Synthesis using aromatic homolytic substitution—recent advances

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This *critical review* aims at presenting recent developments in intramolecular aromatic homolytic substitution which has become one of the common methodologies in modern synthesis. The application of Bu_3SnH-mediated cyclisations have proved especially useful. The *critical review* illustrates the mechanistic considerations required for planning synthetic applications and a wide range of synthetic protocols and natural product syntheses are shown. The latest evidence for the mechanisms involved in aromatic homolytic substitution are presented. (152 references).

Introduction

Aromatic homolytic substitution is defined as replacement of a leaving group X by an attacking radical on an aromatic ring (Scheme 1). The reaction proceeds *via* a sigma (σ) complex and the substitution is completed by loss of the leaving group X, which is normally hydrogen (H•). This step is not fully understood in most reactions because hydrogen is not a likely leaving group. The mechanism contrasts with aromatic electrophilic substitution (attack by an electrophile, cationic σ-complex and loss of a cation) and aromatic nucleophilic substitution S_NAr (attack by a nucleophile, anionic σ-complex and loss of a anion). Many reactions defined as aromatic homolytic substitution involve an oxidative step to convert the radical σ-complex into a cationic σ-complex, followed by rapid loss of a cation X^+, normally a proton (Scheme 1).

Early studies of aromatic homolytic substitution indicated the general mechanism and are well reviewed.[1] The reactions were on the whole not applied to synthesis. Many reactions gave poor yields and intractable mixtures. An exception was the synthesis of biphenyls, *e.g.* the Gomberg reaction. The problems could be overcome by the use of alkyl nitrites to generate aryl radicals from amines. Intermolecular reactions gave poor regioselectivity by comparison to electrophilic and

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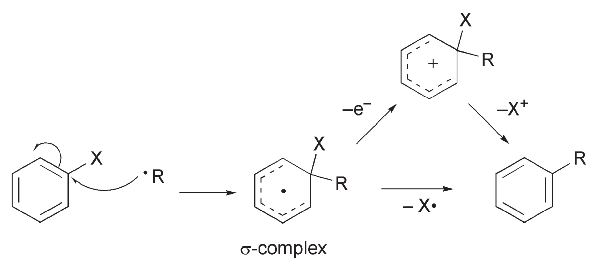

Scheme 1 Aromatic homolytic substitution.

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nucleophilic aromatic substitutions. However, the rapid advances made in radical chemistry in the past twenty years have produced new methods, reagents and mechanistic understanding. These advances also facilitated significant application of intramolecular aromatic homolytic substitution in synthesis and novel routes to the synthesis of complex natural products.

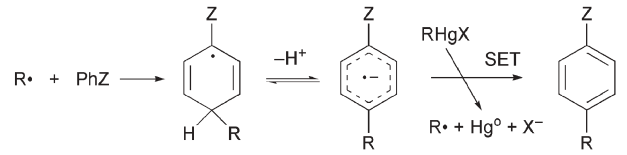
The advent and application of tributyltin hydride (Bu_3SnH)[2–11] and hexamethylditin [$(Me_3Sn)_2$][12] to aromatic homolytic substitution reactions some 15 years ago initiated a major increase in synthetic procedures. These reagents also facilitated the use of halogenoarenes as readily available radical precursors and commonly gave much higher yields. The use of Bu_3SnH is perhaps surprising because normally the reagent facilitates reductive reactions whereas aromatic homolytic substitutions retain the same oxidation level. This aspect is fully discussed later in the review.

This review highlights the synthetic potential and discusses the advances in understanding the mechanisms involved. We have chosen advances since 1990 that were mediated by the application of Bu_3SnH and $(Me_3Sn)_2$. Earlier advances involving the use of oxidants, in particular the Minisci reaction, have been well reviewed and are not covered in this review.[13–15] The Minisci reaction and advances in aromatic homolytic substitution on pyridine and related heteroarenes are well covered by a recent review by Harrowven and Sutton.[14] The extensive review by Studer and Bossart is essential reading[15] along with other reviews that contain useful sections.[16,17]

1. Intermolecular reactions

The addition of aryl radicals to arenes has been intensively studied and well reviewed.[13–16] Reference 16 gives a clear description of the results and the mechanistic factors involved. Polar effects in both the attacking radical and the arenes under attack are important for affecting rates and regioselectivity. These reactions were widely used for the synthesis of biphenyls and aryl–heteroaryl equivalents but were commonly 'dirty' reactions with poor yields and regioselectivities. The modern use of Pd(0)-catalysed reactions has largely superseded this application synthetically.

The rates of addition of alkyl radicals onto arenes is normally too slow to be of synthetic application. However, alkyl radicals add at useful rates to protonated azines, *i.e.* a 100–1000 fold increase relative to the non-protonated azine. The Minisci reaction, which applies this behaviour to aromatic homolytic substitution by alkyl radicals on pyridine and related azines, is well reviewed.[13,14] Russell and co-workers have also shown that alkylmercury halides could be used as precursors for radical addition to arenes[18,19] and protonated azines.[18,20] A radical-anion and single electron transfer (SET) mechanism was proposed (Scheme 2). Alkyl halides can also be used with $(Me_3Sn)_2$ to replace alkylmercury halides.[19b] A base (DABCO) is essential, which strongly suggests the deprotonation step in the mechanism. However, this methodology has not found wide application, possibly due to the use of toxic organomercury precursors and the fact that only electron-deficient arenes can be used.



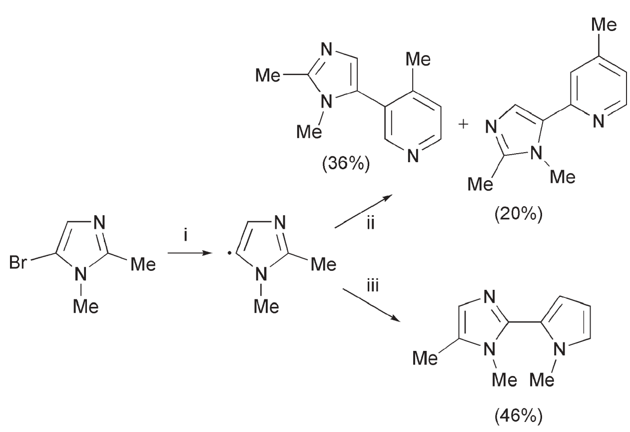
Scheme 2 Alkylmercury halides as precursors: *e.g.* Z = CHO, RHgX = *t*-BuHgI, 4-*t*-Bu-C_6H_4CHO (60%). *Reagents and conditions*: sunlamp, DABCO (4 equiv.), DMSO.

New advances using tributyltin hydride (Bu_3SnH) have largely been reported for intramolecular reactions but also show improved procedures for intermolecular reactions.[21–24] The regioselectivity is still poor and the arene under attack needs to be used in high concentration, or as the solvent, to compensate for poor rates. The first examples showed that alkyl radicals generated from alkyl bromides, iodides[21] and xanthates[22] by Bu_3SnH or $(TMS)_3SiH$ added to protonated azines in moderate to good yields.

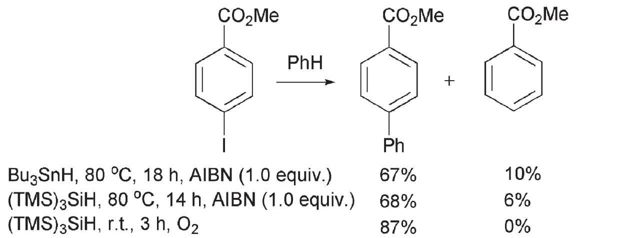
2- And 5-imidazolyl radicals, generated from the respective bromides using Bu_3SnH, undergo addition to a range of arenes and heteroarenes in reasonable yield (*e.g.* Scheme 3).[23] Similar regioselectivity was obtained with phenyl radicals. Pyridyl and aryl radicals have also been added to a range of azines and arenes using similar conditions to yield further carbo- and heterobiaryl compounds.[24]

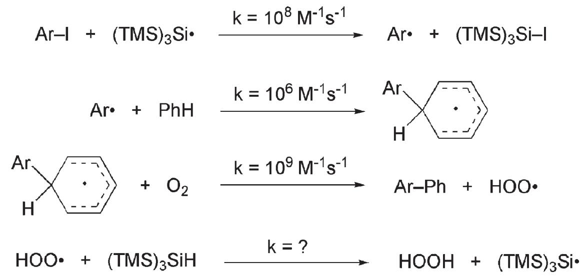
Crich and co-workers have developed a Bu_3SnH-mediated PhSeH-catalysed protocol for trapping the π-radical intermediates in aromatic homolytic substitution reactions to yield aryl-substituted cyclohexadienes (see Sections 2.11 and 3.1).[25,26] In this methodology, addition of aryl radicals onto furans, thiophenes and carbocyclic-arenes yields dihydro-products, but addition to *N*-heteroarenes (pyridine, quinoline, isoquinoline, pyrrole and benzothiazole) yields the fully aromatised products. The PhSeH catalyses the reactions but the mechanism of aromatic homolytic substitution is not clear. Aryl iodides with H-donating groups in the *ortho*-position direct regioselectivity towards the position *ortho* to the nitrogen.

A novel and potentially major advance has been reported for inter- and intramolecular aromatic homolytic substitution using oxygen as the chain carrier (Scheme 4).[27] The method



Scheme 3 *Reagents and conditions*: i, Bu_3SnH, AIBN (3.0 equiv.), PhH, reflux, 2 h; ii, 4-methylpyridine; iii, *N*-methylpyrrole.





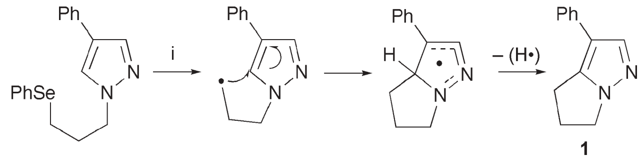
Scheme 4

facilitates rapid reactions (15–30 min) at rt with no initiator. The putative mechanism is shown in Scheme 4. Dioxygen abstracts the hydrogen from the σ-complex to facilitate rearomatisation and form peroxyl radicals, which in turn abstract hydrogen from $(TMS)_3SiH$ to complete the chain reaction. Three of the rates are known and the fourth is assumed to be fast also. These reaction conditions should revolutionise the synthetic use of aromatic homolytic substitution. Pyridine was added to larger scale reactions to neutralise HI formed. $(TMS)_3SiH$ was found to be superior to Bu_3SnH because the slower H-abstraction allows time for the aryl radical to add to the arene rather than be intercepted by the radical reagent. A range of examples were reported but the procedure does not overcome the regioselectivity problems for intermolecular reactions with substituted arenes.

2. Intramolecular reactions

2.1 Synthetic potential

The use of intramolecular reactions largely eliminates the problems of poor regioselectivity obtained in intermolecular reactions and is therefore much more useful in synthesis. The synthetic applications of intramolecular aromatic homolytic substitution are considerable and some initial synthetic examples are shown, *e.g.* a monocyclisation and a domino reaction. The synthesis of the pyrazole alkaloid withasomnine **1** involves a 5-*exo* cyclisation of an alkyl radical onto a heteroarene (Scheme 5).[28] The synthesis of camptothecin **2**, an important anticancer alkaloid, illustrates the use of domino reactions involving aromatic heterocyclic synthesis with an intermediate alkenyl radical as the attacking radical onto a benzene ring (Scheme 6).[29]



Scheme 5 *Reagents and conditions*: i, Bu_3SnH (1.3 equiv.), ACN [1,1′-azobis(cyclohexylcarbonitrile)] (2 equiv.), PhMe, reflux, 4 h, 38% (**1**).

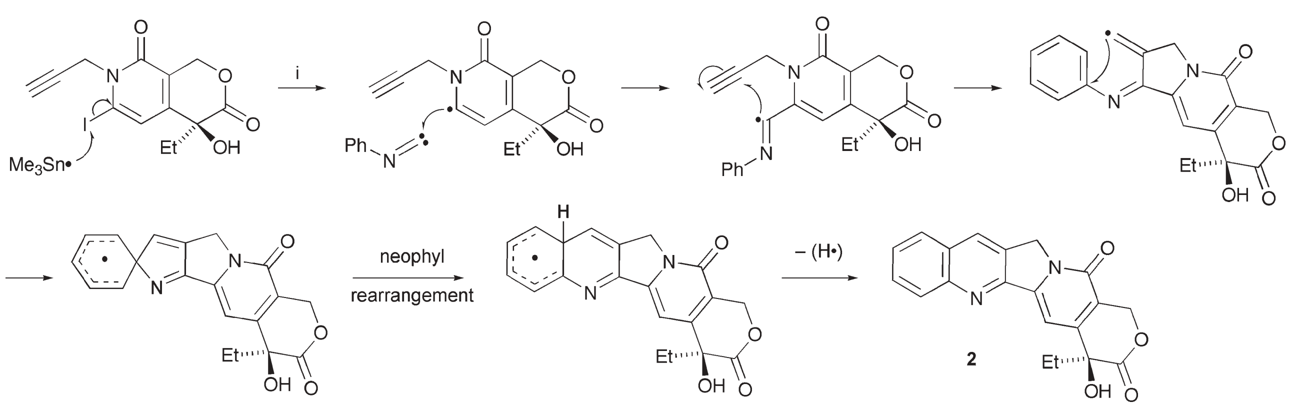
2.2 Kinetic guidelines

A number of general guidelines and concepts of mechanism are helpful in planning syntheses.

2.2a. Kinetics. Several steps need to be considered: abstraction from the precursor to generate the initial radical, rate of cyclisation *versus* rate of trapping the radical and loss of the leaving group in the rearomatisation step. The most common leaving group, hydrogen, needs to be abstracted by another radical species. In the general reactions using Bu_3SnH or related group XIV hydrides, many of the rates are known.

Common precursors are iodo- or bromoarenes. The iodo group is abstracted faster than the bromo group and is therefore a superior precursor. For example, the abstraction from 4-iodoanisole by $Bu_3Sn^{\bullet}$ is $8.8 \times 10^8\ M^{-1}\ s^{-1}$ at 80 °C, whereas for 4-bromoanisole the rate is $2.6 \times 10^6\ M^{-1}\ s^{-1}$ at 80 °C.[30] The rates for $(TMS)_3SiH$ are similar. The rates of abstraction from alkyl halides are also fast and similar for Bu_3SnH, Bu_3GeH and $(TMS)_3SiH$. Phenylselenides (PhSe) have similarly proved good groups for generating radicals from alkyl precursors but not from aryl precursors.

There are no reported rates of cyclisation onto arenes to our knowledge but the rate of addition of phenyl radicals onto



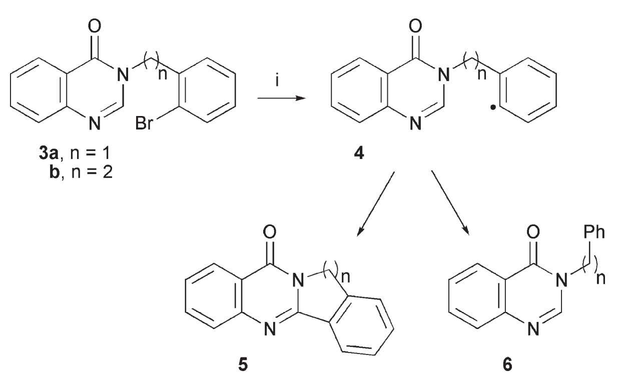
Scheme 6 *Reagents and conditions*: i, $(Me_3Sn)_2$ (1.5 equiv.), PhNC, PhH, sunlamp irradiation, 70 °C, 65% (camptothecin **2**).

benzene is a guide: 10^6 M^{-1} s^{-1} at 25 °C.[31] Reductive trapping of the aryl radical by the radical reagent is a problem and needs to be taken into account. The three common reagents have similar rates of H-abstraction by aryl radicals: Bu_3SnH (6.9×10^8 M^{-1} s^{-1} at 30 °C),[31] Bu_3GeH (2.6×10^8 M^{-1} s^{-1} at 29 °C),[32] $(TMS)_3SiH$ (3.0×10^8 M^{-1} s^{-1} at 20 °C).[33] The rates of H-abstraction by alkyl radicals from Bu_3GeH and $(TMS)_3SiH$ are *ca.* 20 times slower than from Bu_3SnH. These slower rates are useful for facilitating cyclisation over reduction for alkyl radicals but not for aryl radicals.

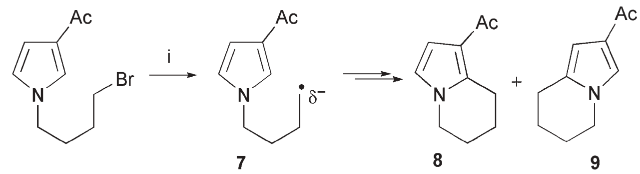
In all of the reactions there is a competition between the rates of cyclisation and reduction of the initial radical by Bu_3SnH. Reduction by Bu_3SnH, which is the most commonly used reagent, can be lowered by syringe pump addition, which keeps $[Bu_3SnH]$ at a minimum. Cyclisation can be facilitated in some reactions by using hexamethylditin $(Me_3Sn)_2$ in place of Bu_3SnH, thereby minimising the reduction of intermediate radicals before cyclisation. An example of the use of hexamethylditin is shown in Scheme 7.[34] The 3*H*-quinazol-4-one precursor **3b** gave largely reduction when Bu_3SnH was used, *i.e.* with a slow cyclisation, the radical **4b** was largely intercepted to yield the uncyclised product **6b**. However, when $(Me_3Sn)_2$ was used, the aryl radical intermediate **4b** cyclised in high yield to the tetracycle **5b**.

2.2b. Ring size. Intramolecular reactions are more favoured than intermolecular reactions if the entropy of cyclisation is favourable, *e.g.* 5–7-membered ring cyclisation. Ring strain caused by sp^2-hybridised atoms in the arene results in 6-membered ring cyclisation being more favoured than 5-membered ring cyclisation. An example is shown in Scheme 7; precursor **3b** gives selective 6-ring cyclisation (92%) over reduction using $(Me_3Sn)_2$, whereas **3a** gives largely reduction (65%) rather than 5-ring cyclisation (18%) under the same reaction conditions.[34] Other examples of this phenomenon are reported in the literature.[28,35–38]

2.2c. Polarity of radicals. Bu_3SnH is a nucleophilic source of hydrogen and therefore intercepts electrophilic radicals faster than nucleophilic radicals, allowing less time for cyclisation of the intermediate radical. Nucleophilic radicals react faster with electron-deficient arenes and *vice versa* for electrophilic



Scheme 7 *Reagents and conditions*: i, Bu_3SnH, Et_3B, PhMe, rt: **3a** yields 0% (**5a**), 96% (**6a**); **3b** yields 8% (**5b**), 55% (**6b**); $(Me_3Sn)_2$, *t*-BuPh, reflux, **3a** yields 18% (**5a**), 65% (**6a**); **3b** yields 92% (**5b**), 0% (**6b**).



Scheme 8 *Reagents and conditions*: i, Bu_3SnH, AIBN, PhMe, reflux, 5 h, 45% (**8**), 0% (**9**).

radicals. However, aryl radicals are only weakly nucleophilic and very reactive. Substituents on the aryl radical or the arene being attacked do not greatly influence rates of attack.[39] The SOMO in aryl radicals lies in the plane of the ring, with no overlap, and therefore substituents have very little effect on reactivity. Aryl radicals react more rapidly than alkyl radicals.

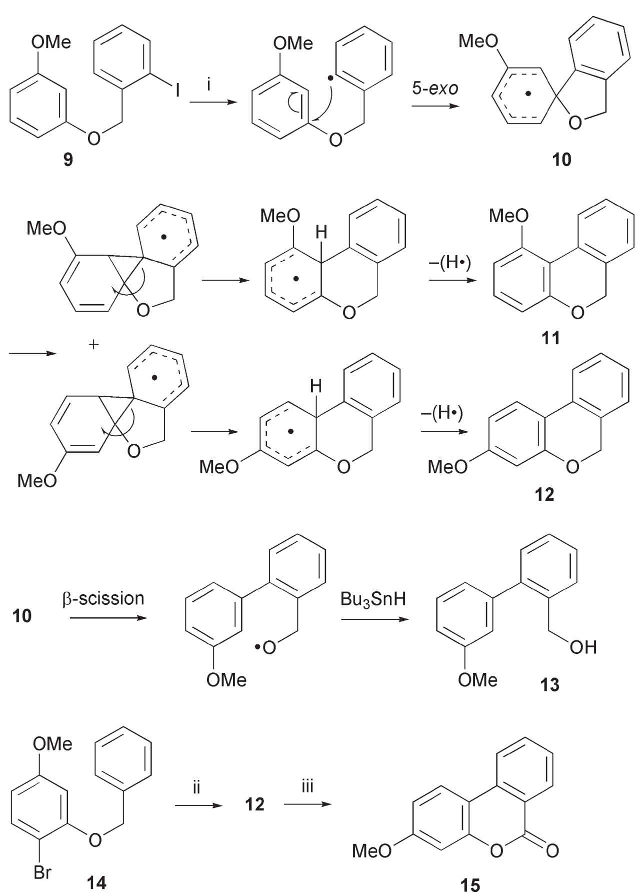
The importance of matching polarity is illustrated in the cyclisation of nucleophilic alkyl radicals onto pyrroles (Scheme 8).[38] The electron-withdrawing group is required to lower the electron density of the electron-rich pyrrole to facilitate cyclisation. The equivalent reaction with no electron-withdrawing group yields only the reduced *N*-butylpyrrole product. This reaction also shows that polarity effects influence regioselectivity. The nucleophilic radical **7** cyclises completely regioselectively onto the more electrophilic 2-C of the pyrrole to yield bicycle **8** with no traces of **9**.

2.2d. *Exo* and *endo* cyclisation. The angle of attack by the radical onto the arene is at *ca.* 100° in the transition state. The difference between *exo* and *endo* cyclisation is not clear in cyclisation onto arenes because the attacking radical reacts with the π-cloud of the arene rather than localised double bonds, so perhaps Baldwin's rules are not directly relevant. However, 5-*exo* substitutions leading to spirodienyl radical intermediates are normally favoured over 6-ring (*endo*?) cyclisation. The spirodienyl intermediates commonly undergo neophyl rearrangements to the 6-ring σ-complexes. The spirodienyl radicals can be trapped and used synthetically (Section 2.11). Factors influencing 5-*exo versus* 6-ring (*endo*?) cyclisation are discussed in Section 3.1.

Where possible regioisomers can be obtained, prior planning of syntheses is required. An example of the neophyl rearrangement is shown in Scheme 9 for the synthesis of the active constituent **15** of shilijat.[40] 5-*exo* Cyclisation of the radical from precursor **9** yields the spiro radical intermediate **10**, which undergoes neophyl rearrangements by two routes to regioisomers **11** and **12**, as well as β-scission to the biphenyl **13**. To selectively obtain the correct regioisomer **12**, the cyclisation needs to be carried out onto the benzene ring from precursor **14**. Similar results have been reported for the radical cyclisation of other halogeno-benzyl phenyl ethers.[41]

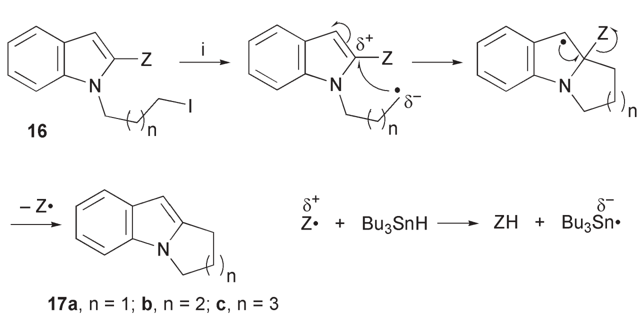
2.3 Good radical leaving groups—*ipso* substitution

Hydrogen is not a feasible leaving group and needs an abstracting radical, whereas leaving groups such as thiyl and sulfonyl radicals provide a mechanism more akin to aromatic and electrophilic substitution. This facet has been exploited in a number of methods.



Scheme 9 *Reagents and conditions*: i, Bu_3SnH, AIBN, PhMe, reflux, 20% (**11**), 20% (**12**), 25% (**13**); ii, Bu_3SnH, AIBN, PhMe, reflux, 40% (**12**); iii, PCC (pyridine chlorochromate), 98% (**15**).

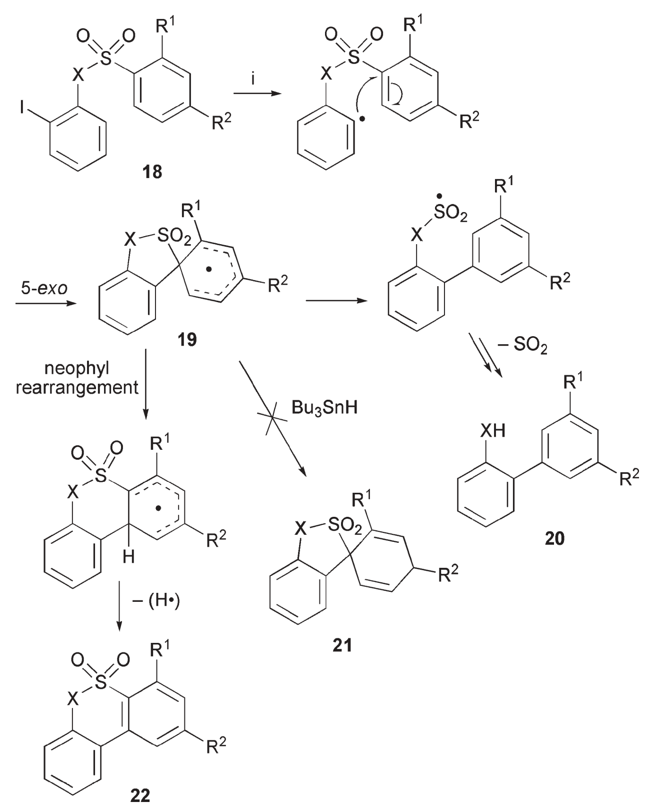
In the first of these methods, the synthesis of fused [1,2-*a*]indoles from precursors **16** (n = 1, 2 or 3) is shown in Scheme 10.[42] The highest yields were achieved for 5-, 6- and 7-membered rings with tosyl as a leaving group. The stronger electron-withdrawing properties of tosyl, as compared to SPh, favour attack by the nucleophilic alkyl radicals. The advantage of this procedure was that regioselectivity was ensured. This same protocol has also been used to facilitate substitution on the benzene ring of indole by placing the tosyl leaving group at 7-C instead of 2-C. Vinyl and aryl radicals can also be used.[42]



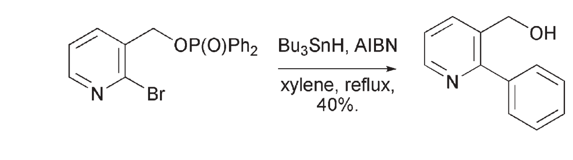
Scheme 10 *Reagents and conditions*: i, Bu_3SnH, AIBN, PhMe, reflux; Z = Ts: n = 1, 71% (**17a**); n = 2, 71% (**17b**); n = 3, 33% (**17c**). Z = SPh: n = 1, 25% (**17a**); n = 2, 51% (**17b**); n = 3, 0% (**17c**). Z = S(O)Ph: n = 1, 46% (**17a**); n = 2, 53% (**17b**); n = 3, 34% (**17c**).

This method has also been used for cyclisation onto the 2-C position of imidazoles (Ts leaving group)[37] and benzimidazole (SPh leaving group).[35,37] A chain reaction mechanism has been proposed in which the electrophilic $Z^\bullet$ leaving group reacts rapidly with the nucleophilic Bu_3SnH to regenerate $Bu_3Sn^\bullet$ radicals to propagate the chain.[37] A catalytic method, with tosyl radicals to replace Bu_3SnH, has been developed that involves addition of the tosyl radicals onto a suitably placed alkyne on the N side-chain.[43] Methoxy radicals can also be replaced in aromatic homolytic substitution.[44]

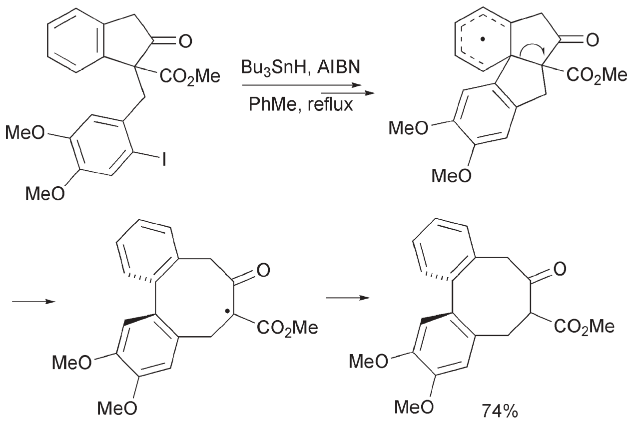
The second method, exemplified in Scheme 11, uses the leaving group as part of the chain connecting the aryl radical and the arene under attack for the synthesis of biphenyls, thereby providing a regioselective replacement for the Gomberg reaction. Cyclisations proceeding by 5- and 6-*exo ipso* substitution work well with sulfonyl radicals as a common leaving group. The methodology is reviewed by Clive and Kang.[45] The spirodienyl radical intermediate **19** has three options: rearomatisation by β-scission (*ipso*-substitution), neophyl rearrangement or reduction to a spirodienyl product (see Sections 2.11 and 3.1). β-Scission is generally faster than neophyl rearrangement or trapping of the spirodienyl radical if a good leaving group is present. Reaction of precursor **18** shown in Scheme 11, which has a good leaving group, yields no spirodienyl product **21**.[46] The *ortho*-Me group favours β-scission to biphenyl products **20**. This could be explained by steric interaction between the *ortho*-Me and sulfone groups, which disfavours 6-ring cyclisation, or buttressing, which accelerates



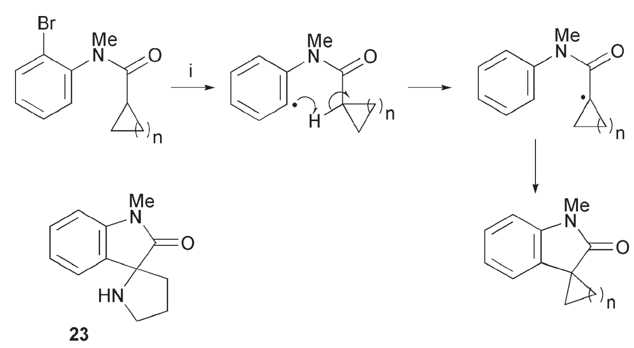
Scheme 11 *Reagents and conditions*: i, Bu_3SnH, AIBN, PhMe, reflux, X = O: R^1 = H, R^2 = Me, 0% (**20**), 63% (**22**); X = O: R^1 = Me, R^2 = H, 23% (**20**), 36% (**22**); X = NMe: R^1 = H, R^2 = Me, 34% (**20**), 39% (**22**); X = NMe: R^1 = Me, R^2 = H, 57% (**20**), 0% (**22**).



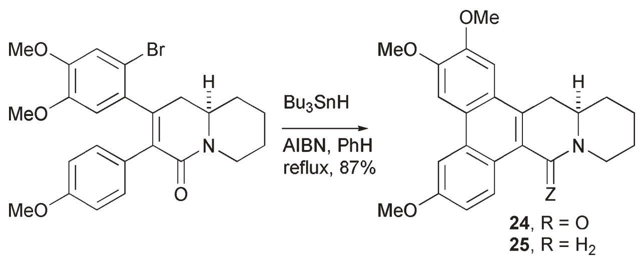
Scheme 12



Scheme 13



Scheme 14 *Reagents and conditions*: i, Bu_3SnH, $(t\text{-BuO})_2$, *t*-BuPh, 160 °C, $n = 1$, 99%; $n = 3$, 96%, $n = 4$, 100%.



Scheme 15 Synthesis of *R*-(−)-cryptopleurine **25**.

the β-scission. A similar procedure has been used involving cyclisation with aryl ketyl radicals instead of aryl radicals, to yield *ortho*-hydroxy biaryl ketones.[47] Reduction of arenediazonium salts can be used to replace aryl halides and Bu_3SnH.[48] The earliest example of the use of Bu_3SnH in aromatic homolytic substitution for the intramolecular translocation of phenyl from phenylsulfonyl amides to alkyl groups, went unnoticed and unexploited for over ten years.[49]

Phosphinates have proved to be useful in this biaryl synthetic procedure and a range of arenes (including pyridines, furans and naphthalenes) and substituents (alkyl, aryl, CN) have been used.[45] An example is shown in Scheme 12.

The procedure has been used in a homolytic aromatic substitution coupled with ring expansion from a 5-membered ring to an 8-membered ring (Scheme 13).[50] This method further illustrates the wide potential of *ipso*-substitution.

2.4 Radical translocation from aryl radicals followed by aromatic homolytic substitution

Beckwith and Storey have developed 1,5-hydrogen translocation to facilitate the use of aryl halides for substitution back onto the arene (Scheme 14).[51] Studies with Bu_3SnD were used to elucidate the mechanism. The protocol has been further exploited in the synthesis of horsfiline **23**.[52]

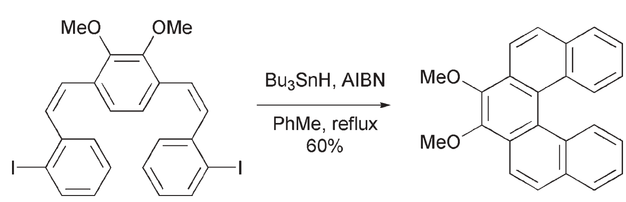
2.5 Aryl radical cyclisation onto arenes

The cyclisation of aryl radicals onto arenes has been widely used and examples of these syntheses are illustrated. The most common targets are phenanthrene derivatives; an example is shown in Scheme 15, of the synthesis of the alkaloid *R*-(−)-cryptopleurine **25** *via* the cyclisation to the amide **24**.[53] Other examples include the syntheses of phenanthrenes,[9,54] dihydrophenanthrenes with a β-lactam ring,[55] phenanthridones,[2] benzophenanthridines,[56] phenanthridines,[6,41,57,58] 6*H*-benzo[*c*]chromen-6-ones[40] and benzopyrans.[40,41,57]

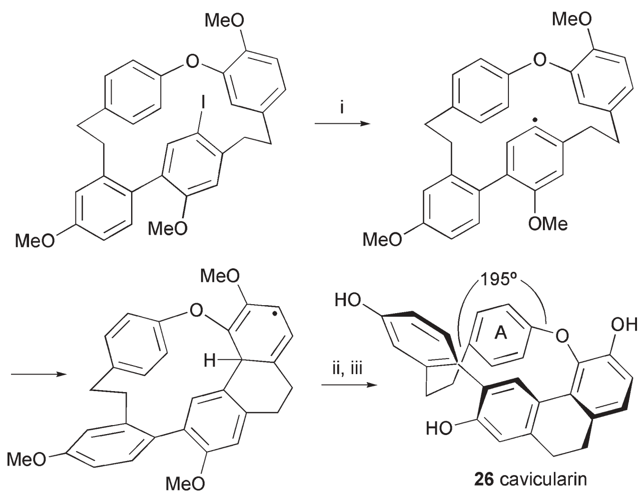
Harrowven *et al.* have used *cis*-stilbenes to form phenanthrenes.[59] The concept has been further expanded and aromatic homolytic substitution has been used to overcome strain in the syntheses of a range of substituted [5]- and [7]-helicenes.[60,61] An example of this double cyclisation method is shown in Scheme 16.[60] An excess of Bu_3SnH (4–5 equiv.) was used to ensure full bicyclisation. The driving force of rearomatisation overcomes the lack of planarity of helicenes.

The use of aromatic homolytic substitution to overcome strain in polyarenes has also proved valuable in the elegant synthesis of cavicularin **26** (Scheme 17).[62] The strained macrocyclic system can only be cyclised because the σ-complex has an sp^3 carbon to relieve steric strain. The driving force of rearomatisation overcomes the ring strain on ring A, where the substituents are at 195° instead of 180°. The radical reaction gave a 2 : 1 mixture of the reduced uncyclised and cyclised products.

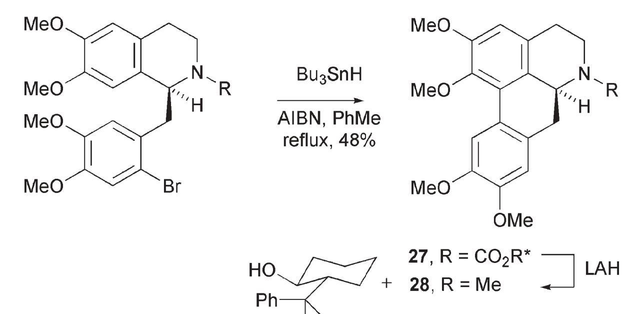
Another general procedure involves cyclisation of pendant bromoarenes onto benzo-heterocycles. In the example shown in Scheme 18, a group pendant to a tetrahydroisoquinoline was cyclised onto 8-C.[63] The precursor was produced in enantiomerically pure form in earlier steps using a cyclohexyl



Scheme 16 Synthesis of helicenes.



Scheme 17 *Reagents and conditions*: i, $(TMS)_3SiH$, AIBN, PhMe, 90 °C; ii, −(H•); iii, BBr_3, CH_2Cl_2, 0 °C, 95% (**26**).



Scheme 18 Synthesis of (+)-glaucine **28**.

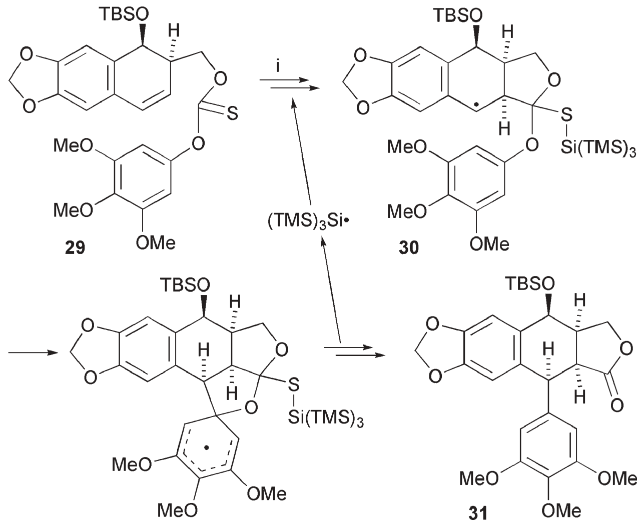
chiral auxiliary. The cyclisation to **27** was accompanied by the uncyclised reduced product (46%). Reduction of **27** to remove the chiral auxiliary and form the NMe group yields the aporphine alkaloid (+)-glaucine **28**. The procedure was based on earlier radical cyclisation studies.[3,64]

Related examples include cyclisation of pendant 2-bromoarenes onto: 3,4-dihydroisosquinolines to yield aporphines;[65] isochroman-3-ones to yield dibenzo[*de*,*g*]chromanes;[66] and indoles to yield pyrrolophenanthridone alkaloids.[67]

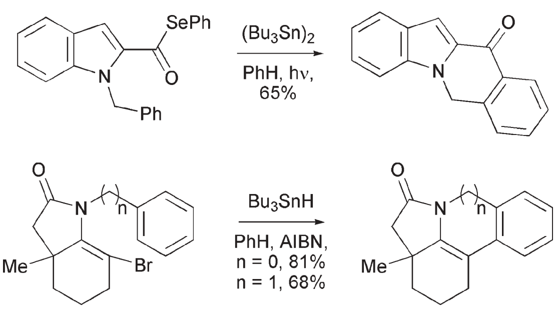
2.6 Alkyl, alkenyl, acyl and iminyl radical cyclisation onto arenes

There are relatively few examples of alkyl radical cyclisation onto arenes. A surprising example uses cyclisation of an intermediate benzylic radical **30** in synthetic studies toward podophyllotoxin, a potent tubulin antimitotic agent (Scheme 19).[68] The thiocarbonate precursor **29** is cyclised to a benzylic radical, which in turn undergoes *ipso*-substitution on the pendant aryl ring to yield **31**, a diastereoisomer of podophyllotoxin. Other useful examples of alkyl radical cyclisation have been published.[69–71]

Examples of acyl[71] and alkenyl[72] radical cyclisation onto arenes are shown in Scheme 20. Alkenyl[73–75] and iminyl radicals[76–78] generated in domino reactions also successfully cyclise onto arenes.



Scheme 19 *Reagents and conditions*: i, $(TMS)_3SiH$, AIBN, PhH, reflux, 38% (**31**).

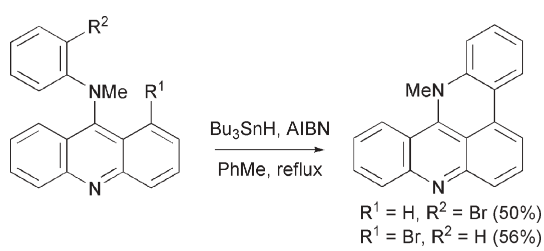


Scheme 20 Aromatic homolytic substitution *via* acyl and alkenyl radicals.

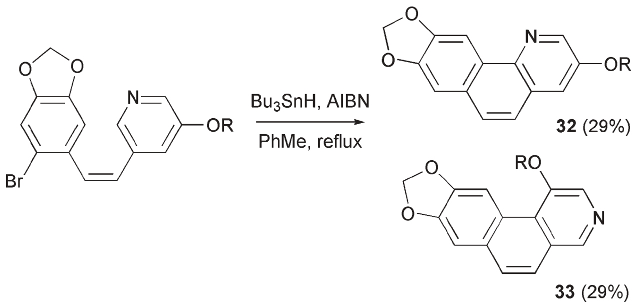
2.7 Cyclisation onto heteroarenes

Synthesis using homolytic aromatic substitution on heteroarenes has been of particular interest because of the importance of polycyclic heteroarenes to the pharmaceutical industry and the occurrence in natural products. There are examples in the literature of radical cyclisation onto most common heteroarenes. Aromatic homolytic substitution on pyridine and related heteroarenes has been reviewed recently by Harrowven and Sutton.[14]

2.7a. Aryl radical cyclisation onto heteroarenes. Examples of aryl radical cyclisation onto heteroarenes are shown for quinazolin-4-ones (Scheme 7) and acridines (Scheme 21).[79]



Scheme 21 Cyclisation onto acridine.

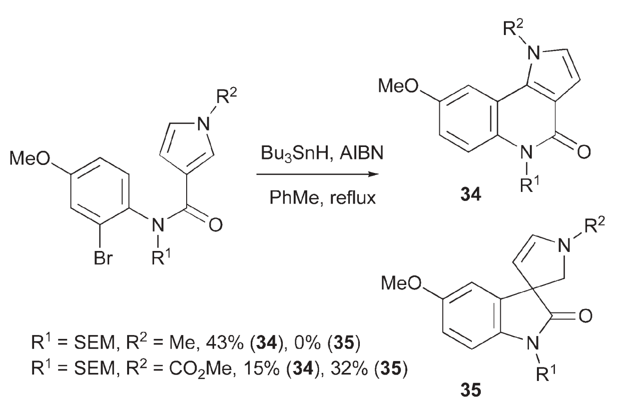


Scheme 22 Synthesis of toddaquinoline **32** (R = H).

The synthesis of the antitumour 13*H*-quino[4,3,2-*kl*]acridines can be facilitated by cyclisation onto the acridine or from the acridine onto the aryl ring.

Harrowven and co-workers have investigated cyclisation onto pyridines[80–83] and quinolines[84] in detail. A good example is shown in Scheme 22 for the synthesis of the alkaloid toddaquinoline **32** (R = H), used in Asian folk remedies.[80,81] With Bu_3SnH, the cyclisation unfortunately gives toddaquinoline methyl ester **32** (R = Me), as well as its regioisomer **33**, but becomes regioselective when the cyclisation is conducted with Co(I).[80a,81] The synthesis of the azaphenanthrene alkaloid eupolauramine has also been facilitated by aryl radical cyclisation onto a pyridine ring.[85] Related cyclisations yield several of the aristolactam group of alkaloids.[86] Other examples of aryl radical cyclisation onto pyridine rings have been reported.[44,87] One example of aryl radical cyclisation onto pyridones has been published.[88]

Aryl radical cyclisation onto 5-membered ring heteroarenes has proved equally useful. An example of cyclisation onto pyrroles is shown in Scheme 23.[89] The direction and rearomatisation can be controlled by use of N-protecting groups on the pyrrole nitrogen. In the cyclisation of aryl radicals, attached through an amide at the 3-C position of the pyrrole, the use of an electron-donating protecting group (Me) gave 6-ring cyclisation and rearomatisation to **34**, whereas use of an electron-withdrawing protecting group (carbamate) gave spiroindole products **35**. The regioselectivity was unaffected by substituents on the arene ring. The reasons for the different behaviour are not clear but Jones and Escolano suggest that, when an electron-withdrawing group is attached to the pyrrole nitrogen, the ring becomes electrophilic and is trapped more rapidly by the nucleophilic Bu_3SnH before a neophyl rearrangement can take place.



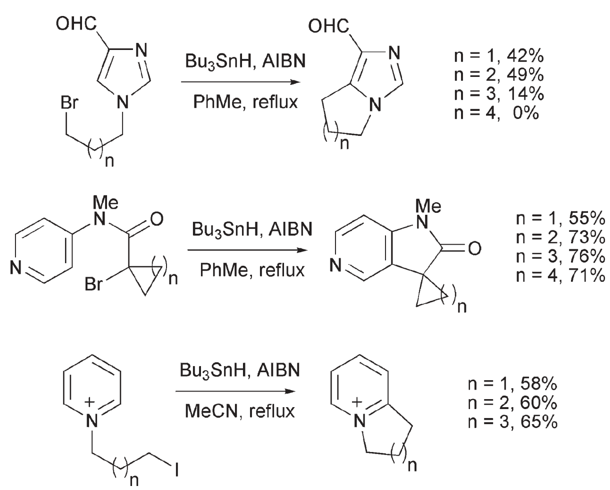
Scheme 23 Aryl radical cyclisation onto pyrroles.

Other examples of aryl radical cyclisation onto 5-membered ring heteroarenes include pyrroles,[36,90] indoles,[36,91] imidazoles,[36,92] pyrazoles[36] and furans.[93]

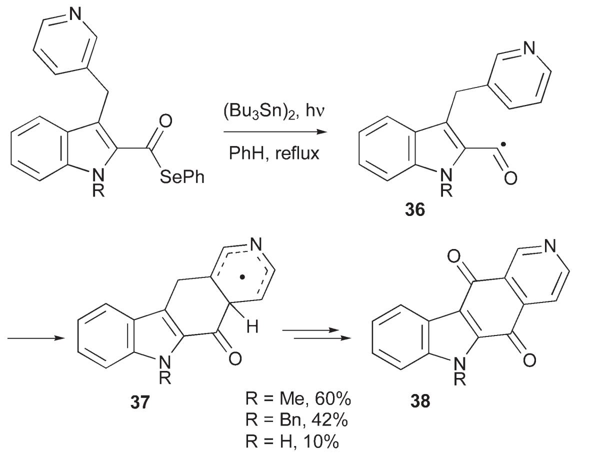
2.7b. Alkyl, acyl and imidoyl radical cyclisation onto heteroarenes. Aromatic homolytic substitution by alkyl radicals onto heteroarenes has been well studied because of the pharmaceutical interest of the products. Examples of alkyl radical cyclisation onto pyrazole and pyrrole are shown in Schemes 5 and 8 respectively. A representative group of alkyl radical cyclisations is shown in Scheme 24, including imidazoles,[38] pyridines[94] and pyridinium salts.[5] A competing reaction in all these examples is reduction of the intermediate alkyl radical by Bu_3SnH to yield reduced uncyclised material. 6-Membered ring cyclisation is most favoured, with little or no reduction, and attempts to synthesise rings greater than 7-membered gave only reduction.

A large number of cyclisations onto the 2-C position on indole proceed by reductive cyclisation and not aromatic homolytic substitution, indicating that reduction of the intermediate radical by Bu_3SnH is faster than rearomatisation, *e.g.* ref. 8. However, when an electron-withdrawing group is present at 3-C, normal aromatic homolytic substitution is largely favoured.[95–99] Other cyclisations of alkyl radicals have been reported, *e.g.* pyrroles,[36,90] 1,3,4-triazoles[100] and 2- and 4-quinolones.[101] There are several reports of cyclisation of radicals at the 5-C of the ribose part of adenosines onto the 2-C of the adenine moiety.[11,12,102]

Novel cyclisations have been carried out by Bennasar and co-workers using aromatic acyl radicals that cyclise faster than loss of CO.[103–105] Indol-2-yl acyl radicals have been cyclised onto a pendant pyridine ring for the synthesis of ellipticine quinone **38** (R = H), a synthetic relay for the anticancer alkaloid ellipticine (Scheme 25).[103] The acyl radicals **36** do not decarbonylate and cyclise selectively onto the 4-position of the pyridine ring to yield the π-radicals **37**. A small amount of cyclisation onto the 2-position also takes place. The monocarbonyl cyclised products were not isolated and further



Scheme 24 Alkyl radical cyclisation onto heteroarenes.



Scheme 25 Syntheses of ellipticine quinones.

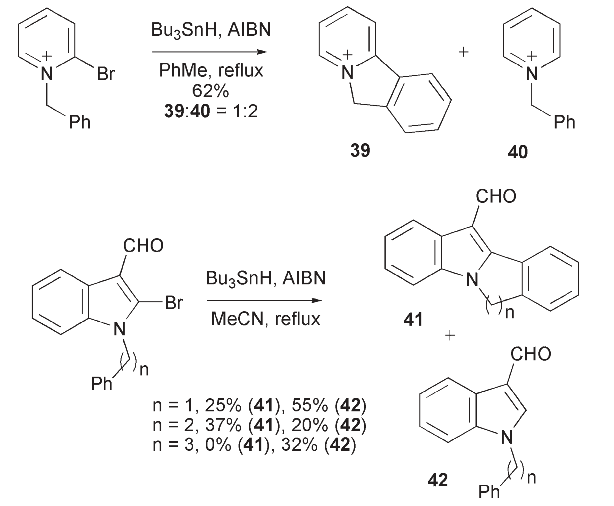
oxidation takes place *in situ* to yield the quinones **38**. The authors suggest that $Bu_3SnOO^{\bullet}$ radicals derived from traces of oxygen in the reaction facilitate the required hydrogen abstractions and oxidation. Indol-2-yl acyl radicals have also been cyclised onto quinolines[104] and in cascade reactions back onto the indole ring.[105]

Alkyl acyl radicals normally decarbonylate rapidly and cannot be used in synthesis. However, if reactions are carried out under a high pressure of CO, intermediate alkyl radicals will add to CO and cyclise onto pyrroles and indoles.[106] A way round the high pressure protocol has been reported wherein the acyl radicals are generated from acyl selenides under an atmosphere of CO.[107] The rate of loss of CO is slower than the rate of addition thereby allowing the alkyl acyl radicals to cyclise onto pyrrole-2- and 3-aldehydes.[107] Imidoyl radicals, generated from imidoyl selenides, have been cyclised onto pyrroles and indoles with electron-withdrawing substituents.[108]

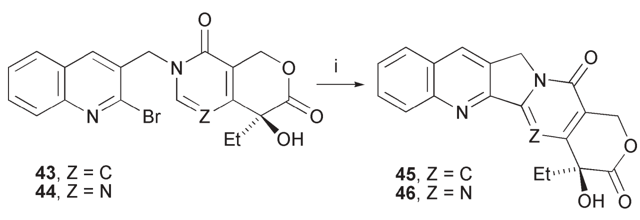
2.8 Heteroaryl radicals

2.8a. Heteroaryl radical cyclisation onto arenes. Heteroaryl radicals behave similarly to aryl radicals and can be used in synthetic procedures. Attachment of a pendant arene by N-alkylation of bromo- or iodo-*NH*-heteroarenes provides a simple methodology, as illustrated in Scheme 26 for the addition of pyridinium radicals to yield **39**[109] and indolyl radicals to yield **41**.[110] Reduced products, **40** and **42** respectively, are also produced. The cyclisation of indolyl radicals provides another example where 6-ring cyclisation is more favoured than 5-ring cyclisation and 7-ring cyclisation is generally not favourable. Other examples of cyclisation onto arenes include radicals at 2-C of indole,[91] 2-C of quinazolin-4-ones,[34] 2-C of pyridine[87b] and 2- and 5-C of imidazoles.[111]

2.8b. Heteroaryl radical cyclisation onto heteroarenes. All the permutations of cyclisation appear possible with aryl or heteroaryl radical cyclisation onto arenes or heteroarenes. Quinol-2-yl radicals have been used in several syntheses of the anticancer alkaloid camptothecin **45**[112] and 14-azacamptothecin **46** and analogues.[113] Two of these syntheses are shown in



Scheme 26 Cyclisation of heteroaryl radicals onto arenes.

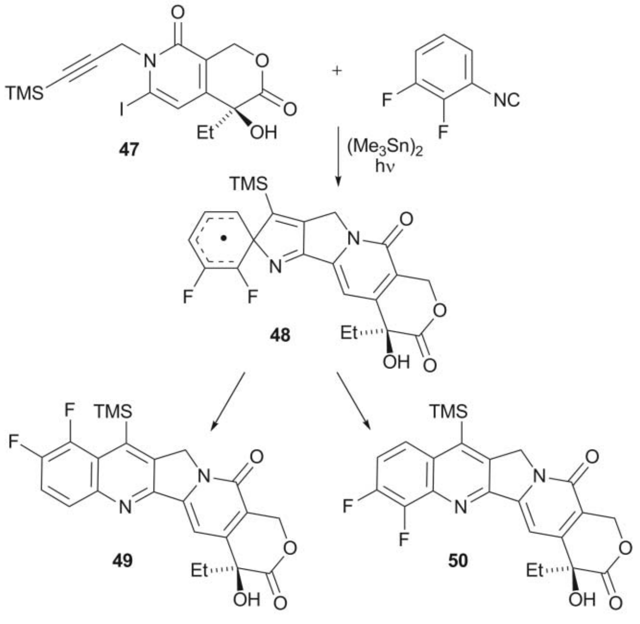


Scheme 27 *Reagents and conditions*: i, **43**, Bu_3SnH, AIBN, PhMe, reflux, 55% (**45**); **44**, $(TMS)_3SiH$, AIBN, PhH, reflux, 28% (**46**).

Scheme 27, from precursors **43** and **44** respectively.[63,113] Cyclisation of indol-2-yl radicals onto quinazolin-4-one has been used for the synthesis of the alkaloid rutaecarpine.[34] Other examples include cyclisation of pyridyl radicals onto pyridones[88] and pyridinium salts.[114]

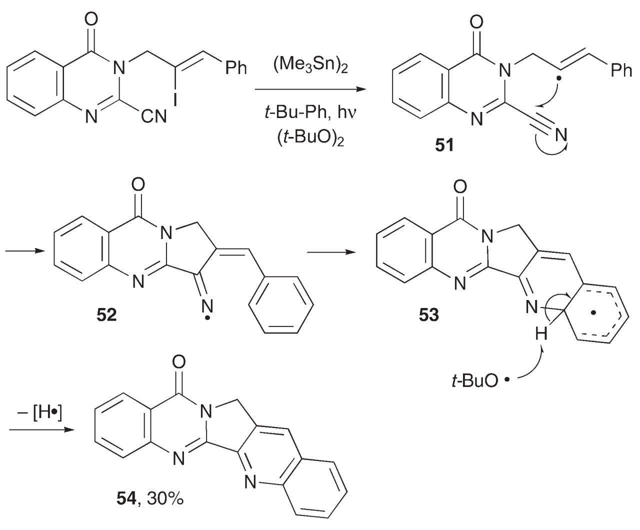
2.9 Domino reactions

The intermediate radicals for aromatic homolytic substitutions can be generated as part of domino reactions, providing notable natural product syntheses. Two general routes have been used. The first starts with a bimolecular radical reaction, *e.g.* addition of aryl/heteroaryl radicals onto isonitriles or thioisocyanates. The second route involves all intramolecular steps. The ground breaking method by Curran and co-workers started with the syntheses of camptothecin by using radical annulation and aromatic homolytic substitution in the final and key step.[13,29] The synthesis of camptothecin **2** is illustrated in Scheme 6. The methodology has been adapted to several other important syntheses. 7-Silylcamptothecins (silatecans), a new group of biologically active camptothecin analogues, are an important spin-off of the protocol.[115,116] An example is shown in Scheme 28. The silyl group is easily introduced using silyl-alkynes, *e.g.* **47**. Two regioisomers, **49** and **50**, were obtained by neophyl rearrangements, indicating a delocalised spiro radical intermediate **48**. This procedure has also been used for the synthesis of the structurally related anticancer alkaloid mappicine,[117] homocamptothecins,[118] luotonin A **54** and analogues (Scheme 32)[119] and sterically hindered camptothecin analogues.[120]

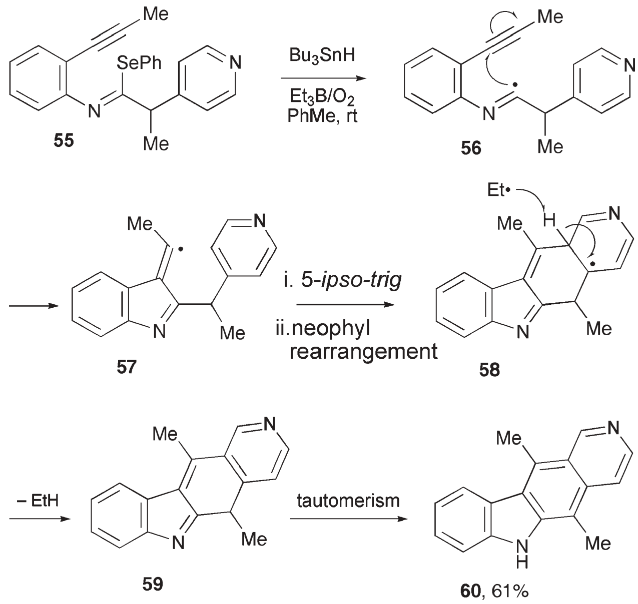


Scheme 28 Synthesis of 7-silylcamptothecins.

Another methodology using all intramolecular reactions has been developed for the synthesis of luotonin A **54**[121a] (Scheme 29) and camptothecin and analogues thereof[121b] by Bowman and co-workers. The methodology is exemplified by the synthesis of luotonin A (Scheme 29). The procedure used cyclisation of vinyl radical **51** onto the nitrile to yield intermediate iminyl radical **52**, which undergoes aromatic homolytic substitution in the final step. The π-radical intermediate **53** undergoes H-abstraction by methyl radical from the breakdown of $Me_3Sn^•$ radicals or *tert*-butoxyl radicals. The method using di(*tert*-butyl)peroxide to generate $Me_3Sn^•$ from $(Me_3Sn)_2$ allows lower temperatures and fewer equivalents of $(Me_3Sn)_2$ to be used. A similar method uses cyclisation of quinol-2-yl radicals onto *N*-acyl cyanamides and subsequent cyclisation of the resulting iminyl radicals for the synthesis of luotonin A.[122]



Scheme 29 Domino synthesis of luotonin A **54**.



Scheme 30 Domino synthesis of ellipticine **60**.

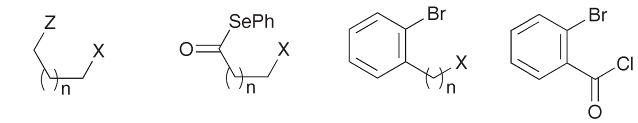
Related domino reactions also use cyclisation onto nitriles to yield iminyl radical intermediates and subsequent homolytic aromatic substitution.[13,29b,76–78]

An intramolecular domino procedure has been used for the synthesis of the anticancer alkaloid ellipticine **60**, carba-ellipticine and analogues thereof (Scheme 30).[75] The procedure uses imidoyl selenides **55** to generate imidoyl radicals **56**, which undergo 5-*exo* cyclisation onto alkynes to yield alkenyl radicals **57**. The alkenyl radicals undergo aromatic homolytic substitution onto the pyridine (or aryl ring for carba-ellipticines) to yield the π-radical **58**. This cyclisation is likely to be by 5-*exo* cyclisation followed by a neophyl rearrangement. The method has the advantage that the pyridine is substituted in the 4-position, so whichever way the neophyl rearrangement takes place the correct product is obtained. The authors propose that ethyl radicals generated from the triethylborane are responsible for the required H-abstraction in rearomatisation to yield **59**. Rapid tautomerism of **59** yields ellipticine **60**.

Thioimidoyl [RN=C($^•$)SR] radicals, generated by aryl radical addition to thiocyanates, also undergo domino reactions involving aromatic homolytic substitution.[73,74] Domino reactions with aromatic homolytic substitution have been used to synthesise isofuro-, cyclopenta- and indolo-quinolines from thiocarbamate precursors.[123] Alkenyl radicals generated by bimolecular addition of aryl radicals to alkynes also undergo aromatic homolytic substitution in domino reactions.[124]

2.10 Building blocks

The use of synthetic building blocks for developing libraries of compounds is also applicable in aromatic homolytic substitution. The tactics use a building block containing a radical leaving group with another leaving group that can be used to facilitate attachment to a wide range of other molecules, *e.g.* by N-alkylation of NH-heteroarenes. Different chain lengths



61, Z = Br, I, SePh alkyl radicals **62** acyl radicals **63** aryl radicals **64** aryl radicals

Scheme 31 Alkyl and aryl radical building blocks.

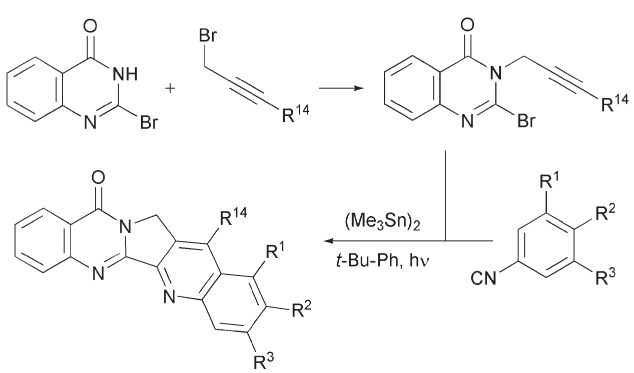
can also be built in for 5-, 6-, and 7-membered ring cyclisation. Examples of building blocks are shown in Scheme 31. The application of *N*-(ω-phenylselenyl)alkyl and *N*-(ω-halo)alkyl building blocks **61** have proved useful for the cyclisation of *N*-(ω-alkyl) radicals onto pyrroles,[37] indoles,[36,42] imidazoles,[36–38] benzimidazoles,[35,38] quinolin-4-ones,[34] pyrazoles,[28,36] 1,2,3-triazoles[100,125] and pyridinium salts.[5] See Schemes 5, 8, 10 and 24 for examples. Acyl radical building blocks **62** have been used for cyclisation onto electron-deficient pyrroles.[107]

Aryl radical buildings blocks **63** have proved useful for 5- and 6-ring cyclisation onto indoles,[36,89] pyrroles,[36,91] 5-amino- and 5-hydroxy-uracils,[126] 2-quinolones,[127] 3*H*-quinazol-4-ones[34] and pyridones.[88] An example is shown in Scheme 7 for 6-ring cyclisation onto 3*H*-quinazol-4-ones. The aryl building block **64** has been widely used but there are only a few examples for aromatic homolytic substitution.[44]

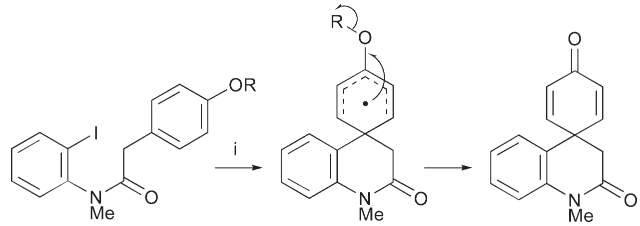
A recent example using a 3*H*-quinazol-4-on-2-yl radical building block facilitates the synthesis of a library of luotonin A **54** analogues (Scheme 32).[119] The procedure incorporates two levels of diversity with both the alkylation and with the bimolecular radical reaction. The procedure is shown in more mechanistic detail in Schemes 6 and 28.

2.11 Trapping of intermediate σ-complexes

The spirocyclic σ-complexes formed in potential aromatic homolytic substitutions are useful for helping to elucidate mechanisms as well as providing novel synthetic methodology. A useful example is the synthesis of spiroquinolones shown in Scheme 33.[128] In both 5- and 6-ring cyclisation there is competition between neophyl rearrangement and elimination to form the spiro product. The better the radical leaving group, the more spiro-product is formed. The trapping of the spiro-product also provides strong evidence for cyclisation to



Scheme 32 Synthesis of luotonin A **54** analogues using a 3*H*-quinazol-4-on-2-yl building block.



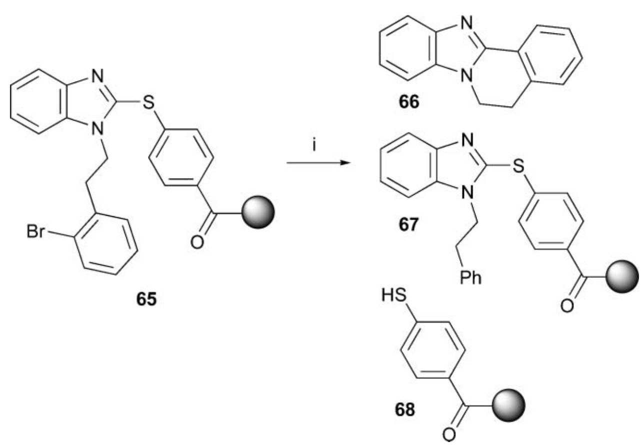
Scheme 33 *Reagents and conditions*: i, $(TMS)_3SiH$, Et_3B, O_2, R = TBS, 49%; R = Tr, 65%.

spiro-intermediates prior to neophyl rearrangement in aromatic homolytic substitution. Crich and co-workers have also trapped spiro-intermediates, by using PhSeH, a very fast H-donor, to trap the spiro radical intermediates in aromatic homolytic substitution reactions.[25,26] Jones and co-workers have developed a domino protocol involving the use of the intermediate σ-complex for a further cyclisation in studies towards the synthesis of the ABCE rings of *Aspidosperma* alkaloids.[129]

2.12 Solid phase synthesis

Although the use of solid phase synthesis has not been widely applied to aromatic homolytic substitution, examples in the literature indicate the potential. Substitution of thiyl radicals at 2-C of benzimidazoles (see Scheme 10) has been studied on solid phase (Scheme 34).[35] In this procedure, the radical leaving group is attached to the resin so that when the reaction is complete, only the product **66** is released from the solid-phase resin and unreacted starting material **65**, the uncyclised reduced product **67** and radical leaving group **68** remain attached to the resin. The reaction also provides a good example of the improved yields and ease of purification on using Bu_3GeH in place of Bu_3SnH. Focused microwave irradiation was found to dramatically speed up the cyclisation.[35]

Aryl radicals have been cyclised onto pyrazoles.[36] In this methodology the product remains attached to the resin by an ester group and has the advantage that reagents can be washed



Scheme 34 *Reagents and conditions*: i, Wang resin: $(TMS)_3SiH$, Et_3B, O_2, rt, 49% (**66**); PhH, reflux, Bu_3SnH, AIBN, 44% (**66**); PhH, reflux, Bu_3GeH, AIBN, 71% (**66**).

away. Conversely, the method has the disadvantage that unreacted starting material and uncyclised reduced products are also cleaved from the resin along with the required cyclised products. Phenanthridines have also been synthesised using solid phase synthesis.[130]

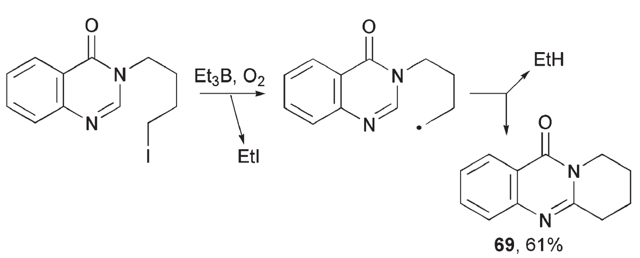
2.13 Radical reagents

Bu_3SnH has been used for the majority of synthetic studies involving aromatic homolytic substitution. However, the problems with the use of Bu_3SnH and other triorganotin hydrides are well known: a. the toxicity rules out their extensive use in pharmaceutical synthesis; b. removal of tributyltin residues from reaction mixtures is problematic; c. Bu_3SnH is unstable and decomposes steadily. Generation of Bu_3SnH *in situ* by reduction of substoichiometric amounts of Bu_3SnCl with borohydrides can be helpful to cut down the amount of stannyl impurities.[82,126]

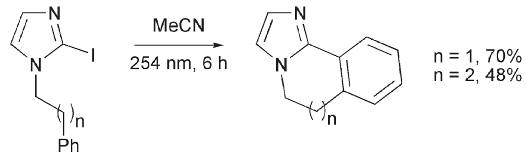
The most common substitute for Bu_3SnH is $(TMS)_3SiH$, a reagent that is commercially available and used in a growing number of aromatic homolytic substitutions.[23–25,28,44,104,105,107,112a,113] An alternative silane, 1,1,2,2-tetraphenyldisilane, has shown promise.[131] Bu_3GeH also provides a clean, non-toxic alternative but has not been widely exploited even though it is easily prepared.[35,36,132] Some useful comparisons have been reported: $(TMS)_3SiH$ and Bu_3SnH;[28,107] Bu_3GeH, $(TMS)_3SiH$ and Bu_3SnH;[35] $(TMS)_3GeH$, $(TMS)_3SiH$, Bu_3SnH, SmI_2 and Bu_3SnCl–$NaBH_4$.[82] Ethylpiperidine hypophosphite (EPHP) and diethylphosphite (DEPO) are non-toxic reagents and have proved superior to Bu_3SnH in the synthesis of horsfiline **23**.[52] DEPO also has the advantage that it can be used in water with a water soluble initiator.[52]

$(Bu_3Sn)_2$[9,103] and $(Me_3Sn)_2$[12,29,34,116–118,121,122] have commonly been used as a source of trialkylstannyl radicals. These reagents have the advantage of no hydrogen source, which allows longer times for intermediate radicals to cyclise. An example of this advantage is shown in Scheme 6. Use of di(*tert*-butyl) peroxide with $(Me_3Sn)_2$ to generate $Me_3Sn^{\bullet}$ radicals allows the temperature and reaction time to be lowered (see Scheme 29).[34,121,122]

AIBN, ACCN and related azo initiators are most commonly used, but increasingly triethylborane (Et_3B) is finding favour because it can be used at room or low temperature and oxygen does not need to be excluded (see Scheme 30).[27,34,75,131] Et_3B can be used as the initiator and radical reagent, as shown in Scheme 35 for the synthesis of mackinazolinone **69**.[34] The ethyl radicals generated from Et_3B are able to abstract iodine from



Scheme 35 Synthesis of mackinazolinone **69**.



Scheme 36 Aromatic homolytic substitution using photolysis.

the radical precursor. The ethyl radicals are also proposed to abstract the hydrogen in the rearomatisation step.

Dicumyl peroxide (DCP) has been used for generating methyl radicals for the abstraction of halogen atoms from halogeno-alkane precursors.[99] Di(isopropyl) dicarboxylate (DPDC) has been used for the abstraction of hydrogen from imines to generate imidoyl radicals.[133]

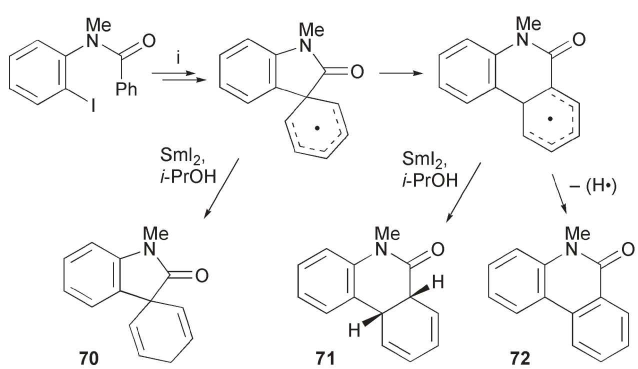
Cobalt(II) complexes have been used for generating radicals for aromatic homolytic substitution. The synthesis of toddaquinoline shown in Scheme 22 has been carried out with cobalt reagents.[12,81] Arene-diazonium salts can be used as precursors of aryl radicals.[73,74,76,78,124,134]

Photolysis of iodo-precursors is possibly involved in many of the reactions, even when initiators are present. For instance, AIBN is commonly broken down using photolysis. Aldabbagh and Clyne have shown that photolysis provides a good method of facilitating aromatic homolytic substitution and is superior to the use of Bu_3SnH.[111] An example is shown in Scheme 36 for the synthesis of tricyclic imidazoles. For 7-membered ring cyclisation, Bu_3SnH gives only uncyclised reduced products, whereas the photolysis procedure gives a good yield with no reduced products.

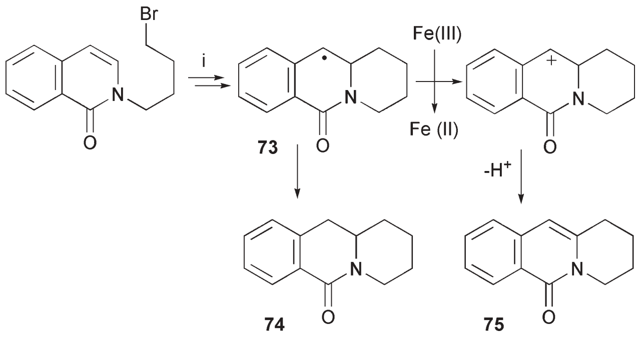
Gas-phase pyrolysis has been used for aromatic homolytic substitution in the synthesis of a range of benzo-heterocycles.[134]

2.14 Cyclisation using redox reagents

Several aromatic homolytic substitution reactions have been facilitated by reduction using SmI_2 to yield initial radicals.[135,136] The conditions are important, as shown in the example in Scheme 37.[135] In the absence of a proton source, the intermediate spirocyclic radical has time to undergo a neophyl rearrangement and rearomatise. However, in the presence of *i*-PrOH, the spirocyclic or π-radical can be intercepted to give reduced products **70** and **71** respectively.



Scheme 37 *Reagents and conditions*: i, SmI_2, HMPA, THF, 0% (**70**), 0% (**71**), 26% (**72**); SmI_2, HMPA, THF, *i*-PrOH, −35 °C, 36% (**70**), 30% (**71**), 0% (**72**).



Scheme 38 *Reagents and conditions*: i, Bu_3SnH, AIBN, 77% (**74**), 0% (**75**); Fe(II), H_2O_2, DMSO, 0% (**74**), 73% (**75**).

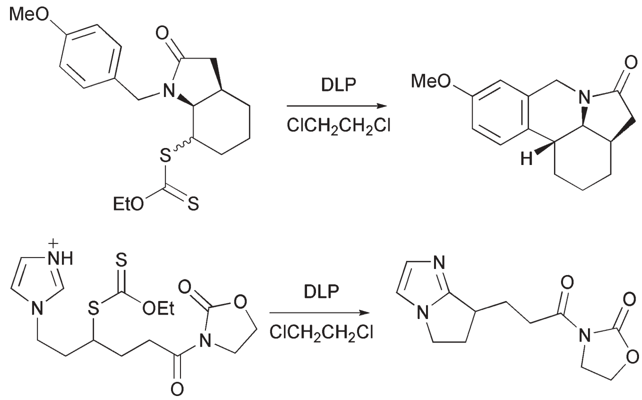
The use of a modified Fenton's reagent [H_2O_2, DMSO, Fe(II)] shows good results with alkyl halide precursors.[98,101] The method builds on early work by Minisci.[13–15] The reagent mixture generates methyl radicals for abstraction of the bromine or iodine to yield the radical precursors for aromatic homolytic substitution. The Fe(III) oxidises the π-radical intermediate (*e.g.* **73**) to the π-cation, followed by rapid loss of a proton in rearomatisation. In the example shown in Scheme 38, the Fenton's reagent gives a good yield of the aromatic homolytic substitution product **75** and none of the reduced cyclised product **74**.[101] However, when the standard Bu_3SnH conditions were used aromatisation did not take place and only the reduced product **74** was obtained. These results indicate good possibilities for using an oxidative reagent in aromatic homolytic substitution.

Bimolecular aromatic homolytic substitutions between electrophilic radicals, generated from α-iodoesters and -nitriles using the modified Fenton's reagent [H_2O_2, DMSO, Fe(II)], and electron-rich heteroarenes give good yields.[137] Acyl radicals, generated by Ag(II) mediated oxidations of α-keto-acids, have been used in aromatic homolytic substitution for the synthesis of 8-aza-ergoline ring systems.[138]

2.15 Zard's protocol with peroxides and xanthates

Zard and co-workers have developed a useful procedure with dilauroyl peroxide (DLP) and xanthate precursors for generating alkyl radicals without the use of group XIV hydrides. The method has been extended to aromatic homolytic substitution and requires a stoichiometric amount of DLP.[139–142] Two examples are shown in Scheme 39.[139,140] The procedure works well with azoles when a catalytic amount of acid is present to protonate the azole to facilitate cyclisation of the nucleophilic alkyl radical onto the electrophilic azole. The cyclisation is regioselective to the 2-position. Protonation of benzimidazole also facilitates cyclisation of alkyl radicals, generated from phenylselenides with Bu_3SnH, onto the 2-C position.[141]

The procedure has been used for a synthesis of lycorane,[142] tetralones[143] and 3-aminochroman.[70] A modified Fenton's reagent [Fe(II), H_2O_2, DMSO] and Zard's method have been compared for cyclisation onto 2- and 4-quinolones.[101] DLP and Et_3B have been used with xanthate precursors for bimolecular aromatic homolytic substitution onto pyrroles, indoles, thiophenes and furans.[144]



Scheme 39 Aromatic homolytic substitution using xanthates.

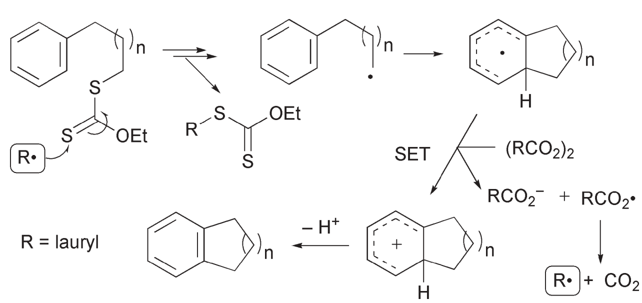
The DLP is required in stoichiometric amount for initiating the radicals as well as rearomatising the σ-complexes in a chain process. The mechanism proposed by several groups indicates that the intermediate π-radicals undergo SET with the peroxide to yield π-cations that rapidly rearomatise by proton loss.[22,101,139] A representative mechanism is shown in Scheme 40. The SET is probably dissociative and yields the carboxylate anion and $RCO_2^{\bullet}$ radicals, which in turn dissociates to the lauryl radicals and carbon dioxide.

3 Mechanism

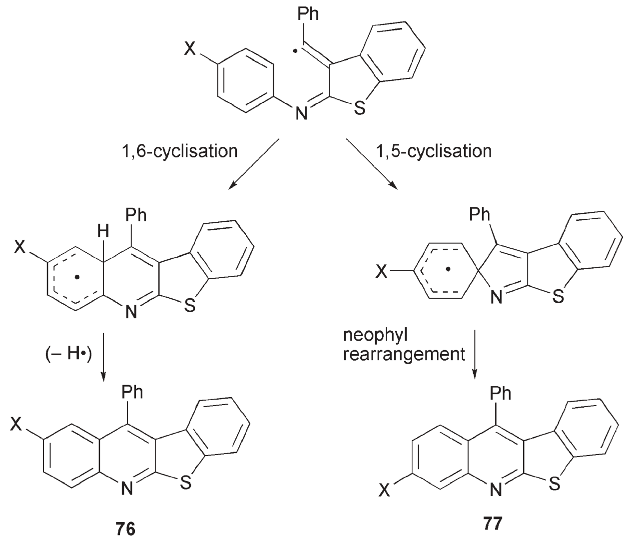
3.1 Neophyl rearrangement

The neophyl rearrangement as illustrated in Schemes 6, 9 and 11 is commonly seen in reactions involving intramolecular homolytic aromatic substitution reactions. For this process to occur, two main prerequisites need to be met. The first of these concerns the lifetime of the initially formed cyclised radical, which must be sufficient to allow rearrangement to occur. That is, the rate of reaction of this radical with other radicals present in the reaction medium must be sufficiently slow to allow rearrangement to take place. The second requirement is that the stability of the intermediate cyclised radical and the final product radical must be such that a sufficient driving force for the rearrangement is achieved. The second of these prerequisites is most readily controlled by careful substrate design.

In a series of investigations targeting the synthesis of benzothienoquinolines (Scheme 41), the nature of the group X played a pivotal role in determining the mode of cyclisation



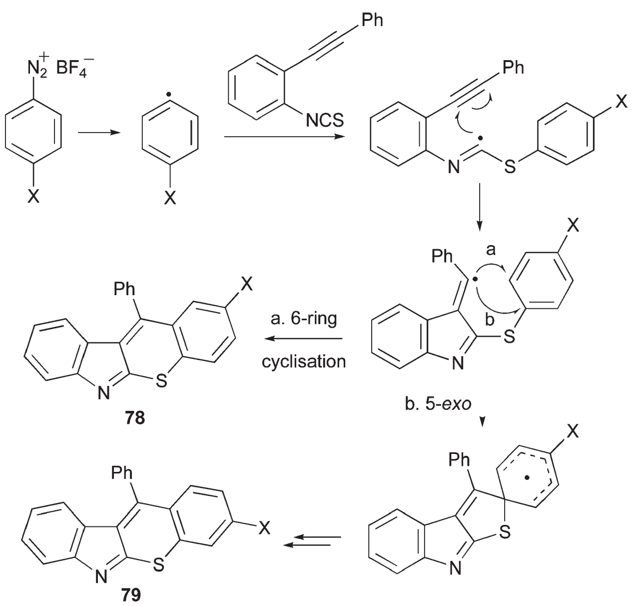
Scheme 40 Putative mechanism of substitution using DLP and xanthates.



Scheme 41 Effect of substituents on neophyl rearrangements.

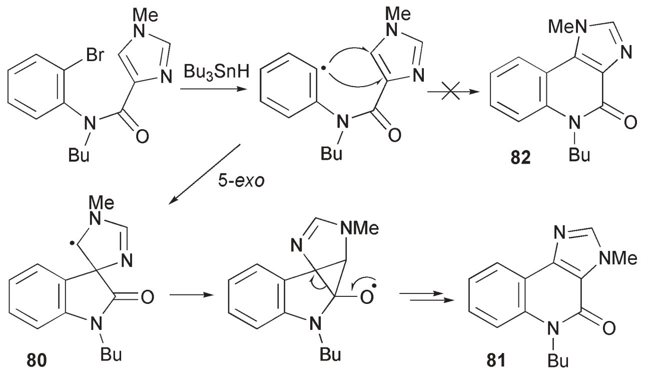
that occurred.[145] Two isomeric quinoline derivatives were isolated, **76** and **77**, which result from 1,6- and 1,5-cyclisation respectively, **77** resulting from neophyl rearrangement. The ratio of products appeared to be dependent upon the electronic nature of the group X, with electron-withdrawing substituents favouring the route *via* rearrangement.

When this effect was investigated in greater detail in the domino synthesis of thiochromeno[2,3-*b*]indoles (Scheme 42), it became apparent that the isomer ratio of products **78** and **79** was once again strongly dependent upon the nature of the aryl substituent X on the aryl ring.[73,74,78] This dependence was correlated with the ability of the group X to delocalise spin density. The results and mechanistic interpretation were well



X	H	CF_3	Cl	OMe	Me	N_3	COMe
78	50	27	27	20	8	4	2
79	-	23	23	20	32	49	43
78/79	-	1.17	1.17	1.00	0.25	0.10	0.05

Scheme 42 Neophyl rearrangements dependent on the ability of substituents X to delocalise spin density.



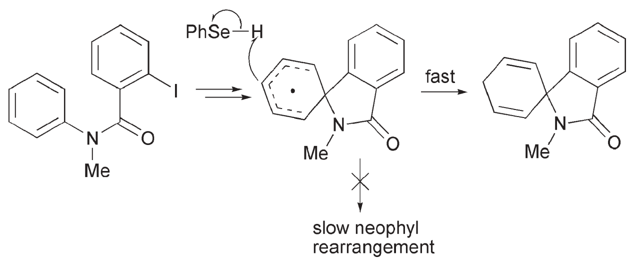
Scheme 43 Neophyl rearrangement in cyclisation onto pyrrole.

supported by semi-empirical and DFT calculations, which point towards the spirohexadienyl radical rearranging *via* ring closure onto the sulfur atom to give **79** rather than the alternative closure onto the carbon which would result in the formation of **78** The results clearly indicate that by careful choice of a suitable group X the selectivity can be well controlled.

Good selectivity has been demonstrated in the synthesis of imidazole[4,5-*c*]quinolin-4(5*H*)-one.[92] Two cyclisation routes are possible, as shown in Scheme 43: 1,5-cyclisation to give the spiro radical intermediate **80** and ultimately **81**, or direct 1,6-cyclisation to give **82**. Under conditions using Pd(0)-catalysis, direct 6-ring cyclisation was observed, but under radical conditions, 5-*exo* cyclisation took place followed by rearrangement. Presumably the high selectivity observed during the radical cyclisation results from the ability of the nitrogen atoms to stabilise the spirocyclic radical intermediate, thus favouring the neophyl rearrangement route.

Another ingenious method devised to control the selectivity of cyclisation between neophyl rearrangement and direct 1,6-cyclisation was developed by Curran and de Turiso in the synthesis of spirocyclohexadienones (Scheme 33). Incorporation of a good leaving group in the acceptor ring facilitated trapping of the spiro σ-complex by the loss of the leaving group, giving the desired spirocyclic system rather than the product resulting from neophyl rearrangement. The better the leaving group ability, the better suppression of rearrangement. This study also provides good evidence for the intermediacy of a spiro-intermediate prior to rearrangement.

Crich *et al.* have provided evidence in support of cyclohexadienyl intermediates in neophyl rearrangements (Scheme 44).[25] By the addition of PhSeH, the normally slow rate of trapping of the intermediate cyclohexadienyl radicals



Scheme 44 Trapping of the spiro-intermediate with PhSeH.

by Bu_3SnH has been overcome, since the rate of H-abstraction from PhSeH is 500-fold faster. This allows the reactive phenyl radicals to cyclise, but the relatively stable cyclohexadienyl radicals become trapped by PhSeH and not by Bu_3SnH. This method not only provides a change in the direction of the reaction, but also makes it a cleaner and higher yielding chain process, which has been used successfully for the synthesis of phenanthridine and phenanthridinone derivatives.

Other examples of neophyl rearrangements are included in references 55, 82, 93 and 128. In one example a spiro-intermediate has been trapped in low yield by 5-*exo* cyclisation onto a pendant alkene.[146]

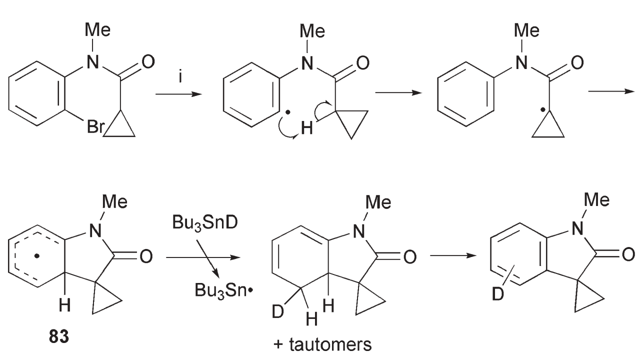
3.2 Abstraction of hydrogen (H$^\bullet$)

In homolytic aromatic substitution the cyclohexadienyl radical intermediate is required to lose a hydrogen atom to achieve aromatisation (Scheme 1). The mechanism by which this process occurs has been an area of debate for some time. A fairly definitive study of the loss of hydrogen in the mechanism has been published.[147]

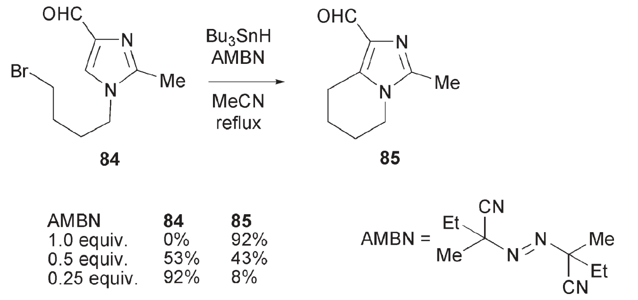
Disproportionation has been suggested as a possible mechanism, or at least a contributory mechanism, by which rearomatisation might occur, but can generally be ruled out because the yields are greater than 50%, often nearly quantitative. Aerial oxidation of dihydro products has been proposed to explain the greater than 50% yield obtained, *e.g.* in the synthesis of cyclopenta-fused pyridines and pyrazines.[148] However, this again can generally be ruled out as in most reactions the dihydro products are air stable.

The direct involvement of Bu_3SnH as a hydrogen transfer agent has been ruled out as a mechanistic possibility by the use of Bu_3SnD (Scheme 45). In these circumstances, if Bu_3SnD were transferring D to give a cyclohexadienyl type adduct **83**, which then underwent oxidation upon work-up, deuterium incorporation in the final product would be expected; none was observed.[147] Furthermore, it is unlikely that other radical carriers that have been used in these types of reactions would behave as H-transfer reagents in the same way as Bu_3SnH.

The production of dihydrogen is also a possible route by which aromatisation could occur followed by SET; this mechanism is discussed fully in Section 3.3 and exemplified in Scheme 50. Careful study of the cyclisation shown in Scheme 45, either with Bu_3SnD or with a deuterated precursor, failed to yield any HD as a product, thereby ruling out



Scheme 45 *Reagents and conditions*: i, Bu_3SnD (1.1 equiv.), AIBN (1.2 equiv.).

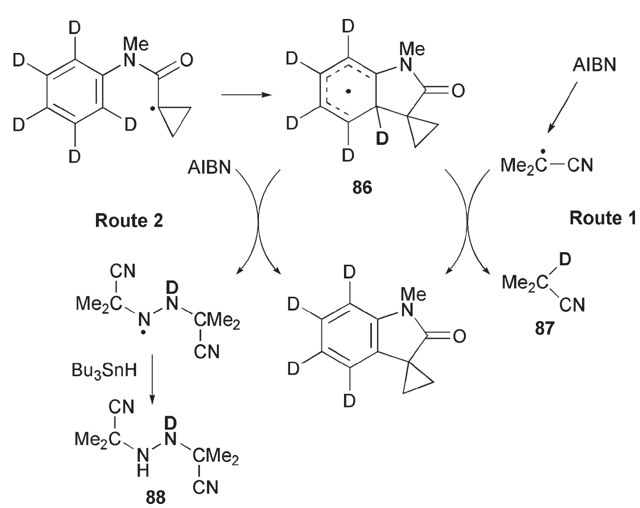


Scheme 46 Role of azo-initiator in H-abstraction.

$Bu_3SnH(D)$ acting as a base to abstract a proton (see Scheme 2).

One of the early studies of Bu_3SnH-mediated cyclisation onto pyridinium rings showed that greater than one equivalent of AIBN was required to achieve good yields of aromatised products.[5] The reliance upon stoichiometric quantities of initiator is a common feature in many homolytic aromatic substitution reactions and a clear dependence upon the amount of initiator used was demonstrated in a series of experiments where the quantity of AMBN (initiator) was varied. Less than one equivalent of initiator resulted in poor yields of the bicyclic imidazole products (Scheme 46).[147]

It has since been suggested that the initiator serves a dual role in some of these reactions (Scheme 47).[147] In the minor of these two roles (route 1, Scheme 47), the cleaved initiator fragment acts by abstracting a H(D)-atom from the cyclohexadienyl intermediate **86**. Evidence in support of this notion was provided by GC-MS showing the deuterated initiator product **87**. However, when 1,1′-azobis(cyclohexylcarbonitrile) (ACN) was used in similar experiments, none of the analogous deuterated initiator product (2-cyano-2-deuteriocyclohexane) was observed.[58] The major role of the initiator (route 2, Scheme 47) was established when it was shown that, for every equivalent of initiator, only 0.3 equivalents of nitrogen gas was evolved, indicating that 0.7 equivalents were not cleaving in the expected way to give nitrogen gas.[147] The scenario postulated was that the initiator acted as an oxidising agent,



Scheme 47 Fate of AIBN in aromatic homolytic substitution.

giving the reduction product **88**. Evidence for H-atom transfer to diazines to form hydrazyl compounds had been previously reported, which supports this notion.[149]

To further complicate the situation in the aryl radical cyclisation onto quinoline using Bu_3SnH and AIBN, Harrowven *et al.* have shown that iodo-precursors require sub-stoichiometric amounts of AIBN, whereas the bromo-precursors require more than one equivalent.[84] This indicates that two mechanisms can operate. The obvious explanation is that the C–I bond can homolyse to initiate the reaction when AIBN has been consumed, whereas the C–Br bond is too strong under the reaction conditions. The mode of rearomatisation in the iodo substrates is postulated to occur *via* a single electron transfer process (see Section 3.3).

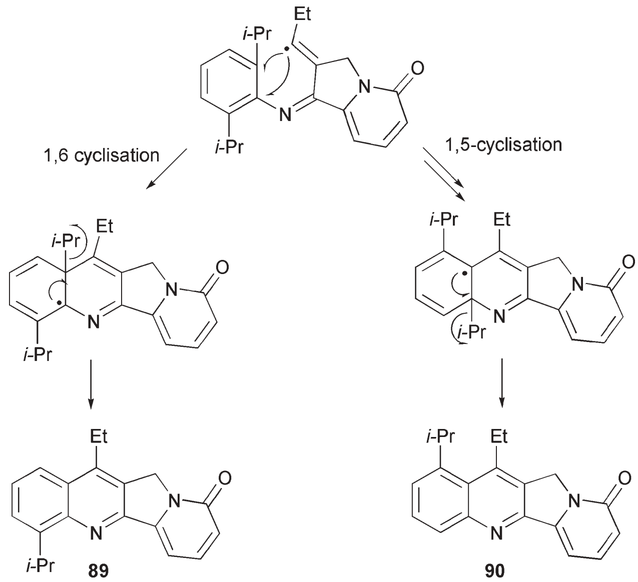
Whilst the evidence adumbrated above can be used to explain the rearomatisation when azo initiators and Bu_3SnH are involved, the successful homolytic aromatic substitution reactions using other initiators and radical carriers need also to be considered. The mechanistic conclusions are likely to be the same for the use of Bu_3GeH and $(TMS)_3SiH$ as reagents (see Section 2.13). The use of Et_3B as a radical initiator has become more popular and works successfully for aromatic homolytic substitutions.[34,75,108,150] Bowman and co-workers have suggested that Et_3B, like AIBN, acts as both the initiator and also the H-abstractor (ethyl radicals) in the rearomatisation steps.[34,75,108,150] While it is likely that the mechanisms are the same, the precise mode of rearomatisation in these systems is as yet unclear.

There are a number of interesting examples of homolytic aromatic substitution that appear not to involve the initiator in the aromatisation process. Curran and Keller have recently shown that oxygen can act as a chain carrier in homolytic aromatic substitution reactions and proposes that dioxygen is involved with the abstraction of a hydrogen atom to facilitate aromatisation (Scheme 4). The details of this mechanism are discussed in Section 1.[27]

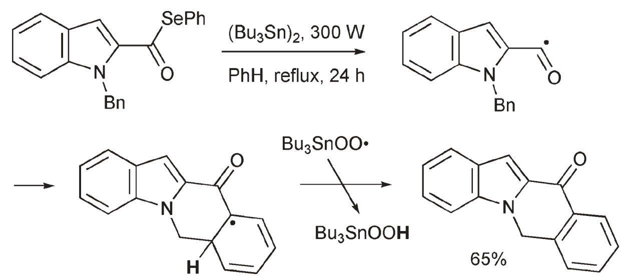
In the synthesis of 7,9-disubstituted camptothecin analogues (Scheme 48), two routes of cyclisation were identified: 1,5-cyclisation to give **90** and 1,6-cyclisation to give **89**, the minor product from the reaction.[120] The intriguing feature of this reaction lies in the aromatisation step, which involves cleavage of an isopropyl group. Loss of *n*-propyl[108,150] and methoxy[41] radicals have also been observed in the rearomatisation step.

In aromatic homolytic substitutions mediated by $(R_3Sn)_2$ with no radical initiator, the identity of the H-abstractor is less obvious. $R_3Sn^{\bullet}$ radicals are not able to abstract hydrogen.[147] In the intramolecular 2-indolyl acyl radical cyclisation mediated by $(Bu_3Sn)_2$ depicted in Scheme 49, peroxy radicals $Bu_3SnOO^{\bullet}$ have been postulated as being involved in H-atom abstraction, resulting in aromatisation of the final product.[71] This could be generated by the reaction of $Bu_3Sn^{\bullet}$ radicals with oxygen *in situ*, a fast reaction. This is probably a common contributor towards H-abstraction because the last traces of oxygen in a reaction mixture are difficult to remove.

Using the similar radical mediator $(Me_3Sn)_2$ in an investigation towards the synthesis of heteroarenes *via* iminyl radical cyclisation (Scheme 29), the putative involvement of methyl radicals was suggested in the H-abstraction step.[121] Breakdown of $Me_3Sn^{\bullet}$ radicals yields methyl radicals and



Scheme 48 Aromatisation by loss of *i*-Pr radicals (53%, **90** : **89** = 8 : 1).



Scheme 49 H-Abstraction with $Bu_3SnOO^{\bullet}$ radicals.

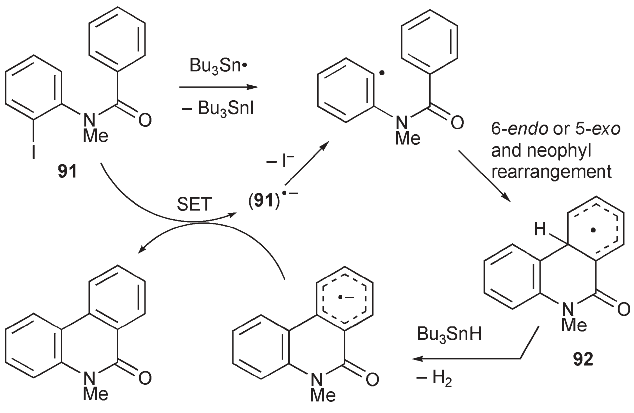
dimethylstannylene (Me_2Sn:), which polymerises. The reactions are accompanied by large amounts of organotin polymers. In the same cyclisations, *tert*-butoxyl radicals ($Me_3CO^{\bullet}$), from homolysis of di(*tert*-butyl)peroxide, were used to speed up the formation of $Me_3Sn^{\bullet}$ radicals from $(Me_3Sn)_2$; the *tert*-butoxyl radicals have been proposed as the H-abstractor (see Scheme 29).[121]

Clearly the process of hydrogen atom abstraction and aromatisation in homolytic aromatic substitution reactions is complicated and largely dictated by the reagent system used for the reaction. The evidence so far strongly indicates that H-abstraction is the main route of rearomatisation. In each reaction a number of radicals are probably responsible for the abstraction, as indicated in the discussion of this section.

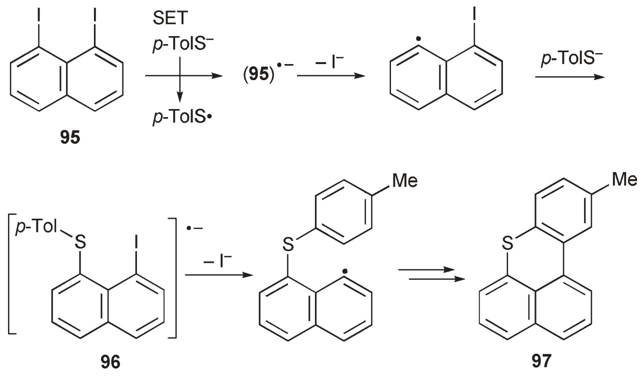
Several radical cyclisations yield intermediate aromatic π-radicals but not *via* radical addition to arenes.[2,108,148,150] H-Abstraction also gives aromatisation to the respective aromatic ring. These reactions are not aromatic homolytic substitutions but provide further evidence for the H-abstraction step.

3.3 SET (single electron transfer) mechanisms

The $S_{RN}1$ mechanism with arene and heteroarene precursors can be regarded as aromatic homolytic substitution and is well reviewed.[151] Studies of $S_{RN}1$ reactions by the research groups



Scheme 50 $S_{RN}1$ type mechanism.



Scheme 52 *Reagents and conditions*: DMSO, 3.5 h, mercury vapour lamp (500 W) irradiation, 55% (**97**).

of Russell[18–20] and Bowman[2,37,38] led them to propose $S_{RN}1$-type mechanisms to explain aromatic homolytic substitutions. These mechanisms involve SET and radical-anion intermediates. An example of the bimolecular studies of Russell and co-workers is shown in Scheme 2. DABCO was found to be essential to facilitate the deprotonation step and electron-withdrawing groups were required on the arene precursors.

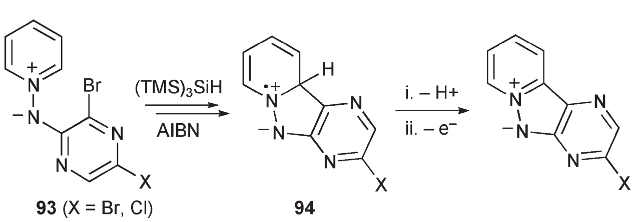
The SET mechanism proposed by Bowman and co-workers to explain the unusual 'oxidised' products resulting from Bu_3SnH-mediated aromatic homolytic substitutions is illustrated for the cyclisation of the iodo-precursor **91** to yield the phenanthridone in Scheme 50.[2] All the steps were well known from $S_{RN}1$ mechanisms, except for the deprotonation of the intermediate π-radical **92** with Bu_3SnH acting as a hydride base. Attempts to replace Bu_3SnH with bases such as DABCO failed. An alternative, but closely related, SET mechanism was proposed by Harrowven *et al.*, in which the intermediate π-radical **92** transferred an electron to the precursor **91** to yield the chain carrying radical-anion.[84] The resulting cation would rapidly re-aromatise with loss of a proton. The attraction of these mechanisms was the chain propagation. However, later studies showed that no hydrogen (H_2) or HD (with use of a deuterated precursor) was produced, indicating that these mechanisms were unlikely to be operative.[147] The normal requirement for greater than one equivalent of AIBN was also not explained by the SET mechanism.

In the synthesis of pyrazolopyridines, good yields were obtained only when potassium carbonate was used in a deprotonation step (Scheme 51).[114] A SET mechanism was proposed, in which the potassium carbonate deprotonates the π-intermediate **94** to yield a radical-anion, which loses an electron by SET, presumably to the starting precursor **93** in a chain reaction. These results and those of Russell *et al.*[19–20] suggest that, in certain circumstances, SET mechanisms may be operative.

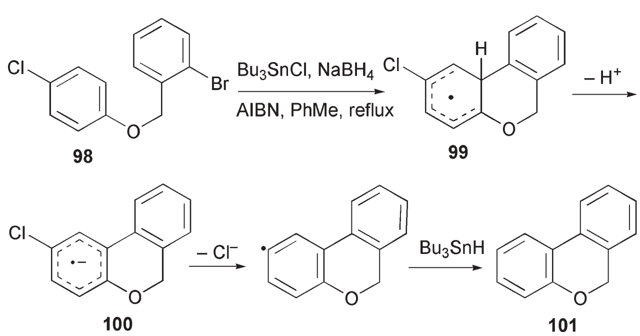
An interesting aromatic homolytic substitution takes place as part of an $S_{RN}1$ reaction, as shown in Scheme 52.[152] The intermediate radical-anion **96** undergoes rapid dissociation with loss of iodide rather than SET to the precursor **95**. This behaviour has been used as a diagnostic tool for the intermediacy of radical-anions in $S_{RN}1$ and other mechanisms. Chloride is also lost from these intermediate radical-anions, even though chloroarenes do not undergo $S_{RN}1$ reactions.[145] This diagnostic test has been used to provide evidence against a SET mechanism in Bu_3SnH-mediated aromatic homolytic substitution in the synthesis of 6*H*-benzo[*c*]chromenes (see Scheme 9), *i.e.* a proton was not abstracted from the π-radical intermediate **99** by Bu_3SnH.[40] The cyclisations were carried out with chloro-precursors, *e.g.* **98** (Scheme 53). 2-Chloro-6*H*-benzo[*c*]chromene was obtained in 42% yield and none of the dechlorinated product **101**, indicating that chloride loss from the putative radical-anion intermediate **100**, as shown in Scheme 53, was not operative.

3.4 Redox mechanisms

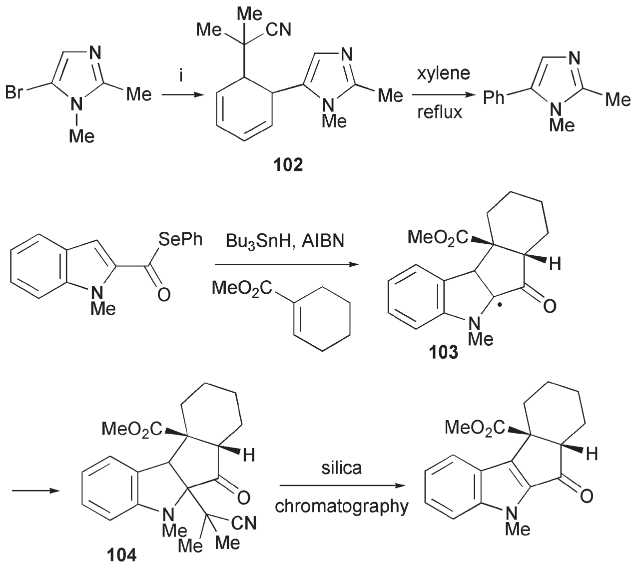
Oxidation of intermediate π-radicals to cations with subsequent rearomatisation by proton loss in aromatic homolytic substitution has been well exploited in the Minisci reaction[13–15] and in the use of xanthates (see Section 2.15). In these mechanisms an oxidant is required and is not comparable to the Bu_3SnH- and $(R_3Sn)_2$-mediated (Section 3.2) or SET mechanisms (Section 3.3) for aromatic homolytic



Scheme 51 Synthesis of pyrazolopyridines.



Scheme 53 Radical-anion dissociation mechanism.



Scheme 54 *Reagents and conditions*: i, Bu_3SnH, AIBN, PhH, reflux.

substitutions. These oxidative mechanisms and procedures are discussed in Sections 2.14 and 2.15.

3.5 Involvement of 2-cyanoprop-2-yl radicals

The involvement of 2-cyanoprop-2-yl radicals from the breakdown of AIBN, the most commonly used initiator, has been reported in several reactions.[17,104,105,108] Some examples are shown in Scheme 54. The intermediates **102** and **104** can be converted to the respective aromatic product by heat or acid catalysis. These results could indicate an uncommon side reaction or possibly suggest that the addition of 2-cyanoprop-2-yl radicals to intermediate π-radicals (*e.g.* **103** to **104**) and subsequent elimination under the reactions conditions could be a contributory mechanism for aromatic homolytic substitution. No mechanistic studies have been carried out to test this hypothesis.

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