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

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Abstract—This review describes the formation of five- and six-membered heterocyclic rings in various organic molecules by radical cyclisation and covers mostly the literature published in 2005.

Contents

☆ Previous review: see Ref. 17d.

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

Abbreviations: ABCVA, 4,4′-azobis(4-cyanovaleric acid); ACCN, 1,1′-azobis(cyclohexanecarbonitrile); CAN, azobis-(cyclohexanenitrile); AIBN, azobis(isobutyronitrile); ATRA, atom transfer radical addition; ATRC, atom transfer radical cyclisation; ATRP, atom transfer radical polymerisation; Bn, benzyl; Bz, benzoyl; BTF, trifluoromethylphenyl; Cbz, carbobenzyloxy; CPT, camptothecin; Cp, cyclopentadienyl; CTAB, cetyltrimethylammonium bromide; CTAN, ceric tetra-*n*-butylammonium nitrate; Cy, cyclohexyl; DEPO, diethylphosphine oxide; DIBAL-H, diisobutylaluminium hydride; DLP, dilauroyl peroxide; DME, dimethoxy ethane; DMF, dimethylformamide; EPHP, *N*-ethylpiperidine hypophosphite; FMO, frontier molecular orbital; HATRC, halogen atom transfer radical cyclisation; HOMO, highest occupied molecular orbital; HMPA, hexamethylphosphoramide; LUMO, lowest unoccupied molecular orbital; MOM, 1′-methoxymethoxyethyl; MW, microwave; NMP, nitroxide-mediated living free radical polymerisation; PMB, 4-methylbenzyl; PMDETA, *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine; PMP, 4-methoxyphenyl; PPTS, pyridinium *p*-toluenesulfonate; PRE, persistent radical effect; RAFT, reversible addition–fragmentation chain transfer; RCM, ring-closing metathesis; SH^i, intramolecular homolytic substitution; SOMO, singly occupied molecular orbital; TBHP, tetra-butyl hydroperoxide; TDPS, *tert*-butyldiphenylsilanyl; TBAF, tetrabutylammonium fluoride; TBS, *tert*-butyldimethylsilanyl; TBTH, tributyltin hydride; TEMPO, 2,2,6,6-tetramethyl-piperidin-1-oxyl; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TMS, trimethylsilyl; TMEDA, *N*,*N*,*N*,*N*-tetramethyl-1,2-ethylenediamine; Tr, trityl; Ts, *p*-toluenesulfonyl; TS, transition state; $TTMSH/(TMS)_3SiH$, tris(trimethylsilyl)silane; VOL(OEt), 2,4-di-*tert*-butyl-6-({[(1*S*)-1-(hydroxymethyl)-3-(methylthio)propyl]imino}methyl)phenol.

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1. Introduction

Application of radical reactions for the synthesis of small molecules has become popular in the past decade, largely in the context of carbon-centred radicals.[1–5] Heteroatom-centred radicals are less common in synthesis, because of the tedious preparations and instabilities of the heteroatom radical precursors. Nitrogen-containing compounds are part of the basis of life and are one of the main classes of pharmacologically active agents. The main goals of synthetic organic chemists are to find many new and advanced methods for their preparations. Due to the extensive research in this field over the past two decades, the addition of radicals to C=N bonds has become a reliable procedure for the syntheses of nitrogenated compounds.[6–8] Around 50% of the industrial polymers are nowadays generated through free radical processes and free radical polymerisations that can be used for the preparation of copolymers with increasing material behaviour.[9] Since its inception in 1982,[10] living free radical polymerisation has been developed[11] extensively, especially through research carried out during the last 10 years. Three different methods, reversible addition–fragmentation chain transfer (RAFT) polymerization,[12] atom transfer radical polymerisations (ATRP)[13] and nitroxide-mediated living free radical polymerisation (NMP),[14] have been introduced as highly useful techniques for living free radical polymerisation. Atom economical transformation is an important development in synthetic organic chemistry,[15] and this has been exemplified by the formation of various 2-substituted cyclic ketones via thiol-catalysed addition reactions of acyl radicals to internal olefins.[16]

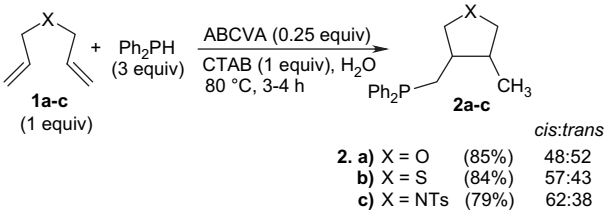
The main aim of this review is to reflect upon, and to summarise, the main developments that have taken place in the application of free radical chemistry to synthesise five- and six-membered heterocycles during 2005. Among the numerous approaches and systems, which have been explored, some representative examples leading to the formation of five- and six-membered heterocycles[17] are discussed.

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

Organotin compounds have found widespread application for carrying out various types of radical reactions.[5] There are, however, number of drawbacks associated with tin-based radical chemistry, like toxicity, hazardous handling and problems with product purification. A useful alternative is the environmentally benign radical cyclisation and addition reactions using the persistent radical effect (PRE).[18] Environmentally benign radical alkoxyamine isomerisation reactions[19] using the PRE have been discussed previously.

Radical carbon–carbon bond-forming reactions are an extremely powerful tool for constructing the skeleton of target molecules.[1,20] Tributyltin hydride[5b] has been widely used in radical reactions in spite of its several drawbacks like toxicity and difficulty of removing tin residues from the desired product. Several alternatives to organotin hydrides have been reported.[21] Phosphorous compounds have proved to be excellent alternatives to organotin hydrides in radical reactions.[22–24]

Water is used as a solvent in many radical cyclisation reactions because of its environmentally friendly nature,[25] but organic reactions in water without using any organic co-solvents are very difficult and, hence, most of the radical reactions in an aqueous medium are performed in organic co-solvents.[26] Recently, Cho and Jang have developed[27] an efficient and mild methodology for preparing heterocyclic compounds with a phosphorous functionality by radical cyclisation of dienes in water without the use of any organic co-solvents. A variety of dienes **1a–c** were allowed to react with diphenylphosphine in the presence of 1 equiv of CTAB in water, producing a moderate to high yield of the cyclised products **2a–c** (Scheme 1).



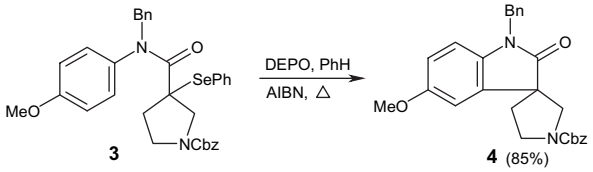
Scheme 1.

The use of solid-phase organic synthesis is an important advance in radical reactions.[28,29] The beauty of the solid-phase synthesis is that the radical precursor is attached to the resin and the $^{n}Bu_3SnH$ used in the reaction can be washed off when the radical cyclisation is complete, thereby eliminating the purification problems and lowering toxicity.

Bowman et al. synthesised[30] 3-methyl-2,3-dihydrobenzofuran by a Bu_3GeH- and $^{n}Bu_3SnH$-mediated radical cyclisation of 2-iodo-1-(prop-2-enyloxy)benzene. The microwave-assisted reaction between azidotrimethylsilane and arylnitrileboronate esters proceeded in dimethoxyethane to produce aryltetrazoleboronates in moderate to good yield, within 10 min, with dibutyltin oxide as catalyst.[31] The oxidative coupling of β-carbonyl imines and allyltrimethylsilane with CTAN were explored in MeCN and CH_2Cl_2[32] and it was found that, in MeCN, the allylation products predominated, whereas, in CH_2Cl_2, the dihydropyrrole products were produced exclusively.

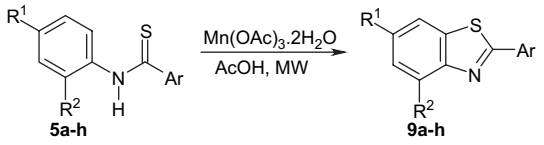
The precursor **3** for horsfiline synthesis was treated[33] with diethylphosphine oxide (DEPO) and AIBN in refluxing dry benzene. The radical-cyclised product **4** was obtained in 85% isolated yield. In order to synthesise the alkaloid, horsfiline, Murphy et al. have used radicals obtained from the phosphorous reagents, *N*-ethylpiperidine hypophosphite (EPHP) and diethylphosphine oxide (DEPO). DEPO proved

to be highly effective for the cyclisations at 80 °C that were difficult or impossible to carry out with Bu_3SnH (Scheme 2).



Scheme 2.

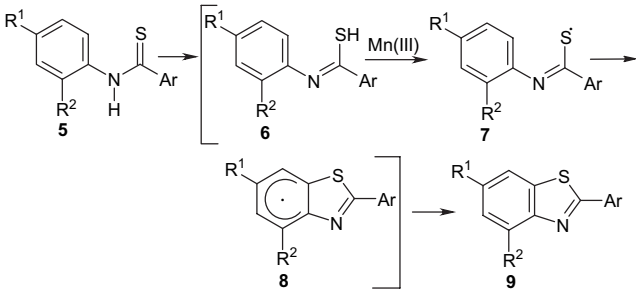
Manganese(III) triacetate is an excellent one-electron oxidant that has been widely employed to produce free radicals for cyclisation reactions.[34] Arylthioformanilides **5a–h** were treated[35] with manganese triacetate [$Mn(OAc)_3 \cdot 2H_2O$] in acetic acid under microwave irradiation. The reaction was complete within 6 min to afford the 2-arylbenzothiazoles **9a–h** (Scheme 3).



	Ar	R^1	R^2	Yield (%)
a)	Ph	H	H	80
b)	Ph	OMe	H	75
c)	*p*-F-C_6H_4	H	H	62
d)	*o*-Cl-C_6H_4	H	H	76
e)	*p*-$C_8H_{17}O$-C_6H_4	OMe	H	83
f)	*p*-$C_8H_{17}O$-C_6H_4	Cl	H	79
g)	*p*-$C_8H_{17}O$-C_6H_4	Br	H	86
h)	*p*-$C_{10}H_{21}O$-C_6H_4	Cl	H	88

Scheme 3.

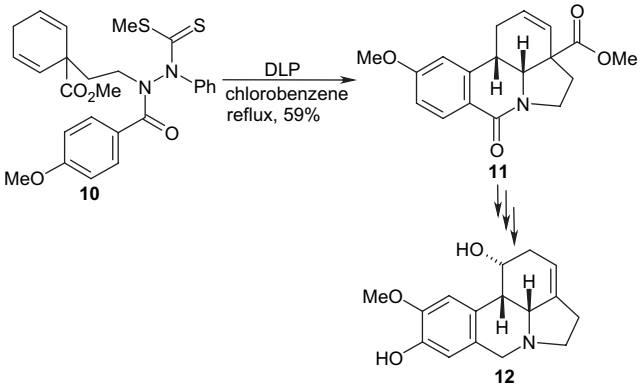
A plausible mechanism for the above conversion suggests that the arylthioformanilides **5** can exist as the thioimidols **6** and react with manganese(III) triacetate to generate the thiyl radicals **7**. During this time, Mn(III) is reduced to Mn(II). 1,5-Homolytic radical cyclisation of **7** followed by aromatisation of radical **8** gives the 2-arylbenzothiazoles **9** (Scheme 4).



Scheme 4.

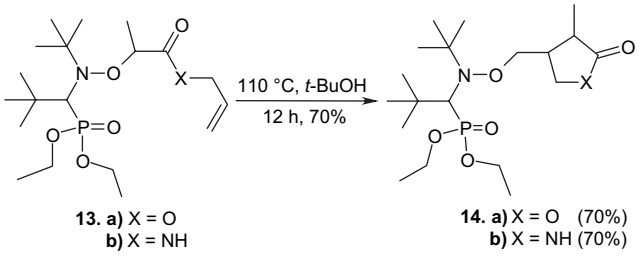
In the preparation of Kirkine **12**, a lycorine-type alkaloid, one of the key steps was the DLP-mediated radical cyclisation[36] of the thiosemicarbazide radical precursor **10** to give the desired cyclised product **11** in 59% yield (Scheme 5).

For decades, chemists have been engaged in the search for new monocomponent initiators for free radical reactions.[37] These initiators should be easy to handle and store, highly



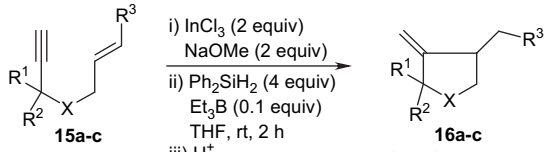
Scheme 5.

selective and non-hazardous. Many new hydrogen donors[38,39] have been developed to replace the tin derivatives, some of which are toxic, environmentally harmful, not easily removable and produce toxic waste.[21a] A number of protocols have been developed including a tin-free Ueno–Stork reaction,[40] the work of Renaud et al.[41] and Oshima[42] et al. on iodine atom-transfer reactions and the search for less toxic hydrogen-donor agents such as Ph_2SiH_2.[43] Rizzardo et al.[44] have developed a new concept by introducing nitroxide in radical chemistry to prepare alkoxyamines by radical addition onto olefins. TEMPO alkoxyamines are found to be unsuitable for the preparation of lactones or lactams.[19b] Recently, new SG-1 alkoxyamines **13a** and **13b** have been prepared[45] and these have been applied to the preparation of a simple lactone **14a** and lactam **14b** (Scheme 6).



Scheme 6.

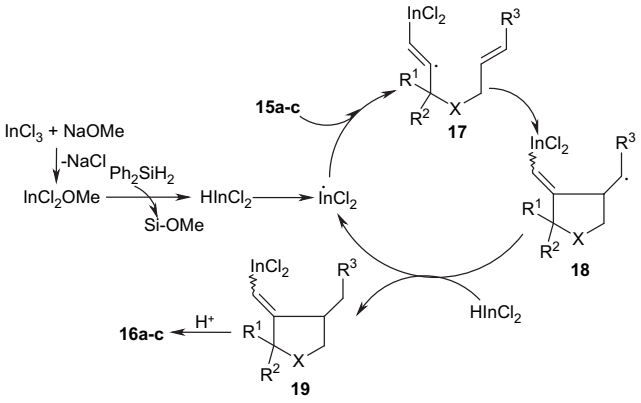
Dihalogenoindium hydrides ($HInX_2$) are effective alternative radical reagents to Bu_3SnH and can be generated from $InCl_3$ or $InBr_3$ and metal hydrides[46–49] like $NaBH_4$,[47] DIBAL-H[48] and Et_3SiH.[49] It was observed[50] that enynes **15a–c** on treatment with $HInCl_2$ (obtained under non-acidic conditions by transmetallation between Ph_2SiH_2 and $InCl_2OMe$) furnished the cyclisation products **16a–c** in good yield (Scheme 7).



16. a) $R^1 = R^2 = H$, $R^3 = Ph$, X = O (89%)
b) $R^1 = R^2 = R^3 = H$, X = NTs (60%)
c) $R^1 = R^3 = Me$, $R^2 = Ph$, X = O (81%, dr = 70:30)

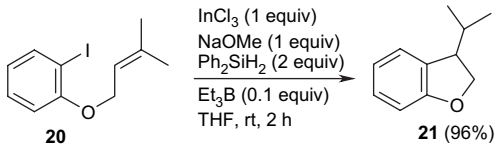
Scheme 7.

The formation of products **16a–c** from **15a–c** may be explained by the following mechanistic pathway. The in situ-generated $InCl_2OMe$ is transmetallated with Ph_2SiH_2 to give $HInCl_2$, which produces an indium radical ($^{\bullet}InCl_2$) by cleavage of the In–H bond. The indium radical ($^{\bullet}InCl_2$) then adds to the C–C triple bond to afford a vinyl radical **17**, which reacts with the remaining alkene moiety to provide the cyclised radical **18**. Finally, the radical **18** is hydrogenated by $HInCl_2$ to give **19** which, after acidic workup, affords the cyclised products **16** (Scheme 8).



Scheme 8.

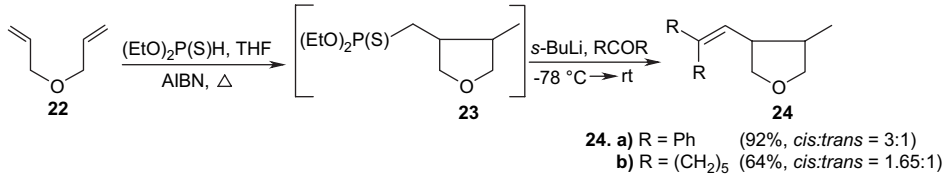
Again, $HInCl_2$-mediated intramolecular radical cyclisation of haloalkene **20** afforded[50] the cyclisation product **21** under similar reaction conditions (Scheme 9).



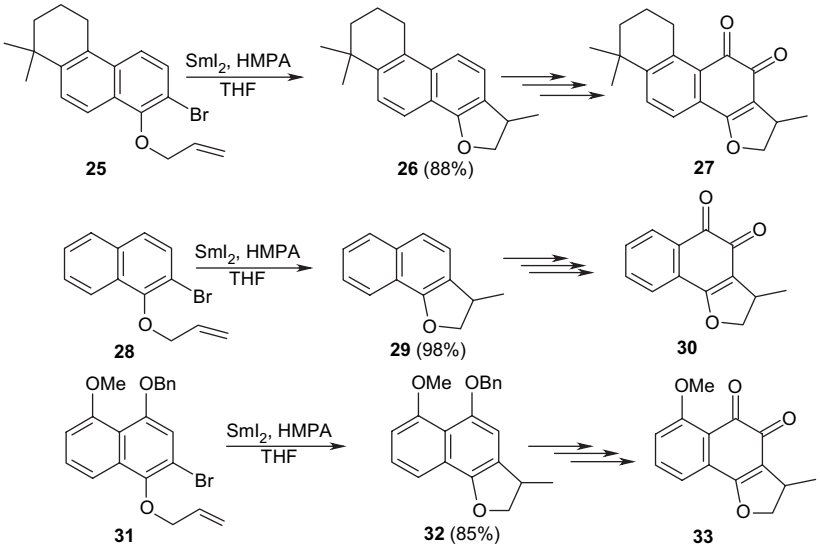
Scheme 9.

Recent research in this area has established that phosphorous hydrides, e.g., hypophosphorous acid (and its salts),[22h,j,23b,24c,51] diethylphosphine oxides[23d] and diethylphosphite[22b,52] are useful alternative reagents[21a,b,53] to Bu_3SnH. Diallyl ether **22** was found to react[54] with diethyl thiophosphite and AIBN to furnish the phosphonothioate **23**, which immediately deprotonated and reacted with dibenzophenone to give the trisubstituted alkene **24a** in good yield. A similar reaction with the cyclohexane afforded the alkene **24b** in 64% yield (Scheme 10).

(±)-Cryptotanshinone **27** and its two new simplified analogues, 2,3-dihydro-3-methylnaphtho[1,2-*b*]furan-4,5-dione **30** and 2,3-dihydro-6-hydroxy-3-methylnaphtho[1,2-*b*]furan-4,5-dione **33**, have been prepared and the key steps were the SmI_2-promoted radical cyclisation[55] of 8-allyloxy-7-bromo-1,1-dimethyl-1,2,3,4-tetrahydrophenanthrene **25** to 1,6,6-trimethyl-1,2,6,7,8,9-hexahydrophenanthro[1,2-*b*]-furan **26** and of 1-allyloxy-2-bromonaphthalene **28** to 2,3-dihydro-3-methylnaphtho[1,2-*b*]furan **29** and of 1-allyloxy-4-benzyloxy-5-methoxynaphthalene **31** to 5-benzyloxy-6-methoxy-3-methylnaphtho[1,2-*b*]furan **32**, respectively (Scheme 11).



Scheme 10.

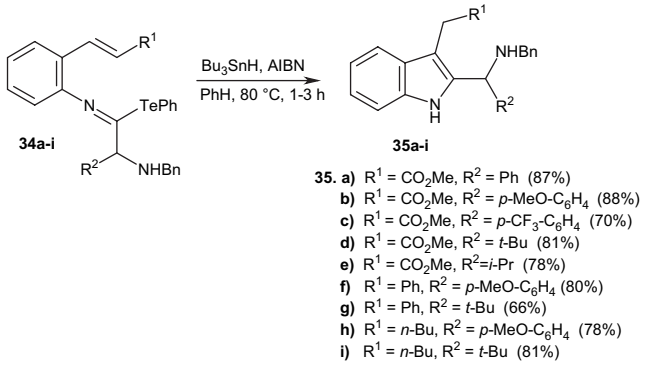


Scheme 11.

3. Synthesis of nitrogen heterocycles

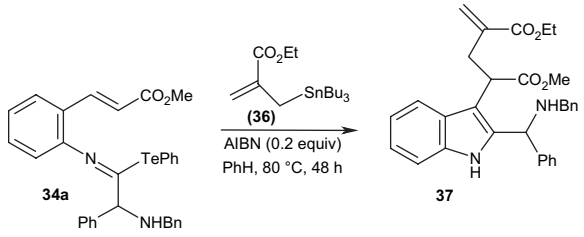
3.1. Imine substrates and related systems

Tributyltin hydride-mediated intramolecular radical cyclisation[56] of imidoyltellurides **34a–i** afforded the 2,3-substituted indoles **35a–i** in excellent yield (Scheme 12).



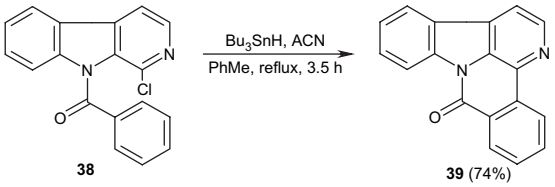
Scheme 12.

It was also observed[56] that compound **34a** on treatment with ethyl 2-(tributylstannylmethyl)acrylate **36** (1.2 equiv) in the presence of AIBN (0.2 equiv) furnished the allylated product **37** in 59% yield (Scheme 13).



Scheme 13.

Recently, Markgraf et al. have synthesised[57] 9*H*-benzo[*c*]-indolo[3,2,1-*ij*][1,5]naphthyridin-9-one **39** in 74% yield by $^{n}Bu_3SnH$ annulated radical cyclisation of 9-benzoyl-1-chloro-β-carboline **38** (Scheme 14).

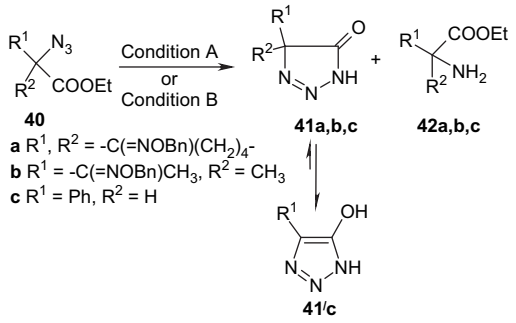


Scheme 14.

These workers have similarly synthesised[57] 9*H*-indolo[3,2,1-*de*]phenanthridin-9-one, 8*H*-[1,6]naphthyridino[8,7,6-*jk*]-carbazol-8-one, 8*H*-[2,6]naphthyridino[4,3,2-*jk*]carbazol-8-one, 8*H*-[2,7]naphthyridino[4,3,2-*jk*]carbazol-8-one and 8*H*-[1,7]naphthyridino[5,6,7-*jk*]carbazol-8-one.

3.2. Substrates with azido oximes and allenamides

The azido oximes **40a–c** were allowed to react under two different conditions.[58] In the first instance, the reaction was carried out in the presence of Bu_3SnH (1.1 equiv) and AIBN (0.1 equiv) in refluxing benzene for ca. 5 h. In the second case, the same reaction was carried out in the absence of AIBN. In both examples, the major product was the triazolones **41a**, **41b** and **41′c**. In general, however, much better yield of **41a**, **41b** and **41′c** were obtained in the absence of AIBN. The diminished yield of triazolones **41a–c** in the presence of AIBN was due to the parallel intervention of stannylaminyl radicals, which would mainly produce unidentified material, along with small amounts of the reduced amines **42a–c** (Scheme 15).

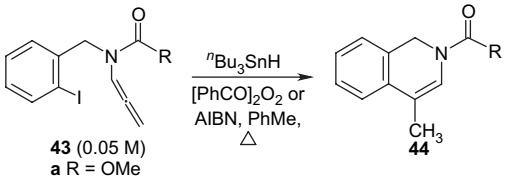


Azide	Reaction Condition	Triazolone	Yield (%)	Amine	Yield (%)
40a	A	**41a**	36	**42a**	10
40a	B	**41a**	70	**42a**	11
40b	A	**41b**	29	**42b**	18
40b	B	**41b**	45	**42b**	18
40c	A	**41′c**	50	**42c**	29
40c	B	**41′c**	48	**42c**	28

Condition A: Bu_3SnH (1.1 equiv), AIBN (0.1 equiv), PhH, reflux
Condition B: Bu_3SnH (1.1 equiv), PhH, reflux

Scheme 15.

Hsung et al. have developed synthetic protocols employing allenamides[59–61] and extended their efforts[62] to the possibility of a radical cyclisation using allenamides. Recently, they have found[62] that an iodobenzyl-substituted allenamide **43a** underwent regioselective radical cyclisation in the presence of AIBN as initiator (compared to benzoyl peroxide) and $^{n}Bu_3SnH$ as hydrogen donor at 80 °C to produce isoquinoline **44a** as the only product. Neither the *endo*-cyclised product (isobenzazepine) nor the *exo*-cyclised product (isoindole) was isolated (Scheme 16).



Substrate	Initiator (equiv)	H-donor (equiv)	Temp. (°C)	Product	Yield (%)
43a	$[PhCO_2]O_2$ (0.2)	*n*-Bu_3SnH (2.0)	60	**44a**	44
43a	AIBN (0.4)	*n*-Bu_3SnH (1.5)	80	**44a**	66

Scheme 16.

The specific regioselectivity was further confirmed by using a range of different allenamides **43b–g** (0.05 M) containing

a urethane, urea or amido substitution, to produce compounds **44b–g** in the presence of $^{n}Bu_3SnH$ (1.5 equiv) and AIBN (0.4 equiv) at 80 °C in refluxing toluene (Table 1).

Table 1

Allenamide	Product	Yield (%)
43b: R=O^{t}Bu	**44b**	75
43c: R=*O*-(+)-menthyl	**44c**	80
43d: R=NMe_2	**44d**	69
43e: R=$(CH_2)_2CH{=}CH_2$	**44e**	55
43f: R=Me	**44f**	58
43g: R=*i*-Pr	**44g**	44

Additionally, Shen and Hsung have also succeeded[62] in achieving *exo*-cyclisation in some cases, leading to the synthesis of isoindoles, and the feasibility of a tandem radical cyclisation using allenamide was found to be effective.

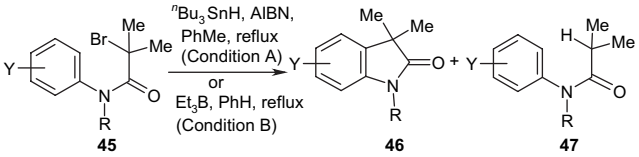
3.3. *N*-Vinylic substrates and related systems

Stevens et al. synthesised[63] the pentacycle, 8*H*-quino[4,3,2-*kl*]acridine, in excellent yield [98% yield in both boiling triglyme (216 °C) and ethanol (78 °C) and 95% yield in methanol (65 °C)] by the radical cyclisation of 9-(benzotriazol-1-yl)acridine in a range of low-boiling solvents. Various spirocyclic compounds have been prepared[64] by $^{n}Bu_3SnH$-mediated radical cyclisation of furan-3-carboxamide. A rare 7-*endo* cyclisation process has been explored[65] to generate octahydrocyclopenta[*b*]azepines in fair yield and excellent stereoselectivity. The vinylogous amide furnished[65] the azaspirocycles via a 6-*exo* ring closure in fair yield and in a 1:1 ratio of diastereomers. Bu_3SnH-mediated radical cyclisation[66] reactions of α-chloroacrylamide and acrylamide have been reported.

Majumdar and Sarkar have demonstrated[67] the radical cyclisation reaction of different 4-[*N*-(2′-bromobenzyl)-*N*-methyl]amino coumarins in dry refluxing benzene under nitrogen with tri-*n*-butyltin chloride and sodium cyanoborohydride in the presence of 0.5–0.6 mol equiv of AIBN.

N-(2-Halogenoalkanoyl)-substituted anilines **45a–j** were treated[68] with $^{n}Bu_3SnH$ and AIBN in boiling toluene to produce 1-substituted 3,3-dimethylindolon-2-ones **46a–j** as the major products, together with 2-methylpropananilides **47a–j** as the minor products.

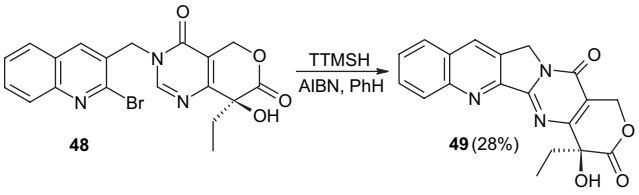
The above reaction could also be performed[68] with triethylborane in benzene or aqueous EtOH to obtain the indolones **46** and the reduction products **47**. The yields, however, were generally lower than those obtained in the tri-*n*-butyltin hydride-mediated reactions (Scheme 17).



	Substituents		Condition A Isolated yield (%)		Condition B Isolated yield (%)	
	R	Y	**46**	**47**	**46**	**47**
45. a)	Ph	H	39	13	21	8
b)	Me	H	48	22	27	13
c)	Me	*p*-Cl	40	20	-	-
d)	Me	*o*-Cl	34	12	-	-
e)	Me	*p*-OMe	36	18	-	-
f)	Me	*o*-OMe	38	12	-	-
g)	Me	*p*-Me	38	24	-	-
h)	Me	*o*-Me	50	28	-	-
i)	Me	*o*-Ac	76	10	1	trace
j)	Me	*o*-Bz	80	7	30	trace

Scheme 17.

14-Azacamptothecin, a potent water-soluble analogue of the antitumour agent, camptothecin, has been prepared[69] by a convergent synthesis, in which the key step involved the radical-mediated cyclisation of compound **48** to produce 14-aza-CPT **49** (CPT=camptothecin) as a colourless solid in 28% yield (Scheme 18).

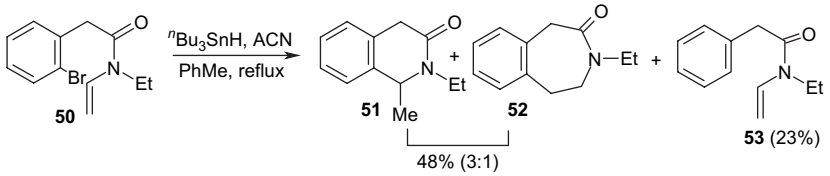


Scheme 18.

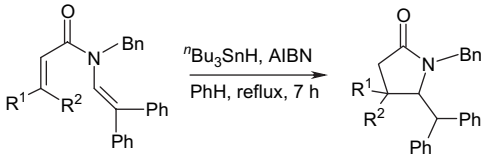
Recently, Ishibashi et al. observed[70] that the Bu_3SnH-mediated radical cyclisation of 2-(2-bromophenyl)-*N*-ethenylacetamide **50** gave a 3:1 mixture of the 6-*exo* cyclisation product, 2-ethyl-1,2,3,4-tetrahydro-1-methylisoquinolin-3-one **51**, and the 7-*endo* cyclisation product, 3-ethyl-2,3,4,5-tetrahydro-1,3-benzazepin-2-one **52** in 48% combined yield along with the simple reduction product **53** (23% yield) (Scheme 19). The above results showed that the position of the carbonyl group on the enamide is extremely important in determining the course of the cyclisation.

Ishibashi et al. also observed[71] that *N*-vinyl-α,β-unsaturated amides **54a–c** on treatment with $^{n}Bu_3SnH$ and a catalytic amount of AIBN in boiling benzene underwent 5-*exo* cyclisation to produce the γ-lactams **55a–c** (Scheme 20).

The formation of lactams **55** from compounds **54** may be explained by the generation of radicals **56** through the attack of



Scheme 19.

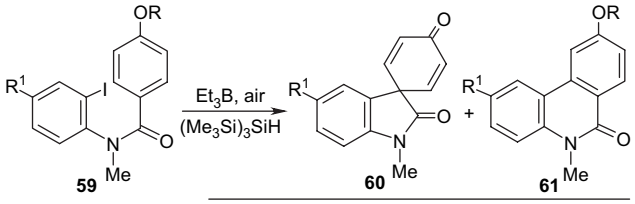


Starting	R^1	R^2	Time (h)	Product	Yield (%)
54a	H	Me	7	*trans*-**55a** + *cis*-**55a**	91(trans:cis = 1.4:1)
54b	Me	Me	9	**55b**	97
54c	H	Ph	1.5	**55c**	93

Scheme 20.

$Bu_3Sn^{\bullet}$ at the carbonyl oxygen atom of the amide **54**. The radicals **56** (stabilised by the resonating structures **56A** and **56B**) undergo 5-*exo* cyclisation to give the radicals **57**, which are stabilised by two phenyl groups. Radicals **57** are trapped with ^{n}Bu$_3$SnH to give the tin(IV) enolates **58** and, finally, the γ-lactams **55** are formed by hydrolysis of the enolates **58** followed by acidic workup (Scheme 21).

It was found[72] that the TBS-protected phenol **59a** (0.15 M in benzene) on treatment with 1.2 equiv of $(Me_3Si)_3SiH$ and 1.2 equiv of Et_3B gave the spirocyclic compound **60a** and the phenanthridinone **61a** as the products and these were isolated by flash chromatography in 13 and 57% yields, respectively. Like the TBS-protected precursor **59a**, the methyl-protected precursor **59e** also afforded the phenanthridinone **61e** as the major product (38% yield). The trityl precursors **59b**,**c** or the benzoyl precursor **59d** furnished the desired spirocyclic compounds **60b**,**c** and **60d**, respectively, as the major products (Scheme 22).

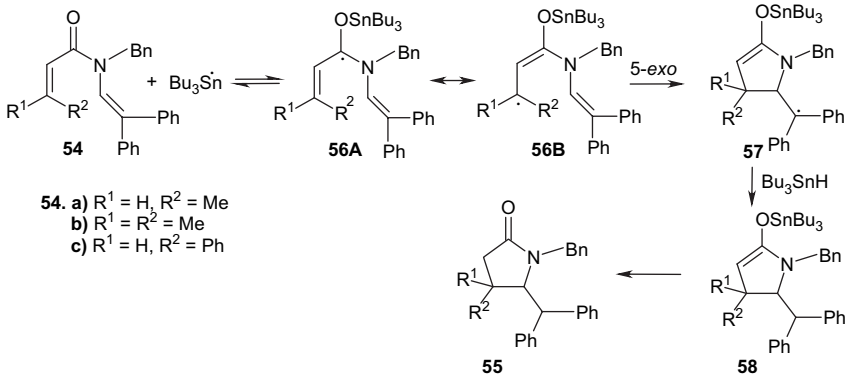


Precursor	R^1	R	Product	Ratio	Yield (%)
59a	H	TBS	**60a/61a**	1/4.4	13, 57
59b	H	Tr	**60b/61b**	2.2/1	43, nd
59c	Me	Tr	**60c/61c**	1/0	53
59d	H	Bz	**60d/61d**	1.5/1	29, nd
59e	H	Me	**60e/61e**	1/2.6	15, 38

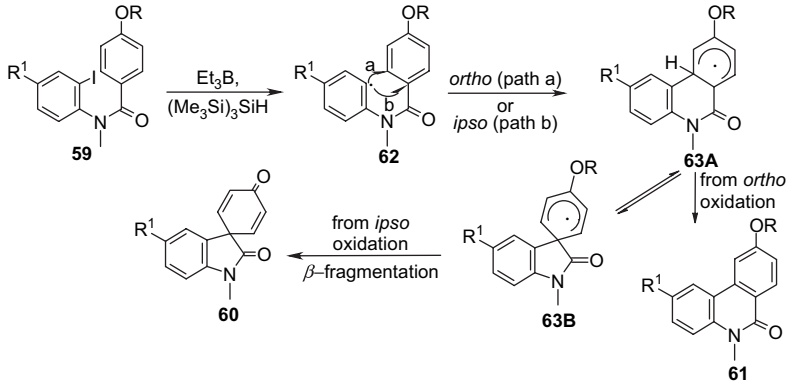
nd = not determined; purification was not possible by column chromatography

Scheme 22.

The mechanism of the reaction is depicted as follows. Aryl radicals **62** obtained from the compounds **59** can cyclise at the *ortho* position (path a) to give **63A** or at the *ipso* position (path b) to give **63B**.[73] These radicals might be in equilibrium through a formal 1,2-shift.[74] Compounds **61** are obtained by the oxidation[75] of **63A**, with the –OR group intact, whereas either oxidation or β-fragmentation[76] of **63B** should give the spirocyclic compounds **60** (Scheme 23).



Scheme 21.



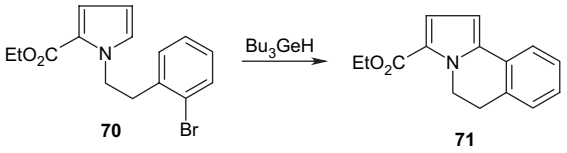
Scheme 23.

Recently, Bremner and Sengpracha have applied[77] the free radical cyclisation of indolyl iodoacetamide derivatives for the synthesis of the pharmacologically significant paullone ring system. *N*-Benzyliodoacetamides **64a–c** on reaction with $^{n}Bu_3SnH$ and AIBN afforded the *N*-benzylated paullone derivatives **65a–c**. When the reaction was carried out in toluene, compound **64a** furnished some spirocyclic product **66a** in addition to compound **65a**. At a higher reaction temperature (boiling mesitylene), the yields of the paullone system were increased significantly (Scheme 24).

The mechanism of this reaction is interpreted as follows. The paullone system could arise either via a 7-*endo-trig* addition of the amidomethyl radical (from the *cisoid* iodoacetamide), followed by oxidation or by 6-*exo-trig* addition at the indole C-2 position, followed by rearrangement and oxidation. There is competition between rearrangement and hydrogen atom abstraction by the indolic C-3 radical, which is responsible for the formation of compounds **65**.

Recently, Bowman and co-workers have used[78] 2-(2-bromophenyl)ethyl groups as building blocks in radical cyclisation reactions onto azoles to synthesise tri- and tetra-cyclic heterocycles. They carried out a $^{n}Bu_3SnH$-mediated radical cyclisation reaction of methyl 1-[2-(2-bromophenyl)ethyl]-1*H*-imidazole-5-carboxylate **67** to produce methyl 5,6-dihydroimidazo[2,1-*a*]isoquinoline-3-carboxylate **69** in 71% yield via the radical intermediate **68**. When the same reaction was carried out in Bu_3GeH, compound **69** was obtained in 54% yield (Scheme 25).

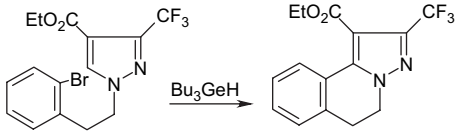
Ethyl 1-[2-(2-bromophenyl)ethyl]-1*H*-pyrrole-2-carboxylate **70** was cyclised using Bu_3GeH to give ethyl 5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate **71** in 82% yield (Scheme 26).[78]



70 **71**

Scheme 26.

Ethyl 1-[2-(2-bromophenyl)ethyl]-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate **72** was also cyclised in good yield using Bu_3GeH to give ethyl 2-(trifluoromethyl)-5,6-dihydropyrazolo[5,1-*a*]isoquinoline-1-carboxylate **73** in 57% yield (Scheme 27).[78]

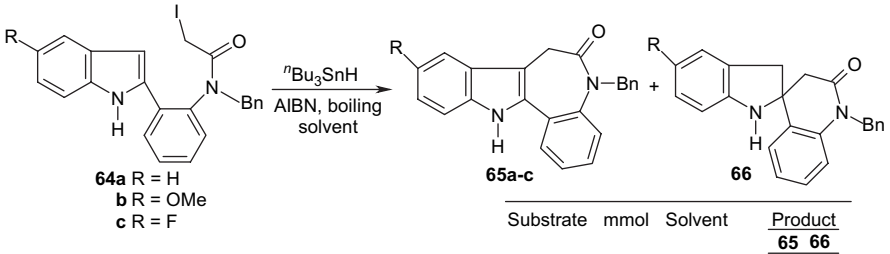


72 **73** (57%)

Scheme 27.

The generalised mechanistic pathway for these radical cyclisation reactions is as follows and they are actually intramolecular aromatic homolytic substitutions. Cyclisation of the intermediate aryl radicals (**B**), obtained from 2-(2-bromophenyl)ethyl groups (**A**), produces new six-membered rings attached to the azoles (**D**) via the intermediate aromatic π-radicals (**C**) (Scheme 28).

N-(2-Bromophenyl)-β-lactams **74a–f** on treatment with Bu_3SnH and AIBN afforded[79] the corresponding condensed tetracyclic biaryl-2-azetidinones **75a–f** in good yield. The β-lactams **74e** and **74f**, however, furnished along with cyclisation products **75e** and **75f**, the C-4 dearylated

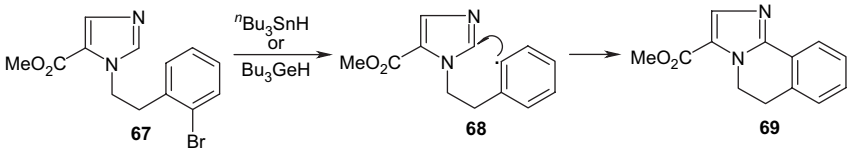


64a R = H
b R = OMe
c R = F

65a-c **66**

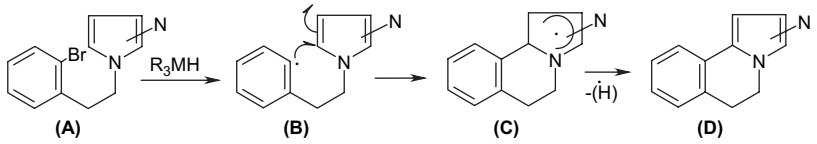
Substrate	mmol	Solvent	Product 65	Product 66
			Yield (%)	
64a	0.13	PhMe	25	-
64a	0.36	PhMe	-	10
64a	0.15	PhMe	8	13
64a	0.13	Mesitylene	52	-
64b	0.11	Mesitylene	25	-
64c	0.10	Mesitylene	45	-

Scheme 24.



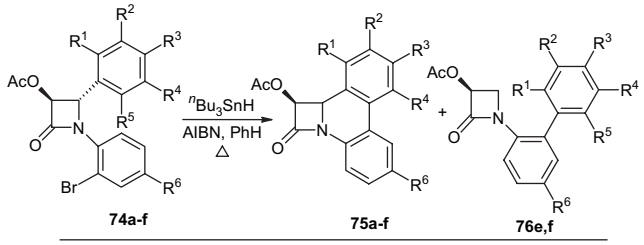
67 **68** **69**

Scheme 25.



Scheme 28.

N-biphenyl-2-azetidinones **76e** and **76f**, respectively (Scheme 29).

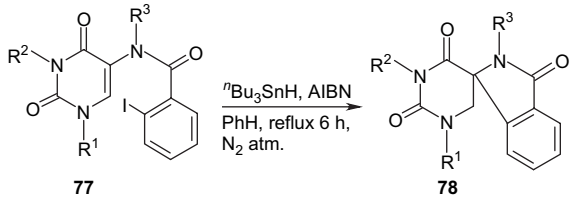


Substrate	R^1	R^2	R^3	R^4	R^5	R^6	Product	**75:76** ratio	Yield **75:76** (%)
74a	H	H	OMe	H	H	H	**75a**	100:0	70
74b	H	H	OMe	H	H	Me	**75b**	100:0	62
74c	H	H	H	H	H	H	**75c**	100:0	66
74d	H	OMe	H	OMe	H	H	**75d**	100:0	51
74e	OMe	H	OMe	H	OMe	H	**75e:76e**	40:30	38:14
74f	Me	H	Me	H	Me	H	**75f:76f**	80:10	58

Scheme 29.

Free radical cyclisation is now a very useful and well-established procedure in heterocyclic chemistry.[80,81] Five-membered ring[82–84] formation via intramolecular free radical cyclisations is more common than those forming six-[17] or seven-membered[85,86] ring, but cyclisation leading to indole-fused eight-membered ring is quite rare. Bremner and Sengpracha presented[87] a versatile route to indolo[2,1-*d*][1,5]benzodiazocine derivatives in a free radical cyclisation approach from 1-substituted indole derivatives with appropriately positioned haloacetamide functionalities. Thus, *N*-substituted iodo- and bromoacetamide precursors afforded indole- and dihydroindole-fused eight-membered ring derivatives in good yield.

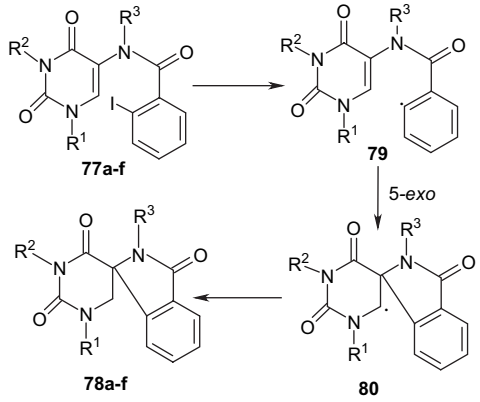
Recently, we have reported[88] the regioselective synthesis of 1,3-dialkyl[5,7′]spiro-[pyrimidine-5,6-1′,7′-tetrahydroisoindole]-2,4,2′-triones **78a–f** by ^{n}Bu$_3$SnH/AIBN-mediated radical cyclisation of 5-(2-iodobenzamido)-1,3-dialkylpyrimidine-2,4-diones **77a–f** (Scheme 30).



78. a) $R^1 = R^2 = R^3 =$ Me (82%)
b) $R^1 = R^2 =$ Et, $R^3 =$ Me (85%)
c) $R^1 =$ Et, $R^2 = R^3 =$ Me (77%)
d) $R^1 = R^2 =$ Me, $R^3 =$ Et (81%)
e) $R^1 = R^2 = R^3 =$ Et (84%)
f) $R^1 = R^3 =$ Et, $R^2 =$ Me (76%)

Scheme 30.

The regioselective formation of the five-membered heterocyclic ring can be explained by the application of FMO theory. Aryl radicals are high-energy species and, hence, are nucleophilic in character. The presence of a highly electron-withdrawing carbonyl group confers considerable electrophilic character to the C-5 position of the uracil moiety. Thus, in the case of the nucleophilic radicals **79**, FMO theory suggests that the mode of ring closure is largely determined by the interaction between the radical SOMO (≡HOMO) and the alkene LUMO of the acceptor (electron-deficient centre) and, accordingly, more favourable bond formation occurs between the radical centre (nucleophilic) and C_5 of the uracil ring for the 5-*exo* products **78a–f** through **80** (Scheme 31).



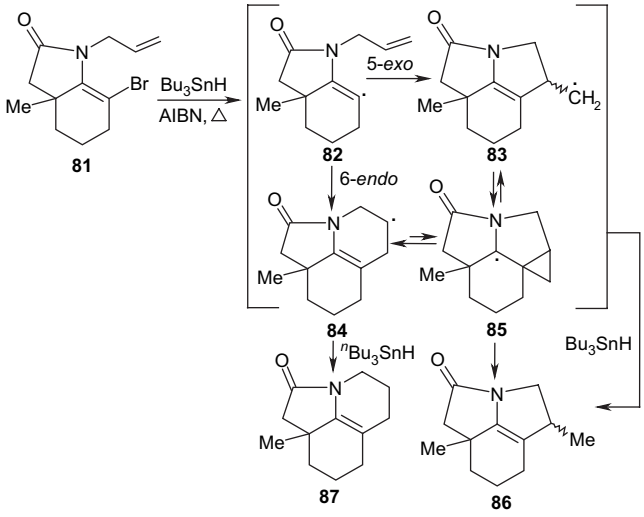
Scheme 31.

3.4. *N*-Allylic substrates and related systems

^{n}Bu$_3$SnH annulated radical cyclisation[89] of selenoesters separated by one methylene group has been discussed under non-reductive conditions (^{n}Bu$_6$Sn$_2$, 300-W sun lamp). The selenoester having a benzyl group at the 3-position of the indole ring also cyclised to give 2,3-fused ring indole derivatives in both reductive and non-reductive conditions.[89] Kamimura and Taguchi reported[66] the radical cyclisation of various α-unsubstituted acrylamides under standard radical cyclisation conditions employing Bu$_3$SnH and AIBN. ^{n}Bu$_3$SnH-mediated radical cyclisation[90] of *N*-allyl-7-bromo-3a-methyl-hexahydroindol-2-one furnished a six-membered ring product that prevails over the isomeric five-membered compound. (*S*)-*N*-Allyl-2-bromo-*N*-(phenylethyl)acetamide, which is a mixture of *E*/*Z* isomers in a ratio of 3:1, favouring the *Z*-rotamer,[91,92] was allowed to react with ^{n}Bu$_3$SnH and AIBN in refluxing benzene, thus producing pyrrolidinones when the *Z*-rotamer was present. The $Ph_{1,5}$-migration product was achieved when the *E*-rotamer was highly populated or the rotation of the amide bond was quite slow.[93] Indole selenoesters, carrying different alkenyl, cyclohexenyl or tetrahydropyridyl moieties at

the nitrogen, were found to cyclise[94] with $^{n}Bu_3SnH$ and AIBN in refluxing benzene. Baldwin et al. reported[95] the spirocyclisation of various benzofuran derivatives under standard radical cyclisation condition using Bu_3SnH and AIBN.

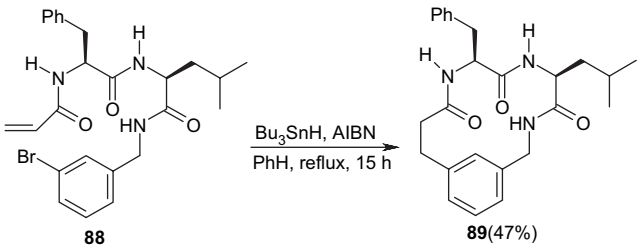
Recently, Padwa and co-workers have observed[96] that the *N*-allyl-7-bromo-3a-methylhexahydroindolinone system **81** preferentially leads to the 6-*endo-trig* cyclisation product **87** under high dilution conditions. Additionally, some 5-*exo-trig* cyclisation product **86** was obtained as a minor product. The six-membered cyclised product **87** was formed through two reaction pathways. The bromide **81** can generate a cyclohexenyl radical **82**, which may undergo 5-*exo-trig* cyclisation to produce the kinetically formed radical **83**, and rearrangement may lead to the thermodynamically more stable radical **84** via **85**. The cyclohexenyl radical **82** may also undergo 6-*endo-trig* cyclisation to produce the radical **84**, which may lead to the product **87**. When compound **81** (0.01 M) was allowed to react with $^{n}Bu_3SnH$ and a catalytic amount of AIBN, the six-membered ring compound **87** was the major product formed in 89% yield. When bromide **81** (0.1 M) was treated with $^{n}Bu_3SnH$, however, the 5-*exo* cyclisation product **86** was produced in 20% yield (3:1 mixture of diastereomers) along with the 6-*endo* cyclisation product **87** in a ratio of 1:3, together with the simple reduction product (19%) (Scheme 32).



Scheme 32.

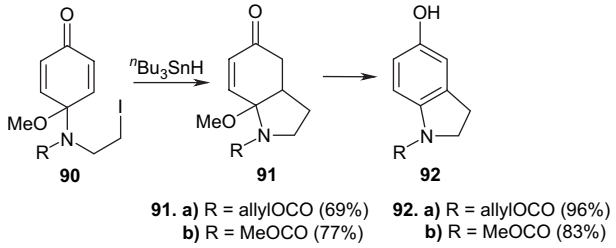
An efficient protocol for the synthesis of cyclic peptides constrained with a 3-(3-aminomethylphenyl)propionic acid linker using a tri-*n*-butyltin hydride-mediated intramolecular free radical reaction has been developed recently.[97] 3-Bromobenzyl-*N*-acryloyl-L-leucine amide **88** in refluxing benzene was subjected to an intramolecular free radical reaction using Bu_3SnH/AIBN to give the corresponding cyclic peptide **89** (Scheme 33). The same procedure has also been utilised to synthesise tripeptides.

Radical cyclisation onto benzene rings is not fully developed and such reactions and their mechanisms[75,83,98] are very difficult, but extremely useful. The most useful procedure involves the use of xanthates with stoichiometric



Scheme 33.

amounts of a diacyl peroxide.[85,99,100] Recently, Clive et al. reported[101] that ketones **90a** and **90b** underwent $^{n}Bu_3SnH$-mediated radical cyclisation to give compounds **91a** and **91b** and on treatment with TsOH, aromatisation is effected to afford the benzo-fused nitrogen heterocycles **92a** and **92b** (Scheme 34).



Scheme 34.

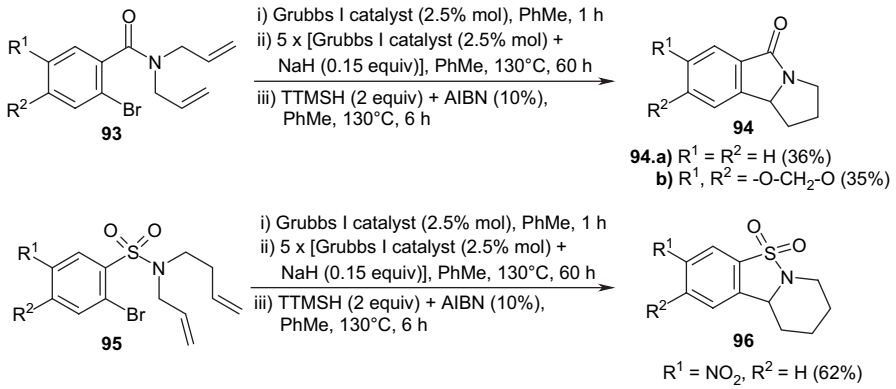
A new one-pot procedure has been developed[102] to synthesise polycyclic lactams and sultams from amides **93a** and **93b** and sulfonamides **95**, respectively. *N*,*N*-Bisallylamides **93a** and **93b** underwent a tandem ring-closing metathesis and subsequent isomerisation followed by a sequential radical cyclisation[103] to produce the polycyclic lactams **94a** and **94b** in good yield. The same process was successfully applied to the bisallylsulfonamides **95** to give the corresponding sultams **96** as the major products (Scheme 35).

Haloaryl-β-lactams (**97a–c** and **98a** and **98b**) under standard $^{n}Bu_3SnH$ annulated radical cyclisation condition afforded[104] the benzocarbapenems (**99a–c** and **100a** and **100b**), respectively, in good yield as single diastereomers (Scheme 36).

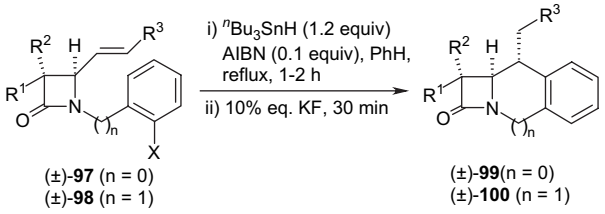
3.5. Cascade/tandem cyclisation

7-Acetyl-3-allyl-4-bromo-6-(*tert*-butyldimethylsilanyloxy)-5,6,6a,7-tetrahydro-3*H*-pyrrolo[2,3-*d*]carbazol-2-one was found to react with $^{n}Bu_3SnH$ and AIBN under slow-addition conditions in refluxing benzene to give 6-acetyl-5-(*tert*-butyldimethylsilanyloxy)-2,3,4,5,5a,6-hexahydro-1*H*-6,12a-diaza-indeno[7,1-*cd*]fluoren-12-one[105] (91%) via an initially generated cyclohexenyl radical, either by a direct 6-*endo-trig* cyclisation or, alternatively, by a vinyl radical rearrangement pathway.[106]

Tandem radical cyclisation of acyclic iodides including [3-(2-iodoethyl)-6,10-dimethyl-undeca-5,9-dien-1-ynyl]-dimethylphenylsilane has been found to give bicyclo[2.2.1]-heptane derivatives in good yield. A radical approach has also been utilised in the total synthesis of racemic-(*Z*)-β-santalol.[107]

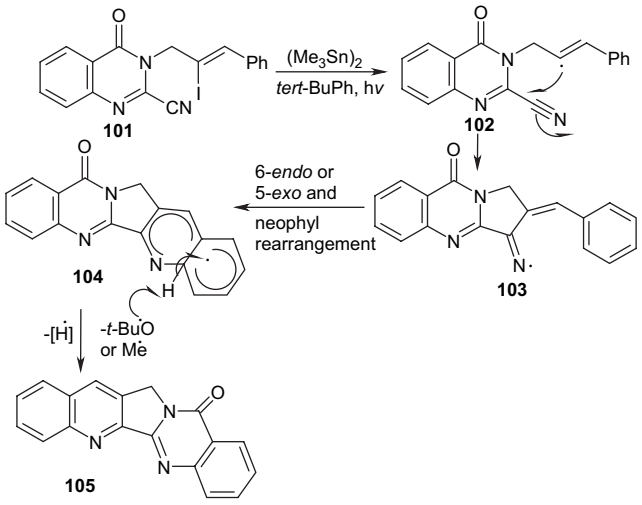


Scheme 35.



Substrate	R^1	R^2	R^3	X	n	Product	Yield (%)
97a	Me	Me	Ph	Br	0	**99a**	65
97b	PhO	H	Ph	Br	0	**99b**	66
cis-**97c**	BnO	H	Ph	I	0	*cis*-**99c**	60
trans-**97c**	BnO	H	Ph	I	0	*trans*-**99c**	65
98a	PhO	H	Ph	Br	1	**100a**	50
98b	BnO	H	Ph	Br	1	**100b**	61

Scheme 36.



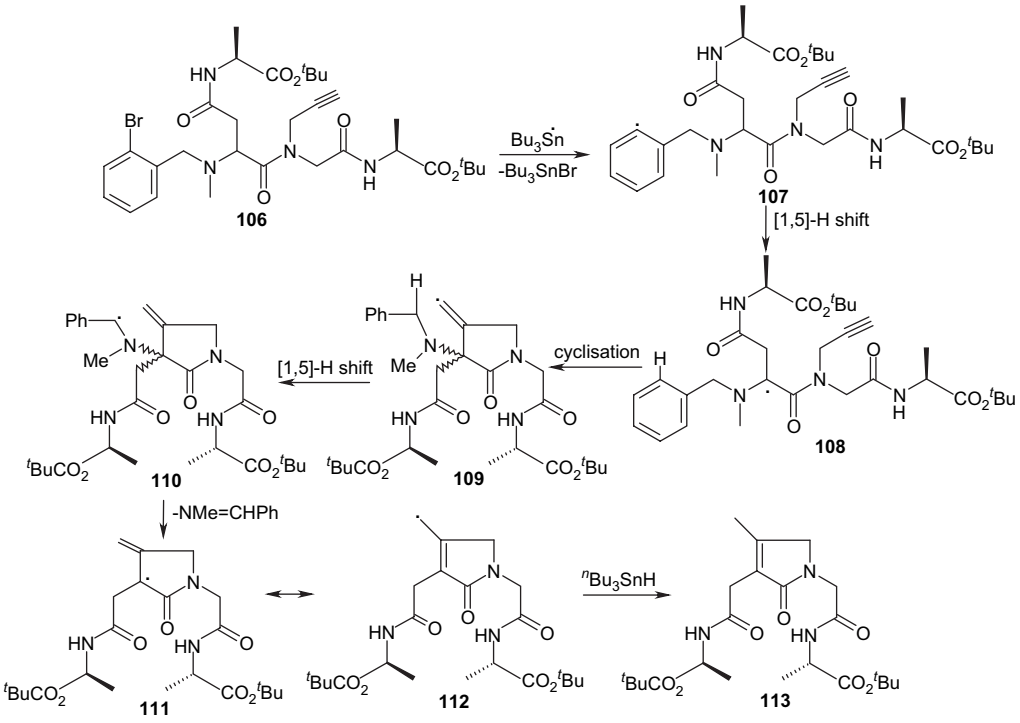
Scheme 37.

The biologically active alkaloid, luotonin A **105**, has been synthesised[108] by a cascade radical cyclisation reaction involving homolytic aromatic substitution. The radical precursor, 3-[(*Z*)-2-iodo-3-phenylprop-2-enyl]-4-oxo-3,4-dihydroquinazoline-2-carbonitrile **101**, was allowed to react under general reaction conditions[109] using hexamethylditin (14 equiv) in *tert*-butylbenzene with sun lamp irradiation at 150 °C for 46 h. Luotonin A **105** was obtained in 21% yield along with other products (30%, *E*/*Z* isomeric mixture). The yield of luotonin A **105** could be improved (30%) under milder reaction conditions using di-*tert*-butyl peroxide.[109] *tert*-Butoxyl radicals are generated by thermal or photochemical homolysis at a lower temperature and rapidly react with hexamethylditin to generate trimethyltin radicals. The *tert*-butylperoxyl radical act as a reactive and efficient H-abstractor for the final re-aromatisation step (from **104** to **105**). The formation of the product luotonin A **105** from **101** may be explained by the following mechanistic interpretation. The vinyl radical **102** obtained from **101** undergoes 5-*exo* cyclisation onto the nitrile and produces the iminyl intermediate **103**, which undergoes 5-*exo* cyclisation onto the phenyl ring followed by a neophyl rearrangement or a 6-*endo* cyclisation to furnish **104**. Finally, luotonin A **105** is formed by hydrogen abstraction from the π-radical intermediate **104** in the second step of the aromatic homolytic substitution (Scheme 37).

α,β-Unsaturated γ-lactams have recently been synthesised[110] by the radical cyclisation of di-, tri- and tetrapeptides containing *N*-2-bromobenzyl-, *N*-methyl-substituted alanine or aspartic acid. The radical precursor **106** on treatment with ^{n}Bu$_3$SnCl in boiling degassed *t*-BuOH in the presence of Na(CN)BH$_3$ and ACCN afforded 2-(2-{1-[(1-*tert*-butoxycarbonylethylcarbamoyl)methyl]-4-methyl-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl}acetylamino)propionic acid *tert*-butyl ester **113** in 51% yield. The mechanistic pathway of this cascade reaction is shown below (Scheme 38). Abstraction of bromine from **106** leads to the aryl radical **107**, which undergoes a [1,5]-hydrogen transfer to produce the radical **108**. Radical **108** then undergoes a 5-*exo-trig* cyclisation to produce the vinyl radical **109** followed by a [1,5]-H shift to generate **110**, which undergoes β-fragmentation to form the radical **111**. Radical **111** can either undergo reduction and subsequent isomerisation of the exocyclic double bond or, more preferentially allylic isomerisation to a more stable conjugated system **112** and, finally, a tin hydride reduction to **113**.

3.6. Diastereoselective radical cyclisation

A diastereoselective synthesis of (±)-9,10-bis-*epi*-stemoamide has been explored[111] in which three of the four contiguous stereocentres were set up in a diastereoselective 7-*exo-trig* radical cyclisation. This also allowed the construction of the tricyclic core of the molecule.

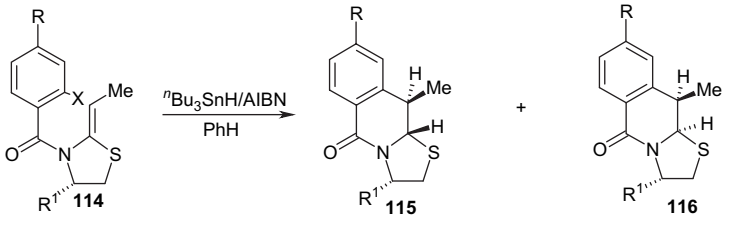


Scheme 38.

N-(2-Halobenzoyl)-cyclic ketene-*N*,*S*-acetals **114a–f** underwent $^{n}Bu_3SnH$-mediated stereo-controlled radical cyclisation[112] to afford (*R*,*S*,*S*)-3-alkyl-10-methyl-2,3,10,10a-tetrahydrothiazolo[3,2-*b*]isoquinolin-5-ones **115a–d** and (*R*,*R*,*S*)-3-alkyl-10-methyl-2,3,10,10a-tetrahydrothiazolo[3,2-*b*]isoquinolin-5-ones **116a–d** (Scheme 39).

The above cyclisation appears to follow two pathways. In the first pathway, the radical **117** derived from compound **114** may lead to either the less stable secondary radical intermediate **118** or the more stable tertiary radical **120**. Naturally, radical **120** may generate the less strained 6/5 ring products **115** and **116** upon hydrogen abstraction from $^{n}Bu_3SnH$. The other possibility of forming the more strained 5/5 ring fusion product **119** from radical **118** by hydrogen abstraction from $^{n}Bu_3SnH$ may be ruled out. Cyclisation of **117** to **118** followed by rearrangement to **120** seems highly unlikely, because this would lead to the generation of both *R*- and *S*-configurations of C-10 in products **115** and **116**. Only the *R*-configuration was observed (Scheme 40).

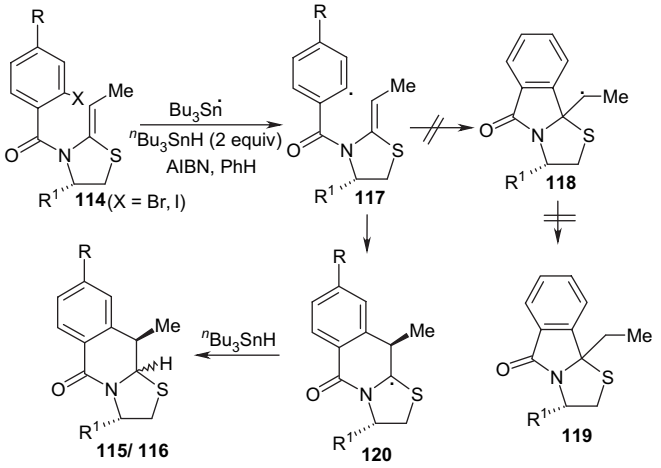
In order to use chiral auxiliaries in radical cyclisations,[113] Jones and McCarthy synthesised dihydroindolones with a very low level of asymmetric induction by the cyclisations of acrylanilides bearing chiral *N*-substituents. Recently, Curran et al. have successfully[114] carried out the radical cyclisation reactions of iodoacrylanilide **121**. From a study by NMR spectroscopy, it is clear that compound **121** exists as an equilibrium mixture of atropisomers (*M*,*S*)-**121**/(*P*,*S*)-**121** in a ratio of 68/32 at room temperature. At 110 °C, radical cyclisation of this mixture afforded the expected 50/50 ratio of products (*R*/*S*)-**122** and (*S*/*S*)-**122** and the ratio increased as the reaction mixture was cooled through 20 °C (78/22) to 0 °C (81/19) and then down to −20 °C (84/16). Cyclisation at −78 °C of a 91/9 ratio of (*M*,*S*)-**121**/(*P*,*S*)-**121** gave (*R*,*S*)-**122** and (*S*,*S*)-**122** in a 95/5 ratio, whereas



114. **a)** X = Br, R = H, R^1 = $CHMe_2$
b) X = I, R = H, R^1 = $CHMe_2$
c) X = Br, R = H, R^1 = CH_2CHMe_2
d) X = I, R = H, R^1 = CH_2CHMe_2
e) X = Br, R = Me, R^1 = $CHMe_2$
f) X = Br, R = Me, R^1 = CH_2CHMe_2

115, 116. **a)** R = H, R^1 = $CHMe_2$ 78%, 115a:116a = 1.4:1
b) R = H, R^1 = CH_2CHMe_2 82%, 115a:116a = 1.5:1
c) R = Me, R^1 = $CHMe_2$ 70%, 115b:116b = 1.1:1
d) R = Me, R^1 = CH_2CHMe_2 68%, 115b:116b = 1.3:1
77%, 115c:116c = 1.5:1
67%, 115d:116d = 1.2:1

Scheme 39.

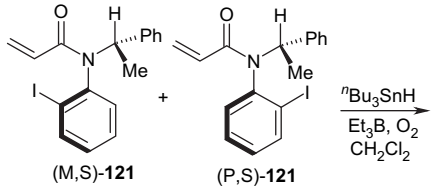


Scheme 40.

a mixture in a 2/98 ratio furnished (*R*,*S*)-**122**/(*S*,*S*)-**122** in 16/84 ratio. This means that each atropisomer of **121** cyclises to different major products **122**, but the results are consistent (Scheme 41).

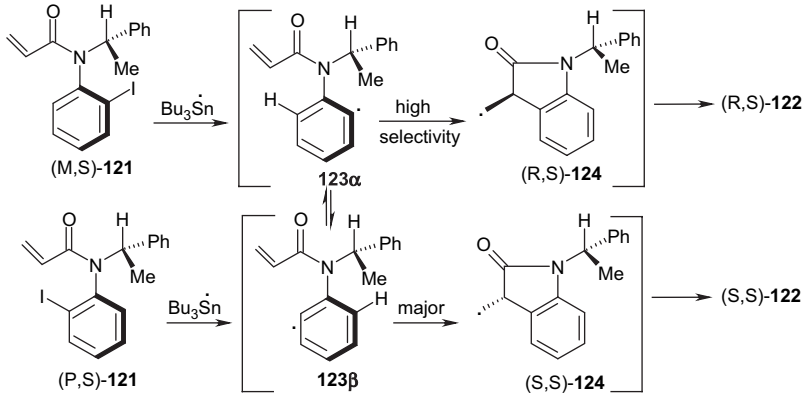
The mechanism of the above reaction may be interpreted as follows. Iodine abstraction from atropisomers (*M*,*S*)-**121** and (*P*,*S*)-**121** by a tributyltin radical takes place with equal rates to generate the radicals **123β** and **123α** in a ratio that reflects the starting iodide ratio. At a higher temperature, interconversion of **123β** and **123α** is more rapid than cyclisation. At low temperatures, below 0 °C, the two radicals **123α**,**β** can no longer interconvert and each undergoes cyclisation with its own selectivity in favour of the opposite diastereomers **124**. Radical **123β** cyclises to (*R*,*S*)-**124**, whereas **123α** cyclises predominantly to (*S*,*S*)-**124**, but with a significant (~20%) leakage to (*R*,*S*)-**124**. This accounts for the formation of different ratios of the product **122** (Scheme 42).

It has been demonstrated[115] that triphenyltin hydride-mediated reactions of β-lactam-tethered bromodienes gave six-, seven- or eight-membered bicyclic ring structure through intramolecular free radical cyclisation. (3*R*,4*S*)-1-Allyl-4-[(*R*)-3-bromo-1-hydroxybut-3-enyl]-3-methoxyazetidin-2-one [(+)-**125a**] underwent tin-promoted radical cyclisation to provide (7*R*,8*S*,9*R*)-7-hydroxy-9-methoxy-5-methylene-1-azabicyclo[6.2.0]decan-10-one [(+)-**126**] (57%) along with (3*R*,4*S*)-1-allyl-4-[(*R*)-1-hydroxybut-3-enyl]-3-methoxyazetidin-2-one [(+)-**127**] (17%). (3*R*,4*SR*)-4[(*RS*)-3-Bromo-1-hydroxybut-3-enyl]-1-(4-methoxyphenyl)-3-vinylazetidin-2-one [(±)-**125b**] under the same reaction conditions afforded the seven-membered ring fused bicycle (±)-**128** as the major product along with the isomeric product (±)-**129** containing a six-membered ring (Scheme 43). Thus, a combination of metal-annulated carbonyl-bromoallylation and free radical cyclisation furnishes a novel

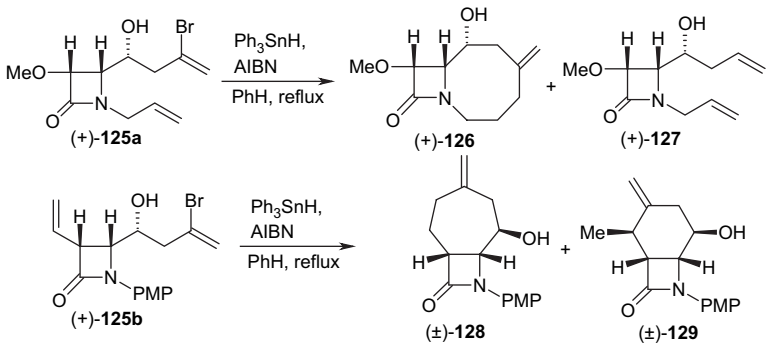


121 (M,S)/(P,S)	T (°C)	122 (R,S)/(S,S)	Yield (%)
68/32	110	50/50	82
68/32	20	78/22	79
68/32	0	81/19	76
68/32	-25	84/16	82
68/32	-78	84/16	73
91/9	-78	95/5	84
2/98	-78	16/84	76

Scheme 41.



Scheme 42.



Scheme 43.

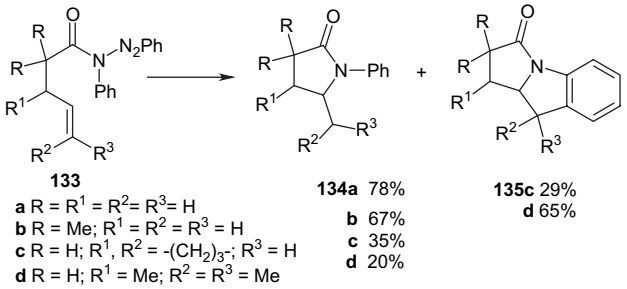
stereocontrolled access to fused bicyclic β-lactams of non-conventional structure.

It has been observed[111] that compound **130** in benzene under high dilution conditions (5.6 mM) at reflux temperature by slow addition of a Bu_3SnH solution (0.2 M) and a catalytic amount of AIBN afforded a 5:1 mixture of two diastereomers **131** and **132** in 41% yield (Scheme 44).

3.7. Synthesis of nitrogen heterocycles with non-conventional reagents

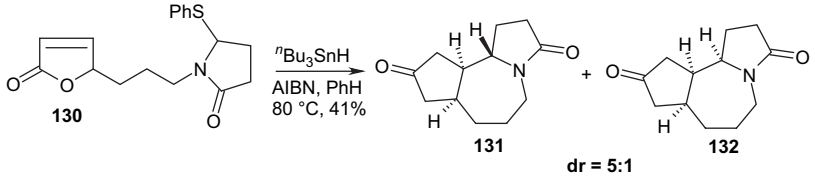
Microwave-assisted solid-phase synthesis of various indol-2-ones has been reported[116] by aryl radical cyclisation of resin-bound *N*-(2-bromophenyl)acrylamides using Bu_3SnH in DMF. Polymer-supported isocyanides reacted[117] with 2-mercaptoethanol and AIBN in DMF at 50 °C to furnish the cyclised products. Addition of a simple triorganogermanium hydride unit into Quadragel™ and Merrifield resins afforded solid-phase triorganogermanium hydrides.[118] 3-Alkylidenehexahydrofuro[2,3-*b*]pyrans (a mixture of *E*- and *Z*-isomers) were prepared[119,120] in good yield with moderate stereoselectivity by the reductive cyclisation with indium and iodine. The two isomers (*Z*/*E*, with the *Z*-isomer preferred) of 4-iodo-3-octenamide, without separation, reacted[121] with *t*-BuOCl and I_2 in CH_2Cl_2 in the dark at room temperature to generate the cyclic iminoketone in 72% yield. Silylation of nitronates, obtained by aza-Michael addition of tosylallylamine to nitroalkenes, furnished the *N*-(silyloxy)-isoxazolidines in 31% yield and these were then diastereoselectively transformed into 3-nitro-4-hydroxymethyl-pyrrolidine after desilylation[122] (52% yield). Compounds bearing a pyridine nucleus fused to a saturated nitrogen-containing ring including 7-azaoxindoles, 7-azaindolines, tetrahydro-[1,8]naphthyridines and tetrahydro-5*H*-pyrido[2,3-*b*]azepin-8-ones were synthesised[123] in good yield starting from various 2,6-dichloropyridines.

Amidyl radicals are highly reactive and electrophilic radicals[124] and synthetic methodologies involving amidyl radicals have not received much attention[125] as amidyl radical precursors are either very unstable or difficult to prepare. Amidyl radical precursors like *N*-halo amides[126] and *N*-hydroxypyridine-2-thienomidate esters[127,128] are very unstable and *N*-(phenylthio)amides[129] or *N*-(*O*-ethyl thiocarbonylsulfanyl)amides[125b] can only be prepared in low yield. *N*-Acyltriazines are found[130] to serve as a convenient precursor for unsaturated amidyl radicals under tin-free and initiator-free conditions. *N*-acyltriazenes **133a** and **133b** with a monosubstituted terminal double bond underwent thermal decomposition to give the 5-*exo* cyclisation product **134a** or **134b**, respectively, in high yield. With substrate **133c** having an internal double bond, the corresponding 5-*exo* cyclisation product **134c** was isolated in 35% yield along with the tetracyclic compound **135c** as a single stereoisomer in 29% yield. The triazine **133d** ($R^2 = R^3 = Me$) afforded the 5-*exo* cyclization product **134d** in only 20% yield whereas the tricyclic product **135d** was produced in 65% yield. The above results indicate that the formation of the tricyclic product is encouraged by the terminal substitution at the C=C bond (Scheme 45).



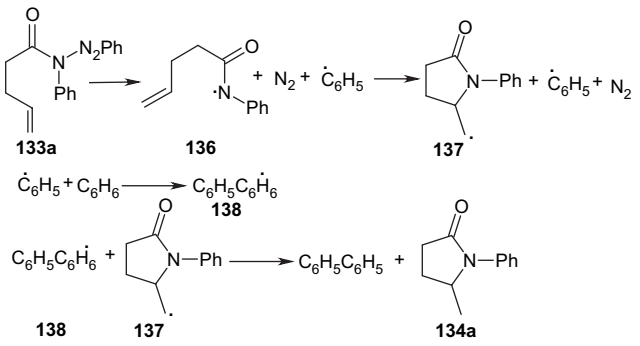
Scheme 45.

The formation of product **134a** from *N*-acyltriazine **133a** may be rationalised as follows. The amidyl radical **136** obtained by the thermal decomposition of **133** might undergo cyclisation to give the cyclised carbon-centred radical **137**. The cyclised radical **137** may abstract hydrogen presumably



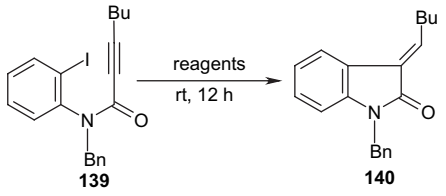
Scheme 44.

from radical **138** to produce the corresponding lactam **134a** as the final product (Scheme 46).



Scheme 46.

Some typical reactions of allylindium reagents[131] involving addition to the unsaturated bond in carbonyl compounds and imines give rise to the corresponding homoallylic alcohols and amines, respectively. Allylated products were also obtained by allylindation of alkynes,[132] allenes[133] and cyclopropenes.[134] Although photochemical reactions involving organocobalt compounds[135] were reported earlier, no photochemical reaction dealing with organoindium compounds has been explored until recently by the work of Araki et al.[136] 8-Bromo-octa-1,6-dienes and indium were refluxed in THF for 3 h to give the allylic indium, which was then irradiated with a high-pressure mercury lamp (100 W, Pyrex filter) in THF to afford the 5-*exo* cyclisation product in 51% yield.[136] This radical cyclisation is also very effective in the presence of benzoyl peroxide as a radical initiator.



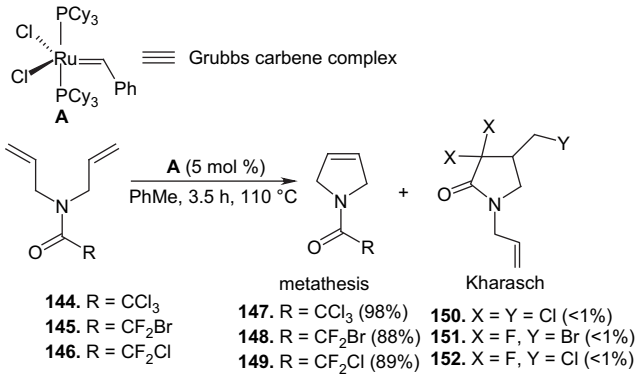
Reagents	Yield (%) **140** (E:Z)	**139**
1.In (2 equivs) + I_2(1 equiv)	40 (E)	45
2.In (2 equivs) + Br_2(1 equiv)	81 (E)	0
3.In (2 equivs) + Py.HBr_3(1equiv)	80(E)	0
4.InI (2 equivs)	32 (E)	55
5.InBr (2 equivs)	45 (E)	40
6.$InCl_3$ (0.1 equiv) + $NaBH_4$ (2equivs)	19(1.1:1)	50
7. Bu_3SnH (1.2 equivs) + Et_3B (1.2 equivs)	59(2:1)	0

Scheme 47.

Recently, Takemoto et al. demonstrated[137] an efficient method for the stereoselective synthesis of various *E*-, *Z*- and disubstituted 3-alkylideneoxindoles via radical cyclisation reactions using tandem indium-mediated carbometallation reactions. 2-Iodoalkynes such as **139** were allowed to react with indium and iodine in DMF,[119] and the desired 5-*exo* cyclisation product **140** was obtained in 40% yield. When bromine was added in place of iodine, the same reaction afforded **140** in 81% yield as a single isomer (Scheme 47). The same reaction may also be carried out by using $InCl_3/NaBH_4$[47,138] and $^nBu_3SnH/Et_3B$.[139]

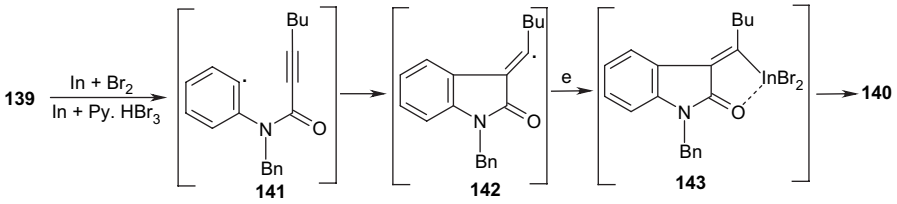
It may be assumed that the indium-mediated cyclisation of **139** may proceed via an sp^2-σ radical intermediate **141** followed by a radical intermediate **142** to give the intermediate **143**, in which coordination of the indium atom to the amide carbonyl group takes place and, thus, the 5-*exo* cyclisation product **140** is ultimately produced (Scheme 48).

It has been observed[140] that amides **144**, **145** and **146** on treatment with the Grubbs carbene complex **A** (5 mol %) in degassed toluene (110 °C, 3.5 h) under an argon atmosphere afforded Δ^2-pyrrolines **147**, **148** and **149**, respectively, in excellent yields (Scheme 49). However, in cases of compounds **144** and **145** Kharasch products (**150** and **151**) were generated in very trace amounts (detected by ^{1}H NMR spectra of the respective crude mixture) whilst compound **152** was not generated at all under this condition.

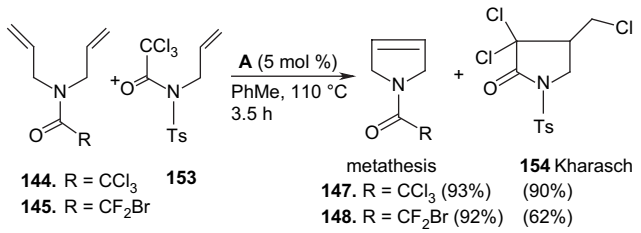


Scheme 49.

A 1:1 mixture of the amide **144** and tosamide **153** was subjected to the standard reaction conditions using the Grubbs carbene complex **A**. The Δ^2-pyrroline **147** (metathesis) and the γ-lactam **154** (Kharasch) products were obtained in excellent yield. A similar result was obtained in the case of the fluoro derivative **145** (Scheme 50).



Scheme 48.



Scheme 50.

It was also found[140] that sequential addition of the amide **144** followed by the tosamide **153** to a solution of the catalyst **143** in refluxing toluene afforded the Δ^2-pyrroline **147** (metathesis) and the lactam **154** (Kharasch) in 95 and 52% yields, respectively. On the other hand, the addition, i.e., sequential addition, of **153** first and then the amide **144** produced the Kharasch product **150** in 85% yield and **154** in 73% yield.

Halogen atom transfer radical cyclisation (HATRC) has been examined[141] on *N*-(indolylmethyl)trichloroacetamides under CuCl catalysis using nitrogen-containing ligands. The chlorinated amides (**155a–d**) upon treatment with CuCl produce the respective radicals (**156a–d**). Since the 3-position of the indole is nucleophilic, the ring closure of the electrophilic dichloro radicals **156a–d** was expected to produce the spiro-indoles (**157a–d**) via a 5-*exo-trig* ring closure (Kharasch ring closure). Now, the 3,3-spiro-3*H*-indoles **158a–d** were formed by losing HCl from compounds **157a–d** (Scheme 51).

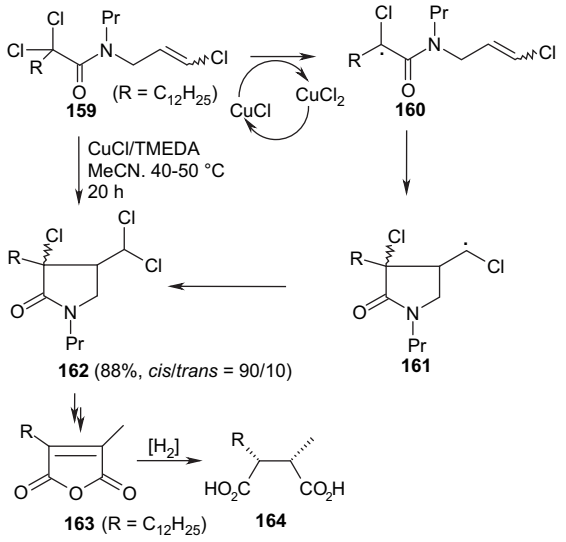
The above reaction may also be performed[141] by using bipyridine (bipy), TMEDA (*N*,*N*,*N*,*N*-tetramethyl-1,2-ethylenediamine) and PMDETA (*N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine) as ligands (Table 2).

Chaetomellic anhydride C **163** and (±)-*erythro*-rocellic acid **164** have been synthesised[142] in which the key step was the CuCl/TMEDA-catalysed atom transfer radical cyclisation of *N*-propyl-*N*-(3-chloro-2-propenyl)-2,2-dichlorotetradecanamide **159** to give *N*-propyl-3-chloro-4-dichloromethyl-3-dodecyl-pyrrolidin-2-one **162** via **160** and **161** (Scheme 52).

Atom transfer radical cyclisation (ATRC) and atom transfer radical addition (ATRA) catalysed by a coordinating

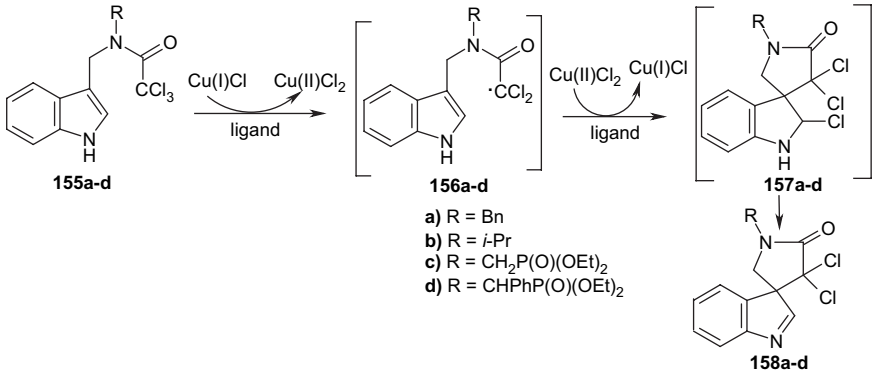
Table 2

Substrate	Ligand	Time (h)	Conditions	Product	Yield (%)
155a	TMEDA	6	Reflux	**158a**	81
155a	TMEDA	24	rt	**158a**	79
155a	PMDETA	24	rt	**158a**	35
155b	PMDETA	3	Reflux	**158b**	79
155c	TMEDA	24	rt	**158c**	51
155c	PMDETA	24	rt	**158c**	75
155c	bipy	24	rt	**158c**	15
155d	TMEDA	24	rt	**158d**	58
155d	TMEDA	4	Reflux	**158d**	57



Scheme 52.

unsaturated diruthenium amidinate complex, $[(\eta^5\text{-}C_5Me_5)\text{-}Ru(\mu_2\text{-}i\text{-}PrN{=}C(Me)N\text{-}i\text{-}Pr)Ru(\eta^5\text{-}C_5Me_5)]^+$ has been compared with atom transfer radical polymerisation (ATRP). *N*-Allyl-*N*-benzyltrichloro acetamide catalysed by the unsaturated diruthenium amidinate complex proceeded[143] at 25 °C to generate 3,3-dichloro-4-chloromethyl-1-benzyl-pyrrolidin-2-one in 94% yield within 30 min. Catalytic species generated in situ from a halide complex, $[(\eta^5\text{-}C_5Me_5)Ru(\mu_2\text{-}i\text{-}PrN{=}C(Me)\text{-}N\text{-}i\text{-}Pr)Ru(\eta^5\text{-}C_5Me_5)(X)$ [X=Cl, Br], and sodium salts of weakly coordinating anions such as $NaPF_6$ and $NaBPh_4$ show high activity.

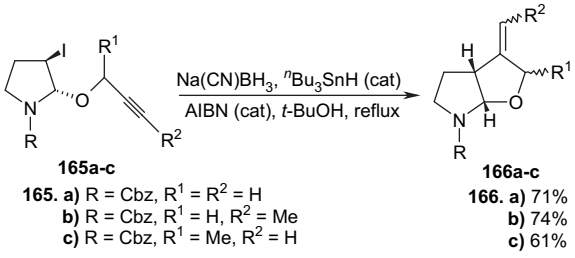


Scheme 51.

4. Synthesis of oxygen heterocycles

The total syntheses of 7(*S*)-hydroxymatairesinol and 7(*S*)-hydroxyarctigenin have been described[144] in which the major step was the $(Me_3Si)_3SiH$-mediated radical cyclisation of thionocarbonates. Clive et al. reported[145] *ent*-norcardione A in which the key step was the Bu_3SnH-mediated radical cyclisation of 8-allyloxy-4-[(1*R*)-2-iodo-1-methylethoxy]-4-methoxy-4*H*-naphthalen-1-one. Majumdar and Mukhopadhyay reported the aryl radical cyclisation of a range of 6-(2′-bromophenoxymethyl)-1,3-dimethyluracils with tri-*n*-butyltin chloride and sodium cyanoborohydride in the presence of AIBN to produce exclusively the 5-*exo* cyclisation products, 1,3-dimethylspiro[pyrimidine-6,3′-2′,3′-tetrahydrobenzofuran]-2,4-diones,[146] in 92–95% yields. Spiro[chroman-3,3′(2′*H*)-benzofurans] have been synthesised[147] in 60–75% yields by Bu_3SnH-mediated radical cyclisation of 3-(2-bromophenoxymethyl)coumarins. We have also synthesised[148] spiro-quinolones and coumarins in 80–85% yields by the application of radical cyclisation reactions of 3-(2′-bromobenzyloxy)quinolin-2-ones and 3-(2′-bromobenzyloxy)benzopyran-7-ones.

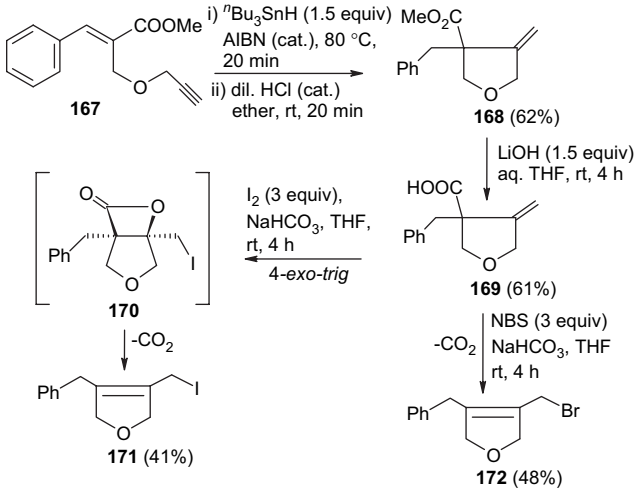
trans-α-Alkoxy-β-iodopyrrolidines **165a–c** underwent free radical cyclisation by sodium cyanoborohydride and catalytic amount of tributylstannane to give the bicyclic compounds **166a–c**, in moderate to high yield.[149] The cyclisations are highly regiospecific with only the cis-fused 5-*exo* or 6-*exo* product being formed (Scheme 53).



Scheme 53.

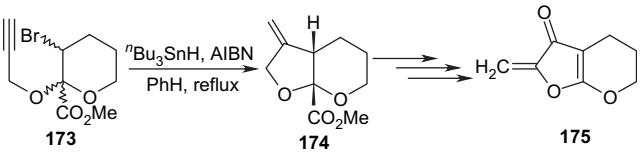
Dihydrofuran and dihydropyrrole derivatives have been synthesised by ring-closing metathesis (RCM) reactions of suitably substituted Baylis–Hillman adducts.[150] In addition to the RCM reaction, a number of synthetic approaches have been reported for the synthesis of these compounds.[151] Recently, Kim et al. have shown[152] that radical cyclisation of the substrate **167** with $^nBu_3SnH$ and a catalytic amount of AIBN,[153] followed by destannylation with aqueous HCl, furnished the tetrahydrofuran derivative **168** in 62% yield. Compound **168** was then treated with LiOH in aqueous THF to yield the acid derivative **169**. Compound **169** in the presence of standard iodolactonisation conditions (I_2, $NaHCO_3$ and THF) afforded the desired 3,4-disubstituted 2,5-dihydrofuran derivatives **171** by a 4-*exo*-*trig* mode via the β-lactone intermediate **170**. Compound **169** under bromolactonisation conditions (NBS, $NaHCO_3$ and THF) gave 3-bromomethyl-4-benzyl-2,5-dihydrofuran **172** in 48% yield (Scheme 54).

The core structure **175** of the fungal metabolite, benesudon,[154] having a wide range of biological properties



Scheme 54.

covering antifungal, antibacterial, cytotoxic, phytotoxic and nematicidal activities, was synthesised in which the key step was the Bu_3SnH-mediated radical cyclisation of the bromide **173** to afford the desired bicyclic skeleton **174** in 77% yield[155] (Scheme 55).

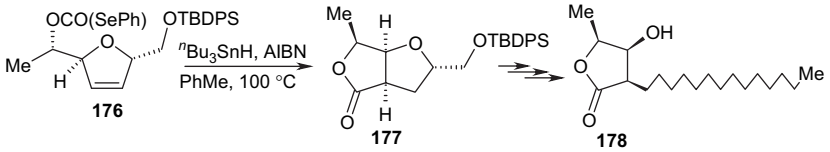


Scheme 55.

Seven-membered oxacycle structural units are found to be present in a variety of natural products,[156] e.g., monocyclic Zoapatanol,[157] polycyclic hemibrevetoxin B[158] and complex polyether toxins such as ciguatoxins and brevetoxins A and B.[159] (3a*R*, 6*R*, 6a*R*)-6-(2-Bromobenzyloxy)-2,2-dimethyl-5-methylene-tetrahydro-furo[2,3-*d*][1,3]dioxole on treatment with TBTH and a catalytic amount of AIBN in refluxing benzene afforded[160] the crystalline tetracyclic ether, (3a*R*,3b*S*,10a*R*,11a*R*)-2,2-dimethyl-3a,3b,5,10,10a,11a-hexahydro-1,3,4,11-tetraoxa-benzo[*f*]cyclopenta[*a*]azulene, in 60% yield. Thus, it is seen that the aryl radical cyclisation reaction can be applied to D-glucose-derived substrates to synthesise tricyclic nucleoside analogues. The synthesis of denbinobin[161] has been achieved via Bu_3SnH-mediated intramolecular radical cyclisation and Fremy's salt-mediated oxidation as the key reactions.

A novel approach to a natural β-hydroxy-γ-lactone **178** has been demonstrated[162] by Takahashi et al. in which one of the key steps of the reaction sequence was a Bu_3SnH-mediated intramolecular radical cyclisation of (1*S*,2′*S*,5′*S*)-1-[5′-(*tert*-butyldiphenylsilanyloxymethyl)-2′,5′-dihydrofuran-2′-yl]-ethyl phenylseleno carbonate **176** to give (2*S*,3a*R*,6*S*,6a*S*)-2-(*tert*-butyldiphenylsilanyloxymethyl)-6-methyltetrahydro-furo[3,4-*b*]furan-4-one **177** in 95% yield (Scheme 56).

Jimenezin **183**, an annonaceous acetogenin has been synthesised[163] via a samarium iodide-mediated radical cyclisation of β-alkoxyacrylate aldehyde **179** to give the oxane



Scheme 56.

derivative **180** and another reaction is the ^{n}Bu$_3$SnH-promoted radical cyclisation of (*E*)-β-alkoxyvinyl-(*S*)-sulfoxide **181** to furnish a single oxolane product **182** (Scheme 57).

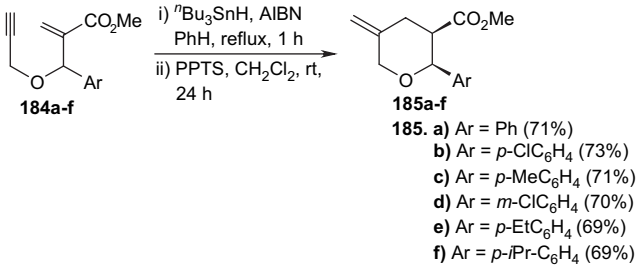
Rolliniastatin 1, rollimembrin and membranacin are annonaceous acetogenins.[164] A radical cyclisation of β-alkoxyvinyl sulfoxides-Pummerer rearrangement and allylation protocol has been utilised[165] to synthesise the *threo*/*cis*/*threo*/*cis*/*erytho* bis-oxolane moiety in rolliniastatin 1, rollimembrin and membranacin.

2,3,5-Trisubstituted and 2,3,5,6-tetrasubstituted oxepanes have been synthesised[153d] by a 7-*endo-trig* cyclisation of homopropargyl and phenyl-substituted homopropargyl derivatives of Baylis–Hillman adducts by using ^{n}Bu$_3$SnH (1.5 equiv) and catalytic amounts of AIBN in benzene at reflux for 12 h.

It was also observed[166] that the propargyl derivatives **184a–f** on treatment with ^{n}Bu$_3$SnH and AIBN afforded the 2,3,5-trisubstituted tetrahydropyran derivatives **185a–f** in good yield via a 6-*endo-trig* cyclisation (Scheme 58).

Enyne ethers **186a–g** under similar reaction conditions furnished[166] the 2,4,5,5-tetrasubstituted tetrahydropyrans **187a–g** as single diastereomers in good yield (Scheme 59).

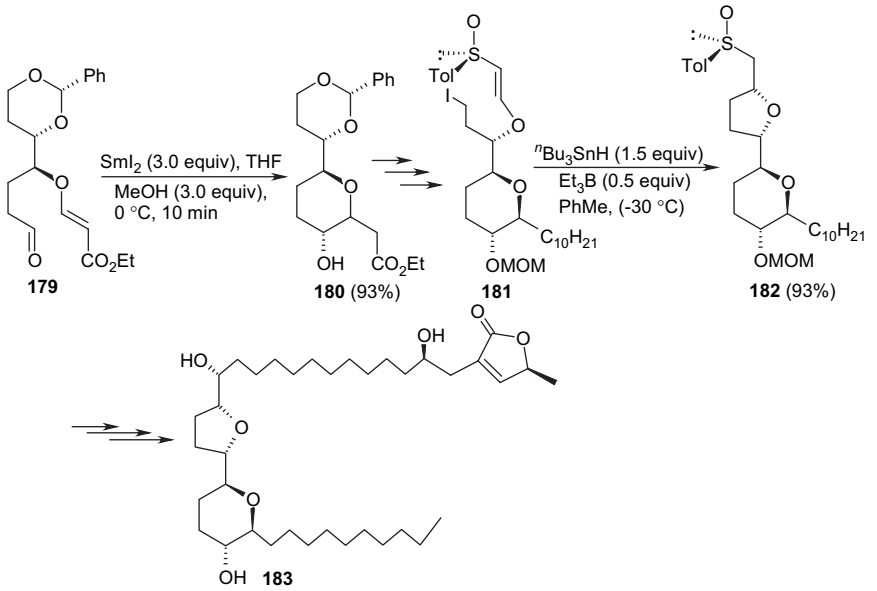
A synthesis of xylobovide **190**, a bis-butyrolactone-containing natural product, has been reported[167] in which the major step was an intramolecular regio- and stereoselective radical cyclisation of the xanthate **188** to give the expected cis-fused bicyclic system **189** in 72% yield (Scheme 60).



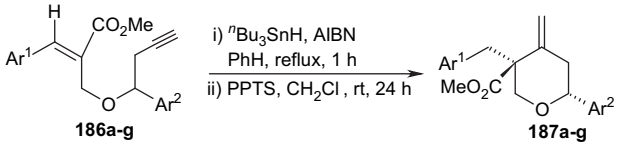
Scheme 58.

Recently, Kim and Tae have investigated[168] a one-pot radical cyclisation/dehydration sequence for β-aryloxyacrylates **191a–i**. Compounds **191a–i** were treated with ^{n}Bu$_3$SnH (1.2 equiv) and AIBN in refluxing benzene at 80 °C. The solvent was removed after completion of the reaction, the residue was treated with 5% HCl/EtOH for 10 min and, finally, the 2,3-disubstituted benzofuran derivatives **192a–i** were obtained (Scheme 61).

α-Halovinylphosphonates **193a–c** were treated with ^{n}Bu$_3$SnH and catalytic amounts of AIBN to give the 5-*exo* radical cyclisation products **198a–c** in excellent yield along with traces of the 6-*endo* cyclisation products **199a–c**.[169] The formation of products **198a–c** and **199a–c** from **193a–c** may be explained by two different pathways, i.e., a direct 6-*endo* cyclisation of **194a–c** to **197a–c** and a 5-*exo* radical cyclisation to **195a–c**, followed by rearrangement into the



Scheme 57.

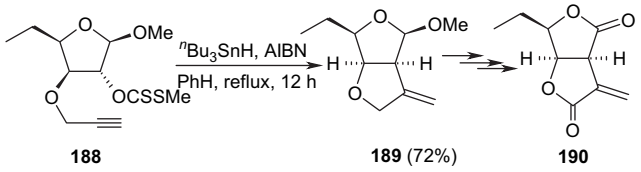


186a-g

187a-g

187. a) $Ar^1 = Ar^2$ = Ph (59%)
b) $Ar^1 = Ar^2$ = *p*-ClC$_6$H$_4$ (56%)
c) Ar^1 = Ph, Ar^2 = *p*-ClC$_6$H$_4$ (58%)
d) Ar^1 = *p*-ClC$_6$H$_4$, Ar^2 = *p*-MeC$_6$H$_4$ (60%)
e) Ar^1 = *p*-MeC$_6$H$_4$, Ar^2 = Ph (55%)
f) Ar^1 = Ph, Ar^2 = *p*-MeC$_6$H$_4$ (58%)
g) Ar^1 = *p*-ClC$_6$H$_4$, Ar^2 = Ph (54%)

Scheme 59.



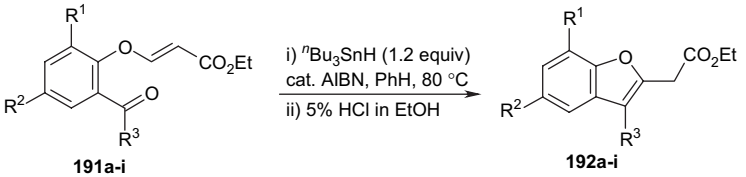
188 189 (72%) 190

Scheme 60.

thermodynamically favourable 6-*endo* radical intermediates **197a–c** via **196a–c** (Scheme 62).

4.1. Diastereoselective radical cyclisation

A stereoselective synthesis of bi- and tricyclic sesquiterpene lactones has been demonstrated[170] in which the key step was the radical cyclisation of appropriately functionalised *trans*-4,5-disubstituted γ-butyrolactones.

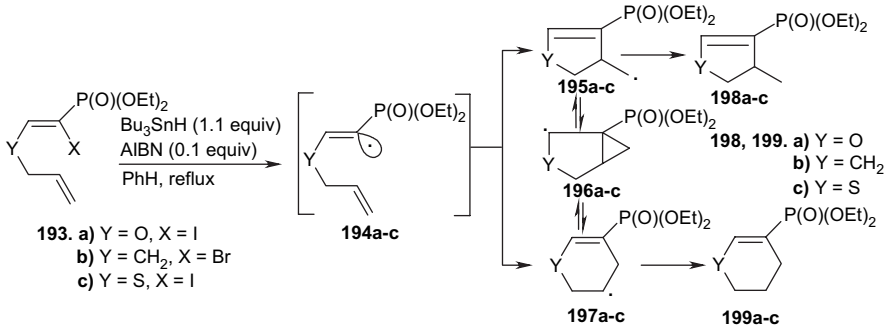


191a-i

192a-i

192. a) $R^1 = R^2 = R^3$ = H (98%)
b) $R^1 = R^2$ = H, R^3 = Me (97%)
c) $R^1 = R^2$ = H, R^3 = *n*-Bu (96%)
d) $R^1 = R^2$ = H, R^3 = Ph (99%)
e) $R^1 = R^2$ = H, R^3 = *i*-Bu (93%)
f) R^1 = H, R^2 = *t*-Bu, R^3 = Me (99%)
g) R^1 = OMe, $R^2 = R^3$ = H (96%)
h) R^1 = OMe, R^2 = H, R^3 = Ph (99%)
i) R^1 = OMe, R^2 = H, R^3 = *i*-Bu (93%)

Scheme 61.



193. a) Y = O, X = I
b) Y = CH$_2$, X = Br
c) Y = S, X = I

194a-c

195a-c 198a-c 196a-c 197a-c 199a-c

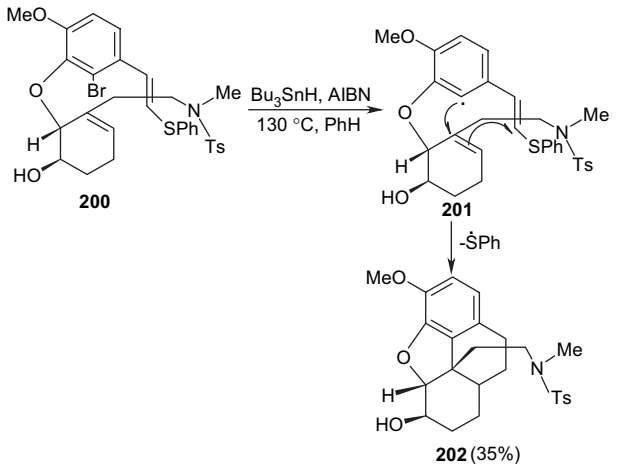
198, 199. a) Y = O
b) Y = CH$_2$
c) Y = S

Vinyl phosphonates **193**	Conditions				
	Concentration (mol^{-1})	Addition time (h)	Time (h)	Yield (**198+199**) (%)	Ratio of **198:199**
193a	0.1	0	3.5	90	**198a:199a** = 99:1
193a	0.025	5	7.0	79	**198a:199a** = 77:23
193b	0.1	0	4.0	73	**198b:199b** = 66:34
193b	0.025	5	8.0	83	**198b:199b** = 8:92
193c	0.1	0	3.5	76	**198c:199c** = 20:80
193c	0.025	5	8.0	77	**198c:199c** = 5:95

Scheme 62.

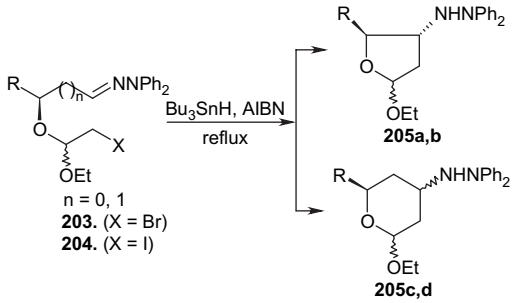
N-(1-Phenyl-6-methyl-5-hepten-1-oxy)thiazolethione reacted[171] with $BrCCl_3$ in AIBN in refluxing benzene at 80 °C to furnish 2-(1-bromo-1-methylethyl)-6-phenyltetrahydropyran (34%, cis/trans=65:35) and 2-phenyl-5-(dimethylvinyl)tetrahydrofuran (46%, cis/trans=50:50). A brominated tetrahydropyran has been reported[172] to be synthesised as a major product (58%, 2,6-cis/2,6-trans=86:14) from the reaction of (*E*)-6-phenyl-5-hexen-2-ol with TBHP, Py·HBr and VOL(OEt). The reaction of (*E*)-vinyl sulfoxide with TBTH and Et_3B at −20 °C in toluene afforded a 94:6 mixture of the tetrahydrofuranyl products.[173]

An asymmetric synthesis of (−)-dihydrocodeinone has been achieved by a radical cyclisation approach to morphine alkaloids.[174] The key step of the above synthetic protocol involved a Bu_3SnH-mediated tandem cyclisation/elimination sequence of the bromoaryl ether **200** to afford the tetracyclic styrene **202** via **201** (Scheme 63).



Scheme 63.

Recently, Friestad and Fioroni have reported the tri-*n*-butyltin hydride-mediated radical cyclisation of haloacetals **203** and **204** (Scheme 64).[175]

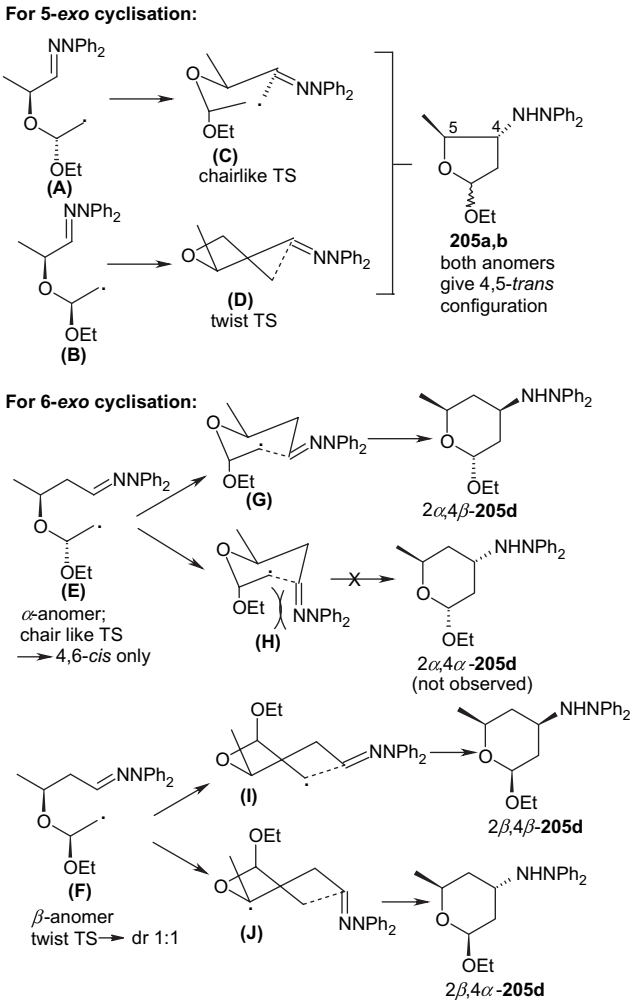


n	R	X	Haloacetal	Cyclised product (yield %)	Configurations (product ratio)
0	H	Br	**203a**	**205a** (69%)	*cis:trans* (2:1)
0	H	I	**204a**	**205a** (68%)	*cis:trans* (2:1)
0	Me	Br	**203b**	**205b** (52%)	2α, 4α:2β, 4α(3:1)
0	Me	I	**204b**	**205b** (64%)	2α, 4α:2β, 4α(3:1)
1	H	Br	**203c**	**205c** (48%)	*trans*:*cis* (3:1)
1	H	I	**204c**	**205c** (70%)	*trans*:*cis* (3:1)
1	Me	Br	**203d**	**205d** (47%)	2α, 4β:2β, 4α:2β, 4β(3:1:1)
1	Me	I	**204d**	**205d** (41%)	2α, 4β:2β, 4α:2β, 4β(3:1:1)

Scheme 64.

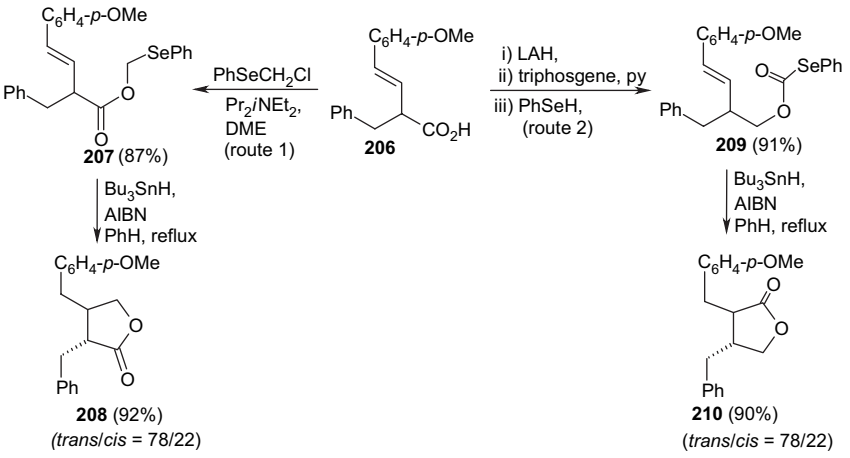
The formation of the 5-*exo* cyclisation products **205a** and **205b** may be due to the fact that the alternative acetal configurations (**A** and **B**) undergo 5-*exo* cyclisation via chairlike (**C**) or twist (**D**) transition state to the same 4,5-trans relative configuration. Again the alternative acetal configurations can lead to matched (α-anomer) (**E**) and mismatched (β-anomer) (**F**) double diastereoselection to give 2α,4β-3d (via **G**), 2β,4β-3d (via **I**) and 2β,4α-3d (via **J**).

The α-anomer (**E**) restricts the conformational freedom of the hydrazone through dipole repulsion between OEt and the imino nitrogen as shown in **H**, and thus the 2α,4α-3d configuration is not favourable. Haloacetals (**203b** and **204b**) each gave the same mixture **205b**, consisting of two of the four possible diastereomers with the 2α,4α configuration favoured (dr 3:1) (Scheme 65).



Scheme 65.

The dibenzylbutyrolactone lignan skeletons have been prepared employing two regio- and stereoselective ^{n}Bu_3SnH-mediated radical cyclisation routes.[176] In the first route, the racemic acid **206** was converted into its phenylselenomethyl ester **207** and this was then allowed to react with Bu_3SnH and AIBN to provide the *trans*-dibenzylbutyrolatone **208** as the major product (trans/cis=78/22). The formation of the *trans*-disubstituted lactone as the major product



Scheme 66.

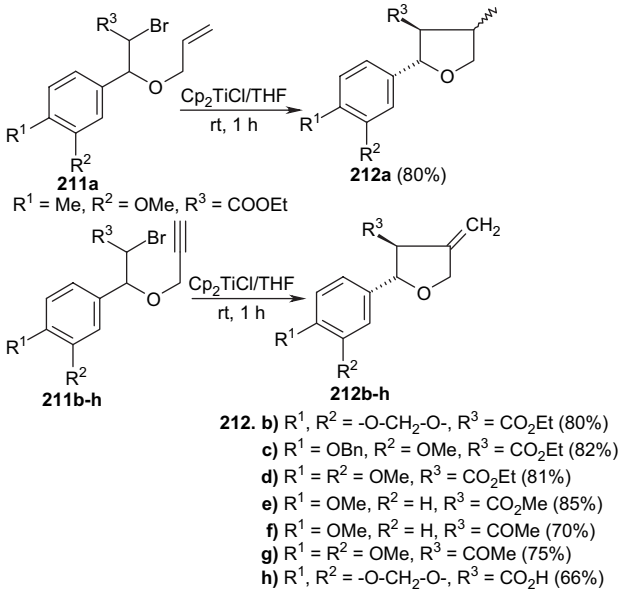
may be explained on the basis of Beckwith's model[177] for stereoselectivity in 5-*exo* radical cyclisations. In the second route, the racemic acid **206** was reduced to the alcohol and then converted into the phenylselenocarbonate **209**. $^{n}Bu_3SnH$-mediated radical cyclisation of **209** afforded the *trans*-dibenzylbutyrolactone **210** (trans/cis=78/22) (Scheme 66).

4.2. Synthesis of oxygen heterocycles with non-conventional reagents

Heterocyclic ring systems can be constructed by molybdenum-catalysed stannylation reactions[178] via subsequent intramolecular Stille coupling. Sulfanyl radical addition–cyclisation of hydroxamates having *o*-benzyloxime ether in the presence of thiophenol and AIBN afforded a ca. 3:1 separable mixture of the amino-1,2-oxazinones in good yield.[179] Alkyl iodides have been prepared as a mixture of stereoisomers (α:β=8:1)[119c] by the reaction of iodoalkenes with indium (2 equiv) and iodine (1 equiv) in MeOH, followed by treatment with 1 N HCl. A novel indium-mediated atom transfer radical cyclisation reaction has been explored[119b] using a catalytic amount of indium and iodine and a reductive radical cyclisation using an excess of indium and iodine without the use of a radical initiator such as AIBN or Et_3B/O_2.

Bromoalkene **211a** and bromoalkynes **211b–h** were found to undergo[180] radical cyclisation using bis(cyclopentadienyl)-titanium(III) chloride, Cp_2TiCl, in THF under an argon atmosphere for 1 h to give the tri-substituted tetrahydrofurans **212a–h** in good yield (Scheme 67).

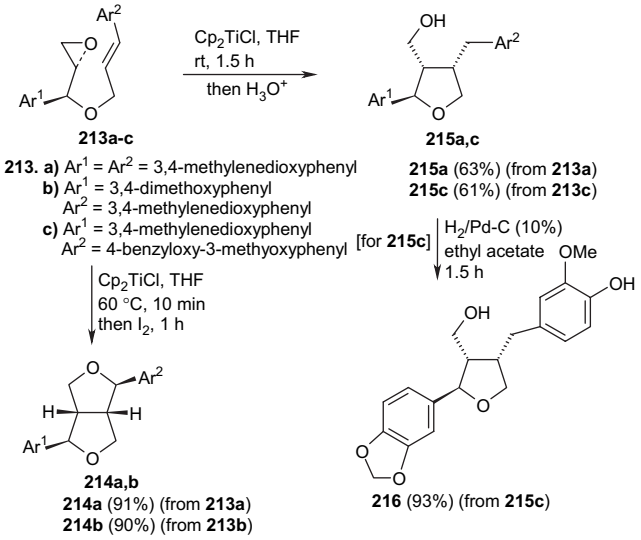
Recently, Banerjee and Roy have reported[181] enantioselective syntheses of furan lignans, (−)-dihydrosesamin **215a** and (−)-acuminatin **216**, and furofuran lignans, (−)-sesamin **214a** and (−)-methyl piperitol **214b**, in 43, 42, 63 and 60% overall yields, respectively, with high optical purity through stereoselective intramolecular radical cyclisation of suitably substituted epoxy olefinic ethers **213a–c** using bis(cyclopentadienyl)titanium(III) chloride as the radical initiator. The epoxy olefinic ether, 5-[(1*E*)-3-{(*S*)-1,3-benzodioxol-5-yl[(2*S*)-oxiran-2-yl]methoxy}prop-1-enyl]-1,3-benzodioxole **213a**, on reaction with Cp_2TiCl in THF at room



Scheme 67.

temperature for 1.5 h followed by acidic workup furnished (−)-dihydrosesamin **215a**. The epoxy olefinic ether **213c** on similar treatment gave the cyclised product **215c**, which on catalytic hydrogenolysis over 10% palladium on charcoal in ethyl acetate furnished (−)-acuminatin **216**. The epoxy olefinic ethers **213a** and **213b** on treatment with Cp_2TiCl in THF at 60 °C, followed by iodination, resulted in (−)-sesamin **214a** (91% yield) and (−)-methyl piperitol **214b** (90% yield), respectively (Scheme 68).

5-Methylenearisteromycin and its 2-fluoro derivatives have been synthesised[182] from D-ribose by stereoselective intramolecular radical cyclisation as the key step. A highly stereoselective synthesis of (−)-erythrodiene has been explored[183] in which the key reactions were an asymmetric methoxycarbonylation of 4-isopropylcyclohexanone and a highly diastereoselective radical cascade involving the addition of a phenylthiyl radical to a terminal alkyne followed by a 1,5-hydrogen transfer and a 5-*exo*-cyclisation. Various alkoxyamines were found to isomerise[184] under microwave irradiation to give the cyclised products within a very short

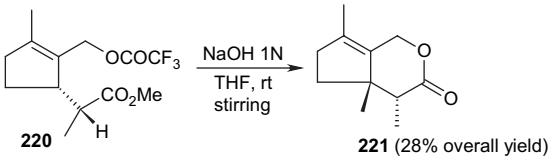


Scheme 68.

reaction time. The photo-induced benzannulation of benzocycloalka[1,2-*b*]furans has been found to give hydrohelicene-type compounds in good yield.[185] A similar type of photoreaction of the spiro[furan-2(3*H*),1′-benzocycloalkane]s furnished dihydrophenalene derivatives in moderate yield.

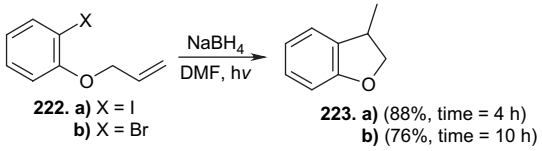
Compound **217** was irradiated with a 60 W desk lamp in the presence of iodobenzene diacetate and iodine in cyclohexane to give the spiroacetal **218** in 86% yield.[186] The *tert*-butyldiphenylsilyl ether was deprotected and the second oxidative radical cyclisation occurred under similar conditions to afford the bis-spiroacetals **219a–d** in 81% yield as a 1:1:1:1 mixture of diastereomers, two of which are major isomers (**219a** and **219b**) and the other two (**219c** and **219d**) are minor isomers (<5%). Indium trichloride is found to be a better reagent than the commonly used reagents like HF·Py, PPTS, $ZnBr_2$ or $ZnCl_2$ for the generation of the thermodynamically favoured isomers **219a** and **219b** (87:13 mixture) (Scheme 69).

Dehydroiridomyrmecin **221** has been synthesised[187] by cyclisation of methyl-7-trifluoroacetoxyirid-1-ene-9-oate **220** on treatment with 1 N NaOH and THF at room temperature (Scheme 70).



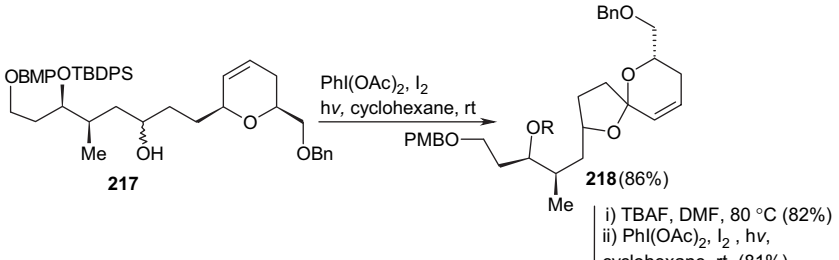
Scheme 70.

A series of *ortho*-allyloxy and *ortho*-but-3-enyloxy-iodo- and -bromobenzenes on direct UV irradiation in the presence of $NaBH_4$ or $Na(CN)BH_3$ afforded radical cyclisation products in high yield.[188] *ortho*-Allyloxy-halobenzenes **222** undergo photo-induced radical cyclisation to afford 3-methyl-2,3-dihydrobenzofuran **223** in high yield (Scheme 71).



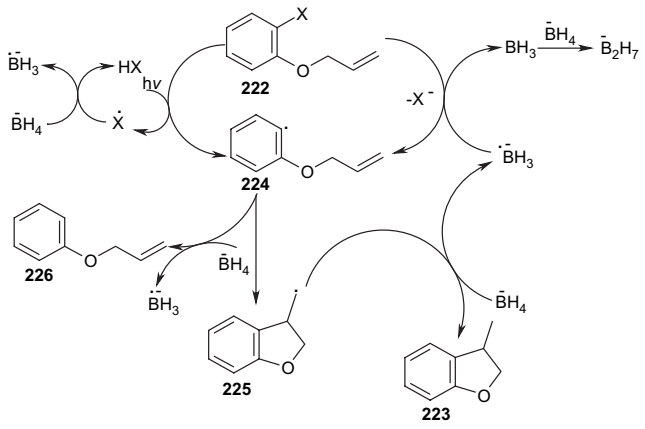
Scheme 71.

The mechanism of the photo-induced cyclisation is depicted as follows. Direct photo-homolysis of the halobenzenes **222** produces initiating radical **224** and the halogen radical X•. The halogen atom abstracts one hydrogen from borohydride and thus produces a propagating borane radical anion, which reacts with **222** to propagate the chain reaction. The intermediate phenyl radical **224** is then converted into the radical **225**, which abstracts a hydrogen from the borohydride to form the cyclisation product **223** and the borane radical anion. Some reduction product **226** may also be obtained by the abstraction of hydrogen from borohydride by the radical **224** (Scheme 72).

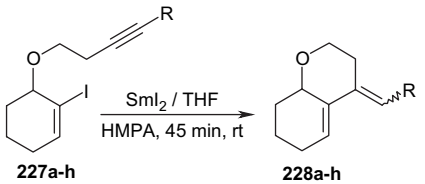


Conditions	Products **219a/219b**	Yield (%)
i) HF.Pyr, MeCN, rt, 12 h	76:24	81
ii) PPTS (0.2 equiv), MeCN, rt, 18 h	~81:19	89
iii) $ZnBr_2$ (0.2 equiv), CH_2Cl_2, rt, 19 h	76:24	95
iv) $ZnCl_2$ (0.2 equiv), CH_2Cl_2, rt, 24 h	~83:17	88
v) $InCl_3$ (0.2 equiv), MeCN, rt, 1 h	87:13	85

Scheme 69.



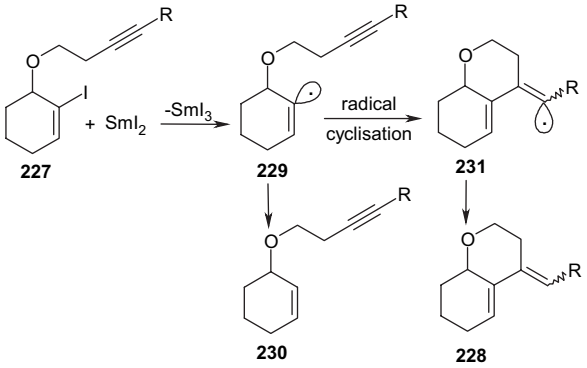
Scheme 72.



a) R = Ph, 71% (E:Z = 1.7:1)
b) R = p-MeO-Ph, 70% (E:Z = 1.9:1)
c) R = o-Me-Ph, 68% (E:Z = 1.9:1)
d) R = thien-2-yl, 58% (E:Z = 1:1.5)
e) R = furan-3-yl, 63% (E:Z = 1:1.1)
f) R = Et, 29% (E:Z = 1.3:1)
g) R = TMS, 30% (E:Z = 1.1:1)
h) R = H, 14%

Scheme 73.

Cyclic allyloxy enones were found to react with SmI_2 in the presence of a mixed THF/MeOH (4:1) solvent at −78 °C to produce a compound in 45% yield as a single diastereomer.[189] There are only a few reports of the 6-(π-*exo*)-*exo-dig* radical cyclisation in the literature.[190] A few years ago,



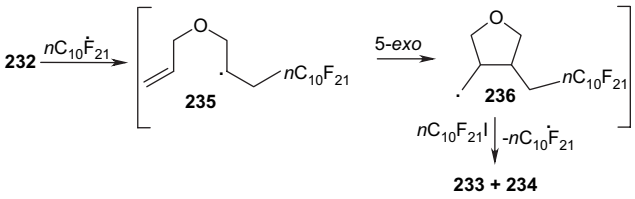
Scheme 74.

the Bu_3SnH-mediated 6-(π-*exo*)-*exo-dig* radical cyclisation of vinyl iodides was reported[191] to give the *exo*-cyclic dienes in moderate to good yield. Recently, Zhan and Lang explored[192] SmI_2-mediated 6-(π-*exo*)-*exo-dig* radical cyclisation of vinyl iodides **227a–h** to give the cyclisation products **228a–h** (Scheme 73).

From a mechanistic point of view, it may be assumed that the vinyl iodides **227** abstract an electron from SmI_2 to generate **229**, which can either undergo intramolecular radical cyclisation leading to the radicals **231** and, finally, the cyclised products **228** or directly abstract a hydrogen from the solvent to give the acyclic products **230** (Scheme 74).

Diallyl ether **232** and $nC_{10}F_{21}I$ in BTF (i.e., $PhCF_3$)[193] upon irradiation with a xenon lamp (500 W) at room temperature for 10 h afforded[194] the iodoperfluoroalkylated cyclisation product **233** in 58% yield, along with a small amount of the acyclic adduct **234** as a byproduct (Scheme 75).

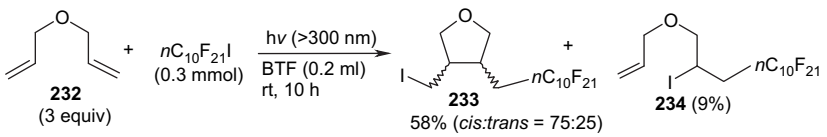
Mechanistically, it may be explained that, under photo-irradiation, $nC_{10}F_{21}I$ undergoes homolytic dissociation to produce $nC_{10}F_{21}^{\cdot}$, which adds to diene **232** to produce the secondary alkyl radical **235** followed by cyclisation in a 5-*exo* route to give the cyclic radical intermediate **236**. The radical intermediate **236** undergoes an S_H^2 reaction with $nC_{10}F_{21}I$ to afford the iodoperfluoroalkylated cyclisation product **233** (Scheme 76).



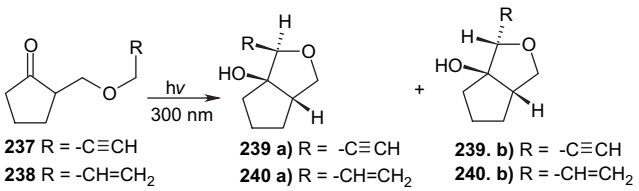
Scheme 76.

Additionally, photo-induced iodoperfluoroalkylation of diynes and enynes has been achieved[194] under similar conditions to those described above by using perfluoroalkyl iodides to furnish the cyclisation products in good yield. Photo-initiated radical cyclisation[195] of allyl- and prop-2-ynyloxymethylcyclopentanones **237** and **238** at a wavelength of 300 nm in dry benzene as well as in a polar solvent such as acetonitrile afforded the bicyclic cyclopentafuranols **239a** and **239b** and **240a** and **240b**, respectively, with high regioselectivity (Scheme 77).

The photo-induced radical cyclisation of compounds **237** and **238** may be explained as follows. The initial step is an (n,π*)-excitation to generate **241** followed by an intramolecular δ-hydrogen atom abstraction to provide a 1,5-biradical **242**. The intermediate **242** leads to the formation of

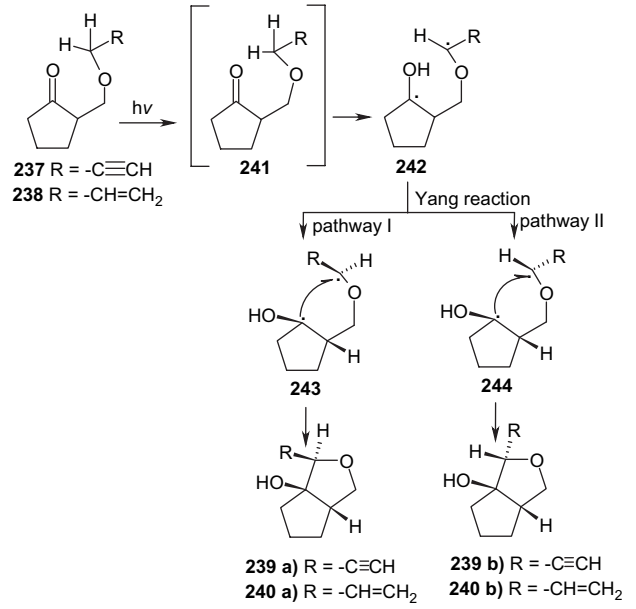


Scheme 75.



Substrate	Conditions	Time (h)	Product	Yield (%)
237	PhH (0.12 M)	20	**239a**	13
			239b	5
237	MeCN (0.12 M)	24	**239a**	14
			239b	4
238	PhH (0.12 M)	53	**240a**	3
			240b	16
238	MeCN (0.12 M)	28	**240a**	4
			240b	12

Scheme 77.



Scheme 78.

the corresponding bicyclic cyclopentafuranols **239** and **240**. When the starting material is **237**, pathway I leads to *cis*-**239a** (via **243**) and *trans*-**239b** (via **244**) through pathway II. Compound **238** can also lead to *cis*-**240a** (via **243**) (pathway I) and *trans*-**240b** (via **244**) (pathway II) (Scheme 78).

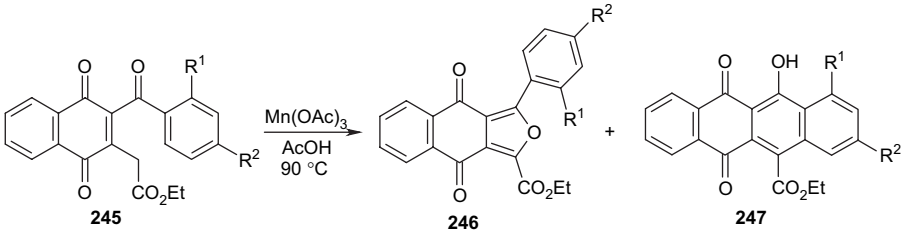
Manganese(III) acetate-mediated radical cyclisation of 2-benzoyl-3-(ethoxycarbonylmethyl)-1,4-napthoquinones **245a–h** afforded the expected 6-hydroxynaphthacene-5,12-diones **247a–h** and naphtho[2,3-*c*]furan-4,9-diones **246a–h** as the major products (Scheme 79).[196]

The formation of products **246** and **247** from **245** may be explained by considering that manganese(III) acetate generates the radical intermediates **248** from **245**, which undergo either a six-membered ring free radical cyclisation onto the C–C double bond of the benzoyl group to give **249** and then **250**, followed by aromatisation to give **247** (path a), or a five-membered ring radical cyclisation followed by oxidation (via **251** and **252**) to give **246** (path b) as the major product (Scheme 80).

Recently, Fujino and Nishino have synthesised[197] spiro-[furan-2-(3*H*),1′-(2-benzocycloalkane)] derivatives **256** and **257a–c** by the oxidation of methylenebenzocycloalkanes **253** and **254** with manganese(III) acetate in the presence of 1,3-dicarbonyl compounds **255a–c** (Scheme 81). A similar oxidation of the benzocycloalkene derivatives afforded the functionalised benzocycloalka[1,2-*b*]furans in good yields.[197]

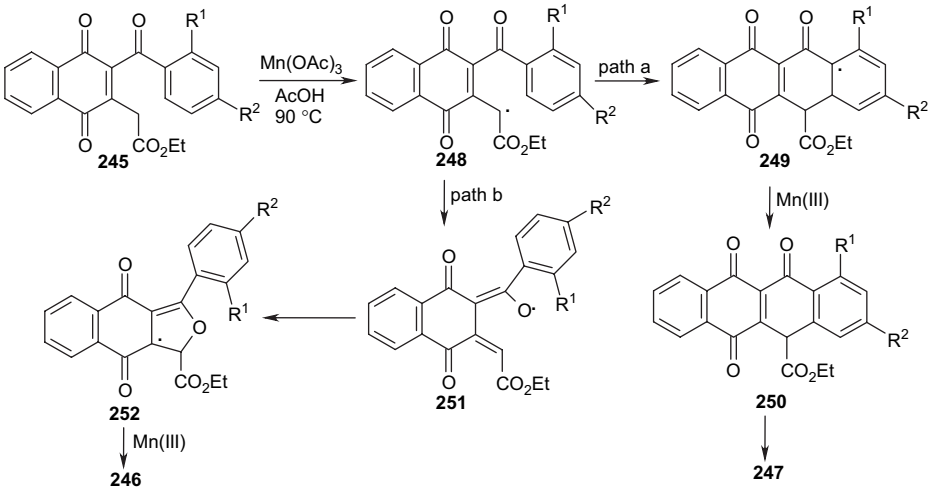
1,1-Disubstituted ethenes **258** were found to react[198] with 2,4-piperidinediones **259** in the presence of a catalytic amount of manganese(III) acetate in acetic acid at room temperature in air to furnish the 4,4-diaryl-1-hydroxy-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-ones **260** as the major products in excellent yield (Scheme 82).

Mechanistically, it may be assumed that, at first, the 2,4-piperidinediones **259** react with manganese(III) acetate to produce the manganese(III)–piperidinedione enolate complexes

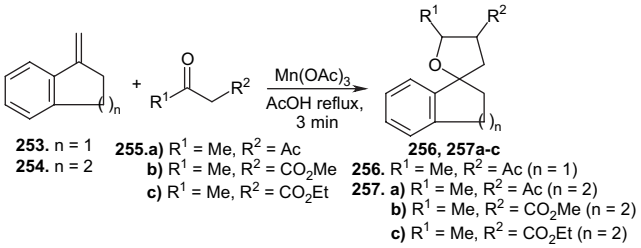


Substrate	Reaction time (h)	Product Yield (%)			
245a: R^1= R^2= H	12	**246a**	43	**247a**	18
245b: R^1 = H, R^2 = Me	14	**246b**	29	**247b**	21
245c: R^1 = H, R^2 = Cl	15	**246c**	42	**247c**	13
245d: R^1 = H, R^2 = Br	12	**246d**	56	**247d**	18
245e: R^1 = Me, R^2 = H	17	**246e**	51	**247e**	8
245f: R^1 = R^2 = Me	20	**246f**	69	**247f**	7
245g: R^1 = Cl, R^2 = H	13	**246g**	62	**247g**	0
245h: R^1 = Br, R^2 = H	13	**246h**	71	**247h**	0

Scheme 79.



Scheme 80.



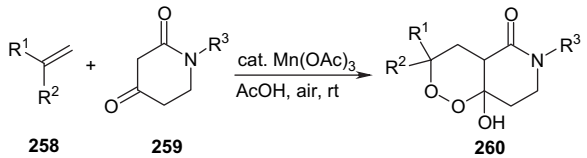
253. n = 1
254. n = 2

255.a) R^1 = Me, R^2 = Ac
b) R^1 = Me, R^2 = CO_2Me
c) R^1 = Me, R^2 = CO_2Et

256, 257a-c
256. R^1 = Me, R^2 = Ac (n = 1)
257. a) R^1 = Me, R^2 = Ac (n = 2)
b) R^1 = Me, R^2 = CO_2Me (n = 2)
c) R^1 = Me, R^2 = CO_2Et (n = 2)

Methylenebenzo-cycloalkane	1,3-Dicarbonyl compound			Product	Yield (%)
		R^1	R^2		
253 (n = 1)	**255a)**	Me	Ac	**256**	72
254 (n = 2)	**255a)**	Me	Ac	**257a**	68
254 (n = 2)	**255b)**	Me	CO_2Me	**257b**	70
254 (n = 2)	**255c)**	Me	CO_2Et	**257c**	71

Scheme 81.

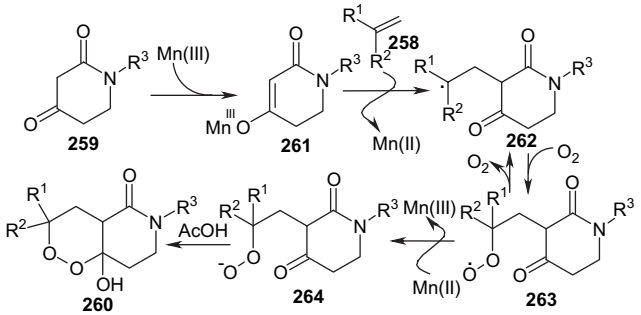


258 **259** **260**

Entry	Alkene (**258**)		Piperidinedione (**259**)	Time (h)	Product (**260**) Yield (%)
	R^1	R^2	R^3		
a	Ph	Ph	Bn	18	99
b	*p*-ClC_6H_4	*p*-ClC_6H_4	Bn	16	77
c	*p*-MeC_6H_4	*p*-MeC_6H_4	Bn	16	87
d	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	Bn	14	66
e	Ph	Ph	Me	14	60
f	Ph	Ph	Et	14	81
g	Ph	Ph	Pr	9	72
h	Ph	Ph	*i*-Pr	18	77
i	Ph	Ph	Ph	30	70

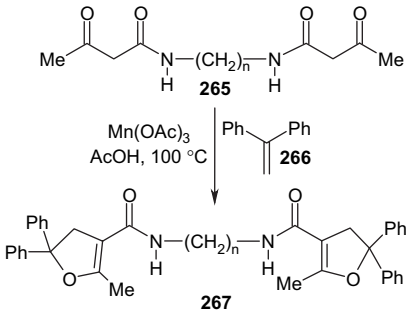
Scheme 82.

261, which then oxidise the alkenes **258** to generate the corresponding carbon radicals **262**. These radicals **262** take up dissolved molecular oxygen in the solvent to generate the peroxy radicals **263**, which could be reduced by manganese(II) species to afford **264** and followed by cyclisation, to finally yield **260** (Scheme 83).



Scheme 83.

N,*N*′-Oligomethylenebis(2-methyl-5,5-diaryl-4,5-dihydrofuran-3-carboxamide)s **267a–f** have recently been synthesised[199] by the reaction of *N*,*N*′-oligomethylenebis(3-oxobutanamide)s **265a–f** with 1,1-diarylethenes **266** in the presence of manganese(III) acetate in acetic acid at 100 °C (Scheme 84).



265
266
267

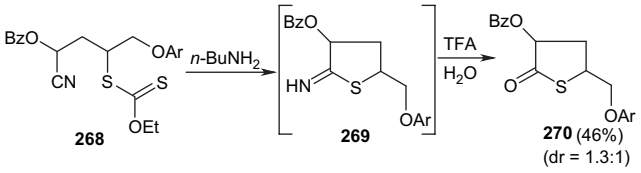
Diamine	Alkene	Time (min)	Product	Yield (%)
265a (n= 3)	**266**	20	**267a**	43
265b (n = 4)	**266**	20	**267b**	40
265c (n = 5)	**266**	14	**267c**	35
265d (n = 6)	**266**	16	**267d**	37
265e (n = 7)	**266**	20	**267e**	35
265f (n = 8)	**266**	23	**267f**	32

Scheme 84.

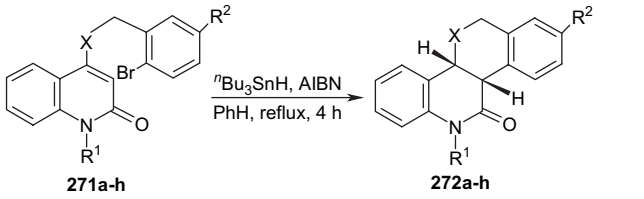
Similarly, the reaction of 3-oxobutanamidoethyl-3-oxobutanoate or *N*,*N*′-(3,6-dioxaoctamethylene)-bis(3-oxobutanamide) with 1,1-diphenylethene afforded (2-methyl-5,5-diphenyl-4,5-dihydrofuran-3-amido)ethyl-2-methyl-5,5-diphenyl-4,5-dihydrofuran-3-carboxylate or *N*,*N*′-(3,6-dioxaoctamethylene)-bis(2-methyl-5,5-diphenyl-4,5-dihydrofuran-3-carboxamide) in moderate yield.[199]

5. Synthesis of sulfur heterocycles

Pentynylthiol esters underwent radical cyclisation reactions with PhSH and AIBN to produce benzaldehyde in excellent yield, along with equal amounts of *E*- and *Z*-dihydrothiophene.[200] Della and Graney developed the regiochemistry of the cyclisation of 5-hexenyl systems bearing a substituent at C-5 and explored the ring closure of α-sulfenyl-, α-sulfinyl-, α-sulfonyl-5-hexenyl- and 5-methyl-5-hexenyl-radicals.[201]



Scheme 85.



271a-d (X = S)
271e-h (X = SO_2)

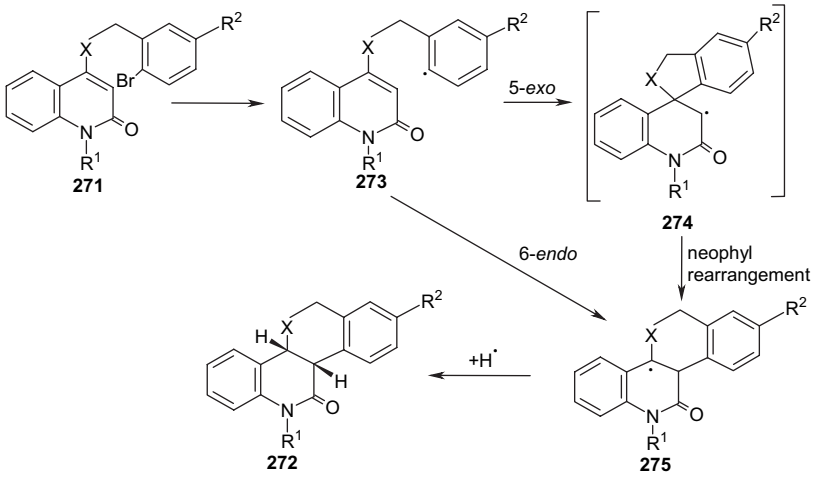
272. a) R^1 = Me, R^2 = H, X = S (65%)
b) R^1 = Me, R^2 = OMe, X = S (63%)
c) R^1 = Et, R^2 = H, X = S (65%)
d) R^1 = Et, OMe, X = S (60%)
e) R^1 = Me, R^2 = H, X = SO_2 (90%)
f) R^1 = Me, R^2 = OMe, X = SO_2(88%)
g) R^1 = Et, R^2 = H, X = SO_2 (85%)
h) R^1 = Et, R^2 = OMe, X = SO_2 (80%)

Scheme 86.

Recently, Zard and co-workers observed[202] that compound **268**, when treated with *n*-butylamine at room temperature, undergoes cyclisation to give dihydrothiophen-2-imine **269** through nucleophilic attack of *n*-butylamine onto the xanthate moiety followed by 5-*exo*-*dig* cyclisation of the sulfide anion formed onto the pendant nitrile.[203] Compound **269** upon treatment with aqueous TFA furnished the corresponding dihydrothiophen-2-one **270** in good overall yield (Scheme 85).

The substrates, 4-(2-bromobenzylsulfanyl)-1-alkyl-1*H*-quinolin-2-ones **271a–d** and 4-(2-bromobenzylsulfonyl)-1-alkyl-1*H*-quinolin-2-ones **271e–h**, were refluxed in dry degassed benzene under a nitrogen atmosphere with ^{n}Bu$_3$SnH in the presence of a catalytic amount of AIBN for 1 h to give the cyclic products, [6,6]-thiopyranoquinoline-2-one derivatives **272a–h,** as the major products along with small amount of the β-scission products (Scheme 86).[204]

The exclusive formation of the six-membered heterocyclic ring in the products **272a–h** from the substrates **271a–h** can be best explained by the addition of a hydrogen radical to the intermediate radical **275**, which, in turn, is formed from the aryl radical **273** by a 6-*endo* ring closure. An alternative route, via 5-*exo*-ring closure to generate the spiro-heterocyclic radical[205] **274** with a subsequent neophyl rearrangement,[206] has also been considered (Scheme 87). The 5-*exo*-cyclisation to form the spiro-heterocyclic radical **274** followed by a neophyl rearrangement is, however, highly unlikely with the systems studied in the present instance. It is known that β-fragmentation of alkylthiyl radicals is very fast[207] ($>10^8$ s^{-1}) compared to neophyl-type rearrangements, which are much slower[74] (about 10^3–10^4 s^{-1}). Therefore, a neophyl rearrangement of radical **274** cannot compete with the β-fragmentation reaction, which would lead to another product. The other reason is that the intermediate tertiary radical **275** is more stable than the spiro-heterocyclic radical **274**. Inspection of a molecular model indicates that the radical intermediate **275** should be highly stabilised, due to excellent overlapping of the p-orbital of the radical centre with the neighbouring aromatic π-system and

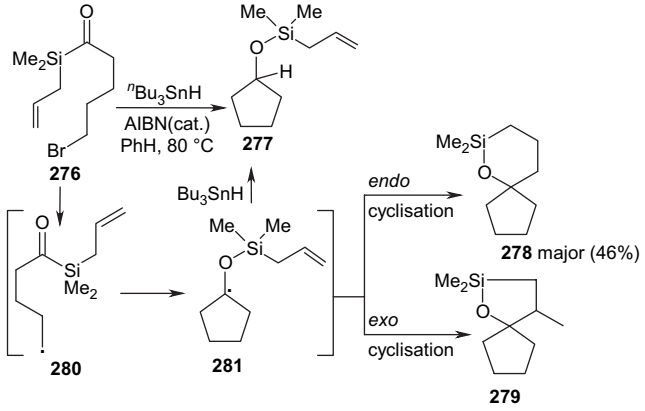


Scheme 87.

also due to a greater polarisation of the sulfur atom.[177,208] The stabilised conformational intermediate radical **275** gives preferably cis-products, the usual reduced products and the dihydro heterocyclic ring are isolated in good yield.

6. Synthesis of silicon-containing heterocycles

Bromomethyldimethylsilyl ethers were found to undergo TBTH-mediated radical cyclisation to generate oxasilacyclopentane products[7a] and, due to their instability, they could only be preserved in benzene at −5 °C without any significant decomposition. 1-(3-Bromopropyl)-3-(trimethylsilyl)-2-propynyl diphenyl(trimethylstannyl)silyl ether reacted with TBTH and AIBN in refluxing benzene to give 2,2-diphenyl-3-(trimethylsilyl)-4,5,6,6a-tetrahydro-2*H*-cyclopenta[*d*][1,2]oxasilole in 84% yield.[209] A few years ago, an intramolecular radical cyclisation of acylsilanes was reported.[210,211] Recently, Tsai et al. have initiated a study[212] of intramolecular radical cyclisation of acylsilanes with radicalphiles attached to silicon to produce spiro products containing a cyclic silyl ether skeleton. 5-Bromo-1-(allyldimethylsilyl)-1-pentanone **276** on treatment with Bu_3SnH (1.2 equiv) at a concentration of 0.05 M in refluxing benzene and AIBN (0.05 equiv) afforded the alloxysilane **277** and spiro silyl ethers **278** and **279**. The initial radical **280** obtained from **276** is transformed to the α-silyloxy radical **281**, which abstracts hydrogen to produce the cyclopentyl ether **277**. The radical intermediate **281** can undergo *endo*- and *exo*-cyclisation to give the spiro silyl ethers **278** and **279**, respectively, out of which only product **278** was isolated in 46% yield (Scheme 88).



Scheme 88.

α-Bromosilyl ether **282** on treatment with allyltri-*n*-butylstannane and ACCN in *n*-heptane, was heated at 100 °C for 24 h to give the silicon heterocycle **284** via **283**.[213] Compound **284** was immediately treated with H_2O_2/KF in THF/MeOH under reflux (Tamao–Flemming oxidation conditions[214]) to give the cyclopentane-substituted diol **285** in 50% overall yield (Scheme 89).

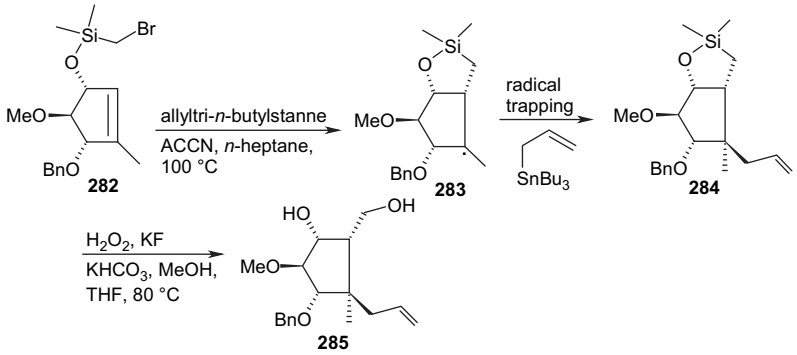
^{n}Bu$_3$SnH-mediated radical cyclisation of 6-(bromomethyl)-dimethylsilyl-1-[3,5-bis-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-D-*erythro*-pent-1-enofuranosyl]uracil **286** afforded the 6-*endo*-cyclised products **288** (58% yield) and **289** (32% yield).[215] The exclusive formation of **288** and **289** may be due to the stabilisation of the anomeric radical **287** by the neighbouring furanose ring oxygen (Scheme 90).

6-(Bromomethyl)dimethylsilyl-1-[3,5-bis-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2-C-methyl-D-*erythro*-pent-1-enofuranosyl]uracil **290** under ^{n}Bu$_3$SnH-mediated radical cyclisation conditions, however, furnished the 5-*exo*-cyclised product **292** as the major product (41%) (Scheme 91). An additional product **295** (29% yield) in this reaction was formed by glycosidic bond rearrangement.[215]

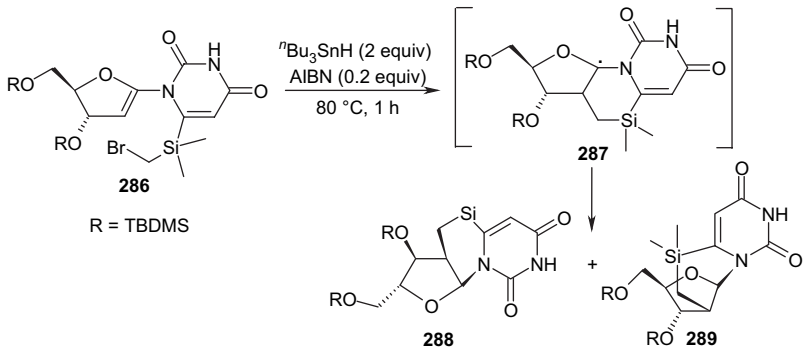
The high preference for C1′-attack of the α-silyl carbon radical obtained from **290** could be due to the formation of an incipient tertiary C2′-radical **291**, in spite of having steric hindrance of the 2-methyl group. Radical **291** after proton abstraction from Bu_3SnH furnished **292**. Again, the formation of **295** may be explained by assuming that **291** is not sufficiently stable enough to react exclusively with Bu_3SnH, and thus may generate the uracil-1-yl radical **293**. This radical can cyclise in a 6-*endo* route to produce a stabilised anomeric radical **294**, which finally gives **295** (Scheme 91).

Stork et al. have reported a facile synthesis of a β-C-glucoside via stereoselective radical cyclisation using a phenyl 1-seleno-β-D-glucose derivative having a phenylethynylsilyl group as a radical acceptor, tethered at the 6-hydroxyl.[216] Recently, Shuto et al. have developed[217] an efficient method for preparing β-C-glucosides via radical cyclisation with a silicon tether based on the conformational restriction strategy.

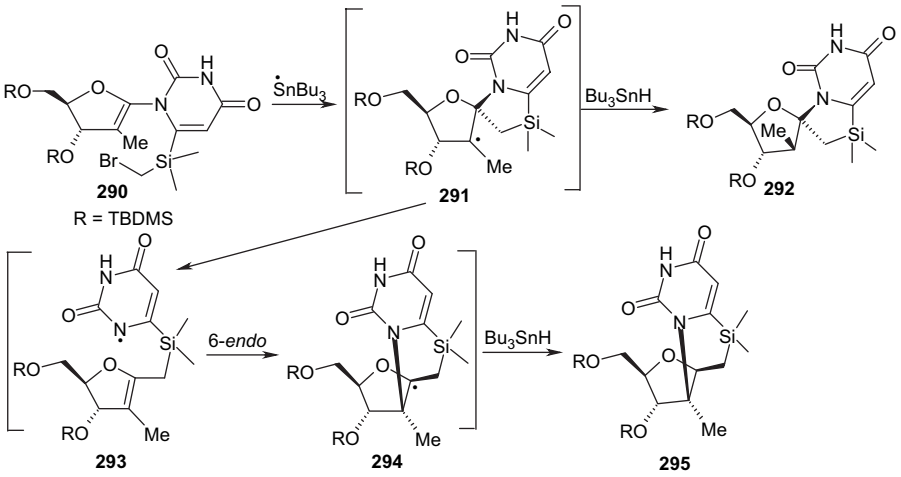
It was observed[218] that the radical cyclisation reaction of phenyl 2-*O*-allyldimethyl-3,4,6-tri-*O*-benzyl-1-seleno-β-D-glucopyranoside **296** in the presence of ^{n}Bu$_3$SnH and AIBN



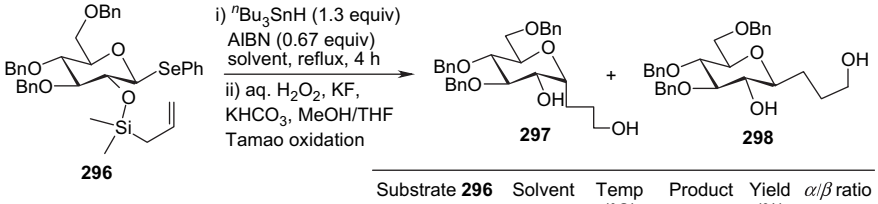
Scheme 89.



Scheme 90.



Scheme 91.



Substrate **296** concn (M)	Solvent	Temp (°C)	Product	Yield (%)	α/β ratio
(0.005)	PhH	80 °C	**297,298**	73	1:2.9
(0.005)	PhMe	110 °C	**297,298**	80	1:4.1
(0.005)	*i*-BuPhH	130 °C	**297,298**	62	1:3.1

Scheme 92.

in refluxing benzene followed by Tamao oxidation,[219] afforded a mixture of the α-C-glucoside **297** and β-C-glucoside **298** (73% yield, α:β=1:2.9). When the above reaction was performed at 110 °C in toluene, the β-selectivity was increased further (80% yield, α:β=1:4.1), while the β-selectivity was decreased (62% yield, α:β=1:3.1) at further higher temperatures (Scheme 92).

7. Conclusions

Nowadays, radical reactions are being increasingly employed in the synthesis of heterocyclic compounds, a reaction that has previously been overlooked. Many new methodologies are continuously developing in this field. The construction of five- and six-membered rings, either in separate or in multistep processes, has dominated many of these developments. In this review, some important efforts in the synthesis of heterocycles by radical cyclisation have been summarised. It is needless to mention that it is a difficult task to cover all aspects within this brief review. Therefore, the major discussions have been limited to the radical cyclisation reactions for the formation of five- and six-membered heterocyclic rings of organic molecules published during 2005. Mechanistic aspects of various radical cyclisations have been included wherever it was felt necessary. Despite

their wide application in organic synthesis radical cyclisation reactions, still offer enormous scope to synthetic organic chemists for the synthesis of target molecules including heterocyclic compounds and will develop more extensively in the near future.

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Biographical sketch

Krishna C. Majumdar received his B.Sc. (1966) and M.Sc. (1968) degrees from the University of Calcutta and Ph.D. from the University of Idaho, completing his doctoral thesis in 1972 as a teaching fellow under the direction of Professor B. S. Thyagarajan and continued as research associate with Professor Thyagarajan at the same University. He moved to the University of Alberta in 1974 as a Postdoctoral fellow with Professor R. K. Brown. Next year he joined the group of Professor J. William Lown at the same University to study the mode of action of cancer antibiotics. After returning to India (1977), he was with Birla Institute of technology and Science as reader for a brief stint. He then moved to the University of Kalyani, first as lecturer (1977) then as reader (1984), professor (1995) and professor and head (2003). He served the Indian Institute of Technology (Kharagpur) for a short period as an associate professor (1990–1991) and also North Eastern Hill University as a visiting professor (1996). His research interests centred around synthetic organic chemistry with more than 190 publications mainly based on sigmatropic rearrangements of which Claisen rearrangement is notable. He is associated with the discovery of sulfoxide- and aminoxide-rearrangements for the synthesis of fused thiophenes and pyrroles. His recent research interests also include radical reactions, design and synthesis of liquid crystals and published a good number of research papers in these areas. He has also authored a number of review articles and two book chapters. He has already supervised 31 Ph.D. students who have already received their Ph.D. degrees. He has affiliation with a number of professional bodies and a fellow of the West Bengal Academy of Science and Technology. He is recipient of the Chemical Research Society of India medal (2004).

Pradipta K. Basu was placed first in first class both in B.Sc. and M.Sc. in Chemistry of the University of Kalyani and received National Merit Scholarship (Govt. of India). He completed his Ph.D. degree in 2003 with a UGC research fellowship from the University of Kalyani under the guidance of Professor K. C. Majumdar. Presently, he is a lecturer in Chemistry (W. B. E. S.) at Hooghly Mohsin College (Govt. of West Bengal). His research interests mainly embrace the synthesis of heterocyclic compounds by radical cyclisation and reagents leading to heterocycles.

Sudip K. Chattopadhyay was born in Bankura, West Bengal. He received his B.Sc. from the Bankura Christian College in 1998 and M.Sc. from the University of Kalyani in 2000. He then joined the research group of Professor K. C. Majumdar to carry out his Ph.D. studies with a CSIR research fellowship in the same University. His research focused on the application of free radical cyclization and sigmatropic rearrangement on the development of new bioactive heterocycles. He is currently working on the palladium-catalysed reaction leading to the synthesis of biologically interesting heterocycles. He is also the co-author of a book chapter.