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Radical aryl migration reactions

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Contents

1. Introduction

Since the first report of a radical aryl migration reaction by Wieland in 1911, many examples have appeared in the literature.[1] The most extensively investigated aryl migration reaction is certainly the 1,2-aryl migration in β-aryl carbon-centred radicals—the neophyl type rearrangement—first described by Urry and Kharasch in 1944 (Section 2.1).[2] Neophyl type rearrangements are used nowadays as radical clocks in kinetic competition experiments. Aryl migrations in free radical chemistry are not restricted to 1,2-migrations. Radical 1,4- and 1,5-migrations of aryl groups are well known. In addition, aryl migrations are not restricted to the 'all-carbon' situation as documented by many examples of aryl migrations between carbon and heteroatom-centred radicals or between two heteroatom-centred radicals. In Fig. 1, the various elements involved in radical aryl migration reactions published so far are presented. It is obvious from this figure, that further elements should participate equally well in radical aryl migration reactions. Future experiments will probably help to fill the gaps in the periodic system shown in Fig. 1.

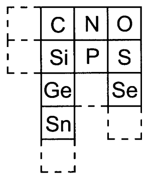

Figure 1. The various elements participating in radical aryl migration reactions.

Aryl migration reactions have also found some applications in natural product synthesis. New methods for the synthesis of biaryls based on radical aryl migrations have been developed during the last decade. Stereoselective radical aryl migration reactions have additionally appeared in the literature. In the present report, the recent achievements in the field of free radical aryl migration reactions are summarized. Previous review articles on this topic cover the literature up to 1980,[3–6] but important work from the older literature will, where relevant, be included in this report.

2. Aryl migrations between group 14 elements and carbon

2.1. The neophyl rearrangement

Almost 60 years ago, Urry and Kharasch discovered the neophyl rearrangement in their study of the cobaltous chloride catalysed reaction of neophyl chloride with

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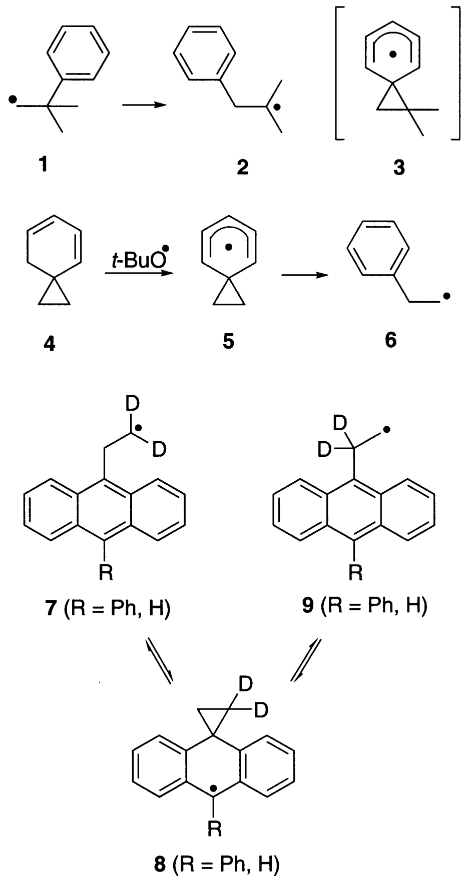
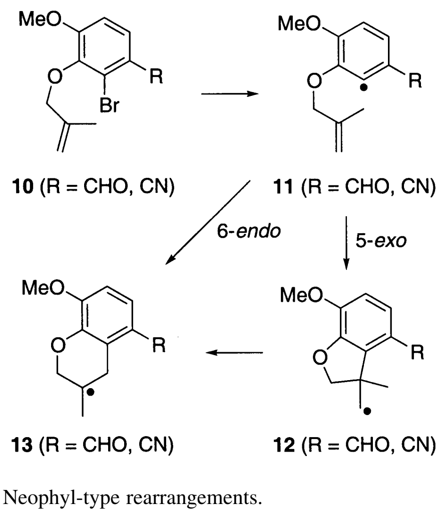


Scheme 1. Neophyl rearrangement.

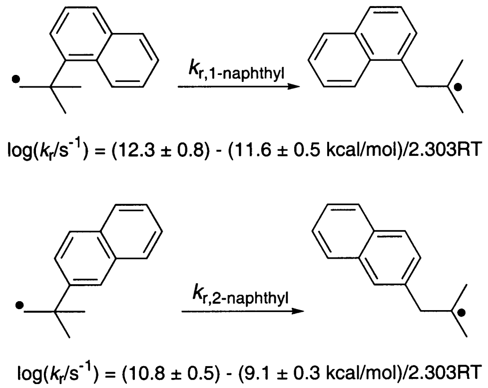
phenylmagnesium bromide.[2] Careful analysis of the products led them to conclude that the initially formed neophyl radical **1** undergoes a 1,2-phenyl migration to the corresponding tertiary radical **2** (Scheme 1). Since that initial report, many papers have appeared in the literature on this reaction, but, despite these efforts, the mechanism of the neophyl rearrangement is still not entirely understood. It is not clear whether the spiro[2,5]octadienyl radical **3** is an intermediate or a transition state in this process. Early EPR[7,8] and CIDNP studies[9–11] did not reveal the occurrence of the intermediate **3**. Later, it was shown by UV spectroscopy that the spiro[2,5]octadienyl radical **5**, independently generated from the cyclopropane **4** by H-abstraction with a *t*-butoxyl radical, decays in the nanosecond time scale to the 2-phenylethyl radical **6**.[12] This experiment does not, however, prove whether the spiro[2,5]octadienyl radical **3** is a genuine intermediate in the neophyl rearrangement. Upon increasing the stability of the spiro intermediate, an Italian group clearly proved the formation of a spiro[2,5]-octadienyl type radical as an intermediate in a neophyl-like rearrangement.[11] The generation of radical **7** in the cavity of an EPR spectrometer only revealed the spectrum of the cyclized radical **8**. The ring-opened radicals **7** and **9** were not detected. The authors provided further experimental evidence that the 2-anthrylethyl radical **7** (R=H) and its phenyl-substituted analogue (R=Ph) are in equilibrium with the corresponding radicals **8** and **9**. The lower limit of the rate constant for the rearrangement of **7** to **9** was estimated to be in the order of $5\times10^7\ \mathrm{s}^{-1}$.

The rate constant k_r of the neophyl rearrangement, used nowadays as a radical clock,[13,14] has been determined by various groups applying different methods. The frequency factor and activation energy for the neophyl rearrangement determined by EPR spectroscopy differ slightly from the values estimated by indirect competition kinetics. In 1973, an activation energy (E_a) of 10.3±2.2 kcal/mol was estimated using EPR spectroscopy.[7] Later, steady-state concentrations were combined with directly determined second-order lifetimes to provide the more exact relation $\log(k_r/\mathrm{s}^{-1})=(11.7\pm1.0)-(13.6\pm1.0\ \mathrm{kcal/mol})/2.303RT$ in the temperature range 283–307 K.[15] Franz et al. determined k_r using the reduction of primary alkyl radicals with Bu_3SnH as a radical clock and arrived at $\log(k_r/\mathrm{s}^{-1})=(11.6\pm0.3)-(11.8\pm0.5\ \mathrm{kcal/mol})/2.303RT$ for 393–492 K.[16] Shortly after this work, similar values were obtained by Ingold et al. using kinetic competition experiments.[17] Recently, Ingold and Walton revised the Arrhenius parameters obtained by Franz using more accurate values for the reduction of the neophyl radical with Bu_3SnH, which was used as the radical clock for determining the rate constant of the neophyl rearrangement. The following 'corrected' equation was obtained: $\log(k_r/\mathrm{s}^{-1})=(11.0)-(10.8\ \mathrm{kcal/mol})/2.303RT$ (k_r (298 K)$=1100\ \mathrm{s}^{-1}$).[18] The newest data has been published by Fischer, who used time-resolved EPR to determine absolute rate constants for the neophyl rearrangement.[19] Arrhenius parameters differ from the 'corrected' values mentioned above ($\log(k_r/\mathrm{s}^{-1})=(12.7\pm0.3)-(13.8\pm0.4\ \mathrm{kcal/mol})/2.303RT$) although, due to error compensation effects, the different Arrhenius parameters yield rather similar rate constants.

Since the neophyl rearrangement is a slow process, there are only scant applications for this reaction in organic synthesis. Often, this rearrangement occurs as a side reaction.[20] Neophyl-type rearrangements in aryl radical cyclizations have first been suggested by Parker et al.[21] They concluded that aryl radicals of type **11**, generated from the corresponding bromides **10** using the tin hydride method, mainly undergo a 5-*exo*-cyclization to provide the primary radicals **12**, which in turn react in a neophyl-type rearrangement to the corresponding ring-enlarged tertiary radicals **13** (Scheme 2). This paper was later challenged by Beckwith, who showed that only under low tin hydride concentration



Scheme 2. Neophyl-type rearrangements.

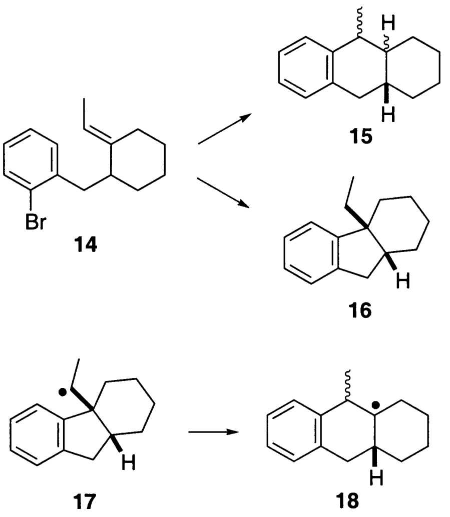


Scheme 3. Arrhenius parameters for the 1,2-migration of the 1-naphthyl and the 2-naphthyl group.

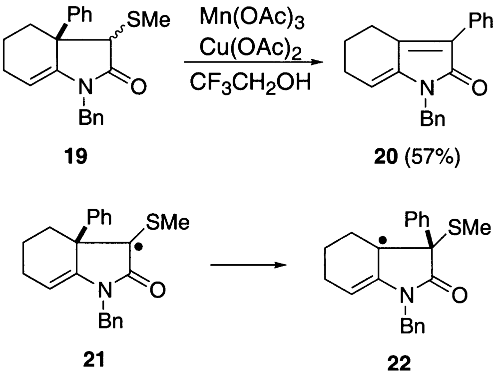
could the rearrangement occur.[22] Part of the ring-enlarged product is formed by a direct 6-*endo* radical cyclization. A rate constant of $1.4\times10^5\ s^{-1}$ was estimated for the rearrangement of **12** to **13** (R=CHO) at 80°C.

Beckwith additionally showed that the neophyl-type rearrangement is facilitated by electron-withdrawing substituents at the migrating aryl group and is faster for radicals containing the naphthalene nucleus (1,2-naphthyl migration). This work has recently been confirmed by Pedulli and Valgimigli, who studied the kinetics of the 1,2-migration of the naphthyl group.[23] In the neophyl-type rearrangement of the 1-naphthyl and the 2-naphthyl group, larger rate constants were measured as compared to the parent neophyl rearrangement ($k_{r,1\text{-naphthyl}}$ (298 K)=6400 s^{-1}; $k_{r,2\text{-naphthyl}}$ (298 K)=14 000 s^{-1}; Scheme 3).

Another example of a neophyl-type rearrangement was described by Ishibashi.[24–26] Radical reaction of the bromide **14** under low tin hydride concentration afforded almost exclusively the formal 6-*endo* cyclization product **15** (79%, mixture of three isomers, Scheme 4). Only trace amounts of the 5-*exo*-compound **16** were isolated. If the reaction was conducted at a high tin hydride concentration, however, the 5-*exo*-compound **16** was formed as the main product with only trace amounts of **15**. At low tin hydride concentration radical **17**, formed via 5-*exo*-cyclization, therefore undergoes a neophyl-type rearrangement to give radical **18**, which eventually affords the formal 6-*endo* product **15**.



Scheme 4. Aryl radical cyclization with subsequent neophyl-type rearrangement.



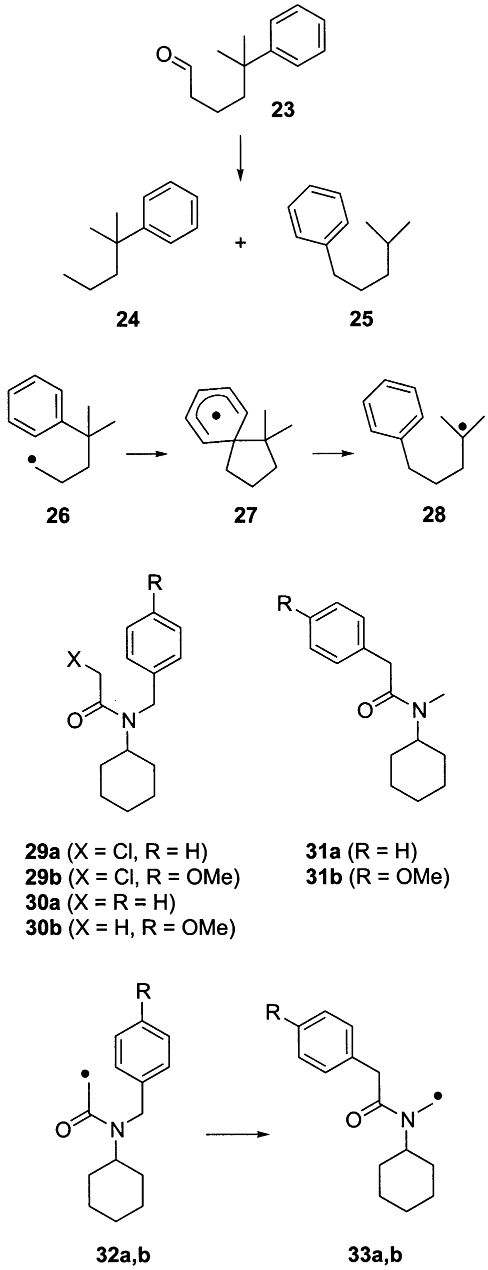
Scheme 5. Neophyl-type rearrangement under oxidative conditions.

A rather high yield of the neophyl-type rearranged product **20** was obtained upon reacting lactam **19** under oxidative conditions using $Mn(OAc)_3$ in the presence of $Cu(OAc)_2$ (Scheme 5).[27] The initially formed tertiary radical **21** undergoes efficient rearrangement to provide the allyl radical **22**, which subsequently eliminates the methylthiyl radical to eventually afford compound **20**.

Neophyl-type rearrangements have also been observed in crystalline bis(3,3,3-triphenylpropanoyl) peroxide[28] and in some pyrolysis experiments.[29,30]

2.2. 1,4- and 1,5-Aryl migrations from carbon to carbon

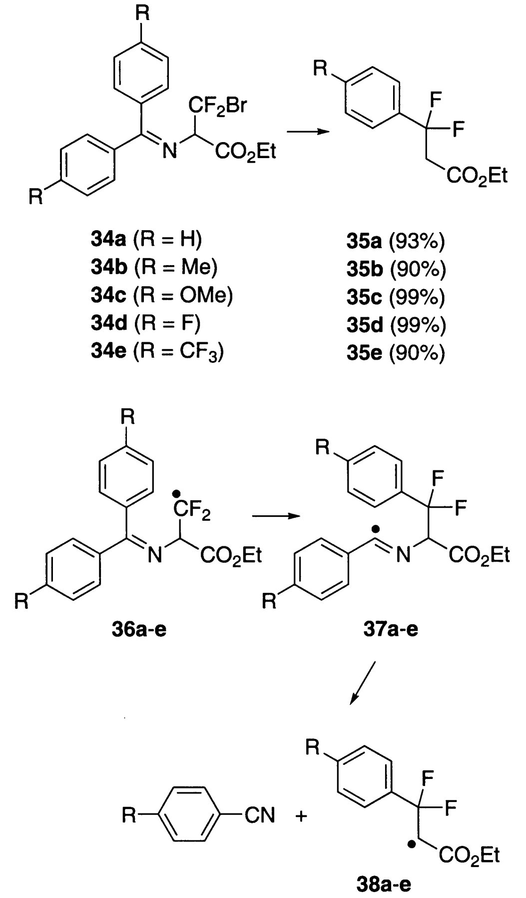
In contrast to 1,3-aryl migration reactions, which have not been observed to date, there are many examples of 1,4- and 1,5-aryl migration reactions from carbon to carbon. The transition state is simply too strained for the 1,3-aryl migration. In 1956, the first example of a radical 1,4-phenyl migration was reported by Winstein et al.[31] Radical decarbonylation of 5-methyl-5-phenylhexanal **23** provided the unrearranged hydrocarbon **24** and compound **25**, along with other side products (Scheme 6). The decarbonylation product **25** is formed via a 1,4-phenyl migration reaction of the primary radical **26** via a cyclohexadienyl radical **27** to the more stable tertiary radical **28**. Radical **26** is formed via decarbonylation of the corresponding acyl radical. Reduction of the radical **28** eventually affords the product **25**. Julia later studied the same reaction more carefully and confirmed the earlier conclusions.[32] More recently, Ishibashi et al. have reported the radical dehalogenation of the α-chloroamide **29a** using Bu_3SnH.[33] Along with the expected dechlorination product **30a** (40%), the *N*-methylamide **31a** was isolated in 31% yield. Besides direct reduction, the radical **32a** undergoes *ipso*-attack with subsequent rearomatization to form the α-aminomethyl radical **33a**. Reduction of **33a** with Bu_3SnH provides the rearranged amide **31a**. Aryl migration of the electron-rich 4-methoxyphenyl group under analogous conditions gave the amide **31b** in 30% yield, along with the corresponding direct reduction product **30b**. The additional substituent at the



Scheme 6. Radical 1,4-aryl migration reactions.

migrating aryl group has obviously no profound effect on the rearrangement. Similar observations have been made in other aryl migration reactions as will be discussed below.

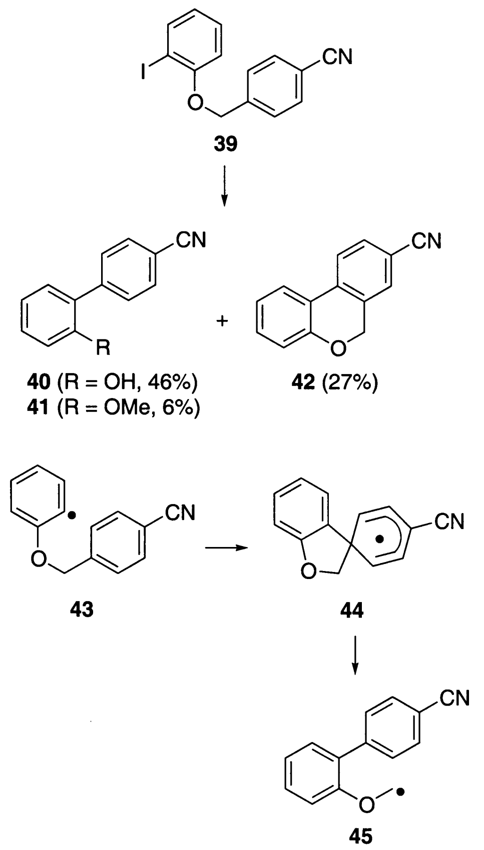
An interesting rearrangement/fragmentation reaction was published by Uneyama et al.[34] Various β-bromo-β,β-difluoroalanine Schiff bases **34a–e** were transformed under radical conditions with Bu_3SnH to the corresponding β-aryl-β,β-difluoroesters **35a–e** in excellent yields (90–99%, Scheme 7). The initially generated α,α-difluoroalkyl radicals **36a–e** undergo 1,4-aryl migration to the iminoyl radicals **37a–e**. β-Fragmentation affords the stabilized radicals **38a–e** and the corresponding aryl nitriles. Reduction of **38a–e** with tin hydride finally leads to the β-arylated esters **35a–e**. As in the previous example, the *p*-substituent of the migrating aryl group has only a small effect on the efficiency of the aryl migration reaction. Electron-rich as well as electron-poor aryl groups underwent the 1,4-migration with high yield.



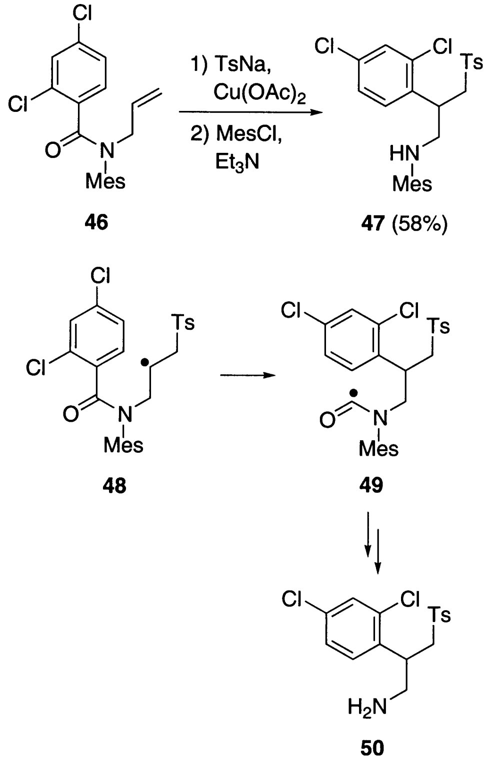
Scheme 7. Radical 1,4-aryl migration/fragmentation reaction.

Radical 1,4-aryl migrations from carbon to carbon have also been used for the synthesis of biaryls.[35] Treatment of the aryl ether **39** under standard tin hydride conditions afforded the homolytic aromatic substitution[36] product **42** (27%) and the biaryls **40** and **41** in 52% combined yield (Scheme 8). *ipso*-Attack of aryl radical **43** generates the cyclohexadienyl radical **44**, which in turn rearomatizes to the more stable α-phenoxymethyl radical **45**. Radical **45** is either reduced with tin hydride to the rearranged methyl ether **41** (6%) or is further transformed to phenol **40** (46%). The mechanism for the transformation of radical **45** to phenol **40** is not known. The benzopyran **42** is formed via *o*-attack of radical **43** with subsequent oxidation.

Chuang et al. have reported radical 1,4-aryl migrations in various benzamides for the preparation of biaryls.[37] Treatment of the allylamide **46** with sodium *p*-toluenesulfinate (TsNa) in aqueous formic acid in the presence of $Cu(OAc)_2$, for example, afforded after sulfonylation the aryl migration product **47** in 58% yield (Scheme 9). Sulfonyl radical addition at the terminal position of the double bond in **46** generates the secondary radical **48**. *ipso*-Substitution (1,4-aryl migration) provides the amidoyl radical **49**, which eventually affords the amine **50**. Sulfonylation finally gives the isolated sulfonamide **47**.



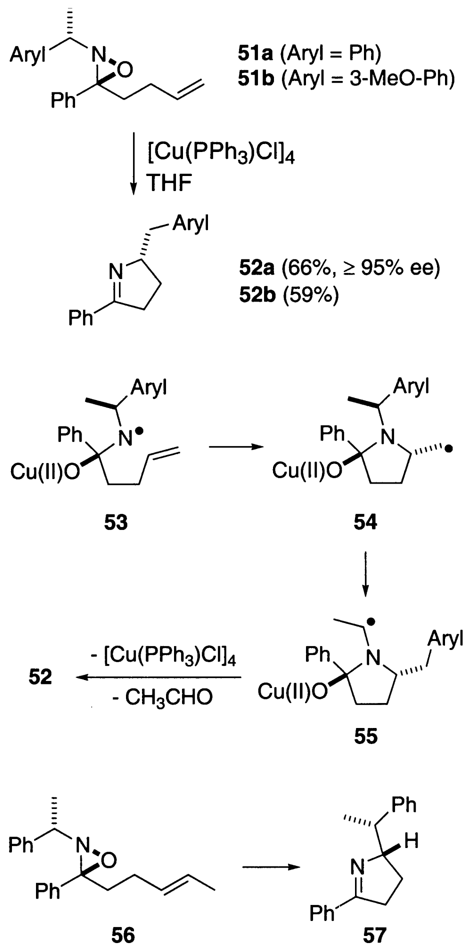
Scheme 8. Radical biaryl synthesis via a 1,4-aryl migration reaction from carbon to carbon.



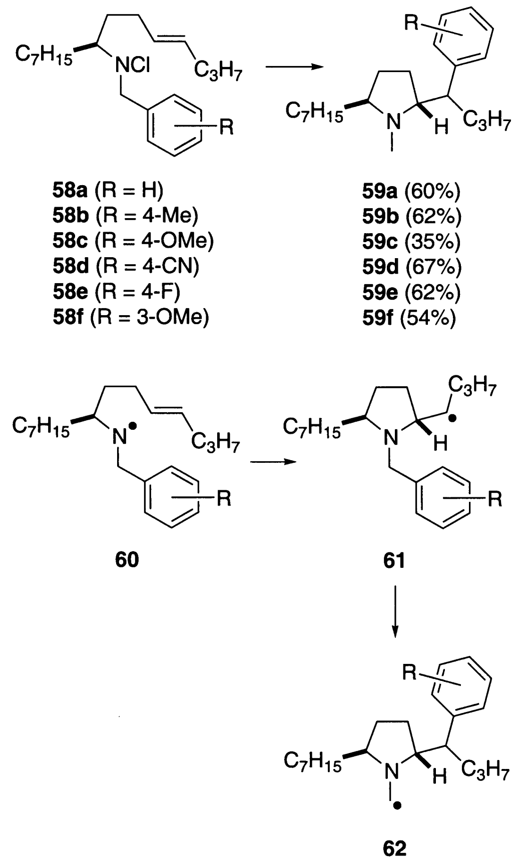
Scheme 9. Radical aryl migration starting from the benzamide **46** (Mes=mesitylenesulfonyl; Ts=toluenesulfonyl).

Interesting radical cascade reactions involving ring opening of oxaziridines followed by stereoselective 5-*exo* cyclizations and subsequent 1,4-phenyl migrations were studied by Aubé in the early 1990s.[38] A copper catalyst was used to initiate these processes. Treatment of the oxaziridine **51a** with the catalyst, for example, afforded the cyclization/phenyl transfer product **52a** with high yield and high stereospecificity (Scheme 10). A similar yield was obtained in the reaction with the oxaziridine **51b** bearing an electron-rich *m*-methoxyphenyl group. Electron transfer from the copper(I) species to the oxaziridine generates the aminyl radical **53**, which undergoes 5-*exo* cyclization to give the primary radical **54**. 1,4-Aryl migration leads to a copper(II) alcoholate **55**, which fragments acetaldehyde and the copper(I) catalyst to provide the isolated products **52**. In the reaction of the substrate **56** under similar conditions, the 5-*exo* cyclization and the phenyl transfer reaction occurred with a high selectivity (→**57**, 42% yield, ee≥95%). This is one of the rare examples where a stereoselective radical aryl migration reaction has been reported. Cu-mediated radical ring-opening/cyclization reactions have been studied more recently by Black et al.[39]

Other examples of stereoselective radical 1,4-aryl migrations have been published by Tokuda and Senboku.[40] Reaction of various *N*-chloroamines **58a–f** under standard tin hydride conditions (AIBN, toluene, reflux) provided the



Scheme 10. Copper(I)-initiated oxaziridine ring openings with subsequent cyclization/aryl migration.

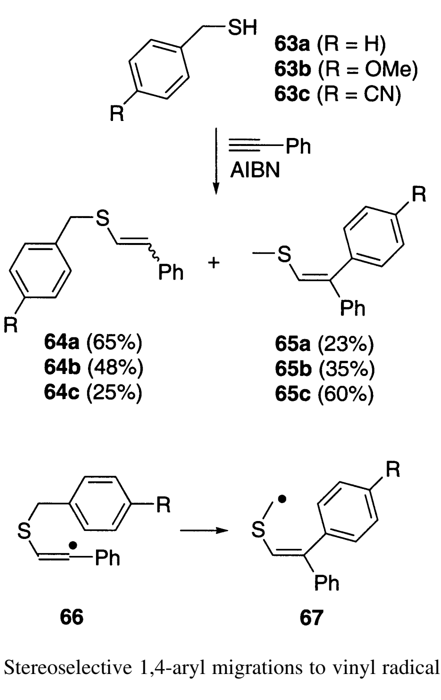


Scheme 11. Stereoselective radical cyclization/aryl transfer reactions.

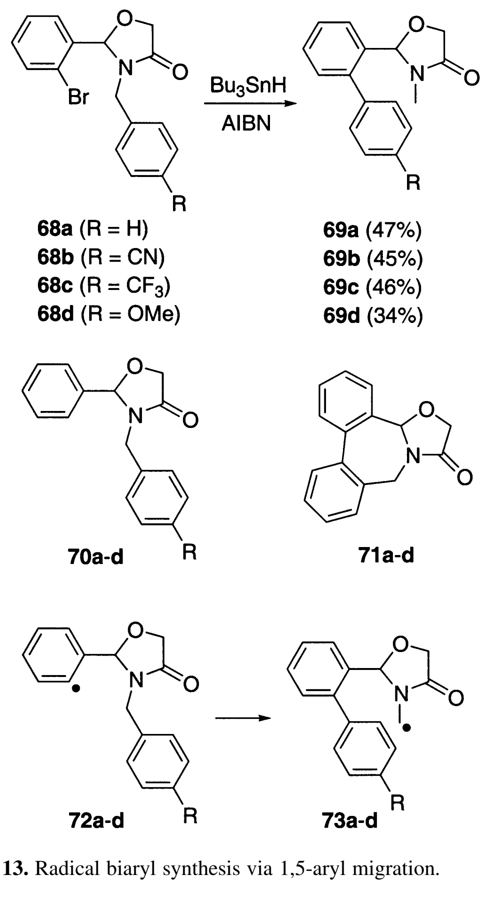
cyclization/aryl transfer products **59a–f** in moderate to good yields (35–67%) with excellent stereocontrol (Scheme 11). Aminyl radicals of the type **60**, generated upon reaction of the starting *N*-chloroamines with tin radicals, undergo highly stereoselective 5-*exo* cyclizations to give secondary radicals of type **61**. A stereoselective (only one isomer formed) aryl migration reaction generates stable α-aminomethyl radicals **62**, which in turn are reduced with tin hydride to propagate the chain. The relative configuration at the newly formed stereogenic centres was not determined. In contrast to the examples discussed above, where the polarity of the arene moiety has only a small effect on the aryl migration reaction, a lower yield was obtained for the reaction including the transfer of the electron-rich *p*-methoxyphenyl group.

Mercapto-substituted vinyl radicals have been shown to undergo stereoselective 1,4-aryl migration reactions.[41,42] The vinyl radicals were generated via thiyl radical addition to the corresponding substituted alkynes. The reaction of benzyl mercaptan (**63a**) with phenyl acetylene under radical conditions (AIBN, benzene, reflux), for example, provided the addition product **64a** (65%) and the methyl vinyl thioether **65a** in 23% yield (Scheme 12). The thioether derives from reduction of the α-thiomethyl radical **67**, which is formed via *ipso*-substitution (1,4-phenyl transfer) of the vinyl radical **66**. 1,4-Aryl migration was even more efficient for the *p*-methoxyphenyl (**63b** to **65b**) and *p*-cyanophenyl (**63c** to **65c**) groups. Both electron-donating as well as electron-withdrawing substituents at the *p*-position of the migrating aryl group accelerate (although to a small extent) the aryl migration.[42] Substituents at the *m*-position do not lead to an acceleration. The effect of the substituents on the stabilization of the intermediate cyclohexadienyl radicals is, therefore, probably more important than their contribution to polar effects.[42]

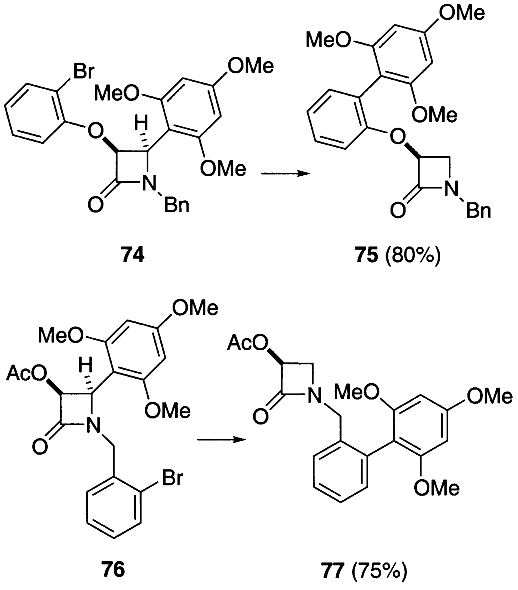
Radical 1,5-aryl migration reactions from carbon to carbon have been used by Renaud et al. for the preparation of



Scheme 12. Stereoselective 1,4-aryl migrations to vinyl radicals.



Scheme 13. Radical biaryl synthesis via 1,5-aryl migration.



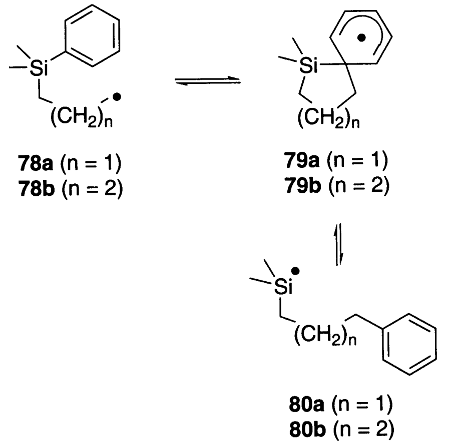
Scheme 14. Radical 1,5-aryl migrations of *o*,*o*-disubstituted aryl groups.

biaryls.[43] Treatment of the aryl bromides **68a–d** with Bu_3SnH/AIBN provided the biaryl derivatives **69a–d** in moderate yields (34–47%, Scheme 13). As side reactions, debromination (→**70a–d**) as well as homolytic aromatic substitution (→**71a–d**) occurred. The aryl radicals **72a–d** undergo *ipso*-sustitution to give the amidomethyl radicals **73a–d**, which are reduced with tin hydride to afford the biaryls **69a–d**. The lowest yield was obtained for the migration of the electron-rich *p*-methoxyphenyl group.

Further examples of 1,5-aryl migrations for the construction of biaryls were published by Alcaide.[44] The bromides **74** and **76** were transformed in high yields under tin hydride conditions to the biaryls **75** and **77** (Scheme 14). In order to suppress the *o*-attack, which would lead to cyclic homolytic aromatic substitution products (compare **71** in the Renaud system), both *o*-positions of the migrating aryl group had to be protected. As for the examples shown in Scheme 13, the driving force of these 1,5-aryl migrations is the formation of a rather stable amidomethyl radical from a reactive aryl radical.

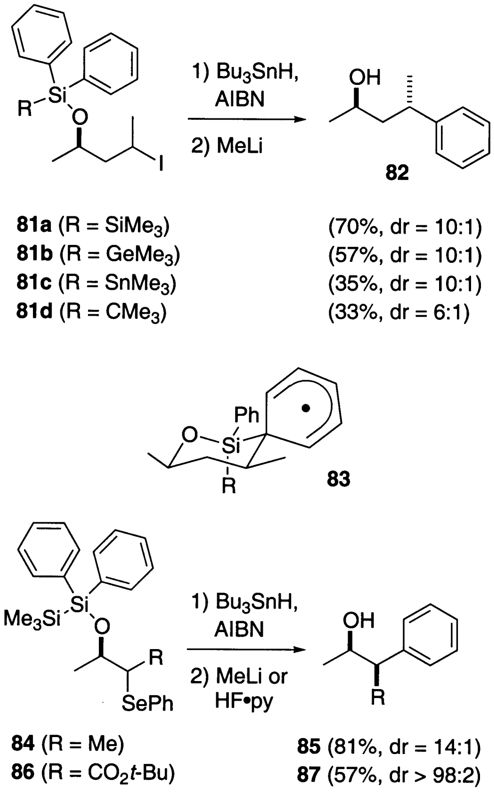
2.3. Aryl migrations involving heavier group 14 elements

The radical 1,2-aryl migration between carbon and silicon ('sila-neophyl type rearrangement') has not been observed to date. In contrast to the parent neophyl rearrangement, the transition state for the analogous process involving a silicon atom is too strained.[45] Back in the 1970s, Wilt et al. studied radical 1,4- as well as 1,5-phenyl migrations from silicon to carbon (Scheme 15).[46–48] The primary alkyl radicals **78a** (n=1) and **78b** (n=2) used in these studies were generated from the corresponding chlorides at 140°C with Bu_3SnH/*t*-BuOO*t*-Bu. Wilt et al. showed that the 1,4-phenyl migration from Si to C via the cyclohexadienyl radical **79a** to give the Si-radical **80a** does indeed occur. In addition, the homologous 1,5-phenyl transfer was observed (**78b**→**80b**) and it was suggested that the phenyl migrations are reversible at high temperatures. Indeed, Sakurai has provided experimental evidence for the reversibility of the radical 1,4- and 1,5-phenyl migration from carbon to silicon.[49] Sakurai also characterized intermediate cyclohexadienyl radicals of the type **79** using EPR spectroscopy.[50]

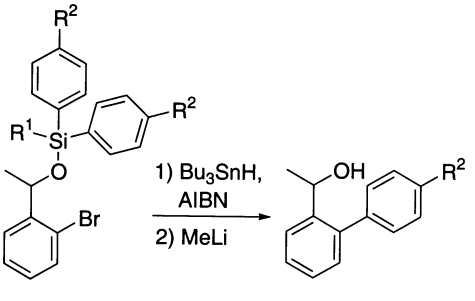


Scheme 15. Radical 1,4- and 1,5-phenyl migrations between carbon and silicon.

Recently, Studer investigated the stereoselective radical 1,5-aryl migration from silicon to secondary C-centred radicals.[51] The 1,5-phenyl migration worked well for diphenyl(trimethylsilyl)silyl ethers. Reaction of the iodide **81a** under radical conditions, for example, afforded after desilylation the phenyl migration product **82** in 70% yield with a good diastereoselectivity (*unlike*/*like*=10:1, Scheme 16). Lower yields for the analogous process were obtained for the corresponding germylated (**81b**, 57%) or stannylated (**81c**, 35%) silyl ethers. For the *t*-butyldiphenylsilyl ether



Scheme 16. Stereoselective radical aryl migration from silicon to carbon.



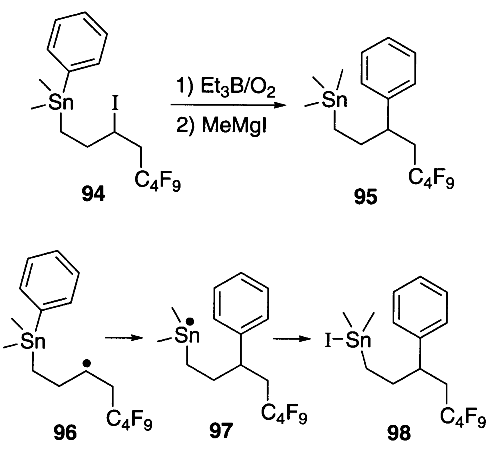
88 (R^1 = Ph, R^2 = H) **89** (71%, R^2 = H)
90 (R^1 = Me, R^2 = OMe) **91** (77%, R^2 = OMe)
92 (R^1 = $SiMe_2Ph$, R^2 = F) **93** (49%, R^2 = F)

Scheme 17. Biaryl synthesis via radical 1,5-aryl migration from silicon to carbon.

81d, the yield and selectivity decreased (33%, *unlike*/*like*=6:1). The cyclohexadienyl radical **83**, with the methyl substituents in a pseudo-equatorial position, was suggested as an intermediate in the formation of the major isomer. It was later shown that functionalized aryl groups can also be transferred to secondary C-radicals using this approach, but the yields are generally lower.[52] The analogous 1,4-aryl migration from *Si* to secondary C-radicals was even more effective, as exemplified by the phenyl selenide **84**, which was readily transformed in good yield and selectivity (81%, *unlike*/*like*=14:1) to the corresponding 1,4-phenyl migration product **85**. α-Arylation of an ester may also be achieved using the radical aryl migration strategy. Radical phenylation of the selenide **86** afforded, after desilylation, the β-hydroxyester **87** in 57% yield with complete stereocontrol.

Recently, it has been shown that the radical 1,5-aryl migration from silicon to carbon can be used for the preparation of biaryls.[53] Transformation of the bromide **88** under tin hydride conditions, for example, afforded after desilylation the biphenyl **89** in 71% yield (Scheme 17). Functionalized aryl groups can also be transferred from silicon to aryl radicals as shown for the transformation of the silyl ethers **90** and **92** to the corresponding biaryls **91** (77%) and **93** (49%).

The first report of a radical aryl migration from tin to carbon was recently published by Oshima et al.[54] Heating the iodide **94** in benzene in the presence of Et_3B/O_2 and subsequent addition of MeMgI afforded the phenyl transfer compound **95** in 70% yield (Scheme 18). The secondary radical **96** reacts in a 1,4-phenyl transfer reaction to give the stannyl radical **97**, which further abstracts an iodine atom from the starting material (→**98**), thereby propagating the chain. Methyl-Grignard addition eventually affords the trimethylstannyl derivative **95**. Functionalized aryl groups can also be transferred using this approach.

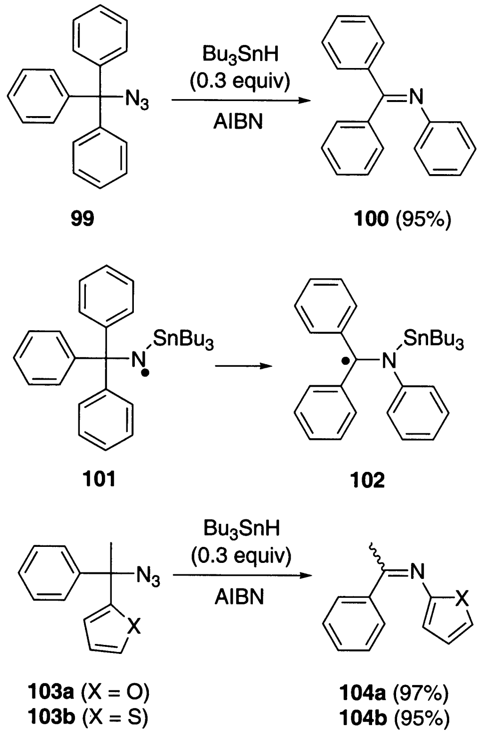


Scheme 18. Radical 1,4-phenyl migration from tin to carbon.

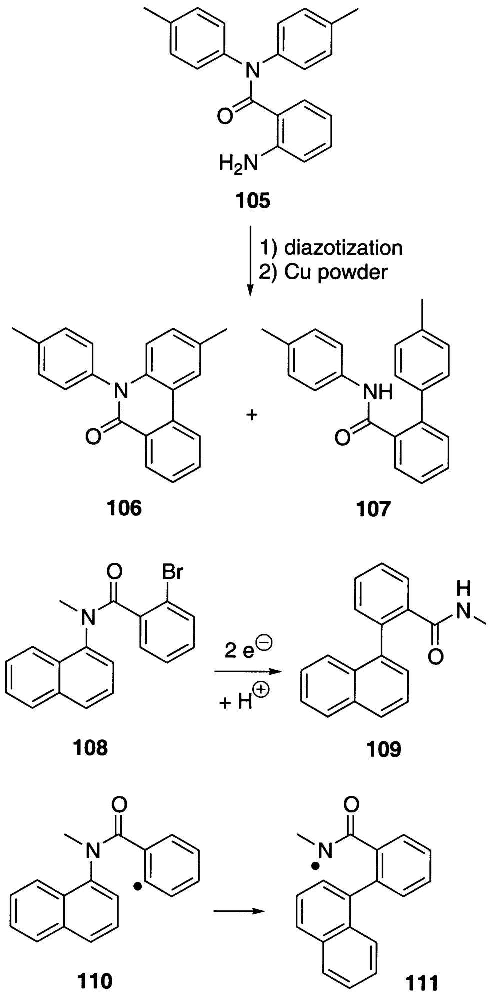
3. Aryl migrations between group 15 elements and carbon

To the best of the authors' knowledge, there is only a single paper on the 1,2-phenyl migration reaction from carbon to nitrogen.[55] Treatment of the azide **99** with tributyltin hydride under radical conditions afforded the imine **100** in 95% yield (Scheme 19). The aminyl radical **101**, generated upon stannyl radical addition to the azide **99**, undergoes a 1,2-phenyl shift to form the diphenylmethyl radical **102**. β-Elimination of the tributyltin radical finally affords the imine **100**. Heteroaryl moieties such as the 2-furyl and the 2-thienyl groups have a stronger migratory aptitude in these 1,2-aryl migration reactions than the phenyl group. Preferential rearrangement of the heteroaryl over the phenyl group was observed in the reaction with the azides **103a** and **103b** to afford the imines **104a** (97%) and **104b** (95%). None of the phenyl migration product was formed in these reactions.

The radical 1,3-phenyl migration between nitrogen and carbon has not been observed to date. In 1959, Hey et al. published the first example of a 1,4-phenyl transfer from



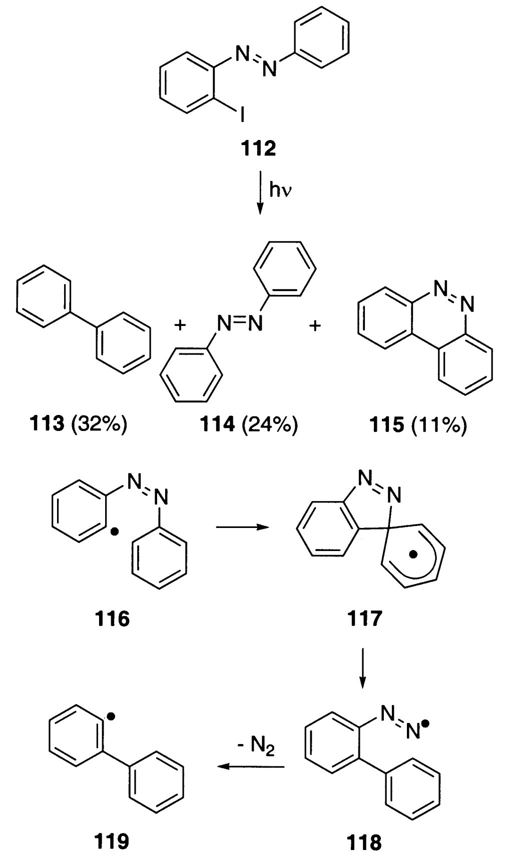
Scheme 19. 1,2-Radical rearrangements of phenyl, furyl and thienyl groups from carbon to nitrogen.



Scheme 20. Radical 1,4-aryl migration from nitrogen to an aryl radical.

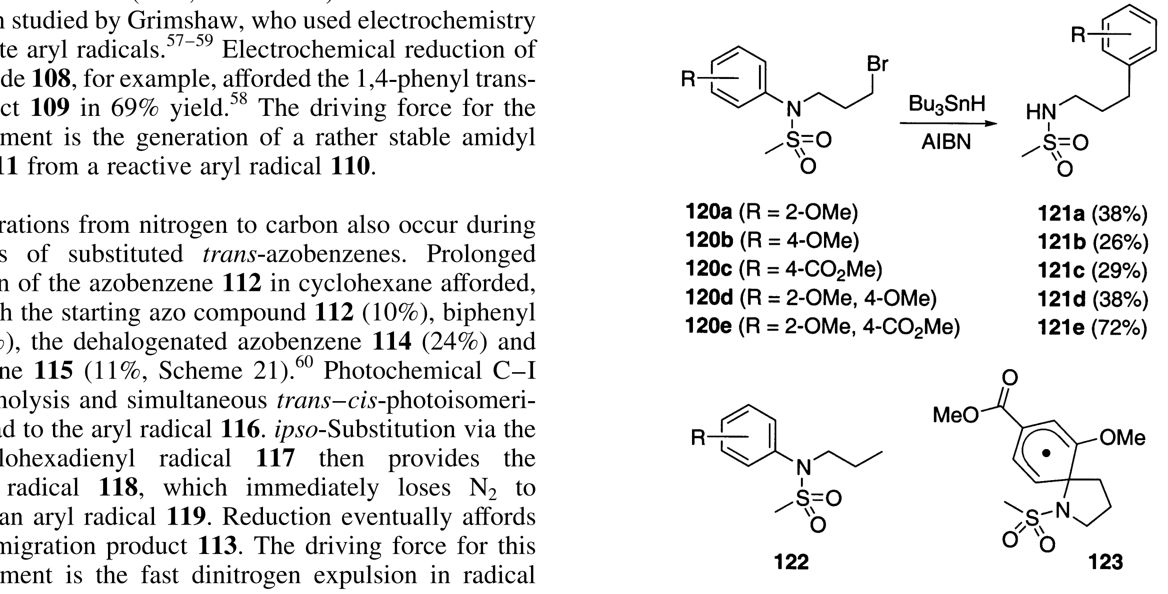
nitrogen to an aryl radical.[56] Decomposition of the diazonium fluoroborate prepared from the amide **105** afforded the Pschorr product **106** (28%) and the phenyl transfer product **107** (58%, Scheme 20). Similar reactions have been studied by Grimshaw, who used electrochemistry to generate aryl radicals.[57–59] Electrochemical reduction of the bromide **108**, for example, afforded the 1,4-phenyl transfer product **109** in 69% yield.[58] The driving force for the rearrangement is the generation of a rather stable amidyl radical **111** from a reactive aryl radical **110**.

Aryl migrations from nitrogen to carbon also occur during photolysis of substituted *trans*-azobenzenes. Prolonged irradiation of the azobenzene **112** in cyclohexane afforded, along with the starting azo compound **112** (10%), biphenyl **113** (32%), the dehalogenated azobenzene **114** (24%) and the diazene **115** (11%, Scheme 21).[60] Photochemical C–I bond homolysis and simultaneous *trans–cis*-photoisomerization lead to the aryl radical **116**. *ipso*-Substitution via the spiro-cyclohexadienyl radical **117** then provides the diazenyl radical **118**, which immediately loses N_2 to generate an aryl radical **119**. Reduction eventually affords the aryl migration product **113**. The driving force for this rearrangement is the fast dinitrogen expulsion in radical **118**. The azo compound **114** derives from reduction of the aryl radical **116** with subsequent thermal *cis–trans*-isomerization. The biphenyl **115** is formed from radical **116** by *o*-addition and subsequent oxidation.



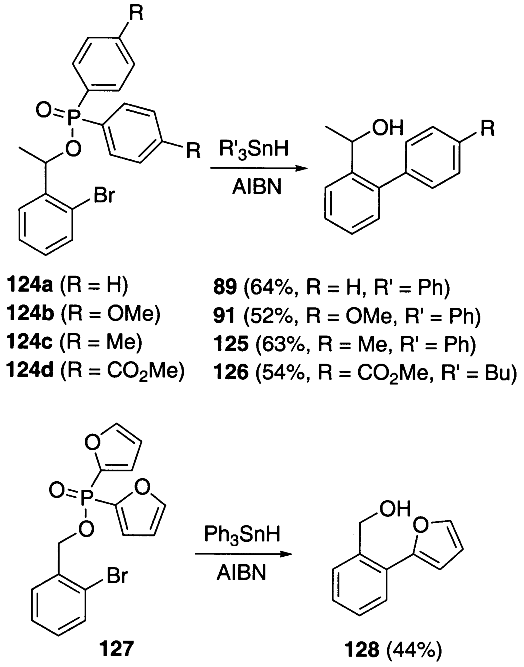
Scheme 21. *ipso*-Substitution in the photolysis of 2-iodoazobenzene.

In a series of experiments, Lee studied the 1,4-aryl migration from nitrogen to primary C-radicals. *N*-arylated sulfonamides and carbamates were used in these studies.[61] Treatment of the sulfonamides **120a–e** with Bu_3SnH/AIBN, for example, afforded the 1,4-aryl migration products



120a (R = 2-OMe)	**121a** (38%)
120b (R = 4-OMe)	**121b** (26%)
120c (R = 4-CO_2Me)	**121c** (29%)
120d (R = 2-OMe, 4-OMe)	**121d** (38%)
120e (R = 2-OMe, 4-CO_2Me)	**121e** (72%)

Scheme 22. Radical 1,4-aryl migration from nitrogen to primary alkyl radicals.



124a (R = H)
124b (R = OMe)
124c (R = Me)
124d (R = CO$_2$Me)

89 (64%, R = H, R' = Ph)
91 (52%, R = OMe, R' = Ph)
125 (63%, R = Me, R' = Ph)
126 (54%, R = CO$_2$Me, R' = Bu)

127

128 (44%)

Scheme 23. Radical 1,4-aryl migration from phosphorous to aryl radicals.

121a–e in moderate to good yields (26–72%, Scheme 22). Dehalogenation (→**122**) was observed as the only side reaction (5–57%). The highest yield for the rearrangement was obtained for the sulfonamide **120e**, for which the intermediate in the 1,4-aryl migration reaction, the cyclohexadienyl radical **123**, is captodatively stabilized.

Radical 1,5-aryl migrations between nitrogen and carbon have not been studied to date. Clive has recently reported the synthesis of biaryls by intramolecular 1,5-phenyl migration from phosphorous to carbon.[62] This is the first example of a radical aryl migration involving a phosphorous atom. The phosphinates **124a–d** were transformed under tin hydride conditions in refluxing xylene to the biaryls **89**, **91**, **125** and **126** (Scheme 23). Heteroarenes can also be transferred to aryl radicals using this approach, as was shown for the reaction of the phosphinate **127** to form the furyl transfer product **128**.

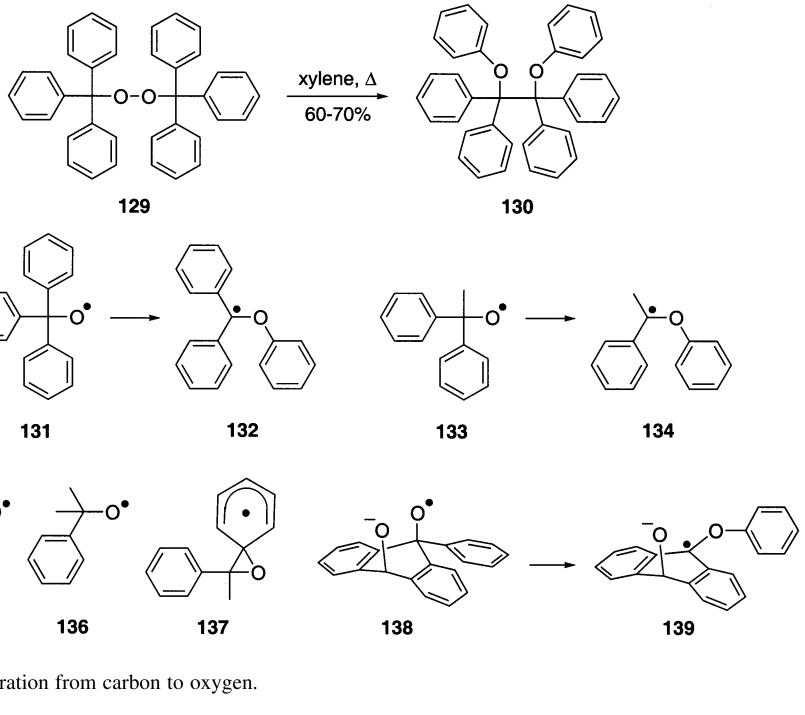
Further radical aryl migration reactions involving heavier group 15 elements are not known.

4. Aryl migrations between group 16 elements and carbon

4.1. Aryl migrations between oxygen and carbon

As mentioned in the introduction, the first report of an aryl migration between carbon and oxygen had already appeared in 1911. In the thermal decomposition of the peroxide **129**, Wieland observed the formation of 60–70% of the bis-phenylether **130** (Scheme 24).[1] Thermal O–O bond homolysis affords the reactive alkoxyl radical **131**, which undergoes a 1,2-phenyl migration to form the stabilized C-radical **132**. Dimerization eventually gives the isolated product **130**. Later, Ingold and Howard observed an analogous 1,2-phenyl shift for the 1,1-diphenylethoxyl radical **133** to form the C-radical **134**.[63] None of the expected β-methyl fragmentation product (benzophenone) was formed, indicating that the phenyl migration must occur with a rate constant $>10^6\ \mathrm{s}^{-1}$. The stability of the tertiary radical **134** is obviously high enough to ensure a fast neophyl-type rearrangement. For ethoxyl radicals bearing a single phenyl substituent such as the benzyloxyl radical **135** and the cumyloxyl radical **136**, however, the aryl migration can neither compete with hydrogen abstraction from the media nor with β-fragmentation (for **136**).[64]

Schuster measured the rate constant for the rearrangement



129

130

131

132

133

134

135

136

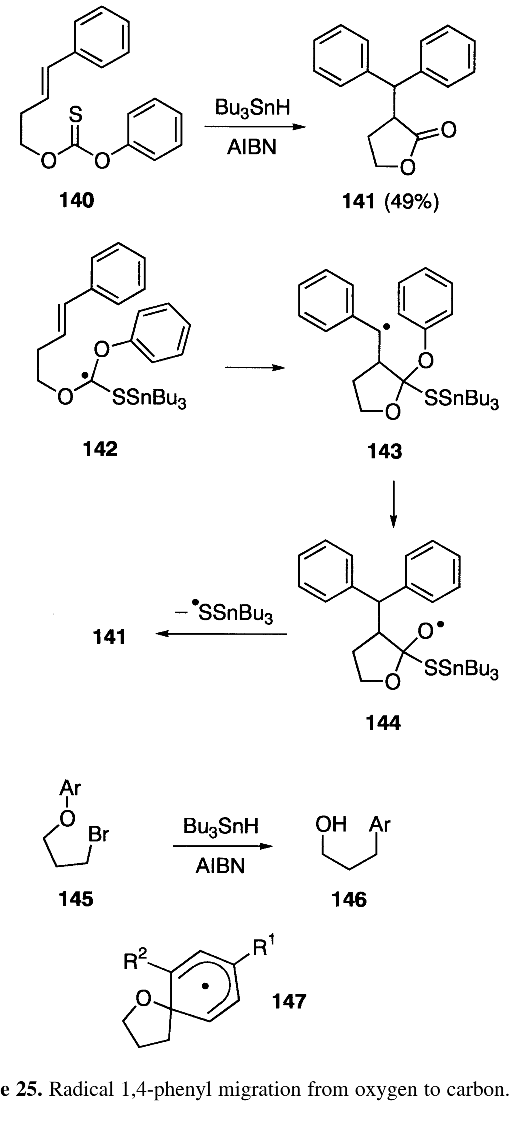
137

138

139

Scheme 24. Radical 1,2-phenyl migration from carbon to oxygen.

of the triphenylmethoxyl radical **131** to form **132** with picosecond time scale absorption spectroscopy and arrived at a rate constant of $>5\times10^{10}\ \mathrm{s}^{-1}$.[65] In the same paper, he also examined the rearrangement of the 1,1-diphenylethoxy radical **133** and claimed the direct detection of the bridged intermediate **137**. Scaiano[66] later determined the Arrhenius parameters for the rearrangement of the alkoxyl radical **133**. He further showed that the intermediate **137** is too short lived to be observed with nanosecond laser photolysis techniques. The spectrum originally assigned by Schuster to the intermediate **137** actually corresponds to the starting alkoxyl radical **133**. Similar conclusions were drawn by Lusztyk in an independent study.[67] Grossi has recently characterized the intermediate **137** using EPR spectroscopy.[68] The alkoxyl radical **133** was generated by photooxidation of the corresponding arylcarbinol with ceric ammonium nitrate. Under these conditions, the intermediate **137** is somehow stabilized by the ceric ion. Analogous phenyl migrations from carbon to oxygen additionally occur in transition metal-catalysed oxidations of tertiary alcohols.[69] An O-neophyl-type rearrangement was also observed in a distonic radical anion.[70] The electrochemically generated radical anion **138** undergoes a highly efficient 1,2-phenyl migration to the corresponding C-centred radical **139**.

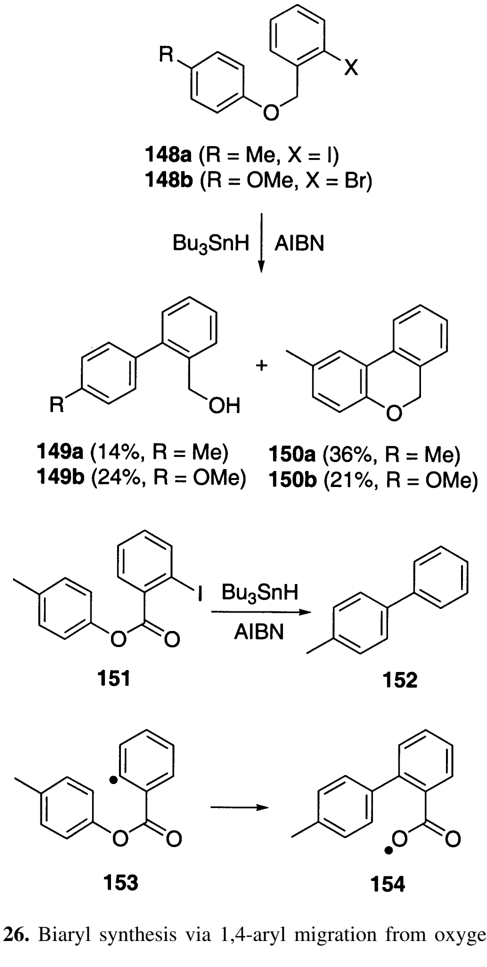


Scheme 25. Radical 1,4-phenyl migration from oxygen to carbon.

The reverse rearrangement, the radical 1,2-phenyl migration from oxygen to carbon, has been observed at high temperatures in pyrolysis[71–73] and in gas phase experiments.[74,75]

As in the all-carbon series, the radical 1,3-aryl migration between carbon and oxygen has not been reported to date. There are, however, some examples of the homologous 1,4-aryl migration. Bachi has published an interesting radical cascade reaction including a 1,4-phenyl migration from oxygen to carbon. Treatment of the phenyl thionocarbonate **140** with tin hydride under radical conditions afforded the diphenylmethyl lactone **141** as the major product in 49% yield (Scheme 25).[76] Initial attack of the stannyl radical onto the C═S double bond provides the tertiary radical **142**, which undergoes a 5-*exo* cyclization to provide the benzylic radical **143**. 1,4-Phenyl migration then affords the alkoxyl radical **144**, which eliminates the tributylstannylthiyl radical to finally give compound **141**.

In a series of experiments, Lee studied the radical 1,4-aryl migration from oxygen to carbon in various bromopropyl aryl ethers **145** (17 different substrates examined) to form the 3-aryl propanols **146**.[77] The efficiency of the *ipso*-substitution is highly dependent on the stability of the intermediate spirocyclic cyclohexadienyl radical **147**. Phenyl transfer with the aryl ether **145** (Ar=phenyl), for example, afforded 3-phenylpropanol in only 2% yield along with 85% of the direct reduction product, phenyl propyl ether. Reaction of the aryl ether **145** (Ar=2-OMe–4-CHO–Ph) under



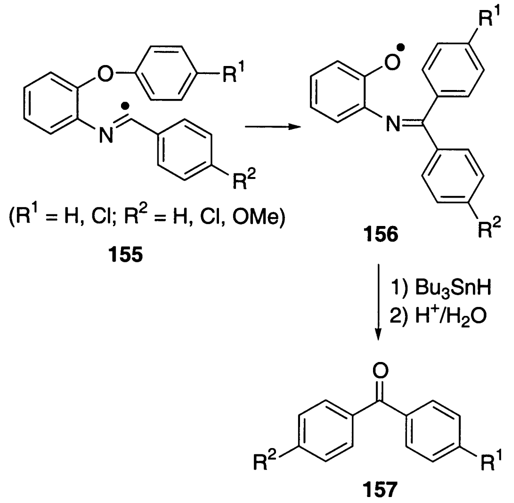
Scheme 26. Biaryl synthesis via 1,4-aryl migration from oxygen to aryl radicals.

analogous conditions, however, provided the corresponding aryl migration product **146** (Ar=2-OMe–4-CHO–Ph) in excellent yield (90%). For the latter reaction, the intermediate cyclohexadienyl radical **147** (R^1=CHO; R^2=OMe) is captodatively stabilized. Analogous 1,4-phenyl migrations in phenyl alkyl ethers from oxygen to aryl radicals to form biaryls also occur, but in low yields.[78,79] Reaction of the aryl halogenides **148a**,**b** under standard tin hydride conditions, for example, yielded the 1,4-phenyl migration products **149a**,**b** in 14 and 24% yield, respectively (Scheme 26).[79] The compounds **150a**,**b**, deriving from *o*-attack with subsequent oxidation, were isolated as side products.

There are only two reports on the radical aryl migration from oxygen to carbon of phenyl esters.[79,80] Treatment of the iodide **151** with Bu_3SnH/AIBN in refluxing toluene, for example, afforded a small amount of the biphenyl **152**.[79] As the mechanism, Bowman suggested an initial *ipso*-substitution of the aryl radical **153** to form the carboxyl radical **154**. Decarboxylation and subsequent reduction eventually provide the biphenyl **152**. Crich has proposed the same mechanism to explain the formation of biphenyl in the reaction of 2-iodophenyl benzoate with tin hydride.[80]

The 1,4-phenyl migration from carbon to oxygen, the reverse process of the rearrangements discussed above, has been observed in the Hunsdiecker reaction of 3,3,3-triphenylpropionic acid[81] and in the thermal decomposition of *t*-butyl 3,3,3-triphenylperpropionate.[82]

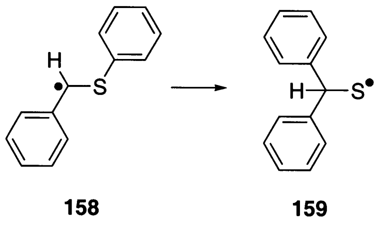
The only examples of radical 1,5-aryl migrations from oxygen to carbon have been published in 1995 by Nanni, who showed that the imidoyl radicals **155** undergo intramolecular *ipso*-substitutions to a small extent to form the phenoxyl radicals **156** (Scheme 27).[83,84] Reduction and hydrolysis eventually afford benzophenone derivatives **157**, which were isolated in up to 18% yield.



Scheme 27. Radical 1,5-phenyl migration from oxygen to carbon.

4.2. Aryl migrations between sulfur/selenium and carbon

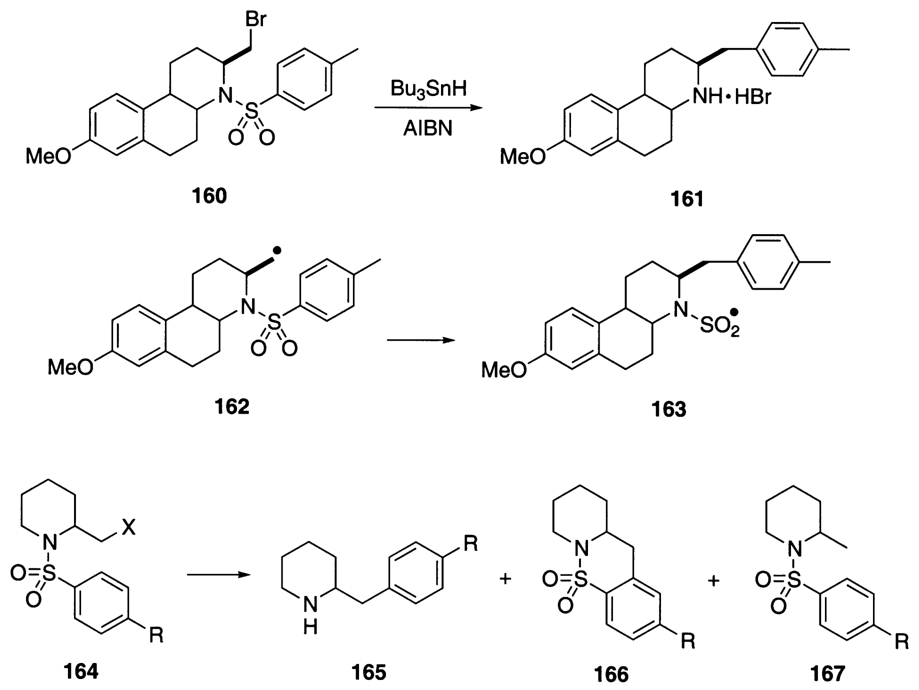
The neophyl-like 1,2-phenyl migration from sulfur to carbon is a known process. Franz determined Arrhenius parameters for the rearrangement of radical **158** to form **159** $(\log(k_r/s^{-1})=(10.65\pm0.74)-(21.4\pm1.55\ \mathrm{kcal/mol})/2.303RT)$.[85] In contrast to the parent neophyl rearrangement (Section 2.1), far higher activation energies have been measured for examples involving sulfur. Migration of the phenyl group from sulfur to carbon for **158** to **159** therefore only occurs at high temperatures (Scheme 28). The reverse process, the 'thia-Wieland-rearrangement', is even slower and has not been observed under the conditions applied.



Scheme 28. 'Thia-neophyl-type' rearrangement.

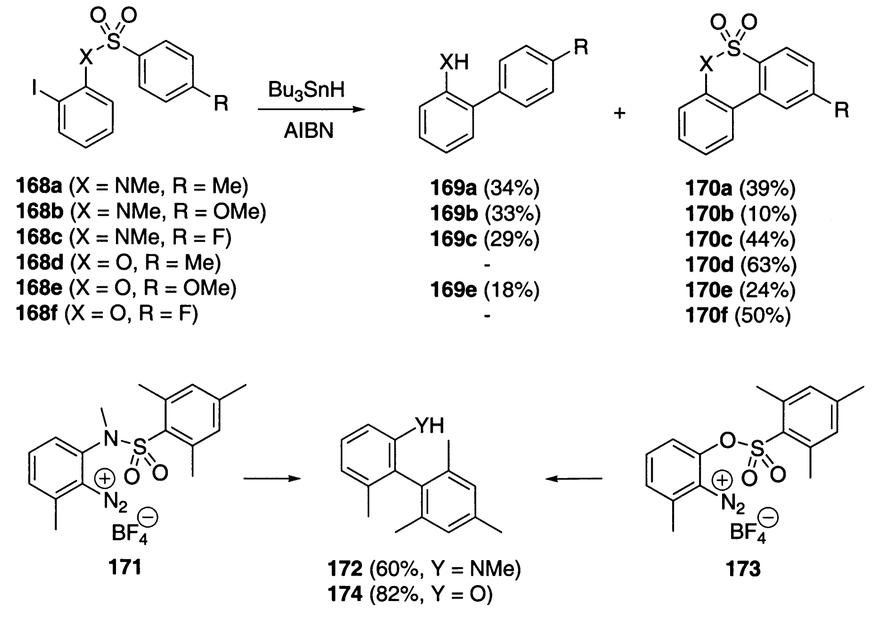
Radical 1,3-aryl migrations from sulfur to carbon are unknown. There are, however, many examples of the homologous radical 1,4-aryl migration reaction. Back in the 1970s, Speckamp and coworkers investigated radical 1,4-aryl migrations from sulfur in sulfonamides to primary and secondary C-radicals (Scheme 29).[86–90] As the first example, they reported the reaction of the bromide **160** with tin hydride under radical conditions in refluxing benzene to afford the tolyl migration product **161** in 88% yield.[86] The primary radical **162**, generated from the bromide **160**, undergoes *ipso*-substitution to give radical **163**, which, after reduction and SO_2 extrusion, yields a secondary amine. Salt formation with HBr, formed during the reaction, finally provides the hydrobromide **161**. In subsequent studies, the reaction of α-halomethyl-substituted piperidine sulfonamides **164** to form the transfer products **165** was carefully investigated.[87–90] As side products in these reactions, the sulfonamides **166** deriving from *o*-attack with subsequent oxidation and the direct reduction products **167** were isolated. It was found that the highest yields of the aryl migration products **165** are obtained at high temperatures. Tolyl transfer at room temperature in anisole, for example, did not yield any of the desired aryl migration product **165** (R=Me). Only the cyclization product **166** (R=Me, 68%) and the direct reduction product **167** (R=Me, 30%) were isolated. The same reaction in diphenyl ether at 190°C, however, provided the aryl migration product **165** (R=Me) in 64% yield along with the cyclization (26%) and the reduction (9%) products.[87] The aryl migration was additionally conducted with a series of *p*-substituted phenyl sulfonamides.[89] In general, the highest yields of the migration product **165** were obtained with π-acceptor substituents at the *p*-position of the migrating phenyl group (R=CO_2Et (53%), R=COMe (57%), R=CN (65%)). Speckamp also showed that aryl groups can be transferred highly stereoselectively to secondary C-radicals in yields of up to 35%.[90] An analogous stereoselective 1,4-phenyl transfer has been observed by Clive.[91]

About ten years ago, Motherwell reported a novel route to biaryls via an intramolecular radical *ipso*-substitution.[92] The aryl sulfonamides **168a**–**c** and aryl sulfonates **168d**–**f** were



Scheme 29. Radical 1,4-aryl migrations in sulfonamides. (X=Br, I; R=H, Me, Cl, Br, F, OMe, CO_2Et, COMe, CN).

reacted with tin hydride under radical conditions to afford the corresponding aryl migration products **169a–c**,**e** (Scheme 30). In contrast to the examples discussed above, aryl radicals were chosen as the attacking species in these reactions. As in the Speckamp studies, side products **170a–f**, deriving from *o*-attack, were observed. From these results, it may be readily seen that the *p*-substituent does not strongly affect the efficiency of the aryl migration reaction in the sulfonamide series. In the sulfonate series, however, aryl transfer occurred only for the electron-rich *p*-methoxyphenyl group. In order to study steric and electronic effects on the aryl migration reaction, the *o*-position of the migrating aryl group was substituted with electron-donating as well as with electron-withdrawing substituents.[93] As expected, direct *o*-addition was suppressed by introducing *o*-substituents for steric reasons. In addition, electron-donating and electron-withdrawing *o*-substituents were found to facilitate the aryl migration reaction. Even heteroarenes can be transferred using this method. Motherwell has recently shown that highly hindered biaryls can be prepared using the radical aryl migration from sulfur to aryl radicals.[94] The introduction of an additional substituent at the *o*-position of the aryl radical further enhances the efficiency of the aryl migration, and diazonium salts have been used, as radical precursors. Mesityl transfer in the sulfonamide **171**, for example, afforded, the biaryl **172** in 60% yield

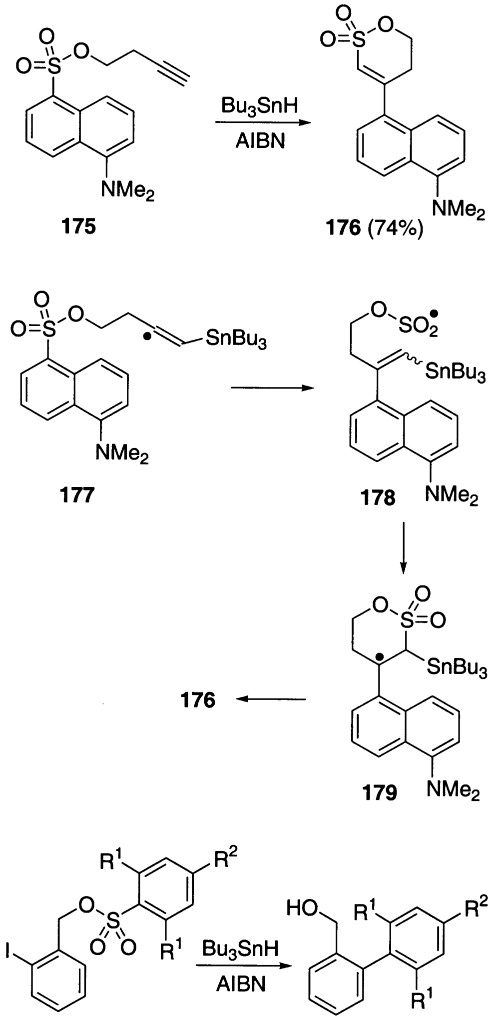


Scheme 30. Radical biaryl synthesis via 1,4-aryl migration from sulfur to carbon.

without the formation of the *o*-addition product. Mesityl transfer for the corresponding sulfonate **173** proceeded even more satisfactorily, and the highly hindered biaryl **174** was isolated in 82% yield.

The 1,4-phenyl migration to vinyl radicals in phenyl sulfides has also been reported.[95] The intermediate vinyl radicals were generated by stannyl radical addition to monosubstituted acetylenes such as $PhSCH_2CH_2CCH$. Further 1,4-phenyl transfers from sulfur to carbon have been observed in gas phase experiments[96] and in photochemistry.[97]

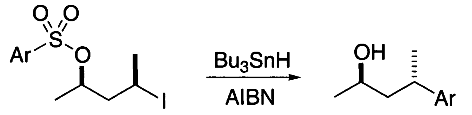
The 1,5-aryl migration from sulfur to reactive vinyl radicals has been studied by Motherwell.[98] The homopropargylic arene sulfonate **175**, for example, was reacted with stannyl radicals to yield the 4-aryl-5,6-dihydro-1,2-oxathiin-2,2-dioxide **176** in 74% yield (Scheme 31). This rather complex cascade reaction includes initial reversible addition of the stannyl radical at the terminal position of the triple bond to form the vinyl radical **177**. The vinyl radical then undergoes an *ipso*-substitution to give the heteroatom-centred radical **178**, which, in turn, reacts in a 6-*endo* cyclization to provide the tertiary radical **179**. β-Fragmentation of the stannyl radical eventually gives the oxathiin-dioxide **176**. The analogous cascade reaction in the sulfonamide series was observed to be less efficient. The same group examined the 1,5-aryl migration from sulfur in sulfonates and sulfonamides to aryl radicals for the preparation of biaryls.[99] The arenesulfonates, deriving from *o*-iodobenzyl alcohols, were reacted with tin hydride under radical conditions. *o*-Substituents at the migrating aryl group were found to be crucial for the *ipso*-substitution, reaction of the sulfonate **180a**, for example, not yielding any of the desired biaryl product. Products deriving from direct *o*-addition were isolated. With the mesityl derivative **180b**, however, aryl migration occurred and the biaryl **181b** was isolated in 36% yield. As for the 1,4-migration, the best results were obtained for the sulfonate bearing a *o*-methoxycarbonyl group (90% yield, not shown). In the analogous series of *N*-methylsulfonamide derivatives, *ipso*-substitution cannot compete with direct *o*-addition.



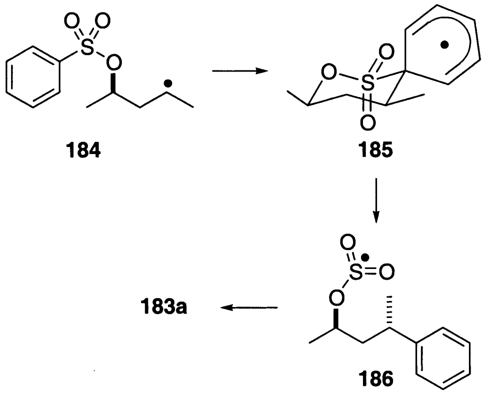
180a (R^1 = H, R^2 = OMe)	**181a** (-)
180b (R^1 = R^2 = Me)	**181b** (36%)

Scheme 31. Radical 1,5-aryl migration to vinyl and aryl radicals.

Studer and Bossart used the radical 1,5-aryl migration from sulfur in sulfonates to secondary C-radicals for stereoselective $C(sp^2)–C(sp^3)$ bond formation.[100] Various aryl groups were transferred with high selectivities and in high yields, as shown for the transformation of the arylsulfonates **182a–e** to the corresponding alcohols **183a–e** (Scheme 32). In order to explain the stereochemical outcome of these aryl migrations, the following model was suggested (phenyl example discussed): The secondary radical **184**, derived from the iodide **182a**, undergoes intramolecular *ipso*-attack at the aryl group of the sulfonate to form the cyclohexadienyl radical **185**. The transition state for the formation of the cyclohexadienyl radical probably resembles a chair with the substituents in equatorial positions. Rearomatization then affords the heteroatom-centred radical



182a (Ar = Ph)	**183a** (76%, dr =13:1)
182b (Ar = 4-FC_6H_4)	**183b** (59%, dr = 10:1)
182c (Ar = 4-$MeOC_6H_4$)	**183c** (50%, dr = 9:1)
182d (Ar = 2-thienyl)	**183d** (74%, dr = 9:1)
182e (Ar = 5-Me_2N-naphthyl)	**183e** (52%, dr = 11:1)



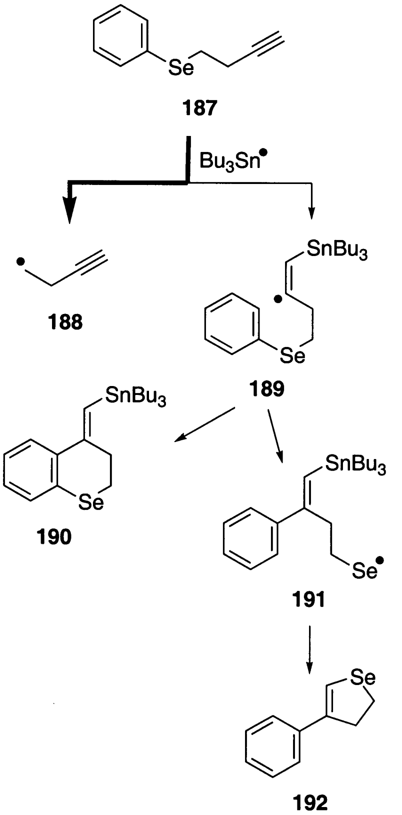
Scheme 32. Stereoselective 1,5-aryl migration reactions.

186, which, after reduction and SO_2-extrusion, gives the alcohol **183a**.

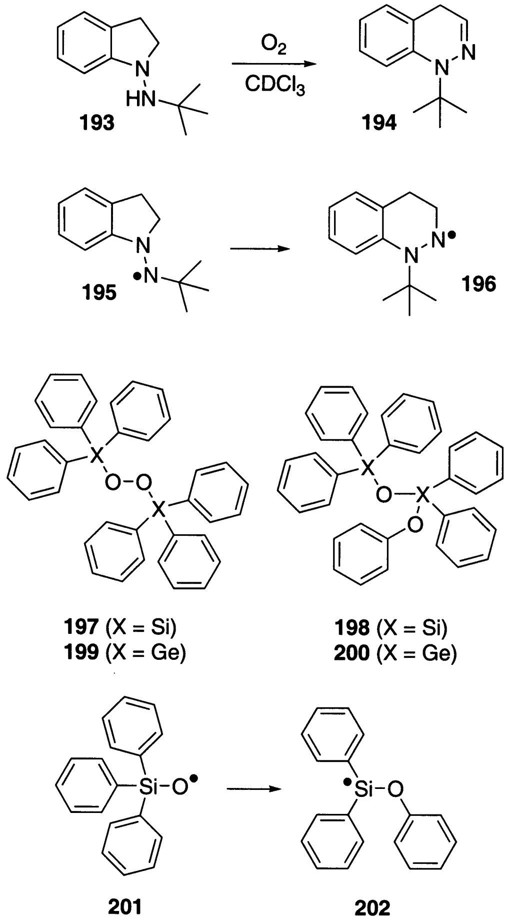
To the authors' knowledge, there is only a single report on a radical aryl migration between selenium and carbon.[95] In the reaction of the phenyl selenide **187** with stannyl radicals, the main reaction pathway is the homolytic substitution at selenium to provide the primary radical **188** (Scheme 33). Stannyl radical addition occurs to a small extent at the terminal position of the triple bond, however, to generate the vinyl radical **189**. The vinyl radical can then undergo *o*-attack to afford the selenocycle **190** or *ipso*-substitution (1,4-phenyl migration) to give the selenyl radical **191**. Cyclization of the selenyl radical **191** eventually affords the selenophene **192**.

5. Aryl migrations between two heteroatoms

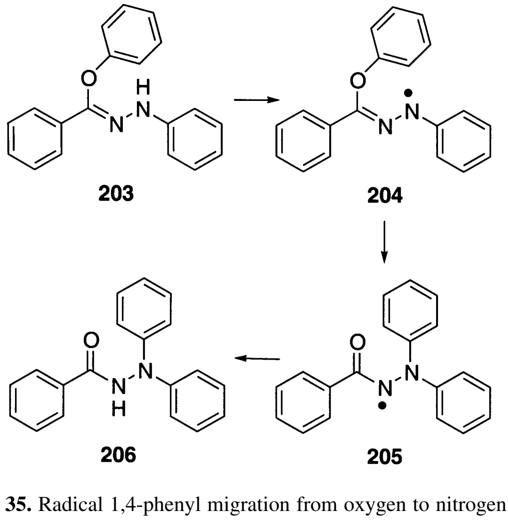
There are very few reports on the radical neophyl-type rearrangement (1,2-aryl migration) between two heteroatoms. Some years ago, Warkentin described an interesting rearrangement of hydrazyl radicals,[101] in which the hydrazine **193** undergoes clean transformation to the cyclic hydrazone **194** on standing under an atmosphere of air in $CDCl_3$ (Scheme 34). The sequence comprises a 1,2-aryl migration between the two nitrogen atoms and is initiated by air oxidation of the hydrazine **193** to form the hydrazyl radical **195**. A neophyl-type rearrangement then affords the radical **196**, which is finally oxidized to the hydrazone **194**. The 1,2-aryl migration between silicon and oxygen has been described 30 years ago.[102] Thermal decomposition of the silylated peroxide **197** provided the rearranged silicon compound **198** in quantitative yield. Thermal O–O-bond homolysis affords a silylated alkoxyl radical **201**, which rearranges to the silyl radical **202**. Radical recombination of **201** and **202** eventually provides the siloxane **198**. The same reaction sequence was observed in the thermolysis of the germylated peroxide **199** to give the rearranged compound **200**.[103]



Scheme 33. Radical 1,4-phenyl migration from selenium to a vinyl radical.



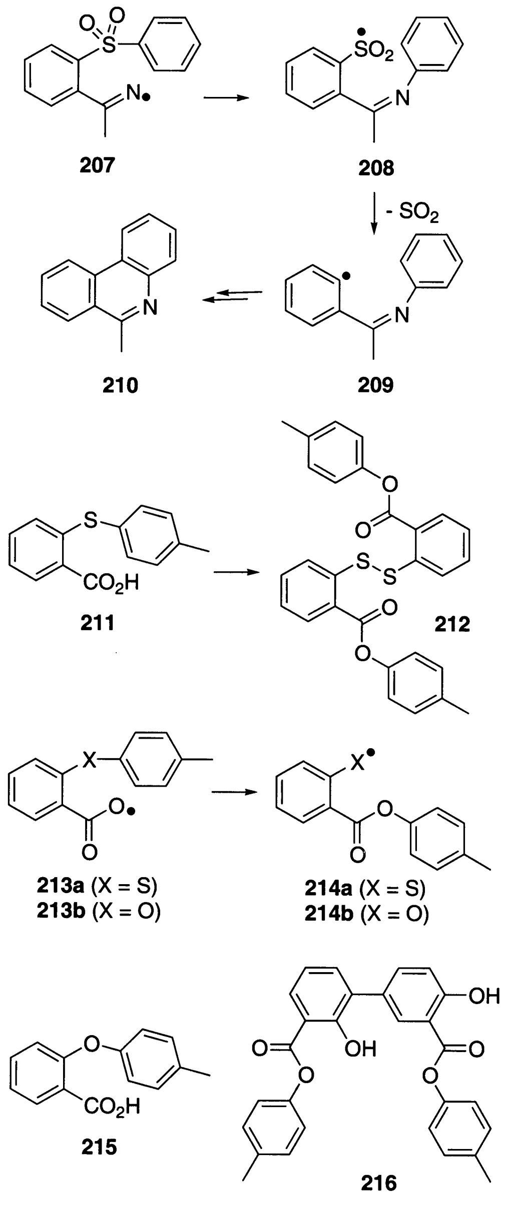
Scheme 34. Radical 1,2-aryl migration between two heteroatoms.



Scheme 35. Radical 1,4-phenyl migration from oxygen to nitrogen.

The radical 1,3-aryl migration between two heteroatoms is unknown. A 1,4-phenyl migration from oxygen to nitrogen has been reported by Hegarty.[104] Oxidation of the hydrazonate **203** with MnO_2 in refluxing benzene affords the N-centred radical **204**, which further reacts in a 1,4-phenyl migration to give the hydrazyl radical **205** (Scheme 35). Reduction, probably with the starting hydrazonate **203** (H-transfer), provides the hydrazide **206**. Further 1,4-aryl migrations between two heteroatoms have been observed in the gas phase.[105]

Very recently, the first radical 1,5-phenyl migration from sulfur to nitrogen has been reported by Leardini.[106] The iminyl radical **207**, generated from the corresponding *t*-butyl iminoxyperacetate, was shown to undergo *ipso*-substitution to a small extent, to give the sulfonyl radical **208** (Scheme 36). SO_2 extrusion then affords the aryl radical **209**, which reacts in a homolytic aromatic substitution to provide the phenanthridine **210** (10% isolated yield).



Scheme 36. Radical 1,5-aryl migration between two heteroatoms.

A 1,5-aryl migration from sulfur to oxygen occurred during persulfate oxidation of the sulfide **211**. The corresponding sulfoxide was isolated as the main product, together with starting material and the diester **212** (15%).[107] The diester is formed by initial oxidation of the acid **211**, providing the carboxyl radical **213a**, which undergoes a 1,5-aryl migration to give the thiyl radical **214a** and dimerization to eventually afford **212**. In an analogous manner, the ether **215** was oxidized to afford the aryl migration/dimerization product **216** in 20–30% yield.[107] *ipso*-Substitution in the carboxyl radical **213b** affords the phenoxyl radical **214b** (1,5-tolyl migration from oxygen to oxygen), which undergoes dimerization to provide the diester **216**.[108] Similar aryl migrations from oxygen in aryl esters to phenoxyl radicals have been observed in pyrolysis experiments.[109]

6. Summary and outlook

In some of the examples discussed in the present article, the radical aryl migration occurs as a side reaction in low yields. There is, however, a increasing number of papers describing the radical aryl migration as an efficient synthetic method for C–C bond formation. Radical biaryl synthesis, for example, using the aryl migration methodology is well developed, and, additionally, there are many radical aryl transfers for which accurate kinetics have been determined. These reactions can nowadays be used as radical clocks in kinetic competition experiments. Despite these achievements, however, a great deal of qualitative and quantitative work remains to be carried out, especially in the area of stereoselective radical aryl migration reactions.

Carbon, silicon, germanium, tin, nitrogen, phosphorous, oxygen, sulfur and selenium have so far been reported to participate in radical aryl migration reactions. As already stated in the introduction, further elements should participate equally well in radical rearrangements comprising aryl transfer reactions. Future experiments will certainly help to fill the gaps in the periodic system shown in Fig. 1.

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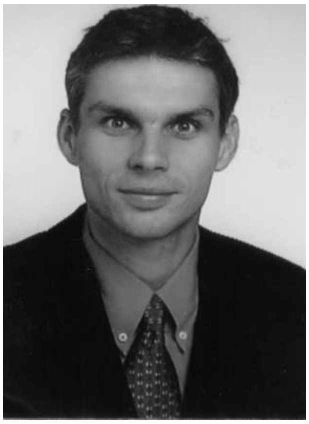
Biographical sketch



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