REVIEW

Synthesis of heterocycles by radical cyclisation

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1 Introduction

The use of radical cyclisation for the synthesis of heterocycles continues to grow and many new methodologies have been published in addition to the use of tributyltin hydride (Bu_3SnH) or related triorganostannanes. The majority of radical cyclisations in heterocyclic chemistry are still carried out using Bu_3SnH. The reaction conditions are generally to use an excess of Bu_3SnH with a smaller equivalent (10–25 mol%) of a radical initiator, most commonly azobisisobutyronitrile (AIBN). The reactions are generally refluxed in benzene or toluene for 1–10 hours. Bu_3SnH mediated reactions are well known and therefore the mechanisms will not be discussed in detail. In Section 12 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.

Most radical cyclisations used for the syntheses of heterocycles proceed by 5-*exo*-*trig* regioselectivity. Therefore, the review has not been divided on the basis of ring size. The review has largely excluded heterocyclic syntheses in which the heterocyclic ring(s) are not part of the radical cyclisation. Therefore, carbocyclic cyclisations in molecules which contain a heterocycle are not included. A new section on macrocyclisation has been included (Section 11). Stereoselective synthesis of heterocycles has become increasingly important and a number of examples are shown.

A number of reviews which include the synthesis of heterocycles *via* radical cyclisation have been published. Reviews on radical chemistry which contain significant sections on heterocyclic synthesis include the use of xanthates in free radical reactions,[1] the formation of C–C bonds mediated by cerium reagents, mainly cerium(IV) ammonium nitrate (CAN)[2] and the use of *N*-aziridinyl imines and azides for the generation of C- and N-centred radicals which can undergo cyclisation.[3] The use of temporarily silicon-tethered molecules in synthesis,[4] in particular the use of (bromomethyl)dimethylsilyl ethers, has been reviewed. Free radical mediated macrocylisations and transannular cyclisations[5] and the synthesis of tetrahydrofuranyl and -pyranyl derivatives by radical cyclisation onto the β-position of β-alkoxyacrylates have also been reviewed.[6]

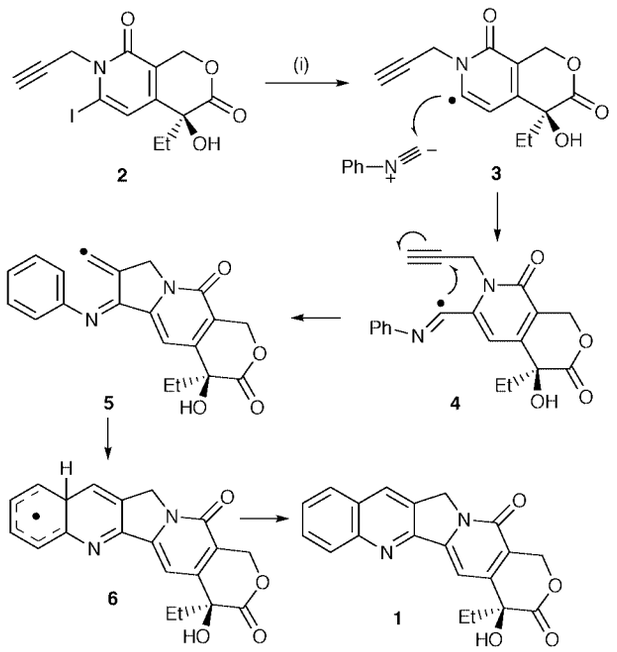
2 Natural product synthesis

Radical cyclisation continues to form one of the central methodologies for the synthesis of natural products containing heterocyclic rings. Complex heterocyclic systems have been constructed with increasing ingenuity in radical cyclisations. These radical cyclisation protocols commonly have several advantages over non-radical methods which require laborious multi-step alternative syntheses. The radical cyclisations which do not generally suffer from steric hindrance or racemisation problems, can be carried out in neutral organic solutions and radical cascade reactions allow the construction of two or more rings in one-pot reactions. In this section a number of illustrative syntheses are discussed while many others are detailed in respective sections defined by the nature of the heterocyclic ring(s).

One of the most novel radical methodologies continues to be developed by Curran and co-workers for the synthesis of the important anticancer alkaloid camptothecin **1**[7,8] and analogues such as mappicine.[9] This cascade methodology is unusual in that a complex heteroarene system is constructed as opposed to alicyclic heterocycles. The development of this protocol indicates the potential for the use of cascade radical cyclisations for the syntheses of complex multi-ring heterocycles, a direction for synthesis which has barely been exploited at this time.

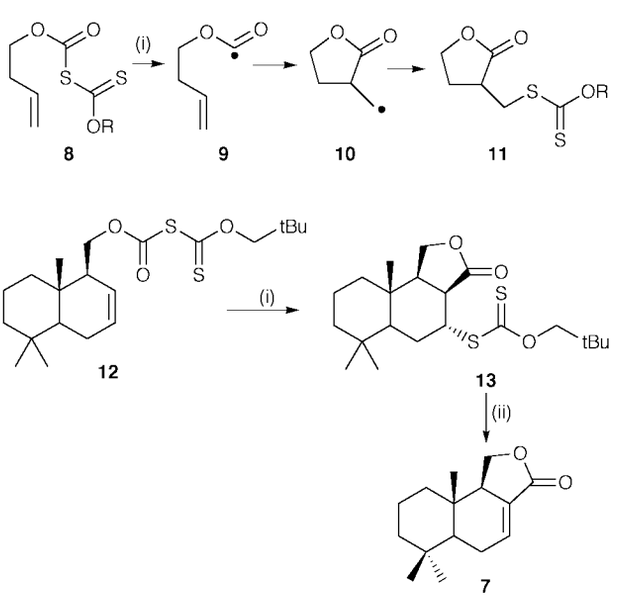
In this protocol, rings B and C are put together in a one-pot radical cascade reaction. The Curran group has now reported the syntheses of most of the camptothecin group of anticancer agents using this protocol as well as new analogues which show promising improved biological activity. The synthesis of camptothecin **1**, the main alkaloid in the group, is shown in Scheme 1 as an example of this protocol. Photolysis of the *N*-propargyl-6-iodo-2-pyridone **2** in the presence of phenyl isocyanide and hexamethylditin generates the pyridone radical **3** which undergoes bimolecular addition to the reactive isonitrile. The new radical **4** thus generated undergoes 5-*exo*-*dig* cyclisation onto the pendant alkyne and the intermediate vinyl radical **5** cyclises onto the benzene ring. The intermediate π-radical **6** undergoes an oxidation by a mechanism which is as yet unclear to yield the pentacyclic camptothecin in good yield. The methodology has been used for a wide range of analogues with substituents on the alkyne, benzene ring A and the pyridone ring.

An area of continuing and important research is to develop new methods of radical generation which avoid the use of the toxic triorganotin hydrides which are also troublesome to separate from reaction products. Zard and co-workers have elaborated a methodology using xanthates as radical precursors.[10,11] Thermal dissociation or treatment with lauroyl peroxide as an initiator generates radicals which are able to



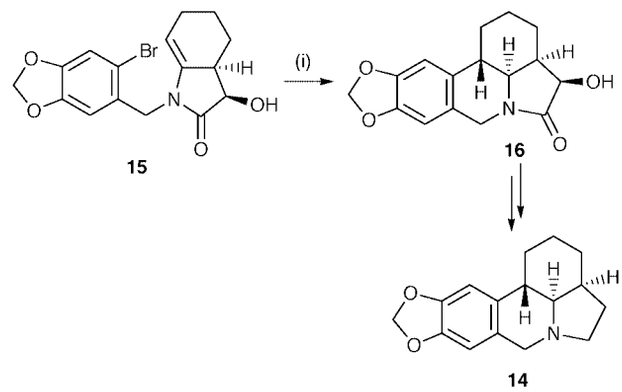
Scheme 1 *Reagents and conditions*: i, PhNC, $(Me_3Sn)_2$, PhH, sun lamp, 70 °C, 8 h, 63%.

undergo cyclisations to yield cyclised radicals which abstract the xanthate groups from the radical precursors to maintain the cycle of radical chain reactions. This protocol is illustrated in Scheme 2 for the synthesis of lactones by 5-*exo* cyclisation.[10] An application of the protocol is also shown in Scheme 2 for the synthesis of the butenolide (±)-cinnamolide **7**.[10] Initial homolysis of the xanthate **8** yields acyloxy radical intermediate **9** which undergoes 5-*exo* cyclisation onto a suitably placed alkene. The cyclised lactone radical **10** completes the chain reaction by the abstraction of the xanthate group to generate the starting radical **9** and the xanthate product **11**. Application of the procedure to starting xanthate **12** yields the lactone **13** in a stereoselective *cis* 5-*exo* cyclisation. Lactone **13** was readily transformed to the natural product **7** to complete the total synthesis. A short synthesis of tetracyclic alkaloid (±)-matrine by a radical cascade from a xanthate precursor as the key step has also been reported by Zard and co-workers.[11]



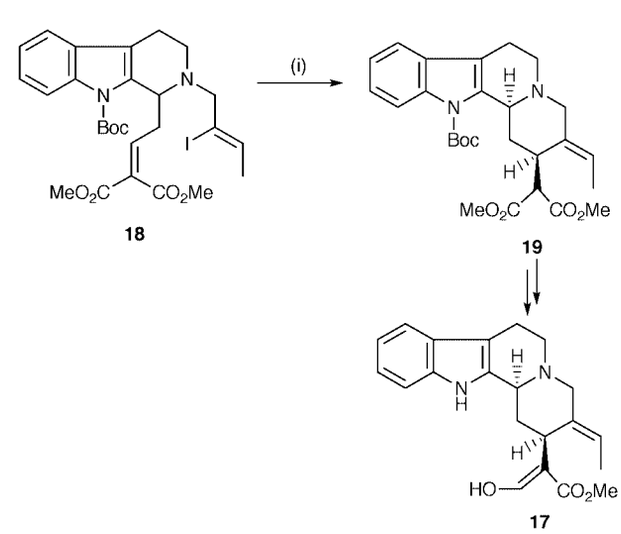
Scheme 2 *Reagents and conditions*: i, *hv* (500 W), PhMe, 111 °C, 9.5 h, 51% from alcohol; ii, DBU, $CHCl_3$, rt, 15 min, 80%.

The use of aryl radical cyclisations to form benzoheterocycles is now a common radical procedure and is illustrated with the synthesis of the *Amaryllidaceae* alkaloid α-lycorane **14** (Scheme 3).[12] The key step involves a 6-*endo* cyclisation of the intermediate aryl radical, generated from starting material **15**, onto the β-position of an enamide using the standard Bu_3SnH procedure. The cyclised galanthan product **16** was obtained in 79% yield as a single diastereomer. The radical synthesis of benzoheterocycles is more fully discussed in section 9.

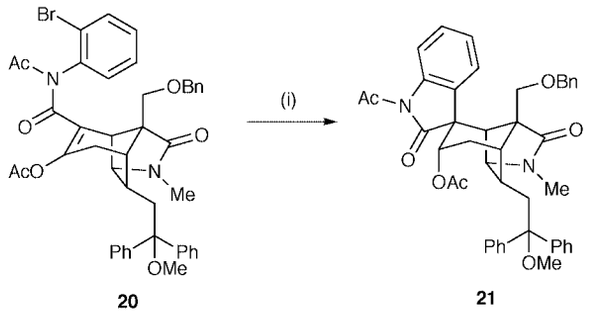


Scheme 3 *Reagents and conditions*: i, Bu_3SnH, AIBN, PhH, reflux, 79%.

A number of syntheses of indole alkaloids have been reported using radical cyclisation. A short synthetic route to (±)-geissoschizine **17** was developed which features the construction of a corynanthe-skeleton **19** *via* a 6-*exo* radical cyclisation of a vinyl radical generated from the starting indole **18** (Scheme 4).[13] The 6-*exo* cyclisation is facilitated by use of an α,β-unsaturated ester to speed up the rate. The synthesis is also notable in the use of triethylborane (Et_3B) with catalytic oxygen as the initiator which allows the reaction to be carried out at room temperature. In studies of the synthesis of the complex indole alkaloid gelsimine, radical cyclisation of the intermediate aryl radical, generated from precursor **20**, yields the oxindole moiety on the gelsimine skeleton **21** in high yield (Scheme 5).[14] The procedure allows the oxindole to be put together at a later stage in the synthesis by a facile route. The oxindole procedure is now well used and normally is selective for 5-*exo* cyclisation of the aryl radical onto the α-position of the α,β-unsaturated amide.

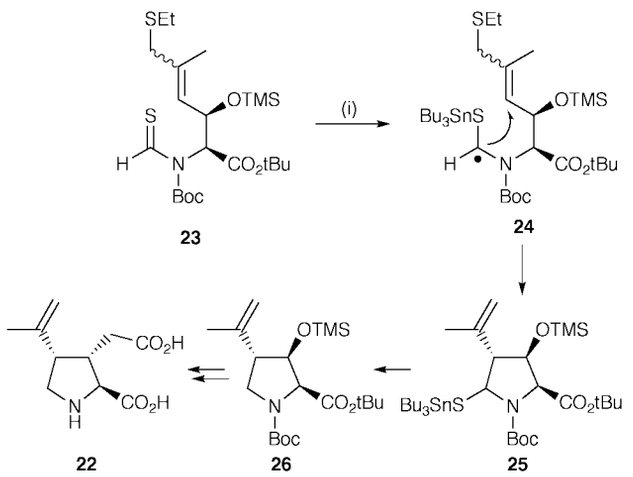


Scheme 4 *Reagents and conditions*: i, Bu_3SnH, Et_3B, PhMe, rt, **19** (*E*) 33%, **19** (*Z*) 17%.



Scheme 5 *Reagents and conditions*: i, Bu_3SnH, AIBN, PhH, *hv*.

The synthesis of (−)-α-kainic acid **22** has been achieved using a novel radical protocol which involves addition of tributyltin radicals to the sulfur atom of a thioaldehyde in precursor **23** (Scheme 6).[15] The resulting radicals **24** undergo stereoselective 5-*exo* cyclisation to yield **25**. The Bu_3SnS-group is reduced off during the radical reaction by further Bu_3SnH to yield the trisubstituted pyrrolidine **26**, which was converted to (−)-α-kainic acid. An equivalent radical cyclisation using thiols in place of Bu_3SnH is reported in the same study.

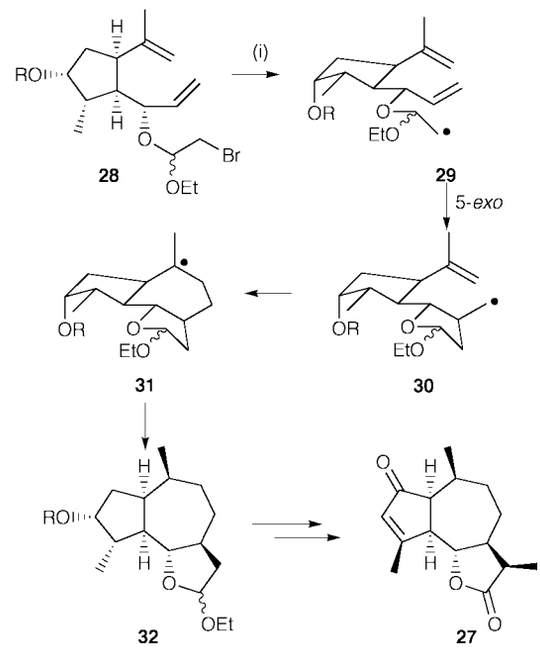


Scheme 6 *Reagents and conditions*: i, Bu_3SnH, AIBN, 73%.

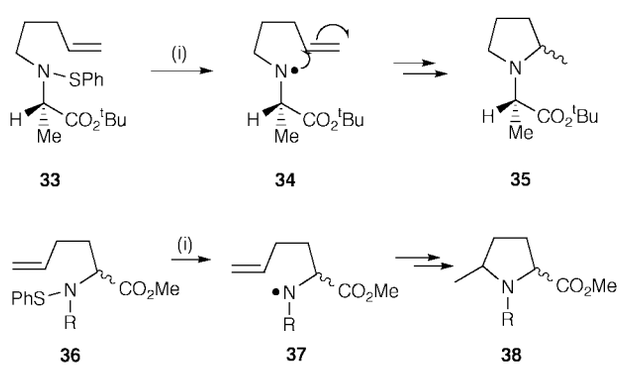
The synthesis of the sesquiterpenes, (+)-cladantholide **27** and (−)-estafiatin, which are representative of guaidanolide lactones have been synthesised using an unusual 5-*exo*, 7-*endo* cyclisation (Scheme 7).[16] The cascade precursor **28** is prepared by the standard method of adding 1,2-dibromo-1-ethoxyethane to a suitable alcohol. The radical **29** generated from the β-bromoacetal undergoes normal 5-*exo* cyclisation using Bu_3SnH. The novel reaction is the second radical cyclisation in the cascade in which the intermediate radical **30** selectively undergoes 7-*endo* cyclisation to yield **32** *via* intermediate **31** to complete the 5,7-membered ring structure which is common in sesquiterpenes. In the second cyclisation, 6-*exo* regioselectivity is disfavoured because of the methyl substituent which creates steric hindrance. However, the selective 7-*endo* cyclisation is nevertheless surprising.

3 Nitrogen heterocycles

The synthesis of nitrogen heterocycles using radical methods continues to be of increasing interest. In particular, the synthesis of pyrrolidines by 5-*exo* cyclisation is well suited to the use of radical cyclisation. The radical can be generated in a number of positions relative to the *N*-heteroatom. The first of these is the use of aminyl radicals and a number of applications have been reported. α-Amino acid aminyl radicals derived from sulfenamide precursors undergo 5-*exo*-*trig* cyclisations onto suitably placed *N*-alkenyl or α-alkenyl chains on the amino acids with reasonable diastereoselectivity (Scheme 8).[17] The



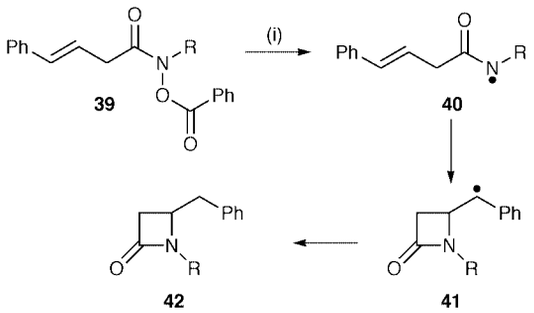
Scheme 7 *Reagents and conditions*: i, syringe pump addition, Bu_3SnH, AIBN, PhH, reflux.



Scheme 8 *Reagents and conditions*: i, Bu_3SnH, AMBN, PhMe, reflux, 6 h, 81%; a. R = H 92%, de = 57%; b. R = Bn 44%.

α-ester of the amino acid imparts electrophilic behaviour to the aminyl radicals and facilitates cyclisation onto alkenes. The aminyl radical precursors are prepared from the α-amino esters using benzenesulfenyl chloride in high yield. Cyclisation of aminyl radicals **34**, generated from α-amino esters with *N*-alkenyl groups **33**, *i.e.* with the α-ester *exo* to the ring, yield pyrrolidines **35** in good yields with reasonable diastereoselectivity but also yield some reduced uncyclised material (Scheme 8). When the aminyl radicals **37** are generated from α-amino esters with side chain alkenyl groups **36**, proline analogues are synthesised (Scheme 8). When the primary sulfenamide **36a** was used a very high yield of the respective proline **38a** was obtained. However, when the *N*-benzyl derivative **36b** was used the yield of **38b** was only 44% with uncyclised reduced products. The effect of the electron donating benzyl group is sufficient to lower the electrophilicity of the aminyl radical centre and make cyclisation less favourable.

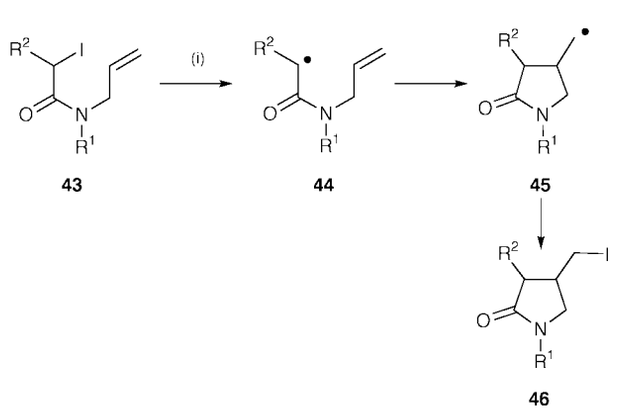
Amidyl radicals which are more electrophilic than aminyl radicals undergo cyclisation more easily. Amidyl radicals **40** generated from Bu_3SnH mediated homolysis of *O*-benzoyl hydroxamic acid derivatives **39** undergo 4-*exo*-*trig* cyclisation to furnish β-lactam derivatives **42** together with reduced and rearrangement products (Scheme 9).[18] The reaction is biased to encourage the unfavourable 4-*exo* cyclisation by use of a styryl side chain which yields a stable intermediate benzylic radical **41**.



Scheme 9 *Reagents and conditions*: i, Bu_3SnH, AIBN, syringe pump 8 h, 1 : 1 cyclohexane–toluene.

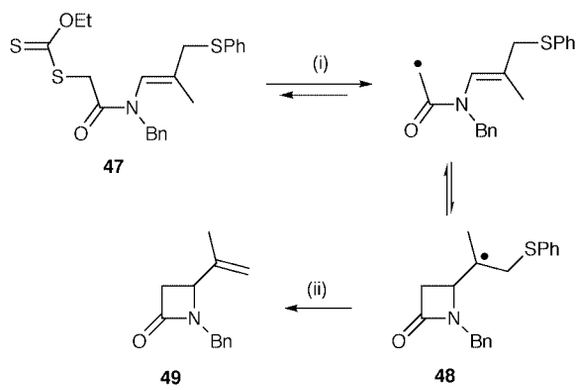
Further studies of the cyclisation of aminyl radicals provide more examples of the potential for synthesis but also useful mechanistic data which will help plan syntheses.[19–21] Different data indicate reversibility[19,20] and irreversibility[21] of 5-*exo* aminyl radical cyclisation. The latest study suggests that the cyclisation is reversible.[20] The problems of reversibility can be overcome by use of Lewis acids to enhance the electrophilic behaviour of aminyl radicals and facilitate ready synthesis of pyrrolidines.[22] The use of amidyl radicals, which are more electrophilic than aminyl radicals, for the synthesis of 5- and 6-membered ring lactams has been further developed with extensive kinetic measurements.[23] Cyclisation of iminyl radicals to yield 5- and 6-membered ring nitrogen heterocycles has also been studied with measurement of the rates of cyclisation.[24]

A large number of radical reactions using cyclisation of radicals, β to the nitrogen atom, onto β-alkenes have been used for the synthesis of a wide range of pyrrolidines. For instance, γ-lactams have been prepared by several methods.[25,26] 2-Iodo-*N*-(prop-2-enyl)acetamides upon treatment with Et_3B in boiling benzene undergo iodine atom transfer cyclisation to afford the 4-(iodomethyl)pyrrolidin-2-ones in high yields (Scheme 10).[25] Triethylborane (Et_3B) and oxygen were used to initiate the reaction thus providing a synthetic route which does not require Bu_3SnH. In the iodine abstraction mechanism, the cyclised radical **45** abstracts iodine from the starting material **43** to yield the product iodide **46** and intermediate radical **44**. The methodology was also extended to the synthesis of γ-lactones. γ-Lactams (pyroglutamates) have been synthesised from dehydroalanines which contain chiral ester auxiliaries *via* 5-*endo* radical cyclisations using Bu_3SnH.[26] No improvement on the cyclisation reaction was found when using triethylborane as the initiator.



Scheme 10 *Reagents and conditions*: i, Et_3B, PhH, reflux; R^1 = Me, Bn, Ts; R^2 = H, Me.

β-Lactams have been synthesised by several methods using radical cyclisation. All the methods have some factor in the mechanism to favour 4-membered ring cyclisation which is otherwise unfavourable. Zard and co-workers[27] have applied their xanthate methodology to β-lactams by cyclisation of *N*-alkenylacetamides. An example is shown in Scheme 11. Lauroyl peroxide is used to initiate the reaction and abstract the xanthate group from starting acetamide **47**. The reversible and unfavourable 4-*exo* cyclisation is pushed to completion by a rapid β-elimination of phenylthiyl radicals from intermediate **48** to yield the β-lactam **49**. A number of similar protocols with xanthates rely on subsequent reactions in the cascade which remove the cyclised radical from the equilibrium. The protocol using xanthates is attractive because it avoids the use of the toxic and troublesome triorganotin hydrides. Zard and co-workers[28] have also synthesised β-lactams from *N*-alkenyltrichloroacetamides using nickel powder for generating the intermediate radicals. β-Lactams can also be synthesised using Bu_3SnH from *N*-alkenyl-α-bromoacetamides which contain a radical stabilising aryl substituent on the β-position of the alkene.[29] The stabilising substituent on the intermediate benzylic cyclised radical pushes the unfavourable equilibrium towards 4-*exo* cyclisation. The CAN oxidation of *N*-alkenyl-α-ethoxycarbonylacetamides affords variously functionalised β-lactams through a 4-*exo-trig* cyclisation of intermediate α-carbamoylalkyl radicals.[30]

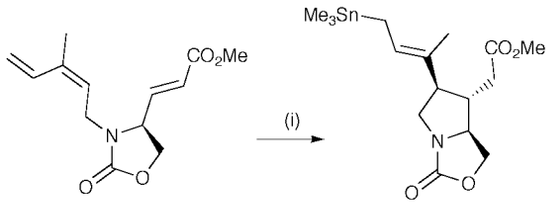


Scheme 11 *Reagents and conditions*: i, dilauroyl peroxide, cyclohexane, reflux; ii, -(PhS$^{\bullet}$), 48%.

The synthesis of pyrrolidines by cyclisation of radicals, β to the nitrogen atom, onto β-alkenes is now a common protocol. An example of this is the cyclisation of *N*-tosyl-β-(phenylselanyl)allylamines to yield *N*-tosylpyrrolidines.[31] However, the synthesis of pyrrolidines by cyclisation of radicals, α to the nitrogen atom, onto γ-alkenes is a less common protocol. A novel variant of this protocol uses the reaction between Bu_3SnH and *N,N*-dialkyl-*N*-(iodomethyl)-but-3-enylamine salts for the synthesis of 5-membered ring ammonium salts.[32] The quaternisation improves the Thorpe–Ingold effect and facilitates improved cyclisation in otherwise difficult to cyclise examples.

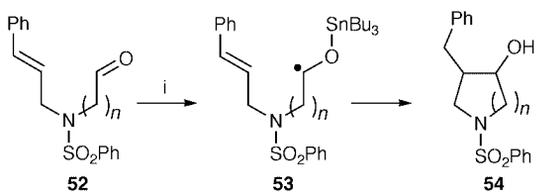
The addition of a radical generating reagent A–B across two alkenyl groups β to a nitrogen moiety continues to be a common synthetic protocol. The addition of a radical reagent A–B can be R_3SnH and is well exemplified in the key step in a synthesis of (−)-α-kainic acid from L-serine using a trimethyltin radical carbocyclisation of a diene precursor[33] to make the C_3–C_4 bond as shown in Scheme 12.[34] The trimethyltin radicals are generated in low dilution from trimethyltin hydride, generated by reduction of trimethyltin chloride with sodium cyanoborohydride, and add to the more reactive *exo* double bond of the diene **50**. Subsequent 5-*exo* cyclisation generates the C_3–C_4 bond of the pyrrolidine ring generating a new α-methoxycarbonyl stabilised radical which in turn abstracts hydrogen from Me_3SnH to yield the synthetic intermediate **51** in good yield. The same cyclisations have also been achieved by using phenylthiol in place of trimethyltin hydride as the radical reagent A–B.[35]

A novel version of this protocol uses addition of tributyltin radicals onto the aldehyde oxygen atom of α- and β-amino aldehydes **52** to form intermediate *O*-stannyl ketyl radicals **53**



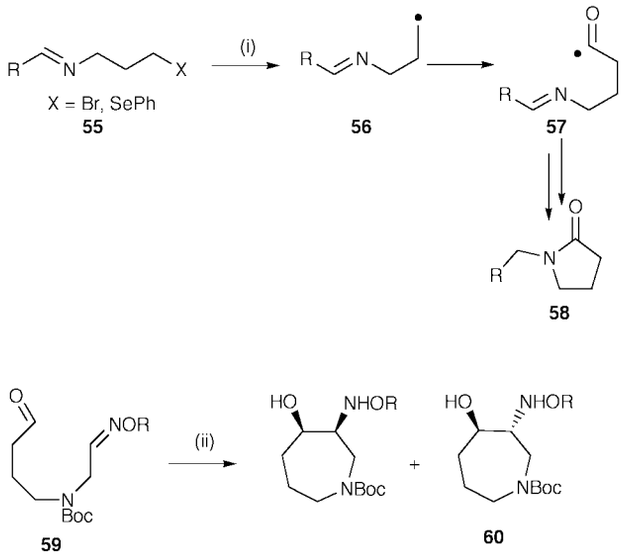
Scheme 12 *Reagents and conditions*: i, Me_3SnCl, $NaCNBH_3$, AIBN, *t*-BuOH, 55% 2.5 : 1 *trans* : *cis*.

rather than addition onto an alkene (Scheme 13).[36] Cyclisation (5- or 6-*exo*) of the ketyl radicals **53** onto suitably placed double bonds, followed by hydrolytic work-up to hydrolyse off the tributyltin group, gives rise to hydroxy-pyrrolidines **54** and -piperidines with good diastereoselectivity. A novel radical cyclisation used radical addition of toluene-*p*-sulfonyl bromide as the radical generating reagent A–B across the alkyne bonds of *N,N*-di(prop-2-ynyl)toluene-*p*-sulfonamide.[37] 3,4-Disubstituted pyrrolidines are formed with 80% diastereomeric excess *via* the addition of TsSePh to dialkyldiallylammonium salts to form the C_3–C_4 bond of the pyrrolidine ring.[38]



Scheme 13 *Reagents and conditions*: i, Bu_3SnH, AIBN, PhH, reflux; *n* = 1, 52% (*exo* : *endo* = 1.6 : 1); *n* = 2, 56% (dr 1.3 : 1).

Radical additions to C=N bonds provides an alternative route to nitrogen heterocycles and two examples are shown in Scheme 14. In the first protocol carbon monoxide is used to trap the intermediate radical.[39] The intermediate radical **56** generated from precursor **55** reacts with carbon monoxide under high pressure to generate a new intermediate carbonyl radical **57** which in turn undergoes an apparent 5-*exo* cyclisation onto the nitrogen of the imine group to yield the pyrrolidin-2-one **58**. The intermediate radical **56** is reluctant to undergo 4-*exo* cyclisation onto the nitrogen of the imine or 5-*endo* cyclisation onto the imine carbon which allows time for the relatively slow addition of carbon monoxide. The procedure is a 4 + 1 type carbonylation–annulation. In the second protocol the known cyclisation onto oxime ethers is used to generate the hexahydroazepine fragment in the total synthesis of (−)-balanol, a potent inhibitor of protein kinase C.[40] The 7-*exo* cyclisation is unusual but is facilitated by polarity effects wherein cyclisation of the intermediate nucleophilic *O*-tributyltin ketyl radical onto the electrophilic carbon atom of the oxime ether is strongly favoured. In this reaction the radical generating reagent A–B is Bu_3SnH which adds initially to the aldehyde group in the precursor **59**. The diastereoselectivity to give preferentially the required *trans* hexahydroazepine **60** further exhibits the usefulness of this protocol. The use of SmI_2 in place of Bu_3SnH promoted cyclisation which gave better selectivity in favour of the desired *trans* isomer. With SmI_2 the intermediate is the *O*-diiodosamarium ketyl.

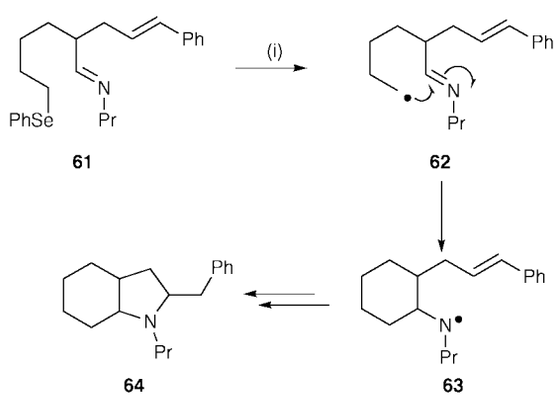


Scheme 14 *Reagents and conditions*: i, CO, AIBN, Bu_3SnH, PhH, reflux, 80 atm, 2 h, 70–80%; ii, R = Me, Bu_3SnH, AIBN, PhH, reflux, 1 : 2, 48%; R = Bn, Bu_3SnH, AIBN, refluxing PhH, 1 : 2.6, 50%; R = Bn, SmI_2, HMPA, *t*-BuOH–THF, 1 : 6.6, 53%.

4 Pyrrolizidines and other bicyclic nitrogen heterocycles

Pyrrolizidines and indolizidines have been common targets for radical cyclisation reactions using a number of different protocols. These protocols have now been applied to a much wider range of different bi- and poly-cyclic nitrogen heterocycles and can be envisaged for synthetic use in most ring systems. We have tried to define both protocols and synthetic targets in this section.

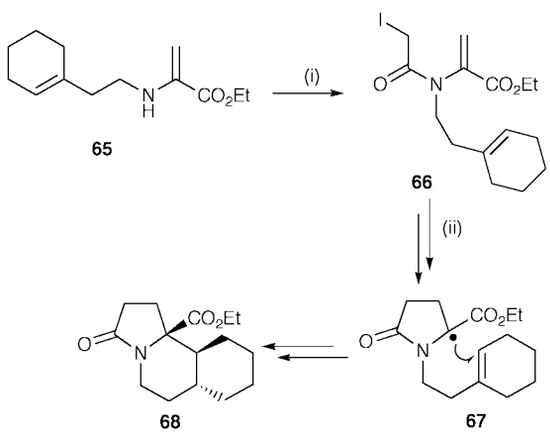
The application of synthetic methods using nitrogen centred radicals continue to be used. For instance, in the total synthesis of the indolizidine alkaloid 223AB the final ring closure step was achieved *via* a Bu_3SnH mediated radical cyclisation of a monocyclic chloramine onto a pendant side chain alkene.[41] The aminyl radical was generated from the chloroamine using reductive cleavage with CuCl and $CuCl_2$. Iminyl radicals, generated from iminodithiocarbonates [=N–N(R)CS_2Me] by irradiation with a sun lamp in the presence of small amounts of hexabutylditin, have been used to synthesise several bicyclic nitrogen heterocycles.[42] This methodology is similar to that for xanthates shown in Scheme 2. Aminyl radicals generated in tandem reactions, initiated by cyclisation of sp^3 carbon-centred radicals onto the electrophilic C-atom of imines, have been used to develop a new protocol for the synthesis of 2-azabicyclo-[3.3.0]octanes and perhydroindolines, spirocyclic amines and indolizidines.[43] An example of this use of imines as intermediates to aminyl radicals is shown in Scheme 15. Selenides, *e.g.* **61**, are used as the radical precursor to avoid reaction between halide substituted carbon atoms and nucleophilic nitrogen atoms in precursor molecules. Cyclisation of the carbon-centred radical **62** onto the imine generates an intermediate aminyl radical **63** which undergoes 5-*exo* cyclisation onto the pendant alkene to give the perhydroindoline **64** in good yield. This protocol can be used to synthesise the analogous 5-5, 5-6 and 6-6 nitrogen bicycles. The yields of the reactions in this general protocol are improved by using Lewis acids to increase the electrophilicity of the imine and the intermediate aminyl radicals.



Scheme 15 *Reagents and conditions*: i, Bu_3SnH, AIBN, PhMe, reflux, 57%.

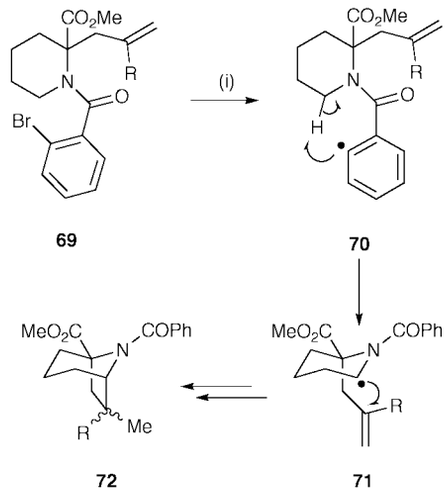
Many of the protocols for synthesising bicyclic nitrogen heterocycles use a nucleophilic nitrogen atom in a larger molecule in alkylation or acylation reactions to attach either a chain containing the group for generating the radical, or a chain containing the unsaturated functionality onto which the 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.

In the first of these protocols, the addition of α-halogenoacyl groups to the nitrogen atom is commonly used. An example of the protocol for the synthesis of pyrrolizidines in which α-iodoacetyl chloride is used in acylation of a suitable nitrogen atom containing precursor is shown in Scheme 16.[44] The starting material **65** is acylated, thereby providing a fast route to yield the radical precursor **66**. Standard Bu_3SnH methodology yields the intermediate stabilised radical **67** by a now well investigated but unusual 5-*endo* cyclisation. The second cyclisation of intermediate **67** to yield product **68** is an example of a stable radical often preferring to undergo the thermodynamically favoured 6-*endo* cyclisation rather than the faster 5-*exo* cyclisation. Other examples in the literature which report the use of this protocol are: α-iodoacetyl chloride for the cyclisation of *N*-(cycloalk-1-en-1-yl)-α-haloacetamides,[45,46] α,α-bis(phenylsulfanyl)acetyl chloride for the synthesis of octahydroindol-2-ones,[47] and trichloroacetyl chloride for the synthesis of a range of bicylic heterocycles including tetrahydro-2*H*-indol-2-ones,[48] 2-azabicyclo[3.3.1]nonanes,[49] and the first total synthesis of the indole alkaloids (±)-melinonine-E and (±)-strychnoxanthine.[50] Other variants of this methodology use alkylation with α-bromoacetates to facilitate the synthesis of selenoesters as radical precursors[33] and for use with manganese(III) acetate as the radical generating reagent.[51] The protocol can be applied the other way round and acylation on nitrogen with acryloyl chloride gives acrylamides which can be used as the alkene moiety onto which radicals can be cyclised to yield γ-lactams.[52]



Scheme 16 *Reagents and conditions*: i, ICH_2COCl, $PhNEt_2$; ii, Ph_3SnH, 5 h, PhH, AIBN, 61%.

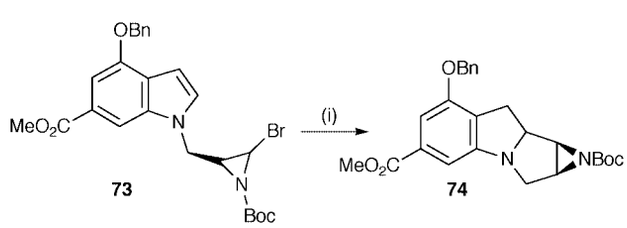
Acylation using ω-halogenoacyl chlorides has also been used in this general protocol, *e.g.* acylation of 1,4-dihydropyridines using 4-iodobutanoyl chloride has been used to prepare precursors for the syntheses of lupinine and epilupine,[53] and 3-bromobutanoyl chloride for the synthesis of the indolizidine framework of pumiliotoxin 251D.[54] A different methodology uses acylation with *o*-bromobenzoyl chloride in order to add a radical generating group which does not itself take part in the cyclisation but instead facilitates 1,5-hydrogen abstraction (Scheme 17).[55] Radical abstraction of the bromine from the precursor **69** yields a reactive aryl radical **70** which abstracts a



Scheme 17 *Reagents and conditions*: i, Bu_3SnH, AIBN, PhMe, reflux, 2 h; R = H, 100% (*exo* : *endo* = 66 : 34); R = Me, 40%.

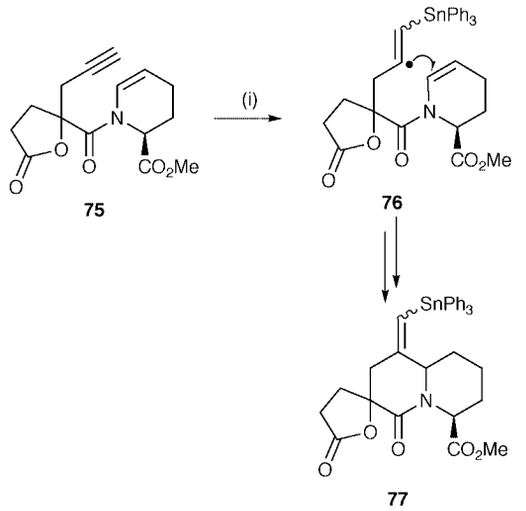
hydrogen atom to yield a new intermediate radical **71** which undergoes 5-*exo* and 6-*endo* cyclisation to yield bridged azabicyclic compounds, *e.g.* **72**. A similar protocol uses vinyl radicals instead of aryl radicals for 1,5-hydrogen abstraction for the synthesis of pyrrolizidines.[56]

Alkylation using ω-halogenoalkyl halides has also been widely used in this general protocol. A useful illustration of this protocol comes from the ongoing studies of Ziegler and coworkers on the synthesis of mitomycin analogues.[57] In this study, an asymmetric route to the core nucleus of the antitumour agent FR-900482 has been facilitated by alkylation with an aziridinylmethyl halide to yield a precursor **73** (Scheme 18). Reaction with Bu_3SnH yields an aziridinyl radical which cyclises onto a functionalised indole nucleus to yield the tetracyclic skeleton **74** which is central to this group of antitumour compounds. There is however competition between cyclisation and reduction by Bu_3SnH of the intermediate aziridinyl radical to yield the uncyclised aziridine. Alkylation with dibromobutane provides precursors for the radical synthesis of the azepinoindole substructure found in several *Stemona* alkaloids by an unusual 7-*endo* radical cyclisation.[58] Reductive *N*-alkylation using 2-(phenylselanyl)ethanal and sodium cyanoborohydride allows the synthesis of 2-(phenylselanyl)ethyl side chains which can be used for generating radicals and cyclising onto suitable alkenes to yield bridged heterocycles, *e.g.* 1,5-dimethyl-1-azabicyclo[3.2.1]octane iodide.[59]



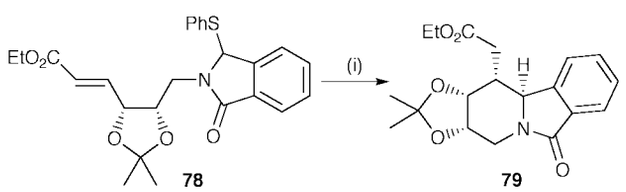
Scheme 18 *Reagents and conditions*: i, Bu_3SnH, AIBN, PhMe, 46%.

The use of vinyl radicals, resulting from alkylation with ω-(vinyl bromides), has been used in a number of alkaloid synthetic studies, *e.g.* mossambine,[60] vincadifformine[61] and the morphinan skeleton.[62] Vinyl radicals can also be generated by *exo* addition of triorganotin hydrides to alkyne precursors, *e.g.* in the synthesis of (±)-A58365B, an inhibitor of angiostensin converting enzyme (Scheme 19).[63] The pendant alkyne is added by acylation of the nitrogen atom to yield the radical precursor **75**. The vinyl radical intermediate **76** undergoes 6-*exo* cyclisation onto the tetrahydropyridine ring to yield a vinyl stannane product **77**.



Scheme 19 *Reagents and conditions*: i, Ph_3SnH, AIBN, PhMe, reflux, 62%.

A protocol using alkylation of α-phenylsulfanyl lactams and treatment of the resulting product using Bu_3SnH methodology to generate radicals α to the nitrogen has been used for some time. The α-phenylsulfanyl lactam precursors are obtained from the corresponding imide in several simple steps. Several further applications of this methodology have been reported.[64,65] In studies aimed towards the synthesis of the indole alkaloid tacamonine, the precursor **78** has been cyclised to yield the all *cis* tetrahydropyrido[2,1-*a*]isoindolone **79** stereoselectively as the major diastereomer (Scheme 20).[64]



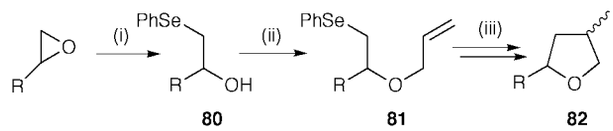
Scheme 20 *Reagents and conditions*: i, Bu_3SnH, AIBN, PhH, reflux, 10 h, 60%.

Several papers report the synthesis of bicyclic spiro amines.[43,66,67] The methodologies shown in Scheme 15 using tandem cyclisation onto imines[43] and the protocol illustrated in Scheme 2 using xanthate transfer[66] have also been applied to the synthesis of spiroamines. A general approach to spiropiperidinyl heterocycles uses aryl radical cyclisation onto alkenes in piperidine rings.[67]

5 Oxygen heterocycles

Oxygen centred radicals, unlike aminyl or iminyl radicals, are not commonly used in the synthesis of *O*-heterocycles, but one example of a tandem process featuring an alkoxyl radical cyclisation onto the β-position of an α,β-unsaturated ester has been reported.[68] The alcohol is reacted with benzeneselenenyl chloride to generate the sulfenate ester (RO–SePh) radical precursor. Treatment of the selenenate ester with Bu_3SnH yields the alkoxyl radical which cyclises to afford 2,3-*trans*-disubstituted tetrahydrofurans, creating two new contiguous stereogenic centres with high levels of 1,2-induction in each step. The reaction is analogous to the use of sulfenamides for aminyl radical precursors (see Scheme 8).

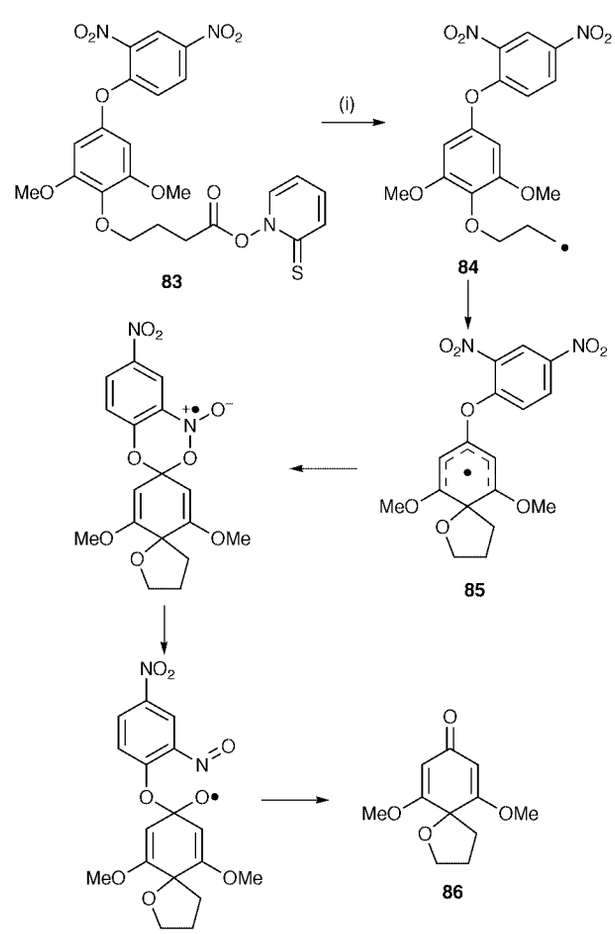
The most commonly used method for the synthesis of *O*-heterocycles is 5-*exo* cyclisation of carbon-centred radicals onto suitable unsaturated bonds to yield tetrahydrofuran derivatives. As discussed for the synthesis of nitrogen heterocycles in Section 3 many of the precursors for *O*-heterocycles are synthesised by addition of the radical generating moiety, or the unsaturated bond moiety, to the oxygen atom of the starting material. This general procedure for the synthesis of tetrahydrofuran derivatives is illustrated in Scheme 21.[69] Aryl selenides or aryl tellurides are added to epoxides to yield β-hydroxy-selenides or -tellurides **80** which are alkylated with sodium hydride and allyl bromide to give the radical precursors **81**. Standard Bu_3SnH methodology gives high yields of tetrahydrofurans **82** whereas the tellurides are sufficiently reactive to undergo radical group transfer using hexabutylditin and light to facilitate the reaction. A number of other examples are reported.[70–76]



Scheme 21 *Reagents and conditions*: i, $ArSe^-$; ii, NaH, allyl bromide; iii, Bu_3SnH, AIBN.

A novel synthesis and mechanistic study involves radical spirocyclisation to form spirodienones with a tetrahydrofuran ring (Scheme 22).[77] The putative biomimetic mechanism outlined in Scheme 22 also helps to explain the biosynthesis of the interiorin and kadsulignan groups of dibenzocyclooctadiene lignans. The Barton ester **83** undergoes homolysis with loss of carbon dioxide to generate an intermediate carbon-centred radical **84** which undergoes 5-*exo* cyclisation onto the arene to yield the spirodienyl radical **85**. An unusual but known rearrangement involving the *o*-nitro group takes place to yield the spirodienone **86** in good yield.

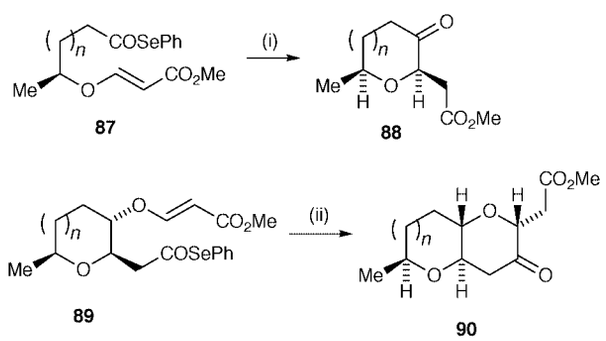
In the synthesis of tetrahydrofurans a number of radical generating methods have been reported other than the use of Bu_3SnH (or related compounds) to abstract a halogen. For



Scheme 22 *Reagents and conditions*: i, *hv*, $-CO_2$, -(PyrS$^\bullet$).

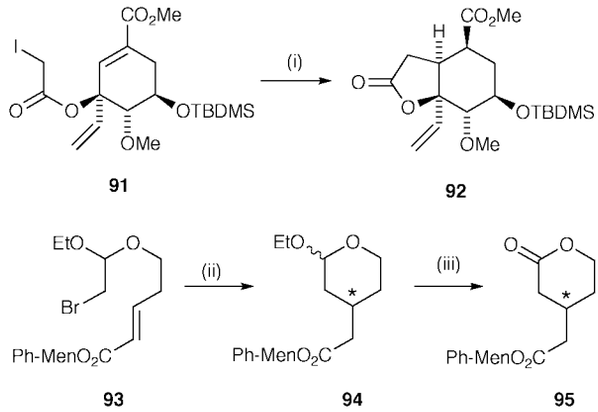
instance, *O*-alkylation with propargyl bromide yields radical precursors for tetrahydrofuran synthesis. Radical addition (phenylthiyl[78] and tributylstannyl[79]) to the alkyne provides an intermediate vinyl radical which rapidly cyclises by 5-*exo* cyclisation onto a suitable alkene. Other reagents for facilitating radical cyclisation of β-iodo or β-bromo allyl or propargyl ethers to yield a range of polyfunctional tetrahydrofurans include diethylzinc coupled with Pd(II) or $Ni(acac)_2$ as catalyst[80] or a catalytic mixed metal system consisting of diethylzinc coupled with $MnBr_2$ and CuCl,[81] and a catalytic amount of cobaloxime, regenerated by reduction with sodium borohydride.[82] Ring opening of strained three membered rings also provides several protocols for generating carbon-centred radicals for synthesising tetrahydrofurans.[83]

Six-membered ring cyclic ethers can be synthesised by similar methods to those for tetrahydrofurans. In studies of the synthesis of the potent antitumour agent mucocin A, a novel route uses intramolecular 6-*exo* radical cyclisation of acyl radicals, generated from acyl selenides.[84] The acyl radicals are cyclised onto *Z*-vinylogous sulfonates to control rotamer population and afford the *cis*-2,6-disubstituted tetrahydropyran-4-ones in high yields. The protocol has been extended to an iterative process to build up fused polycyclic ethers *via* acyl radical cyclisations (Scheme 23).[85] These fused polycyclic ethers are found in a number of natural products such as the newly discovered gamberic acids. In this iterative process, the first acyl selenide **87** undergoes 6-*exo* cyclisation *via* the acyl radical with high *cis* stereoselectivity to yield the monocyclic ketone **88**. The cyclic ketone **88** was converted to the second acyl selenide precursor **89** in a few routine synthetic steps and cyclised again by 6-*exo* cyclisation with complete stereoselectivity, as required in the natural products, to the bicyclic ether **90**. Other protocols for generating six-membered ring cyclic ethers include 6-*exo* cyclisation of nucleophilic 'ketyl' radicals onto the β-position of α,β-unsaturated esters.[86,87] The 'ketyl' radicals are generated by addition of tributylstannyl radicals[86] or samarium diiodide.[87]



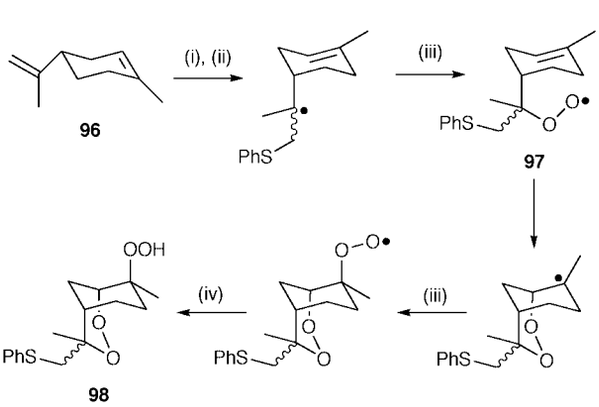
Scheme 23 *Reagents and conditions*: i, $(Me_3Si)_3SiH$, Et_3B, PhH, rt, air; $n = 1$, 94%, *cis*:*trans* = 5.7:1; $n = 2$, 90%, *cis*:*trans* ≥19:1; ii, $(Me_3Si)_3SiH$, Et_3B, PhH, rt, air; $n = 1$, 91%; $n = 2$, 99%.

The synthesis of lactones is a common target of radical cyclisation and two of the common protocols are illustrated in Scheme 24. In both of these protocols the radical precursor is synthesised by reaction between the moiety containing the radical generating group and a suitable allylic alcohol group on the starting material. In the first of these protocols α-substituted esters are used as the radical precursors.[88,89] In Scheme 24, reaction between the α-iodo ester **91** and Ph_3SnH yields the bicyclic lactone **92** in 73% yield.[88] The second method uses intermediate β-bromo acetals as radical precursors which are cyclised and subsequently oxidised to yield the lactone.[90,91] In the example shown in Scheme 24 the precursor **93** contains a chiral auxiliary.[90,91] The cyclisation to the cyclic acetal **94** proceeds with poor diastereoselectivity unless used in tandem with MAD [methylaluminiumbis(2,6-di-*tert*-butyl-4-methylphenoxide)] when a >98% de was obtained. Hydrolysis and oxidation of the product acetal yields the required target lactone **95**. In a third variant of this general protocol, β-bromo- or β-(phenylselanyl)-alcohols have been used to form esters as precursors for radical cyclisation to γ- and δ-lactones for the synthesis of α-hydrazino- and α-(*O*-benzylhydroxylamino)-lactones in 70–82% yields.[92] Alternative methods for the synthesis of lactones use $Mn(OAc)_3$ mediated oxidation of α-keto esters onto suitable alkenyl side chains[93] and SmI_2 mediated radical addition of ketones onto α,β-unsaturated esters followed by cyclisation.[94]



Scheme 24 *Reagents and conditions*: i, Ph_3SnH, AIBN, PhH, reflux; ii, Bu_3SnH, Et_3B, MAD, toluene, −40 °C, 1.5 h, 38%, de > 98%; iii, 10% $HClO_4$, Ag_2CO_3.

Radical cyclisation to yield cyclic peroxides has proved useful for the synthesis of analogues of the important antimalarial compound yingzhaosu isolated from a Chinese herbal medicine which has the unusual 2,3-dioxabicyclo[3.3.1]nonane skeleton.[95] A very novel radical cascade reaction which includes molecular oxygen in the mechanism has been used to synthesise this cyclic peroxide **98** which is illustrated in Scheme 25. In the synthesis, (−)-carvone **96** is used as the precursor for the radical addition of oxygen and also contains the required chiral centre which determines the stereochemistry of the final product. The sequence is initiated by addition of phenylthiyl radicals to the *exo* alkene to yield a radical intermediate which is trapped by oxygen to yield the peroxyl radical **97**. 6-*exo* Cyclisation of the peroxyl radical **97** gives the required 2,3-dioxabicyclo[3.3.1]-nonane skeleton and finally the cyclic peroxide product **98**. The synthesis of 1,2,4-trioxanes and 1,2,4-trioxepanes by NBS/NIS mediated radical cyclisations of unsaturated hydroperoxy-acetals has also been reported.[96]

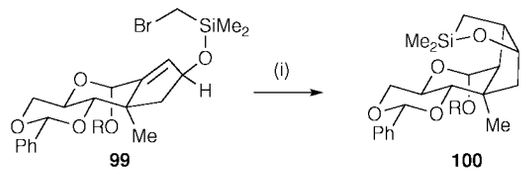


Scheme 25 *Reagents and conditions*: i, PhSH, O_2, DBPO; ii, PhS$^{\bullet}$; iii, O_2; iv, PhSH→PhS$^{\bullet}$.

6 Carbohydrates and nucleosides

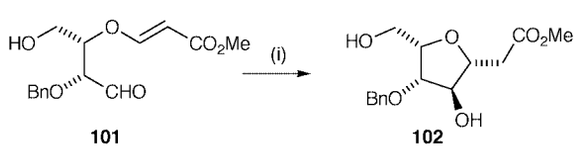
Radical cyclisation has been used in the synthesis of novel carbohydrates as well as using carbohydrates as templates for

radical cyclisation.[97,98] One key advantage of the use of radical cyclisation with carbohydrates is that the hydroxy groups do not normally need protection which can save steps in a synthesis. An example of the use of carbohydrate templates in synthesis is shown in Scheme 26 in which the functionalised monosaccharide **99** is converted to the functionalised cyclopentane derivative **100**.[97] This synthetic sequence illustrates the application of the Stork protocol using cyclisation of silyl methylene radicals for the introduction of new hydroxy functions. An example of the use of radical cyclisation in the synthesis of an optically pure C-glycoside **102** is shown in Scheme 27.[99] Bu_3SnH or PET mediated 5-*exo* cyclisation of the tartaric acid derivative **101** *via* ketyl radical intermediates gave reasonable yields of **102** with high stereoselectivity.



99 **100**

Scheme 26 *Reagents and conditions*: i, R = Me, Bu_3SnCl, $NaCNBH_3$, AIBN, *t*-BuOH, 15 h, 90 °C.



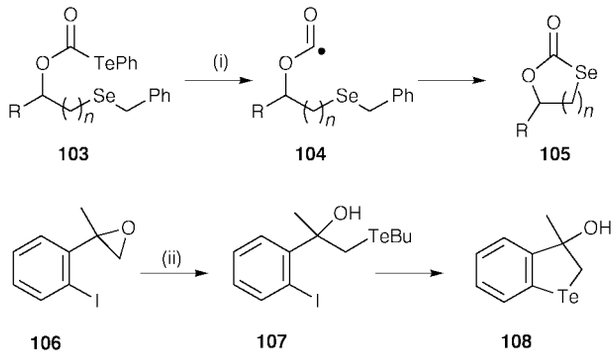
101 **102**

Scheme 27 *Reagents and conditions*: i, Bu_3SnH, AIBN, 40%.

7 Sulfur, selenium and tellurium heterocycles

Free radical chemistry involving sulfur, selenium and tellurium has some marked differences to that of oxygen and nitrogen because of their soft or polarisable nature and the longer and weaker C–S, C–Se, C–Te bonds. S_H2 reactions centred on S, Se and Te have become important and have been used to advantage by Schiesser and co-workers.[100–102] Two of the synthetic reactions using these mechanistic possibilities are illustrated in Scheme 28. In the first the (phenyltelluro)formate precursor **103** undergoes homolysis facilitated by light catalysis to yield intermediate oxyacyl radical **104**. Intramolecular S_H2 (S_Hi) substitution by the acyl radical on selenium with benzyl radical as the leaving group yield the cyclic selenium heterocycle **105** in good yield. The protocol works best with $n = 2$ and when $n > 2$ other mechanisms predominate and yields decline. Reaction of 2-methyl-2-(2-iodophenyl)oxirane **106** with two equivalents of sodium butyltelluroate (NaTeBu), generated from sodium borohydride reduction of dibutyl ditelluride in THF, affords 2,3-dihydro-3-hydroxy-3-methyl-1-benzotellurophene **108** *via* the hydroxy telluride **107** in 57% yield. This mechanism has been shown to involve a tandem $S_{RN}1$–S_Hi sequence. In a further example, γ-thiolactones have been synthesised by carbonylation with carbon monoxide of intermediate free radicals to yield acyl radicals which undergo cyclisation by intramolecular S_H2 (S_Hi) at sulfur.[103]

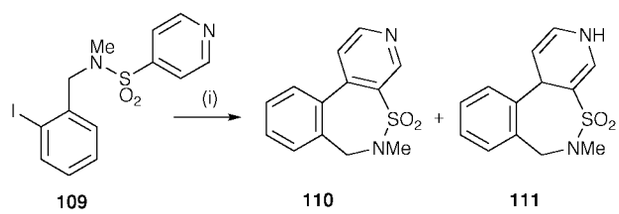
Motherwell and co-workers have carried out several syntheses of unusual *S*-heterocycles involving cyclisation of aryl radicals onto side chains containing sulfonates and sulfonamides.[104–106] In Scheme 29 the synthesis of a biphenyl system containing a seven membered ring sulfonamide is shown as an illustration of this methodology.[104] The benzylic *N*-methylsulfonamide **109** is converted to the cyclised sulfonamides **110** and **111**. In this *ipso* substitution onto arenes there is normally an oxidative step leading to the rearomatised product **110**. These oxidative steps in Bu_3SnH reactions are now well known if there is a driving force to rearomatisation. In some of these reactions the dihydro products without rearomatisation, *e.g.*



103 **104** **105**

106 **107** **108**

Scheme 28 *Reagents and conditions*: *hv*, $n = 2$, 73%; ii, BuTe, THF, 57%.



109 **110** **111**

Scheme 29 *Reagents and conditions*: i, Bu_3SnH, AIBN, slow addition, PhH, reflux; **110** (55%); **111** (24%).

111, are isolable. In this example, benzylic sulfonates and their corresponding benzylic *N*-methylsulfonamides prefer to undergo [1,7] addition reactions rather than [1,6] *ipso*-substitution. *ortho*-Substituents effectively counteract this tendency for addition. The guidelines[104,105] for this synthetic strategy of *ipso* substitution indicate that the synthesis of biphenyls is favoured by the location of electron releasing *o*-substituents around the sulfonyl substituted acceptor ring, thereby leading to hindered products. 4-Aryl-5,6-dihydro-1,2-oxathiine 2,2-dioxides and related heterocyclic systems have been synthesised using this protocol which also involves an unusual rearrangement reaction *via* radical addition to aryl and heteroaryl rings.[106]

The other characteristic of radical reactions involving sulfur atoms which is uncommon for those involving nitrogen or oxygen atoms is the ability to undergo β-scission to give intermediate thiyl radicals. A number of examples in the literature have shown the synthetic potential of using this behaviour for the preparation of thiophenes,[107] dihydrothiophenes[108] and 2,3-dihydrobenzothiophenes.[109]

8 Silicon heterocycles

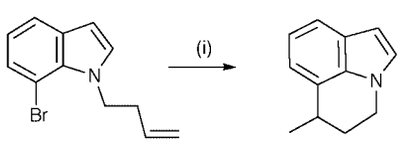
The syntheses of silyloxy heterocycles (with Si–O in the ring) are primarily of interest as synthetic methods rather than as an end in themselves. There has been growing interest in the use of silicon containing tethers attached to hydroxy groups in radical cyclisation for the introduction of new C–C bonds.[4] The well known Stork protocol uses cyclisation of silyl methylene radicals onto alkenes for the introduction of new hydroxy functions. The silyloxy group is oxidised out of the ring to leave two hydroxy groups. An example of the use of this radical cyclisation in synthesis is shown in Scheme 26.[97] New examples use 5-*exo-trig* cyclisations of radicals generated from (bromomethyl)dimethylsilyl propargyl ethers for the synthesis of 5-membered rings with silicon and oxygen heteroatoms,[110] and from (bromomethyl)dimethylsilyl esters of α,β-unsaturated carboxylic acids, for the synthesis of silalactones.[111] A number of examples use cyclisation onto the silicon containing tethers which also have attached alkenes[112] or alkynes.[113]

9 Benzoheterocycles

The synthesis of benzoheterocycles using radical cyclisation can be envisaged by several general routes: a, cyclisation of aryl

radicals onto side chain unsaturated bonds, b, cyclisation of aryl radicals onto pendant arenes/heteroarenes and c, cyclisation of side chain radicals onto arenes/heteroarenes.

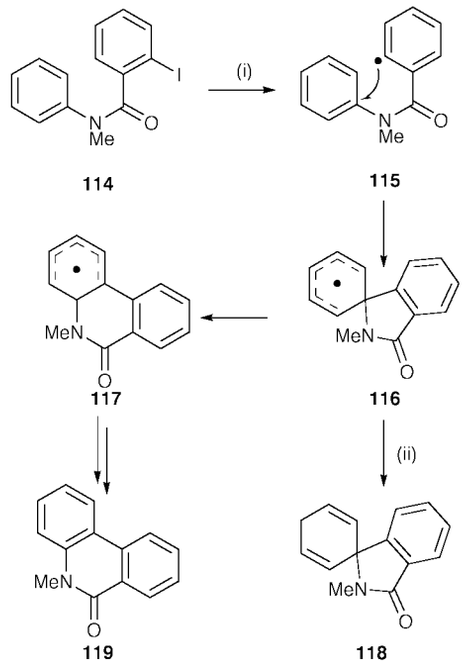
In Scheme 30 the use of cyclisations of radicals generated from *N*-substituted 7-bromoindoles for the synthesis of tricyclic indole analogues is illustrated.[114] The butenyl derivative **112** undergoes 6-*exo* cyclisation to yield the tricyclic indole **113**. The analogous *N*-allyl-7-bromoindole undergoes 6-*endo* rather than 5-*exo* cyclisation due to constraints enforced on the system by the geometry of the indole ring. *N*-(ω-Alkenyl)-2-bromoindoles react to yield intermediate indol-2-yl radicals which undergo 5-*exo* or 6-*exo* cyclisation onto the pendant alkene to yield [1,2-*a*]-fused pyrroles. Indolines have been prepared by cyclisation of aryl radicals generated from *o*-halogeno *N*-alkenylanilines.[115] Other Bu_3SnH mediated aryl radical cyclisations have been used to synthesise isoindolones from *N*-ethenyl-2-bromobenzamides leading to the synthesis of alkaloids lennoxamine and chilenine,[116] isoquinolinones from 2-(2-bromophenyl)-*N*-(ethenyl)phenylacetamides,[117] 2,3-dihydrobenzothiophenes,[118] 2,3-dihydrobenzofurans[119] and isoquinolones and quinazolones.[120] Cyclisation of aryl radicals onto side chain unsaturated bonds using protocols other than Bu_3SnH include: 2,3-dihydrobenzofurans using PhMgBr–$FeCl_2$,[121] carbon monoxide with tri(perfluoroalkyl)tin hydrides[122] and lithium tributylmanganate (n-Bu_3MnLi).[122] Indolines have also been synthesised using lithium tributylmanganate.[123]



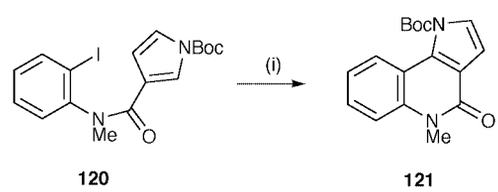
Scheme 30 *Reagents and conditions*: i, Bu_3SnH, AIBN, PhMe, reflux, 12 h.

Cyclisation of aryl radicals onto pendant arenes provides a useful method of constructing biphenyl moieties within polycyclic heterocycles. Phenanthridones have been usefully synthesised by this protocol (Scheme 31).[124] The *o*-iodobenzamide **114** forms an aryl radical **115** which can cyclise by a 5-*exo* route to **116** followed by a neophyl rearrangement to **117** or by a 6-*endo* route directly to intermediate radical **117**. This unknown aspect of the mechanism of these reactions has been solved by using trapping with benzeneselanol (PhSeH) which is an extremely fast hydrogen donor; radical **116** was trapped with PhSeH to yield the spirocyclohexadiene **118** to provide strong evidence for 5-*exo* cyclisation. The intermediate radical **117** rearomatises to yield the phenanthridone **119** by an unknown mechanism which is usual for this synthetic sequence, *i.e.* an oxidation step in a Bu_3SnH mediated cyclisation. This general protocol has been used for the synthesis of phenanthridines leading to the syntheses of the *Amaryllidaceae* alkaloids, vasconine, assoanine, oxoassinine and pratosine.[125] The protocol is attractive by its simplicity; *o*-bromobenzyl bromides are reacted with anilines to yield the radical precursors. The mechanism of the oxidative step is unclear and although a large amount of AIBN is required it does not appear to act as the oxidant.[125] This protocol has also been reported for converting (*o*-bromobenzyl)phenyl ethers to 6*H*-dibenzo[*b,d*]pyrans and a range of precursors with various methoxy and methylenedioxy substituents have been used with success.[126]

This methodology has also been applied to cyclisation of aryl radicals onto heteroarenes (Scheme 32).[127] Radical cyclisation of the *N*-(2′-iodophenyl)pyrrole-3-carboxamide **120** gave the tricyclic pyrrolo[3,2-*c*]quinolone **121**, the ring system found in the recently isolated alkaloid martinelline. This oxidative Bu_3SnH mediated cyclisation of aryl radicals has been used to convert *N*-aroyl-6-bromoindoles into the pyrrolophenanthridone



Scheme 31 *Reagents and conditions*: i, Bu_3SnH, AIBN, PhMe, reflux; ii, PhSeH.

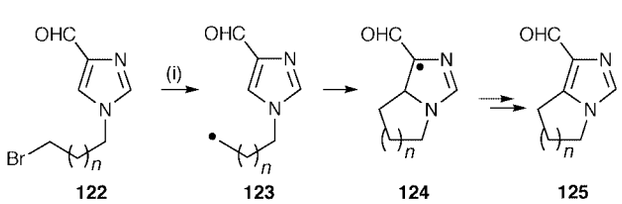


Scheme 32 *Reagents and conditions*: i, Bu_3SnH, AIBN, PhMe, reflux, 52%.

alkaloids, hippadine, pratosinine, pratorimine and pratorinine from various *Crinum* species (*Amaryllidaceae*).[128] The protocol has also been used for the preparation of the pyrrolophenanthridine alkaloids oxoassoanine and anhydrolycorin-7-one from *N*-aroyl-6-bromoindolines.[129]

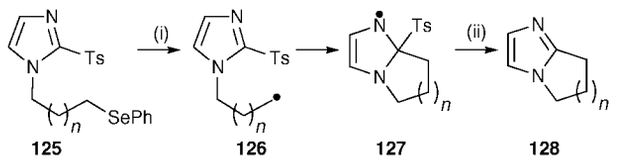
Cyclisation of *N*-(ω-alkyl) radicals onto heteroarenes has been used to annulate pyrrole, imidazole[130] and indole.[131] This oxidative radical cyclisation using Bu_3SnH is illustrated in Scheme 33 for the synthesis of [1,2-*c*]-fused imidazoles **125** from imidazolecarbaldehydes **122**.[130] [1,2-*a*]-Fused pyrroles have been prepared by the same protocol from acylpyrroles. The intermediate nucleophilic *N*-alkyl radicals **123**, generated from the precursor **122**, cyclise onto the imidazole ring to yield the π-radical **124** which undergoes oxidative rearomatisation to **125**. This methodology was applied successfully to 5-, 6-, and 7-membered rings but fails with larger ring cyclisations. A chain mechanism involving single electron transfer has been proposed to explain the unusual oxidative step observed in all these reactions.

Regioselective (*ipso*) aromatic homolytic substitution has been applied to the syntheses of [1,2-*a*]-fused-benzimidazoles,[132] -imidazoles,[132] -indoles[133,134] and uracils.[134] Treatment



Scheme 33 *Reagents and conditions*: i, Bu_3SnH, AIBN, MeCN, reflux, 5 h; $n = 1$, 42%; $n = 2$, 49%; $n = 3$, 14%.

of imidazole precursors **125** with Bu_3SnH under standard radical conditions gave the cyclisation products **128** in reasonable yields without the formation of any uncyclised reduced products (Scheme 34). In these reactions the initial radical **126** cyclises onto the electrophilic C-2 position to yield a π-radical intermediate **127** which rearomatises with loss of tosyl radicals to yield the [1,2-*a*]-fused imidazoles **128**. The tosyl radicals react with Bu_3SnH to regenerate tributylstannyl radicals for carrying the chain reaction.

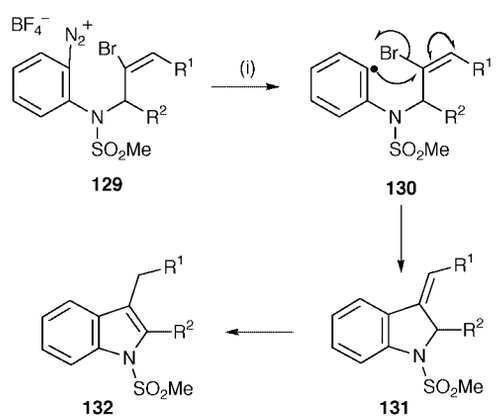


125 **126** **127** **128**

Scheme 34 *Reagents and conditions*: i, Bu_3SnH, AIBN, PhMe, reflux; $n = 1$, 52%; $n = 2$, 48%; $n = 3$, 63%.

10 Heteroarenes

The synthesis of heteroarenes by radical cyclisation is a surprisingly under-studied area with few general protocols. One of the few novel methodologies is illustrated in Scheme 1 for the synthesis of camptothecin. Another novel methodology, by Murphy and co-workers,[135] uses diazonium salts as precursors for the synthesis of indoles which is exemplified in Scheme 35. Reaction between the precursor diazonium salts **129** and iodide yields the initial aryl radical intermediates **130** which undergo 5-*exo* cyclisation onto the vinyl bromides followed by β-elimination of bromide to yield **131**. The *exo*-alkene shifts into the 2,3-position to yield the indoles **132**. This new route avoids the need to use trialkyltin reagents. 2-Cyanoaryldiazonium salts have also been used in a novel cascade radical reaction to generate 2-cyanoaryl radicals which add to aryl isothiocyanates to give α-(arylthio)imidoyl radicals which undergo a 5-*exo*-*dig* cyclisation onto the cyano group eventually leading to tetra condensed nitrogen heterocycles.[136]



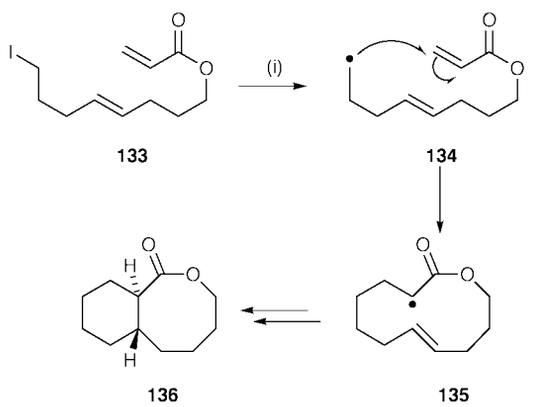
129 **130** **131** **132**

Scheme 35 *Reagents and conditions*: i, NaI, acetone; R^1 = Ph, R^2 = Me, 49%; R^1 = Me, R^2 = H, 83%.

Flash vacuum pyrolysis (FVP) of 2-allyloxypropenoic esters give 1-benzofurans,[137] and oxime ethers give carbazoles, phenanthridines and acridines.[138] Thermal decomposition of *tert*-butyl *o*-(phenoxy)- and *o*-(anilino)-phenyliminoxyperacetates yield acridine, quinazolinone and indole derivatives.[139] 2-Cyanophenylthiyl radicals, generated by photolysis of bis(2-cyanophenyl) disulfide, add to aryl isonitriles to yield imidoyl radicals which cyclise onto the cyano group to eventually afford thienoquinoxalines.[140]

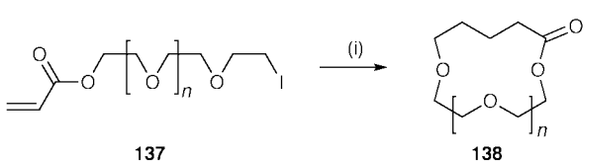
11 Macrocyclisation

The formation of rings with more than seven atoms have unfavourable rates and in radical cyclisation 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 radical onto an electrophilic centre, commonly the β-position of an α,β-unsaturated ketone, ester or amide. Pattenden and co-workers[5,141,142] have studied this methodology extensively and an example of macrocyclisation and transannulation is shown in Scheme 36. The initial radical **134** generated from the acyclic precursor **133** undergoes 12-membered ring *endo* macrocyclisation to intermediate radical **135** which in turn undergoes transannulation to ultimately yield the bicyclic lactone **136** with stereoselective formation of a *trans* ring junction.[141] An excellent example of the polarity effect of the α,β-unsaturated ester is in the exclusive *endo* cyclisation of ω-iodo-poly(oxaalkyl) acrylates **137** to the corresponding cyclic polyethers **138** in excellent yields (Scheme 37).[143] Interestingly, these poly(oxaalkyl) acrylates undergo radical cyclisations more readily than carbon analogues.



133 **134** **135** **136**

Scheme 36 *Reagents and conditions*: i, Bu_3SnH, AIBN, PhH, reflux, 61%.



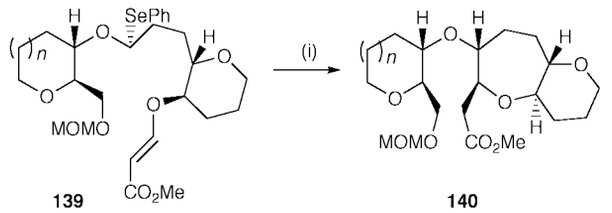
137 **138**

Scheme 37 *Reagents and conditions*: i, Bu_3SnH, AIBN, PhH, reflux; $n = 1$, 76%; $n = 2$, 72%; $n = 3$, 70%; $n = 4$, 63%; $n = 5$, 30%.

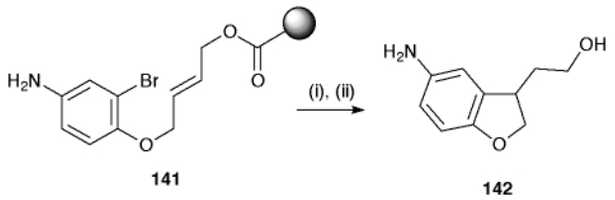
Cyclisation to give 8–10-membered rings requires the same methodology as the larger rings. Radical cyclisation of aryl radicals onto the β-position of α,β-unsaturated amino esters gives good yields of 7–9-membered ring benzocyclic α-amino esters which have the nitrogen atom in the ring.[144] Cyclisation to 10-membered rings was unsuccessful.[144] In studies towards the synthesis of polycyclic ethers, 7-membered ring cyclisation onto the β-position of β-alkoxy acrylates **139** yields 2,7-disubstituted oxepanes **140** with selective *cis* stereochemistry at the 2- and 7-positions of the oxepane.[145] An example of these cyclisations is shown in Scheme 38. The advantage of polarisation can be used in the opposite sense as well, *i.e.* a strongly electrophilic radical can be cyclised onto an electron rich alkene. An example of an 8-*endo* radical cyclisation to yield an eight-membered ring lactone uses cyclisation of a carbon centred radical α to an ester (oxycarbonylmethyl radical).[146] The cyclisation of aryl radicals onto constrained side chain alkenes gives selective 8-*endo* cyclisation. Furo[3,2-*c*][2]benzoxocines[147] and 3,4,5,6-tetrahydro-1-benzazocin-2(1*H*)-ones[148] have been synthesised using this 8-*endo* cyclisation protocol.

12 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



Scheme 38 *Reagents and conditions*: i, Bu_3SnH, AIBN, Et_3B, PhH, reflux; $n = 1$, 82%; $n = 2$, 87%.



Scheme 39 *Reagents and conditions*: i, Bu_3SnH, AIBN, PhMe–*t*-BuOH; ii, NaOMe–MeOH, rt, >90%.

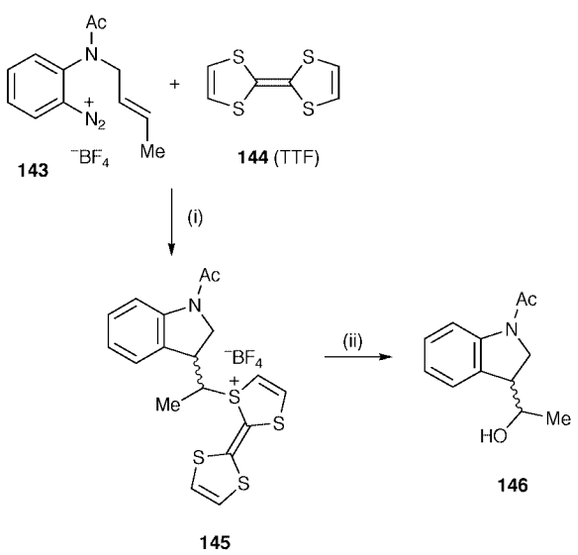
dominant and a very useful reagent. The purification problems can be partially overcome by using Bu_3SnH catalytically. In this methodology Bu_3SnCl is reduced *in situ* with sodium cyanoborohydride or sodium borohydride thereby producing small amounts of Bu_3SnH which is continually used up generating more Bu_3SnX (X = Br, I) in a cycle.[34,69] This also has the advantage of keeping the concentration of Bu_3SnH low to facilitate cyclisation instead of reduction. An example is the reduction and cyclisation of bromoketals in a tandem reaction.[69] Tributylgermanium hydride (Bu_3GeH) is much less toxic and reacts slightly slower thereby facilitating improved cyclisation yields over use of Bu_3SnH but is very expensive. An example is the use in the cyclisation of perfluoroalkenyl radicals.[73] Tris(trimethylsilyl)silane [$(Me_3Si)_3SiH$] is also less toxic and easier to work-up than Bu_3SnH but is also expensive.[33,49,50] While AIBN [azobis(isobutyronitrile)] is the most commonly used radical initiator, there are other diazene initiators, *e.g.* AMBN [azobis(methylisobutyronitrile) = Et(Me)C(CN)–N=N–C(CN)(Me)Et] which is more soluble and can be used in cyclohexane as well as in toluene as solvent.[17] The use of triethylborane and oxygen as an initiator is useful because it allows reactions to be carried out at low or room temperature.[25,46,48,112] Triethylborane can also be used to initiate iodine atom transfer reactions. Cyclohexane is becoming the preferred solvent for Bu_3SnH mediated reactions because of evidence of the possibility of toluene and benzene participating in radical reactions rather than acting only as a solvent. It is also lower boiling than toluene.[17,42]

One major advance in facilitating environmentally acceptable radical reagents has been the use of fluoroalkyl(fluorous)tin hydride.[149] An example of the reagents developed by Curran and co-workers is $(C_6F_{13}CH_2CH_2)_3SnH$. The insolubility of the fluorous reagents in normal organic solvents and water has allowed easy separation of the tin reagents and products. A further development on the use of fluorous tin hydride has been the use of supercritical CO_2. This development is in the very early stages but eventually should serve as the reaction and separation solvent. At present, solubility problems need to be overcome but the potential for clean heterocycle synthesis has been exemplified by the synthesis of indolines in high yield.

Another important advance is the use of solid phase organic synthesis in radical reactions.[150,151] The major advantage with solid phase synthesis is that the radical precursor is attached to the resin and the Bu_3SnH used in the reaction can be washed off when the radical cyclisation is complete, thereby eliminating purification problems and lowering problems of toxicity. An example of the use of solid phase synthesis for 2,3-dihydrobenzofurans is shown in Scheme 39. In this preparation the precursor **141** is attached to TentaGel resin beads and after radical cyclisation the product heterocycle **142** is removed by standard methods. Solid phase synthesis has also been used for the radical synthesis of 2,3-dihydrobenzofurans using samarium diiodide.[151]

A number of alternative reagents to triorganotin hydride continue to be used, *e.g.* use of nickel complex catalysed electroreduction,[152] triethylamine mediated photoinduced electron transfer reactions (PET), [153] catalytic cobaloxime regenerated by reduction with sodium borohydride,[81] manganese triacetate,[51,154] lithium tributylmanganate (n-Bu_3MnLi)[123] and samarium diiodide.[73,87,151]

Murphy and co-workers have continued to develop their novel use of tetrathiafulvalene **144** (TTF) for the reduction of aryldiazonium salts as a method of generating aryl radicals.[155] TTF is an excellent electron donor and transfers an electron to the diazonium salt to yield intermediate aryldiazene radicals ($ArN{=}N^{\bullet}$) which are unstable and rapidly lose nitrogen to yield aryl radicals. Aryldiazonium salts are readily accessed from anilines and are cleanly reduced to aryl radicals. An example of the synthesis of indoline **146** from diazonium salt **143** is shown in Scheme 40. The intermediate cyclised radical is trapped by the TTF to yield the intermediate TTF adduct **145** which undergoes hydrolysis to **146**. This method allows anilines to be used as precursors and avoids the use of the toxic and troublesome Bu_3SnH for generating aryl radicals.



Scheme 40 *Reagents and conditions*: i, Acetone (moist), 59%; ii, water.

Zard and co-workers[1,10,11,27,42,66] have developed their xanthate methodology as a promising alternative to the use of Bu_3SnH and have applied it to a wide range of heterocyclic syntheses, including β-lactams,[27] spirocyclic amines[43] and the tetracyclic alkaloid (±)-matrine.[10] The overall protocol is shown in Scheme 2 and another example for the synthesis of β-lactams[27] in Scheme 11.

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