Chem Soc Rev

Radical Aryl Migration Reactions and Synthetic Applications

Journal:	*Chemical Society Reviews*
Manuscript ID:	CS-REV-12-2014-000467.R1
Article Type:	Review Article
Date Submitted by the Author:	16-Mar-2015
Complete List of Authors:	Chen, Zhi-Min; Shanghai Jiao Tong University, School of Chemistry and Chemical Engineering Zhang, Xiao-Ming; Lanzhou University, State Key Laboratory of Applied Organic Chemistry, Department of Chemistry Tu, Yong Qiang; Lanzhou University, State Key Laboratory of Applied Organic Chemistry + Department of Chemistry

Radical Aryl Migration Reactions and Synthetic Applications

Zhi-Min Chen,[a,†] Xiao-Ming Zhang[b,†] and Yong-Qiang Tu*[a,b]

[a] School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, Shanghai 200240, P. R. China

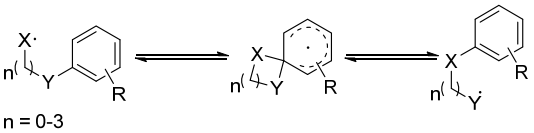
[b]State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. China

[†]These authors contributed equally to this work

Radical aryl migration reactions are of particular interest to the chemical community due to their potential applications in radical chemistry and organic synthesis. The neophyl rearrangements used as radical clocks for examining the radical-molecular reactions have been known for decades. The combinations of these migrations with other radical reactions have provided a wide range of novel synthetic methodologies that are complementary to nucleophilic rearrangements. This review will give an overview of various types of radical aryl migrations, with an emphasis on their mechanistic studies from a historical point of view, as well as their applications in tandem radical reactions.

1. Introduction

Radical aryl migration reactions represent a unique class of organic transformations standing at the intersection of both radical and rearrangement reactions. Specifically, this type of reaction refers to the intramolecular radical migration process of an aryl group from a carbon or heteroatom to a radical center through the formation of a 3, 4, 5, or 6 membered spirocyclic intermediate or transition state. The migration is typically terminated by other radical pathways such as elimination, β-scission, or H-abstraction (Scheme 1). The initial radical species are commonly generated by a radical initiator, an intermolecular radical addition, thermolysis, or photolysis. Unlike most nucleophilic rearrangements, which have been investigated extensively in the past,[1] the exact mechanisms of some radical aryl migration reactions have long been debated, thus piquing the long-term interest of many researchers in validating an unequivocal and reasonable mechanism with the assistance of various spectroscopic techniques and computations. Importantly, the combinations of these migrations with a number of other radical reactions often establish new methodologies capable of synthesizing compounds that are not easily available through nucleophilic rearrangements or other protocols. Therefore, the mechanistic studies of these migration reactions, together with their potential synthetic applications have made them an attractive research field both in radical chemistry and organic synthesis over the past decades.[2]



n = 0-3
X = C, N, O, Si, P, S, Ge, etc.
Y = C, N, O, Si, P, S, Ge, etc.

Scheme 1 Radical aryl migration reactions

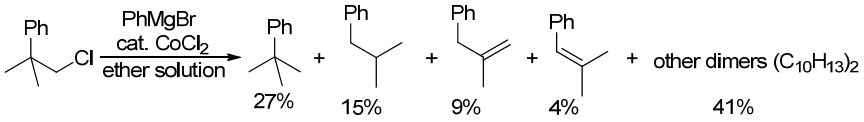
The first aryl migration reaction was disclosed by Wieland in 1911.[3] Since then, a number of examples of aryl migrations have emerged, with the most famous one being the neophyl-type rearrangement first discovered in 1944 by Urry and Kharrasch.[4] The mechanistic studies of these two 1,2-aryl migration reactions have lasted a long time, during which period various other migration types, mainly the 1,4- and 1,5-aryl migrations, have been discovered. Additionally, it has been found that the migrations can take place between carbon and various heteroatoms or even from one heteroatom to another. Despite the extensive research of these radical rearrangements over the last century, their synthetic applications were very limited except for some examples on biaryl synthesis. However, with the recent development of radical chemistry, especially the recent "gold rush" in radical trifluoromethylation, phosphonylation, and azidation reactions, these radical aryl migrations have begun to exhibit their potential impact in organic synthesis. Many of these rearrangements have been incorporated in tandem radical processes to efficiently synthesize the skeletons of natural products and organic compounds containing fluorine, phosphorus, nitrogen, or sulfur. These novel transformations not only enrich the variety of radical aryl migration reactions, but also expand their applications in both the pharmaceutical industry and material science. In this review, we will focus our attention both on recent achievements of radical aryl migrations and their development from the historic perspective. We hope a substantial discussion of the mechanistic studies, reaction designs and synthetic applications of radical aryl migrations can give insights into such reactions.

2. Radical 1,2-aryl migrations

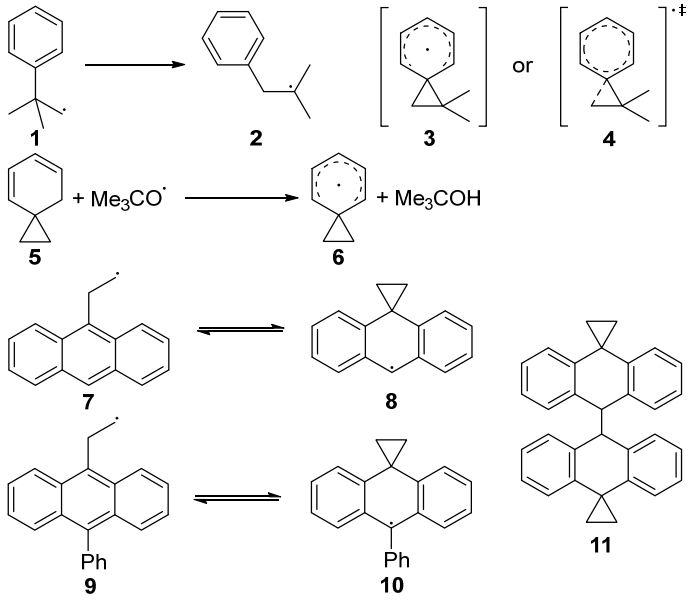
2.1 Neophyl rearrangement

In 1944, when Urry and Kharrasch conducted the Grignard reaction of neophyl chloride, they discovered that the reaction proceeded unusually under a catalytic amount of cobaltous chloride.[4] After carefully examining the products, they surprisingly found 15% isobutylbenzene, 9% 2-methyl-3-phenyl-1-propene, and 4% *β*,*β*-dimethylstyrene (Scheme 2). This unexpected result was attributed to a 1,2-phenyl migration, the neophyl rearrangement, after the formation of neophyl radical **1** (Scheme 3). Since this seminal work, significant efforts have been made to gain a better understanding of the mechanism of this transformation. The first aspect to consider is whether the reaction proceeds through an intermediate **3** or a transition state **4**. Detection of **3** and related spiro[2,5]octadienyl radicals proved difficult in several early reports using electron paramagnetic resonance (EPR) spectroscopy.[5] However, in later experiments, Ingold and co-workers demonstrated that radical **6**, which was formed by H atom abstraction from spirodiene **5**, could be identified by fluorescence spectroscopy with an absorption band at ca. 560 nm characterizing the cyclohexadienyl radical.[6] Although this method validated the existence of the spiro radical intermediate **6** in this specific reaction, the conclusion could not be simply extended to the neophyl rearrangement. To further investigate the intermediacy of a

spiro radical in this rearrangement, Leardini et al. searched other substrates that could *in situ* generate radicals **7** or **9**.[7] After a series of experiments including EPR spectroscopic and chemical studies, they demonstrated the presence of spirocyclic radicals **8** and **10** and their rapid equilibration with the initially formed radicals **7** and **9** in these two neophyl-type rearrangements. It was of particular interest that in the first rearrangement, the self-combination product **11** from radical **8** was isolated and fully characterized by NMR, mass spectrometry, and X-ray diffraction data. The authors also performed calculations using STO-3G at HF, UHF and MP2 levels on the rearrangement of $PhCH_2CH_2^{\cdot}$, but more quantitative DFT calculations were finally performed by Dannenberg in 2001 which, in line with previous reports, strongly suggested that the spiro radical **6** to be a short-lived intermediate rather than a transition state.[8]



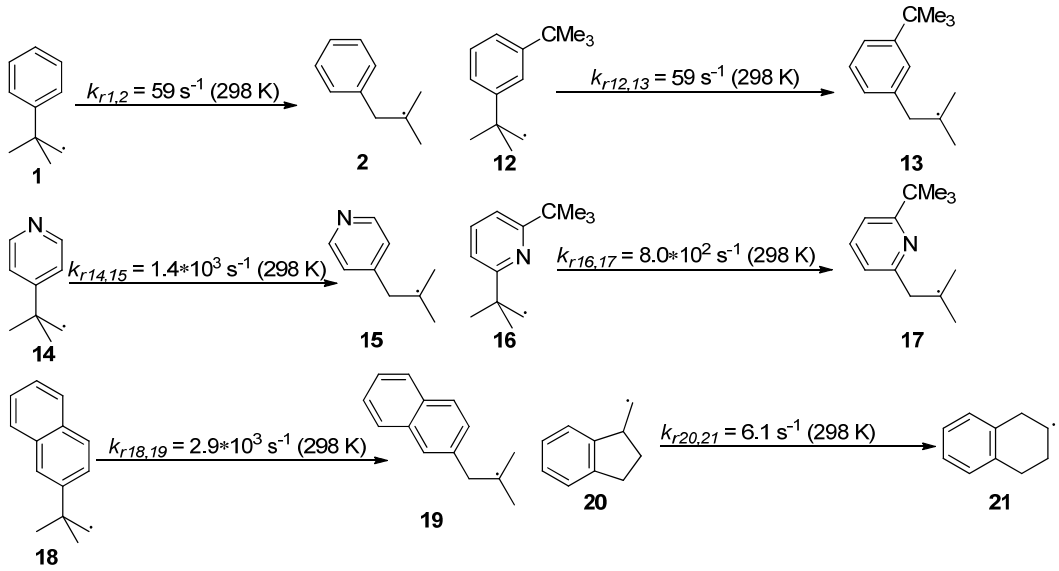
Scheme 2 Neophyl rearrangement



Scheme 3 Mechanistic studies on the intermediacy of spiro[2,5]octadienyl radicals

As another significant aspect in mechanistic studies, the determination of the rate constants k_r of various neophyl rearrangements can provide detailed information on the reaction speed and enable their use as radical clocks for examining the rates of radical-molecule reactions.[9] Measurement of these rate constants was first conducted by Ingold and co-workers using EPR spectroscopy.[10] In their earlier work, they had determined the k_r of five neophyl rearrangements (Scheme 4), with the same rate constant $k_{r1,2}$ or $k_{r12,13}$ = 59 s^{-1} at 298 K for 1,2-phenyl and 1,2-*m*-*tert*-bultylphenyl migrations and quite different constants for the rearrangements of **14**, **16** and **18**,[11] that were $k_{r14,15}$ = 1.4×10^3 s^{-1}, $k_{r16,17}$ = 8.0×10^2 s^{-1} and $k_{r18,19}$ = 2.9×10^3 s^{-1} at 298 K, respectively. In these experiments, the initial radicals **1**, **12**, **14**, **16** and **18** were generated through hydrogen abstraction by *tert*-butoxy radicals. Nearly a decade later, Franz et al. investigated the Arrhenius parameters of different neophyl

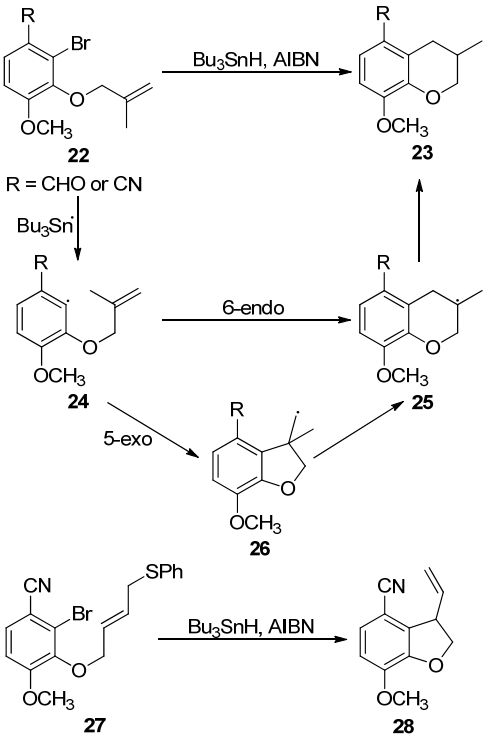
rearrangements.[12] In their work, they employed an indirect method in which the hydrogen abstraction from Bu_3SnH by primary alkyl radicals acted as radical clocks and competed with the rearrangement reactions to help firstly determine the relative rates and then the absolute rates. The absolute rate constant of neophyl rearrangement they refined was $k_{r1,2}$ = 764 s^{-1} at 298 K and that of the migration of 1-indanylmethyl **20** to 2-tetralyl **21** was $k_{r20,21}$ = 6.1 s^{-1} at 298 K. Shortly thereafter, Ingold's group once again studied the kinetics of neophyl rearrangement as well as those of some other 1,2-radical migrations involving non-aryl groups.[13] On this occasion, they used chlorine abstraction from CCl_4 by a primary alkyl radical as a competition reaction. The relative rates of these non-aryl migrations were obtained based on product analysis and the neophyl rearrangement was used as a radical clock to determine the absolute rate constant of the competition reaction, which in turn served as a second radical clock in determining the absolute rate constants of other non-aryl migrations. The same group further revised the rate constant of neophyl rearrangement to be $k_{r1,2}$ = 4.3×10^4 s^{-1} at 373 K.[14] In the latest report, Fischer and Weber re-determined the absolute rate constant of neophyl rearrangement with the aid of time-resolved electron spin resonance (ESR) and finally refined the constant to be $k_{r1,2}$ = 402 s^{-1} at 298 K.[15]



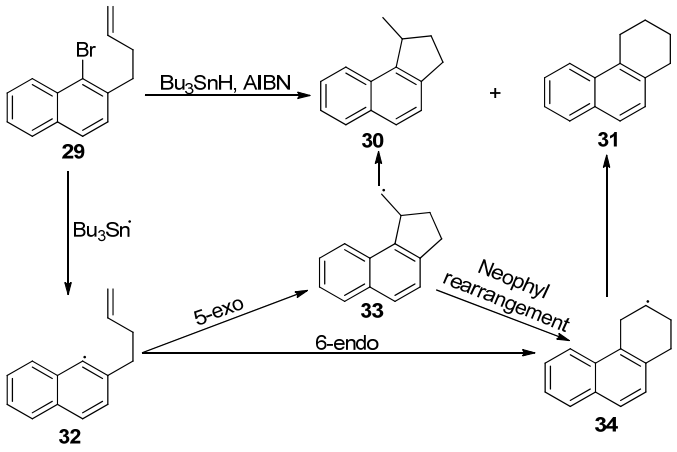
Scheme 4 Determination of the rate constants of various neophyl rearrangements

The initial synthetic applications of neophyl rearrangements were rare except for some examples involved in radical ring closure reactions. Parker and co-workers discovered that when bromides **22** were treated with Bu_3SnH, the resulting radicals **24** underwent cyclization to afford products **23** (Scheme 5).[16] The reaction was proposed to proceed first through *5-exo* cyclization to give primary radicals **26** and then neophyl rearrangement to generate **25** instead of a direct *6-endo* cyclization, evidenced by the exclusive transformation of bromide **27** to the *5-exo* product **28**. These explanations, however, were not consist with the later results reported by Beckwith who showed that both direct *6-endo* cyclization and *5-exo* cyclization/neophyl rearrangement cascade actually coexisted in the transformation of **22** to **23** and the predominant route was determined by the concentration of Bu_3SnH.[17] To further study the mechanism, Beckwith investigated the radical cyclization of

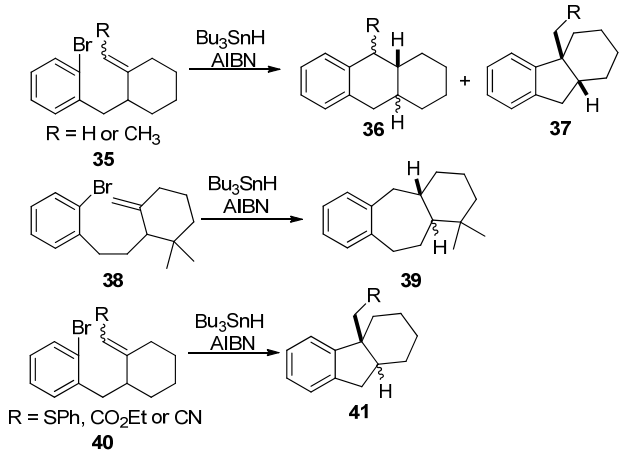
bromide **29** (Scheme 6). High concentrations of Bu_3SnH facilitated the formation of *5-exo* cyclization product **30**, while low concentrations of Bu_3SnH predominantly provided formal *6-endo* cyclization product **31**, indicating that **31** was not entirely generated by *6-endo* cyclization in which case the ratio of **30**:**31** should be independent of the concentration of Bu_3SnH. Similar results were also obtained by Ishibashi et al. in their investigation of the regio-chemistry of aryl radical cyclization of substrates **35** and **38** (Scheme 7).[18] Only at low concentrations of Bu_3SnH were the *endo* cyclization products **36** and **39** exclusively produced. In the same work, they also demonstrated that the regio-selectivity tends to be *5-exo* cyclization if there was a phenylthio, ester or cyano group at the terminus of the methylene. The cyclizations of **40** exclusively generated the corresponding compounds **41**. Apart from these formal radical *6-endo* cyclizations that in fact involve first *5-exo* cyclization and then neophyl rearrangement,[19] other examples of *5-exo* radical cyclization/neophyl rearrangement cascade are more evident. In their efforts to achieve total syntheses of alkaloids (±)-mesembranol and (±)-elwesin using a key radical cyclization of the dichloroacetamides **42**, Ishibashi et al. found an unexpected side product **45** generated via a neophyl rearrangement of **47** taking place after the radical cyclization (Scheme 8). The same result was also obtained in the cyclization of the analogous dichloroacetamides **49**.[20]



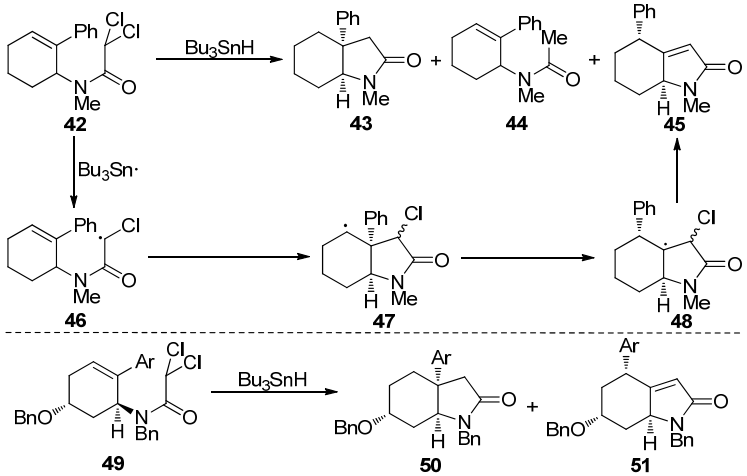
Scheme 5 Initial studies on radical cyclization/neophyl rearrangement



Scheme 6 *5-Exo* radical cyclization and formal *6-endo* radical cyclization determined by the concentration of Bu_3SnH



Scheme 7 *5-Exo* radical cyclization vs. formal *6-endo* radical cyclization in different substrates

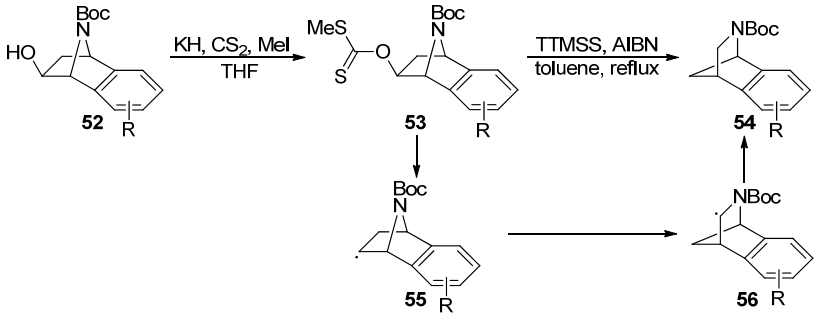


Scheme 8 Other types of tandem *5-exo* cyclization/neophyl rearrangement reactions

The early investigations of neophyl or neophyl-type rearrangements as side reactions or in the context of the mechanistic studies had perhaps, to some extent, prevented them from becoming synthetically useful methodologies. However, the recent exploration of those migrations has demonstrated their potential synthetic applications, especially when combined with other radical reactions.

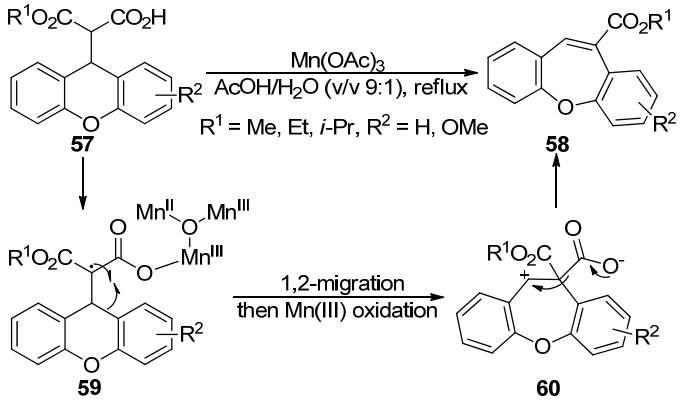
In 2002, Hodgson et al. developed a novel synthetic method to prepare a series of

2-azabenzonorbornanes **54** from 7-azabenzonorbornanols **52** by combining Barton deoxygenation and neophyl rearrangement (Scheme 9).[21] 7-Azabenzonorbornanols **52** were first transformed to xanthates **53**, which were then treated with tris(trimethylsilyl)silane (TTMSS) and azodiisobutyronitrile (AIBN) to afford **54** in moderate to high yields. The driving force of the neophyl rearrangement in this reaction is probably the generation of *N*-stabilized radical **56** from radical **55**.



Scheme 9 Tandem Barton deoxygenation/neophyl rearrangement

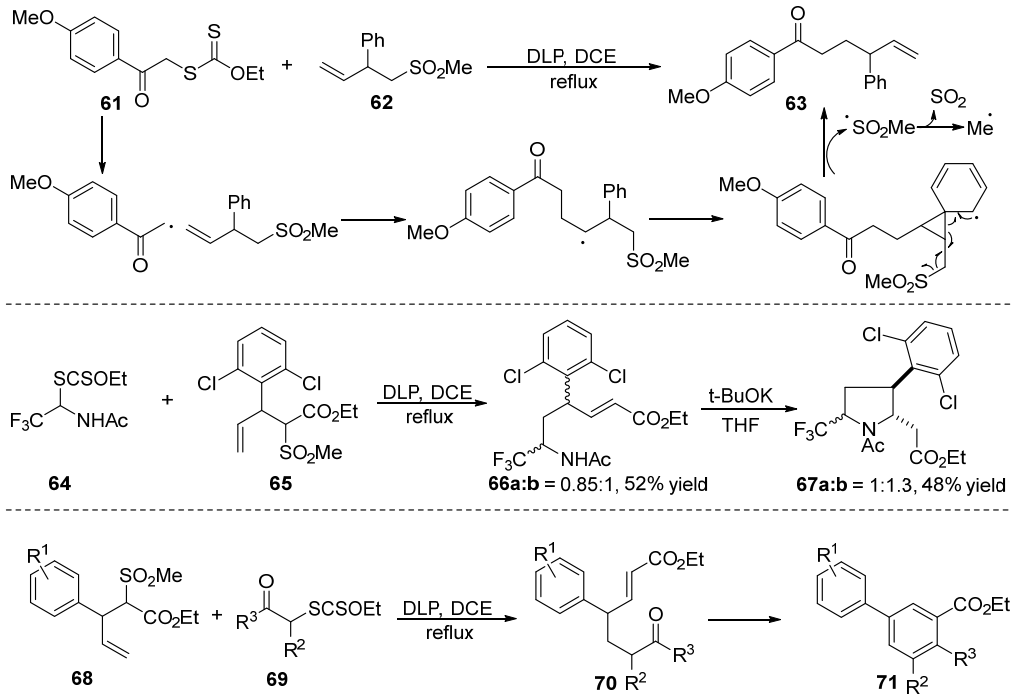
Nishino and co-workers employed a ring-expansion strategy for the preparation of dibenz[b,f]oxepins. The activated C-H bond of malonates **57** was first oxidized by $Mn(OAc)_3$ to initiate the neophyl rearrangement, leading to the formation of a benzyl radical that could then easily be oxidized by Mn(III) to give **60**. The cation-induced decarboxylation of **60** finally afforded **58** (Scheme 10).[22]



Scheme 10 Mn(III) promoted C-H oxidation/neophyl rearrangement

Besides initiating neophyl rearrangement through dehalogenation, deoxygenation or intramolecular cyclization, rearrangements initiated by an intermolecular radical addition have been found in a number of recent examples. Zard and co-workers developed a radical homoallylation reaction which involved xanthate addition, 1,2-aryl migration and β-elimination of a sulfonyl radical for the preparation of various terminal alkenes, α,β-unsaturated esters or ketones (Scheme 11).[23] These radical reactions could serve as useful tools in constructing important building blocks for organic synthesis. For example, the research group applied the cascade process as a central step to synthesize 2,3,5-trisubstituted pyrrolidine **67**, a compound with polytropic pharmacological activities.[24] Although the yield and diastereoselectivity were moderate, the two-step sequence was highly efficient. Some of the products of these tandem radical reactions could also be applied to the syntheses of biaryl compounds **71** via a one-pot reaction. This straightforward route enables the

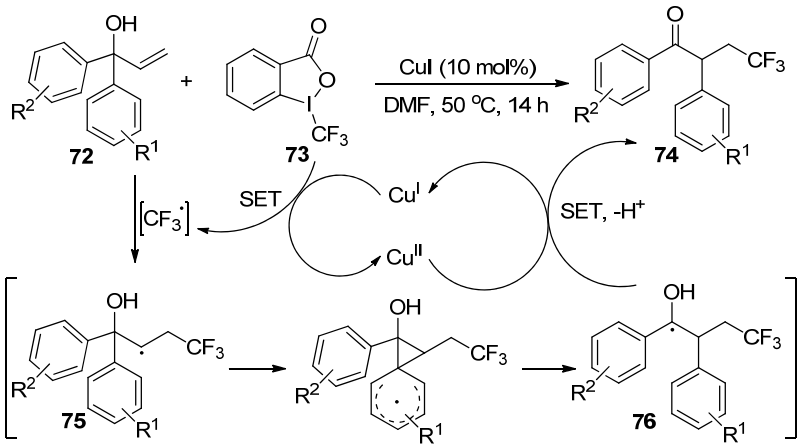
convenient syntheses of various biaryls with functional group patterns quite different from those of biaryls prepared via other existing approaches such as transition metal catalyzed couplings.[25]



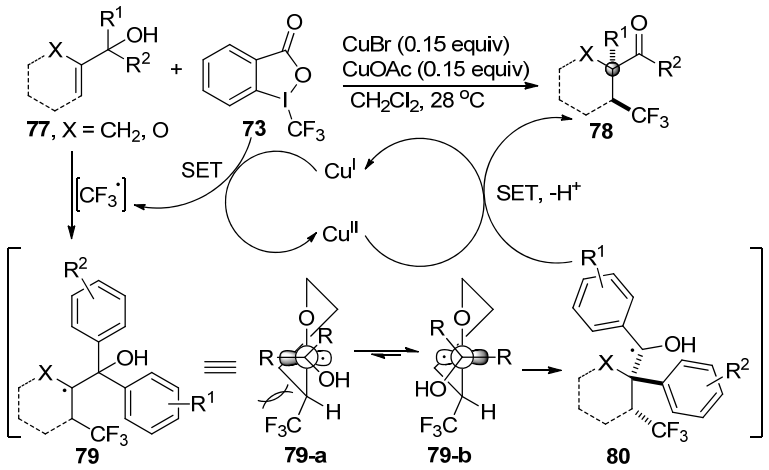
Scheme 11 Tandem xanthate addition/1,2-aryl migration reactions and their applications

With recent advances in radical chemistry, and more specifically in radical alkylation, trifluoromethylation, phosphonylation, and azidation reactions, the combinations of these reactions with neophyl rearrangement have generated novel methods for carbon-carbon bond formation and the syntheses of heteroatom-containing compounds. The first attempts at such tandem reactions were performed independently by Li, Sodeoka and Tu at nearly the same time. In 2013, Li's and Tu's groups reported an interesting copper-catalyzed trifluoromethylation/1,2-migration of allylic alcohols. In both reactions, Togni's reagent **73** first reacted with Cu(I) through a single electron transfer (SET) process to release a CF_3 radical. The addition of the CF_3 radical to the C=C bond of substrates **72** or **77** triggered the radical 1,2-aryl migration to generate radicals **76** or **80**. Oxidation of **76** or **80** by Cu(II) through a second SET process afforded the final products and completed the catalytic circle. Although the possible existence of a cationic intermediate in the reaction of **77** could not easily be ruled out, the experimental results and DFT calculations performed on the reaction of **72** strongly supported a radical rearrangement process (Scheme 12).[26] It is worth mentioning that both reactions have a wide substrate scope and the use of substrate **77** enables the construction of an all-carbon quaternary or oxa-quaternary carbon center in a highly diastereoselective manner (Scheme 13).[27] The work from Sodeoka and co-workers showed that Cu(I) was not the only effective catalyst in this tandem reaction. The reaction was also feasible under a catalytic amount of $Fe(OAc)_2$ (Scheme 14).[28] Significantly, the migratory aptitude of aryl groups in the neophyl rearrangement is quite different from that in the cationic semipinacol rearrangement. For nonsymmetric

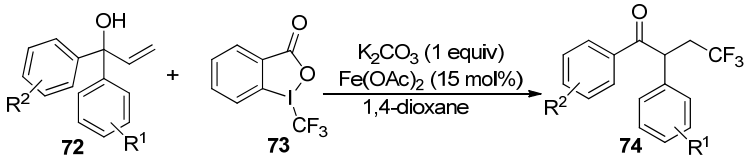
α,α-diaryl allylic alcohols, the aryl group bearing electron-withdrawing group rather than electron-donating group, at *para* or *meta* position would migrate predominantly in the neophyl rearrangement. This aptitude in radical 1,2-migration reactions has also been validated by kinetic studies on the *O*-neophyl rearrangement (see the next section).



Scheme 12 Cu(I)-catalyzed radical trifluoromethylation/1,2-aryl migration



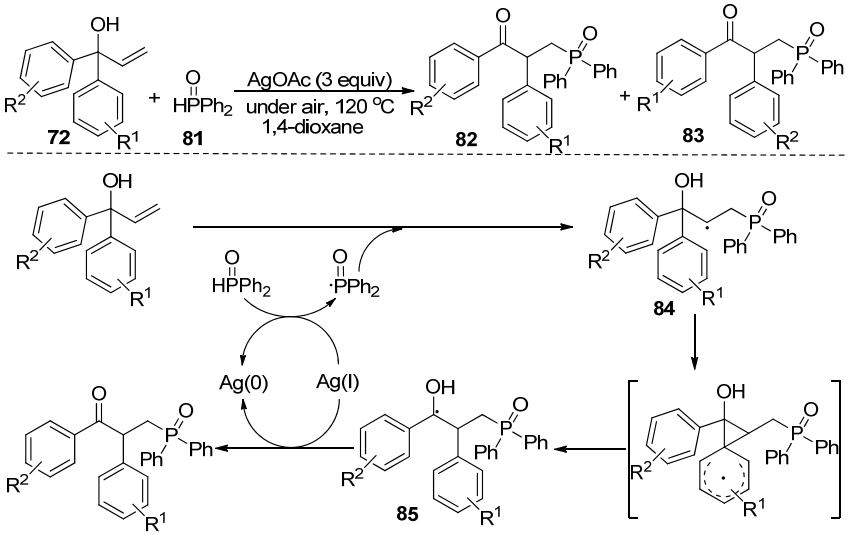
Scheme 13 Cu(I)-catalyzed radical trifluoromethylation/1,2-aryl migration of enolate-type substrates



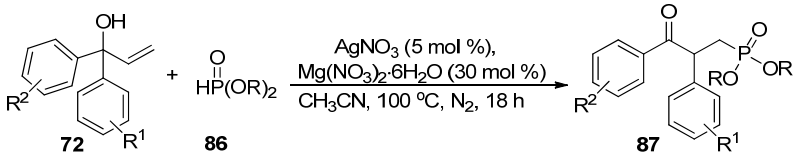
Scheme 14 Fe(II)-catalyzed radical trifluoromethylation/1,2-aryl migration

Following the pioneering work on tandem trifluoromethylation/neophyl rearrangement reactions, Xu and Ji extended the radical 1,2-aryl migration of allylic alcohols to a phosphonylation cascade. In the presence of excess AgOAc (3 equiv.), diphenylphosphine oxide **81** was oxidized to give a *P*-centered radical, which then added to the C=C bond of **72** and initiated the neophyl rearrangement to finally generate α-aryl-β-phosphinylated carbonyl ketones **82** and **83** in moderate to high yields (up to 93 %, Scheme 15).[29] A catalytic version of this tandem reaction was later achieved by Wu and co-workers using $AgNO_3$ as the catalyst and $Mg(NO_3)_2$ as the

additive (Scheme 16).[30] In this case, a dialkyl phosphonate instead of the diphenylphosphine oxide reacted with allylic alcohols **72**.

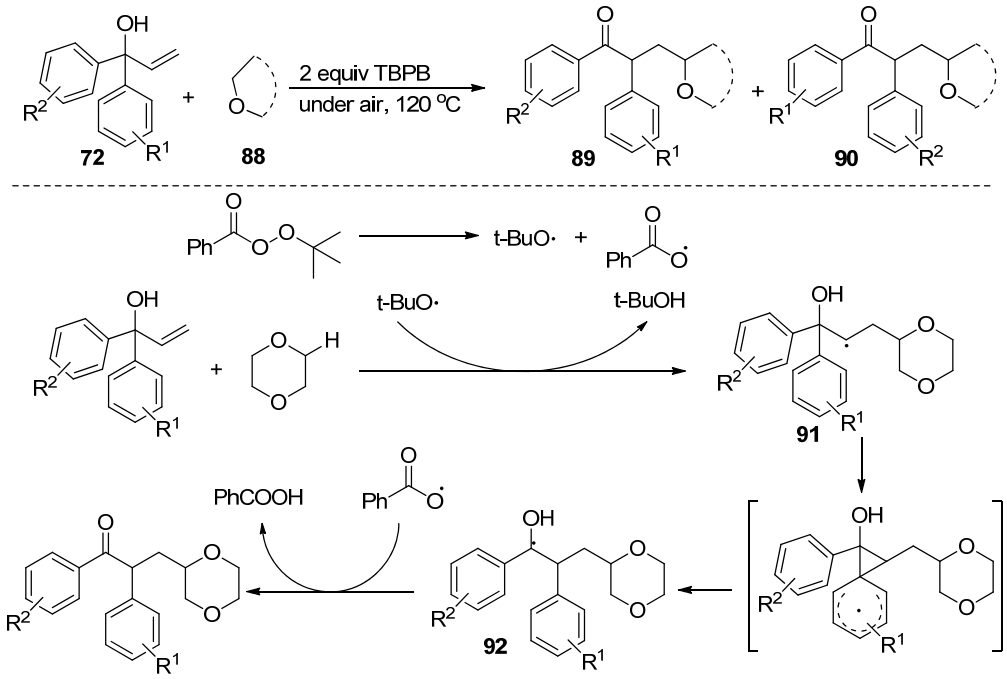


Scheme 15 Ag(I)-mediated radical phosphonylation/1,2-aryl migration

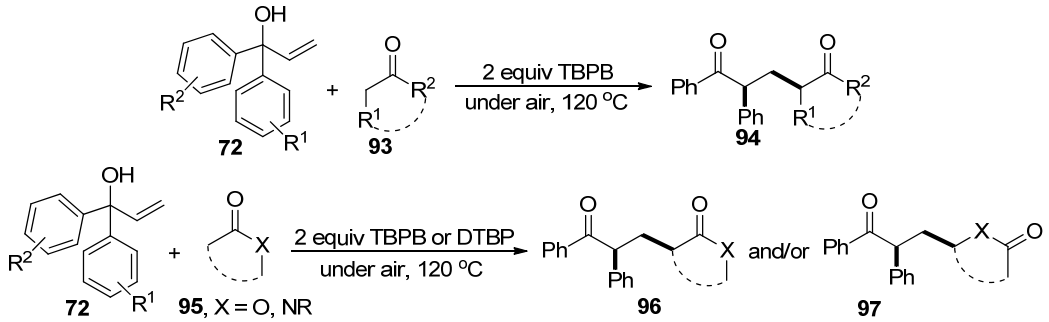


Scheme 16 Ag(I)-catalyzed phosphonation/1,2-aryl migration

Shortly thereafter, Xu and Ji showed that the allylic alcohols were also capable of participating in a radical alkylation/neophyl rearrangement cascade. The *α*-carbon-centered radical generated from ether **88** added to the C=C bond of **72** to induce the 1,2-aryl migration and afford *α*-aryl-*β*-alkylated carbonyl ketones **89** and **90** in high yields. This cascade process successfully combined C(sp^3)-H bond functionalization with neophyl rearrangement (Scheme 17).[31] Notable other tandem radical alkylation/neophyl rearrangement reactions are the oxidative functionalization of *α*-C(sp^3)-H bonds of carbonyl derivatives (Scheme 18) and acetonitriles, the activation of *N*-*α*-C(sp^3)-H bonds of amides and even oxidation of more inert C(sp^3)-H bonds of alkanes.[32]

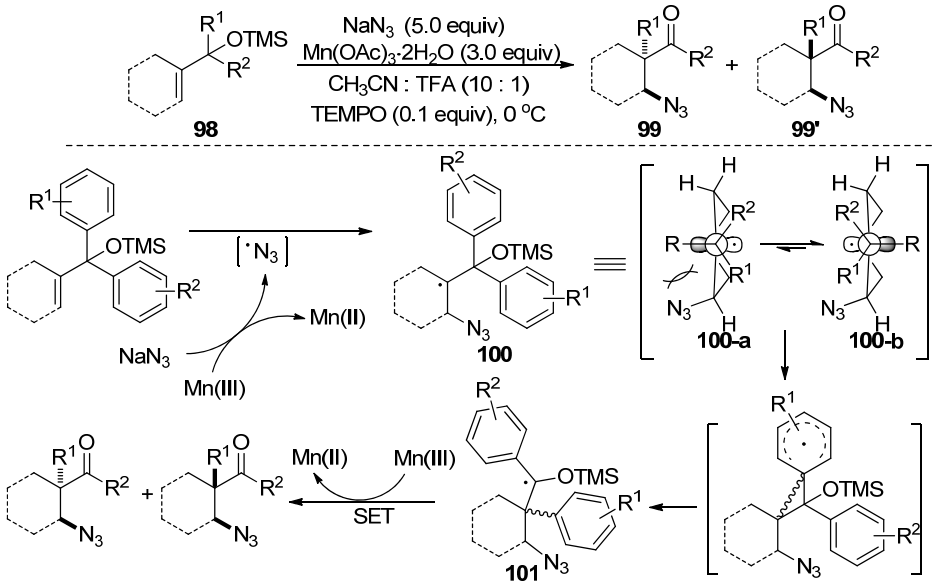


Scheme 17 Radical alkylation/1,2-aryl migration of allylic alcohols with ethers



Scheme 18 Radical alkylation/1,2-aryl migration of allylic alcohols with carbonyl derivatives

Very recently, Tu's group explored a novel radical azidation/1,2-aryl migration cascade process by applying NaN_3 as an azide source and excess $Mn(OAc)_3 \cdot 2H_2O$ as the oxidant. Interestingly, they found that when TEMPO was used as an additive, the yields could be notably improved. Under the optimal conditions, a series of α-quaternary β-azidyl carbonyls were obtained in moderate to excellent yields. Since the steric difference between conformers **100-a** and **100-b** was relatively minor, the corresponding diastereoselectivity was moderate. The transformation provides a straightforward approach to α-quaternary β-amino carbonyl derivatives (Scheme 19).[33]

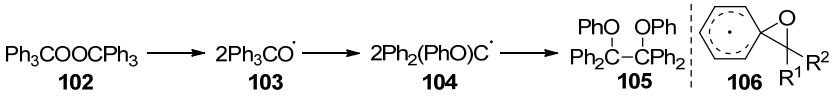


Scheme 19 Mn(III)/TEMPO-mediated radical azidation/1,2-aryl migration

2.2 Radical 1,2-aryl migrations between carbon and oxygen

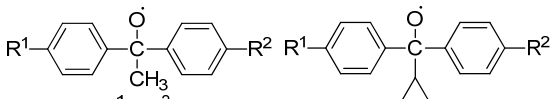
The first radical aryl migration reaction was documented in 1911 when Wieland discovered an unusual coupling product **105** after he decomposed 20 g of peroxide **102** under thermal conditions (Scheme 20).[3] The outcome was attributed to a 1,2-phenyl migration from carbon to its vicinal oxygen, driven by the formation of a more stable radical **104**. In the decades after this work, mechanistic studies of this and other analogous migrations were carried out to deepen the understanding of such radical aryl migrations, namely *O*-neophyl rearrangements. Similar to the investigations of neophyl rearrangement, two main aspects to consider are: (1) whether there is also an analogous oxaspiro radical intermediate **106**; and (2) what the rate constants of these rearrangements are. The existence of intermediate **106**, however, has long been debated. Initial detection of such an intermediate by Schuster using time-resolved laser flash photolysis (LFP)[34] turned out to be incorrect due to misassignment of the absorption band.[35] Later, Grossi et al. reported that they had characterized the spiro radical intermediate **106** by ESR spectroscopy.[36] In this work, the spiro intermediate was proposed to be stabilized by CAN through hydrogen-bonding and thus was detected. However, this observation was doubted by Bietti and co-workers who also made detailed product and time-resolved LFP kinetic studies on the reactivities of various 1,1-diarylalkoxyl radicals with different ring substitution patterns (Scheme 21, radicals **107**-**109** and **114**-**118**).[37] From their results, a concerted mechanism was strongly suggested, indicating that the reaction proceeded via a reactant-like transition state instead of the previously proposed step-wise process through the formation of an oxaspiro[2,5]octadienyl intermediate. Additionally, they demonstrated that the rearrangements of nonsymmetric 1,1-diarylalkoxyl radicals were governed by electronic effects rather than the stabilities of carbon-centered radicals, which provided the following migratory aptitudes: 4-trifluoromethylphenyl > phenyl = 4-methylphenyl > 4-methoxyphenyl. The above paradoxical conclusions

from mechanistic studies induced Ingold et al. to re-examine the original experimental results reported by Grossi.[38] Having repeated the experiments, they found that the early assignment of the spiro radical intermediate **106** was incorrect and the radical observed was actually $C_6H_5O^{\cdot}$. To further address the issue of the intermediacy of spiro radical **106**, Bietti carried out hybrid DFT calculations, performed at the UB3LYP/6-31G(d) level, to obtain additional evidence of the mechanism.[39] They had already demonstrated in their early experimental work that the change of substitution from methyl to cyclopropyl (the differences between radicals **107** and **114**) did not significantly affect the rate constants (2.8×10^6 s^{-1} for **107** and 2.0×10^6 s^{-1} for **114**, respectively) and ΔG° values obtained. Therefore, they only performed calculations on the methyl substituted compounds (radicals **107**, **110**, **111**, **112** and **113**) to avoid calculations of conformational minima involved in cyclopropyl-substituted compounds or radicals. The calculated energetics regarding these 1,2-migrations revealed that, in all cases but the rearrangement of **113**, the oxaspiro radicals were shallow energy minima which validated the step-wise process of these *O*-neophyl rearrangements. Meanwhile, DiLabio's group also independently performed computational studies on various different substrates and drew the same conclusion as Bietti's.[40] Despite the convincing results established by computational studies, there was still a lack of potent experimental evidence. Therefore, Bietti's group made further product and time-resolved kinetic studies on several cumyloxyl radicals.[41] Unlike the 1,1-diarylmethoyl radicals, cumyloxyl radicals typically undergo *β*-scission rather than the *O*-neophyl rearrangement (Scheme 22). In their experiment, they devised and synthesized alcohol **119** bearing a 1,1-diphenyl-1-cyclopropyl group at the *para* position of the phenyl ring. When this substrate was photolyzed, the resulting cumyloxyl radical did not undergo *β*-scission as usual. Instead, the epoxide compound **121** was obtained from **119**. The transformation might have occurred through major events including the formation of an oxaspiro[2,5]diene radical, the opening of the cyclopropane, iodine abstraction and finally substitution by H_2O. This result was in agreement with previous computational studies, strongly supporting the existence of an oxaspiro radical intermediate.



102 **103** **104** **105** **106**

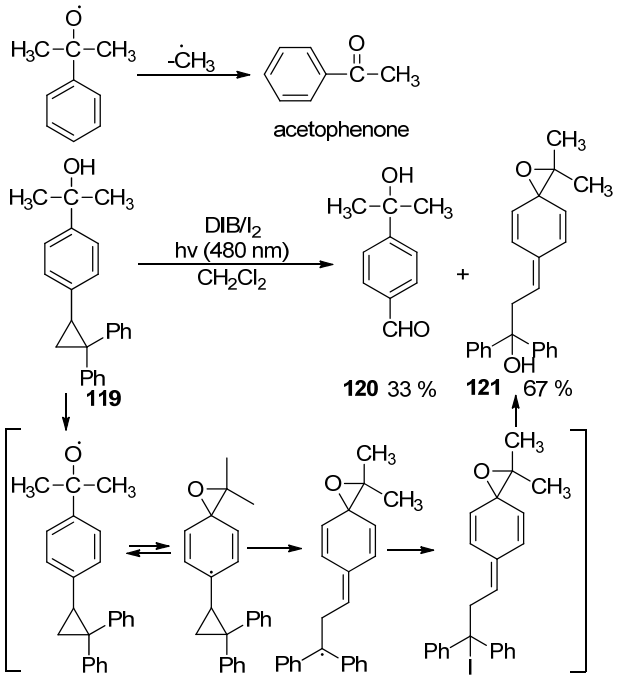
Scheme 20 Wieland rearrangement-the first *O*-neophyl rearrangement



107 $R^1 = R^2 = H$
108 $R^1 = H$; $R^2 = Me$
109 $R^1 = R^2 = Me$
110 $R^1 = R^2 = OCH_3$
111 $R^1 = R^2 = CF_3$
112 $R^1 = R^2 = NO_2$
113 $R^1 = OMe_3$; $R^2 = CF_3$

114 $R^1 = R^2 = H$
115 $R^1 = H$; $R^2 = OMe$
116 $R^1 = R^2 = OMe$
117 $R^1 = H$; $R^2 = CF_3$
118 $R^1 = R^2 = CF_3$

Scheme 21 Radicals investigated in *O*-neophyl rearrangement



Scheme 22 Experimental validation of an oxaspiro radical intermediate

Most rate constants of above-mentioned *O*-neophyl rearrangements were determined either by experimental methods or computations or both. These data are summarized in Table 1 and illustrate the migratory aptitudes of different aryl groups. Applications of *O*-neophyl rearrangements have been rare except for some examples observed as side reactions in the studies of other radical reactions.[43,44]

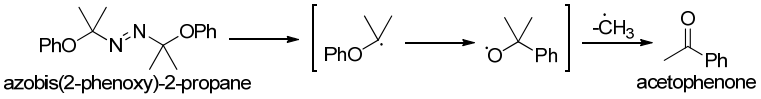
Table 1 Rate constants of *O*-neophyl rearrangements determined by calculations and experiments.

radical	k_{calc} (s^{-1})[a]	k_{exp} (s^{-1})[e]
103	2.0×10^{8} [b,c]	1.4×10^{8} [f,c]
107	9.3×10^{5} [d]	2.8×10^{6} [g]
108		2.4×10^{6} [g]
109		2.0×10^{6} [g]
110	1.5×10^{5} [d]	
111	7.5×10^{6} [d]	
112	5.3×10^{7} [d]	
113	3.8×10^{5} [d]	
114	5.9×10^{5} [d]	2.0×10^{6} [g]
115		5.1×10^{5} [g]
116		2.6×10^{5} [g]
117		5.0×10^{6} [g]
118		1.8×10^{7} [d]

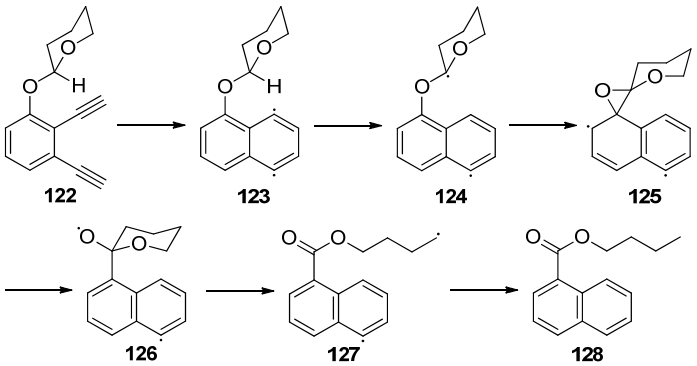
[a] Gas-phase at 298.15 K and 1 atm. [b] Gas-phase at 295.15 K and 1 atm. [c] Ref 42. [d] Ref 39. [e] MeCN solution at 295.15 K. [f] CH_2Cl_2 solution at 295.15 K. [g] Ref 37.

Reverse *O*-neophyl rearrangement, in which the aryl group migrates from oxygen to initial carbon-centered radical, was first discovered by Ohno et al. in 1971 when they decomposed azobis(2-phenoxy)-2-propane under thermal conditions (Scheme

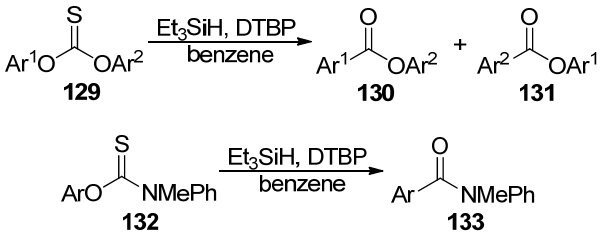
23).[45] The isolation of 50% acetophenone was due to a migration in the 2-phenoxyprop-2-yl radical to afford the 2-phenyl-isopropoxy radical. It was not until 2010 that another example of this type of migration was discovered by Alabugin and co-workers.[46] Ketone **128** was isolated as a side product in the Bergman cyclization of diyne **122** (Scheme 24). Generation of this compound was attributed to a reverse *O*-neophyl rearrangement taking place after the H-abstraction of the naphthalene diradical **123**. The authors carried out calculations to validate the intermediacy of oxaspiro diradical **125** and indeed located it to be an energy minimum. Based on their unexpected discovery, Alabugin designed further analogous radical rearrangements capable of converting phenols into benzoates or benzamides.[47] In their first attempt, they considered the initial steps of the Barton-McCombie deoxygenation reaction and tried to use them to initiate the reverse *O*-neophyl rearrangement.[47a] Therefore, a variety of diphenyl thiocarbonates **129** were prepared, and when treated with triethylsilane (TES) and di-*tert*-butyl peroxide (DTBP), they were successfully transformed to the corresponding esters **130** and **131** via the expected migration followed by a fragmentation (Scheme 25). However, for nonsymmetric diphenyl thiocarbonates, both migration products were obtained with moderate selectivity, a drawback greatly reducing the efficiency of this synthetic method. To solve this problem, Alabugin et al. synthesized various thiocarbamates **132** and examined their reactivities for reverse *O*-neophyl rearrangement (Scheme 25).[47b] Although there was the possibility of *N*-neophyl rearrangement of **132**, the reaction took place exclusively via the *O*-neophyl rearrangement to afford benzamides **133** in high yields (up to 99%). However, unlike their computational studies for the reaction of **122**, DFT calculations on these two migration reactions both suggested a concerted process without the formation of a three-membered oxaspiro radical. These computational results were also different from later calculations performed by Beste et al. on the β-radical of phenethyl phenyl ether, the *O*-neophyl rearrangement of which was suggested to proceed through an oxaspiro[2,5]octadienyl radical intermediate.[48]



Scheme 23 Reverse *O*-neophyl rearrangement



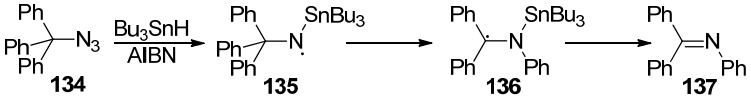
Scheme 24 Discovery of a reverse *O*-neophyl rearrangement in the Bergman cyclization



Scheme 25 Conversion of phenols into benzoates or benzamides

2.3 Radical 1,2-aryl migrations from carbon to nitrogen

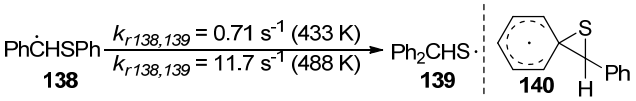
There are very few examples of the radical 1,2-aryl migrations from carbon to nitrogen and still no example of the reverse reaction. The earliest report on such an *N*-neophyl rearrangement was in 1995 (Scheme 26).[49] The transformation of azide **134** to imine **137** proceeded through a 1,2-phenyl shift from the initial nitrogen-centered radical **135** to carbon-centered radical **136**. Similar processes also exist in other tandem radical reactions.[50]



Scheme 26 Radical 1,2-aryl migration from carbon to nitrogen

2.4 Radical 1,2-aryl migrations from sulfur to carbon

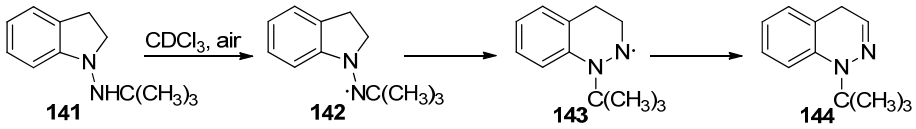
The only example of 1,2-aryl migration from sulfur to carbon was investigated by Franz and co-workers in 1992 (Scheme 27).[51] They determined the rate constant of this reaction to be $k_{r138,139}$ =0.71 s^{-1} at 433 K and their computational studies revealed a concerted mechanism, with **140** being the transition state.



Scheme 27 1,2-Aryl migration from sulfur to carbon

2.5 Radical 1,2-aryl migrations between heteroatoms

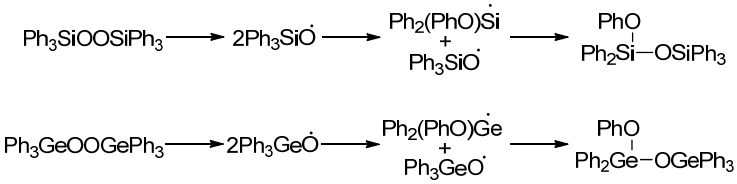
In 1988, Warkentin discovered an interesting 1,2-aryl migration between two nitrogen atoms.[52] Exposure of the $CDCl_3$ solution of 1-aminoindoline **141** to air for 2-3 days led to the clean formation of **144** (Scheme 28). The reaction was initiated by molecular oxygen to generate radical **142**. After the 1,2-phenyl migration of **142**, the so-formed radical **143** underwent *β*-scission to afford the 1,4-dihydrocinnoline **144**.



Scheme 28 Radical 1,2-aryl migrations between two nitrogen atoms

Examples of radical 1,2-aryl migrations from silicon or germanium to oxygen have been known for over 40 years.[53] Similar to the initial discovery of *O*-neophyl rearrangement, these migrations were identified following thermal decomposition of

either bis(triphenylsilyl) or bis(triphenylgermyl) peroxides, and the rearranged products were obtained in high yields for both reactions (Scheme 29).

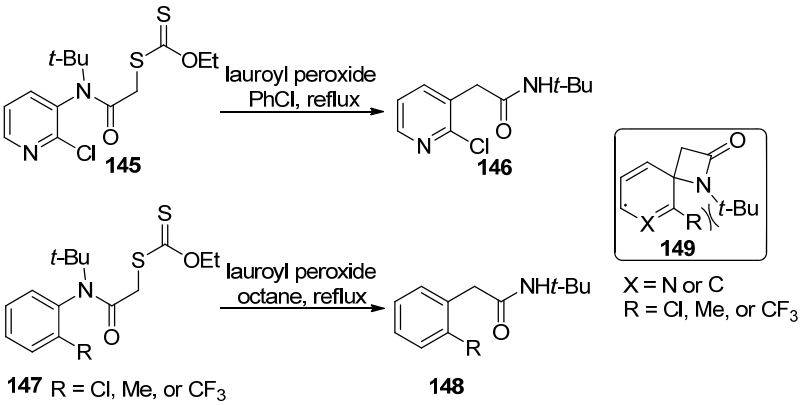


Scheme 29 Radical 1,2-aryl migrations from silicon or germanium to oxygen

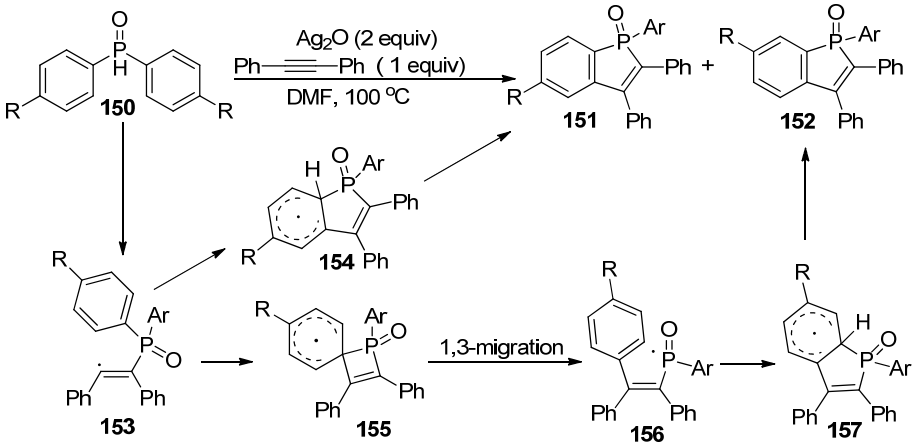
3. Radical 1,3-aryl migrations

Probably because of the requirement of forming a strained four-membered spiro radical intermediate or transition state, radical 1,3-aryl migrations have rarely been observed. In fact, it was not until 2005 that the first example of 1,3-aryl migration was reported by Zard and co-workers.[54] Treatment of *N*-(α-xanthyl)acetylaminopyridines **145** or *N*-(α-xanthyl)acetanilides **147** with dilauroyl peroxide (DLP) under reflux conditions generated rearranged products **146** or **148** (Scheme 30). The *tert*-butyl substitution on the nitrogen atom and the *ortho* substituent on the benzene or pyridine ring were essential factors for the success of this reaction, because the steric repulsion between these two groups compressed the methyl radical toward the benzene or pyridine ring, thus favoring the formation of a spiro[3,5]nondienyl radical **149**.

Another 1,3-aryl transfer process was suggested in a recent C-H activation reaction, although it was not the only reaction pathway. In this work, Duan and co-workers developed a C-H/P-H functionalization method to synthesize benzo[b]phosphole oxides from aryl phosphine oxides and internal alkynes (Scheme 31).[55] The reaction was proposed to proceed via a radical mechanism involving two possible reaction pathways of a direct addition of alkenyl radical **153** onto the aromatic ring and a 1,3-migration of **155** followed by addition of the resulting phosphorous radical **156** onto the aromatic ring. This dual pathway mechanism can explain why the two isomers **151** and **152** were obtained in the transformation.



Scheme 30 Radical 1,3-aryl migrations from nitrogen to carbon



Scheme 31 Radical 1,3-aryl migrations in a C-H/P-H functionalization process

4. Radical 1,4-aryl migrations

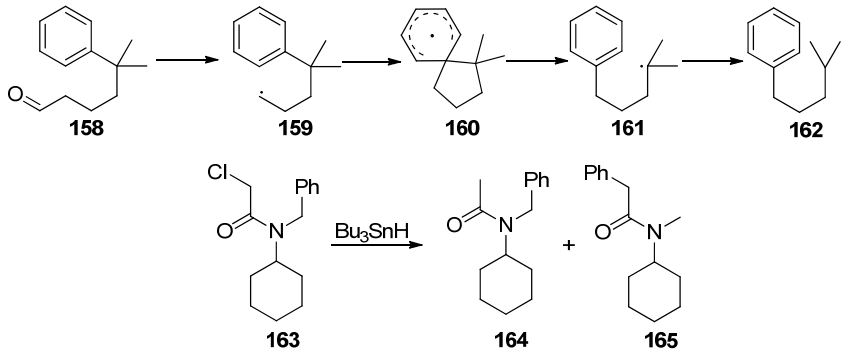
Radical 1,4-aryl migrations incorporate a wide range of reaction types. Among them, aryl migrations between carbon atoms, and migrations from the sulfur atom of a sulfone or a sulfonamide to carbon have been extensively studied and make up the vast majority of reactions in this chapter. Other examples of 1,4-aryl migrations between carbon and other heteroatoms represent only a small proportion of the known examples of this type of reactions.

4.1 Radical 1,4-aryl migrations from carbon to carbon

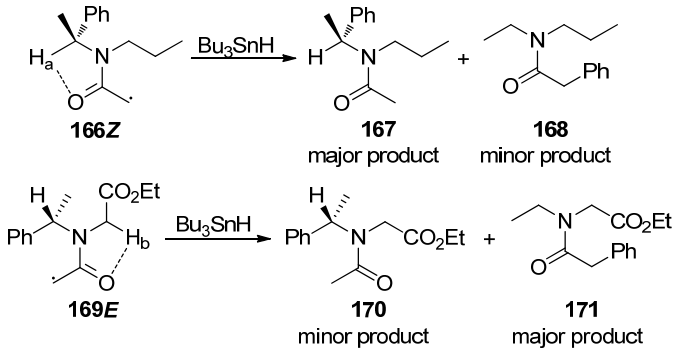
Generally, radical 1,4-aryl migrations between two carbon atoms can be classified into three categories: (1) between sp^3 carbon atoms; (2) from sp^3 carbon to sp^2 carbon; and (3) from sp^2 carbon to sp^3 carbon.

The first radical 1,4-aryl migration was discovered as a side reaction by Winstein and co-workers in 1956,[56] and their initial results were further corroborated in later studies.[57] In this transformation, the unstable primary radical **159** was generated after decarbonylation of **158** and immediately isomerized to the more stable tertiary radical **161**, probably through the formation of a spiro[4,5]decadienyl radical **160** (Scheme 32). Another analogous migration between sp^3 carbon atoms was observed in the dehalogenation of amide **163**. Both expected product **165** and side product **164** were isolated, indicating that a competition between 1,4-aryl migration and the direct reduction took place after the first dechlorination event.[58] Recently, Piscil et al. further investigated this competition and both experimentally and computationally validated the existence of an unprecedented C-H···O interaction that largely influenced the reaction pathway by favoring either the direct reduction or the 1,4-aryl migration.[59] As illustrated in Scheme 33, the substitution at the nitrogen atom determines whether the *Z* or *E* rotamer formed, with alkyl groups favoring the formation of the *Z*-rotamer while the acetyl acetate group facilitates the generation of the *E*-rotamer. In **166*Z***, due to the C-H_a···O interaction, the large distance between the phenyl group and the initial radical inhibits the rearrangement. However, in rotamer **169*E***, the C-H_b···O interaction is favored because of the participation of a more acidic H atom, thus making the migration

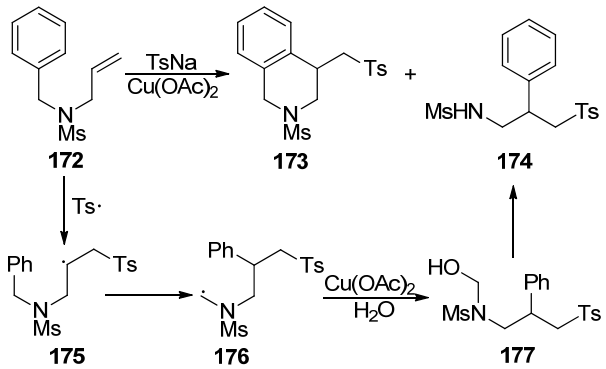
possible to take place. Besides dehalogenation, the initial radical center may also be generated via an intermolecular radical addition. In Chuang and co-workers' synthetic studies towards isoquinoline derivatives, they found an unexpected side reaction from alkene **172** to **174** (Scheme 34).[60] After the addition of a *p*-toluenesulfonyl radical to the terminal alkene **172**, the resulting secondary radical **175** may either undergo a cyclization to produce **173** or a 1,4-aryl migration, followed by oxidation, hydroxylation, and hydrolysis, to afford **174**.



Scheme 32 Early examples of radical 1,4-aryl migrations between carbon atoms



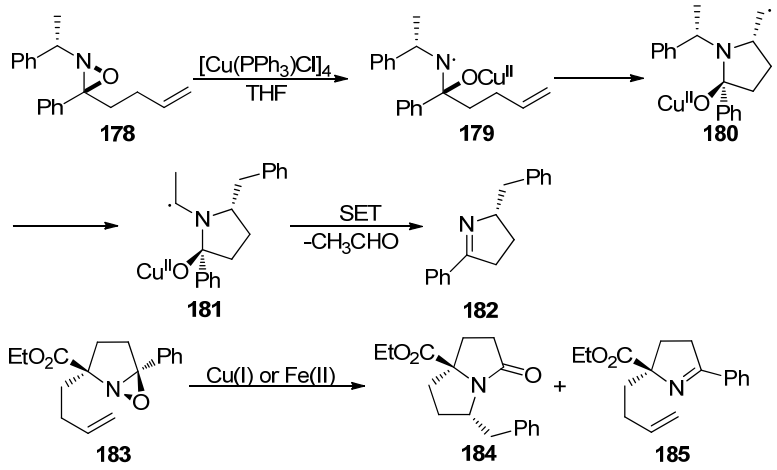
Scheme 33 Direct reduction and 1,4-aryl migration determined by C-H···O interaction of α-amide radicals



Scheme 34 Tandem tosyl radical addition/1,4-aryl migration reaction

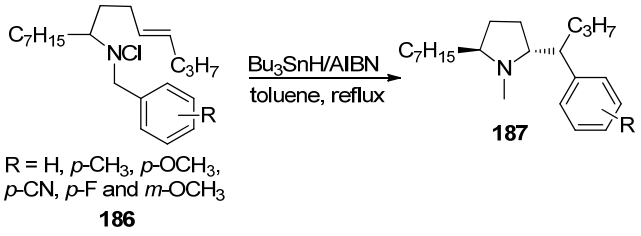
Some examples of 1,4-radical aryl migrations between sp^3 carbon atoms have been combined with radical cyclization reactions. In 1992, Aubé et al. developed an interesting Cu(I)-catalyzed tandem radical reaction of oxaziridine **178** (Scheme 35).[61] A SET process from Cu(I) to optically pure oxaziridine **178** first took place to give rise to radical **179**, which underwent a diastereoselective cyclization to generate primary radical **180**. After the crucial 1,4-aryl migration of **180**, the resulting *N*-stabilized radical **181**

finally took part in another SET process, affording imine **182** and concurrently releasing a molecule of acetaldehyde. The reaction proceeded in a highly diastereoselective manner, with **182** obtained in excellent ee. A similar cascade reaction of cyclic oxaziridine **183** was reported by Black.[62] With Cu(I) catalysis, the lactam **184** was obtained in high yield (82%). However, if Fe(II) was used as the catalyst, **184** was obtained in a relatively low yield because of the formation of side product **185**.



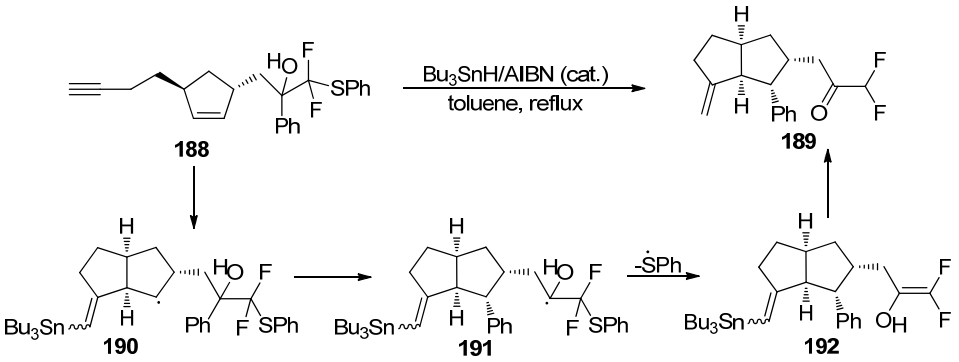
Scheme 35 Tandem N-O cleavage/radical cyclization/1,4-aryl migration reaction

Senboku and Tokuda disclosed another tandem radical cyclization/1,4-aryl migration reaction wherein the rearrangement proceeded with excellent stereocontrol (Scheme 36).[63] They used *N*-chloroamines **186** to generate aminyl radicals. The *5-exo* cyclization of **186** initiated a diastereoselective 1,4-aryl shift and produced a series of *N*-methylpyrrolidines **187** as single diastereoisomers. Given that the *para* position of substituents on the phenyl ring was retained after the rearrangement, the migrations must have proceeded exclusively via *ipso* attack upon the phenyl ring.



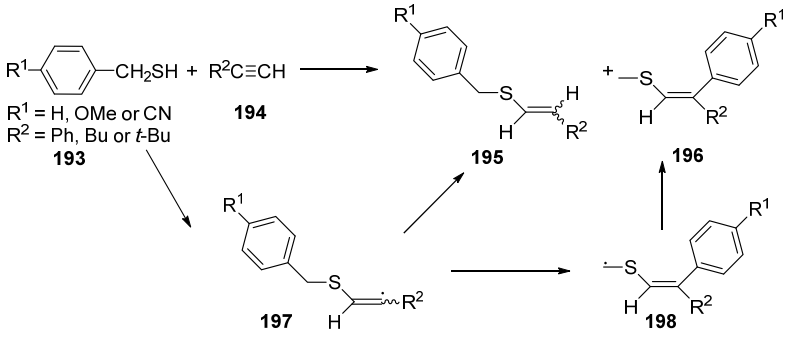
Scheme 36 Radical cyclization/1,4-aryl migration reactions of *N*-chloroamines

An application of tandem radical cyclization/1,4-aryl migration was reported in the very recent asymmetric syntheses of bicyclic octanes (Scheme 37).[64] Enyne **188** was prepared from chiral precursors and subjected to radical cyclization. The enyne cyclization was followed by a diastereoselective 1,4-aryl migration. Controlled by the relative configuration of the 2-propanoyl group on the cyclopentene, the *ipso* attack of radical **190** upon the aryl ring took place exclusively from the convex face of the newly-formed bicyclic octane. Elimination of the phenylthiyl group from **191** ultimately led to the formation of *cis*-bicyclic octane **189**. This reaction has a wide substrate scope, tolerating various substituted phenyl groups. Mechanistic studies revealed that the phenylthiyl group was essential for the 1,4-aryl migration. For enynes without this group, only cyclization products were observed.

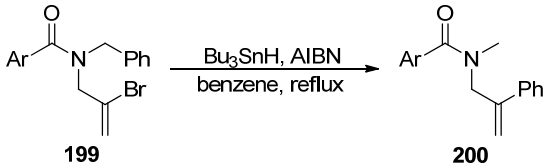


Scheme 37 Asymmetric synthesis of bicyclo[3.3.0]octane

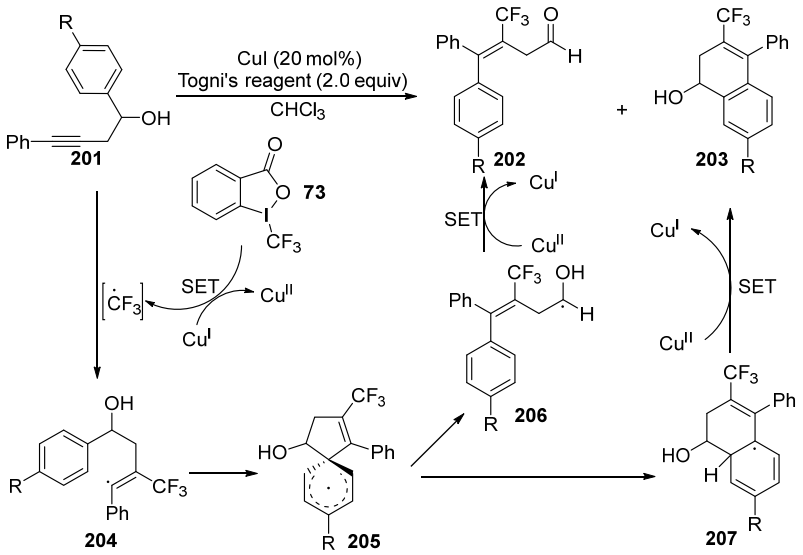
Radical 1,4-aryl migrations from an sp^3 carbon to an alkenyl radical have been investigated since the 1990s. In an early report, a number of 4-substituted benzyl mercaptans **193** reacted with different alkynes **194** under radical conditions to produce both benzyl vinyl sulfides **195** and methyl vinyl sulfides **196** after reduction of radical **197** and rearranged radical **198**, respectively (Scheme 38).[65] Another migration process involving an alkenyl radical was discovered in the debromination of vinyl bromide **199** (Scheme 39).[66] The driving force of this rearrangement is probably the formation of an *N*-stabilized radical. Very recently, Liang et al. devised an elegant Cu(I)-catalyzed one-pot reaction to synthesize CF_3-containing 3-butenal or 3-buten-1-one derivatives.[67] Togni's reagent **73** was reduced by Cu(I) through a SET process to release a CF_3 radical (Scheme 40). Addition of this radical to the alkyne group of homopropargylic alcohol **201** took place regio-selectively to give rise to alkenyl radical **204**, which, after *ipso* attack upon the phenyl ring, formed spiro radical **205**. The ring opening of **205**, followed by the SET oxidation of oxygen-stabilized radical **206**, ultimately furnished the desired product **202**. Alternatively, radical **205** may also undergo a competitive 1,2-aryl migration/oxidation process to afford the side product **203**. EPR studies and DFT calculations validated the mechanism described.



Scheme 38 Reaction of 4-substituted benzyl mercaptans and alkynes

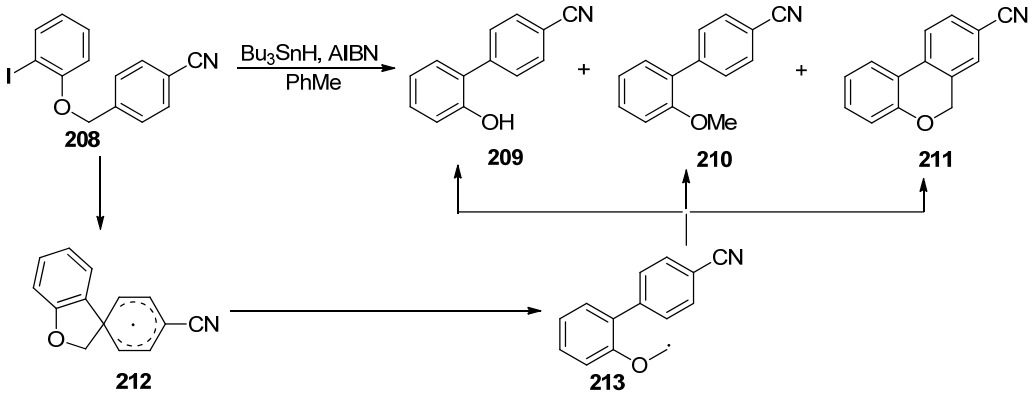


Scheme 39 Debromination of vinyl bromide **199**



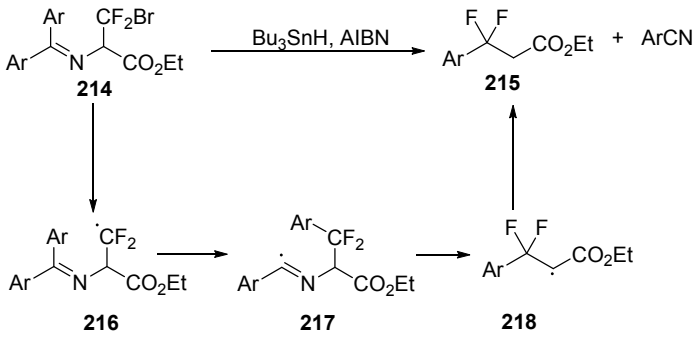
Scheme 40 One-pot trifluoromethylation/aryl migration/carbonyl formation reaction of homopropargylic alcohols

The only example of radical 1,4-aryl migration from an sp^3 carbon to a phenyl radical was reported in 2001. Under standard radical conditions, phenolic ether **208** rearranged to afford phenol **209** and phenolic ethers **210** and **211** in 79% combined yield (Scheme 41).[68] Mechanistically, the migration proceeded through the spiro radical intermediate **212**. Direct reduction of rearranged radical **213** provided **210**, while cyclization of **213** followed by aromatization afforded **211**. However, it is still unclear how phenol **209** was formed.



Scheme 41 1,4-Aryl migration from an sp^3 carbon to a phenyl radical

There is only one example of radical 1,4-aryl migration from an sp^2 carbon to an sp^3 carbon radical. In this case, the phenyl group transferred from the carbon atom of imine **216** to the difluoro primary carbon radical (Scheme 42).[69] The resulting iminoyl radical **217** underwent a fragmentation/reduction sequence to afford ester **215** and release an aryl nitrile.

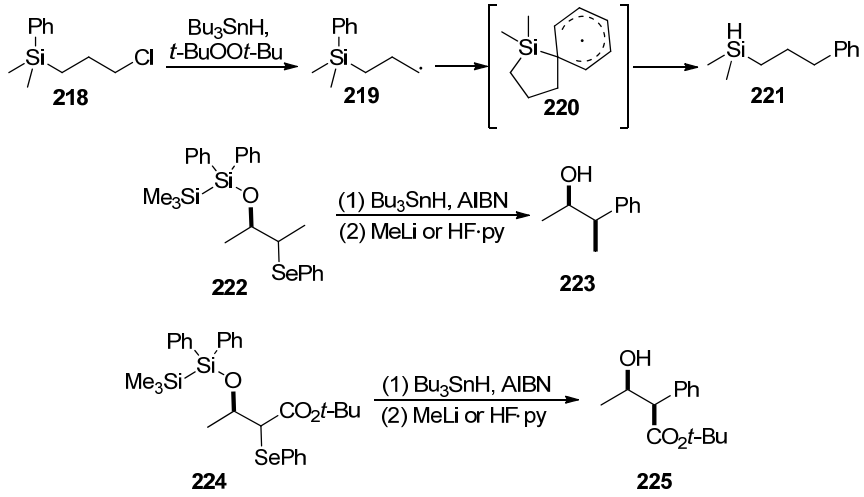


Scheme 42 1,4-Aryl migration from an sp^2 carbon to an sp^3 carbon radical

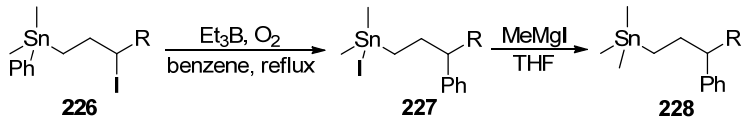
4.2 Radical 1,4-aryl migrations from silicon or tin to carbon

Studies on 1,4-phenyl migrations from silicon to carbon began in the 1970s. Wilt et al. discovered that primary radical **219**, generated from 3-(phenyldimethylsilyl)propyl chloride **218** with DTBP and Bu_3SnH, underwent a 1,4-phenyl transfer to afford silane **221** (Scheme 43).[70] The reaction was later found to be amenable to the migration of various substituted benzenes[71] and the proposed intermediate **220** was characterized by EPR spectroscopy.[72] Analogous diastereoselective 1,4-migration was reported by Studer in 1998.[73] Under similar radical conditions, selenide **222** was converted to alcohol **223** in high diastereoselectivity. Complete stereocontrol was observed even for the transformation of ester **224**. It is interesting to note that this type of migration was also realized on substituted fullerenes, which serves as an effective method to functionalize fullerenes.[74]

The only example of 1,4-aryl migration from tin to carbon was from a report in 2000.[75] Treatment of stannanes **226** with Et_3B under oxygen atmosphere afforded stannane iodides **227**, the rearranged products that could then be transformed to trimethylstannanes **228** using MeMgI (Scheme 44). The resulting trimethylstannyl group can be converted to other functionalities, highlighting the potential synthetic utility of this methodology.



Scheme 43 1,4-Aryl migrations from silicon to carbon

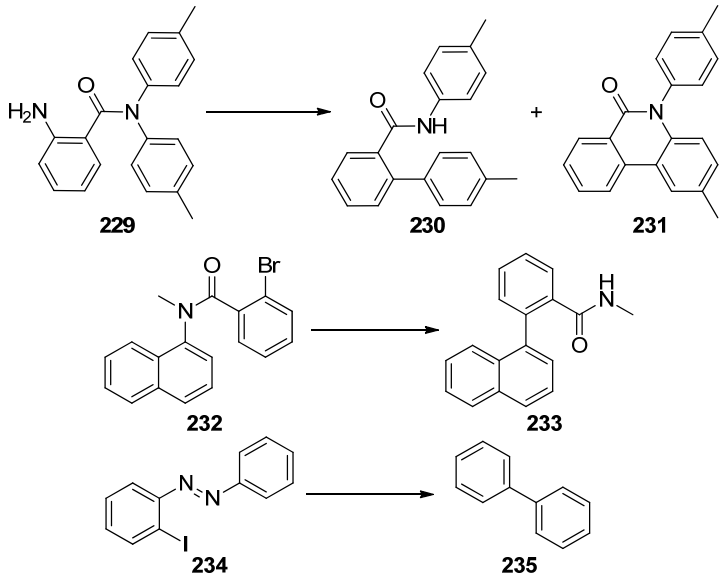


226 227 228

Scheme 44 1,4-Aryl migrations from tin to carbon

4.3 Radical 1,4-aryl migrations from nitrogen to carbon

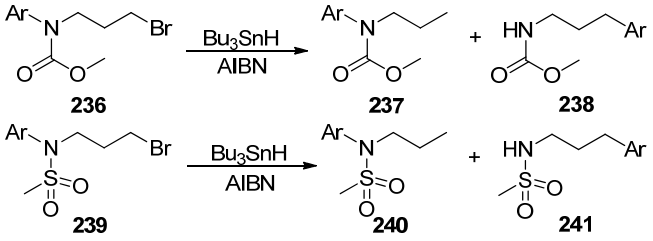
Radical 1,4-aryl migrations from nitrogen to phenyl radicals have been applied to biaryl synthesis (Scheme 45). Diazotization of **229** followed by 1,4-aryl migration mediated by copper powder generated **230** together with a side product **231**.[76] Similarly, the reaction of amide **232** under electroredox condition afforded **233** in moderate yield.[77] Besides amides, *trans*-azobenzene **234** can rearrange under photolysis to provide diphenyl **235**.[78] In this case, before the migration took place, the *trans*-azobenzene first isomerized to its *cis*-isomer and the reaction was completed with the loss of molecular nitrogen.



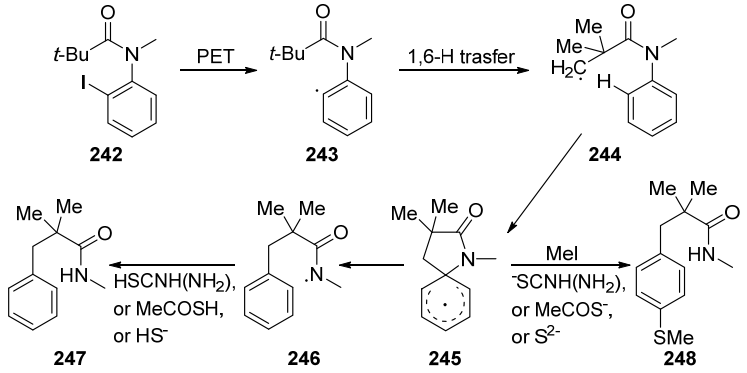
229 230 231 232 233 234 235

Scheme 45 1,4-Aryl migrations from nitrogen to phenyl radicals used in biaryl synthesis

The first example of 1,4-aryl migration from nitrogen to a primary sp^3 carbon radical was reported by Lee et al. in 1995 (Scheme 46).[79] Under standard radical conditions, both *N*-aryl-carbamates **236** and *N*-aryl-sulfoamides **239** could undergo 1,4-phenyl transfer to generate the corresponding rearranged products **238** and **241** respectively, albeit with relatively low yields in most cases because of the competitive direct reductions. In a more recent report, this type of rearrangement was found in an interesting tandem radical process (Scheme 47).[80] Aryl radical **243** was generated from amide **242** by photo electron transfer (PET) and underwent a 1,6-hydrogen transfer to give primary radical **244**. The phenyl group migration of **244** to form a more stable amidyl radical **246** followed by hydrogen abstraction ultimately provided amide **247**. Isolation of another rearranged product **248** indicated the intermediacy of spiro radical intermediate **245** in this transformation.



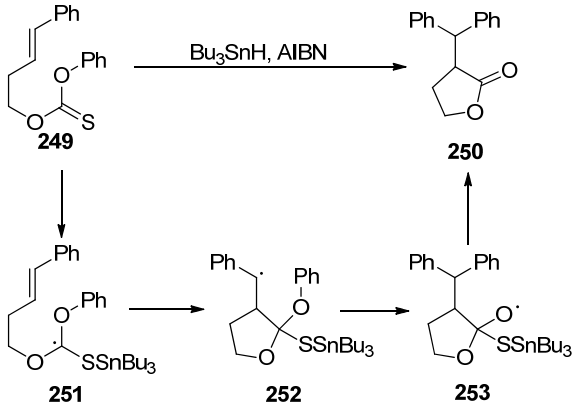
Scheme 46 1,4-Aryl migrations of *N*-aryl-carbamates and *N*-aryl-sulfoamides



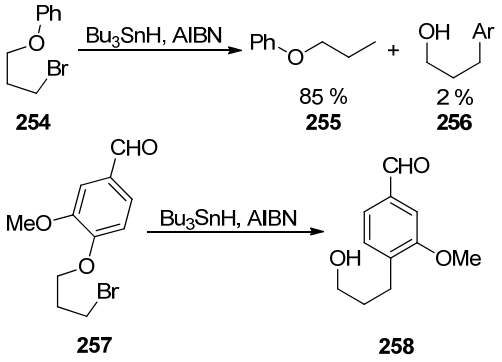
Scheme 47 Tandem photo electron transfer/1,6-H transfer/1,4-aryl migration reaction

4.4 Radical 1,4-aryl migrations between carbon and oxygen

There are almost no examples of radical 1,4-aryl migrations from carbon to oxygen except for some early research on the Hunsdirecker reaction of 3,3,3-triphenylpropionic acid, the mechanism of which is ambiguous.[81] In contrast, the reverse-type aryl migrations from oxygen to carbon have been reported regularly since the early 1990s. Bachi et al. discovered an unusual migration reaction of thioester **249** when studying the radical cyclization of thionocarboxylic acids (Scheme 48).[82] In this tandem process, the key 1,4-phenyl transfer took place immediately after the radical cyclization from **251** to **252** and generated alkoxyl radical **253**, which then eliminated to afford the final lactone **250**. Subsequently, this type of migrations was found in the radical dehalogenation of various 3-bromopropyl aryl ethers by Lee and co-workers.[83] Their experimental results showed that products distributions were highly dependent on the migratory group. Phenyl substituted ether **254** predominantly provided direct reduction product **255**, while 2-methoxyl-4-formyl-1-phenyl substituted ether **257** only afforded rearranged product **258** (Scheme 49).

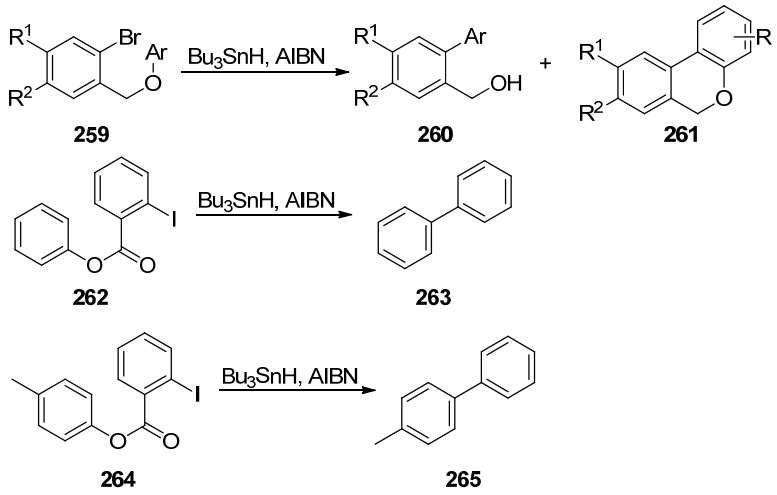


Scheme 48 Tandem radical cyclization/1,4-aryl migration/elimination reaction



Scheme 49 1,4-Aryl migrations of phenyl substituted ethers

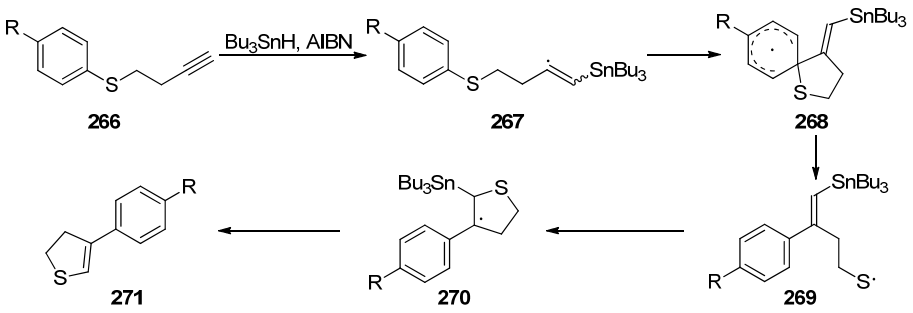
1,4-Aryl migrations from oxygen to phenyl radicals have been used in biaryl synthesis (Scheme 50). Prabhakar and Lobo reported that a range of benzyl phenyl ethers **259** could rearrange under standard radical conditions to give biaryl compounds **260** and **261**, albeit in very low yields.[84,85] Such migratory reactivity was also observed for phenyl esters **262** and **264**,[85,86] which were converted to diphenyls **263** and **265** respectively following decarboxylation.



Scheme 50 1,4-Aryl migrations from oxygen to phenyl radicals used in biaryl synthesis

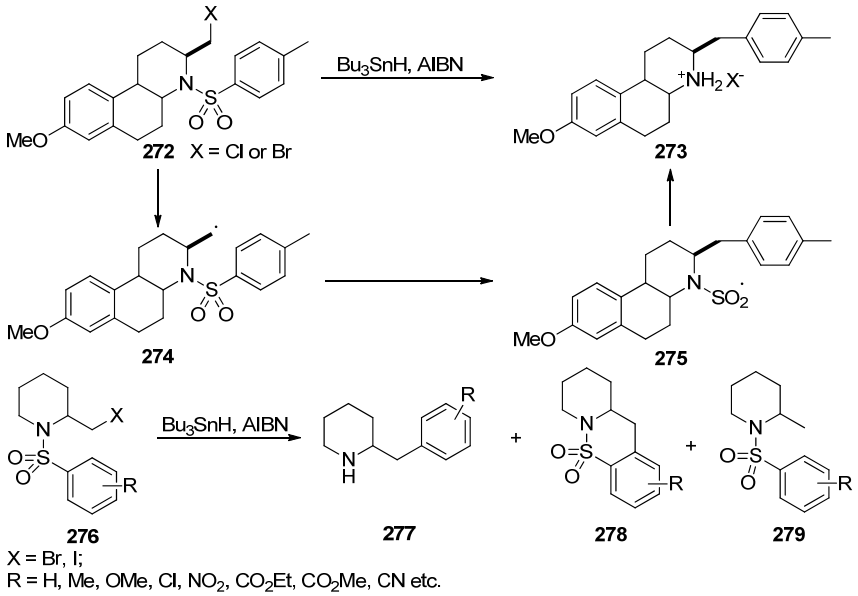
4.5 Radical 1,4-aryl migrations from sulfur to carbon

The majority of reactions discussed in this section are comprised of the radical 1,4-aryl migrations from sulfone or sulfonamide to an initial carbon radical. These reactions have been studied since the 1970s and have recently attracted significant research interest. In contrast, 1,4-migrations from a sulfur atom to carbon are much rarer, and in fact only one example of such migration has been discovered as a side reaction in the radical cyclization of phenylthio alkyne **266** (Scheme 51).[87] Regioselective addition of Bu_3SnH onto the terminal alkynyl group of **266** led to the formation of alkenyl radical **267**. The 1,4-migration process then took place through the formation of spiro radical **268** to generate thiyl radical **269**. Subsequent cyclization of **269** on the adjacent double bond, followed by radical elimination, finally afforded dihydro thiophene **271**.



Scheme 51 1,4-Aryl migrations from sulfur atom to carbon

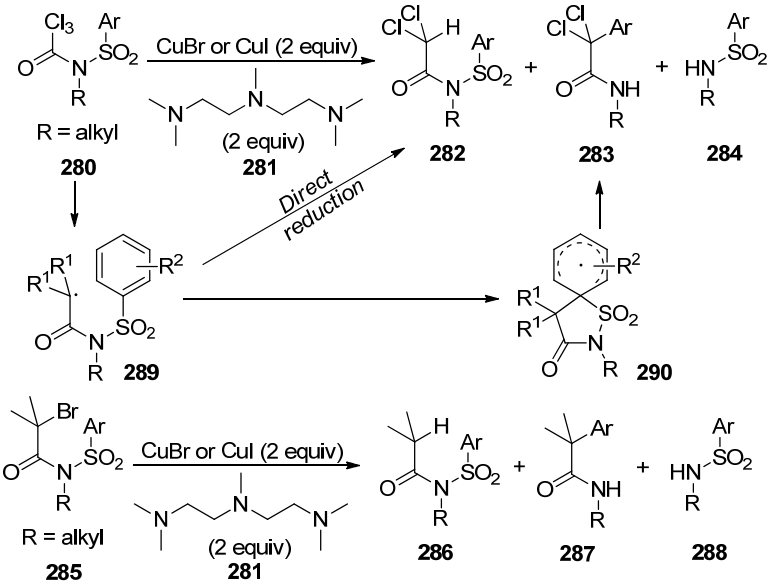
1,4-Aryl migrations from sulfone or sulfonamide to sp^3 carbon have mostly been reported in recent years. Studies on this type of migrations began in 1972 when Speckamp et al. investigated the radical dehalogenation of sulfonamides **272** (Scheme 52).[88] Under standard radical conditions, the *p*-methylphenyl group migrated from the sulfone to the primary radical in **274** to give radical **275**. After subsequent extrusion of SO_2 from **275**, the H-abstraction of the resulting nitrogen radical and *in situ* salification ultimately furnished **273**. Further experiments conducted by the same group demonstrated that this type of migration was also feasible for piperidine sulfonamides **276**.[89] However, the rearranged products **277** could only be obtained at high temperatures. Side products **278** and **279**, formed either by a radical cyclization or a direct reduction, became predominant if the reaction was conducted at room temperature. Later studies revealed that electronic effects of the migratory groups played a significant role in the reaction yields, with better results obtained for electron-deficient aryl groups.



Scheme 52 Radical 1,4-aryl migrations of piperidine sulfonamides

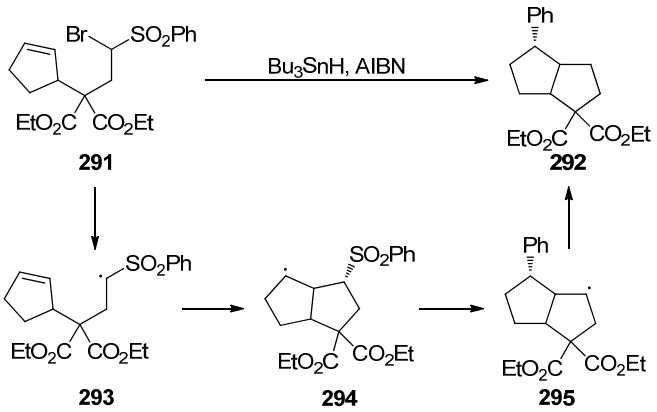
Compared with above-mentioned tandem radical dehalogenation/1,4-migration reactions mediated by toxic organostannane reagents, transition metal-induced or catalyzed reactions often proceed under mild conditions and do not require complex manipulations such as portion-wise addition or high dilution. In a series of studies, Clark and co-workers tried to induce the rearrangements of sulfonamides **280** and **285** using Cu(I) species (Scheme 53).[90] In the presence of two equivalents of Cu(I) halide (both

CuCl and CuBr are applicable) and ligand **281**, various trichlorosulfonamides **280** and monobromosulfonamides **285** were converted to the corresponding amides **283** and **287** through the crucial 1,4-aryl transfer reactions. Direct reduction products **282** and **286** could not be avoided in most examples and in some cases, degradation products **284** and **288** were observed. Generally, the amount of migration was closely related to the reaction temperature, with an elevated temperature largely facilitating the rearrangement. In addition, more rearranged products were obtained in the reaction of monobromosulfonamides **285**, probably because the generation of a more basic carbon radical after dehalogenation favored the *5-exo ipso* attack event in the migration.

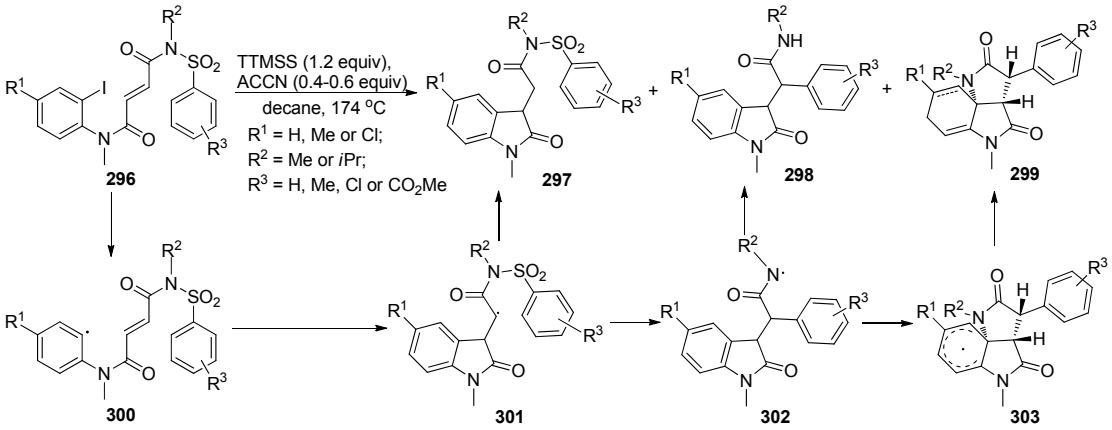


Scheme 53 Cu(I) induced 1,4-aryl migrations of sulfonamides

Besides dehalogenation, 1,4-aryl migrations from sulfone or sulfonamide to carbon can be initiated by an intramolecular radical cyclization. In 1989, Clive and Boivin reported such a tandem process while studying the radical cyclization of cyclopentene **291** (Scheme 54).[91] After *5-exo* cyclization of radical **293**, the phenyl group on the sulfone migrated to the newly-formed secondary carbon radical in **294** to afford the final product **292** after SO_2 extrusion and reduction. In a more recent report, Gérard and Sapi developed another radical cyclization/1,4-aryl migration cascade to synthesize a wide range of 3-(2'-aryl-*N*-methylacetamido)indolin-2-ones **298** (Scheme 55).[92] Treatment of amide **296** with TTMSS and 1,1'-azobis-cyclohexanecarbonitrile (ACCN) initiated the radical dehalogenation and then *5-exo-trig* cyclization process to generate radical **301**. Direct reduction of **301** afforded **297**, while the 1,4-aryl transfer of **301** followed by SO_2 extrusion and reduction furnished the desired product **298**. In some instances, another side product **299** was formed because of an additional cyclization of amidyl radical **302** onto the phenyl ring, taking place after the 1,4-migration.



Scheme 54 Radical cyclization/1,4-aryl migrations of cyclopentene **291**

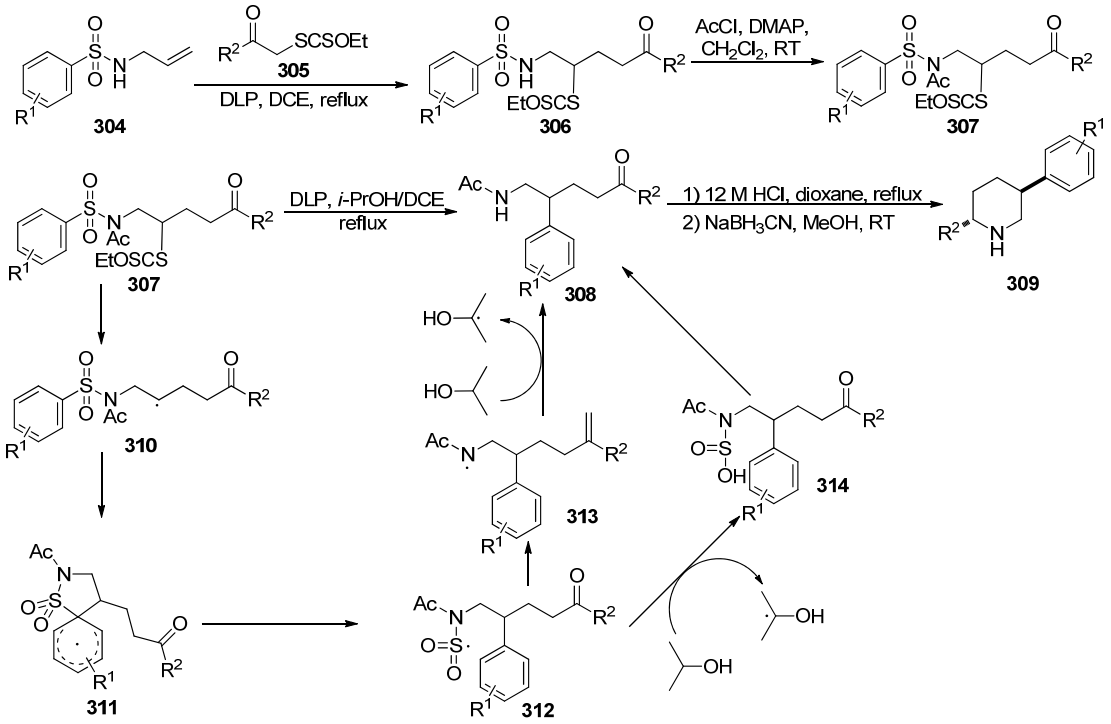


Scheme 55 Radical cyclization/1,4-aryl migrations in the syntheses of 3-(2'-aryl-*N*-methyl acetamido)indolin-2-ones

With recent development of radical chemistry, numerous synthetic methodologies in terms of radical alkylation, trifluoromethylation, phosphonylation, and azidation have been developed. The combinations of these reactions with 1,4-aryl migrations of sulfonamides provide a number of synthetically valuable methods.

In 2005, Zard and co-workers developed a convenient route to synthesize a wide range of piperidine derivatives in which step-wise radical alkylation and 1,4-aryl migration served as key transformations (Scheme 56).[24,93] Various *N*-acetyl substituted sulfonamides **307** were prepared in two steps from olefins **304** and xanthates **305** including a key radical alkylation and a protection procedure. The crucial aryl migrations of **307** were initiated by DLP in the presence of large amounts of 2-propanol and produced the desired *β*-arylacetamides **308** in moderate to high yields. Mechanistically, secondary carbon radical species **310** was first generated under radical conditions and was able to undergo 1,4-aryl migration through the formation of spirocyclic radical intermediate **311** to give radical **312**. After the loss of SO_2 from **312**, H-abstraction from the so-formed amidyl radical **313** provided **308**. In an alternative pathway involving the formation of acid intermediate **314**, the H-abstraction occurred before the extrusion of sulfur dioxide. Acetylation of the nitrogen atom played a dominant role in the success of these transformations. For substrates without such substituents, the sequences were problematic, probably because of the formation of less active aminyl radicals. From

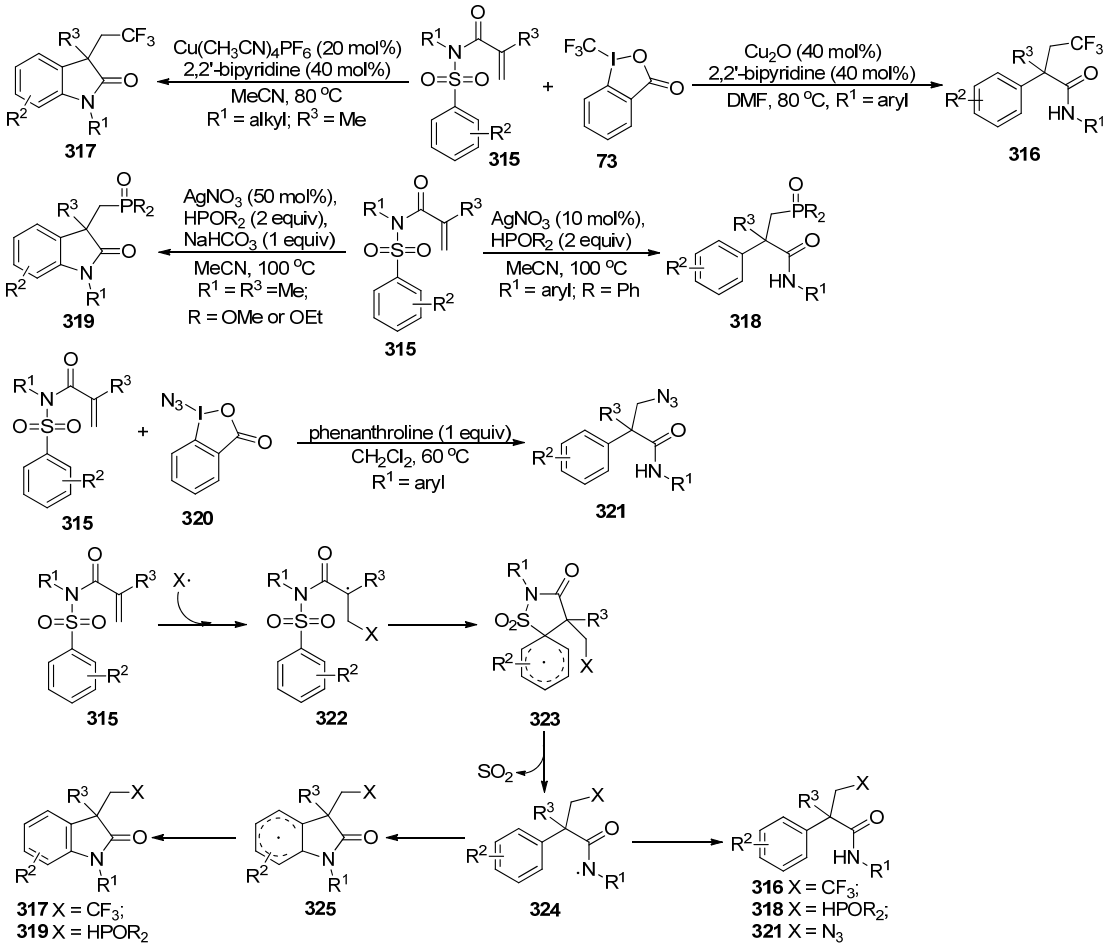
β-arylacetamides **308**, the syntheses of various piperidine compounds **309** were completed after an acid induced deprotection cyclization sequence and a subsequent diastereoselective reduction.



Scheme 56 Syntheses of piperidine derivatives

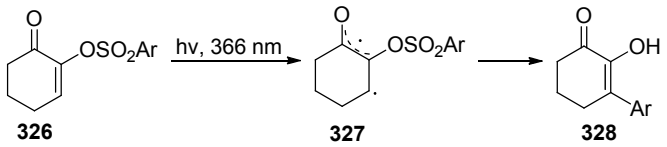
Very recently, Nevado et al. combined the 1,4-aryl migrations of sulfonamides with radical trifluoromethylation, phosphonylation and azidation reactions and realized a series of excellent transition metal catalyzed tandem radical processes capable of synthesizing functionalized amides and oxindoles (Scheme 57). In their systematic studies, they prepared a series of *N*-aryl or *N*-alkyl substituted sulfonamides **315**. Their investigations commenced with the tandem reactions between **315** and Togni's reagent **73**.[94] Under Cu(I) catalysis, the *N*-aryl substituted sulfonamides underwent a trifluoromethylation/1,4-aryl migration cascade to afford *α*-aryl-*β*-trifluoromethyl amides **316** in moderate to high yields, while the reactions of their *N*-alkyl substituted counterparts terminated through an additional cyclization process to produce trifluoromethylated oxindoles **317**. A wide range of substitutents on the migratory aryl group for both reactions are well tolerated, as are different *N*-aryl substitutions for the former reaction, and different *N*-alkyl substitutions for the latter. It is of particular interest that some of the transformations from **315** to **316** can alternatively be catalyzed by nBu$_4$NI, albeit requiring more catalyst (50 mol%).[95] Having successfully realized the aryltrifluoromethylation, the same group further explored the arylphosphonylation and arylazidation of sulfonamides **315**.[96] The arylphosphonylationof **315** took place under Ag(I) catalysis and provided various *α*-aryl-*β*-phosphonyl amides **318** in moderate to high yields, while the arylazidation of **315** with iodine reagent **320** required no catalyst, although the existence of a stoichiometric amount of base, such as $NaHCO_3$ or phenanthroline, greatly improved the yields of *α*-aryl-*β*-azido amides **321** obtained. There is a wide substrate scope for both reactions and the arylphosphonylation can be

further applied for the syntheses of phosphonylated oxindoles **319** when the substrates, like in the above described aryltrifluoromethylation, are *N*-alkyl substituted tosyl amides. Mechanistic studies including control experiments, ^{19}F-NMR investigations, crossover experiments, and deuterium labelling experiments, validated the radical process of all reactions and excluded an intermolecular aryl migration. On the basis of these experimental results, a general mechanism, as suggested in Scheme 57, would involve the generation of radical species X, addition of X to the activated alkene of **315** to give radical **322**, and then a 1,4-aryl migration through the formation of spiro radical **323** followed by desulfonylation to generate amidyl radical **324**. When R^1 is an aryl group, direct H-abstraction of **324** would afford *α*-aryl-*β*-trifluoromethyl amide **316** (X = CF_3), *α*-aryl-*β*-phosphonyl amide **318** (X = $HPOPh_2$) or *α*-aryl-*β*-azido amide **321** (X = N_3), respectively. However, if R^1 is an alkyl group, the more nucleophilic amidyl radical **324** would attack the rearranged phenyl ring to produce oxindoles **317** or **319** after final reduction.



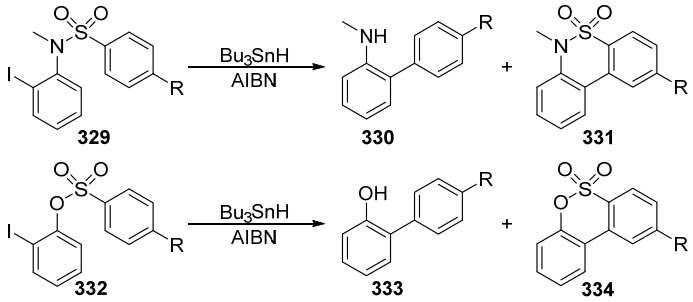
Scheme 57 Tandem radical addition/1,4-aryl migration reactions that involve trifluoromethylation, phosphonylation, and azidation

Until now, the only example of 1,4-aryl migration from sulfone to an sp^2 alkenyl radical is a photoreaction. Irradiation of *α,β*-unsaturated ketone **326** under UV light (366 nm) generated diradical **327**. The aryl group on the sulfone then migrated to the remote carbon radical in **327** and afforded *α*-hydroxy-*α,β*-unsaturated ketone **328** in moderate yield after SO_2 extrusion (Scheme 58).[97]



Scheme 58 Photoreaction of α-sulfonyloxy enones

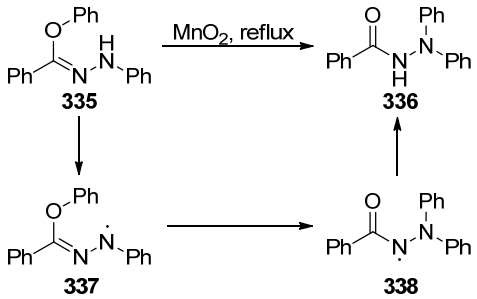
Motherwell et al. demonstrated that the 1,4-aryl migrations from sulfonamide or sulfone to an sp^2 phenyl radical could be used in biaryl synthesis (Scheme 59).[98] Under standard radical conditions, both sulfonamides **329** and sulfonates **332** were converted to biaryls **330** and **333**, respectively, through the rearrangements. The only side reaction that gave side products **331** or **334** were direct *o*-attack of the initially formed radical on the aromatic ring of the tosyl group, which could be suppressed if there was an electron-donating or an electron-withdrawing group at the *ortho* position of the migratory aryl group.



Scheme 59 1,4-Aryl migrations from sulfone or sulfonamide to carbon used in biaryl synthesis

4.6 Radical 1,4-aryl migrations between heteroatoms

The only known 1,4-aryl migration between two heteroatoms was reported by Hegarty and co-workers in 1973 (Scheme 60).[99] The reaction proceeded via a three-step sequence which involved first the oxidation of the N-H bond of **335** by MnO_2 to generate radical **337**, then 1,4-phenyl transfer from oxygen to nitrogen to give radical **338**, and finally reduction of **338** to furnish amide **336**.



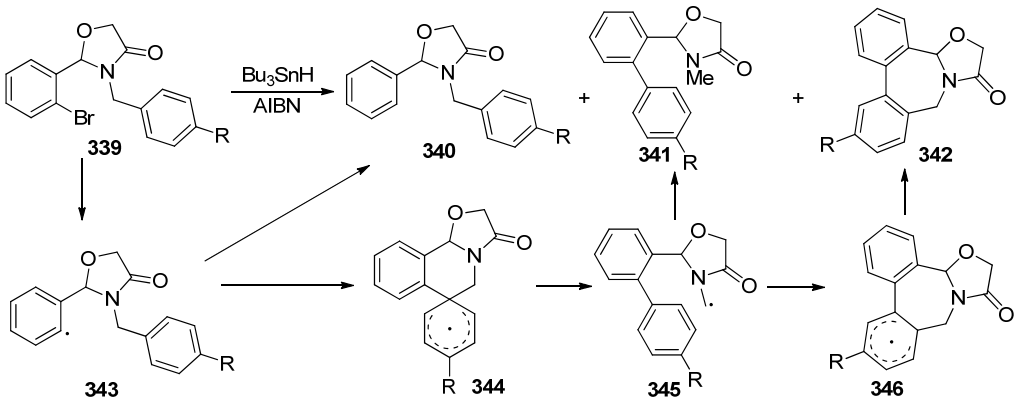
Scheme 60 1,4-Aryl migrations from oxygen to nitrogen

5. Radical 1,5-aryl migrations

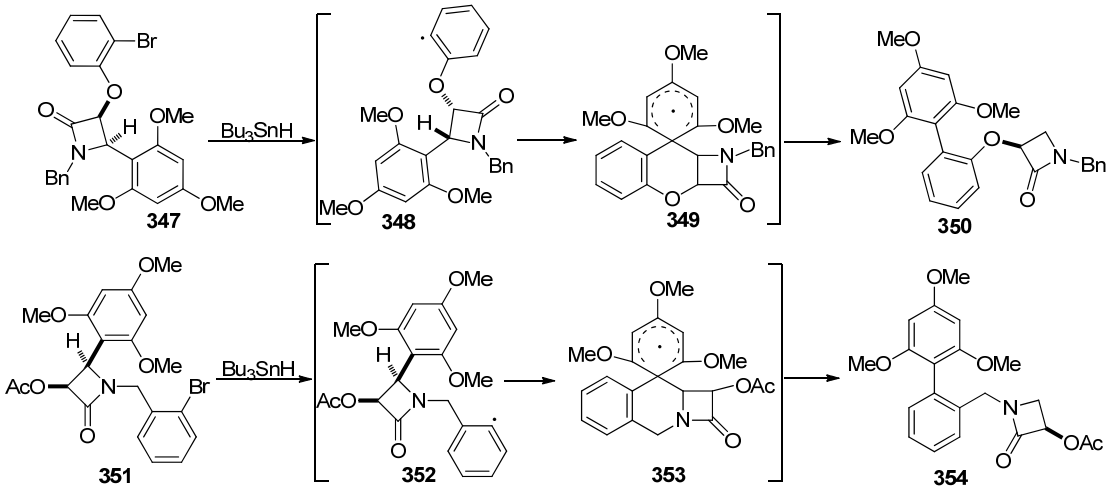
Like the 1,4-aryl migrations we discussed in the last chapter, the 1,5-aryl migrations also incorporate various reaction types, although there are fewer reports of each.

5.1 Radical 1,5-aryl migrations between carbon atoms

The reported 1,5-aryl migration reactions between two carbon atoms are confined to rearrangements from an sp^3 carbon to an initial phenyl radical, which have mainly been employed in the syntheses of biaryl derivatives. In 1997, Renaud and co-workers discovered that when aryl bromides **339** were treated with Bu_3SnH and AIBN, biaryls **341** and their derivatives **342** were obtained in modest yields together with the direct reduction products **340**. The formation of biaryl compounds **341** and **342** was attributed to a 1,5-aryl transfer within phenyl radical **343** to form an *N*-stabilized primary radical **345** (Scheme 61).[100] Subsequently, Alcaide and co-workers reported an example of this type of radical 1,5-aryl migration with more complex substrates. When treated with Bu_3SnH, both bromides **347** and **351** afforded biaryls **350** and **354** respectively. In these examples, the 1,5-aryl migration may proceed via an *ipso*-attack of the radicals **348** or **352** upon the 2,4,6-trimethoxylphenyl group to form the spiro radical intermediates **349** or **353**, which after *β*-scission and reduction would furnish the corresponding product (Scheme 62).[101]



Scheme 61 1,5-Aryl migrations from an sp^3 carbon to a phenyl radical

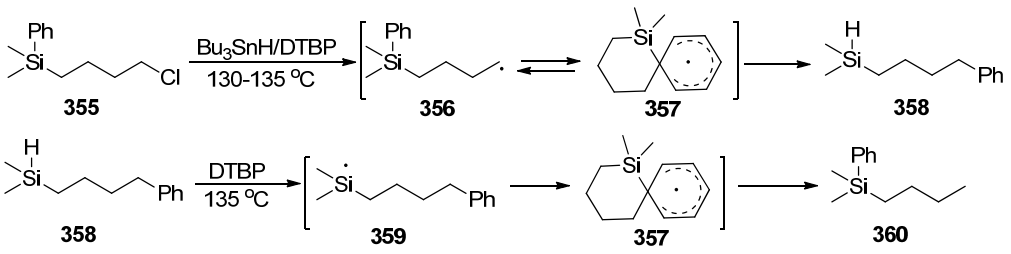


Scheme 62 1,5-Aryl migrations of a bulky 2,4,6-trimethoxyl phenyl group

5.2 Radical 1,5-aryl migrations between silicon and carbon

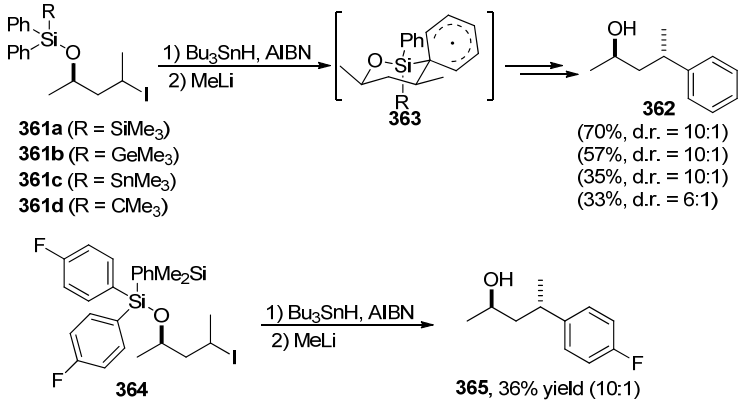
When Wilt et al. studied the radical 1,4-aryl migrations from silicon to carbon in 1970 (see chapter 4), they also investigated the possibility of a 1,5-aryl migration of homologous silane **355**.[70] Dehalogenation of **355** using Bu_3SnH and DTBP at 130 °C readily afforded the 1,5-rearranged product **358**. Later mechanistic studies from the same

group revealed that under such a high temperature, the 1,5-aryl migration actually proceeded via a reversible process, in which the initially formed primary acyclic radical **356** was in equilibrium with the spirocyclic radical **357**.[71] Interestingly, the reverse-type 1,5-aryl migration from carbon to silicon was also realized by Sakurai and co-workers contemporaneously with Wilt's earlier work (Scheme 63).[102] Under similar reaction conditions, dimethyl(4-phenylbutyl)silane **358** was converted to **359** with the formation of the same spirocyclic radical **357**, a genuine intermediate in this reaction that was confirmed by EPR spectroscopy.[72]



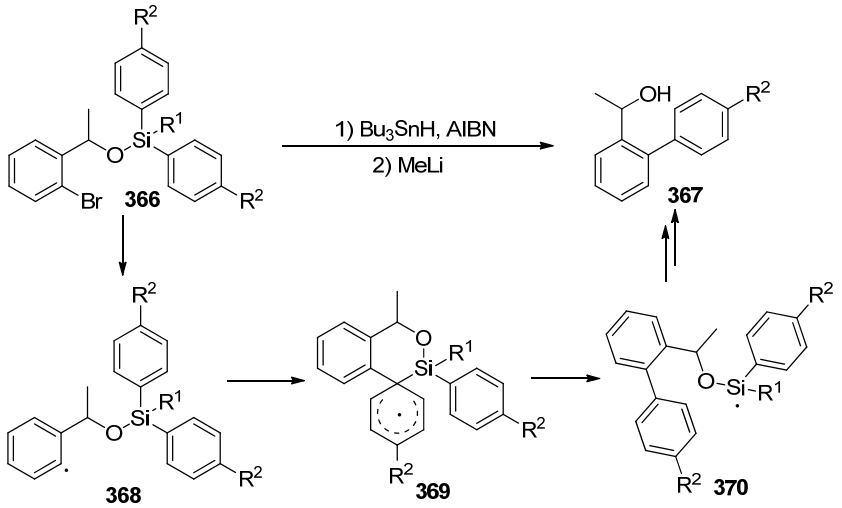
Scheme 63 1,5-Aryl migrations between silicon and sp^3 carbon

Diastereoselective 1,5-aryl migrations from silicon to sp^3 carbon were achieved by Studer and co-workers. Iodides **361** were transformed to alcohols **362** through a two-step sequence including the crucial 1,5-phenyl migration and a subsequent desilication process (Scheme 64). The bulky substituent on the silane atom of **361** played a significant role in determining the yield and diastereoselectivity of the rearrangement reaction, with trimethylsilyl substituted substrate **361a** giving the best results (70 % yield and 10:1 dr).[73] The migration was also feasible for various other phenyl groups with different substituents, although affording lower yields.[103]



Scheme 64 Diastereoselective 1,5-aryl migrations from silicon to sp^3 carbon

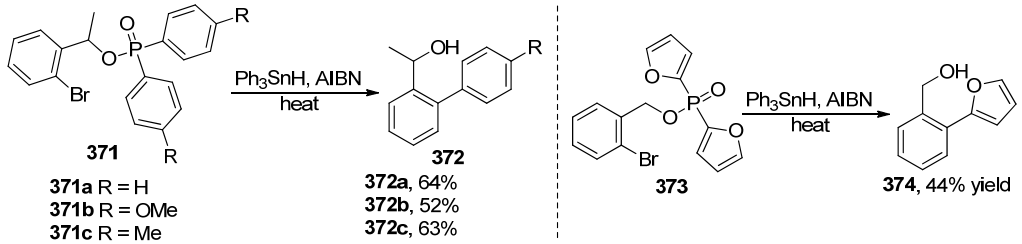
Radical 1,5-aryl migrations from silicon to phenyl radicals have also been used in biaryl synthesis. In 2000, Studer et al. employed this type of migration to convert various silyl ethers **366** to the corresponding biaryl alcohols **367** (Scheme 65).[104] Although the yields of these reactions were moderate, the methodology provides a very convenient way to prepare these biaryl compounds because of the commercial availability of many ethers **366**.



Scheme 65 1,5-Aryl migrations from silicon to sp^2 carbon used in biaryl synthesis

5.3 Radical 1,5-aryl migrations from phosphorus to carbon

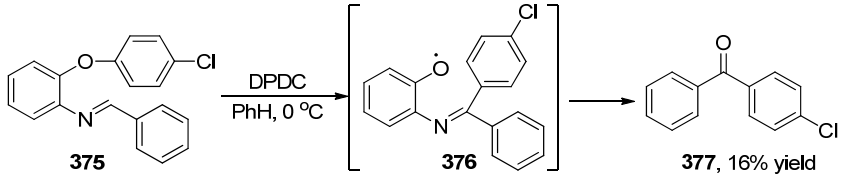
To the best of our knowledge, there is no published example of radical 1,5-aryl migration between nitrogen and carbon to date. However, an example of 1,5-aryl migration from phosphorus to carbon used in biaryl synthesis was reported by Clive and co-workers in 2000 (Scheme 66). When different diaryl phosphinates **371** were treated with Ph_3SnH and AIBN, a series of biaryl alcohols **372** were obtained via the crucial radical 1,5-aryl transfer. The migratory groups could be extended to heteroarenes such as the furane in phosphinate **373**, which produced the corresponding rearranged product **374** in moderate yield.[105]



Scheme 66 1,5-Aryl migrations from phosphorus to sp^2 carbon

5.4 Radical 1,5-aryl migrations from oxygen to carbon

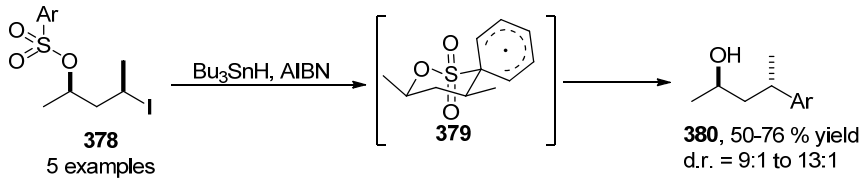
The only example of radical 1,5-aryl migration from oxygen to carbon was reported by Nanni et al. in 1995 (Scheme 67).[106] H-abstraction of **375** by di-*iso*-propylperoxydicarbonate (DPDC), followed by the 1,5-migration of the *p*-chloro phenyl group from oxygen to the imidoyl radical, generated radical **376**. Final reduction and hydrolysis of **376** afforded **377** in low yield (16 %).



Scheme 67 1,5-Aryl migrations from oxygen to carbon

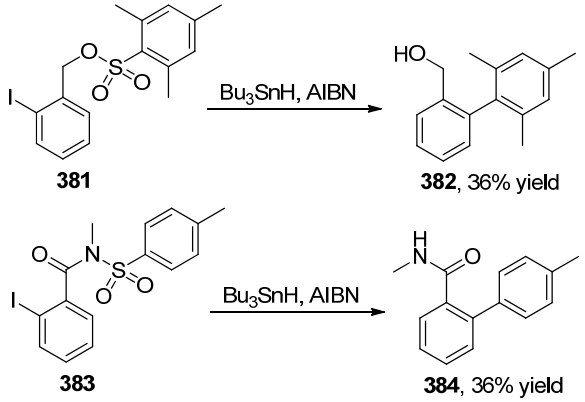
5.5 Radical 1,5-aryl migrations from sulfur to carbon

In general, studies on radical 1,5-aryl migrations from sulfur to carbon are mainly focused on the rearrangements of an aryl group from a sulfonate or sulfonamide to the initially generated carbon-centered radical. In 1998 and 2002, Studer and co-workers developed various examples of migrations from sulfonate to sp^3 carbon. The reactions of **378** with Bu_3SnH and AIBN proceeded in a highly diastereoselective manner, producing alcohols **380** in moderate yields with excellent diastereoselectivities (Scheme 68). The rearrangement had a wide substrate scope with various aryl groups being able to transfer under the standard conditions and the stereocontrol could be explained by the formation of a spiro radical intermediate **379**, which may probably adopt a chair conformation with both methyl groups occupying equatorial positions.[107]

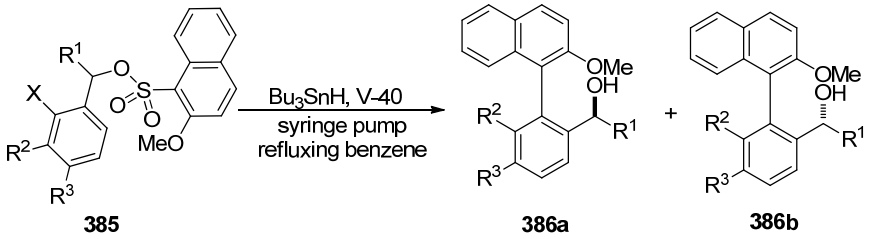


Scheme 68 1,5-Aryl migrations from sulfonate to an sp^3 carbon radical

Radical 1,5-aryl migrations from a sulfonate or sulfonamide to a phenyl radical have also been used in biaryl synthesis, although the examples are limited. In Motherwell and co-workers' early studies, they showed that sulfonate **381** and sulfonamide **383** could be transformed to biaryls **382** and **384** respectively under standard radical conditions, albeit in low yields (Scheme 69).[108] Later, Studer et al. found that the 1,5-aryl migrations of 2-methoxy-1-naphthyl substituted sulfonates took place in an atroposelective manner. Treatment of different sulfonates **385** with Bu_3SnH and 1,1'-azobis(cyclohexane-1-carbonitrile) (V-40) under reflux conditions afforded various separable axially chiral biaryls **386a** and **386b**, which may serve as ligands in asymmetric catalysis (Scheme 70).[109]

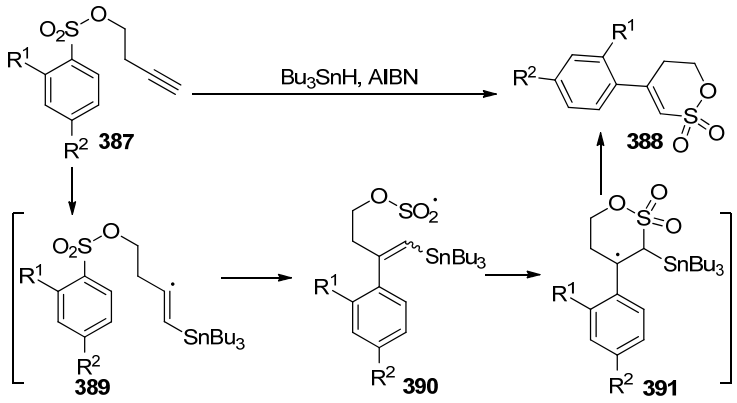


Scheme 69 1,5-Aryl migrations from sulfonate or sulfonamide to a phenyl radical



Scheme 70 Atroposelective radical 1,5-aryl migration reaction from sulfonate to a phenyl radical

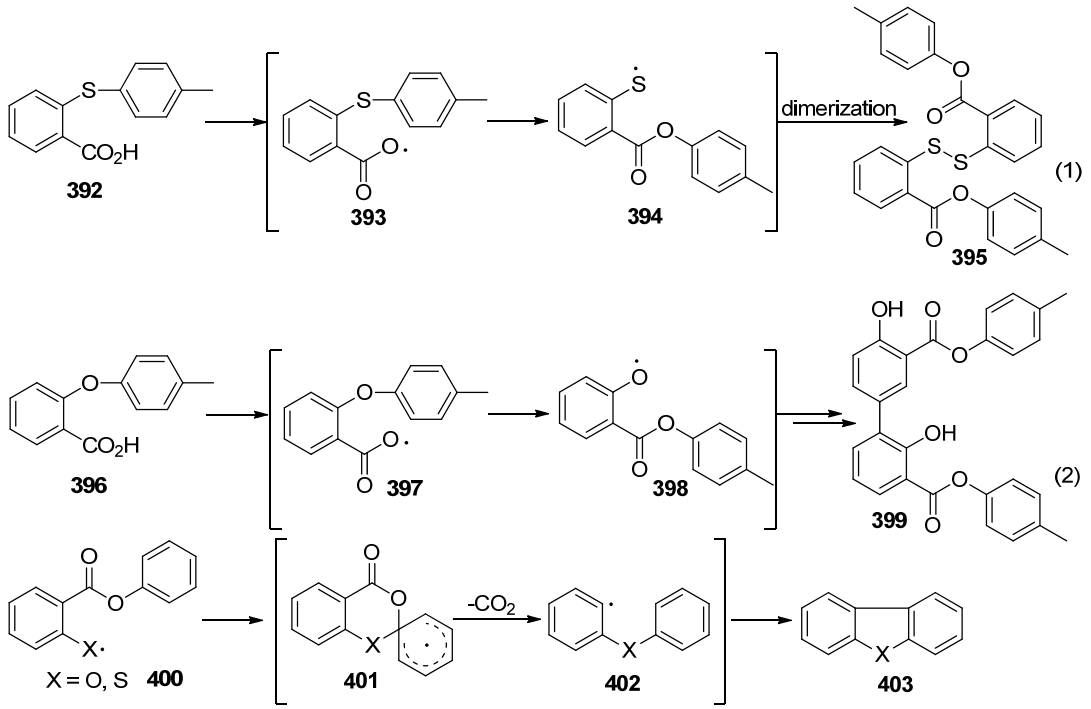
In 1997, Motherwell and co-workers reported an example of radical 1,5-aryl migration from sulfonate to an alkenyl radical. Under standard radical conditions, various sulfonates **387** were transformed to oxathiin-2,2-dioxides **388** in moderate yields.[110] Mechanistically, the cascade process was initiated via the addition of the stannyl radical to the terminal alkyne group of **387** to generate the alkenyl radical intermediate **389**, which then underwent a 1,5-aryl transfer to form the *S*-centered radical **390**. The final *6-endo* cyclization of **390** followed by *β*-fragmentation provided the desired product **388** (Scheme 71).



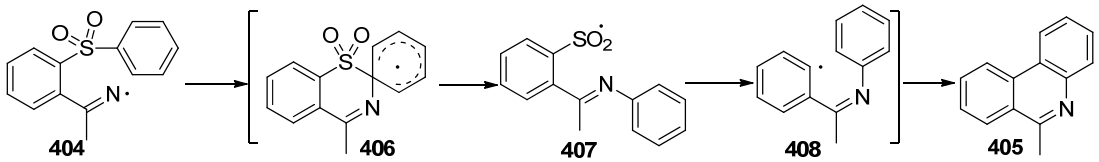
Scheme 71 1,5-Aryl migrations from sulfonate to an alkenyl radical

5.6 Radical 1,5-aryl migrations between two heteroatoms

Radical 1,5-aryl migration from sulfur to oxygen was initially discovered as a side reaction by Thomson's group.[111a] Diester **395** was formed in the persulfate oxidation of carboxylic acid **392** through 1,5-aryl transfer in radical **393** to give **394** followed by dimerization. The corresponding migration between oxygen atoms, however, provided dimer **399** because an isomerization of rearranged *O*-centered radical **398** took place before the final dimerization.[111b] Interestingly, the reverse 1,5-aryl migration of the above type, in which the aryl group migrated from the ester to the initially formed phenoxyl or thiyl radical, were later realized by McNab and Cadogan and used for the syntheses of dibenzofurans and dibenzothiophenes (Scheme 72).[112] The 1,5-aryl migration between nitrogen atoms was reported by McNab and Cadogan,[113] and in a more recent study by Leardini and co-workers, the 1,5-phenyl migration from sulfone to nitrogen was found in the transformation of **404** to phenanthridine **405** (Scheme 73).[114]



Scheme 72 1,5-Aryl migrations between sulfur and oxygen



Scheme 73 1,5-Aryl migrations from sulfone to nitrogen

6. Summary and outlook

In this review, we have introduced the development of radical aryl migration reactions, classified and discussed them based on the migration types and highlighted recent breakthroughs. The long-term efforts in mechanistic studies of neophyl and *O*-neophyl rearrangements, and especially recent investigations with the assistance of modern spectroscopic techniques as well as more accurate computations, have not only deepened the understanding of those radical reactions but also enabled their use as radical clocks in kinetic competition experiments. Although most aryl migrations were originally discovered as side reactions, their extensive variations and modifications have functioned in an increasing number of tandem radical reactions, which serve as efficient methodologies in preparing synthetically useful building blocks. In particular, radical rearrangements in which an aryl group migrates to an initial phenyl radical center have been widely used in biaryl synthesis, and recent combinations of radical trifluoromethylation, phosphonylation, and azidation with 1,2- or 1,4-aryl migration have provided novel methods for the syntheses of various heteroatom-containing compounds with potential pharmaceutical applications. Despite the extensive studies on these radical aryl migrations, there are still challenges in terms of their synthetic applications in natural product synthesis and a need for development of asymmetric

versions, and especially catalytic asymmetric versions. Additionally, most early reported radical aryl migrations required the use of toxic organostannane reagents and harsh conditions, such as high temperature or high dilution, which do not meet the requirements of green chemistry. Therefore, further improvement of these reactions to take place under environmentally benign conditions will be worthwhile. We believe that these highlighted issues in the field of radical aryl migration will remain active topics for researchers who have been or will be engaged in this research field.

Notes and references

1. For selected books and reviews on 1,2-nucleophilic rearrangements, please see: (a) B. Rickborn, in *Comprehensive Organic Synthesis*, Vol. 3 (Eds: B. M. Trost and I. Fleming), Pergamon, Oxford, 1991, pp 721; (b) L. E. Overman, *Acc. Chem. Res.*,1992, **25**, 352; (c) T. J. Snape, *Chem. Soc. Rev.* 2007, **36**, 1823; (d) B. Wang and Y.-Q. Tu, *Acc. Chem. Res.*, 2011, **44**, 1207; (e) Z.-L. Song, C.-A. Fan and Y.-Q. Tu, *Chem. Rev.*, 2011, **111**, 7523; (f) T. Seiser, T. Saget, D. N. Tran and N. Cramer, *Angew. Chem. Int. Ed.*, 2011, **50**, 7740; (g) E. Leemans, M. D'hooghe and N. De Kimpe, *Chem. Rev.*, 2011, **111**, 3268; (h) S.-H. Wang, B.-S. Li and Y.-Q. Tu, *Chem. Commun*., 2014, **50**, 2393; (i) S.-H. Wang, Y.-Q. Tu and M. Tang in *Comprehensive Organic Synthesis*, Vol. 3 (Eds: B. M. Molander and P. Knochel), Elsevier, Oxford, 2014, pp 795.
2. For early books and reviews on radical aryl migrations, please see: (a) *Free Radicals*, Ed. J. W. Wilt and J. K. Kochi, Wiley-VCH, New York, 1973; (b) *Free-Radical Chemistry: Structure and Mechanism*, D. C. Nonhebel and J. C. Walton, Cambridge University Press, Cambridge, 1974; (c) *Advances in Free Radical Chemistry*, Ed. R. Kh. Freidlina, A. B. Terent'ev and G. H. Williams, Heyden, London, 1980; (d) *Rearrangements in Ground and Excited States*, Ed. A. L. J. Beckwith, K. U. Ingold and P. de Mayo, Academic, New York, 1980; (e) A. Studer and M. Bossart, *Tetrahedron*, 2001, **57**, 9649; (f) *Radical Arylations. Encyclopedia of Radicals in Chemistry, Biology and Materials*, S. E. Vaillard and A. Studer, 2012.
3. H. Wieland, *Chem. Ber.*, 1911, **44**, 2550.
4. W. H. Urry and M. S. Kharasch, *J. Am. Chem. Soc.*, 1944, **66**, 1438.
5. (a) Jr., E. J. Hamilton and H. Fisher, *Helv. Chim. Acta*, 1973, **56**, 795; (b) G. Brunton, H. C. McBay and K. U. Ingold, *J. Am. Chem. Soc.*, 1977, **99**, 4447.
6. A. Effio, D. Griller, K. U. Ingold, J. C. Scaiano and S. J. Sheng, *J. Am. Chem. Soc.*, 1980, **102**, 6063.
7. R. Leardini, D. Nanni, G. F. Pedulli, A. Tundu, G. Zanardi, E. Foresti and P. Palmieri, *J. Am. Chem. Soc.*, 1989, **111**, 7723.
8. A. Asensio and J. J. Dannenberg, *J. Org. Chem.*, 2001, **66**, 5996.
9. (a) D. Griller and K. U. Ingold, *Acc. Chem. Res.*, 1980, **13**, 317; (b) M. Newcomb, *Tetrahedron*, 1993, **49**, 1151.
10. B. Maillard and K. U. Ingold, *J. Am. Chem. Soc.*, 1976, **98**, 1224.
11. A recent determination of the rate constant of **18** to **19**, please see: R. Leardini, M. Lucarini, G. F. Pedulli and L. Valgimigli, *J. Org. Chem.*, 1999, **64**, 3726.
12. J. A. Franz, R. D. Barrows and D. M. Camaioni, *J. Am. Chem. Soc.*, 1984, **106**, 3964.
13. D. A. Lindsay, J. Lusztyk and K. U. Ingold, *J. Am. Chem. Soc.*, 1984, **106**, 7087.

14. A. Burton, K. U. Ingold and J. C. Walton, *J. Org. Chem.*, 1996, **61**, 3778.
15. M. Weber and H. Fischer, *J. Am. Chem. Soc.*, 1999, **121**, 7381.
16. K. A. Parker, D. M. Spero and K. C. Inman, *Tetrahedron Lett.*, 1986, **27**, 2833.
17. A. N. Abeywickrema, A. L. J. Beckwith and S. Gerba, *J. Org. Chem.*, 1987, **52**, 4072.
18. (a) H. Ishibashi, T. Kobayashi and D. Takamasu, *Synlett*, 1999, 1286; (b) H. Ishibashi, T. Kobayashi, S. Nakashima and O. Tamura, *J. Org. Chem.*, 2000, **65**, 9022; (c) H. Ishibashi, K. Ohata, M. Niihara, T. Sato and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, 2000, 547.
19. (a) W. R. Bowman and J. M. D. Storey, *Chem. Soc. Rev.*, 2007, **36**, 1803; (b) Y. Wu, S. M. Wang, F. Mao, T. L. Chan and F. Y. Kwong, *Org. Lett.*, 2012, **14**, 5306.
20. (a) H. Ishibashi, T. S. So, K. Okoshi, T. Sato., N. Nakamura, H. Nakatani and M. Iketa, *J. Org. Chem.*, 1991, **56**, 95; (b) H. Ishibashi, A. Toyao and Y. Takeda, *Synlett*, 1999, 1468.
21. (a) D. M. Hodgson, M. W. P. Bebbington and P. Willis, *Org. Lett.*, 2002, **4**, 4353; (b) D. M. Hodgson, M. W. P. Bebbington and P. Willis, *Org. Biomol. Chem.*, 2003, **1**, 3787.
22. Z. Cong, T. Miki, O. Urakawa and H. Nishino, *J. Org. Chem.*,2009, **74**, 3978.
23. G. Ouvry and S. Z. Zard, *Synlett*, 2003, 1627.
24. A. Gheorghe, B. Quiclet-Sire, X. Vila and S. Z. Zard, *Tetrahedron*, 2007, **63**, 7187.
25. B. Quiclet-Sire, G. Revol, and S. Z. Zard, *Org. Lett.*, 2009, **11**, 2832.
26. (a) X. Liu, F. Xiong, X. Huang, L. Xu, P. Li and X. Wu, *Angew. Chem. Int. Ed.*, 2013, **52**, 6962; (b) X. Liu, X. Wu, *Synlett*, 2013, 1882.
27. Z.-M. Chen, W. Bai, S.-H. Wang, B.-M. Yang, Y.-Q. Tu and F.-M. Zhang, *Angew. Chem. Int. Ed.*, 2013, **52**, 9781.
28. H. Egami, R. Shimizu, Y. Usui and M. Sodeoka, *Chem. Commun.*, 2013, **49**, 7346.
29. X.-Q. Chu, Y. Zi, H. Meng, X.-P. Xu and S.-J. Ji, *Chem. Commun.*, 2014, **50**, 7642.
30. X. Mi, C. Wang, M. Huang, Y. Wu and Y. Wu, *Org. Biomol. Chem.*, 2014, **12**, 8394.
31. X.-Q. Chu, H. Meng, Y. Zi, X.-P. Xu and S.-J. Ji, *Chem. Commun.*, 2014, **50**, 9718.
32. (a) X.-Q. Chu, H. Meng, Y. Zi, X.-P. Xu and S.-J. Ji, *Chem. Eur. J.*, 2014, **20**, 17198; (b) J. Zhao, H. Fang, R. Song, J. Zhou, J. Han and Y. Pan, *Chem. Commun.*, 2015, **51**, 599; (c) R.-J. Song, Y.-Q. Tu, D.-Y. Zhu, F.-M. Zhang and S.-H. Wang, *Chem. Commun.*, 2015, **51**, 749; (d) Y. Li, B. Liu, H.-B. Li, Q. Wang and J.-H. Li, *Chem. Commun.*, 2015, **51**, 1024.
33. Z.-M. Chen, Z. Zhang, Y.-Q. Tu, M.-H. Xu, F.-M. Zhang, C.-C. Li and S.-H. Wang, *Chem. Commun.*, 2014, **50**, 10805.
34. D. E. Falvey, B. S. Khambatta and G. B. Schuster, *J. Phys. Chem.*, 1990, **94**, 1056.
35. (a) J. T. Banks and J. C. Scaiano, *J. Phys. Chem.*, 1995, **99**, 3527; (b) D. V. Avila, K. U. Ingold, A. A. Di Nardo, F. Zerbetto, M. Z. Zgierski and J. Lusztyk, *J. Am. Chem. Soc.*, 1995, **117**, 2711.
36. L. Grossi and S. Strazzari, *J. Org. Chem.*, 2000, **65**, 2748.
37. (a) C. S. A. Antunes, M. Bietti, G. Ercolani, O. Lanzalunga and M. Salamone, *J. Org. Chem.*, 2005, **70**, 3884; (b) M. Bietti and M. Salamone, *J. Org. Chem.*, 2005, **70**, 10603; (c) M. Bietti, S. Fiorentini, I. P. Pato and M. Salamone, *J. Org. Chem.*, 2006, **71**, 3167.
38. K. U. Ingold, M. Smeu and G. A. DiLabio. *J. Org. Chem.*, 2006, **71**, 9906.
39. M. Bietti, G. Ercolani and M. Salamone, *J. Org. Chem.*, 2007, **72**, 4515.
40. M. Smeu and G. A. DiLabio, *J. Org. Chem.*, 2007, **72**, 4520.
41. (a) M. Salamone, M. Bietti, A. Calcagni and G. Gente, *Org. Lett.*, 2009, **11**, 2453; (b) M. Bietti, A. Calcagni, D. O. Cicero, R. Martella and M. Salamone, *Tetrahedron Lett.*, 2010, **51**,

4129.
42. G. A. DiLabio, K. U. Ingold, S. Lin, G. Litwinienko, O. Mozenson, P. Mulder and T. T. Tidwell, *Angew. Chem. Int. Ed.*, 2010, **49**, 5982.
43. P. F. Britt, A. C. Buchanan, III, M. J. Cooney and D. R. Martineau, *J. Org. Chem.*, 2000, **65**, 1376.
44. M. Kamata and K. Komatsu, *Tetrahedron Lett.*, 2001, **42**, 9027.
45. A. Ohno, N. Kito and Y. Ohnishi, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 467.
46. A. Baroudi, J. Mauldin and I. V. Alabugin, *J. Am. Chem. Soc.*, 2010, **132**, 967.
47. (a) A. Baroudi, J. Alicea and I. V. Alabugin, *Chem. Eur. J.*, 2010, **16**, 7683; (b) A. Baroudi, P. Flack and I. V. Alabugin, *Chem. Eur. J.*, 2010, **16**, 12316; (c) A. Baroudi, J. Alicea, P. Flack, J. Kirincich and I. V. Alabugin, *J. Org. Chem.*, 2011, **76**, 1521.
48. A. Beste and A. C. Buchanan, III, *J. Org. Chem.*, 2011, **76**, 2195.
49. S. Kim and J. Y. Do, *J. Chem. Soc., Chem. Commun.*, 1995, 1607.
50. J. Tang, S. Nayak, J.S. Costa, A. Robertazzi, R. Pievo, I. Mutikainen, O. Roubeau, S. J. Teat, P. Gamez and J. Reedijk, *Dalton Trans.*,2010, **39**, 1361.
51. M. S. Alnajjar and J. A. Franz, *J. Am. Chem. Soc.*, 1992, **114**, 1052.
52. S. F. Wang, L. Mathew and J. Warkentin, *J. Am. Chem. Soc.*, 1988, **110**, 7235.
53. (a) R. L. Dannley and G. C. Farrant, *J. Org. Chem.*, 1969, **34**, 2432. (b) A. K. Shubber and R. L. Dannley, *J. Org. Chem.*, 1971, **36**, 3784.
54. E. Bacqué, M. E. Qacemi and S. Z. Zard, *Org. Lett.*, 2005, **7**, 3817.
55. Y.-R. Chen and W.-L. Duan, *J. Am. Chem. Soc.*, 2013, **135**, 16754.
56. S. Winstein, R. Heck, S. Lapporte and R. Baird, *Experientia*, 1956, **12**, 138.
57. (a) M. Julia and B. Malassiné, *Tetrahedron Lett.*, 1971, **15**, 987; (b) M. Julia, *Pure Appl. Chem.*,1974, **40**, 553.
58. H. Ishibashi, N. Nakamura, K. Ito, S. Kitayama and M. Ikeda, *Heterocycles*, 1990, **31**, 1781.
59. (a) L. Fuentes, L. Quintero, A. Cordero-Vargas, C. Eustaquio, J. L. Terán and F. Sartillo-Piscil, *Tetrahedron Lett.*, 2011, **52**, 3620; (b) J. Sandoval-Lira, J. M. Hernández-Pérez and F. Sartillo-Piscil, *Tetrahedron Lett.*, 2012, **53**, 6689.
60. S.-F. Wang, C.-P. Chuang, J.-H. Lee and S.-T. Liu, *Tetrahedron*, 1999, **55**, 2273.
61. J. Aubé, X. Peng, Y. Wang and F. Takusagawa, *J. Am. Chem. Soc.*, 1992, **114**, 5466.
62. D. S. Black, G. L. Edwards and S. M. Laaman, *Tetrahedron Lett.*, 1998, **39**, 5853.
63. H. Senboku, H. Hasegawa, K. Orito and M. Tokuda, *Tetrahedron Lett.*, 2000, **41**, 5699.
64. W. Thaharn, D. Soorukram, C. Kuhakarn, P. Tuchinda, V. Reutrakul and M. Pohmakotr, *Angew. Chem. Int. Ed.*, 2014, **53**, 2212.
65. L. Benati, L. Capella, P. C. Montevecchi and P. Spagnolo, *J. Org. Chem.*, 1994, **59**, 2818.
66. (a) M. J. Palframan, K. Tchabanenko and J. Robertson, *Tetrahedron Lett.*, 2006, **47**, 8423; (b) J. Robertson, M. J. Palframan, S. A. Shea, K. Tchabanenko, W. P. Unsworth and C. Winters, *Tetrahedron*, 2008, **64**, 11896.
67. P. Gao, Y.-W. Shen, R. Fang, X.-H. Hao, Z.-H. Qiu, F. Yang, X.-B. Yan, Q. Wang, X.-J. Gong, X.-Y. Liu and Y.-M. Liang, *Angew. Chem. Int. Ed.*, 2014, **53**, 7629.
68. D. C. Harrowven, M. I. T. Nunn, N. A. Newman and D. R. Fenwick, *Tetrahedron Lett.*, 2001, **42**, 961.
69. H. Amii, S. Kondo and K. Uneyama, *Chem. Commun.*, 1998, 1845.
70. J. W. Wilt and C. F. Dockus, *J. Am. Chem. Soc.*, 1970, **92**, 5813.

71. (a) J. W. Wilt and W. K. Chwang, *J. Am. Chem. Soc.*, 1974, **96**, 6194; (b) J. W. Wilt, W. K. Chwang, C. F. Dockus and N. M. Tomiuk, *J. Am. Chem. Soc.*, 1978, **100**, 5534.
72. M. Kira, H. Sugiyama and H. Sakurai, *J. Am. Chem. Soc.*, 1983, **105**, 6436.
73. A. Studer, M. Bossart and H. Steen, *Tetrahedron Lett.*, 1998, **39**, 8829.
74. Y. Zhang, Y. Matsuo and E. Nakamura, *Org. Lett.*, 2011, **13**, 6058.
75. K. Wakabayashi, H. Yorimitsu, H. Shinokubo and K. Oshima, *Org. Lett.*, 2000, **2**, 1899.
76. D. H. Hey and T. M. Moynehan, *J. Chem. Soc.*, 1959, 1563.
77. (a) J. Grimshaw and J. Trocha-Grimshaw, *J. Chem. Soc., Perkin Trans.1*, 1979, 799; (b) J. Grimshaw and R. J. Haslett, *J. Chem. Soc., Perkin Trans. 1*, 1980, 657; (c) J. Grimshaw, R. Hamilton and J. Trocha-Grimshaw, *J. Chem. Soc., Perkin Trans. 1*, 1982, 229.
78. L. Benati, P. Spagnolo, A. Tundo and G. Zanardi, *J. Chem. Soc., Chem. Commun.*, 1979, 141.
79. E. Lee, H. S. Whang and C. K. Chung, *Tetrahedron Lett.*, 1995, **36**, 913.
80. V. Rey, A. B. Pierini and A. B. Peñéñory, *J. Org Chem.*, 2009, **74**, 1223.
81. (a) J. W. Wilt and D. D. Oathoudt, *J. Org. Chem.*, 1958, **23**, 218; (b) Jr., W. H. Starnes, *J. Am. Chem. Soc.*, 1963, **85**, 3708.
82. M. D. Bachi, E. Bosch, D. Denenmark and D. Girsh, *J. Org. Chem.*, 1992, **57**, 6803.
83. E. Lee, C. Lee, J. S. Tae, H. S. Whang and K. S. Li, *Tetrahedron Lett.*, 1993, **34**, 2343.
84. A. M. Rosa, A. M. Lobo, P. S. Branco and S. Prabhakar, *Tetrahedron*, 1997, **53**,285.
85. W. R. Bowman, E. Mann and J. Parr, *J. Chem. Soc., Perkin Trans.1*, 2000, 2991.
86. D. Crich and J.-T. Hwang, *J. Org. Chem.*, 1998, **63**, 2765.
87. (a) L. Capella, P. C. Montevecchi and D. Nanni, *J. Org. Chem.*, 1994, **59**, 3368; (b) P. C. Montevecchi and M. L. Navacchia, *J. Org. Chem.*, 1998, **63**, 537.
88. R. Loven and W. N. Speckamp, *Tetrahedron Lett.*, 1972, 1567.
89. (a) J. J. Köhler and W. N. Seckamp, *Tetrahedron Lett.*, 1977, 631; (b) J. J. Köhler and W. N. Seckamp, *Tetrahedron Lett.*, 1977, 635; (c) W. N. Speckamp and J. J. Köhler, *J. Chem. Soc., Chem. Commun.*, 1978, 166; (d) H. J. Köhler and W. N. Speckamp, *J. Chem. Soc., Chem. Commun.*, 1980, 142.
90. (a) A. J. Clark, S. R. Coles, A. Collis, T. Debure, C. Guy, N. P. Murphy and P. Wilson, *Tetrahedron Lett.*, 2009, **50**, 5609; (b) A. J. Clark, S. R. Coles, A. Collis, D. R. Fullaway, N. P. Murphy and P. Wilson, *Tetrahedron Lett.*, 2009, **50**, 6311; (c) A. J. Clark, D. R. Fullaway, N. P. Murphy and H. Parekh, *Synlett*, 2010, 610.
91. D. L. J. Clive and T. L. B. Boivin, *J. Org. Chem.*, 1989, **54**, 1997.
92. M. Pudlo, I. Allart-Simon, B. Tinant, S. Gérard and J. Sapi, *Chem. Commun.*, 2012, **48**, 2442.
93. A. Gheorghe, B. Quiclet-Sire, X. Vila and S. Z. Zard, *Org. Lett.*, 2005, **7**, 1653.
94. W. Kong, M. Casimiro, E. Merino and C. Nevado, *J. Am. Chem. Soc.*, 2013, **135**, 14480.
95. W. Kong, M. Casimiro, N. Fuentes, E. Merino and C. Nevado, *Angew. Chem. Int. Ed.*, 2013, **52**, 13086.
96. W. Kong, E. Merino and C. Nevado, *Angew. Chem. Int. Ed.*, 2014, **53**, 5078.
97. A. Feigenbaum, J.-P. Pete and D. Scholler, *J. Org. Chem.*, 1984, **49**, 2355.
98. (a) M. L. E. N. da Mata, W. B. Motherwell and F. Ujjainwalla, *Tetrahedron Lett.*, 1997, **38**, 137; (b) E. Bonfand, L. Forslund, W. B. Motherwell and S. Vázquez, *Synlett*, 2000, 475.
99. A. F. Hegarty, J. A. Kearney and F. L. Scott, *J. Chem. Soc., Perkin Trans.2*, 1973, 1422.
100. L. Giraud, E. Lacôte and P. Renaud, *Helv. Chim. Acta*, 1997, **80**, 2148.
101. B. Alcaide and A. Rodríguez-Vicente, *Tetrahedron Lett.*, 1998, **39**, 6589.

102. H. Sakurai and A. Hosomi, *J. Am. Chem. Soc.*, 1970, **92**, 7507.
103. S. Amrein, M. Bossart, T. Vasella and A. Studer, *J. Org. Chem.*, 2000, **65**, 4281.
104. A. Studer, M. Bossart and T. Vasella, *Org. Lett.*, 2000, **2**, 985.
105. D. L. J. Clive and S. Kang, *Tetrahedron Lett.,* 2000, **41**, 1315.
106. (a) S. Guidotti, R. Leardini, D. Nanni, P. Pareschi, and G. Zanardi, *Tetrahedron Lett.,*1995,**36**, 451; (b) F. Leardini, H. McNah and D. Nanni, *Tetrahedron,* 1995, **51**, 12143.
107. (a) A. Studer and M. Bossart, *Chem. Commun.*, 1998, 2127; (b) M. Bossart, R. Fässler, J. Schoenberger and A. Studer, *Eur. J. Org. Chem.*, 2002, 2742.
108. (a) W. B. Motherwell and A. M. K. Pennell, *J. Chem. Soc., Chem. Commun.*, 1991, 877; (b) M. L. E. N. da Mata, W. B. Motherwell and F. Ujjainwalla, *Tetrahedron Lett.*,1997, **38**, 141.
109. B. Schulte, R. Fröhlich and A. Studer, *Tetrahedron,* 2008, **64**, 11852.
110. E. Bonfand, W. B. Motherwell, A. M. K. Pennel1, M. K. Uddin and F. Ujjainwalla, *Heterocycles*, 1997, **46**, 523.
111. (a) P. M. Brown, P. S. Dewar, A. R. Forrester and A. S. Ingram, *Chem. Commun.*, 1970, 849; (b) R. H. Thomson and A. G. Wylie, *J. Chem. Soc (C).*, 1966, 322.
112. (a) J. I. G. Cadogan, C. L. Hickson and H. McNab, *Tetrahedron,* 1986, **42**, 2135; (b) M. Black, J. I. G. Cadogan and H. McNab, *J. Chem. Soc., Chem. Commun.*, 1990, 395.
113. G. Calestani, R. Leardini, H. McNab, D. Nanni and G. Zanardi, *J. Chem. Soc., Perkin Trans. 1,* 1998, 1813.
114. R. Leardini, H. McNab, M. Minozzi and D. Nanni, *J. Chem.Soc., Perkin Trans. 1,* 2001, 1072.

Acknowledgements

We would like to thank the Natural Science Foundation of China (No. 21202073, 21290180, 21272097, 21372104, and 21472077), the “111” Program of MOE, and the Project of MOST (2012ZX 09201101-003) for their financial support.

AUTHOR INFORMATION

Zhi-Min Chen (1986) received his B.S. in chemistry at Fuzhou University in 2009, and his Ph.D. at Lanzhou University in 2014, supervised by Prof. Yong-Qiang Tu. His research mainly focused on rearrangement reactions including neophyl-type rearrangement.

Xiao-Ming Zhang (1985) studied chemistry at Lanzhou University where he received his B.S. in chemistry in 2007. He then joined the research group of Prof. Yong-Qiang Tu and completed his Ph.D. at Lanzhou University in 2013. His research interests involve total synthesis and biomimetic synthesis of natural product.

Yong-Qiang Tu (1958) received his B.S. and M.S. from Lanzhou University in 1982 and 1985, respectively. He obtained his Ph.D. in organic chemistry in 1989 from Lanzhou University under the supervision of Prof. Yao-Zu Chen. After spending three years (1993-95) as a postdoctoral fellow in W. Kitching's group at Queensland University, Australia, he was appointed a full professor position at Lanzhou University in 1995 and became Director of the State Key Laboratory of Applied Organic Chemistry from 2001 to 2010. In 2009, he was elected an Academician of Chinese Academy of Sciences.