intramolecular ring closure reaction with carbanions from α,β-unsaturated amides takes place at the α-C of the carbonyl group (eq 20).[198]



(20)

Ar$^\bullet$ radicals react with the dianion from phenylacetic acid **10** to afford the α-**11** and *p*-**12** arylation products, with a product distribution that depends on the counterion used (eq 21). For example, with K^+



(21)

as counterion, only **12** (73%) is formed, but with Li^+ as counterion, only **11** (77%) is obtained. Similar yields of **11** and **12** are formed with Na^+ as counterion.[199]

Phenylation at the α- and *p*-C was also obtained in the photoinitiated reaction of triphenylmethyl anion.[200a] Another example is the para coupling obtained by reaction of this anion with radicals derived from ring opening and ring rearrangement of *N*-cinnamoyl aziridine radical anions. These products are obtained, after long reaction time, by homolysis of the Michael adduct initially formed through a reversible reaction of the anion with the aziridine.[200b]

The regiochemistry observed in the substitution reaction between phenyl-substituted allyllithiums with *t*-alkyl halides and the tertiary cyclizable probe 6-bromo-6-methyl-1-heptene was explained by competition between polar and ET mechanisms. The polar pathway favors coupling at the C_1 phenyl-

substituted site, whereas for the ET pathway, the C−C formation occurs predominantly at the site far from the phenyl substituent (C_3).[201]

6. Stereochemistry of the Coupling

Further evidence favoring the presence of radicals is stereochemical in nature. In the aliphatic field complete loss of optical activity has been determined in the substitution reaction of the nitro group of optically active 2-(*p*-nitrophenyl)-2-nitrobutane with $^-CMe_2NO_2$, N_3^-, PhS^-, and $PhSO_2^-$ ions.[202] C-alkylation of the $^-CMe_2NO_2$ ion,[203a] the anions of benzylcyanide,[203b] and α-aminonitrile[203b] by optically active 2-(*p*-nitrophenyl)-2-chloroethane also occurs by the $S_{RN}1$ mechanism with complete racemization. On the other hand, C-alkylation of the $^-CH(COMe)CO_2Me$ anion[203b] and S-alkylation of the diethyldithiocarbamate anion[203a] by the same halide involve an $S_{RN}1-S_N2$ competition.

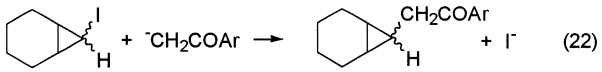
It should be noted, however, that high retention of the configuration has been reported for a cyclohexyl-type radical with EWG. This result was attributed to a fast formation and trapping of a pyramidal radical, avoiding its conversion to a planar intermediate.[204] The proportion of epimers was found to reflect the bulk of the incoming Nu^- relative to the substituent present at the reaction site.[204]

On the other hand, loss of stereochemical integrity has been observed in the reaction of alkyl-substituted cyclohexyl bromide with $LiSnMe_3$ and $LiGeMe_3$, which has been ascribed to the involvement of free radicals intermediates in the alkylation process.[64c,e,205]

Phenylallyllithium reacts with optically active 2-halobutanes, yielding exclusive coupling at C_1 with 100% inversion of configuration. In contrast, 1,1-diphenylallyllithium reacts with (−)-2-halobutanes to form a mixture of coupling at C_1 with complete inversion of configuration and at C_3 with a small but significant loss of stereochemical integrity. These results are in agreement with the proposed preferred regiochemistry for the ET pathway.[201]

Several nucleophiles ($NaSnMe_3$, LiSPh, LiSPr-*i*, LiCN, and $LiPPh_2$) have been shown to react with optically active 2-substituted octanes with loss of optical activity of the product as the leaving group changes to iodide (OTs ∼ Cl ∼ Br > I). It has been suggested that inversion of configuration can result from ET if a rapid geminate coupling of the incipient radicals takes place inside the solvent cage and the leaving group (X^-) protects the front side of the α-carbon. This result will also be observed when RX exists as a tight radical anion pair ($R^{\bullet}X^-$). However, if there is a separation of $R^{\bullet}$ and X^-, some racemization of the probe should occur in the solvent cage (prior to coupling). Finally, when the radical anion pair dissociates and the radical is kinetically free, a completely racemic product should be formed.[64a,b,206]

In the reaction of carbanions with 7-iodonorcarane **13** (a mixture of ca. 1:1 of exo and endo isomers), the substitution products are 93−95% exo isomers, indicating that the coupling of the 7-norcaranyl radical with these carbanions is quite selective (eq 22).[170] The



(22)

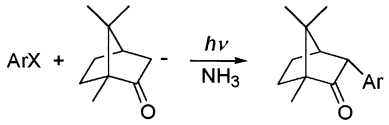
13

same yield of the exo isomer (93−95%) obtained by reaction with $^-CH_2COPh$ ions initiated with inorganic salts ($FeBr_2$ or SmI_2)[106] is evidence of the presence of 7-norcaranyl radicals as intermediates under these types of initiations.

In the reaction of the anion of 4-methoxycarbonyl-1-methyl-1,4-dihydropyridine with bornyl and isobornyl bromide in DMF, the endo and exo products were formed with a small dominance of the inversion product. The percentage of the latter compound increases at lower temperature, indicating a certain participation of an S_N2 pathway.[17c,d] On the other hand, the stereochemical structure is lost in the reaction of anthracene radical anion with bornyl and isobornyl bromide giving the same 1:1 mixture of exo and endo 9-(2-bornyl)-9,10-dihydroantracene.[207] Racemization is mostly observed, although together with detectable amounts of substitution with inversion, by reaction of the anthracene radical anion with optically active 2-octyl halides.[22c] The percentages of inversion are 5, 8, and 11% for I, Br, and Cl as leaving groups, respectively.[22c] Racemization is also obtained in the reaction of the quinoxaline radical anion with optically active *s*-BuBr.[207] In the reductive alkylation of the dianion of a pyrene isomer the involvement of ET is demonstrated by reaction with optically pure RX. In this system racemization of the alkylating agent leads to diastereomers instead of enantiomers, as is the case by reaction with the monoanionic nucleophiles.[53b]

Similar amounts of *E* and *Z* disubstitution products were obtained in the reaction of (*E*)- or (*Z*)-4-chloro-1-iodoadamantane with $LiSnMe_3$, indicating that the 1-substituted-4-adamantyl radical does not show a π-facial selectivity.[208]

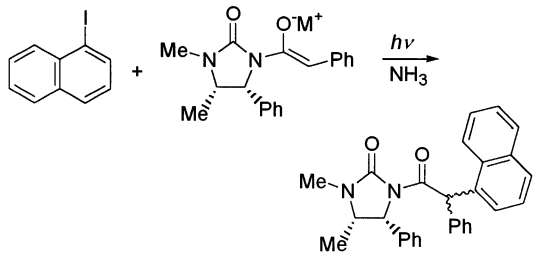
The enolate ion of (+)camphor is arylated by PhBr, PhCl, 1-chloronaphthalene, *p*-$MeOC_6H_4C_6H_4Br$, *p*-PhC_6H_4Br, and *p*-$MeOC_6H_4Cl$.[209] The almost exclusive endo-arylation at C_3 in excellent yields opens a new stereospecific C_3-arylation route of (+)-camphor (eq 23).[209]



(23)

Stereoconvergence was found in the photoinduced $S_{RN}1$ reaction of the $^-CH_2COBu$-*t* ion with (*E*)- and (*Z*)-*p*-anisyldiphenylvinyl bromide. Thus, complete loss of the original stereochemistry of the two precursors was obtained in the substituted and hydrodehalogenated products, giving evidence for the intermediacy of a vinyl radical in this reaction.[210]

1-Iodonaphthalene reacts stereoselectively with chiral-assisted imide enolate ions by the $S_{RN}1$ mechanism (eq 24). In this reaction the diastereomericisomers of the substitution compound are formed, the

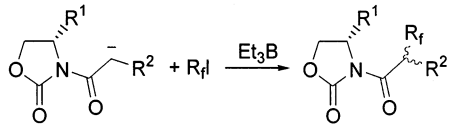


(24)

reaction being highly dependent on the metal counterion used.[211]

All of the ions studied [Li^+, Na^+, K^+, Cs^+, and Ti(IV)] present selection, but the highest is reached with Li^+ as counterion at low temperature (−78 °C) and with Ti(IV) (∼99%).[211]

Similarly, the reaction of R_fI with chiral imide enolate ions induced by Et_3B and oxygen gives the substitution products with diastereomeric excess (eq 25) (55−93%).[212] Asymmetric induction by chiral



(25)

alcohols was also observed in the $S_{RN}1$ reaction of *p*-$O_2NC_6H_4CH_2Cl$ with the α-nitroester anions, reactions in which a variable diastereomeric ratio was obtained (60:40−80:20).[213]

C. Fragmentation of Radical Anions of the Substitution Product

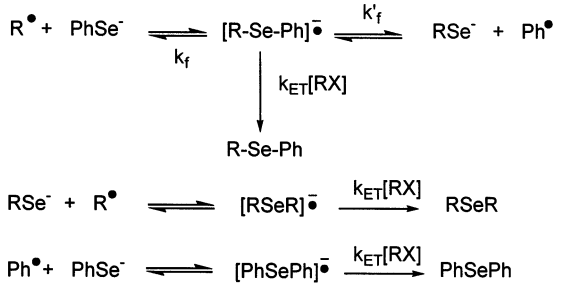
1. Substrates with One Leaving Group

The most common reaction of the radical anion of the substitution product is ET to acceptors present in the reaction media to afford the expected $S_{RN}1$ product. However, in some cases this radical anion can cleave, limiting the synthetic capability of the system. This behavior has been observed in the reaction of radicals with the ions Ph_2As^-, Ph_2Sb^-, $PhSe^-$, and $PhTe^-$. In the reactions of these Nu^-, products from scrambling of aryl rings can be formed, and its distribution has been used as mechanistic evidence.[214] The general situation is presented in Scheme 6 for the reaction of RX with the $PhSe^-$ ion.[215]

The radical anion formed in the coupling of $R^\bullet$ and $PhSe^-$ ions can undergo three competitive reactions: reversion to starting materials by fragmentation of the R−Se bond (k_f), ET to the substrate to give PhSeR, and fragmentation of the Ph−Se bond (k_f') to form the $Ph^\bullet$ radical and RSe^- ion. The RSe^- ion can couple with $R^\bullet$ to finally give R_2Se, whereas $Ph^\bullet$ can react with the $PhSe^-$ ion to form Ph_2Se. The scrambling can be avoided with a high concentration of RX (increasing the rate of k_{ET}[RX]).[216]

When R is an $Ar^\bullet$ radical, the fragmentation of the first formed radical anion depends on the relative energy of its π* and σ* C−Se MOs. For example, fragmentation occurs in the reaction with *p*-anisyl or 2-pyridyl radicals, indicating that the C−Se σ* MO is of similar energy to the π* MO of the aromatic system. On the other hand, for R = 1-naphthyl, 2-

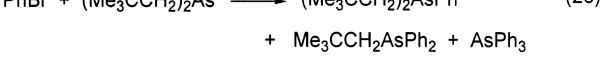
Scheme 6



quinolyl, 4-biphenyl, and 9-phenanthryl only straightforward substitution occurs, indicating that the π* MO is lower in energy than the C−Se σ* MO.[214,215] Either of the conditions k_{ET} (RX) ≫ k_f' (in the case of a radical anion with low-lying π* MO) or k_f ≫ k_f' (for a σ* radical anion) should lead to formation of the straightforward substitution product.

The fragmentation scheme proposed explains the formation of Ar_3As, Ar_2PhAs, $ArPh_2As$, and Ph_3As in the reaction of the Ph_2As^- ion with ArX such as PhX, halonaphthalenes, and halophenanthrenes. Straightforward substitution is achieved by reaction of the anion with 2-chloroquinoline and 4-halobenzophenone.[217,218] On the other hand, only scrambling of aryl rings is obtained by reaction of the Ph_2Sb^- ion with all of the mentioned substrates.[218]

Good yields of straightforward substitution are obtained in the reaction of 1-XAd with $Ph_2As_2^-$ [219] and PhS^- [220] ions, which suggests that in the radical anions formed, unlikely to be of π* type, the cleavage is faster at the aliphatic than at the aromatic C−Z bond (Z = As or S). Formation of AdH (100% yield) in the reaction of 1-$AdPh_2As$ with K metal in liquid ammonia, in which the same radical anion intermediate as in the $S_{RN}1$ reactions is formed, is in favor of the aliphatic cleavage, indicating that indeed k_f ≫ k_f'; otherwise, benzene should be observed.[219] A similar situation holds for the reaction of neopentyl bromide with Ph_2As^- ions in which only the straightforward substitution compound is obtained (80%).[221] On the other hand, dineopentylphenyl arsine (16%), neopentyldiphenylarsine (20%), and triphenylarsine (19%) are formed in the photoinitiated reaction of dineopentyl arsenide ion with PhBr (eq 26), which are the expected products if $k_{f\,neo-As}$ ≫ $k_{f\,Ph-As}$.[222]

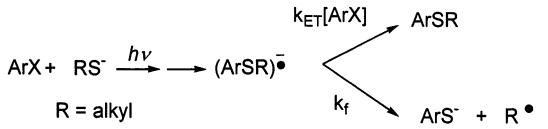


(26)

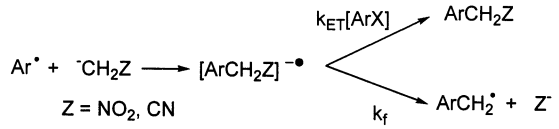
In the reaction of 1-IAd with $PhSe^-$ the three selenides Ph_2Se, 1-AdSePh, and 1-Ad_2Se are obtained in 10, 74, and 16% yields, respectively. The fact that in the reaction of PhI with $1\text{-}AdSe^-$ the three products are formed in similar yields (34, 35, and 32% yields respectively) indicates that $k_{f\,Ph-Se} \leq k_{f\,Ad-Se}$. However, when the reaction is performed with the 1-naphthaleneselenate ion, only straightforward substitution is observed.[220]

1-IAd reacts with $PhTe^-$ ions to afford 1-AdTePh as the main product together with lower amounts of Ph_2Te, whereas the latter is the main product of the

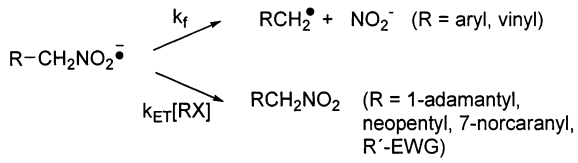
Scheme 7



Scheme 8



Scheme 9



reaction of PhI with 1-AdTe$^-$ ions, indicating that scrambling occurs in both systems.[220]

By treatment of 1-AdZPh (Z = S, Se, or Te) with Na metal in liquid ammonia, it was found that the weaker the bond is, the greater the difference in fragmentation rates [$k_{f\,Ad-Z}/k_{f\,Ph-Z}$ = 3.7 (Z = S), 9.5 (Z = Se), and 13 (Z = Te)], in agreement with the results obtained from the $S_{RN}1$ reactions.[220]

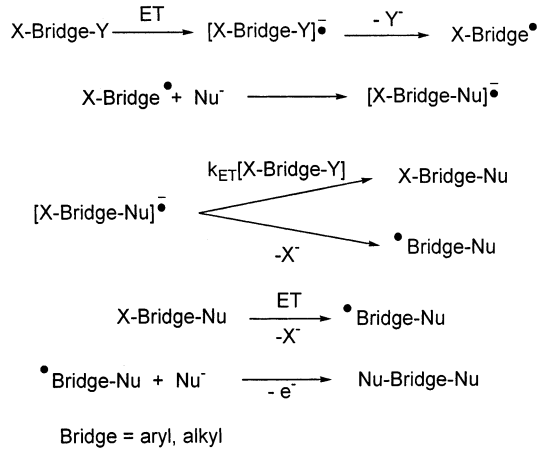
Further evidence indicating that the aliphatic C−S bond fragments more quickly than the Ph-S bond is the formation of fragmentation products in the reaction of PhX with the following thiolate ions: *n*-BuS$^-$,[223] EtS$^-$,[223,224] *t*-BuS$^-$,[223] and $EtO_2CCH_2S^-$.[224] Bond fragmentation is also observed in the reaction of 1-bromonaphthalene with $PhCH_2S^-$ ion, but 2-chloroquinoline, which has a lower π^* MO, gives only the straightforward substitution product (Scheme 7).[223]

Fragmentation has also been observed in the reaction of PhX with $^-CH_2NO_2$ and $^-CH_2CN$ ions. In these radical anions the extra electron is mainly located at Z or at the C−Z bond, favoring fragmentation into stabilized benzyl-type radicals (Scheme 8).

For example, in the reaction of $^-CH_2CN$ with PhX, toluene is the main product. On the other hand, with 1-chloronaphthalene,[98,225] polycyclic aromatic halides,[225] or ArX with substituents, such as a COPh group,[225] or halopyridines,[226] the straightforward substitution products $ArCH_2CN$ are formed. With these substrates the aryl group accommodates the extra electron of the radical anion, avoiding its fragmentation.

Bond fragmentation is always observed by reaction of $^-CH_2NO_2$[79] and $^-CMe_2NO_2$[227] ions with ArX, even with *p*-$C_6H_5COC_6H_4Br$, which has a very low π^* MO. Similarly, vinyl iodides react with $^-CH_2NO_2$ to afford Me-substituted alkenes.[228] On the other hand, straightforward substitution is achieved by reaction of $^-CH_2NO_2$ ions with 1-IAd, neopentyl iodide, and 7-iodonorcarane and by reaction of nitronate anions with aliphatic compounds bearing EWG (Scheme 9). This difference in behavior was explained by differences in the stability of the radicals formed by fragmentation or by the formation of highly stabilized

Scheme 10



radical anions in the case of aliphatic compounds substituted with EWG.

2. Substrates with Two Leaving Groups

One of the main goals of the $S_{RN}1$ mechanism is the possibility to obtain disubstituted compounds when the reaction is performed with substrates bearing two leaving groups. Few examples are known of trisubstitutions[229,230] or of four consecutive $S_{RN}1$ substitutions.[231]

When the substrate receives one electron, it fragments at the more labile C−leaving group bond to give a radical that by reaction with the Nu$^-$ forms the radical anion of the monosubstituted compound. This radical anion can transfer its extra electron to the substrate, and in this case the monosubstituted compound with retention of one leaving group is formed. Another possibility is the intramolecular ET to the second C−leaving group bond; in this case fragmentation will form a new radical, which by coupling with a second molecule of Nu$^-$ will afford the disubstituted compound. The ratio between monosubstitution to disubstitution depends on the relative rate constants for both the intra- and intermolecular ET reactions. In some systems in which the intra-ET is not favored the monosubstitution product can further react to afford disubstitution. The general situation is presented in Scheme 10.

The relative ratio between the intra- and intermolecular ET steps depends on the second leaving group (X), its electron affinity in relation to the substrate that acts as another acceptor, its relative position with respect to the Nu moiety, and the electronic nature and flexibility of the bridge, as well as on the nature of the Nu$^-$. For example, when the bridge is aromatic as in the reaction of *m*-ClC_6H_4I with the $(EtO)_2PO^-$ ion, only replacement of iodide is observed.[232a] The para isomer gives mainly disubstitution with traces of monosubstitution.[233a] On the other hand, mainly replacement of both halogens takes place in the reaction of the meta compound with PhS^- ion in liquid ammonia.[232b] The possibility of the initiation of a second chain by ET from the radical anion of the disubstituted to the monosubstituted products to afford disubstitution has been considered in the reaction of chloroiodobenzenes with different

thiolate ions[234] and of *m*-bromoiodo- or *m*-diiodobenzenes with $(EtO)_2PO^-$ ions.[233b]

In the electrochemically initiated reaction of dihalobenzenes with Nu^-, the fragmentation of the monosubstituted radical anion intermediate can be avoided in some systems by the presence of a redox mediator.[93]

o-Iodohalobenzenes (X = I, Br, or Cl) react in DMSO (under irradiation, as well as under $FeBr_2$ initiation) with the enolate ions of aromatic ketones, such as acetophenone, propiophenone, and 1-(2-naphthyl)ethanone to afford mainly monosubstitution with retention of one halogen. The degree of dehalogenation is discussed in terms of the energetics of the intramolecular ET from the ArCO−π system to the C−X σ bond in the monosubstituted radical anions proposed as intermediates. The lack of ring closure of the radicals formed by dehalogenation of these radical anions has been analyzed in terms of geometric factors.[235]

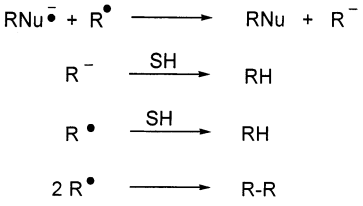
In the case of aliphatic bridges, disubstitution has been achieved in the reaction of 9,10-dibromotriptycene with Ph_2P^- ions.[236] Monosubstitution or disubstitution is obtained in the reaction of 1,4-dihalobicyclo[2.2.2]octanes and 1,3- and 1,4-dihaloadamantanes with different Nu^-. In the reaction of 1-X-4-iodobicyclo[2.2.2.]octane with Ph_2P^- ions disubstitution is obtained for X = Br and I and monosubstitution with X = Cl, indicating that the k_{ET}[substrate] $\gg k_f$ for X = Cl than for X = Br or I.[237]

Disubstitution, monosubstitution, and monosubstitution accompanied by reductive dehalogenation are obtained by reaction of *gem*-dibromocyclopropanes[238,239] with PhS^-, $PhSe^-$, and $PhTe^-$ ions and of *gem*-dichlorocyclopropanes[238] with Ph_2P^- ions. Only bromine substitution is achieved by reaction of 1-bromo-1-chloro-2,2,3,3-tetramethylcyclopropane with PhS^-.[239]

Mainly disubstitution is afforded in the reaction of 1,3-dihaloadamantanes (dichloro, chlorobromo, and dibromo) with Ph_2P^- ions.[240] The percentage of disubstitution decreases and that of monosubstitution with retention of chlorine increases when 1-bromo-3-chloroadamantane reacts in the presence of *p*-DNB. Clearly *p*-DNB does not inhibit the reaction of the substrate as effectively as the intramolecular ET within the chloro-monosubstituted radical anion.[240] Disubstitution and propellane formation occur with $LiSnMe_3$.[241] On the other hand, monosubstitution accompanied by ring fragmentation is observed in the reaction with enolate ions bearing α-hydrogens to the carbanionic center.[175]

1,2-Dichloroadamantane reacts with Ph_2P^- to afford monosubstitution of either chlorine atom with reductive dehalogenation at the other position.[242] In these reactions monosubstitution at position 1 prevails, indicating that in the radical anion of the substrate this position fragments ∼4 times more rapidly than position 2. These results have been used as an $S_{RN}1$ mechanistic evidence; the absence of disubstitution is ascribed to the steric bulk of the radicals and the incoming Ph_2P^- ions[242] (see section VII.C.1).

Scheme 11



Disubstitution is afforded in the reaction of 1-chloro-2-iodo- or 1-iodo-2-chloroadamantane with $^-CH_2COPh$ and $^-CH_2NO_2$ ions.[243] Position 2 is less reactive than position 1 when both bear the same halogen; however, it becomes more reactive than position 1 (X = Br or Cl) when substituted by a better leaving group (X = I). For these compounds the monosubstitution product is an intermediate in the formation of the disubstituted one.[243]

1,3-Diiodo-2,2-dimethylpropane, a dihalide with an aliphatic flexible bridge, reacts with $^-CH_2COPh$ ion to give disubstitution. The iodo-monosubstituted compound is not an intermediate in these reactions.[244]

Two[245−248] and four[231] consecutive $S_{RN}1$ substitutions have been achieved in the reactions of nitronate ions with di- and tetrabenzylic type chlorides bearing a quinone as EWG. Low yields of disubstitution are formed in the reaction of an allylic dichloride with a 5-nitroimidazole ring at the alkene terminus; in this reaction the monochloro-substituted product is an intermediate.[249] *p*-$O_2NC_6H_4CHCl_2$,[250] 1-dichloromethyl-5-nitroisoquinoline,[251] and 2-trichloromethyl-5-nitro-*N*-methylimidazole[252] are monosubstituted by nitronate ions through the $S_{RN}1$ mechanism. This reaction is followed by an elimination radical chain process ($E_{RC}1$), which affords the alkene derivative. On the other hand, *gem*-difluoromethylquinones give mainly the mono-fluorosubstituted product together with very low percentages of the olefin.[253]

V. Termination Steps

ET from the radical anion of the substitution product $RNu^{\bullet -}$ (or from $RX^{\bullet -}$) to a radical intermediate to form its anion is an efficient termination step in solvents that are poor H atom donors such as liquid ammonia (the rate constant for the protonation of R^- is estimated as diffusion control). Hydrogen atom abstraction by the radical from the organic solvent, when this is a good hydrogen donor, is another alternative (Scheme 11).

A quantitative kinetic model describing the propagation cycle and the influence of ET from the intermediate radical anions to $R^\bullet$ as main termination steps as well as hydrogen atom transfer to $R^\bullet$ in the case of organic solvents has been proposed under electrochemical conditions, and most of the conclusions apply to thermal or photochemical reactions.[35]

The following hydrogen abstraction rates have been determined for 9-anthracenyl radicals: 8.5×10^6 s^{-1}, DMSO;[33c] 2×10^7 s^{-1}, MeCN.[33c] For *p*-cyanophenyl radical the rate found was 4×10^7 s^{-1} (MeCN);[33c] and for 1-naphthyl radicals the rates were 2.5×10^5 s^{-1} (MeCN),[254] 3×10^5 s^{-1} (DMSO),[254] 1×10^8 s^{-1}

(DMSO),[33a] and 8×10^6 s^{-1} (DMF)[254]. Taking into consideration the $k_{coupling}/k_H$ determined in MeCN and DMSO for the reaction of 1-naphthyl and 9-anthracenyl radicals with PhZ^- (Z = S, Se, or Te)[255] and pinacolone enolate ions,[159] a k_H value approximately equal to 10^6-10^7 s^{-1} seems to be more adequate.

Even though liquid ammonia has been shown to be one of the most widely used solvents, in some systems better results can be obtained with organic solvents. For instance, the synthesis of phenylseleno- or phenyltellurobenzophenone can be achieved in MeCN under electrochemical induction.[256a] Even though this solvent is a better hydrogen donor than liquid ammonia, the photoinduced reaction in the latter solvent fails due to a competitive addition of the nucleophile to the carbonyl group.[215]

The electrochemical synthesis of 9-anthracenyl phenyl selenide and telluride proceeds with better yields in MeCN than in DMSO. For example, the reaction with $PhSe^-$ in MeCN yields a product ratio for substitution/reduction of 4, whereas in DMSO it is 1.2.[256b] Although MeCN is a better hydrogen donor than DMSO, the aryl radicals couple more quickly with the nucleophiles, giving better yields of substitution in MeCN.[255] The 4,4′-disubstituted biphenyl $PhSeC_6H_4C_6H_4SePh$ was prepared in 46% yield in MeCN,[256b] whereas its synthesis by photostimulation in liquid ammonia failed due to the insolubility of the substrate in this solvent.[215] The solvent effect in the reaction of the $^-CH_2COCH_3$ anion with 2-chloroquinoline has also been investigated (see section VIII.A.2).

Rate constants for bimolecular radical reactions of alkyl radicals with different spin traps, such as TEMPO and TEMIO (1,1,3,3-tetramethyl-2,3-dihydro-1*H*-isoindol-2-yloxyl), and hydrogen and halogen atoms donors have been reviewed by Newcomb.[257] Some examples are the following: THF with $R_3C^•$ ($k_{50} = 2 \times 10^3$ M^{-1} s^{-1}), *c*-$C_5H_9CH_2^•$ ($k_{50} = 6 \times 10^3$ M^{-1} s^{-1}) (pseudo-first order); 1,4-cyclohexadiene with $RCH_2^•$ ($k_{50} = 2 \times 10^5$ M^{-1} s^{-1}), $R_3CCH_2^•$ ($k_{50} = 5 \times 10^5$ $M^{-1}s^{-1}$); DCHP with $RCH_2^•$ ($k_{50} = 7 \times 10^5$ M^{-1} s^{-1}), $R_3CCH_2^•$ ($k_{50} = 1.0 \times 10^6$ M^{-1} s^{-1}), $PhCH_2^•$ ($k_{25} = 2.4 \times 10^3$ M^{-1} s^{-1}); TEMPO with $RCH_2^•$ ($k_{20} = 1.2 \times 10^9$ M^{-1} s^{-1}), $R_2CH^•$ ($k_{18} = 1.0 \times 10^9$ M^{-1} s^{-1}), $R_3C^•$ ($k_{20} = 0.8 \times 10^9$ M^{-1} s^{-1}), and $PhCH_2^•$ ($k_{20} = 0.5 \times 10^9$ M^{-1} s^{-1}).

Radical dimerization in general is not an important termination step with ArX. However, in electrochemically induced reactions, under adequate conditions (fast fragmentation of $ArX^{•-}$, as in the case of *p*-NCC_6H_4X, and a relatively slow rate of coupling between the radical with PhS^- ions), dimerization to 4,4′-dicyanobiphenyl (39%) has been reported.[258] When relatively stable and unreactive radicals are intermediates, such as in the reaction of the 1-Ad• radical with the $^-CH_2COMe$ ion, AdH and 1,1′-biadamanyl are also formed.[259]

Fragmentation of the radical anion of the substitution product into an unreactive radical is another type of termination, such as in the reaction of Ar• radicals with the $^-CH_2NO_2$ or Ph• radical with $^-CH_2CN$ ions.

VI. Aliphatic Substrates with EWG at the α-Carbon

These compounds are presented with the nature of the α-substituent taken into consideration. They are divided into α-substituted nitroalkanes (purely aliphatic compounds), nitrobenzyl and cumyl derivatives, heterocyclic analogues to benzyl, and other activated compounds.

In general, α-substituted nitroalkanes yield substitution by an ET process with carbon, nitrogen, and oxygen nucleophiles. For sulfur and phosphorus ions competition with an X-philic mechanism can take place depending on the nature of leaving group and the Nu^-.

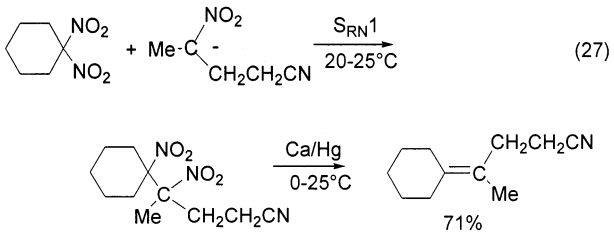
Competition with a polar S_N2 pathway can be avoided by the following approaches: (a) using poorer leaving groups such as alkyl esters, $ArSO_2$, R_3N^+, etc.; (b) photostimulation; (c) substitution at the α-carbon of the *p*-nitrobenzyl system. With the latter substrates, phosphorus nucleophiles can afford competitive products by an X-philic mechanism.

A. α-Substituted Nitroalkanes

These compounds, $XR^1R^2CNO_2$, are some of the most extensively studied in $S_{RN}1$ reactions at an sp^3 carbon. Because 2-bromonitropropane, the first substrate proposed to undergo an $S_{RN}1$ reaction in this series,[2] a wide range of alkyl groups have been reported, including cyclic, heterocyclic, and alkyl groups functionalized by −OH, −CN, and $-CO_2R$[260−263] (Tables 1−10).

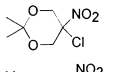
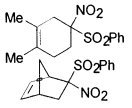
Besides the halides (I, Br, and Cl), the following groups can act as nucleofuges: ArS, $ArSO_2$, ArSO, SCN, and N_3 (Tables 1−6 and 10). When the α-substituent is a CN, COR, CO_2R, Ph, heteroaryl, or a second NO_2 group, the leaving group is the NO_2^- ion (Tables 7−10). For the α-azide nitroalkanes, the NO_2 group is substituted by N_3^-, $PhSO_2^-$, and *p*-$ClC_6H_4S^-$ ions. Meanwhile, the N_3 rather than the NO_2 group is substituted by reaction with the ions $^-CMe_2NO_2$ and $^-CEt(CO_2Et)_2$. This dual nucleofugal behavior is ascribed to the reversibility of both fragmentation pathways of the radical anion intermediate N_3C-$Me_2NO_2^{•-}$ and to a faster coupling reaction of $^•CMe_2$-NO_2 than $^•CMe_2N_3$ radicals with the last pair of Nu^-.[264,265]

These reactions have an important synthetic potential[11a] to obtain tri- and tetrasubstituted olefins principally due to the possibility of nitrous acid (HNO_2) elimination and to the reduction of vicinal dinitro compounds. It also offers the possibility of substitution of the NO_2 group by an Nu^- in a second $S_{RN}1$ process, substitution by hydrogen,[266a] its conversion to thiols,[266b] etc. Equation 27 is a representa-



(27)

Table 1. Photoinduced Reactions of α-Substituted Nitroalkanes with Nitronate Anions in DMSO[a]

$R^1R^2C(X)NO_2$		$^-CR^3R^4NO_2$	Product	Ref.
R^1- R^2	X		(%)	
$R^1 = R^2 = Me$	Br	$R^3 = R^4 = Me$	90[b]	2
	Cl		90[b]	2
	SCN		72	284
	p-$O_2NC_6H_4S$		71[c]	274
	p-ClC_6H_4S		40[c]	274
	N-methylimidazole-2-S		53[d]	286
	1,3-benzothiazole-2-S		25[c]	274
	4,5-dihydro-1,3-thiazole-2-S		16[d]	286
	o-$O_2NC_6H_4S$		13[c]	274
	p-ClC_6H_4SO		42[c]	274
	$PhSO_2$		83	*e*
	p-$MeC_6H_4SO_2$		80	*e*
	N_3		24[d]	265
	p-$O_2NC_6H_4S$	R^3-R^4 = -$(CH_2)_5$-	75[c]	274
	1,3-benzothiazol-2-yl		20[c]	274
	$PhSO_2$		83	*e*
	p-$MeC_6H_4SO_2$		86	*e*
	Cl	$R^3 = Me$, R^4 = 4-nitroimidazolyl	58[f]	268
		$R^3 = Me$, R^4 = *c*-C_3H_5	42[c]	153
		R^3-R^4= -$CH_2OC(Me)_2OCH_2$-	83	118
$R^1 = Me$, $R^2 = Et$	*p*-$MeC_6H_4SO_2$	R^3-R^4 = -$(CH_2)_5$-	86	*e*
$R^1 = Me$, $R^2 = CH_2OThp$	Cl	$R^3 = R^4 = Me$	95 (75)	118 (261)
		$R^3 = Me$, $R^4 = CH_2OThp$	55	261
		R^3-R^4= -$CH_2OC(Me)_2OCH_2$-	80	118
		$R^3 = Me$, $R^4 = CH_2CH_2CO_2Me$	75	118
$R^1 = Me$, $R^2 = CH_2CH_2CO_2Me$		$R^3 = R^4 = Me$	65	261, 118
		$R^3 = Me$, $R^4 = CH_2OThp$	30	118
		$R^3 = Me$, $R^4 = CH_2CH_2CO_2Me$	75	261
		R^3-R^4= -$CH_2OC(Me)_2OCH_2$-	50	118
$R^1 = Me$, R^2 = 4-nitroimidazolyl		$R^3 = R^4 = Me$	60[f]	268
$R^1 = Me$, R^2 = *c*-C_3H_5			78[c]	153
		$R^3 = Me$, $R^4 = CH_2CH_2CH_2CH=CH_2$	56[c]	153
$R^1 = Me$, $R^2 = CH_2CH_2CH=CH_2$	Br	$R^3 = R^4 = Me$	22[c]	154
		$R^3 = Me$, $R^4 = CH_2CH_2CH=CH_2$	60[c]	154
$R^1 = Me$, R^2 = $CH_2CH_2CH_2CH=CH_2$	Cl	$R^3 = R^4 = Me$	63[c]	153
		$R^3 = Me$, R^4 = *c*-C_3H_5	61[c]	153
		$R^3 = Me$, $R^4 = CH_2CH_2CH_2CH=CH_2$	72[c]	153
R^1-R^2 = -$(CH_2)_5$-	SCN	$R^3 = R^4 = Me$	61	265
	N_3		18[d]	284
R^1-R^2 = -$(CH_2)_5$-	$PhSO_2$		85	*e*
	p-$MeC_6H_4SO_2$		85	*e*
R^1-R^2 = -$(CH_2)_5$-	Br	R^3-R^4 = -$(CH_2)_5$-	89	43
R^1-R^2 = -$(CH_2)_5$-	$PhSO_2$		60	*e*
	p-$MeC_6H_4SO_2$		82	*e*
R^1-R^2 = -$(CH_2)_6$-	$PhSO_2$		85	*e*
$R^1 = R^2$ = -$CH_2OC(Me)_2OCH_2$-	Cl	$R^3 = R^4 = Me$	35	118
		$R^3 = Me$, $R^4 = CH_2OThp$	30	118
		$R^3 = Me$, $R^4 = CH_2CH_2CO_2Me$	14	118
		R^3-R^4 = -$CH_2OC(Me)_2OCH_2$-	30	118
		$R^3 = R^4 = Me$	87-90[g]	*h*
			87-90[g, i]	*h*

[a] X as leaving group. [b] Ethanol. [c] DMF. [d] HMPA. [e] Kornblum, N.; Boyd, S. D.; Ono, N. *J. Am. Chem. Soc.* **1974**, *96*, 2580−2587. [f] Isolated as the olefin. [g] DMPU. [h] Wade, P. A.; Murray, J. K.; Shah-Patel, S.; Carroll, P. J. *Tetrahedron Lett.* **2002**, *43*, 2585−2588. [i] Presumably with the nitro group *endo*.

tive example of the synthesis of olefins by reduction of α,β-dinitro compounds.[267]

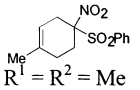
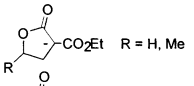
The synthesis of new tetrasubstituted *N*-azolyl (N^9-adenine, 4-nitroimidazole) and of functionalized olefins is possible by two consecutive $S_{RN}1$ reactions followed by a Grob-type fragmentation or $E_{RC}1$ eliminations of the substitution products (Scheme 12).[268] This example illustrates the versatility of the $S_{RN}1$ chemistry and its usefulness for synthesis.

A wide variety of Nu^- participate in these reactions. A comprehensive list is provided in Tables 1−10.

1. Reactions with Carbanions

The most commonly used carbanions are $^-CR^1R^2NO_2$ ions, from the simplest $^-CH_2NO_2$[269] to the more complex nitronates in which R^1 and R^2 are aliphatic, functionalized aliphatic, cyclic, and heterocyclic[261,268,270−275] groups (Tables 1 and 7). Also, an

Table 2. Photoinduced Reactions of α-Substituted Nitroalkanes with *β*-Dicarbonylic, α-Cyano, and α-Sulfonyl Esters ZYR^3C^- in DMSO[a]

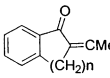
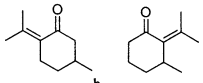
$R^1R^2C(X)NO_2$		ZYR^3C^-	$R^3YC{=}CR^1R^2$	Ref.
R^1, R^2	X		(- NO_2, - Z) (%)	
$R^1 = R^2 = Me$	Br	Y = CN, Z = CO_2Et, R^3 = Me	78[b,c]	66
		Y = CN, Z = $COC(Me)_3$, R^3 = Me	68[b,c]	66
		Y = Z = CN, R^3 = Et	68[b,c]	66
$R^1 = R^2 = Me$		Y = CN, Z = CO_2Et, R^3 = *i*-Pr, *n*-Bu, *n*-C_8H_{17},	62-75[d]	260
R^1 = Me, R^2 = Et		$PhCH_2$		
R^1-R^2 = -$(CH_2)_5$-				
$R^1 = R^2 = Me$		Y = CN, Z = *p*-$CH_3C_6H_4SO_2$, R^3 = Me	69[c,e]	278
R^1-R^2 = -$(CH_2)_4$-			70[c,e]	278
R^1-R^2 = -$(CH_2)_5$			71[c,e]	278
$R^1 = R^2$ = Me,	Cl	Y = Z = CO_2Et, R^3 = Et, *n*-Bu, $PhCH_2$	42-69[d]	260
R^1-R^2 = -$(CH_2)_5$-				
$R^1 = R^2$= Me	*p*-$MeC_6H_4SO_2$	Y = Z = CO_2Et, R^3 = Me	82[b]	*f*
R^1 = Me, R^2 = *c*-C_3H_5	Cl		77[b,c]	153
R^1 = Me, R^2 = $CH_2CH_2CH_2CH{=}CH_2$			62[b,c]	153
R^1-R^2 = -$(CH_2)_5$-	$PhSO_2$		87[b]	*f*
$R^1 = R^2$ = Me	Cl	Y = COMe, Z = CO_2Et, R^3 = Et; *n*-Bu	(51; 60)[d]	260
$R^1 = R^2$ = Me,		Y = CO_2Et, COMe, COPh, Z = H,	(56 – 86)[c]	277
R^1-R^2 = -$(CH_2)_5$-		R^3 = COMe, COPh.		
R^1 = Me, R^2 = CH_2OThp;		Y = CO_2Et, CO_2Me, COMe, Z = H,	58- 86	262
R^1 = $(CH_2)_2CO_2Me$, R^2 = CH_2OThp;		R^3 = CO_2Me, CO_2Et.		
R^1 = $(CH_2)_2CN$, R^2 = CH(Me)OThp;				
R^1-R^2 = -$(CH_2)_4CHOThp$				
R^1 = Me, R^2 = CH_2OThp		Y = CO_2Et, COMe, Z = H, R^3 = CO_2Et.	86; 70	261
R^1 = Me, R^2 = $(CH_2)_2CO_2Me$			70; 55	261
R^1 = CH_2OThp, R^2 = $(CH_2)_2CO_2Me$			30; 20	261
R^1 = CH(Me)OThp, R^2 = -$(CH_2)_2CN$		Y = CO_2Et, Z = H, R^3 = CO_2Et.	25	261
R^1 = Me, R^2 = CH_2OThp		Y = CO_2Et, Z = COMe, R^3 = Me	55[b]	261
		Y = Z = CO_2Et, R^3 = Et	54[b]	261
$R^1 = R^2$ = Me	*p*-$O_2NC_6H_4S$	Y = Z = CO_2Et, R^3 = Et	21[b,c]	274
	Cl	Y = COMe, Z = CO_2Et, R^3 = Et	72[b,d]	260
	$PhSO_2$		84[b]	*f*
	p-$MeC_6H_4SO_2$		83[b]	*f*
R^1-R^2 = -$(CH_2)_5$-	$PhSO_2$		77[b]	*f*
			40[g, h]	*i*
$R^1 = R^2$ = Me	Cl		54[d]	260
R^1 = Me, R^2 = CH_2OThp			70[b]	262
		 R = H, Me	(50, 55)[d]	260
			95[b,d]	260
			67[b]	262
			25[b]	262
				
R^1 = Me, R^2 = *c*-C_3H_5			53[b]	153
$R^1 = R^2$ = Me; R^1 = Me, R^2 = Et		Y = *p*-$MeC_6H_4SO_2$, Z = CO_2Et, R^3 = Me, Et	71-87[d]	260

[a] X as leaving group. [b] Substitution product. [c] DMF. [d] HMPA. [e] Thermal reaction carried out in the dark. [f] Kornblum, N.; Boyd, S. D.; Ono, N. *J. Am. Chem. Soc.* **1974**, *96*, 2580−2587. [g] DMPU. [h] Presumably with the nitro group *endo*. [i] Wade, P. A.; Murray, J. K.; Shah-Patel, S.; Carroll, P. J. *Tetrahedron Lett.* **2002**, *43*, 2585−2588.

intramolecular $S_{RN}1$ reaction was observed when the anion of 2-chloro-2,6-dinitroheptane was photolyzed to give the expected dinitrocyclopentane (22−35%). The cis/trans ratio (60:40) was the same as that observed for the oxidative cyclization of the 2,6-dinitroheptane dianion, indicating a similar TS for cyclization (Scheme 13).[276] A nonchain substitution mechanism can be disregarded, considering the inhibition observed by the presence of *p*-DNB.

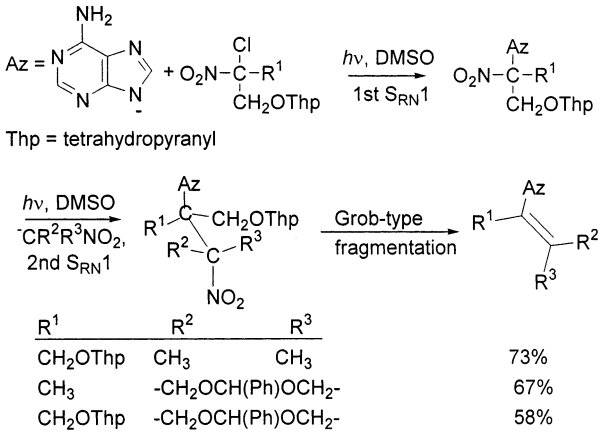
Disubstituted carbanions, such as *β*-dicarbonylic, α-cyano, and α-sulfonyl esters ($ZYRC^-$) react with α-substituted nitroalkanes by the $S_{RN}1$ mechanism (Tables 2 and 8). In the reaction of α-halonitroalkanes and under appropriate experimental conditions, the substitution products, after elimination of the nitro and ester groups, or the nitro and keto groups, give α,*β*-unsaturated ketones and esters,[260,261,277,278] nitriles,[260,278] and sulfones (Scheme 14)[260] (Table 2). The

Table 3. Photoinduced Reactions of α-Substituted Nitroalkanes with Enolate Anions in THF/Hexane (60:40)[a]

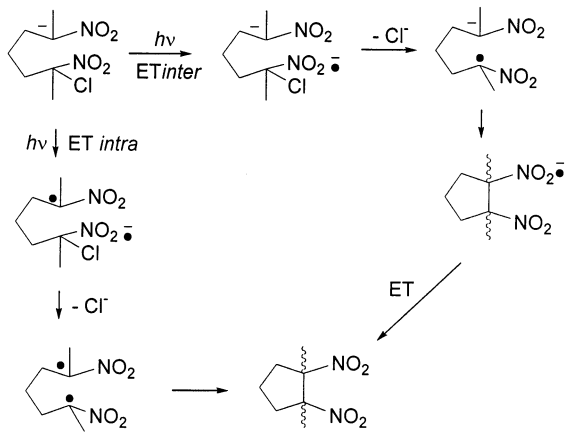
$R^1R^2C(X)NO_2$		$R^3C(O)CHR^4$ [Nu]	Product Distribution (%)			Ref.
R^1, R^2	X		$R^1R^2CNuNO_2$	$R^3(CO)CR^4{=}CR^1R^2$	Nu_2	
$R^1 = R^2 = Me$	Cl	R^3 = *t*-Bu, R^4 = H	-	72	<5	279
	p-$MeC_6H_4SO_2$		-	45	10	32
	NO_2		-	20	30	32
	Cl	R^3 = Ph, R^4 = H	-	97	-	32
		R^3 = Ph, R^4 = Me	78	-	19	279
		R^3 = Ph, R^4 = Et	74	-	13	279
		R^3 = Ph, R^4 = *n*-Bu	38	-	30	279
		R^3 = Ph, R^4 = *i*-Pr	4	-	66	279
		R^3 = Ph, R^4 = Ph	-	-	82	279
		R^3 = Ph, R^4 = OMe	-	66	-	279
		R^3 = *p*-MeC_6H_4, R^4 = Me	52	-	27	279
		R^3 = *p*-MeOPh, *m*-$NEt_2C_6H_4$, R^4 = Me	50-55	-	-	279
		R^3 = *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-NCC_6H_4, *m*-$O_2NC_6H_4$, *m*-ClC_6H_4, R^4 = Me	4-31	7-31	6-26	279
		 n = 1-3		 55, 64, 67		279
R^1-R^2 = -$(CH_2)_5$-		R^3 = Ph, R^4 = Me	-	54	30	279
$R^1 = R^2 = Me$			26[b]	20	3	*c*
		$R^3 = CH_3(CH_2)_5$-, R^4 = H	$CH_3(CH_2)_5COCH{=}CMe_2$ (3.5) : $CH_3(CH_2)_4C(COMe){=}CMe_2$ (1)[b]		-	*c*
				 4 (30%)[b] : 1		*c*

[a] X as leaving group. [b] THF. [c] Russell, G. A.; Jawdosiuk, M.; Ros, F. *J. Am. Chem. Soc.* **1979**, *101*, 3378−3379.

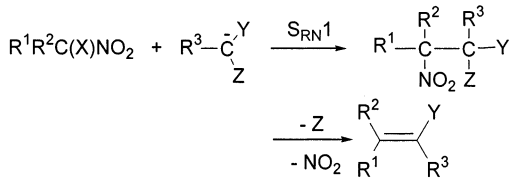
Scheme 12



Scheme 13



Scheme 14

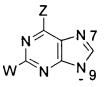
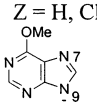
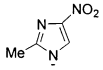
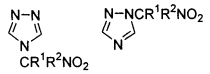


elimination step can be performed by heating with NaBr or LiCl to cause deethoxy carbonylative elimination or by heating with reducing agents to cause deacetylative elimination. The nitro and sulfonyl groups are eliminated from β-nitrosulfones on treatment with reductive one-electron-transfer agents (Na_2S or NaSPh).

When the anions derived from β-dicarbonyl compounds react with α-chloronitroalkanes functionalized with a hydroxy group (protected by tetrahydropyranyl), the corresponding olefins are formed by spontaneous elimination of HNO_2 in the reaction medium. In most cases, alcohol deprotection and lactonization occurred simultaneously under mild acidic conditions to give the butenolides in good yields (Scheme 15).[262]

The reaction with the anion derived from a tertiary malonate gives rise to the quaternary β-dicarbonyl compounds with retention of the nitro group, which

Table 4. Photoinduced Reactions of α-Substituted Nitroalkanes with Nitrogen-Centered Nucleophiles in MeCN[a]

$R^1R^2C(X)NO_2$		Nitrogen	Product (%)	Ref.
R^1, R^2	X	Nucleophiles		
$R^1 = R^2 = Me$	Br	N_3^-	38[b]	265
	SCN		8[b]	284
$R^1 = R^2 = Me$	Br		88-96 (N_9)[c]	187, 184a
$R^1 = Me$, $R^2 = CH_2OThp$			88-96 (N_9)[c]	187, 184a
$R^1 = R^2 = CH_2OThp$			84-94 (N_9)[c]	187
R^1-R^2 = -$CH_2OCHPhOCH_2$-		W = H, NH_2 Z = H, Cl, OMe, NH_2	70-81 (N_9)[c]	184a, 187
$R^1 = R^2 = Me$			96 (N_9 : N_7, 6 : 1)[c]	187
$R^1 = Me$, $R^2 = CH_2OThp$			88 (N_9 : N_7, 9 : 1)[c]	187
$R^1 = R^2 = CH_2OThp$			94 (N_9 : N_7, 3 : 2)[c]	187
$R^1 = R^2 = Me$			92[d]	188
	Cl		11[e]	186
R^1= Me, $R^2 = CH_2OThp$	Br (X = Cl)		97[d] (good yields)	188 (268)
$R^1 = R^2 = CH_2OThp$	Br		86[d]	188
R^1-R^2 = -$CH_2OCH_2OCH_2$-			81[e]	186
R^1-R^2 = -$CH_2OCH(Ph)OCH_2$-			94[d]	188
$R^1 = R^2 = Me$	Br		41[e]	186
	Cl		12[e]	186
$R^1 = Me$, $R^2 = CH_2OThp$	Br		43[f]	184b
	Cl		35[e]	184b
$R^1 = R^2 = Me$	Br		64[f,g]	184b
$R^1 = Me$, $R^2 = CH_2OThp$	Br		87	185
	Cl		29	185
R^1-R^2 = -$CH_2OCH(Ph)OCH_2$-	Br		85	185
	Cl		80	185
	Br		88	185
			30	185
			 (40 : 60) 90	185

[a] X as leaving group. Alkylation on the charged nitrogen otherwise indicated. [b] HMPA under laboratory ligth. [c] DMSO/MeCN, 1:2 ratio. [d] DMSO/MeCN, 1:1 ratio. [e] DMSO. [f] DMF. [g] Disubstitution product.

Table 5. Photoinduced Reactions of α-Substituted Nitroalkanes with NaOMe in MeOH[285]

$R^1R^2CXNO_2$		Product (%)
R^1, R^2	X	
$R^1 = R^2 = Me$	Br	$Me_2C(OMe)_2$ (96)
	NO_2	$Me_2C(OMe)_2$ (84)
	$PhSO_2$	$Me_2C(OMe)_2$ (82)
	N_3	$Me_2C(OMe)_2$ (74)
	p-ClC_6H_4S	$Me_2C(OMe)_2$ (11)
$R^1 = Me$, $R^2 = Cl$	Cl	$MeC(OMe)_3$ (56)
$R^1 = Me$, $R^2 = c$-C_3H_5		*c*-$C_3H_5CMe(OMe)_2$ (68)
$R^1 = Ph$, $R^2 = SO_2Ph$	Br	$PhC(OMe)_3$ (48)

after treatment under acidic conditions yield the β-nitro-γ-butyrolactone (*Er*) in 90% yield (Scheme 16).[262]

The substitution products of α-chloronitroalkanes with the anions of cyclic β-keto esters can either suffer thermal elimination, as described before, or lead to the opened ring olefins, which retain all of the carbon atoms of the parent $S_{RN}1$ products (by NO_2^- ion elimination and fragmentation of the cycloketone, under alkaline conditions, Scheme 17).[263]

Scheme 15

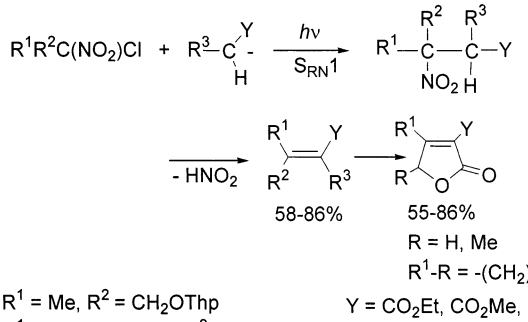
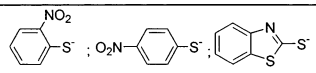
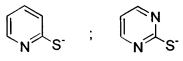
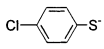
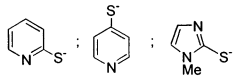
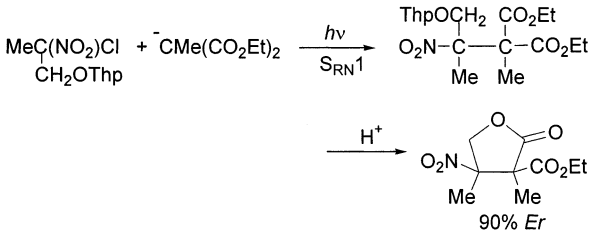


Table 6. Photoinduced Reactions of α-Substituted Nitroalkanes with Sulfur-Centered Nucleophiles in DMF[a]

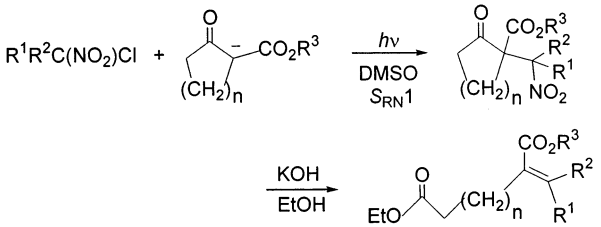
$R^1R^2C(X)NO_2$		Sulfur Nucleophiles	Products (%)[b]	Ref.
R^1, R^2	X			
$R^1 = R^2 = Me$	Br		75 [14], 83, 89	288, 274
			12 [21],[c] 13 [13][c]	286
	Cl		35 [32]	288
	$PhSO_2$		59	288
	SCN		37 [16][d]	284
	p-$MeC_6H_4SO_2$		59[d]	*e*
	Cl		(16, 7, 13)[c]	286
	I	$PhSO_2^-$	87[f]	291
	SCN		49[d]	284
	p-$O_2NC_6H_4S$		32	274
	2,4-dinitrobenzenethiolyl		59	274
	p-ClC_6H_4SO		24	274
$R^1 = Me$, $R^2 = Et$	I		93[f]	291
$R^1 - R^2 = -(CH_2)_n-$, n = 4-6			(93, 92, 85)[f]	291
$R^1 = Me$, $R^2 = CH_2CH_2CH{=}CH_2$	Cl		50	154
$R^1 = R^2 = Me$	I	p-$MeC_6H_4SO_2^-$	90[f]	291
$R^1 = Me$, $R^2 = Et$			85[f]	291
$R^1 - R^2 = (CH_2)_5$			95[f]	291

[a] X as leaving group. [b] Percent yield of the dimer [$(R^1R^2CNO_2)_2$] in brackets. [c] HMPA. [d] DMSO. [e] Kornblum, N.; Boyd, S. D.; Ono, N. *J. Am. Chem. Soc.* **1974**, *96*, 2580−2587. [f] Thermal reaction carried out in the dark. C_6H_4

Scheme 16



Scheme 17

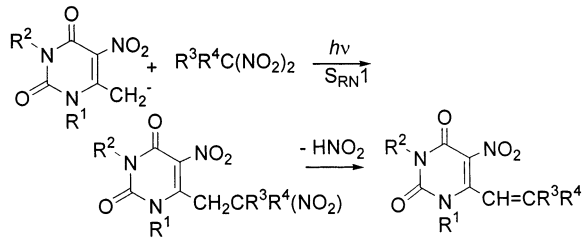


$R^1 = Me$, $R^2 = OMOM$,	n = 1, $R^3 = Me$	30%
$R^1 = R^2 = Me$,	n = 2, $R^3 = Et$	48%
$R^1 = Me$, $R^2 = CH_2OThp$		53%
$R^1 - R^2 = -(CH_2)_5-$		75%
$R^1 = R^2 = Me$,	n = 3, $R^3 = Me$	23%
$R^1 = Me$, $R^2 = CH_2OThp$		32%
$R^1 - R^2 = -(CH_2)_5-$,		47%

OMOM = methoxymethoxy

Russell and co-workers[32,279,280] proposed that simple enolate ions react with α-chloronitroalkanes by an $S_{RN}2$ rather than by an $S_{RN}1$ mechanism; competition with a chain dimerization process was also observed (Table 3). The use of 2 equiv of the enolate ion in the reaction allows complete elimination of HNO_2 to yield α,β-unsaturated ketones. The synthetic potential of these reactions has also been reported.[279] Some examples of their regioselectivity when more than one enolate ion can be formed are included in Table 3.

Scheme 18



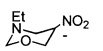
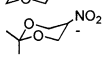
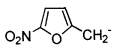
$R^1 = R^2 = Me$; Et	$R^3 = R^4 = Me$	88%; 79%
$R^1 = i$-Pr, $R^2 = Me$		75%
$R^1 = c$-C_5H_9, $R^2 = Me$		90%
$R^1 = R^2 = Me$	R^3-$R^4 = -CH_2OCMe_2OCH_2-$	69%

Stabilized carbanions from 2-methyl-4-nitrofuran,[281] 4,4-dimethyl-2-isopropyl-4,5-dihydro-1,3-oxazole,[282] and 1,3-dialkyl-6-methyl-5-nitrouracil[283] also undergo substitution by the $S_{RN}1$ mechanism (Scheme 18).

2. Reactions with Nitrogen Nucleophiles

Within nitrogen nucleophiles, the N_3^- ion is the most commonly Nu^- used.[264,265,284] N-Centered anions of imidazole and benzimidazole,[185] pyrazole,[185] triazole,[185] 5(6)-nitrobenzimidazole, 5-nitroindazole, 6-nitroindazole, 4-nitroimidazole,[188,268] purine,[184a,187] cytosine,[184b] and thymine[184b] derivatives undergo $S_{RN}1$ reaction with nitroalkanes (Tables 4 and 9). When the thymine ion reacts with 2-bromo-2-nitropropane, the disubstituted product is obtained. Experiments at shorter reaction times indicate that this compound

Table 7. Photoinduced Reactions of α-Substituted Nitroalkanes and α,α-Dinitroalkanes with Nitronates Anions in DMSO[a]

$R^1R^2C(W)NO_2$		$^-CR^3R^4NO_2$ (Nu)	Product (%)	Ref.
R^1, R^2	W			
$R^1 = R^2 = Me$	COPh, CO_2Et	$R^3 = R^4 = Me$	82[b], 95[b]	*c, d*
	CO_2Et	$R^3 = H$, $R^4 = Me$, $R^3 = R^4 = Me$; R^3-R^4 = -$(CH_2)_5$-	(88; 95; 82)[b]	*c*
R^1-R^2 = -$(CH_2)_5$-		$R^3 = R^4 = Me$; R^3-R^4 = -$(CH_2)_5$-	(94; 96)[b]	*c*
$R^1 = Me$, $R^2 = CO_2Et$	CN	$R^3 = R^4 = Me$	75	66
$R^1 = Et$, $R^2 = CO_2Et$	CO_2Et		72	66
$R^1 = R^2 = Me$	CN		90[b]	272
		R^3-R^4 = -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_{11}$-	(81; 92; 71)[b]	272
$R^1 = Me$, $R^2 = Et$		$R^3 = H$, $R^4 = (CH_2)_5CH_3$	77[b]	272
$R^1 = Me$, $R^2 = (CH_2)_4CH_3$		$R^3 = R^4 = H$	77[b]	272
R^1-R^2= -$(CH_2)_4$-		$R^3 = R^4 = Me$; R^3-R^4 = -$(CH_2)_5$-;	(74; 77)[b]	272
R^1-R^2= -$(CH_2)_5$-		$R^3 = R^4 = H$; $R^3 = H$, $R^4 = Me$;	(80; 80)[b]	272
		R^3-R^4 = -$(CH_2)_4$-; -$(CH_2)_5$-	(81; 93)[b]	272
R^1-R^2 = -$(CH_2)_{11}$-		$R^3 = R^4 = H$; $R^3 = H$, $R^4 = Et$; $R^3 = R^4 = Me$;	(83; 71; 75)[b]	272
		R^3-R^4 = -$(CH_2)_{11}$-	54[b]	
$R^1 = R^2 = Me$	NO_2	$R^3 = R^4 = Me$; R^3-R^4 = -$(CH_2)_5$	(82; 85)[b]	*c*
R^1-R^2 = -$(CH_2)_5$-		$R^3 = R^4 = Me$	91	*c*
R^1= R^2= Me			64[b]	270, 271
R^1-R^2 = -$CH_2OC(Me)_2OCH_2$-			60; 50[e]	275
$R^1 = R^2 = Me$			61[f,g]	281
	imidazolyl	$R^3 = R^4 = Me$	65	273
	4-(1,2-dimethyl-imidazolyl		64[h]	*i*
	4-nitroimidazolyl		72	188
$R^1 = R^2 = Me$	imidazolyl	R^3-R^4 = -$CH_2OCH(Ph)OCH_2$-	56	273
$R^1 = Me$, $R^2 = CH_2OThp$	imidazolyl	$R^3 = R^4 = Me$	40	273
	4-nitroimidazolyl		94	188
	*N*9-adenina		*j*	268
$R^1 = Me$, $R^2 = CH_2OThp$	imidazolyl	$R^3 = Me$, $R^4 = CH_2OThp$	25	273
		R^3-R^4 = -$CH_2OCH(Ph)OCH_2$-	50	273
$R^1 = Me$, $R^2 = CH_2OThp$	*N*9-adenina	R^3-R^4 = -$CH_2OCH(Ph)OCH_2$-	67[f]	268
$R^1 = R^2 = CH_2OThp$	4-nitroimidazolyl	$R^3 = R^4 = Me$	82	188
$R^1 = R^2 = CH_2OThp$	*N*9-adenina	$R^3 = R^4 = Me$	73[f]	268
		R^3-R^4 = -$CH_2OCH(Ph)OCH_2$-	58[f]	268
R^1-R^2 = -$CH_2OCH(Ph)OCH_2$-	imidazolyl	$R^3 = R^4 = Me$	80	273
		$R^3 = Me$, $R^4 = CH_2OThp$	65	273
		R^3-R^4 = -$CH_2OCH(Ph)OCH_2$-	72	273

[a] NO_2 as leaving group. [b] Under laboratory light. [c] Kornblum, N.; Stuchal, F. W.; Boyd, S. D. *J. Am. Chem. Soc.* **1970**, *92*, 5783−5784. [d] Kornblum, N.; Boyd, S. D. *J. Am. Chem. Soc.* **1970**, *92*, 5784−5785. [e] MeOH, under laboratory light. [f] Isolated as the olefin. [g] DMF. [h] PTC, PhMe/H_2O, under laboratory light. [i] Crozet, M. P.; Vanelle, P.; Jentzer, O.; Bertrand, M. P. *Heterocycles* **1989**, *28*, 849−855. [j] Informed as good yields of substitution, percentage not given.

is not formed via the monosubstituted product. It is proposed that the monosubstituted radical anion intermediate fragments into NO_2^- ion and a new alkyl radical. This radical reacts with a second molecule of nucleophile to yield, after ET, the disubstitution product by two consecutive $S_{RN}1$ reactions (Scheme 19). Thus, both NO_2^- and Br^- act as leaving groups.[184b]

3. Reactions with Oxygen and Sulfur Nucleophiles

Alkoxide ions derived from primary alcohols react under irradiation with $XCMe_2NO_2$ to yield $Me_2C(OR)_2$ (Table 5).[285] The cation $Me_2C{=}OR^+$ is proposed to be formed from oxidation of the respective radical by $XCMe_2NO_2$. The alkoxy substituent is suggested to be responsible for both the fragmentation of the radical anion of the monosubstituted product $ROCMe_2NO_2^{\bullet -}$ and the oxidation reactions, by stabilization of the $^\bullet CMe_2OR$ radical and the $Me_2C{=}OR^+$ cation, respectively (Scheme 20). It is possible to achieve trisubstitution when three leaving groups are present.[285]

Scheme 19

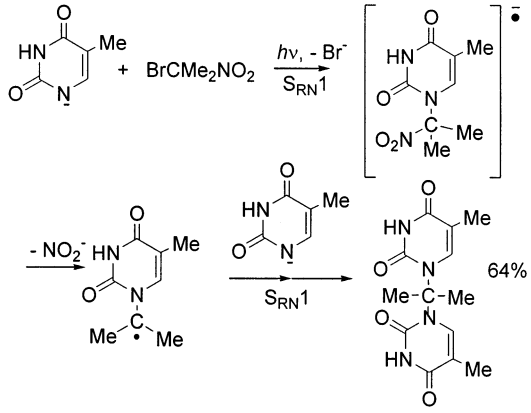
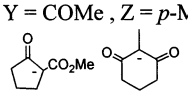
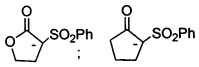
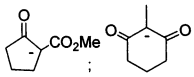
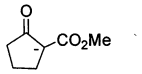
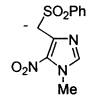
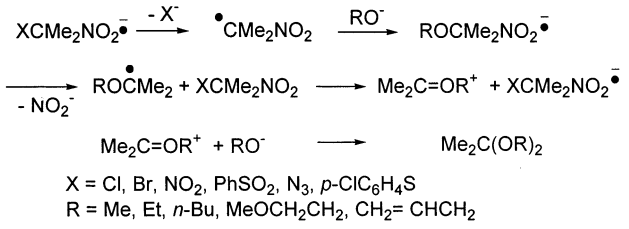


Table 8. Photoinduced Reactions of α-Substituted Nitroalkanes and α,α-Dinitroalkanes with *β*-Dicarbonylic and ZYR^3C^- Anions in DMSO[a]

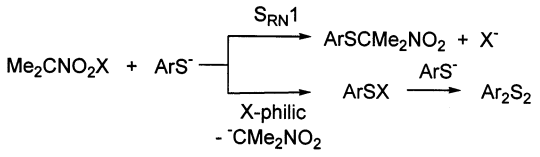
$R^1R^2C(W)NO_2$		ZYR^3C^-	Product (%)	Ref.
R^1, R^2	W			
$R^1 = R^2 = Me$	4-Nitroimidazolyl	$Y = Z = CO_2Et$, $R^3 = Me$	63	188
	NO_2		90	*b*
		$Y = Z = CO_2Et$, $R^3 = Et$	65	43; 66
		$Y = COMe$, $Z = CO_2Et$, $R^3 = Me$; $R^3 = Et$	84; 66	*b*; 66
		$Y = R^3 = COPh$, $Z = H$	63	*b*
		$Y = Z = COMe$; $R^3 = Me$	45[c]	278
		$Y = CN$, $Z = p\text{-}MeC_6H_4SO_2$, $R^3 = Et$, *n*-Bu, *n*-C_8H_{17}	(65; 45; 48)[c,d]	278
		$Y = CO_2Et$, $Z = p\text{-}MeC_6H_4SO_2$, $R^3 = Me$; Et	80[c,d]; 59[c]	278
		$Y = COMe$, $Z = p\text{-}MeC_6H_4SO_2$, $R^3 = Me$	49	278
			86; 71	*b*
			62; 54	278
$R^1 = Me$, $R^2 = Et$		$Y = CN$, $Z = p\text{-}MeC_6H_4SO_2$, $R^3 = Me$	63[c,d]	278
		$Y = CO_2Et$, $Z = p\text{-}MeC_6H_4SO_2$, $R^3 = Me$	70[c]	278
$R^1\text{-}R^2 = -(CH_2)_5-$		$Y = Z = CO_2Et$, $R^3 = Me$	84	*b*
		$Y = COMe$, $Z = CO_2Et$, $R^3 = Me$	81	*b*
		$Y = R^3 = COPh$, $Z = H$	65	*b*
			75; 58	*b*
$R^1\text{-}R^2 = -(CH_2)_{11}-$		$Y = Z = CO_2Et$, $R^3 = Me$	80	*b*
		$Y = COMe$, $Z = CO_2Et$, $R^3 = Me$	64	*b*
			73	*b*
$R^1 = Me$, $R^2 = CH_2OThp$	4-Nitroimidazolyl	$Y = Z = CO_2Et$, $R^3 = Me$	94	188
$R^1 = R^2 = CH_2OThp$			77	188
$R^1\text{-}R^2 = -CH_2OCH(Ph)OCH_2-$			83	188
$R^1 = R^2 = Me$	NO_2	$Y = CN$, $Z = p\text{-}MeC_6H_4SO_2$, $R^3 = Et$; *n*-C_8H_{17}	(74; 77)[c,e]	278
$R^1 = Me$, $R^2 = n\text{-}C_5H_{11}$		$Y = CN$, $Z = p\text{-}MeC_6H_4SO_2$, $R^3 = Me$; *n*-C_8H_{17}	(68; 62)[c,e]	278
$R^1 = R^2 = Me$			30[f]	*g*

[a] Nitro as leaving group. [b] Kornblum, N.; Kelly, W. J.; Kestner, M. M. *J. Org. Chem.* **1985**, *50*, 4720−4724. [c] Thermal reactions carried out in the dark. [d] DMF. [e] α,*β*-Unsaturated nitriles (−NO_2, −Z). [f] With a mixture of 40% of recovered nucleophile and 15% of the olefin from HNO_2 elimination from the substitution product. [g] Crozet, M. D.; Perfetti, P.; Kaafarani, M.; Vanelle, P.; Crozet, M. P. *Tetrahedron Lett.* **2002**, *43*, 4127−4129.

Scheme 20



Scheme 21

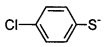
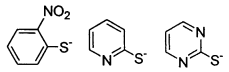
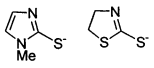
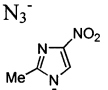


RS^- ions have been shown to react with various aliphatic α-substituted nitro compounds[274,284,286−288] to afford the α-nitro-substituted sulfides or the disulfides, the latter by oxidative dimerization. The substitution reaction is favored by weak nucleophilic RS^-. On the other hand, the redox reaction, which proceeds by an X-philic mechanism, is facilitated by strongly nucleophilic RS^- ions and more easily removed α-substituents (i.e., I > SCN > Br > Cl > NO_2). Thus, *p*-$O_2NC_6H_4S^-$ and 1,3-benzothiazol-2-yl thiolate give only the $S_{RN}1$ α-nitrosulfides product; meanwhile, the phenyl, tolyl, and benzyl thiolate yield the disulfide redox product (Scheme 21). The reactions with *p*-$ClC_6H_4S^-$ and *o*-$O_2NC_6H_4S^-$ ions afford products from both mechanisms, in relative amounts that depend on the leaving groups[288] (Tables 6 and 9).

Reactions that yield $S_{RN}1$ or mixed $S_{RN}1$/redox products in dipolar aprotic solvents yield exclusively redox products in MeOH. This was ascribed to a slower fragmentation of the radical anion $(XCMe_2NO_2)^{\bullet -}$ by strong MeOH solvation, which retards the $S_{RN}1$ reaction.[287]

In most cases the formation of the disulfides is accompanied by a similar amount of the 2,3-dimethyl-2,3-dinitrobutane dimer, which is produced from ET

Table 9. Photoinduced Reactions of α-Substituted Nitroalkanes and α,α-Dinitroalkanes with Nitrogen- and Sulfur-Centered Nucleophiles in DMSO[a]

$R^1R^2C(W)NO_2$		Nucleophile	Products (%)[b]	Ref.
R^1, R^2	W			
$R^1 = R^2 = H$	Ph	PhS^-	77[c]	290
$R^1 = H$, $R^2 = n$-Pr			72[c]	290
$R^1 = H$, $R^2 = CH_2CH_2C(OCH_2CH_2O)CH_3$			74[c]	290
$R^1 = H$, $R^2 = Et$	CO_2Et		58[c]	290
$R^1 = H$, $R^2 = Me$	COMe		28[c]	290
$R^1 = R^2 = Me$	N_3; NO_2		70[d], 69[d,e]	265; 288
	NO_2		55 [9][d,e]; 32[f]; 15 [11][f]	288; 286; 286
			(12; 20 [10])[f]	286; 286
	N_3; SCN; NO_2	$PhSO_2^-$	(70; 49; 81)[d]	265; 284; 43
	N_3	N_3^-	100[d,g]	265
	NO_2		80	186
R^1 = Me, $R^2 = CH_2OThp$			68	184b

[a] NO_2 as leaving group, for nitrogen Nu^-, alkylation on the charged nitrogen atom. [b] Percent yield of the dimer $[(R^1R^2CNO_2)_2]$ in brackets. [c] Reactions in the presence of AIBN in HMPT and temperature. [d] Under laboratory light. [e] DMF. [f] HMPA. [g] PTC, CH_2Cl_2/H_2O.

Table 10. Photoinduced Reactions of α-Substituted Nitroalkanes with Phosphorus Nucleophiles in THF[a]

$R^1R^2C(X)NO_2$		Nucleophiles	Product (%)	Ref.
R^1, R^2	X			
		$(R^3O)_2PO^-$ R^3		
$R^1 = R^2 = Me$	Cl	Me	60[b]	293
		Et	75[b]	293
	p-$MeC_6H_4SO_2$		92[b]	293
R^1 = Me, $R^2 = c$-C_3H_5	Cl	Me	42	153
		Et	72	153
R^1 = Me, R^2 = $(CH_2)_3CH{=}CH_2$		Me	63	153
		Et	49	153
R^1- R^2 = -$(CH_2)_4$-			80[b]	293
	p-$MeC_6H_4SO_2$		75[b]	293
		$(R^3O)_2PS^-$ R^3		
$R^1 = R^2 = Me$	NO_2	Me	30[c]	166
	p-$MeC_6H_4SO_2$	Et	30[c]	166
R^1 = Me, $R^2 = c$-C_3H_5	Cl		86	153

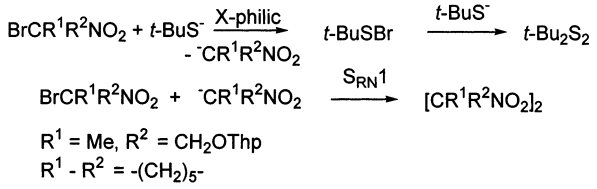
[a] X as leaving group. [b] Thermal reaction carried out in the dark. [c] DMSO.

substitution of the substrate by the nitronate anion (which in turn is generated by an X-philic reaction). Thus, the reaction of t-BuS^- with an α-bromo-α-nitroalkane leads efficiently to the corresponding dinitroalkane and the disulfide in good yields (Scheme 22).[289]

Heterocyclic S−N ambident anions have been shown to react via the sulfur atom with 2-halo-2-nitropropanes by the $S_{RN}1$ mechanism.[286] It was suggested that the addition of ambident anions to alkyl nitro radicals $^{\bullet}CR_2NO_2$ is under kinetic control via the more nucleophilic center (Table 6).

$PhSO_2^-$ ions[284,290] participate in $S_{RN}1$ reactions affording yields of substitution that depend on the structure of the substrate (leaving and substituent

Scheme 22



groups) (Tables 6 and 9). For example, α-nitrosulfones are readily obtained in 85−95% yields by treating α-iodonitroalkanes with sulfinate ions.[291]

SCN^- ion failed to react with 2-bromo-2-nitropropane by an $S_{RN}1$ mechanism, even under entrainment conditions with $^-CMe_2NO_2$.[292]

4. Reactions with Phosphorus Nucleophiles

$(RO)_2PO^-$ ions undergo $S_{RN}1$ reactions with different chloro or p-tolylsulfonyl nitroalkanes to yield the α-nitroalkylphosphonates.[293] The analogous thiophosphite ions react by this mechanism with 2-(*p*-tolylsulfonyl)-2-nitropropane and 2,2-dinitropropane but undergo an X-philic reaction with 2-chloro-2-nitropropane (Table 10).[166,15]

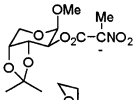
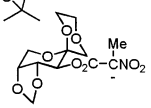
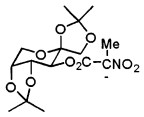
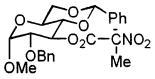
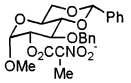
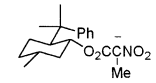
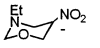
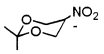
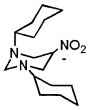
B. Nitrobenzyl and Cumyl Derivatives

1. p-Nitrobenzyl and Cumyl Derivatives

Besides the NO_2 group, other substituentes such as CN, CF_3, and PhCO are known to facilitate the $S_{RN}1$ reaction of this type of compound (see section VI.D). The *p*-nitrobenzyl and the analogous *p*-nitrocumyl derivatives react with a wide range of organic and inorganic nucleophiles, providing a novel and powerful means of synthesis (Tables 11−15).

Besides Cl other groups such as N_3, RSO_2, RSO, RO, NO_2, RS, R_3N^+, and RCO_2, which do not partici-

Table 11. Photoinduced Reactions of *p*-Nitrobenzyl and *p*-Nitrocumyl Derivatives with Nitronate Anions in DMSO[a]

p-$NO_2C_6H_4CR^1R^2X$		$^-CR^3R^4NO_2$	Product (%)[b]	Ref.
R^1, R^2	X			
$R^1 = R^2 = H$	Br; $MeSO_2$	$R^3 = R^4 = Me$	62[c]; 32	111; 298
	Cl		92, 82[d]	43, 112
		$R^3 = Me$, $R^4 = CH_2C(Me)_3$	81 [7]	181b
		$R^3 = Me$, $R^4 = t$-Bu	72 [9]	181b
		$R^3 = R^4 = i$-Pr	16 [50]	181b
		$R^3 = Me$, $R^4 = CO_2Et$	79	295
		$R^3 = Me$, $R^4 = CH_2OThp$	30[e]	261
		$R^3 = Me$, $R^4 = CH_2CH_2CO_2Me$	65	261
			87[f] - *dr* = 50:50	213
			50[f] - *dr* = 60:40	213
			51[f] - *dr* = 60:40	213
			84[f] - *dr* = 60:40	213
			86[f] - *dr* = 62:38	213
			22[f] - *dr* = 80:20	213
			78[g,h]	270 ; 271
			89[h]	275
			74[h]	275b
$R^1 = H$, $R^2 = Me$	Cl	$R^3 = H$, $R^4 = Me$	48	181b
		$R^3 = R^4 = Me$	70 [15]	181b
		$R^3 = Me$, $R^4 = i$-Pr	23 [48]	181b
$R^1 = H$, $R^2 = Et$,		$R^3 = R^4 = Me$	68 [15]	181b
$R^1 = H$, $R^2 = i$-Pr		$R^3 = H$, $R^4 = Me$	66	181b
		$R^3 = R^4 = Me$	7 [55]	181b
$R^1 = H$, $R^2 = t$-Bu		$R^3 = H$, $R^4 = Me$	52 [17]	181b
$R^1 = R^2 = Me$	NO_2; Cl	$R^3 = R^4 = Me$	90; 90	121
	N_3 ; $PhSO_2$; $PhCO_2$		(92; 93; 70)[i]	45
	$PhSO_2$; PhSO, PhS		(60; 50; 28)[i]	298; 298, 45
	NO_2	$R^3 = Me$, $R^4 = Et$	74	181
$R^1 = Me$, $R^2 = Et$		$R^3 = R^4 = Me$	78	181
		$R^3 = Me$, $R^4 = Et$	77	181
$R^1 = Me$, $R^2 = CH_2C(Me)_3$,		$R^3 = R^4 = Me$	76	181
$R^1 = Me$, $R^2 = i$-Pr		$R^3 = H$, $R^4 = Me$	22 [52]	181b
$R^1 = Me$, $R^2 = CH_2CH_2CO_2Me$		$R^3 = R^4 = Me$	42	*j*
		$R^3 = Me$, $R^4 = CH_2CH_2CO_2Et$	35	*j*

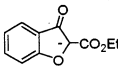
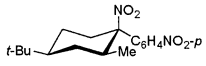
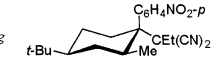
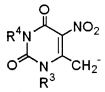
[a] X as leaving group. [b] Yield percent of O-alkylation in brackets; *dr* = diastereomeric ratio. [c] Initiation by sonic waves, darkness reaction vessel in ethanol with 16% O-alkylation. [d] Initiation with microwaves. [e] Together with 35% of the corresponding olefine coming by HNO_2 elimination. [f] DMF. [g] Isolated olefin by the loss of HNO_2 from the substitution product. [h] MeOH under laboratory light. [i] HMPA. [j] Beugelmans, R.; Lechevallier, A.; Rousseau, H. *Tetrahedron Lett.* **1984**, *25*, 2347−2350.

pate in S_N2 displacements, are able to act as leaving groups in ET chain substitution.[45]

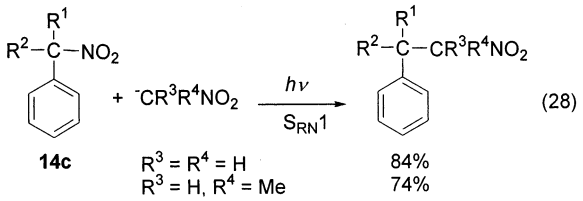
When the reaction of these types of compounds was first described,[43] the presence of the NO_2 group in the phenyl ring was emphasized to facilitate the radical process. However, it was later found that an α-NO_2 group in **14a** ($R^1 = R^2 = H$); **14b** ($R^1 = H$, $R^2 = CH_2CH_2(OCH_2CH_2O)CH_3$, Table 9)[290] and in **14c** ($R^1 = R^2 = Me$)[269,294] can be displaced by PhS^- and $^-CR_2NO_2$ ions, despite a slower rate than for the p-NO_2-substituted compounds (eq 28).[269]

Carbon Nucleophiles. A variety of $^-CR_2NO_2$ ions have been used in reactions with benzylic substrates (Table 11). Secondary and tertiary nitronate ions

Table 12. Photoinduced Reactions of *p*-Nitrobenzyl and *p*-Nitrocumyl Derivatives with β-Dicarbonylic, α-Cyano Esters, β-Dinitriles ZYR^3C^-, and Other Stabilized Carbanions[a]

p-$NO_2C_6H_4CR^1R^2X$		$^-CZYR^3$	Product (%)[b]	Ref.
R^1, R^2	X			
$R^1 = R^2 = H$	Br	Z = Y = COMe, R^3 = H	48[c,d]	*e*
	2,4,6-triphenylpyridinium		63[d,f]	*e*
		Z = COMe; Y = COPh, R^3 = H	84[d]	*e*
		Z = Y = CO*t*-Bu, R^3 = H	56[d]	*e*
		Z = Y = COPh, R^3 = H	82[d]	*e*
R^1 = H, R^2 = *t*-Bu	Cl	Z = Y = CO_2Et, R^3 = Me; Et	(73 [4]; 54 [5])[g]	167
$R^1 = R^2$ = Me	Cl; NO_2; 2-Naphthoxide	Z = Y = CO_2Et, R^3 = H	(90; 90; 62)[h,i]	121; 121; 45
	N_3; $PhSO_2$; PhS	Z = Y = CO_2Et, R^3 = Me	(89; 92; 68)[h,i]	45
	Cl; NO_2	Z = Y = CO_2Et, R^3 = *n*-Bu	(81; 87)[h,i]	121
			(90; 70)[j]	1; 63
R^1 = Me, R^2 = *i*-Pr	NO_2	Z = Y = CO_2Et, R^3 = Me	(20 [13])[g]	167
R^1 = Me, R^2 = $CH_2CH_2CO_2Me$		Z = Y = CO_2Et, R^3 = H	35[h]	*k*
		Z = COMe, Y = CO_2Et, R^3 = H	40[h]	*k*
R^1 = Me, R^2 = 		Z = Y = CO_2Et, R^3 = H	45[h]	*k*
R^1 = H, R^2 = *i*-Pr	Cl	Z = Y = CN, R^3 = *t*-Bu	(52 [10])[g]	167
R^1 = H, R^2 = *t*-Bu,		Z = Y = CN, R^3 = Me; Et, *i*-Pr	(95; 95; 59 [2])[g]	167
R^1 = Me, R^2 = *i*-Pr	NO_2	Z = Y = CN, R^3 = Et; *i*-Pr	(90; 18 [26])[g]	167
R^1 = Me, R^2 = *t*-Bu	Cl	Z = Y = CN, R^3 = Me; Et; *i*-Pr	(90; 73; - [40])[g]	167
		Z = Y = CN, R^3 = Et	50[g] 	*l*
R^1 = H, R^2 = *t*-Bu	Cl	Z = CO_2Et, Y = CN, R^3 = Me; *i*-Pr	(92; 36 [14])[g]	167
R^1 = Me, R^2 = *i*-Pr	NO_2	Z = CO_2Et, Y = CN, R^3 = Me	(31 [10])[g]	167
				
$R^1 = R^2 = H$	Cl	$R^3 = R^4$ = Me	75[h or j]	283
		$R^3 = R^4$ = Et	69[h]	283b
		R^3 = *i*-Pr, R^4 = Me	71[h]	283b
		R^3 = *c*-C_5H_9, R^4 = Me	62[h]	283b
$R^1 = R^2$ = Me	NO_2	$R^3 = R^4$ = Me	40[j]	283a

[a] X as leaving group. [b] Yield percent of the reduction product p-$NO_2C_6H_4CR^1R^2H$ in brackets. [c] Together with 14% of $(p\text{-}NO_2C_6H_4)_2C(COMe)_2$. [d] In the presence of DBU (1,8-diazabicyclo-[5.4.0]undec-7-ene) as initiator, a base with ET ability. [e] Marquet, J.; Moreno-Mañas, M.; Pacheco, P.; Prat, M.; Katritzky, A. R.; Brycki, B. *Tetrahedron* **1990**, *46*, 5333−5346. [f] Together with 31% of $(p\text{-}NO_2C_6H_4)_2C(COMe)_2$. [g] HMPA. [h] DMSO. [i] Under laboratory light. [j] DMF. [k] Beugelmans, R.; Lechevallier, A.; Rousseau, H. *Tetrahedron Lett.* **1984**, *25*, 2347−2350. [l] Norris, R. K.; Smyth-King, R. J. *J. Chem. Soc., Chem. Commun.* **1981**, 79−80.



(28)

have been employed for the study of the regiochemistry of the coupling reaction with series of secondary and tertiary *p*-nitrobenzyl radicals. The change in product distribution from C- to O-alkylation is proposed to depend on steric factors;[181,182] both products are formed by ET (see section IV.B.5).

Among the functionalized $^-CR_2NO_2$ ions used, the anion of ethyl 2-nitropropionate has been employed to synthesize the corresponding α-amino acid (Scheme 23).[295]

Carbanions from β-dicarbonylic, β-dinitriles, α-cyano esters, and uracyl derivatives have also been used in $S_{RN}1$ reactions with *p*-nitrobenzyl and cumyl derivatives (Table 12). The carbanion of *p*-nitrobenzyl phosphonate reacts with *p*-nitrocumyl halides, affording good yields of substitution[296] (see Phosphorus

Scheme 23

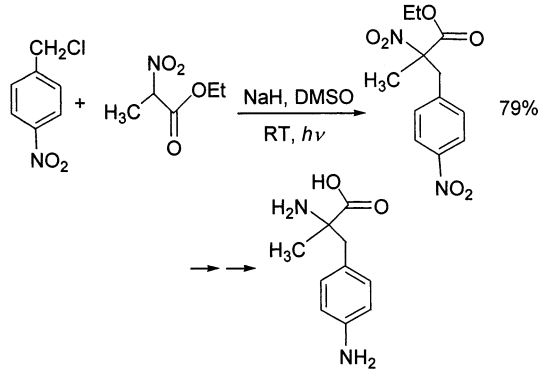
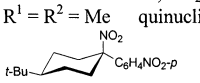
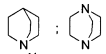


Table 13. Photoinduced Reactions of *p*-Nitrobenzyl and *p*-Nitrocumyl Derivatives with Nitrogen-Centered Nucleophiles in DMSO[a]

p-$NO_2C_6H_4CR^1R^2X$		Nitrogen Nucleophiles	Product (%)	Ref.
R^1, R^2	X			
$R^1 = R^2 = Me$	Cl, NO_2	N_3^-	(95, 94)[b]	121
$R^1 = R^2 = Me$	quinuclidinium		94[b]	45
			85[c]	*d*
$R^1 = R^2 = Me$	Cl	NO_2^-	91[b]	121
	quinuclidinium		83[b]	45
$R^1 = R^2 = Me$	Cl	$MeNH_2$	91[b]	*e*
		Me_2NH	96[b]	*e*
		n-Bu_2NH	67[b]	*e*
		Me_3N	66[b]	*e*
			90[b]	121, *e*
	Cl, NO_2		(91, 77)[b]	121, *e*
	Cl		(90, 80)[b]	121, *e*
$R^1 = R^2 = H$	Cl		72[f]	185
			93[f]	185
			95[f]	185
			100[b]	186
			100[b, g]	186
			26[b, g]	186

[a] X as leaving group. [b] Under laboratory light. [c] HMPA, with retention of configuration. [d] Norris, R. K.; Smyth-King, R. J. *J. Chem. Soc., Chem. Commun.* **1981**, 79−80. [e] Kornblum, N.; Stuchal, F. W. *J. Am. Chem. Soc.* **1970**, *92*, 1804−1806. [f] MeCN. [g] The 4-nitroimidazole isomer is the major product.

Table 14. Reactions of *p*-Nitrocumyl Derivatives with Oxygen Nucleophiles[a]

p-$NO_2C_6H_4CMe_2X$	Oxygen Nucleophiles	O-alkylation (%)[b]	Ref.
X			
NO_2	MeO^-	56[c]	63
	PhO^-	66[d]	63
quinuclidinium		57[d,e]	45
Cl	1-methyl-2-naphthoxide	62[f,g]	121
NO_2		69[d,g]	121

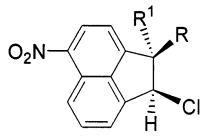
[a] X as leaving group. Reactions carried out under laboratory light. [b] Pure, isolated product. [c] MeOH, 60 °C. [d] DMSO, 25 °C. [e] ~20% of α-methyl-*p*-nitrostyrene was also isolated. [f] DMF, 0°C, 38 h. [g] ~37% of α-methyl-*p*-nitrostyrene was also isolated.

Nucleophiles). The reaction of CN^- ions with p-$O_2NC_6H_4CMe_2Cl$ is another example of an $S_{RN}1$ substitution.[121]

Nitrogen Nucleophiles. Table 13 presents the results of the reactions of *p*-nitrobenzyl and cumyl derivatives with nitrogen nucleophiles. Besides the inorganic N_3^- and NO_2^- ions, the anions of a series of azoles and neutral alkyl and cycloalkylamines afford good yields of substitution.

Recently, substitution via nitrogen was reported in the base-induced reaction of p-$H_2NC_6H_4OH$ with α,*p*-dinitrocumene. The ESR observation of the aryl aminyl radical and of the radical anion of the substitution product suggested that an $S_{RN}1$ process might be accompanied by an alternative path, which involves combination of the phenoxide aminyl with the 4-nitrocumyl radical.[297]

Chart 3



15: R = R^1 = Me
16: R = Me, R^1 = Et
17: R = Et, R^1 = Me

Oxygen and Sulfur Nucleophiles. Oxygen nucleophiles afford O-alkylation not only with α-substituted nitroalkanes[285] but also with *p*-nitrocumyl derivatives[45,63,121] by the $S_{RN}1$ mechanism. Thus, the reaction of MeO^-, PhO^-, and 1-methyl-2-naphthoxide ions with *p*-nitrocumyl derivatives gives the tertiary ethers in moderate yields (Table 14). Concomitant formation of the olefin in about one-third of the product is observed.

The reactions of a series of sulfur-centered nucleophiles are summarized in Table 15. The PhS^- ion is proposed to react with p-$O_2NC_6H_4CH_2Cl$ in EtOH by an S_N2 mechanism.[298] On the other hand, an $S_{RN}1$ pathway was assigned to the reaction of p-$O_2NC_6H_4CH_2Br$ with p-$ClC_6H_4S^-$ ions, without mechanistic evidence.[299] MeS^- ions afford substitution with p-$O_2NC_6H_4CH_2Cl$ by the S_N2 and $S_{RN}1$ mechanisms.[298] As opposed to the behavior of primary benzyl halides, the *p*-nitrocumyl derivatives react by the $S_{RN}1$ process with different RS^- ions in good yields. Products from fragmentation of the radical anion of the substitution product are not formed with these substrates, differing from the behavior observed by reaction of alkyl RS^- ions with some ArX (see section VIII.D.1).

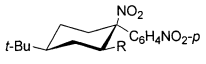
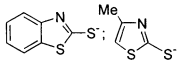
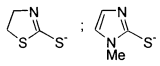
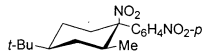
Ambident anions of 2-mercaptoazoles react under irradiation with α,*p*-dinitrocumene, leading to S-alkylated compounds by an $S_{RN}1$ reaction.[300] $ArSO_2^-$ ions also participate in this type of substitution (Table 15).

2-Chloro-1,1-dialkyl-6-nitroacenaphthenes (Chart 3), in which the NO_2 group and the Cl-bearing benzylic carbon are attached to different aromatic rings, give substitution with N_3^- and p-$MeC_6H_4S^-$ ions by the $S_{RN}1$ mechanism.[301]

Stereochemical evidence supports the fact that the reaction of the stereoisomers **16** and **17** takes place through an effectively planar benzylic radical, which is preferentially attacked from the face remote of the α-Et group. The reaction fails with Nu^- such as $^-CMe_2NO_2$, $^-CEt(CN)_2$, and p-$MeC_6H_4SO_2^-$ ions due to the presence of geminal alkyl groups α to the reaction site.

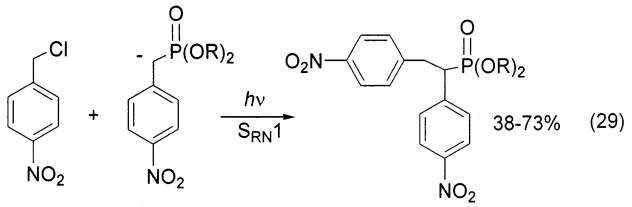
Phosphorus Nucleophiles. A series of $(RO)_2PO^-$ and $(RO)_2PS^-$ ions are known to react with *p*-nitrobenzyl derivatives.[166,302,303] These reactions lead to a variety of products depending on the leaving group and the solvent. The competing processes are $S_{RN}1$ and S_N2 substitutions, halophilic attack by the Nu^- to form the p-$O_2NC_6H_4CH_2^-$ ion, and loss of a benzylic proton to form the p-$O_2NC_6H_4CHX^-$ ion. For example, p-$O_2NC_6H_4CH_2Cl$ reacts with $(RO)_2PO^-$ ions (R = Me, Et,

Table 15. Photoinduced Reactions of *p*-Nitrobenzyl and *p*-Nitrocumyl Derivatives with Sulfur-Centered Nucleophiles in DMSO[a]

p-$NO_2C_6H_4CR^1R^2X$		Sulfur Nucleophiles	Product (%)	Ref.
R^1, R^2	X			
$R^1 = R^2 = H$	Br	p-$ClC_6H_4S^-$	50[b,c]	299
$R^1 = R^2 = H$	Cl	MeS^-	68[c,d]	298
$R^1 = H$, $R^2 = t$-Bu		PhS^-	98	*e*
$R^1 = R^2 = Me$	Cl, NO_2		(95, 96)[c]	121, 63
	$PhSO_2$, 2-naphthoxide		(91, 95)[c]	45
	N_3, PhS	p-$MeC_6H_4S^-$	(88, 79)[c]	45
	PhS	p-(t-Bu)$C_6H_4S^-$	81[c]	45
		PhS^-	55: 45 (retention:inversion)[f]	*g*
			90 (retention)[f]	*g*
$R^1 = R^2 = Me$	NO_2		36[h,i], 86[h]	300
			92[h], 47[h]	300
$R^1 = H$, $R^2 = t$-Bu	Cl	p-$MeC_6H_4SO_2^-$	*j*	*e*
		$2,4,6$-$Me_3C_6H_2SO_2^-$	64[f]	*k*
$R^1 = R^2 = Me$	Cl, NO_2	$PhSO_2^-$	(95, 94)[c]	121
	N_3. $PhSO_2$	p-$MeC_6H_4SO_2^-$	(85, 90)[c]	45
			44 (inversion)[f]	*g*

[a] X as leaving group. [b] Isolated as the sulfone. [c] Under laboratory light. [d] Ethanol. [e] Norris, R. K.; Randles, D. *Aust. J. Chem.* **1979**, *32*, 1487−1509. [f] HMPA. [g] Norris, R. K.; Smyth-King, R. J. *J. Chem. Soc., Chem. Commun.* **1981**, 79−80. [h] DMF. [i] With dimerization (18%), reduction (20%), and elimination (26%) of the benzyl radical intermediate. [j] Not given. [k] Field, L. D.; Hambley, T. W.; Jacobs, B. D.; Wilson, K.; Norris, R. K. *Aust. J. Chem.* **1988**, *41*, 443−452.

n-Pr, *n*-Bu, *i*-Pr, or Ph) in DMSO by an S_N2 process.[303] The carbanion of the substitution product reacts further with p-$O_2NC_6H_4CH_2Cl$ to yield the phosphonate **18** by $S_{RN}1$ (eq 29). In THF or EtOH



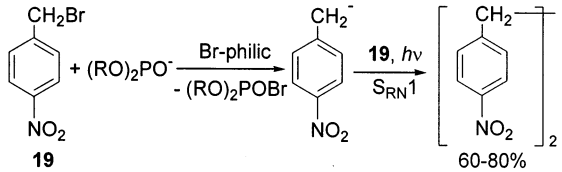
38-73% (29)

18

the S_N2 substitution is much slower and substitution by $(EtO)_2PO^-$ ions proceeds mainly by $S_{RN}1$ under irradiation.[166]

$LiP(O)(OCH_2CF_3)_2$ yields products only by the S_N2 pathway. The latter mechanism becomes slower in DMSO with the hindered $LiPO(OBu\text{-}t)_2$, and the $S_{RN}1$ process predominates. In these reactions, the stilbene derivative p-$O_2NC_6H_4CH{=}CHC_6H_4NO_2$-$p$ is also formed by reaction of the anion p-$O_2NC_6H_4CHCl^-$ with p-$O_2NC_6H_4CH_2^\bullet$ radicals followed by loss of HCl.[303]

p-$O_2NC_6H_4CH_2Br$ **19** reacts with $(RO)_2PO^-$ ions (R = Me, *i*-Pr, or Bn) by a halophilic process, followed by a substitution reaction that mainly occurs by the $S_{RN}1$ mechanism (eq 30).[302,303] With secondary ben-



(30)

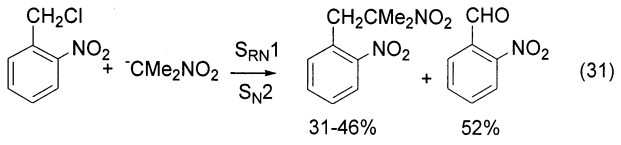
19 60-80%

zylic halides (Br and Cl), the halophilic reaction is the major reaction pathway.[303] A similar behavior has been observed by reaction with other benzylic type bromides unsubstituted by EWG (see section VII.A).

Substitutions of p-$O_2NC_6H_4CH_2Cl$ by $(RO)_2PS^-$ (or their oxygen analogues) proceed by the S_N2 mechanism in DMSO[303]and by the $S_{RN}1$ process in EtOH.[166] p-$O_2NC_6H_4CMe_2Cl$ reacts with $(EtO)_2PO^-$ and $(EtO)_2PS^-$ ions under photoinitiation by the radical mechanism to form the substitution products in 51 and 64% yields, respectively.[166]

2. *o*-Nitrobenzyl Derivatives

The reaction of o-$O_2NC_6H_4CH_2Cl$ with the $^-CMe_2NO_2$ ion proceeds by a competition between the S_N2 and radical anion processes to yield oxygen and carbon alkylation, respectively (eq 31).[5] Carbon substitution is also obtained in moderate yield with functionalized nitroalkanes (Table 16).[261]



(31)

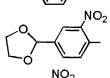
31-46% 52%

The use of *o*-nitrobenzyl compounds with leaving groups that are very difficult to displace in an S_N2 process facilitates the ET reaction. Thus, *o*-nitrobenzyl tolyl sulfones react with $^-CR_2NO_2$ ions with acceptable yields of substitution[304] (Table 16). Although the process is not accelerated by light, it is likely to proceed by a radical mechanism.

3. *m*-Nitrobenzyl and Cumyl Derivatives

m-$O_2NC_6H_4CH_2Cl$ is known to give nucleophilic substitution by an S_N2 process. On the other hand,

Table 16. Photoinduced Reactions of *o*-Nitrobenzyl Derivatives with Nitronate Anions[a]

$ArCH_2X$		$^-CR^3R^4NO_2$	$ArCH=CR^3R^4$ (-HNO_2) (%)	Ref.
Ar	X			
	Cl	R^3 = Me, R^4 = $(CH_2)_2CO_2Me$	45[b]	261
	*p*-$MeC_6H_4SO_2$	$R^3 = R^4$ = Me	75[c]	304
		R^3-R^4 = -$(CH_2)_5$-	50[c]	304
		$R^3 = R^4$ = Me	50[c]	304
			72[c]	304
			17[c]	304
			46[c]	304

[a] X as leaving group. [b] DMSO. [c] H_2O/*n*-PrOH (1:2.5 ratio), under laboratory light.

Table 17. Photoinduced Reactions of *m*-Nitrobenzyl Derivatives with Nucleophiles in HMPA[a]

m-$NO_2C_6H_4CR^1R^2X$		Nucleophile	Product (%)	Ref.
R^1, R^2	X			
$R^1 = R^2$ = H	OCOMesityl	$^-CMe_2NO_2$	36	305
		$^-CMe(CO_2Et)_2$	26	305
R^1 = H, R^2 = *t*-Bu	Cl	$^-CMe_2NO_2$	72[b]	305
		$^-CMe(CO_2Et)_2$	47[c]	305
		$^-CEt(CN)_2$	48	305
		N_3^-	54	305
		p-$MeC_6H_4S^-$	73	305
		p-$MeC_6H_4SO_2^-$	24[d,e]	305
$R^1 = R^2$ = Me	Cl; NO_2	$^-CH(CO_2Et)_2$	(90-94; 96)[e,f]	*g; h*
		$^-C(n\text{-Bu})(CO_2Et)_2$	(87[f], 85[e])[f]	*g; h*
		N_3^-	(87; 87)[f]	*g; h*
		PhS^-	(96; 94)[f,f]	*g; h*
	Cl	$^-CMe_2NO_2$	33[f,j]	*g; h*
		NO_2^-	52[f,h]	*g; h*
		$PhSO_2^-$	59[f,l]	*g; h*

[a] X as leaving group. [b] O-alkylation product by $S_{RN}1$: *m*-$O_2NC_6H_4COR^2$. [c] With 19% of the alcohol presumably from the O-alkylation product. [d] Entrainment with $LiCMe_2NO_2$. [e] DMSO. [f] Cage collapse examples carried out under laboratory light. [g] Kornblum, N.; Davies, T. M.; Earl, G. W.; Holy, N. L.; Manthey, J. W.; Musser, M. T.; Swiger, R. T. *J. Am. Chem. Soc.* **1968**, *90*, 6219−6221. [h] Kornblum, N.; Earl, G. W.; Holy, N. L.; Manthey, J. W.; Musser, M. T.; Snow, D. H.; Swiger, R. T. *J. Am. Chem. Soc.* **1968**, *90*, 6221−6223. [i] DMF. [j] With 35% of the alcohol. [k] With 27% of the alcohol. [l] With 11% of the alcohol.

m-$O_2NC_6H_4CMe_2Cl$ reacts by a mechanism involving free radicals and cage collapse of radical pairs, rather than an $S_{RN}1$ process. However, α-*tert*-butyl-*m*-nitrobenzyl chloride unambiguously undergoes substitution by an $S_{RN}1$ reaction with a variety of ions (Table 17).[305]

C. Heterocyclic Analogues of Nitrobenzyl Derivatives

Different heterocyclic analogues of *p*-nitrobenzyl derivatives react with nucleophiles by the $S_{RN}1$ mechanism (Scheme 24).

2-(Halomethyl)-5-nitrofurans give substitution with $^-CMe_2NO_2$ by the $S_{RN}1$ pathway,[281] whereas they react by S_N2 with different RS^- ions.[306] However, 2-(bromomethyl)-5-nitrofuran was assumed to afford

Scheme 24

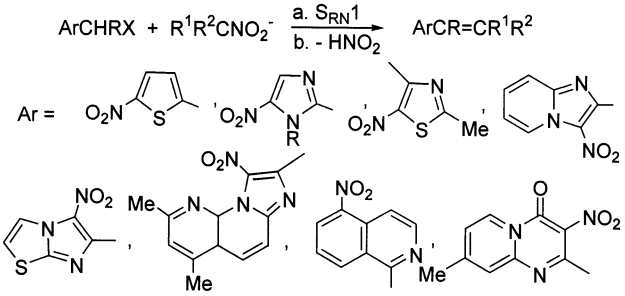
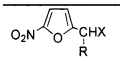
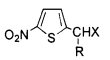
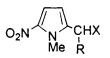


Table 18. Photoinduced Reactions of Nitrofuran, Thiophene, Pyrrole, and Pyridine Alkyl Derivatives with Nucleophiles in DMSO[a]

Substrate	Nucleophile	Products (%)	Ref.
			
R = H, X = Br; $^+NEt_3I^-$	$^-CMe_2NO_2$	(68; 61)[b]	281
R = *t*-Bu, X = Cl	$^-CMe(CN)_2$	49	49a
	N_3^-	>95	49a
	p-$MeC_6H_4S^-$	>95	49a
	p-$MeC_6H_4SO_2^-$	>95	49a
			
R = H, X = Cl	$^-CMe_2NO_2$	71[b,c]	308
	 , n = 4-7	(97, 85, 64, 43)[b,c]	308
		89[b,c]	308
		84[b,c]	308
R = *t*-Bu, X = Cl	N_3^-	70	309
	p-$MeC_6H_4S^-$	74[b]	309
	p-$MeC_6H_4SO_2^-$	90-95	309
			
R = Me, X = $OCOCH_3$	$^-CMe_2NO_2$	17	310
R = Me, X = OCOMesityl		82-88	310
	p-$MeC_6H_4S^-$	81	310
	$^-CMe_2NO_2$	86[d]	*e*
		89[d]	*e*
	PhS^-	73[d]	*e*

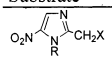
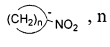
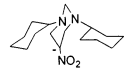
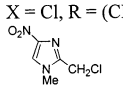
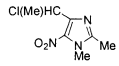
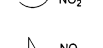
[a] X as leaving group. [b] DMF. [c] Isolated as the olefins by HNO_2 elimination from the substitution product. [d] HMPA. [e] Feuer, H.; Doty, J. K.; Kornblum, N. *J. Heteroatom. Chem.* **1978**, *15*, 1419−1423.

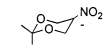
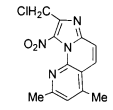
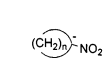
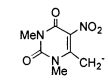
substitution with PhS^- and *p*-$ClC_6H_4S^-$ ions by an $S_{RN}1$ reaction, without mechanistic evidences.[299] This pathway prevails when the benzylic carbon is substituted by a *tert*-butyl group (Table 18).[49a]

The reaction of 2-chloromethyl-5-nitrothiophene with the $^-CMe_2NO_2$ ion was initially reported to proceed with very poor yields of C-alkylation.[307] More recently the reaction was reinvestigated and extended to various nitronate anions under more adequate experimental conditions (Nu^-/substrate ratio 3:1 and 15 min of irradiation). In these $S_{RN}1$ reactions new 5-nitrothiophenes bearing a trisubstituted ethylenic double bond at the 2-position were obtained in good yields[308] (Table 18).

The substitution of neopentylic carbons bearing 4- or 5-nitrothienyl groups proceeds by different mechanisms.[309] Substitutions in the 5-nitro series take place by $S_{RN}1$ (Table 18), whereas those in the 4-nitro

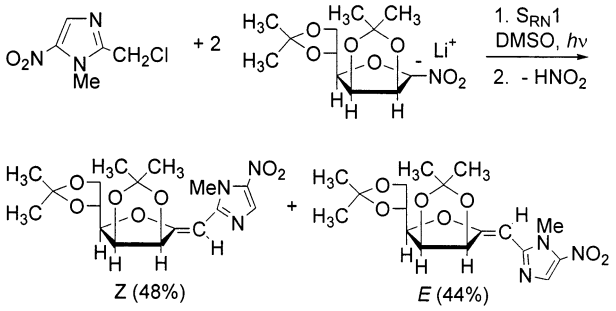
Table 19. Photoinduced Reactions of Nitroimidazole Derivatives with Nucleophiles[a]

Substrate	Nucleophile	Product[b] (%)	Ref.
			
X = Cl, R = Me	$^-CMe_2NO_2$	88[c]	311
		98[d]	315
X = Br, R = Me		8[c]	315
X = NEt_3Cl, R = Me		64[c]	315
X = Cl, R = Me	 , n = 4-6, 11	(84, 76, 95, 65)[d]	311
		94[d]	311
		65[d]	311
		89[e]	275
		84[e,f]	313
		90[e]	271
		70[e]	315, 275b
	$^-CMePhNO_2$	61[d]	311
	$^-CMe(CH_2OThp)NO_2$	46[d]	311
	$^-CMe(CO_2Et)NO_2$	(57)[g,h]	295
			
	Z = O, R^2 = Me, n = 2-4	(85, 44, 17)[i]	314
	Z = O, R^2 = $(CH_2)_3N(CH_3)_2$, n = 2	36[i]	314
	Z = S, R^2 = Me, n = 2	12,5[i]	314
X = Cl, R = $(CH_2)_2OH$	Z = O, R^2 = Me, n = 2	31[i]	314
X = Cl, R = $(CH_2)_2OEt$	Z = O, R^2 = Me, n = 2	41[j]	314
X = Cl, R = $(CH_2)_2OAc$	Z = O, R^2 = Me, n = 2	18[d]	314
	$^-CMe_2NO_2$	77[d,f]	316
		60[f,g]	317
		38[d,f,k]	321c
		(94-95)[c or d]	318
		91[f,l]	112
	$^-CMe(CO_2Et)NO_2$	65[g,m]	295
	 n = 4-7, 11	(62-94)[d]	321a
		84[d]	321a
		70[d]	321a
		79[d]	321a
		65[d]	321a
		66[d]	321a
		39[d]	321a
	$^-CMePhNO_2$	68[d]	321a
	$^-CMe(n\text{-}Pr)NO_2$	77[d]	321a
	$^-CMe[(CH_2)_2CH(CH_3)_2]NO_2$	90[d]	321a
		40[c,f]	283a
		9[f,n]	321c

Substrate	Nucleophile	Product[b] (%)	Ref.
	$^-CMe_2NO_2$	67[l,o]	321b
		83[d]	321c,d
	 , n = 4-7, 11	(80, 62, 54, 43, 29)[d]	321c,d
		53[d]	321c,d
	$^-CMePhNO_2$	65[d]	321c,d
	$^-CMe(CO_2Et)NO_2$	59[d]	321c,d
	$^-CMe[(CH_2)_3CH(CH_3)_2]NO_2$	58[d]	321c,d
	$^-CMe_2NO_2$	(65)[c,p]	320
	 n = 4-7, 11	(59-97)[c]	320
		89[c]	320
	$^-CMe_2NO_2$	99[c]	319
		56[c,f]	283a

[a] X as leaving group. [b] Isolated as the olefins by HNO_2 elimination from the substitution product. [c] DMF. [d] PTC, CH_2Cl_2/H_2O. [e] MeOH, under laboratory light. [f] Substitution product isolated without HNO_2 elimination. [g] DMSO. [h] Together with 36% of substitution. [i] PTC, PhMe/H_2O. [j] PTC, cyclohexane/H_2O. [k] Together with 13% of O-alkylation products. [l] Initiation with microwaves. [m] Together with 30% of substitution. [n] In THF. [o] Substitution product with 4% of the olefin by HNO_2 elimination. [p] Together with 31% of substitution.

Scheme 25



series occur by the ionic S_N(AEAE) process, which involves initial attack of the Nu^- at the 5-position of the thiophene ring.

On the other hand, the analogues 1-methyl-2-(chloroneopentyl)-4- or 5-nitropyrroles react with N_3^-, NCS^-, and *p*-$MeC_6H_4S^-$ ions through an S_N1-type reaction.[310] With poorer leaving groups, such as the acetic or mesitoic esters, the S_N1 pathway is disfavored and the C-alkylated compound with the $^-CMe_2NO_2$ ion is obtained by an $S_{RN}1$ process. Good results have also been found in the reactions with *p*-$MeC_6H_4S^-$ ions (Table 18).

2-(Halomethyl)-1-methyl-5-nitroimidazoles are also good substrates for the $S_{RN}1$ substitution with various aliphatic and cyclic,[311,312] heterocyclic,[271,275,313] functionalized nitronate anions,[295,311] and 3-nitrolactam anions[314] (Table 19). Thus, the $S_{RN}1$ mechanism provides a versatile methodology for the preparation of new 5-nitroimidazoles bearing a tri- or tetrasubstituted ethylenic double bond at position 2.[315] This reaction was recently extended to a nitrosugar anion to give the ethylenic derivative (mixture of Z and E isomers) by nitrous acid elimination from the C-alkylated compound (Scheme 25).[315]

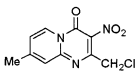
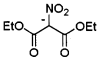
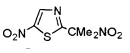
The *m*-nitrobenzyl chloride analogue 2-(chloromethyl)-1-methyl-4-nitroimidazole reacts with $^-CMe_2NO_2$ ions by the $S_{RN}1$ mechanism under PTC. Alkenylimidazole derivatives are obtained by nitrous acid elimination from the C-alkylated product (Table 19).[316]

The $S_{RN}1$ substitution of a nitroimidazole in which the NO_2 group is ortho to the side chain at which substitution occurs is also possible.[317] This process is more efficient than in the *o*-nitrobenzylic series.

Vanelle, Crozet, and co-workers[283a,295,318−321] have reported the $S_{RN}1$ reactions of nitronate ions with a series of imidazoles fused to a heterocycle ring bearing the NO_2 group at C_4 and the chloromethyl group at C_5 of the imidazole ring (ortho to the NO_2 group). In this system the heterocyclic moiety unsubstituted by the NO_2 group was not sufficiently electron-withdrawing to participate in an $S_{RN}1$ reaction. The system constitutes a powerful synthetic tool to obtain nitro-heterocycles with potential pharmacological properties (Table 19).

The reaction of 1-chloromethyl-5-nitroisoquinoline with the $^-CMe_2NO_2$ ion was the first reported example of substitution by the $S_{RN}1$ mechanism in the isoquinoline series.[322] The reaction was further extended to various aliphatic, cyclic, and heterocyclic nitronate ions. By nitrous acid elimination, trisubstituted olefins can be prepared from the C-alkylated product[323] (Table 20).

Table 20. Photoinduced Reactions of Isoquinoline, Pyrimidinone, and Thyazole Derivatives with Nucleophiles in DMF

Substrate	Nucleophile	Product (%)[a]	Ref.
	$^-CMe_2NO_2$	28 [62]	322
	 n = 4-6	28 [30], 35 [52], 49	323
		15 [52]	323
		[68]	323
		- [40]	323
	$^-CMe(n\text{-}Pr)NO_2$	- [50]	323
	$^-CMe[(CH_2)_2CH(CH_3)_2]NO_2$	- [45]	323
	$^-CRHNO_2$ (R = Me, Et, *n*-Pr)	- [77][b], - [61][b] - [54][b]	324 324
	$^-CMe_2NO_2$	- [77][b]	324
	 n = 4-6	- [70][b], - [66][b] - [57][b], - [54][b]	324
		- [53][b]	324
		- [68][b]	324
		- [65][b]	324
	$PhSO_2^-$	56	324
	$PhCH_2S^-$	78	324
		62	324
	$^-CMe_2NO_2$	- [71][c] 72 [10][d]	325 112[c]
	 n = 4, 5	-[12][c], - [18][c]	325
	$^-CMe_2NO_2$	71	326

[a] Together with the olefin by HNO_2 elimination from the substitution product in brackets. [b] PTC, Cl_2CH_2/H_2O. [c] MeOH. [d] Initiation with microwaves.

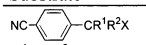
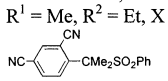
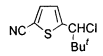
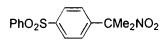
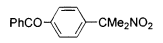
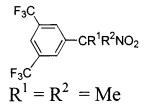
The $S_{RN}1$ process can also be used to prepare new potentially active pyrimidinones. Thus, 2-chloromethyl-3-nitro-substituted pyrimidinones react with various nitronate and malonate anions with good yields of the alkene derivatives. Sulfur-centered nucleophiles and the anion from 4-hydroxycoumarin are also reactive by this pathway[324] (Table 20).

Derivatives of 5-nitrothiazole with the $-CR_2X$ group ortho[325] or para[326] to the NO_2 group also give good yield of substitution with $^-CMe_2NO_2$ ions. The reactions of the chloro derivative with the anion of nitrocyclopentane or nitrocyclohexane proceed with lower yields (Table 20).

D. Other Benzylic Derivatives and Activated Alkyl Halides

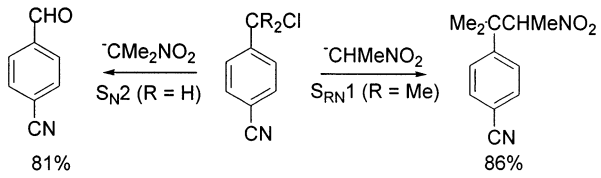
The CN group also facilitates the ET reactions, although not as effectively as an NO_2 group (Table 21). Thus, *p*-$NCC_6H_4CH_2Cl$ gives the aldehyde when treated with $^-CMe_2NO_2$, whereas *p*-$NCC_6H_4CMe_2Cl$ yields the substitution product by $S_{RN}1$ (Scheme 26).[327, 328]

Table 21. Photoinduced Reactions of Aliphatic Halides with a Cyano and Other EWG with Nucleophiles in HMPA

Substrate	Nucleophile	Product (%)	Ref.
			
$R^1 = R^2 = H$, $X = {}^+NMe_3$	$^-CMe_2NO_2$	82[a]	327, 328
$R^1 = R^2$ = Me, X = Cl; NO_2	$^-CHMeNO_2$	86; 94	327, 328
$R^1 = R^2$ = Me, X = NO_2	$^-CMe_2NO_2$	68	294
$R^1 = R^2$ = Me, X = NO_2	$^-CMeEtNO_2$	68	294
R^1 = Me, R^2 = Et, X = NO_2	$^-CMe_2NO_2$	60	294
		84	327, 328
	$^-CMe(CO_2Et)_2$	70	327, 328
	PhS^-	80[b]	327, 328
$NCC(Me)_2Br$	$^-CH_2NO_2$	45	329
	$^-CHMeNO_2$	72	329
	$^-CH[(CH_2)_5CH_3]NO_2$	67	329
	$^-CMe_2NO_2$	82	329
		76	329
$NCCMe_2Cl$	PhS^-	61[a]	330
	$Et_2NCS_2^-$	52[a]	330
	p-$MeC_6H_4S^-$	72[a]	331
	$^-CMe_2NO_2$	71	294
	$^-CMe_2NO_2$	62	294
	$^-CMeEtNO_2$	61	307
			
$R^1 = R^2$ = Me	$^-CMe_2NO_2$	90	294
	$^-CMeEtNO_2$	50	294
R^1 = Me, R^2 = Et	$^-CMe_2NO_2$	60	294

[a] DMSO. [b] DMF.

Scheme 26

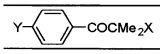


With a poorer leaving group for an S_N2 reaction, such as Me_3N^+, the ET competes favorably and substitution of p-$NCC_6H_4CH_2NMe_3Cl$ by the $^-CMe_2NO_2$ ion is obtained in 82% yield.

An α-CN group is also able to activate an haloalkane. Thus, 2-bromo-2-methylpropionitrile reacts with different nitronate ions by the $S_{RN}1$ mechanism.[329] Poly(α-chloroacrylonitrile) decomposes to low molecular weight compounds when treated with Nu^- ($Et_2NCS_2^-$, PhS^-, and N_3^- ions). An $S_{RN}1$ mechanism was suggested for this reaction, in which an ET to the polymer leads to a radical and a Cl^- ion. Coupling with the Nu^- and decomposition are the main reactions proposed for the radical intermediates. The reaction of $Et_2NCS_2^-$ and PhS^- with 2-chloro-2-methylpropionitrile, as a model compound, has been studied (Table 21).[330]

In the heterocyclic series 4- and 5-cyano thien-2-yl-neopentyl chloride showed a behavior similar to that of the nitro analogues. Thus, only the 5-CN compound undergoes $S_{RN}1$ reaction with the p-$MeC_6H_4S^-$ ion.[331] Other EWGs are CF_3, PhCO, and $PhSO_2$[294] (Table 21).

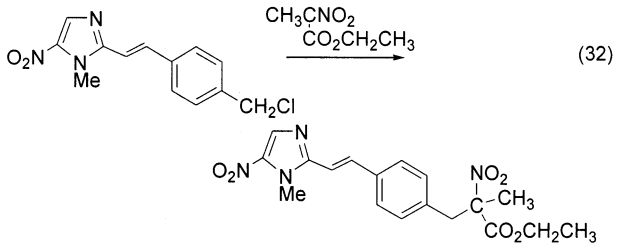
Table 22. Photoinduced Reactions of Aliphatic Halides with a Benzoyl Group with Nucleophiles in DMSO[a]

Substrate		Nucleophile	Product (%)	Ref.
				
Y	X			
NO_2	Cl	$^-CMe_2NO_2$	77	332
	Br		51	332
CN	Cl		69	332
NO_2		$^-CH(CO_2Et)_2$	49	332
		$^-CMe(CO_2Et)_2$	62	332
		$^-CMeCN(CO_2Et)$	66[b]	333
	Br		77	333
	Cl	$^-CMe(CN)_2$	76	333

[a] X as leaving group. [b] HMPA.

Sterically hindered p-CN- or p-NO_2-substituted α-haloisobutyrophenones give C-alkylation products with $^-CMe_2NO_2$,[332] $^-CH(CO_2Et)_2$, $^-CMe(CO_2Et)_2$, $^-CMe(CN)_2$ ions[333] (Table 22).

The benzyl chloride activated through an ethylene bridge by a nitroimidazole group was explored as a possible new substrate for $S_{RN}1$ reactions.[334] These reactions involve a long distance between the EWG and the leaving group. With 2-nitronate anions only the aldehyde (90%) coming from O-alkylation was observed. On the other hand, the less nucleophilic ethyl 2-nitropropionate anion yields a mixture of C-alkylation (55%) and the aldehyde from O-alkylation (35%) (eq 32).

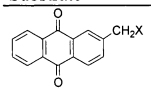
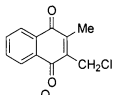
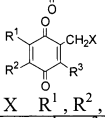
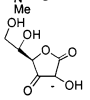
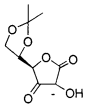
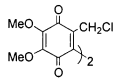


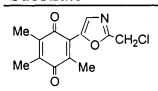
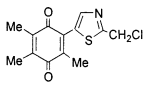
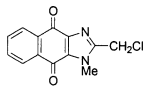
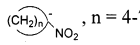
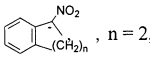
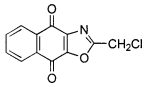
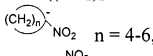
(32)

Benzylic and heterocyclic analogues with a fused or nonfused quinone ring as EWG react with nitronate ions by the $S_{RN}1$ mechanism[113,248] (Table 23). Thus, 4-hydroxycoumarin and 4-aminocoumarin are alkylated by a series of chloromethyl quinones to afford exclusively the 3-substituted-4-hydroxycoumarins in good yields (Table 23).[335]

The reaction of 2,3-bis(chloromethyl)-1,4-naphthoquinone with the $^-CMe_2NO_2$ ion proceeds by two consecutive $S_{RN}1$ reactions leading to a bis-C-alkylated product, which after ring closure gives a 2,3-dihydro-9,10-anthracenedione derivative.[246] A novel and very interesting one-pot synthesis of dialkyl-substituted anthraquinones was performed by this procedure, which consists of two consecutive $S_{RN}1$ processes followed by base-promoted nitrous acid elimination, electrocyclic ring closure, and dehydrogenation.[245] The advantage of this procedure, in comparison with the classical Diels−Alder reaction, is the simplicity of the preparation of the starting

Table 23. Photoinduced Reactions of Aliphatic Halides Activated with a Quinone Group with Nucleophiles in DMSO

Substrate	Nucleophile	Product (%)	Ref.
			
Br	$^-CMe_2NO_2$	65 (18)[a, b]	*c*
Cl		82 (6)[a, b]	*d*
Br	$^-CMe(CO_2Et)NO_2$[e]	20 (35)[a]	295
Cl		62[b]	*c*
	$^-CHMeNO_2$	85[b]	337
	$^-CHEtNO_2$	75[b]	337
	$^-CH(n\text{-Pr})NO_2$	72[b]	337
	$^-CMe_2NO_2$	65[b]	248
			
X R^1, R^2, R^3			
F $R^1 = R^2 = R^3 = Me$	$^-CMe_2NO_2$	42 (28)[a]	336
Cl		83	*f*
	$^-CMe(CO_2Et)NO_2$[e]	65	295
		84[g]	335
$R^1 = R^2 = Me$, $R^3 = H$		72[g]	335
$R^1 = Me$, $R^2 = R^3 = H$		68[g]	335
$R^1 = R^2 = R^3 = OMe$		87[g]	335
$R^1 = R^2 = OMe$, $R^3 = H$		77[g]	335
$R^1 = R^2 = Me$, $R^3 = Br$		88[g]	335
Cl $R^1 = R^2 = R^3 = Me$		89[g]	335
		50[b]	248
		33[g,h]	248
		34[g, i]	248
	$^-CMe_2NO_2$	68[a]	248

Substrate	Nucleophile	Product (%)	Ref.
		88[g]	338
		75[g]	113
		79[a, j]	339
		71[a, k]	113
	 , n = 4-7, 11	(44-68)[a, j]	340
		46[a, j]	340
	 , n = 2, 3	70[a, j] (*E*), 88[a, j] (*E*)	340
		71[a, g]	340
	$^-CMe(n\text{-Pr})NO_2$	65[a, j] (*E*)	340
	$^-CMe((CH_2)_3CHMe_2)NO_2$	72[a, j] (*E*)	340
	$^-CMePhNO_2$	73[a, j] (*E*)	340
		32[a, l] (*E*)	340
	$^-CMe_2NO_2$	75[a]	341
	$^-CMe(n\text{-Pr})NO_2$	71[a] (*E*/*Z* : 8/2)	341
	$^-CMe((CH_2)_2CHMe_2)NO_2$	74[a] (*E*/*Z* : 8/2)	341
	 n = 4-6, 11	(58, 66, 71, 5)[a]	341
		60[a]	341
	$^-CMePhNO_2$	58[a] (*E*/*Z* : 8/2)	341
		70[a] (*E*)	341

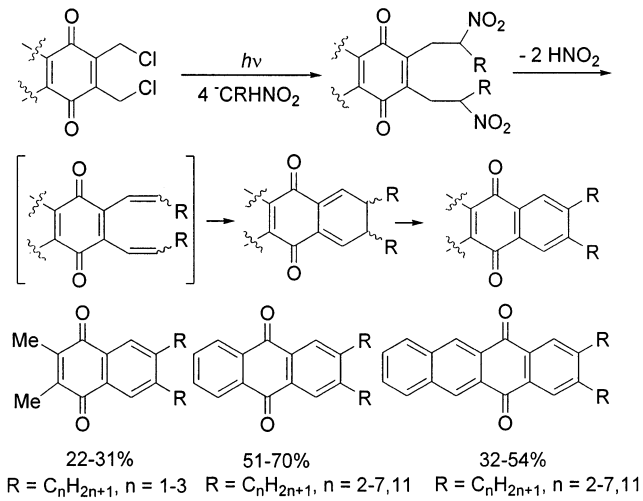
[a] Yield percent of the olefins by HNO_2 elimination from the product. [b] PTC, PhMe/H_2O. [c] Crozet, M. P.; Vanelle, P.; Jentzer, O.; Donini, S.; Maldonado, J. *Tetrahedron* **1993**, *49*, 11253−11262. [d] Crozet, M. P.; Jentzer, O.; Vanelle, P. *Tetrahedron Lett.* **1987**, *28*, 5531−5534. [e] Entrainment with $^-CMe_2NO_2$. [f] Crozet, M. P.; Giraud, L.; Sabuco, J. F.; Vanelle, P.; Barreau, M. *Tetrahedron Lett.* **1991**, *32*, 4125−4128. [g] MeOH. [h] Together with 61% yield of the benzoquinone dimer. [i] Together with 6% yield of the benzoquinone dimer and 2-(hydroxymethyl)-3,5,6-trimethyl-1,4-benzoquinone in 34% yield. [j] DMF. [k] Initiation with microwaves in wet silica gel. [l] PTC, CH_2Cl_2/H_2O.

material. This new annulation method was also applied to synthesize dialkylnaphthacene-5,12-diones[247] and 1,4-naphthoquinones[248] with acceptably good results (Scheme 27).

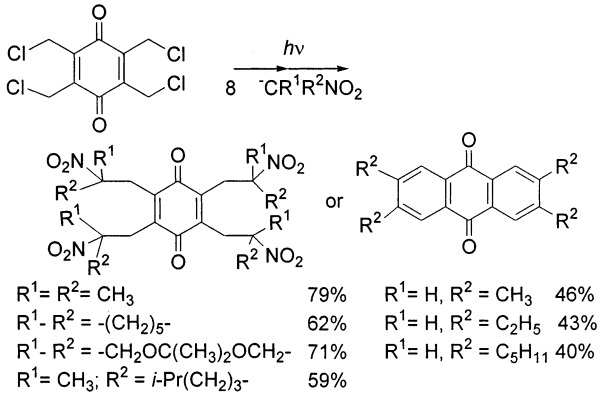
Treatment of a tetrachloride benzoquinone derivative with secondary nitroalkanes under standard $S_{RN}1$ conditions produces 2,3,5,6-tetranitroalkylbenzoquinones in 59−79% yields by four consecutive $S_{RN}1$ reactions. Furthermore, the reaction with primary nitroalkanes under the same experimental conditions renders the 2,3,6,7-tetralkylanthraquinones in 40−46% yield, after four $S_{RN}1$ reactions, followed by four base-promoted nitrous acid eliminations and two electrocyclic ring closures and dehydrogenations (Scheme 28).[231]

The reaction of 2-fluoromethyl-3,5,6-trimethyl-1,4-benzoquinone with the $^-CMe_2NO_2$ ion is the first example of displacement of F by $S_{RN}1$ at an sp^3

Scheme 27

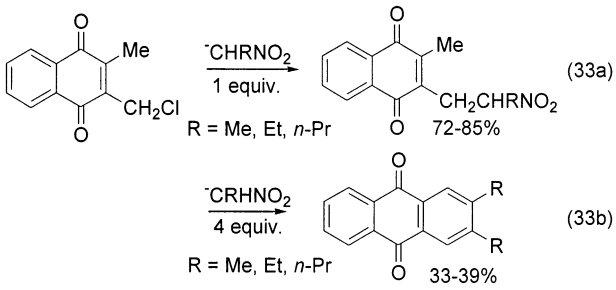


Scheme 28



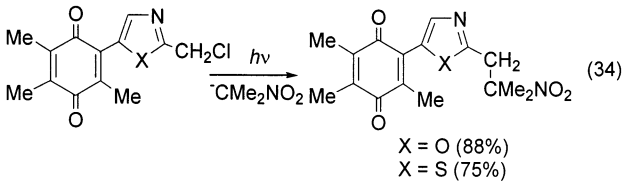
carbon.[336] The reaction was extended to the *gem*-difluoride derivative[253] (see section VI.E).

2-Chloromethyl-3-methyl-1,4-naphthoquinone reacts with primary nitroalkanes to yield the substitution product by a classical $S_{RN}1$ mechanism in good yield (eq 33a) (Table 23).[337] When these reactions are



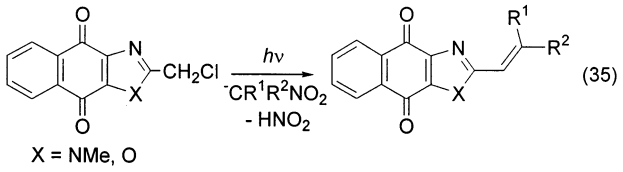
performed with an excess of the anion (4 equiv), 3-alkyl-2-methylanthraquinones are obtained (33−39% yield) (eq 33b). Under these conditions, the Me group in the substitution product is deprotonated, yielding a good Michael acceptor, which in the presence of an excess of anion gives the bis-C-alkylated compound. As indicated previously,[245,247] after oxidation, nitrous acid elimination, electrocyclization, and dehydrogenation, the corresponding dialkylanthraquinones are obtained.

The only example of an $S_{RN}1$ reaction of an oxazole system with the $^{-}CMe_2NO_2$ ion involves activation by a nonfused tetrasubstituted *p*-benzoquinone ring.[338] The thiazole analogue also gives substitution in good yield (eq 34).[113] On the other hand, the corresponding



N-methylimidazole derivative does not react under the same conditions. This can be explained by steric hindrance that avoids the coplanarity of the trimethyl quinone and the heterocyclic moieties in the imidazole derivative.[339]

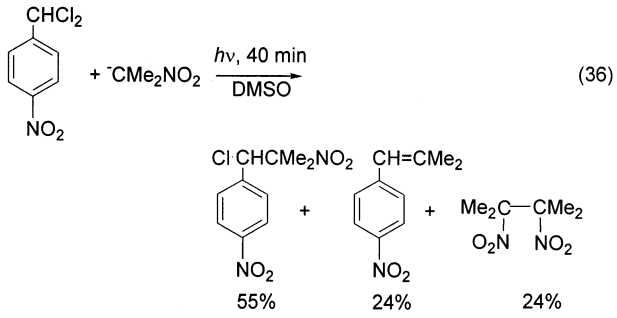
Nevertheless, when the quinone is coplanar with the imidazole ring, for example, in a fused quinone-imidazole system, the $S_{RN}1$ reaction is possible, and it was used as a method for the preparation of naphthoimidazolediones bearing a trisubstituted double bond at the 2-position (eq 35).[339,340] Similar results



are reported for the synthesis of ethylenic naphthoxazolediones from 2-chloromethylnaphthoxazoledione with nitronate ions[341] (Table 23).

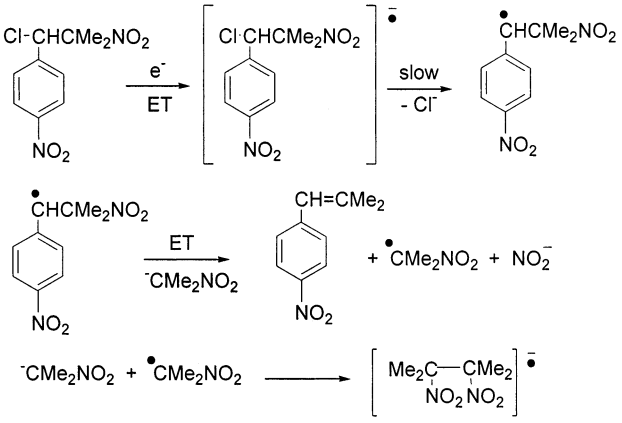
E. Geminal Dihalides and Trihalides

In the *p*-nitrobenzylic system the reactions of geminal dichlorides with nitronate ions have been shown to proceed by an $S_{RN}1$ mechanism followed by an $E_{RC}1$ reaction (eq 36) (Table 24).[250]



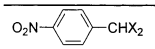
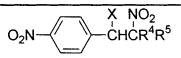
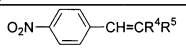
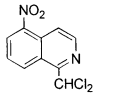
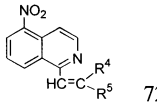
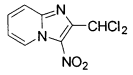
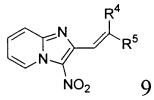
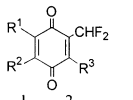
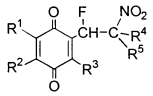
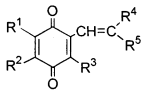
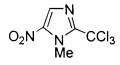
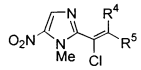
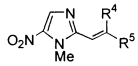
The formation of the monosubstitution compound is ascribed to the high stability of the nitroaromatic radical anions, for which the intermolecular ET is slightly more rapid than the intramolecular ET. The mechanism of formation of the styrene and the dimer of the nucleophile was investigated by reaction of the chloro-monosubstituted compounds. The reaction is proposed to proceed by the $E_{RC}1$ mechanism with the radical anion of the dimer of the nucleophile as the chain carrier (Scheme 29).[250] In the reaction of

Scheme 29



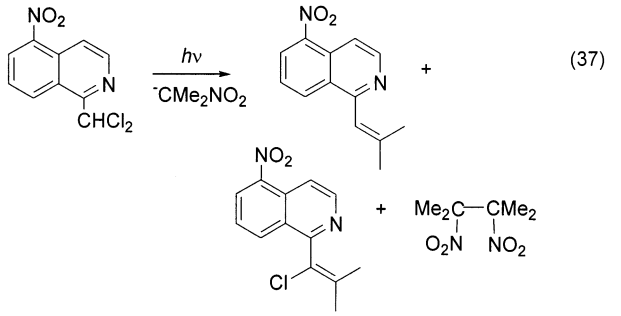
p-nitrobenzylidene dibromide, the monosubstituted bromo compound was not observed. This was explained by a faster dissociation of the corresponding radical anion.[342]

Table 24. Photoinduced Reactions of *gem*-Dihalides and -Trihalides with Nitronate Anions in DMSO

Substrate	$^-CR^4R^5NO_2$	Product (%)		Ref.
				
X = Cl; Br	$R^4 = R^5 = Me$	55; *b*	24[a]; *b*	250
	$R^4 = R^5 = Me$		 72[a,c]	251
	$R^4 = R^5 = Me$		 91[a,d]; 90[a,c]	321c
				
$R^1 = R^2 = Me, R^3 = H$	$R^4 = R^5 = Me$	72	9[a]	253
$R^1 = R^2 = OMe, R^3 = H$		78	6[a]	253
$R^1 = R^2 = R^3 = Me$		74	9[a]	253
$R^1 = R^2 = R^3 = OMe$		87	4[a]	253
$R^1 = R^2 = Me, R^3 = Br$		88	3[a]	253
				
	$R^4 = R^5 = Me$	76	16[a,d]	252
	R^4-R^5 = -$(CH_2)_4$-	65	10[a,d]	252
	R^4-R^5 = -$(CH_2)_5$-	71	12[a,d]	252
	R^4-R^5 = -$(CH_2)_6$-	63	10[a,d]	252
	R^4-R^5 = -$(CH_2)_{11}$-	58	12[a,d]	252

[a] Together with an equimolar amount of the dimer of the nitroalkane. [b] Not given. [c] DMF. [d] PTC, CH_2Cl_2/H_2O.

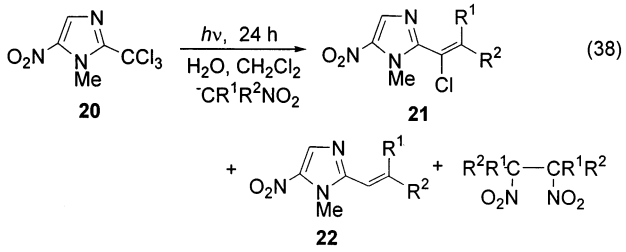
1-(Dichloromethyl)-5-nitroisoquinoline reacts with nitronate ions by $S_{RN}1$ followed by an $E_{RC}1$ mechanism to give 1-isopropylidenemethyl-5-nitroisoquinoline as major product.[251] Although in these reactions the monosubstituted chloro derivative was not found, it has to be formed because the product coming from an E_2 reaction (loss of nitrous acid, competing with the $E_{RC}1$) is observed in low yield in DMF and in higher yield under PTC (eq 37).[251]



(37)

On the other hand, *gem*-difluoromethylquinones give mainly the monofluoro-substituted product (>72%), whereas the olefin coming from a subsequent $E_{RC}1$ process is the minor product (<9%). In this case the intramolecular ET and the fragmentation of the radical anion of the mono-fluorosubstituted derivative is too slow and the main process is the intermolecular ET (Table 24).[253]

Recently, new 5-nitroimidazoles **21**, bearing a tetrasubstituted ethylenic double bond in the 2-position, have been obtained in high yields by the reaction of secondary $^-CR_2NO_2$ ions with a *gem*-trichloromethylimidazole derivative by consecutive $S_{RN}1$ and $E_{RC}1$ mechanisms.[252] Thus, the reaction of **20** with $^-CR_2NO_2$ ions yields the ethylenic chlorides **21** in 58−76% and the alkenes **22** in 10−16% yield, along with the dimer of the nitroalkane (eq 38) (Table 24).



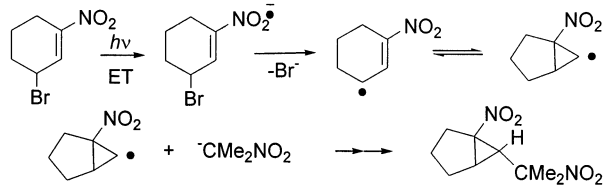
(38)

F. Activated Allyl Derivatives

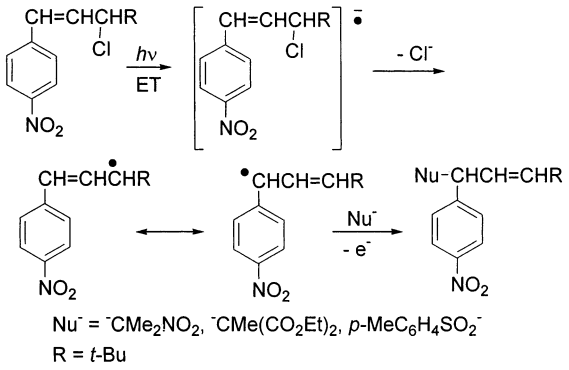
Allyl halides substituted by EWG also give substitution by a radical chain process. Thus, 3-bromo-1-nitrocyclohex-1-ene undergoes reaction with the $^-CMe_2NO_2$ ion to give the product from coupling of the ion with the cyclopropyl radical formed by cyclization of the allyl radical intermediate (Scheme 30).[343] Formation of the rearranged product was ascribed to the low nucleophilicity of the anion, which reacts more rapidly with the unstabilized cyclopropyl radical than with the stabilized nitro-olefin radical.

In the reactions of *p*-nitrophenylallyl chlorides with different carbanions the mechanism involved depends on the alkyl substituent R.[344] The Me derivative undergoes S_N2 or S_N2', the *i*-Pr mixed $S_{RN}1/S_N2$, and the *t*-Bu only the $S_{RN}1$ mechanism (Scheme 31).[49b] The particular regiochemistry of this $S_{RN}1$ reaction can be attributed to the steric hindrance of the R substituent, which disfavors the coupling at the terminal position of the conjugated system.

Scheme 30



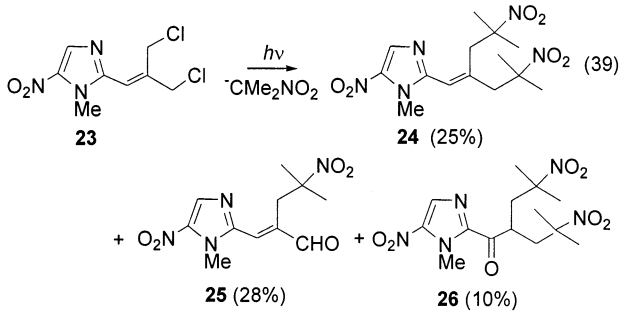
Scheme 31



On the other hand, it has been shown that β-substituted 3-cyclohexenones bearing sulfur leaving groups at the β'-position undergo substitution by stabilized carbanions (Table 25).[345] An interesting application of this reaction is the synthesis of prostaglandin (PGB_1) analogues from cyclopenta-2,4-dienone with an α-functionalized side chain introduced by an $S_{RN}1$ reaction and an alkenyl or alkynyl ω-side chain introduced by Pd(0)-catalyzed cross-coupling reaction (Scheme 32; Table 25).[346]

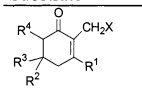
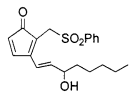
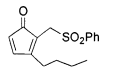
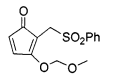
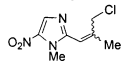
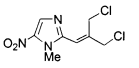
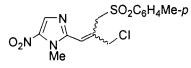
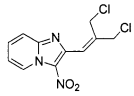
An allyl chloride activated by a 5-nitroimidazole reacts with the $^-CMe_2NO_2$ ion in DMF giving O-alkylation, whereas under PTC (40% Bu_4NOH, H_2O, PhMe), a mixture of C-alkylation and reduction products is isolated. This reaction was extended to the nitrocyclohexane anion (Table 25).[315]

The allylic dichloride analogue **23** affords with $^-CMe_2NO_2$ ions the bis-C-alkylated product **24** by two consecutive $S_{RN}1$ reactions, with two other products proceeding by an initial $S_{RN}1$ mechanism followed by S_N2 or S_N2' and Michael reactions leading, respectively, to the aldehyde **25** and the derivative **26** (eq 39).[249]



The observation of products **25** and **26** implies that the mono-chlorosubstituted product should be an intermediate in the reaction, which means that the intermolecular ET competes effectively with the intramolecular ET to the C−Cl bond (Scheme 33).

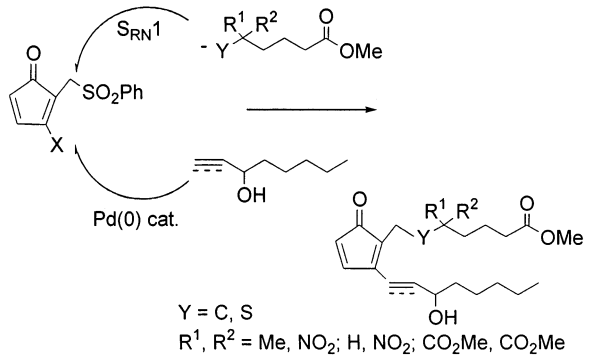
Table 25. Photoinduced Reactions of Activated Allylic Compounds with Nucleophiles in DMF

Substrate	Nucleophile	Product (%)	Ref.
	$^-CMe_2NO_2$	62	345
	$^-CHMeNO_2$	48	345
	$^-CH(CO_2Et)_2$	72	345
X = SPh, R^2 = H, $R^1 = R^3 = R^4$ = Me	$^-CEt(CO_2Et)_2$	72	345
X = SO_2Ph, R^2 = H, $R^1 = R^3 = R^4$ = Me	$^-CMe_2NO_2$	86	345
	$^-CHMeNO_2$	59	345
	$^-CH(CO_2Et)_2$	76	345
	$^-CEt(CO_2Et)_2$	83	345
X = SO_2Ph, R^1 = Me, $R^2 = R^3 = R^4$ = H	$^-CMe_2NO_2$	86	*a*
	$^-CMe(CH_2)_7NO_2$	86	*a*
X = SO_2Ph, $R^1 = R^2 = R^3$ = Me, R^4 = H		66	*a*
X = SO_2Ph, R^1 = OEt, $R^2 = R^3 = R^4$ = H	$^-CMe_2NO_2$	85	345
	$^-CH(CO_2Et)_2$	71	345
	$^-CEt(CO_2Et)_2$	75	345
X = SO_2Ph, R^1 = OTs, $R^2 = R^3 = R^4$ = H	$^-CMe_2NO_2$	66	345
	$^-CH(CO_2Et)_2$	43	345
	$^-CEt(CO_2Et)_2$	60	345
	$^-CMe_2NO_2$	44	346
	$MeO_2C(CH_2)_4C(Me)NO_2^-$	86	346
	$MeO_2C(CH_2)_4C(CO_2Me)_2^-$	75	346
	$MeO_2C(CH_2)_4S^-$	75	346
	PhS^-	71	346
	$MeO_2C(CH_2)_4CHNO_2^-$	65	346
	$MeO_2C(CH_2)_4CMeNO_2^-$	95	346
	$MeO_2C(CH_2)_4CHNO_2^-$	63	346
	$MeO_2C(CH_2)_4CMeNO_2^-$	90	346
	$^-CMe_2NO_2$	(40 *Z*[b] or 30 *E*[c])[d]	315
Z or *E*		(90 *Z* or 70 *E*)[d]	315
	$^-CMe_2NO_2$	25[d,e,f]	249
	$^-CMe(n\text{-}Pr)NO_2$	48[d,e]	347
	 , n = 5, 6	(59, 51)[d,e]	347
		49[d,e]	347
		62[d,e]	347
	$^-CMe_2NO_2$	(40 *E*, 20 *Z*)[d]	*g*
(*E*: *Z*) 1:2			
		29[h]	321c

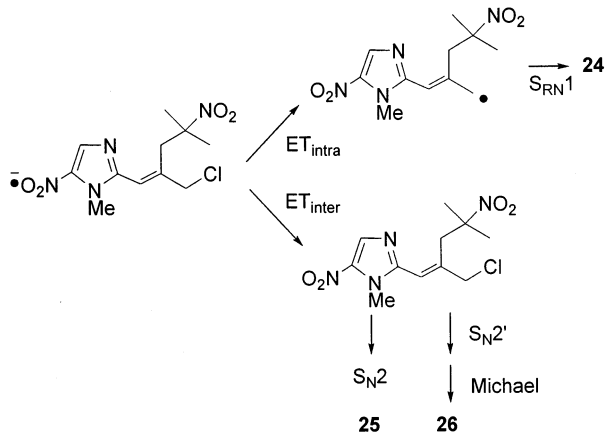
[a] Tamura, R.; Shimono, S.; Fujita, K.; Hirao, K. *Heterocycles* **2001**, *54*, 217−224. [b] Isolated as the olefin by HNO_2 elimination from the substitution product together with 45% yield of the reduction product. [c] Isolated as the olefin by HNO_2 elimination from the substitution together with 30% yield of the reduction product. [d] PTC, PhMe/H_2O. [e] Disubstitution product. [f] Together with two other products coming from an initial $S_{RN}1$ followed by and S_N2 (28%) or and $S_N2'$and Michael reactions (10%). [g] Benakli, K.; Terme, T.; Vanelle, P. *Molecules* **2002**, *7*, 382−385. [h] PTC, CH_2Cl_2/H_2O, disubstitution product isolated as the bis olefin by HNO_2 elimination.

Under PTC (40% Bu_4NOH, H_2O, PhMe), a nucleophile/substrate ratio of 6:1, and irradiation, **23** reacts with crowded nitronate anions to give only bis-C-alkylation products in moderate to good yield (Table 24). The polar competitive reactions are disfavored, and the bis-$S_{RN}1$ reaction predominates, probably due to steric hindrances.[347]

Scheme 32



Scheme 33



VII. Other Aliphatic Substrates

A. Alicyclic Aliphatic Substrates

It is widely accepted nowadays that alkyl halides without EWG may react by ET. Different types of experimental studies have been performed to probe this pathway, some of them criticized as valid mechanistic probes.[348,349]

We will first present the reaction of the simplest derivatives of the family, and then the neopentyl system will be discussed as a particular case at the end of this section.

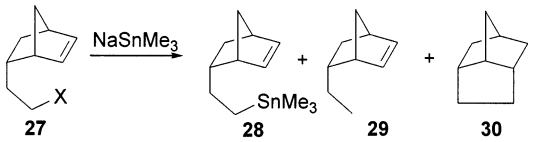
1. Reaction with Triorganylstannyl Anions and Related Nucleophiles

An important number of studies have been carried out with R_3Sn^- ions, which can react with RX through S_N2, ET, and HME. The percentage of each mechanism has been estimated from comparison of the product distribution in the absence and in the presence of DCHP (as radical trap) or *t*-$BuNH_2$ (TBA, as anion trap). However, DCHP can also act as an anion trap and, in some cases, TBA is not acidic enough for trapping the possible anionic intermediates. On the other hand, the radical formed by DCHP after trapping the radical can by itself propagate an ET reaction.

In general, Kuivila found that reactions of $MSnR_3$ with unhindered primary RCl and RBr proceed exclusively by an S_N2 pathway.[18a] On the other hand, Ashby et al. have shown that certain primary RBr react with $NaSnMe_3$ by an ET route.[18b] For example, the reaction of this anion with *n*-BuBr in THF is inhibited (from 100 to 67.7%) in the presence of *p*-DNB. The decrease of the reaction rate on addition of *p*-DNB is more effective by increment of the steric hindrance of the primary RBr to *i*-BuBr and to 2-ethylhexyl bromide. In solvent systems of lower viscosity the reaction with the latter compound produces a larger amount of hydrocarbon (14.6%), which is increased to 40% in the presence of DCHP.

Only the straight-chain product was formed by reaction of the primary radical probe 6-bromo-1-hexene with $LiSnR_3$[350] and $LiGeR_3$ (R = Me or Ph).[64c] However, low yield of the cyclized substitution compound was formed by reaction with $NaSnMe_3$ in different THF−cosolvent mixtures. In these reactions the yield of cyclization decreases in the presence of DCHP with an increase in the amount of straight-chain hydrocarbon.[18b] In addition, TBA shows no effect, indicating that carbanion intermediates are not involved in the reaction.

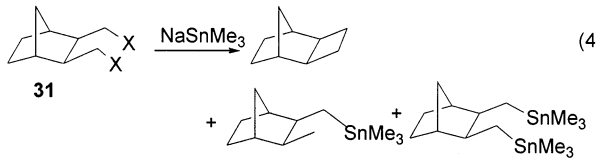
In the reaction of $NaSnMe_3$ with the probe **27** (X = Br) in THF the straightforward substituted product **28** is mainly observed (86%) (eq 40). How-



(40)

ever, ~40% of reduction **29** and cyclized hydrocarbon **30** are obtained in THF−Et_2O or THF−pentane and in the presence of DCHP (eq 40).[18b] In the reaction of the same probe but with iodide as leaving group, three mechanistic pathways (S_N2, HME, and ET) are proposed to occur.[18b]

ET and HME mechanisms are proposed for the reaction of $NaSnMe_3$ with the probe **31** (eq 41) (X = Br or I).[18b]



(41)

The results obtained with these iodide derivatives differ from those found by Kuivila, who has reported that in the reaction of $MSnMe_3$ with unhindered primary alkyl iodides, the HME reaction (32%) competes with the S_N2 mechanism (65%) with no evidence of an ET process.[18a]

Straightforward and rearrangement products were found in the reaction of $LiSnMe_3$ with cyclopropylmethyl bromide and iodide (77 and 82% overall yields, respectively) with straightforward to rearrangement products ratios of 83:17 and 53:47, respectively.[64e,c] Both types of products, with a 70:30 ratio, were formed in the reaction of cyclopentadienyl dicarbonyl iron anion with cyclopropylmethyl iodide (see section IV.B.1).[64e]

Kuivila found that 2-bromooctane reacts with $NaSnMe_3$ by an ET pathway (72%),[18a] and San Filippo reported that (−)-2-bromooctane reacts with the same Nu^- with predominant (90%) inversion of configura-

tion.[351] In general, HME, ET, and S_N2 were found to be operative for secondary RI to variable extents. Further pieces of evidence were found in the reaction of the radical probe 6-halo-1-heptene with $NaSnMe_3$ in THF (eq 42).[64a,b]

(42)

The product distribution leads to the conclusion that for X = OTs, the reaction proceeds by an S_N2 process. In the case of the secondary RCl, it appears that the S_N2 and ET pathways are involved. ET is the major reaction path when X = Br and I, leading to predominantly cyclized products (80−70%). The bromide derivative reacts by the $S_{RN}1$ mechanism.[64b] Similarly, the bromide probe reacts with $LiSnR_3$ and $LiGeR_3$ (R = Me or Ph) in THF affording straightforward and rearrangement substituted cyclic products, with the exception of $LiSnPh_3$.[64c] Rearrangement products were also formed in the reaction of the probe with the Ph_3Si^- anion.[349b]

The alkylation of several anions ($LiSnPh_3$, $LiCPh_3$, and $LiGePh_3$) with optically active secondary RBr and RCl proceeds with high stereoselectivity.[352] The principal exceptions to this behavior are the alkylation of $LiSiPh_3$, which takes place with 70−75% net inversion with the 2-octyl chloride (68% overall yield). The reaction exhibits less stereoselectivity (25−55% net inversion) with 2-octyl bromide in which mainly the hydrocarbon is formed.[352]

The presence of the *n*-$Bu_3Sn^•$ radical was observed, by a stopped-flow technique, in the reaction of the *n*-Bu_3Sn^- ion with *s*- and *t*-BuX (X = Br or I)[353a] as well as with *n*-BuBr[353b] in contrast to a previous report for the latter compound.[353c] The formation of radicals in the reaction with *n*-BuBr and *n*-BuI was also determined by the ^{119}Sn CIDNP technique.[354] In the presence of DCHP, the yields of *n*-Bu_4Sn dropped from 94 to 74% (with *n*-BuBr) and from 69 to 55% (with *n*-BuI). On these bases the yield of the *n*-Bu_4Sn generated through a radical pathway is at least 20%, but it is estimated to be much larger.[354]

2. Reaction with Carbanions

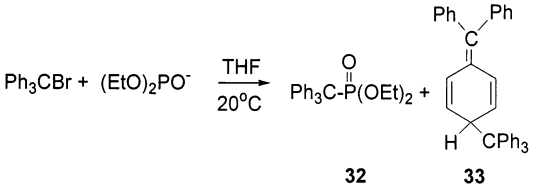
An initial ET step has been proposed in the PTC-catalyzed alkylation of cyclopentadiene and indene anions. In these reactions many tertiary alkyl bromides were employed such as *t*-BuBr, trityl bromide, 2-bromo-2-phenylpropane, and 3-bromo-3-methylpentane as well as secondary alkyl halides. Fair to good yields of alkylation and in some cases dialkylation are obtained depending on the substrate.[355]

The alkylation of C_{60}^{2-} by $PhCH_2Br$ or α,α′-dibromo-*o*-xylene in the synthesis of R_nC_{60} (where *n* = 2 for R = $PhCH_2$− and *n* = 1 for R = *o*-xylyl) is proposed to take place via the rate-determining ET from C_{60}^{2-} to the alkyl bromide.[356]

3. Reaction with Other Nucleophiles

At least two mechanisms (S_N2 and ET) seem to be available for the preparation of alkylcob(III)alamins, (alkyl)porphyrinatocobalt(III)s,[357] and (alkyl)porphyrinatoiron(III) complexes.[20, 55,357] An electrochemical technique for discriminating between one- and two-electron mechanisms in the oxidative addition of alkylating agents to corrinato- and porphyrinatocobalt(I) [Co(I)L] has been proposed on the basis of single-scan voltagrams of [Co(II)L] in the presence of alkyl halides and variable amounts of the radical trap acrylonitrile.[358]

The X-philic substitution is the main process in the reaction between para-substituted benzyl bromides (possessing EWG), Ph_2CHBr, Ph_3CBr, and 9-bromofluorene with >P−O^- nucleophiles, which attack at the bromine atom to yield the benzyl anion analogues. Depending on the redox potentials, these anions can participate in protonation and/or ET processes producing debromination products and/or radical dimers.[359] When the concentration of >P−O^- ion is sufficiently high, it competes for the $Ph_3C^•$ radicals generating the phosphonates by a chain sequence. For example, when the reaction of 1 equiv of Ph_3CBr is performed with 10 equiv of $(EtO)_2PO^-$ ion, product **32** (69%) and the dimer **33** (29%) were obtained (eq 43).[359]



(43)

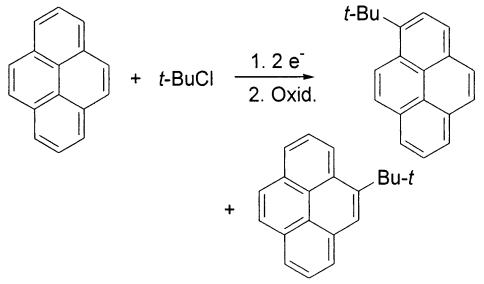
32 **33**

The reaction of RS^- ions (R = *i*-Pr or *n*-Bu) with Ph_3CX (X = Cl or Br) produces the α- and para-substitution products, Ph_3CSR and *p*-$RSC_6H_4CHPh_2$, as well as radical byproducts such as Ph_3CH, dimerization of the trityl radicals (*p*-$Ph_3CC_6H_4CHPh_2$), and dimerization of thiyl radicals (RSSR). The formation of these products suggests the occurrence of ET as the predominant pathway. On the other hand, the reaction of LiSPr-*i* with Ph_3CBr in THF was not affected by the presence or absence of light or the presence of *p*-DNB, thus suggesting the unlikelihood of a radical−radical anion chain process.[360]

4. Reaction with Radical Anions

Differences in the product distribution have been observed in the reaction of radical anions with alkyl halides, depending on the mechanism in play. For example, in the reaction of anthracene radical anion with MeX (X = I, Br, or Cl), the ratio between substitution at the 9-position relative to the 2-position of anthracene increases from 1.4:1 (X = I) to 50:1 (X = Cl), which is taken as an indication of a mechanistic shift from predominantly ET to predominantly S_N2.[22b]

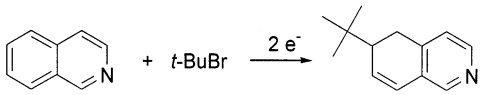
The synthetic possibilities of the coupling reaction have been investigated in a number of cases. For example, *tert*-butylation of the pyrene radical anion results in dihydro derivatives that can be aromatized. The main product is 1-*tert*-butylpyrene (52%), accompanied by 14% of the 4-substituted pyrene (eq 44).[361a] This product distribution follows the expecta-



(44)

tions predicted by the electron density, determined by ESR, at the different positions of the radical anion.[361b]

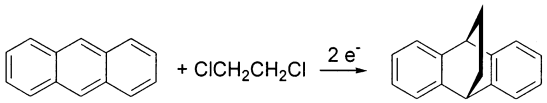
On the other hand, the main attack of the radicals from *t*-BuBr[362a] or 1-BrAd[362b] on the radical anion of isoquinoline occurs mainly at position 6 and less at position 1 (eq 45), in contrast with what would have



(45)

been expected from the ESR spectrum of isoquinoline radical anion.[362c] The regioselectivity of the electrochemical reaction is not as good as the radical alkylation by the method of Minisci et al., which for isoquinoline gives mainly alkylation at C_1.[362d]

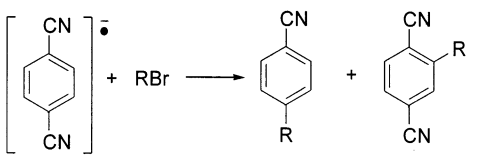
Coupling of 1,2-dichloroethane with the anthracene radical anion affords 9,10-ethano-9,10-dihydroanthracene (57%) probably by an ET followed by a S_N2 reaction (eq 46).[363]



(46)

Besides alkyl halides, other electrophiles may be employed in the coupling reaction with radical anions such as anhydrides or acid chlorides.[114]

The radical anions of PhCN,[364a] 1-naphthonitrile,[364b] and 9-cyanoanthracene[364c] react with alkyl halides in liquid ammonia to afford products from substitution of the CN group by an alkyl group and/or addition of the alkyl fragment at the *ipso* position of the CN group, both products being ascribed to a polar substitution. In going from the radical anion of PhCN to *p*-$C_6H_4(CN)_2$ a change from S_N to ET is proposed for their reaction with primary alkyl bromides.[157,365a] For example, the radical anion *p*-$C_6H_4(CN)_2^{\bullet -}$ reacts with *n*-BuBr to afford *p*-(*n*-Bu)C_6H_4CN and 2-butyl-1,4-dicyanobenzenes (eq 47).[157a] The reaction with



(47)

cyclopropylmethyl bromide leads to compounds with the previous regiochemistry containing both cyclopropylmethyl and 3-butenyl fragments.[157a] Coupling at the para and ortho positions has also been observed with cyclohexyl and cyclooctyl radicals when the reaction is performed in the presence of PhI, the Ph$^\bullet$ radicals formed by dissociation of $PhI^{-\bullet}$ being responsible for the generation of the cycloalkyl radicals by hydrogen atom abstraction from the cycloalkane.[365b]

The dianion *p*-$C_6H_4(CN)_2^{2-}$ reacts in a similar fashion. The ratio of 4-alkylbenzonitriles to 2-alkylterephthalonitriles strongly depends on the alkyl halides and changes in favor of the *ipso*-substitution product, in going from tertiary to primary halides and within primary halides from RI to RCl. In the reaction with *n*-BuX, the S_N path is estimated as 100 and 85% for X = Cl and Br, respectively. With *n*-BuI the contributions of S_N and ET paths are approximately similar. Reactions with secondary and tertiary RX are likely to proceed by an ET mechanism, which is characterized by the absence of an appreciable effect of the nature of the halogen on the regioselectivity of the alkylation. The reaction of the dianion with cyclopropylmethyl bromide as alkylating agent was shown to proceed by polar and ET substitutions.[157b]

A change in the S_N/ET ratio has also been reported in the reaction of the radical anion of 1,4-dicyanonaphthalene with a number of ring-substituted benzyl bromides, as a function of the electron demand of the substituent, by changing the solvent from MeCN to DMF.[22d]

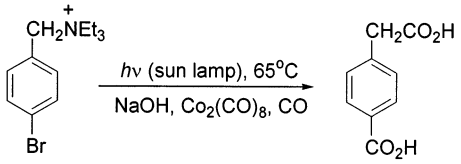
The radical anion or dianion of $PhNO_2$ is also proposed to react with *t*-BuI by $S_{RN}1$ to give *p*-(*t*-Bu)-$C_6H_4NO_2$ (18%).[366]

ET from the ketyl radical anion of *tert*-butyl phenyl ketone, generated electrochemically, to 6-hexene bromide affords the 6-hexenyl radical that undergoes cyclization to the cyclopentylmethyl radical, which results in the formation of both uncyclized and cyclized products mainly at the para and ortho positions of the ketone.[367]

5. Carbonylation Reactions

$PhCH_2NEt_3^+$, *m*-$MeC_6H_4CH_2NEt_3^+$, and β-naphthylmethyltriethylammonium halides afforded the acids in high yields by carbonylation with acetylcobalt tetracarbonyl generated from MeI and $Co(CO)_4^-$ under PTC conditions.[368] The Co-catalyzed carbonylation of $PhCH_2NEt_3^+X^-$ can also be achieved by $Co_2(CO)_8$ under a slow stream of CO in aqueous NaOH, even without organic solvent, provided that the reaction medium is irradiated.[369] The reactions succeeded, affording 75−85% yield of the corresponding acids.[369]

$ArCH_2NEt_3^+$ salts bearing a halogen (Cl or Br) on the aromatic ring are carbonylated to diacids (75−80%) (eq 48). This is an example of an aromatic and aliphatic carbonylation proposed to occur by two consecutive $S_{RN}1$ reactions.[369]



(48)

Allyltriethylammonium halides and benzyl halides can also be carbonylated in high yields.[369] However, carbonylation of *o*-$MeC_6H_4CH_2Br$ led to the corre-

sponding acid in only 25% yield. Cobalt tricarbonyl nitrosyl is another metal catalyst used in the carbonylation of a series of benzyl halides.[370] NaH-NaOAm-*t*-$FeCl_3$-CO promoted the carbonylation of primary, secondary, and, interestingly, tertiary alkyl halides. With the first two types of halides, quite good overall carbonylation yields are obtained.[371]

6. Neopentyl and Related Halides

Neopentyl iodide reacts with 9-phenylfluorenyl anion in THF under irradiation to afford 84% yield of substitution.[372] The irradiated reaction of the anion with 1-iodo-2,2-dimethylhexane gives substitution (54%), the reduced product 2,2-dimethylhexane (29.2%), and the dimer (5.0%) with a quantum yield of 0.98.[372]

In the irradiated reaction of the anion with the radical probe 6-iodo-5,5-dimethyl-1-hexene (THF, − 25 °C), straightforward and cyclized substitution products were obtained. On the basis of the quantum yields and the variation of the product distribution with the concentration of the probe, all of these reactions are proposed to occur by ET with geminate radical coupling within the solvent cage.[372]

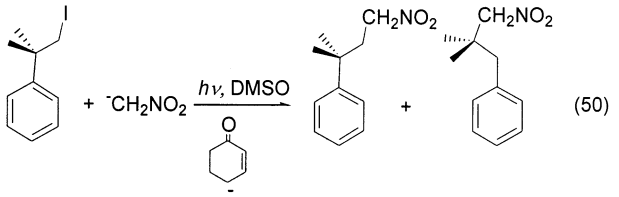
The effects of leaving groups, solvent, and hydrogen atom donors have been investigated in the reaction of LiCHMeCOPh with 6-X-5,5-dimethyl-1-hexenes (X = I, Br, or OTs).[373] In the reaction of the iodo derivative, O- (66%) and C- (11%) alkylation products are formed, together with a small amount of the cyclic hydrocarbon. It is suggested that the reaction takes place in part with radicals as intermediates. The bromide and tosylate derivatives appear to react via the S_N2 pathway.[373]

Several enolate anions such as $^-CH_2COMe$ ions fail to react with neopentyl bromide in liquid ammonia under irradiation. Reduction is the main reaction of neopentyl iodide in the presence of $^-CH_2COMe$ ions in DMSO, whereas substitution is achieved with $^-CH_2COPh$ ions (65% under irradiation,[244] 92% when initiated with $FeBr_2$[106]) (eq 49), and with the anion

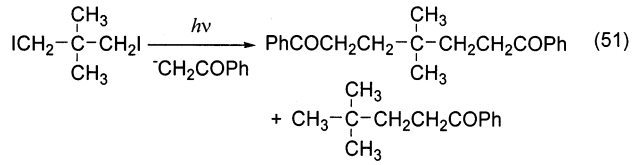
$$Me_3CCH_2I + {}^-CH_2COPh \xrightarrow[DMSO]{h\nu,\ or\ FeBr_2} Me_3CCH_2CH_2COPh \qquad (49)$$

of anthrone (52% under irradiation). Substitution by the $^-CH_2NO_2$ ion, which fails to photoinitiate the process, succeeds (69%) under entrainment conditions (in the presence of $^-CH_2COMe$ ions).[244]

A related substrate, neophyl iodide, in which one Me group of the neopentyl moiety has been replaced by a Ph group, reacts with the $^-CH_2COPh$ ion to afford the straightforward and rearranged substitution compounds (see section IV.B.1). Only C_6H_5Bu-*t* and C_6H_5Bu-*i*, the reduction products arising from hydrogen abstraction by neophyl radical and its rearranged derivative, respectively, are formed by reaction with the anion of 3-cyclohexenone, indicating a slow coupling between the radical and this anion. In agreement with this result, substitution (67%) together with 2% of the rearranged product is obtained with the $^-CH_2NO_2$ ion under entrainment conditions in the presence of the anion of 3-cyclohexenone (eq 50).[87]



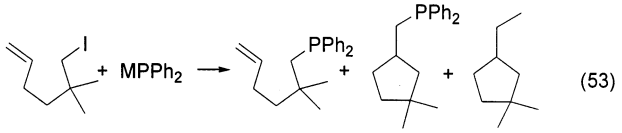
Disubstituted (36%) and monosubstituted reduced (16%) compounds are obtained by reaction of 1,3-diiodo-2,2-dimethylpropane with the $^-CH_2COPh$ ion in DMSO (eq 51). The iodo-monosubstituted compound is not an intermediate of the reaction.[244]



In contrast with the behavior shown by the carbanions, the anions PhS^-, Ph_2P^-, and Ph_2As^- react in liquid ammonia with neopentyl bromide under irradiation with 60, 76, and 82% yields of substitution, respectively.[221] Ph_2P^- ions also react with the neopentyl (R = Me),[222] neophyl (R = Ph),[60] and 2,2-dimethyl-3-phenyl-1-propyl (R = Bn)[60] chloro derivatives affording, after oxidation, the substituted phosphine oxides (70, 74, and 49% yields, respectively) (eq 52).

$$RMe_2CCH_2Cl + Ph_2P^- \xrightarrow[2.\ [O]]{1.\ h\nu,\ NH_3} RMe_2CCH_2P(O)Ph_2 \qquad (52)$$
R = Me, Ph, Bn

When $MPPh_2$ (M = Li, Na, or K) reacts with 6-iodo-5,5-dimethyl-1-hexene in THF, the compounds indicated in eq 53 are formed by ET.[374]



The yields of unrearranged and cyclized substitutions vary between 17 and 43% and between 48 and 75%, respectively, as a function of the counterion. The cyclized hydrocarbon was obtained in 4−11% in all cases. Straightforward substitution is the main reaction with the bromides and chloride derivatives.[374]

Quantitative straightforward substitution is obtained by reaction of the probe with LiSPr-*i*. However, the same reaction, in the presence of DCHP, yielded up to 22% hydrocarbon products. No evidence for this mechanistic pathway was observed with the bromide probe.[360] On the other hand, an ET pathway was proposed for the reaction of the bromide probe with the PhS^- ion in liquid ammonia under irradiation, a reaction in which straightforward and cyclized substitution compounds are formed in similar yields.[148]

Straightforward substitution and scrambled products (symmetrical selenides) are obtained in modest yield by reaction of neopentyl bromide with $PhSe^-$ ions.[221] On the other hand, Na_2Se reacts with neopentyl iodide to give a small amount of dineopentyl

selenide (10%) and dineopentyl diselenide (83%), from oxidation of the neopentyl selenide ion formed (eq 54).[222]

$$Me_3CCH_2I + Se^{=} \xrightarrow[2.\ [O]]{1.\ h\nu} (Me_3CCH_2Se)_2 + (Me_3CCH_2)_2Se \qquad (54)$$

tris-Neopentylarsine (33%) can be obtained by reaction of the "As^{3-}" species, formed from As and Na metals, with neopentyl bromide in liquid ammonia.[222]

The mechanistic pathways followed by the reaction of neopentyl halides with $NaSnMe_3$ in THF have been determined. The chloro derivative reacts mainly by S_N2 (90%) and only 5% by ET, the bromo derivative yields 58% by S_N2, 32% by ET, and 8% by HME, whereas the iodo derivative furnishes 77% by HME and 22% by S_N2.[18a]

Several substitution products and hydrocarbons were formed by reaction of 6,6-dichloro or 6,6-diiodo-5,5-dimethyl-1-hexenes, geminal neopentyl type dihalides, with $NaSnMe_3$ and Ph_2P^- ions in THF.[375,376] The reactions are proposed to occur by an ET route and by an ET followed by a carbene route as well as by an S_N2 pathway.[375,376]

B. Cycloalkyl Halides

1. Halo- and gem-Dihalocyclopropanes and Related Compounds

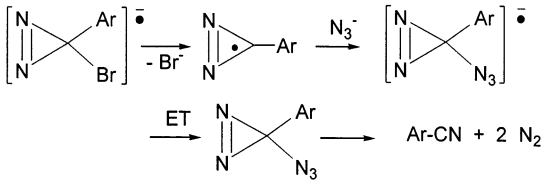
7-Iodonorcarane (7-iodobicyclo[4.1.0] heptane) (ca. 1:1 of exo/endo isomers) affords substitution with $^-CH_2COPh$ ions (87%) and methyl 2-naphthyl ketone (40%) in DMSO under irradiation with high yields of the exo product (see section IV.B.6).[170] The reactions induced by $FeBr_2$ give 90 and 60% yields of substitution, respectively.[106] Substitution (41%) under entrainment conditions is achieved with the $^-CH_2NO_2$ ion with 88% of the exo isomer. The reaction of this anion initiated by $FeBr_2$/$^-CH_2COPh$ ions gives the product in 71% yield (exo 92%), together with 19% of substitution with acetophenone.[106]

7-Bromonorcarane reacts with several Nu^- in liquid ammonia under irradiation. High yields of substitution were obtained with Ph_2P^- (87%) and Ph_2As^- (90%) ions[377] and lower yields with PhS^- (26%)[378] and $^-CH_2COBu$-*t* ions (18%).[378]

On the basis of ^{15}N-labeling experiments, the effect of light, and trapping experiments with radical scavengers, it was concluded that aryl bromodiazirines react with N_3^- ions by $S_{RN}1$ and S_N2' mechanisms to give ArCN.[379] In the case of the chloro derivatives the reaction occurs only by the $S_{RN}1$ process.[380a] In these reactions the radical formed by fragmentation of the radical anion of the diazirine derivative is trapped by N_3^- ions to give the *C*-azidodiazirine radical anion, which by ET to the substrate gives the substitution product. This compound cleaves to afford the observed ArCN (Scheme 34).[380b]

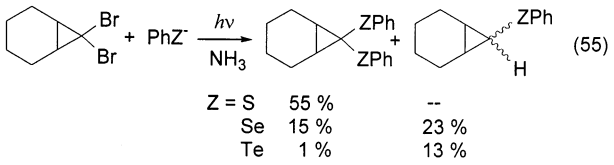
The formation of acetoxyphenyldiazirine in the reaction of phenylbromodiazirine with tetrabutylammonium acetate (45 and 62% yields, the latter under

Scheme 34



superoxide initiation) has been proposed to occur by the $S_{RN}1$ mechanism.[381]

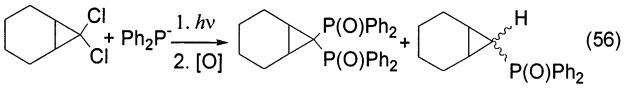
Disubstitution and monosubstitution with reduction occurs, although in overall low yield when 7,7-dibromonorcarane reacts with PhS^-,[238,378] $PhSe^-$,[238] and $PhTe^-$ [238] ions (eq 55). Both types of compounds (5−40%) are formed in the reaction of several 1,1-dibromocyclopropanes with PhS^- ions.[239]



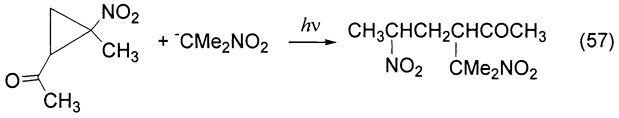
Z =			
S	55 %	--
Se	15 %	23 %
Te	1 %	13 %

Only monosubstitution is formed with the *n*-BuS^- ion (22%), and disubstitution (46%) in the reaction of 7,7-dibromonorcarane with the $^-CH_2COBu$-*t* ion.[378]

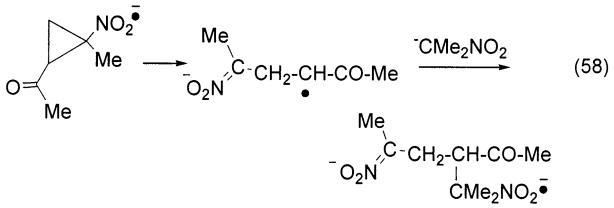
7-Bromonorcarane (87%), formed by an X-philic pathway, is the main product of the reaction of the dibromide derivative with Ph_2P^- ions in liquid ammonia.[382] On the other hand, this anion reacts under irradiation with the dichloride derivative to afford di- and monosubstitution (60 and 15% yields, respectively, eq 56).[238]



In all of these ET reactions there is no opening of the cyclopropane ring. However, rearrangement occurs in the reaction of the following cyclopropane substituted by EWG with $^-CMe_2NO_2$ ions (eq 57).[383]



The radical anion of the substrate cleaves into a distonic radical anion, which couples with the Nu^- to give the radical dianion of the product, responsible for the continuation of the propagation cycle (eq 58).



2. Other Cycloalkyl Halides

The reaction of Ph_2P^- ion has been investigated with different cycloalkyl halides. This anion does not

react with *c*-C_4H_7Cl in liquid ammonia under irradiation, but does react with the bromo derivative to give *c*-$C_4H_7P(O)Ph_2$ (after oxidation) in the dark and under photoinitiation (42 and 83% yields, respectively). The light-catalyzed reaction was partially inhibited by *p*-DNB, suggesting that an $S_{RN}1$ process can be in competition with other mechanisms, probably a cage-collapse pathway.[384]

The Ph_2P^- ion affords substitution with *c*-C_5H_9Cl under irradiation. This reaction was almost completely inhibited by *p*-DNB, whereas *c*-C_5H_9Br reacts by polar and ET pathways.[384] It has been determined that *c*-C_5H_9Cl is substituted (97%) by $NaSnMe_3$ in THF through an S_N2 reaction, but the bromo derivative reacts by ET (90%) with only 7% of a polar component.[18a]

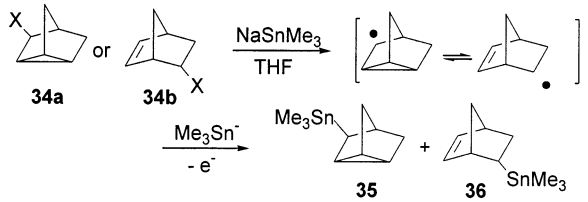
The *c*-$C_6H_{11}Cl$ reacts with Ph_2P^- ions under irradiation to form 33% of substitution by the $S_{RN}1$ mechanism.[150,384] A dark reaction accelerated by light was observed with the bromo derivative to give substitution mostly by the latter mechanism (93%).[384]

Related compounds such as *cis*- and *trans*-4-*tert*-butylcyclohexyl bromide[64e] and *trans*- and *cis*-2-, -3-, and -4-methylcyclohexyl bromides[64c] were found to undergo substitution by $MSnMe_3$ (M = Li, Na, or K) in a non-stereospecific manner. The stereochemical results reveal a product distribution which, in most cases, manifests a predominance of the thermodynamically more stable trans isomer (for the 4-*tert*-butyl, 4-methyl, and 2-methyl halide derivatives) and of the cis isomer (for the 3-methyl halide).[64c,e] The loss of stereochemical integrity was taken as an indication of alkylation proceeding extensively by a free radical pathway.[64c,e]

The reactions of $LiSnPh_3$ with *trans*- and *cis*-2-, -3-, and -4-methylcyclohexyl bromides proceed stereospecifically with inversion at carbon.[64c] The pronounced stereochemical distinction between reactions of $LiSnMe_3$ and $LiSnPh_3$ is not observed in the corresponding reactions of $LiGeMe_3$ and $LiGePh_3$, which are non-stereospecific.[64c] $LiGeMe_3$ reacts with *trans*- and *cis*-4-*tert*-butylcyclohexyl bromide to give the cis and trans products in 86:14 and 76:24 cis/trans ratios, respectively.[205] A similar behavior is observed in the reaction of the anion with *trans*- and *cis*-4-methylcyclohexyl bromide[64c] and *trans*- and *cis*-4-*tert*-butylcyclohexyltrimethyl stannane (Me_3Sn^- as leaving group).[205] The results were considered to be consistent with ET and free radical processes.

In the reaction of 3-bromo- and 3-iodonortricyclene **34a** with $NaSnMe_3$ in THF, 3-nortricyclyltrimethyltin **35** (60% and 72%) and (norborn-2-en-5-yl)trimethyltin **36** (12 and 23%) were, respectively, formed together with the corresponding reduced compounds (12−11%).[385] A similar ratio of product distribution was observed in the reaction of the anion with *endo*- and *exo*-5-bromo- and *exo*-5-chloro-2-norbornenes **34b** (Scheme 35).[385] The increased yield of hydrocarbon formed in reactions in the presence of DCHP showed that the bromides and chloride reacted predominantly by way of free radical intermediates and by geminate reactions. 3-Iodonortricyclene reacted predominantly through an anionic intermediate as shown by trapping with TBA.[385]

Scheme 35



2-Haloadamantanes (2-XAd) are halocyclohexanes that have even lower reactivity toward Nu^- than 1-XAd or the simple halocyclohexanes. However, carbanions react with 2-IAd in DMSO, affording the following variable yields of substitution by photoinitiated reaction with $^-CH_2COPh$ (62 and 88% when the reaction is induced by $FeBr_2$), anthrone (37%), methyl 2-naphthyl ketone (32%), *N*-acetylthiomorpholine (32%), and $^-CH_2NO_2$ ions (88%, with $^-CH_2COMe$ ion as entrainment nucleophile).[243]

The slow substitution of 2-BrAd by Ph_2P^- ions is accelerated by light (64% yield). 2-BrAd was determined to be 0.70 times as reactive as 1-BrAd toward Ph_2P^- ions.[242] 2-ClAd does not react with Ph_2P^- ions.[242] However, 2-ClAd[242] and 2-BrAd[59] are substituted by Me_3Sn^- in liquid ammonia under irradiation (94 and 80% yields, respectively). Substitution of 2-BrAd with $NaSnMe_3$ is also achieved in THF (96%). In the presence of DCHP, AdH was formed in 88% yield (substitution in <5%).[18a] Disubstitution (a mixture of Z and E isomers) is obtained (87−95%) by reaction of 2,4-dibromoadamantanes (Z or E isomers) with $LiSnMe_3$ in THF.[386]

c-$C_7H_{13}Cl$ reacts with Ph_2P^- ions to give substitution (56%) only upon irradiation (3 h). On the other hand, the bromide reacts very quickly in the dark to give the substitution product (96%). The reaction is partially inhibited by *p*-DNB, suggesting that this substrate reacts by both mechanisms (polar and ET), whereas the chloride reacts only by the $S_{RN}1$ process.[384]

The carbonylation reaction of *c*-C_5H_9Cl, *c*-$C_6H_{11}Cl$, *c*-$C_6H_{11}Br$, and *c*-$C_8H_{15}Cl$ with the reducing reagent $NaH-NaOR-FeCl_3$-CO gives a mixture of the acid and the ester derivatives in overall 95, 70−90, and 48% yields, respectively.[371]

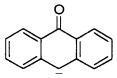
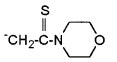
C. Bridgehead Halides

1. 1-Haloadamantanes and Dihaloadamantanes

1-Haloadamantanes. Aliphatic carbanions, such as the $^-CH_2COMe$ or $^-CH_2COBu$-*t* ions, are unsuccessful Nu^- toward 1-XAd in liquid ammonia under irradiation. Even though the 1-Ad$^\bullet$ radicals are formed, they do not couple with carbanions to follow the $S_{RN}1$ cycle, at least at a rate to compete with other reactions (reduction and dimerization).[236] However, substitution succeeded with aromatic ketone enolate ions in DMSO, under irradiation[169,259] or in the presence of $FeBr_2$.[106] The latter initiation also succeeds with thioamide anions[107] (Table 26).

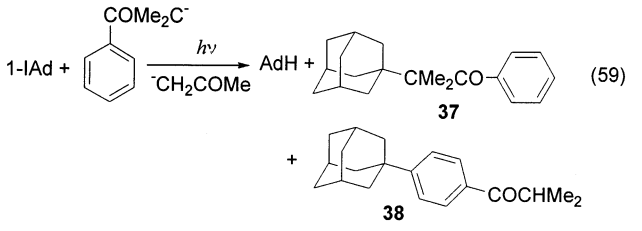
When the carbanion has β hydrogens, as in the case of the $^-CMe_2COPh$ ion, the reduction of the radicals competes with the coupling. A particular regiochemistry was observed in the reaction of this anion (with

Table 26. Reactions of 1-XAd with Nucleophiles

1-XAd, X	Nucleophile	Conditions	Product (%)	Ref.
Br	$^-CH_2COPh$	DMSO, $FeBr_2$	47	106
I	$^-CH_2COMe$	DMSO, *hν*	20[a]	169
	$^-CH_2COPh$		65	169
		DMSO, $FeBr_2$	85	106
		DMSO, *hν*	75	169
		DMSO, *hν*	60	107
		DMSO, $FeBr_2$	65	107
	$^-CH_2NO_2$	DMSO, *hν*[b]	87	169
Cl	Me_3Sn^-	NH_3, *hν*	93	242
Br		THF	95	241
Br, I		NH_3, *hν*	80, 74	59
Cl	Ph_2P^-		29[c]	242
Br			70[c]	219
		DMSO, *hν*	70[c]	168
I			51[c,d]	399
Br	Ph_2As^-	NH_3, *hν*	65	219
I	PhS^-		45	220
Br		DMSO, *hν*	70	168
		SmI_2, DMF-THF	38	109
I		MeCN, *hν*	91	16
	p-$NCC_6H_4S^-$		95	16
	p-$MeC_6H_4S^-$		95	16
	p-$MeOC_6H_4S^-$		95	16
	1-naphthyl-S^-		45[e]	16
	Se^{-2}	NH_3, *hν*	46[f]	220
	$PhSe^-$		74[g]	220
		SmI_2, DMF-THF	62	109
	1-naphthyl-Se^-		50	220
	Te^{-2}		47[h]	220
	$PhTe^-$		69[i]	220
		SmI_2, DMF-THF	52	109

[a] AdH (17%) also was formed. [b] In presence of $^-CH_2COMe$ (entrainment reagent). [c] Isolated as the oxide. [d] AdH (47%) was also formed. [e] In presence of PhS^- (entrainment reagent), 1-AdSPh was also formed (51%). [f] Isolated as $(1\text{-AdSe})_2$. [g] Together with Ph_2Se (10%) and $(1\text{-Ad})_2Se$ (16%). [h] Isolated as $(1\text{-AdTe})_2$. [i] Together with Ph_2Te (31%).

$^-CH_2COMe$ as entrainment reagent) with 1-IAd in which, besides AdH (52%), α-**37** (6%) and *p*-**38** (26%) substitution products were obtained (eq 59). The higher percentage of **38** suggests that the α-C of this nucleophile is strongly sterically hindered.[175]

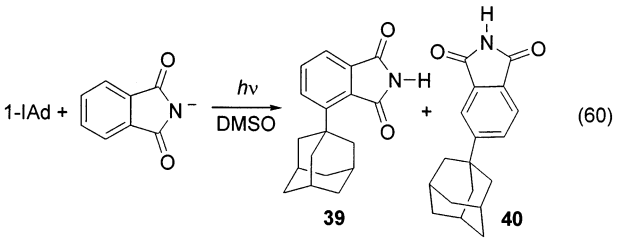


(59)

Adamantyl coupling at C_3 **39** (12%) and C_4 **40** (45%) of the anion of phthalimide is obtained in its reaction with 1-IAd (eq 60). No C−N coupling was observed.[387]

Replacement of halogen in 1-XAd (X = Br or Cl) by CO_2H and CO_2R was achieved with the complex reducing agent NaH-NaOR-$FeCl_3$-CO (80−88% overall yield).[371]

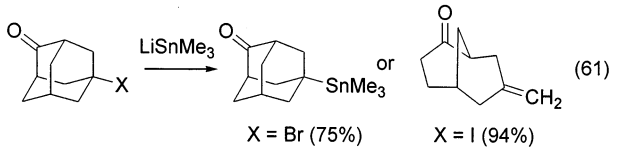
Substitution of 1-XAd is possible with Ph_2P^-, Ph_2As^-, ArS^-, $PhSe^-$, $PhTe^-$, Se^{2-} and Te^{2-} ions (Table 26).



(60)

1-$AdSnMe_3$ (95%) is obtained by reaction of 1-BrAd with $NaSnMe_3$ in THF. In the presence of DCHP only AdH is formed.[18a] The reaction of the anion with 1-IAd was proposed to occur 79% by a radical path and 21% by a carbanion path. However, more recently both compounds were shown to react only by the radical path.[241] Irradiation was needed to achieve the substitution of 1-ClAd and 1-BrAd with Me_3Sn^- ions in liquid ammonia.[59,242]

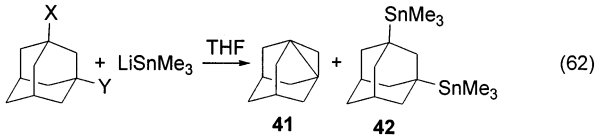
5-Bromoadamantan-2-one reacts with $LiSnMe_3$ in THF to afford the substitution product (75%) by a radical path; however, the iodo derivative furnishes the fragmentation product by a polar reaction (eq 61).[388] Changing the C=O group by $C{=}CH_2$ precludes



(61)

the fragmentation, and both derivatives give the substitution compound (X = Br, 97%; I, 83%).[388]

1,3-Dihaloadamantanes. Propellane **41** and disubstitution **42** products are formed in the reaction of 1,3-dihaloadamantanes with $MSnMe_3$ (M = Li or Na) in THF, besides other minor products (eq 62). The product distribution depends on the halogen, counterion, and experimental conditions.[241]



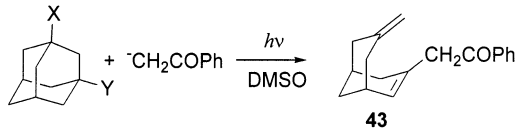
(62)

For example, when X = Cl and Y = Br, **42** is the main product (94−97%); when X = Y = Br, **41** and **42** are formed in similar yields, whereas when X = Br, Y = I, or X = Y = I, **41** is the major product (~80−100%). The $S_{RN}1$ mechanism accounts for the disubstitution. The formation of **41** occurs through a concerted process involving direct nucleophilic attack by the Me_3Sn^- ion on C−I with synchronous cyclization and cleavage of the second C−X bond. In the electrochemical reduction of 1,3-dihaloadamantanes the process was demonstrated to be a one-electron concerted reductive cleavage to yield the halo adamantyl radical, which is further quickly reduced to the carbanion, which can either protonate or give **41**.[389] On the other hand, 1,3 dibromoadamantane affords only disubstitution (60%) in liquid ammonia.[59]

Disubstitution (74−88%) is the main reaction of 1,3-dihaloadamantanes (X = Y = Cl, X = Cl, Y = Br, and X = Y = Br) with Ph_2P^- ions in liquid ammonia under irradiation.[240]

1,3-Dibromoadamantane and 1-ClAd react with $LiSiPhMe_2$ to give 95 and 93% of the di- and monosubstitution products, respectively.[390] No mechanistic information is given for the reaction.

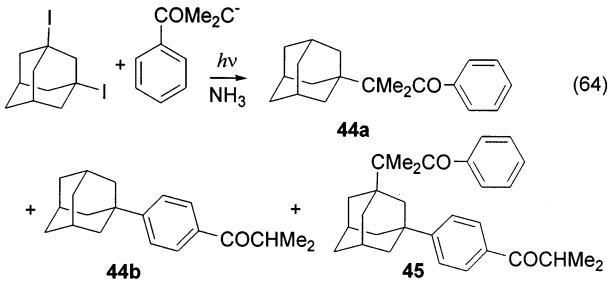
Quite different results were obtained in the photostimulated reaction of 1,3-diiodoadamantane with carbanions in which products from ring opening are formed. For example, in its reaction with the $^-CH_2COPh$ ion, the only product obtained is the ring opened **43** (87%) (eq 63). Lower yields were obtained for X = Y = Br (50%) or X = Br, Y = Cl (21%).[175]



43 (63)

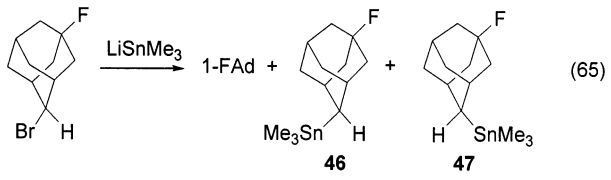
The formation of **43** was ascribed to deprotonation of the halide monosubstituted compound followed by ring opening with halide elimination. The carbanion of the product formed in this reaction, when acidified, affords the more stable isomer **43**. The ring opening reaction was also found with $^-CH_2NO_2$ (67%) and $^-CH_2COBu$-*t* ions (80%).[175]

Ring opening was not observed in the reaction with the $^-CMe_2COPh$ ion, which has no α-hydrogen to give carbanions. The product distribution of the reaction with the diiodide derivative (X = Y = I) depends on the reaction time and shows a particular regiochemistry as previously indicated. For instance, AdH (18%), **44a** (36%), **44b** (13%), and the disubstitution product **45** (14%) (eq 64) were formed after photostimulation (1.5 h).[175]



(64)

1,2- and 1,4-Dihaloadamantanes. The reaction of (*E*)-4-bromo-1-fluoroadamantane with $LiSnMe_3$ in THF gives 1-FAd (8%) and a mixture of the (*E*)-**46** (41%) and (*Z*)-**47** (51%) stannane isomers (eq 65).[208]

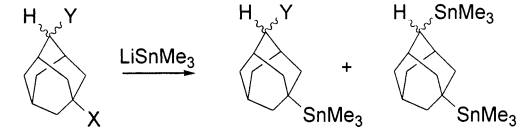


(65)

A similar product distribution was observed in the reaction of the Z isomer, which affords **46** (43%) and **47** (55%). These results were taken as evidence of the intermediacy of 1-fluoro-4-adamantyl radicals in both reactions.[208]

Several 1,4-dihaloadamantanes (Z and E) afford monosubstitution or disubstitution by reaction with $LiSnMe_3$ in THF. In all of the cases, the disubstitution products are a mixture of E and Z isomers (Scheme 36).[388]

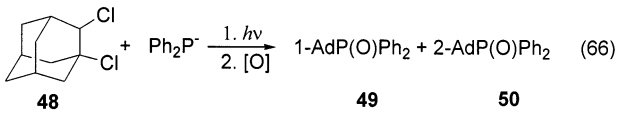
Scheme 36



(*E*) X = Br, Y = Cl	*E* (57%)	*E* (17%), *Z* (19%)
(*Z*) X = Br, Y = Cl	*Z* (73%)	*E* (8%), *Z* (8%)
(*E*) X =I, Y = Cl	*E* (72%)	*E* (9%), *Z* (10%)
(*Z*) X = I, Y = Cl	*Z* (76%)	*E* (6%), *Z* (6%)
(*E*) X = Br, Y = Br		*E* (39%), *Z* (46%)
(*Z*) X = Br, Y = Br	*Z* (4%)	*E* (36%), *Z* (44%)
(*E*) X = I, Y = Br	*E* (11%)	*E* (38%), *Z* (40%)
(*Z*) X =I, Y = Br	*Z* (24%)	*E* (28%), *Z* (28%)

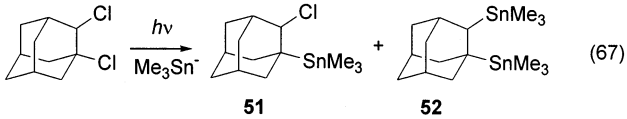
The formation of disubstitution in the case of the chloro bromo and chloro iodo derivatives constitutes evidence for the chain nature of the radical mechanism because the chloro tin compounds are relatively inert toward this nucleophile.[388] The fact that the disubstitution products are formed in equal amounts of E and Z isomers indicates that the 1-substituted 4-adamantyl radical intermediates do not show π-facial selectivity in coupling to Me_3Sn^- ions, although with the dibromide a modest π-facial selectivity is observed. Similar results are observed in liquid ammonia.[59]

The monosubstituted reduced compounds **49** and **50** (quantified as the oxides in 64 and 15% yields, respectively) were formed in the reaction of 1,2-dichloroadamantane **48** with Ph_2P^- ions in liquid ammonia (eq 66) in which no disubstitution was found.[242]



48 **49** **50** (66)

When the dichloride reacts with Me_3Sn^- ions, a nucleophile with less steric bulk than Ph_2P^- ions, mainly the chloro monosubstituted **51** (54%) and the disubstituted **52** (26%) products, are formed (eq 67).

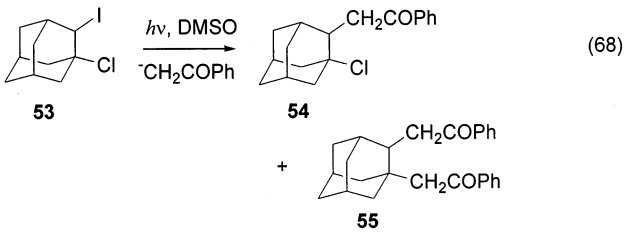


51 **52** (67)

Compound **51** is not an intermediate in the formation of **52** because it fails to react with Me_3Sn^- ions under irradiation.[242]

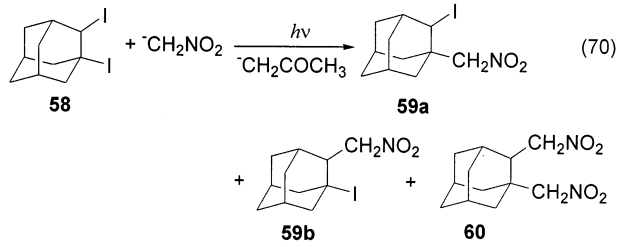
In the case of 1-chloro-2-iodoadamantane **53**, the 2-position fragments more rapidly than the 1-position. Thus, in the reaction of **53** with $^-CH_2COPh$ ions in DMSO, the chloro monosubstituted **54** and the disubstituted product **55** were obtained in a ratio that depends on the irradiation time (eq 68).

After 5 min of irradiation, **54** was the only product observed (52%), but after 3 h **54** and **55** were formed (52 and 45% yields, respectively). These results suggest the reaction to occur through a stepwise mechanism, **54** being an intermediate in the forma-



tion of **55**. Indeed, the photoinduced reaction of **54** gave **55** as product.[243] A similar behavior was found with **56**. In this reaction the chloro monosubstituted compound **57** (53%) is the main product, together with **55** (4%) (eq 69).[243]

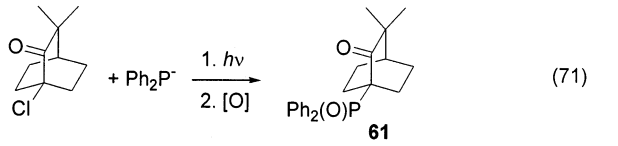
1,2-Diiodoadamantane **58** reacts with $^{-}CH_2NO_2$ under irradiation (induced by $^{-}CH_2COMe$ ions) to give monosubstitution with retention of iodine at either the 2- or 1-position (mainly **59a** and mere traces of **59b**) in ~40% yield and the disubstituted compound **60** in 13% yield (eq 70). Under light



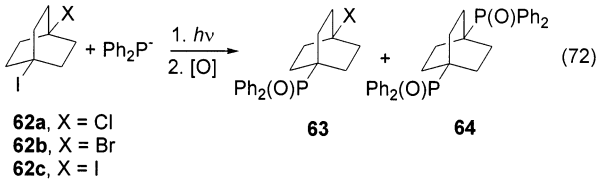
catalysis and longer irradiation time (3 h) almost all of the product formed was **60** (68%) accompanied by mere traces of **59** (<5% yield).[243]

2. 1-Halo- and 1,4-Dihalobicyclo[2.2.2]octanes and Related Compounds

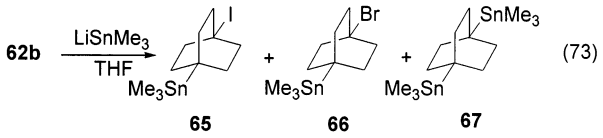
1-Iodobicyclo[2.2.2]octane reacts with Ph_2P^- ions in liquid ammonia under irradiation to give the substitution product (87%, as the oxide). The chloro derivative is unreactive in the dark and under irradiation.[237] However, the 2-oxo derivative of 1-chloro-3,3-dimethylbicyclo[2.2.2]octane (with an C=O π electron acceptor) reacts to afford, after oxidation, a 69% yield of product **61** (eq 71).[58b]



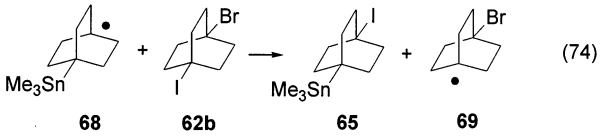
When the substrate has two leaving groups, one of them iodine, such as **62**, the products obtained depend on the nature of the second halogen and the Nu^-. Thus, with **62a** only substitution at iodine occurs (compound **63**, X = Cl, 63%). Both halogens are substituted with **62b** and **62c**, affording mainly **64** (eq 72) (83 and 58%, respectively).[237]



A different pattern is followed by reaction of **62** with $LiSnMe_3$. With **62b** three stannanes **65**−**67** are obtained (eq 73).[391,392]



These results show an unprecedented halogen nucleofugality (Br > I) for an HME or ET reaction. However, competition experiments of 1-iodo- and 1-bromobicyclo[2.2.2]octanes toward $LiSnMe_3$ established that the iodine is about twice as reactive as the bromine derivative.[391] The reaction is proposed to occur by the $S_{RN}1$ mechanism. The major difference is an additional propagation step involving iodine atom abstraction from **62b** by the radical intermediate **68**, to give the substitution product **65** and the radical intermediate **69**, which continues the chain propagation cycle (eq 74).

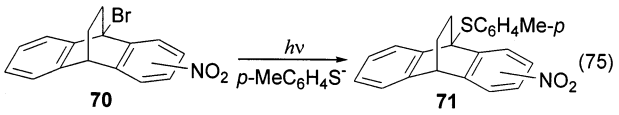


As this anion does not react with 1-chloro-4-methylbicyclo[2.2.2]octane, the substitution at chlorine of **62a** is ascribed to an intramolecular entrainment reaction.[391] When X = F, only substitution at iodine occurs.[391]

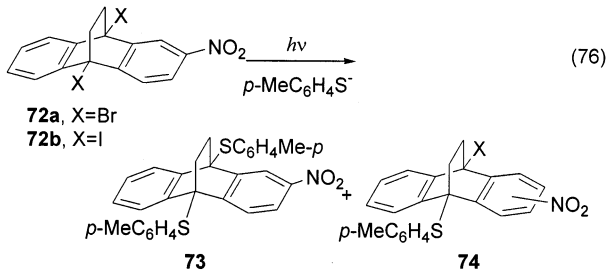
9-Bromotriptycene is another derivative of the family that reacts with Ph_2P^- and Ph_2As^- ions to give substitution (71 and 41% yields, respectively). The reaction of 9,10-dibromotriptycene with Ph_2P^- ion affords disubstitution (49% isolated yield).[236]

Substitution of 9-bromotriptycene by $LiSnMe_3$ was demonstrated to occur through a carbanion pathway, which predominates (~80%) over the radical path (~20%). Similarly, several 9,10-dihalotriptycenes (9,10-dibromo-, 9-bromo-10-iodo-, and 9-bromo-10-chloro-) react with $LiSnMe_3$ to afford mainly monosubstitution, with retention of halogen, and disubstitution, also by competing polar and radical pathways.[388]

A related system, bromonitro-9,10-ethano-9,10-dihydroanthracene **70**, bearing a NO_2 group, is clearly different from the nitrobenzylic system, because the leaving group at the benzylic bridgehead position lies orthogonal to the plane of the nitroaryl group. This compound requires more drastic conditions to be substituted by *p*-toluenethiolate ions to afford **71** (2-NO_2, 75%, and 3-NO_2, 62%, after 24 h, 40 °C) (eq 75).[62]



When the compound bears halogens at both bridgehead positions, such as **72**, the compounds **73** and **74** are formed (eq 76). With **72a** (16 h) only 9% of **73**

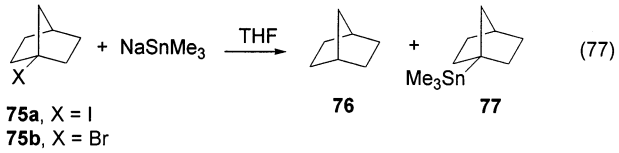


is obtained together with 50% of both isomers **74**. In contrast, **73** is the only product obtained by reaction with **72b** (73% yield, after 30 min of irradiation).[62]

It was concluded that these are $S_{RN}1$ reactions, with the halo-monosubstitution products as intermediates. When the NO_2 group is not present, only reduction products are obtained (5−36%).[62] Similarly, in the reaction of **72** with $^-CMe(CN)_2$ ions, reduction without substitution is observed.[393]

3. 1-Halo- and 1,4-Dihalobicyclo[2.2.1]heptanes (Norbornanes)

1-Iodonorbornane **75a** reacts with $NaSnMe_3$ to give **76** (15%) and **77** (83%) by an ET process; product **77** may be formed by a cage collapse or $S_{RN}1$ reaction (eq 77).[394] However, a reinvestigation of the system

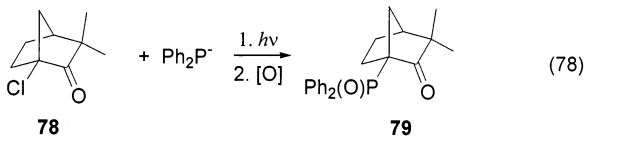


indicates that although **75b** appears to react exclusively by the radical pathway, **75a** reacts by the radical and HME mechanisms.[395a] The partition between radical and HME depends on the counterion. Thus, the reaction of **75a** with $LiSnMe_3$ proceeds by radical (79%) and HME (21%), whereas with $NaSnMe_3$ the radical pathway is estimated to occur to a lesser extent (32%) than the HME (68%) reaction. The origin of this difference has been proposed to lie in differences in the degrees of aggregation in THF.[395]

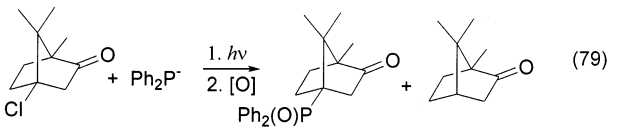
The reactions of **75a** with $LiPPh_2$ and $LiN(Pr\text{-}i)_2$ were sluggish in THF, **76** being the main product. No reaction occurred with $LiCMe_2NO_2$ or with Li-SPr-*i*.[394]

1-Chloronorbornane is unreactive toward Ph_2P^- ions; however, 1-chloro-3,3-dimethyl-2-oxobicyclo-[2.2.1]heptane **78** reacts to give, after oxidation, the product **79** (93%) (eq 78).[58a]

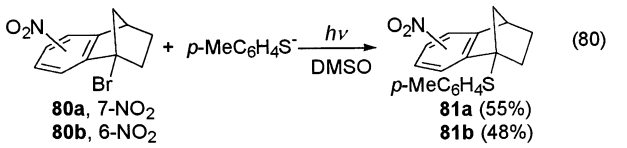
On the other hand, when the C=O group is replaced by a C=C group, no reaction is observed.[58a] 4-Chloro-1,7,7-trimethyl-2-oxobicyclo[2.2.1]-heptane, in which the spatial distance between the leaving group and the C=O is increased with an extra



C−C bond, also affords substitution and reduced products (80 and 8% yields, respectively) (eq 79).[58a]



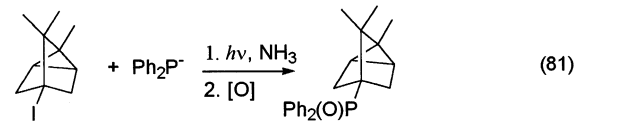
The related system **80** has a reactivity more similar to the bridgehead than to the nitrobenzyl halides. It is substituted by *p*-$MeC_6H_4S^-$ ions after 14 h at 40 °C (eq 80). At 60 °C (7 h) **80b** affords 75% of **81b**.[62]



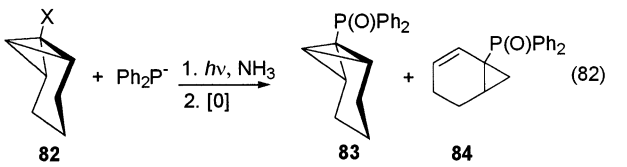
On the basis of the product analysis of the reaction of $LiSnMe_3$ with various 1,4-dihalonorbornanes, it is proposed that in this system a polar mechanism competes effectively with free radical chain processes. The HME pathway is predominant for the dibromo, bromoiodo, and diiodo compounds; a competition between HME and ET was suggested with the chloroiodo compound, and the ET reaction is important for the fluoroiodo and chlorobromo derivatives.[395b]

4. Other Bridgehead Halides

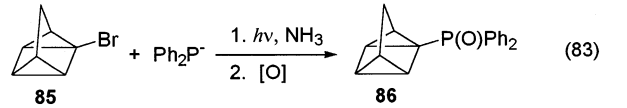
4-Substituted tricyclanes are one of the most unreactive substrates in solvolytic reactions.[396] However, 4-iodotricyclane is substituted by Ph_2P^- ions in 58% yield (eq 81). The 1-chloro derivative is completely unreactive.[397]



1-Bromo- or iodotricyclo[4.1.0.0 ^{2,7}]heptane (**82**) reacts with Ph_2P^- ions to afford a mixture of **83** and **84** (40−52%) (eq 82).[398]

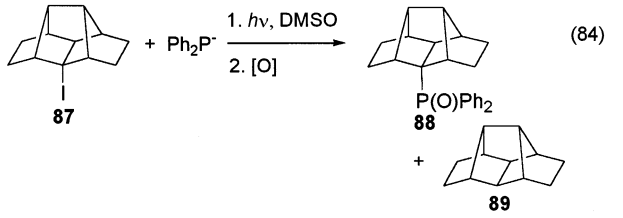


On the other hand, only straightforward substitution is obtained in the reaction of Ph_2P^- ions with 1-bromoquadricyclane **85** (eq 83) (72% yield of **86** in



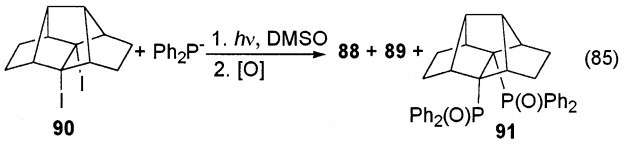
only 15 min of irradiation and after oxidation).[398] The chloro derivatives of **82** and **85** are unreactive.[398]

Iodo and diiodo derivatives of pentacyclo[6.4.0.-0.^{2,10}0.^{3,7} 0^{4,9}]dodecane can also be substituted by Ph_2P^- ions. For example, iodopentacyclo dodecane **87** affords **88** (isolated as the oxide in 34% yield) together with the reduction product **89** (59%) (eq 84). The bromo derivative has a lower reactivity (20% overall yield), and the chloro derivative is unreactive.[399]



(84)

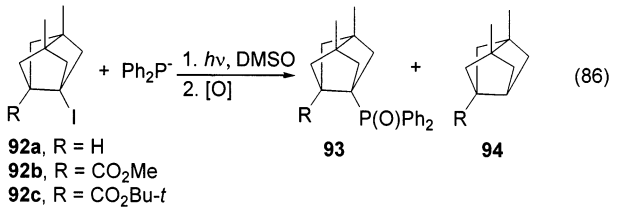
The diiodo derivative **90** gave **88** (24%), **89** (26%), and the disubstitution product **91** (40%) after 10 min of irradiation (eq 85).[399]



(85)

The formation of **91** is remarkable in comparison with the behavior of 1,2-dichloroadamantane, which affords only the reduced monosubstituted compounds by reaction with Ph_2P^- ions in liquid ammonia (see eq 66).

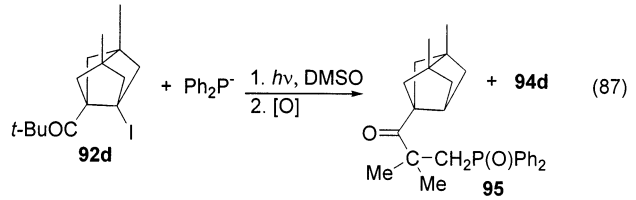
1-Iodo-3,7-dimethyltricyclo[3.3.0.0^{3,7}]octane (**92a**) reacts with Ph_2P^- ions to afford **93** and **94** (55 and 40% yields, respectively) (eq 86). With **92b** only



(86)

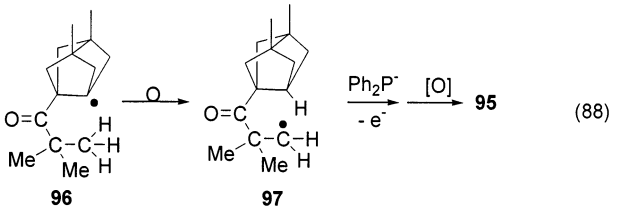
reduction (80%) was obtained; meanwhile, **92c** yields reduction (70%) and substitution (22%).[399]

Quite different results were achieved with the iodo ketone **92d**, which gives the rearranged substitution product **95** (83% yield) and the reduction product **94d** (R = COBu-*t*) (15%) (eq 87).



(87)

The ET to **92d** gives the bridgehead radical **96**. This radical rearranges quite quickly by a 1,5-hydrogen migration to afford the methylene radical **97**, which couples with the Ph_2P^- ion to give the observed substitution product **95** (eq 88). This is the



(88)

first time an intramolecular hydrogen atom abstraction is observed in the propagation steps of an $S_{RN}1$ reaction.

On the contrary, the radical intermediates from **92b** and **92c** do not suffer 1,5- or 1,6-hydrogen migration, respectively.[399]

It has been reported that the reaction of perbromo-D_{2h}-bishomocubane with NaOMe affords the disubstitution product on the cubane structure. This reaction occurs without light stimulation, it is not oxygen sensitive, and it is not inhibited by radical traps. Although the mechanism of this reaction is not known, it has been suggested that the possibility cannot be excluded that it occurs by the $S_{RN}1$ mechanism.[400]

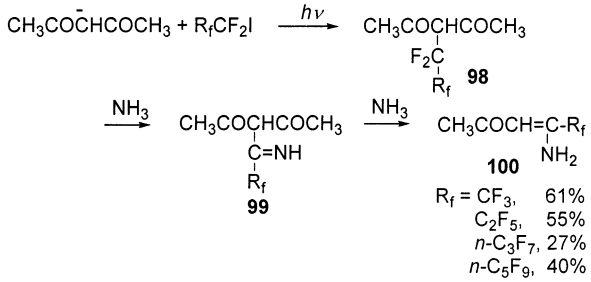
D. Perfluoroalkyl Iodides and Related Compounds

R_fI are able to undergo a variety of nucleophilic substitutions by the $S_{RN}1$ mechanism with different nucleophiles.[401a,b] Some reactions occur in the dark and are accelerated by light, whereas others are induced electrochemically. Cyclic voltammetry has been used to determine the relative reactivity of nucleophiles toward R_fI.[401c]

1. Formation of C–C Bond

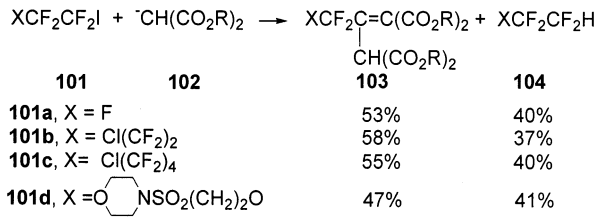
In the reaction of acetylacetone anion with R_fI under irradiation in liquid ammonia, Yagupolskii et al.[402] isolated β-perfluoroalkyl-β-aminovinyl methyl ketones **100**, in which the perfluoroalkyl moiety is one difluoromethylene group shorter than in the initial R_fI. The formation of this product was ascribed to the ammonolysis of the substituted product **98** to afford **99**, which is unstable in alkaline media and eliminates one acyl group leading to **100** and acetamide (Scheme 37).

Scheme 37



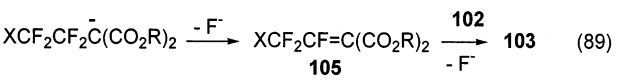
When one acyl group of acetylacetone is replaced by the pivaloyl or benzoyl moiety, compound **99** loses an acyl group, but when it is replaced by trifluoroacetyl, this moiety is eliminated with the formation of the same aminovinyl ketone as from acetylacetone.

Scheme 38



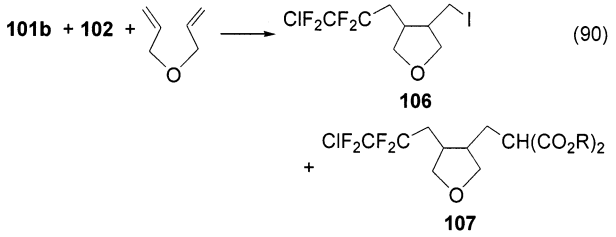
R_fI **101** reacts readily with sodium dimethyl or diethyl malonate **102** in DMF to give the products **103** and **104** (Scheme 38).[403]

The reaction occurred under laboratory light but is accelerated by irradiation and inhibited by *p*-DNB. The anion of the substitution product formed loses F^- ions to give the olefin **105**, which is trapped by **102** to ultimately afford products **103** (eq 89).



R_fI reacts with the ethyl acetoacetate anion to give the substitution product (70−75% yield) in a similar fashion as in Scheme 38.[404] On the other hand, when XCF_2CF_2I (X = Cl or I) was allowed to react with **102**, product **103** was not obtained. Instead, tetrafluoroethylene (85%), a considerable amount of the dimer $[CH(CO_2R)]_2$ (50%), and a small amount of **104** (X = H) (6−11%) were obtained.[403a] The formation of tetrafluoroethylene is due to β−elimination of the β-halotetrafluoroethyl radical intermediate.

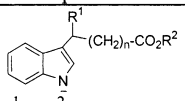
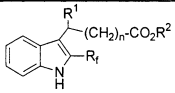
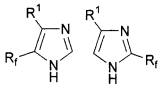
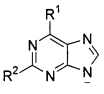
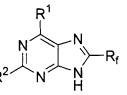
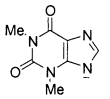
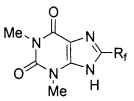
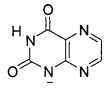
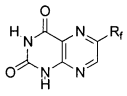
The reactions of **101b** with **102** (R = Me) in the presence of diallyl ether gave no substitution product **103** but the cyclic compounds **106** (26%−traces) and **107** (69−87%) depending on the reaction conditions (R = Me) (eq 90).[403a]



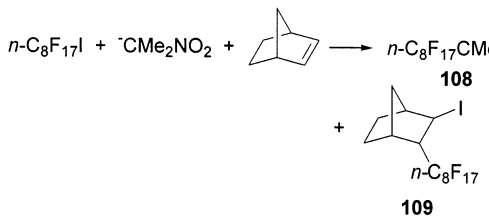
The reaction of the $^-CMe(CO_2Me)_2$ ion with *n*-$C_8F_{17}I$ afforded only *n*-$C_8F_{17}H$ (27%).[405] In the presence of norbornene, the addition of R_fI to the double bond occurred in 67% yields, which demonstrates that there is a radical mechanism involved, even when substitution was not observed.[405] These results seem to indicate that the $^-CMe(CO_2Me)_2$ ion is able to transfer one electron to form radicals but unable to couple with the $R_f^{\bullet}$ radical. For the reaction of $I(CF_2)_3I$ with **102** (R = Et) the analogues to **103** (X = I, 48%, and X = H, 22%) are obtained.[403b]

The reaction of primary R_fI with the $^-CMe_2NO_2$ ion occurs under mild conditions to give substitution in ~80%.[406] The diiodides $I(CF_2)_nI$ (n = 4 or 6) afforded mixtures of mono- and dialkylated products (40−65%) by photoinitiated reaction with the $^-CMe_2NO_2$ ion.[406]

Table 27. Reaction of R_fI with Nitrogen Nucleophiles by Electrochemically Mediated Induction in DMSO[193−195]

R_fI	Nucleophile	Product (%)
n-C_4F_9I		
	$R^1 = R^2 = H$, n = 0	58
	$R^1 = R^2 = H$, n = 3	48
	$R^1 = H$, $R^2 = Me$, n = 0	32
	$R^1 = CF_3$, $R^2 = H$, n = 1	35
	$R^1 = CF_3$, $R^2 = Me$, n = 1	28
n-$C_6F_{13}I$		 A B
	$R^1 = H$	50-55 (A:B = 0.2-0.8)
	$R^1 = NO_2$	65 (A:B = 0.47-0.65)
n-$C_6F_{13}I$		
	$R^1 = NO_2$, $R^2 = Me$	51
	$R^1 = NO_2$, $R^2 = CHO$	35
	$R^1 = H$, $R_2 = p$-$MeOC_6H_4$	56
n-C_4F_9I		
	R^1 = OH	65
	R^1 = NH_2	35
n-C_4F_9I		
	$R^1 = NH_2$, $R^2 = H$	60
	$R^1 = OH$, $R^2 = H$	65
	$R^1 = R^2 = OH$	75
	$R^1 = NHCH_2Ph$, $R^2 = H$	45
	$R^1 = NHCH_2Furyl$, $R^2 = H$	28
	$R^1 = Cl$, $R^2 = H$	52
n-$C_6F_{13}I$	$R^1 = NHCH_2Ph$, $R^2 = H$	34
	$R^1 = Cl$, $R^2 = H$	48
$I(CF_2)_4I$	$R^1 = NH_2$, $R^2 = H$	38
	$R^1 = OH$, $R^2 = H$	40
n-C_4F_9I		35 
n-C_4F_9I		40 

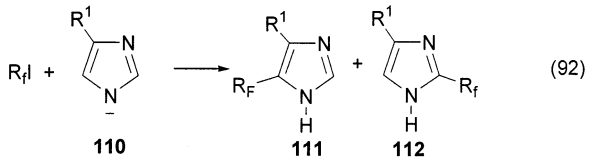
A radical process was demonstrated in the reaction of the $^-CMe_2NO_2$ ion with *n*-$C_8F_{17}I$ in the presence of norbornene.[405] It afforded the product **108** (30%) and the product **109** (50%) that results from the addition of the $R_f^{\bullet}$ radical to norbornene (eq 91).



Perfluoroalkylaryliodonium trifluoromethane sulfonate and perfluoroalkyl phenyliodonium sulfate

react with the $^{-}CMe_2NO_2$ ion (room temperature, DMSO) to give the substitution products in 50 and 30% yields, respectively.[407]

The reaction of R_fI by electrochemical induction in the presence of mediators with several nitrogen nucleophiles is known (Table 27). For instance, imidazole anion and derivatives **110** afford the substitution products **111** and **112** in an overall yield of 50% (eq 92).[193b,194]



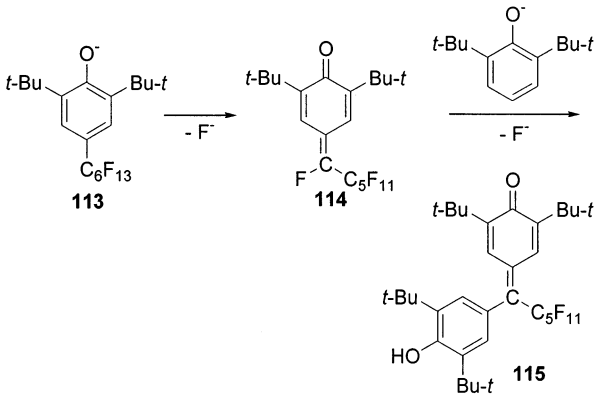
110 **111** **112**

When C_2 has a substituent, only one substitution product is obtained (Table 27).[193] Indirect electrochemical reduction of R_fI in the presence of purine and pyrimidine ions affords the C-perfluoroalkylated nitrogen bases (Table 27). Low yields (25−35%) of monosubstitution products were obtained by reaction of cytosine and uracil anions with 1,4-diiodoperfluorobutane.[194]

The electrochemically induced reaction of R_fI with phenol and derivatives gave the perfluoroalkylation (ortho and para), although in low yields, that increases to ∼30% in the presence of oxygen.[408]

On the other hand, the indirect electrochemical reduction of *n*-C_4F_9I in the presence of barbituric acid leads to a dimeric product, in which two fluorines have been lost.[194b] The same reaction was observed between *n*-$C_6F_{13}I$ and 2,6-di-*tert*-butylphenoxide anion with the formation of **115** (57%). The substitution product is deprotonated to give **113**, which is not stable and loses an F^- ion to give **114**. Then it is attacked by the starting phenoxide, yielding **115** with the loss of a second F^- ion (Scheme 39).[193b]

Scheme 39



Even though C-alkylation takes place in these reactions, O-alkylation has been reported in the reactions of phenolic compounds with 2-(bromodifluorophenylmethyl)benzoxazole (see section VII.D.2).

The reaction of R_fI with chiral imide enolate ions induced by Et_3B and oxygen gives the substitution products with diastereomeric excess (Table 28).[212]

2. Reactions with Sulfur Nucleophiles

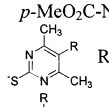
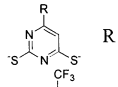
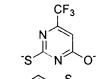
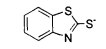
R_fI has been found to alkylate thiols in reactions carried out under irradiation (Table 29).[409,410] In this system the PhS^- ion and its derivatives containing both electron-donating groups and EWG are readily converted into $ArSR_f$ in good yields. The effect of temperature, light, and solvents has been studied for

Table 28. Reaction of R_fI with Chiral Imide Enolate Ions[a,212]

R_fI	R^1	R^2	Product (%)	de
n-$C_6F_{13}I$	*i*-Pr	Me	79	71 (S)
C_2F_5I			74	74 (S)
$(CF_3)_2CF(CF_2)_2I$			75	79 (S)
n-$C_6F_{13}I$	Bn		81	83 (S)
	i-Pr	Bn	70	81 (S)
		n-Bu	73	83 (S)
		t-Bu	57	93[b]
		Ph	63	57[b]
		OBn	59	55[b]

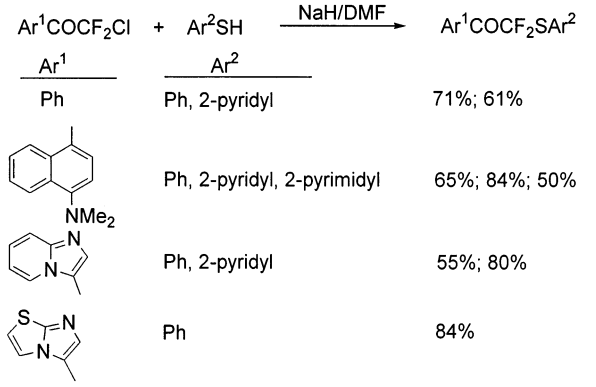
[a] In THF induced by Et_3B. [b] Not indicated.

Table 29. Photoinduced Reactions of R_fI with Thiolate Ions

R_fI	RS^-	Solvent	RSR_f (%)	Ref.
CF_3I	$^-O_2C\text{-}CH_2S^-$	NH_3	83	409
n-C_3F_7I		MeCN	51	410
CF_3I	PhS^-	NH_3	76	409
C_2F_5I		DMF	84	411
n-, *i*-C_3F_7I			83, 76	410, 413
n-$C_6F_{13}I$	$PhSN(Bu)_4$	C_6H_6/H_2O	76	413
n-$C_8F_{17}I$	PhS^-	DMF	92	413
CF_3I	*p*-$RC_6H_4S^-$ R = H, Cl, Me, OMe	Ether/NaOH/ H_2O	52-61	412
n-C_3F_7I	*p*-$RC_6H_4S^-$ R = H, Cl, Me, CO_2Me		71-85	412
i-C_3F_7I	*p*-$ClC_6H_4S^-$		60	412
n-C_6F_{13}			71	412
CF_3I	*o*-$NH_2C_6H_4S^-$	DMF	66	410
n-C_3F_7I		DMF, MeCN	66, 84	410
	p-$MeOC_6H_4S^-$	MeCN	88	410
	p-$RC_6H_4S^-$ R = OH, Cl, CO_2H, CO_2Me	DMF	39-72	410, 409
CF_3I	*o*-$F_2HC\text{-}O_2SC_6H_4S^-$	NH_3	69	409
CF_3I	*p*-$F_3C\text{-}O_2SC_6H_4S^-$		78	409
n-C_3F_7I	*p*-$MeO_2C\text{-}NHC_6H_4S^-$	MeCN, DMF	98, 70	410
CF_3I	 R = H, OH	NH_3	82, 89	*a*
	 R = H, Me		(61, 58)[b]	*a*
			59	*a*
			87	409
n-C_3F_7I		DMF	59	410
$ClCF_2(CF_2)_3I$			57	*c*
$ClCF_2(CF_2)_5I$			78	*c*
$CF_3(CF_2)_5I$			98	*c*
$CF_3(CF_2)_7I$			85	*c*
$ICF_2(CF_2)_5I$			78	*c*
$ClCF_2(CF_2)_3I$			61	*c*
$ClCF_2(CF_2)_5I$			50	*c*
$CF_3(CF_2)_5I$			87	*c*
$CF_3(CF_2)_7I$			85	*c*
$ClCF_2(CF_2)_5I$			43	*c*

[a] Boiko, V. N.; Dashevskaya, T. A.; Shchupak, G. M.; Yagupolskii, L. M. *J. Org. Chem. USSR (Engl. Transl.)* **1979**, *15*, 347−350. [b] Disubstitution products. [c] Chen, Q. Y.; Chen, M. J. *J. Fluor. Chem.* **1991**, *51*, 21−32.

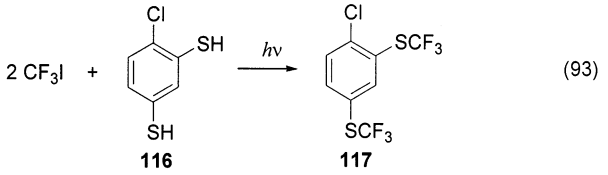
Scheme 40



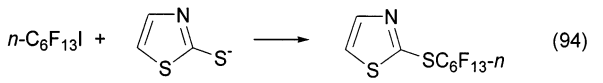
the reactions in the presence of Et_3N.[410] With a primary or secondary R_fI the substitution affords 60−85% of product, but with a tertiary $R_f^•$ no reaction occurred.[411] The reaction can be also performed in PTC (Table 29).[412,413]

Besides substitution, PhSPh and the unsaturated sulfide $CF_3CF{=}CFSPh$ are formed in the reaction with *i*-C_3F_7I under PTC in DMF.[413] An ionic intermediate, namely, the *i*-$C_3F_7^-$ anion, could be involved in the formation of the vinyl sulfide. However, an ET mechanism to give the anionic intermediate cannot be excluded.[413]

The disulfide product **117** (58%) was observed in the reaction of **116** with CF_3I (eq 93).[409] Other examples are collected in Table 29.



Low yields of substitution are obtained by electrochemical initiation in the reaction of *n*-C_3F_7I with *n*-$C_8H_{17}S^-$ (14−16%) and *p*-$MeC_6H_4S^-$ ions (63−68%). Similar results were obtained with *n*-$C_6F_{13}Br$.[414] The anion of 2-mercaptothiazoline is perfluoroalkylated with *n*-$C_6F_{13}I$ (48%) under indirect electrochemical induction (eq 94).[193b]



A series of chlorodifluoromethylated ketones react with ArSH to afford new α-(heteroarylthio)-α,α-difluoroacetophenone derivatives in moderate to good yields (Scheme 40). These compounds may find some biological applications.[415a]

The thermal reactions of 2-(bromodifluoromethyl)-benzoxazole with the anions of heterocyclic thiols and phenolic compounds afford substitution in variable yields (eq 95) (Table 30).[415b]

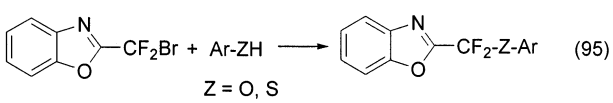
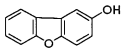
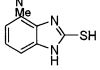


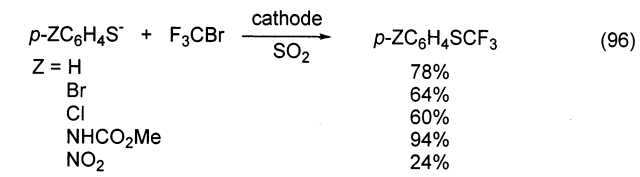
Table 30. Reactions of 2-(Bromodifluoromethyl)-benzoxazole with ArSH and ArOH Nucleophiles[a,415b]

Nucleophile	Product (%)	Nucleophile	Product (%)
	86		70
	82		32
 R = H; Me	51; 76		47
 $R^1 = R^2 = H$; $R^1 = Me$, $R^2 = H$; $R^1 = R^2 = Me$	65; 62 74		44
	72		42
	59		28[b]
	84		

[a] Thermally induced $S_{RN}1$ reactions carried out in DMF with NaH. [b] Monosubstitution product.

R_fBr and R_fCl present different reactivities with Nu^-, but some of them seem to follow an $S_{RN}1$ process. It has been proposed that R_fBr reacts with the RS^- ion by this mechanism.[416] CF_3Br,[417a] CF_2BrCl,[417b] and CF_2Cl_2[417b,418] react with the ArS^- ion in DMF to give substituted or disubstituted product by a radical mechanism. However, it has been suggested that CF_2Br_2 and CF_2BrCl react with PhS^- ions by an ionic pathway.[419] Gaseous CF_3Br does not react if it is simply bubbled through a solution of RS^- ions. However, it reacts under pressure (2 atm) to give 62−83% yield of substitution.[418]

Sulfides have been synthesized electrochemically by the reaction of CF_3Br and ArS^- ions with SO_2 as redox mediator. Except for the *p*-$O_2NC_6H_4S^-$ ions, all of the other ArS^- ions showed a Faraday yield of sulfides of 240−376%, indicating a chain process (eq 96).[420]



A related system, CF_3CH_2X reacts with RS^- ions to give good yields of substitution.[421] These reactions occur in the dark, but they are accelerated by light and inhibited by *p*-DNB and hydroquinone. Thus, CF_3CH_2Cl reacts with PhS^-, *p*-$ClC_6H_4S^-$, *p*-$ClC_6H_4CH_2S^-$, Me_3CS^-, and $CH_2{=}CH_2CH_2S^-$ ions to give the substitution products in 71, 79, 87, 71, and 67% yields, respectively. The leaving ability of halide ions found (I > Br > Cl ≫ F) is in agreement with an ET mechanism.[421]

A series of substrates of the structure $HCF_2(CF_2)_n-CH_2I$ (n = 1, 3, or 5) react (by electrochemical induction) with *p*-$ClC_6H_4S^-$ ions to give substitution in 27, 72, and 66% yields, respectively.[422]

$ArSO_2R_f$ can be obtained (30−35% yield) in one stage by the reaction of R_fI on $ArSO_2H$ acids in liquid ammonia under irradiation.[423] NaO_2SAr and NH_4O_2SAr were also subjected to perfluoroalkylation, but the yield of product decreased to 15 and 25%, respectively. However, when NaO_2SAr was mixed with n-$C_8F_{17}I$ and norbornene in DMF, 100% of 2-perfluorooctyl-3-iodonorbornane was formed, but no substitution was found.[405]

The electrochemical reduction of phenylperfluoroalkyliodonium salts in the presence of *p*-chlorophenylsulfinate ions yields the corresponding sulfone and perfluoropropionic acid (ca. 1:1 ratio) by the $S_{RN}1$ mechanism.[424]

3. Reaction with Other Nucleophiles

The PhSeH has been found to react with CF_3I by irradiation in liquid ammonia, forming the corresponding $PhSeCF_3$ in ~75% yield.[425a] $ArTeC_3F_7$-*n* can be synthesized by irradiation of a mixture of n-C_3F_7I with LiTeAr in ether at 25 °C (41−59%).[425b] No mechanistic consideration was presented.

Polyfluorophenyl pentafluorobenzenesulfonate reacts with NaI to give *p*-$IC_6F_4OC_6F_5$ and *p*-$HC_6F_4OC_6F_5$, a reaction proposed to occur by $S_{RN}1$ and polar pathways.[426]

E. Alkylmercury Halides

RHgX are reagents that have moderate reactivity in electrophilic substitution and low reactivity in S_N2 substitution at carbon because of the unfavorable polarity of the C−Hg bond ($^{-\delta}R-Hg^{\delta+}X$).[427] On the other hand, the RHgX are mild oxidizing agents, which are reduced to R•, Hg^0, and X^- with a reduction potential of ≈−0.6 V versus SCE,[428a,b] making it possible to initiate a chain reaction by addition to an appropriate Nu^-.[428] Thus, RHgX have been proposed to react with $^-CR_2NO_2$ ions by the $S_{RN}1$ mechanism (Scheme 41)[429] (Table 31).

Scheme 41

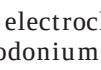
$$R^\bullet + {}^-CR^1R^2NO_2 \rightarrow RR^1R^2CNO_2^{\bullet-}$$

$$RR^1R^2CNO_2^{\bullet-} + RHgX \rightarrow RR^1R^2CNO_2 + R^\bullet + Hg^\circ + X^-$$

This reaction is initiated by light and inhibited by radical scavengers and oxygen. Further mechanistic evidence is the observation of products from the cyclization of the 5-hexenyl radical in the reaction of 5-hexenylmercury chloride with the $^-CMe_2NO_2$ ion.[152] The nature of photoinitiation appears not to involve homolysis, because simple RHgX do not absorb light above 310 nm. Russell et al. proposed an ET to the RHgX from a photoexcited $^-CR_2NO_2$ ion for the initiation path due to the fact that no CTC was detected.[430]

It was suggested that the ET to RHgX is dissociative, on the basis that the reactivity of RHgX in competitive reactions with the $^-CMe_2NO_2$ ion is determined by the stability of the R• radical.[171a] Thus, the reactivity series for RHgX is R = $PhCH_2$ (4.7) > Me_3C (1.0) > Me_2CH (0.07) > n-C_6H_{13} (0.005). Similar results were found using the $^-CH_2COPh$ ion.[431] Vinyl and aryl mercurials do not participate in the reactions, although 1-alkenylmercurials undergo nucleophilic substitution by an addition−elimination mechanism.[432]

Table 31. Photoinduced Reactions of RHgX with Nitronate Anions in DMSO

RHgX	$^-C\,R^1R^2NO_2$	Product (%)	Ref.
R = n-C_6H_{13}, X = Cl, Br, I	$R^1 = R^2$ = Me	90, 50, 80	430
R = $(CH_3)_2CH$, X = Cl		63	430
R = c-$C_5H_9CH_2$, X = Cl		47	430
R = CH_2=$CHCH_2$, X = Cl		50	430
R = $PhCH_2$		100	430
	R^1-R^2 = -$(CH_2)_5$-	87	430
R = c-C_6H_{11}, X = Cl	$R^1 = R^2$ = Me	76	430
	R^1-R^2 = -$(CH_2)_5$-	84	430
R =  , X = Cl	$R^1 = R^2$ = Me	14.5[a]	430
R =  , X = Cl, Br		56, 68	430
X = Cl	R^1-R^2 = -$(CH_2)_5$-	60	430
R = *t*-Bu, X = Cl	$R^1 = R^2$ = H	68	171
	R^1 = H, R^2 = Me	74	171
	R^1 = H, R^2 = Ph	71	171
	$R^1 = R^2$ = Me	69	171
	R^1 = Me, R^2 = Ph	67	171

[a] Cis:trans = 1:8.

Table 32. Photoinduced Reactions of *t*-BuHgCl with Nucleophiles[a]

Nucleophile	Product (%)
NO_2^-	Me_3CNO_2 (71)
Phthalimide ion	4-*tert*-Butylphthalimide (20)[b]
N_3^-	Me_3CN_3 (34)
^-CHPhCN	$Me_3CHPhCN$ (4), $PhCH_2CMe_3$ (11)
$^-CPh_2CN$	Me_3CCPh_2CN (48), Ph_2C=C=$NCMe_3$ (26)
$^-CHPh_2$	Ph_2CHCMe_3 (36)
$^-CPh_3$	Ph_3CCMe_3 (39), 6-*t*-Butyl-3-benzhydrylidene-1,4-cyclohexadiene (21), *p*-$Me_3CC_6H_4CPh_2$ (5)
Fluorenyl ion	9-*t*-Butylfluorene (44)
$^-CPh(CO_2Et)_2$	$PhC(CO_2Et)_2CMe_3$ (43)
$^-CH_2COCMe_3$	$Me_3CCOCH_2CMe_3$ (7)
$^-CPh_2COCMe_3$	$Me_3CCOCPh_2CMe_3$ (6)
$^-CH_2COPh$	$PhCOCH_2CMe_3$ (54)
$^-CHMeCOPh$	$PhCOCH(Me)CMe_3$ (34)
$^-CMe_2COPh$	$PhCOCMe_2CMe_3$ (21)
$^-CHPhCOPh$	$PhCOCHPhCMe_3$ (63)
$^-CPh_2COPh$	$PhCOCPh_2CMe_3$ (57)

[a] In DMSO under nitrogen atmosphere, with equimolar amounts of 18-crown-6 ether.[171] [b] Reference 387.

In addition to nitronates, nucleophiles derived from phenones, stabilized carbanions, and nitrogen nucleophiles such as N_3^-, NO_2^-, and phthalimide ions were found to be reactive toward *t*-Bu• radicals (Table 32). Even though N-alkylation has been reported with the latter anion,[171] only alkylation at C_4 has been recently found.[387] The later regiochemistry of this coupling reaction is similar to that shown by phthalimide anion with the 1-Ad• radical.[387]

Among the anions that failed to give substitution are di- and trinitromethanes, β-dicarbonyl, and β-cyanoketones. The lack of reactivity of these anions can be rationalized in terms of loss of π energy from the stabilized anion to the radical anion of the substitution product.

VIII. Aromatic Substrates

A. Reaction with Carbanions

1. Carbanions Derived from Hydrocarbons

A relatively limited set of carbanions derived from hydrocarbons has been used as Nu^- in $S_{RN}1$ reactions. Among them are the anion of 1,3-pentadiene, 1-(*p*-anisyl)propene, fluorene, and indene.[196] The phenylation of these anions usually affords a mixture of mono- and diphenylated compounds. The regiochemistry of the coupling favors the formation of the most stable radical anion intermediate. For example, in the reaction with the anion of 1,3-pentadiene, 1-phenylpentane (from 57 to 74%) is obtained after hydrogenation.[196] The carbanion from 1-(*p*-anisyl)-propene gives ~3 times as much 3-phenyl- (36%) as 1-phenyl-1-(*p*-anisyl)propane (13%) after hydrogenation. 9-Phenylfluorene (44%) and 9,9-diphenylfluorene (5%) are formed in the reaction of PhBr with the anion from fluorene.[196]

In the photoinitiated reactions of indenyl, 1- and 2-phenyl-, and 2,3- and 1,3-diphenylindenyl anions, mono-, di-, and triphenylation products are formed. The higher yield of substitution is obtained with the 1,3-diphenylindenyl anion, which gives 1,1,3-triphenylindene in 50% yield as well as 1,2,3-triphenylindene (9%) in DMSO.[88a,433]

The products of the reaction of the Ph_3C^- ion[200a] with PhBr, PhI, or Ph_2SO and of cyclooctadienyl anion[434] with PhCl, PhBr, 9-bromoanthracene, and 1-bromonaphthalene are explained on the basis of an $S_{RN}1$ type mechanism.

This mechanism has also been proposed to be responsible for the polymerization of polybromostyryl carbanions[435a] and as a possible mechanism in the formation of polyphenylenes by polymerization of 1-bromo-4-lithiobenzene.[435b,c]

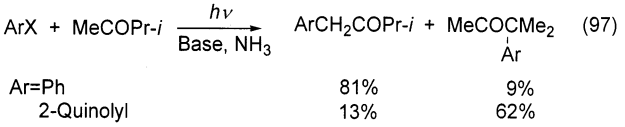
The ions $HC{\equiv}C^-$, $n\text{-}C_3F_7C{\equiv}C^-$, and $PhC{\equiv}C^-$ fail to give substitution under photostimulation with ArX.[80,436]

2. Enolate Ions from Ketones

Substrates with One Leaving Group. The enolate ions of acyclic and cyclic aliphatic ketones react through the $S_{RN}1$ mechanism with ArX, ArSAr′, and $ArN_2SBu\text{-}t$ (Tables 33−38). The solvents and conditions of choice are usually liquid ammonia or DMSO and irradiation. Spontaneous initiation is possible for some systems either in DMSO or in liquid ammonia. For example, PhI reacts with $^-CH_2COR$ ions in DMSO in the dark.[70a] 2-Chloropyrazine and other haloheteroaromatic compounds are examples of substrates able to react in liquid ammonia in the dark. In some cases, products ascribed to a competing ionic process are also formed[72,73] (Tables 33 and 34). The solvent effect was studied in the reaction of the $^-CH_2COCH_3$ ion with 2-chloroquinoline in which the yield of substitution is variable, that is, 90% (liquid ammonia),[437] 82% (THF), 74% (DMF), 37% (DMSO), 28% (DME), 9% (diethyl ether), and 4% (benzene).[438]

When the reactions are performed under Na or K metal stimulation, reduction of the substitution product at the carbonyl group or at the aromatic ring can occur. For example, in the reaction of PhX,[97] $PhNMe_3{}^+I^-$,[97] their derivatives,[27b,97] and $PhOPO(OEt)_2$,[97] with the $^-CH_2COCH_3$ ion, besides phenylacetone (3−71%), 1-phenyl-2-propanol is formed (8−56%). When the anion reacts with 1-iodo- or 1-chloronaphthalene, a mixture of 1-naphthylacetone (6 and 23%) and dihydro- and tetrahydro-1-naphthylacetone (84 and 69%) is obtained, respectively.[98]

With unsymmetric dialkyl ketone, isomeric enolate ions can be formed. The distribution of the two possible arylated products is mainly determined by the equilibrium concentration of the two possible enolates and the selectivity of the attacking radical. For example, phenylation occurred preferentially at the more substituted α-carbon with the anion of 2-butanone (41−61%),[70a,196] whereas with the anion from *i*-propylmethyl ketone the 1-phenyl derivative predominates.[80,196] However, the ratio of tertiary to primary substitution obtained in the reaction of the same anion with 2-chloroquinoline is ≈4.8 (eq 97).[437]



Substituents ortho to the leaving group of the substrate usually favor attack at the primary α-carbon of the anion.[439,440]

The anions of the cyclic ketones can be α-arylated (Table 36).[78,441,442] No substitution product is formed with the enolate ion of cyclohex-2-en-1-one.[78]

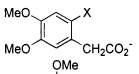
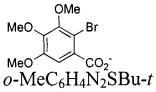
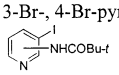
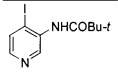
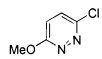
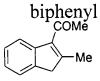
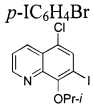
The $^-CH_2COPh$ ion can be arylated and heteroarylated in liquid ammonia by initiation with K metal[72,98] or Na(Hg).[99] Heteroarylation is possible in this solvent under irradiation[72,441] and even in the dark.[73] Low yields are obtained in the reaction of substituted ArI with the anion of 2′,4′-dimethyl-6′-methoxyacetophenone either in DMSO or in liquid ammonia.[443] However, besides heteroarylation, phenylation by PhX succeeded under photostimulation in DMSO[79] (Table 37).

The anions of other aromatic ketones such as methyl 2-naphthyl ketone,[444] 2-acetylfuran,[104,441,445,446] 2-[68b,104] and 3-acetylthiophene,[68b] 2- and 3-acetyl-*N*-methylpyrrole,[105] anthrone,[79] and tetralone[441,446,447] can also be arylated (Table 38).

The arylation and heteroarylation of the anions from several ketones can be achieved in the presence of $FeCl_2$ or $FeBr_2$ in DMSO (Tables 34−38). The reaction of the $^-CH_2COPh$ ion can be carried out in DMSO under SmI_2 catalysis with different ArX[108] (Table 37).

Even though 6-iodo-9-ethylpurines react with the anions of several ketones,[441,445] 2-iodopurine reacts through an ionic process.[448a] 3-Halo (X = Cl, Br, or I) 2-aminobenzo[*b*]thiophene,[448b] 3-iodobenzo[*b*]thiophene,[448c] and 2-chloro- or 2-bromothiophene are poorly reactive[449] (Tables 33, 36, and 38). A slightly higher reactivity is observed with 3-bromothiophene.[449] Hydride elimination is the main reaction of 4-chloro- and 3-bromoquinoline-1-oxide with several ketone enolate ions.[450]

Table 33. Reaction with Acetone Enolate Ions[a]

ArX	Product (%)	Ref
PhX, X = F, Cl, Br, I, SPh, SPh_2^+, SePh, NMe_3^+, N_2SBu-*t*	57-95	*b*
PhI	(88, 60[c])[d]	*e*, *f*, 79, 101
PhBr	61[d]	11c
o-RC_6H_4I, R = CH_2NHCO_2Et,$CH_2NHCOMe$	58, 30	*g*
o-$MeOC_6H_4I$	67	*g*
3,5-$R_2C_6H_3I$, 2,4-$(R)_2C_6H_3Br$ R = OMe	68, 76	11c
2,4,6-$(MeO)_3C_6H_2I$	92	11c
o-, *m*-, *p*- $BrC_6H_4CO_2^-$	85, 80, 70	11c
m-$CF_3C_6H_4I$	35	11c
p -Me_2N, *p*-, *m*-$H_2NC_6H_4I$	90, 33, 66	453, 179
m-Me_2N, *p*-$Et_2NC_6H_4Br$	82, 0	453, 11c
p-PhC_6H_4Br	69	11c
2,4,6-$Me_3C_6H_2I$	82	11c
2,4,6-$Et_3C_6H_2Br$	70	11c
2,5-$R_2C_6H_3I$, R = *i*-Pr, *t*-Bu	78, 26	11c
2,4,6-*i*-$Pr_3C_6H_2$; X = I, Br	16, 2	11c
 X = Br, I	60, 75-80	440
	78	455
o-$MeC_6H_4N_2SBu$-*t*	10[d,h]	68a
m-$RC_6H_4N_2SBu$-*t* R = Me, OMe, COPh	(81, 79, 44)[d]	68a
p-$RC_6H_4N_2SBu$-*t* R = *i*-Bu, *t*-Bu, OMe, COPh	(42,[i] 86, 69, 78)[d]	68a
2,4,6-$Me_3C_6H_2N_2SBu$-*t*	30[d,j]	68a
m-MeC_6H_4SPh	*m*-$MeC_6H_4CH_2COCH_3$ (48) $PhCH_2COCH_3$ (39)	147
p-MeC_6H_4SPh	*p*-$MeC_6H_4CH_2COCH_3$ (38) $PhCH_2COCH_3$ (28)	147
m-$MeOC_6H_4SPh$	*m*-$MeOC_6H_4CH_2COCH_3$ (49) $PhCH_2COCH_3$ (28)	147
p-$MeOC_6H_4SPh$	*p*-$MeOC_6H_4CH_2COCH_3$ (50) $PhCH_2COCH_3$ (18)	147
1-X-naphthalene, X = Cl, I, N_2SBu-*t*	88, 76, 75[d]	98, 11c, 68a
2-X-naphthalene, X = I, N_2SBu-*t*	75, 76[d]	11c, 68a
9-Br-anthracene	98	11c
9-Br-phenanthrene	62	11c
2-X-thiophene, X = Cl, Br	17, 31	449
3-Br-thiophene	51	449
2-X-pyridine, X = F, Cl, Br	40, 85, 100[k]	442
3-Br-, 4-Br-pyridine	65, 28	442
 2-, 4-	90, 90	454
	95	454
2-Cl-quinoline	90	437, *l*
	15, 61[m]	73
 X = Cl, Br R = *t*-Bu	60-65, 75-75 (42, 30)[n]	72
 X = Cl, Br R = Ph	20-25, 25-30 (47, 42)[n]	72
	98[o]	73
	60[o]	73
	70	441, 445
Substrates with two leaving groups (XArY)		
m-FC_6H_4I	56[p]	11c
2-F-4-Br-biphenyl	2-F-4-(3-butyl-2-ona)-biphenyl 62[q]	456
o-$C_6H_4Br_2$ 	64[r]	457
p-$C_6H_4Cl_2$	48[p,s]	93
p-$C_6H_4Cl_2$	42[t]	458
p-IC_6H_4Br	32[t]	458
	73[u]	446

[a] Photoinitiated reaction in liquid ammonia, unless otherwise indicated. The reactions with N_2S−Bu-*t* as leaving group are performed under laboratory light. [b] Rossi, R. A.; Bunnett, J. F. *J. Org. Chem.* **1973**, *38*, 1407−1410. [c] Induced by Fe^{2+} salts. [d] In DMSO. [e] Scamehorn, R. G.; Bunnett, J. F. *J. Org. Chem.* **1977**, *42*, 1457−1458. [f] Bunnett, J. F.; Scamehorn, R. G.; Traber, R. P. *J. Org. Chem.* **1976**, *41*, 3677−3682. [g] Beugelmans, R.; Chastanet, J.; Roussi, G. *Tetrahedron Lett.* **1982**, *23*, 2313−2314. Beugelmans, R.; Chastanet, J.; Roussi, G. *Tetrahedron* **1984**, *40*, 311−314. [h] Together with 70% of indazole. [i] Together with the 2-oxopropanal arylhydrazone derivative (44%). [j] Together with 50% of the substituted indazole and 15% of the 2-oxopropanal arylhydrazone derivative. [k] 64% of substitution under photostimulation in THF. [l] Hay, J. V.; Hudlicky, T.; Wolfe, J. F. *J. Am. Chem. Soc.* **1975**, *97*, 374−377. [m] In THF. [n] Under K stimulation. [o] Dark reaction. [p] Monosubstitution product. [q] After quenching with MeI. [r] Together with other isomers. [s] Induced electrochemically in the presence of mediator. [t] Disubstitution product. [u] Monosubstitution at C_7.

(*Z*)-ArN_2SBu-*t* reacts with aliphatic and aromatic ketone enolate ions under laboratory light in DMSO.[68] Branching at the α-carbon of the enolate decreases the yield of substitution.[68b] In the reactions of substrates bearing benzylic hydrogens in ortho or para position with respect to the azothio group, either indazoles or 2-oxopropanal arylhydrazones are formed (Table 33) (Scheme 42).[68a,451,452]

In this system an acid−base reaction with the enolate ion induces a *t*-BuSH elimination leading to an alkylidene diazocyclohexadiene intermediate. This intermediate cylizes to give indazoles for Ar = *o*-MeC_6H_4, while for Ar = *p*-MeC_6H_4 and *p*-(*i*-Bu)C_6H_4 coupling with the enolate gives 2-oxopropanal arylhydrazones.[68a,452] For this reason the percentage of α-arylation obtained for Ar = *o*-MeC_6H_4, *p*-MeC_6H_4, *p*-(*i*-Bu)C_6H_4, and 2,4,6-$Me_3C_6H_2$ ranges from trace amounts to 42% (Tables 33, 34, and 37).[68]

Scheme 42

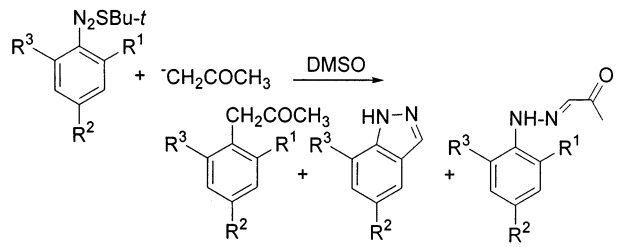
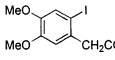
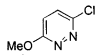
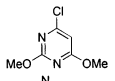
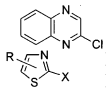
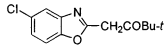
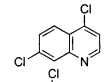
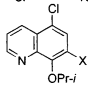
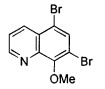


Table 34. Reaction with Pinacolone Enolate Ions[a]

ArX	Product (%)	Ref
PhX, X = Br, SPh	90, 98	78, 84
PhX, X =Br, I, SPh, N_2SBu-*t*, SO_2Ph	(87, 99, 67, 80)[b], 70[c]	*d*, 84, 68a
PhX, X = Br, I	(58, 87)[e]	101
PhX, X = Br, I, PhIBr	(99, 74, 97)[b,e]	102
o-NCC_6H_4Br	46[b,e]	102
o-, *m*-, *p*-$MeOC_6H_4I$,	100, 58,[b,f,g] 81,[b,f]	439, 70b,
p-$MeOC_6H_4Br$	13 [b,e]	*h*, 102
o-RC_6H_4I, R = Ph, NO_2	83, 66	11b, 142
	85-90	440
1-X-naphthalene, X = Br, I	(41, 60)[b,e]	102
1-naphthyl-SPh	1-naphthyl-CH_2COBu-*t* (18)[b] $PhCH_2COBu$-*t* (64)[b]	84
$(1\text{-naphthyl})_2S$	28[c]	84
9-Br-anthracene	46[b,e]	102
2-Br-pyridine	94, 80[b,e]	442, 102
2-Br-3-(*i*-PrO)-pyridine	70	446
 R= OMe, NHMe, NH_2, NHCOBu-*t*	8, 50, 87, 99	454
3-I-4-(*t*-BuCONH)-pyridine	99	454
4-I-3-(*t*-BuCONH)-pyridine	98	454
	72, 38[f]	73
	32	73
 X = Cl, Br, R = *t*-Bu X = Cl, Br, R = Ph	(90, 95); (65, 65)[i] (45, 65); (50, 50)[i]	72
	98	73
	95[f]	73
	70[f,j]	74
R = H, X = Cl, Br	53, 44	
R = 4-, 5-Me, X = Cl	64, 67	460
 *k*	77	460
Substrates with two leaving groups (ArXY)		
p-FC_6H_4I	71[b,f,l]	*h*
o-$C_6H_4Br_2$	62[m]	457
p-$C_6H_4X_2$, X = Cl, Br	(64, 38)[m]	458
p-$BrC_6H_4N_2SBu$-*t*	49[b,m]	68a
2-F-3-I-pyridine	92[l]	454
2,3-; 3,5-; 2,6 -Cl_2-pyridine	(63, 43, 86)[m]	459, 442
2,5-; 2,6 -Br_2-pyridine	(85, 89)[m]	459, 442
	70[n]	459
 X = Cl, I	(70, 70)[o]	446
	60[m]	446

[a] Photostimulated reactions in liquid ammonia unless otherwise indicated. The reactions with N_2S-Bu-*t* as leaving group are performed under laboratory light. [b] Solvent DMSO. [c] Solvent DMF. [d] Scamehorn, R. G.; Bunnett, J. F. *J. Org. Chem.* **1977**, *42*, 1457−1458. [e] Induced by Fe^{2+} salts. [f] Dark reaction. [g] Together with 2-(PhS)-3-(OMe)-C_6H_3I (11%). [h] Scamehorn, R. G.; Bunnett, J. F. *J. Org. Chem.* **1979**, *44*, 2604−2608. [i] Under K stimulation. [j] Together with 2-*tert*-butylfuro[2,3-*b*]quinoxaline (15%) from an ionic mechanism. [k] Obtained by S_NAr substitution of 2,5-dichlorobenzoxazole with the $^-CH_2COBu$-*t* ion. [l] Monosubstitution product. [m] Disubstitution product. [n] Monosubstitution product at C_4. [o] Monosubstitution product at C_7.

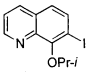
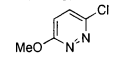
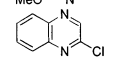
Cyclization of the Substitution Product from Ortho-Functionalized Substrates. The $S_{RN}1$ reaction of ortho-substituted aromatic substrates can be an excellent route to cyclization. For example, the compounds formed in the $S_{RN}1$ reaction of the enolate of a ketone or aldehyde (MeCOR, R = H, Me, *i*-Pr, or *t*-Bu) with *o*-ROC_6H_4X undergo spontaneous cyclodehydration after deblocking of the alkoxy function to afford benzo[*b*]furan **118** derivatives quantitatively, as in the reaction with *o*-$MeOC_6H_4I$ (Scheme 43).[439]

This approach is also useful in the synthesis of furo[3,2-*h*]quinolines (see Substrates with Two Leaving Groups). Furo[3,2-*b*]pyridines are quantitatively formed by acidic treatment of the products obtained in the reaction of 2-bromo-3-*i*-propoxypyridine with the following enolate ions ($^-CH_2COR$, R = Et or *t*-Bu) in liquid ammonia and with the anions ($^-CH_2COAr$, Ar = Ph or *p*-anisyl) in DMSO. Cyclization at the product is also possible by reaction of 2-methoxide-3-iodopyridine with the $^-CH_2COBu$-*t* ion.[446]

Good yield of substitution is obtained in the reaction of the $^-CH_2COMe$ ion with *p*-$Me_2NC_6H_4I$,[453] which decreases with the *m*- and *p*-amino derivatives[179] (Table 33). Even though *m*-$Me_2NC_6H_4Br$ affords substitution in good yields,[453] *p*-$Me_2NC_6H_4$-Br is unreactive[11c] (Table 33). However, indoles can be synthesized through the reaction of *o*-aminohaloarenes with enolate ions (see section VIII.F.1).

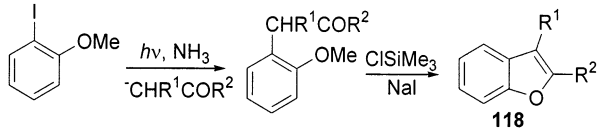
When the amino group is protected as a pivaloylamino derivative, the substitution compounds ob-

Table 35. Reaction with Other Acyclic Ketone Enolate Ions[a]

Substrate	Carbanion from	Product (%)	Ref.
PhBr	EtCOEt	80	78
PhI		70,[b,c] (55)[d]	70a,102
2,4,6-$Me_3C_6H_2X$			78
X = Br, I		14, 24	
		86	446
2-Cl-quinoline		68	437
		70	446
PhBr	*n*-Pr-COPr-*n*	80	78
PhBr	$MeOCH_2COMe$	$PhCH_2COMe$ (17)	78
2-Cl-quinoline	$CH_3COCH(OMe)_2$	88	179
PhX, X = Br, I	*i*-Pr-COPr-*i*	15, 32	80, 78
2-Br-pyridine		97	442
2-Cl-quinoline		98, (65)[e]	437, 438
		88	73
		85[c]	73
		20	73
		43[c,f]	74

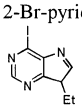
[a] Photostimulated reactions in liquid ammonia unless otherwise indicated. [b] In DMSO. [c] Dark reaction. [d] $FeCl_2$ in DMSO. [e] In THF. [f] Together with quinoxalino[*b*]cyclopentanone and 2-isopropylquinoxaline from an ionic process.

Scheme 43



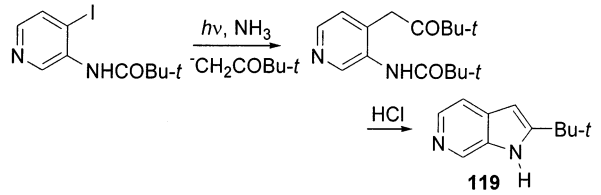
118

Table 36. Photoinduced Reaction of Cyclic Ketones Enolate Ions in Liquid Ammonia

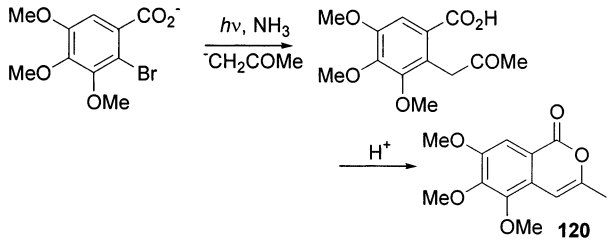
Substrate	Carbanion from	Product (%)	Ref.
PhBr	c-$(CH_2)_3CO$	90	78
	c-$(CH_2)_4CO$	64	78
2-Cl-quinoline		63	437
		65	441, 445
PhBr		90	78
	c-$(CH_2)_5CO$	75[a]	70a
PhI		72, 39[b]	78, 102
2-Br-pyridine		47	442
		50	441, 445
		6[a]	448c
		30[c]	441
PhX, X = Cl, Br		(92, 95)[d]	209
p-$MeOC_6H_4Cl$		71[d]	209
p-PhC_6H_4Br		76[d]	209
1-Cl-naphthalene		100[d]	209
PhBr	c-$(CH_2)_6CO$	58	78
	c-$(CH_2)_7CO$	95	78

[a] DMSO in the absence of photostimulation. [b] $FeCl_2$ in DMSO. [c] Arylation at the most substituted carbon of the enolate ion, together with 7% yield at the less substituted one. [d] Percentage of endo isomer; endo/exo ratio 99:1.

Scheme 44



Scheme 45

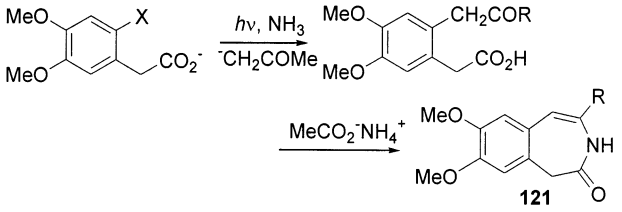


tained by reaction of aminoiodopyridines with $^-CH_2COMe$ or $^-CH_2COBu$-t afford azaindoles in almost quantitative yields after hydrolysis of the pivaloylamino moiety, cyclization, and dehydration under acidic conditions. One example is shown in Scheme 44 of the synthesis of **119**.[454]

The $S_{RN}1$ reaction of o-$HO_2CC_6H_4Br$ and derivatives with the $^-CH_2COMe$ ion affords 78% of substitution product, which by treatment with acid gives the corresponding isocoumarin **120** (90%) (Scheme 45).[455]

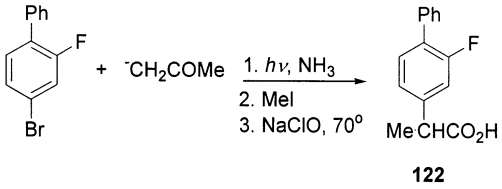
Treatment of the substitution compound obtained in the reaction of (*o*-iodophenyl)acetic acid derivatives

Scheme 46



with enolate ions from ketones ($^-CH_2COR$, R = Me, *i*-Pr, or *t*-Bu) upon ammonium acetate leads to the respective benzazepines **121** (Scheme 46) (50, 60, and 56% respectively).[440]

Substrates with Two Leaving Groups. m-FC_6H_4I[11c] and 2-fluoro-3-iodopyridine[454] react with retention of fluorine. Synthesis of anti-inflammatory drugs, such as fluorobiprophen **122**, can be achieved by reaction of 4-bromo-2-fluorobiphenyl with the $^-CH_2COMe$ ion followed by methylation and oxidative demethylation[456] (eq 98) (Tables 33 and 34).

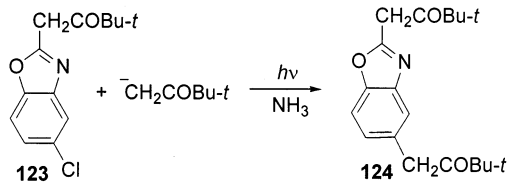


(98)

The products of the reaction of o-$C_6H_4Br_2$ depend on the Nu^- used. For instance, when it reacts with the $^-CH_2COBu$-t ion, disubstitution with no evidence of monosubstitution occurs, but with the $^-CH_2COMe$ ion cyclization from an aldol condensation of the disubstitution product occurs[457] (Tables 33 and 34). *o*-Iodohalobenzenes (X = Cl, Br, or I) react in DMSO under irradiation or $FeBr_2$ initiation with the enolate ions of $^-CH_2COPh$, $^-CH(Me)COPh$, and 1-(2-naphthyl)ethanone to afford mainly monosubstitution with retention of one halogen (Table 37).[235]

Monosubstitution of p-$C_6H_4Cl_2$ can be achieved electrochemically, in the presence of a redox mediator,[93] but disubstitution is possible for p-$C_6H_4Cl_2$, p-$C_6H_4Br_2$, and p-BrC_6H_4I under irradiation.[458] Disubstitution also occurs by reaction of 2,6- and 2,5-dibromopyridines and 2,3-, 3,5-, and 2,6-dichloropyridines with the $^-CH_2COBu$-t ion[442,459] (Table 34).

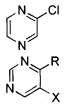
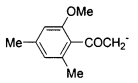
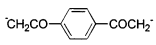
A special behavior is observed with 2,5-dichlorobenzoxazole, which reacts with the $^-CH_2COBu$-t ion to afford the 2-substituted compound **123** by an S_NAr mechanism. This compound is substituted at position 5 by the $^-CH_2COBu$-t ion to give **124** through a light-stimulated $S_{RN}1$ reaction (eq 99) (Table 34).[460]



(99)

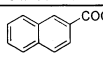
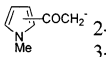
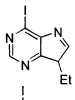
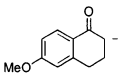
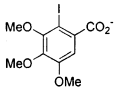
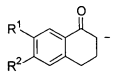
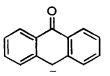
Monosubstitution, resulting from the selective displacement of chlorine from C_4, is obtained in the reaction of the $^-CH_2COBu$-t ion with 4,7-dichloroquinoline,[459] and disubstitution is achieved by its

Table 37. Reaction with the Enolate Ion of Acetophenone, α-Alkyl, and Phenyl Derivatives[a]

Substrate	Nucleophile	Product (%)	Ref
PhI	$^-CH_2COPh$	68,[b] (0,[c] 67[d])[e], 47[f]	79, 78, 80, 108
PhN_2SBu-*t*		95[b]	68a, 451
p-$MeC_6H_4N_2SBu$-*t*		8[b, g]	452, 68b
1-Cl-naphthalene		98,[h] 8,[e] 93[f]	99, 98, 108
1-Br-naphthalene		97[f]	108
2-X-pyridine, X = Cl, Br		75,[h] 77[f]	99, 108
		70[b]	446
2-Cl-quinoline		98,[h] 82,[i] 94[f]	99, *j*, 108
 X = Cl, Br; R = NHBoc		(8, 17)[e]	448b
 X = Cl, Br		82[e,k]	73
R = Ph, *t*-Bu		60-90[e] 35-67[e,l]	72
		70[e]	441, 445
o-BrC_6H_4I		88[m]	235
o-$C_6H_4I_2$		19[n]	235
1-Br-2-I-naphthalene		59[m]	235
PhN_2SBu-*t*	$^-CH_2COC_6H_4OMe$ *o*-, *m*-, *p*-	(71, 76, 77)[b]	68b, 451
p-$MeC_6H_4N_2SBu$-*t*	*m*-	29[b]	68b
	*p*-	98[b]	446
	*p*-	70[e,o]	446
o-RC_6H_4I R = OMe, COMe		18[e], 18[b]	443
p-RC_6H_4I R = OMe, COMe		(19, 13)[b]	443
p-$RC_6H_4N_2SBu$-*t* R = H, Me	$^-CHYCOPh$, Y = Me	(60, 36)[b]	68b, 452
	Y = Et	(52, 24)[b]	
2-Cl-quinoline	$^-CHMeCOPh$	50[e]	437
o-BrC_6H_4I		48[m]	235
1-Cl-naphthalene[p]		30[q]	*r*

[a] Photoinduced reaction unless otherwise indicated. The reactions of substrates with N_2S-Bu-*t* as leaving group are performed under laboratory light. [b] In DMSO. [c] 350 nm. [d] Quartz well. [e] In liquid ammonia. [f] In DMSO induced by SmI_2. [g] Together with 90% of the 2-oxopropanal arylhydrazone derivative. [h] Liquid ammonia in the presence of Na(Hg). [i] Near-UV in liquid ammonia. [j] Hay, J. V.; Hudlicky, T.; Wolfe, J. F. *J. Am. Chem. Soc.* **1975**, *97*, 374−377. [k] Dark reaction. [l] Under K stimulation. [m] Substitution product with retention of bromine. [n] Substitution product with retention of iodine. The reduced substitution product in 25% yield. [o] Monosubstitution product at C_7. [p] Initiated electrochemically. [q] Disubstitution product (15%). [r] Simonet, J.; Dupuy, H. *J. Electroanal. Chem.* **1992**, *327*, 201−207.

Table 38. Reaction with Carbanions Derived from Other Aromatic Ketones[a]

Substrate	Carbanion	Product (%)	Ref.
PhI		49, 92[b]	444, 162
p-$MeCOC_6H_4Br$		54, 56[c]	444
o-BrC_6H_4I		86[d]	235
o-$C_6H_4I_2$		65[e]	235
PhI	 2-	98, 53[b]	105
	3-	89,14[b]	
1-I-naphthalene	2-	78,17[b]	105
PhI		78[f], 88[b]	104
p-$PhCOC_6H_4Br$		63	104
1-I-naphthalene		69	104
9-Br-anthracene		96, 58[b]	104
		80[c]	446
		67[c]	441, 445
PhI	 2-	38,[f] 53[b]	104
p-$RC_6H_4N_2SBu$-*t* R= H, Me		66, 18	68b
PhN_2SBu-*t*	3-	48	68b
		80[c]	441, 445
		75[c]	447
		44[c]	446
		36[g, h]	446
			
	R^1 = H, R^2 = OMe;	60	447
	R^1 = OMe, R^2 = OPr-*i*;	75[c]	447
PhBr		70[i]	99
PhI		95	79

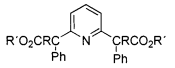
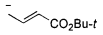
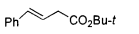
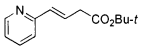
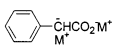
[a] Photostimulated reactions in DMSO unless otherwise indicated. [b] Induced by Fe^{2+} salts. [c] Liquid ammonia. [d] Substitution product with retention of bromine. [e] Substitution product with retention of iodine. [f] Entrainment with CH_3CO-CH_2^- ions. [g] Dark reaction. [h] Monosubstitution product at C_7. [i] Liquid ammonia in the presence of Na(Hg).

reaction with 5,7-dibromo-8-methoxyquinoline[446] (Table 34). On the other hand, monosubstitution at C_7 is the only product obtained with general good yields in the reaction of 5-chloro-7-iodo- or 5,7-dichloro-8-*i*-propoxyquinoline with the carbanions derived from CH_3COR (R = Me, Et, *t*-Bu, 2-furanyl, or *p*-anisyl) (Tables 33, 34, and 38). The furo[3,2-*h*]-quinolines are quantitatively obtained by treatment of the substitution product with HBr 45%/AcOH at 100 °C.[446] Mainly disubstitution takes place in the reaction of the *p*-$BrC_6H_4N_2SBu$-*t* with the $^-CH_2$-COBu-*t* ion (Table 34).[68a]

3. Carbanions Derived from Esters, Carboxylate Salts, N,N-Disubstituted Amides, Thioamides, Imides, and β-Dicarbonylic Compounds

Carbanions Derived from Esters and Carboxylate Salts. α-Arylacetic esters can be obtained through the reaction of ArX with the $^-CH_2CO_2Bu$-*t* ion under light or Fe^{2+} initiation. Lower yields of substitution are

Table 39. Reaction of Carbanions Derived from Esters and Carboxylic Acids in Liquid Ammonia[a]

Substrate	Nucleophile	Product (%)	Ref.
PhBr	$^-CH_2CO_2Bu$-*t*	57, 69[b, c]	80, 103
PhI		82[b, c]	103
o-MeC_6H_4I		55[b, c]	103
p-RC_6H_4Br			
R = Me, OMe		(20, 28)[b]	103
R = OMe		67	173
p-RC_6H_4I			
R = Me, OMe, F		(63, 78, 81[d])[b, c]	103
2-X- pyridine, X = Cl, Br		(22, 89)[b]	103
X = Br		44	461
2-Br-4-Me-pyridine		18[b]	103
3-X-pyridine, X = Br, I		(51,59)[b]	103
2-Cl-quinoline		15[b]	103
		2- (5)[b]; 3-(73)[b, c]	103
PhBr	$^-CHMeCO_2Bu$-*t*	60	80
PhI		51[b]	103
p-PhC_6H_4Br	$^-CHMeCO_2Et$	20	82
2-Br-naphthalene		25	82
PhBr	$^-CMe_2CO_2Bu$-*t*	11	80
p-$MeOC_6H_4Br$		5[e]	173
2-Br-pyridine	$^-CHPhCO_2Et$	77	461
	$^-CRPhCO_2R'$		
	R = H, R′ = Et	84	459
	R = Ph, R′ = Me	42	
PhI		42[f] 	461
2-Br-pyridine		61 	461
PhI			
	M = K	*p*-$PhC_6H_4CH_2CO_2H$	199
	M = Li	(73) Ph_2CHCO_2H (77)	

[a] Under photostimulation unless otherwise indicated. [b] Dark reaction in the presence of $FeSO_4$. [c] Isolated as the acid. [d] Monosubstitution at iodine. [e] Together with 35−50% of reductive dehalogenation of the substrate. [f] Together with other isomers.

usually achieved with the anions of tertiary esters bearing β hydrogens.[80,173] A low percentage of substitution is also obtained in the reaction of the secondary anion of *tert*-butylpropionate with 2-bromonaphthalene and *p*-$C_6H_5C_6H_4Br$ (Table 39).[82]

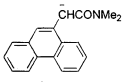
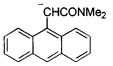
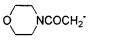
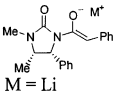
Other carbanions that can be arylated under photoinitiation are the anions of ethyl phenylacetate,[459,461] methyl diphenylacetate,[459] and *tert*-butyl-3-butenate.[461] Phenylation and heteroarylation of the latter carbanion occur at the terminal site of the π system.[461]

The dianion of phenylacetic acid when irradiated in the presence of haloarenes can be arylated at the *p*- or α-carbon depending on the counterion used (Table 39).[199]

Carbanions Derived from N,N-Disubstituted Amide, Thioamide, and Imide Ions. The synthesis of *N,N*-disubstituted α-arylacetamides can be achieved by reaction of ArX with carbanions from *N,N*-disubstituted amides in liquid ammonia under light[462] or Fe^{2+} initiation[103] (Table 40). The K^+ salt of *N*-acetylpiperidine does not react, probably due to its low solubility in liquid ammonia. The anions from acetamide and *N*-methylacetamide are also unreactive.[463]

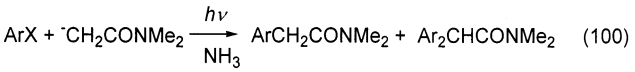
In the reaction of the $^-CH_2CONMe_2$ ion with different ArX, monoarylation is the main reaction

Table 40. Reaction of Carbanions Derived from *N,N*-Disubstituted Amides, Thioamides, and Imides[a]

Substrate	Nucleophile	Product (%)	Ref.
PhX, X = Br, I	$^-CH_2CONMe_2$	80, 63[b]	463, 96
PhI		73[c]	456
p-RC_6H_4I, R = Me, OMe		77, 57	96
p-$PhOC_6H_4Br$		55[c]	456
p-$PhCOC_6H_4Br$		45[d]	96
p-NCC_6H_4Cl		48[e]	96
p-NCC_6H_4X, X = Cl, Br, I		(68, 98, 79)[d]	96
p-$IC_6H_4CO_2^-$		74	96
		18[c,f]	456
1-I-naphthalene		49, 60[c]	96, 456
2-Br-6-MeO-naphthalene		92[b, c]	456
9-Br-phenanthrene		72[c]	456
2-Cl-anthracene		21,[c] 77[c, g]	456
9-Br-anthracene		70,[h] 70[c]	456
2-Br-pyridine		84	461
2-Cl-quinoline		87	461
PhX, X = Cl, Br, I	$^-CH_2CONMePh$	72, 60, 80	463
1-Cl-naphthalene		50	463
9-Br-phenanthrene		80	463
PhI	$^-CH_2CH{=}CHCONMePh$	38[i]	461
2-Br-pyridine		50[i]	461
1-I-naphthalene	$^-CHPhCONMe_2$	26	96
9-Br-phenanthrene		52	96
9-Br-anthracene		30	96
PhI		38	96
PhI		24	96
PhX, X = Cl, Br		75, 56	463
PhX, X = Cl, Br		(46, 70)[j]	103
o-RC_6H_4I, R = F, Me, Ph, OMe		(9,[k] 62, 71, 57)[j]	103
m-RC_6H_4I R = F, Me, OMe		(31,[k]73, 31)[j]	103
p-RC_6H_4I R = F, Me, OMe, Ph, *t*-Bu		(64,[k] 65, 60, 45, 40)[j]	103
2,6-$Me_2C_6H_3I$		44[j]	103
p-XC_6H_4I, X = Cl, I		(51, 55)[j,l]	103
1-I-naphthalene		65[j]	103
2-Br-pyridine		65[j]	103
3-I-thiophene		27[j]	103
PhI		57[j]	103
m-$PhOC_6H_4I$		47[j]	103
p-RC_6H_4I, R = Me, *i*-Bu		(61, 42)[j]	103
PhI	 R = Et, *i*-Pr, *t*-Bu, *n*-C_8H_7	(60, 63, 44, 4)[j]	103
PhX, X = Cl, Br, I		52, 51, 60[b]	462
p-$MeOC_6H_4I$		58	462
1-I-naphthalene		40[m]	462
1-I-naphthalene			
	M = Li	57[n]	211
	M = Ti (IV)	43[n]	211
PhI		(60, 87[o])[p]	107
I-I-naphthalene		70[p]	107

[a] In liquid ammonia under photostimulation unless otherwise indicated. [b] Nucleophile/substrate ratio 15. [c] After quenching with MeI, the product obtained was $ArCHMeCONMe_2$. [d] Under K metal stimulation. [e] Together with 52% of amines from a benzyne mechanism. [f] Together with 65% of products from a benzyne mechanism. [g] In the presence of Na(Hg). [h] Nucleophile/substrate ratio 10. [i] Arylation at the terminal carbon. [j] Induced by $FeSO_4$. [k] Monosubstitution of iodine. [l] Disubstitution product. [m] Product from methylation at the α-C after quenching with MeI. [n] S/R > 99. [o] Induced by $FeBr_2$. [p] Solvent DMSO.

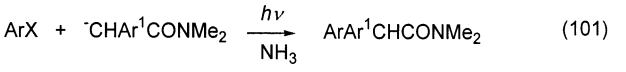
when the nucleophile/substrate ratio is 10−15.[96,456] Diarylation becomes more important when the ratio is equal to 2.[96] Yields of about 50% of monosubstitution and 20% of disubstitution are obtained for most substrates when the ratio is equal to 5 (eq 100).[96, 456]



(100)

Nucleophile addition to the carbonyl group of 4-$C_6H_5COC_6H_4Br$ occurs under photoinitiation (97%), whereas substitution (45%) together with addition to the carbonyl group (14%) occurs under K metal stimulation.[96] Approaches to the synthesis of aryl propionic acids are the photoinitiated reaction of ArX with the anion $^-CH_2CONMe_2$ followed by addition of MeI. The acids are obtained by hydrolysis.[456] Competition with the benzyne mechanism, in the reaction of the anion with 4-bromo-2-fluorobiphenyl, and the addition to the carbonyl group in its reaction with *m*-$C_6H_5COC_6H_4Cl$ are responsible for the low yields of substitution of the amide derivatives of fluorobiprophen and ketoprofen, respectively.[456]

Unsymmetrical α,α-diarylated amides can be prepared by reaction of the anions of the monoarylated products ($ArCH_2CONMe_2$) with ArX (eq 101) (Ar =

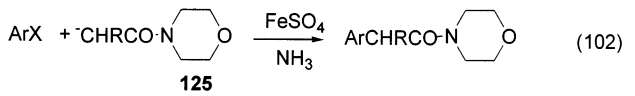


(101)

1-naphthyl, 9-phenanthryl, or 9-anthracenyl and Ar^1 = Ph; Ar = Ph and Ar^1 = 9-phenanthryl or 9-anthracenyl).[96]

The yields of these unsymmetrical diarylamides depend on the substrate−nucleophile pair used. For the same product, and thus for the same radical anion (Ar = Ph and Ar^1 = 9-phenanthryl or vice versa), the best yield is obtained with the less stabilized anion, reaction in which a lesser loss in π energy occurs.

The reaction of ArI with higher *N*-acylmorpholine enolates **125** is another alternative for the synthesis of α-aryl acids (eq 102) (Table 40). The morpholina-



(102)

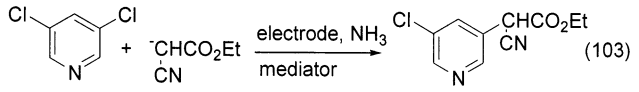
mide of the nonsteroidal anti-inflammatory agent ibuprofen [Ar = *p*-(*i*-Bu)C_6H_4, R = Me] can be obtained by this means.[103]

The anion derived from *N*-acetylthiomorpholine has been successfully arylated by PhI and 1-iodonaphthalene under irradiation or Fe^{2+} initiation in DMSO.[107]

β-Dicarbonyl and Related Carbanions. 1,3-Dianions from β-dicarbonyl compounds react quite well through the terminal carbon site, under irradiation.[78,464] Monoanions do not react with 2-bromopyridine,[442] 2-chloroquinoline,[437] or *o*-$BrC_6H_4CONH_2$ but do react with more electrophilic substrates. The substitution compounds formed in some reactions with the nucleophiles have been further modified by acyl elimination under basic workup, to give the product from a retro-Claisen reaction (Table 41).[177a]

Monoanions from β-dicarbonyl or β-cyanocarbonyl compounds ($^-CHR^1R^2$) react under electrochemical initiation with *p*-$C_6H_5COC_6H_4Br$ and *p*-NCC_6H_4Cl, and in lower yields with 2-chloroquinoline.[465] The presence of a mediator can improve the yield as in the synthesis of *p*-cyanophenyl malononitrile by reaction of the $^-CH(CN)_2$ ion with *p*-NCC_6H_4Cl.[466]

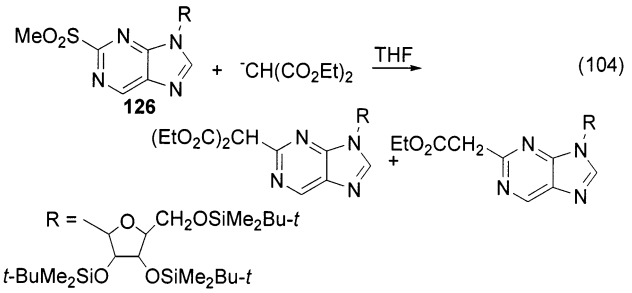
Monosubstitution is obtained electrochemically by reaction of the ethyl cyanoacetate anion with 3,5-dichloropyridine in the presence of a mediator (eq 103),[93] and in the photoinitiated reaction of different



(103)

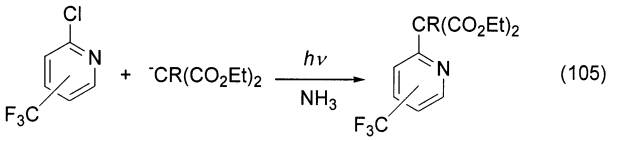
monoanions with 5-chloro-7-iodo-8-methoxide-quinoline or the 8-*i*-propoxide analogues.[467]

Substitution of 2-methylsulfonylnebularine **126** by $^-CH(CO_2Et)_2$ ions is an interesting route to the synthesis of 2-substituted analogues of nebularine, a natural antibiotic (eq 104).[468]



(104)

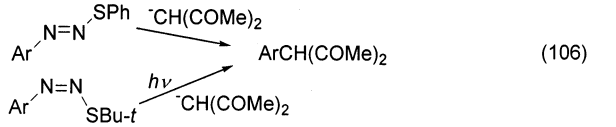
The reactivity of 2-chlorotrifluoromethylpyridines depends on the position of the CF_3 substituent. For example, the reaction with $^-CH(CO_2Et)_2$ ions fails with the C_3- and C_4-substituted derivative (R = H), whereas substitution is obtained with the CF_3 group at C_5 or C_6 (R = Me) (eq 105).[177b]



(105)

A nonchain radical nucleophilic mechanism is proposed to occur in the almost quantitative substitution of *o*-Cl, *o*-Br, and *p*-$O_2NC_6H_4X$ (X = F, Cl, Br, or I) with the anion of ethyl cyanoacetate in DMSO.[469−471]

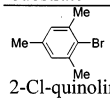
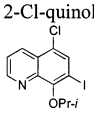
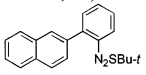
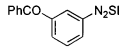
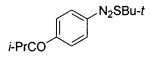
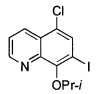
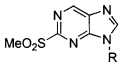
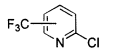
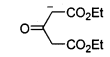
The reactions of (*E*)-ArN_2SPh are spontaneous, whereas sunlamp stimulation is needed for the substitution of (*Z*)-ArN_2SBu-*t*. In the reactions of the latter derivative the reduction products ArH, together with 5−30% of the ArSR sulfides, are also formed (eq 106).[69]



(106)

The higher yields of substitution are formed when the aryl ring of the sulfide is substituted by EWG

Table 41. Reaction of Carbanions Derived from β-Dicarbonyl and Related Nucleophiles[a]

Substrate	Nucleophile	Product (%)	Ref.
			
	R = Me	82[b]	78
2-Cl-quinoline	R = Ph	17-71[b, c, d]	464
o-, *m*-, *p*-NCC_6H_4Br	$^-CH(COMe)_2$	90, 90, 63	177a
p-$PhCOC_6H_4Br$		51[e]	465
		75	177a
2-Cl-quinoline		12[e]	465
		60[f]	467
PhN_2SBu-*t*		7[g,h]	69a
o-$RC_6H_4N_2SBu$-*t*			
R = CN, NO_2		(77, 74)[g,h]	69a
m-$RC_6H_4N_2SBu$-*t*			
R = CN, NO_2, COPh		(84, 71,[c] 58)[g, h]	69a
p-$ZC_6H_4N_2SBu$-*t*			
Z = CN, COMe, COPr-*i*, COPh, Br, OMe		(74,[h] 64,[h] 44, 45,[h] 43,[h] 9[h])[g]	69a, 472
		26[g,h]	69a
3-(*t*-$BuSN_2$)-pyridine		60[g,h]	69a
o-$NCC_6H_4N_2SPh$		67[g,h]	69a
p-$RC_6H_4N_2SPh$, R = COPh, CN, NO_2		(45,[h] 60,[c] 72[c])[g]	69a
	$^-CMe(COMe)_2$	15[i]	74
o-, *m*-, *p*-NCC_6H_4Br	$^-CH(COMe)CO_2Me$	(80, 80, 70)[j]	177a
o-, *p*-NCC_6H_4Br		(90, 70)[k]	177a
		80[k]	177a
		62	467
	$^-CH(R)CO_2Me$ R = COMe, CO_2Me	34,[k, g] 34[k, g]	472
		47-58[k,g]	472
o-NCC_6H_4Br	$^-CMe(COMe)(CO_2Et)$	60[k]	177a
		82[k]	177a
o-NCC_6H_4Br	$^-CH(CO_2Et)_2$	78	177a
		90	177a
		83	467
		50[l]	468
 5-, 6-	$^-CMe(CO_2Et)_2$	100, 44	177b
o-CNC_6H_4Br	$^-CEt(CO_2Et)_2$	80	177a
		92	177a
o-NCC_6H_4Br	$^-CH(CN)CO_2Et$	90	177a
p-NCC_6H_4Cl		48[m]	465
p-$PhCOC_6H_4Br$		94[e]	465
		75[m]	93
		80	177a
o-NCC_6H_4Br		80	177a
		90[k]	177a
p-NCC_6H_4Cl	$^-CH(CN)_2$	85[m, n]	466

[a] Photostimulated reactions. Liquid ammonia as solvent unless otherwise indicated. [b] Arylation at C_1 of the anion. [c] Laboratory light. [d] The percentage of substitution depends in the countercation used. [e] Induced electrochemically in DMSO. [f] Monosubstitution at C_7. [g] DMSO as solvent. [h] Sunlamp. [i] Dark reaction. [j] After HCl addition. [k] Percentage of the aryl acetic ester derivative after quenching with NH_4Cl. [l] In THF, together with 25% of the monodecarboxylated product. [m] Induced electrochemically in liquid ammonia in the presence of mediator. [n] Followed by KOH adddition.

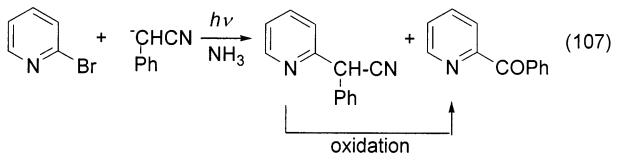
and for Ar = 3-pyridyl.[69] In the reaction with (*Z*)-*p*-$BrC_6H_4N_2SBu$-*t* monosubstitution of the N_2SBu-*t* group is obtained. Substitution is also achieved with ethyl cyanoacetate, ethyl acetoacetate, $^-CH(CN)_2$, and $^-CH(CO_2Et)_2$ ions.[69] The reactions have a limited synthetic scope to ketoprofen and ibuprofen.[472]

4. Carbanions Derived from Nitriles and Nitroalkanes

Anions from Nitriles. The main feature of the $S_{RN}1$ reaction of these nucleophiles is that depending on the ArX involved, straightforward substitution or products from CN elimination can be formed.[473−475] However, α-arylated nitriles are almost exclusively formed by reaction of ^-CHRCN ions (R = H, Me, or Ph) with stabilized π aromatic compounds, such as naphthyl[476] and quinolyl moieties,[477] among others (Table 42).

Besides the $S_{RN}1$ mechanism, the S_NAr amination is also in play in the photoinitiated reaction of the $^-CH_2CN$ ion with 2-bromopyridine.[436] In the reaction of the anion with 2-chloroquinoline, low yields of products from ionic pathways are formed together with the substitution compound.[436]

The nitriles obtained by reaction of the $^-CH(CN)Ph$ ion with heteroaryl halides can lead to the corresponding ketones in excellent yields by oxidative decyanation under PTC (eq 107).[477]

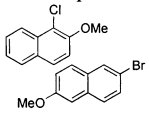
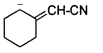


(107)

The excellent yields of substitution obtained in the reaction of 2-chloropyrazine with the $^-CH(CN)Ph$ ion in the dark and the relatively low efficiency of DTBN to inhibit the reaction indicate that it probably takes place by dual radical chain and addition−elimination mechanisms.[73]

Exclusive substitution at C_2 occurs under photostimulation, by reaction of 2,4-dichloropyrimidine with the $^-CH(CN)Ph$ ion.[459] On the other hand, a mixture of monosubstitution, disubstitution, and monosubstitution with reductive dehalogenation occurs in the reaction of this anion and the anion of

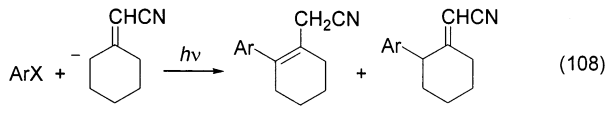
Table 42. Photoinduced Reactions of Carbanions Derived from Nitriles in Liquid Ammonia

Substrate	Nucleophile	Product (%)	Ref.
p-RC_6H_4Cl, R = Ph, PhCO	$^-CH_2CN$	96-97	225
1-Cl-, 2-Cl-naphthalene		89, 98	98, 225
9-Bromophenanthrene		70	225
2-Cl-; 2-Br-pyridine		98, 75[a]	225, 436
3-Br-; 4-Br-pyridine		80, 60	226
2-Cl-quinoline		50	436
 2-, 3-		(35, 38)[b]	475
p-PhC_6H_4Br	^-CHMeCN	52	82
2-Br-naphthalene		77	82
		52	82
		81, 94[c]	82, 476
2-, 3-, 4-Br-pyridine[d]	^-CHPhCN	88, 48,[e] 15[e]	436, 477
2-Cl-quinoline		88	436
3-Br-quinoline		45[e]	477
		82[f]	450
		31	477
		36[g]	459
		58[h]	459
	$^-C(Et)PhCN$	91[f]	450
		25[i]	459
p-$MeOC_6H_4X$, X = Br, I		69-65[j]	197
1-I-naphthalene		60[j]	197

[a] Together with 2-aminopyridine (16%). [b] Together with 6−7% of 1,2-dithienylethane. [c] Solvent $H_2N(CH_2)_2NH_2$. [d] Added as the pyridinium chloride. [e] Ketones from oxidative decyanation of the nitriles are also formed. [f] Solvent HMPA, laboratory light. [g] Disubstitution together with 34% of monosubstitution. [h] Monosubstitution at C_2. [i] Disubstitution together with 17% of monosubstitution and 52% of monosubstitution with reductive dehalogenation. [j] Mixture of two isomers.

2-phenylbutyronitrile with 2,6-dibromopyridine.[459] Both anions react with 3-bromoquinoline 1-oxide to afford the corresponding 3-substituted quinoline 1-oxides by the $S_{RN}1$ mechanism.[450]

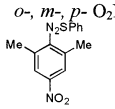
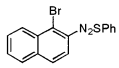
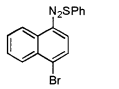
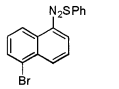
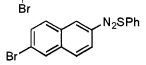
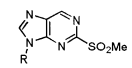
The carbanion of cyclohexylideneacetonitrile reacts to afford good yields of the isomeric substitution products at Cγ together with traces of 2,2-(diaryl)-cyclohexylideneacetonitrile (eq 108).[197]



(108)

Nitronate Ions. These anions are not efficient at initiation (they usually require entrainment conditions to react under irradiation), but they are very efficient in the coupling with radicals. Despite these facts, only products from fragmentation of the radical anion of the substitution product are obtained by reaction with aromatic substrates. An ET and cage collapse mechanism is proposed for the reaction of $Ph_2I^+Br^-$ with the $^-CMe_2NO_2$ ion in MeOH to afford $PhCMe_2NO_2$ and PhI (67 and 88% yields, respectively).[478]

Table 43. Photostimulated Reactions of CN^- Ions in DMSO[a]

Substrate	Product (%)	Ref.
p-$PhCOC_6H_4Br$	95[b]	479, 480, 35a
o-, *m*-, *p*-$NCC_6H_4N_2SPh$	63, 75, 71	119, 143
p-$NCC_6H_4N_2SPh$	80[b]	145c
m-, *p*- $CF_3C_6H_4N_2SPh$	61, 60	119, 143
m-, *p*-$MeOC_6H_4N_2SPh$	35, 9	119, 143
p-$RC_6H_4N_2SPh$, R = F, COMe, COPh, SO_2Ph	37, 50, 69, 74	119, 143
p-$RC_6H_4N_2SPh$ R = COPh, SO_2Ph	(40, 72)[c]	119, 143
o-, *m*-, *p*- $O_2NC_6H_4N_2SPh$	(14, 4, 48)[d]	119, 143
	46[d]	119
	60	119
o-$ClC_6H_4N_2SPh$	53[e]	119
m-, *p*-$BrC_6H_4N_2SPh$	50, 54[e]	119
	27[e,f]	120
	48[e,f]	120
	46[e]	120
	30[e]	120
	40[g]	468

[a] With diazosulfide as leaving group, ArSPh is also formed as minor product. [b] Induced electrochemically in MeCN. [c] Induced electrochemically in DMSO. [d] Daylight. [e] Disubstitution product. [f] Sunlamp. [g] In DMF.

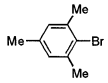
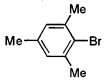
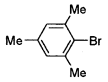
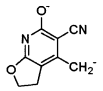
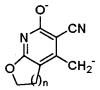
5. Cyanide Ions

One of the less reactive nucleophiles is the CN^- ion, with a rate constant, determined electrochemically, below the diffusion limit.[35,94]

The substitution of *p*-$C_6H_5COC_6H_4Br$ is achieved under controlled potential scale electrolysis, but substitution fails under these conditions with 1-bromonaphthalene.[479,480] On the other hand, the photoinitiated substitution of 2-methylsulfonylnebularine[468] and 1-halo-2-naphthoxide ions[89c] has been reported.

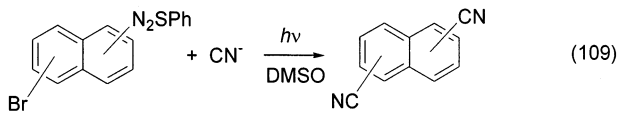
ArN_2SPh are the best compounds to be substituted by CN^- ions in DMSO under irradiation or electrode stimulation.[119,143,145c] Despite the low rate constant for the reaction of the anion with Ar$^\bullet$ radicals, the system is favored by the positive reduction potential of the substrate with respect to the substitution product, which in turn favors the $S_{RN}1$ propagation cycle. In these reactions besides the nitriles, ArSPh are also formed. These compounds result from the competition toward Ar$^\bullet$ or $ArN_2^\bullet$ radicals between CN^- and PhS^- ions, the latter being formed by fragmentation of the radical anion of the substrate.[119,145c] As expected, the best percentages of substitution are obtained with aryldiazo compounds substituted by EWG (Table 43).

Table 44. Photostimulated Reaction of Other Carbanions in Liquid Ammonia

Substrate	Nucleophile	Product (%)	Ref.
PhX, X = Cl,[a] Br, NMe_3I	 2-	48, 73, 66	481
		87	481
PhI[a], $PhNMe_3I$	4-	51, 88	481
		55	481
2-, 4-Br-pyridine		47,[b] 78	436
2-Cl-quinoline		24[c]	436
PhX, X = I, Br		56, 63	461
		94	461
2-Br-pyridine		33[b]	461
2-Cl-quinoline		45[c,d]	461
PhI		62	461
2-Br-pyridine		88	461
PhBr		59	461
2-Br-pyridine		37[b]	461
PhX, X = I, Br		39, 57	461
2-Br-pyridine		94	461
PhI	$^-CH_2P(O)(OMe)_2$	47	461
2-Br-pyridine		68	461
		20[d]	*e*
	 n = 1,2	18[d]	*e*

[a] Initiated by K metal stimulation. [b] Together with 2-aminopyridine. [c] Together with 2-aminoquinoline. [d] Dark reaction. [e] Janin, Y. L.; Huel, C.; Legraverend, M.; Aubertin, A. M.; Bisagni, E. *Synth. Stuttgart* **2001**, 1806−1811.

When Br or Cl is the substituent of the aryldiazo compounds, the introduction of two cyano groups is achieved with more than satisfactory yields.[119] Bromonaphthalenediazonium tetrafluoroborates react with NaSPh in DMSO to give the corresponding diazosulfides, which afford the dinitriles in the presence of an excess of CN^- ions under light stimulation (eq 109) (Table 43).[120]

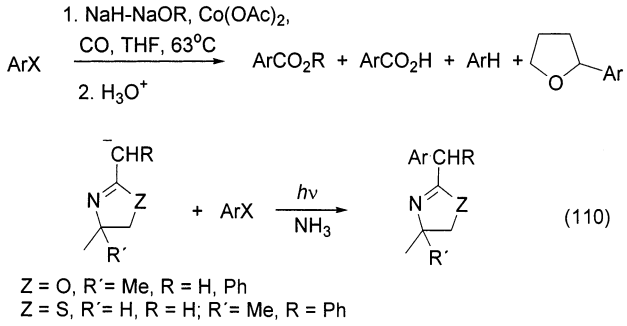


(109)

6. Other Carbanions

Other carbanions proposed to react by the $S_{RN}1$ process are the anions from 2- and 4-methylpyridine,[436,481] 2,4,4-trimethyl-2-oxazoline,[461] 2-benzyl-4,4-dimethyl-2-oxazoline,[461] 2,4-dimethylthiazole,[461] 2-benzyl-4,4-dimethylthiazole,[461] and dimethyl methylphosphonate[461] (Table 44). Competition with a benzyne process has been determined in some of these reactions. Some examples are described in eq 110.

Scheme 47



Carbanions from $MeSO_2Me$, 1,3-dithiane, 2-phenyl-1,3-dithiane, *tert*-butyl α-phenylthioacetate, and *tert*-butyl α-phenylselenoacetate fail to undergo $S_{RN}1$ substitution with 2-bromopyridine under irradiation in liquid ammonia.[461] Even though the $S_{RN}1$ phenylation of dimsyl anion has been proposed to occur under sunlight stimulation in DMSO,[482a] later reports clearly demonstrate that neither PhI nor 2-chloroquinoline reacts with the anion under $S_{RN}1$ conditions in this solvent.[482b]

7. Other C–C Bond Formations

Carbonylation Reactions. The cobalt species Co-CRACO (NaH/NaOR/$Co(OAc)_2$/CO) allows catalytic carbonylation of ArX at atmospheric pressure to give the corresponding acid and ester in good yields.[77,483] The $S_{RN}1$ mechanism has been proposed for these reactions (Scheme 47).[484, 485]

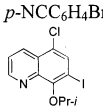
The percentage of reduction formed in these reactions usually varies between 15 and 20%. Formation of 2-aryltetrahydrofuran as well as Ar−Ar is frequently observed in THF, which indicates the presence of Ar• radicals. Except for *p*-$Me_2NC_6H_4Br$, all substituted ArBr are carbonylated in very good yields. Carbonylation of PhI takes place in 70−75% yield and that of PhCl in 35−40% yield.[77,483] Carbonylation of *p*-$C_6H_4Br_2$ gives 60−65% of the diacid *p*-$C_6H_4(CO_2H)_2$.[77] The percentage of carbonylation with halogen retention (X = Cl) increases for the compounds *p*-ClC_6H_4Br and *m*-ClC_6H_4Br.[483]

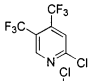
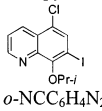
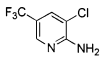
Another possibility to achieve carbonylation is with $Co_2(CO)_8$ under PTC conditions, when the reaction is irradiated.[485,486] Under these conditions, carbonylation of PhI and several ArBr takes place easily in generally quantitative yields and with lower yields for *p*-$O_2NC_6H_4Br$, *p*-$MeOC_6H_4Br$, and *p*-HOC_6H_4Br. Carbonylation does not occur with PhCl; this behavior is used to perform the selective carbonylation of *p*-ClC_6H_4Br to *p*-$ClC_6H_4CO_2H$.[485,486] Carbonylation at the aromatic (major) and benzylic (minor) sites of *p*-$XC_6H_4CH_2CN$ by $Co_2(CO)_8$ under irradiation occurs in NaOMe/MeOH.[487]

Cobalt-catalyzed polycarbonylation of the less reactive polychlorobenzenes can be achieved at the meta or para position to another halogen atom or carboxyl group under photoinitiation in aqueous NaOH under PTC and pressurized CO (2 atm).[230]

In contrast, carbonylation at the ortho position gives a complex mixture of products.[230,488] This situation can be avoided in NaOMe/MeOH (CO 2 atm) and photoinitiation, conditions under which carbonylation at the ortho position to afford benzene poly-

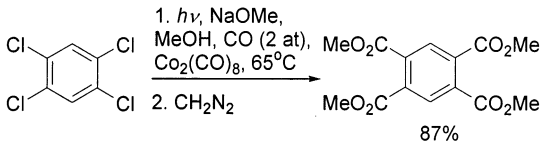
Table 45. Reaction with Phenoxide and Related Ions[a]

Substrate	Nucleophile	Products (%)	Ref.
p-$PhCOC_6H_4Br$	PhO^-	*o*- (40), *p*- (20)[b]	497
p-$NCC_6H_4N_2SR$		*o*- (42), *p*- (20)[c],	498
R = *t*-Bu, R = Ph		*o*- (46), *p*- (14)[d]	
PhN_2SBu-*t*	*p*-$MeC_6H_4O^-$	23[c]	498b
o, *m*, *p*-$NCC_6H_4N_2SBu$-*t*		50, 61, 69[c]	513
m, *p*-$NCC_6H_4N_2SPh$		62, 69[c]	498
o, *m*-$O_2NC_6H_4N_2SBu$-*t*		52, 70[c]	498b
p-$O_2NC_6H_4N_2SPh$		70[d]	498b
m-$PhCOC_6H_4N_2SBu$-*t*		53[c]	498b
p-$RC_6H_4N_2SBu$-*t*			
R = COPh, OMe, Br		(54, 21, 33)[c]	498b
2-(*t*-$BuSN_2$)-naphthalene		28[c]	498b
2-(*t*-$BuSN_2$)-pyridine		58[c]	498b
p-NCC_6H_4Br		20	178
		25	467
PhBr, PhN_2SBu-*t*	*p*-$MeOC_6H_4O^-$	40,[e] 49[c]	178, 498b
o, *p*-$NCC_6H_4N_2SBu$-*t*		62, 76[c]	513, 498b
p-RC_6H_4Br			
R = F, CN, CF_3, OCF_3		15, 65, 20, 45[e]	512, 178
		60[e]	467
o-NCC_6H_4Br	*p*-$CF_3OC_6H_4O^-$	86	512
p-RC_6H_4Br		47, 29,[e] 47	512
R = F, CF_3, OCF_3			
p-$NCC_6H_4N_2SBu$-*t*	*p*-$RC_6H_4O^-$		
	R = CF_3, Br, NO_2	(66, 56, 35)[c]	498b
p-$NCC_6H_4N_2SPh$	R = NO_2	51[f]	
4-Cl-pyridine	2,6-$R_2C_6H_3O^-$	6[g]	505a
	R = Me		
o-, *m*, *p*-NCC_6H_4Cl	R = *t*-Bu	89, (68-80), 78[h]	497b,500, 92, 499
p-NCC_6H_4Cl		(60-68)[h]	499
		70	*i*
p-RC_6H_4Cl			
R = CO_2Me, COMe, NMe_3I, Cl		(50, 50, 85, 67)[g]	503, 506, 93
p-$RO_2SC_6H_4Cl$			
R = Me, Ph, *p*-ClC_6H_4		90[g]	501

Substrate	Nucleophile	Products (%)	Ref.
o-RC_6H_4Br			
R = CN, $CONH_2$, COMe, OMe		88, 85, 60, 78	178
p-RC_6H_4Br			
R = F, CN, CF_3		30, 96, 38	512, 178
R = SMe		40[g]	503
p-NCC_6H_4Br		25[g]	504
4-Br-pyridine		35[g]	504
p-(*p*-$NCC_6H_4)C_6H_4Br$		<10[g]	504
p-$NCC_6H_4N_2SR$			
R = *t*-Bu, Ph		64[c], 58[d]	498
3-, 4-Cl-pyridine		(84, 70)[g]	92, *j*, *k*
		77[g], 70	92, *i*
		30[g,l]	93
		74[g, m]	93
	3-	3- (66)	177b
	5-	5- (85)[e]	
		50[g]	502
		40[g]	502
4-Cl-quinoline		76[g]	503
4-Cl-pyridine	R = *i*-Pr, *n*-C_5H_{11}	(30, 21)[g]	505a
	R = OMe	18	467
o-$NCC_6H_4N_2SBu$-*t*	2,4-$Me_2C_6H_3O^-$	21[c,n]	513
o-,*p*-NCC_6H_4Cl	R = 2,4-(*t*-$Bu)_2C_6H_3O^-$	20[o], 47[g]	500
p-RC_6H_4Br		48, 27, 63	512
R = F, F_3C, F_3CO			
	4, 5, 6	10, 98, 60	177b
		98	177b

[a] Photoinitiated reactions in liquid ammonia unless otherwise indicated. Arylation of PhO^- occurs at *o*- and *p*-carbons. Mono- and disubstituted phenols at positions 4; 2,4; and 2,6 are arylated at the free ortho- or para-position, respectively. [b] Electrochemically initiated in liquid ammonia. [c] Photoinitiated in DMSO. [d] Laboratory light in DMSO. [e] Together with the 2,6-disubstituted phenol. [f] Sunlamp. [g] Initiated electrochemically in liquid ammonia. [h] Initiated electrochemically in DMF. [i] Combellas, C.; Gautier, H.; Simon, J.; Thiébault, A.; Tournilhac, F.; Barzoukas, M.; Josse, D.; Ledoux, I.; Amatore, C.; Verpeaux, J. *J. Chem. Soc., Chem. Commun.* **1988**, 203−204. [j] Combellas, C.; Petit, M. A.; Thiébault, A.; Froyer, G.; Bosc, D. *Makromol. Chem.* **1992**, *193*, 2445−2451. [k] Boy, P.; Combellas, C.; Mathey, G.; Palacin, S.; Persoons, A.; Thiébault, A.; Verbiest, T. *Adv. Mater.* **1994**, *6*, 580−583. [l] Substitution of the chlorine at the C_2. [m] Monosubstituted product. [n] Quenched by addition of MeI. [o] Isolated as the lactone derivative.

carboxylic acids (isolated as Me esters by further reaction with diazomethane) can be easily achieved in high yields (eq 111), with the exception of *o*-$O_2NC_6H_4Br$.[489]



(111)

The combination of light and CoCRACO in THF−alcohol avoids the use of $Co_2(CO)_8$, leading to excellent yields of carbonylation of halo- and dihaloaromatic compounds.[490] Carbonylation can also be performed in general with excellent yields by cobalt(II) salts.[491] When the reactions are performed with the $Co(OAc)_2$ salt, not only halides bearing an EWG but also simple ArCl are carbonylated.

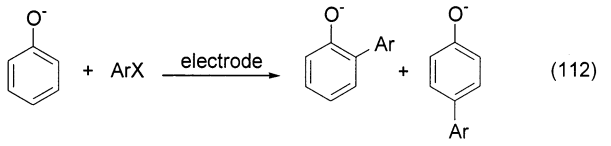
Carbonylation of ArX, bearing amino or hydroxy groups on a side chain ortho to the halogen, is an important route to five- and six-membered ring benzolactams and benzolactones (see section VIII.F.1).[485]

Carbonylation of ArX can also be achieved in the presence of the bimetallic $[Fe(CO)_5-Co_2(CO)_8]$ system.[492−496] When the reaction is performed in the absence of $Co_2(CO)_8$, benzophenone is formed as the major product, given an adequate H_2O/benzene and $PhI/Fe(CO)_5$ ratio as well as NaOH concentration.[495,496]

Reaction with Phenoxide and Related Ions. In the aromatic family, ArO^- ions, mainly 2,6- and 2,4-di-*tert*-butyl phenoxides and 1- and 2-naphthoxide ions, are excellent Nu^- under electrochemical or irradiation conditions. The reaction is a route to biaryls unsymmetrically substituted by EWG and electron

donor groups and to the synthesis of cyclic compounds.

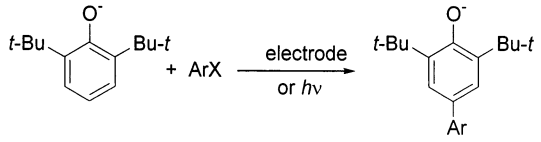
The unsubstituted PhO^- ions have been reported to react with *p*-$C_6H_5COC_6H_4Br$, upon electrolysis in liquid ammonia,[497] and with *p*-$NCC_6H_4N_2SR$ (R = Ph or *t*-Bu), in DMSO under thermal or light initiation,[498] to afford the ortho (≈40%) and para (≈20%) coupling products (eq 112) (Table 45). With



(112)

2-chloroquinoline, only the ortho-substituted compound is formed (27%) in DMSO under electrolyis.[497b]

Arylation of *p*-$MeC_6H_4O^-$ usually gives low yields with PhI,[80,178] *p*-NCC_6H_4Br,[178] and ArN_2SR[498b] under photoinitiation. The yields of substitution increase when the aryl ring is substituted by EWG or the PhO^- ion has electron-donating groups. Thus, *p*-MeO-, 2,6-, and 2,4-di-*t*-Bu phenoxide ions are more reactive than PhO^- ions under electrochemical or light initiation. The *t*-Bu groups substitute two of the three possible coupling positions, which enables a selective synthesis of either the ortho or para isomer. For instance, with the 2,6-disubstituted phenoxide ion the para-substituted compound is obtained (eq 113). The *t*-Bu substituents can be easily removed later.



(113)

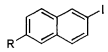
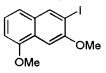
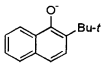
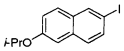
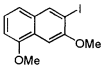
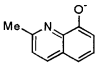
Among the compounds that react with 2,6-di-*tert*-butylphenoxide ion with good yields of substitution under electrochemical induction are chlorobenzonitriles,[92,499,497b,500] chlorophenyl sulfones,[501] and 3- and 4-chloropyridines[92] (Table 45). 2-Chloropyridine gives no substitution unless it is substituted by CN− or CF_3- groups.[92,502] Good yields are also obtained in the mediated reaction of the anion with other ArCl[503] and polyarylbromides.[504]

Electrochemical substitution of 4-chloropyridine has also been performed with other 2,6-dialkyl phenoxide ions (alkyl = *n*-pentyl, *i*-Pr, or Me), although in lower yields than with 2,6-di-*tert*-butyl phenoxide ion.[505a] Quaternization of the substitution product by linear RX, followed by deprotonation, gives pyridiniophenoxide zwitterions.[505]

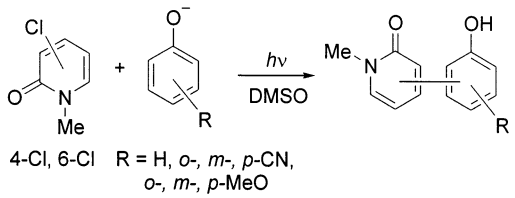
Monosubstitution is obtained in the electrochemically induced reaction of 2,6-di-*tert*-butyl-phenoxide ion with 2,5- and 3,5-dichloropyridines and *p*-$C_6H_4Cl_2$ in the presence of a mediator.[93,506] The product of the latter reaction has been further functionalized by substitution of the remaining chlorine atom.[506]

Arylation of the cesium salt of the PhO^- ion, its *o*-, *m*-, and *p*-Me, and *o*-, *m*-, and *p*-CN derivatives is possible with 4- and 6- chloro-1-methyl-2-pyridones. Low yields are obtained in these reactions (10−60%). A CN group at the ortho position of the anion decreases the yield. However, *m*- and *p*-cyanophenoxides favor the substitution of the 6-chloro (40−54%) with respect to the 4-chloro compound (18−32%). With relation to the regioselectivity of the coupling reaction, ortho-arylation to the hydroxy group is favored (eq 114). However, O-arylation is also obtained with the 6-chloro-1-methy-2-pyridone by a polar pathway.[507]

Table 46. Reaction with 1-Naphthoxide and Related Ions[a]

Substrate	Nucleophile	Coupling at C_2	Coupling at C_4	Ref
p-NCC_6H_4Br	1-Naphthoxide	25	40	178
1-I-naphthalene		22[b]	37[b]	508
2-I-naphthalene		0	36[b,c]	508
1-I-naphthalene			70[b]	508
 R = H, OPr-*i*			(50, 60)[b]	508
			50[b]	508
			57[d]	509
4-Cl-pyridine			80[d]	509
4-Cl-quinoline			85[d]	509
1-I-naphthalene		35[b]	50[e]	508
		47[b,f]		508
2-I-naphthalene		36[b]	34[e]	508
		65[b]		508
		55[b,f]		508
1-I-naphthalene		15[b,g]		511
		*h, g*		511
		51[b]		511
2-I-naphthalene		40[b]		511

[a] Photostimulated in liquid ammonia unless otherwise indicated. [b] Isolated as the isopropyl ether. [c] 2,4-Disubstituted product in 20% yield. [d] Electrochemically initiated in the presence of mediator. [e] Isolated as the C_4 addition compound. [f] In MeCN. [g] In DMSO. [h] Substitution at C_2, C_4, and disubstitution, in 50% yield.

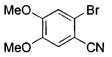
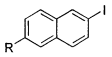
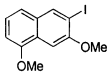
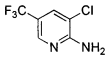


(114)

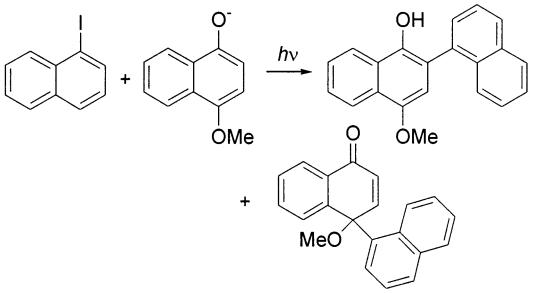
4-Cl, 6-Cl R = H, *o*-, *m*-, *p*-CN, *o*-, *m*-, *p*-MeO

The 1- and 2-naphthoxide ions react under irradiation with different ArX (Tables 46 and 47). In the reaction of 1-naphthoxide ions a mixture of 2- and 4-aryl- together with 2,4-diaryl-1-naphthol is formed.[178,508] Only substitution at C_4 occurs with the 2-Me-substituted anion,[508] whereas in the reaction of the 4-methoxy-1-naphthoxide ion, substitution at C_2 accompanied by addition at C_4 take place (eq 115).[508]

Table 47. Reaction with 2-Naphthoxide Ions[a]

Substrate	Product (%)	Ref.
p-$NCC_6H_4N_2SR$	65-68[b]	498
o-NCC_6H_4Br	76	514
o-RC_6H_4Br, R = NH_2, OMe, $CONH_2$	(40, 25, 25)[c]	86
p-NCC_6H_4Br,	85	178
p-RC_6H_4Br, R = F, CF_3, OCF_3	31, 55, 40	512
	84	514
p-$MeOC_6H_4I$	42	510
1-I-naphthalene	53	510, 508
 R = H, OPr-*i*	(44, 65)[d]	508
	55[d]	508
 5, 6	95, 60	177b
	90	177b
2-, 4-Cl-quinoline	(70, 70)[b, d]	511
3-Br-quinoline	85[b,d]	511
	50[b,d]	511
	74[b,d]	511
	50[b,d]	511
1-I-naphthalene	20[b,d,e]	511

[a] Photoinitiated reactions in liquid ammonia unless otherwise indicated. Substitution product from coupling at C_1. [b] In DMSO. [c] In the presence of KI. [d] Isolated as the isopropyl ether. [e] The anion of 2-hydroxyquinoline as nucleophile.

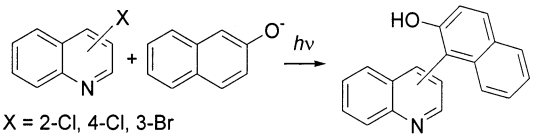


(115)

Good yields of 4-aryl-2-*tert*-butyl-1-naphthols [Ar = 4-pyridyl, 4-quinolyl, or *p*-(4-pyridyl)phenyl] can be achieved by the electrochemically induced reaction of 2-*tert*-butyl-1-naphthoxide ions with ArCl.[509]

2-Naphthoxide ions react with ArX to give substitution only at C_1 of the naphthalene ring.[178,183,508,510] The reactivity of the naphthoxide system allows the synthesis of naphthylquinolines and naphthylisoquinolines via its coupling reaction with haloquinolines (eq 116) and haloisoquinolines, respectively (Table 47).[511]

Another possibility to achieve these compounds is the reaction of iodonaphthalenes with anions from hydroxyquinolines although in lower yields (15−51%).[511]



(116)

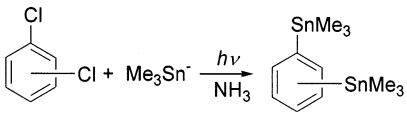
2-Naphthoxide ions as well as 2,4- or 2,6-di-*tert*-butyl-, *p*-MeO^-, and *p*-$F_3COC_6H_4O^-$ ions react with *p*-F-, *p*-CF_3-, and *p*-$F_3COC_6H_4Br$ under photoinitiation to afford fluorinated biaryl derivatives.[512] Depending on the nucleophile and the substrate, ortho disubstitution and 4-addition products can be obtained.[512] Another approach to fluorinated biaryls is the electrochemically[502] or photoinitiated[177b] reaction of CF_3-substituted 2-chloropyridines with 2-naphthoxide or 2,4- or 2,6-di-*tert*-butyl phenoxide ions. In this system synthetically useful yields can be obtained when the CF_3 group is at position 5 or 6 of the pyridine ring.

The reaction of ArO^- ions with *o*-cyanoaryldiazosulfides[513] or *o*-cyanoarylbromides[514] have proved of interest in the synthesis of the dibenzo[*b*,*d*]pyran-6-one skeleton of benzocumarins and related compounds (see section VIII.F.1).

B. Reactions with Tin Nucleophiles

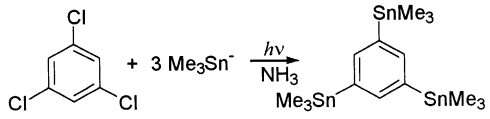
ArCl are substituted by Me_3Sn^- ions in liquid ammonia under irradiation to give the substitution product in high yields (88−100%, Table 48). On the other hand, ArBr and ArI react by an HME pathway.[76]

The reaction of *o*-, *m*-, and *p*-$C_6H_4Cl_2$ with Me_3Sn^- ions gives disubstitution (eq 117).[76,229]



(117)

Even trisubstitution is possible, as in the photostimulated reaction with 1,3,5-$C_6H_3Cl_3$ in liquid ammonia (eq 118).[229]



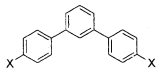
(118)

Different results were found with dichloropyridines. 2,5-Dichloropyridine reacts in the dark (88% of disubstitution), whereas 2,6- and 3,5-dichloropyridine need light to give ~80% yield of disubstitution. These reactions proceed in liquid ammonia by the $S_{RN}1$ pathway.[229]

It is known that haloarenes and haloheteroarenes react with Me_3Sn^- ions in DME, diglyme, and tetraglyme as solvent to yield the substitution product, but no mechanistic studies have been performed. No light was needed to induce these reactions.[64d,f,515a,b] However, recently it has been demonstrated that haloarenes react in diglyme with Me_3Sn^- ions under irradiation by the $S_{RN}1$ mechanism.[515c]

The synthesis of Me_3SnAr from ArOH through $(EtO)_2POAr$ has recently been reported to proceed in high yields.[516a,b] $ArNH_2$ are converted into $ArNMe_3I$,

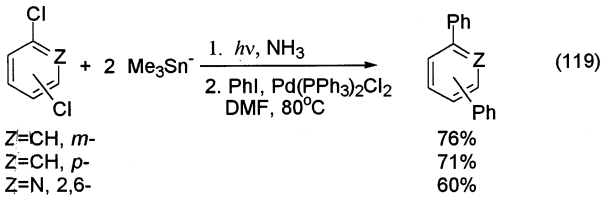
Table 48. Photoinduced Reactions of R_3Sn^- Ions with Aromatic Compounds in Liquid Ammonia

Substrate	R_3Sn^-	Products (%)	Ref.
$PhOP(O)(OEt)_2$	Me_3Sn^-	85	516b
$PhNMe_3I$		89, 98	515c, 516c
p-$MeOC_6H_4X$, X = Cl, $OP(O)(OEt)_2$, NMe_3I		100, 81, 100	76, 516b,c
p-NCC_6H_4Cl		85 (70)[a]	229
p-$H_2NC_6H_4Cl$		95	515c
1-X-naphthalene, X = Cl, $OP(O)(OEt)_2$, NMe_3I		90 (88),[a] 93, 85	76 (515c), 516b, c
2-naphthyl-$OP(O)(OEt)_2$		98	516b
2-X-pyridine, X = Cl, $OP(O)(OEt)_2$		88, 35	229, 516b
3-, 4- pyridine-$OP(O)(OEt)_2$		74, 20	516b
2-Cl-quinoline		96, 65[b]	76
p-PhC_6H_4-$OP(O)(OEt)_2$		80	516b
p-$NCC_6H_4C_6H_4Cl$		94	515c
o-, *m*-, *p*- $Cl_2C_6H_4$		(58, 90, 88)[c]	229
p-ClC_6H_4R, R = $OP(O)(OEt)_2$, NMe_3I		(97, 76)[c]	516
m-, *p*- $C_6H_4[OP(O)(OEt)_2]_2$		79,[c] 95[c]	516b
2,5-, 3,5-, 2,6- Cl_2-pyridine		(88, 80, 86)[c]	229
 X = Cl		0, 79[a,c]	515c
X = NMe_3I		83[c]	515c
1,3,5-$Cl_3C_6H_3$		71,[d] 28[a, d]	229, 515c
1,3,5-$((EtO)_2P(O)O)_3C_6H_3$		57[d]	516b
p-MeC_6H_4Cl	Ph_3Sn^-	75	76
p-$MeOC_6H_4Cl$		30[e]	518, 76
p-MeC_6H_4Br		62	76
1-Cl-naphthalene		80, 72[e]	76, 518
1-Br-naphthalene		75	76
1-, 2-naphthyl-$OP(O)(EtO)_2$		100,[b] 100[b]	516a
2-Cl-pyridine		82[e]	518
3-Cl-pyridine		93[e]	518
2-Cl-quinoline		80	76
p-$C_6H_4Cl_2$		69,[c] 90[c,e]	76, 518
p-$C_6H_4Br_2$		22[c,f]	76
p-$XC_6H_4OP(O)(OEt)_2$, X = Cl, Br, I		100,[c] 100,[c] 40[c]	516b
p-$C_6H_4[OP(O)(OEt)_2]_2$		70[c]	516a

[a] Diglyme as solvent. [b] Dark. [c] Disubstituted product. [d] Trisubstituted product. [e] DMSO as solvent. [f] Only reduction in DMSO.

which by photostimulated reaction with Me_3Sn^- ions in liquid ammonia afford $ArSnMe_3$ in good to excellent yields[515c,516c] (Table 48).

A sequence of $S_{RN}1$ followed by a cross-coupling reaction catalyzed by Pd(0) has been developed to obtain polyphenylated compounds as shown in eq 119.[517] Following the same procedure 1,3,5-triphenyl-



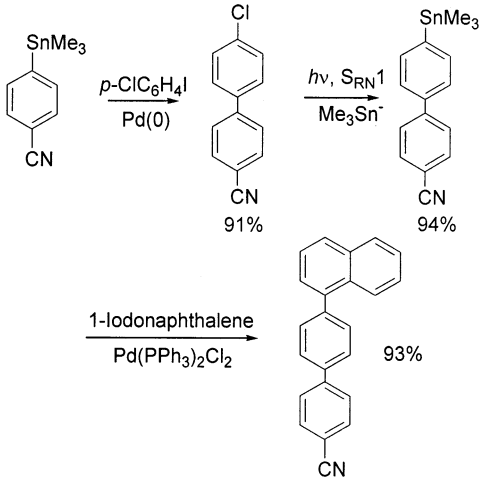
(119)

benzene was obtained in 61% isolated yield from 1,3,5-$C_6H_3Cl_3$ in a one-pot procedure.[517]

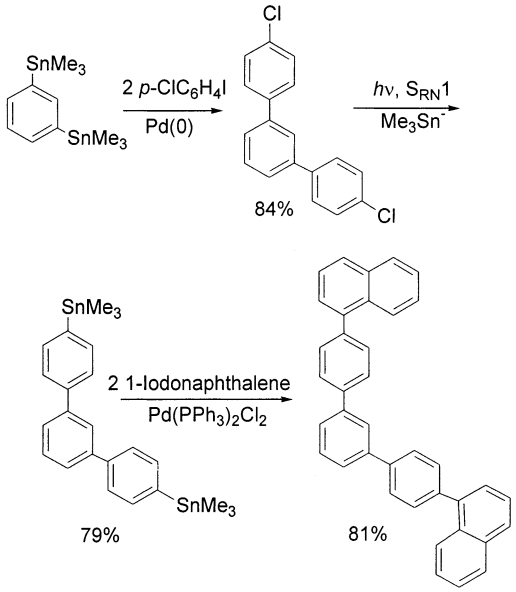
The facts that ArCl react with Me_3Sn^- ions under photostimulation to form Me_3SnAr and that in the Pd-catalyzed reaction with stannanes the reactivity of ArI is much greater than that of ArCl have been used to obtain biaryl chlorides by a chemoselective reaction. This allows the remainder leaving group, Cl, to react further by $S_{RN}1$ to form an organostannyl intermediate, which can ultimately furnish the final arylated product by a second Pd-catalyzed reaction. Thus, following this approach, the sequence of Scheme 48 was carried out.[515c]

With a distannane, and with the same approach, the sequence of Scheme 49 was performed.[515c]

Scheme 48



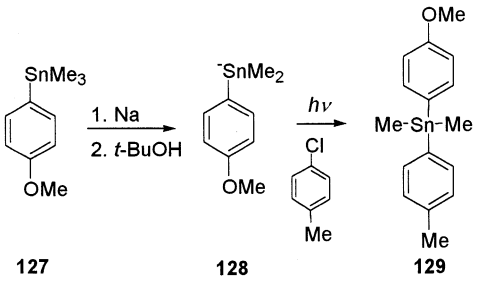
Scheme 49



Good yields of substitution are also obtained by reaction of Ph_3Sn^- ions with ArX in liquid ammonia (Table 48). *p*-$C_6H_4Cl_2$ reacts with Ph_3Sn^- ions to give 75% yield of disubstitution in liquid ammonia,[76] 90% in DMSO,[518] and 44% in MeCN.[518] Although dehalogenation by HME takes place with ArI and 2- and 3-chlorothiophene, good yields of substitution are found with 2- and 3-chloropyridines in DMSO.[518]

Other tin nucleophiles can be prepared by an Sn−alkyl bond fragmentation of an R_4Sn compound. Thus, the treatment of **127** with Na metal in liquid ammonia affords **128**, which reacts with *p*-MeC_6H_4-Cl to yield the asymmetrical substitution product **129** in high yield (eq 120).[519] The latter compound is also obtained (89%) by a one-pot reaction starting from Me_3Sn^- ions and *p*-$MeOC_6H_4Cl$.[519]

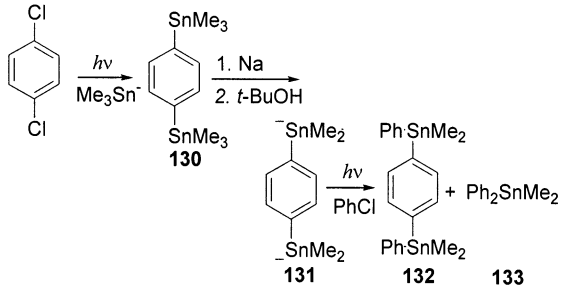
When **130**, the product formed by reaction of Me_3Sn^- with *p*-$C_6H_4Cl_2$, without isolation was first treated with Na metal to produce the Sn−Me bond fragmentation, and then with *t*-BuOH to neutralize the amide ions formed, the dinucleophile **131** was formed. After addition of PhCl and irradiation (90



(120)

min), products **132** and **133** were obtained in a one-pot reaction (70 and 20%, respectively) (Scheme 50).[229]

Scheme 50



C. Reaction with N, P, As, and Sb Nucleophiles

1. Nucleophiles Derived from Nitrogen

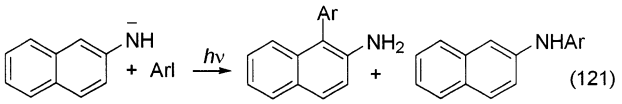
Amide and Aryl Amide Ions. The $S_{RN}1$ mechanism on ArX was discovered through the reaction of NH_2^- ions with 5- and 6-halopseudocumenes in liquid ammonia.[3a] Other compounds that react with NH_2^- ions by this mechanism in liquid ammonia under K metal stimulation are *o*-$MeOC_6H_4X$ (X = Br or I),[3b] 2-iodo-1,3-xylene,[3b] PhOPh,[3b] and 3-bromothiophene[449] to give the amine derivatives in 53−79% yields. 2-Bromothiophene affords the rearranged 3-aminothiophene.[449] $ArOP(O)(OEt)_2$ obtained from PhOH, 2,6-dimethylphenol, and 2-methoxy-4-methylphenol react with NH_2^- ions induced by K metal to afford $ArNH_2$ (73, 79, and 56% yield, respectively).[520]

NH_2^- ions react under photoinitiation with 2-bromomesitylene with good yields of substitution (70%).[160] 2-Bromopyridine fails to react under these conditions; instead, a mixture of 3- and 4-aminopyridines is obtained through addition to a 3,4-dehydropyridine intermediate.[226]

In the K metal stimulated reaction of PhI with KHNPh in liquid ammonia, not only substitution at nitrogen (Ph_2NH, 10%) but also at ortho- and para-carbons of the aromatic ring of the anion (6% yield each) is reported.[3b]

Under photostimulation $PhNH^-$ gives low yields of substitution with ArI.[189] 2-Naphthylamide ions initiate the photo $S_{RN}1$ process of PhI, *p*-$MeOC_6H_4I$, and 1-iodonaphthalene in liquid ammonia. In these reactions the 1-aryl 2-naphthylamines are formed in 47, 63, and 45% yields, respectively (eq 121). The highest yield of nitrogen substitution is obtained with *p*-$MeOC_6H_4I$ (6%).[189]

Heteroaryl Nitrogen Nucleophiles. Arylpyrroles, arylindoles, and arylimidazoles can be synthesized electrochemically, usually in the presence of a mediator, by reaction of pyrrolyl, indolyl, or imidazolyl ions in liquid ammonia.[190−192,194b] Under these conditions in the reaction of pyrrolyl anion with *p*-NCC_6H_4Cl, 4-chloropyridine, 3,5-dichloropyridine (substitution at one chlorine atom), and 4-chloro- and 4-chloro-7-trifluoromethylquinolines, good yields of substitution with coupling at C_2 (52, 60, 67, 53, and 65%, respectively) together with small yields of substitution at C_3 (3−14%) are observed (eq 122).[190] Compounds from disubstitution of the anion at $C_{2,5}$ and $C_{2,4}$ were either detected or isolated.[190]



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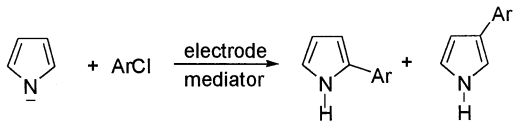


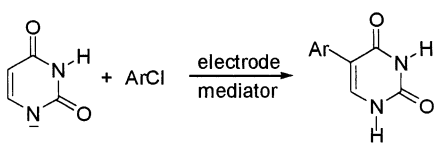
(122)

When the anion bears a *p*-CNC_6H_4 group at C_2, the substitution by *p*-NCC_6H_4Cl at C_5 (60%) is accompanied with substitution at C_3 (20%). With the ion from 2,5-dimethylpyrrole, products from coupling at C_3 (40%) together with addition at C_2 (20%) are obtained with *p*-NCC_6H_4Cl, 4-chloropyridine, 3-chloropyridine, and *p*-$PhSO_2C_6H_4Cl$.[191,192] It is thus concluded that for the anion of pyrrole C_2 is ∼4 times more reactive than C_3. When C_2 and C_5 are substituted, the reaction occurs at C_3.[192] In the case of indolyl anions substitution at C_3 is the main reaction observed (60% yield with 4-chloropyridine and *p*-NCC_6H_4Cl).[190]

On the basis of the percentages of monosubstitution obtained at C_2 and C_5 for the anion of 4-methylimidazolyl, C_5 is ∼4 times more reactive than C_2. When the Me substituent is at position 2, the reaction becomes regioselective and only substitution at $C_{4(5)}$ occurs (40%).[192] Similar results are obtained in the reaction of the anion from 2-(*p*-anisyl)imidazole and 2-Me-5-NO_2-imidazole with fluorinated or CF_3 substituted ArI (35−55% yields).[194b,521]

Although there are reports indicating that certain azaheteroarene anions react through the nitrogen with ArX,[522,523] further studies demonstrated that these are S_NAr processes.[524]

Direct and indirect electrochemical reduction of *p*-$C_6H_5COC_6H_4Br$, *p*-NCC_6H_4Cl, *p*-$O_2NC_6H_4l$, 1-iodo-2-trifluoromethylbenzene, and 1-iodo-2,3,5,6-tetrafluoro-4(1-imidazolyl)benzene in the presence of uracil anion in DMSO yields the corresponding 5-aryluracils (eq 123) in the following respective yields: 55, 50, 55, 38, and 50%.[144,194b]

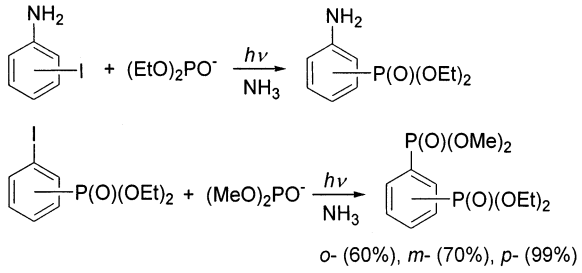


(123)

2. Reactions with Phosphorus Nucleophiles

Diethylphosphite Ions. ArI are substituted by this ion, affording $ArOP(O)(OEt)_2$ (71−96% yields) under irradiation either in liquid ammonia,[232a,c,454,525] in

Scheme 51



MeCN/THF,[526] in DMF, or in DMSO.[527] The synthesis was achieved with the following ArI: PhI, 1-iodonaphthalene, *p*-, *m*- and *o*-RC_6H_4I (R = Me, OMe),[232a] *m*-$CF_3C_6H_4I$,[232a] *o*-, *m*-, and *p*-$H_2NC_6H_4I$,[526,527] 2- and 3-iodopyridines,[526,454] and 3-bromoquinoline.[526] The ion also reacts under Fe^{2+} catalysis with ArI in liquid ammonia[101] but fails to react under these conditions with PhI in DMSO.[102] The electrochemically initiated reaction of the anion in DMSO with *p*-$C_6H_5COC_6H_4$-Br and PhI affords mainly reductive dehalogenation.[227] On the other hand, the yield of substitution obtained from preparative scale electrolysis is quantitative by reaction with *p*-NCC_6H_4Cl in liquid ammonia (rate constant at − 40 °C for the radical−nucleophile coupling is 1.4×10^9 M^{-1} s^{-1}).[35a,528]

ArBr become suitable for preparative use in the presence of NaI, which greatly accelerates the photoinitiated reaction of PhBr, *o*-, *m*-, and *p*-MeC_6H_4-Br, and 2- and 3-bromopyridines in MeCN/THF[85,529] and of ArBr ortho-functionalized by NH_2 (from 60 to 100%), OMe (from 8 to 90%), or $CONH_2$ (from 9 to 63%) in liquid ammonia.[86]

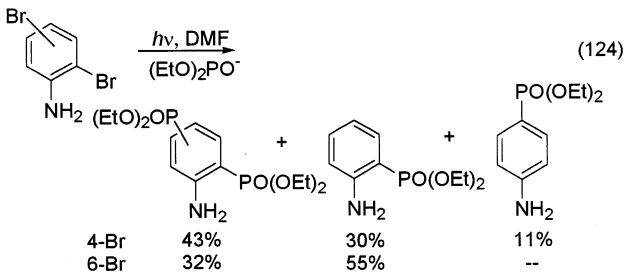
Symmetrical ArSAr, related sulfoxides, and sulfones can also be substituted by $(EtO)_2PO^-$ under irradiation.[84]

The good percentages of substitution obtained with the iodoaniline family (75−98%),[525,530a] derivatives of *o*-bromoaniline (60%),[530a] 1-bromo-2-amino-(85%),[530b,525] 1-amino-2-bromo-(75%),[530b,525] and 1-amino-4-bromo (60%)[525] naphthalenes and 2-amino-5-bromopyridine (60%)[525] have been successfully used to achieve the synthesis of compounds disubstituted by different Nu^- through a second $S_{RN}1$ reaction, after iodination of the product of the first substitution via its diazonium salt (Scheme 51).[525]

Another synthetic possibility for the amino-substituted $ArP(O)(OEt)_2$ (Ar = Ph, pyridyl, or naphthyl) is bromination ortho to the amino group, to form the substrate to be substituted in a second $S_{RN}1$. The disubstituted aromatic amine thus obtained can be further modified to the iodo derivative, which can be substituted in a third $S_{RN}1$ reaction.[525] The second and third substitutions are usually performed with sulfur nucleophiles.[525]

The following substitution behavior has been observed with $(EtO)_2PO^-$ and the four haloiodobenzenes in liquid ammonia under irradiation. Monosubstitution at iodine is obtained with the *o*-,[531] *m*-,[232a] and *p*-fluoro[233a] compounds. Mainly disubstitution is obtained with *o*-[531] and *p*-[233a] chloroiodobenzenes (82 and 59% yields, respectively), whereas the meta isomer gives mainly substitution of iodine (89%).[232a] The *o*-,[531] *m*-,[232a,233c] and *p*-bromo[232b] derivatives give mainly disubstitution. The *o*-,[531] *m*-,[232a] and *p*-$C_6H_4I_2$[232a] give entirely disubstitution products. The ratio of monosubstitution to disubstitution product from either *m*-ClC_6H_4I or *m*-BrC_6H_4I increases linearly with increasing the substrate concentration.[532]

Monosubstitution at bromine (74−60% yield), accompanied by reductive debromination (26−39%), is the main reaction of the anion with 2-fluoro-4-bromo- and 2-bromo-4-fluoroanilines.[527] Disubstitution together with monosubstitution and reductive dehalogenation at C_2 and C_4 or C_6, respectively, are achieved by reaction of the anion with the 2,4 and 2,6-dibromoaniline derivatives (eq 124).[527]



(124)

Monosubstitution at C_7 is obtained under irradiation by reaction of the anion with 5-chloro-7-iodo-8-*i*-propoxyquinoline.[533] 5-Bromo-1,2-dimethylimidazole[534] and 2-iodothiophene[535] fail to react under $S_{RN}1$ conditions with the $(EtO)_2PO^-$ ion. Other $(RO)_2PO^-$ ions that react with PhI are R = Me[232a,233a,525] and R = Bu[232a] derivatives in liquid ammonia under irradiation.

Diphenylphosphide Ions. The reaction of Ph_2P^- ions with methyl and methoxy phenyl halide derivatives,[75,100,110a,160,536] naphthyl[100,110] and quinolyl halides,[100] diarylsulfides,[84] sulfones,[84] and sulfoxides[84] has been reported to afford in general good yields of substitution.

Besides thermal (with *p*-MeC_6H_4l)[75] and photochemical initiation, other means to perform these substitutions are in the presence of Na(Hg), as reported for the compounds *p*-$MeOC_6H_4X$ (X = I or Br), 1-chloronaphthalene, and 2-chloroquinoline (40, 85, 83, and 96% of substitution, respectively)[100,110b] and by ultrasound in liquid ammonia at room temperature and pressure, as reported for the compounds *p*-$MeOC_6H_4I$ and 1-halonaphthalenes (X = Cl, Br, or I) (75, 30, 94, and 70%, respectively).[110]

Other Phosphorus Nucleophiles. The ions $PhP(OBu)O^-$,[537] Ph_2PO^-,[536,537] $(EtO)_2PS^-$,[537] $(Me_2N)_2PO^-$,[537] and $(C_6H_5CH_2)_2PO^-$ [536] react with PhX (X = Br or I) in liquid ammonia under photoinitiation with nearly quantitative yields of substitution in the case of the first three anions when X = I.[537]

The asymmetric bidentate (*R,S*)-methylphenyl(8-quinolyl)phosphine can be prepared in high yields (∼80%) from 8-chloroquinoline and the respective substituted phosphide ion in THF at −78 °C, a reaction for which no mechanistic proposal has been made.[538]

Elemental P affords, by reaction with Na metal in liquid ammonia, a "P^{3-}" species that reacts with PhX (X= I or Cl) under irradiation to form Ph_3P in fair to good yields.[539] Further reaction with Na metal of the

Ph_3P thus obtained affords Ph_2P^- ions that, by reaction with *p*-$MeOC_6H_4Br$, lead to unsymmetrical phosphines in a one-pot reaction.[539]

Di-*p*-tolyliodonium hexafluorophosphate reacts with Ph_3P under irradiation in acetone-d_6 or MeCN-d_3 to give *p*-tolyltriphenylphosphonium salt (50−60%) and *p*-MeC_6H_4I (48−50%).[540] The process is suggested to take place by the $S_{RN}1$ mechanism wherein both the nucleophile and the leaving group are neutral.

3. Reactions with Arsenic and Antimony Nucleophiles

Elemental As or Sb reacts with Na metal in liquid ammonia to afford the "M^{3-}" species able to give Ph_3M in fair to good yields by photoinitiated reaction with PhBr and PhCl.[539] Further reaction of Ph_3As with Na metal gives Ph_2As^- ions, which can give unsymmetrical arsines in one-pot reactions with 2-chloroquinoline under irradiation (90%).[539]

When Ph_2As^- ions, formed by Na or K metal reductive cleavage of Ph_3As or Ph_3AsO in liquid ammonia, react under irradiation with *p*-halotoluenes,[217] *p*-haloanisoles,[217,536] 1-bromonaphthalene,[218] and 9-bromophenanthrene,[218] arsines with scrambled aryl rings are formed. Straightforward substitution is achieved only under light initiation with 2-chloroquinoline[218,536] and in the dark with 4-chlorobenzophenone (76 and 100% yields, respectively).[217] On the other hand, products from scrambling of aryl rings are formed in the reaction of Ph_2Sb^- ions with different ArX, and even with 4-chlorobenzophenone.[218]

D. Reaction with S, Se, and Te Nucleophiles

1. Reactions with Sulfur Nucleophiles

Alkanethiolate Ions. The main disadvantage of the RS^- ions is that, depending on the ArX and the nucleophile involved, the fragmentation reactions may compete with the straightforward substitution process. However, usually the expected straightforward substitution is obtained with compounds bearing EWG or polycyclic or heterocyclic halides (Table 49).

The fragmentation reaction can be useful for the preparation of ArSH by reaction of unactivated ArCl with RS^- ions. For example, *p*-MeC_6H_4Cl reacts with *n*-PrS^- or *n*-BuS^- ions to give *p*-MeC_6H_4SH at 90−96%. Attempts to prepare *p*-benzenedithiol from *p*-$C_6H_4Cl_2$ with *n*-BuS^- ions failed. Instead, *p*-HSC_6H_4-SBu-*n* was formed (94%).[541]

Good yields of substitution are formed by reaction with the $HO(CH_2)_2S^-$ ion. The product obtained with 1-bromo-2-aminonaphthalene cyclizes in good yields to the benzo[*e*]thiazine after replacement of OH by Cl (eq 125).[530b]

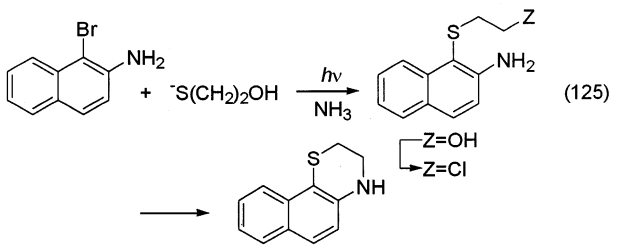
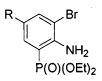


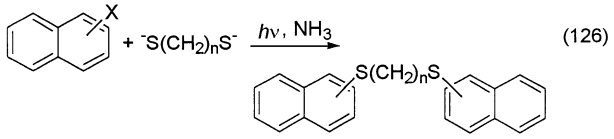
Table 49. Photostimulated Reactions of Alkane Thiolate Ions in Liquid Ammonia

Substrate	Nucleophile	Product (%)	Ref.
4-X-quinoline, X = Cl, Br	MeS^-	(66, 80)[a]	*b*
o-R-C_6H_4Br, R = CN, CHO, COMe, $CONH_2$	EtS^-	70-90	224
m-NCC_6H_4Br		90	224
p-$PhCOC_6H_4Br$		95	224
2-Br-3-R-pyridine, R = H, CN, OMe		61-87	224
2-Cl-3-NH_2-pyridine		35	224
2-Cl-quinoline		85	224
1-Cl-naphthalene	*n*-BuS^-	81	98
2-Cl-pyridine		72-85	223
p-$PhCOC_6H_4Br$	*t*-BuS^-	60[c]	479, 480
1-I-naphthalene		88	223
o-RC_6H_4Br, R = CN, COMe	$PhCH_2S^-$	85,[d] 66	224
2-Br-3-NC-pyridine		82	224
2-Cl-quinoline		69	223
o-NCC_6H_4Br	$HO(CH_2)_2S^-$	85	224
 R = Me, NR_2		65, 80	530a
1-X-naphthalene, X = Cl, Br		71, 74	98
1-(2)NH_2-2(1)Br-naphthalene		85, 88	530b
1-I-2(4)-$((EtO)_2P(O))$-naphthalene		88, 75	525
1-I-2-$((EtO)_2P(O))$-4-(2-S-pyridyl)-naphthalene		74	525
2-I-1-$((EtO)_2P(O))$-naphthalene		75	525
2-X-3-R-pyridine, X = Cl, Br R = H, CF_3, NH_2, CN, OMe, $PO(OEt)_2$		45-100	224, 180, 454, 525
3-I-2-MeO-pyridine		80	454
3-X-2-NH_2-5-R-pyridine X = Cl, R = CF_3		85, 60	180, 525
X = Br, R = $PO(OEt)_2$			
o-NCC_6H_4Br	$EtO_2CCH_2S^-$	100[d]	224
p-$PhCOC_6H_4Br$		68	224
2-Cl-quinoline		75[d]	224
o-NCC_6H_4Br	$EtO_2C(CH_2)_2S^-$	70	224
2-Br-pyridine		32	224
2-(3)Br-3-(4)NC-pyridine		90, 68	224
		65[e]	533
1-X-naphthalene, X = Br, I	$^-S(CH_2)_2S^-$	50[f]	542
2-X-naphthalene, X = Br, I		27, 40[f]	542
1-, 2-I-naphthalene	$^-S(CH_2)_3S^-$	50, 13[f]	542
	$^-S(CH_2)_4S^-$	25, 39[f]	542

[a] Dark conditions. [b] Zoltewicz, J. A.; Oestreich, T. M. *J. Org. Chem.* **1991**, *56*, 2805−2809. [c] Electrochemically induced reaction in DMSO. [d] ArS^- ions, trapped as ArSMe with MeI. [e] With retention of chlorine. [f] Diarylated product.

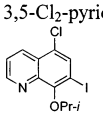
Thiazines and benzo[*g*]thiazine are obtained following the same procedure by reaction of the anion with substituted *o*-bromoaniline[530a] or 2-amino-3-halo- or 3-amino-2-halopyridines (X = Br or Cl), respectively,[525] and with 1-amino-2-bromonaphthalene.[530b]

Double sulfides can be formed in the double-$S_{RN}1$ reaction of 1- or 2-halonaphthalenes (X = Br or I) and the dianions $^-S(CH_2)_nS^-$ (*n* = 2−4) (eq 126).



The percentages of double sulfides obtained are accompanied by small percentages of the dinaphthyl sulfides, formed by fragmentation of the radical anion intermediates.[542]

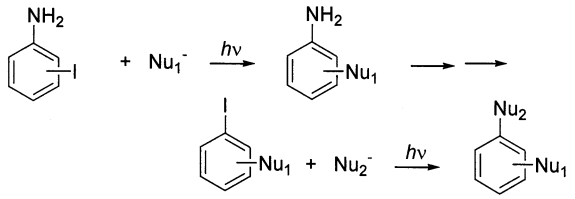
Table 50. Photostimulated Reaction with PhS^- Ions in Liquid Ammonia

Substrate	Product (%)	Ref.
PhX, X = Br, I, N_2BF_4	56,[a] 94, 97[b]	549, 543, 554
o-IC_6H_4R, R = NH_2, P(O)(OEt)$_2$	10,15	525
p-$IC_6H_4P(O)(OEt)_2$	10	525
o-, *m*-IC_6H_4R, R = Me, OMe	68-91	543
m-$IC_6H_4CF_3$	71	543
p-XC_6H_4COMe, X = F, Cl, Br	(84-96)[c]	543
Br	95[a]	550
p-IC_6H_4R, R = Me, OMe, OPh	72-92	543
R = CN	20[a]	479
1-I-2,6-$Me_2C_6H_3$	19	522
p-BrC_6H_4R, R = CN, COPh	(80, 95)[a]	479, *d*, 551, 227
p-BrC_6H_4R, R = CH_2CN, COPh	(91, 97)[b]	546
o-, *p*-$MeC_6H_4N_2BF_4$	(82, 79)[b]	554a
p-$MeOC_6H_4N_2BF_4$	72[b]	554a
m-, *p*-$O_2NC_6H_4N_2BF_4$	(80, 79)[b]	554a
2,6-$Me_2C_6H_3$-1-N_2BF_4	76[b]	554a
1-X-naphthalene, X = Br	(87-100)[a], 43[e]	479, 255, 552, 109
X = I, N_2BF_4	85, 82[b]	543, 554a
2-N_2BF_4-naphthalene	78[b]	554a
2-X-pyridine, X = Br, I	65,[f] 58[c]	547
X = Br	21	436
3-Br-pyridine	23, (24)[c]	226, 547
3-I-pyridine	63[g]	557
2-Cl-quinoline	96,[h] 94,[i] 51[e]	216, 553, 548,109
3-Br-quinoline	78[g]	557
4-Br-isoquinoline	65[g]	556, 557
2-I-thiophene	52[i,j]	535
3-Br-thiophene	64[i]	535
Substrates with two leaving groups		
m-IC_6H_4F	96[k]	543
o-, *m*-, *p*-ClC_6H_4I	(77-89)[l]	234, 232b, 533
m-ClC_6H_4Br	55[l]	232b
m-, *p*-$Br_2C_6H_4$	(92, 64)[l]	232b
p-$IC_6H_4NMe_3I$	95[l]	232b
o-, *m*-, *p*-$FC_6H_4N_2BF_4$	(75-86)[b, k]	554
p-$XC_6H_4N_2BF_4$, X = Cl, Br, I	(63-69)[b, l]	554b
o-$IC_6H_4N_2BF_4$	28[b,l]	554b
o-, *m*-$ClC_6H_4N_2BF_4$	(48, 63)[b, l]	554b
2-Cl-4-Me-1-$C_6H_3N_2BF_4$	34[b,l]	554b
4-(5)Br-1-N_2BF_4-naphthalene	(62, 56)[b, l]	120
	(45, 57)[b, l]	120
3,5-Cl_2-pyridine	60[h,l]	93
	70[m]	533
	65[l]	533

[a] Electrochemical initiation in DMSO or MeCN. [b] DMSO. [c] DMF. [d] Amatore, C.; Pinson, J.; Savéant, J. M.; Thiébault, A. *J. Am. Chem. Soc.* **1982**, *104*, 817−826. [e] Initiation by SmI_2 in DMF/THF. [f] HMPA. [g] NaOMe/MeOH. [h] Electrochemical initiation. [i] MeCN. [j] Together with 10% of fragmentation. [k] Monosubstitution product with retention of fluorine. [l] Disubstitution product. [m] Monosubstitution product on iodine.

Arene and Heteroarene Thiolate Ions. ArI react with PhS^-,[543] substituted PhS^-,[147] 2-naphthalene thiolate,[183,544] and heteroarene thiolate[525,533,545] ions in liquid ammonia under irradiation to afford good yields of ArSPh or heteroaryl-SAr. Substitution of the less reactive ArBr can be achieved under thermal, photochemical,[535,546,547] or electrochemical initiation[227,255,479,548−553] in DMF, MeCN, or DMSO. ArN_2F_4B can be substituted in DMSO at room temperature[554] (Tables 50 and 51). In some systems and depending on the experimental conditions, a competition between ET and the S_NAr mechanisms has been proposed for the reaction with PhS^- ions.[555]

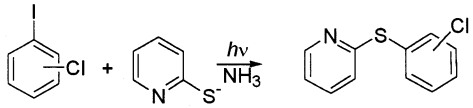
Scheme 52



Substitution of 4-bromoisoquinoline by PhS^- ions takes place in MeOH by an ionic mechanism that is shifted to a radical-chain $S_{RN}1$ type reaction by addition of NaOMe.[556] The substitution of 3-iodopyridine and 3-bromoquinoline is also achieved in this medium under irradiation.[557] 5-Chloro-6-nitroquinoxaline reacts with *p*-$MeC_6H_4S^-$ ions in MeOH to give disubstitution in 56% yield. In this reaction, which is proposed to take place by the $S_{RN}1$ mechanism, both the NO_2 and the Cl act as leaving groups.[555b]

ArN_2F_4B react with Ar^1S^- ions to give $ArSAr^1$ with previous formation of the corresponding ArN_2SAr^1.[554] Electron-releasing groups and EWG in the ArN_2^+ are compatible with high yields of substitution, and nonsteric hindrance is observed in the substrate. Meanwhile, steric hindrance in the Ar^1S^- ions decreases the yield of substitution.[554]

Dihalobenzenes react with PhS^- ion to afford in most cases disubstitution (Table 50).[232b,234] Disubstitution is also the main reaction of the anion with ArN_2^+ salts bearing also a halogen (Cl, Br, or I) (Table 50).[120,554b] On the other hand, *o*-, *m*-, and *p*-ClC_6H_4I react with 2-pyridinethiolate (eq 127) and 2-pyrimidinethiolate ions to afford monosubstitution as the main reaction product (Table 51).[234,533]

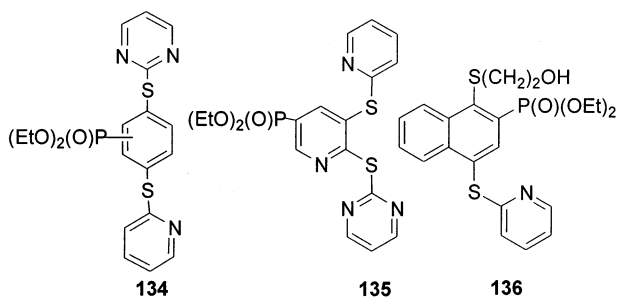


(127)

Disubstitution is the main product formed in the electrochemically initiated reaction, in the presence of a redox mediator, of *p*-$C_6H_4Cl_2$, 2,5-dichloropyridine, and 3,5-dichloropyridine with ArS^- ions.[93] The synthesis of phenyl, naphthyl, and pyridyl unsymmetrical disubstituted compounds bearing the $(EtO)_2PO^-$ and ArS^- moieties, or two different ArS^- groups, can be achieved following the strategy indicated in section VIII.C.2 (Scheme 52) (Table 51).[525]

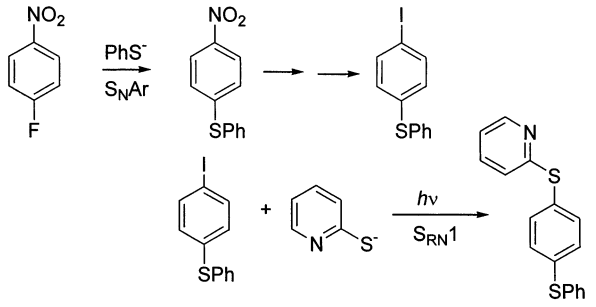
The trisubstituted compounds **134**, **135** (Table 51), and **136** (Table 49) (Chart 4) can be obtained following the same procedure.[525]

Chart 4



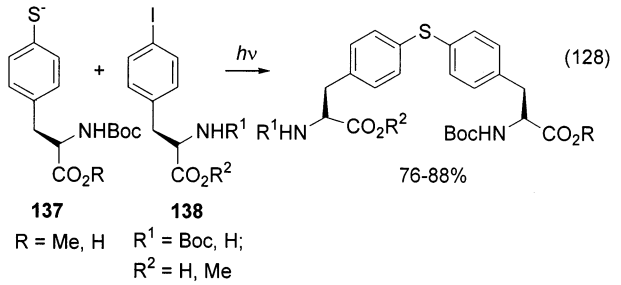
134 **135** **136**

Scheme 53



Substitution of iodoanilines is not successful with PhS^- ions (Table 50). Disubstitution including the latter anion is possible by an $S_NAr-S_{RN}1$ combination in high yield (92%) (Scheme 53).[525]

The Boc-protected *p*-mercaptophenylalanine ester ion **137** (R = Me) and the free acid (R = H) couple with a variety of iodinated aryl amino acid derivatives. For instance, the reaction with iodophenylalanines **138**, either the acid or the amine functionality unprotected, gives the yields indicated in eq 128.[558]



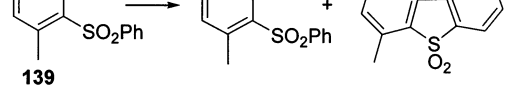
(128)

Racemization observed in the reaction of the glycine derivatives can be avoided by using the unprotected amino acid.[558]

Oligomeric poly(*p*-phenylene sulfide) (PPS) can be synthesized via the $S_{RN}1$ mechanism from *p*-$BrC_6H_4S^-$ ions in DMSO.[559] The polymerization of *p*-$BrC_6H_4S^-$ ions to PPS catalyzed by Cu(I) has been suggested to occur by an $S_{RN}1$ type mechanism.[560a,b] However, the Cu(I)-catalyzed nucleophilic substitution of PhI by PhS^- ions has been shown not to involve ET steps.[560c]

1,4-Dimethyl-2,3-bis(phenylsulfonyl)- and 1,2-bis-(phenylsulfonyl)-3,4,5,6-tetramethylbenzene react with ArS^- ions under irradiation to afford products from substitution of the radical **139** intermediate, together with the corresponding dibenzothiophenes (Scheme 54).[561,562] An ET path is proposed to account for the

Scheme 54



cyclized product, and a competition between the S_NAr and $S_{RN}1$ mechanisms is proposed for the formation of the substitution compounds. Under electrochemical initiation the substitution and cyclic compounds obtained in the presence of PhS^- ions are formed by ET (56 and 41% yields, respectively, for the 1,4-dimethyl derivative).[563, 564]

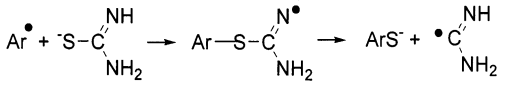
Thiocarboxylate Ions. The reaction of ArN_2F_4B with thioacetate or thiobenzoate ions[565,566] in DMSO leads to the corresponding aryl thioesters (eq 129), which

$$Ar\text{-}N_2^+BF_4^- + RCOS^- \longrightarrow Ar\text{-}SCOR \qquad (129)$$

can either be isolated or react further, providing a convenient one-pot access to other aromatic sulfur derivatives.

The yields of S-aryl thioacetate range from 55 to 60% in the reaction with the following ArN_2F_4B: Ar = Ph, *p*-MeC_6H_4, *o*-MeC_6H_4, *p*-$MeOC_6H_4$, 1-naphthyl, and 2-naphthyl. Lower yields are obtained for Ar = *p*-$O_2NC_6H_4$ (47%) and *p*-IC_6H_4 (41%), and some disubstitution is observed with the latter.[567]

On the other hand, the anion of thiourea reacts with *p*-NCC_6H_4Cl and 2-, 3-, and 4-chloropyridines under electrochemical conditions to afford ArS^-, ArSAr, and ArSSAr ascribed to the fragmentation of the radical anion intermediates (eq 130).[568]



(130)

The rate constants for the coupling reactions of the radicals with the anion have been determined to be 4.2×10^9, 3.3×10^9, 0.98×10^9, and 0.27×10^9 M^{-1} s^{-1} respectively.[568]

Other Sulfur Ions. Oligomeric PPS has been prepared by the reaction of *p*-$C_6H_4Cl_2$ with Na_2S.[569a,b] The reaction is proposed to take place by the ionic S_NAr process even though the $S_{RN}1$ mechanism cannot be totally ruled out.[569c]

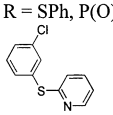
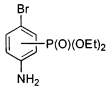
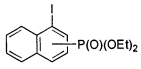
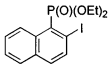
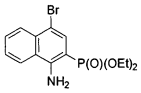
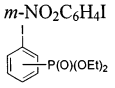
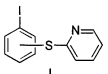
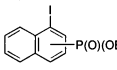
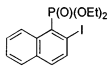
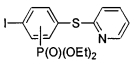
The preparation of the anion S_4^{2-}, generated from a sacrificial S cathode, and its reaction with 3-bromoquinoline in the presence of a redox mediator have led to a mixture of products resulting from $S_{RN}1$ reactions involving three different nucleophiles: S_4^{2-} together with 2-quinolyl-SS^- and 2-quinolyl-S^-, which are formed by fragmentation of the radical anion intermediates.[570]

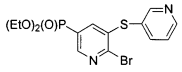
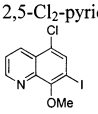
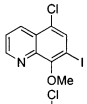
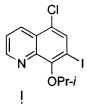
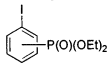
2. Reactions with Selenium and Tellurium Nucleophiles

Selenide and Telluride Ions. Na_2Se can be formed by reaction of Se and Na metals in liquid ammonia and reacts under irradiation with PhI to give $(PhSe)_2$ (78%), after oxidation of the $PhSe^-$ ions formed, together with Ph_2Se (12%).[571] On the other hand, if Na metal is added after irradiation, the $PhSe^-$ ion is the only product formed, isolated as $(PhSe)_2$ (92%); it can also be trapped with MeI as PhSeMe (67%) or further react under irradiation with ArX to afford the ArSePh. For example, 1-naphthyl phenyl selenide (98%) is formed by reaction with 1-iodonaphthalene.[571] With the same procedure the irradiated reaction of Se^{2-} with *o*-MeC_6H_4I followed by Na metal and MeI addition affords *o*-MeC_6H_4SeMe (87%).[571]

Alkali metals react with elemental Se or Te in dipolar aprotic solvents (DMF, NMP, and HMPA) to form, depending on their relative concentration, M_2Z_2 or M_2Z (Z = Se or Te).[572,573a,b] The anions thus formed

Table 51. Photostimulated Reaction with ArS^- Ions in Liquid Ammonia

Substrate	Thiolate Ion	Product (%)	Ref.
PhN_2BF_4	*p*-$MeC_6H_4S^-$	82[a]	554
p-$NCCH_2C_6H_4Br$		90[a]	487
p-RC_6H_4I, R = H, OMe	*p*-$MeOC_6H_4S^-$	71-73	147
2-Cl-quinoline	*p*-$ClC_6H_4S^-$	80[b]	553
PhN_2BF_4	2,4,6-$Me_3C_6H_2S^-$	67[a]	554
p-$MeOC_6H_4I$	2-naphthyl-S^-	65[d]	183
1-I-naphthalene		95	183
o-ClC_6H_4I		81[c]	544
PhI		68	545
o-, *p*-$NO_2C_6H_4Cl$		25, 12	545
o-RC_6H_4I			
R = NH_2, $P(O)(OEt)_2$		74, 81	525
m-RC_6H_4I			
R = NH_2, $P(O)(OEt)_2$, NO_2		56, 50, 44	525, 545
p-RC_6H_4I			
R = SPh, $P(O)(OEt)_2$		92, 60	525
		95	234
		60-56	525
		2- (75) 4- (68)	525
		65	525
		85	525
2-Br-5-$(EtO)_2P(O)$-pyridine		65	525
3-Br-6-NH_2-pyridine		60	525
2-NH_2-3-Br-5-$(EtO)_2P(O)$-pyridine		98	525
o-, *m*-, *p*-ClC_6H_4I		(70, 83, 87)[a, c]	234, 533
2,5-Cl_2-pyridine		40[b,d]	93
PhI		47	545
o-$NO_2C_6H_4Cl$		32	545
m-$NO_2C_6H_4I$		32	545
		50-60	525
		68-90	525
		2- (75) 4- (65)	525
		73	525
		54-78	525

Substrate	Thiolate Ion	Product (%)	Ref.
		62-96[e]	180
3-Br-5-$(EtO)_2P(O)$-pyridine		77	180
		60	180
m-, *p*-ClC_6H_4I		100[c]	533
p-$Cl_2C_6H_4$		52[b, d]	93
2,5-Cl_2-pyridine		45[b, d]	93
		90[c]	533
		45-98[e]	180
		100	533
		88[c]	533
		2- (49) 4- (39)	525 525
		5- (80) 3- (92)[f]	180 180
		75[c]	533
2- Cl-pyridine		21	180
		5- (53) 3- (98)[f]	180 180
		100[c]	533
		80[c]	533
		3- (78) 5- (95)[f]	180 180
		77[c]	533
		5- (95) 3- (96)[f]	180 180
		100[c]	533

[a] In DMSO. [b] Electrochemical induction. [c] Monosubstitution product on iodine. [d] Disubstituted product. [e] Yields of the 6-, 5-, and 3-substituted compounds. The 4-CF_3 derivative gives low yield of substitution. [f] The 4-CF_3 derivative gives low yield of substitution.

undergo the thermal substitution of ArX (Table 52). For example, in the reaction of Na_2Se with *p*-$C_6H_4Br_2$ poly(*p*-phenylselenide) (PPSe) is formed in 65−80% yield;[572b,573b] 5% of PPSe is obtained with *p*-$C_6H_4Cl_2$, whereas *p*-$C_6H_4I_2$ reacts with Na_2Te to afford 70−75% of PPTe in DMF.[573b]

p-$C_6H_4Br_2$ and 9,10-dibromoanthracene react with Na_2Se_2 to give polyarene diselenide in 85 and 69% yields, respectively. *o*-PPSe can be prepared from *o*-$C_6H_4Br_2$ and Na_2Se_2 in DMF (26%).[573c]

M_2Te_2 reacts with 9-bromoanthracene and 2-chloronaphthalene with 40 and 20% yields of Ar_2Te_2, respectively.[572a] Lower yields are obtained with 1-chloronaphthalene, PhI, and PhBr.[572a] Di-2-naphthyl ditelluride is also formed by reaction of the anion with 2-chloro- or 2-bromonaphthalene in the presence of sodium naphthalenide as initiator (22%).[573c]

Na_2Te can also be formed from Te metal with Rongalite (NaO_2SCH_2OH) in dilute aqueous alkali or from Te and NaH in dry DMF.[574,575] Better yields are obtained when the ion is formed by the Rongalite method (Table 52). However, changing the solvent from DMF to NMP remarkably improves the yields of the NaH method.[575] Under the latter experimental

Table 52. Reactions of Z^{2-} (Z = Se and Te) and Related Nucleophiles

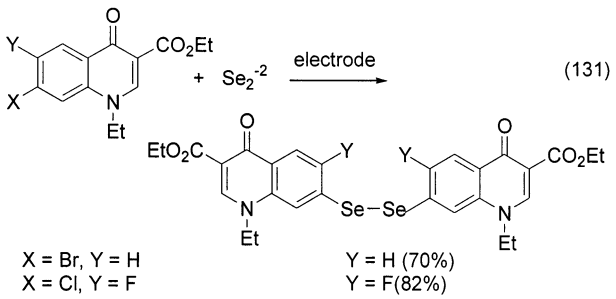
Substrate	Nu^-	Products (%)	Ref.
2-Br-naphthalene	$Se^=$	ArSeAr (30)[a]	572a
9,10-Br_2-anthracene		-($C_{14}H_8Se)_n$- (38)[b]	573c
p-$PhCOC_6H_4Br$	$Se_2^=$	ArSeAr (20)[c]	577
		$ArSe_2Ar$ (40)[c]	
9-Br-anthracene		$ArSe_2Ar$ (54)[c]	576
2-Cl-quinoline		$ArSe_2Ar$ (79)[c] (70)[c]	578, 576
9-Br-anthracene		$ArSe_nAr$ n = 1(22)[b]	573c
		n = 2(28)[b]	
PhI	$Te^=$	PhTePh (71-77)[d]	574, 575b
m-, *p*- MeC_6H_4I		ArTeAr (84, 81)[b]	574
p- $MeOC_6H_4I$		ArTeAr (74)[b]	574
2,4-$Me_2C_6H_3I$		94[b]	574
2,4,6- $Me_3C_6H_2I$		77[b]	574
1-I-naphthalene		ArTeAr (35)[e], 59[b]	571, 575a
2-X-naphthalene, X = Cl, Br		ArTeAr (27-30)[a]	572a, 573a
X = I		61[b]	575a
3-I-fluorene		ArTeAr (48)[b]	575a
1-I-pyrene		ArTeAr (60)[b]	575a
2-Cl-quinoline	$Te_2^=$	$ArTe_2Ar$ (50)[c]	576, 552

[a] HMPA, temperature. [b] DMF, temperature. [c] Electrochemical induction in MeCN. [d] DMF or NMP and temperature. [e] Liquid ammonia, irradiation.

conditions and with an ArI/Te ratio within 1.1−1.5, the Ar_2Te is obtained in good yields [PhI (77%), *o*- (55%) and *p*- (42%) MeC_6H_4I, *p*-$MeOC_6H_4I$ (58%), 1-iodo (76%) and 2-iodo (61%) naphthalenes, 1-iodo-2-methylnaphthalene (53%), and C_6F_5I (56%)].[575b] When the ratio ArI/Te is 0.45−0.60, NaTeAr are obtained. Oxidation leads to satisfactory yields of Ar_2Te_2; treatment with an excess of an RX affords the ArTeR in 52−67% yields.[575b]

Another approach to Z_2^{2-} (Z = Se or Te) is the electrogeneration from the metals using sacrificial Z electrodes in MeCN.[576] Under these conditions, the synthesis of ArZZAr is possible by performing the electrolysis in the presence of ArX (Table 52).[576] When the reaction of *p*-$C_6H_5COC_6H_4Br$ is performed with an Se or Te electrode, besides the diaryldichalcogenide (Ar_2Se_2, 40%; Ar_2Te_2, 14%), the Ar_2Z (Z = Se or Te) is also formed due to the generation of the anion *p*-$PhCOC_6H_4Se^-$ by cathodic reduction of Ar_2Z_2 (Table 52).[577]

The use of an undivided cell equipped with a Mg sacrificial anode, with addition of F^- ions to avoid the precipitation of the Z_2Mg, is an improvement of this technique.[578] Under these conditions, 2-chloroquinoline reacts with Se_2^{2-} ions to give 79% yield of substitution. With this methodology the following diselenides can be prepared (eq 131). The yields with Te_2^{-2} are lower.[578]



(131)

The cathodic reduction of the diseleno intermediate followed by addition of MeI leads to the 7-methylselenoquinolone derivatives.[579]

Table 53. Reaction of $PhSe^-$ and $PhTe^-$ Ions

Substrate	PhZ^-	Product (%)	Ref.
PhI	$PhSe^-$	73,[a] 45[b]	215, 109
o-, *m*-, *p*-NCC_6H_4X, X = Cl, Br		36-73[c,d]	581, 582, *e*, *f*, 552
p-PhC_6H_4X, X = Cl, Br		52,[a] 65[d]	*g*, 215, 256b
p-$PhCOC_6H_4Br$		62-86[d]	256a,581, *h*
4,4′-$C_6H_4C_6H_4Br_2$		46[d,i]	256b
p-BrC_6H_4I		70[a,i]	215
1-X-naphthalene, X = Cl; Br		73[a], 88[j], 72[b]	*g*; 215, 216, 109
9-Br-anthracene		74[d]	256b
9-Br-phenanthrene		72[a]	*g*, 215
3-I-fluorene		53[d]	256b
2-Br-pyridine		72,[a] 72[b]	161, 109
2-Cl-quinoline		98,[a] 70,[j] 66[b]	*k*, 216, 109
PhI	$PhTe^-$	90[a]	*l*, 215
p-$MeOC_6H_4I$		73[a,c]	215
o-, *m*-, *p*-NCC_6H_4X, X = Cl, Br		20-53[c,d]	581, 582, *f*
p-$PhCOC_6H_4Br$		45-75[c,d]	256a, 581
4,4′-$C_6H_4C_6H_4Br_2$		16[d,i]	256b
p-BrC_6H_4I		40[a,c,i]	215
1-X-naphthalene, X = Cl, Br		41, 53,[a,c] 75[b]	*l*, 215, 109
9-Br-anthracene		68[c,d]	256b
2-Cl-quinoline		43,[a,c] 50[b]	161, 109

[a] Liquid ammonia under irradiation. [b] Initiation by SmI_2 in DMF/THF. [c] Some scrambled products were also formed. [d] Electrochemical induction in MeCN. [e] Degrand, C. *J. Org. Chem.* **1987**, *52*, 1421−1424. [f] Degrand, C. *J. Chem. Soc., Chem. Commun.* **1986**, 1113−1114. [g] Pierini, A. B.; Rossi, R. A. *J. Organomet. Chem.* **1978**, *144*, C12−C14. [h] Prest, R.; Degrand, C. *J. Chem. Soc., Perkin Trans. 2* **1989**, 607−611. [i] Disubstitution product. [j] Under irradiation in MeCN. [k] Peñéñory, A. B.; Pierini, A. B.; Rossi, R. A. *J. Org. Chem.* **1984**, *49*, 3834−3835. [l] Pierini, A. B.; Rossi, R. A. *J. Organomet. Chem.* **1979**, *168*, 163−165.

A tandem $S_{RN}1/S_Hi$ sequence has been recently proposed for the preparation of dihydrotellurophenes (62%) by reaction of 1-(2-iodophenyl)-1-methyloxirane with *n*-$BuTe^-$ ions generated by reduction of $(n\text{-BuTe})_2$.[580] A similar reaction of 1-(benzylseleno)-2-phenyl-2-propanol affords the selenophene derivative (74%).[580]

$PhSe^-$ and $PhTe^-$ Ions. These ions substitute different ArX in varying yields under irradiation, in liquid ammonia. Straightforward and scrambled products are obtained with both Nu^- depending on the substrate employed (Table 53). Disubstitution of *p*-BrC_6H_5I can also be achieved.[215]

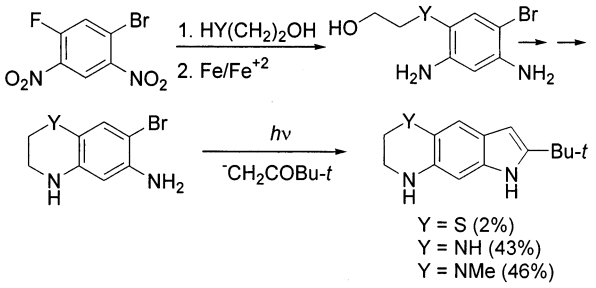
Bromobenzophenones, bromobenzonitriles, and dibromides, among others, can be substituted in MeCN by the mediated cathodic reduction of the substrates in the presence of $PhTe^-$ or $PhSe^-$ ions, prepared by electrochemical reduction of the corresponding diphenyl dichalcogenide.[256,581,582] The reaction is also successful with chlorobenzonitriles.[581,582]

E. Other Organometallic Nucleophiles

Few examples are known of the substitution of aryl halides by iron(I) porphyrins under electrochemical induction. On the other hand, the electrochemically induced reaction of metal carbonyl anions forms Cp-(CO_3)M-σ-Ar (M = W, Mo; Ar = Ph, *p*-C_6H_4 NO_2) in ∼30% yields.[583]

The compounds $PhFe(CO)_2Cp$ (30%) and *p*-$CH_3C_6H_4$-$IFe(CO)_2Cp$ (43%) were obtained by reaction of PhI and *p*-$CH_3C_6H_4I$ with the anion $[Fe(CO)_2Cp]$, after preparative electrolysis in the presence of *o*-dicy-

Scheme 55

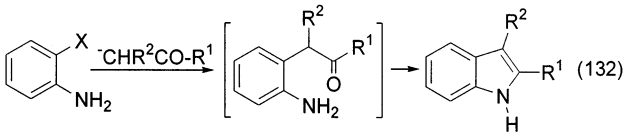


anobenzene as redox mediator. This nucleophile reacts with *p*-NCC_6H_4Br to afford, under electrochemical induction, the substitution product in 45% yield.[584]

F. Ring Closure Reactions

1. $S_{RN}1$ Substitution Followed by a Ring Closure Reaction with an Ortho Substituent

One of the most widely studied approaches to ring closure reactions is the $S_{RN}1$ substitution of aromatic compounds that have an appropriate substituent ortho to the leaving group. The synthesis of substituted indoles by the photostimulated reaction of *o*-iodo and *o*-bromoanilines with carbanions from ketones is an important example of substitution followed by spontaneous ring closure in the reaction media (eq 132).[179,453,585] When the reaction is performed with the enolate ion of an aldehyde, 3-substituted indoles are obtained.[179] These reactions can also be initiated electrochemically[586] or by Fe^{2+} ions (Table 54).

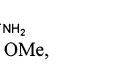
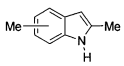
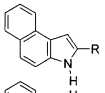
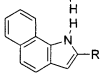
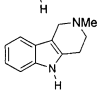
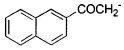
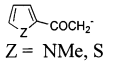
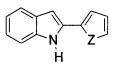
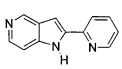


Indoles bearing a −CHO or −COMe functionality at the 2-position are synthesized after hydrolysis of the corresponding dimethylacetals obtained from the reaction of *o*-iodoaniline with $^{-}CH_2COCH(OMe)_2$ or $^{-}CH_2COC(OMe)_2Me$ ions, at 45 and 55%, respectively.[179] Benzo[*e*]- and benzo[*g*]indoles can be obtained through the reaction of 1-bromo-2-amino or 1-amino-2-bromonaphthalene, respectively, with the enolate ion of pinacolone.[530b] The reaction of *vic* aminohalo pyridines leads to azaindoles (Table 54). Aromatic ketones do not react in liquid ammonia, but they cyclize to indoles in DMSO under light or Fe^{2+} initiation (Table 54).[587]

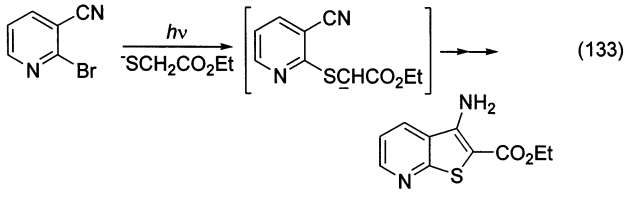
2-*tert*-Butylindoles bearing substituents in the phenyl ring and tricyclic indoles can be synthesized by a combination of S_NAr, reduction of the nitro group, and $S_{RN}1$ reactions. An example is presented in Scheme 55.[530a]

Thienopyridine rings can be obtained by reaction of $EtO_2CCH_2S^{-}$ ions with 2-bromo-3-cyanopyridine and 3-bromo-4-cyanopyridine in 90 and 98% yields, respectively (eq 133).[224]

Table 54. Synthesis of Indoles[a]

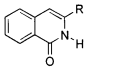
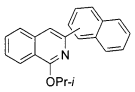
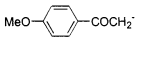
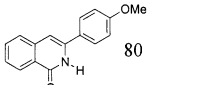
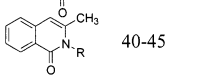
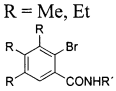
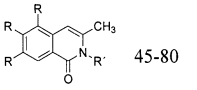
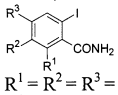
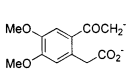
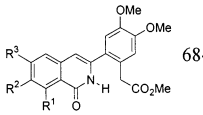
Substrate	Nucleophile	Indole (%)	Ref.
o-$IC_6H_4NH_2$	$^{-}CH_2CHO$	(75, 93[b]) Indole	585, 179, 586
	$^{-}CHRCHO$ R = Me, Et, *i*-Bu	(26-49) 3-R-indoles	179
o-$ClC_6H_4NH_2$	$^{-}CH_2COMe$	(51)[c] 2-Me-indole	101
R = Ph, OMe, CO_2H		42-89 	453
o-$BrC_6H_4NH_2$	$^{-}CH_2COR$ R = Me, *i*-Pr, *t*-Bu	(84-94) 2-R-indoles	453
 3, 4, and 5	$^{-}CH_2COMe$	80-88 	453
	$^{-}CH_2COR$ R = *t*-Bu, $CH(OMe)_2$	67, 52 	530b
	$^{-}CH_2COR$ R = *t*-Bu, $CH(OMe)_2$	82, 65 	530b
o-$IC_6H_4NH_2$	$^{-}CH_2COR$ R = Me, *i*-Pr, *t*-Bu	(100-53) 2-R-indoles (75-87)[b]	585,179 586
	$^{-}CH_2COMe$	(63)[d] 2-Me-indole	587
		40 	585
		22 	179
	$^{-}CH_2COPh$	88,[d] 83[e] 2-Ph-indole	587
		(73)[d] 2-naphthyl-indole	587
	 Z = NMe, S	(93, 82)[e] 	587
	$^{-}CHRCHO$ R = H, Me	62, 59 	*f*
	$^{-}CH_2COR$ R = Me, *i*-Pr, *t*-Bu	48, 61,100 	453, *g*, *f*
		52 	*f*
 R = H, Me, COBu-*t*	$^{-}CH_2COR^1$ (R^1 = Me, *t*-Bu)	70-95 	454
		21 	*f*

[a] Photostimulated reactions. Solvent liquid ammonia unless otherwise indicated. [b] Electrochemical initiation, in liquid ammonia. [c] In liquid ammonia under Fe^{2+} initiation. [d] Under photostimulation in DMSO. [e] Under Fe^{2+} catalysis in DMSO. [f] Fontan, R.; Galvez, C.; Viladoms, P. *Heterocycles* **1981**, *16*, 1473−1474. [g] Beugelmans, R.; Boudet, B.; Quintero, L. *Tetrahedron Lett.* **1980**, *21*, 1943−1944.



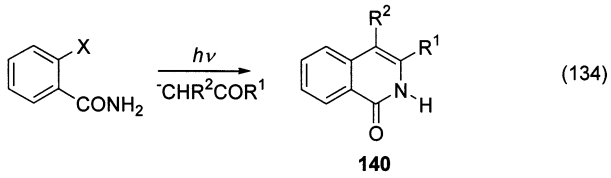
Isocarbostyrils **140** are accessible by the reaction of *o*-bromo- or *o*-iodobenzamides with carbanions (Table 55). The yields in the cyclization are better

Table 55. Photostimulated Reactions of *o*-Halobenzamides with Carbanions in Liquid Ammonia

Substrate	Nucleophile	Product (%)	Ref.
	$^-CH_2COR$		*a*
	R = Me, *i*-Pr, *t*-Bu	90	
	R= $^-CHMeCOEt$	70	
		60-70 	511
	1. *hν*,[b] 2. *i*-PrBr		
		 80	*a*
	$^-CH_2COMe$	 40-45	*a*
X = Br, I			
R = Me, Et			
	$^-CH_2COMe$	 45-80	455
R = H, OMe			
R′= H, Me			
		 68-85[d]	*c*
$R^1 = R^2 = R^3 = H$			
R^1 = H,			
$R^2 = R^3$ = OMe			
$R^1 = R^2$ = OMe,			
R^3 = H			

[a] Beugelmans, R.; Bois-Choussy, M. *Synthesis* **1981**, 730−731. [b] DMSO. [c] Beugelmans, R.; Bois-Choussy, M. *Tetrahedron* **1992**, *48*, 8285−8294. [d] After treatment with BF_3, MeOH, reflux for 1 h.

when the benzamides are not N-methylated (eq 134).[455]

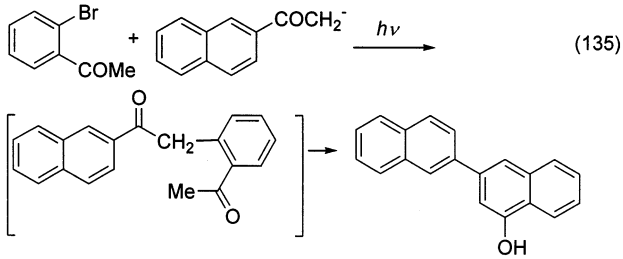


(134)

140

The $S_{RN}1$ mechanism can be a route to isoquinoline rings and derivatives by reaction of *o*-iodobenzylamines with ketone enolate ions under irradiation (Table 56).

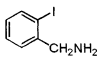
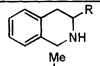
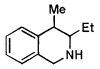
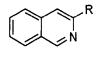
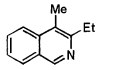
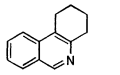
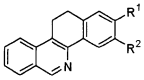
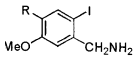
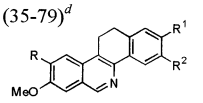
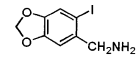
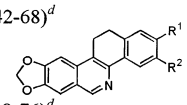
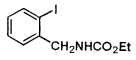
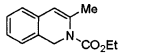
The 2,2′-binaphthyl can be obtained by reaction of the enolate ion of methyl 2-naphthyl ketone with *o*-$C_6H_5COC_6H_4Br$, under irradiation in liquid ammonia (72%) or in DMSO (82%) (eq 135).[444] Unsymmetrically substituted binaphthyls can also be synthesized according to this procedure.[444]



(135)

Naphthylquinolines and naphthylisoquinolines can be achieved by reaction of 3-acetyl-2-chloro- and

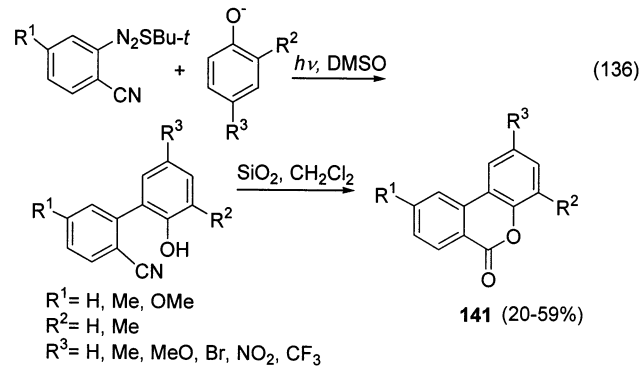
Table 56. Photostimulated Reactions of *o*-Halobenzylamines with Carbanions in Liquid Ammonia

Substrate	Nucleophile	Product (%)	Ref.
	$^-CH_2COR$		
	R = Me, *i*-Pr	(90, 60)[a] 	*b*
	$^-CHMeCOEt$	(90-100)[a] 	*b*
	$^-CH_2COR$		
	R = Me, *i*-Pr,	(38-100)[c] 	*b*
	t-Bu, $^-CHMeCOEt$		
	$^-CHMeCOEt$	77[c] 	*b*
		43[c] 	*b*
			
	R = H, OMe, OPr-*i*	(35-79)[d]	447
			
R = OMe, OPr-*i*	R = H, OMe, OPr-*i*	(42-68)[d]	447
			
	R = H, OMe, OPr-*i*	(38-76)[d]	447
	$^-CH_2COMe$	41 	*b*

[a] After treatment of the reaction product with $NaBH_4$. [b] Beugelmans, R.; Chastanet, J.; Roussi, G. *Tetrahedron Lett.* **1982**, *23*, 2313−2314. Beugelmans, R.; Chastanet, J.; Roussi, G. *Tetrahedron* **1984**, *40*, 311−314. [c] After treatment of the reaction product with Pd/C. [d] After air oxidation.

4-acetyl-3-chloropyridines with the anions from methyl 1- or 2-naphthyl ketone.[511] Another approach involves reaction of *o*-$BrC_6H_4CONH_2$ with the same nucleophiles.[511]

The reaction of ArO^- ions with ortho-substituted ArN_2SBu-*t* is an important route to the benzopyranone family. The dibenzo[*b*,*d*]pyran-6-one skeleton of benzocumarins **141** and related compounds can be synthesized through a rather straightforward two-step route by 2-cyanoarylation of a phenol in DMSO, followed by lactonization under very mild conditions (eq 136). There is no need to isolate the intermediate hydroxybiaryl.[513]

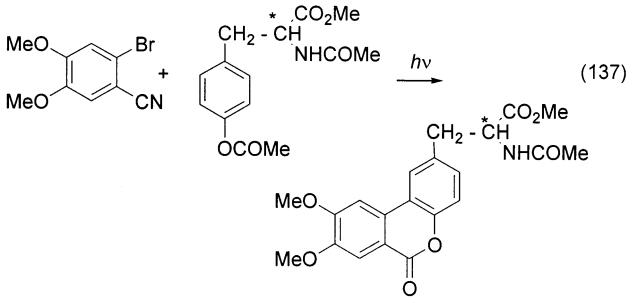


(136)

141 (20-59%)

Another approach to the same type of compounds is the ortho-arylation of substituted phenoxide ions by *o*-NCC_6H_4Br followed by SiO_2-catalyzed lacton-

ization. The phenoxide ions of the amino acids (*S*)-tyrosine, protected as *N*,*O*-diacetyl methyl ester, do not racemize under the standard $S_{RN}1$ and can be used to obtain the optically active dibenzo[*b*,*d*]pyran-6-one (52% yield) (eq 137).[514] Racemic dibenzopyra-

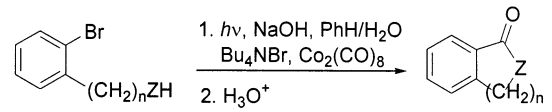


(137)

nones are obtained by the reaction of the anion from the *N*-acetyl methyl ester of (*R*)-hydroxyphenylglycine with *o*-NCC_6H_4Br and 2-cyano-4,5-dimethoxybromobenzene (65 and 79%, respectively).[514]

The reaction of 2-naphthoxide ion with *o*-NCC_6H_4Br is a route to the synthesis of benzonaphthopyranone.[514]

An important approach to five- and six-membered ring benzolactams and benzolactones is the carbonylation under PTC catalysis conditions of ArX bearing $-NH_2$ or $-OH$ groups on a side chain ortho to the halogen (eq 138).[485]

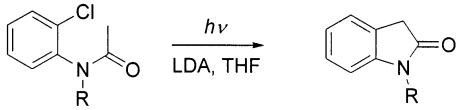


(138)

n = 1, Z = NH	60%
n = 1, X = NCH_2Ph	78%
n = 1, Z = O	95%
n = 2, Z = NH	72%
n = 2, Z = O	95%
n = 2 (1-Et substituted), Z = O	92%

2. Intramolecular $S_{RN}1$ Reactions

Cyclization of *N*-alkyl-*N*-acyl-*o*-haloanilines to afford *N*-alkyl-1,3-dihydroxy-indol-2-one can be achieved in the presence of LDA in THF or KNH_2 in liquid ammonia (eq 139).[198,588,589]



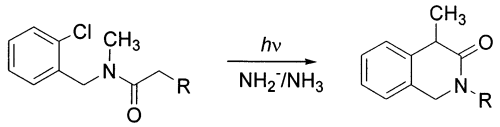
(139)

R = Me (81%)
R = $PhCH_2$ (32%)

N-Methyl α,β-unsaturated anilides undergo intramolecular arylation exclusively at the α-position to afford 3-alkylideneoxindoles. The best results are obtained with KNH_2/NH_3 under photoinitiation (see eq 20).[198]

Photocyclization of the carbanions from *N*-acyl-*N*-methyl-*o*-chlorobenzylamines formed by reaction with KNH_2 in liquid ammonia gives 1,4-dihydro-2*H*-isoquinolin-3-ones in fair to good yields (eq 140).[198]

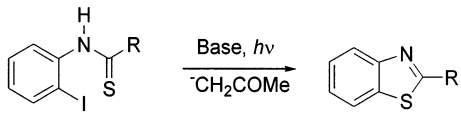
Preparation of 2-methyl- and 2-phenyl-1,3-benzothiazoles is possible in excellent yields (100%) by



(140)

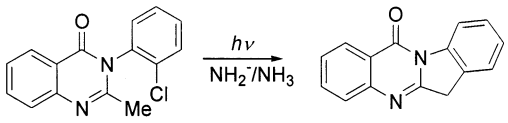
R = H 62%
R = Me 60%
R = Et 54%

intramolecular $S_{RN}1$ reaction from *o*-iodothiobenzanilide and *o*-iodothioacetanilide under entrainment conditions with $^-CH_2COCH_3$ ions in DMSO (eq 141).[590]



(141)

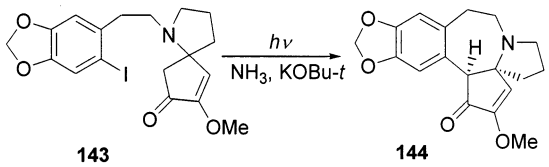
The carbanion derived from 3-(*o*-chlorophenyl)-2-methyl-3*H*-quinazolin-4-one cyclizes in liquid ammonia under irradiation to yield 6*H*-indolo[2,1-*b*]-quinazolin-12-one (**142**) (60%) (eq 142).[591]



(142)

142

The cyclization of iodoketone **143** leads to **144** under metal or light stimulation (45 and 94% yields, respectively) (eq 143).[592]

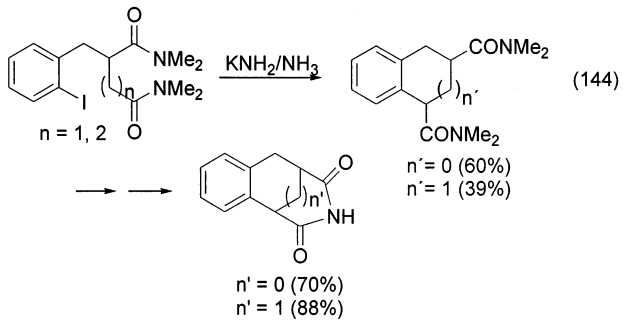


(143)

143 **144**

Studies of the system were extended to other analogues to determine the ring size preferences in the cyclizations, the effects of β-hydrogens on the carbonyl group, and the regioselectivity with ketones that can give two enolate ions.[80,173,592]

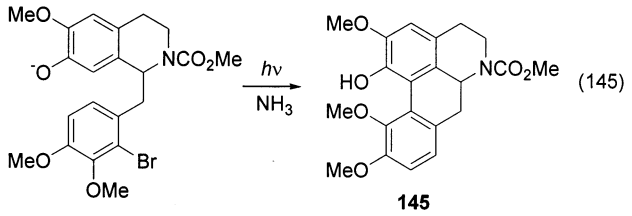
The synthesis of tricyclic compounds can be accomplished by initial intramolecular arylation of enolates derived from diamides (eq 144). Evidence for competing aryne and $S_{RN}1$ pathways was provided.[593]



(144)

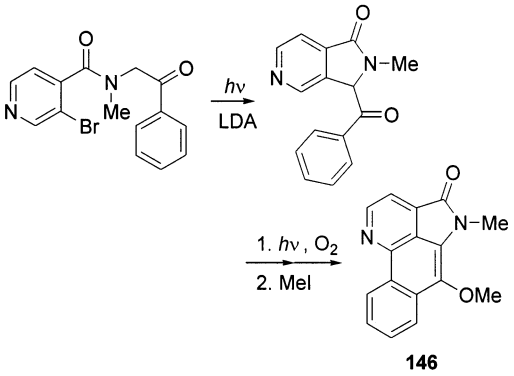
Dibenz[*d*,*f*]azonine alkaloids such as bractazonime can be synthesized through the $S_{RN}1$ mechanism based on the bidentate behavior of phenoxide ions.[594]

A similar approach has been used for the synthesis of the aporphine skeleton **145**, although in low yield (19%), as shown in eq 145.[595]



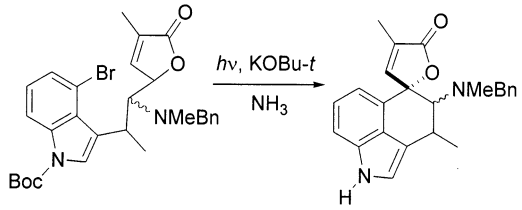
(145)

The key step in the synthesis of the azaphenanthrene alkaloid eupoulauramine **146** (56% yield) is an intramolecular $S_{RN}1$ reaction, followed by in situ stilbene photocyclization and further methylation (eq 146).[596a] A similar strategy is followed in the synthesis of (±)tortuosamine (54%).[596b]



(146)

The $S_{RN}1$ mechanism has proved to be an excellent alternative to achieve the following intramolecular cyclization reaction in 51% yield (eq 147), which constitutes one of the steps in the synthesis of an Ergot type alkaloid.[597]



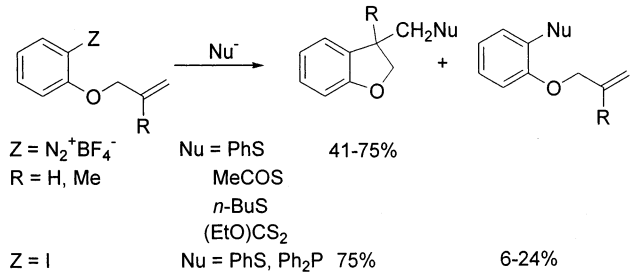
(147)

3. Miscellaneous Ring Closure Reactions

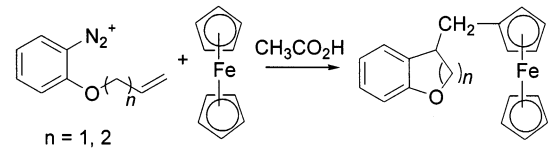
ArX and ArN_2^+ salts ortho-substituted by a radical probe offer the possibility to obtain cyclic compounds by ET reaction with Nu^-. In these systems compounds from straightforward substitution may also be formed. Some examples of this approach are the reaction of the *o*-(3-propenyloxy)phenyl probe with PhS^-, Ph_2P^- (liquid ammonia under irradiation),[148] PhS^-, *n*-BuS^-, $(EtO)CS_2^-$,[149b] and $MeCOS^-$ ions[565] in DMSO (Scheme 56).

Lower yields have been reported by reaction of the iodide probe with *n*-$BuTe^-$ ions.[580] Good yields of cyclic substituted compounds are obtained by reaction of the *o*-(3-propenyloxy)- and *o*-(3-butenyloxy)benzene diazonium salts (tetrafluoroborates or hexafluorophosphates) with ferrocene (65 and 49% yields,

Scheme 56

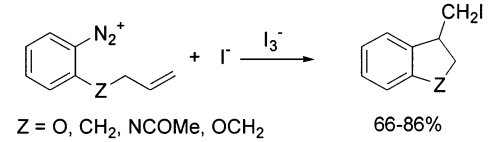


respectively) or mixtures of ferrocene and ferrocenium ions (eq 148).[598]



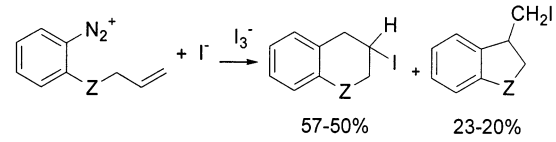
(148)

The iododediazoniation is proposed to occur by the $S_{RN}1$ process (eq 149).[599a]



(149)

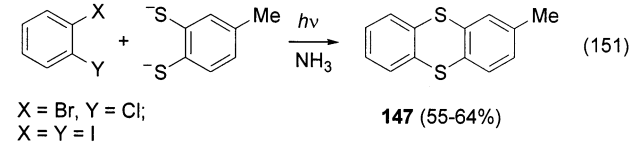
Cyclization or direct iodination of the aromatic radical can be formed depending on the Z moiety. For example the latter reaction prevails for Z = $O(CH_2)_2$, CO_2. When Z = $SO_2NCH_2CH{=}CH_2$ or SO_2NH the following products are formed (eq 150):[599a]



(150)

When the dediazoniation reaction of *o*-(3-butenyloxy)benzene diazonium salts is performed in the presence of *n*-BuS^- or PhS^- ions in DMSO, the 3-*n*-butyl (63%) and 3-phenyl (60%) sulfanylmethyl-2,3-dihydrobenzofurans are obtained, respectively.[599b]

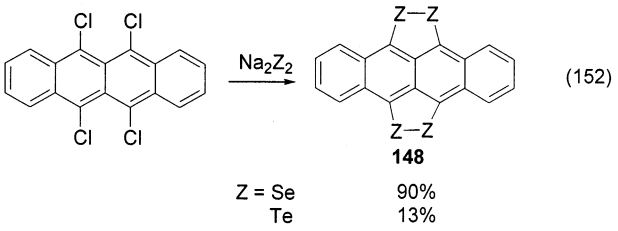
Another possibility to achieve cyclization is through the reaction of *o*-$C_6H_4X_2$ with dinucleophiles. Some examples are the reactions of *o*-$C_6H_4I_2$ and *o*-ClC_6H_4-Br with 3,4-toluendithiolate ion to afford 2-methylthianthrene **147** (eq 151).[600]



(151)

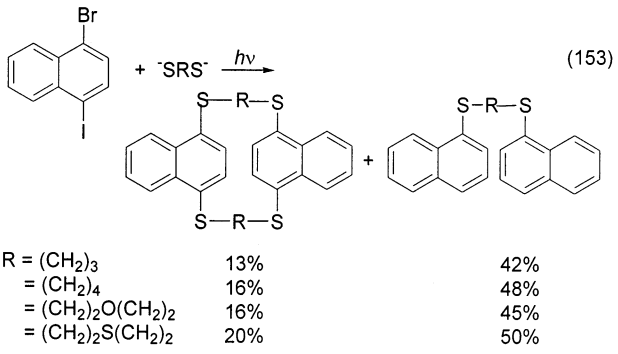
Other examples are the reaction of 1,8-dichloronaphthalene with S^{2-} and Se_2^{2-} (HMPA, 46–69%)[601] and of 1,2-diiodoindane with Te^{2-} (DMF, 35%).[575a] When the reaction of the latter anions is performed with aromatic compounds, tetra-halosubstituted in adequate positions, compounds with two diheterocyclic rings **148** can be formed (eq 152). No

mechanistic evidences have been reported for these reactions.[602]



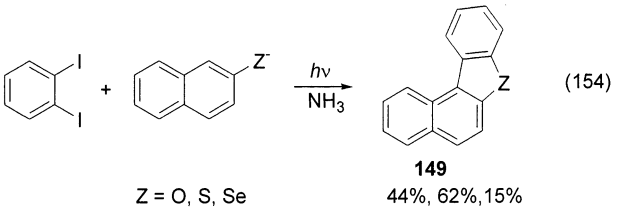
(152)

The formation of 18-, 20-, or 22-membered heteromacrocycles can be performed by four $S_{RN}1$ reactions of dithiolate ions with 1-iodo-4-bromonaphthalene (eq 153).[603]



(153)

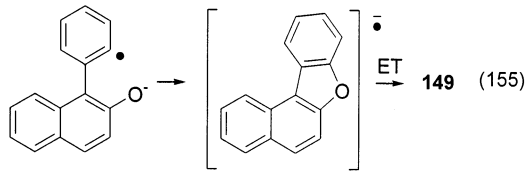
Furo- and thiophene rings **149** have been successfully obtained by reaction of *o*-dihalobenzenes with 2-naphthoxide and 2-naphthylthiolate ions, respectively (eq 154). In the reaction with 2-naphthoxide



(154)

ion the best yield of cyclization, accompanied by traces of monosubstitution, is achieved with *o*-$C_6H_4I_2$. Low yields of cyclization are obtained with the seleno analogue nucleophiles.[544,604]

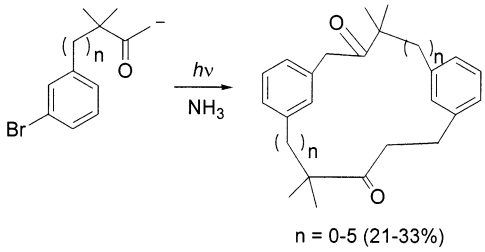
It is remarkable that phenoxy anions react only at C in *intermolecular* reactions, but due to proximity effects, an *intramolecular C−O* bond formation is possible to finally afford **149** (Z = O) (eq 155). This



(155)

is the only example known of a reaction between an aromatic radical with an oxyanion center.[544]

The preparation of *m*- and *p*-cyclophanes is possible through the $S_{RN}1$ reaction of *m*- and *p*-$C_6H_4Br_2$ with appropriate dianions, although in low yields.[605] Another approach to these compounds is a combination of inter- and intramolecular substitutions with substrates bearing the leaving group and nucleophilic center in the same molecule (eq 156).[606]



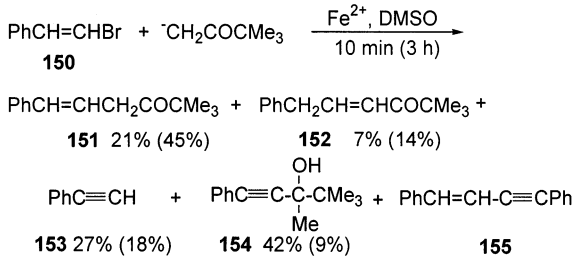
(156)

IX. Other Systems

A. Vinyl Halides

Many years after the first report suggesting the occurrence of an $S_{RN}1$ route for the substitution of vinyl halides by $^-CH_2COMe$ and PhS^- ions,[607] new evidence has indicated the competition with an ionic elimination−addition pathway. Thus, *β*-bromostyrene **150** reacts with $^-CH_2COBu$-*t* ions under Fe^{2+} catalysis to give a mixture of products **151**−**155** in yields that depend on the reaction time, 10 min or 3 h (Scheme 57).

Scheme 57

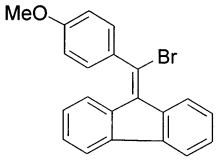


The yield of **151** and **152** was reduced by the presence of *p*-DNB, whereas that of **154** was unaffected. The formation of **154** was ascribed to the reversible addition of the conjugated base of the elimination product **153** to the ketone carbonyl. This step is likely to be reversible and will gradually allow the buildup of compound **151**, through an alternative route to the $S_{RN}1$ process.[608]

Different competitive mechanisms are possible for the nucleophilic substitutions of vinyl halides. For an exclusive vinylic $S_{RN}1$ process to operate, the substrate should not have vinylic or allylic hydrogens to avoid the alternatives of α−α and α−*β*′ elimination−additions, respectively. On the other hand, the presence of a conjugated group such as phenyl or anisyl is necessary to stabilize the intermediate radical anion of the substitution product favoring substitution instead of hydrogen abstraction of the vinyl radical (reduction process) in the reactions with nucleophiles derived from ketones. Nucleophilic addition to a rearranged radical from a 1,3-hydrogen shift is possible when the vinyl halides have *γ*-hydrogen.[609]

Compounds *β*-substituted with EWG such as NO_2, I, or Br gave exclusively formation of an acetylene derivative by two consecutive ETs with contribution

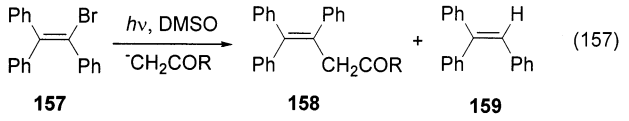
Chart 5



156

of an ionic halophilic route, whereas compounds β-substituted with CHO afforded a novel ionic deformylation process. Another possible competitive mechanism is the addition−elimination reaction for vinyl halides with EWG at the β-carbon able to stabilize a carbanion. Thus, the fluorenylidene derivative **156** (Chart 5) yields the substitution products in the reactions with RS^- and $^-CH_2COBu$-*t* ions by a nucleophilic addition−elimination pathway, favored by the aromaticity of the fluorenylidene moiety of the intermediate carbanion.[610] Taking into account the above considerations, it follows that the spectrum of possible substrates for which a vinylic $S_{RN}1$ can exclusively take place is very narrow.

Triphenylvinyl bromide **157** reacts with $^-CH_2COMe$ to yield 52% of Br^- ion with only traces of the substitution product, whereas with $^-CH_2COBu$-*t* ion the substitution compound **158** (R = CMe_3, 93%) is obtained exclusively by an $S_{RN}1$ mechanism together with a minor amount of the reduction product **159** (eq 157).[228] Catalyst with Fe^{2+} yielded principally



157 **158** **159** (157)

product **159**, probably from reduction of the vinyl radical intermediate by the ferrous ion.[609]

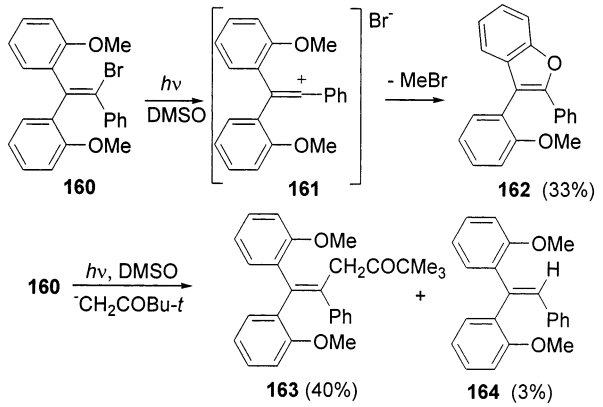
Under entrainment conditions ($^-CH_2COMe$ ion as initiator) the $^-CH_2COPh$ ion afforded 90% of substitution **158** (R = Ph). Under similar conditions the $^-CH_2NO_2$ ion yields 1,1,2-triphenylpropene, due to fragmentation of the radical anion formed by coupling of the anion with the vinyl radical.[228]

The relative reactivity of $^-CH_2COPh$ and $^-CH_2$-COBu-*t* ions toward the 1,1,2-triphenylvinyl radical was estimated to be ~3.7.[228] This result is consistent with the reactivities determined toward PhI (7.5)[79] and 1-IAd (11).[169]

Photolysis of vinyl halides can induce both heterolysis of the C−X bond, thereby generating vinyl cations, and homolysis, giving vinyl radicals.[611] Thus, the photoinduced reaction of the vinyl bromide **160** gave a fairly good conversion to the benzofuran derivative **162** through a cationic intermediate **161** (Scheme 58). Products from an $S_{RN}1$ mechanism (**163** and **164**) are formed in the presence of the $^-CH_2$-COBu-*t* ion without competition with a heterolysis process.[611]

In the reaction of *p*-anisyl diphenyl vinyl bromide with $^-CH_2COBu$-*t* ions, complete loss of the original stereochemistry of the (*E*)- and (*Z*)-bromide isomers is observed in the substituted and dehalogenated reduced products.[210] The stereoconvergence observed indicates that the intermediate vinyl radical has

Scheme 58



160 **161** **162** (33%) **163** (40%) **164** (3%)

Table 57. Photoinduced Carbonylation of Vinyl Bromides and Chlorides[a]

Vinyl Halide (VyX)	Method[b]	Time (h)	Product (%) $VyCO_2H$	Product (%) $VyCO_2Me$	Ref.
1-Bromocyclohexene	A	2.5	98		485
	B	22	8	59.5	490
1-Chlorocyclohexene	A	2.5	97		485
	B	38	5	78	490
1-Bromocyclooctene	A	4.5	97		485, 486
	B	38	11.5	65.5	490
1-Chlorocyclooctene	B	62	10.5	67.7	490
trans-PhHC=CHBr	A	15	85[c]		485
	B	41	4[c]	65[c]	490
cis-PhHC=CHBr	A	15	38,[d] 42[c]		485
$(CH_3)_3CC(Cl)=CH_2$	A	2	95		485
n-PrC(Br)=CH_2	B	62	10.5	62.5	490
$C_6H_{11}CH_2C(Br)=CH_2$	B	91	5	65	490
$C_6H_{11}CH_2C(Cl)=CH_2$	B	120	13	54.5	490
	B	57	13	71	490

[a] Photostimulation was assured by a sunlamp. [b] Method A (PTC): $Co_2(CO)_8$, C_6H_6/5 N NaOH (aq), CO, $Bu_4N^+Br^-$, 65 °C. Method B (CoCRACO): NaH, NaOAm-*t*, $Co(OAc)_2$, CO, THF/MeOH, 40 °C. [c] Trans. [d] Cis.

either a linear *sp* or an "average linear" structure due to a rapidly interconverting *E*,*Z* mixture of sp^2 bent radicals. Theoretical calculations of some α-substituted vinyl radicals indicate that for π-type substituents, the vinyl radicals are linear, whereas for σ-type the radicals are bent.[612]

The $S_{RN}1$ mechanism has been proposed for the photoinduced catalytic carbonylation of vinyl bromides and chlorides with $NaCo(CO)_4$ under PTC conditions at atmospheric pressure, which constitutes a very interesting synthesis of α,β-unsaturated carboxylic acids[485,486] (Table 57) (see section VIII.A.7). Alkoxycarbonylation of vinyl halides can be performed under atmospheric pressure of CO in the presence of a cobalt catalyst (CoCRACO)[490] (Table 57).

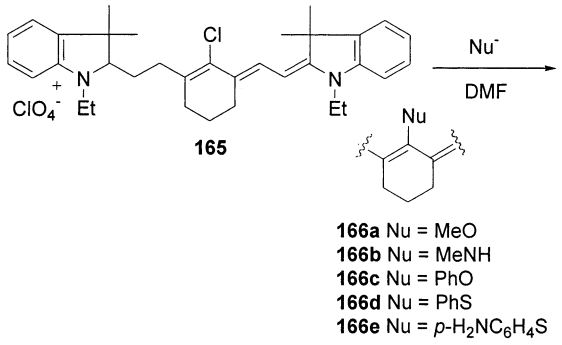
The synthesis of σ-vinyliron porphyrins can be achieved by reaction of the electrogenerated iron(I) porphyrins with 1-bromo-2,2-bis(4-chlorophenyl)ethylene under electrochemical stimulation. The Fe(II) σ-vinyl porphyrin obtained can be reoxidized electrochemically into the Fe(III) σ-vinyl complex.[613] This method was applied to the synthesis of σ-vinyl derivatives of η^5-cyclopentadienylirondicarbonyl anion [$CpFe(CO)_2^-$] by electrochemical reaction with polyfluorovinyl halides[614] and by using homogeneous redox catalysis with (*E*)- and (*Z*)-bromostilbene[615] (Table 58).

Table 58. Electrochemically Induced Reactions of Vinyl Halides with $CpFe(CO)_2^-$ Anion[a]

$R^1R^2C=CR^3X$ R^1, R^2, R^3	X	Isomer	$R^1R^2C=CR_3[FeCp(CO)_2]$ (%) Z	E	Ref.
$R^1=(CF_3)_3C$, $R^2=R^3=F$	F		40	traces	614
	Cl	Z	15	traces	614
	Br	Z	14	traces	614
$R^1=Ph$, $R^2=R^3=F$	F		42	5	614
	Cl	Z	32	3	614
	Cl	E	10	5	614
$R^1=R^3=Ph$, $R^2=H$	Br	Z[b]	13	32	615
		E[b]	20	41	615

[a] Electrolysis of the mixture of vinyl halides and $[CpFe(CO)_2]_2$ in MeCN (Hg electrode, 0.25 M n-Bu_4NBF_4, Ag^+/AgCl/KCl, 20 °C). [b] *o*-Dicyanobenzene as redox mediator.

Scheme 59

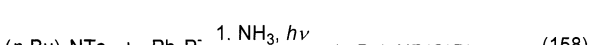


The reaction of the dye **165** with different nucleophiles has been reported to yield the corresponding derivatives **166a**−**e** (Scheme 59).[616]

It was suggested that **165** reacts by an $S_{RN}1$-type mechanism leading to products **166b**−**e** with radical cations as intermediates. On the other hand, the reaction with NaOMe/MeOH to give **166a** may involve an addition of MeO^- followed by elimination of Cl^- ions.

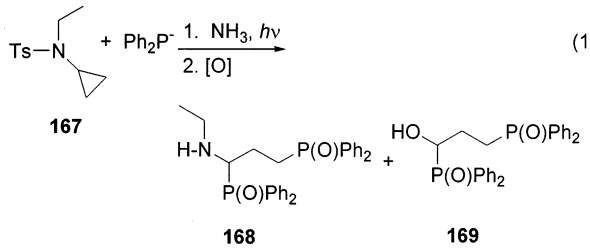
B. *N*,*N*-Dialkyl-*p*-toluenesulfonamides

There are few reports of $S_{RN}1$ reactions of nitrogen-centered radicals with Ph_2P^- ions. For example, the photoinitiated reaction of *N*,*N*-di-*n*-butyl-*p*-toluensulfonamide gives the substitution product, isolated as the oxide in 79% yield (eq 158).[617]



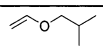
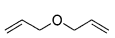
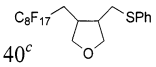
(158)

N-Cyclopropyl-*N*-ethyl-*p*-toluensulfonamide **167** reacts with Ph_2P^- ions to give 1,3-bis(diphenylphosphinyl)-1-(*N*-ethyl)propylamine **168** (69%) and 1,3-bis(diphenylphosphinyl) 1-propanol **169** (24%), isolated as the oxides (eq 159). These products are taken as



(159)

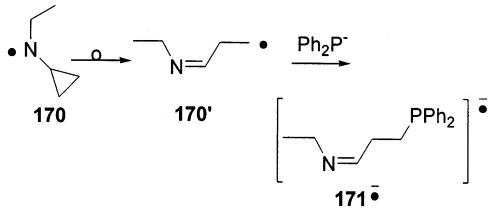
Table 59. Perfluoroalkyl Sulfenylation of Olefins[620]

R_fX	p-XC_6H_4SNa (ArSNa) X	Olefin	Ar-S, R^1, R_f (%)
n-C_4F_9I	OMe		87[b]
n-$C_6F_{13}I$			93[b]
n-$C_8F_{17}I$			86
			88[b]
	H		92
			80[c]
	Cl		88
			80[c]
	NO_2		45[b]
	H		39[c,d]
			 40[c]

[a] Reactions carried out adding the R_fI and the olefin to a solution of p-XC_6H_4SNa in dry ether under N_2 atmosphere under reflux, otherwise indicated. [b] In the presence of NaSePh. [c] In the presence of p-$MeOC_6H_4SeNa$. [d] Diastereomeric mixture trans/cis 71:29.

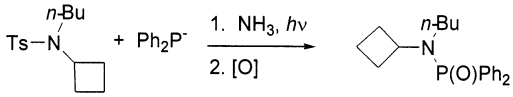
evidence of the presence of cyclopropylaminyl radicals as intermediates, which open to ultimately afford the indicated products.[618] When DMSO is added under N_2 atmosphere, after irradiation, only **168** is obtained.

The aminyl radical **170** rearranges to radical **170′** more rapidly than the coupling with the Ph_2P^- ion. Radical **170′** is trapped by the nucleophile to afford radical anion **171**$^{\bullet-}$, which by ET to the substrate gives the imine **171**. Addition of the Ph_2P^- ion to **171** ultimately gives **168** after oxidation (eq 160).[618]



(160)

In the reaction of *N*-(*n*-butyl)-*N*-cyclobutyl *p*-toluenesulfonamide with the Ph_2P^- ion, *N*-(*n*-butyl)-*N*-cyclobutyl diphenylphosphonamide is formed in 94% yield, isolated as the oxide (eq 161); no ring-opened



(161)

products are observed.[618] The order of the magnitude of the rate constant for the coupling reaction of a dialkylaminyl radical with the Ph_2P^- ion is proposed to be between those of the rearrangements of the cyclopropyl and cyclobutylaminyl radicals (2×10^9 and 1.6×10^6 s^{-1} at 50 °C in benzene, respectively).[619]

C. Perfluoro Alkylation of Dienes and Ensuing Reactions

The reaction of R_fX with PhZ^- (Z = S, Se, or Te) in the presence of olefins has been shown to be a route to the synthesis of α,β-perfluoroalkylphenylchalconides (Tables 59−61).[620−622] The $R_f^\bullet$ radicals generated by ET from PhZ^- to R_fI add the olefin to afford

Table 60. Perfluoroalkyl Selenation of Olefins[621]

R_fX	R^1	R^2	Products (%) PhSe, R^1, R^2, R_f	R_fSePh
CF_3Br[b]	H	n-C_6H_{13}	26	34
	H	OBu-*i*	38	32
n-C_4F_9I	H	n-C_4H_9	55	20
	H	n-C_6H_{13}	57	17
	H	OBu-*i*	78	2
n-$C_6F_{13}I$	H	n-C_4H_9	53	27
	H	n-C_6H_{13}	47	22
	H	OBu-*i*	84	6
n-$C_8F_{17}I$	H	n-C_4H_9	63	25
	H	n-C_6H_{13}	59	19
	H	OBu-*i*	86	7
	H	SBu-*i*	66	-
			15	60
			39	42

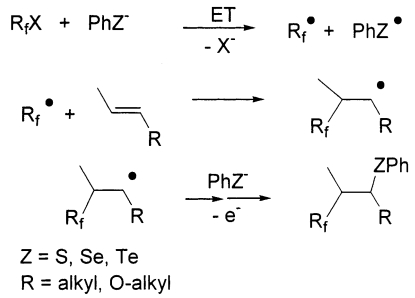
[a] Reactions carried out by addition of R_fI and the olefin to a solution of NaSePh in dry EtOH under N_2 atmosphere at room temperature otherwise indicated. [b] In EtOH/DME, (1:2), at room temperature under a CF_3Br gas atmosphere.

Table 61. Perfluoroalkyl-Telluration of Olefins[622]

R_fX	R^1	PhTe, R^1, R_f (%)
CF_3Br	H	44[b]
	n-C_6H_{13}	57[c]
	OBu-*i*	30[c,d]
	CH_2CN	44[c]
n-C_4F_9I	H	63[e]
	n-C_6H_{13}	81
	OBu-*i*	64[d]
	CH_2CN	58
n-$C_8F_{17}I$	H	47[e]
	n-C_6H_{13}	59
	OBu-*i*	54[d]
	CH_2CN	39

[a] Reactions carried out by addition of the R_fI and the olefin to a solution of NaTePh in dry EtOH under N_2 atmosphere at − 40 °C, otherwise indicated. [b] DMF/ether, (1:2) at − 100 °C. [c] DMF at − 100 °C. [d] Perfluoroalkyl ethoxylation giving $R_fCH_2CH(OEt)(OBu\text{-}i)$. [e] DMF/ether, (1:2) at − 80°C.

Scheme 60



a new radical, which after coupling with the PhZ^- gives the intermediates that continue an $S_{RN}1$-like propagation cycle (Scheme 60). A similar behavior has been observed with the alkyne derivatives.[623]

X. Appendix: Acronyms

Φ	quantum yield
Ad	adamantyl
BDE	bond dissociation energy
CIDNP	chemically induced dynamic nuclear polarization
CTC	charge transfer complex
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCHP	dicyclohexylphosphine
DFT	density functional theory
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
p-DNB	*p*-dinitrobenzene
DTBN	di-*tert*-butylnitroxide
$E_{RC}1$	elimination radical chain process
ESR	electron spin resonance
ET	electron transfer
EWG	electron-withdrawing group
HME	halogen metal exchange
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
MO	molecular orbital
NHBoc	*N*-*tert*-butoxycarbonyl
NMP	1-methyl-2-pyrrolidinone
PPS	poly(*p*-phenylene sulfide)
PTC	phase transfer conditions
R	aryl or alkyl, otherwise indicated
R_f	perfluoroalkyl
SCE	saturated calomel electrode
S_Hi	intramolecular homolytic substitution
S_N(AEAE)	nucleophilic substitution process by addition−elimination, addition−elimination sequence
SOMO	single occupied molecular orbital
TBA	*tert*-butylamine
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
THF	tetrahydrofuran
TS	transition state
Ts	*p*-toluenesulfonyl (tosyl)

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XII. References and Notes

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