Synthesis of heterocycles by radical cyclisation

W. Russell Bowman,* Martin O. Cloonan and Sussie L. Krintel

Department of Chemistry, Loughborough University, Loughborough, Leics, UK LE11 3TU

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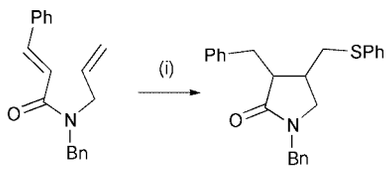
1 Introduction

Radical cyclisation for the synthesis of heterocycles is now a well established and commonly used methodology. Many new protocols are being developed to synthesise the wide range of novel natural products which are of interest to organic chemists. The majority of radical cyclisations in heterocyclic chemistry are still carried out using tributyltin hydride (Bu_3SnH) but other radical generating procedures are becoming more common. Bu_3SnH mediated reactions are well known and therefore the mechanisms will not be discussed in detail. In Section 13 at the end of the review the different reagents and methods for generating the radicals are discussed. Photochemical reactions not proceeding by chain reactions, *e.g.* by photochemical generation of biradicals, have been excluded.

The review has not been divided on the basis of ring size because most radical cyclisations used for the syntheses of heterocycles proceed by 5-*exo*-*trig* regioselectivity. The review has excluded heterocyclic syntheses in which the heterocyclic ring(s) are not part of the radical cyclisation. Therefore, carbocyclic cyclisations in molecules which contain a heterocycle are not included. Stereoselective synthesis of heterocycles and synthesis of macrocycles have become increasingly important and are discussed in Sections 11 and 12.

A number of reviews which include the synthesis of heterocycles *via* radical cyclisation have been published. The use of samarium diiodide for ring expansions and cyclisation reactions has been reviewed.[1] A review on heteroatom radical addition–cyclisation and its synthetic applications contains mainly heterocyclic examples, *e.g.* the conversion of radical precursor **1** into pyrrolidinone **2** (Scheme 1).[2] An extensive review covers the use of radicals for the synthesis of medium sized rings.[3] A review of the use of furanoses as 'off-template' sites for the stereoselective radical synthesis of annulated furanoses provides a good example of the use of carbohydrates in radical chemistry.[4] Photoinduced electron transfer (PET) decarboxyltaion of alkanecarboxylates in water has been reviewed.[5] The protocol leads to primary, secondary or tertiary carbon radicals



1 **2**

Scheme 1 *Reagents and conditions*: i, *hv*, PhSH, PhSSPh, 71% (*cis* : *trans* = 1 : 1).

which undergo C–C bond coupling reactions in either an intra- or intermolecular fashion. Intramolecular reactions give rise to heterocyclic ring systems (*e.g.* lactams, lactones, cyclopeptides, cyclic ethers and crown ethers) with ring sizes from 5 to 28 and a broad range of functionalities.

2 Natural product synthesis

The challenge of complex natural product synthesis has continued to attract ingenuity of design using radical cyclisations. The use of radicals in natural product synthesis allows complex ring systems to be put together without much functional group protection or problems of racemisation. These advantages, along with the use of one-pot cascade reactions, facilitate syntheses which avoid time consuming multi-step protocols. Radical reactions are also increasingly used to facilitate stereoselective cyclisations. In this section a number of examples of syntheses are presented and others are detailed in later sections defined by the heterocyclic rings.

Zard and co-workers have continued to exploit their methodology which avoids the use of toxic triorganotin hydrides by using thioxanthates as radical precursors. In this example of the protocol, the total synthesis of (±)-cinnamolide and (±)-methylenolactocin **7** have been achieved using irradiation with visible light of *S*-alkoxycarbonyl xanthates which give rise to alkoxycarbonyl radicals which undergo intramolecular addition to double bonds to produce lactones.[6] The protocol is exemplified in Scheme 2 for the preparation of the γ-lactone **6** in the synthesis of (±)-methylenolactocin **7**. The strength of this protocol depends on the reversible and degenerate step which involves the equilibrium between the starting material **3** and the intermediate acyl radical **4**, *i.e.* the intermediate radical either goes back to starting material or cyclises because there is no Bu_3SnH to trap the intermediate radical by reduction. Therefore, this chain transfer reaction does not compete with the synthetically useful cyclisation step. The chain reaction is completed by the cyclised radical **5** abstracting the thioxanthate group from the starting precursor **3** to regenerate the intermediate **4**. Another example of this protocol uses xanthate derivatives of hydrazides to generate amidyl radicals in the synthesis of (±)-γ-lycorane.[7] The synthesis of (−)-dendrobine has also been achieved by cyclising amidyl (urethanyl) radicals in the key step of the synthesis.[8] In this case the urethanyl radicals were generated from *O*-benzoyl-*N*-hydroxyurethanes using Bu_3SnH.

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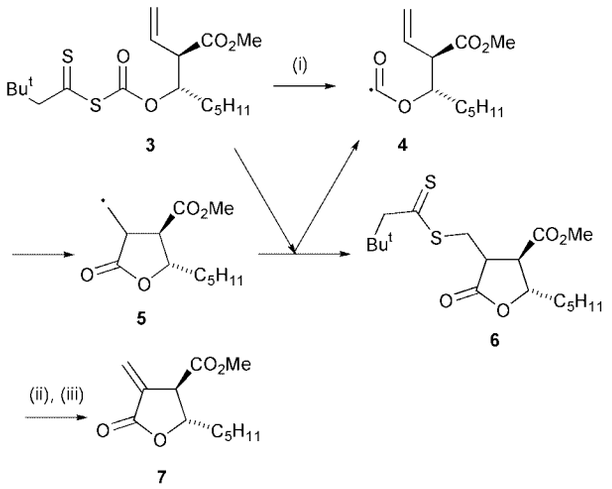
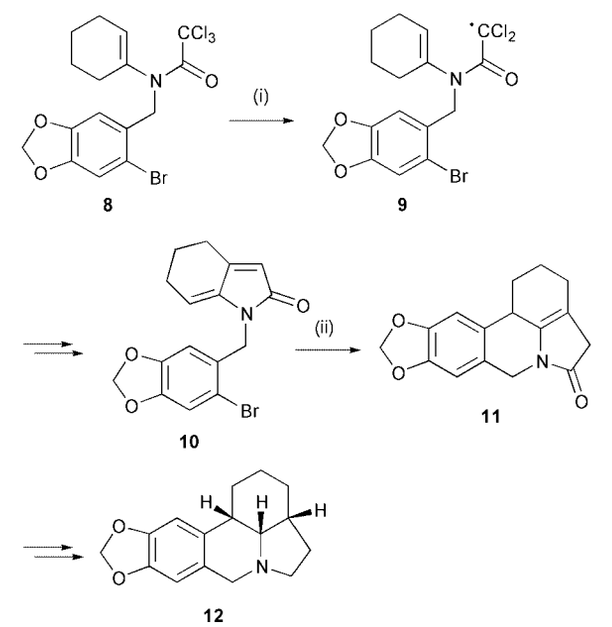


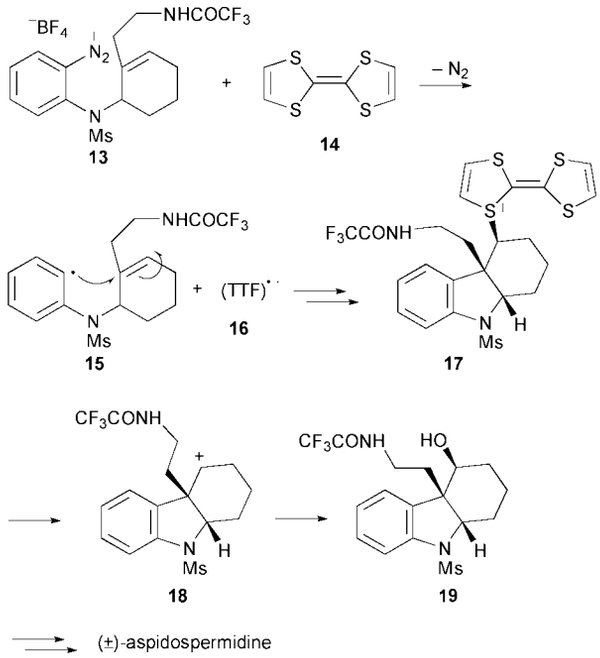
Scheme 2 *Reagents and conditions*: i, *hv*, toluene, reflux 63%; ii, Cu, heat, distillation, 62%; iii, HCl, butanone, reflux, 73%.

(±)-γ-Lycorane **12** has also been synthesised by Zard using two successive radical cyclisations (Scheme 3).[9] The first cyclisation uses nickel to generate α-amidyl radicals **9** from the precursor **8** to yield the synthetic intermediate **10**. The second cyclisation (**10** to **11**) uses the traditional Bu_3SnH for 6-*exo* cyclisation of an aryl radical onto an alkene. Another synthesis of (±)-γ-lycorane **12** has been reported using an initial aminyl radical cyclisation followed by cyclisation of an aryl radical onto the resulting indolizidine moiety.[10]



Scheme 3 *Reagents and conditions*: i, Ni, NaOAc, propan-2-ol, reflux 60%; ii, Bu_3SnH, 1,1′-azobis(cyclohexanecarbonitrile), toluene, reflux, 65%.

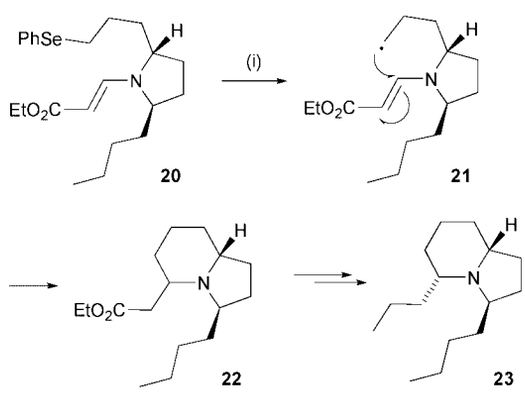
Cyclisation of an aryl radical onto an alkene to form an intermediate indoline has been reported in the total synthesis of (±)-aspidospermidine.[11] Murphy and co-workers have applied their tetrathiafulvalene (TTF)-induced radical–polar crossover protocol to promote the aryl radical cyclisation (Scheme 4). TTF **14** acts as an electron donor to the diazonium radical precursor **13** which generates the TTF radical cation **16** and the aryl radical **15** by loss of nitrogen gas. This procedure for generating aryl radicals has the advantage of avoiding the use of toxic triorganotin hydrides. Radical **15** undergoes cyclisation and the cyclised radical adds on the TTF radical cation to give **17**. The radical–polar crossover comes into play leading to S_N1 substitution by water *via* a cation **18** to yield **19**, a synthetic



Scheme 4 *Reagents and conditions*: tetrathiafulvalene **14** (TTF), moist acetone.

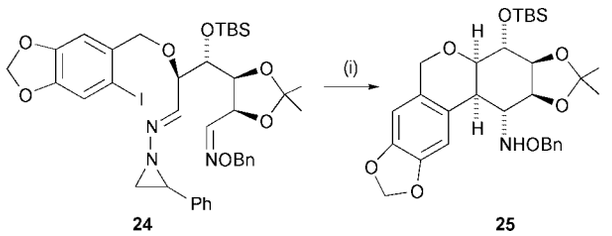
intermediate used for further elaboration for the synthesis of (±)-aspidospermidine.

A good example of the cyclisation of alkyl radicals in natural product synthesis is shown in Scheme 5 for the synthesis of (−)-indolizidine 223AB **23** from a *trans*-2,5-disubstituted pyrrolidine precursor **20**.[12] The rate of the 6-*exo*-cyclisation is enhanced by the cyclisation of a nucleophilic alkyl radical **21** onto the electrophilic β-position of an α,β-unsaturated ester to yield the indolizidine synthetic intermediate **22**.



Scheme 5 *Reagents and conditions*: i, Bu_3SnH, AIBN, benzene, reflux, two diastereomers: 58% and 13%.

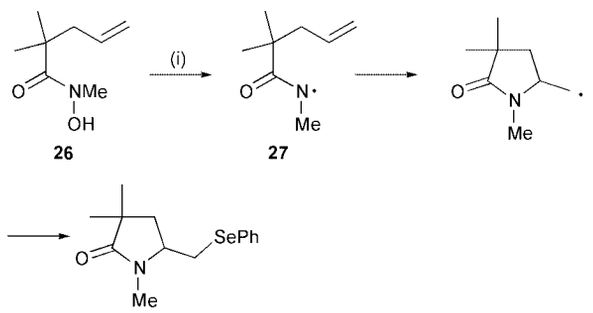
A Ph_3SnH-mediated radical cyclisation is used as a key step in the synthesis of the naturally occurring alkaloid (+)-7-deoxypancratistatin (Scheme 6).[13] The synthesis uses the protocol developed by Kim in which an aryl radical cyclises onto the imine bond of an arizidinyl hydrazone to yield a radical intermediate which breaks down to yield a new *C*-centred radical which can cyclise again. In this example the radical cyclises again onto an imine bond (oxime ether). The precursor **24** undergoes a cascade reaction to give the key synthetic intermediate **25** by two successive cyclisations onto imine moieties. 2,4-Dinitrophenyl oxime ethers have also been used to generate iminyl radicals by a single electron transfer procedure.[14] The iminyl radicals undergo 5-*exo* cyclisations onto alkenes. The protocol has been used for the synthesis of the pyrrolizidine xenovenine.



Scheme 6 *Reagents and conditions*: i, Ph_3SnH, AIBN, benzene, reflux, loss of N_2 and styrene, 78%.

3 Nitrogen heterocycles

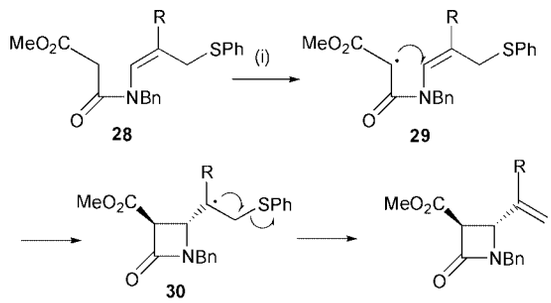
The synthesis of nitrogen heterocycles using radical cyclisation, especially the synthesis of pyrrolidines using 5-*exo* cyclisation, is one of the most common uses of radicals. The radical can be generated in various positions relative to the *N*-heteroatom. The use of aminyl radicals is an obvious application and a novel protocol uses amidyl radicals generated from *N*-sulfonyl amides which are synthesised *in situ* from *N*-hydroxy amides.[15] An example is shown in Scheme 7. The *N*-sulfonyl amide, generated *in situ* from the *N*-hydroxy amide **26**, decomposes on warming from −50 °C to generate the amidyl radical **27** which undergoes 5-*exo* cyclisation. The cyclised radicals are trapped with diphenyl diselenide or disulfide and TEMPO. A range of monocyclic and bicyclic nitrogen heterocycles have been synthesised using this protocol. Amidyl radicals have also been generated by reaction between Bu_3SnH and *O*-benzoyl hydroxamic acid derivatives and undergo 5-*exo* cyclisation to give mixtures of *cis* and *trans* *N*-acyl pyrrolidinones in 60–70% yield (de = 54–74%).[16] Aminyl radicals have been generated from *N*-chloramines using Bu_3SnH and undergo 5-*exo* cyclisation to yield *trans* 1,5-disubstituted pyrrolidines.[17] A combined theoretical (high level molecular orbital study) and experimental study of the cyclisation of *N*-methyl *N*-penten-5-yl radicals has been published.[18] In the experimental studies, the aminyl radicals are generated from sulfenamides using Bu_3SnH. The evidence presented in the paper indicates that cyclisation of aminyl radicals is irreversible which is at odds with other reports in the literature which indicate reversibility.



Scheme 7 *Reagents and conditions*: i, *tert*-$BuSO_2Cl$, $(PhSe)_2$, diisopropyl(ethyl)amine, CH_2Cl_2, −50 °C to rt, 64%.

Iminyl radicals have been generated by several routes and cyclised to give a range of monocyclic 5-membered nitrogen rings.[19] Irradiation of ketoxime *O*-(*S*-methyl)xanthates containing γ,δ-double bonds leads to dihydropyrroles through cyclisation of an intermediate iminyl radical in a radical chain reaction.[19] The last propagation step involves transfer of a dithiocarbonate group. The protocol has also been used for bicyclic nitrogen heterocycles. Generation of iminyl radicals from *N*-acyl oximes using nickel powder in conjunction with a weak carboxylic acid provides another methodology for cyclising iminyl radicals.[20] This protocol has also been applied to bicyclic and polycyclic nitrogen heterocycles. Iminyl radicals have also been generated from β-allenylbenzoyl oximes using Bu_3SnH as the radical reagent to synthesise dihydropyridines, 3*H*-pyrroles and alkylidenepyrrolines.[21]

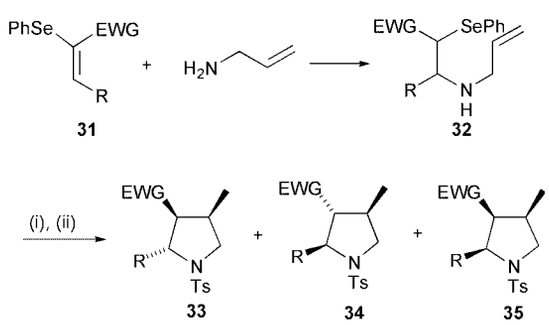
Synthesis of β-lactams is unfavourable and can only be achieved using radical cyclisation if the method has some factor in the mechanism to favour 4-membered ring cyclisation, *e.g.* formation of a very stable cyclised radical or subsequent fragmentation. Oxidation of β-ketoamides with $Mn(OAc)_3$ has been used to synthesise β-lactams, *e.g.* Scheme 8.[22,23] In this protocol, the cyclisation is driven by elimination of phenylsulfanyl radicals from the cyclised radical **30**. β-Dicarbonyl compounds (*e.g.* **28**) are readily oxidised by Mn(III) to carbinyl radicals centred (*e.g.* **29**) on the carbon atom between the two carbonyl groups and in this case undergo 4-*exo*-*trig* radical cyclisation. The effects on the reaction course of different substituents both on amide nitrogen atom or double bond, were analysed. The overall reaction was stereoselective, leading to *trans*-azetidinones.



Scheme 8 *Reagents and conditions*: i, $Mn(OAc)_3$ (1 equiv.), AcOH, 70 °C, 30 min, 36–58%, R = H, Me, Ph.

Pyrrolidines can also be synthesised by cyclisation of radicals α to the *N*-heteroatom. A range of pyrrolidines have been prepared by samarium diiodide mediated 5-*exo* radical cyclisation of α-amino radicals generated from *N*-(α-benzotriazolylalkyl)alkenylamines.[24] The alkene can be unsubstituted but the reaction gives better yields with electron withdrawing substituents.

A large number of radical reactions using cyclisation of radicals, β to the nitrogen atom, onto alkenes have been used for the synthesis of a wide range of pyrrolidines. For instance, a useful synthetic procedure uses Michael addition of allyl- or propargyl-amines to α-phenylselanyl-α,β-unsaturated-esters, -amines, -ketones, -nitriles and -sulfones **31** to yield precursors **32** in which the phenylselanyl group is abstracted by tris-(trimethylsilyl)silane [$(TMS)_3SiH$] with triethylborane (Et_3B) as initiator.[25] The resulting radicals undergo 5-*exo* cyclisation reactions to give the corresponding pyrrolidine or dihydropyrrole derivatives which are isolated as the tosylates (Scheme 9). A mixture of diastereomers **33** and **34** are formed but the all-*cis* diastereomers **35** were not formed in the procedure. In a related study, *N*-allyl-β-aminoalkyl phenyl selenides were used as precursors of 3-azahex-5-enyl radicals.[26] The effect of various *N*-protective groups on diastereoselectivity were studied in these cyclisations. *N*-Unprotected derivatives afforded predominantly *trans*-2,4-disubstituted pyrrolidines, whereas *N*-protection with

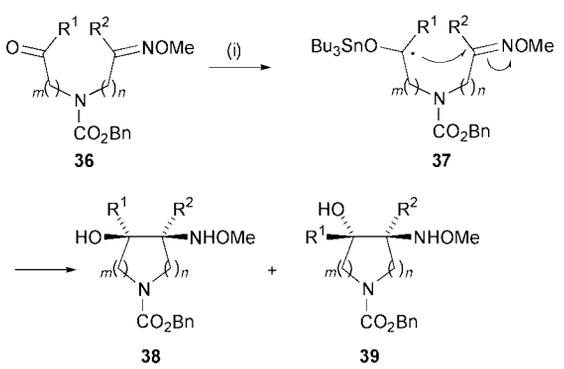


Scheme 9 *Reagents and conditions*: i, $(TMS)_3SiH$, Et_3B, O_2, toluene; ii, tosyl chloride, Et_3N, two diastereomers, 36–89%.

the diphenylphosphinyl group gave cyclisation in a highly *cis*-selective manner.

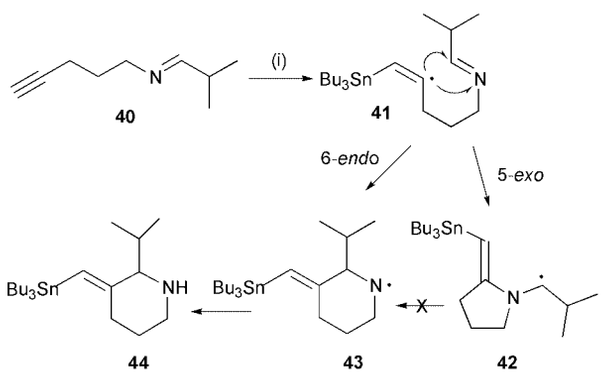
β-Alkenyl radicals, generated from alkenyl iodides using Bu_3SnH and AIBN, also undergo 5- and 6-*exo-dig* cyclisation onto alkynes to give five- and six-membered rings with exocyclic dienes in good yields.[27] A new approach to the synthesis of 3,3-difluoro proline methyl esters and methyl α-aminoadipates uses cyclisation of difluoroalkyl radicals in the β-position of α-amino esters onto alkenes β to the amino group.[28] New reagents have been used in several of these cyclisations to synthesise pyrrolidines, *e.g.* ferrocenium hexafluorophosphate as a SET oxidant[29] and an activated manganese species derived from Li_2MnCl_4.[30]

Cyclisation of radicals onto unsaturated groups other than alkenes is playing an increasing role in the synthesis of pyrrolidines. For instance, cyclisation of radicals β or γ to the nitrogen atom onto oxime ethers has been well explored.[31–34] A useful example is shown in Scheme 10 in which $Bu_3Sn^{\bullet}$ radicals are added to aldehyde or ketone substrates **36** and the resulting radicals **37** cyclised onto oximes.[31] The *trans* diastereomer **39** is predominant over the *cis* isomer **38** and this is explained by instability of the *cis*-transition state due to steric hindrance. The protocol has been used for the synthesis of 5-, 6- and 7-membered nitrogen heterocycles with hydroxy and amino substituents. The protocol has also been extended to cyclisation of oxime ethers or α,β-unsaturated oxime ethers connected by a tether to α,β-unsaturated aldehydes or ketones and provides a new entry to the adjacently functionalised pyrrolidines.[34] This procedure has also been adapted for solid phase synthesis[34] and SmI_2 has been used in place of Bu_3SnH.[35] The use of cyclisation of radicals generated γ to the nitrogen atom has also been applied to 5-*exo* addition onto the β-position of α,β-unsaturated esters in a stereoselective SmI_2 mediated synthesis of *trans*-2-oxohexahydro-2*H*-furo[3,2-*b*]pyrrole, a novel elastase inhibitor.[36]



Scheme 10 *Reagents and conditions*: i, Bu_3SnH, AIBN, benzene, reflux, 38–71%.

Another example of *endo* cyclisation has been reported in the cyclisation of alkenyl radicals onto imines (Scheme 11).[37] $Bu_3Sn^{\bullet}$ radicals are added to the terminal alkyne **40** to generate

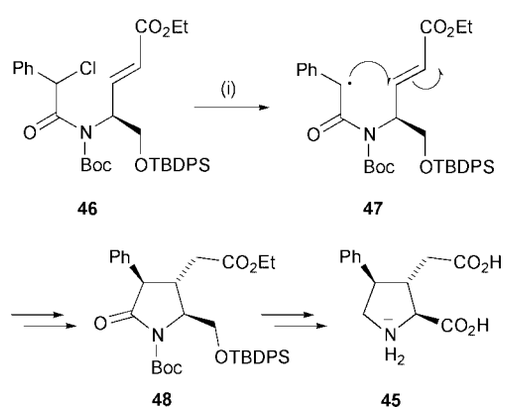


Scheme 11 *Reagents and conditions*: i, Bu_3SnH, AIBN, benzene, reflux, 27–43%.

the alkenyl radical **41** which undergoes 6-*endo* cyclisation to **43** rather than 5-*exo* cyclisation to **42**. Rearrangement of **42** to **43** is possible but was ruled out in the study and only **44** was isolated as a cyclised product. Reaction using $(TMS)_3SiH$ gave only 6-*endo* cyclisation and no uncyclised reduced material. The same regioselectivity was observed when the alkenyl radical was generated from the corresponding alkenyl iodide. The regioselectivity of 6-*endo* over 5-*exo* cyclisation for alkenyl radicals is the same as observed for aryl radicals but opposite to that observed for alkyl and acyl[38] radicals.

The synthesis of γ-lactams (pyrrolidin-2-ones) is particularly well suited to radical cyclisation.[38–47] The cyclising radical has been generated in each position relative to the nitrogen atom. Amidyl radicals generated from *O*-benzoyl hydroxamic acid precursors using Bu_3SnH undergo 5-*exo* cyclisation onto alkenes to give mixtures of *cis* and *trans* pyrrolidin-2-ones.[39] Yields varied from 22–82% with diastereomeric excesses of 10 to 43%. The diastereoselectivity of reaction caused by substituents in various positions followed the Beckwith rules. Radicals (carbamoyl) have also been generated on acyl groups (carbamoyl) for the synthesis of γ-lactams.[40] Carbamoyl radicals generated from reaction between phenylselenocarbamates and $(TMS)_3SiH$ undergo 5-*exo* cyclisation onto alkenes in 31–68% yield. Bicyclic nitrogen heterocycles were also synthesised when cyclisations onto cyclic alkenes were undertaken. Kinetic studies indicate that the rate constant exceeded 1×10^8 s^{-1} in several cases. Carbonyl radicals, generated by addition of carbon monoxide under 80 atm pressure to alkyl radicals, undergo 5-*exo* cyclisation onto the N-atom of imines to yield *N*-alkyl pyrrolidin-2-ones.[38]

5-*exo* Cyclisations of radicals β to the nitrogen atom, *i.e.* α to the amide carbonyl group (α-amide radicals), onto alkenes have been used for the synthesis of a wide range of pyrrolidin-2-ones. A good example of this methodology is shown in Scheme 12 for the synthesis of the biologically active phenyl allokainic acid analogue **45**.[41] The starting precursor **46** was readily prepared by *N*-acylation and Bu_3SnH mediated cyclisation gave an intermediate radical **47** α to the amide carbonyl group which cyclised onto the α,β-unsaturated ester to yield three diastereomers. The predominant stereochemistry contained a *trans*-(C-3, C-4) isomer, consistent with a reversible cyclisation which results from using a stabilised radical **47**. The major diastereomer **48** was converted through to the target allokainic acid analogue **45**. The protocol is reported in detail for 5-*exo-trig* cyclisation of a variety of secondary haloamides to yield a wider range of kainic acid analogues.[42]



Scheme 12 *Reagents and conditions*: i, Bu_3SnH, AIBN, toluene, reflux, 79%, dr 8.9 : 3.5 : 1.

Pyrrolidin-2-ones have also been synthesised from the same precursors using dimanganese decacarbonyl $[Mn_2(CO)_{10}]$ and light catalysis to facilitate iodine- or bromine-atom transfer cyclisations.[43] Other methods of generating α amide radicals for the synthesis of pyrrolidin-2-ones include use of the radical

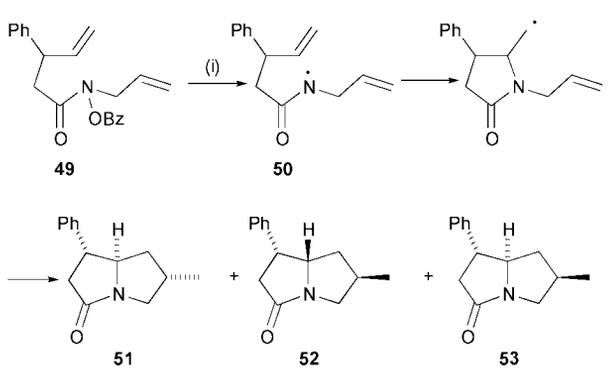
initiators 4,4′-azo(4-cyanopentanoic acid) and 2,2′-azo(2-methylpropanamidine) dihydrochloride in water[44] and photolysis of PTOC [*N*-(pyridine-2-thio)oxycarbonyl] derivatives.[45] The development of the use of Cu(I) derivatives by Clark and co-workers has provided a useful new methodology for radical cyclisation without using the toxic Bu_3SnH.[46] The reagents facilitate iodine atom transfer and have been thoroughly investigated for the synthesis of pyrrolidin-2-ones. The ligands used for complexing the copper include bipyridine, pyridinemethanimines and tris(*N*,*N*-dimethylaminoethylene)amine (trien-Me_6). The pyridinemethanimines have also been attached to solid phase supports to facilitate catalysis in which the Cu(I) is bound to the solid support.[47]

The addition of a radical generating reagent A–B across two alkenyl groups β to a nitrogen moiety continues to be a common synthetic protocol. For example, addition of $PhSO_2Br$ under sunlamp irradiation to diene and enyne esters promotes γ-lactam formation.[48]

4 Pyrrolizidines and other bicyclic nitrogen heterocycles

Pyrrolizidines and indolizidines remain common targets for radical cyclisation reactions but a much wider range of bi- and poly-cyclic nitrogen heterocycles are now also targets for synthesis. We have attempted to discuss both protocols and synthetic targets in this section. One of the factors which aids radical synthesis of polycyclic nitrogen heterocycles is the ability to attach by *N*-alkylation, either a chain containing the group for generating the radical, or a chain containing the unsaturated functionality onto which the radical intermediate will cyclise. Alternatively both chains, *i.e.* one containing the group for generating the radical and a chain containing the unsaturated functionality onto which the radical intermediate will cyclise, are added to a central nitrogen atom. These alkylation reactions of nitrogen atoms provide fast and facile routes into the syntheses of complex nitrogen heterocyclic targets.

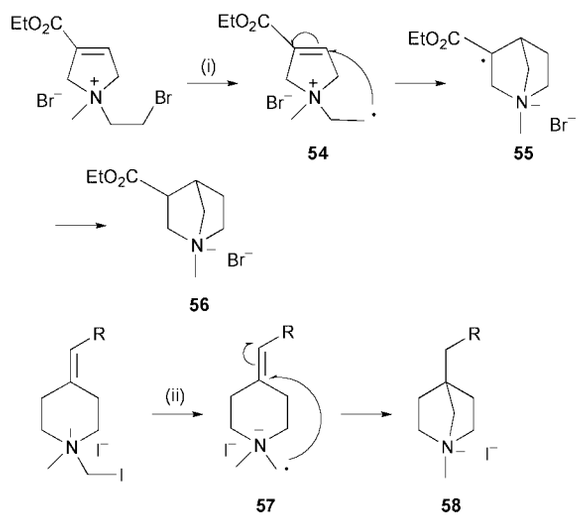
The use of *N*-centred radicals is an obvious starting point for the synthesis of polycyclic nitrogen heterocycles. Amidyl radicals, generated from *O*-benzoylhydroxamic acid derivatives using Bu_3SnH, have been used to synthesise pyrrolizidines and other bicyclic nitrogen heterocycles (Scheme 13).[49] The precursor **49** was synthesised by *N*-acylation and reacted with Bu_3SnH to generate an intermediate amidyl radical **50** which undergoes two 5-*exo* cyclisations to yield a mixture of diastereomeric pyrrolizidines **51**–**53**. A similar synthesis of pyrrolizidines has been reported using tandem cyclisation with aminyl radicals generated from *N*-chloramines with Bu_3SnH.[50] The synthesis of bicyclic lactams and bicyclic carbamates has been facilitated by 5-*exo* cyclisations of cyclic amidyl radicals, generated by photolysis of the corresponding *N*-chloramine precursor, onto a pendant alkene side chain.[51] The synthesis of (±)-γ-lycorane **12** has been reported using aminyl radicals generated from chloramines[10] and also from amidyl radicals generated from xanthate derivatives of hydrazides as precursors.[7] Aminyl radicals generated by ring opening of aziridinylmethyl radicals have been used in a tandem cyclisation for the synthesis of pyrrolizidines.[52] Reductive ring opening of oxaziridines to yield monocyclic aminyl radicals which then undergo cyclisation onto pendant alkenes also yields pyrrolizidines.[53]



Scheme 13 *Reagents and conditions*: i, Bu_3SnH (syringe pump addition), AIBN, benzene–toluene, reflux, dr **51** : **52** : **53** = 3 : 2 : 1.

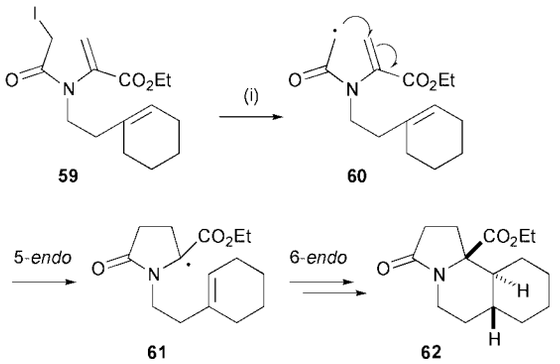
One route for the synthesis of bicyclic *N*-heterocycles uses cyclisation between two chains attached to a heterocycle, *i.e.* one containing the group for generating the radical and the other chain containing the unsaturated functionality onto which the radical intermediate will cyclise. An example of this general protocol is the synthesis of (−)-indolizidine 223AB **23** using a cyclisation of an alkyl radical generated from a *trans*-2,5-disubstituted pyrrolidine precursor **20** (Scheme 5).[12] This protocol which uses cyclisation onto β-aminoacrylates has been used for the synthesis of a range of bicyclic nitrogen heterocycles.

The second route uses cyclisation of a pendant side chain onto a ring *endo* or *exo* alkene. The synthesis of bridged *N*-heterocycles has been achieved by a novel protocol using cyclisation of pendant α- and β-ammonio radicals onto ring alkenes (Scheme 14).[54,55] The cyclisations are governed by steric and polar factors. The radical **54** cyclises rapidly with high stereoselectivity to yield the intermediate radical **55**, *i.e.* polar effects are dominant.[54] Finally abstraction of a hydrogen atom from Bu_3SnH yields 3-ethoxycarbonyl-1-methyl-1-azoniabicyclo[2.2.1]heptane bromide **56**. In contrast, the α-ammonio radical **57** undergoes 5-*exo* cyclisation onto the *exo* double bond to yield the substituted 1-methyl-1-azoniabicyclo[2.2.1]-heptanes **58**.[55] Bridged tricyclo-*N*-heterocycles, *i.e.* tricyclic tropane analogues, have been synthesised by making use of radical cyclisation of *N*-alkyl radicals onto alkenes in cocaine analogues.[56] Regio- and diastereo-selective radical cyclisations of 1-(4-iodoalkanoyl)-3-formyl-4-methyl-1,4-dihydropyridines using various radical reagents have been used for the synthesis of lupinine and epilupinine.[57] The diastereoselectivity is accounted for by steric interactions.



Scheme 14 *Reagents and conditions*: i, Bu_3SnH, AIBN, *tert*-BuOH, reflux, 85%, dr *exo* : *endo* = 10 : 90; ii, Bu_3SnH, AIBN, *tert*-BuOH, reflux, 88%.

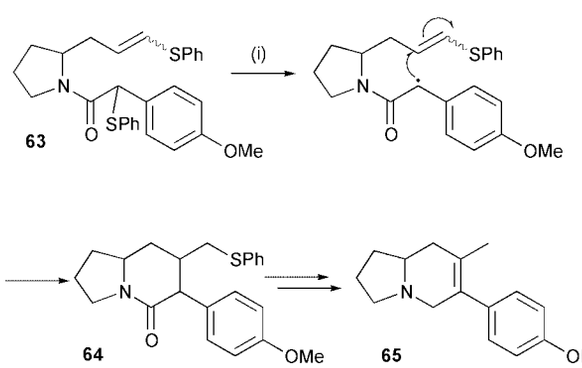
Methods for the annulation of pyrrolidin-2-ones onto cycloalkenes are similar to those used for the synthesis of monocyclic pyrrolidin-2-ones (see Section 3). However, an interesting protocol uses a tandem cyclisation for the synthesis of bi- and tricyclic indolizidinone.[58] An example of this protocol is shown in Scheme 15 for the synthesis of the tricyclic indolizidinone **62** from precursor **59**. The first step involves a 5-*endo* cyclisation of the α-amidyl radical **60** onto an alkene, an unusual regioselectivity. However, 5-*endo* cyclisation of α-amidyl radicals onto the β-position of dehydroamino esters is



Scheme 15 *Reagents and conditions*: i, Ph_3SnH, AIBN, benzene, reflux, 5 h, 61% (and 26% monocyclised product).

now well accounted for in the literature and is the normal regioselectivity. A second unexpected 6-*endo* cyclisation takes place to yield **62**. This is probably explained by thermodynamic control of cyclisation of the stabilised α-amino ester radical **61**.

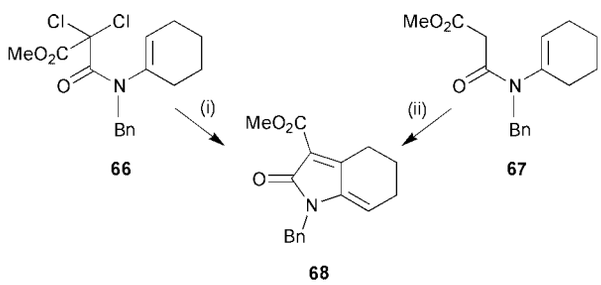
The use of α-amidyl radicals has also been applied to the synthesis of (±)-ipalbidine **65** (Scheme 16).[59] This synthesis uses cyclisation between two chains attached to a heterocycle **63**, *i.e.* one containing the group for generating the radical and the other chain containing the alkene onto which the radical intermediate will cyclise. The intermediate α-amidyl radical undergoes 6-*exo* cyclisation to yield the indolizidine **64**. Further synthetic elaboration yields (±)-ipalbidine **65**. Other variations in the synthesis of bicyclic pyrrolidin-2-ones include Bu_3SnH mediated cyclisation of various *N*-acryloxy-2-aminocyclohex-2-enones in which the radical is generated by addition of $Bu_3Sn^{\bullet}$ radicals to the oxygen of the cyclohexenone to generate a radical β to the amine for cyclisation onto the acryl side chain.[60]



Scheme 16 *Reagents and conditions*: i, Ph_3SnH, AIBN, benzene, reflux, 65%.

There have been a large number of reports of α-amidyl radical cyclisation onto cycloalkenes. 5-*exo* Cyclisation of *N*-(2-arylcyclohex-2-en-1-yl)trichloroacetamide using CuCl(bipyridine) to generate the α-amidyl radicals gives the 3a-phenyloctahydroindole ring system of the mesembrane alkaloids.[61] The product was converted to the alkaloids (±)-mesembrane and (±)-irinane. Xanthate transfer initiated by AIBN or di-*tert*-butyl peroxide has also been used to generate side chain α-amidyl radicals for 6-*exo* cyclisation onto cyclohexenes in the synthesis of octahydroindole ring systems.[62] 6-*exo* Cyclisation of α-amidyl radicals generated from trichloroacetamido precursors has been used to synthesise 2-azabicyclo[3.3.1]-nonanes.[63,64] The use of a chiral substituent on the nitrogen of the amide facilitates the stereoselective formation of diastereomers which allows enantiomerically pure 2-azabicyclo[3.3.1]-nonanes to be prepared.[64]

5-*endo* Cyclisation of α-amidyl radicals onto cycloalkenes has been thoroughly examined in the development of new radical generating reagents as alternatives to Bu_3SnH. Two representative examples are shown in Scheme 17.[65–67] Both reagents, CuCl(bipyridine)[65,66] and $Mn(OAc)_3$,[65,67] generate intermediate α-amidyl radicals, which undergo 5-*endo* cyclisation to octahydroindole radical intermediates. The dichloro acetamido precursor **66** is reduced by CuCl with loss of chloride to give an intermediate monochloro acetamido radical which cyclises.[65,66] In the $Mn(OAc)_3$ protocol,[65,67] the β-diketo precursor **67** is oxidised by Mn(III) to give a radical centred between the two carbonyl groups. The cyclised intermediates were both oxidised to the corresponding cation [Cu(II) and Mn(III)] which lost a proton to give the 1,4,5,6-tetrahydroindol-2-one **68**. The Cu(I)-mediated cyclisations are very efficient while the corresponding Mn(III) reactions were generally more problematic. Other studies of new radical generating reagents for similar precursors have been reported; CuBr with a range of ligands;[68] AcOH and propan-2-ol;[69] and Ni(0), $Cu(Ac)_2$, AcOH and *tert*-butyl alcohol.[70] Bu_3SnH has also been used on related α-amidyl radicals onto cycloalkenes.[71]

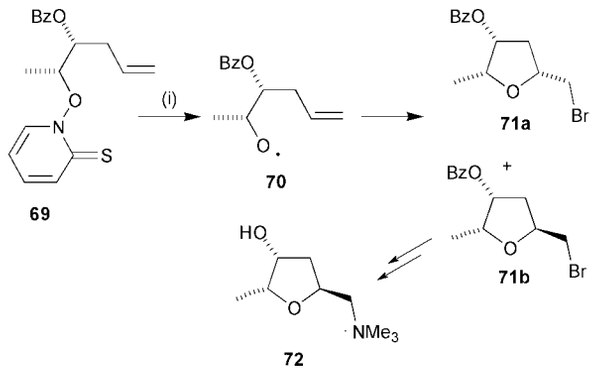


Scheme 17 *Reagents and conditions*: i, CuCl(bipyridine) (0.5 equiv.), toluene, reflux, 84%; ii, $Mn(OAc)_3$ (4 equiv.), MeOH, reflux, 38%.

5 Oxygen heterocycles

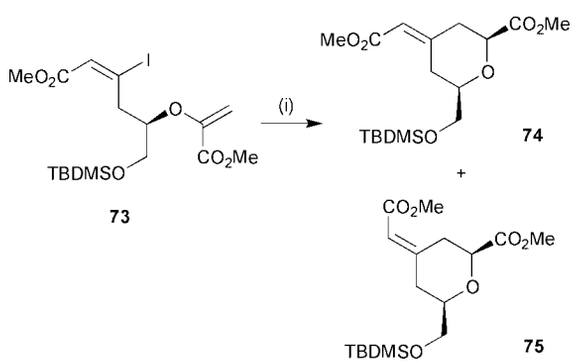
Many protocols can be used for both oxygen and nitrogen heterocycles and examples of both γ-lactones and lactams[44] and pyrrolidines and tetrahydrofurans[27,30] have been detailed in Section 3. The synthesis of tetrahydrofurans is one of the most commonly used radical procedures. As detailed for *N*-heterocycles in Section 3 the radicals can be generated in various positions relative to the oxygen atom. Oxygen centred radicals have not commonly been used in the synthesis of *O*-heterocycles. One example reports the use of the reactions between *N*-alkoxyphthalimides and Ph_3SnH as a means of generating alkoxy radicals.[72] A novel method uses *N*-alkoxypyridine-2-thiones for the generation of alkoxy radicals. This adaptation of the Barton reagent uses bromotrichloromethane as the chain carrier to yield a 2-bromomethyl tetrahydrofuran (Scheme 18).[73] The method is exemplified by the photolysis of the *N*-alkoxypyridine-2-thione precursor **69** which gives the alkoxy radical intermediate **70**. The expected 5-*exo* cyclisation results in two diastereomers **71a** and **71b** with no diastereoselectivity. One of the newly prepared tetrahydrofurans **71b** was used for the synthesis of (+)-*allo*-muscarine **72**, a muscarine alkaloid.

5-*exo* Cyclisation of carbon-centred radicals onto suitable unsaturated bonds to yield tetrahydrofuran derivatives is now a well established procedure for the synthesis of *O*-heterocycles. Addition of tri-2-furanylgermyl radicals, generated from tri-2-furanylgermane with triethylborane as initiator, to the γ-position of diallyl ethers results in a β-radicals which undergoes 5-*exo* cyclisation onto the other allyl group to give 3,5-disubstituted tetrahydrofurans.[74] A novel methodology uses ammonium hexanitratocerate (CAN) to oxidise nitronate anions to nitroalkyl radicals which undergo stereoselective 5-*exo* and 6-*exo* cyclisation onto alkenes to yield 3-nitro-4-hydroxymethyltetrahydrofurans and 2,3-dialkyl-4-methyl-3-nitrotetrahydropyrans respectively.[75] The stereochemistry is discussed in terms of the Beckwith–Houk transition state model.



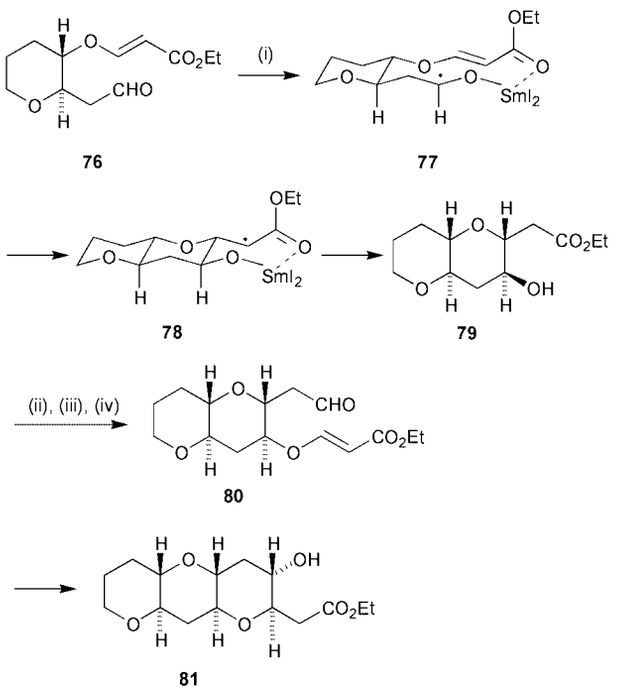
Scheme 18 *Reagents and conditions*: i, $BrCCl_3$, *hv*, benzene, 80%, dr of **71a** : **71b** = 1 : 1.

6-Membered ring cyclic ethers can be synthesised by similar methods to those for tetrahydrofurans and an interesting example is shown in Scheme 19 for the synthesis of the C(10)–C(16) fragment of bryostatins.[76] *cis*-2,6-Disubstituted 4-(methoxycarbonylmethylene)tetrahydropyrans, *e.g.* **74** and **75**, are prepared by Bu_3SnH mediated radical cyclisations. In Scheme 19 the precursor **73** gives a vinyl radical intermediate which undergoes stereoselective 6-*endo* cyclisation to yield the tetrahydropyrans **74** and **75**. The geometry of the exocyclic alkene reflects the faster cyclisation of the (*Z*)-component of the rapidly equilibrating mixture of the (*E*)- and (*Z*)-vinylic intermediate radicals.



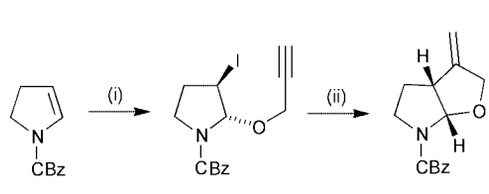
Scheme 19 *Reagents and conditions*: i, Bu_3SnH, AIBN, benzene, reflux, 45 min, 85%, dr of **74** : **75** = 80 : 20.

A novel iterative methodology for the synthesis of *trans*-fused poly-tetrahydropyran ring systems has been developed using samarium diiodide (SmI_2)-induced reductive intramolecular cyclisation of an aldehyde onto the β-position of β-alkoxy acrylates.[77] The methodology is illustrated in Scheme 20. The initial *trans* ring junction in the first radical precursor **76** undergoes reduction with SmI_2 to yield the radical intermediate **77** which cyclises to give a new *trans* ring junction in radical intermediate **78**. The stereoselectivity is explained by the samarium binding with the ester carbonyl thereby holding a chair conformation. Simple elaboration of **79** gives a new precursor **80** which also undergoes SmI_2-induced reductive intramolecular cyclisation to **81** in high yield. The methodology has been expanded to include highly stereoselective syntheses of *trans*-fused 6,6- and 6,7-membered ether ring systems having an angular methyl group using SmI_2-induced reductive intramolecular cyclisation between an aldehyde or a methyl ketone and a β-alkoxy acrylate.[78] More recently the protocol has also been used to prepare six–seven–six, six–seven–seven and the six–seven–seven–six *trans*-fused polycyclic ethers. The latter sub-structure is found in the potent neurotoxin brevetoxin B.[79] In a similar procedure, *cis*-fused tetrahydrofurans have been synthesised using Bu_3SnH-mediated reductive intramolecular cyclisation onto the β-position of β-alkoxy acrylates.[80]



Scheme 20 *Reagents and conditions*: i, SmI_2, THF–MeOH, 92%; ii, DIBAL, toluene, −78 °C; iii, propane-1,3-dithiol, BF_3–Et_2O, CH_2Cl_2, 0 °C; iv, ethyl propiolate, *N*-methylmorpholine, CH_2Cl_2, rt; MeI, aqueous MeCN; v, SmI_2, THF–MeOH, 86%.

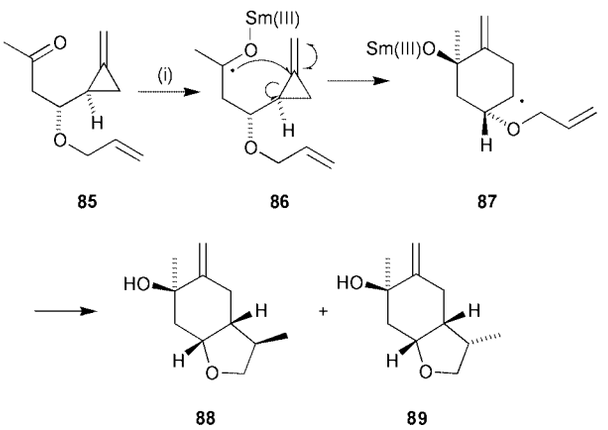
In the same way as the synthesis of bicyclic nitrogen heterocycles, chains on a monocyclic ring can be cyclised to yield a new bicyclic oxygen-containing heterocyclic ring. Cyclisation from a radical on the ring onto a side chain has been used for the synthesis of perhydrofuro[2,3-*b*]pyran (and furan)-3-yl methanols in one step from various 3-iodo (or bromo)-2-allyoxy perhydro-pyrans and -furans in high yields.[81] Use of the cobalt complex Co(salen) was more convenient than the Bu_3SnH system. The reaction is general and was successfully applied to carbohydrate derived substrates. Hexahydrofuro-[2,3-*b*]pyrroles have been prepared by the generation of radicals on the pyrrolidine rings and cyclisation onto the side chain of alkynyl ethers using a catalytic Bu_3SnH and sodium cyanoborohydride system (Scheme 21).[82] In the example shown in Scheme 21, the precursor **83** is conveniently synthesised from dihydropyrrole **82** using an acyliminium intermediate. The catalytic reaction with Bu_3SnH gave high yields of the *trans* hexahydrofuro[2,3-*b*]pyrrole **84**. The method has been used with a range of side chain alkynes and alkenes to add tetrahydro-furan and -pyran rings.



Scheme 21 *Reagents and conditions*: i, propargyl alcohol, NIS, −78 °C, 80%; ii, Bu_3SnH, $Na(CN)BH_3$, AIBN, *tert*-BuOH, reflux, 71%.

Addition of electro-generated nitrate radicals to the alkyne bond in alkyne ethers yields tetrahydrofurans with high diastereoselectivity.[83] This diastereoselective formation of tetrahydrofurans uses a nitrate radical induced oxidative, self-terminating radical cyclisation cascade. Octahydrobenzofurans have been synthesised by tetrahydrofuran formation using arylmethaniminyl and alkyl radicals generated from di- and trimethoxyphenyl aldoxime esters by photolysis in the presence of 4-methoxyacetophone.[84] Intermediates were detected by

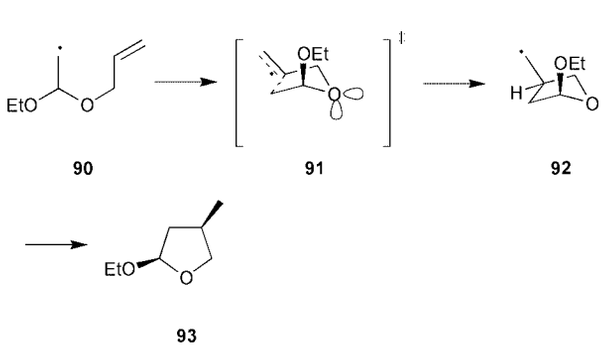
EPR spectroscopy to confirm radical intermediates. Another strategy is a novel cascade sequence which initially forms the first ring followed by a second radical cyclisation to give the tetrahydrofuran ring (Scheme 22).[85] These studies aimed at the synthesis of paeonilactone begin with samarium(II) iodide mediated formation of a ketyl radical **86** from the precursor methylenecyclopropane **85**. The samarium ketyl radical cyclises onto the methylenecyclopropane moiety which undergoes ring opening to yield the radical intermediate **87**. The last step in the cascade reaction forms the bicyclic tetrahydrofurans **88** and **89** with good stereoselectivity except for the methyl group.



85 **86** **87** **88** **89**

Scheme 22 *Reagents and conditions*: i, SmI_2, *tert*-BuOH–HMPA, 35%, **88** : **89** = 1 : 1.

Lactones are a common target of radical cyclisation and a number of common protocols continue to be used. The synthesis of γ-lactones using the Ueno–Stork reaction with α-halogeno-acetal precursors continues to find good application and overcomes the problem of unfavourable stereochemistry of α-ester radicals. A number of advances of the methodology have been reported. In the first of these reports, the stereoselectivity of cyclisation is strongly directed by the anomeric effect as observed in carbohydrate chemistry thereby giving the opposite stereochemistry to that observed and predicted in the Beckwith transition state model (Scheme 23).[86] The intermediate radical **90** generated from a halogenoacetal precursor lines up in the Beckwith transition state **91** but the anomeric effect pushes the alkoxy group into the axial conformation rather than the normal equatorial conformation. The cyclised acetal radical **92** gives the *cis* 1,3-disubstituted cyclic acetal **93**. The stereochemical outcome of these radical cyclisation reactions for cyclic acetal precursors is influenced in the same manner, *e.g.* 2-allyloxytetrahydropyran-3-yl radicals also show stereoselectivity that is explained by the anomeric effect.[87] In a second advance, the radical cyclisation of β-bromoethylacetals has been carried out on solid support (see Section 13).[88] Oxidative cleavage from the solid phase using the Jones reagent



90 **91** **92** **93**

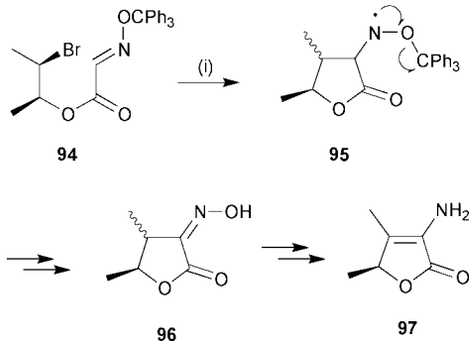
Scheme 23 *Reagents and conditions*: Bu_3SnH, $Bu^tON{=}NOBu^t$, pentane, 40 °C, 61%, dr *cis*/*trans* = 5.8.

gives γ-butyrolactones in good yield. A third advance reports the development of stereoselective radical cyclisation of β-bromoacetals using chiral auxiliaries on the oxygen atom of the acetal.[89–91] One protocol uses cyclisation onto allenes in the synthesis of (±)-botryodiplodin.[89,90] A fourth protocol uses desymmetrisation of 1,4-dien-3-ols and related compounds *via* Ueno–Stork radical cyclisation. The iodoacetal is placed on the alcohol of the 1,4-dien-3-ol and cyclised.[91] The stereochemistry of the cyclisation is controlled by the acetal centre giving high diastereoselectivity.

Synthesis of α,α-difluoro-γ-lactones has been facilitated through intramolecular 5-*exo* radical cyclisation involving allyl *O*-(trimethylsilyl)-α-bromo-α,α-difluoroacetates.[92] The cyclisations were regioselective and gave predominately the *trans* configuration with high yields. The cyclic acetals were hydrolysed and oxidised to the γ-lactones using PDC or Dess–Martin oxidation. Both enantiomers of difluoroeldanolide, analogues of sex pheromones of the male African sugarcane borer, were synthesised. Radical cyclisation reactions using 2-halogenoethanal allylic acetals yield tetrahydrofuran ring systems using an activated manganese species derived from Li_2MnCl_4.[30,93]

Acyloxy radicals have been used for 5-*exo* cyclisation onto alkenes and alkynes to synthesise γ-lactones. The acyloxy radicals have been generated from selenocarbonates (and cyclised onto alkynes[94] and *Z*-vinylogous sulfonates[95]) and *S*-alkoxycarbonyl xanthates.[6] An unusual synthesis of γ-lactones has been carried out using reaction between 4-hydroxycyclobut-2-enones with lead acetate which leads to the formation of furan-2(5*H*)-ones due to the radical-mediated ring expansion and 5-*endo* cyclisation of an acyl radical onto the carbonyl group in the ring opened intermediate radical.[96] In another unusual procedure, δ-lactones are synthesised from saturated alcohols using lead tetraacetate oxidation to yield intermediate alkoxy radicals which undergo 1,5-hydrogen abstraction to yield carbon centred radicals.[97] CO is added to these radicals to form acyl radicals which then undergo oxidative cyclisation with the primary alcohols to give the δ-lactones.

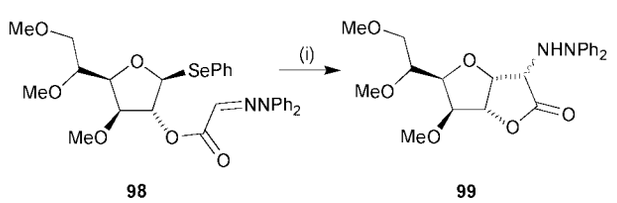
The last of the routes for the preparation of γ-lactones uses cyclisation of radicals α to the carbonyl group of allyl esters. All of these procedures require 5-*exo* cyclisation with the ester in the thermodynamically unfavoured *cis* conformation and hence appear to override the problem of the preferred *trans* conformation. The addition of a radical generating reagent A–B across two alkenyl groups β to a heteroatom continues to be a common synthetic protocol. In the synthesis of γ-lactones using this procedure, chemoselectivity was observed in the addition and cyclisation reactions of $PhSO_2Br$ to allyl acrylates due to the higher reactivity of the acrylic double bond towards the sulfonyl radical than that of the allyl alkene.[98] Studies towards the synthesis of a precursor to (±)-botryodiplodin *via* 5-*exo*-*trig* ring closures onto allylic sulfones of α-ester radicals was found to be problematic because of the ester conformation and only moderate yields were achieved.[99] Highest yields were achieved when the iodine-atom transfer methodology was used as opposed to the use of Bu_3SnH. Use of iodine-atom or phenylselanyl-group transfer methodology has also been reported to overcome the ester conformation problem with phenylselanyl and iodo derivatives of allyl and propargyl malonate esters.[100] In contrast, no problems were encountered when oximino lactones were synthesised from *O*-trityl oximino-esters using Bu_3SnH-induced radical cyclisation onto the oxime ether with 41% to 80% yields (Scheme 24).[101] The oxime function is regenerated by loss of the trityl group after cyclisation. For example, the precursor **94** was cyclised to yield the aminyl radical intermediate **95** which on fragmentation, reduction and tautomerism yields the cyclised oxime **96**. Further elaboration gave the biologically active naturally occurring substance **97** present in the flowers of the tree *Quararibea funebris* (Llave).



Scheme 24 *Reagents and conditions*: i, Bu_3SnH, AIBN, toluene, reflux, **96** (68%).

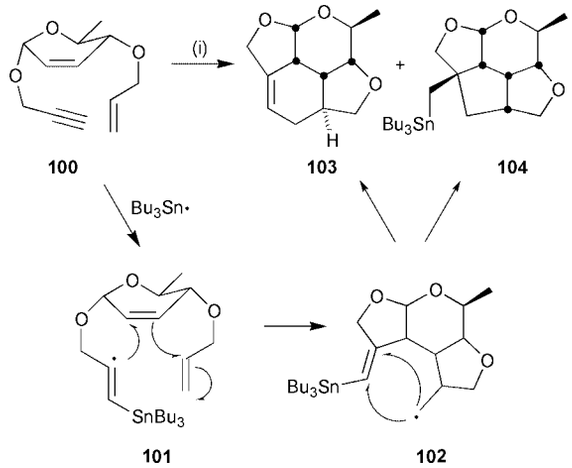
6 Carbohydrates and nucleosides

Radical cyclisation has been used in the elaboration of novel carbohydrates as well as using carbohydrates as templates for radical cyclisation. The use of furanoses as 'off-template' sites for the stereoselective radical synthesis of annulated furanoses has been reviewed.[4] A key advantage of the use of radical cyclisation with carbohydrates is that the hydroxy groups do not normally need protection which saves time in a synthesis. A continuing number of papers report the cyclisation of radicals, generated on the monosaccharide rings onto side chain unsaturated bonds, usually for elaboration of the substituents on the monosaccharides. The synthesis of *C*-glycosides using radical cyclisation has been reviewed.[102] A useful application of this protocol is the cyclisation of radicals on the anomeric carbon onto pendant hydrazones, and an example is illustrated in Scheme 25.[103] The phenylselanyl precursor **98** was converted to the 1-C centred radical which undergoes 5-*exo* cyclisation (annelation) onto the hydrazone with low diastereoselectivity to the γ-lactone **99**. The synthesis of 5- and 7-membered lactones was also reported using this protocol. The cyclised lactones have been converted to *C*-glycosyl α-amino acids.[103] The synthesis of *C*-glycosides *via* radical cyclisation onto vinylsilyl tethers[104] on 2-C and propargyloxy tethers[105] on 5-C have also been reported. Radical cyclisation from 3-C of monosaccharides onto vinylsilyl tethers on 2-C has also been used for alkylation of 3-C.[106] Radical cyclisation from 3-C of a monosaccharide onto a propargyloxy tether on 2-C has been used to synthesise a *cis*-fused bicyclo[3.3.0]octane system for the synthesis of dicosiolide, a natural product.[107]



Scheme 25 *Reagents and conditions*: i, Bu_3SnH (syringe pump addition over 10 h), AIBN, toluene, reflux, 82%, dr = 42 : 40.

A monosaccharide template has been used for Bu_3SnH-mediated cyclisation of a radical generated on the 5-C side chain onto a 4-C β-oxyacrylate side chain to give highly functionalised *cis*- and *trans*-fused bicyclic ethers of various ring sizes.[108] This protocol provides another route to these polycyclic ethers as detailed in references 78–81 and Scheme 20. A novel protocol uses a cascade reaction in which three rings are constructed in a single reaction and an example is illustrated in Scheme 26.[109] Treatment of precursor **100** with Bu_3SnH gives a vinyl radical **101** which cyclises onto the monosaccharide 2,3-alkene to yield a carbon-centred radical at 3-C which in turn undergoes 5-*exo* cyclisation onto the pendant allyl ether on 4-C to yield the radical intermediate **102**. Further cyclisation yields

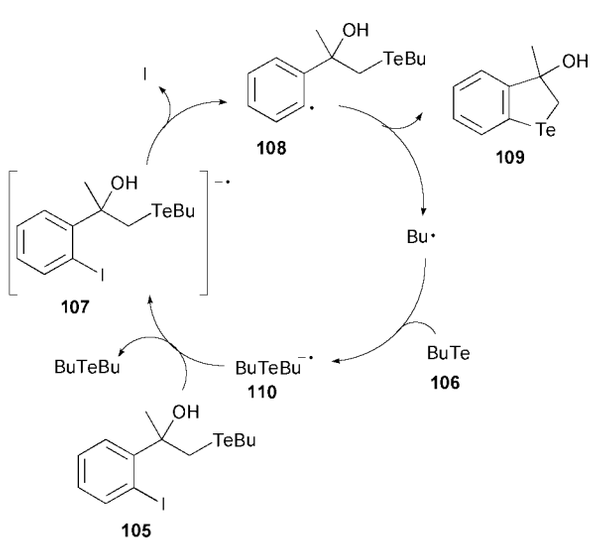


Scheme 26 *Reagents and conditions*: i, Bu_3SnH (syringe pump addition), AIBN, toluene, reflux, **103** (43%) and **104** (17%).

two products **103** and **104** by 6-*endo* or 5-*exo* cyclisation respectively.

7 Sulfur, selenium and tellurium heterocycles

Radical cyclisations involving sulfur, selenium and tellurium have some marked differences to that of oxygen and nitrogen because of their polarisable nature and the longer and weaker C–S, C–Se and C–Te bonds. S_H2 reactions centred on S, Se and Te have become important and have been used to advantage in the synthesis of S, Se and Te containing heterocycles. In a fascinating example of the application of S_H2 chemistry to tellurium compounds, a combined $S_{RN}1$ and S_{HI} reaction has been reported (Scheme 27).[110] In this reaction, the starting material **105** is generated *in situ* and reacted with butyl telluride **106** which is also generated *in situ*, from the reduction of dibutyl telluride with sodium borohydride. The butyl telluride **106** initiates the $S_{RN}1$ reaction by SET to the precursor **105** to generate the chain carrying radical anion **107**. The radical anion **107** dissociates to give the aryl radical intermediate **108** which undergoes an intramolecular S_H2 substitution on the tellurium atom to yield the 2,3-dihydro-3-hydroxy-3-methylbenzo[*b*]tellurophene product **109**. The butyl radical generated in this S_{HI} substitution on the tellurium atom reacts with the butyl telluride **106** to form a new chain carrying radical anion **110** to complete the $S_{RN}1$ chain reaction. Similar reactions of 1-(benzylseleno)-2-phenylpropan-2-ol afford 2,3-dihydro-3-hydroxy-3-methylbenzo[*b*]selenophene.



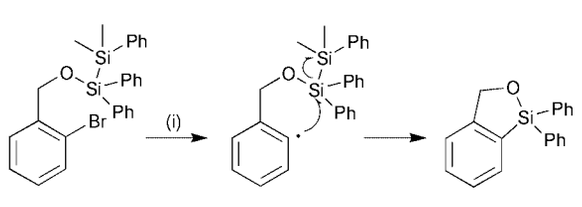
Scheme 27 *Reagents and conditions*: BuTeBu, $NaBH_4$, THF, rt, overnight, 62%.

Intramolecular S_H2 has also been used for the synthesis 5-seleno-D-pyranoses.[111] Reaction between the aldehyde of 2,3,4-tri-*O*-benzyl-5-benzylseleno-5-deoxyribose and samarium(II) iodide yields an intermediate ketyl radical which attacks the selenium atom and displaces benzyl radicals in a S_Hi reaction to afford 2,3,4-tri-*O*-benzyl-5-deoxy-5-seleno-D-ribopyranose. Xylo- and arabino-pyranoses are prepared in similar manner. Intramolecular S_H2 has been used to synthesise benzothiophene and 2,3-dihydrobenzothiophene.[112] In these reactions, aryl radicals generated by reduction of arenediazonium salts with tetrathiafulvalene (TTF) in 'radical–polar crossover' reactions, attack the sulfur atom in the side chain with a five-membered ring transition state to displace suitable alkyl radicals.

A range of other protocols have been used to prepare sulfur heterocycles. Cyclic sulfides with 4-, 5- and 6-membered rings have been synthesised by ring closure of thiyl radicals, generated *in situ* by a nickel complex catalysed electro-reduction of the thioacetates and thiosulfonates, onto alkenes or alkynes.[113] Thiabicyclic compounds have been obtained from monocyclic precursors using cyclisations of radicals, generated from thionocarbonate radical precursors, onto the β-position of β-thioacrylates.[114] The synthesis of 5- and 6-membered ring sultams has been facilitated using cyclisation of α-sulfonamidyl radicals which were generated by reaction between α-halomethyl sulfonamide precursors and Bu_3SnH.[115] In larger ring cyclisations, 7-*endo* cyclisation predominates over the 6-*exo* alternative. 1,3-Dithiol-2-ones can be prepared in a one pot reaction from diisopropyl xanthogen disulfide and alkynes under radical conditions using AIBN as an initiator.[116]

8 Silicon and boron heterocycles

The synthesis of silyloxy heterocycles (with Si–O in the ring) is primarily of interest as a synthetic method for the introduction of hydroxymethyl groups. There has been continuing interest in the use of the well known Stork protocol which uses silicon containing tethers attached to hydroxy groups in radical cyclisation for the introduction of new C–C bonds.[117] Cyclisation of the intermediate silyl methylene radicals onto alkenes gives new C–C bonds from which the silyloxy group is oxidised out of the ring to leave two hydroxy groups. SmI_2-promoted intramolecular reductive cyclisation *via* silyl methylene radicals onto a carbonyl group provides a new method for generating the radicals.[118] The radical chemistry of organosilanes is still poorly understood but recent studies have shown that S_Hi reactions on silicon by carbon-centred radicals proceeds smoothly in chain reactions.[119,120] One of these reactions is illustrated in Scheme 28 for the precursor **111** in which an intermediate aryl radical **112** cyclises onto the silicon atom by displacing a silyl group to yield the benzocycle **113**.[119] The resulting dimethylphenylsilyl radical carries on the chain reaction. A novel ring-expansion reaction of (3-oxa-2-silacyclopentyl)methyl radicals into 4-oxa-3-silacyclohexyl radicals has also been reported showing that *C*-centred radicals react *via* a three-membered ring pentavalent silicon-bridging radical transition state.[120] Silyl methylene radicals have been cyclised by a double 7-*endo* radical route onto allylsilanes to yield a bridged spiro[6.6]silatridecane.[121]



111 **112** **113**

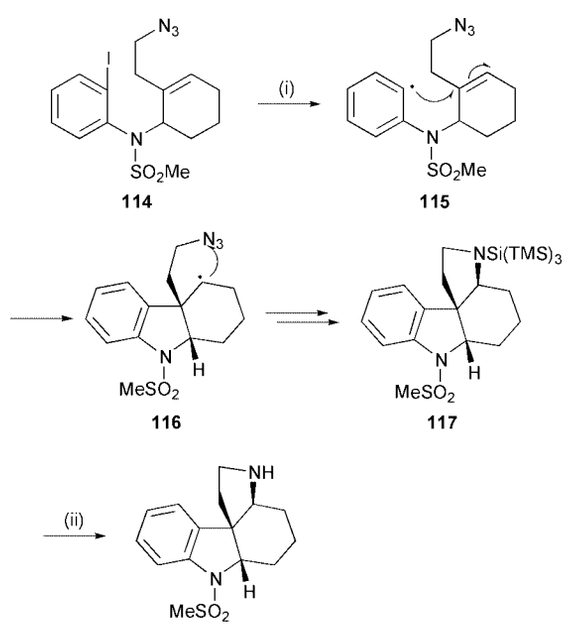
Scheme 28 *Reagents and conditions*: i, Bu_3SnH (0.2 equiv.), AIBN, benzene, reflux, 80%.

The use of boroalkyl radical cyclisation has been developed which parallels that of the silyl systems.[122] These radicals readily undergo regioselective 5-*exo* cyclisation onto alkene and alkynes tethered *via* a C–B–O linkage. The use of boron–oxygen tethers has been expanded in the same way as the silicon–oxygen tethers and B–O tethered alkyl radicals have been cyclised onto alkene groups attached to the boron atom.[123] These alkyl radicals which are β to the boron atom are able to undergo ring expansion *via* three-membered ring cyclisation onto the boron atom, as observed for the silicon equivalent.

9 Synthesis of non-aromatic heterocyclic rings on arene/heteroarene rings

In this section, the radical cyclisations to form non-aromatic heterocyclic rings on arene or heteroarene rings is described, whereas in the next section, the heterocyclic rings formed by cyclisation are heteroarenes. These radical cyclisations can be carried out by several general routes: *a*. cyclisation of aryl/heteroaryl radicals onto side chain unsaturated bonds, *b*. cyclisation of aryl/heteroaryl radicals onto pendant arenes/heteroarenes and *c*. cyclisation of side chain radicals onto arenes or heteroarenes.

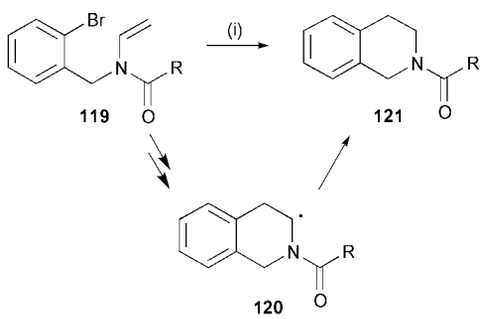
The synthesis of benzoheterocycles using cyclisation of aryl radicals onto side chain unsaturated bonds using triorganotin hydrides remains one of the most commonly used radical methodologies. An interesting example has been reported for the stereoselective synthesis of the tetracyclic core of *Aspidosperma* alkaloids (Scheme 29).[124] The aryl radical **115** was generated from the aryl iodide precursor **114** using $(TMS)_3SiH$ and gave 5-*exo* cyclisation onto the alkene. The resulting tricyclic radical intermediate **116** undergoes cyclisation onto the azide with loss of nitrogen to form the silylamine **117** which on hydrolysis results in a high yield of the tetracyclic aspidospermine skeleton **118** with the correct stereochemistry. Several other examples of these cyclisations of aryl radicals onto alkenes have been discussed earlier in the review and include a 6-*exo* cyclisation in the syntheses of (±)-γ-lycorane (Scheme 3)[9,10,125] and a Ph_3SnH-mediated 6-*exo* cyclisation of an aryl radical onto the imine bond of arizidinyl hydrazones is used as a key step in the synthesis of the naturally occurring alkaloid (+)-7-deoxypancratistatin (Scheme 6).[13] The synthesis of indolines by 5-*exo* cyclisation of aryl radicals onto *o*-allylamino side chains is commonly used.[126]



114 **115** **116** **117** **118**

Scheme 29 *Reagents and conditions*: i, $(TMS)_3SiH$, AIBN, benzene, reflux; ii, water, 83%.

Aryl radical cyclisation normally has a high *exo* : *endo* ratio indicating a stronger preference for *exo* cyclisation than alkyl radicals. However, this preference can be reversed by cyclisation to stabilised radicals.[127–129] An example of this preference is illustrated in Scheme 30 where *N*-(*o*-bromobenzyl)enamide precursors **119** undergo 6-*endo*-*trig* cyclisation to stable α-aminoalkyl radical intermediates **120**.[127] The only cyclised products were the tetrahydroisoquinoline derivatives **121** and no 5-*exo* cyclisation was observed but some reduced uncyclised products are also obtained. The mode of cyclisation can be shifted to a 5-*exo*-*trig* manner by introducing a phenylthio group at the terminus of the *N*-vinylic bond. The authors discuss the influence of conformation and radical stability on these cyclisations. Similarly, radical cyclisation of 2-(ω-haloalkylthio)enones yields predominantly fused thiapolycycloalkanones by 6-*endo* cyclisation.[128] In the synthesis of 3-benzazepines, *o*-bromophenethylenamides undergo 7-*endo*-*trig* radical cyclisation onto the enamides *via* α-aminoalkyl radical intermediates.[129]

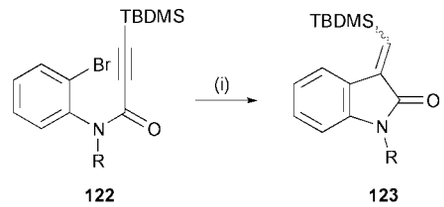


Scheme 30 *Reagents and conditions*: i, Bu_3SnH, 1,1′-azobis(cyclohexanecarbonitrile), toluene, reflux, **121**, R = Et (80%) and R = H (43%).

All of the above examples have used Bu_3SnH for generating the aryl radicals. An increasing number of alternative protocols are being reported. The first of these protocols developed by Murphy and co-workers is the use of tetrathiafulvalene (TTF)-induced reduction of arenediazonium salts which yield aryl radicals after loss of nitrogen. An example of this protocol is shown in Scheme 4 which shows the cyclisation of an aryl radical onto an alkene to form an intermediate indoline in the total synthesis of (±)-aspidospermidine by using their tetrathiafulvalene (TTF)-induced radical–polar crossover protocol to generate the aryl radical cyclisation.[11] The protocol has also been used for the synthesis of dihydrobenzofurans and other indolines.[130] A water-soluble tetrathiafulvalene reagent has been developed and applied to a range of arenediazonium tetrafluoroborates and chlorides.[131] Cyclic ethers and amines are obtained by the use of polymer-supported tetrathiafulvalene in radical–polar crossover reactions with slightly lower yields than in the corresponding solution-phase reactions.[132] The polymer can be reused after regeneration with sodium borohydride.

Other new methods for the cyclisation of aryl radicals onto side chain alkenes include the synthesis of indolines and dihydrobenzofurans using *N*-ethylpiperidine hypophosphite to generate the aryl radicals.[133] Methods for limiting the problem of the toxic triorganotin hydrides have been reported, *e.g.* the use of catalytic Bu_3SnCl with generation of Bu_3SnH *in situ* by reaction with polymethylhydrosiloxane and KF[134] and use of solid phase resins for attaching the substrate so that tributyltin residues can be washed away.[135]

Oxindoles are commonly synthesised using cyclisation of aryl radicals onto side chain α,β-unsaturated amides. An example of these reactions is illustrated in Scheme 31 with the synthesis of silyl substituted 3-methylene oxindoles using cyclisation onto alkynyl amides.[136] The intermediate aryl radical generated from the precursor **122** undergoes 5-*exo*-*dig* cyclisation to yield mixtures of *E* and *Z* isomers of **123** (59–67%) with dr's of *E* : *Z* = 1 : 3 (R = Me), 1 : 4.7 (R = allyl) and 1 : 3.5 (R = CH_2-dioxolane). Various factors influence the balance between 5-*exo* and 6-*endo* cyclisation for cyclisation of aryl radical onto side chain α,β-unsaturated amides to give oxindoles and dihydroquinolones respectively.[137] In an interesting set of experiments, Curran and co-workers have shown that there is transfer of chirality in radical cyclisations to synthesise oxindoles which illustrates the presence of a certain memory effect in the cyclisation.[138] Cyclisation of *N*-vinylic 2-iodobenzamides gave 2,3-dihydroisoindol-1-ones (5-*exo* cyclisation) and 3,4-dihydro-2*H*-isoquinolin-1-one (6-*endo* cyclisation).[139] Synthesis of ketospiro-2,3-dihydroisoindol-1-ones has been achieved by cyclisation of aryl radicals onto 2-bromo-*N*-alkyl-*N*-(3-oxocyclohex-1-enyl)benzamides.[140] Benzo[*a*]quinolizidines have been synthesised from 2-iodobenzamide derivatives by radical cascade reactions in which the first steps are 6-*exo* cyclisations of aryl radicals onto *N*-vinylic substituents.[141]

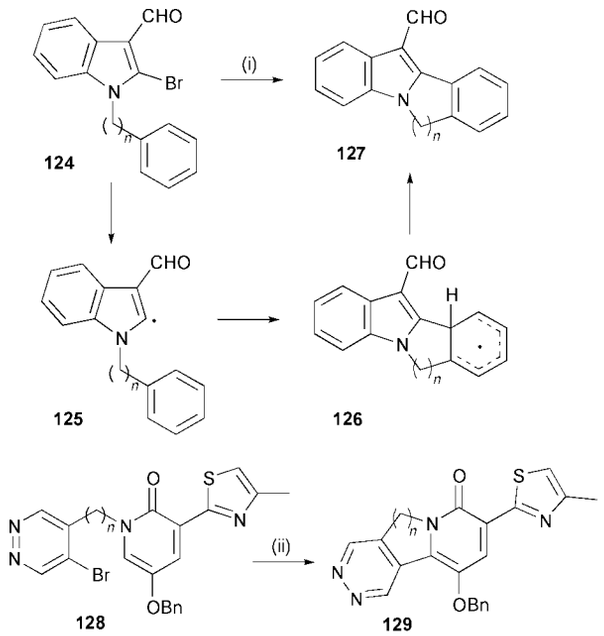


Scheme 31 *Reagents and conditions*: i, Bu_3SnH (syringe pump addition), AIBN, toluene, reflux, **122** (R = Me, 62%; R = allyl, 59%; R = CH_2-dioxolane, 67%).

The analogous esters have also been cyclised to produce isobenzofurans, *e.g.* 2-bromobenzoic acid 3-oxocyclohex-1-enyl esters give keto spiro-γ-lactones.[140,142] These cyclisations are surprising because they require the esters to be in the higher energy *cis* conformations rather than in the lower energy *trans* conformations.

The second route to benzoheterocycles is the cyclisation of aryl or heteroaryl radicals onto pendant arenes/heteroarenes. The mechanism of these Bu_3SnH-mediated 'oxidative' cyclisations is still unclear. A good example is the cyclisation of indol-2-yl radicals onto phenyl rings as shown in Scheme 32.[143] The precursors **124** (*n* = 1–3) initially give reactive indolyl radicals **125** which cyclise to yield the π-radicals **126** and after loss of a hydrogen atom yield the tetracyclic isoindolo-[2,1-*a*]indoles **127**. In each reaction of **124** (*n* = 1–3) some of the corresponding uncyclised reduced *N*-(phenylalkyl)indole-3-carbaldehyde was obtained. In a related series of cyclisations to synthesise the tricyclic pyridones **129** from precursors **128**, Bu_3SnH-mediated 'oxidative' cyclisations are facilitated by 5-, 6- and 7-*exo* cyclisation of pyridyl radicals onto the pyridone ring.[144] The pyridone ring is sufficiently aromatic to act as a driving force for rearomatisation (Scheme 32). However, in analogous cyclisations of aryl radicals onto 1*H*-pyrimidine-2,4-dione rings, only reductive cyclisation takes places to yield the corresponding isoindole products 4a,9a-dihydro-4*H*-indeno[2,1-*c*]pyridine-1,3,9-triones.[145] The 1*H*-pyrimidine-2,4-dione ring is obviously less aromatic in character and 'normal' reductive cyclisation takes place. Hindered biaryls with bridging sulfonamide rings have been prepared by the use of an intramolecular radical [1,5]-*ipso* substitution and provides an example of aryl radical cyclisations onto arenes. The aryl radicals are generated by reduction of *o*-(arylsulfonamido)benzene diazonium salts. The introduction of an additional substituent ortho to the diazonium group in the aryl ring enforces the formation of *ipso* substitution products.[146]

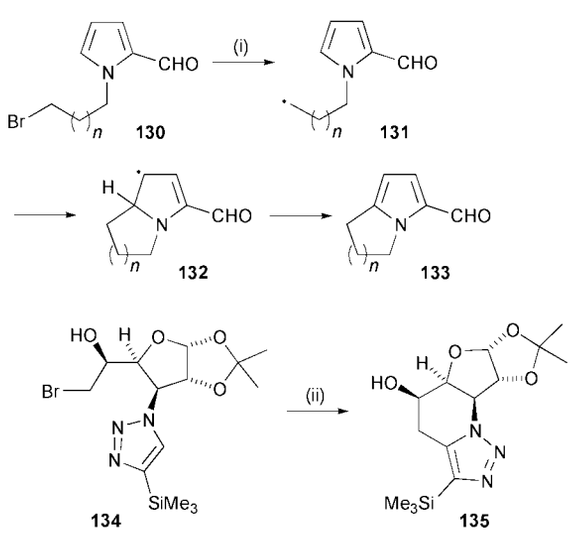
The Bu_3SnH-mediated cyclisation of alkyl radicals onto arenes and heteroarenes provides a good route to benzoheterocycles. Xanthate precursors are used to generate the radicals with peroxide initiators.[147] Indolines have been synthesised by cyclisation of β-(arylamino)-alkyl radicals onto the aryl rings in



Scheme 32 *Reagents and conditions*: i, Bu_3SnH (syringe pump addition), AIBN, MeCN, reflux, **127** (n = 1, 25%; n = 2, 65%; n = 3, 37%); ii, Bu_3SnH, AIBN, benzene, reflux, **129** (n = 1, 37%; n = 2, 35%; n = 3, 50%).

oxidative cyclisations[147a] and a similar procedure has been applied to the cascade synthesis of (±)-γ-lycorane[7] and the synthesis of 4-substituted 1,2,3,4-tetrahydroisoquinolin-1-ones.[147b]

Cyclisation of *N*-(ω-alkyl) radicals onto heteroarenes has been used to annulate pyrrole, imidazole and indole. An example of these oxidative radical cyclisations using Bu_3SnH is illustrated in Scheme 33 for the synthesis of [1,2-*a*]fused pyrroles.[148] Treatment of the precursors **130** with Bu_3SnH yield *N*-(ω-alkyl)pyrrole radicals **131** which cyclise onto the pyrrole rings to form the cyclised π-radicals **132**. In an oxidative step a hydrogen atom is lost to yield the [1,2-*a*]-fused pyrroles **133** in reasonable yields (28–55%). [1,2-*c*]-Fused imidazoles have been synthesised by the same methodology.[148] This methodology has been extended to 6-*exo* cyclisation of a sugar moiety onto 1,2,3-triazoles, *e.g.* the cyclisation of *N*-substituted triazole **134** resulted in a 36% yield of the polycyclotriazole **135**.[149] In a novel addition to this methodology, 1-(2-iodoethyl)-pyrroles and -indoles are used to generate *N*-(ω-alkyl)-pyrrole and -indole radicals which add to carbon monoxide under 80 atm pressure to form intermediate acyl radicals which then undergo

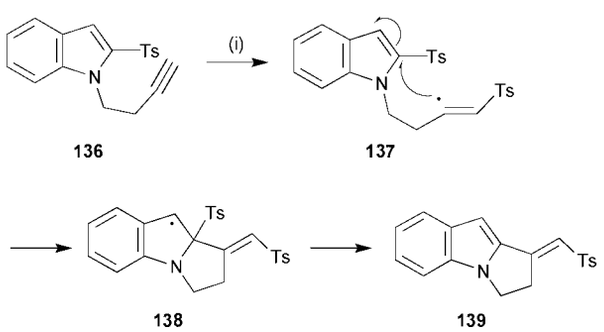


Scheme 33 *Reagents and conditions*: i, Bu_3SnH (syringe pump addition), AIBN, MeCN, reflux, **133** (n = 1, 28%; n = 2, 55%; n = 3, 40%); ii, $(TMS)_3SiH$, AIBN, toluene, reflux, 36%.

5-*exo* oxidative cyclisation onto the pyrrole or indole ring to form 2,3-dihydropyrrolizin-1-ones or the corresponding indole derivatives.[150] As with all of these examples, electron withdrawing or stabilising groups are required on the heteroarene ring. Oxidative cyclisations onto indole rings and arenes have also been reported for *N*-(ω-allylsulfonylalkyl)indoles.[151] The radical reactions were induced by phenylsulfonyl radicals generated from the benzenesulfonate anions using copper diacetate.

[1,2-*a*]-Fused benzimidazoles,[152] imidazoles,[152] and indoles[153] have been synthesised using regioselective (*ipso*) aromatic homolytic substitution. The [1,2-*a*]fused imidazoles were synthesised from *N*-(ω-phenylselanyl)alkyl-2-(phenylsulfonyl)-imidazoles by cyclisation of intermediate *N*-(ω-alkyl) radicals, generated using Bu_3SnH, with displacement of the phenylsulfonyl groups.[152]

Similarly, the [1,2-*a*]fused benzimidazoles were synthesised from *N*-(ω-phenylselanyl)alkyl-2-(phenylsulfanyl)benzimidazoles with displacement of phenylsulfanyl leaving groups. Phenylselanyl groups were used as radical leaving groups on the side chains to avoid problems in the *N*-alkylation of imidazoles and benzimidazoles.[152] A new protocol uses catalytic tosyl radicals to add onto *N*-(ω-alkynyl)indoles for the synthesis of [1,2-*a*]-fused indoles.[153] An example of the protocol is shown in Scheme 34 for the conversion of the alkynyl precursor **136** to cyclised indole **139**. The initiator sets off the reaction and tosyl radical adds to the alkyne, followed by cyclisation of the intermediate vinyl radical **137** to **138** and loss of a new tosyl radical, thereby completing the chain reaction. The protocol was also used for 6-membered ring cyclisations and with *N*-(ω-alkenyl)-indoles.[153] In another methodology, primary alkyl radicals, generated (AIBN–Bu_3SnH) from *N*-(2- or 3-haloalkyl)-2-methylsulfonylpyrroles, are intercepted by carbon monoxide (at 80 atm) to form acyl radicals. These acyl radicals undergo intramolecular cyclisation with loss of the sulfonyl moiety thereby giving bicyclic ketones.[154]

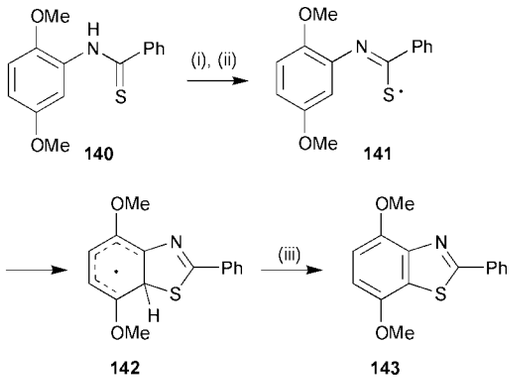


Scheme 34 *Reagents and conditions*: i, TsSePh (0.25 equiv.), AIBN, benzene, reflux, 72–89%.

10 Heteroarenes

In this section, the term 'heteroarenes' is used to describe radical cyclisations to form heteroarene rings as opposed to the previous section which describes cyclisations to form non-aromatic heterocyclic rings on arene or heteroarene rings.

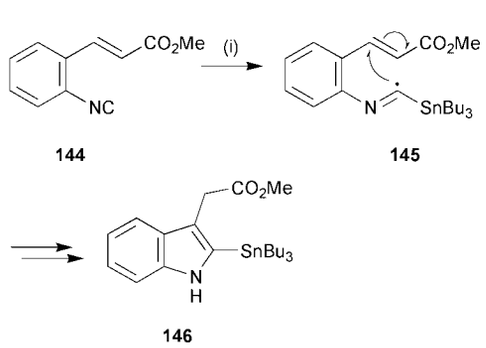
The synthesis of heteroarenes by radical cyclisation has been a surprisingly little studied area with few general protocols. A hundred year old synthetic procedure which has found new uses is the Jacobsen synthesis of benzothiazoles which involves ferricyanide oxidation of thioamides.[155,156] The methodology has been used in the synthesis of analogues of the biologically active marine natural product kuanoniamine A (Scheme 35).[155] The thioamide **140** gives the benzothiazole **143** in high yield. While no full mechanism has been proposed, we suggest that the anion of the thioamide **141** will readily oxidise to the thiyl radical which undergoes addition to the ring to yield an aromatic π-radical **142**. Further oxidation of the aromatic π-



Scheme 35 *Reagents and conditions*: i, $K_3Fe(CN)_6$, 1.5 M NaOH; ii, Fe(III)⟶Fe(II); iii, Fe(III)⟶Fe(II), $-H^+$, 80%.

radical gives an aromatic π-cation, followed by loss of a proton, to yield the benzothiazole. The authors carried out benzothiazole synthesis with a range of substituents on both arenes using this protocol. The Jacobsen reaction has also been used in the development of 2-(4-aminophenyl)benzothiazoles as anticancer compounds.[156,157] However, the problem is that while *o*-and *p*-substituted thioanilides give only one regioisomer, *m*-substituted thioanilides give both possible regioisomers.[157] This problem has been overcome by cyclising the thioamide anion onto thioanilide rings with *o*-bromo groups. The bromine group is substituted by the thioanilide anion. No mechanism has been proposed but it is likely to be an intramolecular $S_{RN}1$ reaction.

Several procedures have been reported for the radical synthesis of indoles.[158–161] A new protocol using the addition of $Bu_3Sn^{\bullet}$ radicals onto isonitriles of 2-alkenyl phenyl isocyanides (*e.g.* **144**) facilitates the synthesis of 3-substituted indoles, *e.g.* **146** (Scheme 36). Radicals are known to add readily to isocyanide groups generating imidoyl radicals.[158] In this protocol the intermediate imidoyl radical **145** undergoes 5-*exo* cyclisation onto the *o*-alkene group. Isomerisation of the cyclised imine yields the aromatic indole products. A range of substituents can be used on the alkene and the 2-tributyltin group has been displaced with substituents using Stille couplings to give a variety of 2,3-disubstituted indoles.[158] This protocol has been furthered with the use of 2-alkynyl substituents using intramolecular Bu_3SnH and benzenethiol mediated radical cyclisation of imidoyl radicals generated from isocyanides.[159] Another novel methodology, by Murphy and co-workers, uses diazonium salts as precursors for the synthesis of indoles.[160] The indoles are produced by cyclisation of aryl radicals, generated by reduction of diazonium salts, onto pendant vinyl halides by a radical addition–elimination route. The radicals are produced using "clean methodology" either by reaction of iodide ions with arenediazonium salts or by reaction of phosphorus-centred radicals. Imidoyl radical intermediates have also been used in the [4 + 1] radical annulation reactions of vinyl isonitriles with iodoalkynes or iodonitriles affording cyclopenta-fused pyridines, and pyrazines (6,7-dihydro-5*H*-cyclopentapyrazines) respectively.[161] Lastly, indoles as part of tetracyclic indolo[2,1-*a*]isoquinolines, have been synthesised by Bu_3SnH-mediated aryl radical cyclisations of 1-(2-bromobenzyl)isoquinoline precursors.[162] The intermediate aryl radicals cyclise onto the nitrogen atom of 3,4-dihydroisoquinolines followed by an oxidative step to yield the indole structures.



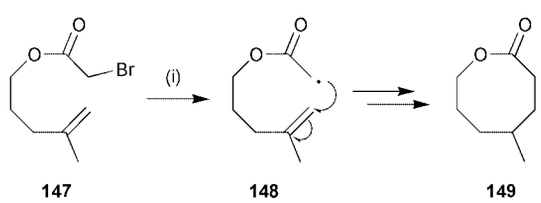
Scheme 36 *Reagents and conditions*: i, Bu_3SnH, AIBN, MeCN, reflux, 91%.

Toddaquinoline, a biologically active alkaloid with a benzo[*h*]quinoline skeleton, has been synthesised by Bu_3SnH-mediated cyclisation of aryl radicals onto the 2-position of a pendant pyridine ring.[163] The aryl radical also cyclises onto the 4-position of the pyridine ring. The protocol has been improved by using cobalt(I)salophen to improve the yield and regioselectivity of the synthesis of toddaquinoline.[164]

Benzothiophenes have been prepared by thiyl radical addition to alkynyl group of several different phenyl alkynyl derivatives.[165] The resulting vinyl radicals undergo cyclisations to yield benzothiophenes and other products. New benzofuran and benzothiophene ring systems have been synthesised by flash vacuum pyrolysis (FVP) of stabilised phosphorus ylides.[166]

11 Macrocyclisation

In general, the formation of rings with more than seven atoms using radical cyclisation have unfavourable rates and the interception of intermediate radicals by hydrogen donors such as Bu_3SnH is a problem. The most common method of overcoming this rate problem is to use favourable polarity, *e.g.* cyclise nucleophilic alkyl radicals onto electrophilic centres or *vice versa*. Synthesis of bicyclic heptanolactones (8-membered ring lactones) by an 8-*endo* cyclisation of (alkoxycarbonyl)methyl radicals has been reported (Scheme 37).[167] In the example shown, the α-bromoester precursor **147** gives an electrophilic α-ester radical **148** which cyclised onto the weakly nucleophilic alkene to yield the product of 8-*endo* cyclisation **149**. This favourable balance of philicity is essential to overcome the problem of unfavourable entropy. Theoretical calculations indicate that 8-*endo* cyclisation is favoured over 7-*exo* cyclisation which is not observed in any of the actual reactions. Some uncyclised reduced products are obtained in each reaction.



Scheme 37 *Reagents and conditions*: i, Bu_3SnH (syringe pump addition), AIBN, benzene, reflux, 38% (uncyclised reduced product 18%).

The most commonly used method for overcoming the unfavourable entropy is to use cyclisation of nucleophilic alkyl radicals onto the β-position of α,β-unsaturated ketones, esters or amides. A detailed study, including rates of cyclisation, has been reported for the synthesis of 12-, 15-, 18-, 21- and 24-membered macrocyclic lactones from ω-iodopolyoxaalkyl acrylates derived from tri-, tetra-, penta-, buta- and heptaethylene glycols. The radical reactions yield mixtures of uncyclised reduction products and macrocyclic ethers formed by *endo* cyclisation.[168] In these cyclisations the nucleophilic β-alkoxyethyl radicals were cyclised onto the β-position of α,β-unsaturated esters. This general protocol has also been adapted for use with water as a solvent using triethylborane as the initiator.[169] The same advantageous philicity has been applied to the synthesis of bicyclic rings containing a β-lactam and 7-, 8- and 9-membered carbocyclic rings.[170] The radical cyclisation is facilitated *via* cyclisation of *N*-pendant vinyl radicals,

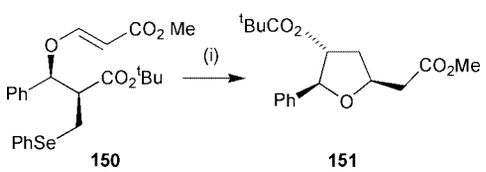
generated by addition of $Ph_3Sn^{\bullet}$ or $PhS^{\bullet}$ radicals onto the *exo* position of *N*-pendant alkynes, onto the β-position of α,β-unsaturated ketones attached to the 4-position of the β-lactams.

Other methodologies include the synthesis of silylated 11-membered ring stilbene lactams by intramolecular addition of aryl radicals onto trimethylsilyl-alkynes.[171] New 12- to 22-membered macrocyclic lactones have been prepared by macrocyclisation of radicals centred on the central carbon atom of β-ketoesters, generated from oligomethylene di-3-oxobutanoates using $Mn(OAc)_3$ oxidation, onto α,α,ω,ω-tetraphenylalka-α,ω-dienes.[172]

Photoinduced electron transfer (PET) decarboxylation of alkylcarboxylates in water has been reviewed, including reports of the lactams and lactones with ring sizes from 5 to 28 and a broad range of functionalities.[5]

12 Stereoselectivity

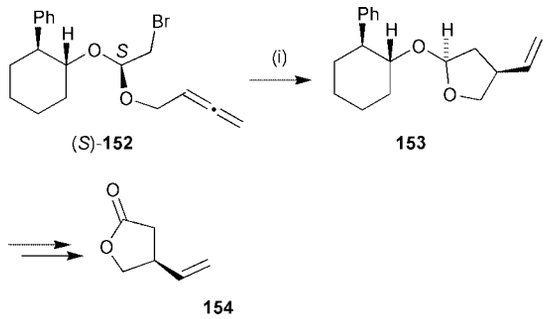
The application of protocols used in stereoselective synthesis in general continue to be applied to radical cyclisation reactions. Diastereoselectivity in 5- or 6-*exo* cyclisation is commonly observed in radical cyclisation and used for the synthesis of heterocycles. An example[31] is illustrated in Scheme 10 for cyclisation onto oximes in which the *trans* diastereomer is predominant and is explained by instability of the *cis*-transition state due to steric hindrance.[31] This protocol facilitates the synthesis of 5-, 6- and 7-membered nitrogen heterocycles with hydroxy and amino substituents **39**. The use of SmI_2 normally gives higher diastereoselectivity than Bu_3SnH.[36] An interesting example to illustrate the potential of diastereoselectivity in radical cyclisations is the synthesis of trisubstituted tetrahydrofurans using standard Bu_3SnH methodology (Scheme 38).[173] The alkyl radical generated from the phenylselanyl precursor **150** cyclises with total diastereoselectivity onto the β-position of the α,β-unsaturated ester to give the tetrahydrofuran **151** in 90% yield. A similar diastereoselective synthesis of a bicyclic γ-lactam has been achieved by radical cyclisation of a β-aminoacrylate derived from 4-(2-bromoethyl)azetidin-2-one.[174]



150 **151**

Scheme 38 *Reagents and conditions*: i, Bu_3SnH, AIBN, toluene, reflux, 90%.

The addition of enantiomerically pure chiral auxiliaries to radical precursors which facilitates the formation of diastereomers after cyclisation has been reported for several protocols. These diastereomers can be separated and following removal of the auxiliary, pure enantiomers are obtained. An example is the synthesis of enantiomerically pure 2-azabicyclo[3.3.1]nonanes.[64] An illustrative protocol uses cyclisation onto allenes in studies aimed at the synthesis of (*S*)-botryodiplodin.[89,90] The protocol uses the Ueno–Stork reaction with a bromoacetal precursor for generating γ-lactones. (±)-Botryodiplodin has been synthesised using the protocol.[89] Use of a chiral auxiliary [(1*R*,2*S*)-2-phenylcyclohexanol] in the enantiomerically pure precursor (*S*)-**152** facilitates a largely diastereoselective cyclisation to the tetrahydrofuran **153** (dr 90 : 10) (Scheme 39).[90] Separation of the diastereomers and oxidative removal of the auxiliary yields the enantiomerically pure (ee >99%) γ-lactone **154**. In a further example, enantiomerically pure perhydro-1,3-benzoxazines derived from (−)-8-aminomenthol as the chiral auxiliary undergo regio- and stereo-selective 5-*exo*-*trig* radical cyclisations leading to diastereomeric five-membered lactams.[175] These products were



(*S*)-**152** **153** **154**

Scheme 39 *Reagents and conditions*: i, Bu_3SnH, Et_3B, O_2, toluene, −78 °C, 88% (ee >99%).

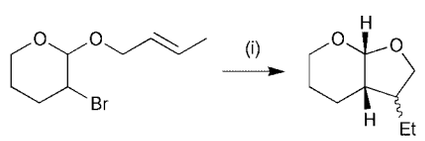
transformed into enantiomerically pure 3,4-disubstituted pyrrolidines by removal of the (−)-8-aminomenthol auxiliary.

A third advance reports the development of stereoselective radical cyclisation of α-bromoacetals using desymmetrisation of 1,4-dien-3-ols and related compounds *via* Ueno–Stork radical cyclisations. The iodoacetal was placed on the alcohol of the 1,4-dien-3-ol and cyclised.[91] The stereochemistry of the cyclisation is controlled by the acetal centre giving high diastereoselectivity.

13 Reagents for radical cyclisation

The synthesis of heterocycles using radical cyclisation depends on the same advances in radical synthetic methodology as non-heterocyclic systems. The use of Bu_3SnH continues to be dominant and a very useful reagent even with the problems of work-up. The toxicity of organotin compounds precludes use on a large scale by the pharmaceutical industry. The purification problems can be partially overcome by using Bu_3SnH catalytically. In this methodology Bu_3SnCl is reduced *in situ* with sodium borohydride or sodium cyanoborohydride thereby producing small amounts of Bu_3SnH which is continually used up generating more Bu_3SnX (X = H, Br, I) in a cycle. This also has the advantage of keeping the concentration of Bu_3SnH low to facilitate cyclisation instead of reduction. Polymethylhydrosiloxane and KF have also been used for regeneration of Bu_3SnH.[134] Tris(trimethylsilyl)silane $(TMS)_3SiH$ is commonly used in place of Bu_3SnH.[13,25,40,62,122] For instance, phenylselanyl groups are abstracted using tris(trimethylsilyl)silane and triethylborane (Et_3B) as initiator in the synthesis of pyrrolidines.[25] Carbamyl radicals generated from reaction between phenylselenocarbamates and $(TMS)_3SiH$ undergo 5-*exo* cyclisation onto alkenes to yield γ-lactams.[40] Tri-2-furanylgermane with triethylborane and oxygen as initiator has been used in place of Bu_3SnH in the synthesis of 3,5-disubstituted tetrahydrofurans.[73]

Hypophosphorous acid (H_3PO_2), and the corresponding 1-ethylpiperidine salt, *N*-ethylpiperidine hypophosphite (EPHP), have been recently developed for radical generation in both aqueous and organic media.[133,176,177] The method avoids many of the problems associated with tributyltin hydride based methodology. A range of halogeno substrates can be used and an example is shown in Scheme 40 for the conversion of precursor **155** to the bicycloheterocycle **156** in high yield.[176] EPHP has been used for the diastereoselective synthesis of tetrahydrofurans using a carbohydrate auxiliary from vinylogous esters/carbonates.[177] Aryl iodide and alkyl bromide



155 **156**

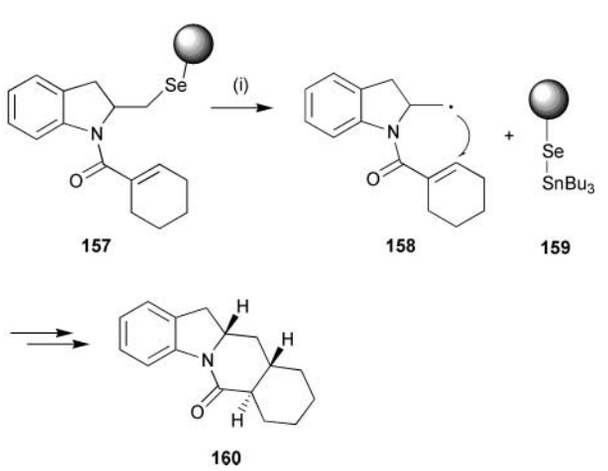
Scheme 40 *Reagents and conditions*: i, *N*-ethylpiperidine hypophosphite (EPHP), AIBN, benzene, reflux, 74%.

substrates were subjected to these conditions and yields ranged from 63–94%, *e.g.* the synthesis of indolines and dihydrobenzofurans using EPHP to generate the aryl radicals.[133] Hypophosphorous acid has also been used for the reduction of arenediazonium salts to generate aryl radicals in the synthesis of indoles.[160]

The most commonly used radical initiator has been azoisobutyronitrile (AIBN). However, most fine chemical companies have now phased out the sale of AIBN and sell the cyclohexyl analogue, 1,1′-azo(cyclohexanecarbonitrile) (ACCN). Examples of the use of this initiator are reported in the literature.[8] Benzene is a listed carcinogen in Europe and is becoming less used as a solvent in favour of toluene. Cyclohexane is becoming the preferred solvent for Bu_3SnH mediated reactions because of evidence of toluene and benzene participating in radical reactions rather than acting only as a solvent; it also has a lower boiling point than toluene.[16,38] The use of triethylborane and oxygen as an initiator is useful because it allows reactions to be carried out at low or room temperature.[25,34,35,73,89] Triethylborane can also be used to initiate iodine atom transfer reactions.

The use of water as a solvent for carrying out radical reactions is a welcome start to using the most environmentally safe and cheap solvent. Water soluble initiators have been developed for carrying out radical reactions in water. Pyrrolidin-2-ones have been synthesised using the radical initiators 4,4′-azo(4-cyanopentanoic acid) and 2,2′-azo(2-methylpropanamidine) dihydrochloride in water.[44] A water-soluble tetrathiafulvalene reagent has also been developed and applied to a range of arenediazonium tetrafluoroborates and chlorides.[131] In the macrocyclisations of nucleophilic β-alkoxyethyl radicals onto the β-position of α,β-unsaturated esters the protocol using triethylborane as the initiator with water as a solvent shows improved yields.[169]

The use of solid phase synthesis has started to be applied to radical reactions but is obviously an area that will see expansion in the future. The advantage with solid phase synthesis is that the radical precursor is attached to the resin and the Bu_3Sn-products can be washed off when the radical cyclisation is complete. Alternatively, the Bu_3Sn-product can be left attached to the resin and the product washed off. This protocol is exemplified with the use of selanyl-attached precursors (Scheme 41).[178] The precursor is attached to the resin **157** and reacted with Bu_3SnH to yield an intermediate radical **158** which is released from the resin leaving the Bu_3Sn moiety attached to the resin **159**. The radical undergoes a useful 6-*endo* cyclisation to the tetracycle **160**. Other examples of the use of solid phase synthesis include the cyclisation onto oximes in the synthesis of pyrrolidines with hydroxy and amino substituents shown in Scheme 10.[34] Dihydrobenzofurans have been prepared by



Scheme 41 *Reagents and conditions*: i, Bu_3SnH, AIBN, toluene, 90 °C, 36%.

cyclisation of aryl radicals onto side chain allyloxy groups.[135] Radical cyclisation of β-bromoethylacetals has been carried out on solid support.[88]

Another methodology for the use of solid phase synthesis is to attach the radical generating reagents to solid phase resins with the radical precursors in solution. Solid phase supported Cu(I) catalysts have been developed for atom-transfer radical cyclisation of 2-haloacetamides for the synthesis of pyrrolidin-2-ones[47] and cyclic ethers and amines have been obtained by the use of polymer-supported tetrathiafulvalene in radical–polar crossover reactions with slightly lower yields than in the corresponding solution-phase reactions.[132]

Zard's methodology using thioxanthates and related compounds to generate radicals can use Bu_3SnH but alternative reagents such as peroxides can be used with the aim of avoiding use of Bu_3SnH.[16,62] Xanthate transfer initiated by AIBN or dialkyl peroxides has proved useful for non-triorganotin hydride syntheses, *e.g.* to generate side chain α-amidyl radicals for 6-*exo* cyclisation onto cyclohexanes in the synthesis of octahydroindole ring systems.[62]

A number of reductants can be used for generating radicals in heterocyclic synthesis. The use of samarium diiodide for ring expansions and cyclisation reactions has been reviewed[1] and used in a number of useful synthetic procedures.[35,36,85] For instance, reduction of benzotriazole groups α to a nitrogen atom generates α-aminoalkyl radicals which have been used in the synthesis of pyrrolidines.[24] The use of a tetrathiafulvalene (TTF) as a reductant of arenediazonium salts for the generation of aryl radicals continues to be developed by Murphy and co-workers in their TTF induced radical–polar crossover protocol (see Scheme 4).[11] This procedure for generating aryl radicals also avoids use of toxic triorganotin hydrides. The protocol has been adapted for use in water[131] and on solid phase supports.[132] The use of nickel powder to generate radicals has also been developed but only works with reactive precursors such as α,α,α-trichloroamides[9,69,70] (see Scheme 3) and *N*-acyl oximes to generate iminyl radicals.[17]

The application of metals and organometallics in radical heterocyclic synthesis continues. The use of Cu(I) with ligands has provided a useful new methodology[46,61] for radical cyclisation without using the toxic Bu_3SnH and has proved particularly successful for the generation of α-amidyl radicals.[61,65,66,68] Ferrocenium hexafluorophosphate has been used as a SET oxidant[29] and an active manganese species derived from Li_2MnCl_4.[30,93] The synthesis of pyrrolidinones using iodine- or bromine-atom transfer cyclisations has been facilitated using dimanganese decacarbonyl $[Mn_2(CO)_{10}]$ and light catalysis which generates $[^{\bullet}Mn(CO)_5]$ *in situ*.[43] The procedure requires weak carbon–halogen bonds for efficient halogen-atom abstraction. Cobalt complexes [Co(salen)–$NaBH_4$–O_2] continue to be used as an alternative to Bu_3SnH, *e.g.* in the synthesis of perhydrofuro[2,3-*b*]pyran (and furan)-3-yl methanols.[81]

Mn(III) oxidation has been used with β-dicarbonyl compounds as precursors for generating carbinyl radicals centred on the carbon atom between the two carbonyl groups which undergo cyclisation (*e.g.* Scheme 8).[19] The procedure is effective but largely limited to β-dicarbonyl compounds.[19,20,65,67]

Photoinduced electron transfer (PET) decarboxylation of alkylcarboxylates in water has been reviewed.[5] The protocol leads to primary, secondary or tertiary carbon radicals which undergo C–C bond coupling reactions which give rise to heterocyclic ring systems (*e.g.* lactams, lactones, cyclopeptides, cyclic ethers and crown ethers) with ring sizes from 5 to 28 and a broad range of functionalities. Other applications of PET include the generation of silicon-centred radical species for the synthesis of bicyclic tetrahydrofurans and benzotetrahydrofurans[179] and a PET catalysed radical cation hetero Diels–Alder reactions for the synthesis of highly functionalised tetrahydrocarbazole derivatives.[180]

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