Recent progress in the generation and use of nitrogen-centred radicals†

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Nitrogen-centred radicals hold much promise as useful synthetic intermediates. Even though their popularity is still extremely limited and very far from matching that of carbon radicals, the recent development of various routes allowing their generation under mild conditions and a better appreciation of their reactivity thanks to the increased availability of absolute rate constants should encourage their use. It is hoped that this *tutorial review* will help increase the awareness of synthetic chemists and help revive the interest in these forgotten species.

1. Introduction

Despite the continuing popularity of radical reactions in organic synthesis, the field is far from being exhausted and much remains to be explored. Nitrogen-centred radicals, for instance, have not received the attention they deserve and their considerable synthetic potential has remained largely unappreciated.[1] Progress in this area has been slow, hampered hitherto by a dearth of convenient routes for generating these reactive species and a lack of awareness concerning their reactivity. The purpose of this *tutorial review* is to survey the main methods for creating and capturing nitrogen radicals, to provide an idea of their reactivity through the display of typical transformations, and to illustrate their utility with a few recent synthetic applications.

There are broadly two approaches for generating nitrogen radicals. The more general route involves the scission of a weak N–X bond, where X is a halogen (excepting fluorine), a nitrogen, an oxygen, or a sulfur group. Cleavage of the generally strong N–C bond is possible in special cases, such as in aziridinylmethyl radicals or in cyclohexadienyl systems, where aromatisation provides the necessary driving force. We shall also include in this category the less common, direct oxidation reactions, where an N–H bond is ultimately broken. The second strategy is indirect; it relies on a radical addition to an unsaturated nitrogen group such as a nitrile, an imine, an oxime, a hydrazone, or an azide. Only cases were the ensuing nitrogen radical is captured to produce a new C–N bond, and not merely reduced by hydrogen atom transfer, will be discussed.

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† This paper is dedicated with respect to Professor Steven M. Weinreb.

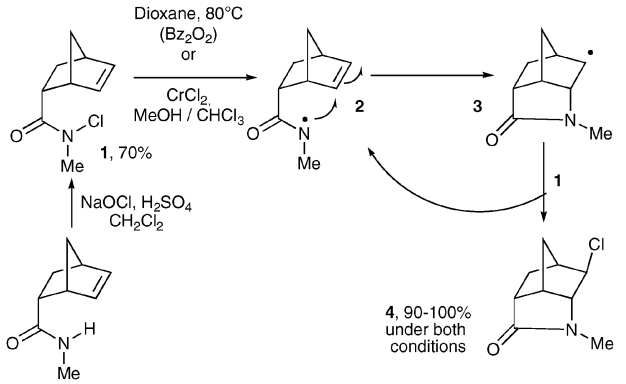
Samir Z. Zard was born in 1955 in Ife, Nigeria. His training as a chemist started at the American University of Beirut, then at Imperial College, London, and finally at the Université Paris-Sud, France, where he received his doctorate under the supervision of Professor Sir Derek Barton. His main research interests concern the study and development of new reactions and processes. In addition to a number of scientific awards, he received in 2007 the Croix de Chevalier de la Légion d'Honneur.

2. Methods for the generation of nitrogen-centred radicals

2.1 Cleavage of N–halogen bonds

N-Halo nitrogen derivatives have often been used as precursors to nitrogen radicals.[1] The photochemical or thermal decomposition of *N*-chloro amines in a strongly acidic medium, known as the Hoffmann–Löffler–Freytag reaction, is of historical importance, as it represents perhaps the earliest instance of a nitrogen radical generation. It is applied—very rarely now—to the synthesis of pyrrolidines by an initial abstraction of a hydrogen atom, even from an unactivated C–H bond. A milder, and synthetically much more interesting solution to the difficult problem of remote functionalisation of unactivated C–H bonds, one of several devised by Barton and his collaborators, is the photolysis of *N*-iodoamides.[2] The amidyl radical produced upon photolysis is sufficiently reactive to uproot the hydrogen atom without the need for activation with a strong acid.

Transformations whereby the intermediate nitrogen-centred radical generated from the *N*-halo precursor is captured with an olefin are often more easily accomplished by the use of a chemical initiator or suitable one-electron reducing agents. *N*-Chloro derivatives are most commonly used because of their ease of preparation and relative stability, as compared with their *N*-bromo and *N*-iodo analogues. Furthermore, *N*-chloroamines and *N*-chloroamides and related derivatives (*N*-chlorocarbamates, *N*-chlorosulfonamides *etc.*) are readily reduced with low-valent transition metal salts or complexes [*e.g.* Ti(III), Fe(II), Cu(I), or Cr(II)], and the free or metal-complexed (in the case of aminyls) nitrogen radical can be captured with a conveniently positioned internal olefin.[1] Much more rarely,



Scheme 1

an external olefin may be used as the trapping agent. Following ring closure or intermolecular addition, a halogen atom transfer normally takes place from the starting material to the intermediate carbon radical.

An example of such a chain process, taken from the extensive work of Lessard *et al.*, is pictured in Scheme 1.[3,4] In this example, the radical chain could be initiated with equal efficiency, either with chromous chloride at low temperature[3] or with benzoyl peroxide in refluxing dioxane.[4] The *N*-chloroamide precursor **1** is readily prepared by reaction of the parent amide with bleach in an acidic medium. Heating compound **1** in the presence of benzoyl peroxide triggers a chain process: carbon radical **3**, formed in the cyclisation step, exchanges a chlorine atom with *N*-chloroamide **1** to give product, lactam **4**, and the initial amidyl radical **2**, which can thus propagate the chain. The same amidyl radical **2** can be created by a one-electron transfer from chromous chloride.

The transformation outlined in Scheme 2, devised by Oshima and co-workers,[5] illustrates an annelation sequence where the first step is the intermolecular addition of a sulfonamide radical. The process is initiated by chlorine atom abstraction from compound **5** by ethyl radicals generated by autoxidation of triethylborane. Addition of the resulting sulfonamidyl **6** to styrene is followed by rapid ring closure to **7** and chlorine atom exchange with the starting material to give the expected pyrrolidine **8** in high yield. It is interesting to note that the starting material **5** was itself made by a radical chain addition of *N*,*N*-dichlorophenylsulfonamide to butadiene. Intermolecular additions of nitrogen radicals are relatively uncommon. In the case of nitrogen radicals with electrophilic character such as amidyls and sulfonamidyls, one complicating factor is their propensity for allylic hydrogen abstraction.

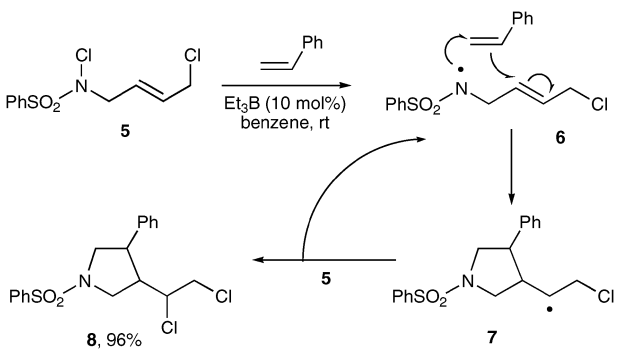
As stated above, *N*-bromo and *N*-iodo derivatives tend to be more reactive and more sensitive to handling. Furthermore, complications arising from unwanted ionic side reactions are not always easy to suppress. Their use in cyclisations has therefore been less extensive than the corresponding *N*-chloro compounds. In one recent report, a 5-*endo* ring-closure of amidyl radicals derived from *N*-iodoamides was put forward, but the evidence for the radical nature of the process is not incontrovertible.[6]

2.2 Cleavage of N–N bonds

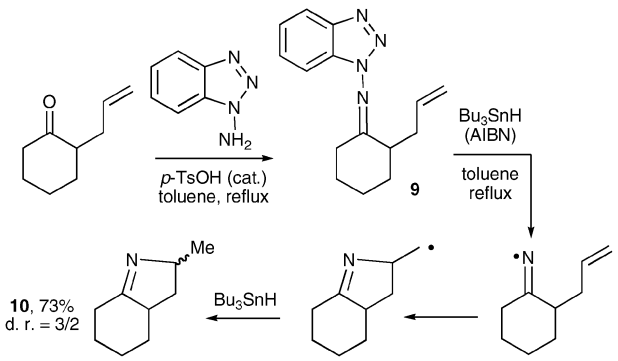
Several routes to nitrogen radicals rely on the rupture of the relatively weak N–N bond. One early approach, which has since been very seldom employed, consists in the photolysis with UV light of *N*-nitrosoamides.[7] More recently, El Kaim and Meyer discovered that imines derived from *N*-aminobenzotriazole were convenient precursors for iminyls through the action of stannyl radicals, generated in the usual manner from tributytin hydride.[8] The synthesis of pyrroline **10** from *N*-benzotriazolylimine **9**, which need not be isolated, is typical. The logical extension of this chemistry to the generation of other nitrogen radicals has not been established but appears feasible in principle (Scheme 3).

Azides react with stannyl radicals to produce stannyl-substituted aminyl radicals following loss of molecular nitrogen. An example, taken from the pioneering work of Kim *et al.* and displayed in Scheme 4, concerns the addition of tributylstannyl radical to azide **11** to provide radical **13**.[9] This species undergoes scission of the N–N bond to give a molecule of nitrogen and aminyl radical **14**. The latter closes onto the carbonyl group of the cyclobutanone, and the alkoxy radical **15** thus produced undergoes rapid ring opening. After aqueous work up, eight-membered ring lactam **12** is obtained in excellent yield.

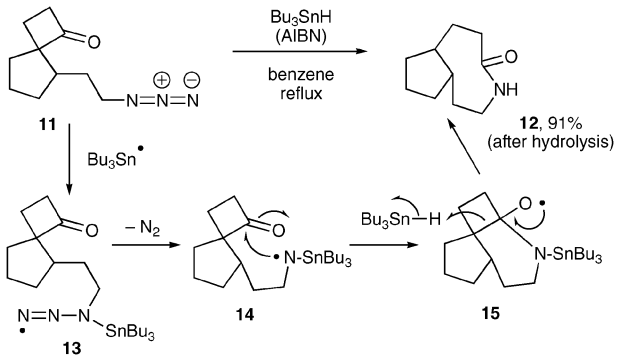
Another contrivance to create amidyl radicals hinges on the thermolysis, in refluxing toluene, of *N*-acyltriazenes such as **16**, as outlined in Scheme 5.[10] Cleavage of the weak N–N bond and loss of molecular nitrogen are again the main driving forces for this process, the generality of which is not clear since all the examples provided involve *N*-aryl derivatives. The ring closure is presumably followed by hydrogen atom abstraction from the solvent to give pyrrolidone **17** in the present case.



Scheme 2



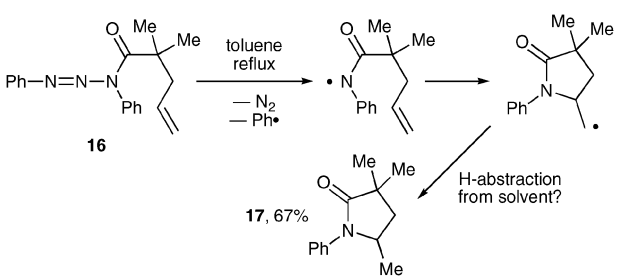
Scheme 3



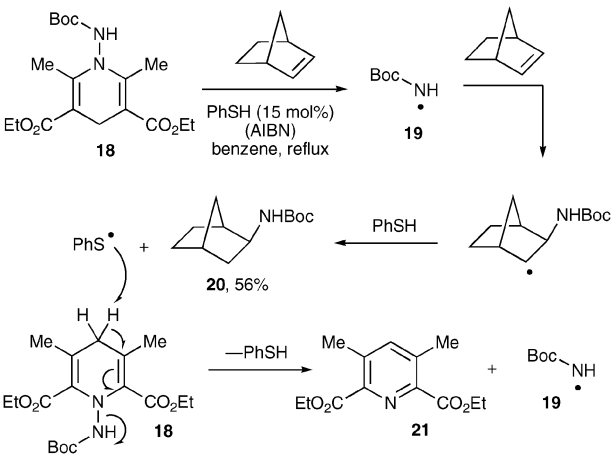
Scheme 4

Studer and co-workers disclosed very recently a more promising, and potentially quite general, approach to nitrogen-centred radicals.[11] It is based on the clever exploitation of the subtle effects that polar factors play on the reaction rate constants and on the strong driving force gained upon aromatisation to form a pyridine ring. The key reagent, dihydropyridine **18**, is trivially made in two steps on a large scale by an extension of the classical Hantzsch synthesis. In the hydroamination of norbornene leading to carbamate **20** pictured in Scheme 6, the step that creates the carbamyl radical **19** involves abstraction by a phenylthiyl radical of one of the two doubly allylic hydrogens in dihydropyridine **18**. This causes aromatisation into pyridine **21** through rupture of the N–N bond of the hydrazine moiety and formation of radical **19**. Thiophenol acts as a catalyst in the process: it is a fast reducing agent for most carbon-centred radicals and, at the same time, a better hydrogen abstractor in the present case because of its greater electrophilic character. The latter step regenerates the thiophenol and closes thus the catalytic loop. This principle of "catalysis by polarity reversal", as it is commonly called, deserves to be more widely appreciated by the synthetic community. In the present case, the desired transformation can be initiated thermally with a chemical initiator, such as AIBN, or by the use of Et_3B/O_2, or just simply by stirring under air, letting the slow aerial oxidation of thiophenol generate the needed starting thiyl radicals.

Thiosemicarbazides and thiosemicarbazones have proved to be very practical progenitors of various nitrogen radicals.[12] They are easy to prepare, can be used with standard stannane chemistry or sometimes under tin-free conditions, and the reactivity of the precursor may be modulated by modifying the substituents. The example in Scheme 7 shows the synthesis of the precursor and a typical 5-*exo* ring closure of an iminyl radical. Condensation of glucose-derived ketone **22** with thio-



Scheme 5

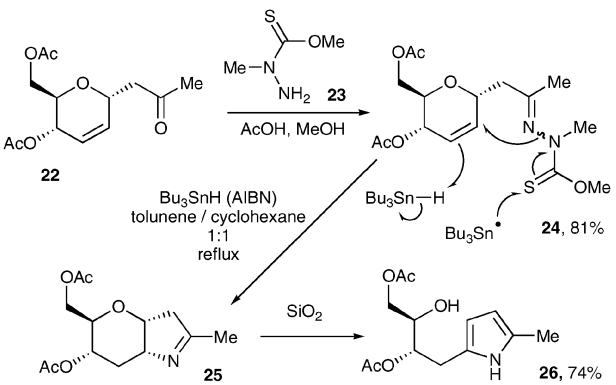


Scheme 6

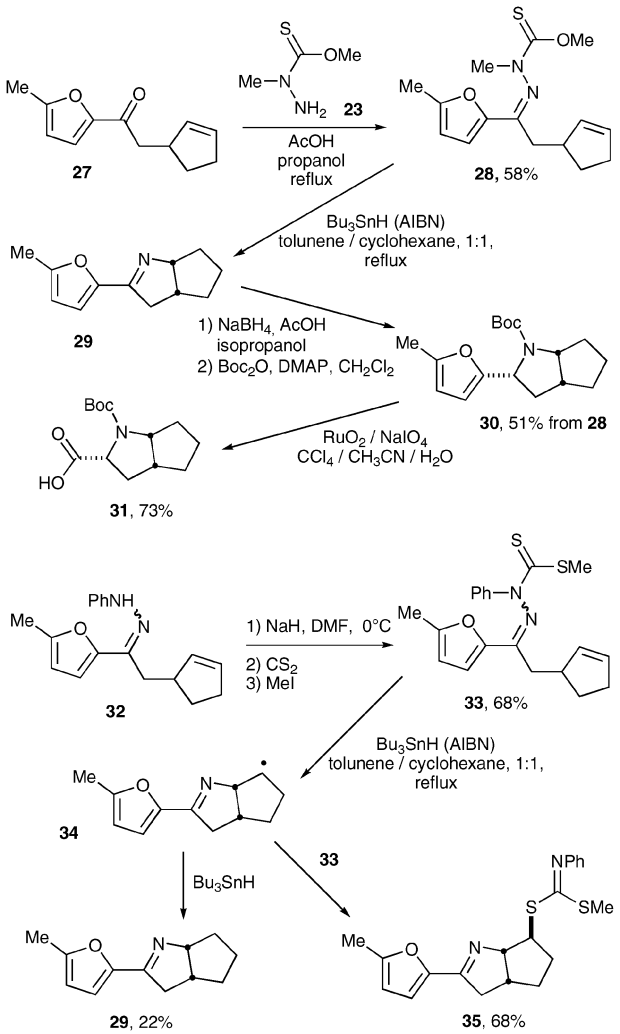
semicarbazide **23** furnishes cleanly carbazone **24**. Upon treatment with tributylstannane under the usual conditions, this material is smoothly converted into the expected pyrrolenine **25** which, in this particular case, is unstable towards chromatography on silica and is further transformed into the interesting pyrrole **26** in good overall yield.

In the sequence depicted in Scheme 8, the generation and ring closure of an iminyl radical is used to construct the bicyclic amino acid motif **31** found in the drug Ramipril, an angiotensine-converting enzyme inhibitor. Condensation of ketone **27** with thiosemicarbazide **23** requires more drastic conditions but furnishes nevertheless carbazone **28** in acceptable yield. Treatment of this compound with tributylstannane under the usual conditions leads to bicyclic pyrrolenine **29**, which is not isolated but selectively reduced from the *exo* face with sodium borohydride and protected as carbamate **30**. Finally, oxidative destruction of the furan ring gives the desired amino acid component **31** in good yield.[13]

Interestingly, when phenylhydrazone **32**, derived from the same ketone **27**, is subjected in sequence to base, carbon disulfide, and methyl iodide, another very convenient precursor to the iminyl radical is obtained. However, when dithiosemicarbazone **33** is subjected to the standard stannane treatment, the major product is not the expected pyrrolenine **29**, formed in only 22%, but rather the non-reduced derivative **35**, isolated in 68% yield.[13] In this case, the reaction of intermediate carbon radical **34** with dithiosemicarbazone **33**



Scheme 7

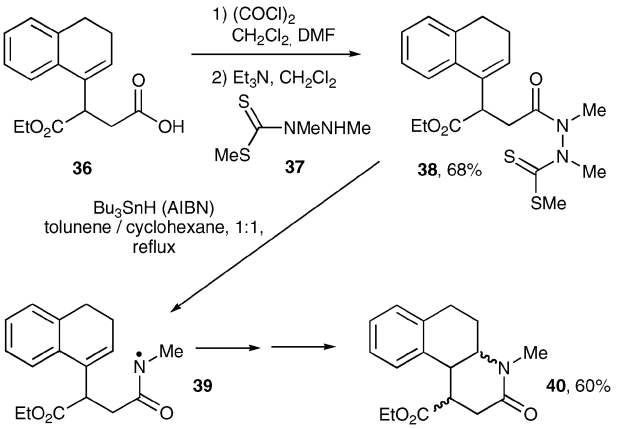


Scheme 8

becomes strongly competitive with respect to hydrogen abstraction from tributylstannane. This behaviour is not observed with precursor **28**, demonstrating the powerful influence of the substituents on the ease of transfer of the sulfur group.

The possibility of transfer of sulfur groups opens access to more densely functionalised structures.[14] The reaction can be carried out under tin-free conditions by using, for example, a peroxide as initiator, which is advantageous if the compounds are destined for biological testing and have to be free of heavy metal residues. Irradiation with a sunlamp in the presence of hexabutylditin is also effective in promoting the radical transfer process. The use of the distananne combats the formation of inhibitors and often ensures reproducibility.

The formation of amidyl radicals is also straightforward, owing to the ease of synthesis of the required precursors. One example is outlined in Scheme 9, starting from carboxylic acid **36**, a compound made in one step by a Stobbe condensation with 1-tetralone.[13] Dithiosemicarbazide **37** is also prepared in one step by treating 1,2-dimethylhydrazine with carbon disulfide and methyl iodide. Coupling of the two components to produce compound **38** is accomplished through the acid



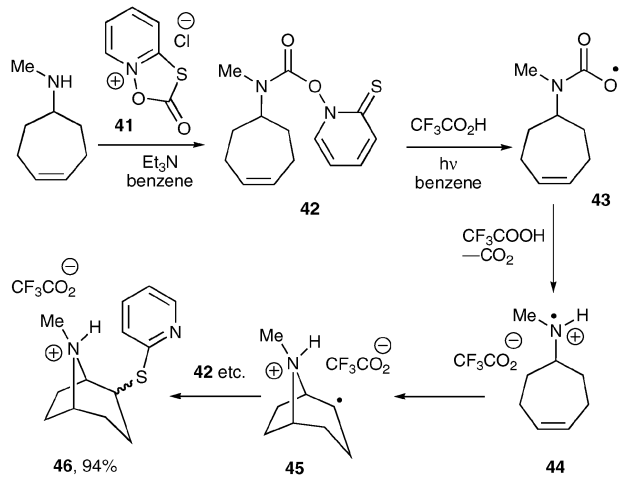
Scheme 9

chloride of **36**. Upon exposure to tributylstannane under the usual conditions, compound **38** undergoes ring-closure to give tricyclic derivative **40** *via* the intermediacy of amidyl **39**. Such 6-*endo* cyclisations of amidyl radicals are apparently unprecedented.[15]

2.3 Cleavage of N–O bonds

N–O Bonds are generally weaker than N–N bonds, and their easy rupture is the basis of several methods for the production of nitrogen radicals. Thus, various derivatives of oximes and hydroxamic acids have been exploited, in some cases indirectly as in the modification of Barton's decarboxylation reported by Newcomb and his collaborators.[16] This conception is illustrated by the behaviour of carbamate derivative **42** of *N*-hydroxy-2-thiopyridone upon irradiation with visible light in the presence of trifluoroacetic acid (Scheme 10). Homolysis of the N–O bond is followed by a rapid fragmentation of the incipient carbonyloxyl radical **43** to give a molecule of carbon dioxide and the desired protonated aminyl radical **44**. This species is vastly more reactive than the neutral aminyl (hence the use of trifluoroacetic acid) and undergoes a fast ring closure into the bicyclic carbon radical **45**. The last step of the radical sequence involves attack of radical **45** on the thiocarbonyl group of the starting Barton ester **42**, allowing in this way propagation of the chain. The presence of the pyridinethiyl group in the product, **46**, is a tremendous asset since it is a springboard for numerous subsequent transformations.

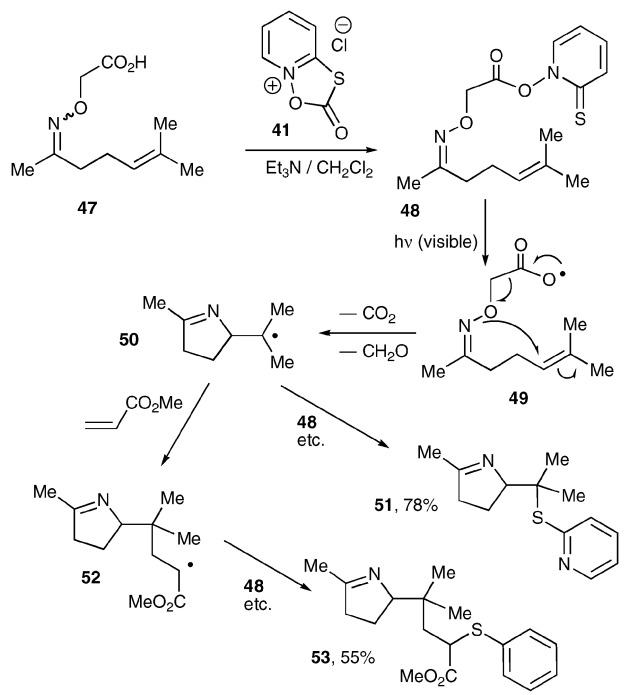
By applying the Barton decarboxylation to modified oximes, such as **47** in Scheme 11, it is possible to generate iminyl radicals easily and efficiently.[17] The corresponding Barton ester **48** can be obtained using the same reagent **41** employed in the previous scheme. In this alternative route, the decarboxylation of carboxylic radical **49** is followed by loss of formaldehyde to give the expected iminyl radical, which cyclises into carbon radical **50**. This strategy is based on an earlier, pioneering work by the group of Forrester,[18] who relied on a more drastic process for performing the decarboxylation step. In the absence of an external trap, pyrrolenine **51** is formed by transfer of a pyridylthiyl group from the starting Barton ester **48**. It is possible to obtain more complex structures by intercepting radical **50** with an olefinic trap that is sufficiently



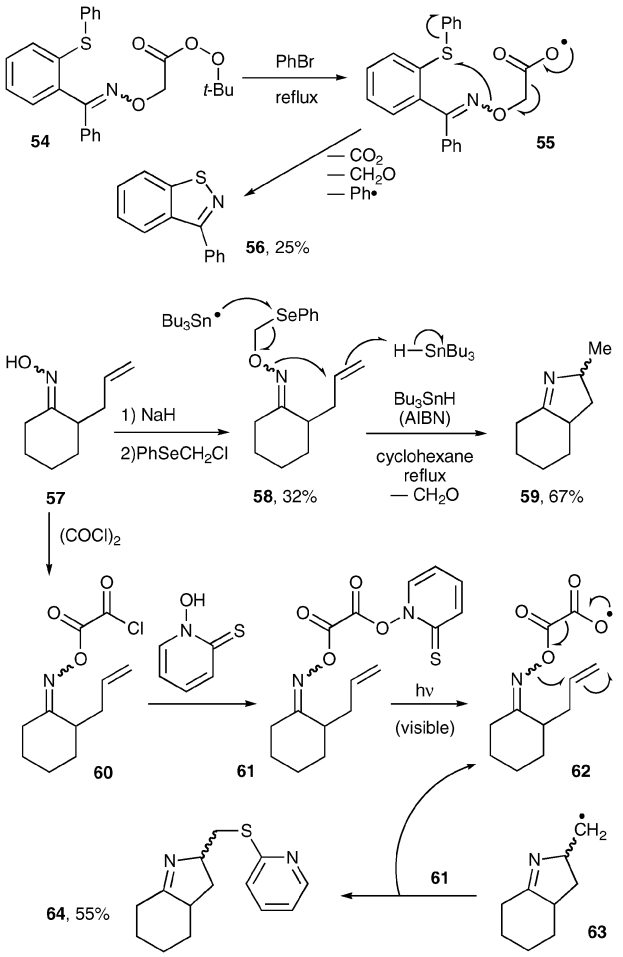
Scheme 10

reactive to compete successfully with the starting Barton ester **48**. In this manner, compound **53** was obtained using methyl acrylate as the radical trap.

Recently, Leardini and co-workers used the thermal decomposition in boiling bromobenzene of peresters such as **54** to produce the desired iminyl radical (Scheme 12).[19] Decarboxylation and loss of formaldehyde, as above, is followed in the present case by attack of the resulting iminyl radical on the neighbouring sulfur atom and expulsion of a phenyl radical to give finally benzothiazole **56** in modest yield. Various other products are formed concomitantly, including the three isomeric bromobiphenyls, derived from addition of the phenyl radical to bromobenzene. In the second transformation in Scheme 12, the iminooxymethyl radical is made directly from the parent selenide **58** using stannane chemistry. Even though the formation and capture of the iminyl radical to give **59** is



Scheme 11

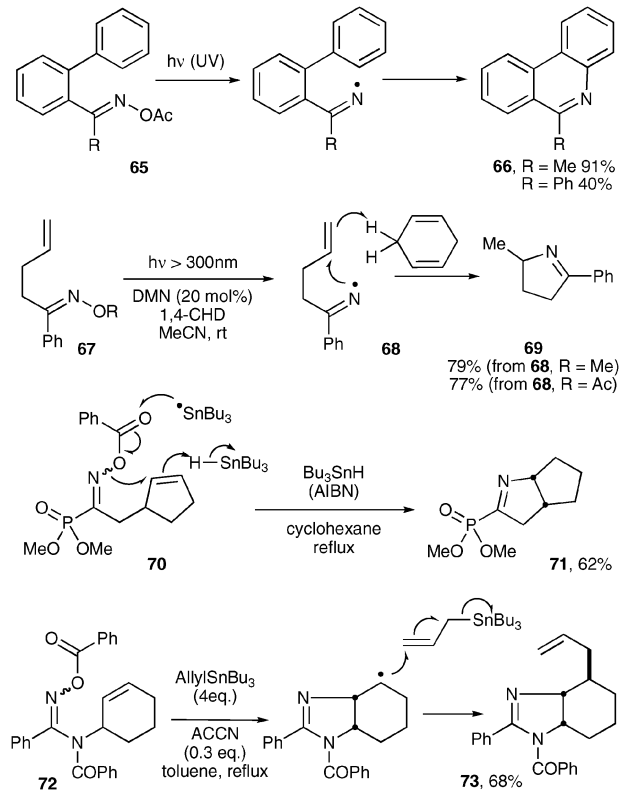


Scheme 12

efficient, the synthesis of precursor **58** from the oxime still needs improving.[17]

The last route displayed in the scheme relies on the double decarboxylation of oxalate esters of oximes. In the example shown, the Barton oxalate ester **60** derived from oxime **57** undergoes fragmentation upon irradiation to give first carboxylic radical **62**, which in turn evolves into the iminyl radical by expelling two molecules of carbon dioxide. Ring closure into **63** and transfer of the pyridylthiyl group lead to bicyclic pyrrolenine **54** in a useful overall yield.[17] This approach appears highly promising but its scope remains to be more fully explored.

Simple esters of oximes, hydroxamic acids, and related compounds can be cleaved photochemically, thermally, through exposure to stannyl radicals, or by electron transfer from a suitable reducing agent or a dissolving metal. The ease of access to the precursors makes this approach quite attractive for synthesis. Some examples are pictured in Scheme 13. The first reaction illustrates access to aza-phenanthrenes **66** by irradiation of oxime acetates **65** with UV light.[20] The ring closure of the intermediate iminyl onto the aromatic nucleus is followed by rearomatisation through the formal loss of a hydrogen atom, but the mechanism of this latter step has not been ascertained. The second sequence is taken from the extensive work of the group of Narasaka.[21] Irradiation of

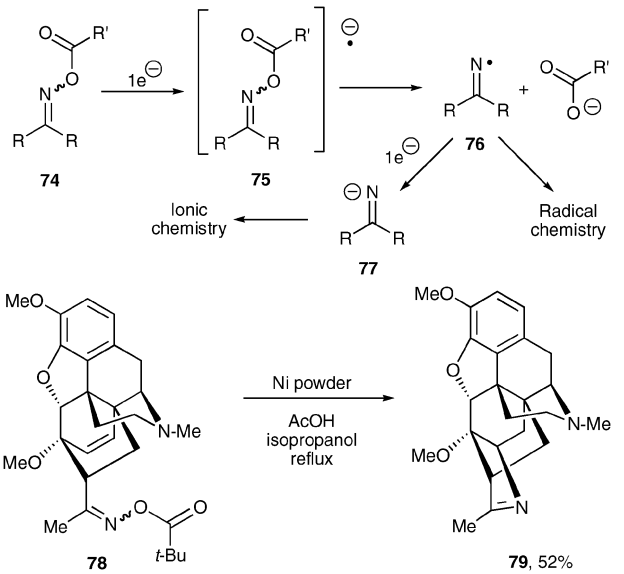


Scheme 13

oxime acetate or even methyl ether **67** in the presence of 1,5-dimethoxy-naphthalene (DMN) and 1,4-cyclohexadiene (1,4-CHD) leads to pyrrolenine **69** in good yield by cyclisation of iminyl radical **68** followed by hydrogen abstraction from 1,4-CHD.

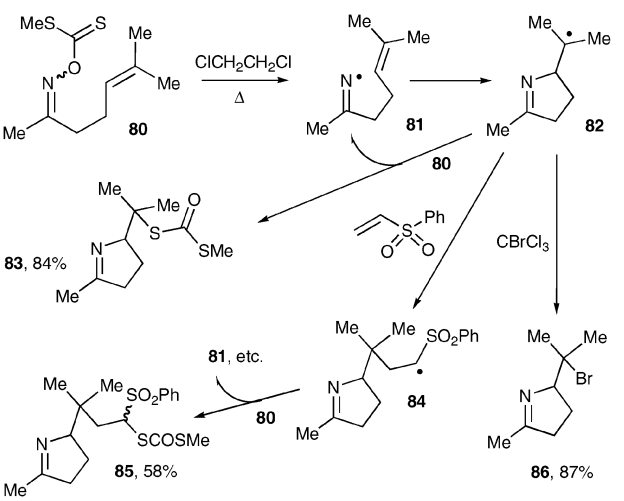
Even though most esters are not normally cleaved by tributylstannane, those derived from oximes, hydroxamic acids, and related derivatives, undergo a smooth reduction to give the corresponding nitrogen-centred radical. Stannyl radicals add reversibly to the carbonyl group of esters, but the subsequent β-scission does not occur except when a weak bond is concerned, which is indeed the case with N–O bonds. Oxime benzoate **70** is thus readily converted into pyrrolenine phosphonate **71**, an interesting precursor to cyclic aminophosphonic acids.[22] The transformation starting with benzoate **72** illustrates the formation and capture of an amidyl radical, as well as the coupling of the cyclisation with an allylation step to give imidazoline **73** in good overall yield.[23]

Iminyl radicals may be generated from oxime esters by electron transfer reduction. A one-electron transfer converts the oxime ester **74** into radical anion **75**, which rapidly collapses into an iminyl radical **76** and a carboxylate anion (Scheme 14). Most often, further reduction of the former takes place leading to iminyl anion **77**; however, if a sufficiently slow reducing agent is used, it is possible to capture the iminyl radical before it gets reduced to the anion. Dissolving nickel powder in a mixture of acetic acid and isopropanol has proved especially useful in this respect.[24] In the example shown, oxime pivalate **78** derived from thevinone furnishes cyclised derivative **79**. The isopropanol acts as the ultimate hydrogen atom donor in the sequence.

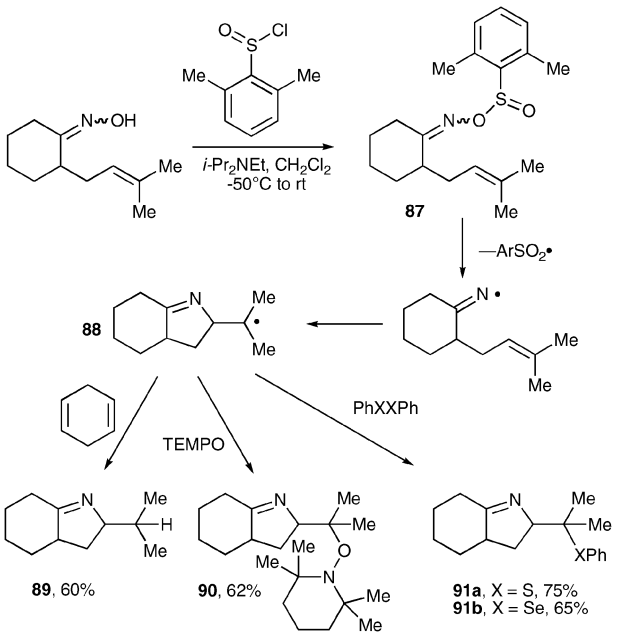


Scheme 14

Two further approaches relying on the scission of N–O bonds have been devised. The first uses xanthates derived from oximes and operates by a chain reaction as briefly outlined in Scheme 15.[25] The oxime is first converted into xanthate **80** by reaction with base, carbon disulfide, and methyl iodide. This derivative is not purified but simply warmed gently to trigger a radical chain reaction starting with iminyl **81**, which cyclises to give carbon radical **82**. In the absence of an external trap, this radical reacts with the initial xanthate **80** to furnish pyrrolenine dithiocarbonate **83**. If a reactive electrophilic olefin is incorporated into the medium before heating, then the reaction leads to compound **85** *via* adduct **84** in the case of phenyl vinyl sulfone. Intermediate radical **82** may also be captured by bromotrichloromethane to efficiently produce bromopyrrolenine **86**. In the exchange of the bromine atom, a trichloromethyl radical (not shown) acts as the propagating species. This approach relies on earlier work by Hudson and collaborators, who found that thiocarbonyl derivatives of oximes were thermally and photochemically unstable, and rearranged



Scheme 15



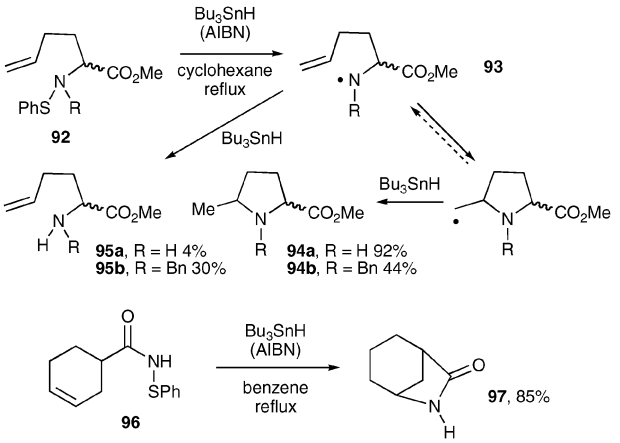
Scheme 16

into the sulfenamide isomers.[26] This decomposition was assumed to involve caged radicals and this was supported by ESR studies, but no attempt was made to incorporate an intramolecular trap to capture the presumed reactive species.

The second approach also derives from prior observations by Hudson.[26] In a set of ingenious and mechanistically insightful experiments, Weinreb and his co-workers demonstrated that the nitrogen radicals arising from the thermal decomposition of sulfinates and trivalent phosphorus derivatives of oximes and hydroxamic acids can be intercepted by an alkene, and the resulting carbon radical in turn quenched by various radical traps.[27] The richness of this process is showcased by the series of transformations pictured in Scheme 16. Sulfinate **87** decomposes upon warming to give carbon radical **88** by cyclisation of the intermediate iminyl. Hydrogen atom transfer from cyclohexadiene leads to pyrrolenine **89**, whereas capture with TEMPO gives alkoxyamine **90**. Finally, sulfides and selenides **91a,b** may be obtained using the appropriate dichalcogenide as the radical trap. Overall, these are not chain processes but rely on the stoichiometric thermal decomposition of the initial oxime derivative.

2.4 Cleavage of N–S bonds

Homolysis of N–S bonds also offers rich opportunities for the generation of N-centred radicals. Perhaps the most direct is the cleavage of various sulfenamine derivatives with stannyl radicals. Essentially all nitrogen radicals can be made this way, the only limitation being the access to the sulfenyl precursor. Some examples involving aminyl and amidyl radicals are gathered in Scheme 17. Sulfenamide **92** is the precursor of aminyl radical **93**, which undergoes cyclisation with an efficiency that depends on the substituent on the nitrogen atom. This may be appreciated by observing the difference in the yield of pyrrolines **94a** and **94b** as compared with that of the corresponding non cyclised amines **95a** and **96b**.[28] Bowman

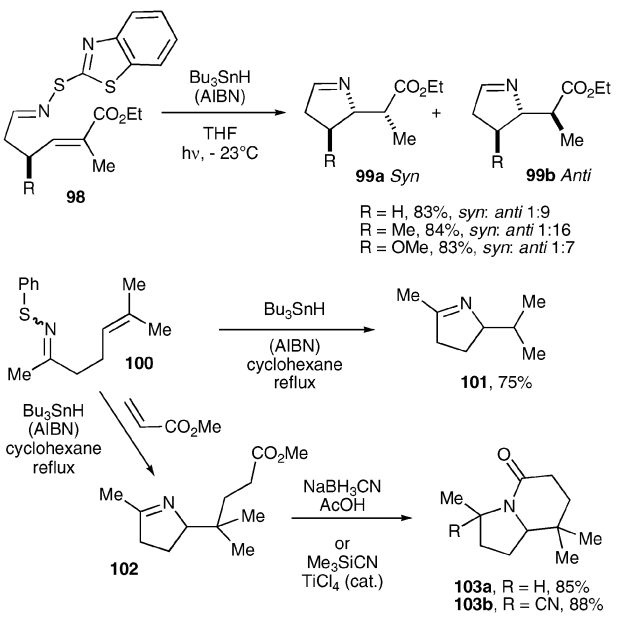


Scheme 17

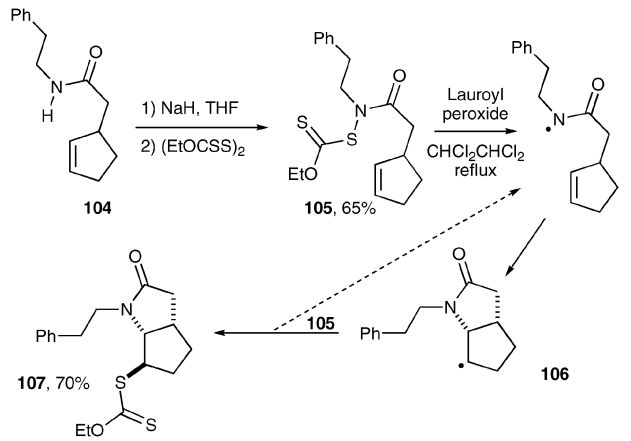
and collaborators, from whose extensive study this example was selected, have demonstrated that the cyclisation of neutral aminyl radicals may be reversible.[29] The trick of operating under acidic conditions in order to enhance the reactivity of the aminyl radical (as the protonated species) cannot be applied here because of the incompatibility of tributylstannane with acids, and the general fragility of sulfenamides, even in relatively weak acidic media. The cyclisation of **96** into **97** represents a rare case of ring closure of a non-substituted amidyl radical recently disclosed by the group of Lessard.[30]

The sequences presented in Scheme 18 highlight the use of sulfenimines as progenitors of iminyl radicals. The first is taken from a study of the stereoselectivity of the cyclisation of amidyl and iminyl radicals reported by Guindon *et al.*[31] Quite useful selectivities can be attained, as demonstrated by the elevated ratio of epimers **99b**/**99a** observed upon treatment of benzothiazole precursor **98** with tributylstannane.

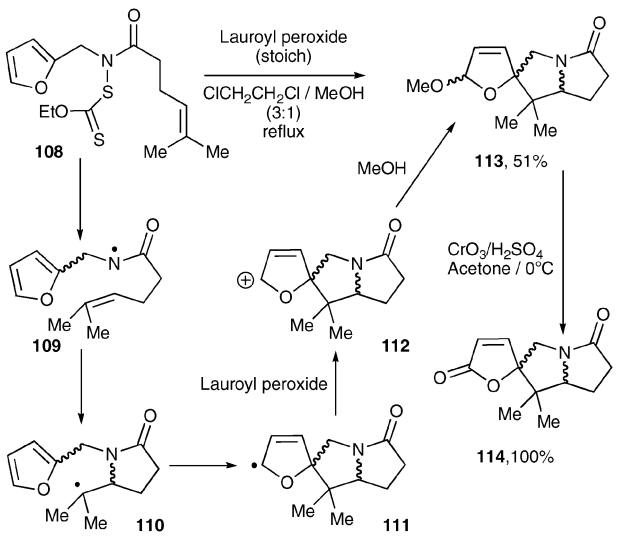
The second series of transformations exemplifies the facile construction of the indolizidine nucleus through the combination of ring closure and intermolecular capture by methyl



Scheme 18



Scheme 19



Scheme 20

acrylate, followed by an ionic lactam formation.[32] Starting from sulfenamide **100**, pyrrolenine **101** is obtained in the absence of acrylate while pyrrolenine **102** is produced in its presence. The imine nitrogen in **102** does not cyclise spontaneously onto the ester group, but ring closure to indolizidinones **103a,b** takes place upon reduction or addition of a nucleophile such as cyanide, which leads to a more nucleophilic aminyl nitrogen.

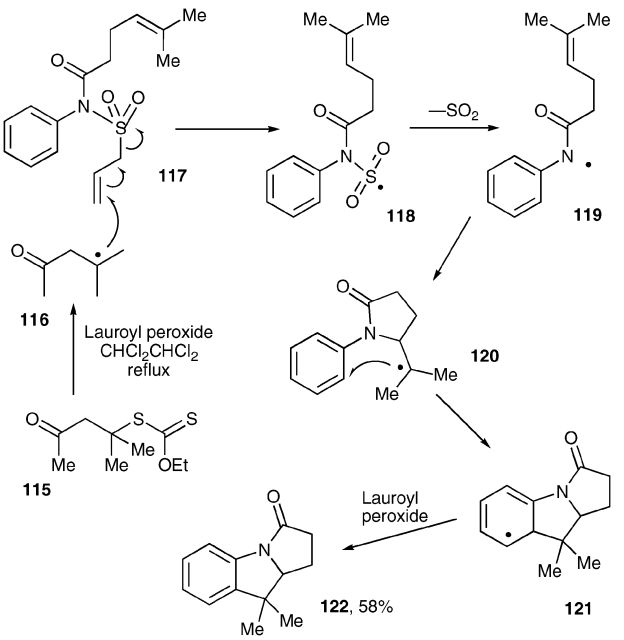
The sulfur groups in the preceding sulfenamine precursors are not sufficiently radicophilic to sustain a chain process without the mediation of an organotin reagent. In contrast, *N*-xanthyl derivatives such as **105** possess a vastly more reactive thiocarbonyl group, and chain processes can be readily implemented under tin-free conditions (Scheme 19).[33] The somewhat fragile starting material is prepared by reaction of an amidyl anion with a bis-xanthate, and the radical chain may be triggered with the help of a peroxide. In the present case, amide **104** is converted into lactam **107** in good overall yield. The fast transfer of the xanthate group from substrate **105** onto the *exo* face of intermediate radical **106** regenerates the amidyl radical and propagates the desired chain.

The cascade in Scheme 20 illustrates a case where the peroxide acts both as the initiator and as a stoichiometric oxidant. Starting from derivative **108**, the first cyclisation of amidyl **109** is followed by an *ipso* closure of radical **110** to the furan ring to give allylic radical **111**. This radical is too stabilised to undergo efficient exchange of the xanthate group, but is easily oxidised into the corresponding cation **112** by electron transfer to the peroxide. Finally, quenching of the cation with methanol gives acetal **113** in reasonable overall yield. This compound is best characterised as spirolactone **114**, formed in quantitative yield by oxidation with the Jones reagent.[33]

The degenerative transfer of xanthates and related dithiocarbonyl groups is a broadly applicable process, and one of its main features is to provide the intermediate radicals with sufficient lifetime to undergo additions to ordinary, non-activated alkenes.[34] This property can be exploited to devise yet another route to nitrogen radicals, proceeding by fragmentation of an allyl sulfonamide.[35] An example of this route is outlined in Scheme 21, where *N*-arylaminyl **119** is created by extrusion of sulfur dioxide from sulfonyl radical **118**. The latter derives from allyl sulfonamide **117** by addition–fragmentation of tertiary radical **116**, generated from xanthate **115** by the action of lauroyl peroxide. Ring closure of **119** produces carbon radical **120**, which undergoes cyclisation onto the aromatic ring to afford finally tricyclic lactam **122**. In this transformation, the peroxide is required in stoichiometric amounts to execute the final re-aromatisation of intermediate cyclohexadienyl radical **121**. This approach works best with a stabilising group on the nitrogen atom, which facilitates the loss of sulfur dioxide and limits side reactions arising from capture of the amidosulfonyl radical **118** by the olefin.

2.5 Cleavage of N–C and N–H bonds

The nitrogen–carbon bond is generally too strong to undergo scission. In fact, one of the important advantages of radical methods is the small tendency of oxygen and nitrogen groups



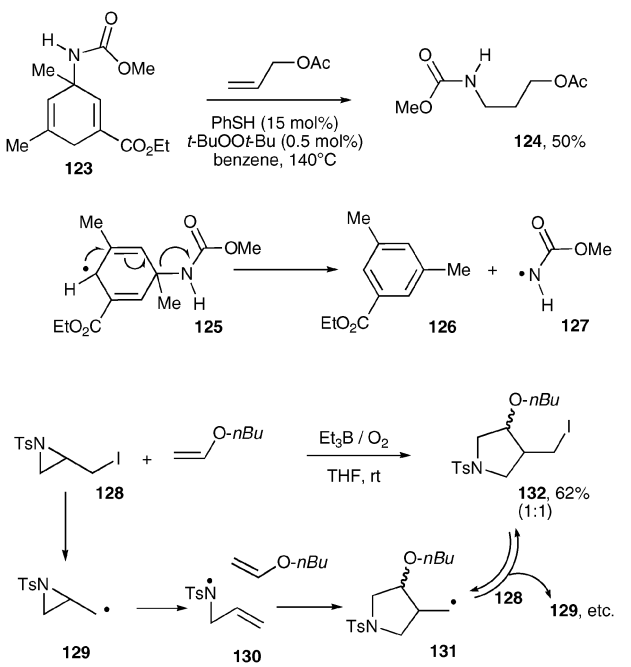
Scheme 21

towards β-elimination by homolysis, in contrast to ionic processes. However, in special cases, β-elimination does take place and this may be used to generate nitrogen-centred radicals. For instance, the first route to nitrogen-centred radicals devised by Studer and his students is conceptually related to the one described in Scheme 6 above.[36] It exploits the tendency of aminocyclohexadienyl radicals to fragment owing the powerful driving force of aromatisation. As shown in the first example of Scheme 22, a carbamyl radical **127** can be generated from cyclohexadiene **123** and captured with allyl acetate to give adduct **124** in 50% yield.[36] The fragmentation of intermediate cyclohexadienyl radical **125** to afford ethyl 3,5-dimethylbenzoate **126** proceeds readily even though it involves scission of a carbon–nitrogen bond. In fact, cyclohexadienyl radicals can aromatise by cleavage of quite strong bonds that would not normally rupture in other systems.[37] Catalysis by polarity reversal, through the adjunction of thiophenol, also served in this case to enhance the kinetics of some of the key steps and to improve the overall efficiency.

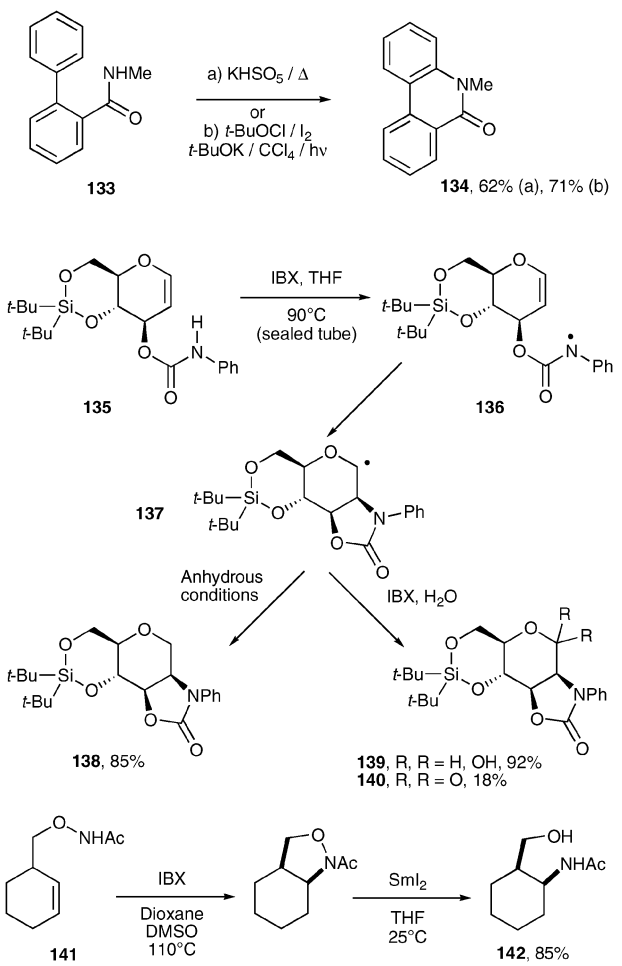
Another situation conducive to a β-fragmentation concerns strained structures such as aziridinemethyl radicals. The ring opening occurs by rupture of the carbon–nitrogen bond to give a nitrogen-centred radical, which can undergo addition to an alkene in the usual manner. Thus, in the sequence depicted in the lower part of Scheme 22, Taguchi and co-workers constructed pyrrolidine structure **132** by a formal 3 + 2 annelation reaction starting with aziridine iodide **128**.[38] Iodine abstraction furnishes radical **129**, which opens rapidly to give sulfonylamidyl radical **130**. Addition to butyl vinyl ether, cyclisation, and iodine exchange finally leads to the desired product while propagating the radical chain at the same time.

One of the earlier methods for creating nitrogen-centred radicals consisted in the formal abstraction of a hydrogen atom from an N–H bond in the parent compound. This requires generally a strong oxidising agent, which explains the rather limited scope of this approach. Only sturdy substrates that can withstand the harsh conditions are normally tolerated. The ring closure of amide **133** to give lactam **134** using potassium persulfate, described by Forrester and displayed at the top of Scheme 23, represents one such example.[39] The same conversion may be accomplished *via* the *N*-iodoamide under milder conditions.[40]

A milder and synthetically more interesting method was discovered a few years ago by the group of Nicolaou, who found that *o*-iodoxybenzoic acid (IBX) was capable of generating amidyl radical from *N*-aryl amides and carbamates.[41] Thus, reaction of glucose-derived carbamate **135** reacts with IBX in THF at 90 °C in a sealed tube to give cyclic carbamate **138** under anhydrous conditions. The reaction proceeds by way of carbamyl radical **136**, which cyclises into radical **137**, and this is followed by hydrogen abstraction from the solvent. In the presence of water as the co-solvent, the polarity of the medium increases considerably and radical **137** is oxidised by IBX to the cation. Quenching with the water leads then to cyclic hemiacetal **139**. In the presence of excess IBX, the hemiacetal is further oxidised to lactone **140**. The exact mechanism of the first oxidation step is still not clear. It could involve an initial electron transfer to IBX or the formation then homolysis of an amide N–I intermediate (or its isomeric imino ether hypoiodide). Recently, Janza and Studer extended



Scheme 22



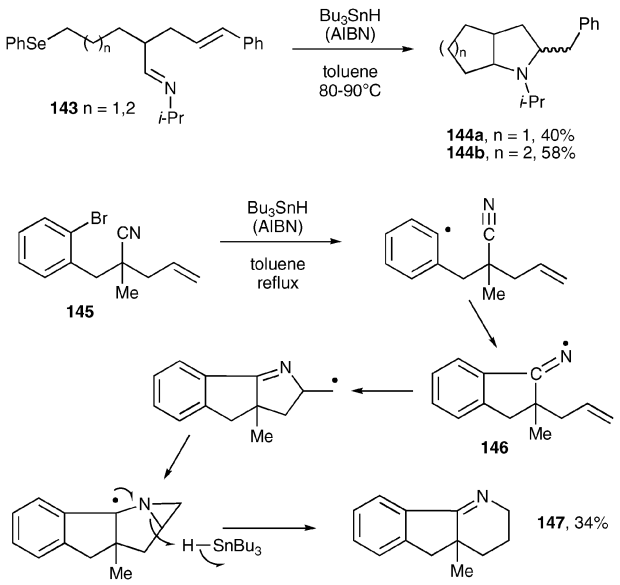
Scheme 23

the use of IBX to *N*-acylhydroxylamines such as **141**.[42] The ring closure leads to a cyclic *N*-acetylhydroxylamine, which could be smoothly cleaved by reduction with samarium diiodide into acetamido alcohol **142**.

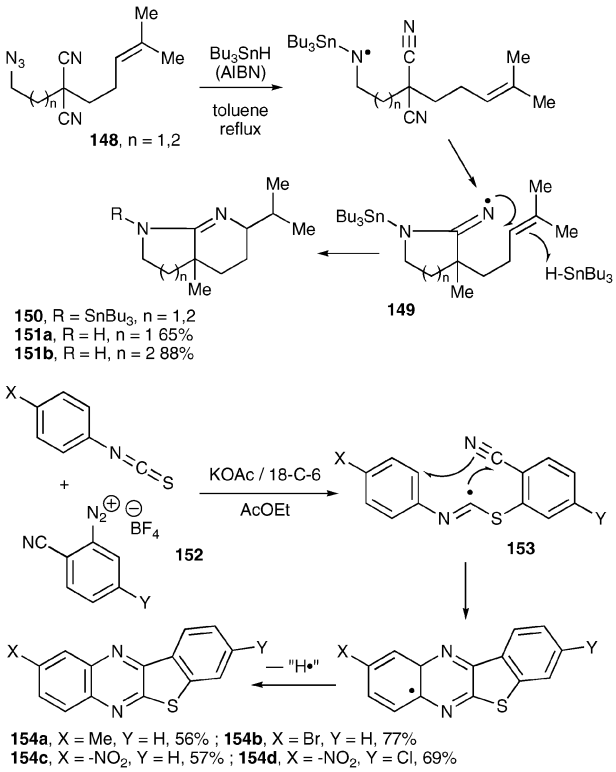
2.6 Indirect methods

Indirect ways for creating nitrogen radicals involve addition of a radical to an unsaturated nitrogen derivative, such as a nitrile, an imine, an oxime, a hydrazone, or an azide. In initial studies, additions to nitriles resulted in a transfer of the nitrile group, but later work demonstrated the broader synthetic utility of this process through the capture of the intermediate iminyl radical. Two examples from the studies of Bowman are presented in Scheme 24. The first relates to the synthesis of bicyclic derivatives **144a,b** by two sequential ring closures starting with the carbon radical generated from selenides **143**.[43] The second involves a cascade whereby the radical derived from bromide **145** closes onto the nitrile to give iminyl radical **146**, and this in turn undergoes cyclisation and ring expansion to furnish tricyclic derivative **147**.[44] In both cases, stannane chemistry is employed to mediate and control the radical sequence.

A variation on this approach is outlined in Scheme 25. In this example, taken from the results of Leardini, Spagnolo, and co-workers, the cascade begins with an aminyl radical produced from azides **148**.[45] Cyclisation leads to the corresponding iminyl radical **149**, and finally to bicyclic derivatives **151a,b** upon hydrolysis of stannylamines **150** on work up. Another example of a cascade from the Leardini group may be found in the same scheme. It relies on generating an aromatic radical by decomposition of a diazonium salt such as **152** in the presence of an aryl isothiocyanate.[46] The aryl radical thus produced adds to the thiocarbonyl group of the isothiocyanate to afford radical **153**, which then undergoes two successive cyclisations to furnish, after an aromatisation step, the tetracyclic aromatic derivatives **154a–d**, depending on the substituents in the starting reagents.



Scheme 24

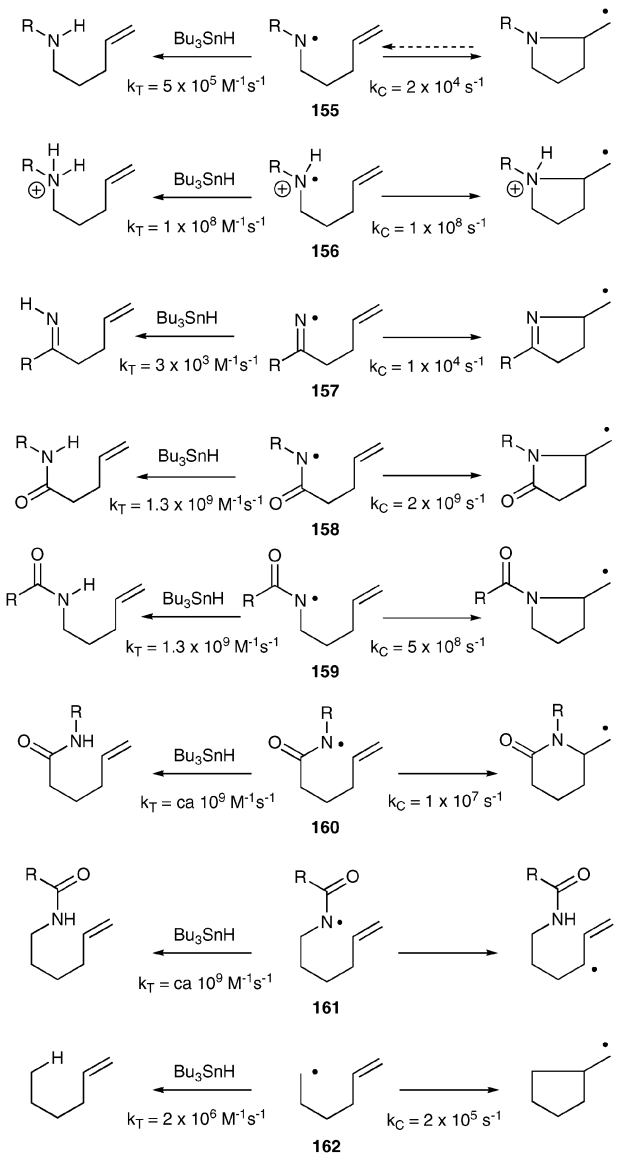


Scheme 25

3. Rate constants for the reaction of nitrogen-centred radicals

In radical chemistry, it is important to have some knowledge of the rate constants of basic transformations in order to guide the design of viable reaction sequences and to aid in establishing the best experimental parameters. The rates for some of the more important ring closures of nitrogen-centred radicals are collected in Scheme 26. Most have been taken from the seminal work by Horner and Newcomb.[47] For comparison purposes, the rate of cyclisation of the all-carbon 5-hexenyl radical **162** has been included at the bottom of the list. For the neutral aminyl radical **155**, the rate constant for cyclisation, k_C, is one order of magnitude slower than that for **162**, whereas the rate constant for the transfer of a hydrogen atom from tributylstannane, k_T, is only 4 times slower than that for hydrogen abstraction by a primary carbon radical. The competition between the desired cyclisation and premature hydrogen abstraction from the stannane is therefore somewhat less favourable in the case of aminyl **155** than for hexenyl radical **162**. Furthermore, as stated above, Bowman has shown that the ring closure of aminyls may be reversible, resulting in a significant decrease in the yield of cyclised product in many cases.[29] In contrast, the protonated aminyl counterpart, **156**, is vastly more reactive, but requires acidic conditions, which limits its synthetic scope.

The ring closure of iminyl **157** is also about an order of magnitude slower than that of hexenyl radical **162**; however, the rate constant for hydrogen abstraction from the stannane is nearly a thousand times slower than that of a primary carbon radical. The cyclisation process can therefore compete



Scheme 26

more favourably, and is indeed very easy to implement. Furthermore, the imine group in the product is a more useful functionality than a simple amine because it opens up many more possibilities for subsequent transformations and allows ultimately a more convenient control of the stereochemistry.

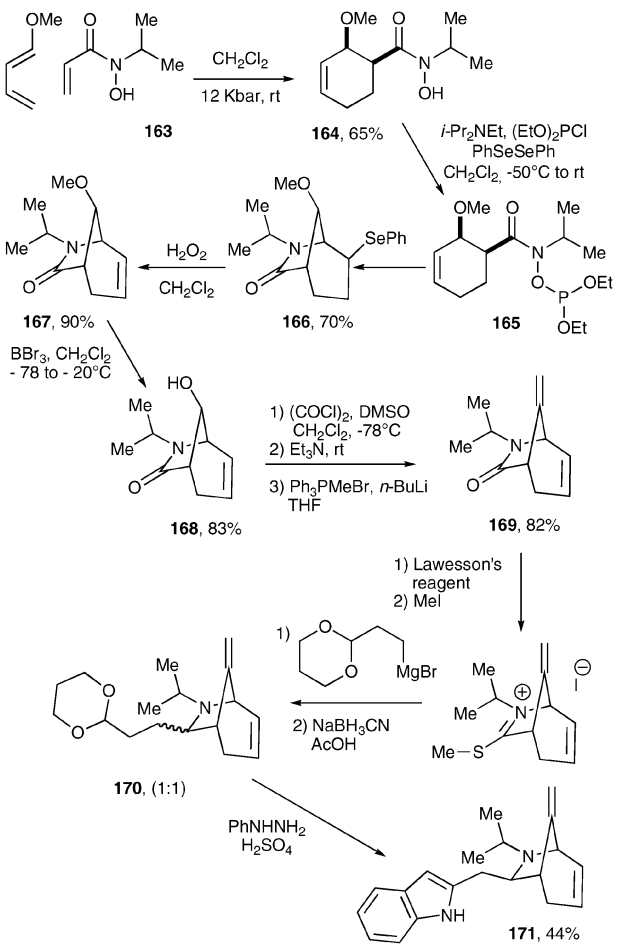
As would be expected, amidyl radicals are especially reactive. Even though the rate constant for reaction with tributylstannane is essentially diffusion controlled, the ring closure is sufficiently rapid to compete successfully under appropriate reaction conditions. It is interesting to note that the 5-*exo* closure of amidyl **158** to give a γ-lactam is significantly faster than that of **159**, where the carbonyl group of the amide ends up outside the pyrrolidine ring.

The 6-*exo* ring closure of amidyl **160** is approximately a hundred-fold slower, so that the competition with premature hydrogen abstraction now becomes especially difficult to overcome. Such cyclisations are indeed quite rare.[48] In the case of amidyl **161**, the normally undesired allylic hydrogen atom abstraction overwhelms the cyclisation process.

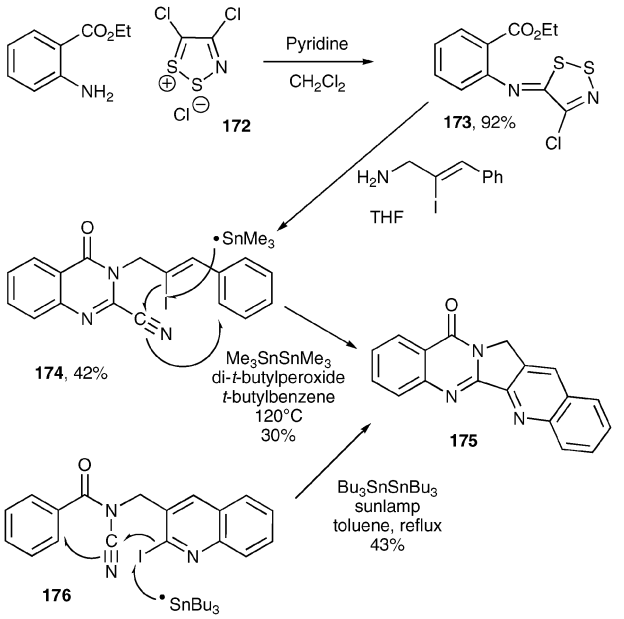
4. Applications in total synthesis

4.1 Synthesis of peduncularine

By and large, synthetic organic chemists have overlooked the potential of nitrogen-centred radicals for the construction of complex structures. The examples that follow summarise some recent contributions in this area. The formal synthesis of peduncularine, **171**, reported by Weinreb and co-workers, is an application of the route to nitrogen radicals developed by the same group and discussed earlier (see Scheme 16).[27] The synthetic route, displayed in Scheme 27, requires the formation of an alkene following the creation of the C–N bond. Thus, Diels–Alder cycloaddition of 1-methoxybutadiene with *N*-hydroxyacrylamide **163** under very high pressure furnishes hydroxamic acid **164**. The corresponding phosphite **165** is allowed to decompose in the presence of diphenyl diselenide to give bridged lactam **166** in good overall yield. *Syn* elimination of the selenoxide produces the desired alkene **167** and cleavage of the methoxy group with boron tribromide affords alcohol **168**, which is subjected to a Swern oxidation and Wittig olefination to give diene **169**. Hiemstra *et al.* had previously converted this compound into peduncularine **171** by a sequence involving methylation of the corresponding thioamide and transformation of the resulting iminium salt



Scheme 27



Scheme 28

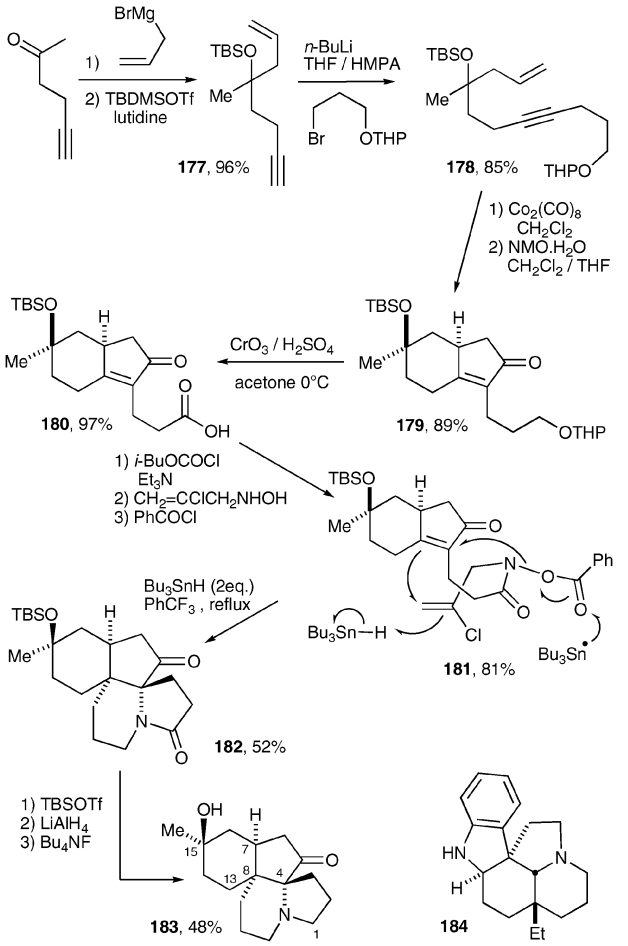
into protected aldehyde **170**, followed by a Fischer condensation to form the required indole ring.[49]

4.2 Synthesis of luotonine A

The use of cascade reactions can lead to highly efficient syntheses. One such example is the expedient route to the anticancer compound luotonine A, **175**, conceived by Bowman, and detailed in Scheme 28.[50] Reaction of ethyl anthranilate with Appel's salt **172** leads efficiently to intermediate **173**, which undergoes condensation with 2-iodocinnamylamine to form key precursor **174** in moderate yield. This compound is then subjected to the action of trimethyltin radicals, generated by thermolysis of di-*t*-butyl peroxide in the presence of hexamethylditin. Iodine abstraction followed by cyclisation to the nitrile group and closure of the resulting iminyl onto the phenyl ring completes the synthesis of the target molecule **175**. A conceptually similar approach to luotonine A was recently reported by Courillon *et al.*, where the radical cascade is initiated from isomeric iodide **176**.[51] Even though the yield of the double cyclisation is marginally better, the synthesis of precursor **176** is significantly more laborious.

4.3 Synthesis of 13-deoxyserratine

The use of cascades involving nitrogen radicals may considerably simplify the synthesis of alkaloids containing an indolizidine subunit, as illustrated by the synthesis of 13-deoxyserratine **183**, belonging to the lycopodium family of alkaloids.[52] The synthetic route, outlined in Scheme 29, starts with the standard chain elongation of the very simple enyne **177** into the homologous derivative **178**, which is then subjected to a Pauson–Khand annelation to give bicyclic enone **179** in high yield. The fabulous Pauson–Khand reaction thus allows the very swift assembly of two of the four rings found in 13-deoxyserratine, with the correct relative stereochemistry at the centres corresponding to C-7 and C-15 in the target molecule.



Scheme 29

Oxidation using Jones' conditions furnishes carboxylic acid **180** directly from the tetrahydropyranyl precursor. Activation of the carboxylic function as the mixed anhydride and reaction with *N*-(2-chloroallyl)hydroxylamine affords, after benzoylation, the requisite amidyl radical precursor **181** in a one-pot procedure. Slow addition of two equivalents of tributylstannane and azo-bis(cyclohexanenitrile) (ACCN) as initiator to a solution of **181** in trifluoromethylbenzene results in the formation of tetracyclic derivative **182**.

The amidyl radical produced undergoes first a 5-*exo* then a 6-*endo* cyclisation, and finally reductive removal of the chlorine atom. The presence of the chlorine atom is crucial: in its absence, the second cyclisation occurs in a 5-*exo* fashion to give a pyrrolizidine arrangement instead. The chlorine atom thus plays an important directing role in the process. Furthermore, it may be worth noting that the vinylic chloride in the substrate is not easily abstracted by the stannyl radical but, once the second cyclisation takes place, the chlorine becomes attached to an aliphatic secondary carbon and can therefore be reductively removed. In this manner, the remaining two rings can be put together in one step, at the same time as the two adjacent quaternary centres corresponding to C-4 and C-8 in 13-deoxyserratine. The stereoselective assembly of these two quaternary centres represents the main synthetic hurdle in

these structures and has considerably complicated their previous syntheses by more traditional routes.

To complete the synthesis of 13-deoxyserratine, the ketone in **182** is protected as the silyl enol ether and the lactam selectively reduced with $LiAlH_4$ before removal of the two protecting silyl groups by exposure to tetrabutylammonium fluoride.

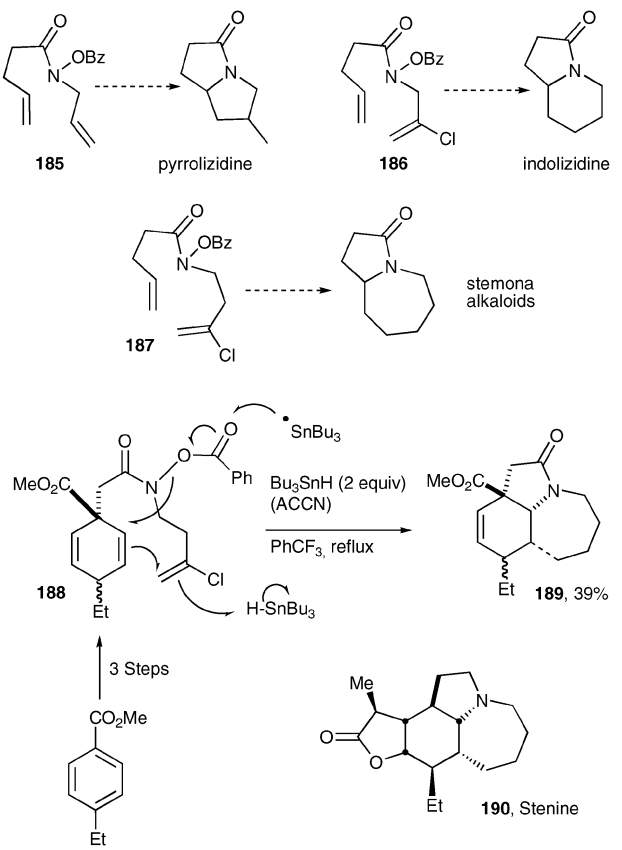
An identical approach was used for the construction of the indolizidine portion of aspidospermidine **184**.[53] Both of these syntheses highlight in fact a general strategy for the formation of both the indolizidine and pyrrolizidine skeletons, which are ubiquitous in the alkaloid kingdom. As summarised in Scheme 30, by placing (as in **186**) or not placing (as in **185**) a chlorine atom (or other substituents) at the 2-position of the allyl side chain, either the former or the latter skeleton can be built. Furthermore, it turns out to be even possible to form the 5–7 ring combination found in a small number of alkaloids, such as those of the stemona family, by appending a homoallyl chain on the nitrogen atom as in compound **187**. The moderately effective conversion of benzoate **188** into tricyclic lactam **189** is an example of such a transformation. Thus, three of the four rings found in stenine **190** can be assembled in only four steps starting from methyl *p*-ethylbenzoate.[53]

4.4 Synthesis of fortucine

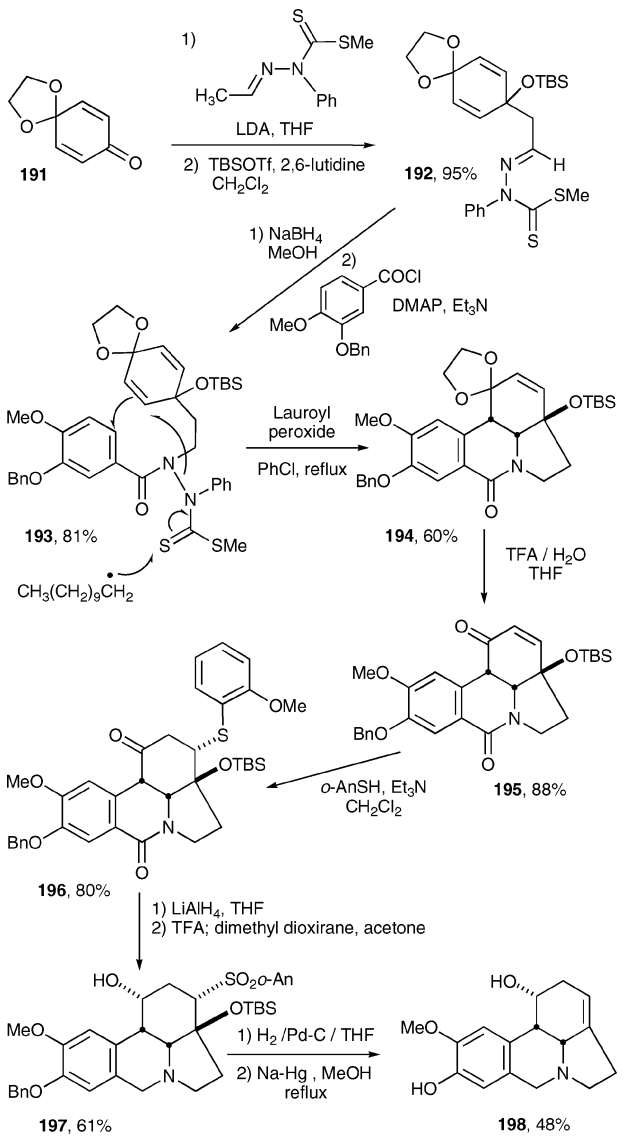
The above strategy to the indolizidines can be adapted to access lycorine alkaloids possessing the *cis*-ring junction found in γ-lycorane. In fact, to obtain the desired galanthan framework, it suffices to replace the second (6-*endo*) ring closure by a cyclisation to an aromatic ring. The potential of this approach is illustrated in Scheme 31 by the synthesis of fortucine **198**, an alkaloid isolated from the 'Fortune' variety of narcissus.[54]

The obtention of the required dithiosemicarbazide precursor **193** is accomplished by attaching the corresponding dithiocarbazone fragment to monoprotected benzoquinone **191**, protection of the intermediate tertiary alcohol, followed by reduction of resulting hydrazone **192**, and, finally, acylation. Addition of lauroyl peroxide to a refluxing solution of dithiosemicarbazide **193** in chlorobenzene triggers the desired radical sequence and gives rise to key intermediate **194** in acceptable yield and regioselectivity. In this manner, the tetracyclic core of fortucine is constructed in only five steps and it only remains to adjust the functional groups adorning the central framework.

First, the ketone is deprotected with trifluoroacetic acid to reveal enone **195**, which undergoes a clean, stereoselective Michael addition of 2-methoxythiophenol leading to sulfide **196**. Reduction of both the ketone and the lactam is effected



Scheme 30



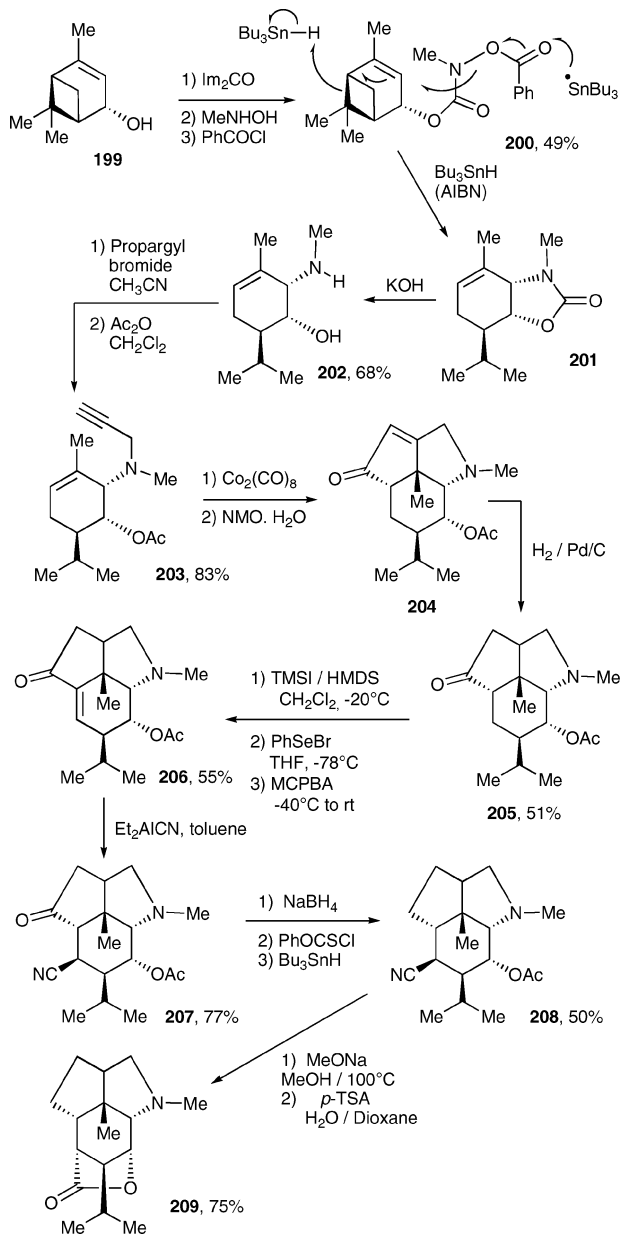
Scheme 31

with $LiAlH_4$ and the resulting tertiary amine protected as the trifluoroacetate to allow selective oxidation of the sulfide group into sulfone **197** using dimethyldioxirane. Finally, the benzyl group is cleaved by catalytic hydrogenation, and both the sulfone and the protected tertiary alcohol eliminated with sodium amalgam in methanol to give fortucine **198** through a Julia-type olefination process.

4.5 Synthesis of dendrobine

The synthesis of (−)-dendrobine, **209**, the last to be discussed in this section, exemplifies yet another way to exploit the chemistry of nitrogen-centred radical on a strategic level. Dendrobine possesses seven asymmetric centres, six of which are around the central cyclohexane ring. The synthetic plan, depicted in Scheme 32, hinges on the cyclisation of a carbamyl radical to control the stereochemistry of the remaining centres.[55] Thus, the radical cascade applied on intermediate **200** serves to attach the nitrogen atom in a *cis* disposition with respect to the alcohol function initially present in the starting (+)-*trans*-verbenol **199** and to introduce the isopropyl group found in dendrobine with the correct absolute stereochemistry. Furthermore, the opening of the cyclobutane ring causes a shift of the olefinic bond to a position, allowing implementation of a subsequent Pauson–Khand annelation. Thus, treatment of benzoate **200** with tributylstannane gives cyclic urethane **201**. This compound is not isolated but cleaved with base into amino alcohol **202**. Propargylation and acetylation affords amine **203**, which is converted into tricyclic enone **204** through the Pauson–Khand reaction. Because of inbuilt strain, this enone is rather sensitive and it is therefore immediately reduced to ketone **205** by catalytic hydrogenation.

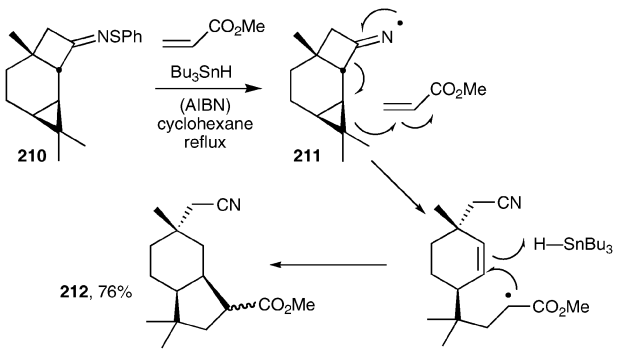
The synthesis of (−)-dendrobine is completed by introduction of the missing carbon by conjugate addition of cyanide to enone **206** and removal of the ketone group in **205** by reduction and Barton–McCombie deoxygenation. The stereochemistry of the nitrile group in the product **205** has to be inverted for lactone formation. This is accomplished by treatment with hot methanolic potassium hydroxide, which cleaves the acetate and epimerises the nitrile group, causing ring closing into an imino ether, which in turn can be hydrolysed by acid into (−)-dendrobine **209**.



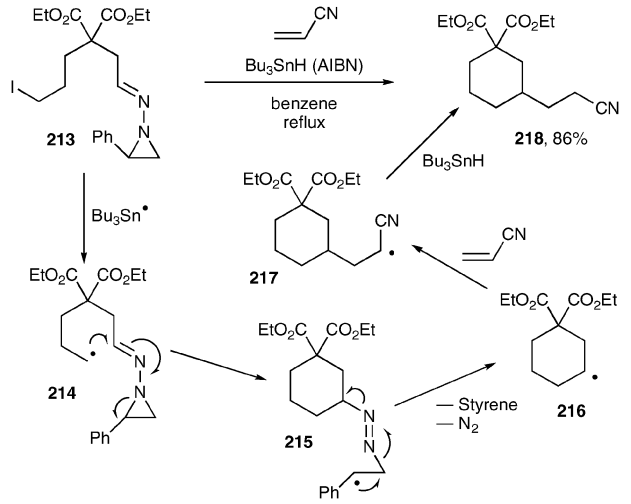
Scheme 32

5. Conclusions

This brief review of the chemistry of nitrogen-centred radicals has focused on the methods that have been devised to generate these reactive species, as well as on synthetic transformations leading the formation of C–N bonds, where the nitrogen atom is part of the main framework of the end molecule. There are of course numerous other ways to use nitrogen radicals without the nitrogen atom becoming ultimately embedded within the main structure. It is for example possible to use iminyl radicals as a way to rupture strained rings, as shown by the cascade displayed in Scheme 33.[56] The ring opening of cyclobutyliminyl radical **211** derived from sulfenimine **210** is followed by opening of the cyclopropane, addition of the resulting tertiary radical to methyl acrylate, and, finally, ring closure and hydrogen atom transfer from the stannane to give bicyclic structure **212**. The nitrogen atom thus ends up in the nitrile group and not as part of the main skeleton.



Scheme 33



Scheme 34

The ingenious sequence imagined by Kim, pictured in Scheme 34, converts hydrazone **213** into cyclohexane **218** in high yield.[57] The hydrazyl radical formed upon closure of radical **214** onto the hydrazone triggers a concomitant opening of the cyclopropane ring to afford radical **215**, which collapses with loss of styrene and molecular nitrogen into secondary radical **216**. Addition to acrylonitrile gives radical **217**, and hydrogen atom transfer from the stannane finally produces compound **218**.

Nitrogen-centred radicals hold much promise as useful synthetic intermediates. Even though their popularity is still extremely limited and very far from matching that of carbon radicals, the recent development of various routes allowing their generation under mild conditions and a better appreciation of their reactivity thanks to the increased availability of absolute rate constants should encourage their use. It is hoped that this overview will help increase the awareness of synthetic chemists and help revive the interest in these forgotten species.

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