Synthesis of heterocycles by radical cyclisation

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Reviewing the literature published between January 1994 and June 1996

Introduction

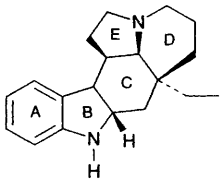
The most successful radical cyclisations proceed by 5-*exo-trig* regioselectivity and provide the main protocols used in heterocyclic synthesis. Therefore, as the majority of the heterocycles synthesised by radical cyclisations have five-membered rings, the review has not been divided on the basis of ring size. The review has largely excluded heterocyclic syntheses in which the heterocyclic ring(s) are not part of the radical cyclisation. For example, carbocyclic cyclisations in molecules which contain a heterocycle are not included.

The majority of radical cyclisations in heterocyclic chemistry have been carried out using tributyltin hydride (Bu_3SnH) or related triorganostannanes. The reaction conditions are generally similar, using a slight excess of Bu_3SnH with a smaller equivalent (10–25 mol%) of a radical initiator, normally azobisisobutyronitrile (AIBN). The reactions are generally carried out in boiling benzene or toluene for 1–10 h. It is assumed that readers have a general knowledge of the mechanism of Bu_3SnH facilitated reactions and therefore the mechanisms have not been discussed in detail. At the end of the review a section has been included which discusses different reagents and methods for generating the radicals.

A number of reviews which include synthesis of heterocycles *via* radical cyclisation have been published. Reviews include the use of transition metal-promoted[1] and redox-induced[2] radical reactions, tandem radical reactions,[3] radical reactions as key steps in natural product syntheses[4] and radical protocols for the synthesis of heterocycles.[5]

2. Natural product synthesis

The application of radical cyclisation to the synthesis of natural products containing heterocyclic rings provides practical examples of how the protocols using radicals can be used. In recent years some ingenious and time-saving radical cyclisation protocols have been used in the synthesis of biologically active heterocyclic natural products.



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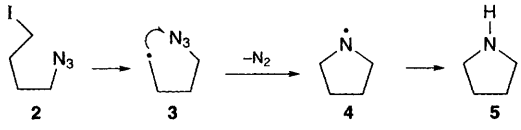
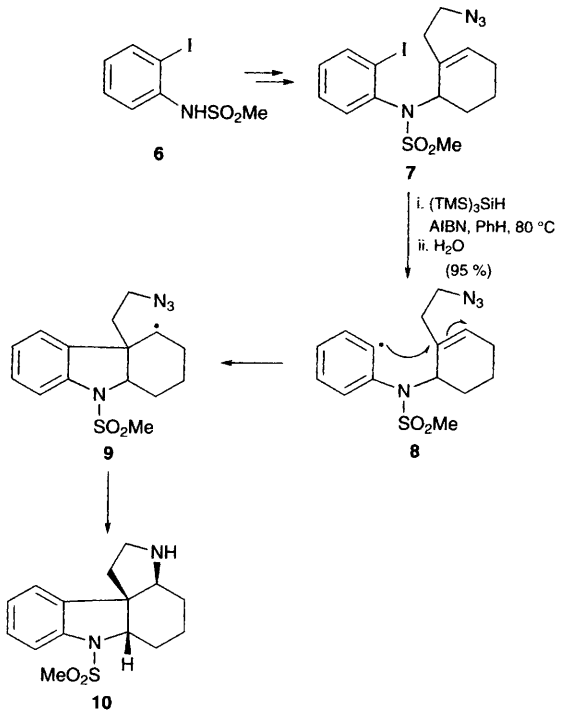


2 **3** **4** **5**

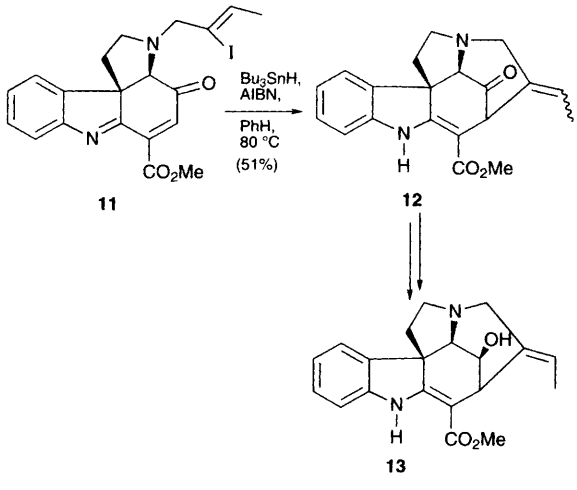
Murphy and Kizil[6] have synthesised the ABCE tetracycle of aspidospermidine **1** and related alkaloids by a tandem cyclisation which includes using the protocol of Kim and co-workers.[7] This latter protocol is shown (**2**→**5**) and involves the cyclisation of an alkyl radical **3** onto an azide with loss of nitrogen to yield an intermediate aminyl radical **4**. The aminyl radical is reduced by hydrogen abstraction from tris(trimethylsilyl)silane, $(TMS)_3SiH$, to pyrrolidine **5**. Murphy's synthesis starts from a simple arene **6** to give the radical precursor **7** in several steps. Treatment of **7** with $(TMS)_3SiH$ initially generates the aryl radical **8** which undergoes 5-*exo* cyclisation to form ring B. Radical **9** smoothly undergoes cyclisation onto the azide to give the tetracyclic aspidospermidine analogue **10** (**Scheme 1**). The synthesis proceeds with excellent stereoselectivity and in high yield. Kuehne and co-workers[8] have also used radical cyclisation to great advantage to facilitate the final cyclisation (**11** to **12**) in the pentacyclic *Strychnos* skeleton, (±)-mossambine **13**. The cyclisation step



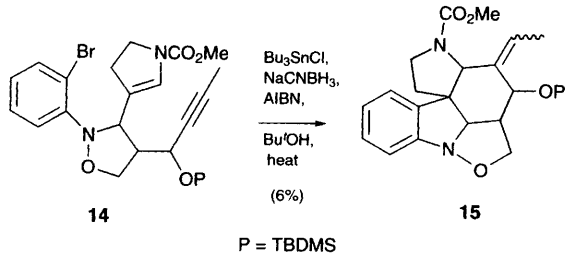
Scheme 1

involves a novel 6-*exo* cyclisation onto the β-position of an α,β-unsaturated imine (**Scheme 2**).

Several noteworthy syntheses using complex tandem heterocyclisation have come from Parsons *et al.* In the first of this group of syntheses,[9] the skeleton of models of the *Pseudocopsinine* and *Aspidosperma* alkaloids have been synthesised, albeit in lowish yields, *e.g.* the 5-*exo*, 6-*endo* cyclisation of **14** to **15** (**Scheme 3**). In these studies the second cyclisation proved difficult to carry out and was only successful with considerable care in the choice of positioning groups. In the example shown, the use of catalytic tributyltin hydride (Bu_3SnH) generated



Scheme 2

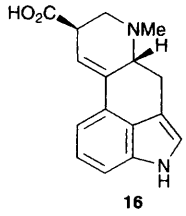


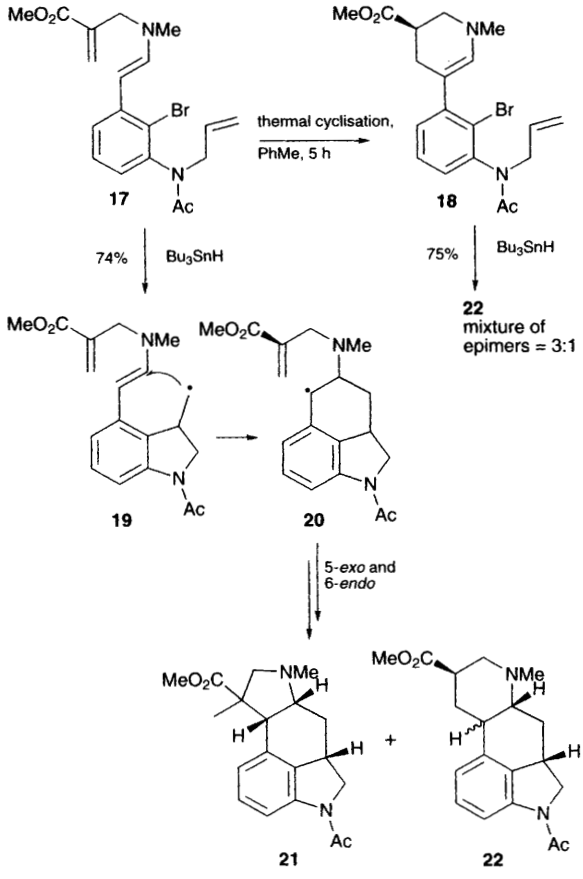
Scheme 3

in situ by reduction of tributyltin chloride with $NaCNBH_3$ allowed successful tandem cyclisation. This methodology allows minimal Bu_3SnH to be present in the reaction and thus facilitates cyclisation rather than reduction of the uncyclised intermediate radical. Several novel free radical cascade reactions (*e.g.* **17** to **21** and **22** and **18** to **22**, **Scheme 4**) for the syntheses of derivatives of lysergic acid **16** have also been reported.[10] All proceed *via* generation of an aryl radical from a radical precursor, *e.g.* **17** or **18**, which cyclises initially to yield a 3,4-disubstituted dihydroindole **19** by 5-*exo* cyclisation. Both of the resulting indole-3-methyl radical intermediates undergo 6-*endo* cyclisation to form the C-ring of the lysergic acid skeleton (**19** to **20** and that derived from **18** to **22**). In the case of the precursor **17** a third cyclisation, of intermediate radical **20**, in the cascade sequence gives a mixture of 6-*endo* cyclisation to the lysergic acid skeleton of **22** and the unwanted 5-*exo* cyclisation to **21**. The syntheses provide an interesting example of how the normally favoured 5-*exo* cyclisation can be forced towards 6-*endo* by steric or structural constraints. The stereoselectivity is also of note.

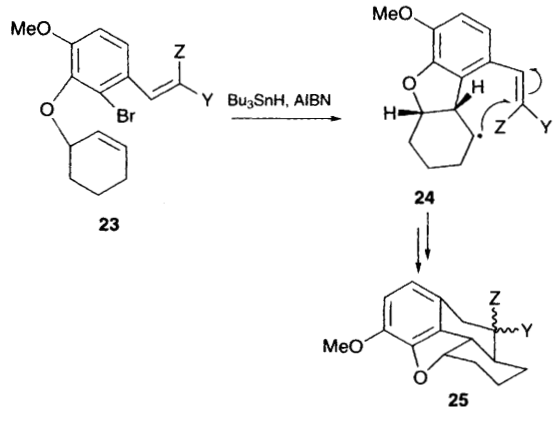
Tandem cyclisation has been used in the synthesis of the *cis*, *cis*-hydrophenanthrofuran part of the morphine skeleton.[11] The aryl radical generated from precursor **23** undergoes 5-*exo* cyclisation to give a radical intermediate **24** which undergoes 6-*endo* cyclisation onto the styryl moiety. The resulting stable benzylic radical facilitates 6-*endo* cyclisation to yield the correct skeleton of the product **25** (**Scheme 5**).

The use of halogenoacetals as masked esters has been widely used in the synthesis of natural products and provides a useful protocol for the preparation of lactones *via* radical cyclisation. The formation of the lactone intermediate **27** in the synthesis of the sesquiterpene (3*S*,4*R*)-luffariolide *E* **28** has been accomplished by 5-*exo* cyclisation onto

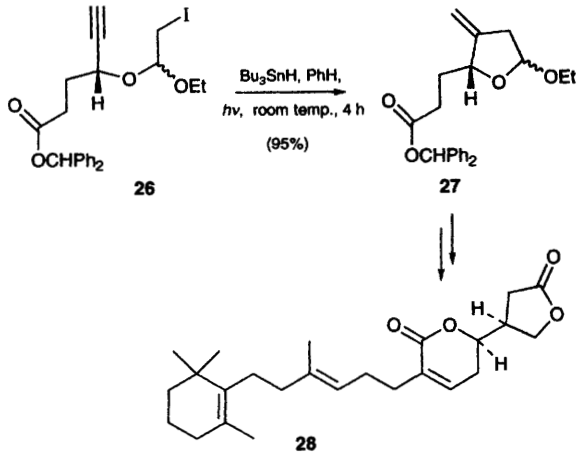




Scheme 4



Scheme 5

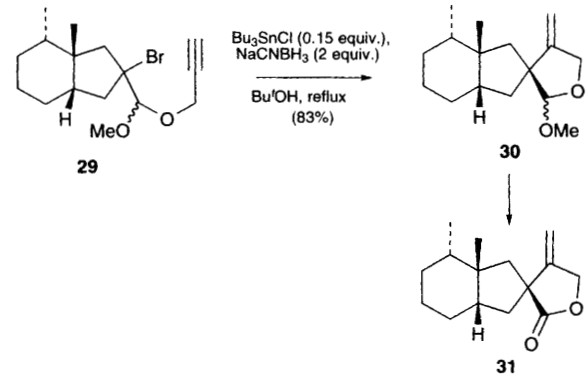


Scheme 6

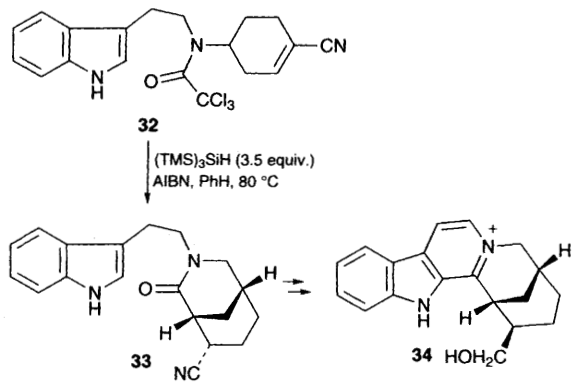
the alkyne bond in radical precursor **26** (**Scheme 6**).[12] A further example of this protocol is shown in the total synthesis of 4-epibakkenolide-A **31**.[13] The masked ester **29** is used for carrying out the central spirocyclisation step to yield **30** which was hydrolysed to give the butyrolactone ring present in the product **31** (**Scheme 7**).

In the first total synthesis[14] of the alkaloid (±)-melionine-E **34**, the central 2-azabicyclo-[3.3.1]nonane ring system was synthesised from the intermediate trichloroacetamide **32**. One of the chlorines is abstracted by $(TMS)_3SiH$ to generate the radical for cyclisation and the other two chlorines are reductively removed after the cyclisation to yield **33** (**Scheme 8**). The use of halogeno-substituted radicals has been used to great effect to synthesise the *cis*-linked pyranopyran ring system in the synthesis of the marine natural product (3*Z*)-dactomelyne **39** (**Scheme 9**).[15] Two cyclisations onto α,β-unsaturated esters (**35** to **36** and **37** to **38**) were carried out, each leaving behind one of the halogens required in the synthesis.

One of the most novel radical cyclisation protocols has been developed by Curran[16] using radical annulation with isonitriles for the synthesis of a range of the camptothecin family of anticancer

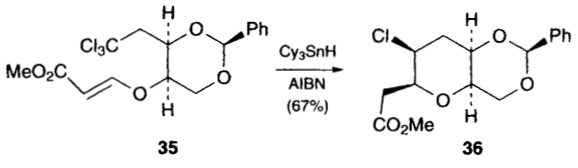


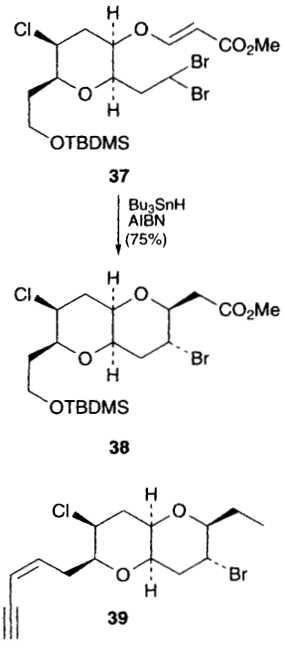
Scheme 7



Scheme 8

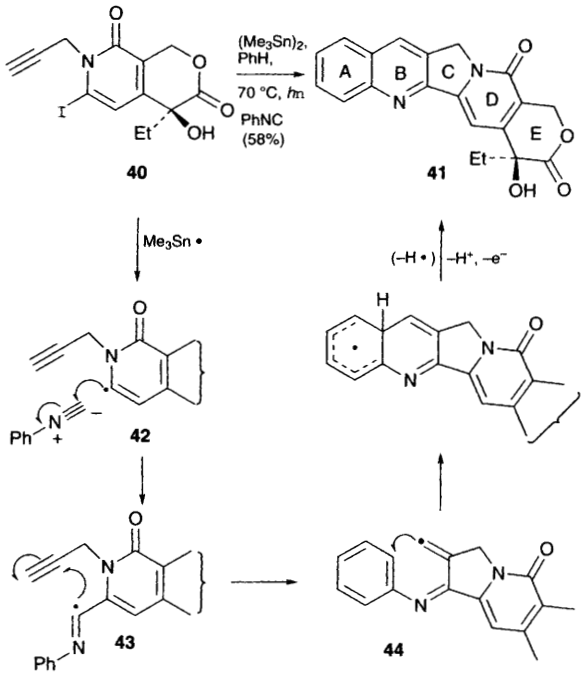
compounds, *e.g.* **41**. The protocol can be easily adapted to the synthesis of most of the camptothecin family because of the tolerance of radical reactions to functional groups on rings A and B and the retention of the chiral centre in ring E without racemisation. This protocol is a good example of the application of radical cyclisation to a commercially viable and adaptable synthesis. The protocol is exemplified by the synthesis of camptothecin **41** from radical precursor **40** (**Scheme 10**). The first radical **42** in the cascade, generated by iodide





Scheme 9

abstraction by the trimethyltin radical, undergoes bimolecular addition to the reactive phenyl isocyanide. The intermediate α-iminyl radical **43** gives 5-*exo* cyclisation onto the pendant alkyne, followed by cyclisation of the vinyl radical **44** onto the arene. Loss of hydrogen (or loss of a proton and an electron) by an as yet undefined mechanism yields the pentacyclic product.

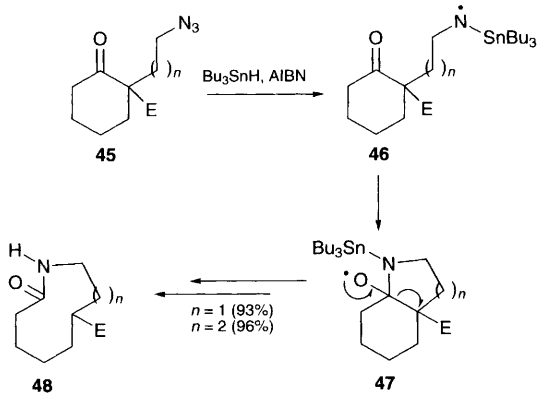


Scheme 10

3 Nitrogen heterocycles

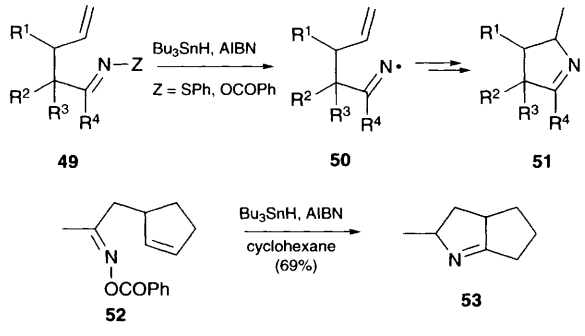
Nitrogen heterocycles can be synthesised by radical cyclisation with the nitrogen atom in various positions relative to the radical centre. The first of these options which has the radical on the nitrogen, *i.e.* aminyl radicals, continues to gain attention. Pyrrolidines have been synthesised by radical cyclisation of aminyls using sulfenamides,[17] disulfenamides,[18] nitrosamines[19] and *O*-benzoyl oximes[20] as precursors. Large ring lactams **48** have been synthesised by a novel route involving intermediate tributylstannylaminyl radicals **46** (**Scheme 11**). The latter can be generated by addition of tributyltin radicals onto azides **45** with loss of nitrogen.[7,21] These intermediate aminyl radicals are nucleophilic and readily add to ketones or aldehydes to yield intermediate alkoxyl radicals **47** which may undergo β-scission with ring opening to provide a novel synthetic route to large ring lactams. The driving force for this reaction is the reformation of the carbonyl group to yield the lactam and the forma-

tion of a stable α-ester radical in the ring-opened intermediate.



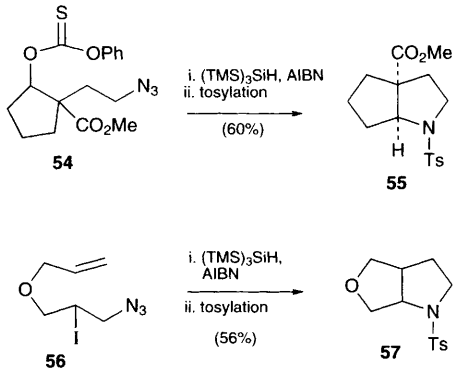
Scheme 11

The generation of iminyl radicals and their use for the synthesis of nitrogen heterocycles continues to be exploited by Zard and co-workers. *O*-Benzoyl oximes[20] and phenylsulfanylimines[22] have been used as radical precursors to generate the iminyl radicals. The iminyl radicals are electrophilic and readily cyclise onto weakly nucleophilic alkenes by 5-*exo* cyclisation. The general cyclisation is shown in the cyclisation of **49** to **51** *via* the iminyl radical **50**, and a bicyclic example (**52** to **53**) shows the wider versatility (**Scheme 12**).



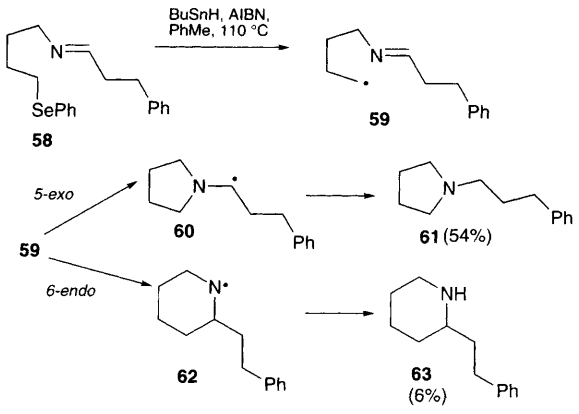
Scheme 12

The second option for the synthesis of nitrogen heterocycles is cyclisation onto a nitrogen atom in an unsaturated group. The innovative work of Kim and co-workers[7,21] has shown a variety of cyclisations of carbon centred radicals onto azides with loss of nitrogen to yield pyrrolidines *via* intermediate aminyl radicals (**2**→**5**). Murphy has exploited the protocol in the synthesis of the ABCE tetracycle of aspidospermidine **1**.[6] Some further examples of the uses of this novel protocol are shown: **54** to **55** and **56** to **57** (**Scheme 13**).[7,21]

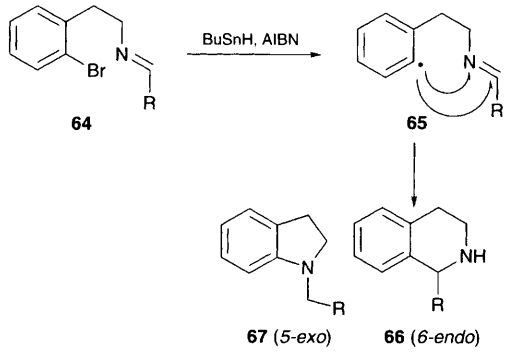


Scheme 13

In recent years there has been considerable study of the cyclisation of radicals onto imines, a reaction which had previously been ignored.[23,24] Depending on the relative position of the radical and the nitrogen of the imine, the cyclisation can take place onto the nitrogen or the carbon with 5-*exo* or 6-*exo* cyclisation being the main determining factor. Carbon radicals are weakly nucleophilic and prefer to add onto the electrophilic carbon centre. The rates of cyclisation are faster for both 5- and 6-*exo* cyclisation onto imines as compared to the rates of cyclisation onto the corresponding alkenes. The protocol for tandem cyclisations is discussed further in the next section. Cyclisation of alkyl radicals, *e.g.* **59**, generated from an *N*-(3-phenylpropylidene)-ω-(phenylselanylamine, *e.g.* **58**, gives predominantly 5-*exo* cyclisation onto the nitrogen atom of the imine to yield the pyrrolidine **61** *via* **60** but with some 6-*endo* cyclisation onto carbon to yield the piperidine **63** *via* intermediate radical **62** (**Scheme 14**).[23] In general the alkyl radicals cyclise as predicted from reactions with alkenes. However, aryl radicals have a strong preference for 6-*endo* cyclisation and this thereby provides a useful synthesis for tetrahydroisoquinolines.[24] The cyclisation has also been shown to proceed with good stereoinduction if a α-chiral alkyl group is attached. An example of the protocol is shown for the imine **64** which reacts *via* aryl radical **65** to yield largely the 6-*endo* tetrahydoisoquinoline product **66** and very little of the 5-*exo* indoline product **67** (**Scheme 15**).



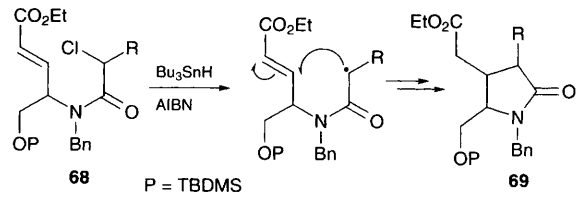
Scheme 14



Scheme 15

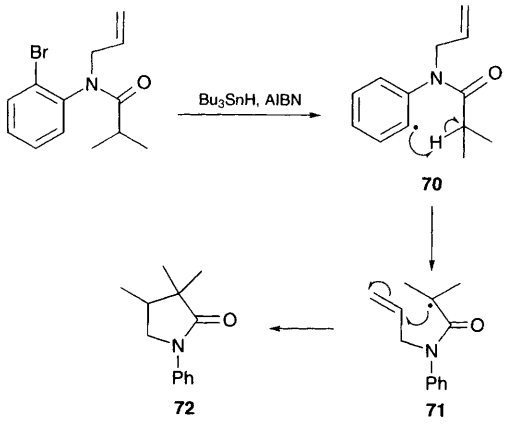
A third option for cyclisation is to generate the radical centre α to the nitrogen atom. SET photosensitised reactions of α-silylaminoenones and ynones[25] and Cu(bpy)Cl metal-catalysed cyclisation of α-chloroaminoesters[26] have been reported. The fourth option using cyclisation of radicals onto the carbon α to the amine, *i.e.* an enamine function, is less commonly used but a few examples have been reported.[27]

The fifth and most common route to pyrrolidine ring systems is cyclisation of a radical β to the nitrogen atom onto an unsaturated bond which is also β to the nitrogen.[28–32] Piperidine rings have been similarly prepared by cyclisation of a radical γ to the nitrogen onto a β-alkene.[28] The radical β to the nitrogen has been generated by a number of methods. There are a number of examples of the generation of the required radicals by abstraction of a suitable radical leaving group (chlorine,[29] iodine[30] and thiocarbonates[31]) by Bu_3SnH and also by electrochemical generation by anodic decarboxylation from carboxylic acids.[32] For example, with the use of Bu_3SnH, DL-serine derived α-chloroamides **68** undergo cyclisation in good yield (58–95%) to give a mixture of diastereoisomeric pyrrolidinones **69** by 5-*exo* cyclisation (**Scheme 16**). The effect of a wide variety of substituents was determined for this cyclisation with the aim of synthesising kainic acid analogues.



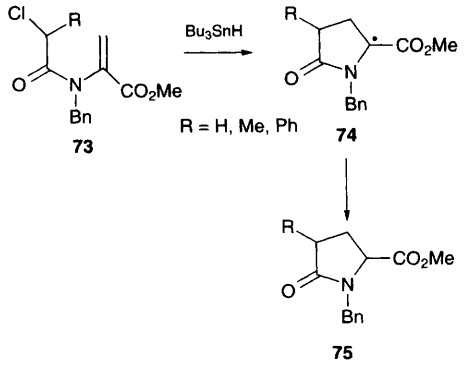
Scheme 16

The protocol of radical translocation has been used for synthesising pyrrolidines.[33,34] In this protocol an aryl radical is generated from a stable and unreactive halogenoarene which will not interfere with other synthetic manipulations. In the example shown in **Scheme 17**,[33] the aryl radical **70** abstracts hydrogen from an unactivated position by 1,5-hydrogen abstraction to generate a new radical **71** which undergoes 5-*exo* cyclisation to yield a pyrrolidinone ring **72**. The advantage is that the halogenoarene can be easily introduced and does not react until radical conditions are initiated.

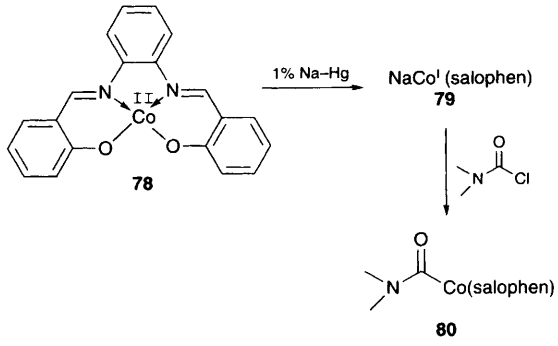


Scheme 17

A useful synthesis of proline analogues **75** (47–74%) has been reported[35] using *N*-(α-chloroacetamido)dehydroalanine derivatives **73** in which the cyclisation proceeds *via* an unusual 5-*endo* cyclisation. The α-acetamido radical cyclises onto the dehydroalanine to generate stable captodative α-amido ester radicals **74** (**Scheme 18**). These stable cyclised radicals may be the driving force for the unusual 5-*endo* cyclisation, or a SET mechanism may be involved. A related 5-*endo* cyclisation onto α-acetamidostyrenes has also been reported.[36]



Scheme 18

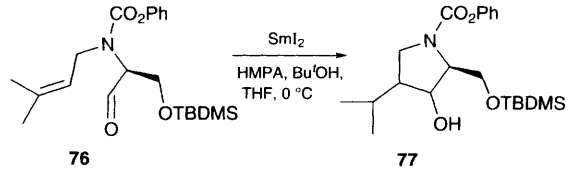


Scheme 20

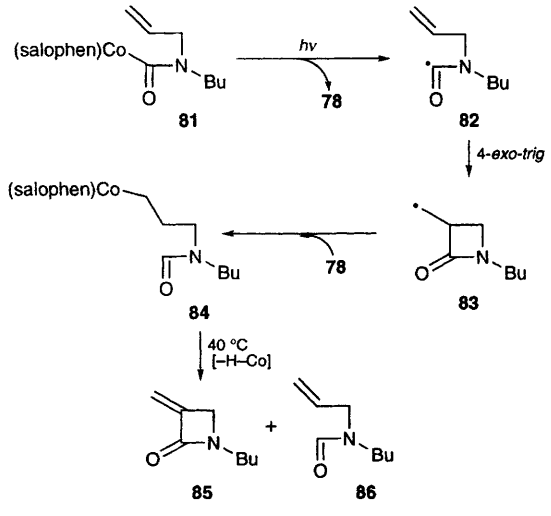
The protocol using precursors with two unsaturated bonds β to the nitrogen (alkenes, alkynes, aldehydes, oxime ethers) for the synthesis of pyrrolidines continues to be reported.[37-44] The protocol requires generation of a radical on one of the unsaturated bonds which undergoes 5-*exo* cyclisation to yield a 3,4-disubstituted pyrrolidine derivative. The radicals are generated by addition of a radical to the unsaturated bond or by reduction.[37] This reductive method has been applied to the synthesis of proline analogues, *e.g.* **77** (**Scheme 19**). The aldehyde on the radical precursor **76** is reduced with samarium diiodide (SmI_2) to yield a ketyl radical which undergoes 5-*exo* cyclisation onto the alkene. In SmI_2 radical reactions the resulting radical abstracts hydrogen from the THF solvent.

Several syntheses of β-lactams have been reported using radical cyclisation.[44-46] Pattenden and co-workers[44] have applied their methodology using the cobalt(II) salophen complex **78** to facilitate 4-*exo* cyclisation of carbamoyl radicals (**82** to **83**). The method for generating the carbamoylcobalt(III) salophen compounds is shown (**78**→**80**). The use of the cobalt is illustrated for the reaction with *N*,*N*-dimethylcarbamoyl chloride. The cobalt(II) salophen complex **78** is activated by reduction to the Co^{I} oxidation state which undergoes oxidative addition to the C–Cl bond of *N*,*N*-dimethylcarbamoyl chloride to yield the carbamoylcobalt(III) salophen compound **80** (**Scheme 20**). In the β-lactam synthesis, irradiation of the intermediate carbamoylcobalt(III) salophen compound **81** yields the intermediate carbamoyl radical **82** and regenerates the starting cobalt(II) salophen complex **78**. 5-*endo* Cyclisation is very unfavourable and 4-*exo* cyclisation is normally readily reversible. However, the intermediate cyclised radical **83** is trapped by the cobalt(II) salophen complex **78** to yield a new cobalt(III) salophen complex **84** which prevents the fast ring opening that would otherwise take place. Although these intermediate cobalt(III) species appeared to be stable under 40 °C, dehydrocobaltation took place under the conditions of the reaction. The unsaturated β-lactam **85** was produced as the main product along with some ring-opened material **86** (**Scheme 21**). γ- and δ-Lactams were also synthesised by the same protocol *via* 5- and 6-*exo* cyclisation respectively.

Another method[45] for facilitating the 4-*exo* cyclisation required for β-lactam synthesis is to place benzenesulfenyl groups on the alkene in order to stabilise the cyclised 4-*exo* radical and hence prevent the reverse ring opening. The use of *N*-ethenyl-α-bromoamides with benzenesulfenyl groups attached to the alkene gives reasonable yields of β-lactams. A 7-*endo* cyclisation has been reported[46] for the synthesis of an aza-5-silabicyclo[5.2.0]nonan-9-one with two pendant groups attached to the β-lactams.



Scheme 19



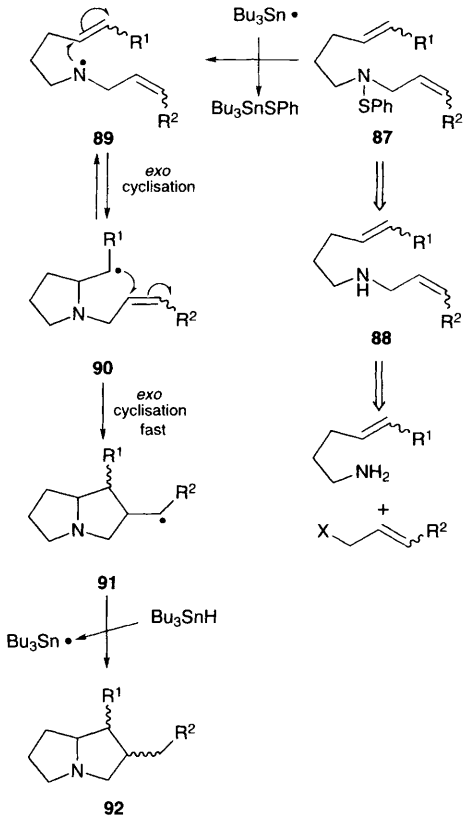
Scheme 21

4 Pyrrolizidines and other bicyclic nitrogen heterocycles

The synthesis of bicyclic nitrogen heterocycles using radical cyclisation continues to be a developing area of study. The protocols can be split into two areas: acyclic precursors which undergo tandem cyclisation or monocyclic precursors which undergo one cyclisation.

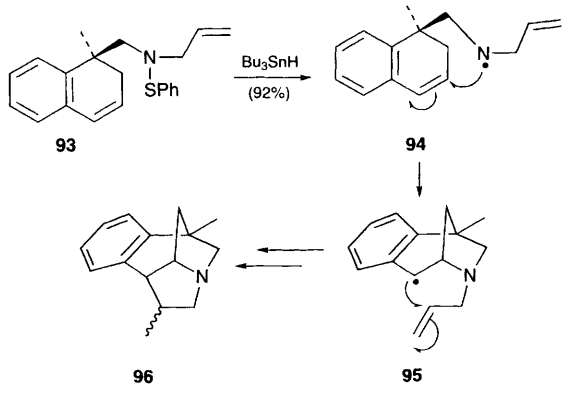
A number of novel methodologies for tandem cyclisation to yield pyrrolizidines have been published and show the utility of radical cyclisation for synthesising complicated heterocycles in one pot reactions. Tandem radical cyclisations of aminyl radicals generated from sulfenamide precursors have been used for the synthesis of pyrrolizidines and other polycyclic nitrogen heterocycles.[47] The general procedure is shown in the conversion of **87** into **92** (**Scheme 22**). The starting amines **88** are easily prepared and converted to the sulfenamide precursors **87** using benzenesulfenyl chloride. The aminyl radicals **89** are generated by reaction between sulfenamide precursors and Bu_3SnH. The 5-*exo* cyclisation of the aminyl radical **89** to the monocyclic radical **90** is reversible but trapping in the tandem reaction to yield the bicyclic pyrrolizidine **91** prevents ring opening of **90**. The pyrrolizidine product **92** is obtained by hydrogen abstraction from Bu_3SnH by **91**. The procedure allows a wide variety of pyrrolizidines and indolizidines to be prepared and is exemplified by the synthesis of an unusual tetracyclic heterocycle **96** containing the pyrrolizidine ring system.[47] The sulfenamide precursor **93** undergoes 5-*exo*, 5-*exo* tandem cyclisation *via* intermediate radicals **94** and **95** (**Scheme 23**).

The use of aminyl radical intermediates for the synthesis of bicyclic nitrogen heterocycles has been further exploited by generation in tandem reactions.[48] A range of bicyclic nitrogen heterocycles have been synthesised by tandem cyclisation of sp^3 carbon-centred radicals onto the C=N double bonds of imines to generate intermediate aminyl radicals, which undergo further cyclisation onto suitably positioned alkenes. Three of the retrosyntheses are illustrated in **Scheme 24**, including 2-azabicyclo[3.3.0]octanes and perhydroindolines **98** (*via* 5- or 6-*exo*, 5- or 6-*exo* cyclisation), spiroamines **97** (*via* 5- or 6-*exo*, 5- or 6-*exo* cyclisation) and indolizidines **99** (*via* 6-*endo*, 5-*exo* cyclisation). The protocol is exemplified by the synthesis of spiroamines **104** ([5.5], [5.6], [6.6]) which proceed in 30–60% yields (**Scheme 25**). The tandem cyclisations are better facilitated by the use of the Lewis acid magnesium dibromide–diethyl ether which bonds to the nitrogen atom, thereby making both the imine and intermediate aminyl radical more electrophilic and increasing the rates of cyclisations to prevent side reactions. In this protocol the benzeneselenyl group is abstracted from **100** by tributyltin radicals to yield intermediate radical **101** which undergoes cyclisation onto the imine to yield the intermediate aminyl radical **102**. A second cyclisation by the intermediate aminyl radical yields the bicyclic radical **103** followed by abstraction of hydrogen from Bu_3SnH.

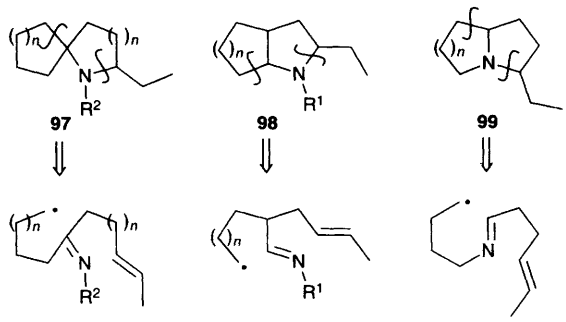


Scheme 22

A range of syntheses of bicyclic nitrogen heterocycles has been reported[49–52] using monocyclic precursors which a radical cyclisation to add the second ring. A good example[49] of this methodology is the preparation of indolizidines, *e.g.* **106**, using standard Bu_3SnH-mediated cyclisation from precursors, *e.g.* **105** (**Scheme 26**). By suitable changes in ring size and side chain length, pyrrolizidines and quinolizidines were also synthesised in high yield. Other similar cyclisations to prepare quinolizidines and pyrrolizidines using Bu_3SnH have

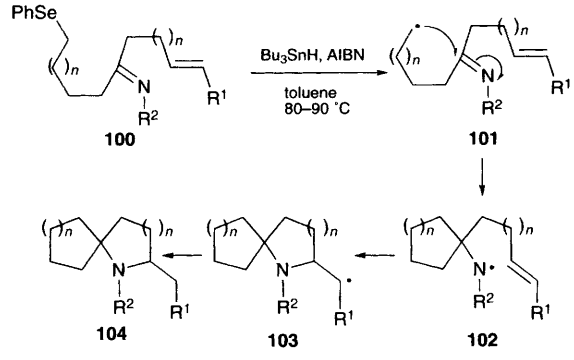


Scheme 23

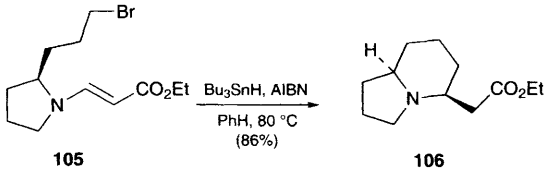


Scheme 24

been reported.[50] Copper(I)-catalysed chlorine transfer has been used for the synthesis of a range of bicyclic nitrogen heterocycles from α-chloroglycine derivatives with a 3-alkenyl side chain.[26] The cyclisations proceed *via* captodative glycinyl radicals. Photosensitised electron transfer (PET) of α-silylmethylamines has been used for the synthesis of pyrrolizidine alkaloid, (−)-retronecanol.[51] Pyrrolizidines, indolizidines and spirobicyclic amines have been prepared using photosensitised ring annulation between amines and acrylates *via* α-aminoalkyl radicals.[52]



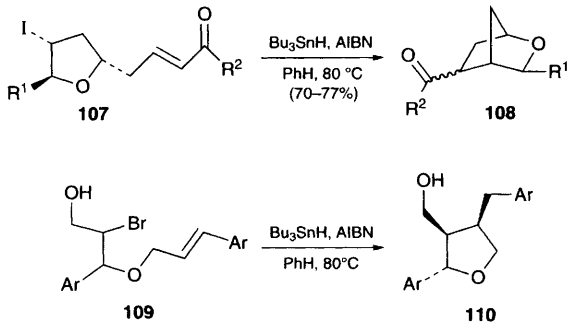
Scheme 25



Scheme 26

5 Oxygen heterocycles

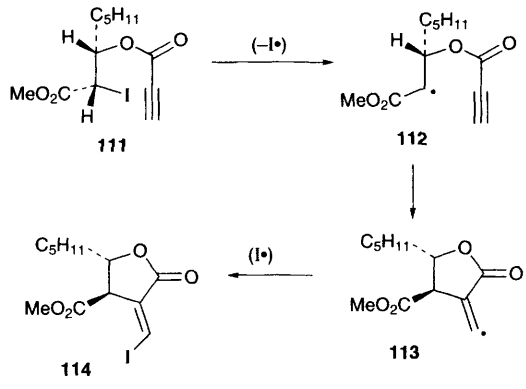
Radical cyclisation of halogenoalkenes with an oxygen atom in the chain to yield tetrahydrofuran derivatives is probably the most commonly used radical-based synthesis of heterocycles. Two examples are used to illustrate the synthetic possibilities, *e.g.* synthesis of 2-oxabicyclo[2.2.1]heptanes **108**[53] from β-iodo-substituted furans **107** and furanolignans, *e.g.* (±)-dihydrosesamin **110** (Ar = 4-hydroxy-3-methoxyphenyl), from the bromo alkene **109 (Scheme 27)**.[54] Other 5-*exo* cyclisations onto alkenes reported include cyclisations onto α,β-unsaturated esters using Bu_3SnH as the radical generating reagent,[15,55] stereoselective cyclisation of alkyl halides onto α,β-unsaturated sulfones,[56] cyclisation of difluoroalkyl radicals onto alkenes to give α,α-difluoro-γ-lactones[57] and cyclisation of bromoketals[58] and iodoacetals[59] to yield tetrahydrofurans. Intramolecular addition of acyl radicals generated from selenol esters to vinylogous carbonates provides a stereoselective and high yielding synthesis of 2-oxotetrahydropyrans.[60] Several cyclisations of alkylhalogeno alkynes to yield tetrahydrofurans with an exocyclic methylene group have been reported.[61] The cyclisation of vinyl bromides onto trimethylsilyl-alkynes *via* 5-*exo* cyclisation of the intermediate vinyl radicals onto the alkyne yields 3-methylene-4-(trimethylsilylmethylene)tetrahydrofurans.[62]



Scheme 27

Other methods of generating radicals for cyclisation to yield tetrahydrofurans include use of organocobalt intermediates[63] and Cp_2TiCl_2 activated by zinc for cyclisation of epoxyalkynes in the synthesis of the exocyclic methylene tetrahydrofuran, (±)-methylenolactocin.[64]

Use of the iodine atom transfer protocol with α-iodo esters provides a high yielding route to the antitumour antibiotic methylenolactocin.[65] The reaction is initiated by dibenzoyl peroxide to generate the initial α-methoxycarbonyl radical **112** which undergoes 5-*exo* cyclisation onto the alkyne to yield the methylene radical **113 (Scheme 28)**. This unstable radical abstracts iodine from the starting material **111** to yield the more stable intermediate radical **112** which is stabilised by the α-methoxycarbonyl group. The driving force for the iodine atom transfer protocol is the conversion of a weak C–I bond into the stronger vinyl iodide bond. The iodine is removed from the product **114** to yield the antibiotic methylenolactocin. The iodine atom transfer method has also been used for the synthesis of fluorinated α-alkylidene-γ-butyrolactone deriva-

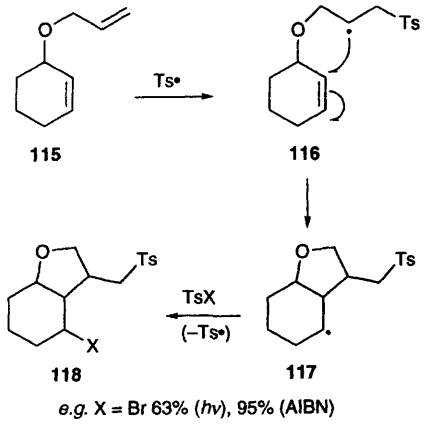


Scheme 28

tives[66] and dioxatriquinanes and doubly annulated glycosides.[67] The Speckamp group[68] have also applied their copper(I)-catalysed chlorine atom transfer methodology to the conversion of 2-(alk-3-en-1-oxy)-2-chloroacetates to 3-(chloroalkyl)-2-methoxycarbonyltetrahydrofurans.

The cyclisation of ethers with two β-alkenes or a β-alkene and a β-alkyne has been achieved by addition of compounds with labile bonds, *e.g.* diphenyl diselenide,[69,70] diphenylphosphine,[69] benzenethiol[71] and tosyl iodides, bromides, chlorides and selenides.[69,70,72] These reactions are initiated with AIBN or photolysis to cleave the labile bond. The protocol is exemplified by the synthesis of tetrahydrofurans using tosyl iodides, bromides and selenides.[69] Initiation with either light or AIBN yields the initial tosyl radical which adds to the diene **115** to give an intermediate radical **116** which undergoes 5-*exo* cyclisation to **117**. The chain is completed by **117** abstracting an iodide, bromide or benzeneselenolate group to yield **118** and to regenerate the chain carrying tosyl radical (**Scheme 29**). The advantage of these reactions is that the use of toxic triorganotin compounds is avoided.

Two examples of the generation of intermediate alkoxyl radicals in the synthesis of tetrahydrofurans



Scheme 29

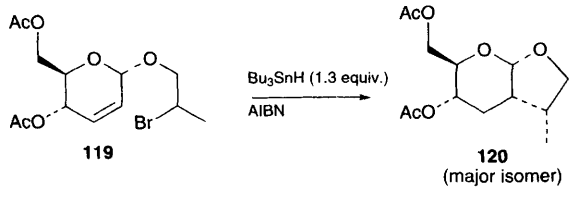
have been reported. The first method involves treatment of benzenesulfenic acid esters (ROSPh) and *N*-(alkoxy)pyridine-2(1*H*)-thiones with Bu_3SnH to generate alkoxyl radicals followed by 5-*exo* cyclisation onto alkenes.[73] The second method uses lead tetraacetate oxidation of alcohols.[74]

6 Carbohydrates and nucleosides

Radical cyclisation methods are well suited to carbohydrate molecules because of the tolerance of radical reactions to functional groups, thereby avoiding the need for protecting all of the alcohol groups. The use of radical cyclisation in the syntheses of oxygen heterocycles in carbohydrates can be split into several strands of methodology: cyclisation of a side chain radical onto an alkene in the monosaccharide ring (normally furanoses), cyclisation of a radical on the one of the ring carbon atoms onto a pendant side chain containing an unsaturated bond, cyclisation of a side chain radical onto an alkene on a side chain, monocyclisation to form the monosaccharide ring, and lastly, cyclisation from the monosaccharide ring onto a nucleoside base. The syntheses are used for both the synthesis of carbohydrate natural products and analogues, and for synthetic manipulations using carbohydrate templates.

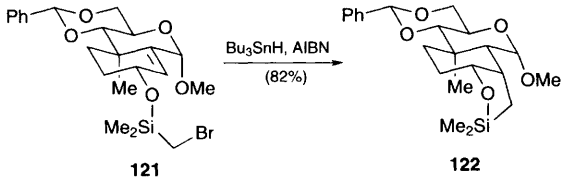
Several examples illustrate the cyclisation of a side chain radical onto a double bond in the monosaccharide ring.[75,76] Radical cyclisation of alkyl hex-2-enopyranosides yields furanopyrans with a *cis* ring junction as normally predicted (**119** to **120**, **Scheme 30**).[75]

The Stork methodology using side chain dimethylsilylmethylene radicals continues to be used.[77–80] The side chain moiety can be added onto a ring alcohol with ease using $ClSiMe_2CH_2Br$. A radical is generated from the resulting side chain for cyclisation onto the monosaccharide ring. The silicon group is normally removed by treatment with H_2O_2 and KF to yield the original, and the new, hydroxymethyl groups. Jenkins[77] has used this protocol with success (**121** to **122**, **Scheme 31**) for the synthesis of an intermediate in his studies on the synthesis of Taxol from glucose. The general protocol has also been used for attaching an alkyne group onto a ring alcohol with $RC{\equiv}CSiMe_2Cl$.[81] 5-*exo* Cyclisation of a radical on C-2 or C-3 of the monosaccharide ring onto the pendant alkyne is then carried out to yield an *exo*-methylene group which can be further functionalised as required. The protocol has been

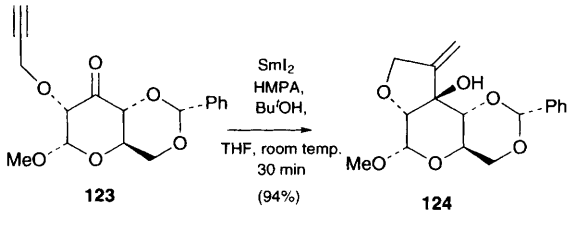


Scheme 30

extended by using the ability to add an alkenyl or alkynyl side chain onto one of the ring hydroxyl groups.[82–84] For example,[82] in the synthesis of the carbohydrate part of the nucleoside antibiotics miharamycins A and B, addition of $HC{\equiv}CCH_2Br$ to the C-2 hydroxy of a pyranose yields the radical precursor **123**. Treatment of **123** with SmI_2 gives 5-*exo* cyclisation as well as generating the ring-junction hydroxy in **124** (**Scheme 32**). This protocol facilitates the addition of a tetrahydrofuran ring onto a monosaccharide ring without undue synthetic elaboration. In other examples, the ring radical is generated using Bu_3SnH, followed by cyclisation onto a side chain alkyne,[83] alkene[84] and α,β-unsaturated ester.[85]

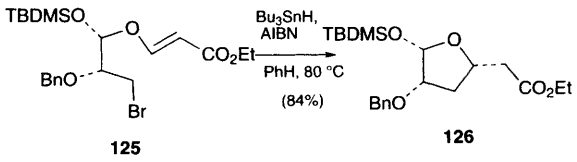


Scheme 31



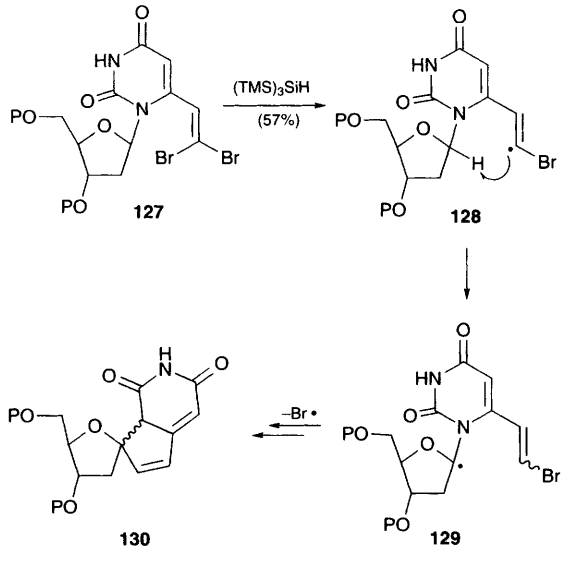
Scheme 32

One example in the literature[86] exploits the cyclisation of a side chain β-acetal radical onto an alkene on a side chain α,β-unsaturated ester. The anomeric effect is crucial in understanding the stereoselectivity of these cyclisations. In several examples, monocyclisation to form the monosaccharide ring has been used.[87,88] The protocol is exemplified[87] by the stereoselective synthesis of C-glycosides which has been accomplished *via* Bu_3SnH-mediated radical cyclisation of β-alkoxyacrylates, *e.g.* **125** to **126** (**Scheme 33**).



Scheme 33

Several reported syntheses show the potential for cyclising a radical on the monosaccharide moiety onto the nucleoside base. These reactions are of importance because of the evidence that they can be responsible for the DNA damage caused by certain drugs such as neocarzinostatin, a member of the enediyne family of antibiotics. A novel synthesis of an anomeric spironucleoside has been accomplished with a 2′-deoxyuracil nucleoside using a novel 1,5-radical translocation procedure.[89,90] One of the syntheses[89] starting with the protected 2′-deoxyuracil nucleoside **127**, forms the intermediate vinyl radical **128** and by 1,5-radical translocation generates a radical at the anomeric position **129**. The 1,5-translocation is favoured because the vinyl radical is very reactive and the abstraction yields a stabilised α-alkoxyl radical at the anomeric position. The anomeric radical undergoes cyclisation followed by elimination of bromine to yield an anomeric mixture of two cyclic spironucleosides **130** (**Scheme 34**). The radical generated at C-5′ from 5′-deoxy-5′-iodo-adenosine has been cyclised onto the C-2 carbon of the adenine.[91]

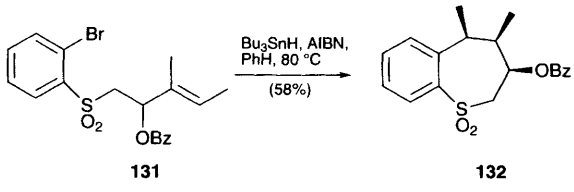


Scheme 34

7 Sulfur heterocycles

Remarkably few synthetic applications have been reported for cyclisations to give sulfur heterocycles.

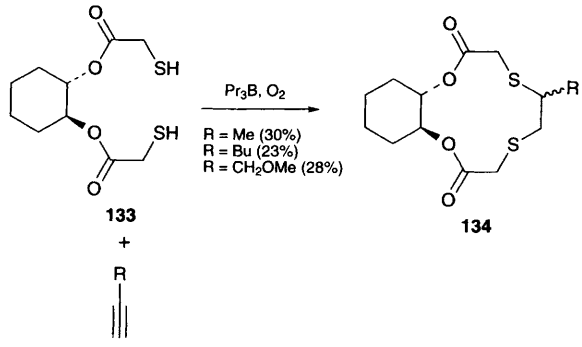
Simpkins *et al.* have cyclised aryl radicals derived from *o*-bromophenyl sulfones onto side chain alkenes to yield benzo-fused six- and seven-membered ring sulfones.[92] Higher than normal preference for *endo* cyclisation is observed in some of these reactions, which is in keeping with cyclisations involving sulfur in the ring because of the relatively long C–S bond, *e.g.* the *o*-bromophenyl sulfone **131** gives only the *endo* benzo-fused seven-membered ring sulfone **132** (**Scheme 35**). Cyclisation of aryl radicals onto side chain dithioesters yields 6-, 7- and 8-*endo* cyclisation onto the sulfur atom of the dithioesters to yield benzo-fused five-, six- and seven-membered rings.[93] The authors compare the cyclisation of aryl radicals and aryllithium compounds and report that the only successful aryllithium cyclisation is 8-*endo*. Cyclisation of aryl radicals onto side chain thioesters gives dihydrobenzothiophenes.[94] The reaction proceeds *via* S_H2 substitution on the sulfur atom *via* a five-membered ring transition state with an acyl radical as the leaving group. Similar cyclisation of aryl radicals onto side chain thioethers gives dihydrobenzothiophenes *via* S_H2 substitutions.[95]



131 132

Scheme 35

Intramolecular S_H2 substitutions on sulfur and selenium by carbon-centred radicals yield four-, five- and six-membered ring sulfur and selenium heterocycles.[95,96] Treatment of but-1-ynyl phenyl selenide with Bu_3SnH yields almost exclusively dihydroselenophene.[96] An unusual radical annulation reaction dithiols derived from *cis*- and *trans*-cyclohexanediols and alkynes yields cyclohexano-fused 12-membered crown thioethers.[97] The radical reaction is initiated with tripropylborane and oxygen *via* thiyl radicals. In the example shown, the dithiol derivative from *trans*-cyclohexanediol **133** initially undergoes addition to the alkyne to give an intermediate vinyl thioether followed by a 12-membered ring *endo* cyclisation by the other thiol group to give the 12-membered crown thioether **134** in 23–30% yield (**Scheme 36**).[97] A mixture of isomers at the alkyl substituent on the dithioethane part of the molecule was obtained. The addition of thiols to alkynes and alkenes is well known but this is the first example of a large ring annulation by this protocol.



133 + R 134

Scheme 36

Two radical cyclisations onto thiophene have been reported for the synthesis of tetrahydrobenzothiophenes.[98,99] In the first synthesis, 5-thienylpent-1-enes are cyclised using tosyl radicals which add onto the side chain alkene followed by oxidative cyclisation of the resulting radical onto the thiophene ring.[98] In the second synthesis α-malonyl radicals, resulting from $Mn(OAc)_3$ oxidation of (3-thienyl)methyl-malonate, were added to alkenes and the resulting radicals oxidatively cyclised onto the thiophene rings.[99]

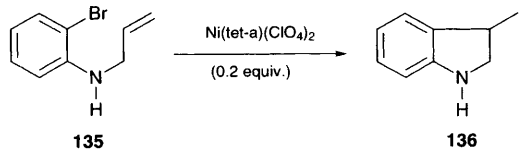
8 Heterocycles with heteroatoms other than *N*, *O* and *S*

The only other group of heterocyclic syntheses involve silicon heterocycles, *e.g.* aza-5-silabicyclo-[5.2.0]nonan-9-one[46] and 9-silylphenanthrenes.[100] The Stork methodology using side chain dimethylsilylmethylene radicals discussed in Section 6[77–80] has also been used on other hydroxyalkenes.[101,102] $ClSiMe_2CH_2Br$ reacts with the alcohol to form the $ROSiMe_2CH_2Br$ derivative which cyclises onto a suitably placed alkene to form a five-membered ring containing oxygen and silicon. One of these papers[101] reports the stereoselective synthesis of the side chain of the steroid brassenolide using the Stork protocol.

9 Benzoheterocycles

Indolines can be easily synthesised by cyclisation of an aryl radical onto an *ortho*-alkenyl chain by 5-*exo* cyclisation. Examples of this protocol have been shown in some of the natural product syntheses in Section 2, *e.g.* Murphy's synthesis[6] of the tetracyclic aspidospermidine analogue **10** (**7**→**10**, **Scheme 1**) and the syntheses by Parsons *et al.*[9,10] of the skeleton of models of the *Pseudocopsinine* and *Aspidosperma* alkaloids (**14** to **15**, **Scheme 3**). The indoline nucleus is also present in the synthesis of the pentacyclic *Strychnos* skeleton, (±)-mossambine **13** by Kuehne and co-workers (**Scheme 2**).[8] A straightforward example of cyclisation to indolines has been carried out using a nickel(II) complex to generate the aryl radical by electroreduction.[103] *N*-Allyl-*o*-bromoaniline **135** gives 3-methylindoline **136** in 58% yield

(**Scheme 37**). The use of nickel and reduction avoids toxic triorganotin hydrides. Cyclisation of *N*-allenylmethyl-*N*-tosyl-*o*-bromoaniline gives a mixture of 5-*exo* cyclisation to the corresponding 3-vinylindoline as well as 6-*endo* cyclisation onto the central allene carbon atom to yield the corresponding 4-methyl-1,2-dihydroquinoline.[104]

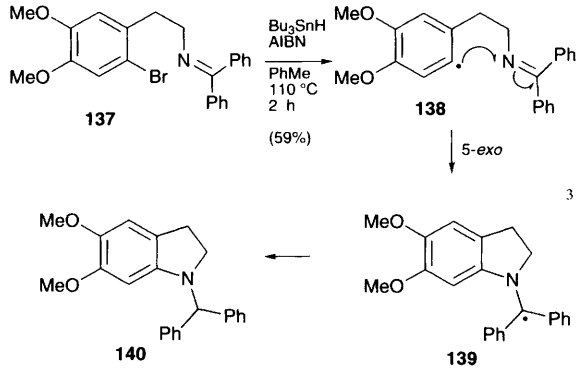


135 **136**

tet-a = hexamethyltetraazacyclotetradecadiene

Scheme 37

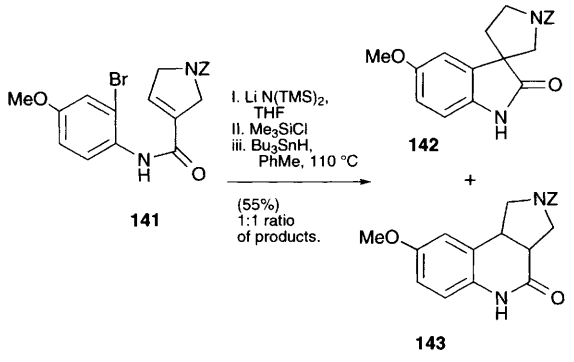
The synthesis of indolines by cyclisation of aryl radicals onto side chain imines[24,105] normally gives 6-*endo* cyclisation, e.g. **64** gives tetrahydoisoquinoline **66** and very little of the 5-*exo* indoline product **67** (**Scheme 15**). However when groups are attached to stabilise the radical resulting from 5-*exo* cyclisation onto the nitrogen atom of the imine *e.g.* phenyl, 5-*exo* cyclisation becomes more favourable. The radical **138**, resulting from bromine abstraction from *the* o-bromophenyl imine **137**, proceeds by selective 5-*exo* cyclisation to give the stable diphenylmethyl radical **139** (**Scheme 38**).[105] The indoline **140** is the only product, but when alkyl groups in place of aryl groups are present the cyclisation is selective to 6-*endo* cyclisation.[24,105]



137 **138** **139** **140**

Scheme 38

Oxindoles have been synthesised by cyclisation of aryl radicals onto the α-carbon of the double bond in α,β-unsaturated amides chain by 5-*exo* cyclisation. The aryl radicals have been generated by Bu_3SnH,[106] by use of cobalt(II) chloride and a Grignard reagent[107] and by reduction with SmI_2.[108] The starting α,β-unsaturated amide needs to have an *N*-substituent to force some of the amide into the *cis* conformation to allow cyclisation. This problem has been overcome by using a one pot reaction involving silylation followed by cyclisation.[109] An example of this methodology is shown in the studies towards the synthesis of the alkaloid horsfiline. The amide **141** is treated with $LiN(TMS)_2$ followed by TMSCl to make the *N*-TMS derivative. The silylation is effective at forcing the amide into the conformation in which the alkene is *cis* to the aromatic ring, but is also sufficiently bulky to force 6-*endo* cyclisation to **143** as well as 5-*exo* cyclisation to the required oxindole **142** (**Scheme 39**). Zard *et al.*[110] have synthesised a range of oxindoles by use of a protocol with nickel powder in acetic acid as a reductant. α-Keto radicals are generated by nickel(0) reduction of α-halogenoanilides. The resulting α-keto radicals are electrophilic and cyclise onto the arene. Loss of an electron and a proton from the aromatic π-radical yields the oxindole.



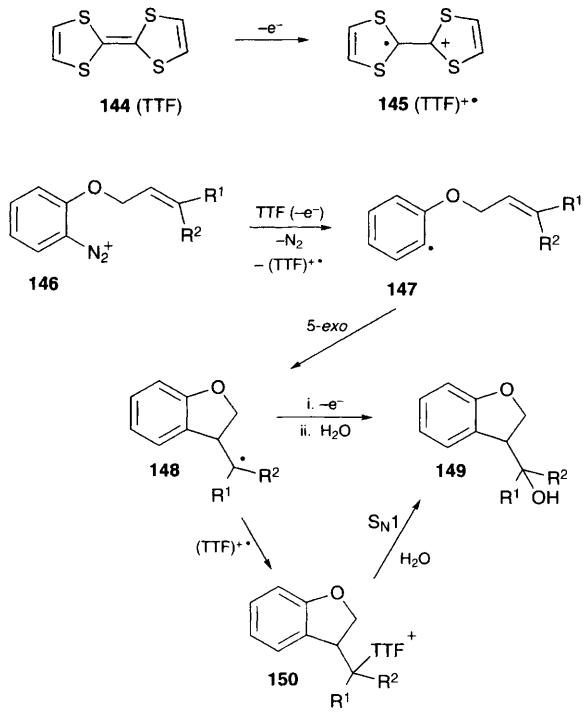
141 **142** **143**

Scheme 39

The synthesis of dihydrobenzofurans by cyclisation of aryl radicals onto side chain allyl ethers is well known. The aryl radicals are normally generated by Bu_3SnH reduction of the corresponding *o*-halogenophenyl allyl ether. An excellent illustration of the use of this protocol has been the synthesis of the *cis*-,*cis*-octahydrodibenzoisobenzofuran part of the morphine skeleton (**23**→**25**, **Scheme 5**).[11] Other methods for reducing the *o*-halogenophenyl allyl ethers in order to generate the aryl radicals include the use of a titanium complex-catalysed reduction by sodium borohydride in dimethylacetamide,[111] use of a nickel(II) complex to generate the aryl radical by electroreduction[103,112] and by use of cobalt(II) chloride and a Grignard reagent.[107]

However, the most novel new method has been developed by Murphy and co-workers[113] with the use of tetrathiafulvalene (TTF) **144** as an oxidant to generate an aryl radical. An example of the protocol is shown in the cyclisation of **146** (**Scheme 40**). The diazonium fluoroborate **146** is reduced by TTF to yield an intermediate aryldiazene radical which rapidly decomposes liberating nitrogen and generating the intermediate aryl radical **147**. The aryl radical undergoes 5-*exo* cyclisation to yield a cyclised radical **148** which can either be further oxidised by TTF to an intermediate cation or add to

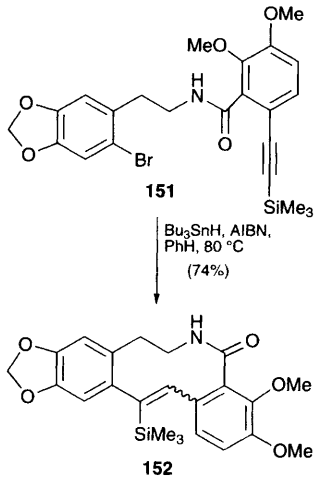
the TTF radical cation **145** to yield **150**. The intermediate cation adds water to give the alcohol **149**. S_N1 Substitution by water on the TTF adduct **150** also yields the alcohol **149**. The protocol is being further developed to use the intermediate cation for further synthetic manipulations, *i.e.* a tandem radical cyclisation followed by a cationic cyclisation.



Scheme 40

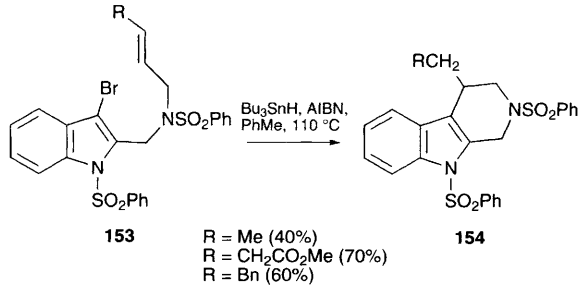
A method for the synthesis of chromans has been developed using Fe^{II}/Cu^{II} oxidation of 3-(4-methoxyphenyl)propyl hydroperoxide.[114] The alkoxyl radicals resulting from Fe^{II}/Cu^{II} oxidation undergo cyclisation onto the arenes to yield intermediate π-radicals. Loss of an electron and a proton from the aromatic π-radicals yield isomeric 6- and 7-methoxychromans.

Isoindolones have been prepared by flash vacuum pyrolysis of *O*-allyl salicylic alkylamides and alkyl esters.[115] The mechanism involves generation of the phenoxyl radical, regiospecific hydrogen atom transfer from the alkylamide and cyclisation. A novel synthesis of a benzo[*d*]indeno[1,2-*b*]azepine has been achieved using photolysis of a bromoaryl vinylogous amide.[116] A 3,6-epoxy-3,4,5,6-tetrahydro-2-benzoazocin-1(2*H*)-one has been synthesised *via* a β-scission from a photoadduct of acrylonitrile and a protected 4-hydroxyisoquinolin-1(2*H*)-one.[117] In studies towards the synthesis of the aporphoedane group of alkaloids, a ten-membered ring lactam **152** was obtained by intramolecular cyclisation of an aryl radical, generated from the bromobenzene **151**, onto a trimethylsilylalkyne group (**Scheme 41**).[118] This unusual large ring cyclisation tests the limits of ring size in radical cyclisations.



Scheme 41

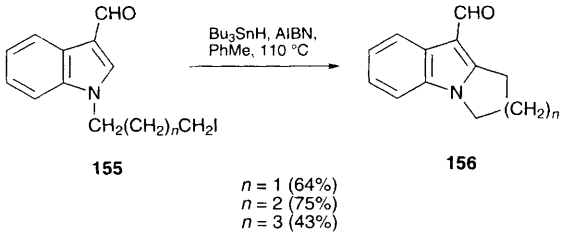
Cyclisation involving indole ring systems has proved a useful area.[119–121] Indol-3-yl radicals, generated from 3-bromoindoles **153** using Bu_3SnH, have been cyclised onto side chain alkenes on the indole 2-position to yield 4-substituted-1,2,3,4-tetrahydro-β-carbolines **154** in good yields (**Scheme 42**).[119] Two useful methods for cyclisation at the 2-position of indoles have been reported.[120] Firstly, *N*-alkenyl-2-bromoindoles have been used in cyclisation studies.[120a] The indol-2-yl radicals undergo 5-*exo* and 6-*exo* cyclisation to yield the corresponding cyclised indole derivatives. The 5-*exo* cyclisation is of interest because the tetrahydropyrrolo[1,2-*a*]indoles represent the same basic nucleus as in the mitosenes. Secondly, (*N*-bromo- and *N*-iodo-alkyl)indoles, substituted in the 2-position by benzenesulfenyl, benzenesulfinyl and tosyl groups, undergo *ipso* aromatic homolytic substitution to yield fused [1,2-*a*]indoles.[120b] The *N*-alkyl radicals cyclise onto the 2-position of the indoles to yield intermediate indole π-radicals which rearomatise with the expulsion of the benzenesulfenyl, benzenesulfinyl or tosyl groups. Five-, six- and seven-membered rings have been synthesised using this protocol.



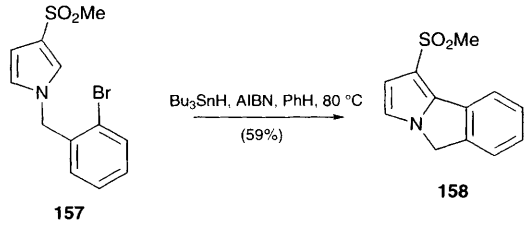
Scheme 42

These fused [1,2-*a*]indole ring skeletons have also been synthesised by an alternative route by cyclisa-

tion of 1-(ω-iodoalkyl)indole-3-carbaldehydes, *e.g.* **155**, by Moody and Norton.[121] A representative group of these reactions is shown in **Scheme 43** (**155** to **156**) but the protocol also tolerates a range of substituents (OMe, OBn) on the benzene ring. In this procedure the iodoalkylindoles are reacted with Bu_3SnH to generate alkyl radicals which cyclise onto the 2-position of the indole ring. These intermediate radicals are stabilised by the 3-carbaldehyde. The radicals are aromatised by an oxidative process which is discussed briefly in the paper. Good yields of 30–75% of the tricyclic indole-3-carbaldehydes are obtained. Cyclisations of 1-(ω-iodoalkyl)indole-3-carboxaldehydes, and analogues with other electron withdrawing substituents in the 3-position have also been carried out using Fe^{II}/H_2O_2 in DMSO as an oxidant.[122] Sonication is required to oxidise the iodoalkyl groups to radicals for cyclisation. The oxidation generates hydroxyl radicals which react with the DMSO to generate methyl radicals which then abstract the iodine from the iodoalkyl groups. This oxidative protocol was also used for carrying out cyclisations on 1-(ω-bromoalkyl)pyrrole rings substituted in the 2- or 3-positions with electron withdrawing groups. The same cyclisations of 1-(ω-bromoalkyl)- and 1-(2-bromophenyl)-pyrroles, substituted in the 2- or 3-positions, were also carried out using Bu_3SnH to yield bicyclic and tricyclic pyrrole derivatives, *e.g.* **157** to **158** (**Scheme 44**).[123] The authors also propose an oxidative mechanism to explain the apparent oxidation during the Bu_3SnH mediated cyclisations.

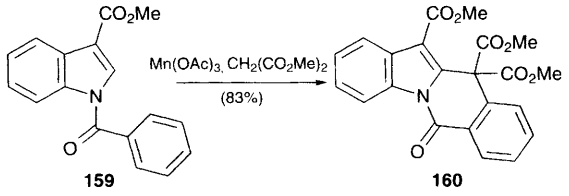


Scheme 43



Scheme 44

Indolo[2,3-*a*]isoquinolones have been prepared by $Mn(OAc)_3$ oxidative addition of dimethyl malonate radicals across the C-2 position of indole with electron withdrawing groups at C-3 and the *ortho*-position of N-benzoyl substituents.[124] A typical example, *e.g.* 159, with an indole-3-methoxycarbonyl substituent cyclises onto the *N*-benzoyl group in 83% yield (**Scheme 45**). The range of examples of this protocol include indoles with nitrile and ketone substituents in the 3-position as well as *para*-substituents on the benzoyl ring (methyl, phenyl and methoxy).

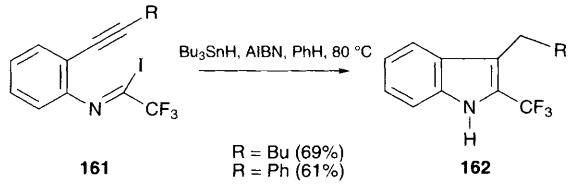


Scheme 45

Benzo-fused six- and seven-membered ring sulfones have been synthesised by Simpkins *et al.* by cyclisation of aryl radicals derived from *o*-bromophenyl sulfones onto side chain alkenes, *e.g.* **131** to **132** (**Scheme 35**).[92]

10 Heteroarenes

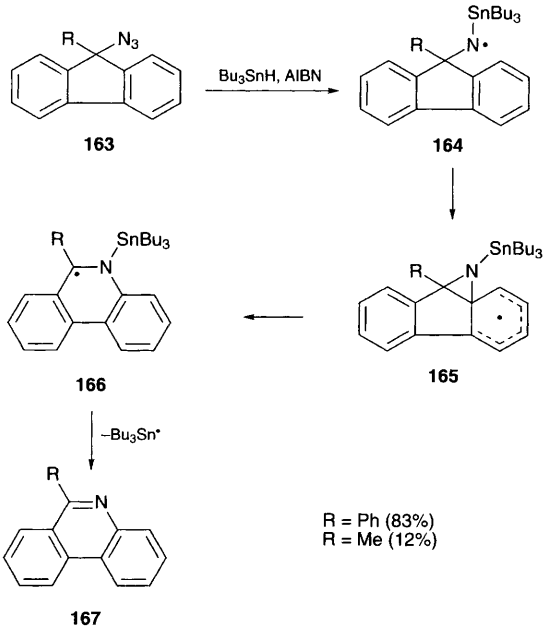
The synthesis of heteroarenes has been carried out by a variety of different reactions. The first group of syntheses uses the normal Bu_3SnH methodology.[125] For example, 2-(trifluoromethyl)indoles (*e.g.* **162**) have been synthesised from α-iodoimines (*e.g.* **161**) *via* intermediate *N*-aryltrifluoroacetimidoyl radicals using Bu_3SnH to generate the radicals (**Scheme 46**).



Scheme 46

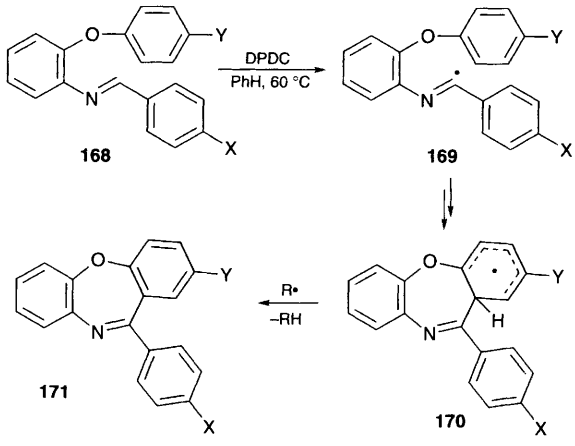
Generation of radicals by abstraction of iodine with tributyltin radicals from 2-alkylidenamino-2′-iodobiphenyls yields mainly 5-*exo* cyclisation onto the nitrogen of the imine to yield 9-substituted carbazoles.[126] Small amounts of 2-substituted phenanthridines deriving from a minor route *via* 6-*endo* cyclisation onto the carbon atom of the imine were also isolated. 2-Substituted phenanthridines **167** have been synthesised from 9-azido carbazoles **163** by 1,2-aryl migration (**Scheme 47**).[127] The ratio of 2-substituted phenanthridines to unrearranged 9-(tributylstannylamino)carbazoles depends on the nature of the 9-substituent. When

the substituent is phenyl the main product is 2-phenylphenanthridine, whereas when the substituent is methyl the main product is the unrearranged 9-methyl-9-(tributylstannylamino)carbazole. The tributyltin radicals add onto the azide generating intermediate aminyl radicals **164** which either are reduced or undergo 1,2-aryl migration to **166** *via* **165**. Elimination of tributyltin radicals from 166 yields the phenanthridine product **167**.



Scheme 47

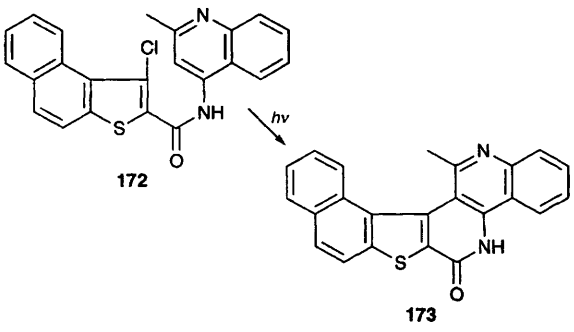
Unusual heteroarenes have been generated by heating a variety of substrates in the presence of radical initiators. The reaction between 4-methoxyphenyl isocyanide, phenylethyne and AIBN produces a novel cyclopenta-fused quinoxaline *via* addition of the 2-cyanopropyl radical onto the phenylethyne. The overall process is an example of a [4+1] radical annulation.[128] The use of isonitriles has been particularly well applied in Curran's studies on the synthesis of camptothecin (**40** to **44**, **Scheme 10**).[3,16] Oxidation of 5-amino-3-anilinopyrazoles with dibenzoyl peroxide give products with a novel ring system, pyrazolo[1,5-*a*]benzoimidazole, *via* radical cyclisation of the pyrazole radical on the *N*-1 position.[129] Dibenzooxazepines **171** have been synthesised from *o*-phenoxyaniline imines **168** *via* intermediate α-iminyl radicals **169** obtained by hydrogen abstraction with DPDC (diisopropyl peroxydicarbonate).[130] The intermediate iminyl radical either undergoes 7-*endo* cyclisation onto the phenoxy ring to yield the intermediate radical **170** directly, or undergoes a 6-*exo* cyclisation to a spirocyclohexadienyl radical which rearranges to **170** (**Scheme 48**). The process involves a novel 1,5-aryl radical translocation from an oxygen to a carbon atom. The cyclisations also proceed with chloro and methoxy groups on *para*-positions of the phenyl rings.



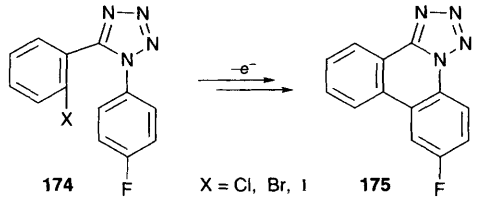
DPDC = diisopropyl peroxydicarbonate

Scheme 48

Photolysis remains a technique for radical cyclisation of heteroarenes, although less regioselective than the use of more modern radical generating reagents such as Bu_3SnH. Photolyses of 'linked' aryl (heteroaryl) rings can undergo a well known formation of biaryls (biheteroaryls). Several examples have been recently reported. For example, *N*-(2-halogenobenzyl)anilines and *N*-benzyl-2-halogenoanilines have been photolysed to yield phenanthridines as the major products.[131] An example of these photolytic coupling reactions is shown for the photolytic coupling of the naphtho[2,1-*b*]thiophene derivative **172**, which yields the polynuclear heteroarene **173** (**Scheme 49**).[132] A similar photolytic cyclisation has been reported for a related thiophene analogue.[133] Biphenyl bond formation has also been achieved by electrochemically induced radical cyclisation of 1,5-diaryltetrazoles **174** to form the corresponding tetracylic tetrazole derivatives **175** (**Scheme 50**).[134] The electrochemical reduction of the halogenoarenes **174** yields intermediate aryl radicals which result from dissociation of the initially formed aryl radical anions. The aryl radicals then undergo 6-*endo* cyclisation onto the other arene ring to yield cyclised π-aromatic radicals which after hydrogen abstraction loss yields 175.



Scheme 49



Scheme 50

Other methods for generating radicals for the synthesis of heteroarenes includes FVP (flash vacuum pyrolysis). Two papers report the syntheses of benzothiophenes and benzofurans from β-oxophosphorus ylides using FVP at 850 °C.[135]

11 Reagents for radical cyclisation

The purpose of this section is to provide an overview of methods reported recently in the literature which are potentially useful for the synthesis of heterocycles by radical cyclisation. As stated in the introduction the majority of radical cyclisations in heterocyclic chemistry have been carried out using Bu_3SnH. In many reactions, tris(trimethylsilyl)silane [$(TMS)_3SiH$] has a number of advantages over Bu_3SnH but is considerably more expensive. In several instances different reaction routes are observed. For example, the protocol of Kim and co-workers[7] (**2**→**5**) involves the addition of tributylstannyl radicals to azides with loss of nitrogen to yield intermediate aminyl radical[21] but reaction with $(TMS)_3SiH$ gives addition to ketones in preference to azides with different results. Bu_3SnH may be generated *in situ* by reduction of Bu_3SnCl with $NaBH_4$ or $NaCNBH_3$ in order to keep the concentration of tributyltin radicals low and also to diminish the problems of separating tributyltin residues in the work-up, *e.g.* the syntheses of the skeleton of models of the *Pseudocopsinine* and *Aspidosperma* alkaloids by Parsons *et al.* (**14** to **15**, **Scheme 3**).[9]

The use of SmI_2 has become popular as an alternative to Bu_3SnH. For example, this reductive method has been applied to the synthesis of proline analogues by Baldwin *et al.*,[37] (**76** to **77**, **Scheme 19**), and nucleoside antibiotics miharamycins A and B (**123** to **124**, **Scheme 32**).[82] However, **a note of warning is required**, although several papers report that it is non-toxic, natural samarium contains two radioactive isotopes, ^{147}Sm (15.1%) and ^{148}Sm (11.3%), both of which are weak alpha emitters. Pure samarium is just above the legal limit in the UK for use in a normal laboratory but SmI_2 will be below. Nevertheless, extra safety precautions should be taken for work with radioisotopes and ingestion or inhalation must be avoided. The use of Ni powder by Zard *et al.* shows promise as a reductant for the generation of radicals.[110] Ni^{II} complexes along with anodic reduction have also been used.[103,112]

The use of cobalt(II) salophen complexes has been successfully developed by Pattenden *et al.*,[44] *e.g.* to facilitate 4-*exo* cyclisation in β-lactam synthesis (**78** to **86**, **Schemes 20** and **21**). The method has also been used for oxindole[107] and tetrahydrofuran syntheses.[62]

Photosensitised electron transfer (PET)[51,52] provides a protocol in which electrons are generated from a tertiary amine in the presence of a photosensitiser, *e.g.* anthraquinone or 1,2-dicyanonaphthalene, for the synthesis of pyrrolizidine alkaloid, (−)-retronecanol,[51] and pyrrolizidines, indolizidines and spirobicyclic amines.[52]

Atom transfer methods have shown promise, *e.g.* copper(I)-catalysed chlorine atom transfer in the synthesis of proline derivatives by Speckamp *et al.*[26,65] Iodine atom transfer, initiated by use of a radical initiator such as AIBN or $(Bu_3Sn)_2$, has been used for the synthesis of the antibiotic methylenolactocin (**111** to **114**, **Scheme 28**),[65] α-alkylidine-γ-butyrolactone derivatives[66] and dioxatriquinanes and doubly annulated glycosides.[67] A similar method has been achieved by addition of compounds with labile bonds, *e.g.* diphenyl diselenide,[69,70] diphenylphosphine,[69] benzenethiol[71] and tosyl iodides, bromides, chlorides and selenides[69,70,72] to 1,6-dialkenes for the synthesis of tetrahydrofurans (*e.g.* **115** to **118**, **Scheme 29**) and pyrrolidines.

Lastly, a method with considerable promise has been developed by Murphy *et al.*[113] with the use of tetrathiafulvalene (TTF) as an oxidant to generate aryl radicals from arenediazonium fluoborates which has been used for the synthesis of benzofurans (**144** to **150**, **Scheme 40**). The protocol is being further developed to tandem radical cyclisations followed by cationic cyclisations.

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