Synthesis of heterocycles by radical cyclisation

W. Russell Bowman,* Anthony J. Fletcher and Graeme B. S. Potts

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

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REVIEW

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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.

A new reference series for free radical chemistry has been published which replaces the well used and known two volume series by Kochi. This new two volume series edited by Renaud and Sibi has been published with chapters covering many important aspects of radical chemistry and most are pertinent to the synthesis of heterocycles using radical cyclisation.[1]

A general review discusses the use of cascade, domino or tandem cyclisation processes in synthesis which includes many heterocyclic examples.[2] The authors describe a method of classifying these reactions. A review on heteroarene synthesis includes radical protocols and discusses them in the context of other non-radical methodologies.[3]

A number of reviews report general methodologies in radical chemistry which contain useful discussions of heterocyclic protocols, *e.g.* annulations and related cascade processes,[4] translocation reactions[5] and the use of three-membered rings.[6] The application of radical carbonylation using addition of carbon monoxide to alkyl radicals generated by atom transfer reactions from iodoalkanes has been reviewed.[7] The Baldwin rules for cyclisation state that 5-*endo-trig* cyclisations are disfavoured and this is generally correct. However, a steadily increasing number of exceptions are being elucidated in radical cyclisation reactions and most are in cyclisations for the synthesis of heterocycles.[8]

The use of particular functional groups in radical cyclisation have been reviewed. The utilisation of alkoxyl radicals in the synthesis of tetrahydrofurans with emphasis on the stereochemical factors has been reviewed.[9] Hypervalent iodine compounds have been used to generate radicals centred on nitrogen and oxygen which are used to synthesise heterocycles.[10] The electrophilic and radical behaviour of α-halosulfones in cyclisations to cyclic sulfones has been reviewed.[11] Heterocyclic examples are included in reviews of the cyclisation of carbon-centred radicals onto imines and related functional groups,[12] α,β-unsaturated electron-withdrawing groups[13] and enamides.[14] Carbon–carbon bond-forming cyclisations using sulfanyl radical addition–cyclisation have been reviewed.[15]

A number of reviews discuss alternative reagents to Bu_3SnH, *e.g.* tetrathiafulvalene (TTF)-mediated radical-polar crossover reactions of arenediazonium salts to aryl radicals and hypophosphite salts and hypophosphorous acid.[16] Two reviews discuss a wide range of alternatives to Bu_3SnH.[17,18] A review on the use of water in radical cyclisation reactions provides a most interesting development.[19] Organoboranes as sources of radicals including heterocyclic syntheses have been reviewed.[20]

2 Natural product synthesis

In the last two years the number of total syntheses using radical cyclisations to make heterocyclic rings has grown considerably indicating the increasing use in natural product synthesis. A review uses four syntheses of relatively simple natural products as examples of the introduction of stereo-controlled radical cyclisations.[21] The use of radical cyclisation for the synthesis of naturally occurring indole alkaloids has also been reviewed.[22]

A [3+2] annulation has been used to synthesise (±)-13-deoxyserratine **4** *via* a homoallyl amidyl radical (Scheme 1).[23] The amidyl radical **2** was generated from the *O*-benzoyl-*N*-allylhydroxylamine **1** by reaction with Bu_3SnH. Interestingly, the annulation in toluene gave the unwanted 5-*exo* product whereas reaction in α,α,α-trifluorotoluene and a chloroallyl analogue **1** gave a 52% yield of the 6-*endo* product **3**. The annulation takes place from the least hindered face. The xanthate-mediated methodology developed by Zard and co-workers for a wide range of related polycyclic alkaloids has been further applied to the syntheses of (±)-lepadin B using a radical cyclisation–vinylation sequence[24] and (±)-lupinine and (±)-*cis*-deethyleburnamine.[25]

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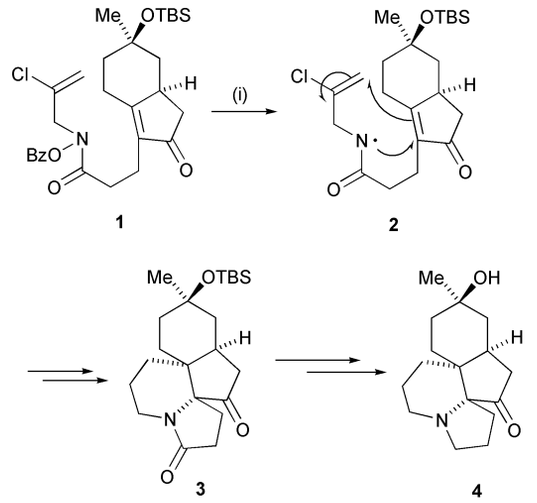
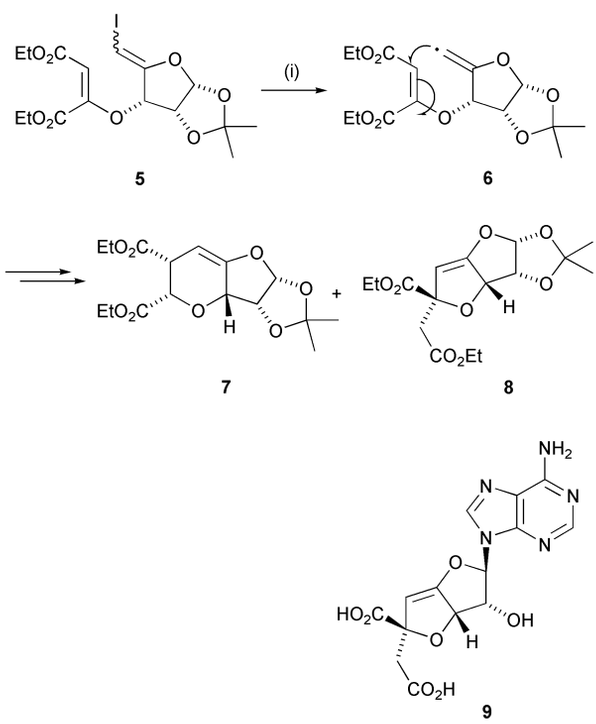


Scheme 1 *Reagents and conditions*: i, Bu_3SnH (2 equiv.), ACCN, $PhCF_3$, **3**, 52%.

Griseolic acid B **9**, a recently discovered nucleoside, has been synthesised using a radical cyclisation as the key step in the formation of the unusual monosaccharide (Scheme 2).[26] The

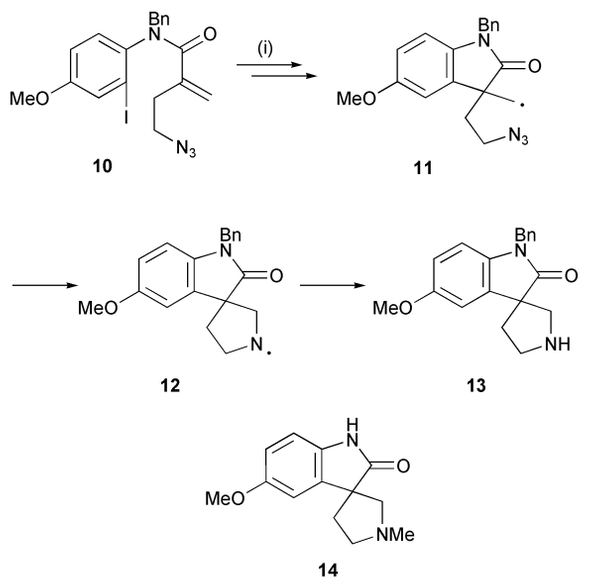


Scheme 2 *Reagents and conditions*: i, Bu_3SnH, AIBN, benzene, 80% (**7** : **8** = 3 : 2).

synthesis uses a cyclisation of a vinyl radical **6** onto an alkene. The use of vinyl radicals is surprisingly not common and can be expected to have much wider application. The intermediate vinyl radical, generated from a vinyl iodide precursor **5**, undergoes the desired 5-*exo*, as well as, the undesired 6-*endo* cyclisation in good yield. The dihydrofuran product **8** was converted into the nucleoside griseolic acid B **9**. The stereoselective synthesis of trisubstituted tetrahydrofurans by 5-*exo*-*dig* radical cyclisation of radicals α to an ester onto alkynes using a hypophosphite salt has been used for the syntheses of (±)-dihydrosesamin.[27]

The syntheses of the trisubstituted tetrahydrofurans of furano-lignins, *e.g*. lariciresinol and acuminatin, and furofuran-lignans, *e.g*. sesamin and eudesmin, have been achieved by stereoselective radical cyclisation of epoxides using a transition metal radical source.[28] The Ti(III) reagent bis(cyclopentadienyl)titanium(III) chloride is generated *in situ* from titanocene dichloride by reduction with zinc. The Ti(III) reagent adds to the epoxide oxygen to generate a carbon-centred radical which undergoes 5-*exo* cyclisation onto suitably placed alkenes.

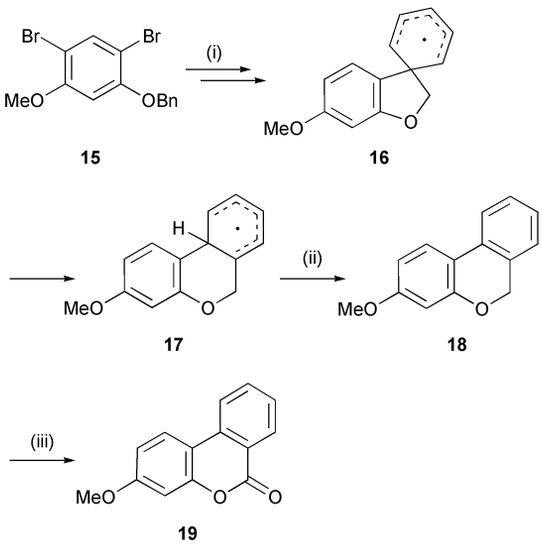
A number of total syntheses use the cyclisations of aryl radicals onto pendant side chain alkenes. Elegant examples using this initial radical cyclisation step have been developed by Murphy and co-workers.[29–31] In this protocol, the aryl radical cyclises onto an alkene which in turn undergoes a further cyclisation onto an azide with the elimination of nitrogen gas as a driving force. The protocol is illustrated by the synthesis of (±)-horsfiline by the tandem radical cyclisation strategy from an iodoarene precursor **10** (Scheme 3). The intermediate alkyl



Scheme 3 *Reagents and conditions*: i, $(TMS)_3SiH$, AIBN, benzene, 60%.

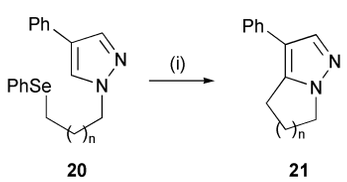
radical **11**, formed by the initial aryl 5-*exo* cyclisation, undergoes cyclisation onto the azide with the formation of an aminyl radical **12** which is reduced by the tris(trimethylsilyl)silane [$(TMS)_3SiH$ or TTMSS] to yield the spirocyclic product **13**. Minor elaboration gives horsfiline **14**. The protocol has also been used for the total syntheses of (±)-aspidospermidine[30] and (±)-vindoline.[31] Further examples of the use of aryl radical cyclisation onto side chain alkenes in total synthesis have also been published. The synthesis of the *Erythrina* alkaloid skeleton including (±)-α-lycorane has been achieved by a 6-*endo*-*trig* cyclisation onto side chain enamides.[32] Cyclisation of aryl radicals onto the double bond of pendant quinolones has been used to prepare the pavine alkaloid (±)-argemonine (referred to as algemonine in the reference) and the proto-berberine skeleton.[33] A related protocol has been applied to the synthesis of (±)-argemonine.[34] (−)-Aphanorphine has been synthesised by aryl radical cyclisation onto a vinyl thioether on a chiral side chain.[35]

Cyclisation of aryl radicals onto a second arene ring is also commonly used, *e.g*. cyclisation of *o*-(benzyloxy)aryl and *o*-(aryloxy)aryl radicals yields 6*H*-benzo[*c*]chromenes.[36] The protocol has been used to synthesise 3-methoxy-6*H*-benzo[*c*]chromen-6-one **19**, the main constituent of *shilajit*, a herbal medicine used in countries surrounding the Himalayan mountains (Scheme 4). The cyclisation of the aryl radical generated from **15** proceeds *via* a 5-*exo* cyclisation to yield the spiro intermediate **16** which undergoes a neophyl rearrangement to the 6-*endo* product **17**. Loss of a hydrogen atom by abstraction by a species derived from the initiator AMBN [azo-bis(methylisobutyronitrile)] yields the cyclised benzochromene **18**. Oxidation yields the required benzochromen-6-one natural product **19**. Evidence is provided for the mechanism of the



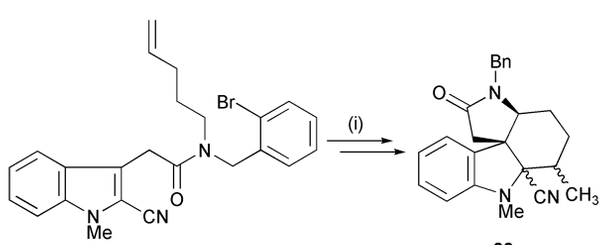
Scheme 4 *Reagents and conditions*: i, Bu_3SnH, AMBN, cyclohexane, reflux, 8 h, 40%; ii, (-H$^{\bullet}$); (iii) PCC, 100%

now common Bu_3SnH-mediated 'oxidative' cyclisation. This protocol has also been used for the short synthesis of withasomnine **21** (n = 1), one of the few pyrazole natural products (Scheme 5).[37] In this example a side chain alkyl radical



Scheme 5 *Reagents and conditions*: i, Bu_3SnH, ACCN, toluene, reflux, 4 h, n = 1, 38%; n = 2, 63%.

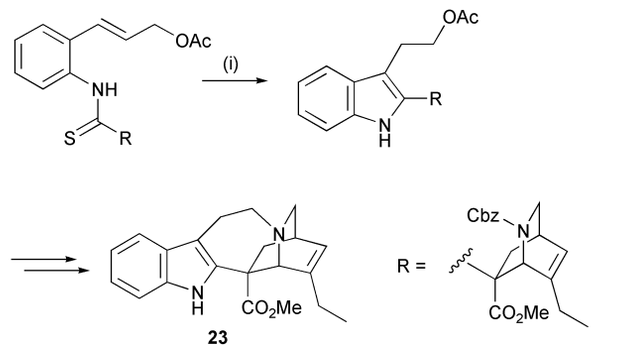
generated from the precursor selanide **20** cyclises onto the pyrazole ring with subsequent loss of hydrogen atoms by a similar oxidative process. Interestingly, the unnatural 6-membered compound **21** (n = 2) is formed in greater yield due to less ring strain in the cyclisation step. In studies of tandem cyclisations in the synthesis of rings ABCE of the *Aspidosperma* and *Strychnos* alkaloids, the final step involves cyclisation of an alkyl radical onto the indole ring (Scheme 6).[38] Contrary



Scheme 6 *Reagents and conditions*: i, Bu_3SnH, *tert*-butyl-*m*-xylene, reflux, 6 h, 43%.

to the two previous examples, the cyclisation onto the indole ring yields an indolin-2-yl radical intermediate which cyclises further to yield the 'reduced' product **22** as normally observed for Bu_3SnH reactions and not the rearomatised indole ring. The synthesis also uses a novel aryl radical abstraction to initiate the cascade reaction.

Very few syntheses use radical cyclisation for heteroarene formation. A new protocol for the synthesis of 1,3-disubstituted indoles uses radical cyclisations of thioamides onto alkenes (Scheme 7).[39] The mechanism is not clear but aromatisation by elimination after cyclisation is likely to yield the indole. The protocol has been used to synthesise the



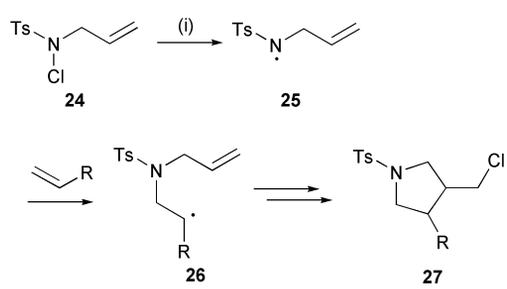
Scheme 7 *Reagents and conditions*: i, AIBN, H_3PO_2, Et_3N, *n*-PrOH, 90 °C, 50%.

alkaloid (±)-catharanthine **23**. The protocol uses hypophosphorous acid in place of Bu_3SnH, thereby replacing the toxic Bu_3SnH.

3 Nitrogen heterocycles

The synthesis of biologically important γ-lactams using cyclisation of enamides has been reviewed.[14] These cyclisations can proceed *via* either 4-*exo* or 5-*endo* pathways, to produce β- or γ-lactam products, respectively. One of the most common uses of radical cyclisation is the synthesis of nitrogen heterocycles, especially 5-*exo* cyclisation for the preparation of pyrrolidines. The radical can be generated in various positions relative to the *N*-heteroatom. Generation of aminyl radicals provides the first of the protocols. Improved methods for the generation of aminyl radicals continue to be published. For example, the use of chloramines to generate aminyls for cyclisation is the oldest method and Cu(I)[40] or Sm(II)[41] catalysis generates aminyl radicals which undergo 5-*exo* cyclisation to produce 2-chloromethyl pyrrolidines which rearrange to piperidines. Lewis acids have been used to carry out stereoselective cyclisation of chloramines *via* cationic aminyl radicals to yield 2,4-disubstituted pyrrolidines without rearrangement to piperidines.[42] The non-radical rearrangement is also prevented with Cu(I) catalysed cyclisation of aminyls generated from *N*-benzoyloxyamines for 5-*exo* cyclisation to pyrrolidines.[43] 2,5-*trans*-Disubstituted pyrrolidines result from the 5-*exo*-*trig* cyclisation of aminyls generated from sulfenamides with Bu_3SnH.[44] Similar results were obtained with iminyl radicals to yield 2,5-*trans*-disubstituted pyrrolenines.

A novel strategy uses radical [3+2] annulation of *N*-allyl-*N*-chlorotosylamide **24** with alkenes *via* an atom-transfer process with triethylborane (Et_3B) as the initiator (Scheme 8).[45] The



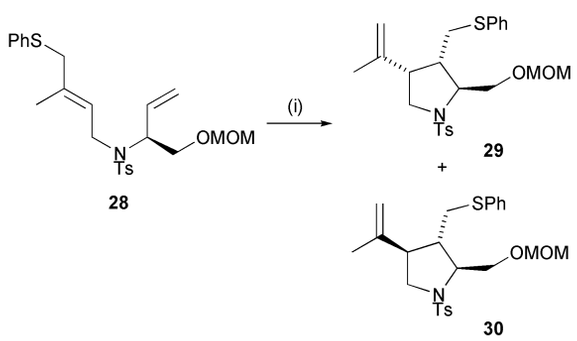
Scheme 8 *Reagents and conditions*: i, Et_3B (0.1 equiv.), benzene, rt, 3 h, 96% (R = Ph), 80% (R = Me_3SiCH_2)

Et_3B induces chlorine abstraction to give an electrophilic sulfonamidyl radical **25** which attacks the nucleophilic alkene trap added in a two-fold excess. The resultant alkyl radical **26** then proceeds to cyclise in a 5-*exo*-*trig* manner followed by the cyclised alkyl radical abstracting chlorine from the starting material and continuing the radical chain to yield the 3-chloromethylpyrrolidine product **27**. A wide range of

alkenes were successfully used in the protocol. A similar [3+2] annulation protocol using enol ethers and *N*-allyltosylamidyl radicals, generated from *N*-tosyl-2-(iodomethyl)aziridines by iodine atom abstraction and ring-opening, has also proved successful.[46] Enol ethers are used for the annulations to ensure electron rich alkenes to react with the electrophilic tosylaminyl radicals. Iodine-atom transfer is used to avoid reduction of intermediate radicals prior to cyclisation. Little or no diastereoselectivity was observed.

Cyclisations of radicals, β to the nitrogen atom, onto alkenes continues to be used for the synthesis of a wide range of pyrrolidines. A recent example uses $PhSeSiR_3$, activated to $[PhSeSiR_3]^{-\bullet}$ radical anions by visible light (410 nm), as a means of generating trialkylsilyl radicals which abstract phenylselanide groups from the β-position.[47] A number of methodologies report the cyclisation of radicals β to the nitrogen atom onto β-oxime ethers. In these protocols, the β-radicals are generated by phenylsulfanyl radical addition to a β-alkene,[48] $Bu_3Sn^{\bullet}$ addition to β-allenes,[49] $Bu_3Sn^{\bullet}$ abstraction of oxythiocarbonylimidazolides[50] and addition of propyl radicals, generated by Et_3B initiated abstraction of iodine, onto β-alkenes.[51]

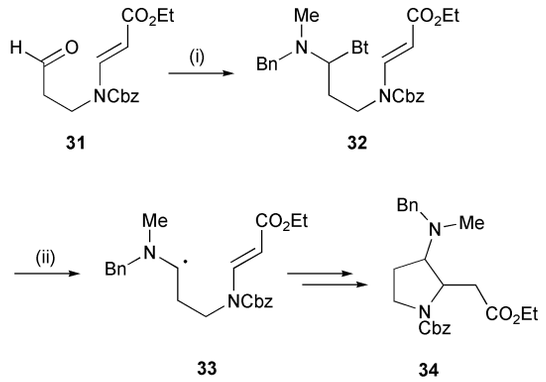
The addition of a radical generating reagent A–B across two alkenyl groups β to a nitrogen atom moiety with a 5-*exo-trig* cyclisation continues to be a common synthetic protocol and a model system for testing new radical reagents. For example, use of CCl_4 in the presence of diethyl phosphite or diphenylphosphine oxide has been investigated.[52] These reactions involve addition of the trichloromethyl radical to the β-alkene followed by a 5-*exo-trig* cyclisation reaction. The resultant cyclic primary radical can abstract a chlorine atom from CCl_4 or alternatively, abstract a hydrogen atom from the solvent or the organophosphorus compound. Similar cyclisations have been carried out with CCl_4 using decacarbonyldimanganese $[Mn_2(CO)_{10}]$ as the initiator.[53] Another new protocol involves the use of silylated cyclohexadienes which add silyl groups and hydrogen atoms in a hydrosilylation–cyclisation process.[54] Synthesis of (−)-kainic acid *via* phenylthiyl ($PhS^{\bullet}$) has been carried out by radical addition–cyclisation–elimination reactions (Scheme 9).[55] The thiyl radical adds to the β-alkene of



Scheme 9 *Reagents and conditions*: i, PhSH (0.2 equiv.), AIBN, benzene, reflux, 95% (**29** : **30** = 1 : 1.5)

the precursor **28** followed by 5-*exo-trig* cyclisation and $PhS^{\bullet}$ elimination to form the pyrrolidines **29** and **30** with poor diastereoselectivity. The diastereomer **29** was further elaborated to give a formal total synthesis of (−)(α)-kainic acid. Related cyclisations to yield 3,4-disbustituted pyrrolidines have involved employment of two allenyl groups β to a nitrogen moiety using TsBr and TsSePh as the reagents to add across the two allenes.[56] A second example uses the addition of Bu_3SnH onto β-alkynes followed by cyclisation onto β-alkenes to give 3,4-*exo*-cyclic alkenes on a pyrrolidine ring.[57]

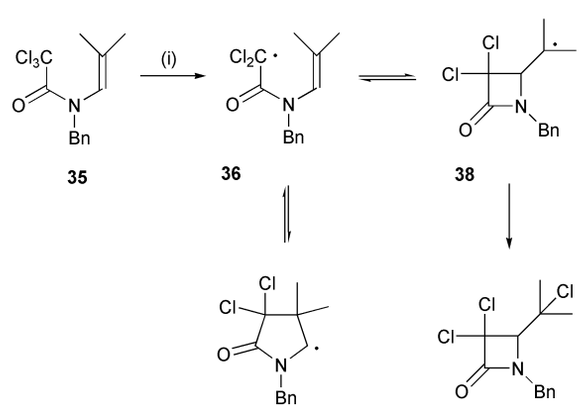
Generation of the cyclising radical can take place at any of the positions relative to the nitrogen. Synthesis of 3-aminopyrrolidines by cyclisation of neutral *C*-centred α-aminoalkyl radicals γ to the nitrogen atom (*e.g.* **33**) has been achieved in good yield (Scheme 10).[58] The radical precursor **32**



Scheme 10 *Reagents and conditions*: i, *N*-Methylbenzylamine, Bt–H; ii, SmI_2, *tert*-BuOH, −78 °C to rt, 82% for both steps.

was synthesised from the respective aldehyde **31** by addition of an amine and α-benzotriazole (Bt–H) and treated with SmI_2 in a one-pot reaction. The nucleophilic α-amino radicals readily cyclise onto the electrophilic β-position of the α,β-unsaturated ester to yield the β-amino ester **34**. The diastereoselectivity is poor. Generation of the radical α to an ammonium nitrogen gives unusual regioselectivity.[59] 2-Azonia-2,2,5-trimethyl-5-hexenyl radicals, derived from treatment of 1-iodo-2,2,5-trimethyl-2-azonia-5-hexenyl iodide with Bu_3SnH, was found to give an 8 : 3 : 1 mixture of the isomeric 5-*exo*, 6-*endo* and acyclic ammonium salts. A rationale for the observed regioselectivity is proposed, and a comparison is made with the behaviour of the corresponding all-carbon radical. Benzeneselanol (PhSeH) showed similar behaviour, but an order of magnitude superior as a H-atom transfer reagent.

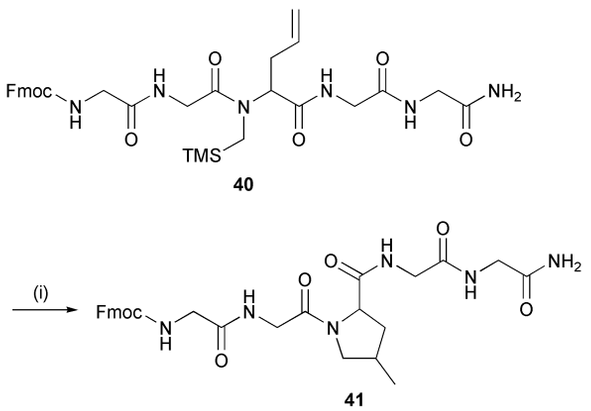
Radical cyclisation for the synthesis of β-lactams is unfavourable and can only be achieved using a method which has some factor in the mechanism to favour 4-membered ring cyclisation. Cu(I) complex catalysis of suitable precursors provides an important route into β-lactams.[60,61] The importance of the complex is illustrated in the cyclisation of halo-enamides, *e.g.* **35**, where the use of different complexes directs the cyclisation to 5-*endo* cyclisation *via* **37** to a γ-lactam (bipyridine complex) or *via* 4-*exo* cyclisation to **38** and finally to the β-lactam product **39** (TMEDA complex) (Scheme 11).[60] The



Scheme 11 *Reagents and conditions*: i, CuCl (0.5 equiv.), MeCN, TMEDA (0.5 equiv.), heat, 86%.

difference in reaction route is explained by the equilibrium between the two cyclised radicals **37** and **38** and the ring-opened intermediate **36**. Generation of aminoacyl radicals using 'tin-free' conditions by homolysis of 1-carbamoyl-1-methylcyclohexa-2,5-dienes provides a new route to β- and γ-lactams.[62] The radical induced homolysis of the precursor yields toluene and aminoacyl radical intermediates which were found not to decarbonylate under the reaction conditions and either cyclised or reduced to yield minor products.

Photochemically induced electron transfer (PET) has been used to catalyse radical cyclisations of amino acids in peptides to yield peptide products with a pyrrolidine ring present which induces structural changes in the peptides (Scheme 12).[63] PET



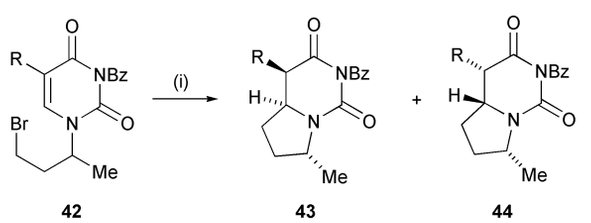
40 41

Scheme 12 *Reagents and conditions*: i, 20 mol% BP, 30 mol% ADC, MeOH : MeCN (3 : 2), irradiation $\lambda > 345$ nm, 64%.

can be carried out under mild, non-oxidising, and non-toxic conditions in neutral medium and can be used in peptide chemistry. An example is shown in Scheme 12 where the single electron transfer (SET) between the electron donor BP (biphenyl) and electron acceptor ADC (9,10-anthracenedicarbonitrile) is facilitated under light catalysis. The BP radical cation removes an electron from the trimethylsilylmethylamino moiety of the peptide precursor **40** to yield a radical cation on the peptide chain. The radical cation dissociates to a trimethylsilyl cation and a *N*-methyl radical on the peptide chain which undergoes 5-*exo* cyclisation with the pendant alkene to yield the new peptide **41**.

4 Pyrrolizidines and other bicyclic nitrogen heterocycles

Synthesis of bicyclic nitrogen heterocycles by radical cyclisation remains an important area of research. The most common route is to start with one ring and carry out a cyclisation onto the ring from a side chain radical or from a radical on the ring to cyclise onto a side chain. The former of these two approaches has been utilised for the stereoselective synthesis of the azabicyclic core of the polyguanidinium alkaloids batzelladine A and D (Scheme 13).[64] The radical was generated

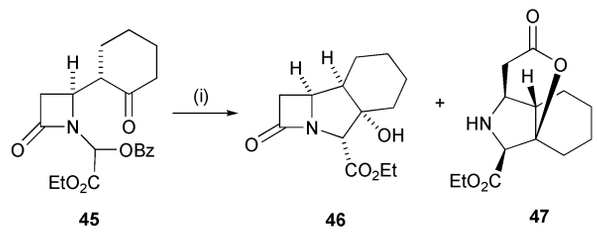


42 43 44

Scheme 13 *Reagents and conditions*: i, $(TMS)_3SiH$, Et_3B, benzene, rt, air, **43**, R = H (78%), **43**, R = Me (72%).

using $(TMS)_3SiH$ on the side chain of the precursor **42** and cyclises stereoselectively onto the ring alkene. Diastereomer **43** was predominantly obtained with a diastereomer ratio of **43 : 44** > 19 : 1. The origin of the diastereocontrol at C-5 is presumed to be as a consequence of conformational bias of the azabicyclic core derived after the cyclisation which results in reduction at the more accessible convex face. A new methodology has been developed for generation and cyclisation of iminyl and amidyl radicals under mild conditions which involves treatment of oximes with 2,6-dimethylbenzenesulfinyl chloride or hydroxamic acids with *tert*-butylsulfinyl chloride to give nitrogen radicals which cyclise onto pendant olefin groups.[65] Radical traps $(PhSe)_2$, $(PhS)_2$ and TEMPO can be used to terminate the cyclisation in order to give a functionalised product suitable for further transformation. Generation and reaction of alkene radical-cations under non-oxidising conditions has been used for the synthesis of the pyrrolizidine nucleus.[66]

Several protocols use β-lactam rings as a template for radical cyclisation. SmI_2-mediated cyclisations of derivatised β-lactams, *e.g.* **45**, have been used for highly diastereoselective construction of functionalised β-lactams and prolines (Scheme 14).[67]

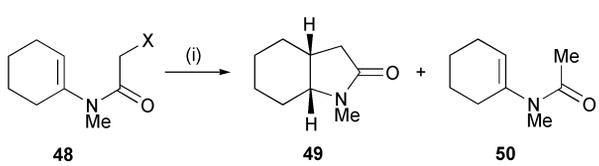


45 46 47

Scheme 14 *Reagents and conditions*: i, SmI_2, THF, 20 °C, **46**, 55%; **47**, 28%.

Depending on the conditions of the reactions the route can be pushed to selective β-lactam **46** or proline **47** synthesis. The SmI_2 forms an intermediate radical centred on the carbon between the ester and amine. The proline product can be selectively produced by the addition of *tert*-butanol to facilitate protonation of the intermediates after acyl migration. Other protocols using a β-lactam template include the synthesis of novel tricyclic β-lactams from radical cyclisations of methylenecyclopropyl azetidinones[68] and conversion of cephalosporins to 1-carba(dethia)cephalosporins *via* ring opening and closing.[69]

The synthesis of γ-lactams (pyrrolidin-2-ones) by 5-*endo* cyclisation of *N*-alkenyl-α-haloamides has proved a popular methodology and continues to be exploited. The effect of the halogen atom as a leaving group in Bu_3SnH-mediated 5-*endo-trig* radical cyclisation of *N*-(cyclohex-1-enyl)-α-haloamides was examined (Scheme 15).[70] The cyclisation of

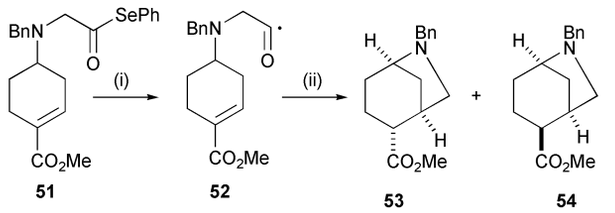


48 49 50

Scheme 15 *Reagents and conditions*: i, Bu_3SnH, AIBN, toluene, **49** (X = Cl, 63%, X = I, 0%); **50** (X = Cl, 8%, X = I, 54%.

the α-chloroamide **48** (X = Cl) occurred with a high degree of efficiency to yield the bicycle **49**, while the corresponding α-iodo analogue **48** (X = I) gave only limited quantities of the cyclisation products and largely reduced uncyclised material **50**. This behaviour is rationalised by consideration of rotamers, with the iodo-rotamer preferring the *trans* conformation which does not lead to cyclisation. Use of Bu_3SnCl or Bu_3SnF as additives appears to restore the effectiveness of the cyclisation of α-iodoamides. The protocol has been applied to the synthesis of lycoranes. The effect of phenylsulfanyl (PhS) groups on the reactivity of the alkene have also been explored.[71] Two studies report protocols using $Mn(OAc)_3$ for the synthesis of the erythrinane skeleton.[72] A novel route to spirocyclic pyrrolidin-2-ones has been developed *via* 1,5-hydrogen atom abstraction from the position α to the carbonyl group by a pendant aryl radical and 5-*exo* cyclisation of the new radical intermediate onto an alkene.[73]

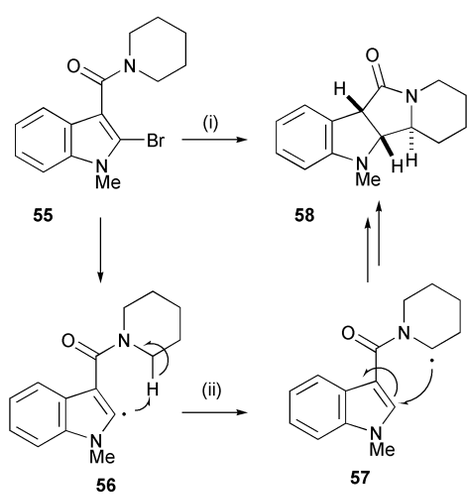
Radical cyclisation provides a facile route to bridged nitrogen ring systems. A general method for 6-azabicyclo[3.2.1]octane synthesis using decarbonylative radical cyclisation of α-amino selenoesters upon electrophilic alkenes has been reported (Scheme 16).[74] Treatment of the acyl selanide precursor **51** and



Scheme 16 *Reagents and conditions*: i, Bu_3SnH, AIBN, toluene; ii, –CO, cyclisation, **53**, 34%; **54**, 40%.

analogues with Bu_3SnH or $(TMS)_3SiH$ yields an intermediate acyl radical **52** which undergoes loss of CO followed by regioselective 5-*exo* cyclisation onto the electrophilic cycloalkene to yield a mixture of 6-azabicyclo[3.2.1]octanes **53** and **54**. Azabicyclo[4.2.1]decanes were synthesised using the same methodology.[74] 6-Azabicyclo[3.2.1]octanes,[75,76] 1-azabicyclo[2.2.2]octanes,[75] and 1-azabicyclo[2.2.1]heptanes[75] have also been synthesised by radical cyclisation from bromide or phenylselanide precursors. 2-(4-Trimethylsilyl-1-oxobut-3-ynyl)piperdines have been used to synthesis 9-azabicyclo[3.3.1]nonanes in high yield.[77] *o*-Iodobenzoyl groups were used to generate aryl radicals which give 1,5-H translocation to yield α-amino radicals, which undergo 6-*exo* cyclisation onto the pendant alkyne. New tricyclic tropane † skeletons for structure activity relationship studies of cocaine analogues have been prepared by 6- and 7-*exo*-*trig* radical cyclisation.[78] Radical cyclisation of *N*-(α-methyl)benzyl substituted trichloroacetamides onto α,β-unsaturated nitriles has yielded morphan † derivatives.[79]

Manipulations of indole derivatives provide a number of interesting examples of radical cyclisation. Generation of indol-2-yl radicals **56** from the bromide precursor **55** followed by 1,5-hydrogen atom transfer (radical translocation) yields the more stable α-aminyl radical intermediate **57** and finally 5-*endo*-*trig* cyclisation back onto the indole ring gives the tetracyclic indole **58** (Scheme 17).[80] The methodology has also been used



Scheme 17 *Reagents and conditions*: i, Bu_3SnH, AIBN, toluene, reflux, 36 h; ii, 1,5-H abstraction; **58**, 54%.

for the equivalent 5- and 7-membered rings. Easy entry into berbane and *allo*-yohimbane alkaloids has been achieved *via* a 6-*exo* radical cyclisation using xanthate radical methodolgy.[81] In studies towards the synthesis of the alkaloid geissoschizine, a novel pentacyclic 1-azatricyclo[5.3.0.0.^{4,8}]decane system has been generated *via* tandem radical cyclisation of a tryptophan derivative.[82]

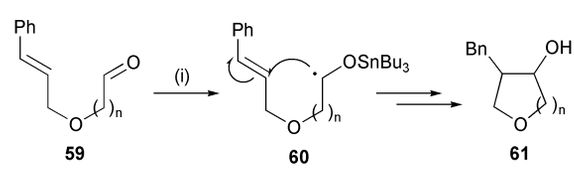
Radical cyclisation has been applied to the preparation of spirocyclic nitrogen heterocycles. A new route to spirooxindoles has been developed by tandem cyclisation of an indol-3-yl side chain radical onto the 3-position of a 2-cyanoindole.[83] $Mn(OAc)_3$ mediated cyclisation of β-keto carboxamides was found to be successful for formation of azaspiro[4.5]decanes and azaspiro[4.4]nonanes.[84]

5 Oxygen heterocycles

The synthesis of tetrahydrofurans by radical cyclisation is a most common general route. The first of many options for general protocols is 5-*exo* cyclisation of alkoxy radicals. This obvious protocol has been hampered by problems of synthesis of alkoxy radical precursors. Two new methodologies have been published. The first methodology uses photolysis of *N*-alkoxy-4-(*p*-chlorophenyl)thiazolyl-2(3*H*)-thiones as alkoxyl radical precursors. Thiols of different polarity and molecular size were selected as the hydrogen atom donor.[85] The protocol has also been compared with the classical bromine cyclisation.[86] The second procedure uses reactions between *N*-alkoxydithiocarbonates and Bu_3SnH.[87]

As with cyclisation to pyrrolidines, the analogous cyclisation of radicals, β to the oxygen atom, onto alkenes β to the oxygen to prepare tetrahydrofurans is a common reaction used to test new radical generating methodologies. Most of these methodologies have also been tested on cyclisations to yield 2,3-dihydrobenzofurans (*o*-allyloxyaryl radicals) and bicyclic acetals, *e.g.* 3-methylhexahydrofuro[2,3-*b*]pyran (2-allyloxytetrahydropyran-3-yl radicals). These protocols include the use of EPHP (1-ethylpiperidine hypophosphite) with VA-061 {2,2′-azobis[2-(2-imidazolidin-2-yl)propane]} in water as a solvent,[88] hypophosphorous acid (H_3PO_2) in EtOH or water as solvent,[89] indium(III) hydride, generated by reduction of $InCl_3$ with $NaBH_4$,[90] 1-phenylcyclohexa-2,5-diene-1-carboxylates as hydrogen atom sources[91] and tri(2-furyl)germanium hydride in solvents such as THF, EtOH and water with Et_3B and VA-70 {[2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrite)]} as initiators.[92]

Aldehydes in the β-position to the oxygen atom can also be used as sources of generating the radical (Scheme 18).[93] $Bu_3Sn^{\bullet}$

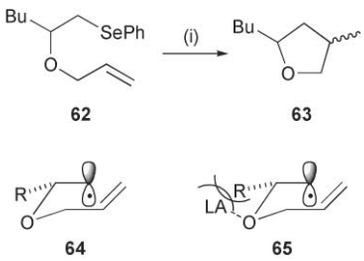


Scheme 18 *Reagents and conditions*: i, Bu_3SnH, AIBN, benzene, reflux; ii, **61**, $n = 1$ (59%), $n = 2$ (44%).

radical attack onto the aldehydes **59** form *O*-stannyl ketyl intermediates **60** which cyclise to form tetrahydrofurans **61** ($n = 1$) and pyrans **61** ($n = 2$) depending on chain length. Little diastereoselectivity was observed. Nitrogen heterocycles were also prepared by this protocol as well as addition of $Bu_3Sn^{\bullet}$ radicals to ketones and α,β-unsaturated ketones.

Depending on the substitution pattern all these cyclisations show some diastereoselectivity. Diastereocontrol can be obtained by use of trialkylaluminiums in the synthesis of tetrahydrofurans *via* radical cyclisation.[94] An example of the cyclisation to yield 2,4-disubstituted tetrahydrofurans, *e.g.* **63**, from phenylselanide precursors, *e.g.* **62**, is shown in Scheme 19. A reversal of diastereoselectivity was observed when the major isomer obtained was not derived from the transition state (TS) with the equatorial substituent (**64**, Beckwith TS). A variety of Lewis acids were utilised of which the trialkyl aluminiums proved most effective in terms of yield and diastereocontrol (Me_3A1, Et_3A1 and Bu_3A1). Of these, Et_3A1 imparted the highest diastereoselectivity and also gave good yields. Due to clashes with the steric bulk of the complexed Lewis acid as

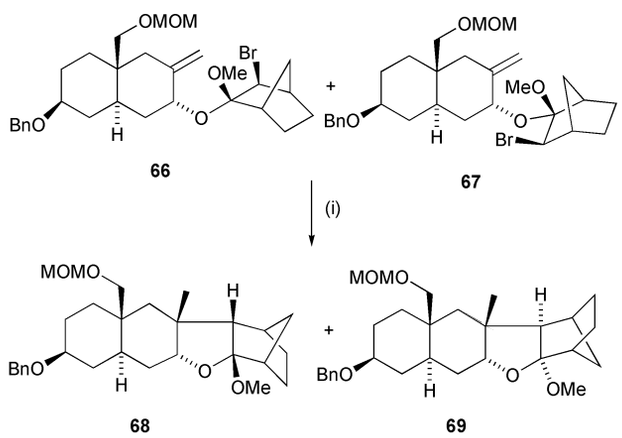
† The IUPAC name for tropane is 8-azabicyclo[3.2.1]octane. The IUPAC name for morphan is 2-azabicyclo[3.3.1]nonane.



Scheme 19 *Reagents and conditions*: i, Bu_3SnH, AIBN, Et_3Al, benzene, 17 °C, *hv*, 79% (*cis* : *trans* = 5.1 : 1).

shown in intermediate **65**, the substituent is forced into the axial or twist boat position in the TS. A highly diastereoselective cyclisation strategy leads to the formation of 2,3,4- and 2,3,4,5-substituted furan rings.[95] Excellent levels of 2,4-*trans* selectivity are observed in accordance with the Beckwith–Houk model for selectivity in 5-*exo* radical cyclisations.

Tetrahydrofuran ring synthesis has proved useful in the synthesis of larger and more complex molecules. Construction of the crowded C8–C14 bond of azadirachtin, a natural product which exhibits a potent insect antifeedant activity, has been achieved by radical cyclisation (Scheme 20).[96] A mixture

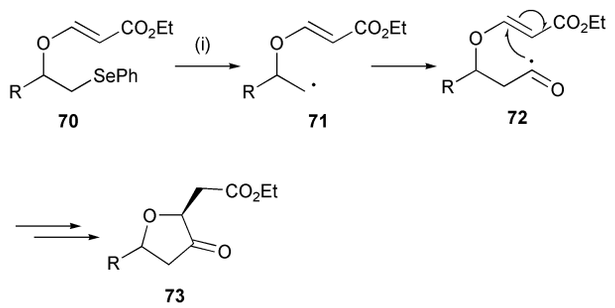


Scheme 20 *Reagents and conditions*: i, **66** : **67** = 1 : 1.5, Bu_3SnH, AIBN, toluene, reflux, 70% (**68** : **69** = 1 : 1.5).

of diastereomers **66** and **67** gives an equivalent mixture of diastereomers **68** and **69** around the newly formed tetrahydrofuran ring. The synthetic studies are a useful illustration of the application of the common cyclisation to tetrahydrofuran derivatives to complex natural product synthesis. Other useful examples include synthesis of heteroannular acetals,[97] spiroenones[98] and the eudesmane framework.[99]

Acyl radicals have been used in the synthesis of 5-, 6- and 7-membered oxygen heterocycles. Tetrahydrofuran-3-ones, *e.g.* **73**, have been synthesised from phenylselanyl precursors, *e.g.* **70**, *via* radical carbonylation–reductive cyclisations (Scheme 21).[100] The initially formed alkyl radical **71** is carbonylated using high pressure CO to give an acyl radical **72** which facilitates 5-*exo*-*trig* cyclisations onto vinyl ethers with electron withdrawing groups. This protocol provides a new synthon to acyl radicals and avoids the use of acyl selanides as precursors. An analogous protocol uses acyl selanide precursors to carry out cyclisations onto α-branched vinylogous carbonates for the synthesis of tetrahydrofuran-3-ones, -pyran-3-ones and -oxepin-3-ones using $(TMS)_3SiH$, Et_3B and air.[101]

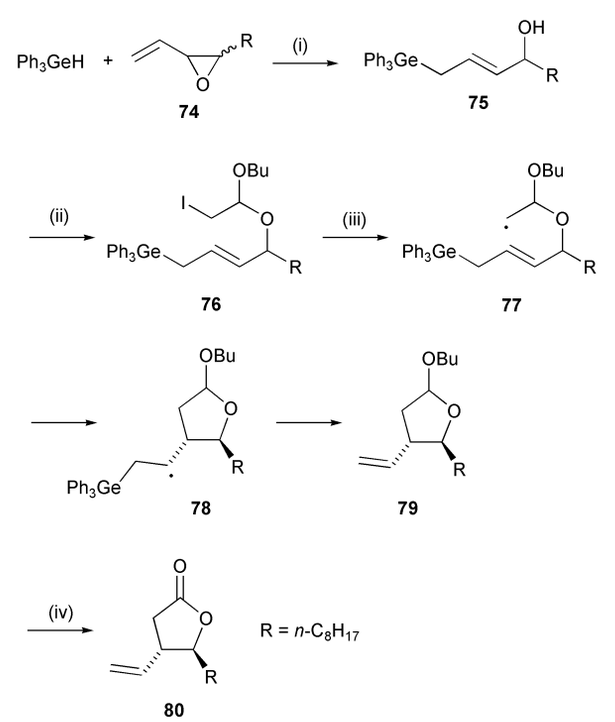
γ-Lactones are an important target for radical cyclisations but the obvious method of 5-*exo* cyclisation of alkyl radicals onto alkenes joined by esters has a major problem because the lower energy *trans* conformation is favoured for the ester which gives reduction rather than cyclisation. An early method round this problem which is still commonly applied is to use Stork's protocol with α-bromoacetals.[102] In a most important develop-



Scheme 21 *Reagents and conditions*: i, $(TMS)_3SiH$, AIBN, CO 80 atm, R = Bn (88%, dr 9 : 1), R = $BnOCH_2$ (42%, dr 7 : 1), R = Ph (64%, dr 8 : 1)

ment the use of water or mixtures of water with EtOH with Et_3B to initiate iodine-atom transfer reactions, esters are held in the higher energy *cis*-conformation allowing high yields of cyclisation.[103] Theoretical calculations have been used to support the preferred *cis*-conformation of ester radicals in water. β-Disubstituted γ-lactones have been prepared by a novel protocol using sulfonyl radical addition–cyclisation of dienes connected with hydroximates. The cyclised hydroximates are converted to the γ-lactones after radical cyclisation.[104a] This protocol also overcomes the problem of equivalent ester cyclisation to γ-lactones which are unsuccessful because of the preferred *trans* conformation of the ester. Likewise use of the esters of glyoxylic acid hydrazones for the synthesis of 3-(2,2-diphenylhydrazino)-γ-lactones by radical cyclisation also overcomes the problem of ester conformation.[104b] The precursors are prepared by condensation of 2-bromo- and 2-(phenylselanyl)ethanols with the glyoxylic acid hydrazones. Hydrogenolysis of the cyclisation product yields 3-amino-γ-lactones.

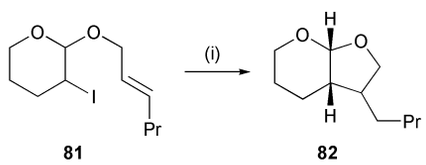
A new protocol for the synthesis of 4-vinyltetrahydrofuran-2-ones uses radical reactions of triphenylgermanium hydride in several steps (Scheme 22).[105] Triphenylgermanium hydride is added to vinyloxiranes **74** to yield allyl alcohols **75** and then converted to the iodoacetal **76**. The next reaction is the same as the Stork protocol and radical reaction with Ph_3GeH promotes



Scheme 22 *Reagents and conditions*: i, Ph_3GeH, Et_3B, hexane; ii, NIS, CH_2=CHOBn; iii, Ph_3GeH, Et_3B, hexane; iv, Jones oxidation, 78% overall.

cyclisation of radical **77** to cyclised radical **78** which eliminates triphenylgermanyl radicals to yield the cyclised acetal **79**; in this reaction the $Ph_3Ge^{\bullet}$ is regenerated to continue in the cycle. Standard Jones oxidation gives the γ-lactone **80**. A radical addition–cyclisation method involving iodine atom transfer facilitates cyclisation of radicals α to the ester onto β-oxime ethers and overcomes the problem of ester conformation.[106] Iodine atom transfer reactions with dilauroyl peroxide as initiator abstract iodine to form carbon centred radicals α to the esters which cyclise onto β-alkenes to form lactones, lactams and cyclic acetals depending on the alkene used.[107] Macrolactonisation and cyclisation onto aromatic rings is also possible.

Bicyclic acetals, *e.g.* **82**, are good targets of radical cyclisation. The precursors, *e.g.* **81**, are easily prepared by addition of the allylic alcohols to the cyclic enol ethers in the presence of an electrophile such as NBS. The use of hypophosphorous acid has proved successful for preparing high yields of the acetals (Scheme 23).[89] Similar syntheses have been carried out with Et_3B



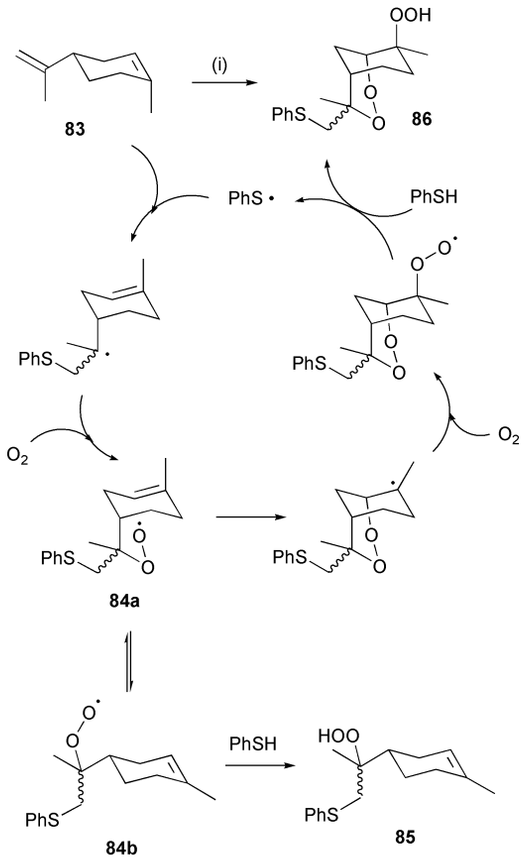
81 **82**

Scheme 23 *Reagents and conditions*: i, H_3PO_2 (10 equiv.), $NaHCO_3$ (15 equiv.), AIBN, EtOH, reflux, 30 min, 98% (dr 74 : 26).

as the initiator in water,[89] with gallium hydride ($HGaCl_2$) with Et_3B as the initiator[108] and Bu_3SnH but using a chiral allylic alcohol.[109] Similar procedures employ alkynes with indium metal[110] and oxime ethers with Co(I) and electroreduction.[111]

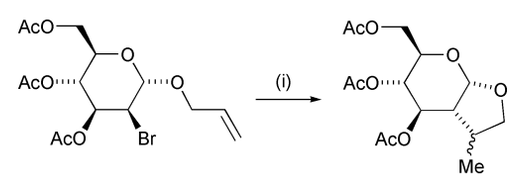
Further studies have been reported on the iterative synthesis of *trans*-fused polycyclic ethers *via* SmI_2-induced cyclisation.[112] The iterative syntheses include *trans*-fused 6,6,6,6-membered and 6,7,7,6-membered rings in tetracyclic ethers and *trans*-fused 6,7,6-membered in tricyclic ethers.

An efficient synthesis of bridged-bicyclic peroxides structurally related to the antimalarial yingzhaosu A have been achieved using PhSH as a mediator in the presence of oxygen (Scheme 24).[113] This process provides an efficient method for the preparation of peroxides containing the 2,3-dioxabicyclo-[3.3.1]nonane system characteristic of the yingzhaosu A family. The thiyl radical adds to the alkene of limonene **83**, followed by trapping with oxygen to give the peroxy radicals **84a** and **84b**. The equatorial peroxyl **84b** gives the unwanted product **85** whereas the axial peroxyl **84a** cyclises to give a new radical which traps a second molecule of oxygen eventually yielding the peroxide product **86**.



83 **86** **84a** **84b** **85**

Scheme 24 *Reagents and conditions*: i, O_2, PhSH, rt, AIBN, MeCN, 10 h, 44%.



87 **88**

Scheme 25 *Reagents and conditions*: i, $Ph_4Si_2H_2$, Et_3B, EtOAc, 84% (dr = 52 : 48).

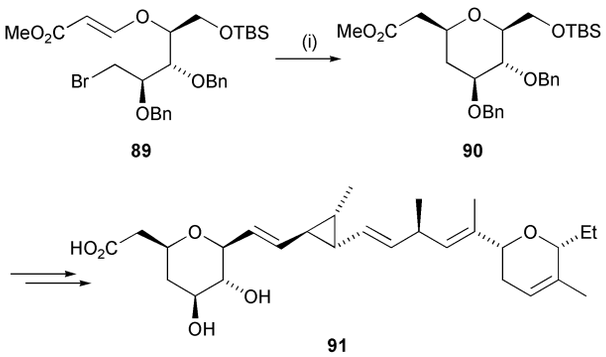
6 Carbohydrates and nucleosides

Radical cyclisations involving carbohydrates can be split into cyclisations from a radical on the carbohydrate ring onto side chain unsaturated bonds or from a radical on the side chain onto the carbohydrate ring. The former route is exemplified by radical cyclisation of *O*-glycosides using 1,1,2,2-tetraphenyldisilane ($Ph_4Si_2H_2$) as the radical reagent for the preparation of bicyclic sugars (Scheme 25).[114] $Ph_4Si_2H_2$ is an easily handled reagent due to its stability in contrast to other silyl hydrides available. Bicyclic sugars were formed through alkyl radical cyclisations onto allylic ethers in good yields to give *cis*-fused 5-*exo* cyclisation products, *e.g.* cyclisation of the anomeric allyl ether **87** to the bicyclic **88**.

There are several examples using cyclisation of a radical on the side chain onto the carbohydrate ring. A simple chiral synthesis of *cis*- and *trans*-pyrano[3,2-*c*]benzoxocines in good yields (60–75%) through regioselective 8-*endo-trig* aryl radical cyclisation of the D-mannose derived enopyranosides with Bu_3SnH has been described.[115] 5-*exo-dig* And 5-*exo-trig* cascade radical cyclisations onto furanose templates have been used to synthesise oxa- and dioxa-triquinone skeletons.[116] In the synthesis of enantiomerically pure (−)-tetrodotoxin, radical cyclisation onto an oxime ether on a mannose analogue from a side chain was carried out using standard slow addition of Ph_3SnH to yield a key intermediate.[117] Oxazaspirobicycles with the oxygen-containing ring as a monosaccharide have been synthesised *via* H-transfer and cyclisation of aminyl radicals onto the anomeric position using (diacetoxyiodo)benzene (DIB) and iodine as radical generating reagents.[118]

Cyclisations on carbohydrate templates can also be facilitated by the radical and the unsaturated radical acceptor being positioned on side chains. For example, 11-*endo* cyclisation has been used to make 11-membered ring lactams by cyclisation of aryl radicals onto alkenes but when both groups are pendant on a β-D-glucose template higher yields are obtained.[119]

Monosaccharide rings are also synthesised directly by cyclisation of acyclic radicals. A good example of this methodology is exemplified by a key step in the synthesis of the ambruticin, a natural antifungal agent **91** using radical cyclisation as the key step to elaborate the monosaccharide portion (Scheme 26).[120] The nucleophilic alkyl radical generated from **89** readily



Scheme 26 *Reagents and conditions*: i, Bu_3SnH, AIBN, benzene, reflux, 2 h, 83% (2,6-*cis* : *trans* = 10 : 1).

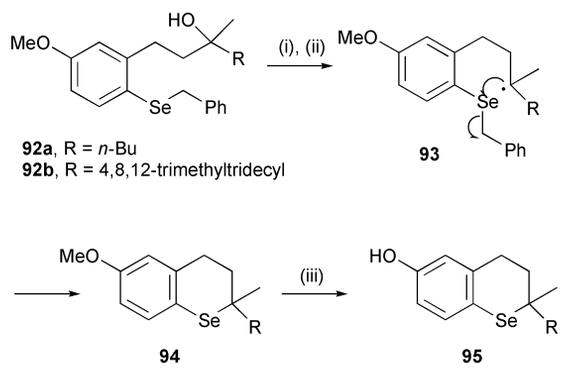
undergoes 6-*exo* cyclisation onto the electrophilic β-position of the α,β-unsaturated ester. The cyclised monosaccharide product **90** which was achieved with a good diastereoselectivity was further elaborated to yield ambruticin **91**. Radical annulation onto monosaccharides provides a new route to bicyclic saccharide derivatives containing an amino substituent.[121] The protocol uses addition of $Bu_3Sn^{\bullet}$ radicals onto aldehydes and the resulting radical undergoes 6-*exo* cyclisation onto oxime ethers.

Two examples use 5-*exo* radical cyclisation of substituents at N-1 of nucleoside bases to synthesise the monosaccharide moiety of the nucleoside.[122]

7 Sulfur, selenium and tellurium heterocycles

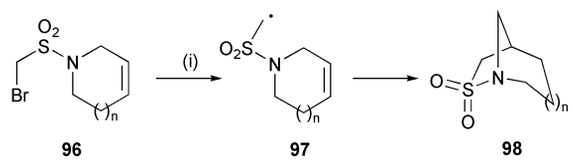
The Baldwin rules for cyclisation state that 5-*endo-trig* cyclisations are disfavoured. However, in a useful review, there is a reminder that these rules only apply to first row elements which in particular excludes sulfur. Therefore in the synthesis of S-, Se- and Te-heterocycles, 5-*endo* cyclisation should always be considered.[8] In the cyclisation of radicals α to sulfides or sulfones onto alkenes a mixture of 5-*exo* and 6-*endo* products are obtained.[123] The results were also explained by the intermediate radicals experiencing greater difficulty attaining the transition state required for 5-*exo-trig* cyclisation due to longer C–S bond lengths compared to C–O bond lengths leading to a significant proportion of 6-*endo*-cyclisation. However, in the reported synthesis of thiabicyclic heterocycles of 8-aza-3-thiabicyclo[4.3.0]nonanes and 3-thiabicyclo[4.4.0]-decanes and 8-thiabicyclo[4.3.0]nonanes, cyclisation onto the β-position of β-thioacrylates, 6-*exo* cyclisation is dominant over possible 7-*endo* cyclisation.[124]

Intramolecular S_H2 substitution on Se with the displacement of benzyl radicals has been used to good advantage for the synthesis of important selenium analogues of natural products. In Scheme 27, the synthesis of selenium analogues of vitamin E using this protocol is illustrated.[125] The alcohols **92a** and **92b** were converted to radical intermediates **93** using Barton esters. The tertiary radicals undergo cyclisation by S_H2 substitution on the Se to yield the cyclised Se-heterocycles **94** which were converted in the same one-pot reaction to the required phenols **95a** (48%) and **95b** (62%) in good yield. The long chain hydrocarbon analogue **95b** is closely related to vitamin E. Se analogues of β-lactams (selenocephems and selenopenams with Se replacing sulfur in the 6-membered ring)[126] and 5-seleno-pyranoses[127] have also been synthesised using this protocol. Radical cyclisation *via* S_H2 substitution on sulfur has also been used.[128] In this protocol *tert*-butyl radicals are displaced from sulfur in the final step in *tert*-butylthiyl radical mediated cascades for the synthesis of thiabicyclo[3.3.0]octanes.



Scheme 27 *Reagents and conditions*: i, $(COCl)_2$, benzene; ii, sodium salt of 2-mercaptopyridine *N*-oxide, DMAP, benzene; iii, BBr_3, DCM, **95a**, 48% from **92a**; **95b**, 62% from **92b**.

The use of radicals from α-halosulfono compounds in cyclisations to prepare cyclic sulfono compounds has been reviewed.[11] The general methodology has been further exploited by Paquette and co-workers in the synthesis of the first bridgehead sultams (*e.g.* Scheme 28).[129] The protocol

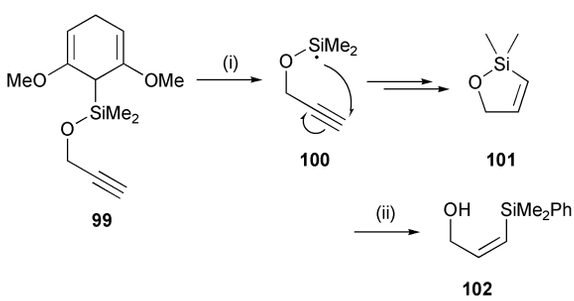


Scheme 28 *Reagents and conditions*: i, $(TMS)_3SiH$, AIBN, benzene, reflux, **98** (*n* = 1, 16%; *n* = 2, 69%; *n* = 3, 37%).

exploits the electrophilicity of α-sulfonyl radicals and their propensity to undergo intramolecular ring closure with weakly nucleophilic alkenes. In the examples shown in Scheme 28, 5-*exo* cyclisation of **97** was dominant but reduced uncyclised material was obtained in each reaction. The α-bromosulfonamides yield the electrophilic intermediate radicals **97** which cyclise to give the bridgehead sultams **98**. The yields were better when less strain was involved, *e.g.* when **96** (*n* = 0) was reacted, no cyclised product was obtained. In the cyclisation of **96** (*n* = 1) both 5-*exo* and 6-*exo* products were obtained but when *n* = 2 and 3, only 5-*exo* products were obtained.

8 Silicon heterocycles

The synthesis of silyloxy heterocycles (with Si–O in the ring) is primarily of interest as a synthetic method which uses silicon containing tethers attached to hydroxyl groups in radical cyclisation for the introduction of new C–C bonds. The general protocol has been applied to the synthesis of (+)-juruenolide C by using a cascade radical reaction to a bicyclic ring system containing a γ-lactone and a silyloxy ring[130] and to the diastereoselective addition of vinyl groups to chiral hydrazones *via* tandem thiyl radical addition and silicon-tethered cyclisation.[131] In a most interesting application of Baldwin's rules, the first 5-*endo-dig* cyclisation has been reported (Scheme 29).[132] In this cyclisation, a new protocol which uses the driving force of aromatisation and avoids the toxic Bu_3SnH has been used. The radical precursor **99** was subjected to the radical initiator, di-*tert*-butylhyponitrite, to yield the silyl radical intermediate

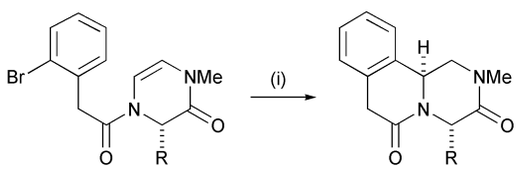


Scheme 29 *Reagents and conditions*: i, *t*-BuO–N=N–O*t*-Bu, hexane, 80–85 °C; ii, PhLi, 55%.

100 which undergoes the 'allowed' 5-*endo*-*dig* cyclisation to yield the silyloxy heterocycle **101**. This heterocycle was unstable and treatment with phenyllithium gave the allylic alcohol **102** in good yield.

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

One of the most widely used general protocols remains the cyclisation of aryl radicals onto side chain alkenes to yield benzoheterocycles. The protocol is illustrated by the synthesis of novel amino acid derived heterocycles which can be used as peptidomimetic scaffolds as shown in Scheme 30.[133] Amino



103a, R = Bn
103b, R = *i*-Pr
103c, R = Me

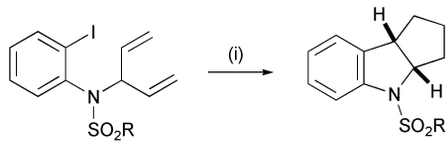
104a, R = Bn
104b, R = *i*-Pr
104c, R = Me

Scheme 30 *Reagents and conditions*: i, Bu_3SnH, AIBN, toluene, reflux, 16 h, **104a**, 80%; **104b**, 70%; **104c**, 71%.

acids were used to synthesise a range of enamido radical precursors, *e.g*. **103a**–**c**. The aryl radicals were generated using Bu_3SnH which cyclised by 6-*exo* selectivity to yield the peptide mimics **104a**–**c** in good yield. Only one diastereomer was obtained in each reaction which is explained by the radical approaching from the opposite face of the amino acid side chain. The anthelmentic drug praziquantel was also synthesised by this protocol.

Further examples of this general methodology using Bu_3SnH include the following examples. Naphthyl radicals have been generated and undergo 5-*endo*-*trig* cyclisation to synthesise analogues of tetracyclic phytoalexin pterocarpans.[134] The unfavoured cyclisation is facilitated by the formation of radical intermediates stabilised by aryl and ether substituents. The required *cis*-ring junction was obtained as expected from cyclisation onto a cycloalkene. Synthesis of constrained arylpiperidines, *e.g*. hexahydrobenzofuro[2,3-*c*]pyridines, was carried out using Bu_3SnH-mediated generation of aryl radicals from iodo- and bromoarene precursors. In this procedure aryl radicals undergo 5-*exo* cyclisation onto pendant tetrahydropyridines.[135] The radical route gave much better yields than related intramolecular Heck reactions. A new approach to the tetracyclic galanthan alkaloid ring system using radical cyclisation of aryl radicals has been reported.[136] Isoindoles and tetrahydroisoquinolines have been prepared using aryl radical 5-*exo* and 6-*exo* cyclisation onto the β position of side chain enaminone esters respectively.[137] Spirolactones have been synthesised by aryl radical cyclisation onto enol esters.[138] Cyclisation of heteroarenyl radicals onto side chain alkenes continues to be exploited for the synthesis of new heterocyclic rings. A recent example shows the use of thien-2-yl radicals for the synthesis of thieno[3,2-*b*]pyrroles and 5,6-dihydrothieno[3,2-*b*]pyrroles.[139] Finally, 2,3-dihydrobenzofurans have been synthesised using silylated cyclohexadienes as a new replacement for Bu_3SnH.[140]

A range of tricyclic indolines (*e.g*. **106**) containing the strained tricyclo ring systems have been synthesised by cyclisation of aryl radicals onto *o*-alkenylamino groups in precursors such as **105** (Scheme 31).[141] The resulting radical from the initial 5-*exo* aryl radical cyclisation undergoes further cyclisation by an unfavoured 5-*endo*-*trig* route. The unusual 5-*endo* cyclisation was carried out on a number of related dienes. Other products from monocyclisation and rearrangements resulting from 4-*exo*

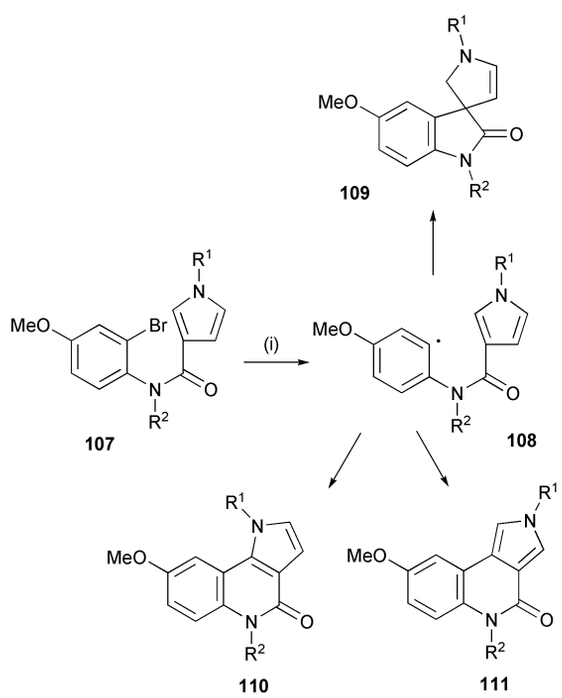


105 **106**

Scheme 31 *Reagents and conditions*: i, Bu_3SnH, AIBN, **106**, R = Me (30%), R = *p*-MeC_6H_4 (29%), R = CF_3 (25%).

instead of 5-*endo* cyclisation were also observed. Another unusual tandem *endo*-cyclisation has been reported for the synthesis of pyrrolo[1,2-*b*]isoquinoline derivatives.[142] Cyclisation of the initial aryl radicals onto a pendant enamide proceeds by the 6-*endo* mode due to the effect of the *N*-atom. The second cyclisation of the second intermediate radical undergoes a now well known 5-*endo* cyclisation onto an α,β-unsaturated amide.

Further examples of the now common Bu_3SnH-mediated 'oxidative' cyclisation have been used for cyclisations onto arenes and heteroarenes. The first group of these syntheses involves the cyclisation of reactive aryl radicals onto arenes and heteroarenes, *e.g*. the synthesis of 3-methoxy-6*H*-benzo[*c*]-chromen-6-one **19**, the main constituent of *shilajit*, a herbal medicine used in countries surrounding the Himalayan mountains (Scheme 4).[36] A similar methodology has been used for the synthesis of 6*H*-benzo[*c*]chromenes.[143] Interestingly, in the synthesis of aza-6*H*-benzo[*c*]chromen-6-one, cyclisation *via* the *cis*-ester conformation and *ipso*-substitution of methoxy groups has been achieved.[144] The direction of cyclisation of aryl radicals **108**, derived from amide precursors **107**, onto pyrroles to give spiropyrrolidinyloxindoles and pyrrolo[3,2-*c*]quinolines is strongly influenced by the *N*-substituents as shown in Scheme 32.[145] When the pyrroles were substituted with electron donating



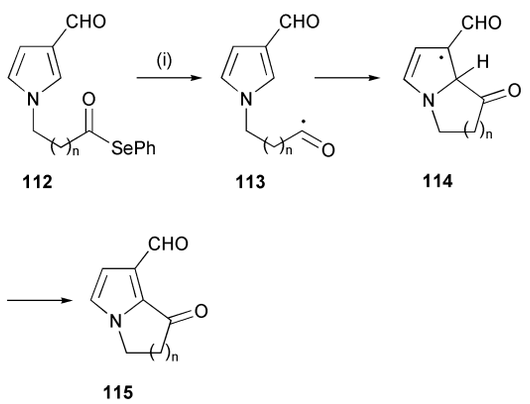
Scheme 32 *Reagents and conditions*: i, Bu_3SnH, AIBN, toluene, reflux. R^1 = H, R^2 = Me, **109** (0%), **110** (37%), **111** (15%) R^1 = CO_2Me, R^2 = SEM, **109** (32%), **110** (15%), **111** (0%) R^1 = Me, R^2 = SEM, **109** (0%), **110** (43%), **111** (0%).

groups (Me) on N-1 only the pyrrolo[3,2-*c*]quinoline (**110**, R^1 = Me, R^2 = SEM) was obtained. When the pyrroles were substituted on N-1 with electron withdrawing groups (*e.g*. CO_2Me) the spiropyrrolodinyloxindole (**109**, R^1 = CO_2Me, R^2 = SEM) was also obtained. Cyclisation onto the C-2 position of the

pyrrole was favoured but smaller amounts of cyclisation onto C-4 were also obtained. In the routes to **110** and **111** loss of hydrogen atoms takes place to yield the re-aromatised products. Therefore, access to both ring systems from common intermediates can be facilitated depending on substitution patterns present.

Alkyl radicals have also been shown to cyclise onto arenes with re-aromatisation. In the first example the side-chain radicals are generated using lauroyl peroxide and cyclisation yields indolines with side chain alkynyl alkenes.[146] In the second example, electrophilic side chain radicals (α-CO_2Me and α-sulfones) add to the electron-rich benzene rings with re-aromatisation to yield quinolinones and indolinones.[147] Cyclisation of electrophilic side chain radicals (α-CO_2Me) also has been reported to take place onto the electron-rich 3-position of indoles.[148] In this protocol, 1-(2-iodoethyl) indoles were reacted with hexabutylditin to generate intermediate radicals which add to methyl acrylate with subsequent cyclisation to yield benzoindolizidine ring systems.

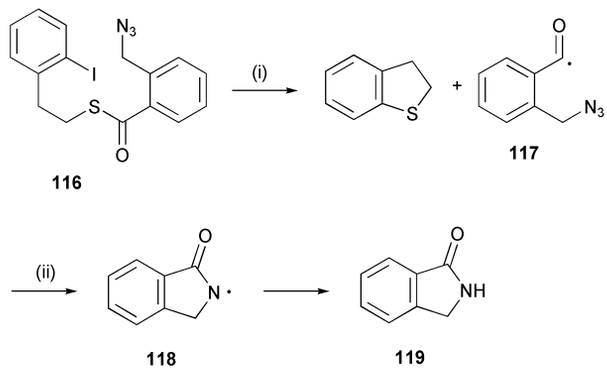
Acyl and alkyl radicals have also been shown to cyclise onto heteroarenes with re-aromatisation. Acyl selanide precursors (*e.g.* **112**) have been used to generate *N*-(ω-acyl) radicals for cyclisation onto pyrrole rings in the synthesis of useful [1,2-*a*] fused pyrroles **115**, *e.g.* 2,3-dihydro-1*H*-pyrrolizidines substituted in the 1- and 7-positions (Scheme 33).[149] Loss of CO from



Scheme 33 *Reagents and conditions*: i, Bu_3SnH, AIBN, CO atmosphere, 5 h, **115**, $n = 1$ (32%), $n = 2$ (50%), $n = 3$ (38%).

the intermediate acyl radicals **113** was prevented by carrying out the reactions in an atmosphere of CO. Mechanistic studies suggest a central role for azo radical initiators as oxidants of the intermediate π-radicals **114**. Two examples report the cyclisation of alkyl radicals onto triazoles.[150,151] Radical cyclisation onto 1,2,3-triazoles has been used to synthesise potential glycosidase inhibitors similar to nagstatin. The carbohydrate moiety is cyclised onto the triazole *via* a 6-membered ring followed by an oxidative process. Electrophilic *N*-(ω-alkyl) radicals (α-CO_2Me), generated by oxidation of the ester with silver nitrate and ammonium persulfate, gave cyclisation onto the 5-position of 1,2,4-triazoles in moderate yields (35–60%). As normal for cyclisation onto azoles, 5-*exo* cyclisation is less efficient than 6- and 7-*exo* cyclisations.[151]

Benzoheterocycles can also be prepared by cyclisation of a side chain radical onto a side chain unsaturated group. An interesting example is provided by the synthesis of 5- and 6-membered benzolactams **119** by cyclisation of acyl radicals **117** onto azides (Scheme 34).[152] The acyl radicals **117** were generated from iodoarene precursors **116** by aryl radical mediated S_H2 substitution on the *S*-atom of the thiol ester giving 2,3-dihydrobenzothiophene as a by-product. Cyclisation onto azides is now well known and yields the amidyl radicals **118** with loss of nitrogen. $(TMS)_3SiH$ gave similar results to those using Bu_3SnH. Acyl radicals have also been generated from acyl hydrazines using PbO_2 and TEMPO and used in the

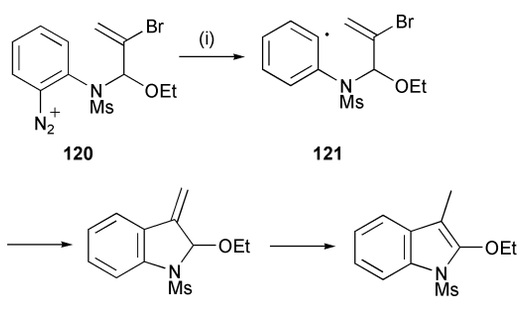


Scheme 34 *Reagents and conditions*: i, Bu_3SnH, AIBN; ii.–N_2, **119**, $n = 1$ (87%), $n = 2$ (87%).

synthesis of chroman-4-ones.[153] The acyl radicals undergo 6-*endo* cyclisation and the resultant radicals were trapped with TEMPO.

10 Heteroarenes

Although very few syntheses have used radical cyclisation for heteroarene formation, a number of important protocols are now being reported. Several protocols for the radical synthesis of indole have been described. The first uses arenediazonium salts, *e.g.* **120**, as precursors to generate aryl radicals **121** which undergo *ipso*-substitution to yield various substituted indoles, *e.g.* **122** (Scheme 35).[154] Hypophosphorous acid can be used in



Scheme 35 *Reagents and conditions*: i, NaI, acetone, rt, 44%.

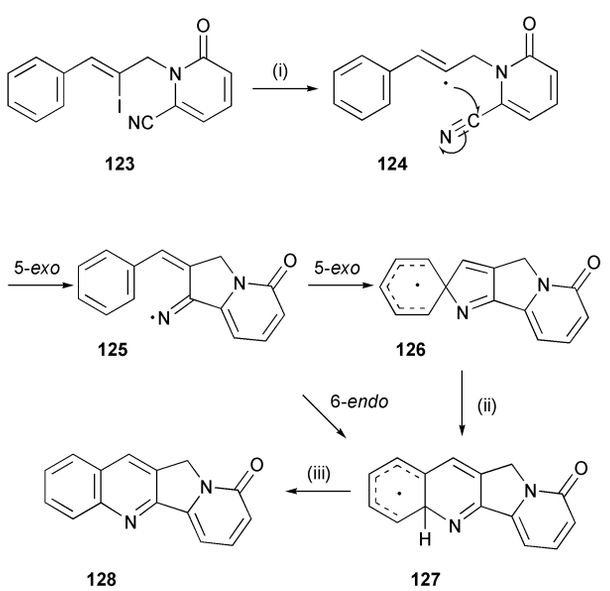
place of NaI and the protocol is compatible with a range of substituents. Intermediate imidoyl radicals have been used for the synthesis of indoles.[155,156] Addition of $Bu_3Sn^{\bullet}$ radicals to arene isonitriles yields intermediate imidoyl radicals which undergo 5-*exo* cyclisation onto *o*-acetylenes.[155] Some 6-*endo* cyclisations to quinolines were also observed depending on the substituents on the alkyne. Bulky alkyne substituents led to mainly indoles whereas less bulky substituents gave largely the quinoline. Protodestannylation was used to remove the tributyltin group at C-2. In a related method, ethanethiyl radicals are used in place of $Bu_3Sn^{\bullet}$ radicals for the synthesis of 2-(ethylsulfanyl)indoles.[156] *N*-Arylimidoyl radicals, derived from treatment of the respective imidoyl phenylselanides with Bu_3SnH gave 5-*exo*-*trig* cyclisation onto α,β-alkenes in the *ortho* positions of the substituted arenes to yield 3*H*-indoles. Isomerisation during work-up yielded the substituted indoles.[157] A new protocol for the synthesis of 1,3-disubstituted indoles uses radical cyclisation of thioamides onto alkenes (Scheme 7).[39]

A range of different heteroarenes have been prepared by various methods. Dihydroisoindoles have been synthesised using 5-*exo* aryl radical cyclisation onto enamides upon treatment of aryl bromide precursors with Bu_3SnH.[158] A range of substituted benzothiazoles have been prepared by CAN (ceric ammonium nitrate) treatment of arylthiols and cyanobenzenes.[159] SmI_2-mediated coupling between 1,1-diaryl-2-

cyanoethenes and aromatic nitriles yields polysubstituted 3*H*-pyrroles.[160] FVP (flash vacuum pyrolysis) of oxime-ethers yields 1,3-benzoxazines[161] and benz[*d*]isothiazoles and benzothiophenes from oxime sulfides.[162] Thermal decomposition of *tert*-butyl *o*-(phenylsulfanyl)- and *o*-(phenylsulfonyl)phenyliminoxyperacetates yields benzoisothiazoles and phenanthridines.[163] Treatment of *N*-azinylpyridinium *N*-aminides with $(TMS)_3SiH$ gave pyrazolopyridines.[164]

Studies aimed at the synthesis of the anticancer alkaloid camptothecin and analogues by radical cyclisation has remained an important area of research. Curran and co-workers have continued to report syntheses of analogues of camptothecin using their novel [4+1] radical annulation cascade methodology with isocyanides.[165–167] Improved syntheses of mappicine and mappicine ketone have been developed using combinatorial techniques to prepare libraries of analogues.[165] The route is flexible and could be developed further to prepare larger libraries of compounds. The methodology has been applied to the synthesis of ring E analogues but with poor results for biological activity.[166] A promising new synthetic analogue of camptothecin, silatecan (7-*tert*-butyldimethylsilyl-10-hydroxycamptothecin), is showing promising activity in clinical trials.[167] This promising anti-cancer drug has also been synthesised by their radical cascade methodology.

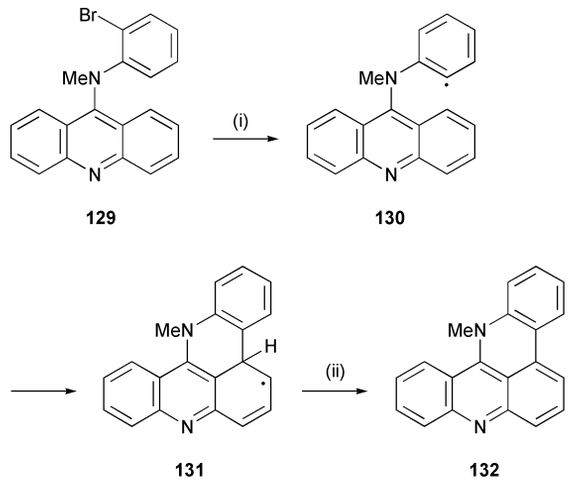
A new radical cascade protocol for the synthesis of camptothecin, mappicine and analogues uses vinyl radical cyclisation onto nitriles.[168] An example of the protocol for the synthesis of rings A–D is shown in Scheme 36. Vinyl radicals **124**, generated



Scheme 36 *Reagents and conditions*: i, $(Me_3Sn)_2$, *tert*-butylbenzene, 150 °C, 48 h, *hν*; ii, neophyl rearrangement; iii, (-H$^{\bullet}$), 73%.

from vinyl iodide precursors **123** using $Me_3Sn^{\bullet}$ radicals from homolytic cleavage of hexamethylditin, undergo 5-*exo* cyclisation onto the nitrile group. The intermediate iminyl radicals **125** give 5-*exo* cyclisation onto the arene to give the spirodienyl intermediate **126** followed by a neophyl rearrangement to **127**. Loss of a hydrogen atom from **127** yields the tetracylic **128**, rings A–D of camptothecin and analogues. Methyl radicals from thermal breakdown of $Me_3Sn^{\bullet}$ radicals was suggested to explain the H-abstraction step. Use of di-*tert*-butyl peroxide gave faster and cleaner reactions and allowed lower temperatures to be used. A short synthesis of camptothecin uses 5-*exo* radical cyclisation of quinolin-2-yl radicals onto a pendant dihydropyridine ring.[169] Benzothieno[2,3-*b*]quinolines have been prepared by a novel cascade reaction of 2-(phenylalkynyl)aryl radicals with 4-substituted isothiocyanates.[170] In the key step, the intermediate imidoyl radicals cyclise onto the alkyne which in turn cyclises onto the arene ring.

Penta- or hexacyclic 9-anilinoacridines, *e.g.* **132**, with important antitumour activity have been prepared by radical cyclisation of aryl radicals onto acridine rings (Scheme 37).[171]

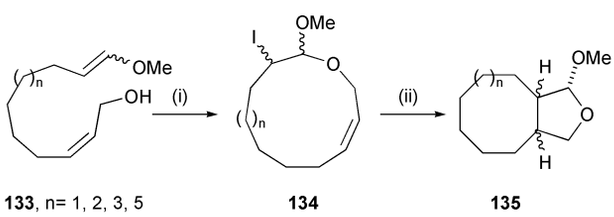


Scheme 37 *Reagents and conditions*: i, Bu_3SnH, AIBN, toluene, reflux, 12 h, 50%.

Standard Bu_3SnH generation of aryl radicals **130** from precursor **129** gives cyclisation onto the acridine ring system. The intermediate π-radical **131** loses a hydrogen atom by an 'oxidative' step to yield the pentacyclic acridine analogue **132**.

11 Macrocyclisation

11-*endo* Cyclisation has been used to make 11-membered ring lactams by cyclisation of aryl radicals onto alkenes but when both groups are pendant on a β-*D*-glucose template higher yields are obtained.[119] Bicylic rings containing a 5-membered ring joined to 8-, 9-, 10- and 12-membered rings have been formed in radical transannulation (Scheme 38).[172] The macro-



Scheme 38 *Reagents and conditions*: i, NIS, DCM; ii, Bu_3SnH, Et_3B, hexane, 2.5 h, **135**, *n* = 1 (64%), *n* = 2 (64%), *n* = 3 (59%), *n* = 5 (70%).

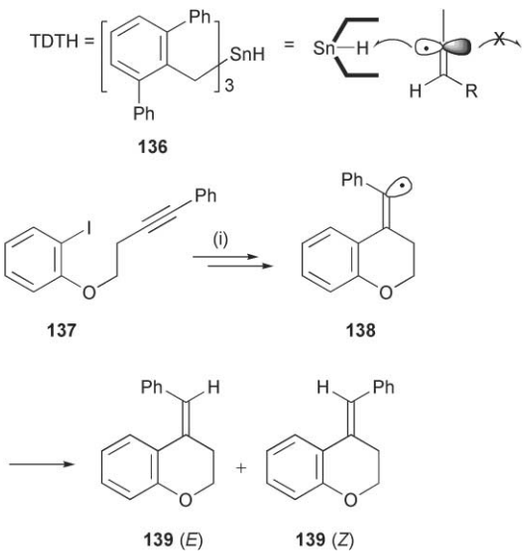
cycles **134** were initially prepared by iodoacetal formation from starting materials **133** using NIS. The radical transannulations proceeded in good yield with good diastereoselectivity to the *cis* ring junction products **135**. The diastereoselectivity was high for the 8-, 9- and 10-membered rings but less so for the 12-membered ring. Cyclisations with starting materials containing a *trans* alkene were less stereoselective. A most important development is the use of water in radical reactions for macrocyclisations to large ring lactones albeit in low yield.[103] In these reactions electrophilic radicals with an α-ester group have been cyclised onto weakly nucleophilic alkenes. The stereochemistry of the ester group in the chain is not important and the water appears to favour the *cis* conformation. A similar cyclisation to yield 8-membered rings has been achieved using iodine-atom transfer reactions.[173]

A 7-membered ring cyclisation forms the key step in the synthesis of rings EFGH in ciguatoxin, a seafood poison isolated from moray eels.[174] The macrocyclisation was facilitated by the use of a nucleophilic radical cyclising onto the electrophilic β-position of an α,β-unsaturated ester. A

conformationally restricted dipeptide mimetic containing an 8,5-fused bicyclic lactam was synthesised *via* regio- and stereoselective radical cyclisation onto the β-position of a pendant *N*-acetyl acrylamide.[175]

12 Stereoselectivity

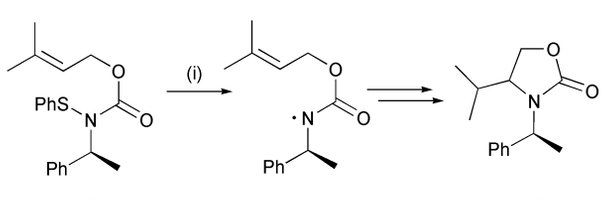
Tris(2,6-diphenylbenzyl)tin hydride (TDTH) **136** has been developed to facilitate high diastereoselectivity in the synthesis of oxygen heterocycles in which cyclisation onto a pendant alkyne is a key step (Scheme 39).[176] Cyclisation of the precursor



Scheme 39 *Reagents and conditions*: i, cat. Et_3B, DCM; Bu_3SnH, 71% (*E*–*Z* = 1.5 : 1); $(TMS)_3SiH$, 57% (*E*–*Z* = 44 : 1); TDTH, 76% (*E*–*Z* > 100 : 1).

137 yields an intermediate vinyl radical **138**. H-abstraction by **138** can take place to give **139** with either the (*E*)- or (*Z*)-stereochemistry. The TDTH has a Sn–H bond positioned in a bowl structure forcing delivery of a hydrogen atom from the less hindered face of the vinyl radical intermediate. Whereas Bu_3SnH gives slight diastereoselectivity, $(Me_3Si)_3SiH$ gives a high selectivity but TDTH is almost completely selective. The example shown in Scheme 39 clearly shows the effect of the extra steric hindrance.

Numerous examples of stereoselectivity have been discussed in previous sections and schemes. α-Chiral aminyl radicals do not give as good stereoselectivity as expected (Scheme 40).[177]



Scheme 40 *Reagents and conditions*: i, Bu_3SnH, AIBN, toluene, reflux, 6 h, **142**, 58% (dr = 2 : 1).

Cyclisation of aminyl radicals generated from sulfenamides of α–amino acid esters yields novel proline derivatives but with little diastereoselectivity. However, the use of α-chiral aminyl radicals **141**, generated from sulfenamide precursors **140**, yield cyclic urethanes **142** with better diastereoselectivity when bulky groups are present. The bulky isopropenyl side chain gave moderate diastereoselectivity but cyclisation onto vinyl or styryl analogues gave low diastereoselectivity.

The use of (−)-8-aminomenthol as the chiral relay has been applied to heterocyclic cyclisation. 6-*exo*-*trig* Cyclisation of perhydrobenzo-1,3-oxazines derived from (−)-8-aminomenthol gave good diastereoselectivity to tricyclic compounds containing a piperidine ring.[178] Hydrolysis of the cyclised product yielded enantiopure 3-alkylpiperidines. H-bonding has been used to obtain moderate stereocontrol in 5-*exo* cyclisations for the synthesis of enantiopure 3-alkyl and 2,3-dialkylpyrrolidines.[179] The 1,3-aminoalcohol radical precursor gave diastereoselectivity which is explained by H-bonding. The cyclic diastereomers were separated and hydrolysed to yield the enantiopure pyrrolidines.

Novel 3,6,6,4-tetracylic compounds containing β-lactams have been synthesised in a diastereoselective cyclisation forming a new 6-membered oxygen heterocycle.[180] Both the alkene and the side chain containing the bromide for generating the radical are attached to the 4- and 3-positions of the β-lactam respectively. A range of bicyclic [3.3.0], [4.3.0] and [5.3.0] systems containing tetrahydrofuran or pyrrolidine have been synthesised with high diastereoselectivity using titanocene(III) catalysts.[181] Diastereoselective SmI_2 mediated cascade radical cyclisations of methylenecyclopropane derivatives have been reported for the syntheses of paeonilactone B and 6-*epi*-paeonilactone A.[182]

13 Reagents for radical cyclisation

The drive to find alternatives to toxic Bu_3SnH has been growing and has been well reviewed in the last two years. The pharmaceutical industry is reluctant to use Bu_3SnH and has largely avoided the use of radical protocols for this reason. Environmentally cleaner chemistry is leading to considerable research of new clean radical methodologies and reagents. The use of a range of radical generating reagents are contrasted with Bu_3SnH in the synthesis of biologically important γ-lactams using cyclisation of enamides.[14] Improved triorganotin hydrides continue to be reported for use in heterocyclic synthesis. For example, a triorganotin hydride designed to facilitate removal of tin species from products of triorganotin hydride mediated radical reactions uses an acetal side chain which is easily hydrolysed to a carboxylic acid which can be extracted by aqueous $NaHCO_3$.[183]

A wide range of alternatives to Bu_3SnH is further reviewed.[17,18] Organoboranes as a source of radicals for initiation including heterocyclic syntheses have been reviewed.[20] The use of tetrathiafulvalene (TTF)-mediated radical-polar crossover reaction uses arenediazonium salts to generate aryl radicals which cyclise onto suitable alkenes. The resulting alkyl radicals couple with TTF radical cations to yield sulfonium salts which, in turn, undergo solvolysis.[16] Dilauroyl peroxide, a relatively safe peroxide, has been developed for iodine atom transfer reactions, *e.g.* the synthesis of the alkaloid (±)-α-lycorane.[32]

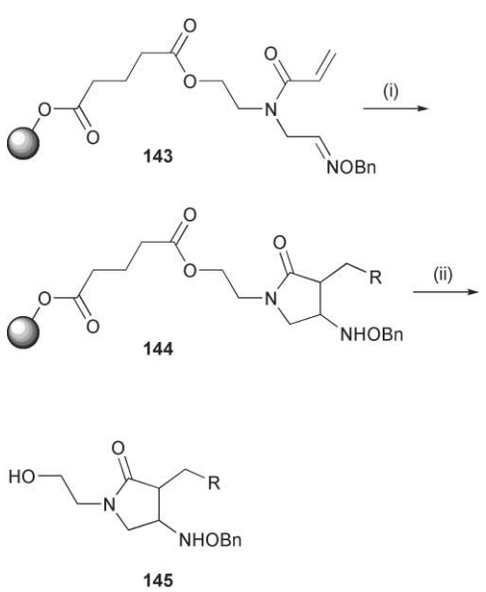
Alternative donors of hydrogen atoms to replace Bu_3SnH are being developed. The most obvious are other group XIV hydrides. The non-toxic *tris*-(trimethylsilyl)silane [$(TMS)_3SiH$ or TTMSS] is increasingly used in place of Bu_3SnH. In many protocols it gives different behaviour to that of Bu_3SnH which is often advantageous. An example is the tandem protocol developed by Murphy and co-workers which includes a cyclisation onto azides using $(TMS)_3SiH$.[29–31] In the cyclisation of acyl radicals onto azides, $(TMS)_3SiH$ gave very similar results to those with Bu_3SnH.[152] $(TMS)_3SiH$ and Et_3B in place of Bu_3SnH and AIBN in cyclisation onto pyrazoles also avoids elimination of phenylselenide groups to yield unwanted alkenes.[37] $(TMS)_3SiH$ has been utilised for the stereoselective synthesis of the azabicyclic core of the polyguanidinium alkaloids batzelladine A and D (Scheme 13).[64] The second obvious replacements are triorganogermanium hydrides. Mono- and bicyclic tetrahydrofurans and dihydrobenzofurans have been synthesised in high yield from bromo and iodo precursors using tri-2-furylgermanium hydride as the radical mediator.[92] This new reagent can be used in THF, EtOH and water.

The use of hypophosphorous acid (H_3PO_2) or salts of hypophosphorous acid shows good potential for replacing the toxic Bu_3SnH.[16] The stereoselective synthesis of trisubstituted tetrahydrofurans by 5-*exo*-*dig* radical cyclisation of radicals α to an ester onto alkynes using a hypophosphite salt has been used for the syntheses of (±)-dihydrosesamin.[27] Hypophosphorous acid has been used as the radical mediator in the synthesis of 1,3-disubstituted indoles using radical cyclisation of thioamides onto alkenes (Scheme 7).[39] Aryl radicals for the synthesis of indoles have been generated by reaction between arenediazonium salts and hypophosphorous acid (Scheme 35).[154]

The use of water in radical cyclisation reactions provides a most interesting development of a cheap and environmentally safe solvent and indicates an important route forward for radical syntheses of heterocycles.[19,103] Mono- and bicyclic tetrahydrofurans and dihydrobenzofurans have been synthesised using tri-2-furylgermanium hydride as the radical mediator in water.[92] Et_3B which is water stable and V-70 {[2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrite)]}, a soluble form of AIBN, were used as initiators. These reactions use a non-toxic radical generator as well as environmentally friendly water as a solvent. Tetrahydrofurans were prepared using EPHP (1-ethylpiperidine hypophosphite) with VA-061 {2,2′-azobis-[2-(2-imidazolin-2-yl)propane]} in water as a solvent.[88] Surfactant concentrations used in these reactions was within range of micelle formation and therefore micellar reaction cannot be ruled out.

Hypophosphorous acid (H_3PO_2) has also been applied to the synthesis of tetrahydrofurans in EtOH or water as solvent.[89] 4-Amino-γ-lactams have been synthesised in water as a solvent with Et_3B initiation.[51]

Radical reactions including heterocyclic cyclisations are being developed on solid supports and have been reviewed.[184] An example of the use of solid phase in heterocyclic cyclisation is the preparation of 4-amino-γ-lactams on Wang resin with Et_3B initiation (Scheme 41).[185] The required precursor was



Scheme 41 *Reagents and conditions*: i, RI, Et_3B, hexane–toluene, 100 °C; NaOMe, MeOH, THF, water, 20 °C, **145**, R = *iso*-Pr (69%), R = c-hexyl (54%), R = c-pentyl (59%), R = *sec*-Bu (55%).

attached to the Wang resin by ester formation using a hydroxyethyl chain attached to the *N*-atom. The combined radical cyclisation of precursors **143** to cyclised product **144** and removal from the resin to yield the 4-amino-γ-lactams **145** proceeded in good yields. A new supported reagent for the generation of radicals has been developed by adding *N*-hydroxythiazole-2(3*H*)-thione onto Wang resin, *i.e*. a solid phase version of the Barton reagent.[186] The formation of esters with the solid phase reagent and carboxylic acids allows the formation of alkyl radicals for various reactions. The esters were decomposed by photolysis. Tetrahydofurans were synthesised using this solid phase reagent.

The use of metals for the generation of radicals in heterocyclic synthesis continues, *e.g*. Ti(III) reagent bis(cyclopentadienyl)titanium(III) chloride,[28] Sm(II),[41,67,99] Co(II),[187] Cu(I) complexes,[60,61,68,188] $Mn(OAc)_3$,[84,72,73] indium(III) hydride (generated by reduction of $InCl_3$ with $NaBH_4$)[90] and indium metal.[110]

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