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Radicals in organic synthesis: part 2

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Abbreviations: ABCVA, 4,4′-azobis(4-cyanovaleric acid) (VA-501); Ac, acetyl; ACCN, 1,1′-azobis(cyclohexanecarbonitrile) (V-40 or VAZO-88); AIBN, azobisisobutyronitrile; Ar, aryl; ATRA, atom transfer radical addition; ATRC, atom transfer radical cyclisation; ATRP, atom transfer radical polymerisation; bipy, 2,2′-bipyridine; Bn, benzyl; BTAC, benzyltriethylammonium chloride; Bu, butyl; Bz, benzoyl; CAN, cerium(IV) ammonium nitrate or ceric ammonium nitrate or diammonium cerium(IV) nitrate; Cp, cyclopentadienyl; CTAB, cetyltrimethylammonium bromide; DCP, dicumyl peroxide; DEPO, diethylphosphine oxide; dHbipy, 4,4′-di-*n*-heptyl-2,2′-dipyridyl; DLP, dilauroyl peroxide or lauroyl peroxide or dodecanoyl peroxide; DMA, *N*,*N*-dimethylacetamide; DMF, dimethylformamide; DMP, 1,4-dimethylpiperazine; DMSO, dimethylsulfoxide; EDC, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; EH, 2-ethylhexanoate; EPHP, 1-ethylpiperidinium hypophosphite; Et, ethyl; Fmoc, 9-fluorenylmethoxycarbonyl; h, hour; HMPA, hexamethylphosphoramide; HOBt, 1-hydroxybenzotriazole; HWE, Horner–Wadsworth–Emmons; IBX, 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide; *i*Pr, *iso*propyl; MAP, 4-methoxyacetophenone; Me, methyl; min, minute(s); MOM, methoxymethyl; MS, molecular sieves; MW, microwave; Ph, phenyl; PMB, *para*-methoxybenzyl; PMDETA, *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine; PMP, *para*-methoxyphenyl; PRC, polarity-reversal catalyst/catalysis; PRE, persistent-radical effect; RCM, ring-closing metathesis; SET, single electron transfer; SEM, 2-(trimethylsilyl)methoxymethyl; TBDPS, *tert*-butyldiphenylsilyl; TBHN, di-*tert*-butyl hyponitrite; TBHP, *tert*-butyl hydrogen peroxide; TBPP, *tert*-butyl peroxypivalate; TBS, *tert*-butyldimethylsilyl; TBST, tri-*tert*-butoxysilanethiol; TBTH, tributyltin hydride; TEMPO, 2,2,6,6-tetramethylpiperidine-1-oxyl radical; Tf, trifluoromethanesulfonyl or triflyl; THP, tetrahydropyran; TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; TMS, trimethylsilyl; Tr, trityl; Ts, toluenesulfonyl or tosyl; TSE, 2-tosylethyl; TTMSS, tris(trimethylsilyl)silane.

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1. Introduction

For many years, radicals were considered too reactive to be used productively in organic synthesis. This myth has been dispelled and, somewhat ironically, it is now clear that radicals frequently offer higher levels of selectivity and predictability than analogous ionic reactions. Even with this increased understanding, radicals have still to find widespread acceptance in organic synthesis and in the chemical industry in particular. The purpose of the current reviews is to highlight the potential offered by radicals and to encourage synthetic chemists to employ these fascinating species.

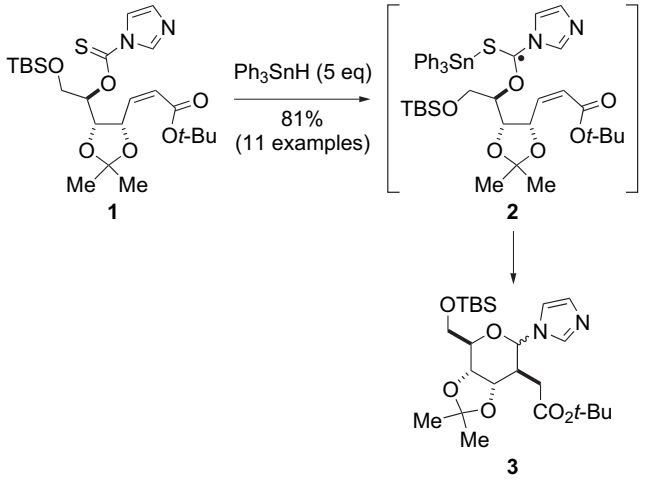
The review is not intended to be comprehensive, but to highlight those advances that are of most interest to synthetic chemists, and is based on the Author's contributions to *Annual Reports on the Progress of Chemistry: Section B*,[1] covering the literature from 2002 to 2007; key publications from 2008 have been included, but the year was not meticulously surveyed. Part one[2] covered radical reagents and intermolecular radical additions; part two provides an overview of radical cyclisations and rearrangements. A comprehensive list of reviews published over the last six years is given in part one.

2. Radical cyclisations

Radical cyclisations are the most abundant class of radical transformation, due to the high degree of regio-, chemo- and stereoselectivity associated with such reactions. There have been a number of reviews covering various aspects of radical cyclisations including samarium(II) iodide-promoted cyclisations in natural product synthesis,[3] 5-*endo*-*trig* radical cyclisations,[4] unusual radical cyclisations,[5] synthesis of heterocycles via radical cyclisation[6] and the formation of five- and six-membered heterocycles via radical cyclisations.[7] This section has been subdivided according to the nature of the radical donor and acceptor as well as the type of cyclisation involved.

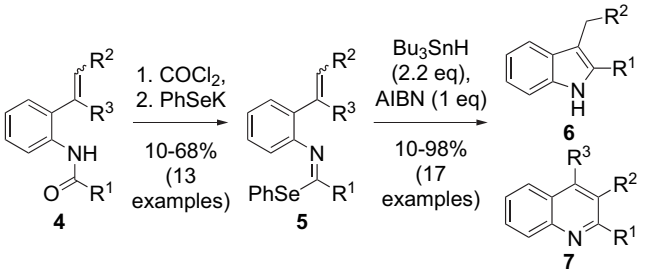
2.1. Cyclisation of C-centred radicals on to carbon–carbon multiple bonds

The Barton deoxygenation reaction has been adapted to allow a simple radical route into nucleoside-like molecules (**3**; Scheme 1).[8] The methodology is based on the interception of intermediate **2** prior to fragmentation and deoxygenation. Successful reaction required the slow addition of a dilute solution of **1** to an excess of a good hydrogen donor; deviation from this procedure led to the formation of a thiolactone. The methodology permits the synthesis of nucleosides with either a carbon or a nitrogen substituent at C2, depending on whether the radical acceptor was an activated alkene or an imine, and the formation of either five- or six-membered heterocycles. There is absolute stereocontrol at C2, but a mixture of anomers is normally formed. Not only does this report present a rapid entry to a range of nucleosides, but it also confirms both the intermediacy of radical **2** in the Barton deoxygenation reaction and its utility; it is this latter factor that may be of greatest importance in the future.



Scheme 1.

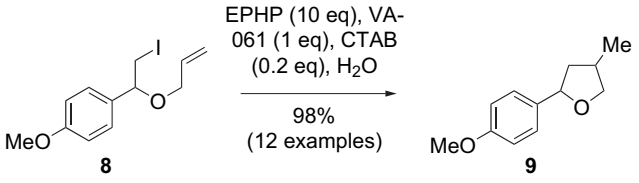
The use of amides as radical precursors is highly attractive as they are readily synthesised and expedite increased structural diversity within molecules. Bowman has devised a methodology that converts amides **4** into indoles **6** or quinolines **7** via the cyclisation of radicals derived from imidoyl phenyl selenides **5** (Scheme 2).[9] The cyclisation is viable for a range of precursors with the various substituents affecting the mode of ring closure. When R^2 is a radical-stabilising group and the alkene is activated, 5-*exo*-*trig* cyclisation to give the indole **6** is normally observed. If the hydride source is added slowly, then rearrangement via a cyclopropyl intermediate alters the outcome of the reaction and permits the formation of quinolines **7**, albeit in considerably lower yields. Addition of a substituent to the other end of the alkene, R^3, favours direct 6-*endo*-*trig* cyclisation to give the quinolines **7**. The methodology appears to be a powerful route to imidoyl radicals from amides (see Section 2.5. for further examples), but has the disadvantage that it utilises phosgene to form the imidoyl chloride. Imidoyl radicals can also be formed by the addition of stannyl radicals to isonitriles. Such methodology permits the formation of 2-stannyl indoles that can be used directly in a 'one-pot' cyclisation–Stille coupling procedure.[10] This highlights the compatibility of radicals with more orthodox methodology.



Scheme 2.

There is a need for more environmentally benign methods for performing radical transformations. Phosphorus-based reagents can act as water-soluble chain carriers and 1-ethylpiperidinium hypophosphite (EPHP), in the presence of the water-soluble initiator, 2,2′-azobis[2-(2-imidazolin-2-yl)propane] (VA-061), has been employed in the cyclisation of hydrophobic substrates such as **8** in aqueous media (Scheme 3).[11] The optimum yields required the addition of a surfactant, thus **9** was formed in 98% yield after 2 h with just 0.2 equiv of cetyltrimethylammonium bromide (CTAB). The reaction gives satisfactory yields for a range of hydrophobic allyl ethers and amines, but they must be in the form of iodides, since bromides give poor results. The reaction can also be performed 'on water;' addition of a 'salting out' agent, such as NaCl, which decreases the solubility of hydrocarbon substrates in water results in an improved yield of 88% (10 equiv of NaCl), compared to 64% for no additive. The improvement is believed to be the result of an increase in the internal pressure that encourages the substrate to adopt the more compact, *E*-conformation, which is essential for cyclisation. Interestingly, addition of greater quantities of NaCl led to a rapid decrease in yield, presumably as the substrate, the radical-chain carrier and the initiator precipitate from the solution. EPHP has also been employed as the hydride source during a study

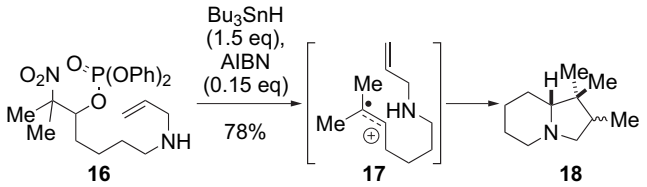
on the efficiency of cyclisations of solid-supported iodides. The best conditions were found to involve JandaJel® as the solid support, whilst performing the reactions in THF/EtOH, which is believed to allow the greatest penetration of EPHP and AIBN into the polymer matrix.[12]



Scheme 3.

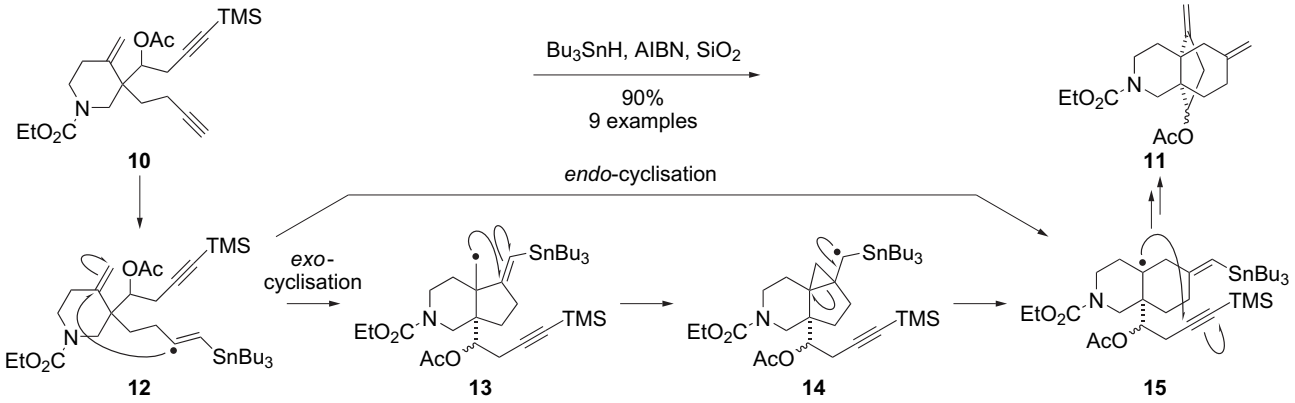
The use of cascade radical cyclisations to form the tricyclic skeleton of the propellanes and related compounds has been known for many years. The majority of these syntheses employ the reductive radical cyclisation of iodides with all the inherent disadvantages associated with their use. This limitation can be ameliorated by the use of an alkyne as the radical precursor, thus leaving functionality in the product. Furthermore, the choice of an alkyne as the substrate improves the regioselectivity with the reaction occurring with exceptional selectivity favouring the formation of the product of an initial *endo* cyclisation. The high regioselectivity occurs as both the *endo* and *exo* cyclisations ultimately give the *same product* **11** (Scheme 4).[13] Addition of a stannyl radical to **10** gives the highly energetic alkenyl radical **12** that undergoes non-selective cyclisation via both the *endo* and *exo* pathways to give **15** and **13**, respectively. Intermediate **15** proceeds directly to **11**, whilst the primary radical formed from the *exo* cyclisation (**13**) undergoes a rapid 3-*exo*-*trig* cyclisation to form a cyclopropylcarbinyl intermediate **14**. Rapid ring opening of **14** (see Section 3) results in skeletal rearrangement to give **15**, the product of *endo* cyclisation. The methodology has been employed to give six- and seven-membered rings and was used in the synthesis of modhephene.

cation. An enantioselective variant of this methodology has been developed that relies on the concept of 'memory of chirality' to induce selectivity (see Section 2.9.). Whilst this methodology gives enantiomerically enriched nitrogen heterocycles, the enantioselective step is the ionic cyclisation and it will therefore not be discussed in this review.[16]



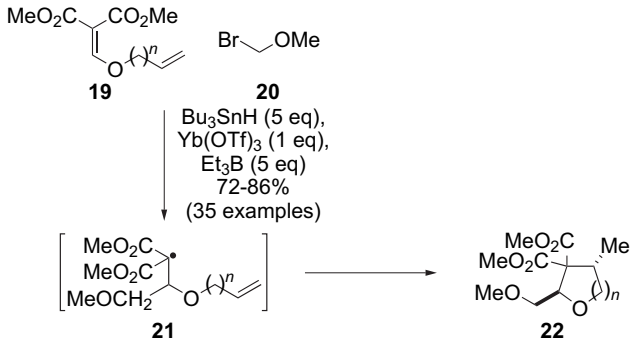
Scheme 5.

The development of general reaction platforms for the synthesis of whole classes of compounds instead of individual molecules can be problematic; subtle alterations to the sterics and/or the electronics can have a profound affect on the chemo-, regio- and stereoselectivity of the reaction. Sibi has investigated these issues in order to develop a versatile route to oxacycles via a tandem radical addition–cyclisation reaction protocol.[17] The transformation involves the intermolecular radical addition of **20** to an electron-deficient alkene **19**, followed by cyclisation of the resulting electrophilic C-centred radical **21** on to an electron-rich acceptor to give **22** (Scheme 6). The reaction is aided by the addition of a Lewis acid, which facilitates the intermolecular addition and enhances the electrophilicity of the intermediate radical. The reaction permits the formation of tetrahydrofurans by a 5-*exo*-*trig* cyclisation in good yield and high diastereoselectivity favouring the *trans* product. Primary, secondary and tertiary radicals, as well as acyl radicals, can be employed as the initial donor. The substituents on the electron-rich alkene are very important; addition of terminal substituents erodes the stereoselectivity, whilst a substituent at the α-position shuts down the 5-*exo*-*trig* pathway and promotes



Scheme 4.

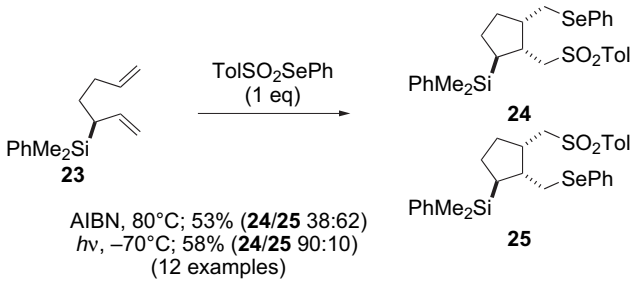
The reactivity of radical cations is an important facet of radical chemistry and has recently been the subject of a dedicated issue of Tetrahedron.[14] Crich has developed an elegant route to nitrogen heterocycles, based on trapping alkene radical cations.[15] Treatment of **16** with tributyltin hydride results in homolytic cleavage of the nitro group; fragmentation of the resulting β-(phosphatoxy)alkyl radical then gives an alkene radical cation **17** and a phosphate anion (Scheme 5). 6-*Exo* ionic cyclisation of the amine on to the cation gives the piperidine ring and a subsequent 5-*exo*-*trig* radical cyclisation results in the formation of the second ring **18**. Quite remarkably, the initial ionic cyclisation can be forced down a 6-*endo* pathway, a process equivalent to nucleophilic attack on a primary cyclisation via a 6-*endo*-*trig* pathway; the latter route permits the synthesis of functionalised tetrahydropyrans. Again, the reaction tolerates a range of nucleophilic radicals, but cyclisation occurs with reduced stereoselectivity. The methodology can be extended to allow the synthesis of both seven- and eight-membered rings; the former is achieved by biasing the cyclisation for 7-*endo* over 6-*exo* ring closure, whilst the latter occurs by the preferential 8-*endo* versus 7-*exo* cyclisation. Not only does this methodology demonstrate the utility of free radicals in the construction of multiple C–C bonds in a single operation and present a general route to substituted oxacycles, but it also highlights the potential of radicals in the construction of medium-sized ring systems (see Section 2.3.).



Scheme 6.

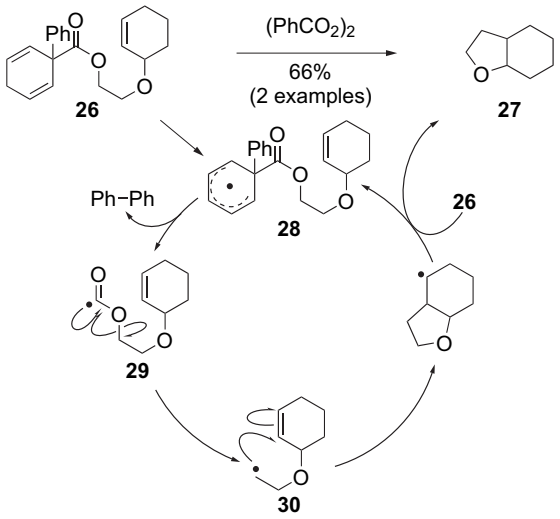
A similar strategy has been described for the synthesis of functionalised pyrrolidines via a tandem radical addition–cyclisation–ionic addition sequence.[18] Di-*n*-butylzinc is used as a radical initiator and trap, thus promoting the first two steps and furnishing a functionalised alkylzinc species that participates in the final anionic addition step. The generality of the methodology is unclear as only a few examples are given. At present, the major limitation is the range of alkyl radicals that can be utilised in the initial intermolecular addition; primary halides are unlikely to be suitable precursors, due to the inefficient halogen-atom exchange initiated by the *n*-butyl radical. Even so, the methodology constitutes an elegant 'one-pot,' two- or three-component synthesis of valuable nitrogenous building blocks.

A range of cyclopentanes can be prepared by a simple tandem coupling–cyclisation–addition sequence.[19] Reaction of a silyldiene, such as **23**, with stoichiometric sulfonoselenoate permits the synthesis of sulfones **24** and **25** (Scheme 7). The regioselectivity of the reaction is highly temperature dependent; thermal initiation results predominantly in the formation of **25** in which the sulfonyl radical has attacked the non-activated alkene first. If the reaction is performed at low temperature under photo-initiation conditions, then the selectivity is reversed and **24**, arising from addition of the sulfonyl radical to the allylsilane, predominates. It appears that, at low temperature, the electrophilic sulfonyl radical adds preferentially to the more electron-rich allylsilane, but, at higher temperatures, it adds to the less sterically demanding alkene. The issue of regioselectivity can be circumvented by the addition of a thiyl radical derived from di-*tert*-butyl disulfide, which results in the formation of bicyclic sulfides as single isomers. If the initial diene is an allyl sulfone, then treatment with sub-stoichiometric sulfonoselenoate facilitates an apparent cycloisomerisation by the addition of a tosyl radical followed by 5-*exo*-*trig* cyclisation and β-fragmentation to give the product and regenerate the sulfonyl radical chain carrier.[20]



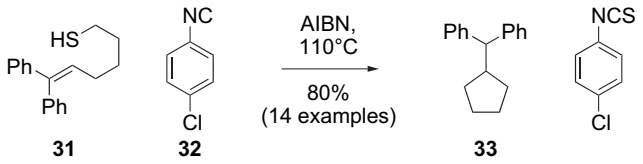
Scheme 7.

The concept of re-aromatisation as a driving force for radical reactions has been extended beyond the development of new reagents (see Part 1, Section 2.10.1) to the preparation of radical precursors. Thus, 2,5-cyclohexadiene **26** acts as an effective precursor for the generation of simple alkyl radicals, such as **30** (Scheme 8).[21] Initiation results in the formation of the delocalised cyclohexadienyl radical **28** that undergoes β-scission to afford an alkoxycarbonyl radical **29** and biphenyl. Radical **29** extrudes carbon dioxide to generate alkyl radical **30**, which can finally be trapped by an internal alkene to give **27** in good yield. The 1-phenyl substituted precursors are an improvement over the earlier 1-alkyl cyclohexadiene precursors, which suffered from low yields, due to competitive β-scission of the alkyl group instead of the desired carboxylate; this is not observed with the phenyl derivative, as the formation of aryl radicals is energetically disfavoured. The main drawback of this methodology is the difficult preparation of the precursor and this hurdle probably precludes this strategy from gaining wider acceptance.

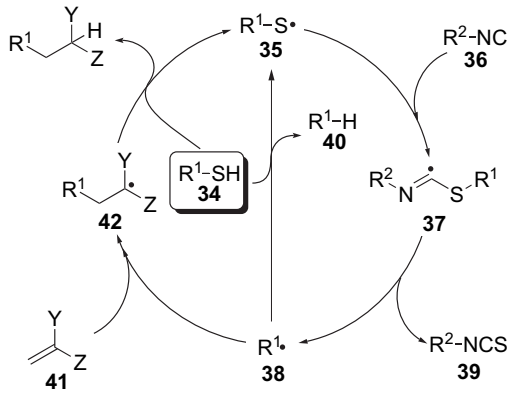


Scheme 8.

Recently, it has been shown that simple thiols can, in the presence of an isocyanide, act as alkyl-radical precursors.[22] Thus, treatment of thiol **31** with isocyanide **32** and AIBN gives the cyclopentane **33** and isothiocyanate in good yield (Scheme 9). The rapid rate of 5-*exo*-*trig* cyclisation means that no product of direct reduction by a second equivalent of thiol is observed. The reaction is initiated by AIBN, which converts thiol **34** into sulfinyl radical **35** that attacks isocyanide **36** to give the thioimidoyl radical **37** (Scheme 10). β-Fragmentation generates the alkyl radical **38** and an isothiocyanate **39**. In the absence of a radical acceptor, hydrogen abstraction from another equivalent of thiol gives the product of reduction **40** and regenerates **35** to propagate the chain reaction. If an appropriate acceptor **41** is present, then addition can give **42**, which then continues the chain reaction. For both simple reductions (desulfurisation) and intermolecular additions, the optimum isocyanide was *tert*-butyl isocyanide; it is commercially available and both it and the resulting isothiocyanate are volatile, thus facilitating simple work-up. Presumably, it was not used in the cyclisation of **31** as it boils at 91 °C, whilst these reactions are performed at 110 °C; **32** melts at 71 °C and is more suitable. Alkyl radicals formed from this methodology readily add to nucleophilic alkenes, but give poor results with electrophilic alkenes, due to rapid hydrogen transfer from the thiol. Even with its present limitations, the simplicity of this methodology is highly attractive and further advances will undoubtedly be reported in the future.

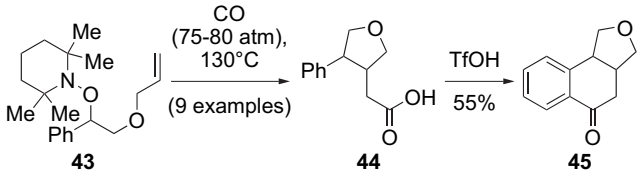


Scheme 9.



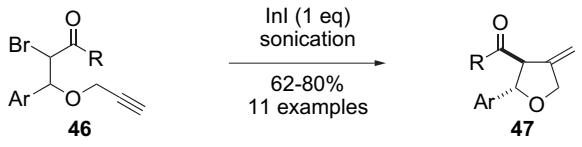
Scheme 10.

The persistent-radical effect (PRE; see Part 1, Section 2.10.2.) is ideally suited to cyclisation reactions, and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) derivatives, such as **43**, have been employed in an efficient 'one-pot' route to 3,4-cyclopenta-1-tetralones via the formation of two C–C bonds by radical processes followed by intramolecular Friedel–Crafts acylation (Scheme 11).[23] Commencing from alkoxyamine **43**, thermal homolysis of the C–O bond generates a radical that cyclises to give a reactive primary radical. The latter reacts with carbon monoxide to give an acyl radical, that is, presumably trapped by TEMPO. The acyl-TEMPO adduct could only be isolated in low yield and was found to readily hydrolyse to the acid **44**. Isolation of either product could be avoided if the reaction mixture was treated with trifluoromethanesulfonic acid, which promotes Friedel–Crafts acylation and formation of cyclic ketones such as **45**.



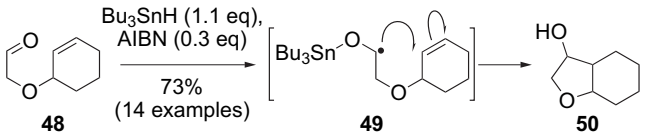
Scheme 11.

The cyclisation of simple halides can be achieved with low-valent indium.[24] Sonication of a mixture of bromo-alkyne **46** and indium(I) iodide gave the alkene **47** (Scheme 12). Whilst the reaction normally proceeds in good yield, it has a number of limitations; firstly, it appears that the substrate must contain an electron-rich aryl ring and, secondly, the α-bromocarbonyl moiety is essential. The requirement for activation of the C–Br bond by the carbonyl group is understandable, but the need for the electron-rich aryl ring is less explicable. Empirical evidence favours a radical and not an ionic mechanism, as both TEMPO and benzoquinone, excellent radical quenchers, arrest the transformation completely. Of more general interest is the fact that sonication is also essential, with both simple stirring and conventional heating failing to furnish the desired product. Clearly, indium-mediated reactions show considerable potential, but current vagaries limit their acceptance.

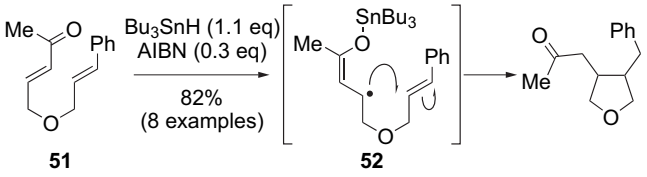


Scheme 12.

The cyclisation of ketyl radicals is particularly attractive as the products retain functionality. Normally, such reactions employ samarium(II) iodide, but it is possible to use tributyltin hydride. Thus, addition of tributyltin hydride to **48** results in the formation of an *O*-stannyl ketyl radical **49** that efficiently cyclises to give the bicyclic tetrahydrofuran **50** (Scheme 13).[25] Aldehydes are good precursors, but alkyl ketones are unreactive. Furthermore, 6-*exo*-*trig* cyclisations were less efficient than 5-*exo*-*trig* cyclisations, due to a competing 1,5-hydrogen atom transfer–fragmentation pathway. Both limitations can be ameliorated if an aryl ring is incorporated into the tether connecting the donor and acceptors. Presumably, the benzene ring confers stability on the ketyl radical and introduces rigidity into the transition state. α,β-Unsaturated ketones, such as **51**, are more versatile and permit the formation of allylic *O*-stannyl radicals **52**, analogous to Skrydstrup's samarium methodology (see Part 1, Section 3.1.),[26] which efficiently participate in either 5-*exo*-*trig* or 6-*exo*-*trig* cyclisations (Scheme 14).



Scheme 13.

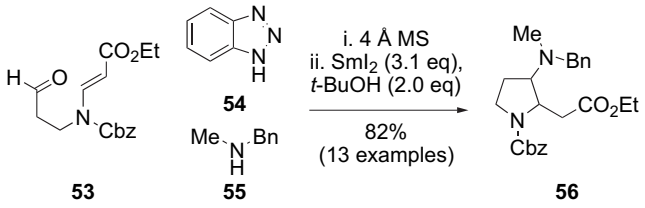


Scheme 14.

The reverse of Scheme 13, the cyclisation of alkyl radicals on to aldehydes, can be problematic; fragmentation of the alkoxy radical intermediate frequently proceeds faster than chain propagation or termination, thus preventing isolation of the cyclic product. One possible solution to this problem is the cyclisation of α-stannyl radicals followed by a 1,3-stannyl shift.[27] The cyclisation precursors are relatively simple to prepare and the reaction proceeds in moderate yields. The value of this study arises from the information garnered about both the rate of cyclisation on to aldehydes and the rate of the stannyl shift, and not from the products themselves, which can be formed by more conventional methodology. Prudent use of this information may permit more constructive processes to be developed. Curiously, a recent report suggests that β-scission of cyclic alkoxy radicals is not always an issue.[28] If there is no radical-stabilising group adjacent to the aldehyde, then the rate of fragmentation is sufficiently slow to allow efficient trapping of the alkoxy radical by tributyltin hydride. This appears to contradict many earlier studies, but bodes well for future radical methodology.

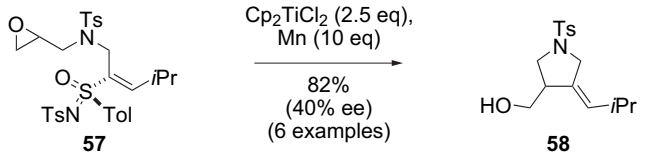
C-Centred α-aminoalkyl radicals have been prepared from α-aminoalkyl benzotriazoles,[29] which are conveniently prepared by the condensation of a secondary amine **55**, benzotriazole **54** and the appropriate aldehyde **53**. The precursors are not isolated, but directly reduced with samarium(II) iodide to give pyrrolidines such as **56** in moderate-to-good yields (Scheme 15). Only enamines protected with an electron-withdrawing group, either

a sulfonamide or a carbamate, furnish the desired pyrrolidines. The attraction of this methodology is the simple and rapid preparation of the cyclisation precursors and its amenability to the synthesis of a range of pyrrolidines with different substitution patterns. Unfortunately, the methodology is marred by the fact that all the cyclisations proceed with poor diastereoselectivity.

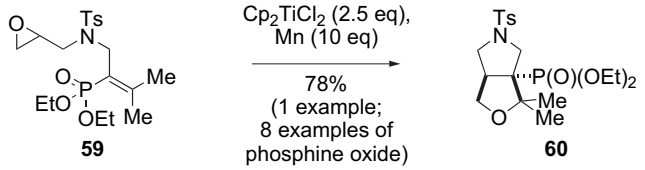


Scheme 15.

Radical alkenylations offer a mild alternative to the more conventional palladium(0)-mediated cyclisations, such as the Heck reaction. There are two possible strategies for achieving this transformation, the simplest of which involves radical addition to an alkyne, but this limits the number of substituents. Alternatively, alkenylation can be achieved by the addition of a radical to an alkene bearing a leaving group in the α position, permitting β-elimination to reform the alkene.[30] Sulfoximines can be both a chiral auxiliary and a leaving group in an intramolecular alkenylation strategy (Scheme 16); treatment of **57** with excess titanocene(III) chloride gave pyrrolidine **58** in good yield. Unfortunately, the low stereoselectivity observed does not compensate for the tortuous synthesis of these compounds. A conceptually similar intramolecular alkenylation involving chiral alkenyl sulfoxides provides enantiopure cyclopentanes with good stereoselectivity; unfortunately, the methodology relies on the use of tributyltin hydride.[31] As an alternative, phosphine oxides have been employed as the leaving group, in one of the few examples of the β-elimination of phosphinoyl radicals.[30,32] The phosphine oxide analogues of **59** are readily prepared and undergo cyclisation to the *exo*-alkylidenepyrrolidines in good yield. Tri- and tetra-substituted alkenes can be prepared, with the cyclisation of the former normally occurring with retention of the alkene geometry. Replacing the phosphine oxide with a diethyl phosphonate (**59**) altered the course of the reaction and led to a fused pyrrolidine-tetrahydrofuran (**60**) instead of the *exo*-alkylidene (Scheme 17). Formation of the bicycle can be explained if the phosphonoyl radical is assumed to be a less efficient leaving group than its phosphinoyl counterpart; cyclisation first gives a long-lived β-phosphono radical that preferentially undergoes a Ti–O bond-breaking 5-*exo*-*tet* radical cyclisation on to the oxygen atom, rather than elimination.

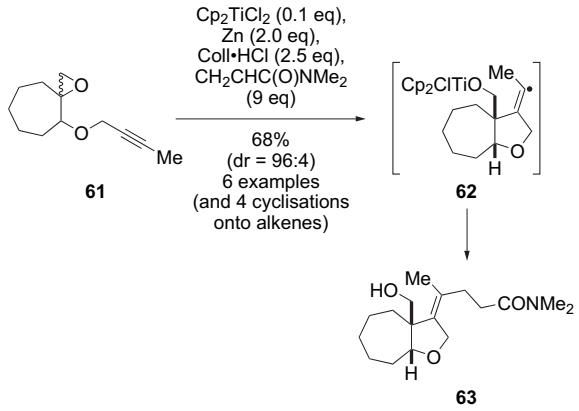


Scheme 16.



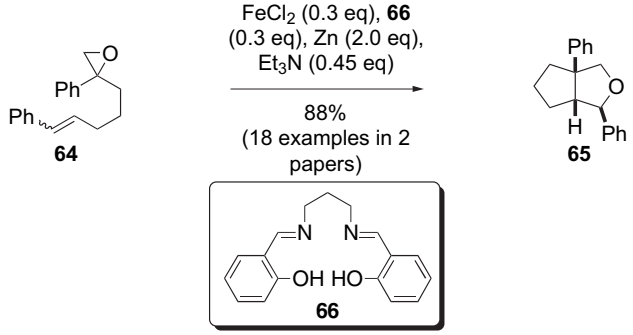
Scheme 17.

Titanocene(III)-mediated reactions are suitable for tandem reaction sequences including an elegant ring-opening–cyclisation–intermolecular addition process (Scheme 18).[33] Formation of a β-alkoxy radical from **61** was followed by 5-*exo*-dig cyclisation to give the alkenyl radical **62**, which participated in an intermolecular addition to give a tetrasubstituted alkene **63**. The reaction proceeds in good yield and stereoselectivity; control of the alkene geometry is thought to arise via the titanium–oxygen complex blocking the approach of the acrylate to one face. The choice of solvent is critical to the success of the tandem reaction. Ethyl acetate was found to be the optimum solvent, balancing a low hydrogen-donor ability, thus inhibiting premature reduction of **62**, with an ability to promote fast reduction of the titanocene(IV) pre-catalyst in order to maintain the catalytic cycle.



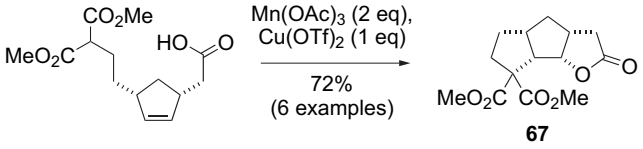
Scheme 18.

The use of iron complexes as catalysts is an attractive goal, due to their low toxicity and abundance.[34] A low-valent iron complex has been utilised to generate alkyl radicals from epoxides (such as **64**)[35] in a reaction comparable to the more common titanocene(III)-mediated chemistry already described. The resulting β-alkoxy radicals readily undergo cyclisation prior to oxidation to a cationic intermediate. An ionic cyclisation then gives substituted tetrahydrofurans **65** (Scheme 19). The reaction utilises catalytic iron with a stoichiometric reductant comprised of zinc and triethylamine. It was found that the choice of ligand for the iron had a profound influence on the reaction, improving both the stereoselectivity and yields. The optimum ligand, salen **66**, even permits intermolecular coupling of epoxides and alkenes; a reaction normally plagued by polymerisation. The scope of this reaction has recently been expanded to allow the synthesis of a wide range of bicyclic compounds including lignan precursors.[36] Furthermore, the requirement for the alkene acceptor to be activated by a phenyl group has been negated and other radical-stabilising moieties such as alkynes can be employed instead. It will be interesting to see if this reagent system will find as many applications as the analogous titanocene(III) system.



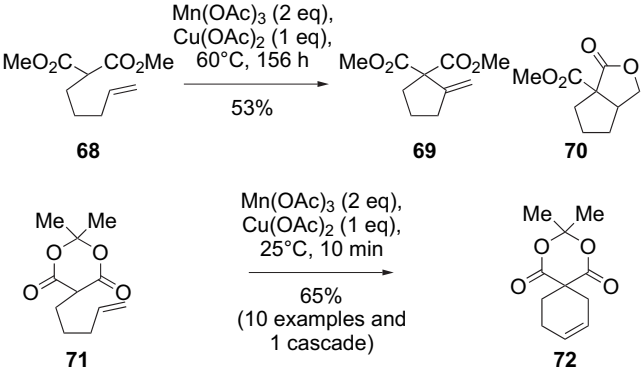
Scheme 19.

Manganese(III) also mediates radical–polar crossover reactions to give oxygen heterocycles. Essential to the viability of this reaction is a copper(II) complex with a non-coordinating anion that facilitates oxidative C–O bond formation (see Part 1, Section 2.8.). This methodology has been employed in the synthesis of a tricyclic lactone **67** (Scheme 20).[37] The reaction is quite remarkable when it is considered that both new rings are formed on the more sterically demanding face of the molecule. An analogous reaction performed in the absence of copper(II) triflate failed to provide satisfactory yields of the cyclisation product.



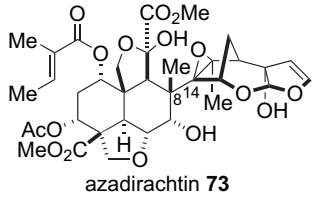
Scheme 20.

The majority of manganese(III)-mediated reactions involve malonates or β-keto esters.[38] Surprisingly, derivatives of Meldrum's acid have been largely ignored.[39] The reactions of such substrates occur more rapidly and at lower temperature, due to the increased acidity of the methylene position of Meldrum's acid; it is approximately 8.5 pK_a units more acidic than a malonate. This is ably demonstrated by the comparison of **68** and **71** (Scheme 21). The reaction of malonate **68** takes 156 h at 60 °C, whilst the reaction of **71** has a half life of <5 min at 25 °C and only 2 h at −30 °C. More significantly, there is a change in the mode of cyclisation, with **68** preferentially undergoing 5-*exo* cyclisation to give **69** and **70**, whilst **71** predominantly proceeds via a 6-*endo* cyclisation to give **72**. This suggests that there are two fundamental mechanisms in operation; the cyclisation of **68** is believed to occur via the α-carbonyl radical, whilst **71** appears to occur via the enolate to give a cyclic radical without the intermediacy of an acyclic α-carbonyl radical. The ability to perform these reactions at low temperature and their preference for the formation of cyclohexenes, as opposed to cyclopentanes, makes them a valuable companion to the more common malonate-derived methodologies.



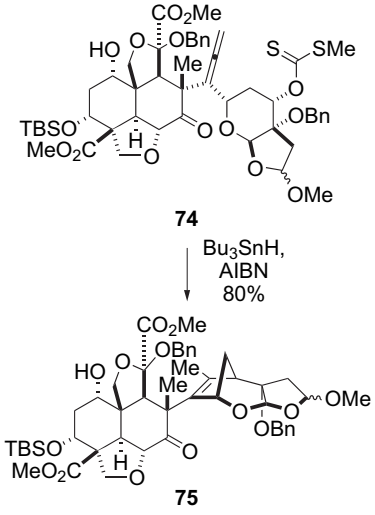
Scheme 21.

An exemplary illustration of the utility of radical cyclisations in total synthesis is found within Ley's landmark synthesis of azadirachtin **73** (Fig. 1).[40] Azadirachtin presents a multitude of synthetic challenges and highlights the fascinating complexities of organic synthesis. The key step is a 5-*exo* cyclisation of xanthate **74** to give the alkene **75** in excellent yield (Scheme 22). Early model studies indicated that the desired *endo*-alkene would be the exclusive product of cyclisation,[41] with the thermodynamically disfavoured primary radical abstracting a hydrogen atom instead of forming the relatively stable tertiary C14 radical. The authors suggest that the highly congested nature of the tertiary radical prevents approach of the hydrogen source and results in the hydrogen adding to the more accessible primary radical centre (C18). The high yield of this step demonstrates the tolerance of radicals to a host of functionalities including acetals, free hydroxyl groups and a variety of protecting groups. The regiochemistry of radical cyclisations on to allenes is the focus of a recent theoretical study.[42]



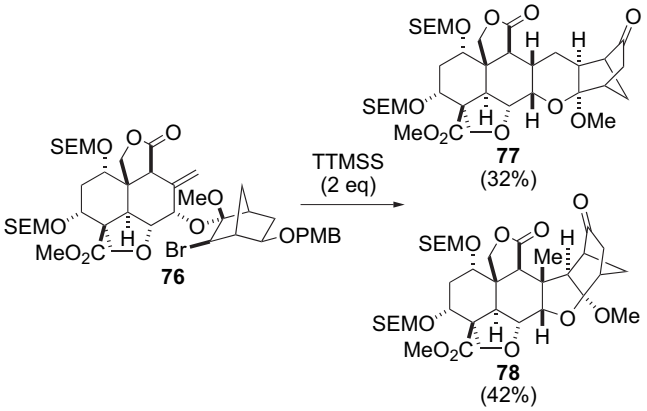
azadirachtin **73**

Figure 1.



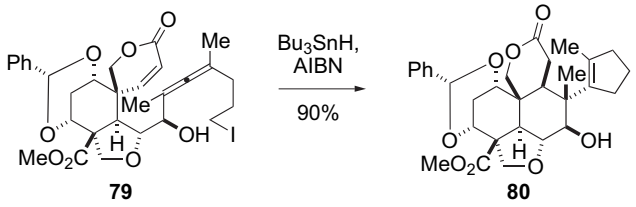
Scheme 22.

Nicolaou has also used a radical cyclisation in an approach to azadirachtin.[43] In these studies, the cyclisation was employed to form the highly problematic C8–C14 bond. The frustrations of total synthesis are highlighted in these studies; cyclisation of precursor **76** results in both 6-*endo*-*trig* and 5-*exo*-*trig* cyclisation to give, after a 1,5-hydrogen shift and concomitant oxidation/deprotection of the C21 alcohol, **77** and **78**, respectively (Scheme 23). Cyclisation of the analogous model system, missing the tetrahydrofuran ring, proceeds by the desired 5-*exo*-*trig* cyclisation exclusively. Of the two products, only **78** has the potential to be employed in the total synthesis of azadirachtin. These vagaries indicate the difficulty in planning syntheses and the potential pitfalls of model systems.



Scheme 23.

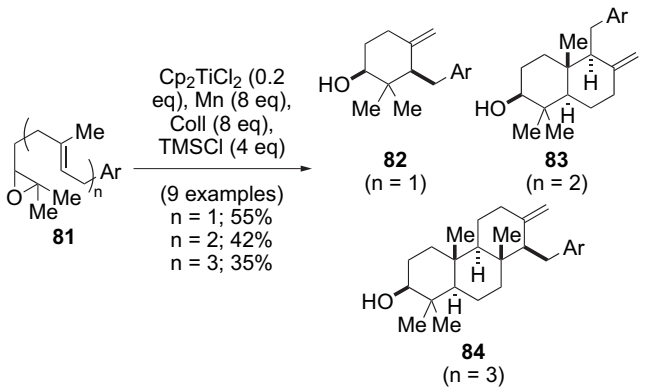
A third radical-based route towards **73** has recently been reported. Ambitiously, this strategy involved coupling suitable precursors for both the left- and right-hand sides of the molecule *prior* to the formation of the B-ring of the decalin moiety.[44] Such a strategy permits the formation of the problematic C8–C14 bond early in the synthesis and, thus, hopefully avoids the steric and chemical issues reported by both Ley and Nicolaou. Thus, precursor **79** was prepared and subjected to a tandem radical cyclisation (Scheme 24). Quite remarkably, the hexacyclic compound **80** was formed as a single isomer in an astonishing 90% yield. The success of this strategy is partly due to the rigidity of the spirolactone ring of the starting material that encourages the final cyclisation. Cyclisation of a more flexible precursor, in which the conjugated alkene is not part of a ring, occurs in a mere 28% yield. It is possible that this route may offer a short route to azadirachtin, as long as a suitable synthesis of the right-hand side can be developed, and the cyclisation proceeds with a more complex precursor.



79 **80**

Scheme 24.

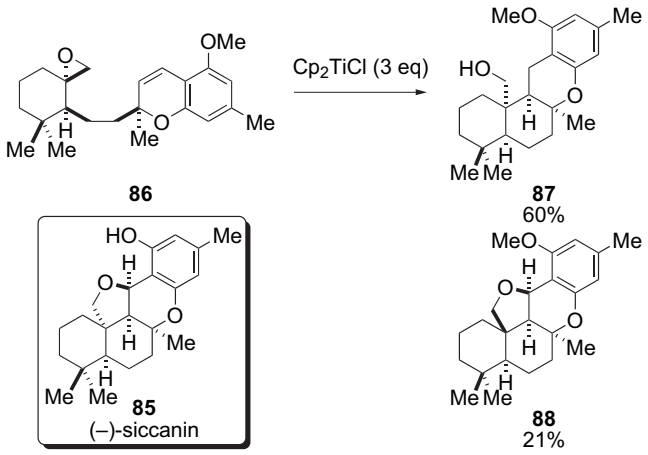
Titanocene(III)-mediated radical reactions have found considerable use in total synthesis. An elegant example comes from the synthesis of polycyclic meroterpenoids via a radical cascade cyclisation sequence.[45] Treatment of the epoxypolyprenes **81** (n=1, 2 or 3) under catalytic titanocene(III) conditions (see Part 1, Section 2.7.1.) led to the formation of mono- **82**, di- **83** or tri-cyclic **84** compounds in moderate yields (35–55%) (Scheme 25). Whilst the yields appear low, the fact that the cascade gave the tricyclic **84**, which contains six stereogenic centres, as exclusively the *trans*/*anti*/*trans*-fused isomer from among more than 190 possible regio- and stereoisomers is quite extraordinary. The radical cascade is more efficient than conventional cationic polycyclisations, as it does not suffer from side reactions due to competitive nucleophilic attack on the cation. Furthermore, as the final step of the catalytic cycle is β-hydride elimination, an alkene is formed that permits further elaboration. In the synthesis of sclareol oxide[46] and puupehdione,[47] the *exo*-alkene was utilised to build additional rings after the radical cascade. A similar radical cascade was exploited in the synthesis of malabaricane and its 13β-epimer.[48] This reaction permitted the synthesis of malabaricane in just two steps from the commercially available squalene.



81 **82** (n = 1) **83** (n = 2) **84** (n = 3)

Scheme 25.

Titanocene(III) chloride has been employed in a biomimetic-inspired synthesis of (−)-siccanin **85** (Scheme 26).[49] Originally, a Lewis acid-catalysed sequence of cyclisations was intended to convert demethyl-**86** directly into **85**, but this route proved unsuccessful. Pleasingly, radical-mediated cyclisation with excess titanocene(III) chloride was more successful, furnishing a mixture of **87**, **88** and an allylic alcohol product formed by simple epoxide ring opening and reductive elimination. Whilst **88** is the wrong diastereoisomer, the major product **87** could readily be converted into **85**. Once again, the mild conditions inherent in most radical reactions overcame the limitations of the ionic pathway.



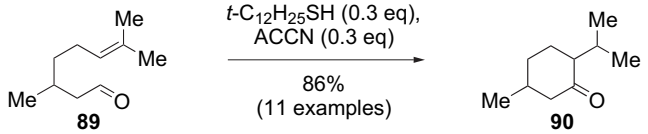
86 **87** **88** **85** (−)-siccanin

Scheme 26.

The cyclisation of alkyl radicals remains probably the most common radical reaction employed in organic synthesis, due to its ease and versatility. As the examples above reveal, it has many advantages over the analogous ionic processes in terms of functional-group compatibility and the formation of numerous C–C and C–heteroatom bonds.

2.2. Cyclisation of acyl and aminoacyl radicals

The intramolecular addition of acyl radicals and aminoacyl (carbamoyl) radicals on to multiple bonds is a useful method for the synthesis of cyclic ketones and lactams. There has been a noticeable trend towards the development of new methodologies for the generation of acyl radicals. In the past, the majority of acyl radicals have been derived from acyl aryl selenides, as this moiety readily partakes in radical-chain processes; unfortunately, these compounds suffer from many shortcomings. Ultimately, the ideal precursor would simply be an aldehyde, but homolytic scission of the C–H bond has long thought to be too demanding. Amazingly, a number of reports have emerged that show that C(O)–H bond scission can readily be achieved under simple reaction conditions (see Part 1, Section 3.1.1.). Tomioka has shown that a sub-stoichiometric quantity of thiol, employed as a polarity-reversal catalyst (PRC; see Part 1, Section 2.5.), can generate acyl radicals *directly* from either alkyl **89** or aryl aldehydes and that these readily cyclise to give ketones such as **90** in a radical variant of the Stetter reaction (Scheme 27).[50] In many respects, the reaction is superior to the

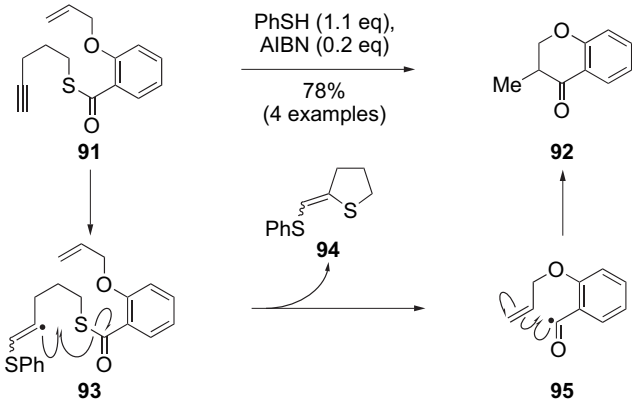


89 **90**

Scheme 27.

anionic Stetter reaction; it is operationally simple and, more importantly, both activated and non-activated alkenes participate in the cyclisation. The choice of thiol catalyst is crucial; if it is too small, hemithioacetal formation or conjugate addition becomes an issue and, if it is too bulky, the reaction is suppressed. An additional limitation is that the thiyl radical cannot be stabilised. The optimum thiol was found to be the odourless *tert*-dodecanethiol. It will be interesting to see if an enantioselective variant that can compete with ionic asymmetric Stetter reactions can be developed.

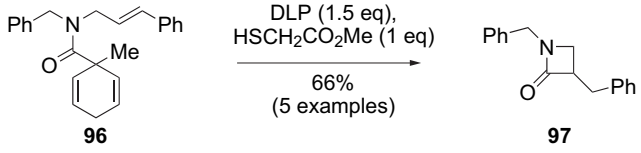
Thiol esters are more attractive precursors than their seleno counterparts, as they are readily prepared and are more stable. Hitherto, this potential has been unfulfilled, due to their sluggish reaction with chain-transfer reagents that makes chain propagation unviable. Incorporating an additional propagation step that employs a facile intermolecular addition to expedite homolytic substitution at the sulfur via an intramolecular process can circumvent this limitation. Initially, aryl iodides in combination with either toxic tin reagents or expensive silanes were used,[51,52] but more appealing methodology has now been developed.[53] Cyclisation of the readily prepared precursor **91** is achieved by the addition of thiophenol and AIBN (Scheme 28). Addition of the thiyl radical to the alkyne gives an alkenyl radical **93** that then undergoes *intramolecular* addition to the thiol ester to give a mixture of the dihydrothiophene **94** and the desired acyl radical **95**. Cyclisation then furnishes a primary alkyl radical that abstracts hydrogen from thiophenol to give the product **92** and propagate the chain reaction. In all cases, small quantities of the product of direct reduction of the sulfanylalkenyl radical **93** were isolated. This methodology has been extended to allow the formation of aminoacyl radicals and, thus, the synthesis of lactams. The reaction is sensitive to the structure of the cyclisation precursor and the nature of the nitrogen-protecting group.[54] The optimum linker between the aminoacyl moiety and the alkene is an aryl group; if it is a simple alkyl chain then, cyclisation still proceeds, but the yield is compromised by significant quantities of the non-cyclised compound. *N*-Benzyl-protected precursors gave the best yields, with *N*-tosyl analogues suffering a competitive β-scission pathway.



Scheme 28.

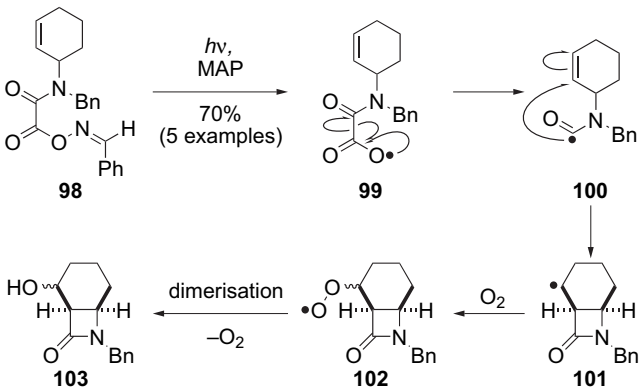
Thioesters have also been employed as acyl radical precursors in a nickel complex-catalysed eletroreduction.[55] Electrochemistry is a promising technique for performing clean radical reactions, but is viewed as beyond the scope of the present review; interested readers are directed towards a review by Duñach as a useful introduction to electrochemical reductive cyclisations.[56]

Walton has developed an elegant precursor to carbamoyl (aminoacyl) radicals, based on the re-aromatisation of derivatives of 1-methylcyclohexa-2,5-diene-1-carboxylates (see Part 1, Section 2.10.1.).[57] Aromatisation of the diene moiety is the driving force for the formation of a stabilised carbamoyl radical from **96** (Scheme 29). This reaction displays none of the competitive scission of both 1-alkyl and 1-methyl substituents observed in the non-carbamoyl analogue (see Section 2.1.; Scheme 8). Cyclisation of the carbamoyl radical gives the desired lactam; simple pyrrolidinones were prepared in good yield, but the more substituted variants gave less satisfactory yields. More promisingly, cinnamyl-substituted amide **96** underwent 4-*exo*-*trig* cyclisation to give the β-lactam **97** in good yield when the reaction was performed in the presence of dilauroyl peroxide (DLP) and a thiol. The latter presumably acts as a PRC and facilitates chain propagation (see Part 1, Section 2.5.). This elegant work has been exploited by Myers during the enantioselective synthesis of stephacidin B.[58] The power of the radical chemistry in total synthesis was highlighted when this methodology gave the desired bridged amide in 62% yield, whilst all attempts to install the bridging amide moiety by standard ionic chemistry failed. The carbamoyl radicals generated by this methodology add to other radical acceptors such as oxime ethers.[59]



Scheme 29.

An alternative family of aminoacyl radical precursors are the oxime oxalate amides **98** (Scheme 30).[60] These contain a weak N–O bond, which, on fission, generates an iminyl radical and an acyloxy radical **99**. The former causes little interference with the subsequent steps in the reaction process and is believed to simply abstract a hydrogen from the solvent,whilst the latter readily extrudes carbon dioxide to furnish the desired carbamoyl radical **100**. The oxime oxalate amides are easily prepared from the corresponding oxime and oxalyl chloride followed by treatment with the appropriate primary or secondary amine. The reaction is initiated by photolysis in the presence of a 3-fold excess of 4-methoxyacetophenone (MAP) as photosensitiser. Both γ- and β-lactams can be prepared in good yields, although the latter must proceed via the formation of a stabilised secondary or benzylic radical if satisfactory yields are to be obtained. In these cases, the β-lactams are isolated as the hydroxylated compounds, such as **103**, presumably due to the stabilised radical **101** having a sufficient half-life to react with oxygen in the solvent. The resulting peroxyl radicals **102** dimerise prior to extruding dioxygen and generating the required alkoxy radical that can finally abstract a hydrogen. This methodology allows a rapid route to highly functionalised bicyclic lactams utilising clean radical technology, the major side product being a simple aldehyde or ketone derived from the hydrolysis of the imine.



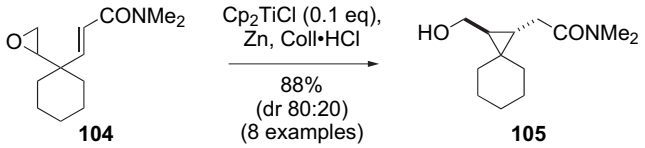
Scheme 30.

Acyl radicals can be formed via radical carbonylation reactions, thus bypassing the need to form specific acyl radical precursors; this attractive methodology is outlined in Part 1, Section 3.1.7. The cyclisation of acyl radicals and their equivalents is rapidly becoming a valuable route to cyclic ketones, lactones and lactams. Whilst many problems still exist, mostly involving the synthesis of the precursors, their stability and competitive decarbonylation, these issues are gradually being addressed and it is clear that this area of radical chemistry will continue to advance in the coming years.

2.3. Cyclisation of C-centred radicals to give 'unusual' ring sizes

Radical cyclisations readily generate five-, six- and seven-membered rings; the formation of other ring sizes is less common. The formation of small rings by radical cyclisation is a taxing endeavour and, whilst kinetically feasible, it is usually thermodynamically disfavoured with ring opening occurring faster than ring closure. In fact, the radical-mediated ring opening of cyclopropanes is often used as a mechanistic probe to determine the intermediacy of radicals. Like many ionic reactions, the formation of medium rings is disfavoured on entropic grounds and the problem is further exacerbated by competitive 1,5-hydrogen abstraction. Walton has published a comprehensive review of unusual radical cyclisations.[5]

The ring opening of a cyclopropylcarbinyl radical to a homoallylic C-centred radical (butenyl radical) is one of the fastest known radical reactions ($k \approx 10^8\ s^{-1}$), but it should be noted that the reverse process, cyclisation, is also fast ($k \approx 10^4\ s^{-1}$). Addition of a suitable radical-stabilising group can make the cyclisation process thermodynamically favourable. Catalytic titanocene(III)-mediated 3-*exo* cyclisation of a variety of activate epoxyalkenes was studied in order to identify such groups.[61] The best results were achieved with carbonyl derivatives, such as **104**, which gave cyclopropanes **105** in good yields (Scheme 31). The high diastereoselectivity suggests that the cyclisation is reversible and that trapping of the cyclopropylcarbinyl radical by a titanium species is slower than ring opening. Other radical-stabilising functionalities, such as phenyl or alkenyl substituents, were not successful. Whilst it is suggested that this is the result of the trapping of the cyclopropylcarbinyl radical being too slow in the latter examples, it is interesting to speculate whether the success of the carbonyl-containing functionality is actually due to the oxophilicity of the titanium reagent trapping the delocalised enoyl radical (alkoxide radical). The resulting titanium enolate is then protonated under the reaction conditions followed by rapid tautomerisation.



Scheme 31.

The importance of the carbonyl functionality has been demonstrated in the work of Fernández-Mateos;[62] ring opening of epoxyalkene **106** to give a tertiary radical is followed by 3-*exo-trig* cycliastion in quantitative yield whilst, the analogous substrate without the carbonyl group furnishes the dienol **107** formed by ring opening and elimination (Fig. 2). Furthermore, the importance of trapping an alkoxy radical was demonstrated by the cyclisation of **108**, which still results in the formation of a cyclopropane. The product arises from irreversible attack on the carbonyl group in preference to 4-*exo*- or 5-*endo-trig* cyclisation on to the activated alkene. Presumably, the titanocene(III) reagent acts as both an alkoxy radical trap, preventing the reverse reaction from dominating, and as a Lewis acid, activating the carbonyl moiety. The influence of the carbonyl group on the product distribution was probed further by varying the length of the tether between the tertiary radical and the radical acceptor. From these studies, it is clear that many factors influence the outcome including stereoelectronics and the ability to trap either the C- or O-centred radical.

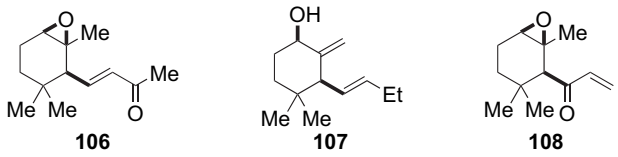
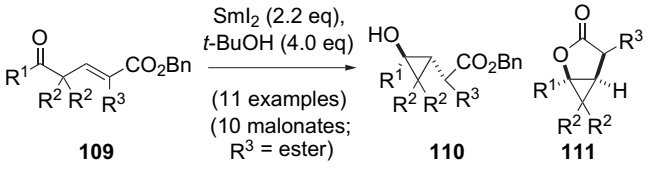


Figure 2.

Samarium(II) iodide can also mediate the formation of cyclopropanes via 3-*exo-trig* cyclisations. In a series of experiments, various γ,γ-disubstituted δ-keto enoates and δ-aldehydes **109** were converted into a mixture of *trans* cyclopropanol **110** and lactone **111** (Scheme 32).[63,64] Only disubstituted substrates ($R^2 \neq H$) were tested in order to prevent isomerisation of the alkene. Aromatic ketones (**109**, R^1=Ar) gave the desired cyclopropanes with complete or very high diastereoselectivity in favour of the *trans* isomer. With alkyl ketones, increasing amounts of the lactone were formed, with the cyclopropyl-substituted ketone (**109**, R^1=C_3H_5) giving exclusively the lactone **111**. Aldehydes (**109**, R^1=H) gave low yields, compared to the ketones, and with little selectivity; an earlier communication that states differently should be discounted.[64]



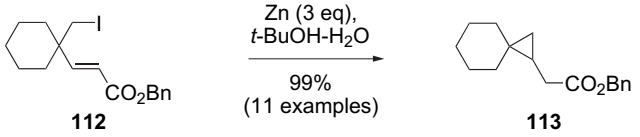
Scheme 32.

It is apparent that the orthodox mechanistic rationale for this reaction does not explain the results. Samarium would be expected to reduce the carbonyl moiety to a ketyl radical that adds to the activated alkene. A second single-electron reduction then forms a stabilised enolate anion and inhibits ring opening. Yet, if this mechanism is correct, ring opening of the cyclopropane-substituted ketone (**109**, R^1=C_3H_5) should be observed instead of the clean transformation into **111** (R^1=C_3H_5). It is possible that the *enoate* moiety is reduced first to give a radical enolate that attacks the ketone in a 3-*exo-trig* process. The resultant alkoxy radical is trapped by samarium, thus retarding the reverse reaction; Skrydstrup has observed an analogous process in the coupling of *N*-acyl oxazolidinones and acrylamides (see Part 1, Section 3.1.1.).[26] Alternatively, pre-coordination of the donor and acceptor may result in a rapid cyclisation before ring opening occurs, as observed in the intramolecular pinacol reaction of cyclopropyl ketone (See Part 1; Section 2.7.4.).[65] It is possible that both mechanisms operate; with the aromatic ketones, the reaction proceeds via the ketyl radical, the one-electron reduction of aromatic ketones being approximately 10^4 times more rapid than the reduction of alkyl ketones by samarium(II), whilst, with the alkyl ketones and aldehydes, it is the enoate, that is, reduced first.

The mechanistic picture is further complicated when the reaction is applied to the cyclisation of malonate derivatives (**109**; R^1=Ar, R^3=ester).[66] The reaction of aromatic ketones with methyl malonate derivatives gave poor selectivity, whilst alkyl ketones (**109**; R^1=alkyl, R^3=ester) gave better results. This is the opposite

pattern to that observed with the simple enoates. Changing to *tert*-butyl esters gave better results and uncovered an interesting dependency on the proton donor. Phenol was found to be superior to *tert*-butanol, giving higher yields and complete stereoselectivity for the *trans* cyclopropanol **110**; oddly, applying these new conditions to the simple enoates proved to be unsatisfactory. This methodology is not only interesting due to the scarcity of the methods for the formation of cyclopropanes by radical cyclisation, but, more importantly, by highlighting the possibility that enoates can be utilised as radical donors as well as radical acceptors, it might open the way to a fascinating form of umpolung.

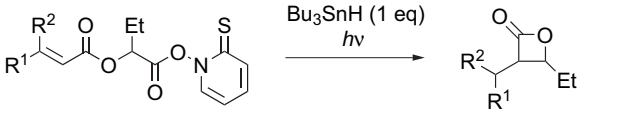
Other single-electron transfer (SET) reagents are capable of mediating radical cyclopropanation by trapping the intermediate cyclopropylcarbinyl radical. An environmentally benign method to achieve this is the use of zinc powder in a mixture of *tert*-butanol and water (Scheme 33).[67,68] The reaction proceeds by single-electron reduction of the iodide **112** to a primary radical followed by 3-*exo*-*trig* cyclisation on to an activated alkene. A second electron transfer reduces the newly formed secondary radical to furnish an anion, that is, rapidly protonated to give the product **113**. The reaction proceeds with moderate-to-good yields for a range of iodides, but fails with bromides. The alkene can be activated by a number of different electron-withdrawing groups including esters, amides, ketones, sulfones and nitro moieties. One structural requirement for successful cyclisation is the presence of dialkyl groups at the 4- or 5-position. Presumably, this confers a favourable conformation on the cyclisation precursor. A similar methodology permits the synthesis of cyclopropanes by 3-*exo*-tet cyclisation of diiodides.[67] Simple treatment of the diiodide with zinc powder in ethanol at reflux gives the cyclopropane in excellent yield. The reaction appears to be radical in nature, as it can be performed under conventional tributyltin hydride/AIBN conditions. These methodologies are complementary to the most common methods for the preparation of cyclopropanes; reactions of carbenes/carbenoids, such as the Simmons–Smith reaction, generally require electron-rich alkenes. This radical reaction employs nucleophilic alkyl radicals and thus needs electron-poor alkenes.



112 **113**

Scheme 33.

Like three-membered rings, the synthesis of four-membered rings via radical ring closure is taxing, due to their strained nature. The synthesis of β-lactones exacerbates this problem by incorporating an sp^2-hybridised carbonyl group within the ring. Sweeney has reported the first example of a radical 4-*exo*-*trig* cyclisation to yield β-lactones (Scheme 34).[69] Photochemical initiation of the pyridine-2-thione-*N*-oxycarbonyl (PTOC) precursors **114a–c** resulted in the formation of the desired β-lactones **115a–c** and the products of direct reduction with no trace of the 5-*endo*-cyclisation products. The key to the success of this reaction is the judicious choice of radical-stabilising group and the slow addition of the tin hydride. Just one stabilising group gives **115a** in poor yield, but this could be remedied by the addition of a second stabilising group and the diphenyl derivative **114b** gives the *gem*-diphenyl compound **115b** in higher yield. The thioacetal moiety of **114c** is also an efficient radical-stabilising group and results in the formation of the lactone **115c** in a comparable yield with the added bonus that it is more suited for further elaboration. The current limitation to this reaction appears to be the premature reduction of the intermediate radical; it should be possible to overcome this shortcoming by utilising non-reductive radical conditions such as those based around the use of xanthates or the PRE effect and thus permit the development of a powerful new strategy for the synthesis of these valuable building blocks.

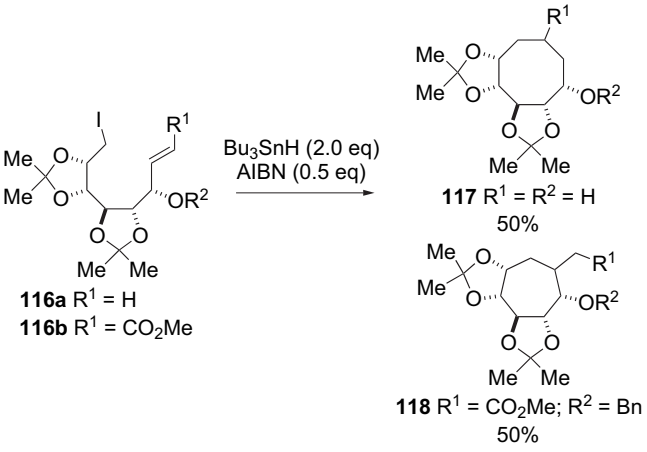


114a R^1 = Ph R^2 = H
114b R^1 = R^2 = Ph
114c R^1 = R^2 = SPh

115a R^1 = Ph R^2 = H 22%
115b R^1 = R^2 = Ph 59%
115c R^1 = R^2 = SPh 55%

Scheme 34.

Like small rings, medium and large rings are often difficult to synthesise by conventional means, due to unfavourable entropic and enthalpic factors. A number of recently developed radical methodologies appear to overcome the inherent disinclination for such systems to cyclise; many radical additions show a propensity for 8-*endo* over 7-*exo* cyclisations as illustrated in the cyclisation of carbohydrates **116a**,**b** (Scheme 35).[70] Non-activated alkene **116a** (R^1=H) cyclises to give **117** in moderate yield under standard radical reaction conditions. It was necessary to add an activating group to the alkene **116b** (R^1=CO_2Me) to promote the 7-*exo*-*trig* process and furnish **118**. An acyl selenide displayed a similar preference for 8-*endo*-*trig* cyclisation,[71] whilst thiyl radicals have been used to initiate the 8-*endo*-*trig* cyclisation of alkenyl radicals derived from alkynes[72] and for the synthesis of heterocycles.[73]



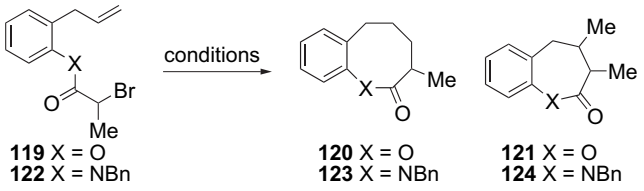
116a R^1 = H
116b R^1 = CO_2Me

117 R^1 = R^2 = H
50%

118 R^1 = CO_2Me; R^2 = Bn
50%

Scheme 35.

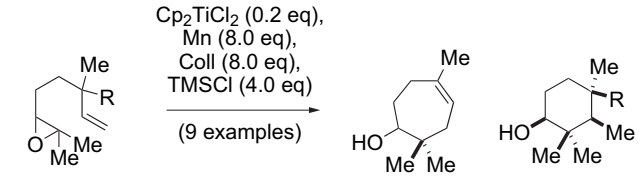
Phosphorus reagents are particularly well suited for the synthesis of large rings, as the slower rate of hydrogen transfer, compared to tin hydrides, favours cyclisation over premature reduction. The ester **119** underwent 8-*endo*-*trig* cyclisation to give **120** exclusively when either 1-ethylpiperidinium hypophosphite (EPHP) or diethylphosphine oxide (DEPO) were used (Scheme 36).[74] In neither case was 7-*exo*-*trig* cyclisation to give **121** or premature reduction observed. DEPO gave higher yields and was more practicable, as it could be added to the reaction in one portion, whereas EPHP required slow addition via a syringe pump. Lactams could be prepared from amide **122** under these conditions, but with reduced regioselectivity favouring 7-*exo*-*trig* cyclisation (**124**) over formation of the eight-membered ring **123**; this change in selectivity is not explained, but could result from conformational changes due to amide rotamers. Interestingly, the reaction could be performed in water with a slightly increased yield of **123** and a comparable decrease in the yield of **124**. It should be noted that lactone formation could not be performed in water, due to ester hydrolysis.



EPHP (10 eq), ACCN (0.4 eq); **120** = 75%, **121** = 0%
DEPO (10 eq), ACCN (0.5 eq x2); **120** = 91%, **121** = 0%
EPHP (10 eq), ACCN (0.4 eq); **123** = 32%, **124** = 65%
DEPO (10 eq), ACCN (0.5 eq x2); **123** = 32%, **124** = 65%
DEPO (10 eq), ABCVA (0.5 eq x2), H_2O; **123** = 43%, **124** = 50%

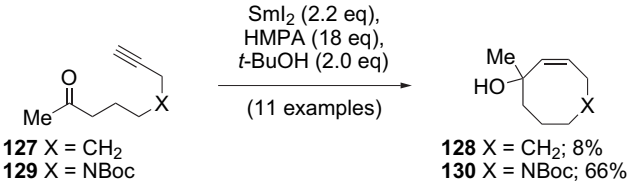
Scheme 36.

It is commonly believed that a combination of entropic factors and the propensity of 6-heptenyl radicals to undergo 6-*exo* instead of 7-*endo* cyclisation hamper the formation of seven-membered rings.[75,76] Even activated alkenes rarely cyclise selectively and give mixtures of six- and seven-membered rings. Intriguingly, 5-oxygenated 6-heptenoyl radicals offer a powerful control element for cyclisations and permit the selective synthesis of seven-membered carbocycles. The cyclisation of **125** and **126** highlights the dramatic effect of the acetate group on the mode of cyclisation (Scheme 37). A simple alcohol has a similar effect, but with reduced yields due to premature reduction. The main argument for the high regioselectivity is that the transition state for the 6-*exo* cyclisation experiences disfavourable 1,3-diaxial interactions, which are not an issue in the 7-*endo* cyclisation. If this is the reason, then any disubstitution of the 5-position should be sufficient to favour 7-*endo* cyclisation and the acetate itself is unnecessary. Without further experimental data, it is impossible to comment on either hypothesis, but an alternative argument involving coordination between the titanocene species and the acetate should also be considered. Use of the acetate control element described above has permitted a cascade 6-*endo*-*trig*–7-*endo*-dig cyclisation to give bicyclic carbocycles.[75] It is believed that this is the first example of a radical 7-*endo*-dig cyclisation. The titanocene(III) methodology has also enabled 8-*endo*-dig cyclisations to be performed, as long as the acceptor and donor functionalities are separated by an aryl group.[77] Presumably, the latter restriction reduces conformational freedom and negates the unfavourable entropic factors.



Scheme 37.

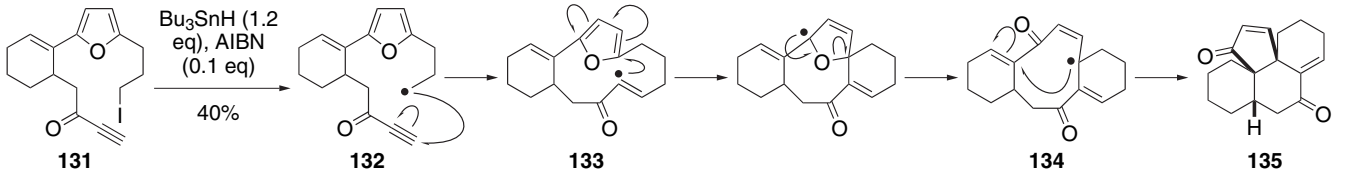
Samarium(II) iodide has also been applied to the synthesis of eight-membered rings. As with other systems, the regioselectivity of the competing 8-*endo*-dig and 7-*exo*-dig cyclisations is hard to predict, with electronic, steric and conformational effects all influencing the outcome. It is clear that the presence of an aryl spacer group between the radical donor and the acceptor greatly facilitates 8-*endo*-dig cyclisation. Additionally, heterocycles appear to be more efficient than the analogous carbocyclic compounds; cyclisation of **127** (X=CH_2) results in only 8% of **128**, whilst the carbamate **129** (X=NBoc) gives 66% of the desired product **130** (Scheme 38).[78] It is apparent that a full investigation of such cyclisations is required to understand these effects and thus develop a general methodology.



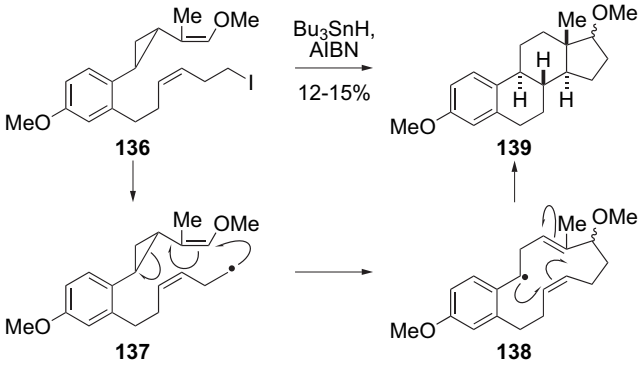
Scheme 38.

Alkynes show a propensity for the formation of large rings. In particular, the terminal conjugated ynone moiety is an ideal component in radical-cascade processes, permitting facile macrocyclisation–transannular cyclisations sequences. This property has been employed in the synthesis of complex ring-fused systems.[79] Whilst the results of these protocols are not always predictable, they are often spectacular! Treatment of **131** with tributyltin hydride forms the alkyl radical **132** that readily undergoes 13-*endo*-dig cyclisation to give the alkenyl radical **133** (Scheme 39). 6-*Exo*-*trig* cyclisation on to the furan is followed by fragmentation to give the doubly allylic tertiary radical **134** that participates in a second 6-*exo*-*trig* cyclisation and hydrogen-atom abstraction to give the fused tetracycle **135**. Whilst **135** was not the desired steroidal product, the rapid increase in complexity to give the functionalised **135** is still highly advantageous and shows great potential.

Pattenden has used the capability of radicals to form large rings to set up an appealing radical cascade to give (±)-oestrone.[80] In the key step, iodide **136** undergoes four successive C–C bond-forming reactions; macrocyclisation of **137** by 12-*endo*-*trig* cyclisation and subsequent cyclopropane ring-opening gives the benzylic radical **138**. Subsequently, a transannular ring-closing cascade comprising a 6-*exo*-*trig* and a 5-*exo*-*trig* cyclisation furnishes **139** (Scheme 40).



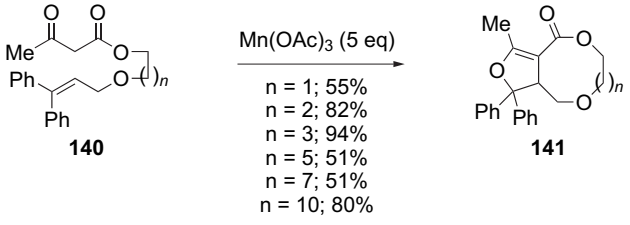
Scheme 39.



Scheme 40.

Although the reaction proceeds in poor yield (12–15%), the main product being derived from halide reduction (40–50%), it is quite remarkable in terms of selectivity, giving exclusively the *trans*,-*anti*,*trans*-oestradiol derivative **139**. A similar transannular radical cascade is at the heart of a synthesis of the 5,5,5-tricyclic triquinane skeleton. The cascade involves a 5-*exo*-dig cyclisation of a silyl ether followed by the transannular cascade [5-(π-*endo*)-*exo*-*trig*/8-(π-*exo*)-*endo*-*trig*]–[5-*exo*-*trig*/5-*endo*-*trig*] cyclisation that eventually furnishes the product.[81]

A remarkable manganese(III)-based methodology efficiently prepares large heterocycles. A range of allyl ethers **140** undergo oxidative radical macrocyclisation, followed by dihydrofuran formation, presumably by a second oxidation and subsequent ionic cyclisation, to give the bicyclic **141** (Scheme 41).[82] The reaction requires an excess of manganese(III) acetate and must be carried out at reflux to avoid side reactions. The methodology allows the formation of eight- to seventeen-membered rings in moderate-to-excellent yields and, remarkably, the cyclodecane ring, which is both kinetically and thermodynamically the hardest ring to form by intramolecular cyclisation, is prepared in 94% yield. Inexplicably, 5-*exo*-*trig* cyclisation to give a five-membered ring, normally a favourable cyclisation, failed to give *any* product!.

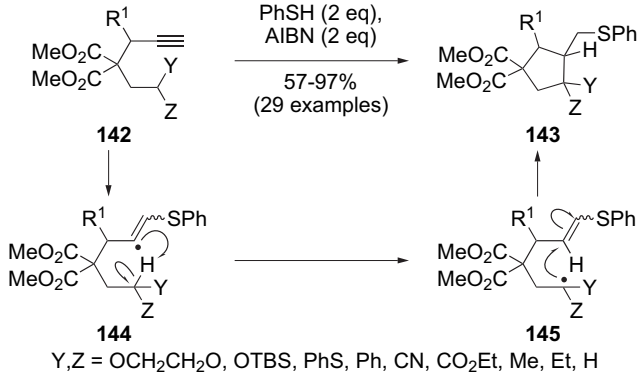


Scheme 41.

Radical cyclisations are highly amenable to the formation of 'unusual' ring sizes. It is possible that this arises due to the highly reactive nature of radicals that can help to overcome unfavourable entropic factors. Additionally, the possibility of trapping radicals, either by careful selection of reagent or by sequencing radical cascades, hampers ring-opening processes from competing. It is likely that these properties will allow radicals to be employed in the synthesis of natural products with 'unusual' ring sizes.

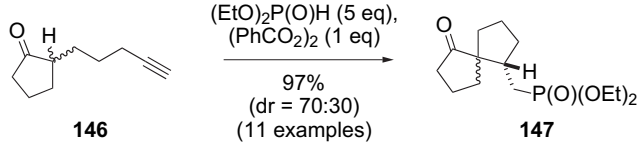
2.4. Radical translocation and cyclisation

The functionalisation of remote, unactivated C–H bonds remains a challenging task in organic chemistry. Few classical methods allow such a reaction, but radical chemistry routinely achieves such transformations via hydrogen-atom abstraction/transfer or radical translocation. A 1,5-hydrogen transfer combined with cyclisation of the resulting radical has led to the development of a powerful route to five-membered rings and a recent review covers this methodology in more detail.[83] The principle is best demonstrated via the following example for the synthesis of cyclopentanes **143** (Scheme 42).[84] Addition of a thiyl radical to alkyne **142** gives a reactive alkenyl radical **144** that abstracts a hydrogen, thus allowing functionalisation of a remote position. Alkyl radical **145** undergoes 5-*exo*-*trig* cyclisation and reduction by thiophenol to yield the product **143** and regenerate the thiyl radical. Curiously, the process is not a chain reaction and optimum yields are obtained with two equivalents of both thiophenol and AIBN. The reaction is a considerable improvement on the analogous tin variant, which suffered from premature reduction of the alkenyl radical prior to cyclisation. The reaction is general, giving excellent yields in all examples in which the translocated radical **145** is stabilised. Even non-stabilised radicals give the desired product, but with a reduced yield. The only limitation to the reaction appears to be the necessity for either homopropargylic disubstitution, in order to promote the Thorpe–Ingold effect, or *vicinal*-disubstitution, which fosters a similar conformational effect. The radical translocation step negates the need to synthesise complex or unstable cyclisation precursors. If the precursor contains a pre-existing ring, then this approach can used for the synthesis of both fused bicyclic or spirocyclic compounds. In fact, radical translocations form the basis for arguably the most common radical approach to spirocyclic compounds. This strategy has been employed in the synthesis of (−)-erythrodiene[85] and in the synthesis of bicyclic pyrrolidinones and piperidinones.[86]



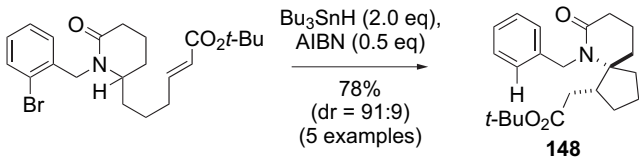
Scheme 42.

The thiophenol-mediated spirocyclisation is not without its limitations; the reaction requires a high dilution and slow, syringe-pump, addition of the thiophenol. In addition, certain substrates undergo slow hydrogen transfer, which can result in premature reduction of the alkenyl radical or its cyclisation on to the *S*-phenyl moiety. As diethyl phosphite is a less efficient hydrogen donor than thiophenol, it can alleviate some of these shortcomings. Reaction of **146** with an excess of the phosphite permits the synthesis of spirocyclic phosphonates **147** in good yield and diastereoselectivity (Scheme 43), thus opening up the possibility of carrying out further manipulations such as the Horner–Wadsworth–Emmons reaction (see Part 1, Section 3.1.8.).[87]



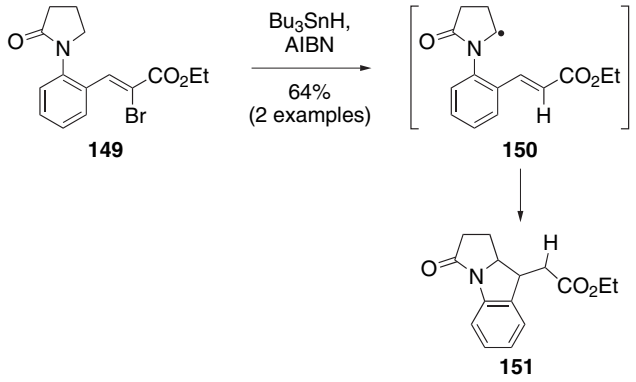
Scheme 43.

The use of halogenated aryl rings as a means of functionalising remote positions by 1,5-hydrogen abstraction has found considerable use. Such moieties are readily introduced via simple alkylation or acylation and form highly reactive aryl radicals that are highly amenable to radical translocation. Examples are found in the synthesis of the azaspirocyclic nucleus of halichlorine **148** (Scheme 44),[88] oxaspiro-γ-lactams,[89] and bridged bicyclics such as 9-azabicyclo[3.3.1]-nonanes.[90] Care should be taken when applying this methodology to benzamide derivatives, as problems can arises from the existence of rotamers, which can have very different reactivities.[91]



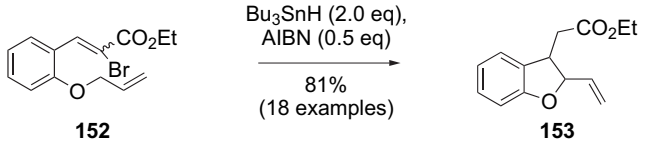
Scheme 44.

Compared to 1,5-hydrogen transfers, the related 1,6-hydrogen transfer is a more challenging concern. The former is favoured on entropy grounds, with the transition state resembling a six-membered ring; the transition state for the 1,6-hydrogen transfer is the disfavoured seven-membered ring. A 1,6-hydrogen transfer can occur, but it is normally a side reaction, and, if it is desired, then a conformational bias towards the seven-ring is required or the hydrogens of the δ-carbon must be removed.[92] Taking the latter approach, Parsons has utilised a 1,6-hydrogen-atom transfer followed by 5-*exo*-*trig* cyclisation in the synthesis of the core of the mitomycin system **151** (Scheme 45).[93] The precursor **149** was readily prepared and reacted efficiently with tributyltin hydride to generate a reactive alkenyl radical that rearranged to form the more stable pyrrolidinone radical **150**. Finally, 5-*exo*-*trig* cyclisation occurred in good yield, with only a trace of the unwanted 6-*endo*-*trig* cyclisation.



Scheme 45.

An analogous 1,6-radical translocation has been employed in the synthesis of oxygen and nitrogen heterocycles such as **153** (Scheme 46).[94] The key to the success of this methodology is the aromatic tether and the stabilisation of the translocated radical by two groups. The rigid benzene ring restricts the conformational freedom of **152**, whilst the stabilising groups are required to activate the hydrogen. All other structural and electronic variables can be varied with no detriment to the reaction. This synthesis highlights the power of the radical-translocation methodology to form radicals that would otherwise be difficult to access.



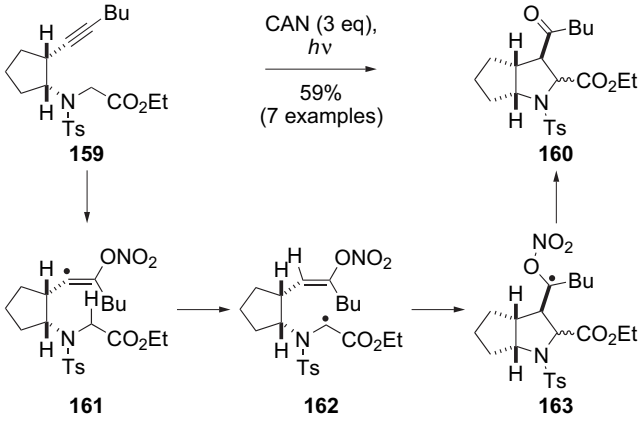
Scheme 46.

Intramolecular hydrogen-atom abstraction forms the basis of a common radical method for the synthesis of spiroacetals and related compounds. Treatment of the alcohol **154** with (diacetoxyiodo)benzene and iodine under irradiation conditions results in the formation of an alkoxy radical **155** that abstracts the α-ether hydrogen atom (Scheme 47).[95] The resultant C-centred radical **156** is oxidised by an excess of the reagent to furnish an oxonium cation **157**, that is, trapped by the alcohol to give the spirocycle **158**. A similar methodology has been employed in a number of total synthesis studies including the preparation of ritterazine[96] and the synthesis of the bis-spiroacetal moiety of spirolides B and D where two sequential spirocyclisations were used.[97]

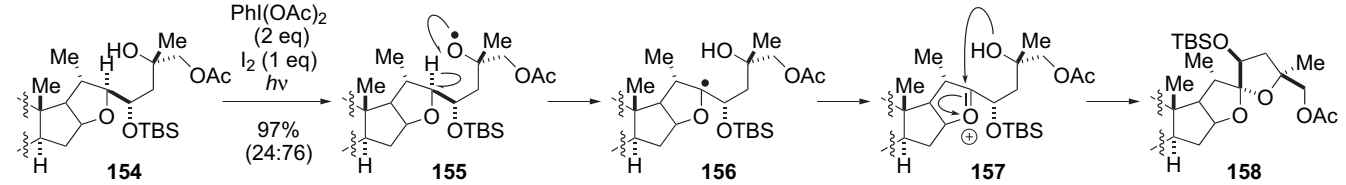
Spirolactams can be prepared by an analogous process.[98] The use of amidyl radicals to facilitate hydrogen transfer has been known for many years, but is beset by one major problem, namely that the cationic intermediate can be attacked by either the oxygen or the nitrogen, leading to either the γ-lactone or the γ-lactam. The hard–soft properties of the cation control the product distribution and can be influenced by neighbouring groups. If simple protected amines are employed instead of amides, then competition is not a problem and oxa-aza spirobicycles can easily be prepared.[99] A comparable hydrogen-abstraction methodology has been used to functionalise the side chain of isoleucine and leucine and thus permit access to a wide range of modified amino acids.[100]

Fused bicyclic acetals can be prepared by the same strategy.[101] With 3,7-anhydro-2-deoxyoctitols, either 1,5-hydrogen abstraction, to give hexahydro-2*H*-furo[3,2*b*]pyran systems (fused bicyclic rings), can occur or, 1,6-hydrogen-atom abstraction, to give the bridged bicyclic moiety (2,9-dioxabicyclo[3.3.1]nonanes), can compete.[102] It appears that the nature of the C4 substituent controls the outcome of the reaction; simple ethers favour 1,5-hydrogen abstraction at C4, leading to the fused system, whilst electron-withdrawing esters inhibit C4–hydrogen-atom abstraction and give the bridged system formed by abstraction of the C7 hydrogen. Even 1,8-hydrogen abstractions have been observed in disaccharides, thus permitting the remote functionalisation of specific sugars within more complex frameworks.[103] It is clear that choice of the correct C4 substituent is able to control the regioselectivity of hydrogen abstraction, thus making this methodology very versatile.

The combination of hydrogen translocation and certain O-centred radicals that participate in the so-called 'self-terminating radical oxygenation' permits an exciting route to fused bicyclic systems. This strategy is ably demonstrated in the synthesis of the fused pyrrolidine **160** (Scheme 48).[104] The initial inorganic O-centred radical was produced by the photolysis of a dilute solution of



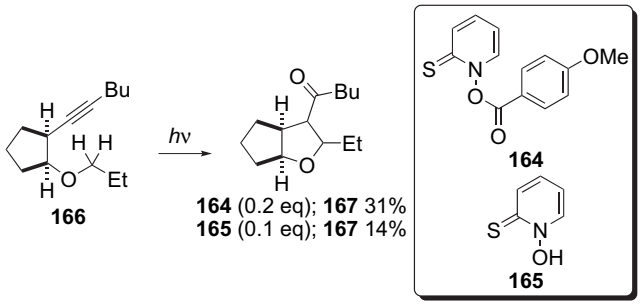
Scheme 48.



Scheme 47.

cerium(IV) ammonium nitrate (CAN) and this adds to the alkyne of **159** to give an alkenyl radical **161**. Hydrogen-atom transfer furnishes **162**, which cyclises to give the radical **163** that undergoes homolytic fragmentation to yield **160** and a radical leaving group. The best results are also obtained when there is an electron-withdrawing substituent adjacent to the amine and the nitrogen is protected with a tosyl group. Both inorganic[105] and organic O-centred radicals[106] participate in similar reactions.

The ability of organic compounds, such as **164** and **165**, to act as single oxygen-atom donors is quite remarkable (Scheme 49). For **164** to mediate oxidative radical cyclisation of **166** requires the unprecedented homolytic cleavage of an acyl–oxygen bond.[107] Equally astonishing is the fact that **165** allows the hydroxyl radical •OH to be employed as an oxygen source, as demonstrated in the synthesis of **167**.[108] If the proposed mechanism is correct, then the reaction proceeds by the loss of a hydrogen atom to form the ketone. Whilst this methodology is of no preparative use, the reaction reveals that the hydroxyl radical can act as an oxygen-atom donor and provides invaluable empirical information.



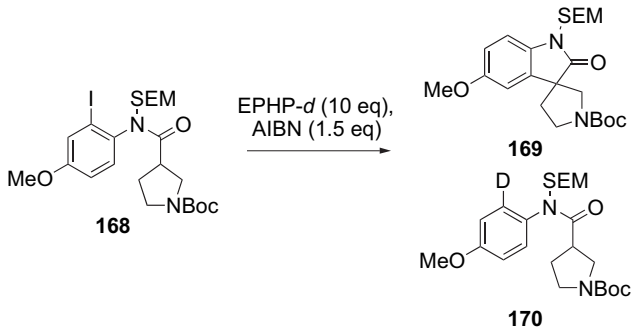
Scheme 49.

Radical translocations offer an incredibly versatile method for the remote functionalisation of C–H bonds and it is somewhat surprising that this chemistry has not been further exploited in synthesis.

2.5. Cyclisation of C–centred radicals on to aromatic rings

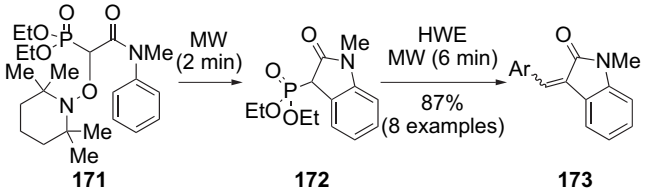
The intramolecular addition of alkyl and aryl radicals to aromatic rings offers a valuable route to functionalised bicyclic systems without recourse to transition-metal catalysts or harsh reaction conditions. As can be seen below, many elegant synthetic procedures have been reported, but far less effort has been invested in answering the fundamental mechanistic question, namely, how, if the majority of reactions are performed under reductive radical conditions, does the *oxidative re*-aromatisation step occur (see Part 1, Section 3.1.5.)? An authoritative review on the addition of radicals to aromatic systems has recently been published by one of the chief proponents of this strategy.[109]

Murphy has utilised a 1,5-hydrogen atom translocation–cyclisation strategy in the synthesis of (−)-horsfiline.[110] Key to the success of this route was the use of the deuteriated ethylpiperidine hypophosphite (EPHP-*d*), which led to the formation of the desired spirocycle **169** in 60% yield along with 36% of **170** from iodide **168** (Scheme 50). Use of the deuteriated reagent almost doubles the yield of the spiro compound, compared to simple protonated EPHP; presumably the increased strength of the P–D bond, compared to the P–H bond, retards premature reduction. In keeping with this hypothesis, tin hydrides give poor results. Use of diethylphosphine oxide (DEPO), which possesses an even stronger P–H bond, allows oxindoles analogous to **169** to be prepared in quantitative yield in an aqueous medium.[111] The major drawback of the DEPO methodology is the excessive reaction times; the transformations can take up to 6 days with a large excess of DEPO (20 equiv).



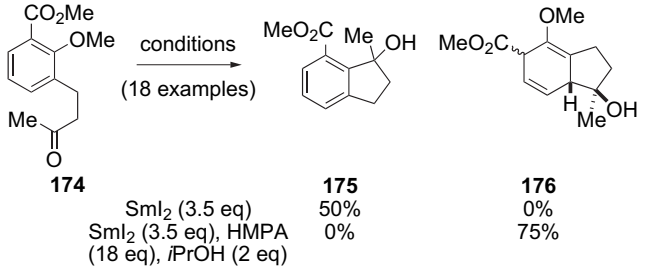
Scheme 50.

The persistent radical effect (PRE), with the (apparent) extended lifespan it engenders in alkyl radicals, facilitates the cyclisation of alkoxyamines, such as **171**, via radical aromatic substitution. The resulting phosphonates **172** can be subjected to Horner–Wadsworth–Emmons (HWE) alkenylation to give good yields of oxindoles **173** in a 'one-pot' reaction (Scheme 51).[112] Remarkably, the entire conversion of **171** in to **173** can be achieved in less than 10 min; homolytic aromatic substitution requires microwave heating at 180 °C for 2 min before the reagents for the alkenylation are added and the reaction then needs to be heated for a further 6 min. Conventional heating results in a pitiful 32% for the initial cyclisation. Currently, the exact mechanism for the aromatic cyclisation and, more specifically, *re*-aromatisation after radical addition to the aryl ring, is not clear.



Scheme 51.

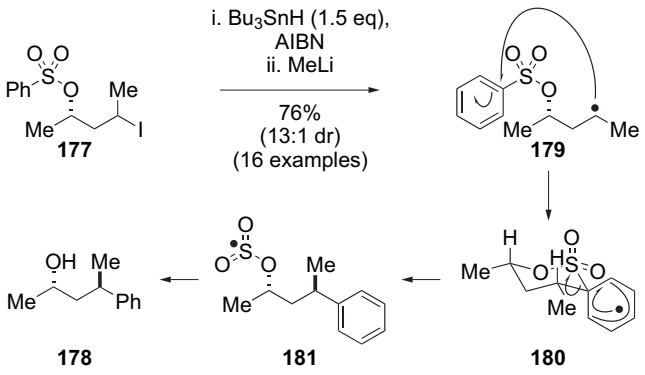
The product distribution for the samarium(II) iodide-mediated cyclisation of ketyl radicals on to aryl systems, such as **174**, is governed by the additive employed (Scheme 52).[113] Cyclisation with concomitant aromatic substitution of the methoxy group gives **175** in acceptable yields if there is an electron-withdrawing group *ortho* to the leaving group. Addition of HMPA and *iso*propanol alters the chemoselectivity, with the addition occurring *para* to the ester and resulting in the destruction of aromaticity to give the 1,4-cyclohexadiene **176**. It is assumed that the samarium directs ketyl-radical approach to the *ipso* methoxy position by binding to the ester; alternatively, when HMPA is added, the bulky samarium alkoxide attacks the less hindered *para*-position. *Iso*propanol is essential for the isolation of the diene **176**; in its absence, only starting material is returned. Presumably, the *iso*propanol protonates the intermediate cyclohexadienyl anion and shifts the equilibrium in favour of cyclisation. The simple ability to control both the regiochemistry and



Scheme 52.

chemoselectivity of the reaction by altering an additive is highly beneficial and permits a variety of different compounds to be readily accessed. The cyclisation of radicals that were formed by the deoxygenation of secondary alcohols was also studied, but with less satisfactory results.

Ipso substitution appears to be a common pathway in radical cyclisations on to aryl rings and it forms the basis of an intriguing stereoselective C(sp^2)–C(sp^3) coupling.[114] The starting sulfonates are readily prepared and migration of **177** to **178** is a general process, working for a wide range of electron-rich and electron-poor aromatics and heteroaromatics (Scheme 53). Unfortunately, the yields and selectivities can vary significantly and there is no clear trend in the reactivity. The reaction is sensitive to both the steric and electronic environment of the initial C-centred radical **179**; neither primary nor tertiary radicals appear to be as effective as secondary radicals. The reaction is thought to proceed by *ipso* attack and formation of the cyclohexadienyl radical **180**. Re-aromatisation with expulsion of the S-centred radical furnishes **181**; the reduction of this species is believed to be very slow and terminates the chain process, thus necessitating the use of excess reagents. The second step, treatment of the reaction mixture with methyllithium, facilitates purification by forming tributyl(methyl)stannane, which is readily removed by chromatography. Currently, aryl migration from sulfonates to secondary radicals appears to be the only efficient process; the analogous reactions with sulfinates, sulfoxides and sulfonamides are all less promising.

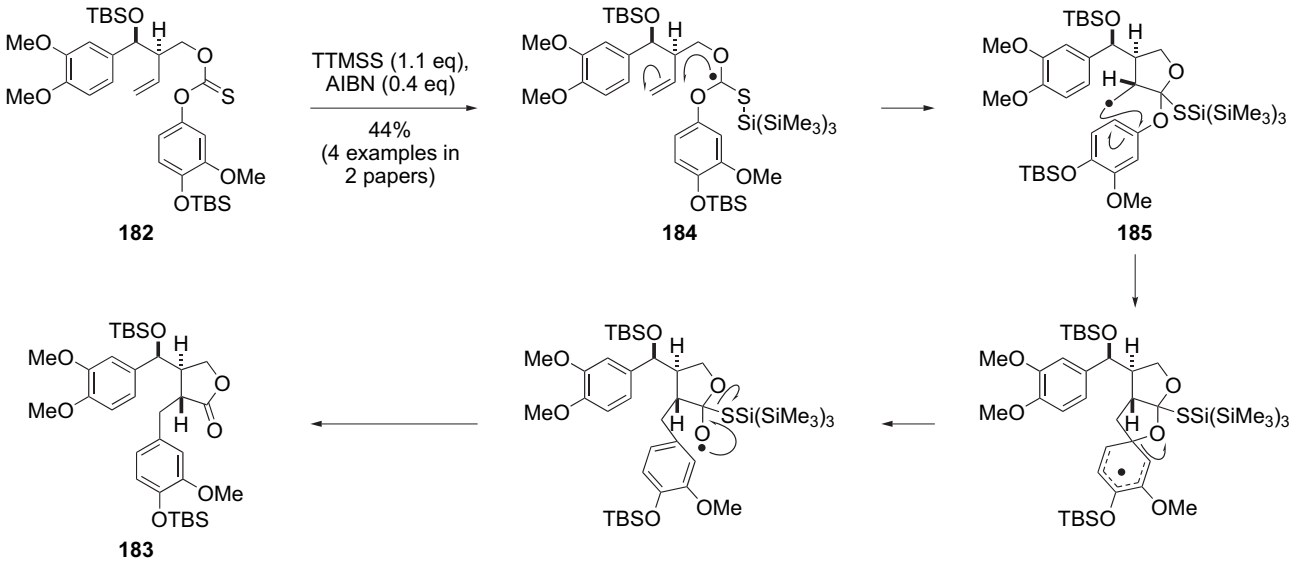


Scheme 53.

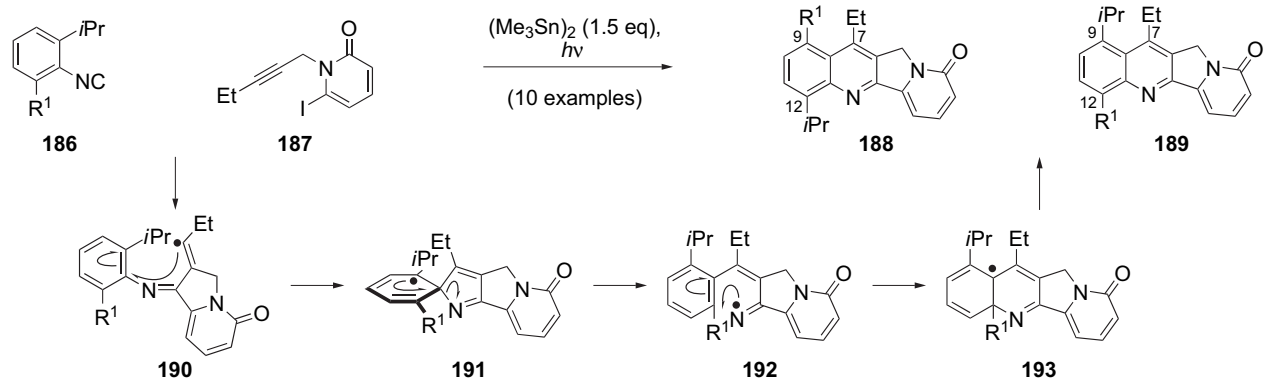
Aromatic *ipso* substitution is the basis of an elegant cascade carboxyarylation that has been employed in the formation of a number of natural products.[115] Treatment of **182** with a silyl radical results in 5-*exo* cyclisation of the acyl radical equivalent **184** on to the alkene to generate a masked lactone and simultaneously tether the aryl ring in close proximity to the new primary alkyl radical **185** (Scheme 54). The tether effectively controls the regiochemistry of the subsequent aryl-transfer step. Elimination and collapse of the resulting alkoxy radical give the desired compound **183**. The radical reaction is quite remarkable involving, addition, two 5-*exo* cyclisations and two elimination steps. A similar strategy has been used in an approach to podophyllotoxin, in which the cascade not only controls the regiochemistry, but also the relative stereochemistry, during the introduction of the aryl ring.[116]

The 11*H*-indolizino[1,2-*b*]quinolin-9-one ring system of camptothecin and related compounds is readily prepared by a cascade radical annulation of an aryl isonitrile **186** and an *N*-propargyl-6-iodopyridone **187** (Scheme 55). The effects of substituents on the regioselectivity have been thoroughly studied, permitting the synthesis of most substitution patterns; only the valuable 7,9-disubstituted analogues are hard to access. As expected, *ortho-iso*propylphenyl isonitrile **186a** (R^1=H) gives the 12-substituted product **188**.[117] Surprisingly, employing *ortho*,*ortho*-di*iso*propylphenyl isonitrile **186b** (R^1=*i*Pr) does not result in the incorporation of two *iso*propyl groups, but gives an 8:1 mixture of 9- **189** (R^1=H) and 12-substituted **188** (R^1=H), favouring the sterically more demanding 7,9-disubstituted compound. The reaction is relatively general, tolerating a range of substituents on the alkyne. Counter-intuitively, replacing the ethyl-substituted alkyne with the sterically demanding *tert*-butyl derivative gives the 7,9-disubstituted product *exclusively*. These results can be rationalised if the intermediate **190** undergoes *ipso* cyclisation to **191**. Fragmentation of the latter generates an iminyl radical **192** that participates in *ortho* cyclisation to give **193**. Re-aromatisation with concomitant loss of the *iso*propyl radical gives the product **189**. Overall, this is a remarkable process, as one *ortho*-substituted group is lost, whilst the other has migrated in relation to the isonitrile functionality. Curran has employed the same methodology in approaches to the lutotonins.[118]

A comparable two-component annulation has been reported for the synthesis of substituted thiochromeno[2,3-*b*]indoles[119] and a number of alternative methods have been developed for the synthesis of related compounds; once again, all are based on the



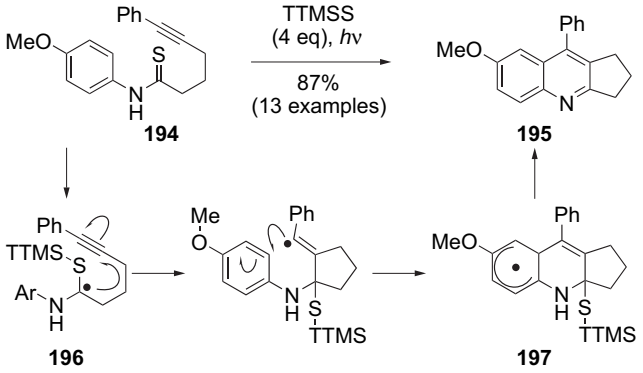
Scheme 54.



Scheme 55.

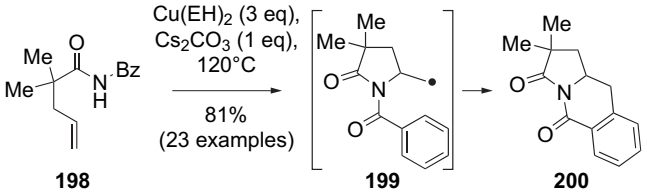
addition of radicals to aryl rings. Bowman has employed addition to a nitrile followed by cyclisation of the resulting iminyl radical on to an aryl ring.[120]

Thioamides are attractive precursors for the formation of the synthetic equivalent of imidoyl radicals and participate in an elegant cascade that forms quinolines **195** under 'tin-free' conditions. Irradiation of **194** and tris(trimethylsilyl)silane (TTMSS) results in the reversible addition of the silyl radical to the thiocarbonyl group to give the stabilised radical **196** (Scheme 56).[121] A 5-*exo*-dig cyclisation followed by a 1,6-cyclisation on to the aryl ring gives **197**; empirical evidence suggests that *ortho* and not *ipso* substitution occurs under these conditions. Finally, oxidative re-aromatisation and loss of the thiol furnishes the product **195**. This methodology shows excellent generality, being equally effective with alkyne-substituted thioureas and thiocarbamates as well as with the simple thioamide **194**. The precursors are readily prepared, but care must be taken during the radical cascade, as the initially formed α-thioamino radical is subject to captodative stabilisation, which can inhibit cyclisation. The ease of assembly of the radical precursors combined with the power of this radical cascade make this an excellent method for the formation of an assortment of fused heterocycles. A related method employs imidoyl selenides and has been employed in a short synthesis of ellipticine, but, more importantly, it is highly amenable to the preparation of analogues.[122]



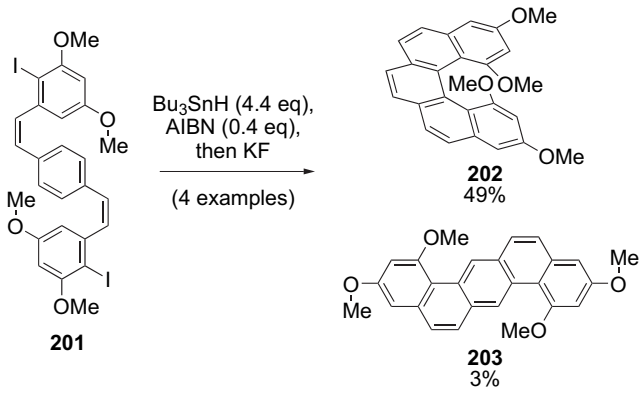
Scheme 56.

Polycyclic lactams, such as **200**, can be prepared by a beautiful cascade reaction involving copper(II)-mediated carboamination and radical cyclisation (Scheme 57).[123] The first step of this reaction is a *syn* aminocupration of the alkene **198** by an amine-coordinated copper species. The resulting unstable organocopper intermediate undergoes homolytic scission to give a primary radical **199** that can cyclise on to alkenes or arenes. Key to the success of the reactions is the use a soluble copper(II) salt, copper(II) 2-ethylhexanoate [$Cu(EH)_2$], and relatively high temperatures (120–190 °C). The cascade proceeds in moderate-to-good yields for a variety of amides, sulfonamides and imides. Detailed mechanistic studies on the sulfonamide series suggest that no nitrogen radicals are formed and that the initial cyclisation is mediated by a copper species.[124] An enantioselective variant has been devised, but it should be noted that the stereoselectivity is induced in the non-radical step.[125] Earlier reports from the same group show the versatility of this strategy.[126]



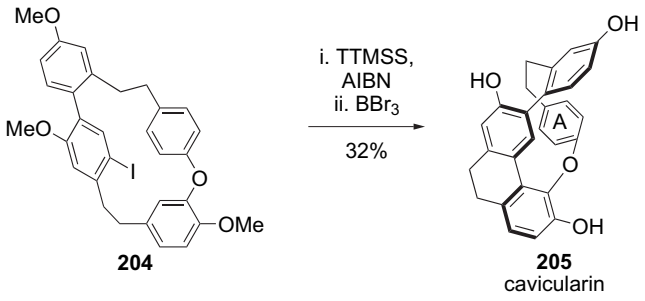
Scheme 57.

Radical aromatic substitution permits the synthesis of helicenes, a class of compound, that is, often hard to access via conventional means. Initially, an iterative strategy, based on two consecutive cyclisations, was developed.[127] This evolved into a more appealing, tandem radical cyclisation method that delivered the desired helicenes in one-step (Scheme 58).[128] Treatment of the diene **201** under standard conditions resulted in the formation of two products, the desired helicene **202** and dibenzo[*a*,*h*]anthracene **203**. The latter is almost certainly formed in a higher yield than stated, but material is lost during the work-up. Even so, the reaction appears to be highly selective for the helicene formed by the cyclisations on to C2 and C3 of the central arene, rather than the compound **203** formed via cyclisation on to C2 and C5. This selectivity is thought to reflect a better SUMO–LUMO interaction at C3.



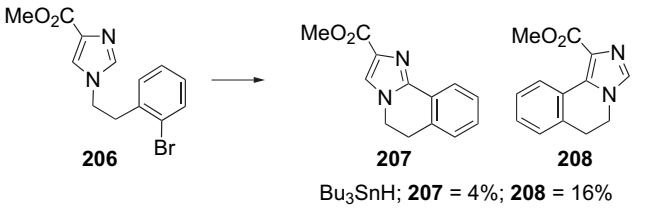
Scheme 58.

Considering the plethora of natural products containing biaryl systems, it is surprising that radical chemistry is rarely employed. One interesting example comes from the synthesis of cavicularin **205** (Scheme 59).[129] The macrocycle structure of **205** is so strained that the A-ring adopts a boat-like conformation and is twisted out of the plane by ≈15° in the solid state. Therefore, macrocyclisation was avoided and a radical-induced transannular ring contraction was used to form the tricyclic moiety in the penultimate step; the advantages of such a strategy include the synthesis of a larger, less-strained, macrocycle earlier in the sequence and, by constraining the reactive partners in a ring, the radical donor and acceptor are held in close proximity. Reaction of **204** followed by deprotection gives cavicularin **205** in 32% along with the product of direct reduction, the natural product, riccardin C, in 63% yield.



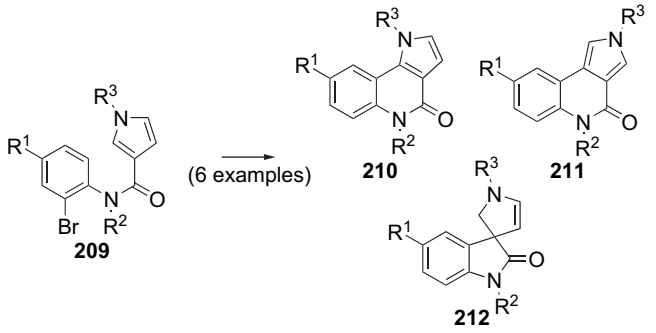
Scheme 59.

Radical cyclisation on to *N*-heteroaromatics is relatively common, due to the ease of synthesising the cyclisation precursors and the inherent electronic bias towards certain regioisomers.[6,130] Premature reduction prior to cyclisation can be a serious problem and the addition of tributyltin hydride is invariably performed using a syringe pump. The reduced rate of hydrogen abstraction from tributylgermanium hydride, TTMSS and similar reagents curtails premature reduction, making these reagents more practical. Reaction of **206** with tin hydride gave **207** in a meagre 4% yield along with 16% yield of **208** (Scheme 60).[131] Addition of the germanium hydride reagent in one portion improved the yield of both products (**207**=19% and **208**=38%), whilst TTMSS gave the best results (**207**=30% and **208**=30%). Interestingly, performing the reaction with the germanium hydride in the presence of a PRC gave **208** exclusively. Alkyl radical cyclisations on to the imidazole moiety also exhibit complete regioselectivity, with only the product of addition to C-5 being observed.[132] This selectivity presumably arises due to the lower reactivity of alkyl radicals, compared to aryl radicals. The methodology works equally well for other azoles, including indoles, pyrroles and activated pyrazoles. In each of these examples there is no possibility of regioisomers being formed and the yields of the germanium-mediated cyclisations are considerably higher than those observed in Scheme 60.



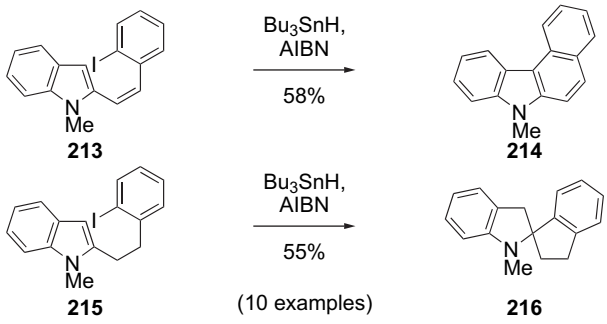
Scheme 60.

Cyclisation on to pyrroles can suffer from regiochemistry issues (Scheme 61).[133] In the reactions of amides **209** the regiochemistry is governed by the substituent on the pyrrole nitrogen; unsubstituted pyrroles (R^3=H) gave a 2:1 mixture of pyrroloquinolines **210** and **211** formed by a 6-*endo*-*trig* or 6-*exo*-*trig* cyclisation followed by *re*-aromatisation. Only the product of 6-*endo*-cyclisation **211** was observed when an electron-donating alkyl substituent was employed (R^3=Me). When the substituent was an electron-withdrawing group, such as carbamate (R^3=CO_2Me), the main product was the spirocycle **212**. Curiously, treatment of the carbamate with TTMSS instead of tributyltin hydride gave only the two products arising from 1,6-cyclisation (**210** and **211**). This change of product distribution probably results from the slower hydrogen-atom transfer from TTMSS, suggesting that the fused products are actually derived from the spirocyclic radical intermediate via rearrangement.



Scheme 61.

The effect of different tethers on the cyclisation of aryl radicals on to indoles has been investigated.[134] Reaction of the *Z*-alkene **213** under standard tin-mediated conditions resulted in the formation of the benzo[*c*]carbazole **214**, whilst the saturated derivative **215** gave the spirocycle **216** (Scheme 62). Similar results were obtained with the C-3 substituted indole; the alkene-based precursor gave the fused benzo[*a*]carbazole (90%), whilst the substrate with the alkyl tether gave a mixture of spirocyclic (63%) and fused (36%) compounds. Either the alkene adds sufficient rigidity to prevent *ipso*-radical attack or the additional ring strain engendered by two sp^2 centres accelerates radical rearrangement of the spirocyclic intermediate. Radical addition to the indole nucleus has found use in the total synthesis of (−)-vallesamidine and related natural products.[135]

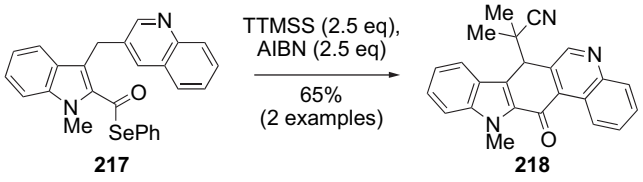


Scheme 62.

Harrowven has extensively studied similar systems and has reported a number of differences in the cyclisations of aryl radicals on to pyridines,[136] compared to quinolines.[137] Generally, it was found that aryl iodides gave the best results, with the optimum tether being a *Z*-alkene. Aryl bromides led to alkene isomerisation, whilst saturated alkyl tethers resulted in a mixture of three compounds, the product of direct reduction, the expected fused system and a regioisomer derived from the rearrangement of a spirocyclic

intermediate. In the intramolecular addition of aryl radicals to quinolines, the effect of the tether saturation is less pronounced, but still important.[137] Predicting the outcome of such cyclisations should be approached with some trepidation.

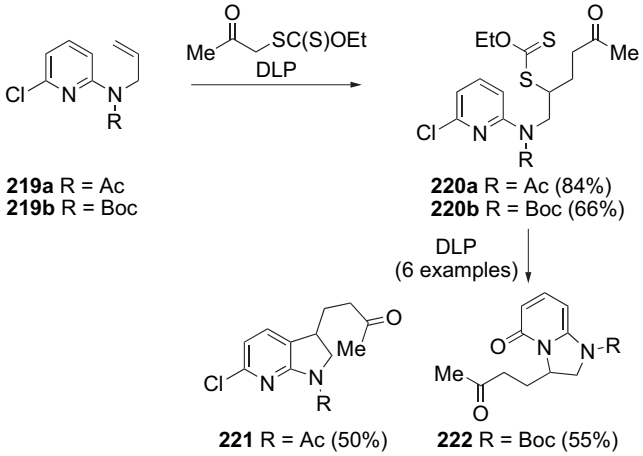
The addition of acyl radicals to aromatic and heteroaromatic systems is scarce, in comparison to their alkyl and aryl counterparts. Acyl selenide **217** undergoes cyclisation to give **218** upon treatment with TTMSS and AIBN (Scheme 63).[138] Unusually, the 2-cyano-2-propyl moiety from the initiator was incorporated into the final product. The doubly benzylic methylene position is sufficiently activated to allow hydrogen-atom abstraction followed by trapping with the 2-cyano-2-propyl radical. Somewhat surprisingly, simply changing the nitrogen substituent to a MOM group alters the course of the reaction and the initiator is no longer integrated into the product. Currently, it is unclear why there is such a different in the reactivity of the two compounds. If the quinoline ring is replaced by a pyridine, the reaction must be performed under non-reductive conditions to avoid premature reduction of the acyl radical. This is due to the reduced susceptibility of pyridines to aromatic substitution; cyclisation and auto-oxidation of the benzylic position occurs in moderate yield (42–60%).[139] If the pyridine is attached via the indole nitrogen, the cyclisation is less efficient.[139] Whilst this methodology can still be improved, it shows great potential, permitting rapid access to highly functionalised heteroaromatics. A similar chemistry, the cyclisation of 2-indolylacyl radicals on to alkenes, has been employed in the synthesis of the pyrido[4,3-*b*]carbazole alkaloid, guatambuine.[140]



Scheme 63.

Dicumyl peroxide (DCP) is an excellent reagent for radical cyclisations on to heteroaromatics; the methyl radical formed from its decomposition allows efficient atom transfer and it can act as an oxidant for *re*-aromatisation.[141] Use of DCP has permitted radical cyclisation on to 2-pyridones, a class of molecule that has been reported to be inactive under tin-mediated cyclisations. These reaction conditions also permit cyclisation–oxidation on to substituted benzene rings.

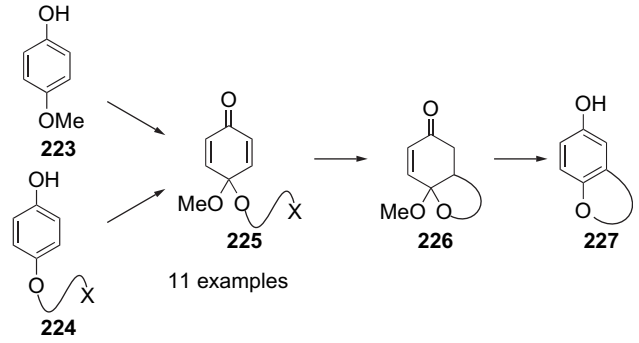
A remarkable effect of the nitrogen-protecting group has been uncovered in the cyclisation of the xanthates **220a** and **220b** (Scheme 64).[142] Group-transfer addition of a xanthate to acetamide



Scheme 64.

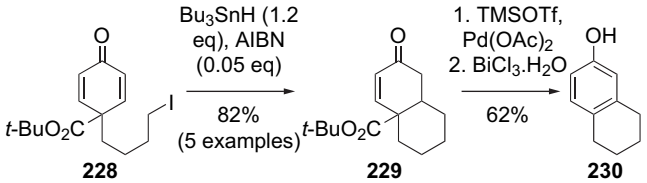
219a followed by cyclisation gave the expected azaindoline **221**, but, cyclisation of carbamate **220b**, derived from **219b**, resulted in an unprecedented ring closure on to the pyridine nitrogen to give **222**. It is possible that the two protecting groups favour different rotamers of the cyclisation precursor and this explains the dramatic change in selectivity. The chlorine of the pyridine ring is also essential for the formation of **222** and, presumably, it increases the radicophilicity of the nitrogen. This reaction opens up a route into a rare class of heterocyclic compound and should permit a wide range of substrates to be prepared, as there appears to be few limitations on the nature of the xanthate or the substitution pattern of the pyridine ring.

The problems encountered during the addition of C-centred radicals to benzene systems have been circumvented by an ingenious method that allows the transformation to be performed indirectly. Cross-conjugated ketones **225** can be prepared from phenol derivatives such as **223** by oxidation in the presence of an excess of halo alcohol or from diphenols by alkylation to give **224** followed by oxidation in methanol (Scheme 65).[143,144] Intramolecular conjugate addition on to the enone occurs in good yield if the reaction is carried out in hot, but not refluxing, solvent. The resulting bicyclic **226** is readily elaborated, permitting a range of aromatic compounds to be prepared, including simple phenols such as **227**. The value of this methodology was demonstrated by the synthesis of (+)-nocardione.[143,145]



Scheme 65.

The methodology has been extended to permit the synthesis of nitrogen heterocycles[146] and carbocycles.[147] The preparation of the cyclisation precursors is more challenging than that for the ether analogues, but the cyclisations and *re*-aromatisation are still highly efficient (e.g. **228**→**230**; Scheme 66). The synthesis of the carbocycle precursors is the most complex part of the procedure and involves Birch reduction of the corresponding benzoate, trapping of the intermediate anion and subsequent allylic oxidation of the resulting diene. Cyclisation is achieved under standard tin-mediated radical conditions and gives the bicycle **229** in good yield. The aromatic ring can be regenerated in two steps to give **230** in high yield. The methodology works for the preparation of five- and six-membered rings, but fails for larger ring sizes. Instead of producing phenols such as **230**, treatment of **229** with a reducing agent gives the non-substituted bicyclic aromatic system, whilst reaction with a Grignard reagent gives the substituted analogue. This methodology, along



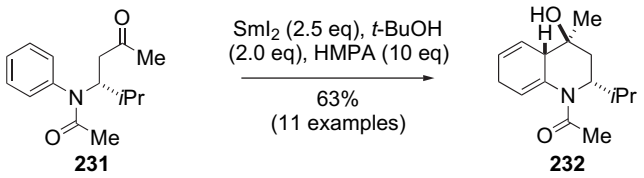
Scheme 66.

with the heterocylic variants, offers a high-yielding, versatile strategy for the synthesis of a variety of fused systems. Unlike much of the methodology discussed in this section, the chemistry is well understood and does not involve a 'black-box' *re*-aromatisation step and is thus ideal for planning synthetic ventures.

Radical cyclisation on to aromatic rings offers convenient functionalisation of these valuable motifs. As our knowledge of the mechanism improves, more versatile methodologies are being developed and it is clear that these will play an important role in organic synthesis. It must be stressed that it is essential that more research is undertaken to delineate the mechanism of oxidative *re*-aromatisation in reactions carried out under essentially reductive conditions.

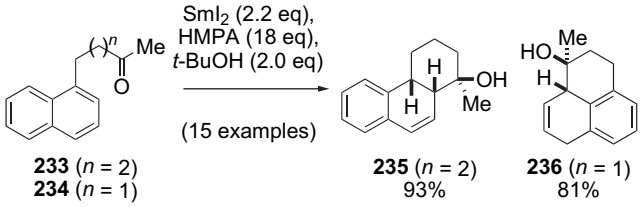
2.6. Cyclisation of C-centred radicals on to aromatic rings with destruction of aromaticity

Many radical additions to aryl rings result in the disruption of aromaticity and this allows rapid access to highly functionalised cyclic systems. Hexahydroquinoline derivatives **232** can be prepared by a highly diastereoselective 6-*trig* cyclisation (Scheme 67).[148] Regioselective protonation occurs in an analogous fashion to the Birch reduction and furnishes 1,4-cyclohexadienes. As ketyl radicals are nucleophilic, electron-deficient aniline derivatives give the best results. The nitrogen substituent affects the outcome of the reactions; not only does the electron-rich *N*-methyl analogue of **231** afford the bicyclic product in low yield, but it also undergoes *re*-aromatisation. Electron-withdrawing substituents such as carbamates and acetamides give the best yields. The yield could be improved considerably by replacing *tert*-butanol with phenol; the lower basicity of the phenolate anion possibly reduces the generation of side products or the increased acidity allows the intermediate cyclohexadienyl anion to be trapped more readily. A full paper was recently published on related non-anilide cyclisations.[149]



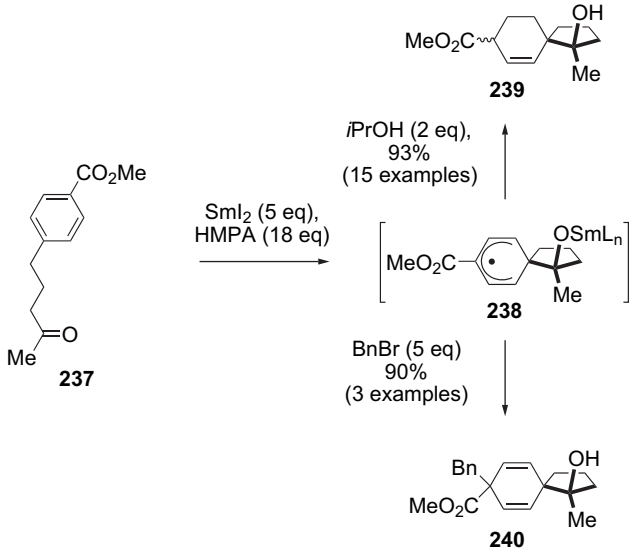
Scheme 67.

γ-Naphthyl-substituted ketones are effective precursors for this reaction, due to their reduced aromaticity.[150] A range of ketones smoothly cyclise to give functionalised fused-ring systems. There is a strong preference for the formation of six-membered rings, with only two conformationally biased systems forming different ring sizes. This selectivity is demonstrated by comparing the cyclisation of δ-naphthyl-substituted ketone **233** and β-naphthyl ketone **234**. As expected, **233** (n=2) cyclises on to the C-2 position to give **235**, but **234** (n=1) favours the formation of **236** by cyclisation on to C-8 over the formation of the five-membered ring (Scheme 68). Further extension of this chemistry permits the synthesis of aza-steroid derivatives.[151]



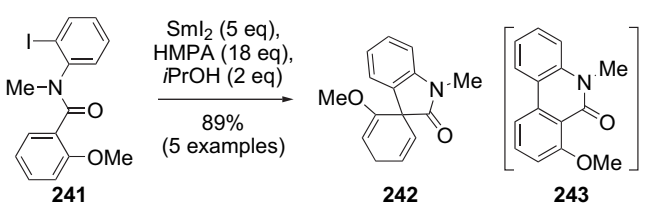
Scheme 68.

It appears that many of these reactions proceed via *ipso* attack to give spirocyclohexadienyl radical species that normally rearrange to fused-ring systems. The reactions can be biased to permit trapping of the spirocyclic compounds.[152] Thus, ketone **237** was converted into the diastereoisomeric alkenes **239** in an impressive 93% yield (Scheme 69). *Ipso* addition requires HMPA to be added to the reaction. The relative orientation of the hydroxyl group and the alkene is rationalised by the internal delivery of a second equivalent of samarium(II), which facilitates the reduction of the alkene positioned adjacent to the hydroxyl group. A variety of ketones can be employed in the reaction including those that result in the formation of four-, five- and six-membered rings. Sterically congested derivatives often require an increased amount of *iso*propanol to prevent the recovery of starting material, indicating that formation of cyclohexadienyl radical **238** is reversible. The ester substituent must be in the *ortho* or *para* position for the spirocyclic compounds to be formed; if it is in the *meta* position, then only the fused bicyclic compounds are isolated. Other substituents are tolerated in either the *ortho* or *meta* positions if the substrate retains the *para* ester group. Curiously, only esters and amides activate the aryl ring to spirocycle formation, both nitriles and sulfonates giving the fused bicyclic products. The synthetic value of this reaction has been extended by incorporating it in a radical cyclisation–ionic alkylation sequence that allows the formation of two C–C bonds in 'one pot' (such as the formation of **240**).



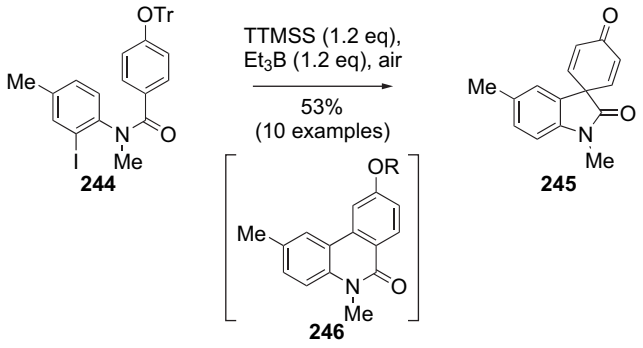
Scheme 69.

Aryl halides such as **241** undergo spirocyclisation under the influence of samarium(II) iodide and an alcohol to furnish dienes (**242**) in excellent yield (Scheme 70).[153] In the absence of the proton source, fused heterocycle **243** was the predominant product, presumably formed via rearrangement of the spirocyclohexadienyl radical. The best yields were obtained from compounds that possessed an *ortho*-substituent. It is argued that these substituents retard the rearrangement and thus the intermediate radical has sufficient time to be reduced to an anion and then protonated.



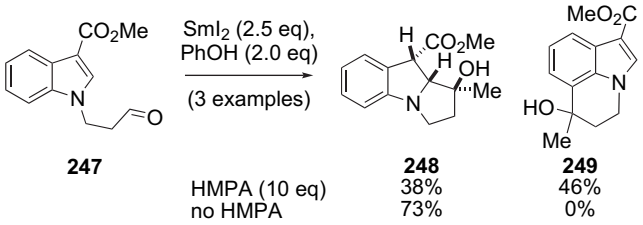
Scheme 70.

An alternative method to trap the spirocycle is to use a phenol derivative that can undergo β-fragmentation to retard rearrangement or ring opening from occurring. For the conversion of **244** into **245** (Scheme 71), the choice of protecting group was crucial;[154] both *O*-benzoyl and *O*-trityl derivatives were found to give the spirocycle, whilst other *O*-substituents gave the fused product **246**. Once again, these results suggest that the intermediate cyclohexadienyl-like radical intermediates of *ortho* and *ipso* cyclisation are in equilibrium through a formal 1,2-shift or that the initial addition is reversible and that it is the subsequent fate of this initial adduct that determines the product distribution. Interestingly, if the length of the tether is extended by one carbon, then the product of *ipso* cyclisation is formed exclusively, regardless of the *O*-substituent. The utility of this methodology was demonstrated by the synthesis of the key intermediates for the synthesis of both SR121463A and aza-galanthamine.



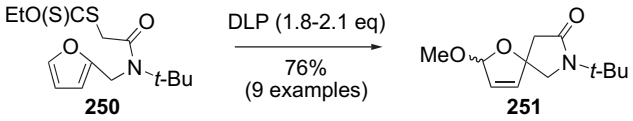
Scheme 71.

Cyclisation on to heteroaromatic systems can also proceed with loss of aromaticity. Ketyl radicals cyclise on to pyrroles and indoles to furnish functionalised pyrrolizidines and indolizidines in good yields and high diastereoselectivity.[155] For the cyclisation of **247**, the co-solvent has a dramatic effect on the regioselectivity (Scheme 72). In the presence of HMPA, cyclisation of **247** gave a mixture of **248** and **249**, whereas without HMPA only the tricyclic pyrrolizidine **248** was formed. More research is required before it is clear whether this is a substrate-specific example or if HMPA will alter all cyclisations. It is clear that highly electron-deficient indoles react efficiently in the absence of HMPA to give attack at the pyrrole nucleus. This methodology has been extended to allow the formation of seven- and eight-membered rings.[156] Intriguingly, both pyrrole and indole derivatives react to give seven-membered rings, but only the indole derivatives permit the formation of fused eight-membered rings.



Scheme 72.

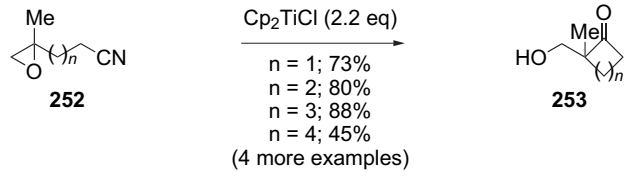
Furans are prone to spirocyclisation, due to their reduced aromaticity. Treatment of xanthate **250** with stoichiometric quantities of lauroyl peroxide results in the formation of the acetal **251** (Scheme 73).[157] *Ipso* cyclisation gives an allyl radical, that is, oxidised to an oxonium cation by electron transfer to lauroyl peroxide. Finally, nucleophilic attack by methanol generates the spirolactam. The substituent on the nitrogen is important for obtaining high yields; bulky alkyl groups are optimum, whilst a carbamate-protecting group gave poor results. The bulky groups must encourage a conformation in which the radical acceptor and donor are in close proximity. Substituents are tolerated on the non-aromatic part of the molecule, thus permitting the synthesis of tricyclic systems. Pyrrole derivatives bearing an electron-withdrawing *N*-substituent can be employed in the reaction as well. It is not clear if this is required to stabilise the final product or to reduce the aromaticity of the pyrrole to permit the initial attack.



Scheme 73.

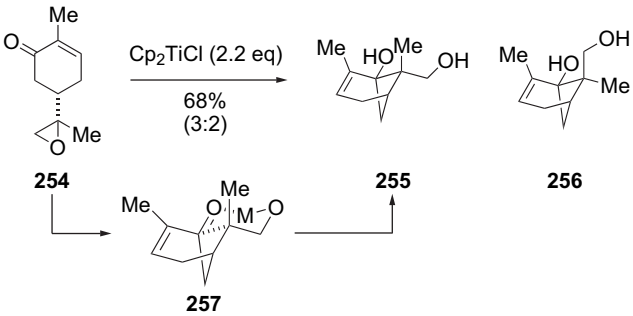
2.7. Cyclisation of C-centred radicals on to heteroatom-containing acceptors

Radical cyclisations on to C=X can be problematic, due to the reversibility of such processes, but with the correct choice of radical reagent this limitation can be overcome (see Part 1, Section 3.1.6.). The ability of titanocene(III) reagents to act as radical traps allows them to shift the equilibrium in favour of the products. As a result, they permit the range of radical acceptors to be expanded beyond simple alkenes or alkynes. Radical cyclisation on to the nitrile moiety is a slow process; a 5-*exo*-dig cyclisation has $k=4.0\times10^3\ s^{-1}$, compared to $1\times10^4\ s^{-1}$ or $2.5\times10^5\ s^{-1}$ for the equivalent cyclisation on to an alkyne or alkene. Furthermore, nitrile translocation or 1,5-hydrogen shift side reactions frequently interfere. By trapping the N-centred iminyl radical, titanocene(III) permits the cyclisation of epoxy nitriles **252** to occur efficiently to give a range of carbocycles **253** (Scheme 74).[158] Four- to seven-membered rings can be formed although the yield of the latter is reduced, due to premature reduction. A catalytic variant of the reaction (see Part 1, Section 2.7.1.) was attempted, but with only moderate success; the reaction took four days and still only produced the product in a meager 37%. A more in-depth study of this reaction was recently reported.[159]



Scheme 74.

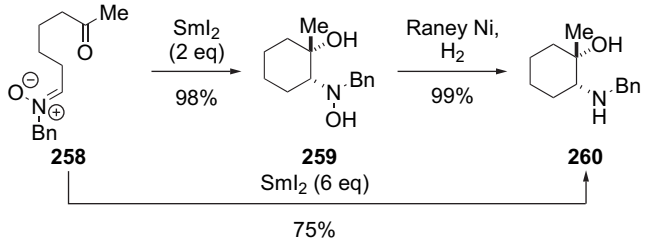
Trapping O-centred radicals with oxophilic reagents can prevent fragmentation during additions to carbonyl compounds. As a result, **254** can be converted into a mixture of the two diastereoisomers **255** and **256** in good yield (Scheme 75).[160] The predominant diastereoisomer **255** is believed to arise from the stability of complex



Scheme 75.

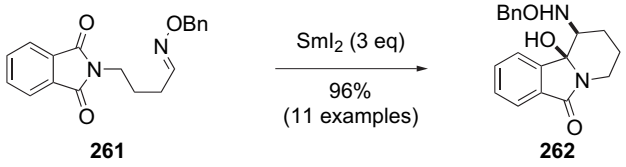
257 that is formed by chelation of the oxygen functionality to the titanium centre. A more comprehensive study of the mechanism and the kinetics of this reaction have recently been reported.[159]

Considering that many C=N functionalities have been employed in radical additions, it is somewhat surprising that nitrones have only recently been used in pinacol-like couplings with aldehydes.[161] Nitrone **258** undergoes efficient cyclisation to give either the *N*-hydroxyamine **259** or the amine **260**, depending on the quantity of samarium(II) iodide employed in the reaction (Scheme 76). The use of two equivalents of samarium resulted in the formation of the *N*-hydroxyamine **259**, whilst use of a greater excess led to deoxygenation. All of the experimental evidence suggests that the samarium(II) species reduces the nitrone first to give a C-centred radical that attacks the carbonyl, instead of the expected pathway via the ketyl radical and attack on the nitrone. It is thought that the high oxophilicity of the samarium encourages cyclisation by tethering the two oxygen functionalities.



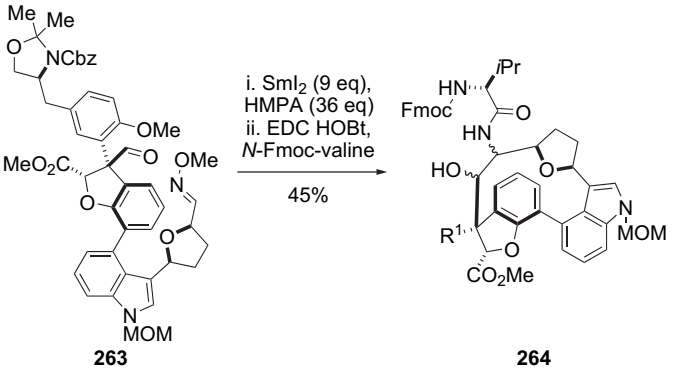
Scheme 76.

A number of functional groups undergo preferential single-electron reduction more rapidly than ketones or aldehydes. During the attempted synthesis of a 1,2-diaminocyclopentane, Chiara discovered that samarium(II) iodide preferentially reduced an *N*-phthalimido protecting group, instead of a ketone or oxime ether.[162] A comprehensive study[163] of this reaction showed that *N*-alkylphthalimides, such as **261**, react with a variety of tethered acceptors including imides, oximes, nitrones and α,β-unsaturated esters as well as undergoing intermolecular coupling with alkenes (Scheme 77). DFT calculations suggest that phthalimides are inherently better SET acceptors than other carbonyl species. The highly functionalised cyclic products (**262**) should be valuable intermediates. Once again, this shows the value of undesired reactions and the isolation of unexpected side products can allow the development of new methodology.



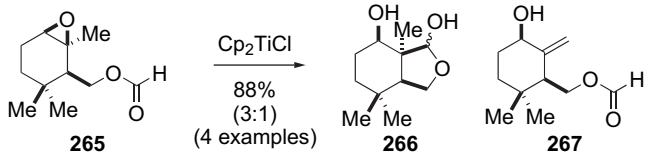
Scheme 77.

Nicolaou has used samarium(II) iodide in the key macrocyclisation step in studies aimed at the synthesis of diazonamide A.[164] The reaction constitutes one of the first examples of a hetero-pinacol reaction leading to a large-sized ring. It is believed that the treatment of **263** with a large excess of samarium(II) iodide and HMPA results in the reduction of both the aldehyde and the oxime ether to give a diradical intermediate that undergoes C–C bond formation. The excess samarium–HMPA complex then cleaves the N–O bond and the resulting amino alcohol was subjected to in situ peptide formation to give **264** in good yield (Scheme 78). It is clear that the HMPA ligand plays a crucial role in the tandem cyclisation–N–O bond-cleavage reaction; when the reaction was performed in the absence of HMPA, no hetero-pinacol reaction was observed. If the ratio of samarium to HMPA was reduced from 4:1 to 2:1, then cyclisation occurs, but considerable amounts of material with the N–O bond still intact are isolated.



Scheme 78.

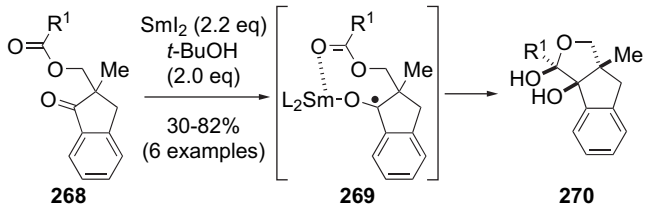
Radical addition to carboxylic acid derivatives is a challenging reaction. Whilst cyclic ketones can be prepared if the acid derivative contains a highly efficient radical leaving group, such as a thioester, a selenoester or an acyl germane, addition to simple esters is fraught with problems. The alkoxy radical tetrahedral intermediate readily collapses to regenerate the C=O double bond via expulsion of either a C-centred radical or an alkoxide anion or radical. Titanocene(III) can act as an efficient oxophilic reductant and inhibit fragmentation. Treatment of the epoxide **265** with titanocene(III) readily induces epoxide ring opening and the resulting β-hydroxy radical either cyclises on to the formate ester to give **266** or undergoes elimination to give **267** (Scheme 79).[165] Whilst the reaction works well in this example, there are a number of limitations that need to be overcome before the methodology is of general synthetic utility; the cyclisation only proceeds with formate esters, all other esters tested giving unsaturated hydroxy esters analogous to **267**. This means that the ether-type oxygen must be situated between the initial radical and the carbonyl acceptor. Furthermore, only 5-*exo* cyclisations proceeded with acceptable yields, all other ring sizes giving increasing amounts of the alkene. Whilst this methodology marks an important advance, it is clear that further study is required before it will become synthetically useful.



Scheme 79.

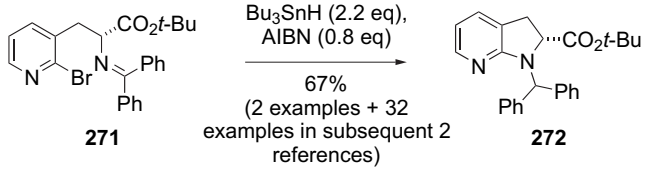
Samarium is also oxophilic and mediates an analogous reaction to furnish cyclic hemiacetals such as **270** (Scheme 80).[166] The reactivity of the samarium(II) system mirrors that of the titanocene(III) reagents; successful cyclisation is only achieved when the ether-like oxygen is situated between the radical donor and acceptor. The reaction of the keto ester in which the ether-type oxygen is '*exo*' results in fragmentation. The samarium(II) reaction is more versatile than the titanocene(III) methodology, working with a greater range of esters. Whilst the best results are still achieved with formyl esters (**268**; R^1=H), the samarium variant also tolerates acetates (R^1=Me) and benzoates (R^1=Ph). The titanium reagent was also limited to the formation of five-membered rings, whilst the samarium system can form larger cycles, although the yields are disappointing. Coordination of the samarium and the two carbonyl

groups, giving **269**, is believed to be key to the success of this reaction; not only does it permit the rapid trapping of the alkoxy radical, thus retarding fragmentation, but it also encourages ketyl-ester coupling over simple reduction. Both the titanocene(III) and samarium(II) methodologies expand the repertoire of effective radical acceptors and show great potential for the formation of cyclic hemiacetals that are closely related to biologically relevant molecules.



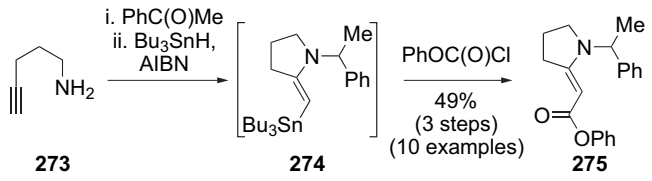
Scheme 80.

Radicals can cyclise on to heteroatoms of multiple bonds and this has led to the development of a mild, radical-mediated amination, that is, complementary to transition-metal-mediated reactions. The methodology is exemplified by the synthesis of a 7-azaindoline α-amino acid **272** via the 5-*exo* cyclisation of **271** (Scheme 81).[167] Choice of the correct imine moiety is vital, as the substrate must be kinetically and thermodynamically biased to attack the nitrogen and not the carbon. This can be achieved by incorporating bulky groups on the carbon to deter attack at this position and by choosing groups that stabilise a C-centred radical. The optimum ketone for imine formation was benzophenone; this stabilises the tertiary radical formed and, unlike acetone, does not encourage the premature reduction of the aryl radical. Although the neutral conditions have many advantages over metal-mediated variants of this reaction, care must still be taken to avoid racemisation of the α-amino stereocentre or translocation of the protected amine.[168] Both processes are thought to occur by a reversible ring opening of the adduct radical. The 1,4-group transfer of the amine can be encouraged and this permits the synthesis of the protected anilines. The reaction is tolerant of a range of substituents at virtually all positions on the indoline structure and a large number of ketones can be employed to form the ketimine. The only limitation appears to be that at least one substituent must be a radical-group and that dialkyl ketones, generally cannot be used as they give predominantly the product of direct aryl reduction.[169]



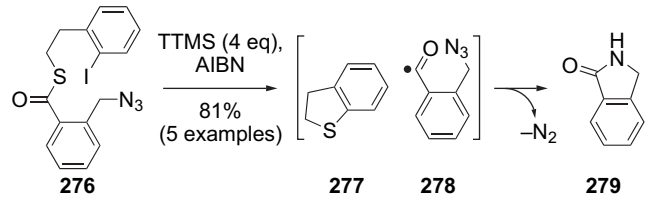
Scheme 81.

This methodology has been applied to the preparation of enamines via the amination of alkenyl radicals. This is a far more challenging proposition than the synthesis of indolines, due to the greater conformational freedom of the precursors and the high reactivity of the enamine products.[170] In an elegant 'one pot' reaction, amino alkynes, such as **273**, are treated with a ketone followed by the addition of a stannyl radical to initiate the radical cyclisation and give the reactive stannane **274**. In situ acylation gives the isolatable **275** (Scheme 82). The alkenyl radical can also be prepared from alkenyl bromides. Generally, the cyclisations occur in moderate yields, not due to inherent inefficiencies in the radical reaction, but due to the volatility of the products and their high reactivity. A further limitation is that only 5-*exo* cyclisations are possible; attempts to achieve 6-*exo* cyclisations were unsuccessful and only furnished the product of direct radical reduction. Radical-mediated amination is rapidly becoming a powerful strategy for the formation of *N*-heterocycles; it permits aryl amination under mild, neutral reaction conditions that should permit a wide range of functionality to be tolerated. Additionally, by altering the radical precursor, the regioselective formation of reactive, non-stabilised enamines can be achieved and applied to synthetically useful cascade processes.



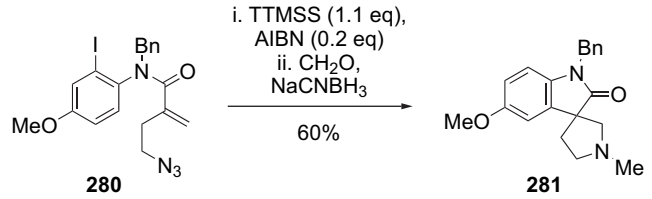
Scheme 82.

The intramolecular addition of C-centred radicals on to azides provides a route to lactams.[51] Generation of an aryl radical from the thioester **276** leads to the formation of dihydrobenzothiophene **277** (see Scheme 28) and an acyl radical **278** (Scheme 83). Addition of the radical **278** to the azide yields the lactam **279** and nitrogen. The radical nature of this transformation was confirmed by replacing TTMS with allyltributylstannane, which resulted in the formation of the *N*-allylated indolinone and **279** in a 1:1 ratio. The methodology permits the formation of five- and six-membered indolinones and quinolones. Attempts to prepare alkyl-derived lactams missing the aryl backbone were more problematic, with competitive decarbonylation consuming the majority of the material.



Scheme 83.

Murphy has exploited an elegant radical cyclisation cascade that culminates with radical attack on an azide to furnish spirocyclic pyrrolidines. Horsfiline can be prepared from the iodoaryl azide **280** via the formation of an aryl radical that undergoes 5-*exo*-*trig* cyclisation on to the alkene to give an unstable primary radical that reacts with the azide to furnish the free amine; in situ methylation then furnishes **281**, a protected form of horsfiline, in good yield (Scheme 84).[171] An analogous reaction has been utilised to create the tetracyclic core of (±)-vindoline, thus demonstrating the potential of this methodology for the rapid preparation of complex alkaloids.[172]



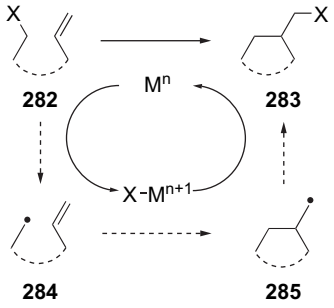
Scheme 84.

2.8. Atom- and group-transfer radical cyclisations

Atom- and group-transfer radical reactions are amongst the most important radical reactions for the formation of carbon–carbon bonds. Such reactions are attractive, as they are isomerisations,

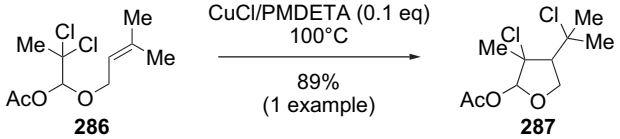
and so no functionality is lost from the molecule. This is in contrast to the majority of radical reactions, which are reductive in nature and result in the removal of functionality. Atom- and group-transfer radical reactions (henceforth collectively termed atom-transfer reactions) can be classified into three basic categories: intermolecular atom-transfer radical addition (ATRA), atom-transfer radical cyclisation (ATRC) and atom-transfer radical polymerisation (ATRP). From the synthetic organic chemists perspective it is the former two reaction classes that are of interest; for readers interested in atom-transfer radical polymerisation, two reviews have been published by Matyjaszewski.[173]

It has long been known that a variety of transition metals can catalyse atom-transfer reactions and considerable effort has been expended in the development of cheap, non-toxic alternatives to ditin compounds for these reactions. The mechanism of the metal-catalyzed ATRA is routinely described as a redox reaction involving M^n and M^{n+1} complexes and an organic radical (Scheme 85); the initial step is halide abstraction from **282** to give a stabilised radical **284** and $M^{n+1}X$; a requirement of this systems is that the metal centre, M, must be co-ordinatively unsaturated to enable atom abstraction. M should also have a suitable redox potential to facilitate catalytic turnover. This is followed by radical addition or cyclisation forming a C–C bond **285**. Finally, the new, less stable radical reacts with $M^{n+1}X$ to furnish the product **283** and regenerate the catalyst M^n. For the initial atom abstraction to occur, the C–X bond must be activated and this invariably requires the presence of several electron-withdrawing groups to sufficiently weaken the bond. Whilst this mechanism explains most observations, it is an oversimplification.



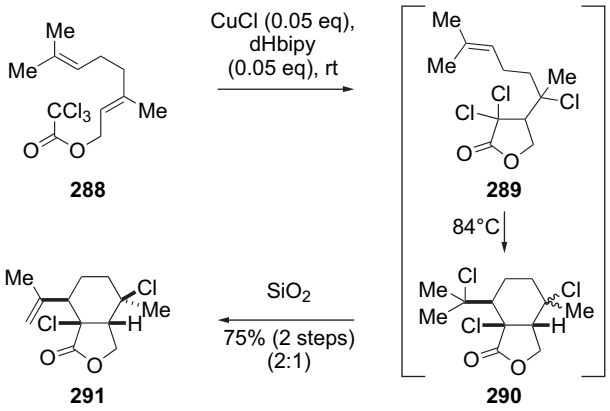
Scheme 85.

Complexes of copper(I) are by far the most common reagents for ATRC and a review has covered this area in detail.[174] Examples of copper-mediated ATRC of chlorides that are not adjacent to a carbonyl group are surprisingly scarce; lowering of the C–Cl LUMO by a carbonyl group is the most common form of activation. Cyclisation of 2,2-dichlorohemiacetal **286** requires a highly active catalyst system; standard bipyridine-based systems are insufficiently reactive (Scheme 86).[175] The optimum results were found using copper(I) chloride-*N*,*N*,*N*′,*N*″,*N*″-pentamethylethylenetriamine (PMDETA) in acetonitrile at 100 °C to give **287** in good yield; other catalyst systems gave incomplete conversion. This compound could be further elaborated to prepare (±)-botryodiplodin. Interestingly, an earlier example using a *tri*chlorohemiacetal was sufficiently reactive to employ the 'standard' copper(I) chloride–bipyridine system.[176] The synthesis of β-lactams by the ATRC of deactivated systems has been studied in detail by Clark.[177]



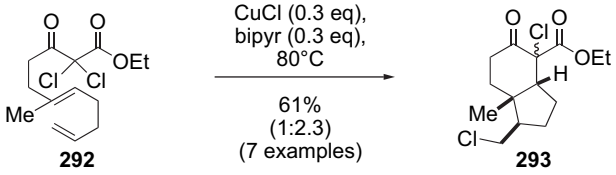
Scheme 86.

During studies towards the synthesis of the core of the eunicellins, Quayle developed the first example of a tandem ATRC process (Scheme 87).[178] Treatment of the diene **288** with a pre-formed copper(I) catalyst, first at room temperature and then at reflux, brings about two cyclisations; the monocyclic lactone **289** is formed at room temperature and then harsher reaction conditions are required to mediate the second cyclisation, due the less activated nature of the α-dichloro moiety of **289**. The resultant diastereoisomeric chlorides **290** are unstable and undergo spontaneous elimination of hydrogen chloride in the presence of silica to give predominantly the diastereoisomer **291** (2:1).



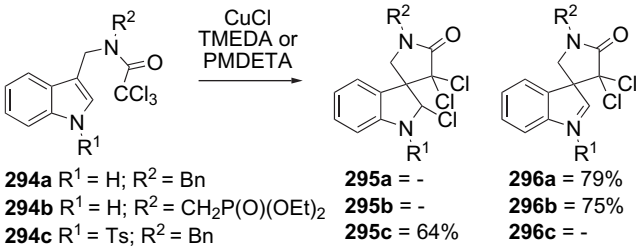
Scheme 87.

An alternative ATRC cascade utilises α-dichloro-β-ketoesters **292** (Scheme 88).[179] The tandem cyclisation of **292** yields the fused 5,6-bicyclic ring systems **293** in good yield as a mixture of diastereoisomers at the remaining α-chloro position. Arguably, the second cyclisation occurs prior to chlorine-atom transfer, which would result in a deactivated alkyl chloride that would terminate the reaction. This methodology offers an efficient route to highly functionalised bicyclic compounds.



Scheme 88.

In one of the rare examples of ATRC on to an aromatic ring, amides **294** cyclised to give **295** and **296** (Scheme 89).[180] It is slightly frustrating that the cyclisation conditions appear to be substrate dependent; TMEDA gave the best yields for the cyclisation of the simple benzyl derivative **294a** (79 vs 35% for PMDETA), whilst PMDETA (pentamethyldiethylenetriamine) gave the best yield for the phosphonate **294b** (75 vs 51%). Whilst it is clear that the intended ATRC occurs to give **295a,b**, these spontaneously



294a R^1 = H; R^2 = Bn
294b R^1 = H; R^2 = $CH_2P(O)(OEt)_2$
294c R^1 = Ts; R^2 = Bn

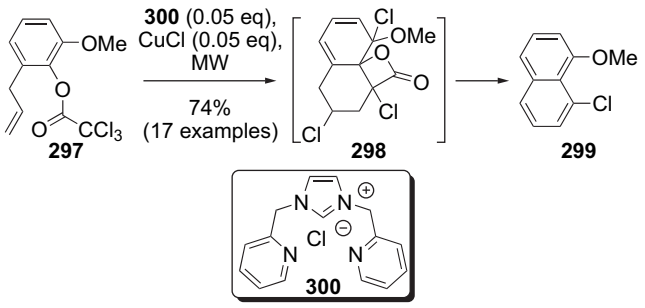
295a = -
295b = -
295c = 64%

296a = 79%
296b = 75%
296c = -

Scheme 89.

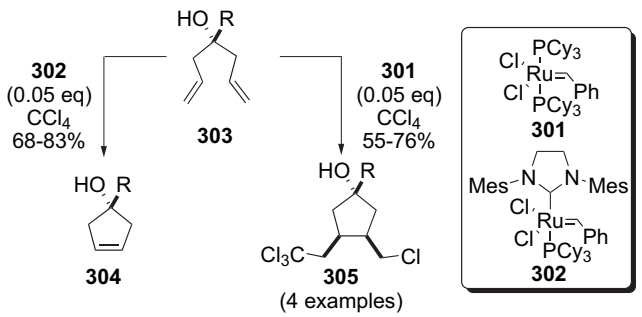
eliminate hydrochloric acid to give the imino compounds **296a,b**. This elimination can be stopped if the indole was protected as the tosylate **294c** and the reaction carefully monitored, thus permitting the formation of the chloride **295c** with no trace of **296c**.

ATRC has permitted the development of a novel benzannulation protocol for the formation of naphthyl chlorides.[181] Readily available aryl trichloroacetates such as **297** were subjected to copper(I) chloride-**300** complex-mediated ATRC in a microwave at 200 °C to give the naphthalene derivatives **299** (Scheme 90). The reactions occur with complete regiochemical control and can tolerate both an electron-donating and an electron-withdrawing functionality, although the nitro group appears to cause a reduction in yield. A plausible pathway for the reaction is via the expected 8-*endo-trig* ATRC reaction followed by a second transannular 4-*exo-trig* ATRC reaction to give **298**. Rapid loss of carbon dioxide by a retro-[2+2]-cyclisation gives a putative trichloro species that can undergo dehydrochlorination with concomitant *re*-aromatisation. This methodology offers an efficient route to these interesting aromatic compounds. ATRC to give unusual ring sizes has also been studied by Clark.[177]



Scheme 90.

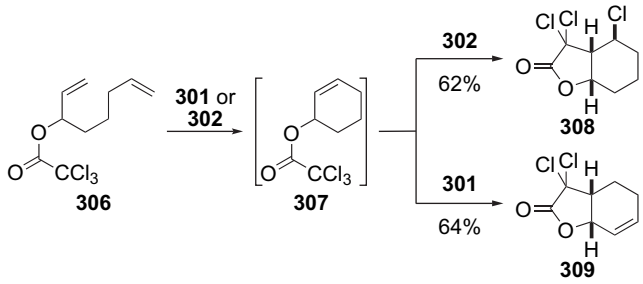
Ruthenium-based reagents have shown great potential in atom-transfer processes. One of the most reactive reagents is a diruthenium species that is exceptionally efficient at both ATRC and ATRA,[182] but it is not expected to find widespread acceptance, as there is no commercial source. The most convenient ruthenium complex for the generation of radicals is Grubbs' alkylidene complex **301** (Scheme 91). It was shown as early as 1999[183] that **301** could catalyse both ATRA and ATRC, but it is only recently that its activity has been explored in depth. Interestingly, the bis(phosphine) pre-catalyst **301** and the more active metathesis catalyst, imidazolylidene-substituted pre-catalyst **302**, show very different activity under otherwise identical reaction conditions;[184] treatment of the diallyl carbinol **303** with **302** gave the product of ring-closing metathesis (RCM) **304** in good yield, but, if **301** was employed, then a tandem radical addition–cyclisation–atom transfer process was observed, giving **305** in comparable yields. Currently, the identity of the active species has not been ascertained; there must be some interaction between either the pre-catalyst or the catalyst with the hydroxyl group, as reaction of the methyl ether leads exclusively to



Scheme 91.

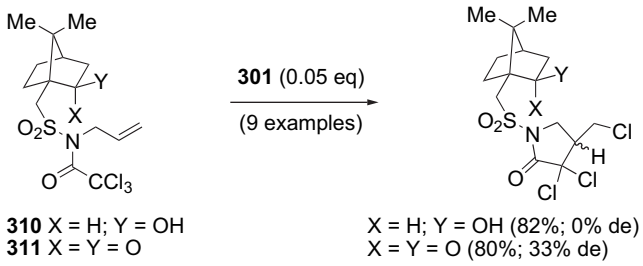
the ether of **304** (71%). It is thought that the hydroxyl group competes with the terminal alkene for the vacant coordination site on the ruthenium, reducing the metathetical activity of **301**; the imidazolylidene catalyst has a much lower tendency towards coordination with Lewis bases and, hence, is still active for RCM.

Catalysts **301** and **302** also display surprisingly different activity during the preparation of the lactones **308** and **309**. Whilst **302** gave **308**, **301** did not catalyse the expected RCM–ATRC process and gave the alkene **309** instead; the regiochemistry of the latter suggests that it is not the product of chloride elimination (Scheme 92).[185] Both reactions are believed to proceed via RCM of **306** to give **307**; **302** then promotes ATRC, whilst **301** causes the trichloroacetate moiety to be eliminated to give cyclohexadiene that then participates in *intermolecular* ATRA followed by nucleophilic displacement to give the lactone **309**.



Scheme 92.

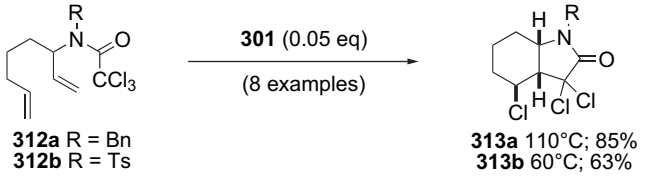
Ruthenium alkylidene catalyst **301** also mediates the ATRC of both trichloroacetamides and trichloroacetates, thus permitting the formation of γ-lactams and γ-lactones.[186] Rather intriguingly, attempts to influence the stereochemistry of the cyclisation met with mixed results; cyclisation of the alcohol **310** resulted in no detectable asymmetric induction, yet cyclisation of the ketone **311** occurred with a diastereoselectivity of 33% de (Scheme 93). At present, the origin of this effect is unclear.



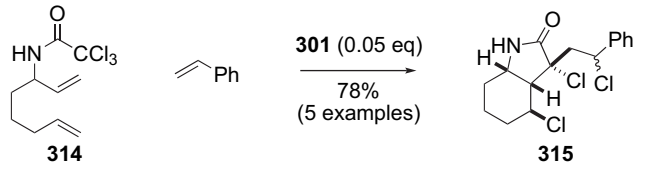
Scheme 93.

The ability of **301** to catalyse RCM, ARTC and ATRA has been employed to develop a remarkable tandem process that permits the formation of up to three new C–C bonds and two new C–Cl bonds in a 'one-pot' process.[187] At room temperature, substrate **312a** undergoes RCM and only heating to reflux initiates ATRC to furnish the bicyclic compound **313a** in good yield (Scheme 94). The unveiling of the radical activity at elevated temperatures destroys the catalyst's metathetical activity. As with all γ-lactam preparations by ATRC, the nature of the nitrogen-protecting group makes a significant difference to the reactivity of the species; the tosylate **312b** reacts, to give **313b**, at nearly half the temperature of benzylate **312a**. The reason for this is undoubtedly due to the populations of different amide rotamers. The stereoselectivity of the reaction supports the belief that the second cyclisation proceeds via a radical mechanism and not a ruthenium-mediated oxidative addition/reductive elimination pathway. Chlorides unable to undergo

ATRC can participate in ATRA and this has enabled a remarkable tandem RCM–ATRC–ATRA sequence that converts **314** into lactam **315** in a remarkable 78% yield (Scheme 95).

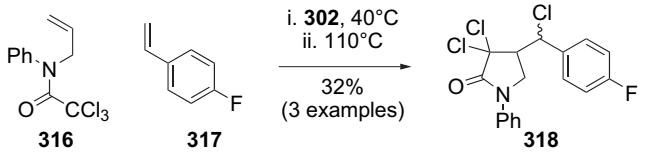


Scheme 94.



Scheme 95.

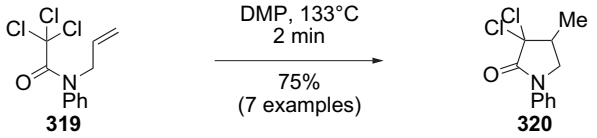
An alternative reaction sequence utilises **302** to initiate cross metathesis of two alkenes, **316** and **317**, prior to ATRC (Scheme 96).[185] Whilst the reaction is far from optimised, it is highly promising as a method for the rapid assembly of heterocycles **318**. The initial cross metathesis must be carried out below 80 °C; above this temperature, catalyst decomposition generates the species responsible for radical activity. Both coupling partners in the metathesis reaction should be carefully selected in order to limit co-metathesis and/or isomerisation of the alkenes to enamides. In contrast to previous reports, the imidazolylidene pre-catalyst **302** was found to be the optimum reagent. These exciting reaction sequences allow the rapid and operationally simple construction of highly substituted cyclic compounds, and bode well for the future development of atom-economic synthesis.



Scheme 96.

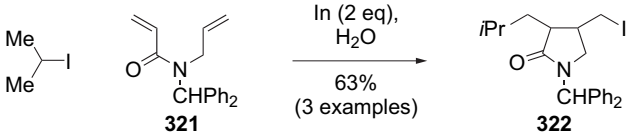
At present, there is little information about the structure of the active species responsible for promoting radical behaviour. Quayle has studied the different modes of reaction and found that metathesis is normally the more rapid process, with the half-life of simple acetamides being approximately five minutes at room temperature.[188] The radical reaction is only initiated at temperatures in excess of 60–70 °C. It appears that the active species in the radical reaction is formed by the decomposition of the metathesis catalyst and that the catalyst responsible for the radical activity is incapable of metathetical reactivity. It will be interesting to see if this catalyst is related to the transition-metal catalysts used in the radical couplings with Grignard reagents and boronic acids (see Part 1, Section 2.7.5.) and whether the catalysts will be interchangeable.

Whilst discussing ATRC, it is worth focusing on a recent example of the reductive cyclisation of trichloroacetamides;[189] cyclisation occurs simply by heating the precursor **319** in an amine solvent. There is no need to add any metal catalyst/reagent. The optimum amine is 1,4-dimethylpiperazine (DMP), which permits **319** to undergo rapid cyclisation to give **320** in an excellent 75% yield in just two minutes (Scheme 97). The reaction can be achieved at room temperature if an additive with a high dielectric constant, such as dimethylsulfoxide, is added. A 1:1 mixture of DMSO:DMP gave **320** in 50% yield after 6 h. Dichloroacetamides also cyclise, but at an appreciably slower rate. The ease and simplicity of this methodology will undoubtedly lead to its further exploitation[190] and it is hoped that both the versatility of this methodology and the mechanism will be delineated in the near future. The latter is especially intriguing, considering the similarity between this reaction and the copper(I) methodology.



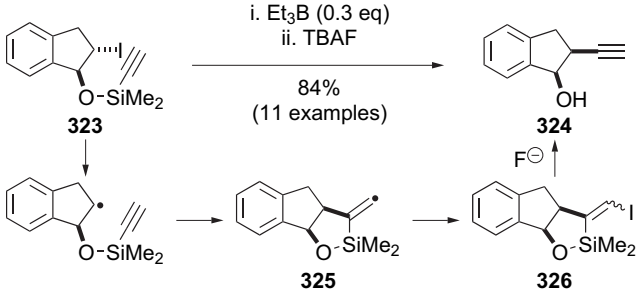
Scheme 97.

Indium(0) also mediates atom-transfer processes and was successfully employed in a tandem radical addition–cyclisation–trap sequence, which converts diene **321** into lactam **322** (Scheme 98).[191] The reaction proceeds by SET to give an alkyl radical that adds to the activated acrylate moiety. The carbonyl-stabilised radical then undergoes 5-*exo*-*trig* cyclisation to give a primary alkyl radical. Finally, atom transfer regenerates the initial radical and propagates the chain reaction. Both secondary and tertiary iodides add to **321**, but primary iodides are unreactive. An attractive feature of this methodology is that the reaction is considerably faster in pure water than in organic solvents.



Scheme 98.

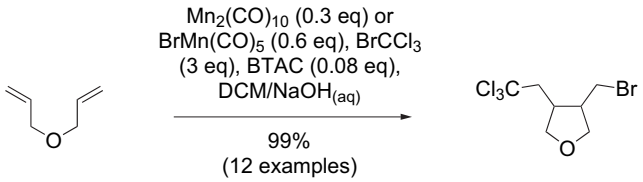
ATRC has been employed in the regio- and stereoselective introduction of the alkyne moiety into cyclic structures. This can be a taxing challenge if a *cis* relationship with the existing substituents is required, with most reactions preferentially delivering the *trans* isomer. One way to overcome this problem is via a temporary silicon-tethered radical cyclisation (Scheme 99).[192] Radical cyclisation of the ethynyldimethylsilyl ether, **323**, is initiated with sub-stoichiometric quantities of triethylborane to give an alkenyl radical **325**. This reactive species abstracts an iodine atom from the starting material to give the alkenyl iodide **326** and propagate the chain. Treatment of **326** with tetrabutylammonium fluoride (TBAF) results in elimination to furnish **324** in good yields. The reaction works for a range of cyclic structures, but is more problematic with acyclic substrates.



Scheme 99.

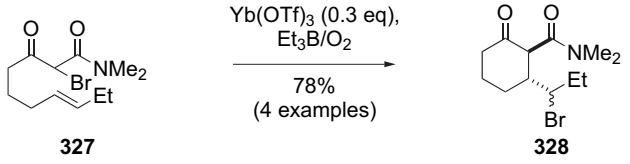
The photolysis of the Mn–Mn bond of decacarbonyldimanganese ($Mn_2(CO)_{10}$) forms a pentacarbonylmanganese radical, which can abstract halides from the appropriate substrates and initiate radical

reactions. Drawbacks of the $Mn_2(CO)_{10}$ methodology include the need for stoichiometric quantities of the manganese compound and the removal of the pentacarbonylmanganese halide side product. Parsons has developed a simple biphasic system that overcomes both these limitations.[193] Performing the reactions in dichloromethane and aqueous sodium hydroxide in the presence of a phase-transfer catalyst (benzyltriethylammonium chloride, BTAC) results in the formation of water-soluble manganese salts, easing the purification and permitting the regeneration of $Mn_2(CO)_{10}$, thus facilitating the use of sub-stoichiometric quantities. A range of efficient radical couplings, cyclisations (Scheme 100) and intermolecular addition reactions could be performed. The decacarbonyldimanganese reagent can be replaced by pentacarbonylmanganese bromide with no change in the yield of product. It is assumed that the $BrMn(CO)_5$ is converted in situ into $Mn_2(CO)_{10}$ and that it is this latter reagent, that is, the precursor to the active species. Whilst this methodology presents a practical method for radical generation, it should be noted that the conditions do not work for all reactions; trichloroamides analogous to **319** were simply reduced under these conditions and did not undergo the desired cyclisation.



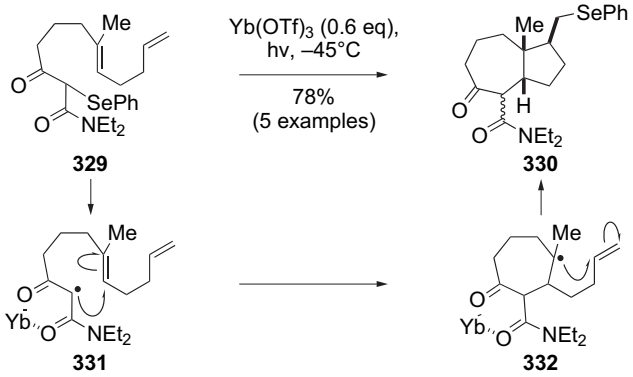
Scheme 100.

An alternative strategy for the promotion of ATRC is the use of Lewis acids in conjunction with a radical initiator; the Lewis acid is essential, as no product is formed when it is omitted. Presumably, the Lewis acid activates the radical precursor and increases the radical's electrophilicity, permitting the addition to unactivated alkenes. Many α-halo- and α-seleno-β-ketoesters are unstable unless an α-alkyl substituent is present. Bromides of β-ketoamides, such as **327**, do not share this limitation and are relatively stable, making them ideal candidates for Lewis acid-mediated ATRC.[194] Mono-cyclisations occur in good yields to give the *trans* product **328** with excellent stereoselectivity for two out of three stereocentres (Scheme 101). Surprisingly, tandem cyclisations to furnish bicyclic compounds fail, even though such processes are possible with α-bromo-β-ketoesters.



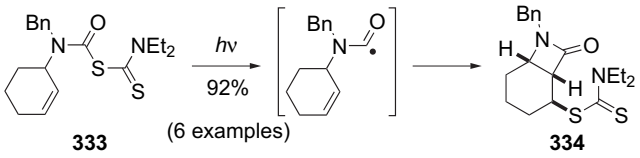
Scheme 101.

Lewis acids also mediate the group-transfer reactions of phenyl selenides. Once again, α-phenylseleno-β-ketoamides, such as **329**, are the most attractive precursors. Irradiation with UV light in the presence of a suitable Lewis acid furnishes the cyclised group-transfer product **330** in good yield (Scheme 102).[195] Radicals are intimately involved in the reaction, as the six-membered ring, the product of an ionic cyclisation, is observed if the reaction is not irradiated. The reaction proceeds with sub-stoichiometric quantities of the Lewis acid, but fails in the absence of a Lewis acid. The slow rate of phenylseleno transfer, compared to either the Br or I atom-transfer processes, permits the synthesis of fused-medium rings such as **330**. The α-radical **331** participates in regioselective cyclisation on to the least hindered end of the internal alkene to give a stabilised tertiary radical **332**. The second cyclisation step then occurs faster than radical chain-termination by phenylseleno group transfer. A highly diastereoselective version of this reaction has been developed using α-phenylseleno-β-hydroxy esters.[196] This represented the first example of stereoselective group-transfer radical cyclisation that occurred via 1,2-asymmetric induction and it was utilised in an elegant formal synthesis of (−)-wilforonide.



Scheme 102.

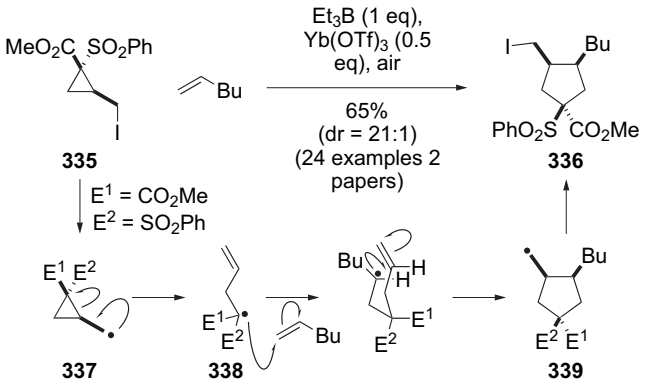
Xanthates, and related groups, are good precursors for group-transfer reactions and this has been exploited in an elegant synthesis of functionalised lactams. The formation of carbamoyl radicals from xanthates is relatively simple, but, unfortunately, access to the prerequisite carbamoyl xanthate is problematic. Grainger has overcome this limitation by utilising *N*,*N*-diethyldithiocarbamates as replacements for the xanthate moiety.[197] The cyclisation precursor **333** was readily prepared from the corresponding carbamoyl chloride and the commercially available sodium diethyldithiocarbamate, and underwent radical cyclisation to the lactam **334** in high yield (Scheme 103). Four-, five-, six- and eight-membered lactams could all be formed in moderate-to-excellent yields (37–96%). An improved protocol for the preparation of the radical precursors has been applied to the formal synthesis of (−)-aphanorphine.[198] This methodology highlights both the power of radical-transfer reactions as a strategy for the efficient elaboration of simple structures into useful intermediates and the value of *N*,*N*-diethyldithiocarbamates as attractive alternatives to the more common xanthates.



Scheme 103.

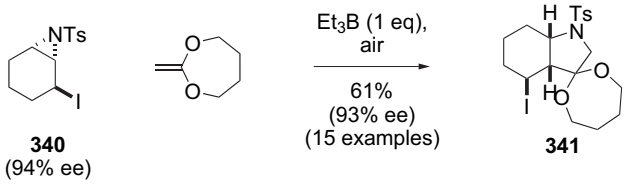
The ring opening of the cyclopropylcarbinyl radical to give homoallylic radicals forms the basis of a powerful strategy for the preparation of cyclopentanes by a formal [3+2] cycloaddition. Whilst this general reaction has been known for a number of years,[199] it has only recently been refined. A highly diastereoselective cyclisation of the disubstituted cyclopropanes **335** has been developed (Scheme 104).[200] This methodology generates functionalised cyclopentanes **336** with up to three stereocentres. Treatment of **335** with triethylborane in the presence of a Lewis acid abstracts the iodine to give the cyclopropylcarbinyl radical **337**, which rearranges to **338**. A radical addition–cyclisation sequence then furnishes the primary alkyl radical **339**, which acts as the chain carrier and abstracts an iodine to give the product **336** and regenerate **337**. The ytterbium(III) triflate is necessary for good yields, but does not affect the diastereoselectivity of the reaction. The reaction can be performed with electron-rich and electron-poor

alkenes, as well as 1,1-disubstituted alkenes and ketene acetals. The ytterbium Lewis acid required for the reaction of neutral alkenes is unnecessary with electron-rich alkenes and is in fact detrimental to the reaction of ketene acetals. It is thought that the Lewis acid may increase the reactivity of the homoallylic radical simply by making it more electrophilic or it is possible that coordination to the ester moiety increases the rate of iodine abstraction. The methodology has been extended to permit a radical cascade that forms two rings in one step by reacting a cyclopropylcarbinyl radical precursor analogous to **335** with either a 1,4-diene or a 1,4-enyne.[201]



Scheme 104.

A comparable methodology employs *N*-tosyliodoaziridines and permits the synthesis of pyrrolidines.[202] The reaction works for a range of electron-rich alkenes including enol ethers, ketene acetals and simple alkyl-substituted alkenes. A number of different iodoaziridines can be employed in the reaction including bicyclic examples such as **340**, which allow the rapid synthesis of hydroindoles such as **341** (Scheme 105). This reaction can be performed utilising enantiomerically pure aziridines to generate enantiomerically enriched products. It is apparent that some racemisation is observed, but the degree to which this occurs is dependent on the nature of the alkene coupling partner; racemisation is believed to occur by the abstraction of the active allyl hydrogen to give a captostabilised radical. The rate of this reaction will be dependent on the stability of the initial adduct radical.



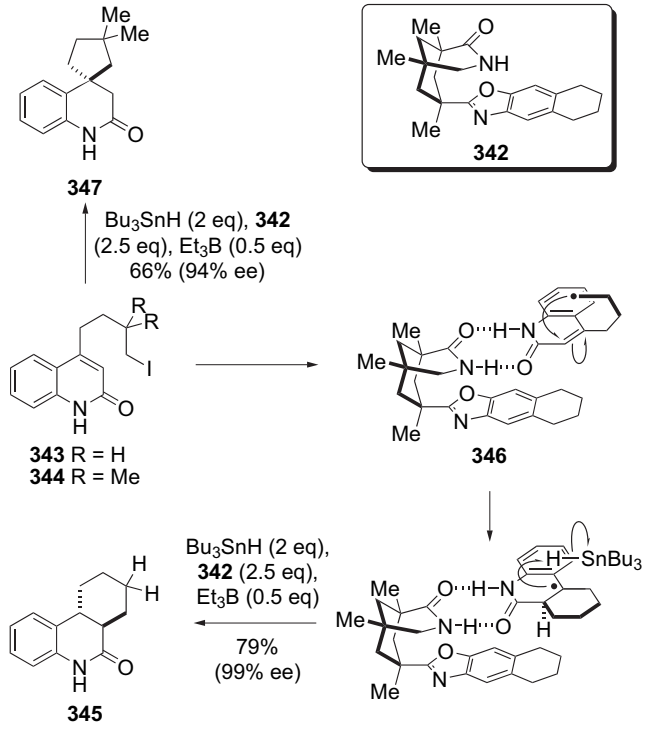
Scheme 105.

Atom- and group-transfer radical reactions are useful reactions for the formation of complex molecular architectures. The retention of functionality in the molecule after cyclisation is a clear advantage over conventional radical processes. Due to the different rates of reaction for radical cyclisations versus transfer processes, tandem reactions are possible, allowing the formation of multiple carbon–carbon bonds in 'one pot.' The potential of these systems is extremely high, especially due to the enantioselective variants now possible via chiral Lewis acid catalysis (see Part 1, Section 3.1.2., 3.1.4. and Part 2, Section 2.9.).

2.9. Stereoselective cyclisations

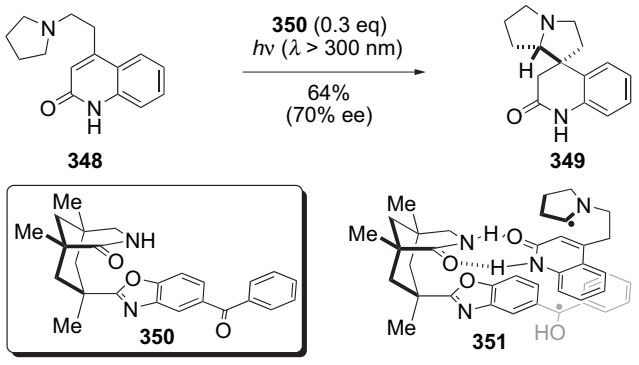
It now seems superfluous to comment on the fact that radicals can participate in highly selective reactions; radicals are simply organic molecules subject to the same influences as ionic reactions and therefore many examples show exquisite control of regio-, chemo- and stereoselectivity. Many excellent reviews cover this material, including reports on diastereoselective radical reactions,[203] enantioselective radical reactions,[204] asymmetric additions to C=N bonds,[205] stereoselective conjugate additions[206] and organocatalysis in radical chemistry.[207] An issue of *Tetrahedron: Asymmetry* was dedicated to stereoselective radical reactions.[208] Chiral catalysis in free-radical chemistry is still relatively scarce and the high reactivity of radicals makes non-selective background reactions a constant issue. Most enantioselective radical reactions require a stoichiometric quantity of chiral additive and, whilst great advances have been made to overcome this limitation in intermolecular additions, enantioselective cyclisations are both much harder and less well studied.

In all areas of chemistry, the use of organic molecules as catalysts (organocatalysts) and reagents is becoming increasingly popular, and radical chemistry is no exception. One of the most fascinating examples is the chiral lactam **342**, which has been employed as a hydrogen-bond donor catalyst in a host of reactions including the cyclisation of iodides **343** and **344** (Scheme 106).[209] The reaction of unsubstituted **343** (R=H) furnishes **345** in excellent yield and selectivity. Lactam **342** binds to **343** by complementary hydrogen bonding between the carbonyl and N–H moieties (**346**), thus controlling the face of the radical addition. Whilst superstoichiometric quantities of **342** gave the best selectivity (2.5 equiv gave 99% ee), the use of sub-stoichiometric amounts still resulted in chiral amplification, with just 0.1 equiv affording **345** in 55% ee The correct choice of solvent is pivotal for high enantioselectivities in the catalytic variant; the reaction mixture must be heterogeneous throughout the reaction, with the substrate dissolving only on complexation with **342**, thus forcing cyclisation to occur in a chiral environment. A dramatic change in regioselectivity was observed when the dimethylated precursor **344** (R=Me) was used and the cyclisation gave the spiro compound **347** exclusively in good yield and stereoselectivity.



Scheme 106.

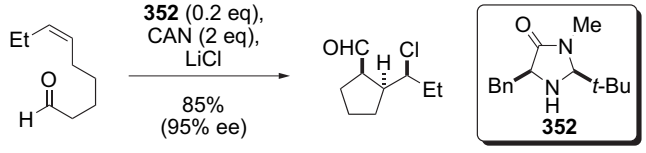
An exciting variation on this system has permitted a highly enantioselective, catalytic, photoinduced electron-transfer reaction that furnishes tetracycle **349** (Scheme 107).[210] Key to the success of this reaction is the catalyst **350** that acts as both the chiral template and an antenna for harvesting the light required to activate the substrate. Excitation of **350** expedites electron transfer from the amine **348** to **350** and permits the formation of the α-aminoalkyl radical **351**. Cyclisation of the complexed radical **351** occurs from the top face, as the catalyst blocks the bottom face of the alkene. Just 0.3 equiv of **350** are required for the reaction to occur in high yield and enantioselectivity. The simplicity of this methodology and its use of just two reagents coupled with the rapid increase in molecular complexity ensure that this methodology has a bright future.



Scheme 107.

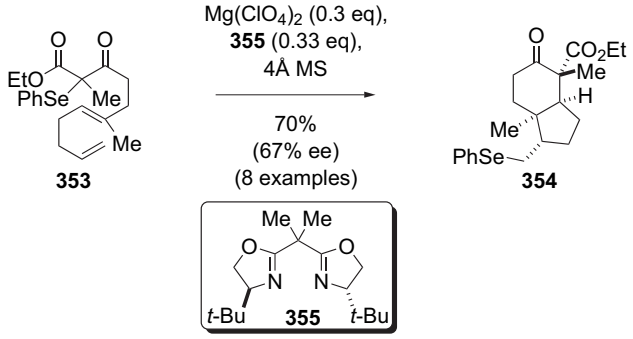
Lactam **342** has been employed in a number of other radical cyclisations[211] and both inter- or intramolecular [2+2]-photocycloaddition reactions.[212] It will be very interesting to see if other hydrogen-bond donors can be used as Lewis acid catalysts in radical reactions, especially considering that one of the first uses of a urea as a Lewis acid was in a radical reaction[213] and as such donors are known to function in aqueous media. A review of chirality control in photochemical reactions has recently been published.[214]

MacMillan has reported an exciting enantioselective radical cyclisation that is mediated by a sub-stoichiometric quantity of a chiral imidazolidinone **352** and a super-stoichiometric amount of the oxidant, diammonium cerium(IV) nitrate (CAN) (Scheme 108).[215] The full potential of this new methodology is discussed in greater detail in Part 1, Section 3.1.4.



Scheme 108.

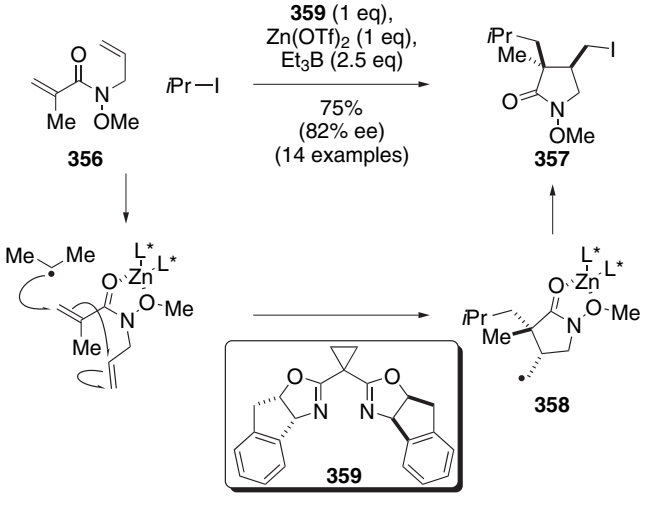
Lewis acid-promoted atom/group-transfer reactions (see Section 2.8.) are ideally suited to the development of catalytic enantioselective cyclisation. One of the earliest examples of a catalytic enantioselective radical cyclisations was a phenylseleno transfer–cyclisation protocol. Selective mono-cyclisation occurs, even with a sub-stoichiometric quantity of Lewis acid (0.3 equiv) formed from $Mg(ClO_4)_2$ and bis(oxazoline) **355**; there is only a slight drop in enantioselectivity, compared to the stoichiometric variant.[216] It is essential that 4 Å molecular sieves are included in the catalytic version of the reaction; without this additive, the reaction is too sluggish to be practical. All substrates employed in the reaction are α-methyl-α-phenylseleno substituted β-ketoesters; without the methyl substituent, the substrates are relatively unstable. This methodology permitted one of the first examples of an asymmetric radical cascade. The diene **353** readily participates in two consecutive cyclisations to give **354** in good yield and moderate enantioselectivity (Scheme 109).



Scheme 109.

The same group have also achieved similar atom-transfer radical cyclisation cascades with α-bromo-β-ketoesters.[217] It is hard to draw a definitive pattern with these reactions, as they appear to be substrate specific; optimum ligand, Lewis acid and solvent all vary, depending on the size and number of rings being formed, as well as the nature of the substituents. More intriguing is the effect of 4 Å molecular sieves, which reverses the enantioselectivity of the reaction; unfortunately, there is no explanation for this observation.[217,218] Overall, it appears that selenides generally give better yields and enantioselectivities than bromides. A diastereoselective variant, employing a chiral oxazolidinone auxiliary, has also been reported.[219]

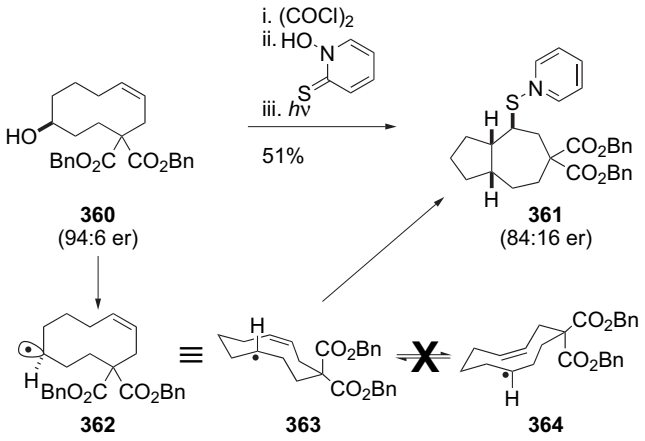
Even though enantioselective cyclisations have received far less attention than their intermolecular counterparts, it is still surprising to find that 2006 saw the first report of an enantioselective tandem reaction sequence involving both inter- and intramolecular steps.[220] In this reaction, a range of hydroxamate esters, such as **356**, underwent a radical addition–cyclisation–atom-transfer sequence to furnish chiral γ-lactams, **357** (Scheme 110). Hydroxamate esters were chosen as the cyclisation precursors to facilitate bidentate co-ordination to the chiral Lewis acid, formed from zinc(II) triflate and **359**, and formation of rigid chelates that controlled rotamer population. The structure of the *N*-alkoxy substituent is crucial, with groups larger than methyl inducing lower enantioselectivity. For efficient chain propagation, it is important that a primary radical **358** is formed after cyclisation and



Scheme 110.

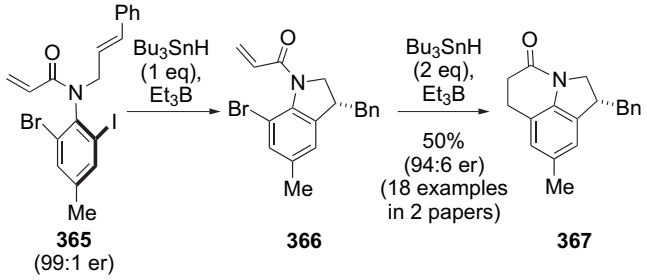
that the initial alkyl halide is either a secondary or a tertiary halide. If these caveats are not met, iodine transfer becomes problematic. The potential of this reaction is self-evident; a remarkable three bonds are formed including a tertiary and a quaternary stereogenic centre.

An intriguing concept that can be employed in enantioselective radical reactions is the 'memory of chirality.' In such reactions, the chirality of the starting substrate is preserved, even though the reaction passes through a configurationally labile intermediate. As the rate of reaction of many radicals is faster than the rate of many common conformational changes, it is possible for chiral radicals to react faster than they racemise. Rychnovsky has investigated the transannular cyclisation of radical **362** formed by the deoxygenation of alcohol **360** (Scheme 111).[221] The in situ formation of an oxalate is followed by photolysis and cyclisation to give **361** in moderate yield. The reaction proceeds via a 5-*exo*-*trig* cyclisation with a remarkable 90% chirality transfer. Presumably, it is essential for the initially formed secondary radical to be non-stabilised, thus encouraging cyclisation to be faster than racemisation through 'ring flipping' (**363**↔**364**) of the cyclodecenyl ring.



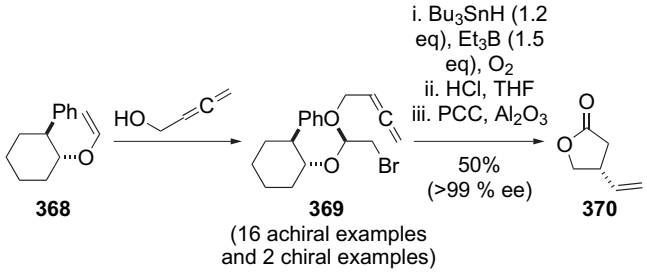
Scheme 111.

Curran has also utilised the concept of 'memory of chirality' to convert axial chirality into centrochirality. Aryl amides with two *ortho*-substituents can exist as stable atropisomers at room temperature and radical reactions can occur faster than N–Ar bond rotation. Therefore, it is possible to form an aryl radical and achieve transfer of chirality to the new stereocentre before racemisation of atropisomers. In initial studies, Curran utilised a methyl group as the second *ortho*-substituent, the first being the iodide radical precursor, and this resulted in an impressive >90% chirality transfer.[222] Unfortunately, the methyl group restricts the variety of compounds that can be formed and was therefore replaced with either a trimethylsilyl moiety or a bromine atom, thus incorporating a temporary substituent. This more general methodology allowed up to 96% chirality transfer during cyclisation.[223] The bromide **366** incorporated in this methodology can participate in a second radical reaction and, thus, in 'one pot,' *N*-acryloyl *N*-cinnamyl precursor **365** underwent a double cyclisation to give tricyclic product **367** in good yield (50%) and with excellent chirality transfer (94%; Scheme 112). The reaction proceeds with complete regioselectivity via 5-*exo*-*trig* cyclisation followed by the slower 6-*endo*-*trig* cyclisation. Aryl amides missing the second *ortho*-aromatic substituent *can* still be employed in these reactions if care is taken.[224] Mono-*ortho*-substituted anilides can be resolved and, in many cases, have a half life of several hours. Each atropisomer undergoes radical cyclisation with little racemisation. Therefore, rapid treatment of a resolved *ortho*-anilide permits the transient chirality to be locked into a new stereogenic centre on cyclisation. This suggests that it may be possible to perform dynamic kinetic resolution of such species if the reaction were to be performed in the presence of the correct chiral Lewis acid.



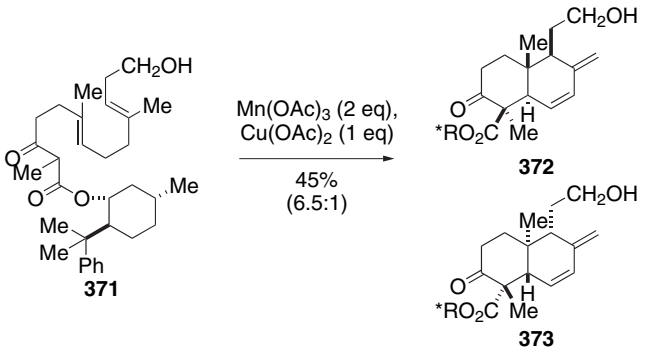
Scheme 112.

The most common strategy for the synthesis of enantiomerically pure compounds in radical chemistry is the use of chiral auxiliaries and these reactions have been covered in previous reviews.[203,204,205] Two very different examples are worth discussing. The first involves the Ueno-Stork radical 5-*exo* cyclisation of bromoacetals in the synthesis of γ-lactones. Diastereoselective variants of this reaction are well known, with the selectivity normally controlled by the allylic alcohol stereocentre and rationalised by the Beckwith-Houk model; the acetal stereocentre is largely ignored. Renaud has revealed that, in many cases, this is a simplification and that the acetal stereocentre influences the diastereoselectivity.[225] In an elegant example, enol ether **368**, containing a chiral auxiliary, is transformed into separable acetal diastereoisomers **369** (Scheme 113). Diastereoisomer **369** was then cyclised to give, after hydrolysis and oxidation, **370** in 50% yield (for three steps) and an impressive >99% ee The selectivity can be rationalised if the alkoxy auxiliary of the acetal is assumed to adopt the axial position of a chair-like transition state. Presumably, this maximises the anomeric stabilisation. Renaud showed that the structure of the anomeric substituent does not affect the stereochemical outcome of the cyclisation and thus, it can be assumed that the auxiliary's role is over after the formation of **369**. Computer modeling was also performed to investigate the selectivity in more detail and to confirm the importance of the anomeric effect on the favoured conformation of the cyclisation precursor.[226] This model was later used to permit the stereoselective preparation of (−)-botryodiplodin.[227]

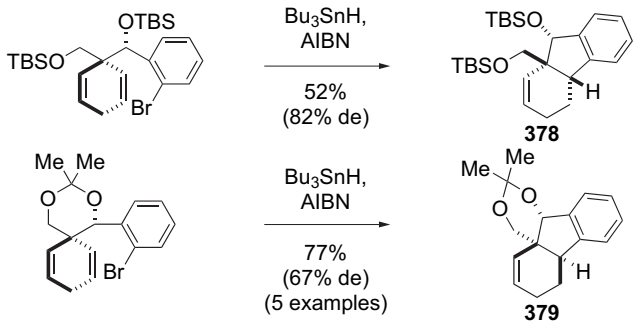


Scheme 113.

The second example highlights one of the advantages of manganese(III)-mediated cyclisations. As the precursors are often β-ketoesters, they permit chiral auxiliaries to be readily incorporated.[228] Under standard conditions, i.e., acetic acid as solvent at 25 °C, **371** undergoes bicyclisation to give **372** and **373** with low selectivity (2:1), but, by changing the solvent to methanol, the reaction could be performed at 0 °C and the selectivity improved considerably (6.5:1; Scheme 114).



Scheme 114.



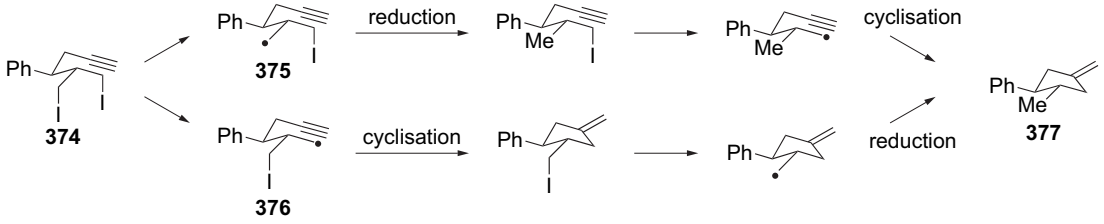
Scheme 116.

Curran has introduced a very different concept for diastereoselective cyclisation, namely, stereocontrol at the steady state in which two radical *precursors* compete for one acceptor, as opposed to the traditional approach that employs one precursor and two acceptors.[229] Under these conditions, the stereoselectivity of the radical cyclisation of the acyclic dihalide **374** is not due to two competing stereoisomeric transition states, but is the result of the two stereoisomeric intermediates **375** and **376** undergoing different chemical reactions (Scheme 115). For brevity, only the two pathways leading to the major diastereoisomers are illustrated. For stereoselection to occur, the initially formed radicals **375** and **376** must undergo either reduction or cyclisation at different rates. As long as **375** undergoes reduction more rapidly than cyclisation and **376** undergoes faster cyclisation compared to reduction, then both pathways will give the same diastereoisomer **377** as the major product. The results show that it is possible to achieve reasonable, predictable selectivities by extending the principles of the Beckwith–Houk model and open up the possibility of a new method for the introduction of chirality into a molecule.

Radical cyclisations are amongst the most thoroughly studied radical reactions. The diastereoselectivity of most cyclisations is understood, yet catalytic enantioselective radical cyclisations remain elusive. This situation is gradually being ameliorated and it is anticipated the next decade will see many more examples of such transformations.

2.10. Radical cyclisations of heteroatom-centred radicals

In the preceding section, C-centred radicals were employed to synthesise complex cyclic structures. Many of these reactions utilised heteroatom-centred radicals as reagents for initiation or chain propagation, yet heteroatom-centred radicals are rarely used to form bonds to carbon. The paucity of examples is starting to come to an end, as more thermodynamic and kinetic data for the reactivity of such species are becoming available. Reviews covering the use of N-centred[232] and O-centred[233] radicals in C–X bond formation give a more detailed analysis of this area, as does a review on the use of inorganic radical reagents.[105]



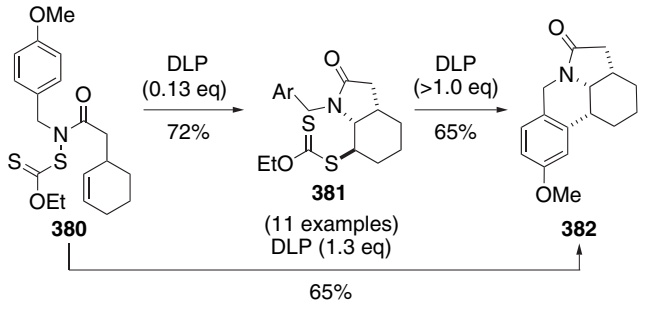
Scheme 115.

It has long been understood that hexenyl radicals bearing a large substituent on the radical carbon cyclise to give 1,2-*trans*-substituted cyclopentanes, unlike most other hexenyl radical cyclisations, which favour the *cis* product; it was thought that eclipsing strain disfavoured the normal *cis* selectivity. Curran has disproved this long-held notion in a comprehensive study of such cyclisations and it now appears that the early work in this area may have mis-assigned the configuration of the original products.[230] As such, this study shows that there are very few exceptions to the generalisation that hexenyl radicals bearing 1-substituents cyclise with *cis* selectivity.

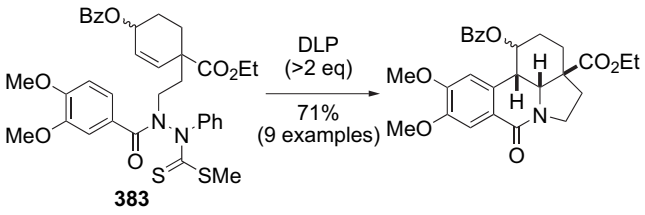
Diastereoselectivity in radical cyclisations has been comprehensively studied over the last two decades, but there are still many applications of this knowledge yet to be explored. The desymmetrisation of cyclohexadiene systems offers a rapid entry into highly functionalised carbocyclic systems. Whilst investigating the cyclisation of aryl radicals on to cyclohexadiene rings, it was found that the conformation of the cyclisation precursors could be altered simply by changing the protecting groups utilised, thus permitting one diol to be converted into either diastereoisomer of the tricyclic product (**378** vs **379**; Scheme 116).[231] Such flexibility from a single precursor shows great potential for divergent synthesis.

2.10.1. Cyclisation of N-centred radicals. The cyclisation of nitrogen-centred radicals is undoubtedly the most studied reaction for C–X bond formation. This popularity arises from nitrogen's valency, which allows multiple substituents and thus enables modulation of the radical's reactivity with relative ease. The addition of the N–H bond across an alkene is problematic, as it is almost thermoneutral. This shortcoming can be overcome by the use of high-energy amidyl radicals. Such amide-derived N-centred radicals have found more synthetic utility than their aminyl or amine-derived radical counterparts. The reasons for the popularity of amidyl radicals are twofold; firstly, they are more electrophilic than aminyl radicals and therefore react more readily with alkenes. Secondly, there are more methods for their generation and the precursors are often more stable. Even so, there is little kinetic data for amidyl radical reactions, a situation, that is, only slowly being ameliorated.[234] Unfortunately, the majority of *N*-radical precursors are still relatively unstable and difficult to prepare. Xanthates are being investigated as a potential solution to these shortcomings. Radical precursors, such as **380**, can be prepared from bis(ethoxythiocarbonyldisulfane) and cyclise in good yield with only sub-stoichiometric quantities of dilauroyl peroxide (DLP) to give the γ-lactam **381** (Scheme 117).[235] An advantage

of the xanthate methodology (see Part 1, Section 2.10.3.) is that transfer of the xanthate moiety permits further elaboration and, thus, tricycle **381** can be converted into the tetracycle **382** in good yield by a second radical reaction. Alternatively, **380** can be transformed in to **382** directly without the need to isolate **381**. The xanthate can be replaced by a thiosemicarbazide, as in **383**; these are more readily prepared and are more stable (Scheme 118).[236]

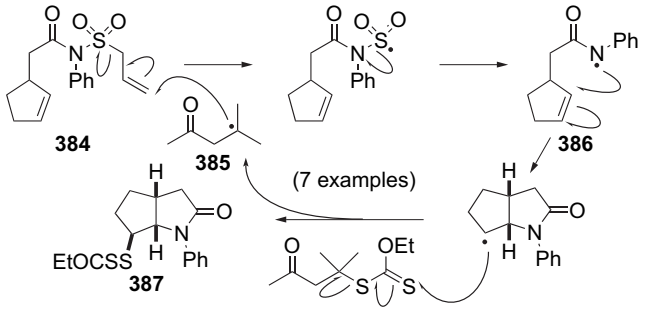


Scheme 117.



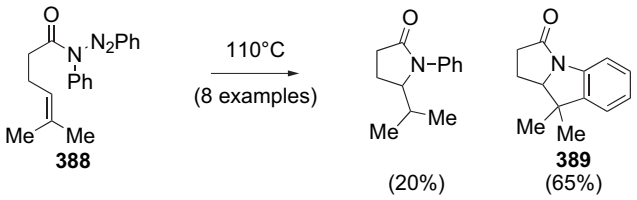
Scheme 118.

Xanthates have also been utilised in the generation of amidyl radicals from *N*-allylsulfonamides, such as **384** (Scheme 119).[237] In this methodology, the xanthate is a precursor for the alkyl radical **385**, which is required for the addition–fragmentation sequence that generates the amidyl radical **386**. Cyclisation followed by xanthate-group transfer furnishes the product **387** and perpetuates the chain mechanism. For selective activation of the *N*-allyl sulfonyl moiety, a nucleophilic tertiary alkyl radical, like **385**, is necessary; less nucleophilic radicals hinder the extrusion of sulfur dioxide and result in the formation of cyclic sulfonamides. Furthermore, the choice of substituent on the nitrogen is also important; alkyl groups inhibit sulfur dioxide extrusion, resulting in varying amounts of cyclic sulfonamide. The phenyl substituent encourages the formation of the desired lactams, presumably due to the increased stability of the N-centred radical **386**. Whilst this strategy has yet to be optimised, the ease of formation and the stability of sulfonamides make them promising precursors for amidyl radicals.



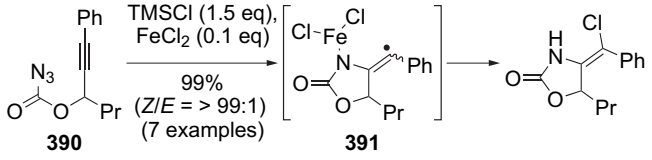
Scheme 119.

N-Acyltriazenes are potentially good precursors to amidyl radicals;[238] they can be prepared in a 'one pot' process by reacting primary amines with arenediazonium salts and then treating the resulting intermediates with an acyl chloride. They are stable at reflux in benzene, but cleanly decompose to give nitrogen, an aryl radical and the desired N-centred amidyl radical when heated to 110 °C. Simple monosubstituted alkenes readily cyclise to give five-membered rings in good yields, but precursors containing an internal alkene, such as **388**, give complex product mixtures that normally favour tricyclic compounds, such as **389** (Scheme 120). The propensity for a second cyclisation is due to the stability of the secondary or tertiary radical formed in the initial step. Whilst the methodology appears promising, it is currently limited to the formation of five-membered rings; six-membered rings are conspicuous by their absence.



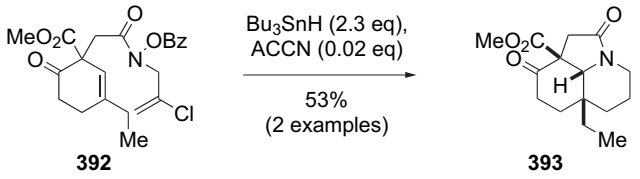
Scheme 120.

Acyl azides are readily prepared and provide an excellent source of amidyl radicals. Treatment of simple 2-alkenyloxycarbonyl azides with catalytic iron(II) chloride and trimethylsilyl chloride results in clean cyclisation, furnishing 4-chloroalkyl substituted oxazolidinones.[239] The power of this methodology is highlighted by the intramolecular chloroamination of alkynes such as **390** (Scheme 121). The addition of N-centred radicals on to alkynes is uncommon. In this work, consistently high yields are achieved, with a preference for the *Z* configuration, due to quenching of the thermodynamically more stable alkenyl radical **391**. An analogous methodology has permitted a high-yielding and practical method to convert carboxylic acids directly into pyrrolidinones via a 'one pot,' two-step process involving acyl azide formation–amidyl radical cyclisation.[239,240] The temperature must be kept below 0 °C or Curtius rearrangement of the azide prior to amidyl radical formation becomes a competing process. Unfortunately, whilst this methodology offers an elegant route to useful heterocycles, it still exhibits a number of limitations; it appears that only five-membered rings can be formed and tandem bicyclisations are too slow to compete with radical capture by the reagents.



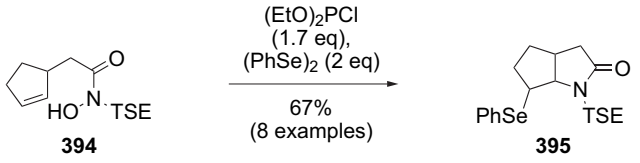
Scheme 121.

Hydroxamic acid derivatives are effective radical precursors for the synthesis of γ-lactams. Zard has employed such species in an elegant cascade radical cyclisation that rapidly constructs the core of (±)-aspidospermidine.[241] Treatment of **392** with tributyltin hydride generates an N-centred radical that undergoes a 5-*exo* cyclisation followed by a 6-*endo* cyclisation to give **393** (Scheme 122). It is essential that there is a chlorine atom on the alkene in order to control the regiochemistry; in its absence, only a pyrrolizidine structure, formed by two consecutive 5-*exo* cyclisations, was isolated. The use of the chlorine as a directing group permitted this methodology to be extended to allow a cascade 5-*exo*–7-*endo*-cyclisation sequence to prepare the core of the *Stemona* alkaloids. A similar methodology was also employed in the synthesis of (±)-13-deoxyserratine; once again, the presence of a chlorine substituent on the terminal alkene was essential to ensure 6-*endo*-cyclisation over the alternative 5-*exo* process.[242] It is clear that alkenyl halides permit exquisite regiochemical control in many radical cyclisations.



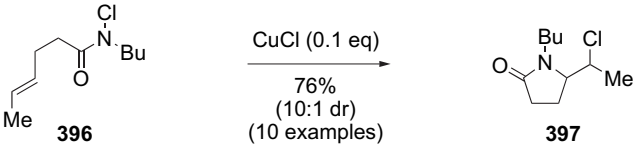
Scheme 122.

Weinreb has devised an efficient 'one pot' functionalisation–cyclisation of β-tosylethyl-protected (TSE) hydroxamic acids, such as **394**, to prepare lactams **395** (Scheme 123).[243] Treatment of **394** with diethyl chlorophosphite in the presence of diphenyl diselenide generates a phosphite that undergoes spontaneous homolysis to form the amidyl radical that cyclises to give, after quenching the product **395**. A variety of mono-, bi- and tri-cyclic lactams can be prepared in good yield, showing the general utility of this methodology. The ease of this methodology is only tempered by the use of unpleasant reagents such as diphenyl diselenide.



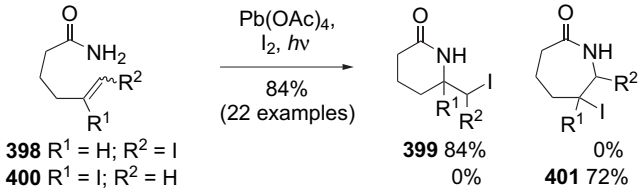
Scheme 123.

Copper(I) catalysts can be utilised in the ATRC of N–Cl precursors. The copper reagent plays multifarious roles in the reaction; it acts as the radical initiator, activates the N-centred radical to electrophilic attack and scavenges the carbon radical formed upon cyclisation. Treatment of a range of chloroamides (**396**) with copper(I) chloride in methanol results in excellent yields of the γ-lactams **397** (Scheme 124).[244] Low yields were only obtained with two substrates, one in which the amide carbonyl is *exo* to the ring and the other, which involves an internal carbamate. In both cases, unfavourable conformation/rotamers are blamed for the reduced yield. This operationally simple method for the formation of lactams compares favourably with other radical approaches. Nitrogen–halide bonds are frequently unstable and can be formed in situ; an elegant example of this approach is found in the synthesis of γ-lactams by Li.[245]



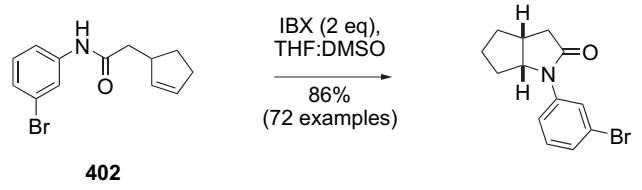
Scheme 124.

Whilst the high reactivity of amidyl radicals is normally advantageous, it can cause diminished regioselectivity. The addition of a halogen substituent to the pendant alkene radical acceptor can greatly improve the regioselectivity of cyclisations (see Scheme 122).[246] For example, photolysis of iodide **398** in the presence of lead(IV) acetate/iodine gave the 6-*exo* product **399** exclusively in an excellent 84% yield (Scheme 125). If the reaction was performed in the dark, a roughly 1:1 mixture of lactam **399** and lactone was observed. The lactone is formed by ionic cyclisation followed by hydrolysis and confirms the radical nature of the cyclisation that yields **399**. Simply altering the position of the iodide alters the mode of cyclisation; treatment of the internal iodide **400** results in 7-*endo* cyclisation to give **401**. Other halides can be utilised instead of the iodide, resulting in the synthesis of mixed halogen–halogen acetals.[247] This strategy permitted the first examples of both the 7-*exo* and the 8-*endo* cyclisation of an amidyl radical. Removal of the halide substituent from any of the previous examples results in reduced regioselectivity and contamination with the lactones formed via the ionic pathway.



Scheme 125.

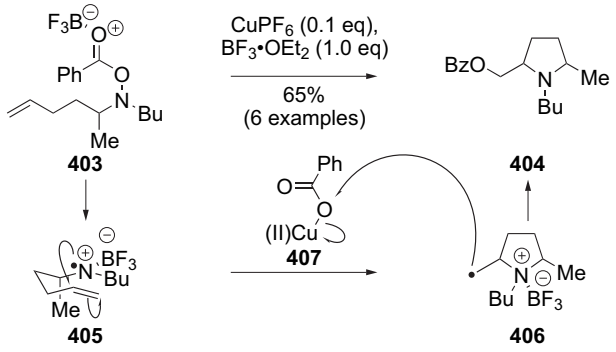
Nicolaou has shown that *o*-iodoxybenzoic acid (IBX) can be used to mediate the oxidative radical cyclisation of a broad range of *N*-aryl amides such as **402** (Scheme 126).[248] The reaction is operationally simple and does not require rigorously anaerobic or dry conditions. The efficiency of the reaction is independent of the functionality on the *N*-aryl ring; electron-rich, electron-deficient and sterically demanding substrates all undergo cyclisation. Mono-, di- and tri-substituted alkenes are all effective substrates, but electron-deficient alkenes fail to cyclise, confirming the electrophilic nature of amidyl radicals. In this study, the only prerequisites for successful cyclisation were that the molecule contained an *N*-aryl group with a free *ortho* position and an *N*-carbonyl moiety; thus, appropriately substituted amides, ureas and carbamates will undergo cyclisation, whilst all other functionalities fail. Furthermore, the methodology is limited to 5-*exo*-*trig* cyclisations; attempts to produce other ring sizes met with failure. The reaction is believed to proceed via an SET process, resulting in the oxidation of the aryl amide group. It is postulated that THF is vital for this process and activates IBX by coordinating to the iodine atom, thus forming a strong oxidant, and provides the final source of hydrogen atoms to terminate the reaction. Studer has shown that *N*-alkoxyamides undergo a similar reaction.[249] An acetyl-protecting group was found to be vital for activity; all other protecting groups failed to give the desired products. This system allowed both 5-*exo* and 6-*exo* cyclisations to occur. Clearly, the direct generation of amidyl radicals from an N–H bond is an attractive process that bypasses the need to synthesise specific radical precursors.



Scheme 126.

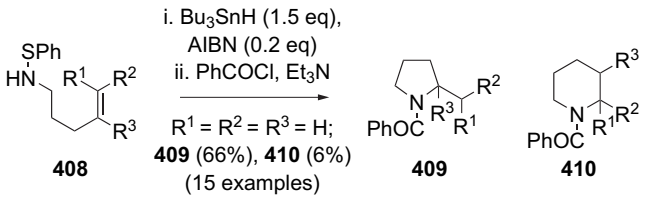
Aminyl radicals have not been studied as comprehensively as their amidyl counterparts. The reason for this disparity stems from the relatively unreactive nature of neutral aminyl radicals. In fact, most cyclisations reportedly involving simple N-centred radicals are not aminyl radicals at all but aminium radicals, in which the nitrogen is coordinated to a Lewis or Brønsted acid. Aminyl radicals are nucleophilic, whilst aminium radicals are electrophilic and thus react with neutral alkenes. One of the most attractive examples of the cyclisation of an aminium radical involves a catalytic aminohydroxylation process (Scheme 127).[250] Overall, the reaction is a radical group-transfer cyclisation mediated by a combination of copper(I) catalyst and stoichiometric Lewis acid. The Lewis acid is believed to have two roles; it complexes the benzoyloxy carbonyl oxygen **403**, activating the N–O bond, and it co-ordinates the resulting N-centred radical **405**, facilitating cyclisation. The

copper(I) catalyst is required to reduce the N–O bond, furnishing the desired aminyl radical and a copper(II) complex **407**. Subsequently, aminium radical formation and cyclisation generate an alkyl radical **406**, that is, oxidised by the copper(II) species to give **404**. Performing the reaction without the copper(I) species or with a conventional radical initiator such as AIBN suppresses the reaction and results in the recovery of the starting material. This suggests that whilst the process is radical and not ionic, the copper species more than just a simple initiator and is an integral reagent in the oxidation process. *N*-Chloroamines have been employed in an analogous reaction and used to prepare piperidines.[251] The reaction is believed to proceed via 5-*exo*-atom transfer to give a pyrrolidine that rearranges through an aziridinium ion to give the final product. As with all radical transfer reactions, the atom economy of these transformations is highly attractive and it is curious that further reports on this reaction have not been forthcoming.



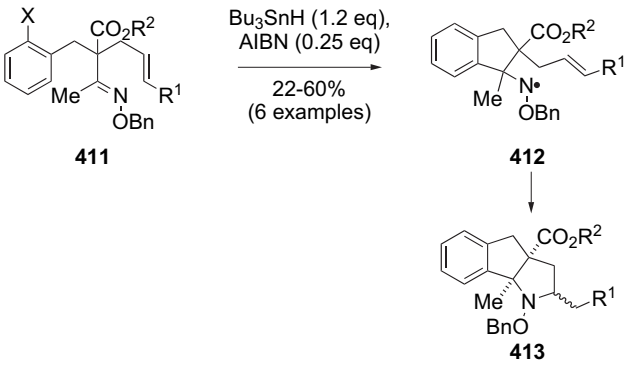
Scheme 127.

Surprisingly, the cyclisation of *primary* aminyl radicals has garnered scant investigation. It appears that such radicals are far more effective than their secondary aminyl counterparts; benzenesulfenamide **408** readily undergoes cyclisation and gives a mixture of **409** and **410** in good overall yield (Scheme 128).[252] These reactions almost certainly proceed via aminyl radicals and not aminium species. The nature of the internal substituent (R^3) on the alkene has a profound effect on the regiochemistry of the cyclisation. As the size of this substituent increases, so does the preference for 6-*endo* cyclisation to give **410**. Interestingly, if a phenyl group is present, then no 5-*exo* cyclisation is observed. This is an electronic effect, rather than a steric interaction, as 4-chloro analogues all preferentially form the piperidine **410** as well. The addition of terminal substituents gives exclusively the product of 5-*exo* cyclisation. This methodology adds to the repertoire of radical routes to nitrogen heterocycles and will undoubtedly see use in total synthesis. It would be interesting to see if the aminyl radicals could be generated without tin.



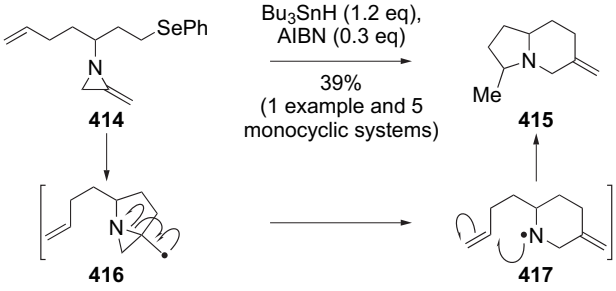
Scheme 128.

Aminyl radicals can be formed as a result of radical addition to a nitrogen-containing functionality. This is best illustrated in the cascade radical reactions of aryl halides **411** to give tricycles **413** (Scheme 129).[253] Reaction of aryl halide **411** with either tributyltin hydride/AIBN or triethylborane/oxygen results in the formation of an aryl radical that can undergo two possible reactions; it can cyclise on to either the pendant alkene to furnish a carbocycle or the oxime ether. The latter reaction predominates, due to the increased radiophilicity of oximes and the kinetic favourability of 5-*exo* cyclisations versus 6-*endo* cyclisations. If the alkene is activated (R^1=electron-withdrawing group), then the neutral alkyl oxyaminyl radical **412** adds to the alkene to give **413** in moderate yield. If the substituent (R^1) is electron donating, then a 1,5-hydrogen transfer process results in quenching of the aryl radical. These results suggest that the neutral alkyl oxyaminyl radical is nucleophilic. Whilst the current methodology has not been fully optimised, it is the first example of the intermolecular capture of an alkyl oxyaminyl radical and it clearly displays the potential of this methodology for the synthesis of complex alkaloid structures.



Scheme 129.

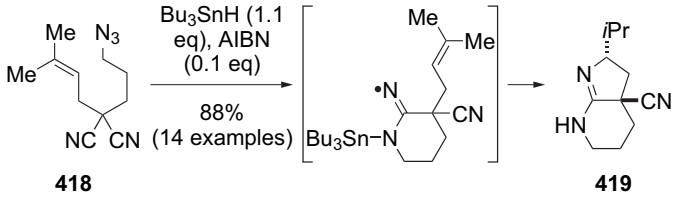
Highly strained 2-alkylidenaziridines can be utilised in the generation of aminyl radicals by a radical rearrangement mechanism and this has permitted an elegant entry into the indolizidine alkaloid framework.[254] Crucial to the success of this methodology is the use of the phenylselenide group as the alkyl radical precursor **414**; other precursors do not survive the harsh reaction conditions required to form the 2-alkylidenaziridine. Formation of the indolizidine core is achieved via a radical cyclisation–rearrangement–cyclisation cascade (Scheme 130). *Exo*-cyclisation of the initial radical gives the primary radical **416**, which undergoes rearrangement with C–N bond fission to release the ring-strain energy found in the fused aziridine and generate the aminyl radical **417**. Finally, a second 5-*exo* cyclisation gives the indolizidine **415**. The low yield is believed to arise from difficulties encountered in the isolation and purification of **415** and not the radical cascade. Cyclisation–rearrangement to form piperidine rings is efficient, but attempts to form larger, azepane rings proved futile, due to a disfavoured radical cyclisation on to the 2-alkylidenaziridine.



Scheme 130.

Azides are a powerful radical functionality, as they can act as both acceptors and as precursors. Stannyl radicals readily add to azides to give, after loss of nitrogen, *N*-stannylaminyl radicals. Metallated aminyl radicals are more reactive than neutral aminyl radicals,

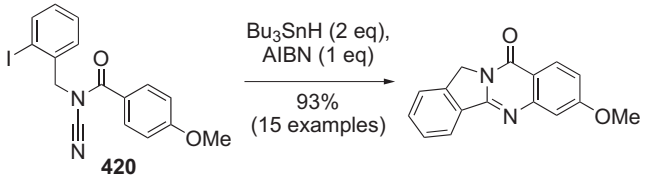
showing increased nucleophilicity, and will add to nitriles permitting the development of an efficient method for the formation of amidines.[255] Azide **418** undergoes a radical cascade involving both nitrile and alkene acceptors to give the bicyclic amidine **419** (Scheme 131). The efficiency of the second cyclisation appears to be governed by the stability of the resultant alkyl radical; terminal alkenes fail to cyclise, due to the instability of the final primary radical.



Scheme 131.

Indium(III) chloride and triethylsilane have been employed in a more environmentally benign variant of this reaction.[256] A wide range of aromatic azides can be cleanly reduced to amines in excellent yields, whilst alkyl azides give lower yields. The methodology displays a wide functional-group compatibility, selectively reducing the azide moiety in preference to cyano, iodo and ester groups. The nitro group is partially reduced under standard conditions (0 °C), but this side reaction could be curbed if the temperature is lowered to −20 °C. Once again, highly efficient cyclisation on to nitriles furnishes cyclic amidines in excellent yields. Cyclisation is independent of the nature of the azido and/or cyano moieties, with a range of both alkyl and aromatic derivatives giving yields of over 85%. The reaction does not need a radical initiator, but it is considerably faster in the presence of triethylborane, whilst the addition of a radical trap (TEMPO) results in inhibition of reduction. This lends credence to a radical pathway, although an ionic mechanism involving two separate SET processes cannot be ruled out. It will be interesting to see if this methodology can be employed in a cascade process similar to that shown in Scheme 131.

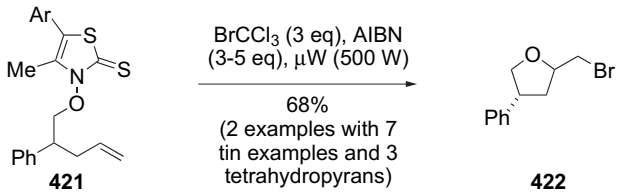
Iminyl radicals can also be prepared by the unprecedented cyclisation of aryl radicals on to *N*-acylcyanamides such as **420** (Scheme 132).[257] The iminyl radicals readily undergo cyclisation on to simple alkenes or aromatic rings.



Scheme 132.

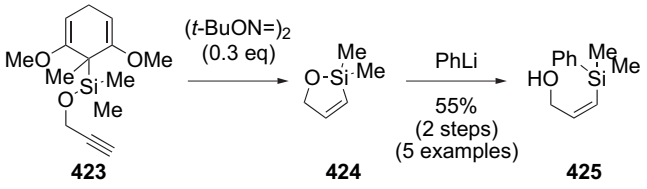
The cyclisations of N-centred radicals have been studied more comprehensively than other heteroatomic radicals, but there remains much to be achieved. The two main goals should be the development of more practicable radical precursors and an enantioselective cyclisation.

2.10.2. Cyclisation of other heteroatomic radicals. The cyclisation of other heteroatom-centred radicals has received less attention than their nitrogen-based counterparts. O-Centred radicals can be prepared from *N*-(alkoxy)thiazole-2-(3*H*)-thiones such as **421** to give tetrahydrofurans in moderate-to-good yield (Scheme 133).[258] For tin-mediated reactions, microwave heating not only accelerates the reaction, but also reduces the amount of reagent required from 4.0 to 2.5 equiv. The tin reagent can be replaced by water-soluble thiols or bromotrichloromethane; the latter reagent facilitates an atom-transfer process, so that functionality is not lost in the product **422** (Scheme 133). Once again, microwave activation was a major improvement over conventional modes of heating, requiring shorter reaction times and less trapping reagent. Additionally, it is compatible with both aqueous and organic solvents and does not require an inert atmosphere. 5-*Exo-trig* cyclisations of alkoxy radicals are relatively simple; 6-*exo-trig* cyclisations to give tetrahydropyrans are considerably harder, due to the reactivity of alkoxy radicals, which encourages 1,5-hydrogen transfer or β-fragmentations to compete. It is possible to overcome this limitation by removing the δ-hydrogen or by biasing the conformation of the cyclisation precursor to favour cyclisation over these side reactions.[259] An alternative method to encourage 6-*exo-trig* cyclisation is to incorporate a radical-stabilising group on to the alkene. Current applications of this strategy are promising but need to be improved if this methodology is to become more widely accepted.



Scheme 133.

Studer has investigated the use of cyclohexadiene-based radical precursors (see Part 1, Section 2.10.1.) as a means of generating silyl radicals for intramolecular hydrosilylations.[260] Cyclisation of silanes such as **423** was achieved using di-*tert*-butyl hyponitrite as initiator and proceeds in good yields, but the products are prone to hydrolysis; in situ treatment with phenyllithium gives stable alcohols such as **425** (Scheme 134). The reaction tolerates a variety of monosubstituted alkenes, but the yields decrease significantly with increasing alkene substitution. This methodology permitted the first example of a 5-*endo*-dig radical cyclisation to exclusively yield the *Z*-alkene **424**. The observed stereoselectivity rules out the possibility that the reaction occurs via an intermolecular pathway. An intermolecular variant of this reaction, for the hydrosilylation of alkenes, has been developed.[261]



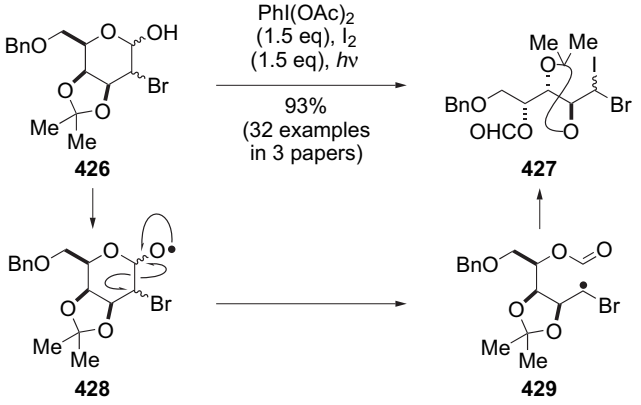
Scheme 134.

It is clear that considerably more research is required on the cyclisation of heteroatom-centred radicals.

3. Radical rearrangements and fragmentations

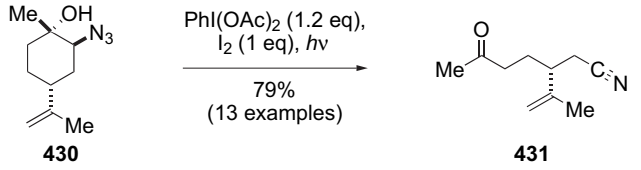
All the advantages of radical addition reactions are equally true of radical rearrangements and fragmentations including the ability to sequence such transformations in elegant reaction cascades and tandem processes. The fragmentation of alkoxy radicals with the attendant formation of a carbonyl group and an alkyl radical is the basis of a variety of productive rearrangements. Suárez has developed an elegant route to a range of functionalised carbohydrate derivatives based on the fragmentation of anomeric alkoxy radicals.[262] Halogen,halogen-acetals are valuable substrates, yet their synthesis is highly problematic with very few general methodologies existing.[247] Suárez's methodology permits the synthesis of virtually any combination of halogen acetal or mixed acetal (Scheme

135).[262] The precursors **426** are prepared from the 2-deoxy derivatives by halohydrin formation. Alkoxy radical fragmentation is instigated by treatment with (diacetoxyiodo)benzene, which presumably forms a hypoiodite intermediate that breaks down to give the radical **428**. Fragmentation results in the formation of **429** that can either be oxidised by the hypervalent iodine agent or trapped by iodine to give **427**. The latter reaction predominates, due to the electron-withdrawing nature of the C2 halogen substituent, which hampers oxidation. The reaction is incredibly versatile, tolerating esters, acetals, silyl ethers and ethers as protecting groups on the carbohydrate, as well as proceeding efficiently with both galactopyranose and glucofuranose derivatives. Not unsurprisingly, the reaction can also be applied to the synthesis of 1,1,1-trihaloalkyls simply by changing the starting material.[263] This methodology works equally well for the formation of 1-bromo-1-halo acetals.[264]



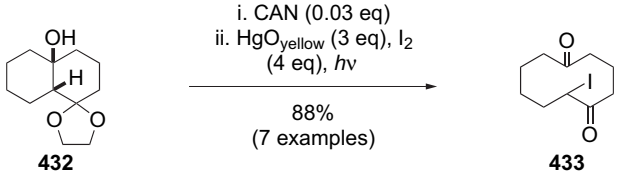
Scheme 135.

An extension of this methodology allows the preparation of chiral nitriles.[265] The reaction was initially established with carbohydrate derivatives, but is applicable to any β-hydroxy azide compound, such as **430** (Scheme 136). Fragmentation of the alkoxy radical leads to a ketone and an azide stabilised C-centred radical. The radical is oxidised by the hypervalent iodine to give a carbocation, which generates the nitrile **431** after deprotonation and loss of nitrogen. The methodology can also be applied to sequential radical fragmentation–intermolecular allylation to give highly oxygenated alkene substrates.[266] The power of the anomeric alkoxy radical fragmentation methodology arises due to the mild reaction conditions that tolerate a wide range of functionality coupled to the abundance of many different carbohydrate derivatives. The range of reactions that the resulting radicals can undergo further enhances this chemistry and it is anticipated that the methodology will see far greater use in the future.



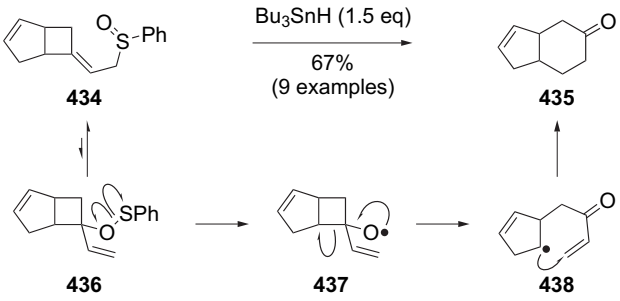
Scheme 136.

One of the most common uses of radical fragmentations in organic synthesis is in the preparation of medium-sized rings via ring expansion. A range of acetals, such as **432**, can be deprotected and then subjected to mercury-mediated fragmentation. The optimum reagents for the fragmentation are yellow mercury(II) oxide and iodine, which furnish α-iodoketones **433** in good yields (Scheme 137).[267] The relative stereochemistry of the fused bicycles is immaterial to the success of the fragmentation and the reaction permits the formation of nine-, ten- and eleven-membered rings. For the fragmentation of fused bicyclic six-rings, such as **432**, yellow mercury(II) oxide/iodine gave superior results to (diacetoxyiodo)benzene/iodine, but this preference was reversed for the expansion of fused bicyclic cyclobutanols.[268] It is not clear why these subtle differences arise.



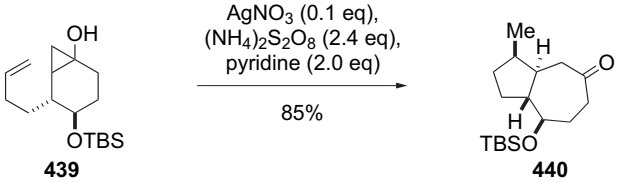
Scheme 137.

Intriguingly, most radical ring expansions are limited to either one-, three- or four-carbon expansions, with two-carbon expansions being conspicuous by their absence. One of the few exceptions is the sulfoxide-based methodology developed by Renaud.[269] In this reaction, the alkenyl sulfoxide **434** was converted into the ketone **435** in moderate yield (Scheme 138). The expansion occurs via a cascade process consisting of a [2,3]-sigmatropic rearrangement of the allylic sulfoxide to a sulfinate **436** followed by the formation of the alkoxy radical **437**. Fragmentation gives **438** that readily undergoes 6-*endo*-cyclisation. The regioselectivity of the ring expansion reaction is governed by the fragmentation step; if there is not sufficient difference between the stability of the two potential alkyl radicals, then no selectivity is observed.



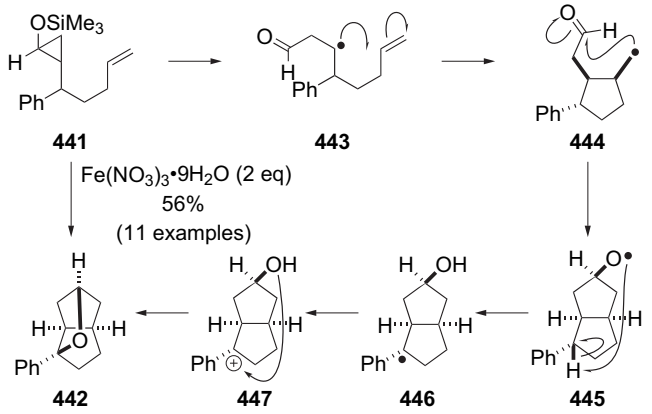
Scheme 138.

The fragmentation of cyclopropanols has long been known, but such methods invariably involve the use of a stoichiometric quantity of metal promoter. Narasaka has developed a silver(I) nitrate-catalysed variant for the generation of β-keto radicals[270] and has applied this in the synthesis of (−)-sordarin.[271] The use of substoichiometric silver(I) nitrate in conjunction with a stoichiometric *re*-oxidant formed from ammonium persulfate and pyridine permits the rearrangement to be efficiently scaled up. Utilising these new conditions, cyclopropanol **439** could be converted into **440** in high yield on a 10 g scale, thus making it possible to complete the total synthesis (Scheme 139). Once again, the key step is the fragmentation of an alkoxy radical to form a ketone, ring opening of the cyclopropane and the formation a C-centred radical. A comparable methodology utilising stoichiometric amounts of an iron(III) salt has been applied to the synthesis of (±)-kessane.[272]



Scheme 139.

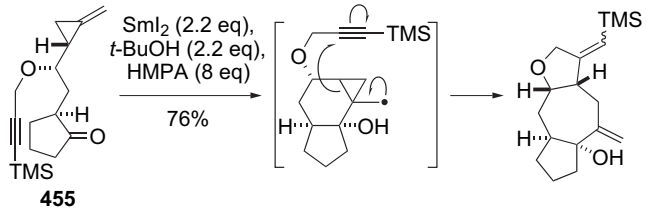
Cyclopropyl silyl ethers **441** can be employed in an interesting cascade that produces fused tricyclic compounds **442** (Scheme 140).[273] The reaction proceeds via fragmentation to give a β-keto radical **443** that undergoes 5-*exo*-*trig* cyclisation to **444**. This is followed by a cyclisation on to the carbonyl moiety to give a second alkoxy radical **445**. It is believed that 1,5-hydrogen atom abstraction then occurs to give a benzylic radical **446**, which is oxidised by excess iron(III) reagent to the cation **447** that undergoes cyclisation with the nucleophilic alcohol to give **442**. It is important that the reactions are run in an aprotic solvent to retard the reduction of radical **444** prior to the second cyclisation.



Scheme 140.

Alkoxy radicals can also be formed by the radical fragmentation of epoxycarbinyl radicals, such as **450**, and this has been employed in the elegant conversion of **448** into hydroazulene **449** (Scheme 141).[274] Methyl radical formation followed by epoxide ring opening generates an alkoxy radical **451** that undergoes β-cleavage to give the nine-membered ring **452**. Transannular addition of the newly formed radical yields an unstable primary radical **453** that reacts with the adjacent carbonyl to give a fused 3,6,5-tricyclic ring system **454**. Finally, a second alkoxy radical fragmentation gives **449**. The relative stereochemistry of the final product is independent of the epoxide stereochemistry as both stereocentres are destroyed in intermediate **452**. The reversibility of cyclopropane formation under radical conditions has often been used to bring about the ring expansion. Donohoe has utilised this property for the synthesis of tetrahydropyridines from pyrrolines.[275] The reaction proceeds via the formation of a primary radical that undergoes 3-*exo*-*trig* cyclisation followed by a retro 3-*exo*-*trig* reaction to give the six-membered ring.

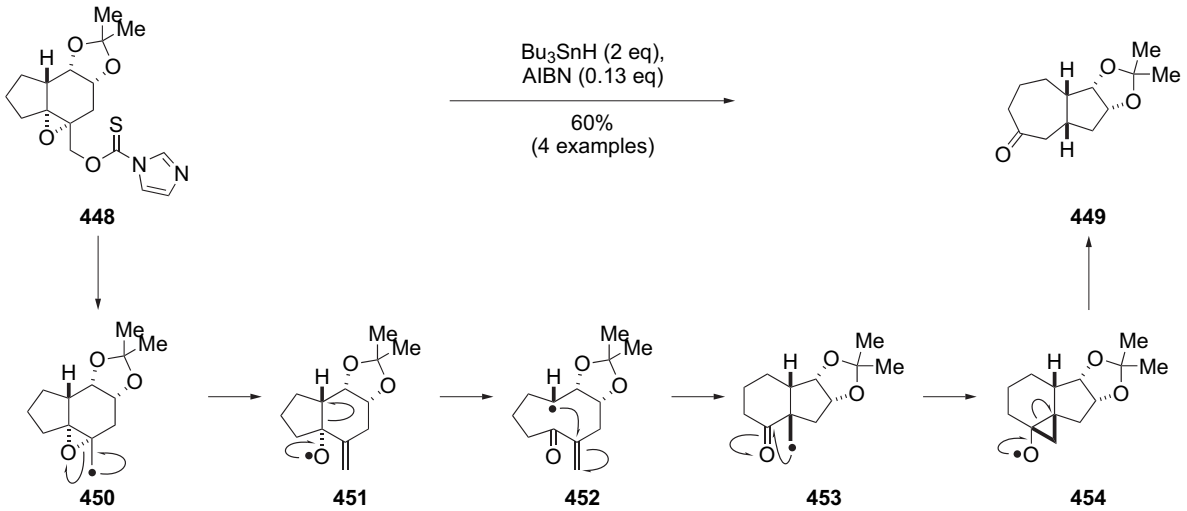
The rearrangement of cyclopropylcarbinyl radicals with its concomitant release of ring strain is a powerful driving force in radical reactions and has been incorporated into an interesting radical cascade involving 6-*exo*-*trig* cyclisation–ring expansion–5-*exo*-dig cyclisation (Scheme 142).[276] The problem with this, and comparable sequences, is that a number of competing processes, including direct reduction, hydrogen transfer and 7-*exo*-dig cyclisation, can occur. In fact, these reactions show a high stereochemical dependency and, of the four diastereoisomers of **455**, only the one shown gave a clean reaction. This dependency is true of other cyclisations on to the methylenecyclopropyl moiety and stems from the differences in the conformations that each diastereoisomer can adopt. An analogous methodology has been employed in the preparation of a bicyclooctane skeleton.[277]



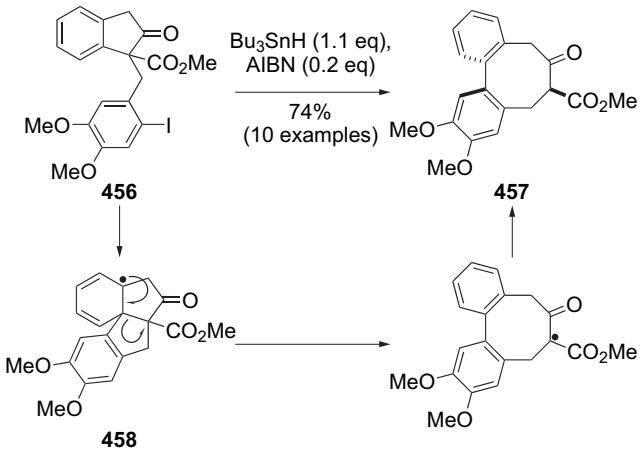
Scheme 142.

A beautiful example of a radical ring expansion as part of a cascade has been utilised in an approach to the stegane family of biaryl lignan natural products (Scheme 143). The radical formed from **456** smoothly cyclises on to the aromatic ring to give **458**, which fragments with concomitant *re*-aromatisation to generate the fused medium ring **457**.[278] It appears that the initial aryl radical must be electron rich; aryl iodides with alkoxy substituents participate cleanly in the reaction, whilst an unsubstituted aryl ring gives poor yields. Attempts to form higher analogues were less successful; starting from a tetralone, instead of the five-membered indanone, led to a mixture of the desired nine-membered ring and the tetracyclic product of cyclisation on to the *ortho* position. Presumably, the mixture arises because of the additional flexibility in the tetralone series, which permits the radical to approach the *ortho*-position.

Hodgson has extensively studied the radical rearrangement of azabicyclic systems and has found that the stability conferred to a radical by an adjacent nitrogen has a powerful directing effect on



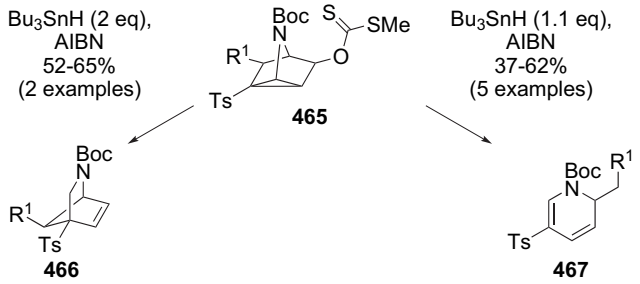
Scheme 141.



Scheme 143.

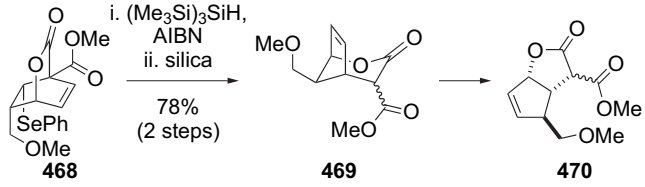
the selectivity of these skeletal reorganisations; an overview of this work was recently published.[279] A powerful tandem intermolecular radical addition–homoallylic radical rearrangement sequence has been developed for the synthesis of kanoid-like amino acids.[280] Alkyl radicals add in a highly regio- and stereoselective manner to the diene **459** (Scheme 144); addition is only observed on the *exo*-face of the sulfone-activated alkene. The resulting sulfone-stabilised radical **460** then undergoes homoallylic radical rearrangement to give the cyclopropane **461** that then partakes in β-cleavage/ring opening to generate first **462** and then the product **463**. The stabilising effect of the α-nitrogen on the C-centred radicals is important for controlling this rearrangement. Normally, only two out of a possible 16 products are observed; these are the non-rearranged product **464** and the desired product **463**. The ratio of the two compounds is strongly influenced by the bulk of the incoming alkyl radical, with sterically demanding groups resulting in a greater proportion of the non-rearranged compound. This probably arises due to the stereoelectronic requirement for the sulfone and alkyl group to be in an eclipsed conformation for rearrangement; obviously, this is less likely to occur the bigger the alkyl group. Simple non-activated bicyclic nitrogenous dienes undergo the same rearrangement upon treatment with alkyl or aryl thiols.[281] The homoallylic rearrangement has also been applied to the synthesis of dehydroisoquinuclidines, such as the alkaloid, (+)-ibogamine.[282]

1,2-dihydropyridines **467** are formed. This methodology demonstrates both the potential of radical rearrangements to generate valuable substrates and the sensitivity of these reactions to a range of factors that often make prediction of the final product difficult. Analogous chemistry has been applied to 7-azabenzonorbornadiene derivatives. The transformation requires harsher reaction conditions, due to the disruption of aromaticity, but it is a valuable route to tricyclic heterocycles.[281,284]



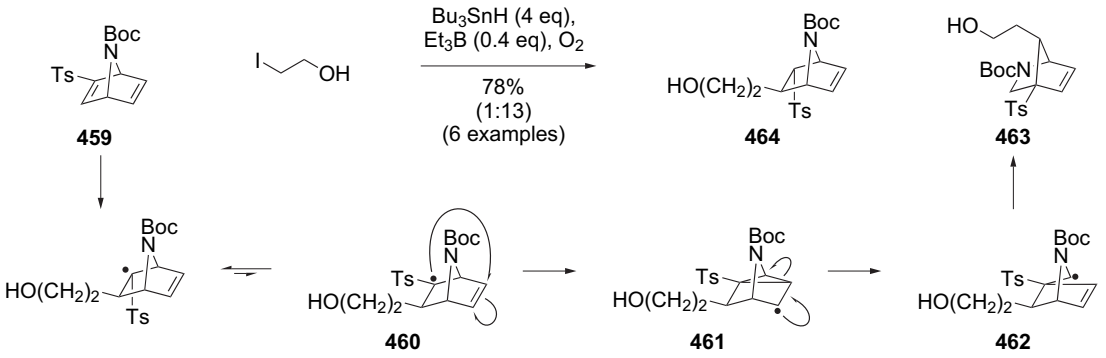
Scheme 145.

A related rearrangement has been used to prepare 'Corey's lactone.'[285] The precursor **468** is simply prepared by a Diels–Alder reaction,[286] and then treated with TTMSS to give **469** (Scheme 146). Simply stirring the bridged bicycle with silica gel results in acid-catalysed translocation to furnish the desired fused-ring system **470** in excellent yield. This is the key intermediate in a rapid, five-step, relatively high-yielding (40%) synthesis of 'Corey's lactone'.



Scheme 146.

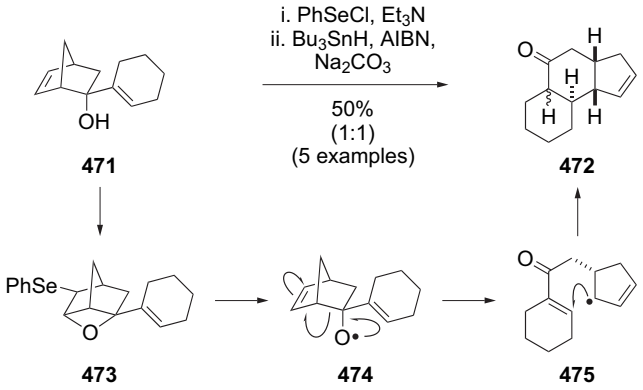
The anionic oxy-Cope rearrangement has emerged as a powerful tool in organic synthesis, but it is not without its limitations; this sigmatropic rearrangement requires the two double bonds to be in



Scheme 144.

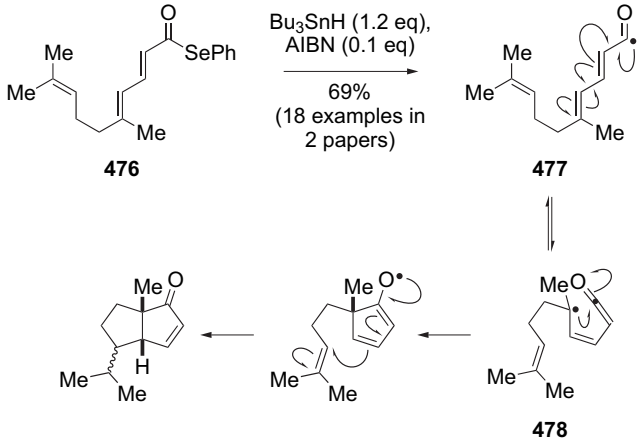
Related radical rearrangements, again based on the stability of α-*N* radicals, allow access to a number of other heterocyclic systems. Deoxygenation of **465** gives rise to either **466** or **467**, depending on the nature of the substituent R^1 (Scheme 145).[283] When R^1 is an alkyl group, radical deoxygenation gives the anticipated **466**, formed via β-elimination with concomitant cyclopropane ring opening. Alternatively, if R^1 is an aryl or an alkoxy group, close proximity and correctly oriented for successful transformation. In norbornenone derivatives, this can be problematic as addition of the alkenyl group to the ketone furnishes the wrong diastereoisomer (**471**). Whilst inversion of the stereochemistry is possible, this route is lengthy and low yielding. Radical fragmentation followed by isomerisation and 6-*endo*-*trig* cyclisation overcomes this shortcoming.[287] Alcohol **471** can be treated with phenylselenyl chloride to

afford a tricyclic selenide **473**, the key intermediate. The crude selenide **473** is reacted under standard tin conditions to give **472**, the formal product of the oxy-Cope rearrangement of **471** (Scheme 147). The reaction proceeds via β-elimination to give the alkoxy radical **474** followed by a second β-fragmentation to produce the allyl radical **475**; cyclisation of **475** yields the product **472**. The independence of this methodology on the relative stereochemistry of the starting material makes it a welcome addition to the canon of sigmatropic-like rearrangements.



Scheme 147.

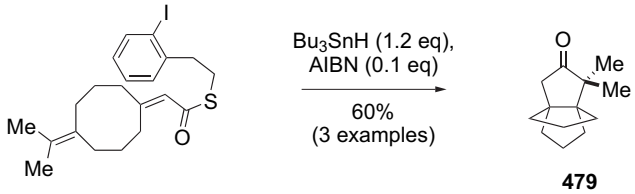
Pattenden has comprehensively studied the cyclisations of ketene radicals prepared by the rearrangement of conjugated acyl radicals or cyclopropyl acyl radicals.[71,288,289] A variety of mono-, bi- and tri-cyclic compounds can be prepared in quite remarkable yields, as demonstrated by the reaction of the α,β,γ,δ-unsaturated selenyl ester **476** (Scheme 148).[288] It is apparent that acyl radicals, such as **477**, only rearrange to ketene radicals **478** if the alkene (or cyclopropane) is substituted and, thus, can confer a degree of stability on the new radical. Ketones should be avoided as the stabilising group, as they can react via the O-centred enolate radical instead of the desired C-centred radical. Five-, six- and seven-membered rings can be prepared, as well as the tricyclic core of



Scheme 148.

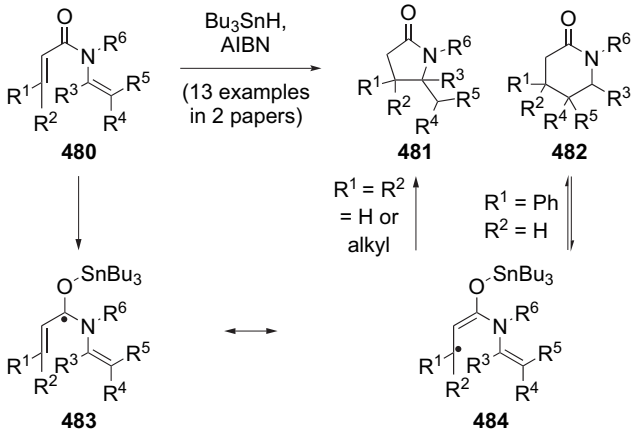
pentalenene, an angular triquinane, and modhephene, a propellane. The latter occurs via a 5-*exo-trig* cyclisation followed by a 5-*exo*-dig cyclisation on to the ketene to give **479** in 60% yield (Scheme 149).[289]

The high reactivity of radicals means that a number of productive pathways are frequently open to them. Therefore, it is important to 'tune' the electronics correctly to favour one route over another. The synthesis of either γ-lactams **481** [290] or piperidin-2-ones **482** [291] via either 5-*exo-trig* or 6-*endo-trig* cyclisation from



Scheme 149.

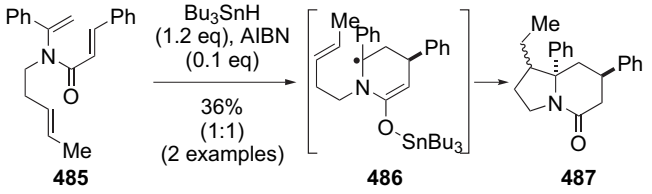
similar starting substrates **480** impressively illustrates this issue (Scheme 150). The key structural requirements for the successful synthesis of **481** via the 5-*exo-trig* cyclisation include a substituent at the β-position of the α,β-unsaturated amide moiety (R^1 and/or R^2), to prevent conjugate addition of the tin radical competing with the formation of the postulated *O*-stannyl ketyl radical **483**, and a radical-stabilising group at R^4 and/or R^5, to encourage 5-*exo-trig* cyclisation, whilst concurrently hampering 6-*endo-trig* cyclisation. Attempted cyclisation of **480** (R^1=R^2=R^3=H; R^4=R^5=Ph; R^6=Bn) results in a meagre 10% of the desired pyrrolidinone **481**; with the addition of a single methyl group to the α,β-unsaturated amide moiety (R^1=Me), the yield dramatically increases to 91%. The effect of substitution on the alkenyl group (R^4 and R^5) can be seen by comparing the yields of **481** (R^4=R^5=Me), **481** (R^4=Ph; R^5=H) and **481** (R^4=R^5=Ph), which are 64, 71 and 97%, respectively, thus indicating how increasing stability of the final radical improves the yield of 5-*exo-trig* cyclisation. For the formation of the six-membered ring **482**, it appears that a substituent is required at the α-position of the enamine moiety (R^3) to stabilise the radical formed from the 6-*endo-trig* cyclisation and to promote attack at the β-position on steric grounds. This is not sufficient to ensure 6-*endo* cyclisation however, and it is essential that there is a radical-stabilising group at the β-position of the α,β-unsaturated amide moiety (R^1=Ph). The preference for the formation of the six-ring can be explained if the cyclisation process is reversible (**484**↔**482**) and is governed mainly by thermodynamic control. Thus, judicious choice of the correct substituents allows either **481** or **482** to be formed. This methodology has been incorporated into a radical–ionic crossover sequence that permits the tin enolate to be employed in an aldol reaction.[290]



Scheme 150.

This chemistry has been incorporated into a radical cascade that allows two cyclisations and access to the indolizidine skeleton. Initial 6-*endo-trig* cyclisation of **485** results in the formation of the stabilised radical **486** that can undergo a 5-*exo-trig* cyclisation to give **487** as a mixture of epimers (Scheme 151).[291] These studies show that enamides of α,β-conjugated acids can easily undergo radical cyclisation to a variety of heterocyclic ring systems. It is clear that the substitution pattern of **485** has a profound influence on the

efficiency and regioselectivity of the cyclisations. Once again, the value of radical reactions for performing multiple bond-forming processes was illustrated in the synthesis of highly functionalised compounds.



Scheme 151.

Radical rearrangements allow rapid increase in molecular complexity; when this is combined with the propensity of radicals for sequenced and cascade processes, this opens the door to the synthesis of surprisingly elaborate compounds from simple starting materials.

4. Conclusions

Hopefully, this review has given an overview of the rich chemistry of radical cyclisations, fragmentations and rearrangements. The mild reaction conditions, in conjunction with the functional-group tolerance of radical reactions and their ability to be sequenced into both inter- and intramolecular multiple bond-forming processes, make radical chemistry a valuable tool in the synthetic chemist's repertoire, as demonstrated by the key role radical chemistry played in the synthesis of azadirachtin and other complex natural products.

Many chemists mistakenly believe that radical cyclisations are limited to the synthesis of normal, five- and six-membered rings, but this no longer the case; all ring sizes are accessible, from small strained rings such as cyclopropanes to macrocycles. Furthermore, the variety of both radical acceptors and donors that can be utilised in cyclisations is being rapidly expanded. Of particular interest are the radical variants of the Stetter reaction that allow the cyclisation of acyl radicals and the use of the carbonyl moiety and analogous groups as radical acceptors. Atom/group-transfer cyclisations should also be attractive to synthetic chemists, as these are effectively isomerisations and therefore retain functionality for subsequent elaboration. New and more efficient catalyst systems are continually being established; probably the most exciting of these is the use of Grubbs alkylidene catalyst in both cascade and multicomponent reactions. This, combined with the advent of enantioselective Lewis acid-catalysed ATRC, will ensure the continued growth of this field. Enantioselective cyclisations are amongst the most challenging radical reactions; whilst they remain underdeveloped, many exciting examples have been reported in recent years. Stereochemical induction using hydrogen-bond donors, as reported by Bach, is particularly attractive and it is anticipated that these scaffolds will see increased use along with the more accessible chiral (thio)ureas. Undoubtedly, enantioselective radical cyclisations mediated by MacMillan's enamine catalysts will be one of the next popular reactions to be exploited within radical chemistry. The cyclisation of heteroatom-centred radicals offers exciting possibilities and the author anticipates that a combination of these methodologies with enantioselective catalysis will soon be developed.

Radical fragmentations and rearrangements allow the conversion of simple starting materials into complex products. They are complementary to 'conventional' ionic and pericyclic reactions.

The two review articles have shown that radical chemistry is a vibrant avenue of research; its comparative immaturity when compared to the study of ionic processes means there is considerable scope for exciting new breakthroughs.[292] It is hoped that these articles inspire synthetic chemists to overcome their fear of single electrons and attempt some radical chemistry.

Acknowledgements

First and foremost, I would like to thank all my colleagues who have helped in the preparation of parts 1 and 2 of this review and the preceeding *Annual Reports*; these people have made me look far more competent than I deserve and include, in no particular order, Prof. Philip Page, Prof. William Motherwell, Associate Prof. Trevor Kitson and Prof. James Hanson. I am grateful to all the practising (it is a long time since I actually performed a radical reaction myself) radical chemists I have had contact with over the last few years for all the comments and advice (especially Mukund Sibi). Apologies to everyone I have forgotten and especially to those researchers whose work I have not included (shockingly, the review could have been much longer), or to those whose work I have included but I have failed to do justice to. Finally, Dr. Kate Arentsen for (a lot of) proof reading and everything else.

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Biographical sketch

Gareth J. Rowlands was born and raised in Horsham, West Sussex, UK. He obtained his first degree from Imperial College, London and stayed there to complete his PhD under the supervision of Donald Craig. In 1996 he joined Prof. Steven V. Ley's group at Cambridge University as a Royal Commission for the Exhibition of 1851 Research Fellow. After three years, he moved to Brighton to take up a lectureship in organic chemistry at the University of Sussex. Seven years and a few grey hairs later, he moved to New Zealand where he is currently enjoying life as a senior lecturer at Massey University. He loves chemistry a little too much to be healthy and, when forced to narrow his interests, he professes to be intrigued by enantioselective catalysis, organocatalysis, radicals and, of course, the chemistry of [2.2]paracyclophane. He cannot survive without music and has to acknowledge Resident in Brighton for feeding his addiction.