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Formation of five- and six-membered heterocyclic rings under radical cyclisation conditions

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Contents

1. Introduction

A few years ago, radicals were the subject of mechanistically oriented research and there has been increasing interest for several years in the chemistry of radical cyclisation. Important efforts have been made towards the synthesis of various heterocycles and many new methodologies have been developed in the field of radical cyclisations. Since their first appearance in literature, various types of *exo*- and *endo*-cyclisations of radicals onto internal unsaturated bonds have been described. The kinetics of various radical processes was known in the mid

Keywords: Radical cyclisation; Five- and six-membered heterocycles; Tributyltin hydride; Cascade cyclisation; Sulphur heterocycles.

Abbreviations: TBTH/Bu_3SnH, tributyltin hydride; Me_3SnH, trimethyltin hydride; Ph_3SnH, triphenyltin hydride; TTMSH/$(TMS)_3SiH$, tris(trimethylsilyl)silane; Bu_3GeH, tributylgermanium hydride; Bu_3SnCl, tributyltin chloride; Bu_3SnF, tributyltin fluoride; AIBN, azobis(isobutyronitrile); AMBN, azobis(methylisobutyronitrile); ACN, 1,1′-azobis(cyclohexanecarbonitrile); VA-061, 2,2′-azobis[2-(2-imidazoline-2-yl)propane]; EPHP, *N*-ethylpiperidine hypophosphite; CTAB, cetyltrimethylammonium bromide; $Zn(OTf)_2$, zinc(II)triflate; $(EtO)_2P(O)H$, diethylphosphite; TMEDA, *N*,*N*,*N*,*N*-tetramethyl-1,2-ethylenediamine; $Mn(OAc)_3$, manganese triacetate; $Cu(OAc)_2$, copper diacetate; HOMO, highest occupied molecular orbital; $Na(CN)BH_3$, sodiumcyanoborohydride; PhSH, thiophenol; THF, tetrahydrofuran; $Cp_2Zr(H)Cl$, Schwartz reagent; SmI_2, samarium diiodide; DLP, dilauroyl peroxide; DFT, density functional theorem; ATRC, atom transfer radical cyclisation; HPLC, high-performance liquid chromatography.

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1970s. The kinetic and structural information on various reactive intermediates was the first step in modern synthetic radical chemistry.[1–9] Beckwith[10] and Stork[11] reported that, under tin hydride annulated reaction conditions, a 5-*exo*/6-*endo* type of vinyl radical **1** cyclisation onto a C=C bond gives a mixture of both 5-*exo* and 6-*endo* products. The kinetic study of Beckwith[10] also showed that the initially formed five-membered ring radical **2** undergoes further isomerisation to produce the six-membered ring **3**. The fact that the five-membered ring closure is kinetically favoured is further supported by the work of Crich et al.[12] They pointed out the preferential formation of the 5-*exo* products by carrying out the reaction in a very rapid radical quenching system using PhSeSePh–Bu_3SnH (Fig. 1).

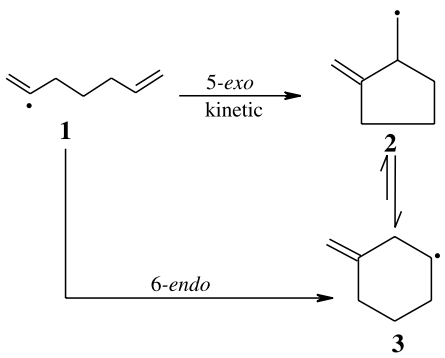


Figure 1. Vinyl radical cyclisations onto C=C bonds.

Similarly, a 5-*exo*/6-*endo* cyclisation of acyl radical **4** also gives a mixture of both 5-*exo* and 6-*endo* products (**5** and **6**, respectively) and, accordingly, the 5-*exo* cyclisation of acyl radicals onto a C=C bond is a kinetically favoured process[13a,b] (Fig. 2).

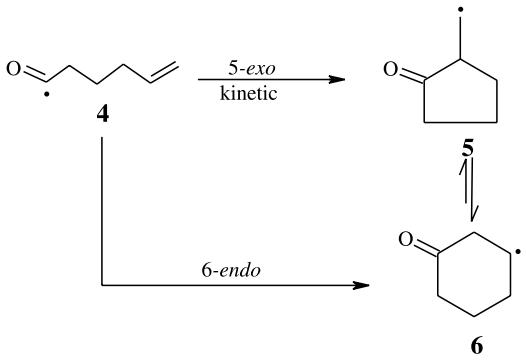


Figure 2. Acyl radical cyclisations onto C=C bonds.

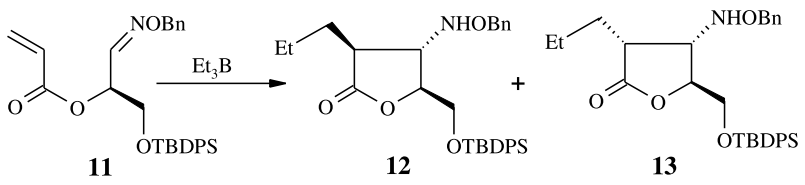
Among the numerous approaches and systems, which have been developed, some representative examples related to the formation of five- and six-membered heterocycles[13c] are discussed in this review.

2. Reagents, solvents and radical initiators used in radical cyclisation

Tin hydrides (Bu_3SnH, Me_3SnH and Ph_3SnH)[14] have been successfully employed in the synthesis of heterocycles using radical cyclisation. Generally, an excess of the tin hydrides with a smaller equivalent of a radical initiator like azobisisobutyronitrile (AIBN) are used in this type of reaction. An alternative procedure involves the use of a small amount of tri-*n*-butyltin chloride with sodium cyanoborohydride for the in situ generation of tri-*n*-butyltin hydride. Certain organotin compounds such as the trimethyltin derivatives are highly toxic,[15] whilst tributyl- and triphenyltins are only moderately toxic for mammals and moreover, it is very difficult to completely remove the toxic triorganotin byproducts, which are produced in stoichiometric amounts during the reaction. One of the most useful processes is the transformation of the excess, unreacted trialkyltin or triphenyltin halides to the corresponding easily removable, non-volatile, insoluble polymeric triorganotin fluoride by using aqueous potassium fluoride.[16] Purification of the product is, therefore, very difficult and various attempts have been made to overcome this problem. Due to this difficulty, various efforts have been directed towards tin-free radical chemistry.[17] Tris(trimethylsilyl)silane [$(TMS)_3SiH$] is commonly used in place of Bu_3SnH[18–22] and is slightly less reactive than Bu_3SnH, but very expensive,[23–26] and the reaction conditions are analogous to the tin hydride-mediated reductions using AIBN as initiator in refluxing benzene or toluene. Tributylgermanium hydride (Bu_3GeH) is another expensive reagent that can be used for an improved cyclisation yield. One such example is the cyclisation of perfluoroalkenyl radicals[27] using Bu_3GeH. Generally germanes are more reactive than silanes, but less reactive than tin hydrides. In most cases, AIBN is used as the radical initiator. There are, however, other diazine initiators, for example, azobis(methylisobutyronitrile) [AMBN], which is more soluble and can be used in cyclohexane as well as in toluene as the solvent. Cyclohexane is found to be the preferred solvent for Bu_3SnH-mediated reactions because toluene and benzene not only act as a solvent, but may also participate in the radical reactions.

The use of water as a solvent is a tremendous development in the field of radical cyclisation. The radical reaction in aqueous media is advantageous from the point of view of cost, safety and environmental concern. Additionally, most of the organic radical species are stable in water. Water-soluble initiators are used for carrying out the radical reactions in water. Mono- and bicyclic tetrahydrofurans and dihydrobenzofurans have been synthesised by the use of tri-2-furylgermanium hydride as the radical mediator in water.[28]

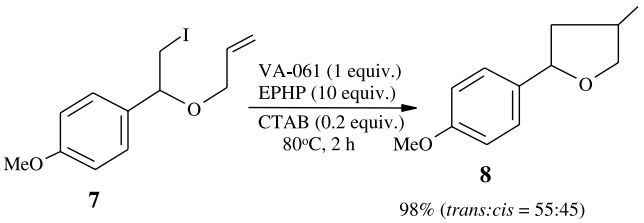
Recently, the radical cyclisations of hydrophobic substrates in water using the combination of 2,2′-azobis[2-(2-imidazolin-2-yl)propane] (VA-061), 1-ethylpiperidine hypophosphite (EPHP) and cetyltrimethylammonium bromide (CTAB) have been reported by Nambu et al.,[29] who observed that, when 2-iodo-1-(4-methoxyphenyl)-1-prop-2-enyloxy ethane **7** was treated with VA-061 as the water-soluble initiator and EPHP as the chain carrier, the cyclised product, 1-methoxy-4-(4-methyl-2-oxolanyl)benzene **8** was formed in 64% yield. By using 1–10 equiv. of NaCl as a 'salting out' salt, however, the reaction of the compound **7** proceeded more effectively and the yield of the product **8** was found to increase. It is important to note that a large quantity of a 'salting in' salt such as guanidine hydrochloride was necessary to facilitate the cyclisation reaction



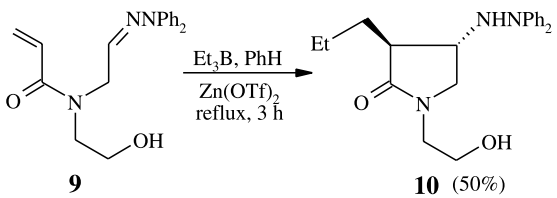
Solvent	T°C	Yield	Selectivity (**12**:**13**)
i) PhMe	reflux	70%	8:1
ii) PhH	reflux	64%	12:1
iii) PhMe	20°C	53%	18:1
iv) CH_2Cl_2	20°C	53%	10:1
v) H_2O/MeOH (1:4, v/v)	reflux	55%	9:1

Scheme 1.

of compound **7**. On the other hand, the reaction of **7** was best observed by using various surfactants (e.g., CTAB) in the presence of VA-061 and EPHP. The reaction did not go to completion in the presence of the commonly used radical initiator, AIBN.

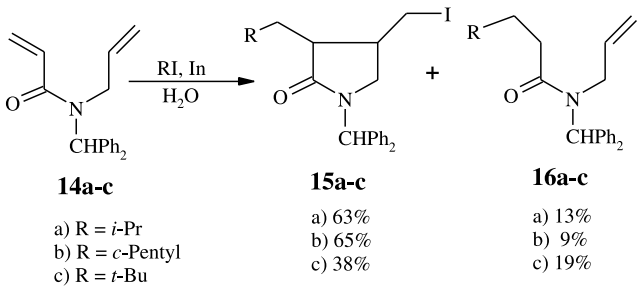


Triethylborane (Et_3B) is a useful reagent for radical cyclisation. The novel tandem radical addition cyclisation of oxime ethers and hydrazones intramolecularly concerted with the α,β-unsaturated carbonyl group is reported[30] by Miyabe et al. to give the heterocycles via a tandem C–C bond-forming process. The tandem reaction of the hydrazone **9** in the presence of the Lewis acid, $Zn(OTf)_2$, furnished only the *trans* cyclic product **10** and no *cis* isomer was formed.



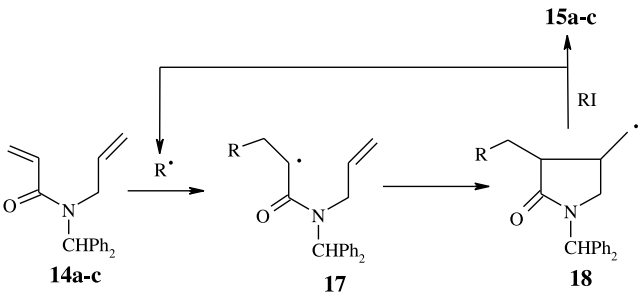
The radical addition cyclisation reaction of substrates having two different radical acceptors such as acrylate and aldoxime ether moieties has also been described. The reaction of the chiral oxime ether **11** in the presence of triethylborane in refluxing toluene proceeded smoothly to give a major diastereomer **12** in 70% yield, along with a small amount of another diastereomer **13**. The tandem reaction of **11** proceeded smoothly, even in aqueous media, providing a novel method for the asymmetric synthesis of γ-butyrolactones and β-amino acid derivatives[30] (Scheme 1).

Indium metal can be used for tandem carbon–carbon bond forming reactions as a single-electron-transfer (SET) radical initiator in aqueous media.[31] The radical addition–cyclisation reaction of hydrazones gave the functionalised cyclic products. The tandem addition–cyclisation trap reaction[31] of the substrate **14a** having acrylate and olefin moieties gives the desired cyclic product **15a** in 63% yield as a *trans*/*cis*-mixture in 3.2:1 ratio, along with 13% yield of the addition product **16a** (Scheme 2).



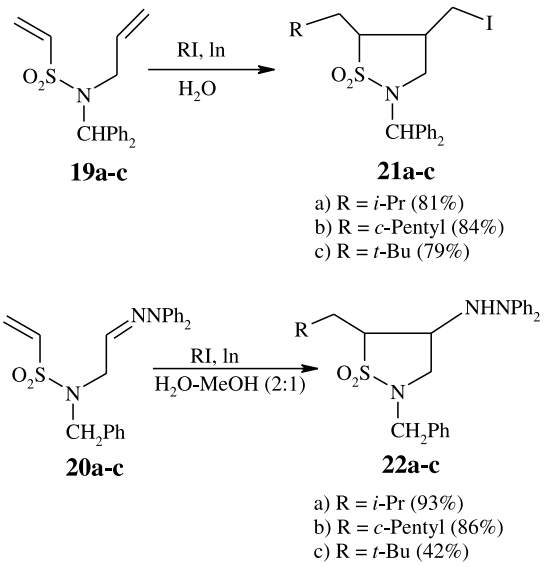
Scheme 2.

The preferential formation of the cyclic products **15a-c** over the addition products **16a-c** from **14a-c** could be explained by a radical mechanism. The indium-mediated reaction was initiated by single-electron-transfer to RI, with the generation of an alkyl radical. This radical then attacked the electrophilic acrylate moiety of **14** to generate the carbonyl-stabilised radical **17**. The cyclic products **15a-c** were obtained via the intramolecular reaction of the radical **17** with the olefin moiety, followed by an iodine atom transfer reaction from RI to the intermediate primary radical **18** (Scheme 3).



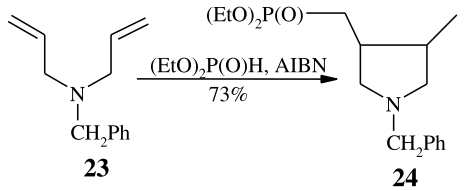
Scheme 3.

Similarly, the sulphonamides **19a-c** and the hydrazones **20a-c** produced only the cyclic products **21a-c** and **22a-c**, respectively. In these cases, other byproducts are not formed, due to the good reactivities of the sulphonamides and hydrazones as electron-deficient olefins (Scheme 4).

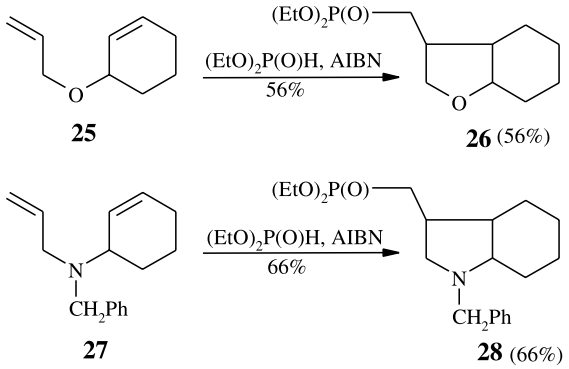


Scheme 4.

Diethyl phosphite, $(EtO)_2P(O)H$, an alternative and more versatile reagent for radical cyclisation was recently investigated by Parsons et al.[32] The reaction of the benzamide **23** with diethyl phosphite gave the pyrrolidine **24** in 73% yield when AIBN was used as the initiator or in 75% yield with Et_3B/O_2[33] at room temperature.



Bicyclic oxygen and nitrogen heterocycles could also be prepared by applying this methodology.[32] The cyclisation of the compounds **25** and **27** involved the reaction of diethyl phosphite with intermediate secondary (rather than primary) carbon-centred radicals to furnish **26** and **28** in 56 and 66% yield, respectively (Scheme 5).



Scheme 5.

The reaction of diethyl phosphite with tertiary carbon-centred radicals has also been demonstrated.[32] The yield for the cyclisations involving the intermediate tertiary carbon-centred radicals was rather lower and this may be explained by the greater stability of the tertiary carbon-centred radicals, which results in lower rates of hydrogen-atom transfer from diethyl phosphite.[34] In comparison to tin hydrides, phosphorous hydrides such as diethyl phosphite are inexpensive and non-toxic and it is also much easier to change the substituents on phosphorous.

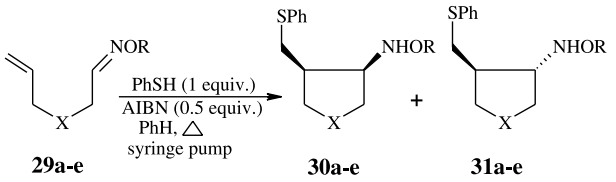
3. Synthesis of nitrogen heterocycles

3.1. Imine and enamine substrates and related systems

Bowman et al. have reported[35] alkyl radical cyclisations onto imino groups. Ryu et al. elaborated[36] the fact that a 5-*exo*/6-*endo* type of acyl radical cyclisation onto an N=C bond furnished 2-pyrrolidinones in a selective 5-*exo* manner. Recently, they also observed[37] that a 5-*exo*/6-*endo* type of vinyl radical cyclisation onto an aldimine N=C bond proceeds selectively in a 6-*endo* manner, to produce the methylenepiperidines.

9-(2-Bromoanilino)acridine was reported[38] to cyclise with tributyltin hydride and AIBN in boiling toluene to produce the pentacyclic acridines in very low yield (31%). The yield may be increased in the radical cyclisation reaction of *N*-alkylacridines to furnish 8-alkylquinoacridines.

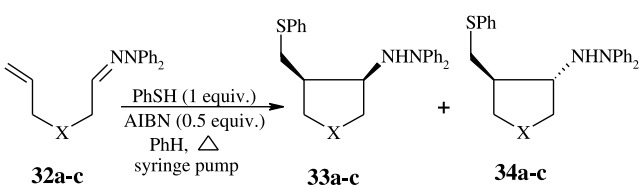
Naito et al. investigated[39] the radical cyclisation of various oxime ethers **29a-e** and obtained a mixture of the *cis* **30a-e** and *trans* compounds **31a-e** in combined yield (Scheme 6).



a) X = C(COOEt)$_2$, R = Me 76% (*cis*:*trans* = 4.0:1)
b) X = CH$_2$, R = Me 49% (*cis*:*trans* = 3.3:1)
c) X = NTs, R = Me 88% (*cis*:*trans* = 2.0:1)
d) X = NBoc, R = Me 62% (*cis*:*trans* = 3.0:1)
e) X = O, R = Bn 72% (*cis*:*trans* = 3.0:1)

Scheme 6.

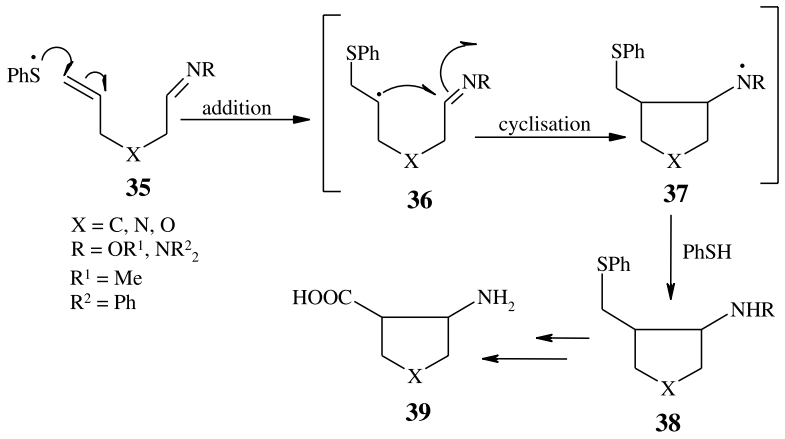
After the successful cyclisation of the oxime ethers **29a-e**, they investigated[39] the sulphanyl radical addition–cyclisation of various hydrazones **32a-c** to give a mixture of the *cis* **33a-c** and *trans* compounds **34a-c** in good combined yield (Scheme 7).



a) X = CH$_2$ 73% (*cis*:*trans* = 2.0:1)
b) X = NTs 75% (*cis*:*trans* = 1.5:1)
c) X = O 84% (*cis*:*trans* = 1.3:1)

Scheme 7.

Naito et al. then synthesised[39] the cyclic β-amino acids by a combination of sulphanyl radical addition–cyclisation of



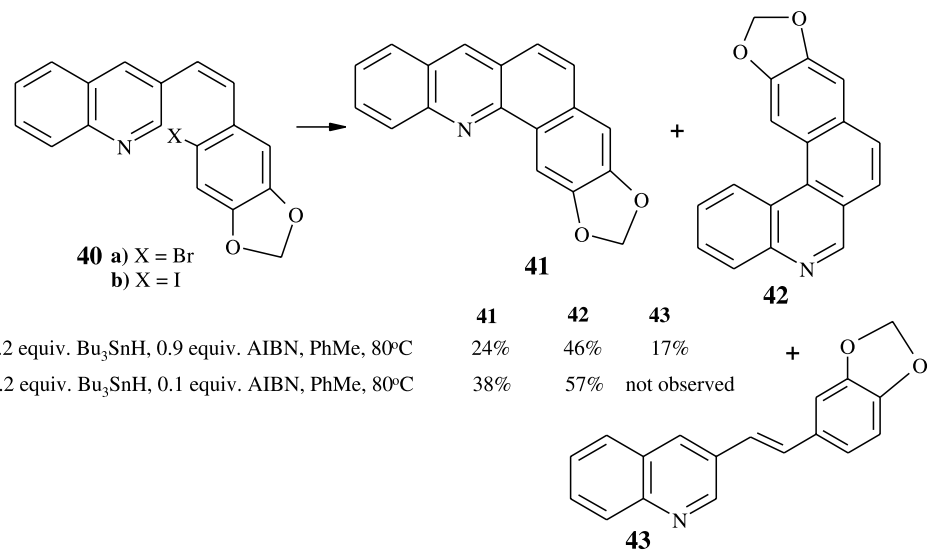
Scheme 8.

oxime ethers or hydrazones connected with alkenes and subsequent conversion of a phenylsulphanylmethyl group to a carboxyl unit. In this approach, a sulphanyl radical would attack the terminal alkenyl group in the substrates **35** to provide the alkyl radical species **36**, which are expected to form the substituted cyclic amines **38** via the aminyl radicals **37** as a result of 5-*exo-trig* cyclisation of **36**. Subsequent conversion of the phenylsulphanylmethyl group into the carbocyclic moiety would furnish the desired β-amino acid **39** (Scheme 8). This methodology has been successfully applied for the synthesis of a wide range of both natural and unnatural cyclic β-amino acids.

Radical additions to C-2, C-3 and C-4 of a quinoline have all been shown to proceed under neutral conditions.[40] In each case, the formation of heteroaromatic products, rather than dihydroquinolines, was observed by an oxidative tin hydride pathway. Treatment of the *cis*-azastilbene **40a** with tributyltin hydride under radical-forming conditions led to a separable mixture of the C-2 addition product **41** (24%) and the C-4 addition product **42** (46%), along with some *trans*-azastilbene **43** (17%). Similarly the iodo compound **40b** gave a mixture of compound **41** and **42** in 38 and 57% yield, respectively. In this case compound **43** was not obtained (Scheme 9).

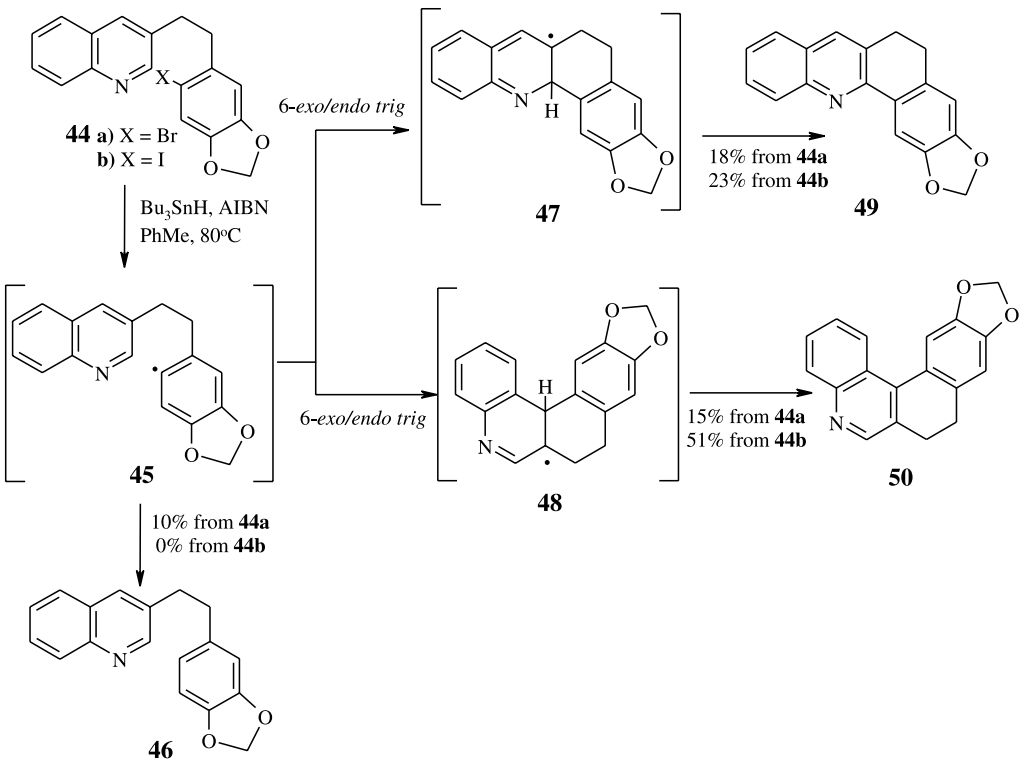
The cyclisation of **44a**,**b**, where a saturated two-carbon chain conjoined the quinoline and the aryl halide, led to a complex product mixture. The bromo derivative, 3-[2-(6-bromo-1,3-benzodioxol-5-yl)-ethyl]quinolone **44a** furnished the cyclisation product **49** in 18% via intermediate **47** and compound **50** (15%) via intermediate **48**. Additionally some recovered starting material (27%) and the dihydroazastilbene **46** (10%) following intermediate **45** could also be isolated. The reaction with the corresponding iodo compound **44b** proceeded more efficiently, however, yielding dihydrobenzo[*c*]acridine **49** and dihydrobenzo[*k*]-phenanthridine **50** in 23 and 51% yield, respectively in the same manner (Scheme 10). It is important to note that 5-*exo*/5-*endo-trig* radical cyclizations to quinolines fail and therefore appear to be more akin to 5-*endo-trig* processes than 5-*exo-trig* processes.

The radical addition to C-3 of quinoline can occur in different ways, for example, substrates in which the radical precursor was tethered at C-2 or C-4 of the quinoline moiety



	41	42	43
40 a: 1.2 equiv. Bu_3SnH, 0.9 equiv. AIBN, PhMe, 80°C	24%	46%	17%
b: 1.2 equiv. Bu_3SnH, 0.1 equiv. AIBN, PhMe, 80°C	38%	57%	not observed

Scheme 9.



Scheme 10.

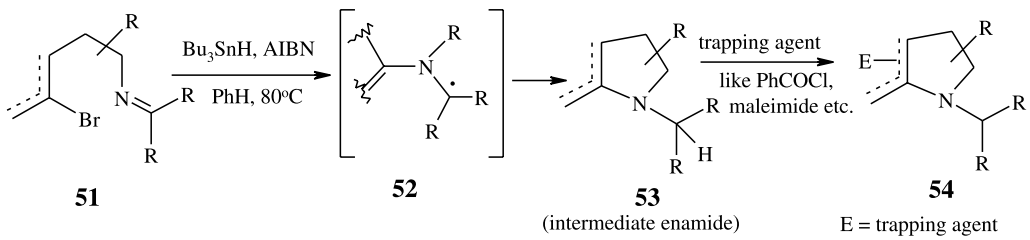
afforded different six-membered cyclised products in variable yields.

Ketimines derived from *o*-bromophenethylamine were reported[41] to cyclise to the *N*-substituted indolines under *n*-Bu_3SnH-mediated radical cyclisation conditions.

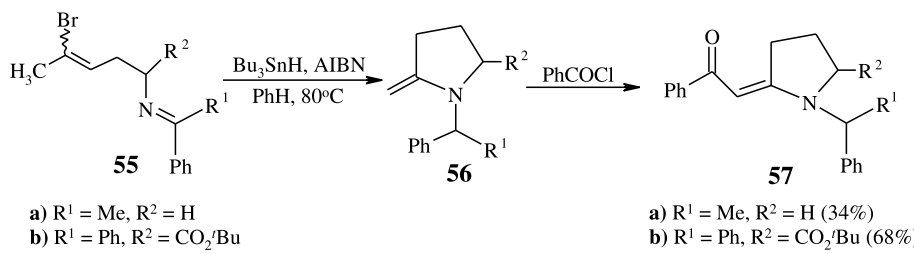
Johnston et al. have described[42,43] the free radical-mediated vinyl amination by non-conventional vinyl radical addition to azomethine nitrogen, following 5-*exo-trig* cyclisation, and this protocol is shown in Scheme 11, this involve sequential conversion of compound **51** to **54** via the intermediate **52** and **53**, respectively.

It was observed that compounds **55** on treatment with Bu_3SnH–AIBN furnished compounds **56**, which were trapped with benzoyl chloride to generate the final compound **57** (Scheme 12).

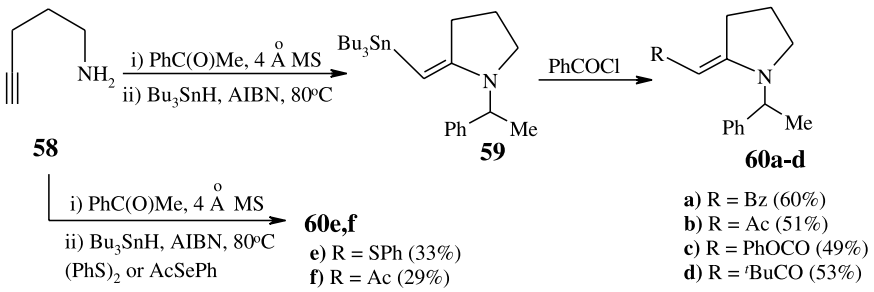
This new vinyl amination protocol is very useful for synthetic access to non-stabilised *N*,*N*-dialkyl enamines and tandem bond-forming processes.[42] Vinyl radicals might also



Scheme 11.



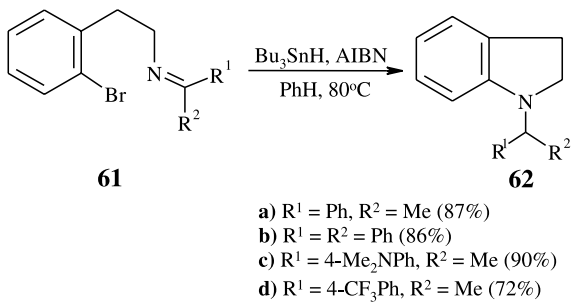
Scheme 12.



Scheme 13.

be produced by the addition of heteroatom-centred radicals to alkyne π-bonds and, accordingly, aminostannation was achieved by the addition of a stannyl radical to the ketimine obtained from the alkyne **58** in a highly regio- and stereoselective manner to give the β-stannyl enamine **59**. This enamine **59** was acylated at low temperature without the use of additives. A variety of acid chlorides varying in oxidation state and steric hindrance furnished the vinylogous amides and carbamates **60a-d**, ranging from 49 to 60% yield. Again, aminothiolation of the intermediate iminoalkyne provided the β-arylthioenamine **60e** in 33% yield with diphenyl disulphide as the thiyl radical precursor. Similarly, phenylselenoacetate and tributylstannane gave the product of aminoacylation **60f** in 29% yield (Scheme 13).

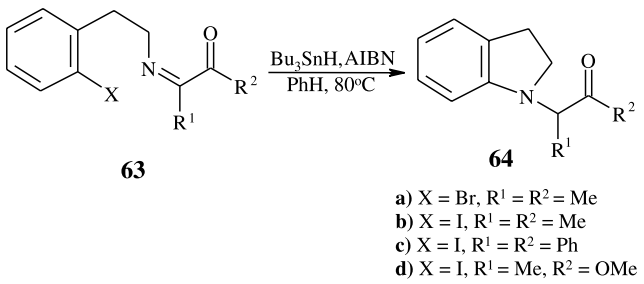
Recently, the tributyltin hydride-mediated radical cyclisation of various ketimines **61a-d** to provide **62a-d** was carried out to analyse the aryl radical additions to the nitrogen of azomethines.[44] Aryl, trifluoromethyl, alkyl and α,β-unsaturated ketimines are engaged in regioselective aryl nitrogen bond formation via 5-*exo* cyclisations of an aryl radical to the azomethine nitrogen. C–N bond formation is more selective than C–C bond formation and competes only with direct aryl radical reduction by the stannane (Scheme 14).



Scheme 14.

In the case of α-ketoimines **63a-d**, no such competitive aryl radical reduction was observed. The reaction conditions are pH 7 and are therefore the mildest methods available for the amination of an aromatic ring. Here, only indoline products **64a-d** were isolated and the reduction products arising of the aryl halides could not be identified in the crude reaction mixture (>200:1 cyclised/ArH) (Scheme 15).

Oxime benzoates have already been found to be convenient precursors for iminyl radicals.[45] Analogously, amidoxime



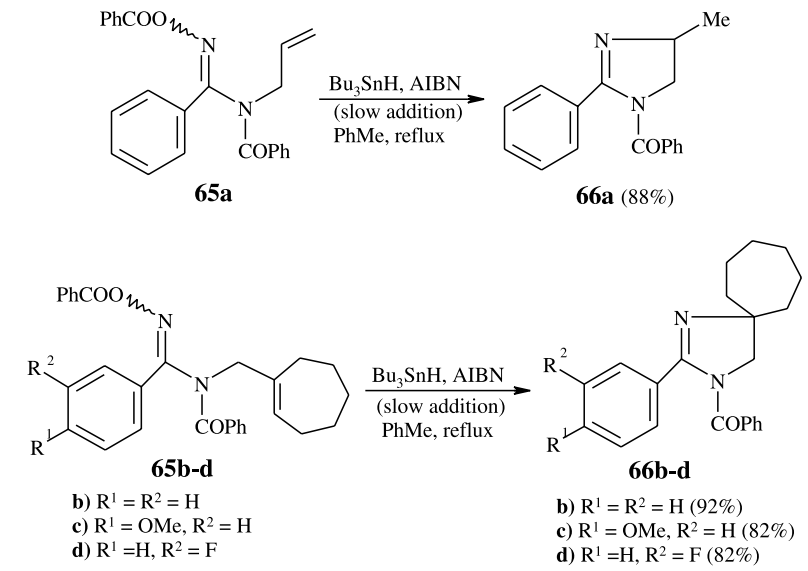
Scheme 15.

benzoates could act as substrates for generating the corresponding amidinyl radicals. The tri-*n*-butylstannane-mediated reactions of various amidoxime benzoates **65a-d** resulted in the smooth formation of the corresponding imidazolines **66a-d** in excellent yield.[46] Some reported examples are shown in Scheme 16.

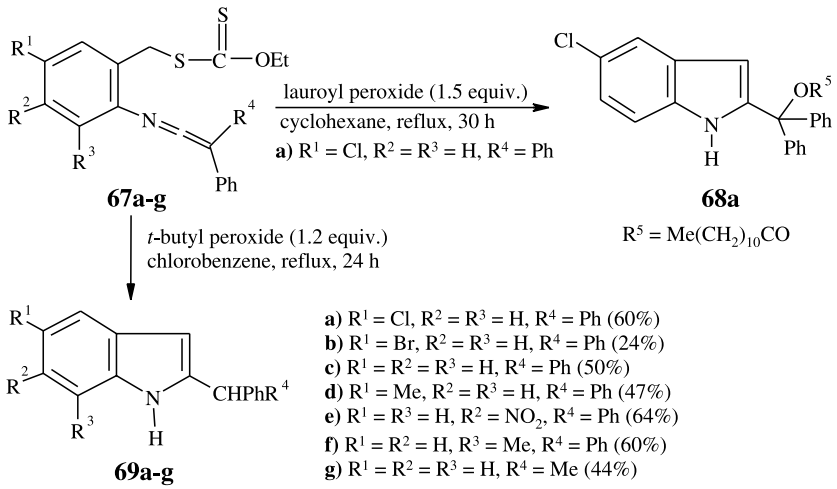
3.2. Substrates with ketenimine functions

A novel radical annulated synthesis of 2-alkyl indoles based on the intramolecular addition of benzylic radicals onto the central carbon atom of a ketenimine function following a 5-*exo-dig* cyclisation was described very recently.[47] Here, the radical cyclisation of the ketenimine **67a** was initiated by lauroyl peroxide in refluxing cyclohexane to furnish the indole-containing lauroyloxy fragment **68a** in 38% yield, along with a small amount of 5-chloro-2-diphenylmethylindole **69a**. On the other hand, if the reaction of the ketenimine **67a** was carried out in boiling chlorobenzene with stoichiometric amount of *t*-butyl peroxide, compound **69a** was obtained in 60% yield as the only product. When the ketenimine **67b-g** were initiated by *t*-butyl peroxide (1.2 equiv.) in refluxing chlorobenzene compounds **69b-g** were isolated in varying yield (Scheme 17).

The mechanism for the formation of **68** and **69** from **67** may be explained as follows. The radical $(R_o)^{\cdot}$ produced by the thermal decomposition of the peroxide initiator exchanges the xanthate group with the ketenimines **67** to give the expected benzylic radicals **70**, which then undergo a 5-*exo* addition of the radical moiety onto the central carbon of the ketenimine function, followed by a prototropic imine–enamine equilibrium, favouring the indole from **73**. The stabilised tertiary radicals **73** may undergo reduction to give indoles **69** or electron transfer to the lauroyl peroxide to produce the carbocations **74**. These carbocations **74** were then quenched by the carboxylate anion generated in the redox process to give the compounds **68**. The conversion of



Scheme 16.



Scheme 17.

67 to **69** is a reductive process and the source of hydrogen atom that quenched the radicals **73** is not obvious[48] (Scheme 18).

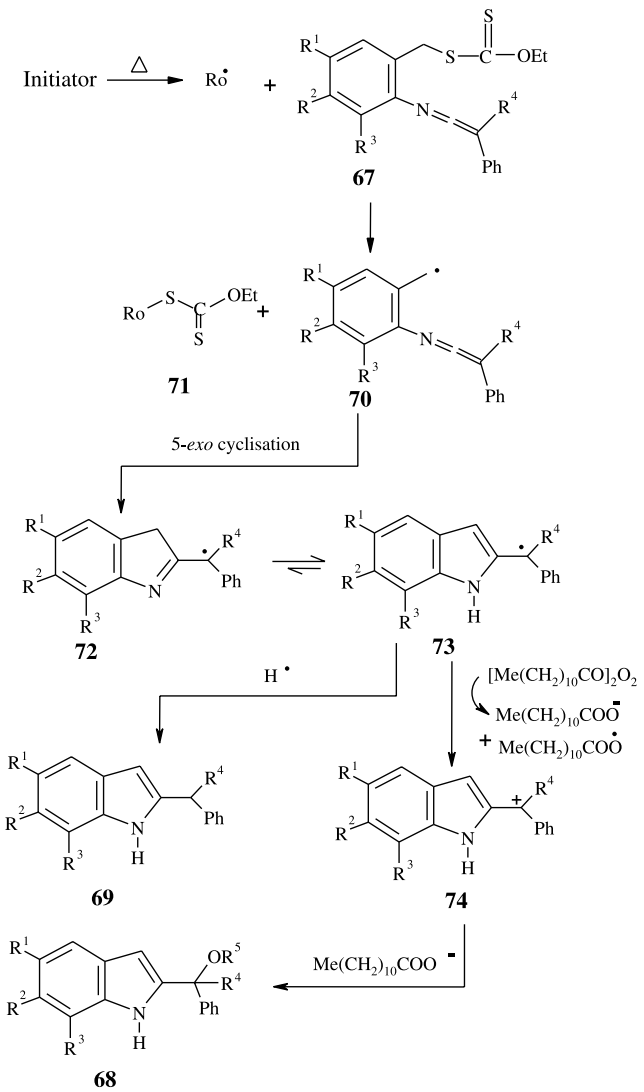
1-(2-Bromoethyl)-2-isocyanatobenzene **75** was allowed to react with tributyltin hydride by using thermal initiation with AIBN, photochemical initiation and conditions of slow organotin addition.[49] The main product, 3,4-dihydro-1*H*-quinolin-2-one **80**, was evidently formed by 6-*endo* cyclisation of the radical **76** to give the acylaminyl radical **77** that abstracted a hydrogen atom from the tin hydride. Alternatively, the cyclisation might be considered as 6-*exo*. Hydrogen atom abstraction by the O-centred mesomer of **77** might afford an iminol that would tautomerise to **80**. 2,3-Dihydroindole-1-carbaldehyde **81** was formed by 5-*exo* cyclisation at the *N*-terminus of the isocyanate group via **78** and this is followed by the abstraction of a hydrogen atom from tin hydride. A small amount of the direct reduction product **79** was also formed. The rate constants for the two processes were estimated and compared with reaction enthalpies computed by the density functional theorem (DFT) method (Scheme 19).

3.3. *N*-Vinylic substrates and related systems

9-(2-Bromo-*N*-methylanilino)acridine was cyclised[38] under normal radical cyclisation conditions to produce the 1,3-methylquinoacridine as the major product (50%). Similarly, 1-bromo-9-(*N*-methylanilino)acridine undergoes radical cyclisation to furnish the same product in 56% yield.

Aryl radicals generated by the homolysis of the Ar–Br bond by *n*-Bu_3SnH–AIBN have been used extensively as the key step in the establishment of the C_{aryl}–C_{alkyl} bond. This method has been applied to construct a variety of systems such as dihydroindoles,[50] benzofurans,[51] tetrahydro-β-naphthols[52] and oxindoles.[53]

In the synthesis of pyrrolophenanthridine alkaloids, *N*-(2-bromo-4,5-dimethoxybenzyl)-*N*-(2′-β-hydroxyethylphenyl)-



Scheme 18.

amine was prepared[54] in one of the steps and it was then refluxed for 12–13 h in benzene in the presence of AIBN by the slow addition of TBTH in benzene. Cyclisation of the tin-free residue obtained after chromatography furnished the phenanthridine alcohol as a colourless solid (27% yield).

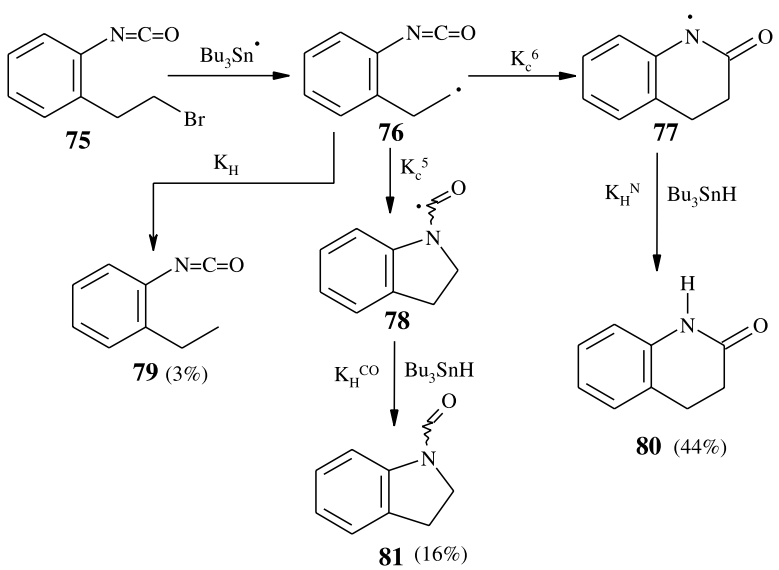
Tamura et al. have examined[55] the effect of a halogen atom in the 5-*endo* radical cyclisation of α-haloamides by employing the *N*-benzyl amides **82a**-**c**. The cyclisation ability decreased from the chloro to bromo to iodo amide (**82a→b→c**). $(TMS)_3SiH$ annulated reactions have exhibited the same tendency (Scheme 20).

The compound **82a** under normal radical cyclisation conditions (Bu_3SnH in the presence of AIBN in boiling toluene) afforded the cyclisation product **83** in 92% yield, while the compound **82b** gave a mixture of compound **83**, enamide **84** and the α,β-unsaturated product **85** in 55, 11 and 11% yield, respectively. The reaction of the α-iodo amide **82c** furnished the simple reduction product **86** in 68% yield, along with very small amount of the cyclisation products **84** and **85**. The effectiveness of the cyclisation of the α-iodo amides was restored by using Bu_3SnCl[56] or Bu_3SnF as additives (Scheme 20).

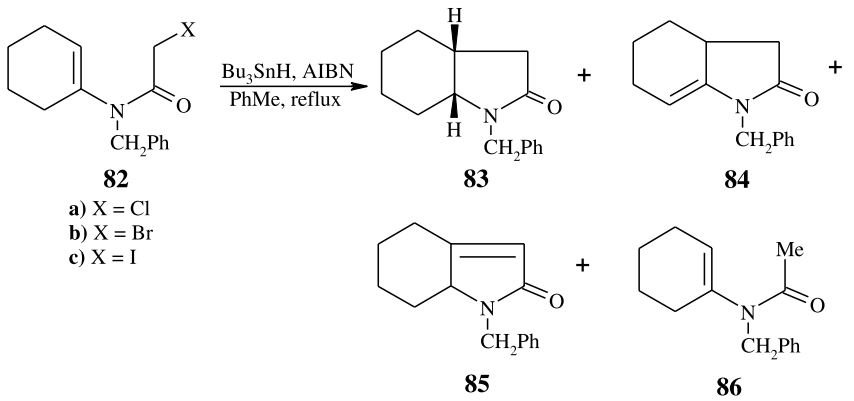
N-(α-Haloacetamido)dehydroalanine derivatives on treatment with tributyltin hydride in boiling benzene or toluene afforded the pyroglutamates in a disfavoured 5-*endo-trig* manner.[57] The *N*-benzyl substituent was found to be essential for this type of cyclisation, because the corresponding N–H derivatives furnished no pyroglutamate.

Dichloro and trichloroamides are found to be more efficient for the effective formation of pyroglutamate. The cyclisation of the S-phenyl derivative also furnished the pyrrolidinone as a 2:1 mixture of diastereomers in only 28% yield. Parsons et al. have explored[58] the Bu_3SnH-mediated radical cyclisation of various *N*-acryloxy-2-amino-2-cyclohexanones to afford the bicyclic lactams.

Influenced by radical-stabilising substituents such as



Scheme 19.



82
a) X = Cl
b) X = Br
c) X = I

83 **84** **85** **86**

Scheme 20.

methyl, phenyl, phenylthio, dimethyl or dichloro groups, the γ-lactam was prepared exclusively via 5-*endo-trig* cyclisation from a range of 2-halo-*N*-(3,4-dihydro-2-naphthyl)-acetamides.[59]

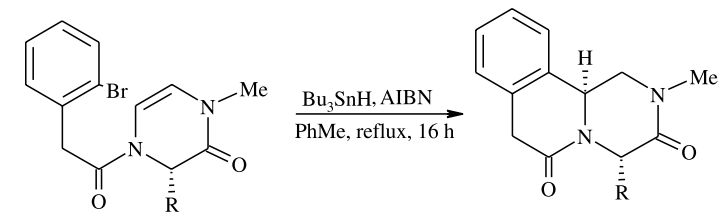
Ikeda et al. reported[60] the Bu_3SnH- or $(TMS)_3SiH$-mediated 5-*endo-trig* radical cyclisation of *N*-(cyclohex-1-enyl)-*N*-(4-methoxybenzyl)-2-(3,4-methylenedioxyphenyl)-2-(phenylseleno)acetamide to give a mixture of *cis*-fused (3*R**,3*aS**,7*aS**)- and *trans*-fused (3*R**,3*aS**,7*aR**)-3-aryloctahydroindol-2-ones, respectively. On the other hand, 5-*exo-trig* radical cyclisation of *N*-(cyclohex-2-enyl)-*N*-(4-methoxybenzyl)-2-(3,4-methylenedioxyphenyl)-2-(phenylthio)acetamide furnished *cis*-fused (3*R**,3*aS**,7*aR**)-3-aryloctahydroindol-2-ones in a stereoselective manner.

A novel radical cyclisation involving tributyltin hydride has been demonstrated[61] to form tri- and tetracyclic ring systems related to the Amaryllidaceae or Erythrina family of alkaloids. The radical cyclisation of dichloroethanamides was reported to generate a 5,6-bicyclic ring system.

The chloroethanamide having a ketone group at C-3 (instead of C-6) under tributyltin hydride-mediated radical cyclisation conditions furnished a very small amount (16%) of octahydroindolone. This clearly suggests that the efficiency of the 5-*endo* cyclisation is influenced only when the ketone group is placed at C-6.

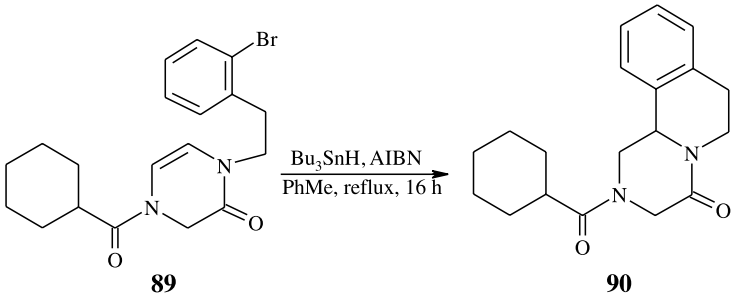
The tributyltin hydride-mediated radical cyclisation of *N*-(2-phenylthiocyclohex-1-enyl)-α-haloamides has also been reported.[62] Bromoacetamides having no substituent α- to the halogen atom cyclised exclusively in a 4-*exo-trig* manner, whereas the fully substituted haloamides gave the 5-*endo-trig* cyclization products. This clearly indicates that the mode of cyclisation is affected by the size of the substituents around the radical centre.

Radical cyclisations providing five-membered rings are



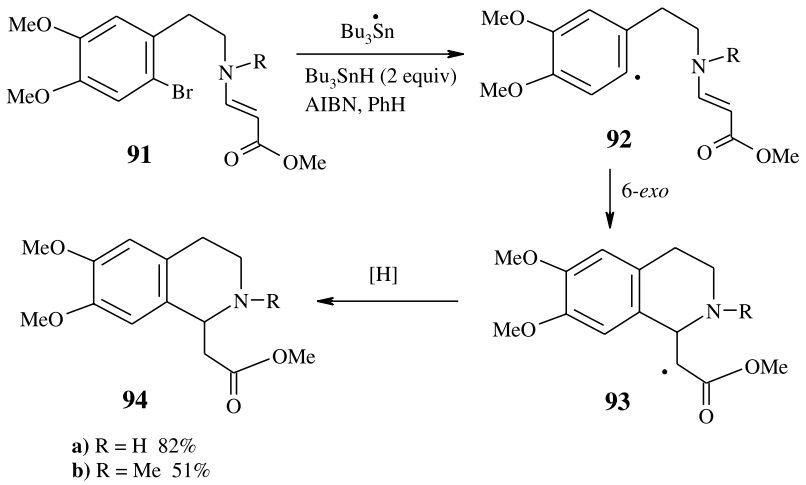
87

88
a) R = Bn (80%)
b) R = *i*-Pr (70%)
c) R = Me (71%)



89 **90**

Scheme 21.



Scheme 22.

highly stereoselective.[63–66] Although the formation of six-membered rings via radical cyclisations is less common compared to the five-membered rings, it still has an important role in synthesis. The Bu_3SnH-mediated radical cyclisation of *o*-iodobenzamide was reported to produce phenanthridone via 6-*endo* cyclisation.[67]

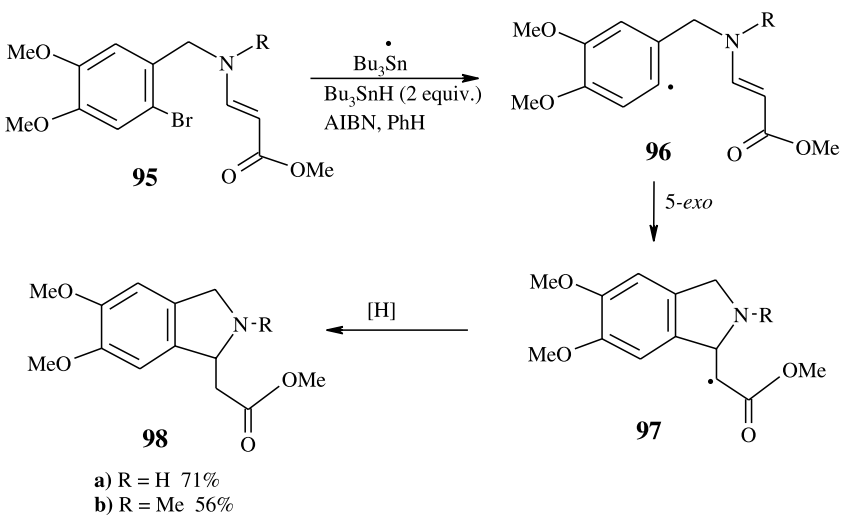
Ishibashi et al. reported[68] that *N*-vinylic-*o*-iodobenzamides upon treatment with Bu_3SnH–ACN gave mainly the 5-*exo* cyclisation product. The enamide having a phenyl substituent on the vinyl carbon atom α- to the nitrogen atom, however, gave predominantly the 6-*endo* cyclisation product.

Todd et al. encountered difficulty in developing a general synthesis of the fused-ring system via the acyliminium intermediate and therefore turned their attention to radical cyclisation as an alternative approach. Influenced by the success of Rigby et al.[69] and Ishibashi et al.[70] with the ring closure of aryl radicals onto acyclic enamides, Todd et al. applied a similar protocol to the acyl pyrazinone intermediate **87**.[71] Tri-*n*-butyltin hydride-mediated radical cyclisation of the bromophenyl dihydropyrazinone **87** furnished the peptide mimics **88** in good yield via 6-*exo* selectivity (Scheme 21).

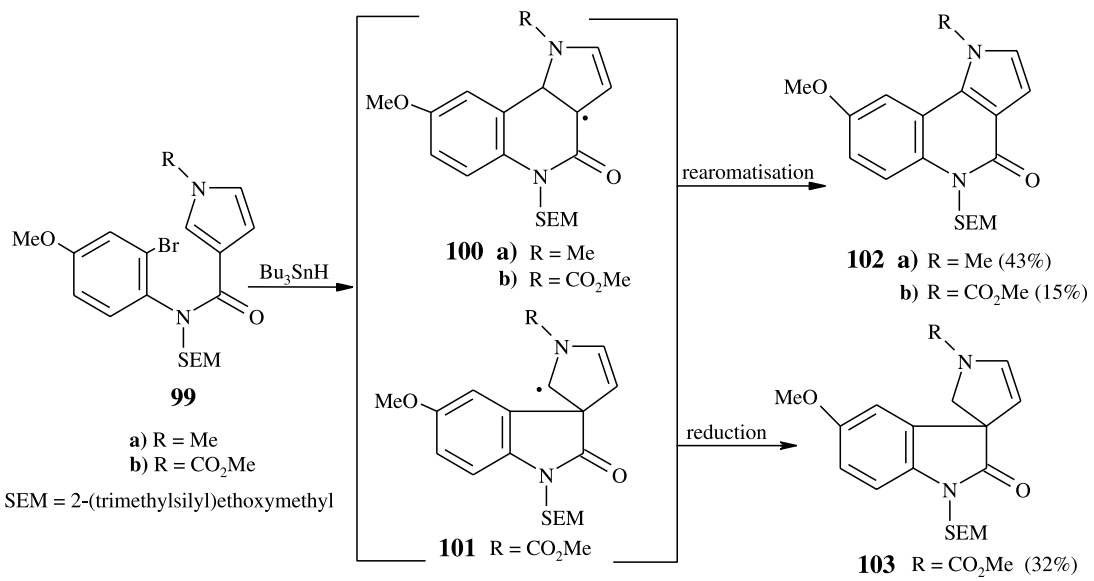
The anthelmintic drug praziquantel **90** has been synthesised[71] following the radical-initiated cyclisation of the pyrazinone **89**. The tetracyclic galanthan alkaloid ring system has also been prepared by a Bu_3SnH-mediated radical cyclisation of aryl radicals[72] (Scheme 21).

Radical cyclisations of highly reactive aryl radicals onto double and triple bonds are very useful to construct carbocycles and heterocycles[1,8a,73] and especially aza heterocycles.[73b] Various sizes of aza heterocycles have been obtained by radical addition to *N*-vinyl amides (enamides).[70,74,75] *N*-Vinyl unit-containing compounds like enamines,[76] *N*-sulfonyl enamines[77] and enaminones[78,79] are less common substrates for the additions.

Aryl radical cyclisation in *N*-phenyl, *N*-benzyl and *N*-phenethyl enaminones has been developed.[80] The tetrahydroisoquinolines **94** have been produced from the *N*-phenethyl enaminones **91** via aryl radical **92** and H-abstraction of the 6-*exo* ring closure product **93** (Scheme 22).



Scheme 23.



Scheme 24.

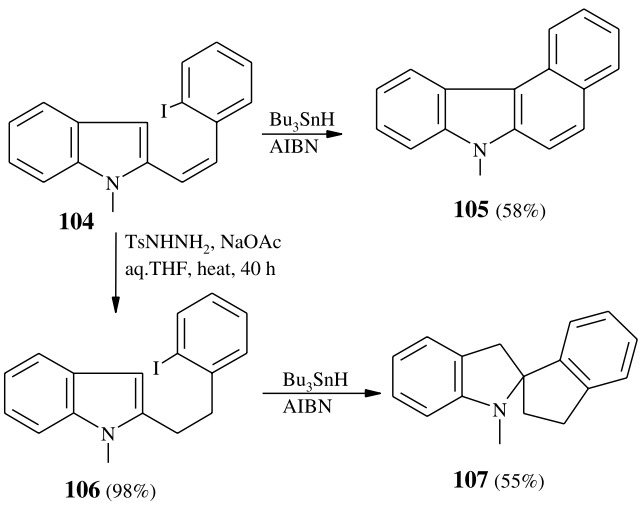
Similarly, the radical cyclisation of *N*-benzyl enaminones **95** afforded isoindoles **98** via intermediate radical **96** and H-abstraction of the 5-*exo*-ring closure product **97** in good yield (Scheme 23). No cyclised product was obtained from the *N*-phenyl enaminones.

Aryl radical cyclisation has been proved to be very useful in the development of modern heterocyclic chemistry and also in the synthesis of natural products.[81] Jones et al. have reported[82] that the regiochemistry of the cyclisation of aryl radicals onto pyrroles attached through an amide at the C-3 position is influenced by the *N*-substituent on the pyrrole. Pyrroles substituted with an electon-donating group (methyl) on nitrogen, for example, **99a**, gave exclusively 8-methoxy-1-methyl-5-(2-trimethylsilylethoxymethyl)-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinolin-4-one **102a** in 43% yield arising from 6-*endo* cyclisation following intermediate **100a**. No 5-*exo* or 6-*exo* cyclisation product was isolated from the reaction. On the other hand, pyrroles substituted on nitrogen with an elecron-withdrawing group (carbamate) such as **99b** gave cyclisation product **103** (32%) via intermediate radical **101**, along with a small amount of aromatised product **102b** in 15% yield via radical **100b** (Scheme 24). From the consideration of the above results, it has been concluded that the formation of either the spiropyrrolidinyloxindole or pyrrolo[3,2-*c*]qinoline nucleus from a common intermediate can be controlled by changing the substituent on the pyrrole, and the regiochemistry is not influenced by the substituents on the benzene ring.

2-Bromo-3-carboxamide was found to provide hexahydro-pyrrolo[3,4-*b*]indole[83] when refluxed in toluene in the presence of Bu_3SnH and a catalytic amount of AIBN. Some reduction product was also encountered from the reaction. This reaction is believed to involve the generation of the expected C-2 radical, followed by [1,5]-H atom abstraction to give the α-amidoyl radical and then 5-*endo-trig* cyclisation to the indole double bond, followed by hydrogen abstraction to give the indoline. Snieckus and Curran termed the first two steps in this process as radical translocation.[84]

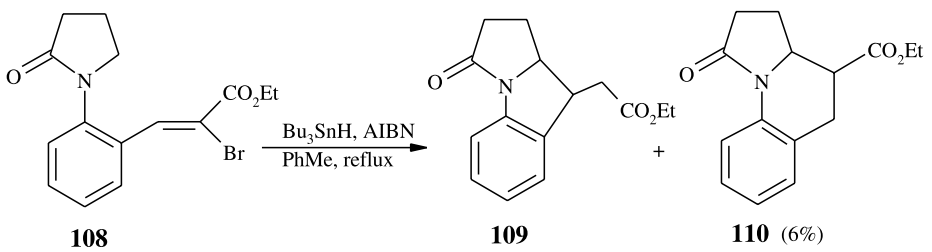
A few years ago, the synthesis of 2-stannylindoles was reported[85] by the radical cyclisation of 2-alkenyl-phenyl-isonitriles. With this result in view, Tokuyama et al. have synthesised[86] 2,3-disubstituted indoles by a Bu_3SnH annulated radical cyclisation of 2-alkenylthioanilides. The *cis*-isomer of the 2-alkenylthioanilide on treatment with Bu_3SnH–AIBN in toluene at 80 °C for 5 min furnished the expected 2-*n*-pentyl-3-(acetoxymethyl)indole in 93% yield. The same product was obtained within 5 min at room temperature by using Et_3B as the radical initiator.[87]

Recently, it was observed[88] that the tributyltin hydride-mediated radical cyclisation of the 2-styrylindole **104** took place at C-3 of the indole via a 6-*endo-trig* pathway to produce the benzo[*c*]carbazole **105** in 58% yield as the major product. On the other hand, the radical cyclisation of the indole **106** generated the spirocycle **107** as the major product in 55% yield (Scheme 25).



Scheme 25.

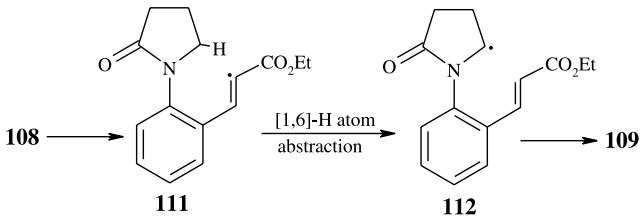
Parsons et al. have shown[89] that the 5,5,6-ring system present in mitomycins can be prepared via tandem radical



Scheme 26.

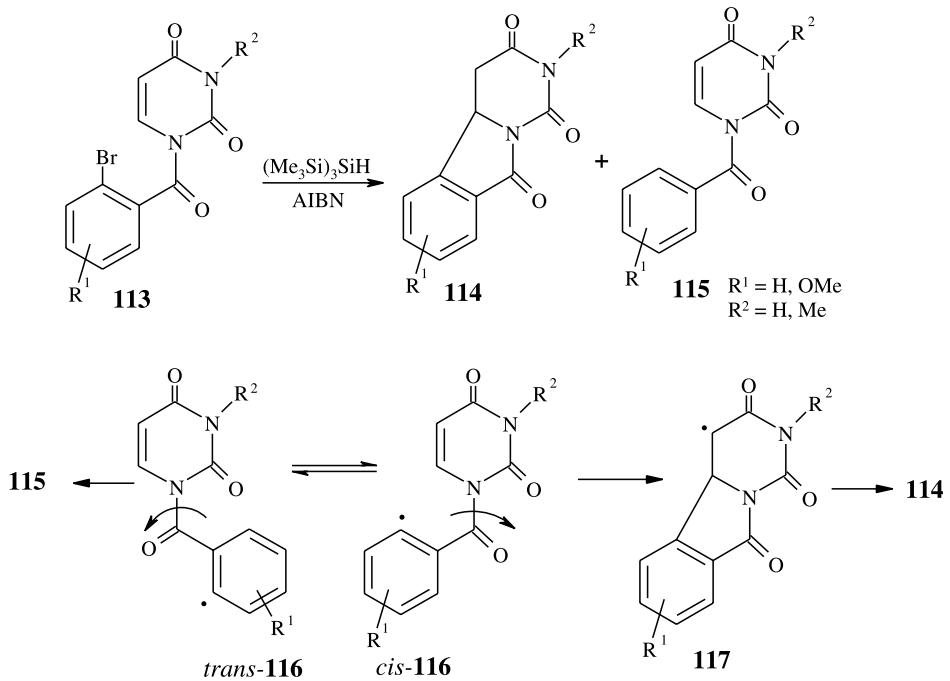
cyclisation sequences involving either a tandem 5-*endo*/5-*exo* radical cyclisation or, alternatively, a [1,6]-hydrogen-atom transfer, followed by a 5-*exo* cyclisation sequence. The reaction of compound **108** with tributyltin hydride and AIBN furnished the desired 5,5,6-tricycle **109** in 64% isolated yield as a 1.4:1 mixture of diastereomers. It is very important to note that the 6-*endo* product **110** was formed in only 6% yield (as a single diastereomer) and no simple reduced product was isolated (Scheme 26).

The ability to control the ratio of 5-*exo*/6-*endo* radical cyclisation pathways by appropriate substitution of the precursor is of particular mechanistic interest, as is the novel [1,6]-hydrogen-atom transfer reaction. The formation of the product **109** from **108** is based on the following mechanistic approach. Reaction of the compound **108** with the tributyltin radical should produce a reactive vinyl radical **111**, which could undergo a rearrangement reaction to form the more stable pyrrolidinone radical **112**. Such an intermediate pyrrolidinone radical **112** could not be formed from a classical halogen-atom transfer route because of the difficulty in preparing the requisite 5-halopyrrolidinone precursor (Scheme 27).

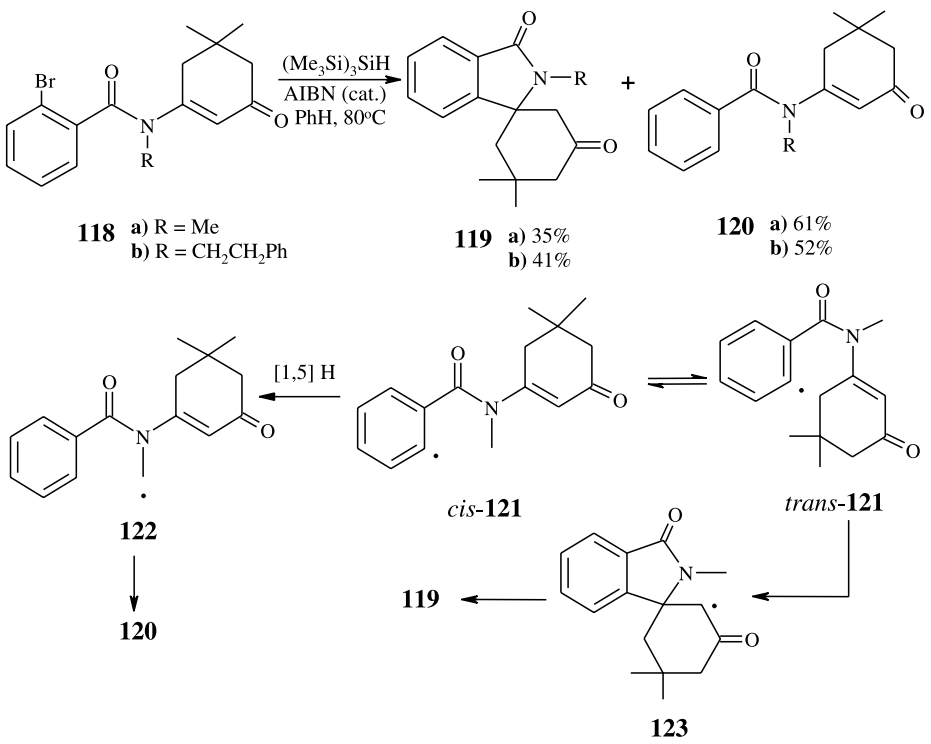


Scheme 27.

Recently, Zhang et al. have described[90] a general method for constructing a variety of nitrogen heterocycles. They treated the *N*-acylated cyclic nitrogen compounds **113** with $(TMS)_3SiH$ and AIBN to generate the tricyclic isoindolinones **114** as the major product via radical **117**, along with some reduction product **115**. In this case, the initial radical **116** is generated from **113** and is equilibrated between the *cis*- and *trans*-amide conformation. Only the *cis*-amide conformation (*cis*-**116**) underwent the conjugate radical cyclisation to give **114**. The *trans*-amide conformation (*trans*-**116**) gave the direct reduction product **115** (Scheme 28).



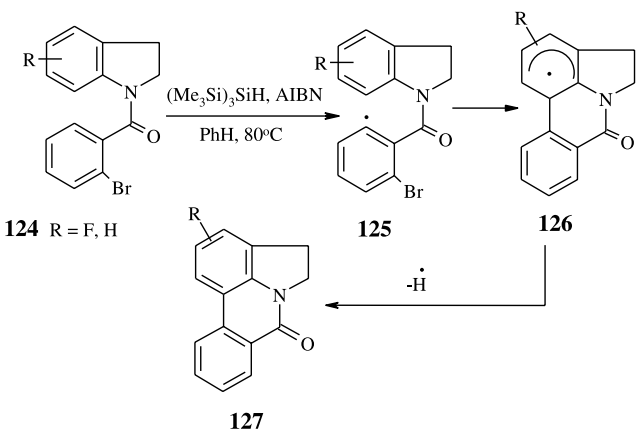
Scheme 28.



Scheme 29.

By the application of a similar protocol,[90] they prepared the spiroisoindolinones **119** from **118** via intermediate radical **123**. In this case, the yields of the cyclisation products were very low (35–41%) and significant amounts of the direct reduction products **120** were obtained (52–61%). It was proposed that the equilibrium between *cis*-**121** and *trans*-**121** favours the formation of *cis*-**121** and the relatively stable α-amidomethyl radical **122** is generated from *cis*-**121** by a [1,5]-H atom transfer (Scheme 29).

Zhang et al. then extended their protocol to the synthesis of various tetracyclic isoquinolinones[90] **127** from compound **124** through the intermediates **125** and **126**. One such reported case is depicted in Scheme 30.

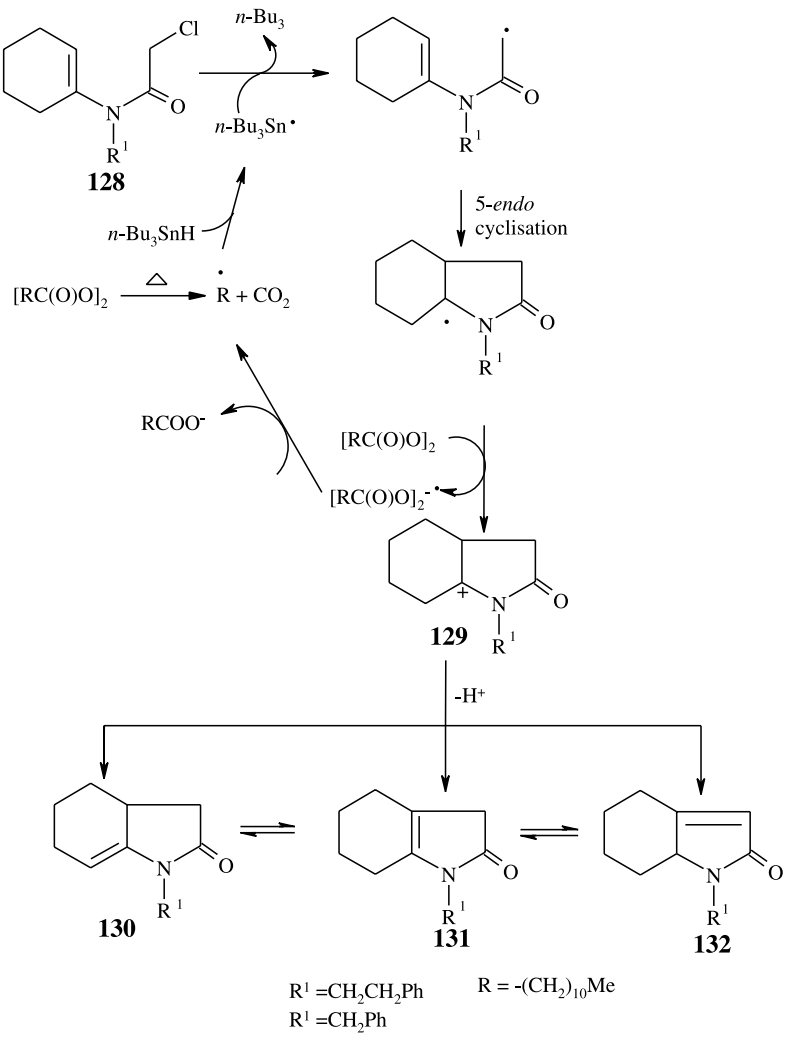


Scheme 30.

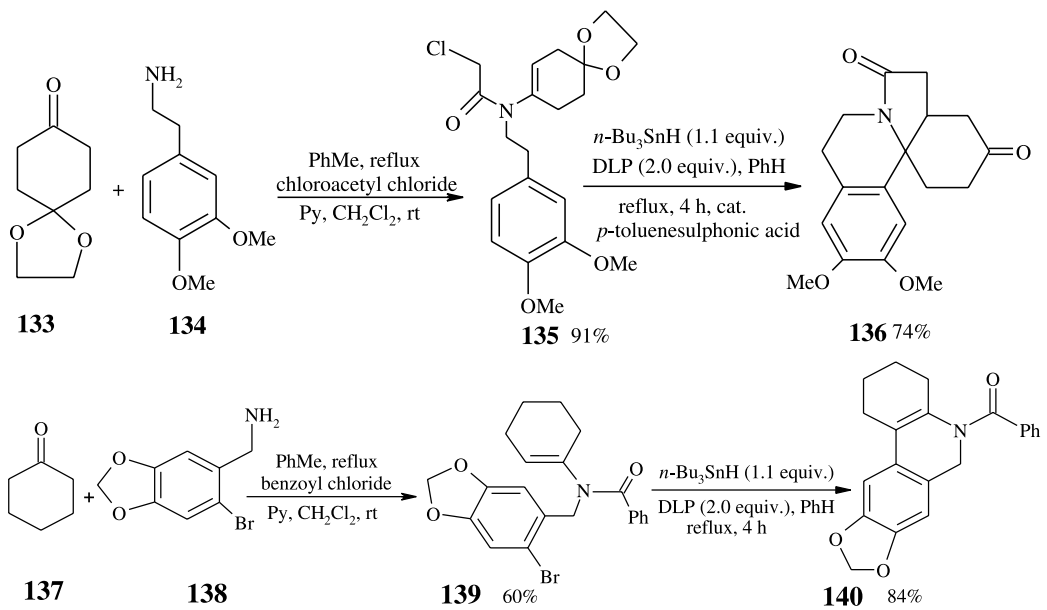
The oxidative radical cyclisation of enamides **128** by using *n*-Bu_3SnH and dilauroyl peroxide has recently been reported by Miranda et al.[91] and an efficient 5-*endo* and 6-*endo* oxidative radical cyclisation was observed. *n*-Bu_3SnH and dilauroyl peroxide were used both as radical initiator and oxidant in cyclisations onto enamide systems. Dibenzoyl peroxide and dicumyl peroxide were also tested in the same reaction and the product yields were very similar to those obtained with dilauroyl peroxide.

The effectiveness of dibenzoyl peroxide and dicumyl peroxide in this process was also examined. The combined product yields were quite similar to those obtained with dilauroyl peroxide (DLP), but the product distribution was rather different with the dibenzoyl peroxide-mediated reaction. The tendency for the latter reaction to give mainly the most stable olefin **132** may be explicable by a faster conversion of **130** and **131** into **132** by the more acidic benzoic acid produced in this reaction (Scheme 31).

The erythrina and phenanthridine framework was constructed in a two-step sequence featuring the novel cyclisation. The chloroacetamide **135** was prepared in a two-step process from commercially available ketone **133** and amine **134**. The dibenzoyl peroxide mediated reaction failed to effect cyclisation of **135**, in the absence of *n*-Bu_3SnH. However, erythrina derivative **136** was isolated in 74% yield by adding a catalytic amount of *p*-toluenesulphonic acid to the reaction mixture after **135** had been consumed in the *n*-Bu_3SnH–DLP mediated radical cyclisation. The new *n*-Bu_3SnH–DLP oxidative radical cyclisation process was extended to an aryl bromide. The bromide **139** was prepared in two steps from the piperonal derived amine **138** and cyclohexanone **137** in moderate yield. Reaction of **139** under the above mentioned oxidative radical conditions furnished the thermodynamically stable olefins **140** exclusively in good yield (Scheme 32).

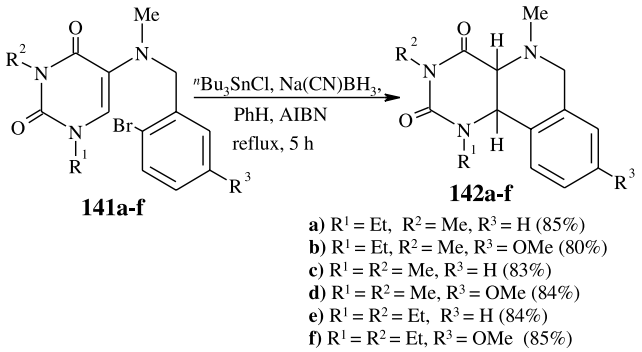


Scheme 31.



Scheme 32.

Recently we have reported[92] the regioselective synthesis of a number of pyrimidino[3,2-*c*]tetrahydroisoquinolin-2,4-diones **142a-f** from the 1,3-dialkyl-5-(*N*-2′-bromobenzyl,*N*-methyl)amino pyrimidine-2,4-diones **141a-f** by the intramolecular addition of an aryl radical to the uracil ring bearing the amino nitrogen atom (Scheme 33).



Scheme 33.

The formation of a six-membered heterocyclic ring in the products **142a-f** from the substrates **141a-f** may be easily explained by the initial formation of the aryl radical **143**, followed by a 6-*endo* ring closure to give a tertiary radical **146**, which may then accept a hydrogen radical to afford the final products **142a-f**. In an alternative route, the aryl radical **143** may undergo a 5-*exo*-ring closure to generate a spiroheterocyclic radical[93] **144**, which may be converted into the tertiary radical **146** via the radical **145** by a neophyl rearrangement[94] (Scheme 34).

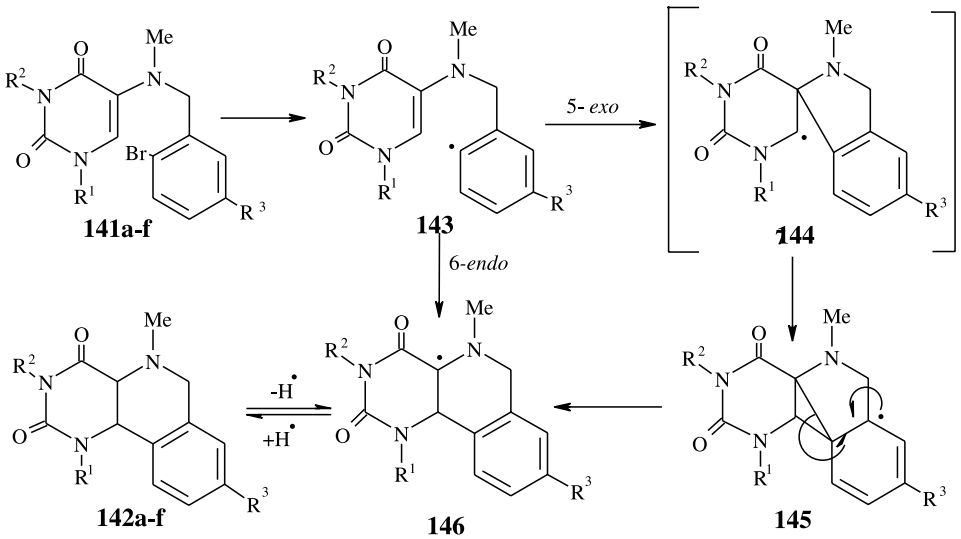
An interesting feature of this reaction sequence is that the usual aerial oxidation in this type of cyclisation with $^{n}Bu_3SnH$ is not observed and the dihydro compounds are isolated in excellent yield. The usual course during this type of cyclisation is that the initially formed dihydro products give oxidized products by aerial oxidation, that is, an oxidation step in the *n*-Bu_3SnH-mediated cyclisation.[9b,54,95]

3.4. *N*-Allylic substrates and related systems

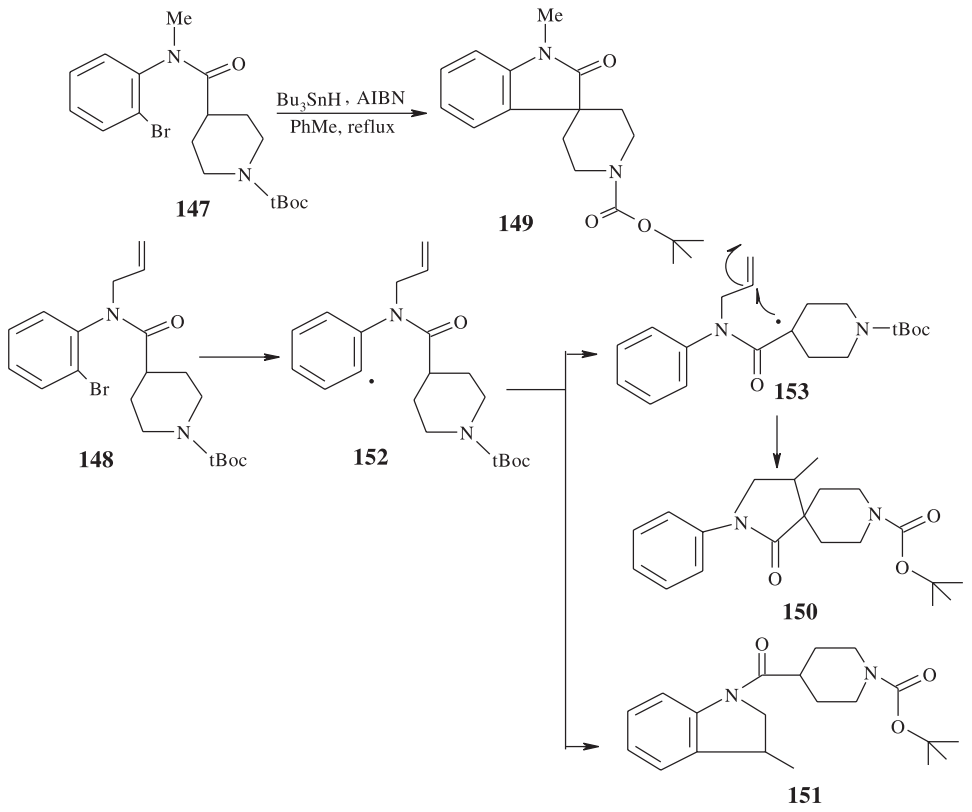
Several methods have been employed for the preparation of γ-lactams.[96,97] The formation of γ-lactams by the use of 5-*exo* or 5-*endo* cyclisation of a carbamoylmethyl radical has received considerable attention by researchers and the interest continues to grow.[1,5,8a,13c,95a,b,98] It is now well established that, in the Bu_3SnH-mediated radical cyclisations of ω-haloalkenes, an iodine atom is a better leaving group than a bromine or chlorine atom,[5] because of the lower C–I bond dissociation energy compared to that of a C–Br or C–Cl bond.[5] The result of using a chlorine atom as a leaving group for the radical cyclisation of ω-haloalkenes is therefore, an increase in the amount of the uncyclised reduction products. This trend was proved to be true in the Bu_3SnH-mediated 5-*exo* radical cyclisation of *N*-(cyclohex-2-enyl)-α-haloacetamides.[99,100] The fact that an iodine atom is a better leaving group for the Bu_3SnH-mediated radical cyclisation of ω-haloalkenes is not applicable to the 5-*endo-trig* cyclisation of α-haloamides having an alkenic sp^2 carbon atom α- to the amide nitrogen atom.

Storey[101] has described a novel synthesis of a series of spirocyclic pyrrolidin-2-ones under standard radical cyclisation conditions. The pyrrolidin-2-ones were obtained in excellent yield and are the result of a [1,5]-hydrogen atom transfer, followed by 5-*exo-trig* cyclisation.

The reaction of the compound **147** has been explored[102] in toluene solution with TBTH in the presence of AIBN at 100 °C for 2 h to synthesise the compound **149**. The formation of compound **149** in this study is difficult to rationalise, but there are several reported examples in the literature[103] relating to the formation of oxidation products during TBTH-mediated reactions. Under similar reaction conditions, the compound **148** produced a mixture of two compounds **150** (75% yield) and **151** (8% yield). Reaction of the compound **148** to give **150** and **151** could be rationalised as follows. The initial radical **152** undergoes *exo*-cyclisation, followed by abstraction of the newly formed radical by hydride to give **151**. The compound



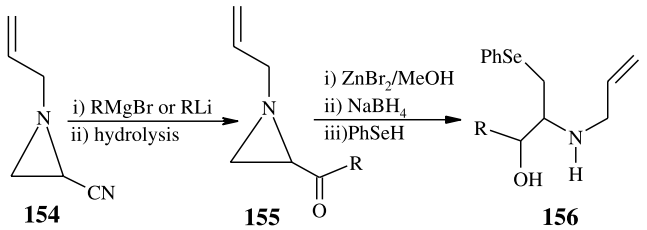
Scheme 34.



Scheme 35.

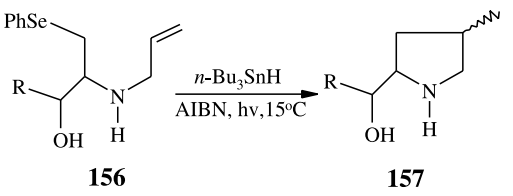
150, on the other hand, was formed by the rearrangement of **152** to the more stable radical **153**, followed by *exo*-cyclisation (Scheme 35).

Diasterocontrol by a hydroxyl auxiliary in the synthesis of pyrrolidines via radical cyclisation has been demonstrated by Engman et al.[104] Organoselenium radical precursors of 3-aza-5-hexenyl radicals carrying a 1-hydroxyalkyl group in the 2-position were prepared by the addition of organometallic reagents to *N*-allyl-2-aziridinecarbonitrile **154**, reduction of the resulting aziridine ketones **155** and regioselective benzeneselenol ring opening of the aziridines (Scheme 36).



Scheme 36.

Reductive radical cyclisation of compound **156** was achieved by photolysis in benzene in the presence of tributyltin hydride and AIBN at 15 °C. This cyclisation was highly selective, affording the corresponding *trans*-2,4-disubstituted pyrrolidine **157** (*cis*/*trans* ca. 1:10) as the major diastereomer (Scheme 37). Recrystallisation afforded material that was substantially more enriched in the *trans*-isomer (*cis*/*trans*<1:25). In this connection, it is important to note that cyclisation of radical precursors carrying a



a) R = Ph 82% (*cis*:*trans* = 1:9)
b) R = 2-thienyl 80% (*cis*:trans = 1:9)
c) R = *n*-Pentyl, 96% (*cis*:*trans* = 1:10)
d) R = *i*-Pr 81% (*cis*:*trans* = 1:12)
e) R = 2-(1,3-diox- 84% (*cis*:*trans* = 1:9)
olan-2-yl)ethyl

Scheme 37.

hydroxyl auxiliary in the side chain are much more *trans*-selective than they would be if the hydroxyl group was missing.

The high *trans*-selectivity (*cis*/*trans*=1:14) for the phenoxymethyl substituent could be due to intramolecular hydrogen bonding,[105] favouring an equatorial orientation of the 2-substituent in a chair-like transition state **A** (Fig. 3).

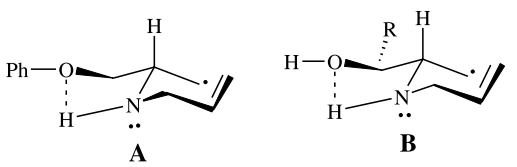
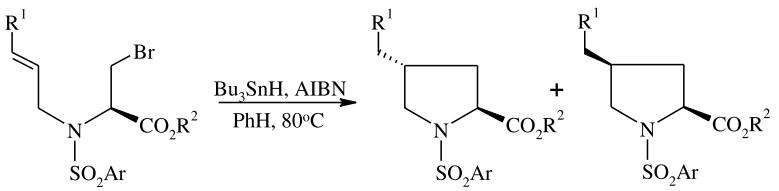


Figure 3. Hydrogen bonding in the transition state of the radical ring closure.



158a-f **159a-f** **160a-f**

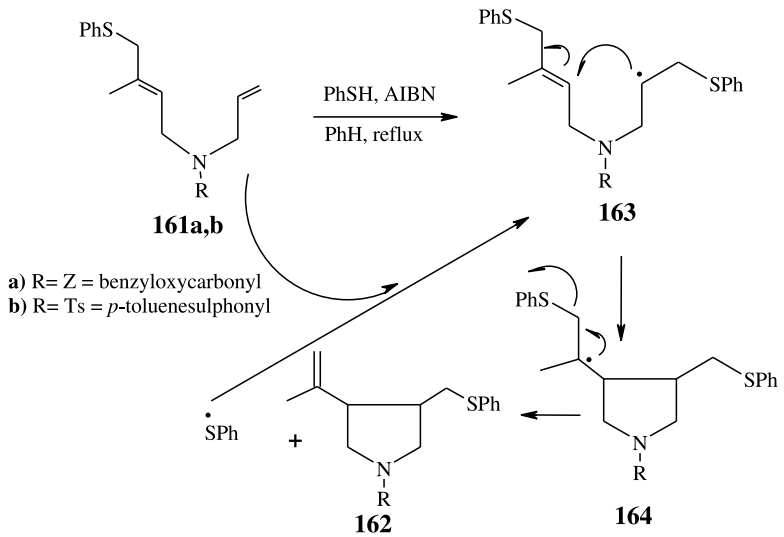
a) R^1 = H, R^2 = Bn, Ar = *p*-Tolyl	159a:160a = 3:1	80%
b) R^1 = H, R^2 = Bn, Ar = *p*-Nitrophenyl	159b:160b = 4:1	83%
c) R^1 = H, R^2 = Bn, Ar = *p*-Chlorophenyl	159c:160c = 4:1	85%
d) R^1 = H, R^2 = Bn, Ar = 2-Naphthyl	159d:160d = 8:1	85%
e) R^1 = H, R^2 = $CHPh_2$, Ar = *p*-Tolyl	159e:160e = 3:1	82%
f) R^1 = Ph, R^2 = Bn, Ar = *p*-Tolyl	159f:160f = 1.7:1	85%

Scheme 38.

Engman et al. have used a similar protocol to employ a hydroxyl substituent in the side chain as an auxiliary (favouring the transition state **B** in Figure 3) to increase the *trans*-selectivity in the cyclisation of 2-substituted 3-aza-5-hexenyl radicals.

Basak et al. subjected[106] the *N*-arylsulphonyl-*N*-allyl-3-bromo-L-alanines **158a-f** to tributyltin hydride-mediated intramolecular radical cyclisation to obtain enantiopure 4-substituted L-proline derivatives **159a-f** and **160a-f** in excellent yield. The predominant product was the *trans* isomers **160a-f** and the reaction followed an exclusive 5-*exo*-addition in all cases (Scheme 38).

The radical cyclisation of the carbamate **161a** has been demonstrated[107] in the presence of 1 equiv. of thiophenol and 0.5 equiv. of AIBN in benzene under refluxing condition to produce a mixture of the *cis*- and *trans*-pyrrolidines **162a** having an isopropenyl group in 22% combined yield as an inseparable mixture. The same reaction with 2 equiv. of thiophenol furnished the compound **162a** in 63% yield. Treatment of **161b**



161a,b

a) R= Z = benzyloxycarbonyl
b) R= Ts = *p*-toluenesulphonyl

163 **162** **164**

Substrate	PhSH (equiv.)	AIBN (equiv.)	Yield (%)
161a	1.0	0.5	22
161a	2.0	1.0	63
161a	0.2	0.2	16
161b	0.2	0.2	50

Scheme 39.

containing *N*-tosyl group with 0.2 equiv. of thiophenol afforded a 1:1 mixture of the *cis*- and *trans*-pyrrolidines **162b** in moderate yield. The mechanism of the reaction is shown in Scheme 39.

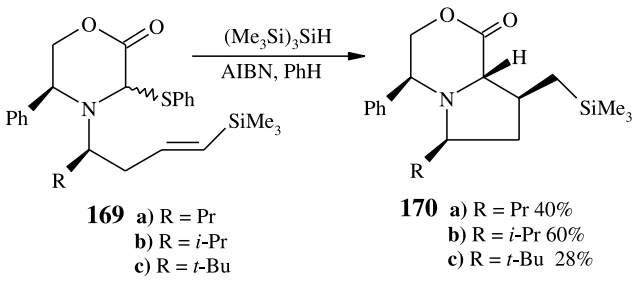
The first step of the reaction is the intermolecular addition of a phenylsulphanyl radical to the terminal olefin of **161**, producing the carbon-centred radical **163**, and then ring closure to the radical **164**, followed by subsequent β-elimination, leading to the isopropenylpyrrolidine **162** and a sulphanyl radical, which reacts with **161** to give back the radical **163**.

3.5. *N*-Propargylic substrates and related systems

The radical cyclisation of dipeptides proceeds smoothly to give five- and seven-membered rings in good to moderate total yield using Stork's catalytic tin hydride method.[108] The *N*,*N*-substituted dipeptides **165a-h** having a triple bond on a side chain were allowed to react with Bu_3SnH to furnish the products **167a-h** in good to moderate yield. Two types of side products were associated with the main product, one of which reflected the direct reduction of the radicals before any further cyclisation (**166a-h**). The second type of products (**168a-h**) resulted from a possible [1,5]-H transfer from the *N*-methyl group, followed by 7-*exo* cyclisation (Scheme 40).

3.6. Diastereoselective 5-*exo-trig* radical cyclisation

Recently, Agami et al. carried out[109] the transformation of β-amino alcohols having a vinylsilane functionality **169a-c** into the bicyclic derivatives **170a-c** via a diastereoselective 5-*exo-trig* radical cyclisation. The yield of **170c** may, however, be increased to 40% by using triethylborane as initiator and tris(trimethylsilyl)silane as hydrogen donor in refluxing benzene (Scheme 41).



Scheme 41.

It is important in this connection that two stereogenic centres are generated during these cyclisations. Here, the radical reacts with the double bond of the vinylsilane moiety by assuming a chair-like transition state[110] according to an axial approach[111] in a relative *anti* position to both the phenyl group and the R substituent. The radical undergoes 5-*exo-trig* cyclisation[112] and the chair-like transition state in which the vinylsilane adopts a pseudoequatorial position explains the absolute configuration of the second centre (Fig. 4).

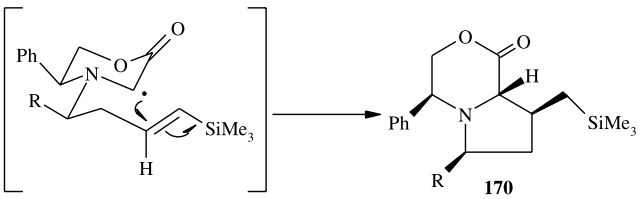
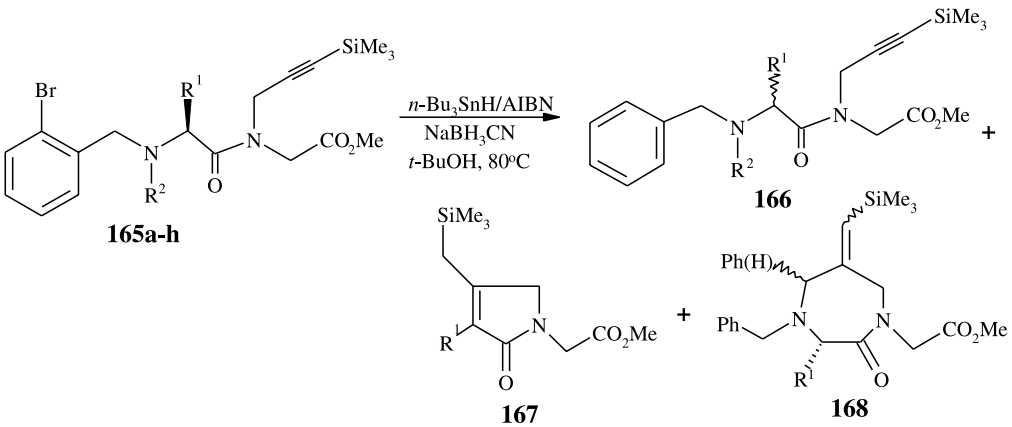


Figure 4. Stereochemical view point for the synthesis of enantiopure proline derivative.

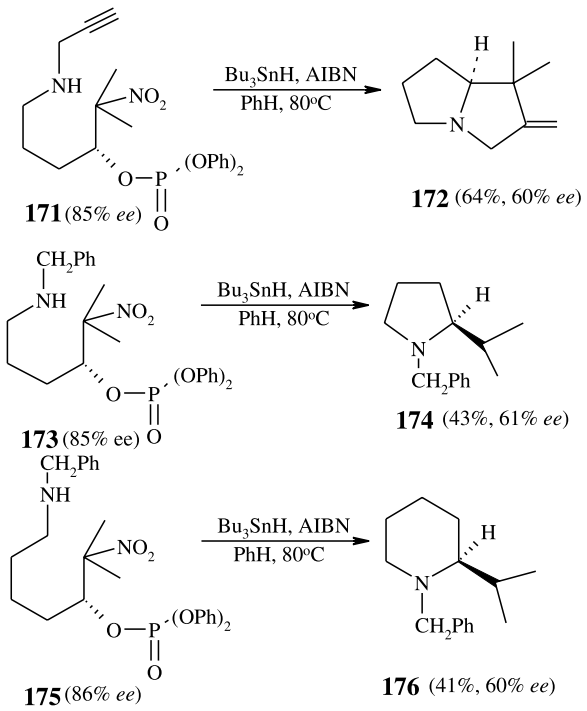
3.7. Enantioselective radical cyclisation

Crich et al. synthesised[113] pyrrolidines and piperidines with



	R^1	R^2	**166** (%)	**167**(%)	**168**(%)
165a)	H	Me	4	90	
165b)	Me	Me	17	68	9
165c)	Me	Bn	8	39	49
165d)	Et	Me	14	45	11
165e)	CH_2Ph	Me	17	37	10
165f)	*i*-Pr	Me	22	32	13
165g)	*i*-Bu	Me	36	32	11
165h)	$-CH_2CH_2CH_2-$		23	39	

Scheme 40.



Scheme 42.

significant enantioselectivity (~60% ee) from enantiomerically enriched β-(diphenylphosphatoxy)nitroalkanes by radical ionic fragmentation, induced by tributyltin hydride and AIBN in refluxing benzene. Substrate **171** (85% ee) under a tandem polar radical cross over reaction furnished the pyrrolizidine **172** in 64% yield (60% ee). Compound **173** on treatment with tributyltin hydride and AIBN in refluxing benzene resulted in the isolation of the pyrrolidine **174** in 43% yield and 61% ee. Considering the 85% ee of the substrate, it is readily calculated that **174** with 71% ee would be obtained if enantiomerically pure **173** were used in the cyclisation. The cyclisation of the next higher homologue **175** provided **176** in a very similar enantiomeric excess, demonstrating the extension of the model to the formation of piperidines (Scheme 42).

The absolute configuration of compound **173** and **175** is consistent with the model shown in Figure 5 in which nucleophilic attack occurs within the initial contact of the radical ions pair and on the face of the alkene radical cation opposite to that shielded by the departing phosphate group (as shown in the intermediate **177**).

3.8. Cascade/tandem cyclisation

Ishibashi et al. investigated[114] the radical cyclisation of enamide **178a** in the presence of 1.5 equiv. of Bu_3SnH and a catalytic amount of 1,1′-azobis(cyclohexanecarbonitrile) (ACN) in refluxing toluene to give a complex mixture of products from which **179a**, **180a** and **181a** were isolated in 11, 13 and 3% yield, respectively. Unfortunately, no expected radical cascade product was obtained from **178a**. The formation of **180a** and **181a** might be the result of 6-*exo* and 7-*endo* aryl radical cyclisations with the *N*-acryloyl group, respectively. The *N*-crotonoyl congener **178b** also furnished no cascade product; only the 6-*endo* and 6-*exo* aryl radical cyclisation products **179b** and **180b** were formed in 39 and 28% yield, respectively. In this case, no 7-*endo* cyclisation product **181b** was formed (Scheme 43).

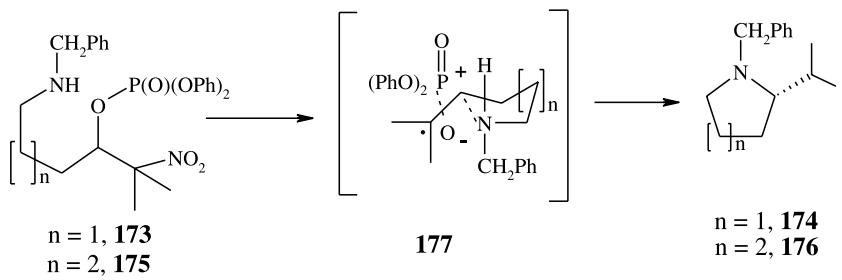
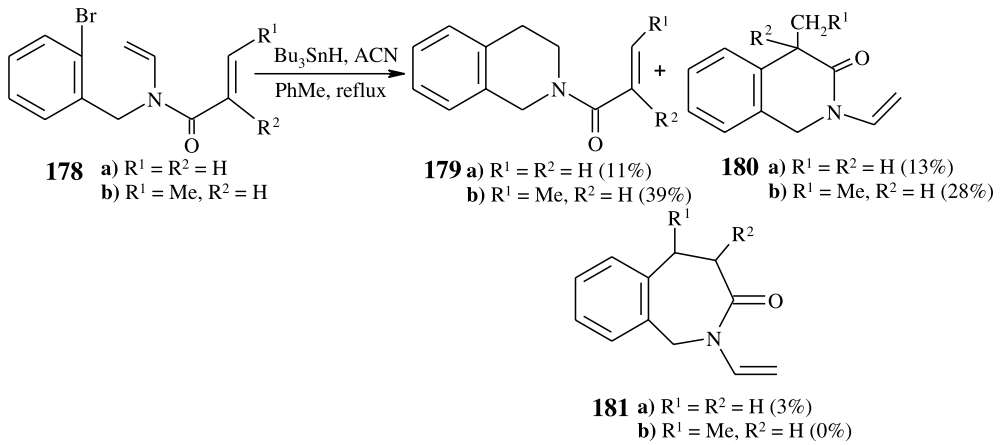
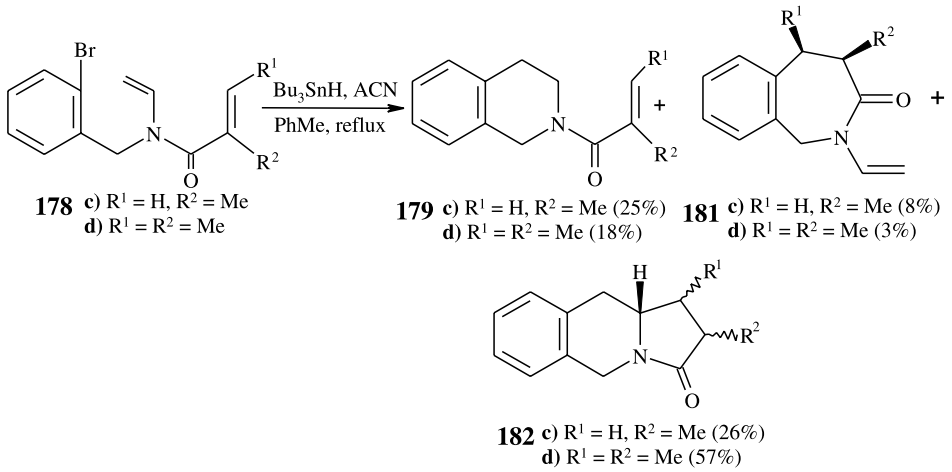


Figure 5. Enantioselective formation of heterocycles.



Scheme 43.

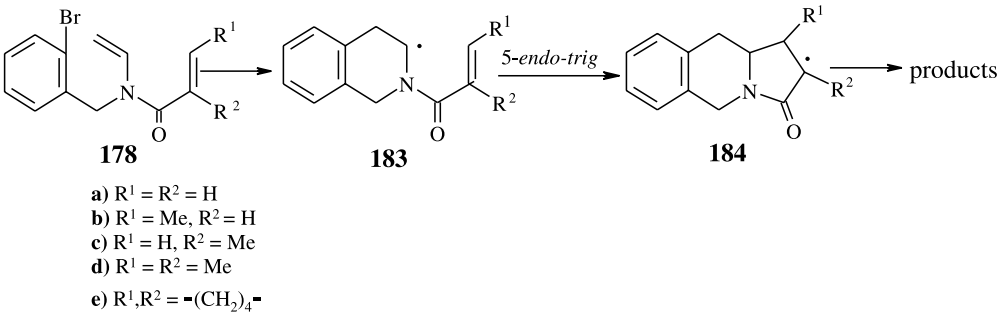


Scheme 44.

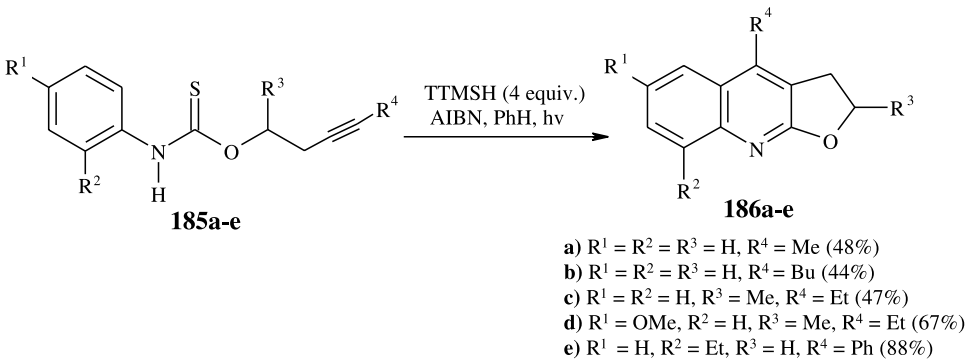
Treatment of the *N*-methacryloyl congener **178c** with Bu_3SnH/ACN, however, afforded the expected radical cascade product, 1,2,3,5,10,10*a*-hexahydro-2-methyl-pyrrolo[1,2-*b*]isoquinolin-3-one **182c**, in 26% yield as a mixture of two stereoisomers in a ratio of ca. 3:2, along with **179c** and **181c** in 25 and 8% yield, respectively. The same workers, encouraged by the above results, treated compound **178d** under similar radical cyclisation conditions, to furnish **179d**, **181d** and **182d** in 18, 3 and 57% yield, respectively (Scheme 44).

The formation of **182c** strongly suggests that the methyl substituent at the α-position of the *N*-acryloyl group in **178c** acts as an effective radical-stabilising group for the radical **184** (R^1=H, R^2=Me) generated by 5-*endo-trig* cyclisation of the α-amidoyl radical **183** (R^1=H, R^2=Me). The formation of the 6-*exo* cyclisation product **180** (R=Me) might be prevented due to the steric interference of the methyl group (Scheme 45).

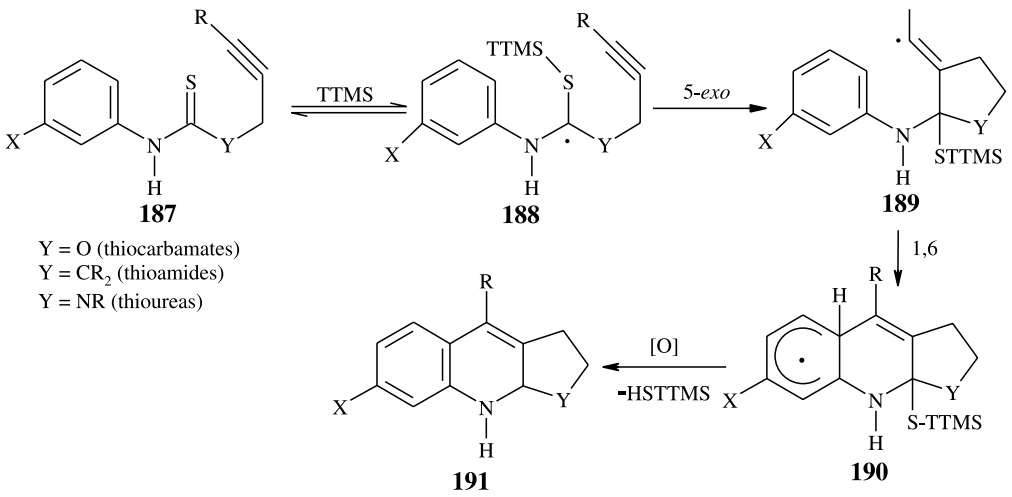
Curran et al. observed[115] that phenylcarbamic acid pent-3-ynyl esters **185a-e** in the presence of AIBN (1 equiv.) and tristrimethylsilylsilane (TTMSH) (4 equiv.) in benzene under standard conditions involving UV irradiation furnished the furoquinolines **186a-e** (Scheme 46). Additionally, the same workers focused the standard radical cyclisation of various thioamides and thioureas to furnish 2,3-dihydro-1*H*-cyclopenta[*b*]quinoline and indoloquinoline derivatives, respectively.



Scheme 45.



Scheme 46.



Scheme 47.

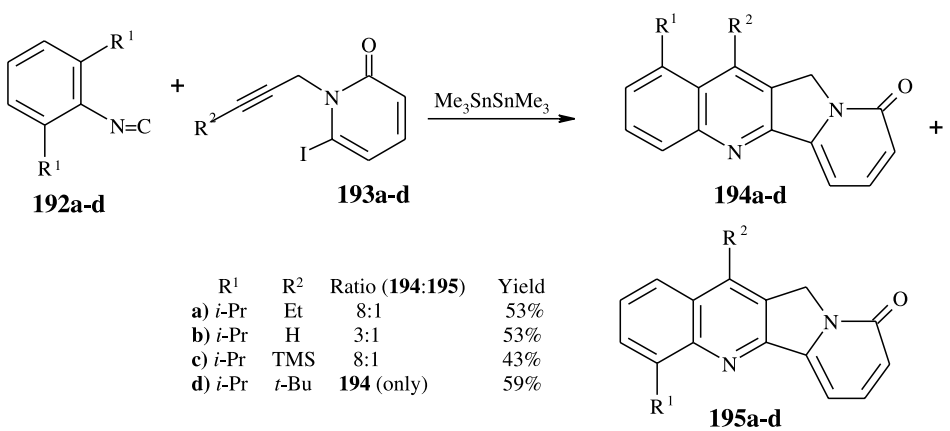
The suggested mechanism for this reaction is the reversible addition of the TTMS radical to the thiocabonyl group of **187** to give the stabilised radical **188**, which undergoes cyclisation to the vinylic radical **189**. 1,6-Cyclisation to one of the vacant *ortho* sites provides the delocalised radical **190**, from which oxidative re-aromatisation[103] is followed by ionic loss of the thiol to give **191** (Scheme 47).

Cascade [4+1] radical annulation of *o*,*o*′-dialkyl-substituted aryl isonitriles **192a-d** with *N*-propargyl-6-iodopyridones **193a-d** furnished a mixture of the 7,9-isomers **194a-d** and 7,12-isomers **195a-d** of 11*H*-indolizino[1,2-*b*]quinolin-9-ones with significant regioselectivity in favour of the more crowded product[116] (Scheme 48). The usefulness of the method is illustrated with a regioselective synthesis of (20*S*)-7-trimethylsilyl-9-isopropyl camptothecin. The 11*H*-indolizino[1,2-*b*]quinolin-9-one ring forms the core of the camptothecin and mappicine families of natural products. Camptothecin is the parent of one of the most important families of antitumour agents,[117] while analogues of mappicine exhibit antiviral activity.[118]

The formation of the products **194** and **195** by the annulation of *o*,*o*′-dialkyl-substituted aryl isonitriles with *N*-propargyl-6-iodopyridones may be explained as follows. The vinyl radical **197** was produced by the standard addition of the 6-pyridinyl radicals **196** to the isonitrile **197a** followed by 5-*exo*-cyclisation. This vinyl radical **197** partitions between 1,6-cyclisation to the *ortho* carbon to give **198** and 1,5-cyclisation to the *ipso* carbon to give **199**. β-Fragmentation of the isopropyl group from **198** provided the minor 7,12-isomer **195a**. Fragmentation of **199** to the iminyl radical **200**, followed by reclosure in a 1,6-fashion, furnished the rearranged radical **201**, which, upon loss of the isopropyl radical, provided the major 7,9-isomer **194a**. As the size of the *ortho* aryl substituent on the isonitrile increases, the partitioning of the radical **197** is directed away from 1,6-cyclisation due to the crowding in the intermediate **198** and this results in the formation of the less-crowded spirocycle **199** via 1,5-cyclisation.

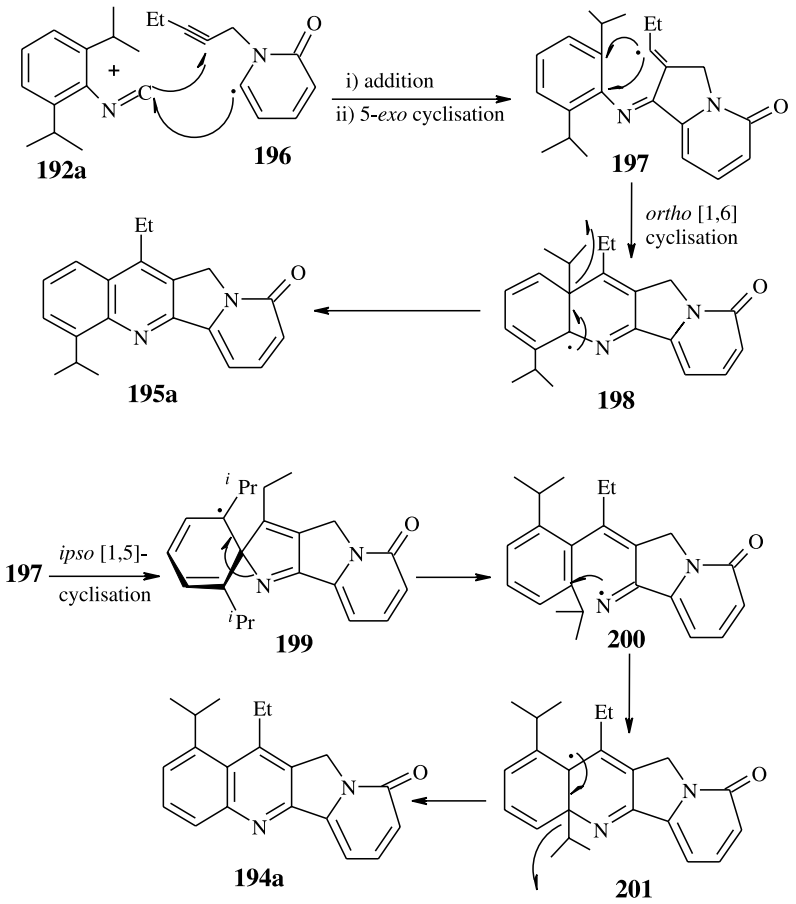
As the fates of the products are determined by the partitioning of **197**, the end result is the formation of the more-crowded 7,9-isomer **194a** by subsequent ring cleavage, reclosure and loss of the isopropyl group (**199→200→201→194a**) (Scheme 49).

Cascade radical reactions via α-(arylsulphanyl)imidoyl radicals were successfully applied[119] for the competitive [4+2] and [4+1] radical annulations of alkynyl isothiocyanates such as **204** with aryl radicals **203** (from **202**) leading to a new class of compounds, the thiochromeno[2,3-*b*]indoles. These derivatives were formed as a mixture of the substituted analogues **205** and **206** (Scheme 50).



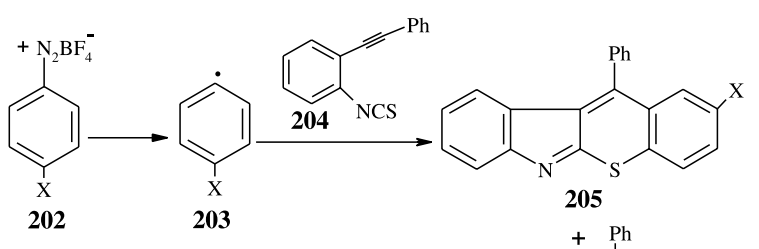
R1	R2	Ratio (**194**:**195**)	Yield
a) *i*-Pr	Et	8:1	53%
b) *i*-Pr	H	3:1	53%
c) *i*-Pr	TMS	8:1	43%
d) *i*-Pr	*t*-Bu	**194** (only)	59%

Scheme 48.



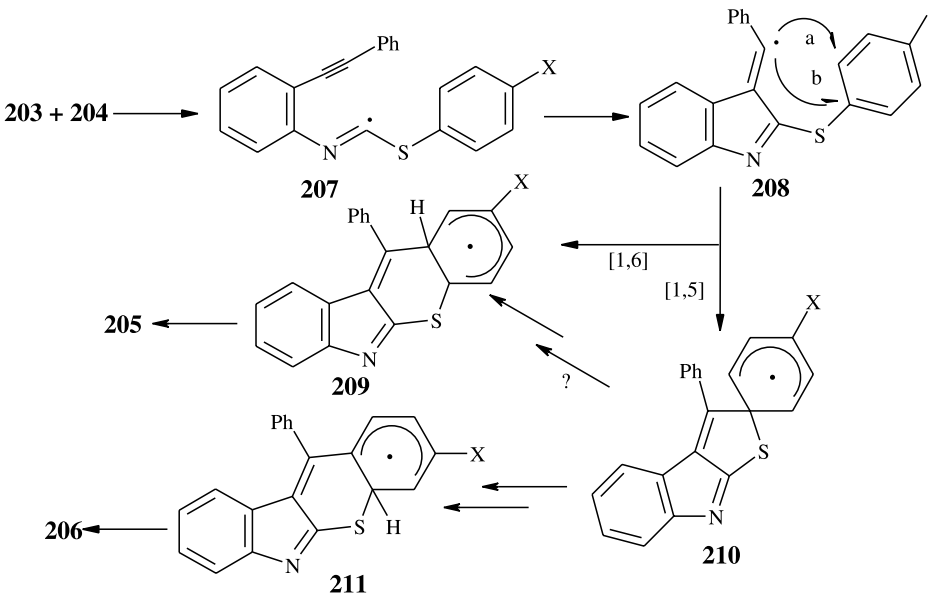
Scheme 49.

The isomer ratio is strongly dependent on the aryl substituent and has been correlated to its ability to delocalise the spin density. The presence of a methylsulphanyl group in the *ortho* position of the initial aryl radical results in complete regioselectivity and better yield. This is due to both strong spin delocalisation effect, which promotes exclusive [4+1] annulation, and a good radical leaving group ability, which facilitates the aromatisation of the final cyclohexadienyl radical. The reaction outcome can be accounted for through the initial addition of the aryl radical to the sulphur atom of the isothiocyanate to give the imidoyl radical **207**, with the subsequent cyclisation of **207** onto the C–C triple bond leading to the vinyl radical **208**. This radical eventually undergoes two competitive 1,5- and 1,6-cyclisations onto the aromatic ring of the starting aryl radical. In one route, 1,6-ring closure leads directly to the formation of the thiochromeno ring, the sulphurated part of which can be taken as arising from a [4+2] radical annulation between the radical **203** and the isothiocyanate **204**. Aromatisation of the cyclohexadienyl radical **209** eventually gives the compound **205**. In another route, 1,5-cyclisation produces the spirohexadienyl radical **210**, the thiophene ring of which is the result of [4+1] annulation between **203** and the isothiocyanate **204**. Ring expansion of



Series	X	**205** (%)	**206** (%)
a)	H	50	
b)	CF_3	27	23
c)	Cl	27	23
d)	OMe	20	20
e)	SMe	8	32
f)	N_3	4	40
g)	C(O)Me	2	43

Scheme 50.



Scheme 51.

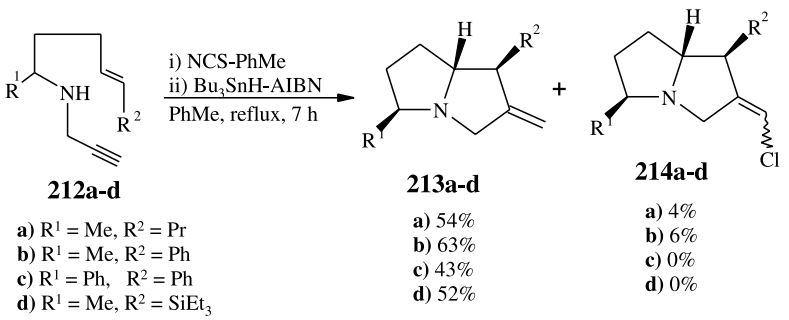
the radical **210** onto the sulphur atom to **211**, followed by aromatisation, affords the isomeric compound **206** (Scheme 51).

Theoretical calculations support the hypothesis of competitive, independent [4+2] and [4+1] annulation pathways and suggest that rearrangement onto the sulphur atom of the [4+1] intermediate does not occur via a sulphuranyl radical, but rather through either a transition state or a sulphur-centred (thioamidyl) radical. The latter is possibly the preferred route in the presence of an *o*-methylsulphanyl moiety that can act as a leaving group in the final *ipso*-cyclisation process.

Tandem cyclisation of *N*-propargylaminyl radicals produced by *N*-chlorination of (*E*)-alk-4-enylamines **212a-d**, followed by treatment with the tributyltin radical using *n*-Bu_3SnH and catalytic AIBN, afforded the 2-methylene-pyrrolizidines[120] **213a-d** and the reaction is highly stereoselective. The atom-transferred products **214a** and **214b** were also obtained in low yield in the case of **212a** and **212b** (Scheme 52).

The transition state **C** for the aminyl radical cyclisation is found to be chair-like, in which R^1 possesses a pseudo-equatorial position.[64b,121] The first ring closure produces a *trans*-2,5-disubstituted pyrrolidine intermediate **D**, and this is then followed by 5-*exo* cyclisation on to the C≡C bond efficiently to give the pyrrolizidine intermediate **E** as a diastereomer. This then abstracts a hydrogen atom from the tributyltin hydride to give the product **213** (Fig. 6).

The synthesis of the spiropyrrolidinyloxindoles, horsfiline and coerulescine, has been described,[122] in which the key



Scheme 52.

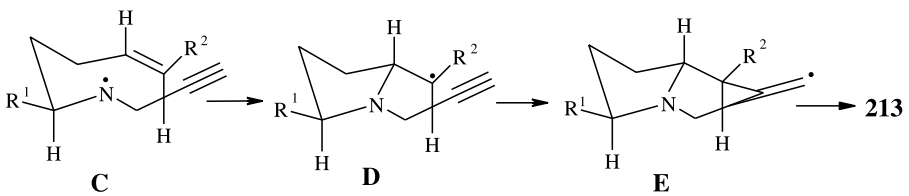
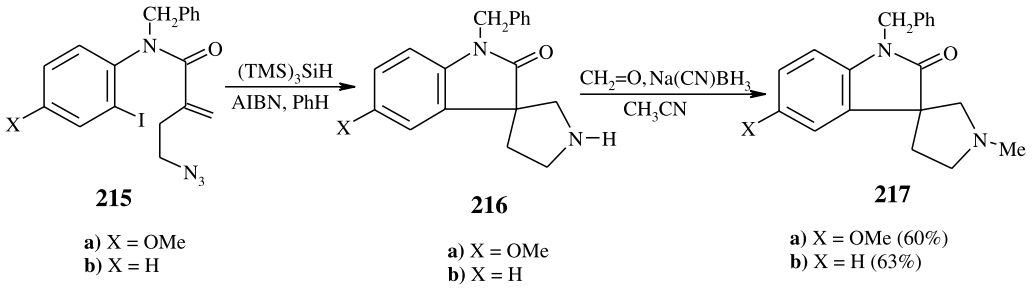
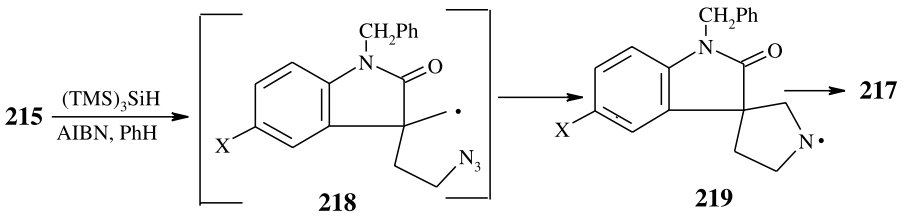


Figure 6. Chair-like transition state of aminyl radical in which R^1 possesses a pseudo-equatorial position.



Scheme 53.



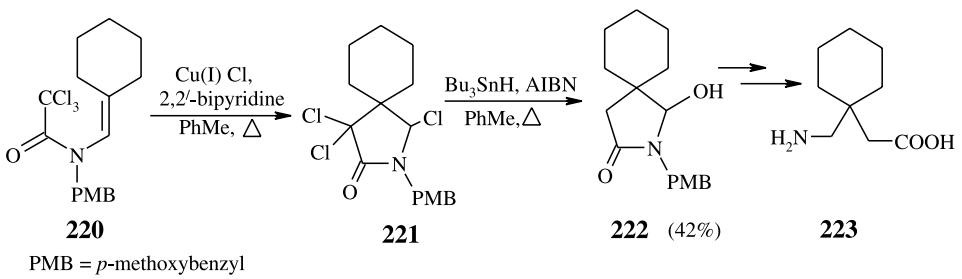
Scheme 54.

step was the tandem radical cyclisation of iodoaryl alkenyl azides. The radical cyclisation of 2-(2-azidoethyl)-*N*-benzyl-*N*-(2-iodo-4-methoxyphenyl)acrylamide **215a** by using $(TMS)_3SiH$ and AIBN in refluxing benzene furnished 1-benzyl-5-methoxy-1*H*-spiro[indole-3,3′-pyrrolidin]-2-one **216a** and this was subjected to in situ methylation to produce 1-benzyl-5-methoxy-1′-methyl-1*H*-spiro[indole-3,3′-pyrrolidin]-2-one **217a** in 60% yield. A similar protocol was followed for the conversion of **215b** to **217b** via **216b** (Scheme 53).

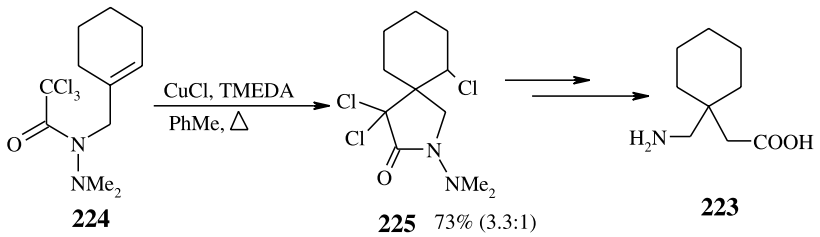
Compound **215** after passing through two intermediates **218** and **219** (nitrogen radical intermediate) furnished the final product **217**. The mechanism for the conversion of **215** to **217** is depicted in Scheme 54.

3.9. Synthesis of nitrogen heterocycles with non-conventional reagents

The radical cyclisation of unsaturated organohalides[95a,123] is very common for preparing five-membered nitrogen heterocycles and a variety of pyrrolidinones[124] have been prepared following the favoured 5-*exo-trig* pathway. Recently, it was reported that the 5-*endo-trig* radical cyclisation of haloenamides[125] also furnished pyrrolidinones. This cyclisation is unusual in the sense that the initial carbamoylmethyl radical reacts to form a five-membered, rather than a four-membered (or a β-lactam), ring. The formation of a β-lactam ring following the favoured 4-*exo-trig* cyclisation is generally observed when radical-stabilising (aromatic) groups are introduced on the enamide C=C bond.[126] Tributyltin hydride annulated 5-*endo* cyclisations have provided efficient approaches to substituted pyroglutamates.[57,127] It is very difficult to use tributyltin hydride, as the tin-containing byproducts are often difficult to remove and the cyclisation leads to the reduction of C–halogen and C=C bonds. In view of these circumstances, Parsons et al. have developed[128] a more straightforward and versatile approach, in which the 5-*endo-trig* radical cyclisation reaction of enamides with manganese(III) acetate or copper(I) chloride/bipyridine have been utilised to produce functionalised pyrrolidinones. Both of the reagents are cheaper, the metal byproducts are more easily removed and a functional group (generally a double bond or a halogen atom) is introduced into the product after cyclisation. The copper(I)-mediated cyclisations are very efficient and the bicyclic dienes can be isolated in >80% yield, while the corresponding manganese(III) reactions are generally more problematic, producing the dienes in lower yield (35–52%). Bryans et al. carried out[129] the radical cyclisation of a variety of haloenamides with copper(I) or ruthenium(II) complexes. They observed that the copper(I)/bipyridine reactions gave predominantly the γ-lactams via a 5-*endo* route, whereas the β-lactams were mainly produced via a 4-*exo* pathway by using dichlorotris(triphenyl phosphine)-ruthenium(II) or copper(I)/TMEDA(*N*,*N*,*N*,*N*-tetramethyl-1,2-ethylenediamine). *N*-Allyl-*N*,*N*-dimethyl-2,2-dichlorohydrazides were found to react with CuCl/TMEDA in



Scheme 55.



224 **225** 73% (3.3:1) **223**

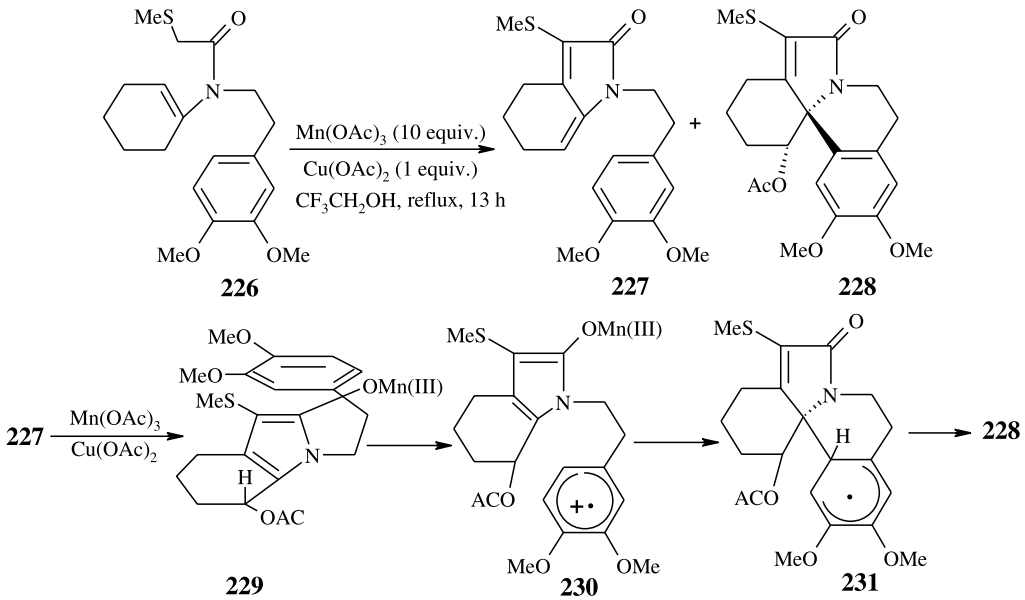
Scheme 56.

ethyl acetate to afford *N*-(dimethylamino)-2-pyrrolidinones[130] as a mixture of inseparable diastereomers.

In another report,[131] the radical cyclisation of halo-amides has been utilised to afford functionalised pyrrolidinones via 5-*endo-trig* and 5-*exo-trig* radical cyclisation pathways. The trichloro-enamide **220** was heated with copper(I) chloride/bipyridine to give the desired trichlorinated spirocycle **221**, following 5-*endo-trig* cyclisation. The spirocycle **221** was then reacted with tributyltin hydride (3.3 equiv.) to remove all three chlorine atoms. It is very important to note that hydrolysis, rather than reduction, of the chlorine atom α- to the nitrogen occurs to give the hydroxypyrrolidinone **222** in 42% yield. By applying this methodology, Parsons et al.[131] have synthesised the anti-epileptic drug, gabapentin **223**, after several multistep synthetic reactions (Scheme 55).

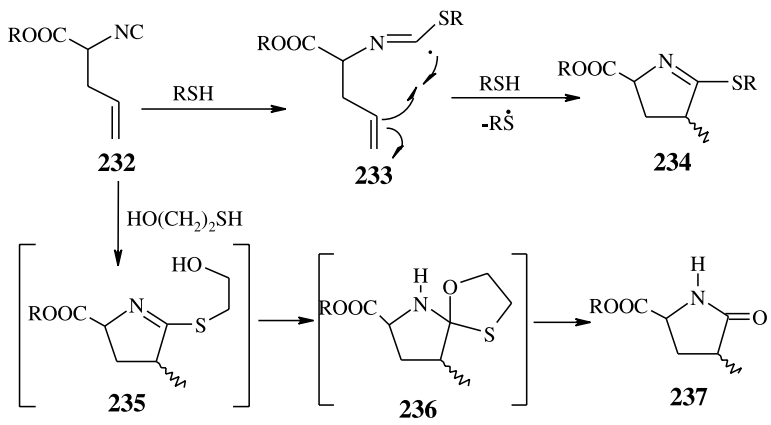
Although the formation of gabapentin **223** following a 5-*endo-trig* approach offers an alternative strategy, the overall yield of **223** from the copper(I)-catalysed reaction is only 2%, mainly because of the inefficient formation of the trichloroenamide **221**. A more efficient synthesis of **223** has been achieved by using 5-*exo* radical cyclisation, in which the key step involved the radical cyclisation of the cyclohexene derivative **224**, bearing an *N*-dimethylamino protecting group. The trichloride **224**, on treatment with copper(I) chloride and TMEDA resulted in the formation of the desired heterocycles **225** in 73% yield as a 3.3:1 mixture of separable diastereomers (Scheme 56). Following the successful formation of spirocyclic compounds using copper(I)-mediated atom transfer radical cyclisation (ATRC) reactions, Parsons et al. also succeeded in forming the unsaturated pyrrolidinone, pulchellalactam, by using 5-*endo* cyclisation.[131]

Ishibashi et al. observed[132] that the treatment of *N*-[2-(3,4-dimethoxyphenyl)ethyl]-α-(methylthio) acetamide **226** with $Mn(OAc)_3$ in the presence of $Cu(OAc)_2$ gave the tetrahydroindol-2-one **227**, which then cyclised with $Mn(OAc)_3$ to give 4-acetoxyerythrinane **228**. The formation of **228** from **227** may be depicted as follows. When the 3,4-dimethoxyphenyl and pyrrole rings of the acetoxy-substituted intermediate **229** were brought very close together, a mutual π−π interaction[133] between the two aromatic rings becomes evident. If the HOMO level of this system is enhanced, either the 3,4-dimethoxyphenyl or pyrrole ring would be readily oxidised. A more rapid oxidation of the electron-rich 3,4-dimethoxyphenyl ring than that of the pyrrole ring might result in the formation of the cation radical **230**. This is then followed by a nucleophilic attack of the pyrrole ring on the cation radical **230** to give the radical **231**. A further oxidation of **231** and deprotonation of the resulting cation would give **228** (Scheme 57). Mn(III)/Cu(II)-mediated oxidative radical cyclisation was applied to a formal synthesis of 3-demethoxyerythratidinone, a naturally occurring Erythrina alkaloid.



226 **227** **228** **229** **230** **231**

Scheme 57.



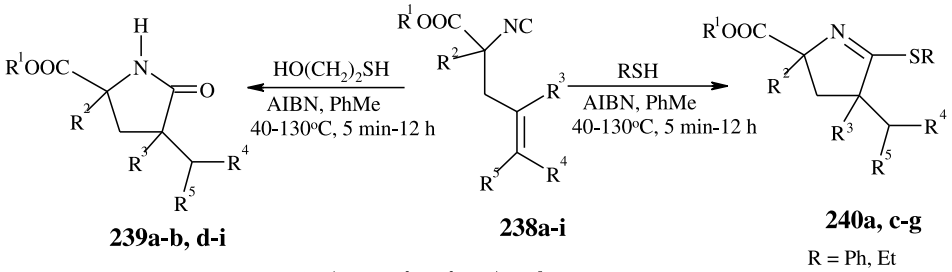
Scheme 58.

Kilburn et al. have reported[134] the microwave-assisted free radical cyclisation of alkenyl and alkynyl isocyanides with thiols to give the five-membered nitrogen heterocycles. In a typical reaction a thiyl radical (RS) was found to add to an alkenyl isocyanide **232**, generating a thioimidoyl radical **233** which underwent 5-*exo* cyclisation and subsequent hydrogen atom abstraction to afford *cis*- and *trans*-pyrrolines **234**. By using 2-mercaptoethanol *cis*- and *trans*-pyroglutamates **237** were obtained, through the intermediate **235** and also through the intermediate of a cyclic derivative **236** which underwent hydrolysis during the reaction (Scheme 58).

Microwave flash heating was found to give a better yield than the traditional thermal heating techniques. Alkanethiols and 2-mercaptoethanol were found to provide different products when treated with alkenyl isocyanides. Cyclisation of the isocyanides, **238a** and **238g**, afforded the *cis*- and *trans*-pyrrolines **240a** and **240g** in satisfactory yield (60 and 40%, respectively) under thermal conditions. The yield of the same products **240a** and **240g** may be increased to 75 and 78%, respectively, by the use of microwave flash-heating within 5 min. When 2-mercaptoethanol was used *cis*- and *trans*-pyroglutamates **239a**-**b** and **239d**-**f** were obtained in excellent yield, both under thermal and microwave conditions. However, the microwave reactions furnished slightly better yield and were completed in much shorter times. Cyclisation were also attempted by the use of benzenethiol and 2-mercaptoethanol in the absence of radical initiator. Isocyanides **238a**-**d** and **238f** all cyclised in good yield. However, the yields were lower than with radical initiator but still comparable to thermal methods. In order to carry out such reactions the reaction time had to be increased to 10 min with 4 equiv. of thiol (Scheme 59).

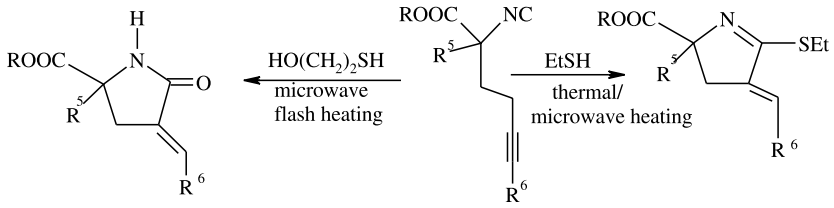
Similarly ethanethiol and 2-mercaptoethanol also provided different cyclised products from alkynyl isocyanides under standard thermal conditions, cyclisation of alkynyl isocyanides **241a**, **241c** and **241d**, using 2-mercaptoethanol, gave surprisingly poor yield of the corresponding pyroglutamates **242a**, **242c** and **242d**. However, with microwave flash-heating dramatically good yields were obtained. Again, high yield of pyrrolines (**243a**, **243c** and **243d**) were also obtained under thermal and microwave assisted condition by the use of ethanethiol (Scheme 60).

Pyrrolines and pyroglutamates have been synthesised in good to excellent yield by employing the microwave flash heating technique. The reaction times were dramatically reduced and the cyclisations of alkynyl isocyanides, which gave poor results under traditional thermal conditions, were improved.



a) R^1 = Et, R^2 = R^3 = R^4 = R^5 = H
b) R^1 = Et, R^2 = $CH_2CH{=}CH_2$, R^3 = R^4 = R^5 = H
c) R^1 = Et, R^2 = R^4 = R^5 = H, R^3 = Me
d) R^1 = Et, R^2 = $CH_2C(Me){=}CH_2$, R^3 = Me, R^4 = R^5 = H
e) R^1 = Et, R^2 = R^3 = H, R^4 = R^5 = Me
f) R^1 = PMB, R^2 = R^3 = R^4 = R^5 = H
g) R^1 = Bn, R^2 = R^3 = R^5 = H, R^4 =Ph
h) R^1 = Bn, R^2 = R^4 = R^5 = H, R^3 =Me
i) R^1 = Bn, R^2 = $CH_2C(Me){=}CH_2$, R^3 = Me, R^4 = R^5 = H

Scheme 59.



242a-d **241a-d** **243a, c-d**

a) R = Et, R^5 = H, R^6 =TMS
b) R = $PhCH_2$, R^5 = H, R^6 = TMS
c) R = $PhCH_2$, R^5 = $CH_2C{\equiv}CTMS$, R^6 = TMS
d) R = Et, R^5 = $CH_2C{\equiv}CH$, R^6 = H

Scheme 60.

4. Synthesis of oxygen heterocycles

γ-Lactams have been prepared by several methods.[96,97] The formation of these heterocycles by tin hydride-mediated radical cyclisation is often practical.[135,136] A general route to γ-lactones has been developed by Stork[137–139] and by Ueno[140–142] and this has been increasingly applied in their synthesis.[143–145]

The synthesis of tetrahydrofurans by the radical cyclisation of bromo acetals and bromo ketals is well known. Srikrishna et al. have utilised[146] the tributyltin hydride annulated radical cyclisation reaction to produce 2-alkoxy-4-methylenetetrahydrofurans from the suitable bromo acetals. Srikrishna et al. also reported[147] the radical cyclisation reactions of various bromo acetals, followed by aromatisation, to produce the 2,3,5-tri- and 2,3,4,5-tetrasubstituted furans, respectively. They also demonstrated[148] the tributyltin hydride-mediated radical cyclisation of the bromo ketal, 3-[(2-bromo-1-methoxy-1-phenyl)-ethoxy-propyne, with tri-*n*-butyltin chloride and $Na(CN)BH_3$ in the presence of a catalytic amount of AIBN. Tributylchlorostannane acts as a Lewis acid in the presence of sodium cyanoborohydride in the regioselective reductive demethoxylation of dimethyl and mixed ketals.[149]

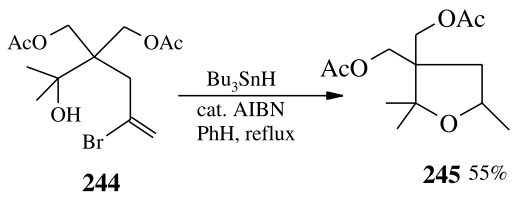
Beckwith et al. have pointed out[150] the Bu_3SnH-prompted radical cyclisation of various acyclic bromo acetals. One of the methods for the synthesis of tetrahydrofurans by radical cyclisation is the 5-*exo* cyclisation of alkoxy radicals. A novel method for the generation of alkoxy radicals has been introduced[151] from *N*-alkoxydithiocarbamates by a radical reaction with Bu_3SnH/AIBN in refluxing benzene for 3 h to furnish 4-phenoxy-1-butanol in 95% yield. The alkoxy radical was also generated under tin-free conditions[152,153] using PhSH as a radical mediator in the presence of AIBN in refluxing benzene.

A combination of sulphanyl radical addition–cyclisation of dienes connected with hydroximates, followed by conversion of the resulting cyclic hydroximate to the lactone, has proved to be an unique method for the construction of α,β-disubstituted γ-lactones.[154] The radical cyclisation of (*Z*)-hydroximates in the presence of thiophenol and AIBN furnished a mixture of the cyclised *cis*- and *trans*-products in 82% combined yield. No such cyclised product was, however, obtained from the corresponding (*E*)-hydroximates. Clive et al. have described[155] a method for making spiro enones from bromo acetals such that the stereochemistry at the spiro centre is controlled by the stereochemistry of an adjacent hydroxyl group. Several novel bridged spiro lactones can be prepared by the tandem radical cyclisations of α,β-unsaturated cyclohexanone derivatives bearing an appropriate allyl side chain via a double radical cyclisation of the enol ester radical.[156]

Acyl radicals participate in a wide range of inter- and intramolecular reactions and they are therefore very useful synthetic intermediates.[157] A few years ago, Evans et al. reported[158] the $(TMS)_3SiH$ annulated radical cyclisation of acyl selenides to furnish the cyclic ethers in 90–96% yield, with 33:1 diastereoselectivity (by HPLC) at C-3′. Acyl radicals have also been used in the synthesis of five-, six- and seven-membered oxygen heterocycles. Substituted tetrahydrofuran-3-ones can be easily prepared[159] from *o*-vinylated-β-hydroxyalkyl phenyl chalcogenides via carbonylation or reductive cyclisation. The initially formed alkyl radical is carbonylated using a high pressure of CO to give an acyl radical, which facilitates 5-*exo-trig* cyclisations onto vinyl ethers with electron-withdrawing groups.

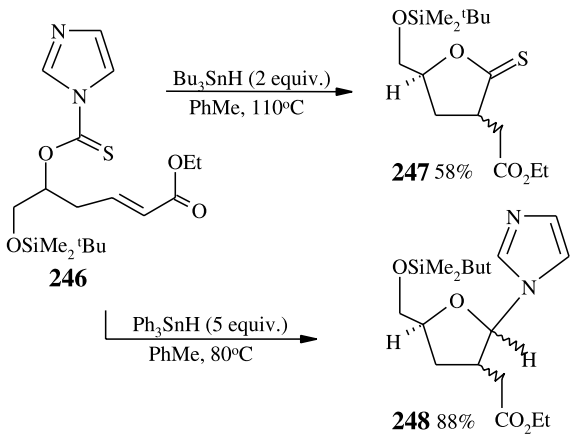
Recently, the Bu_3SnH-mediated radical cyclisation of unsaturated organohalides has attracted considerable interest to synthetic organic chemists.[95a,b,123a,160] Under mild, neutral reaction conditions, a large number of five- and six-membered rings may be prepared by employing this methodology. Various hydroxy-tetrahydrofurans[161] have been prepared under normal radical cyclisation conditions. The use of an allylic *o*-stannylketyl radical cyclisation to form a chroman by the 6-*exo-trig* cyclisation of the diene was also reported.[162]

In 2003, Yokota et al. have achieved[163] the tri-*n*-butyltin hydride-mediated radical cyclisation of the hydroxy vinyl bromide **244** via a 5-*exo-trig* cyclisation of an alkoxy radical and it is thought to be produced by an unusual [1,5]-hydrogen shift from the hydroxyl group to vinyl radical to generate an unusual furan **245** in 55% yield as the major product (Scheme 61). Similar results were obtained by using primary and secondary alcohols as the substrates. The conformation of the carbon chain is controlled by the presence of the quaternary carbon centre at the β-position to the hydroxyl group.



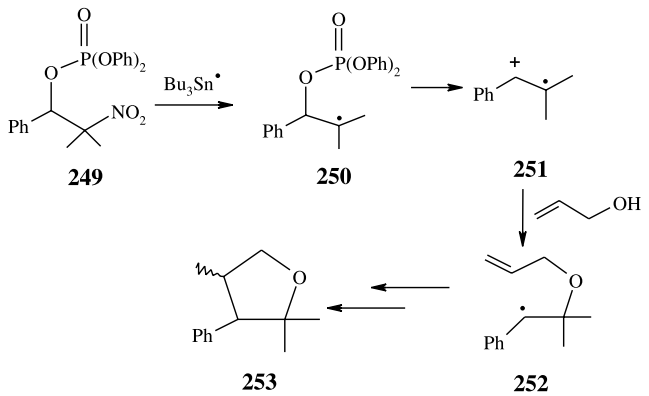
Scheme 61.

The thiolactone **247** (*cis*/*trans*=2.1:1.0) was produced[164] in 58% yield by a Bu_3SnH-mediated radical cyclisation reaction of a simple carbohydrate-derived imidazole thioate **246**. When a dilute solution of the substrate **246** in benzene was added to an excess of Ph_3SnH at 80 °C (reverse addition), however, the immediate result was the formation of an imidazole glycoside **248** in 88% yield (Scheme 62).



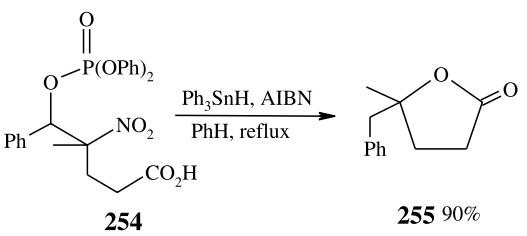
Scheme 62.

The diphenyl phosphate **249** was synthesised[165] and was then subjected to reflux with tributyltin hydride in 3:1 mixture of benzene and allyl alcohol. The immediate result was the formation of a (1:10) *trans*/*cis* mixture of 2,2,4-trimethyl-3-phenyltetrahydrofuran **253** via **250**, **251** and **252**, respectively. The reaction sequence is depicted in Scheme 63.



Scheme 63.

The formation of the γ-lactone **255** in 90% yield was achieved by refluxing the phosphorylated nitro acid **254** with triphenyltin hydride and AIBN in benzene[165] (Scheme 64).

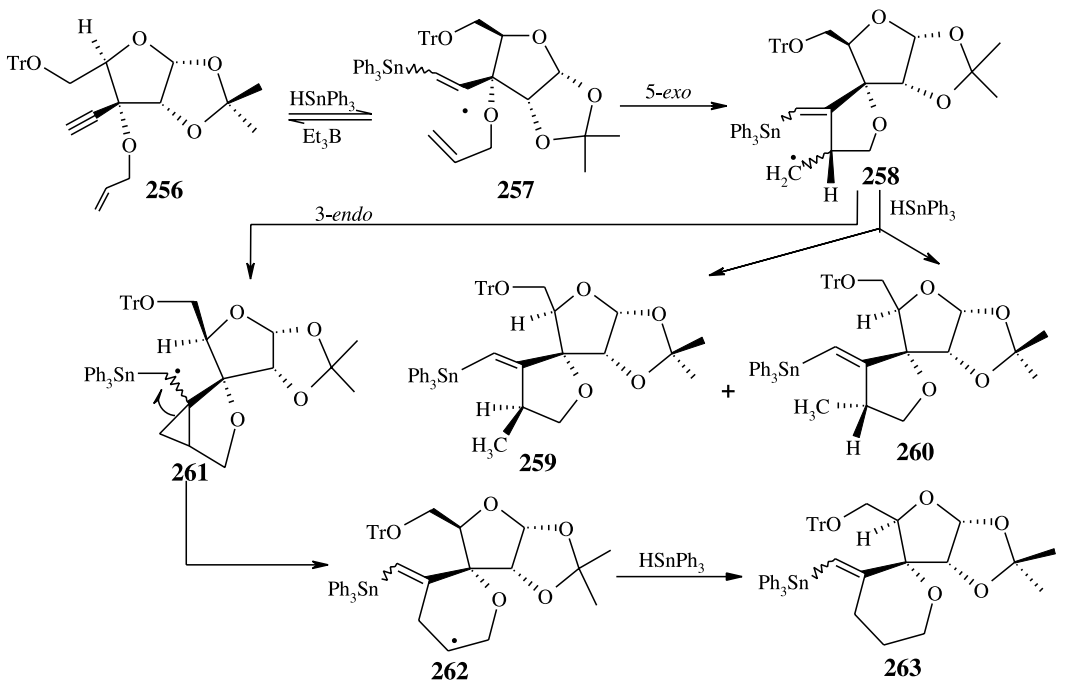


Scheme 64.

The triphenyltin hydride-mediated free radical cyclisation of the radical precursor **256**, a new stereoselective entry into the 1,7-dioxaspiro[4,4]nonane ring system, has recently come to light.[166] The cyclisation of the precursor **256** gave a mixture of products, two 5-*exo* products **259** and **260** (via **257** and **258**) and one 6-*endo* product **263** following the sequential route (**258→261→262→263**), in a 1:1:1 ratio. The cyclisation of compound **256** was modelled using semi-empirical PM 3 calculations, while taking into account the preferred conformers in the transition state for the eight possible structures, the *E*/*Z* stereochemistry at the *exo*-double bond and the *R*/*S* configuration at the newly formed stereocenters, via either chair or boat conformations, to give the 5-*exo* products. From the energy calculations at a density functional theorem (DFT) level on these optimised structures to obtain more accurate differences in energy between all the possible structures in the transition state, it is clear that the chair forms were more stable than the boat forms (Scheme 65).

Intramolecular homolytic *ipso* substitution has already been used for the preparation of benzo-fused ring systems such as phenanthridinones[67,103] and benzochromenes.[167] Here, Zhang et al. achieved a novel double *ipso* substitution process for the synthesis of azabenzoisocoumarins.[90] In this case, the initial radical **265**, generated from the radical precursor **264**, underwent 1,5-*ipso* substitution by a radical attack at the 2-position of the pyridine ring to produce the carbonyloxy radical **267** through **266**. This then underwent a second 1,6-*ipso* substitution to displace the methoxy group from **268** to furnish 10-oxa-4-azaphenanthren-9-one **269**. The yield of the rearrangement product **269** was decreased to <10% in the absence of the methoxy group and this suggests the important role of the methoxy group in the promotion of the double *ipso* rearrangement (Scheme 66).

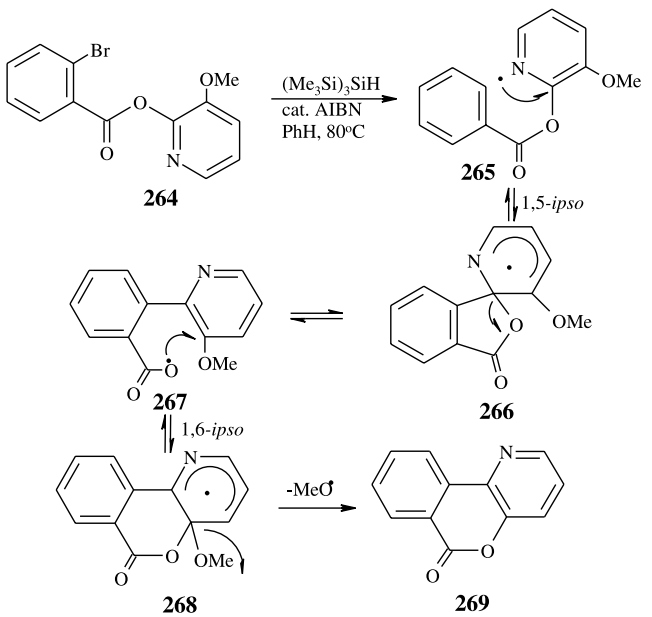
The cyclization of aryl radicals onto 2-bromo-*N*-alkyl-*N*-(3-oxocyclohex-1-enyl)benzamides furnished the ketospiro-2,3-dihydroisoindol-1-ones.[168] Analogously, 2-bromobenzoic acid 3-oxocyclohex-1-enyl esters gave the keto-spiro-γ-lactones.[168,169] Recently, Zhang et al. described[170] a straightforward two-step parallel synthesis for structurally diversified spiro compounds, where 2-bromobenzoic acids **270** were used as common building blocks to couple with a series of conjugated enols or enamines. Sequential intramolecular free-radical Michael additions lead to the formation of spirobenzolactones, spirobenzolactams, spirobenzolactone-lactams, spirobenzolactone-thiolactones, spirodilactones and bridged-spirolactones. Substituted 2-bromobenzoic acids (**270**) reacted with teronic acid (**271**) to give the intermediate enol ester **272**. Compounds **272** were reported to have antifungal activity and cyclised in the presence of $(Me_3Si)_3SiH$ and catalytic amount of AIBN



Scheme 65.

to afford spirodilactones **273**. Compounds **273** possess a unique heterocyclic system that was also found in natural product altenuic acid II. Again, substituted 2-bromobenzoic acids (**270**) on reaction with thiotetronic acid (**274**) furnished the intermediates **275**. These then underwent radical spirocyclisation to give spirolactone–thiolactone **276**.

In a similar manner spirolactone ester **279** was synthesised by coupling of 2-bromobenzoic acid (**270**) with a β-keto ester **277** followed by radical cyclisation of **278** (Scheme 67).



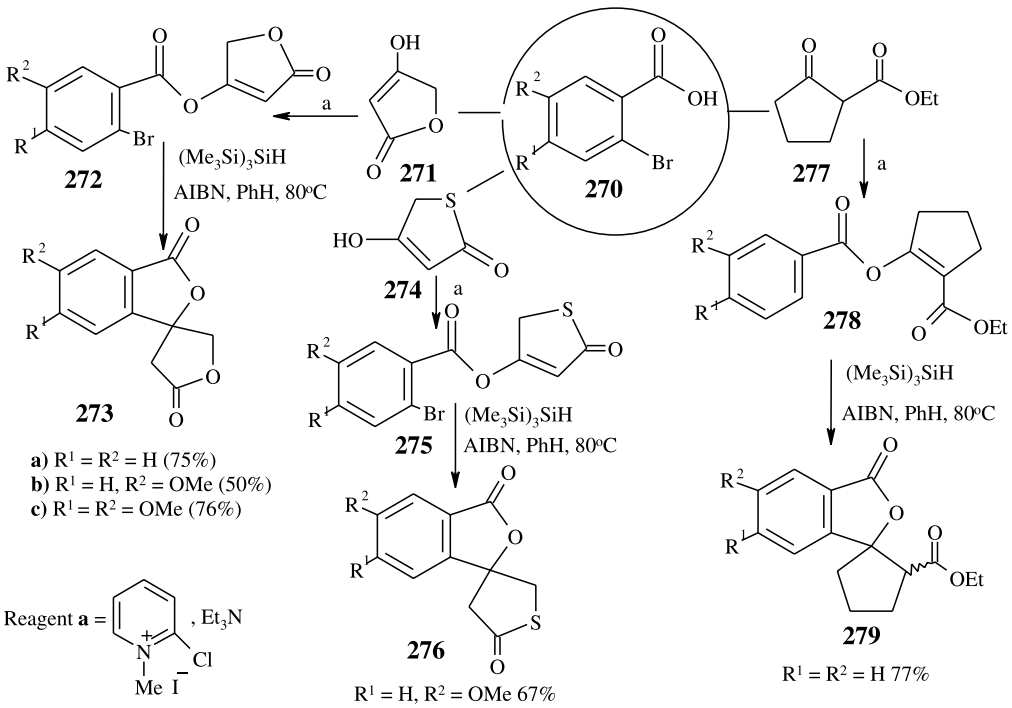
Scheme 66.

Recently, we have reported[171] the regioselective synthesis of 1*H*,3*H*,6*H*-[2]benzopyrano[4,3-*d*]pyrimidine-2,4-diones **281a-f** (75–85%) and 12*H*-benzopyrano[3,2-*c*][1]benzopyran-5-ones **283a-h** (70–85%), respectively, by radical cyclisation reactions. The starting materials, the 5-(2′-bromobenzyloxy)pyrimidine2,4-diones **280a-f** or 4-(2′-bromobenzyloxy)benzopyran-7-ones **282a-h**, were separately refluxed in benzene under a nitrogen atmosphere with tri-*n*-butyltin chloride and sodium cyanoborohydride in the presence of a catalytic amount of azobisisobutyronitrile (AIBN) for 3–4 h to give the cyclic products **281a-f** or **283a-h**, respectively (Scheme 68).

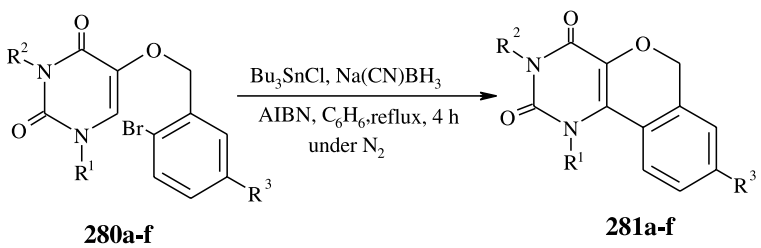
The exact reason why the 6-*endo*-cyclisation product is exclusively formed is not clear at present. The formation of the products **281a-f** from **280a-f** may, however, be explained by the generation of an aryl radical **284**. Subsequent 5-*exo* cyclisation may give a spiroheterocyclic radical[93] **285** (not isolated), followed by neophyl rearrangement,[94] to give the more stable intermediate radical **286** (benzylic radical) or by a 6-*endo* route directly to give the intermediate radical **286**, which then re-aromatises to yield the products **281a-f**, by an unknown mechanism, which is usual for this type of synthetic sequence, that is, an oxidation step in *n*-Bu_3SnH-mediated cyclisations[9b,54,95] (Scheme 69).

A similar mechanism is also operative for the formation of the products **283a-h** from **282a-h**.

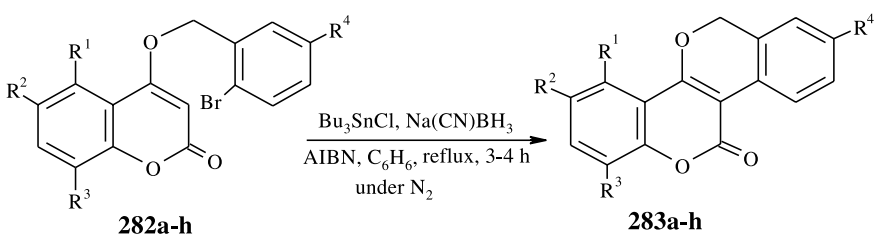
Recently, we have extended our efforts[172] in the regioselective synthesis of 2*H*-benzopyrano[3,2-*c*]quinolin-7(8*H*)-ones **288a-f** by a Bu_3SnH-mediated radical cyclisation of 4-(2′-bromobenzyloxy)quinolin-2(1*H*)-one derivatives **287a-f** (Scheme 70).



Scheme 67.

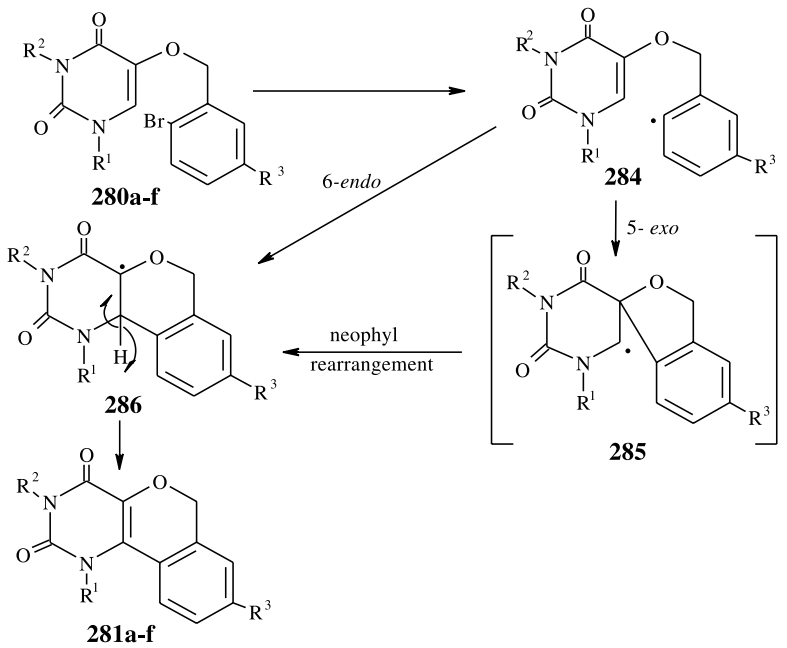


a) $R^1 = R^2 = Me$, $R^3 = H$ (80%)
b) $R^1 = R^2 = Me$, $R^3 = OMe$ (75%)
c) $R^1 = R^2 = Et$, $R^3 = H$ (85%)
d) $R^1 = R^2 = Et$, $R^3 = OMe$ (80%)
e) $R^1 = Et$, $R^2 = Me$, $R^3 = H$ (82%)
f) $R^1 = Et$, $R^2 = Me$, $R^3 = OMe$ (84%)



a) $R^1 = R^2 = R^3 = R^4 = H$ (75%)
b) $R^1 = R^2 = R^3 = H$, $R^4 = OMe$ (78%)
c) $R^1 = R^3 = R^4 = H$, $R^2 = Me$ (70%)
d) $R^1 = R^3 = H$, $R^2 = Me$, $R^4 = OMe$ (72%)
e) $R^1 = R^3 = Me$, $R^2 = R^4 = H$ (76%)
f) $R^1 = R^3 = Me$, $R^2 = H$, $R^4 = OMe$ (85%)
g) $R^1 = R^2 = R^4 = H$, $R^3 = Me$ (82%)
h) $R^1 = R^2 = H$, $R^3 = Me$, $R^4 = OMe$ (78%)

Scheme 68.



Scheme 69.

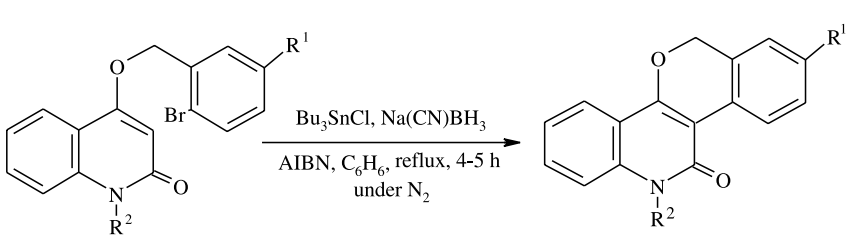
We have also synthesised[173] various spiroheterocycles **292a**,**b** by the tri-*n*-butyltin hydride-induced radical cyclisation of 5-(*o*-bromoaryloxymethylene)-6,7,8-trihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **289a**,**b**. These heterocycles can additionally be obtained under acid-catalysed enol–ether cleavage conditions. The formation of the products **292a**,**b** from **289a**,**b** may be explained by the formation of an aryl radical **290**, followed by 5-*endo-trig* cyclisation, to give the spirocyclic radical **291**, which may then give the final spiroheterocycles **292a**,**b** (Scheme 71).

4.1. Synthesis of oxygen heterocycles with non-conventional reagents

The reduction of halides with bis(cyclopentadienyl)zirconium chloride hydride [$Cp_2Zr(H)Cl$; Schwartz reagent] proceeded smoothly via a radical process, which is similar to the reduction with *n*-Bu_3SnH, in the presence of triethylborane as an initiator.[174] It was reported[175] that the haloacetals[137,141] on treatment with $Cp_2Zr(H)Cl$ in the presence of Et_3B in THF at 25 °C for 3 h furnished the cyclised products in excellent yield.

Hypophosphorous acid (H_3PO_2) and the corresponding 1-ethylpiperidine salt, *N*-ethylpiperidine hypophosphite (EPHP), are now well established for the generation of radicals in both aqueous and organic media.[72,176,177] This method has a good potential to replace the moderately toxic Bu_3SnH.[167a]

The samarium diiodide-induced reductive radical cyclisation of various haloalkenes has been developed.[178] Jiang et al. have synthesised[179] (±) cryptotanshinone and tanshinone IIA from the readily available 1,5-naphthalenediol **293**, in which the key step is the SmI_2-promoted intramolecular radical cyclisation of the compound **294** to produce the cyclic product **295** in 88% yield.[180] The compound **295** is found to serve as a suitable precursor to cryptotanshinone and tanshinone IIA (Scheme 72).

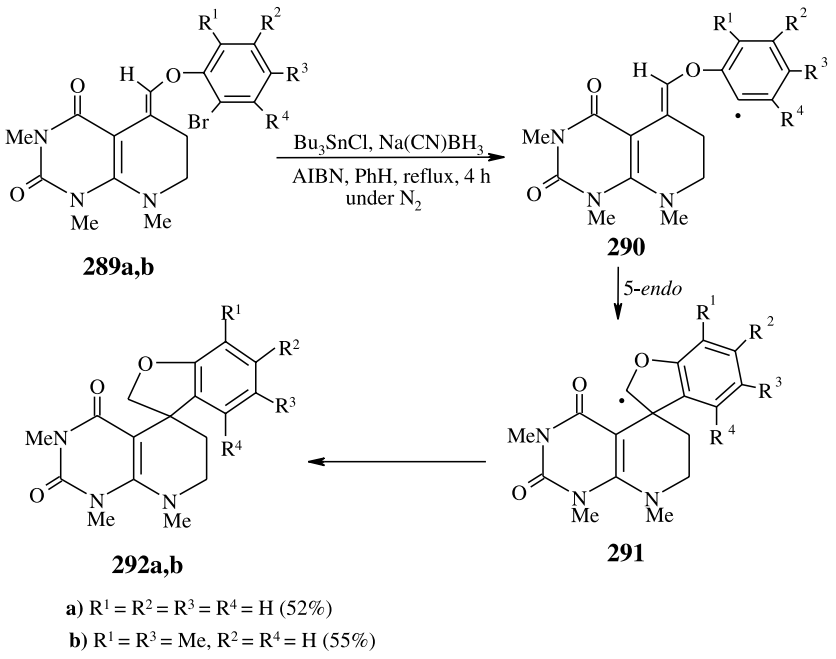


287a-f

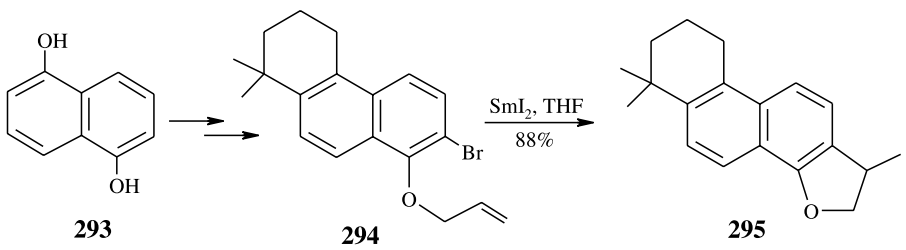
288a-f

a) R^1 = H, R^2 = Ph (80%)
b) R^1 = OMe, R^2 = Ph (76%)
c) R^1 = H, R^2 = Me (70%)
d) R^1 = OMe, R^2 = Me (73%)
e) R^1 = H, R^2 = Et (70%)
f) R^1 = OMe, R^2 = Et (76%)

Scheme 70.



Scheme 71.



Scheme 72.

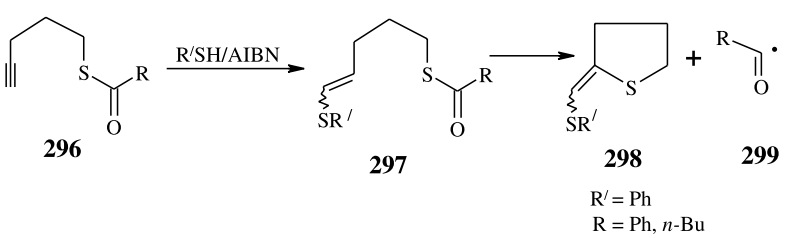
5. Synthesis of sulphur heterocycles

A few years ago, the Bu_3SnH-mediated radical cyclisation of di-isophenol-ω-haloalkyl ethers from oxapolycycloalkanones was reported.[181] Influenced by this result, Ponaras et al. extended this methodology to the sulphur-containing 2-(ω-haloalkylthio)enones to produce predominantly the fused thiapolycycloalkanones.[182]

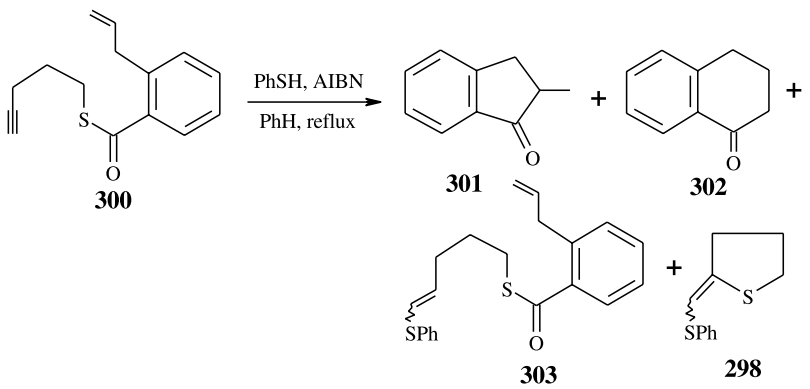
Acyl and aryl selenides are often the precursors of choice for acyl radicals, due to their capability to take part in chain sequences with tri-*n*-butylstannane and tris(trimethylsilyl)-silane.[183–185] The replacement of acyl selenides by thiol esters has been carried out, but these are normally very poor sources of acyl radicals[183] and this lack of reactivity may be increased by the inclusion of an additional propagation step, in which an aryl radical brings about an intramolecular homolytic substitution at sulphur.

Crich et al. prepared[157e] the iodothiol ester precursors by the reaction of (iodophenyl)ethanethiol with appropriate acyl chlorides. Benati et al. have utilised[186] this idea to prepare the thiophene **298** by the reaction of thiol ester **296** with R′SH and AIBN in refluxing benzene via the intermediate formation of **297**. In this case aryl radical **299** was also generated (Scheme 73).

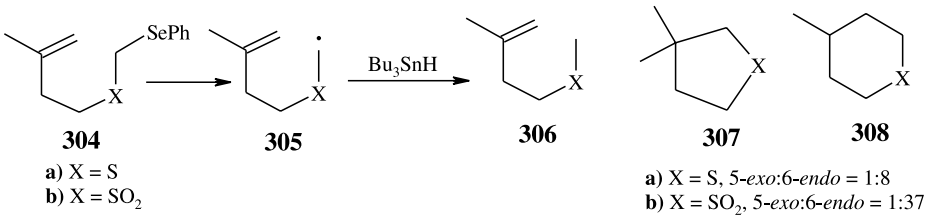
The radical reactions of some thiol esters were carried out[187] by adding a benzene solution of PhSH and AIBN under refluxing conditions. The thiol ester **300** led to the isolation of the cyclised indanone **301** and tetralone **302** in ca. 96:4 ratio (overall 73% yield), along with comparable amounts of



Scheme 73.



Scheme 74.



Scheme 75.

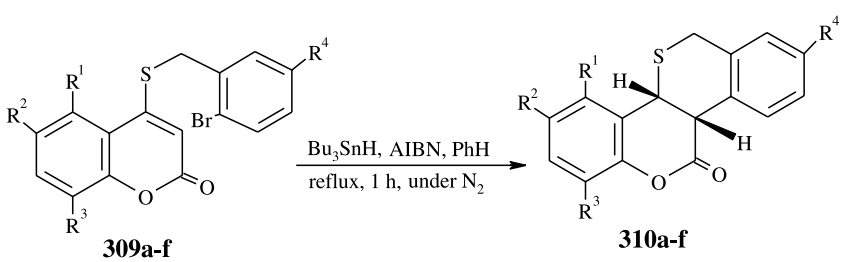
the (*E*)- and (*Z*)-dihydrothiophene **298**. Small amounts of the (*E*)- and (*Z*)-vinyl sulphide adduct **303** were the additional products (Scheme 74).

A few years ago, Della et al. reported[188] the results of a parallel study of the cyclisation of the 2-thia- and 2-sulphonyl-5-hexenyl radicals and obtained mixtures containing substantial quantities of both the 5-*endo* and 6-*exo* products, respectively. Recently, Della et al. also pointed out[189] the regioselectivity of the ring closure of 2-thia- and 2-sulphonyl-5-methyl-5-hexenyl radicals. The selenides **304** were the selected precursors to the radicals **305**. Ring closure of the α-substituted radicals **305** (X=S, SO_2) was found to be irreversible and led to significant amounts of the 6-*endo*-cyclisation products **308**. In the case of the sulphonyl radical **305** (X=SO_2), the extent of 6-*endo*- versus 5-*exo*-ring closure was enormously enhanced and the ratio of the 5-*exo* to 6-*endo* (**307/308**) product was 1:37. Very little acyclic reduced species **306** (X=SO_2) was detected. The high regioselectivity in the case of the radical ring closure of the sulphone **305** (X=SO_2) is a combination of two predominant factors, the steric effect and the frontier molecular orbital interaction (Scheme 75).

Recently, we have described[190] a simple convergent synthesis of the *cis*-benzothiopyrano[3,2-*c*]benzopyran-7(2*H*)-ones **310a-f** (70–75%) through the implementation of a regioselective 6-*endo-trig* aryl radical cyclisation of the respective 4-(2′-bromobenzyl)thiobenzopyran-7-ones **309a-f** with tributyltin hydride in the presence of a radical initiator (AIBN) (Scheme 76).

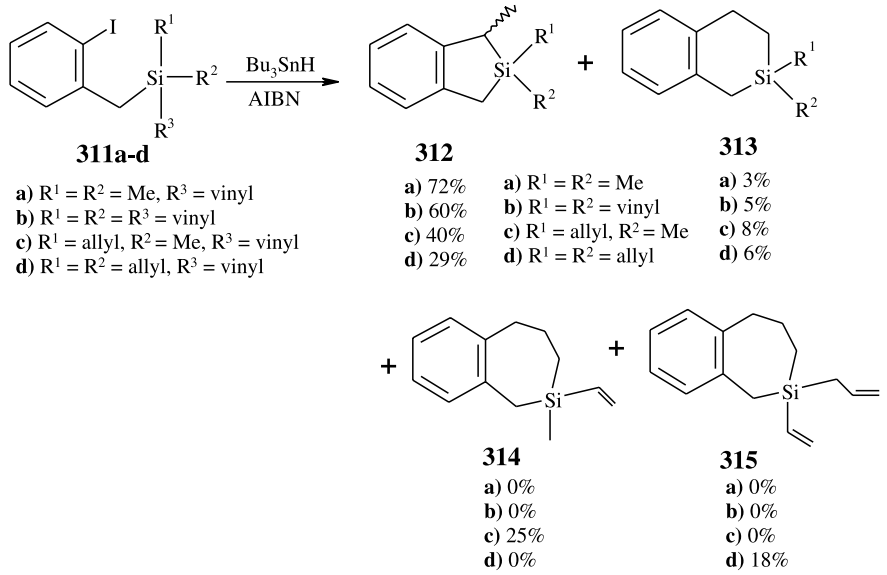
6. Synthesis of silicon-containing heterocycles

The intramolecular free-radical mediated formation of C–C bonds has been studied for a long time and is one of the most important methods for the synthesis of carbocyclic compounds.[123a] Tributyltin radical-induced intramolecular radical reactions of *ortho*-substituted phenyl halides have



a) $R^1 = R^2 = R^3 = H$, R^4 = OMe (75%)
b) $R^1 = R^2 = R^3 = R^4 = H$ (72%)
c) $R^1 = H$, R^2 = Me, $R^3 = H$, R^4 = OMe (72%)
d) $R^1 = H$, R^2 = Me, $R^3 = R^4 = H$ (70%)
e) R^1 = Me, $R^2 = H$, R^3 = Me, R^4 = OMe (74%)
f) R^1 = Me, $R^2 = H$, R^3 = Me, $R^4 = H$ (70%)

Scheme 76.



Scheme 77.

been explored for the preparation of indanes, dihydroindoles, dihydrobenzofurans and tetrahydrobenzopyrans.[180,191–195] It was reported[196] that, when *o*-iodobenzyldimethylvinylsilane **311a** was treated with tributyltin hydride and AIBN, the siloles **312a** and **313a** were obtained in 72 and 3% yield, respectively, that is, the 5-*exo-trig* cyclised product was exclusive. A similar result was obtained in the cyclisation of compound **311b**. Treatment of the *o*-iodobenzylallylvinylmethylsilane **311c** under radical cyclisation conditions furnished the products **312c** (mixture of diastereomers) and **313c**, as well as **314** in 40, 8 and 25% isolated yield, respectively. In this case, the 7-*endo* cyclisation is competitive with the 5-*exo* cyclisation, while the 6-*endo* reaction seems to be rather slow. The compound **311d** under similar reaction conditions furnished the siloles **312d** and **313d** via a 5-*exo* and 6-*endo* cyclisation in 29 and 6% yield, respectively. In the case of **311d**, the compound **315d** was additionally formed in 18% yield via a 7-*endo* cyclisation. The results with **311c**,**d** are indicative of the fact that the vinyl group reacts in preference to the allyl group (Scheme 77).

7. Conclusions

As already stated, the literature on the synthesis of heterocycles by radical cyclisation is vast and it is beyond the scope of this review to include all aspects of the topic. Therefore, only the introduction, mechanism and recent representative examples have been included. The application of the radical cyclisation for the formation of the pyran and furan rings in heterocycles is incorporated. Mechanistic aspects of various radical cyclisation reactions have been studied in detail. In recent years, there has been a considerable study of the cyclisation of radicals on heterocyclic compounds, a reaction that had previously been ignored. Radical cyclisation reactions, however, still offer enormous challenges to synthetic organic chemists.

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Biographical sketch

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