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FORMATION OF FIVE- AND SIX-MEMBERED HETERO-CYCLIC RINGS BY RADICAL CYCLIZATION

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Abstract - This review describes the formation of different five- and six-membered heterocyclic rings in various compounds by radical cyclization.

The chemistry of free radical occupies a prominent position in the synthetic organic chemistry for the last few years.[1] The construction of five- and six-membered rings, either in separate or multi step processes has dominated many of these developments. Radical reactions are important in many industrial processes-especially for producing a whole class of useful 'plastics' or 'polymers' such as polyethylene, teflon, polystyrene and so on. Radical reactions are of vital importance in biology and medicines also.[2,3] A number of reviews have been reported[4,6] regarding general methodologies in radical chemistry containing useful discussions of heterocyclic protocols. The kinetics of various radical processes was known in the mid 1970's. The kinetic and structural information of various reactive intermediates was the first doorstep of the modern synthetic radical chemistry.[7-9] Beckwith[10] and Stork[11] reported that under tin hydride annulated reaction condition 5-*exo*/6-*endo* type of vinyl radical cyclization onto C=C bond gives a mixture of both 5-*exo* and 6-*endo* products. The kinetic study of Beckwith[10] also showed that the initially formed five-membered ring radical undergoes further isomerisation to produce the six-membered ring. The fact that the five-membered ring closure is kinetically favored[12,13] is further supported by the work of Crich *et al*. This new review has the same goal as its predecessors to provide the most effective works possible. The main aim of this review is to reflect upon, and to summarize, the main developments that have taken place in the application of free radical chemistry to synthesize five- and six-membered heterocycles. In order to keep the review to an acceptable length, coverage has been focused only on

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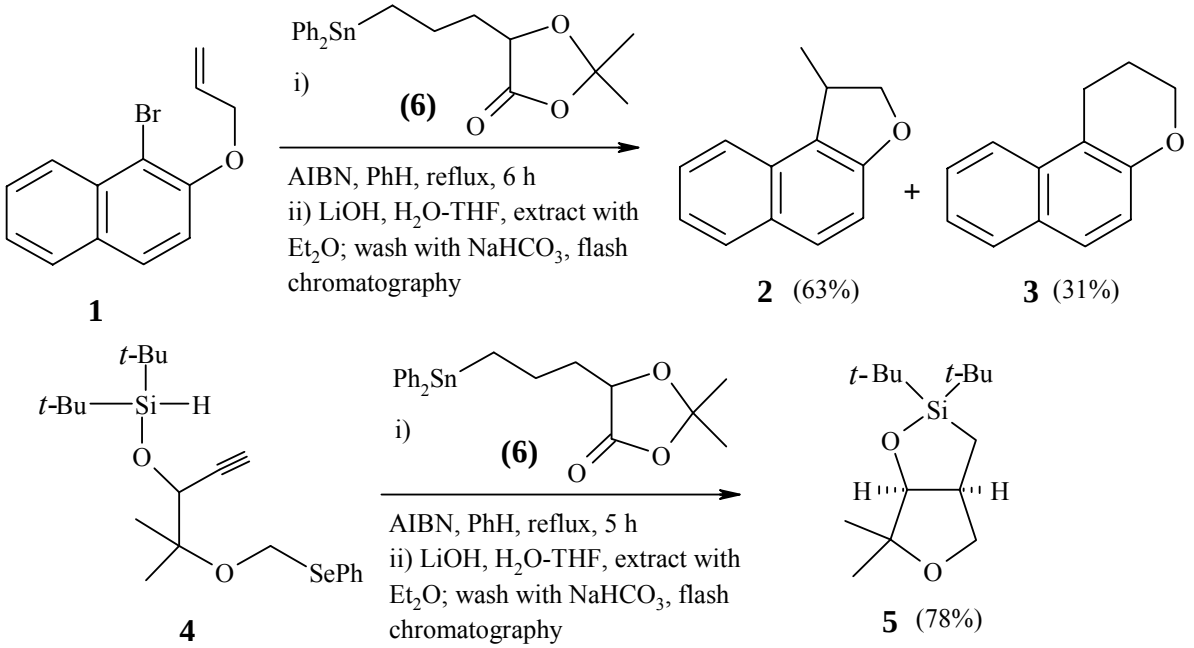
heterocyclic ring constructions and has largely excluded heterocyclic syntheses in which the heterocyclic ring(s) are not part of radical cyclization.

Among radical reducing reagents, tributyltin hydride is the most useful one in intermolecular radical additions using alkyl halides and unsaturated compounds such as alkenes and alkynes.[14] Except Bu_3SnH, other tin hydrides such as Me_3SnH and Ph_3SnH[14] have also been successfully employed in the synthesis of heterocycles using radical cyclization. Generally, an excess of tin hydrides with a smaller equivalent of a radical initiator like azobisisobutyronitrile (AIBN) are used in this type of reaction. The alternative procedure involves the use of small amount of tri-*n*-butyltin chloride with sodium cyanoborohydride for *in situ* generation of tri-*n*-butyltin hydride. Organotin compounds are highly toxic.[15] It is well established that there are occasional difficulties in removing tin species from the products of stannane-mediated radical reactions. One of the most useful processes is the transformation of the excess, unreacted trialkyltin halides to the corresponding easily removable, non-volatile, insoluble 'polymeric' tin fluoride by using aqueous potassium fluoride.[16] Purification of the product is therefore, very difficult and various attempts have been made to overcome this problem. Clive *et al*. have synthesized[17] a triorganotin hydride of the type (**6**) whose structural features simplify product isolation. It facilitates the removal of tin species in triorganotin hydride mediated radical reactions in which an acetal side chain is easily hydrolyzed to a carboxylic acid and that can be extracted by aqueous $NaHCO_3$. The performance of the stannane (**6**) was evaluated for a range of radical cyclization reactions onto a carbon-carbon double bond or in the radical cyclization onto a triple bond as indicated below (**Scheme-1**).



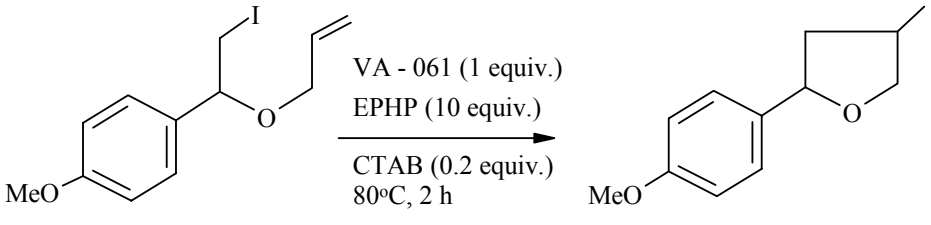
Scheme-1

Recently, various efforts have been directed towards tin free radical chemistry.[18] Tris(trimethylsilyl)silane [$(TMS)_3SiH$] is commonly used in place of Bu_3SnH[19-23] and it is slightly less

reactive than Bu_3SnH, but is very expensive[24-27] and the reaction conditions are analogous to the tin hydride mediated reductions using AIBN as initiator in refluxing benzene or toluene. Tributylgermanium hydride (Bu_3GeH) is another such expensive reagent that can be used for the improved cyclization yield. One such example is the cyclization of perfluoroalkenyl radicals[28] using Bu_3GeH. Generally germanes are more reactive than silanes, but less reactive than tin hydrides. In most cases AIBN is used as radical initiator. However, there are other diazine initiators, *e.g*. AMBN [azobis(methylisobutyronitrile)]. It is more soluble and can be used in cyclohexane as well as toluene as solvent. Cyclohexane is found to be the preferred solvent for Bu_3SnH mediated reactions because toluene and benzene not only act as a solvent but also may participate in radical reactions.

The use of water as a solvent is a tremendous development in the field of radical cyclization. The radical reaction in water media is advantageous from the point of view of its cost, safety and environmental concern. Additionally, most of the organic radical species are stable in water. Water-soluble initiators are used for carrying out radical reactions in water. Mono and bicyclic tetrahydrofurans and dihydrobenzofurans have been synthesized by the use of tri-2-furylgermanium hydride as the radical mediator in water.[29]

Recently the radical cyclization of hydrophobic substrates in water using the combination of 2,2/-azobis[2-(2-imidazolin-2-yl)propane] (VA-061), 1-ethylpiperidine hypophosphite (EPHP) and cetyltrimethylammonium bromide (CTAB) have been reported.[30] Nambu *et al*. observed that 2-iodo-1-(4-methoxyphenyl)-1-prop-2-enyloxyethane (**7**) when treated with VA-061 as water soluble initiator and EPHP as the chain carrier the cyclized product, 1-methoxy-4-(4-methyl-2-oxolanyl)benzene (**8**) was formed in 64% yield. However, by using 1-10 equiv. of NaCl as 'salting out' salt the reaction of compound (**7**) proceeded more effectively and the yield of the product (**8**) was found to increase. It is



7 **8**

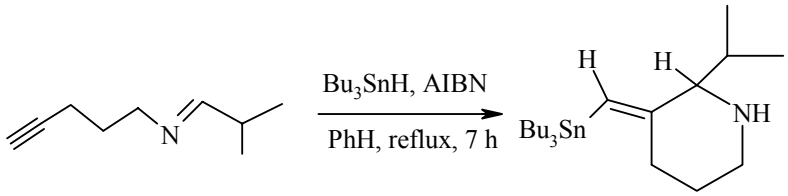
98% (*trans:cis* = 55:45)

important to note that large quantity of 'salting in' salt like guanidine hydrochloride was necessary to facilitate the cyclization reaction of compound (**7**). On the other hand, the reaction of **7** was best observed by using various surfactants (*e.g*. CTAB) in the presence of VA-061 and EPHP. The reaction did not go to completion in presence of commonly used radical initiator, AIBN.

Bowman *et al*. reported[31] the alkyl radical cyclizations onto imino group. Ryu *et al*. elaborated[32] the fact that 5-*exo*/6-*endo* type of acyl radical cyclization onto N=C furnished 2-pyrrolidinones through selective

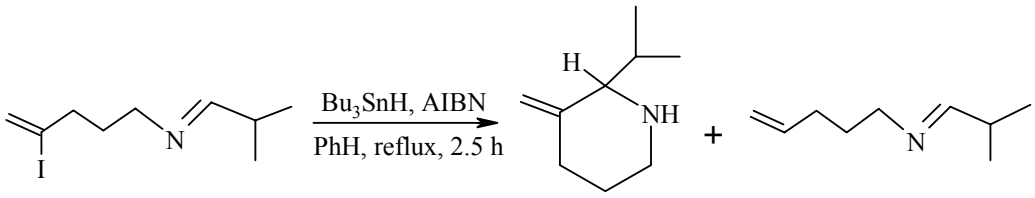
5-*exo* manner. Recently they also observed[33] that 5-*exo*/6-*endo* type of vinyl radical cyclization onto aldimine N=C proceeds selectively in 6-*endo* manner to produce methylenepiperidines.

An azaenyne (**9a**) was treated with tributyltin hydride and a catalytic amount of AIBN; six membered ring product (**10a**) was formed in 43% yield as a single stereoisomer along with some hydrostannylation product (21%). No five membered ring product was detected in the reaction mixture.



9a **10a** (43%)

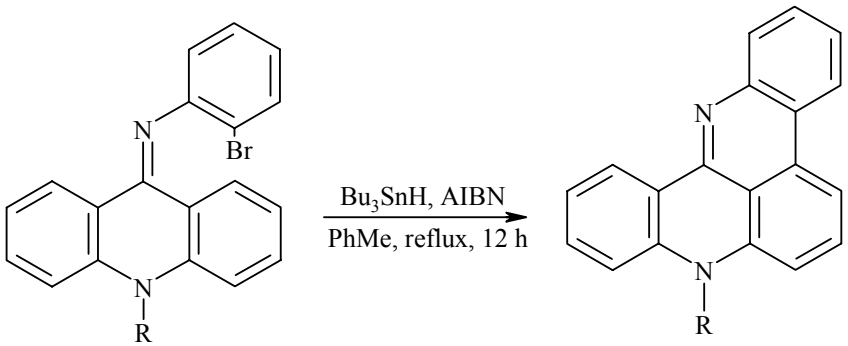
The vinyl iodide (**9b**) under normal radical cyclization condition furnished 3-methylenepiperidine (**10b**) (30%) together with a comparable amount of reduced product (**11b**). In this case no five membered ring product was detected (**Scheme-2**).



9b **10b** (30%) **11b**

Scheme-2

9-(2-Bromoanilino)acridine was reported[34] to cyclize with tributyltin hydride and AIBN in boiling toluene to produce the pentacyclic acridines in very low yield (31%). The yield may be increased by the radical cyclization reaction of *N*-alkylacridines (**12a-c**) to furnish 8-alkylquinoacridines (**13a-c**) (**Scheme-3**).

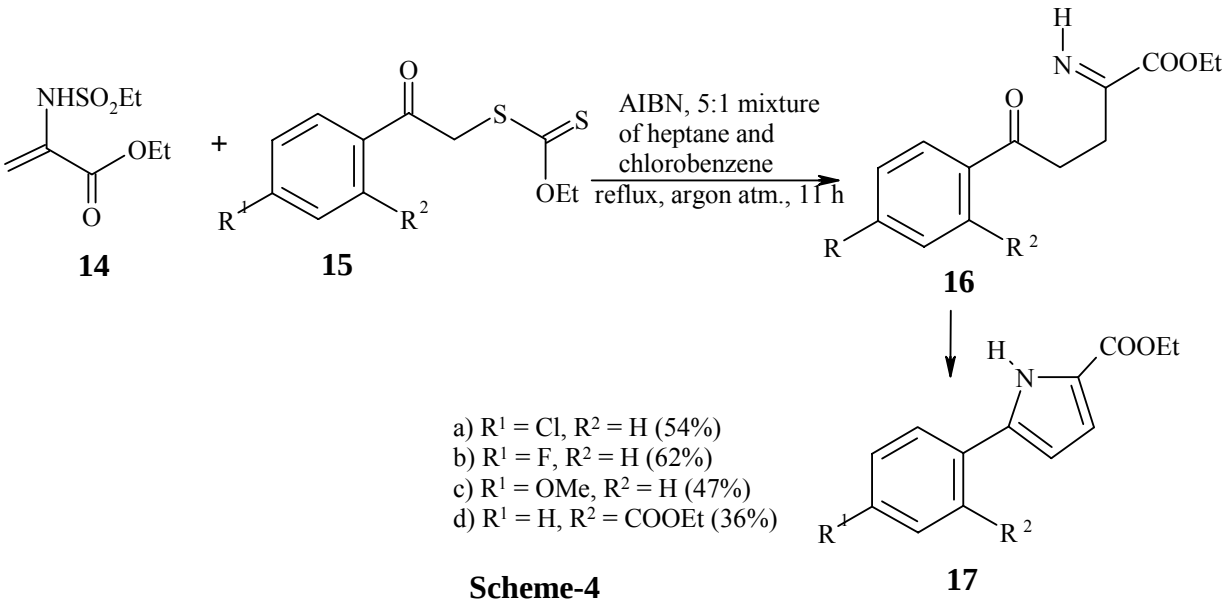


12a-c **13a-c**

a) R=Me (69%)
b) R= Et (79%)
c) R= Pr (54%)

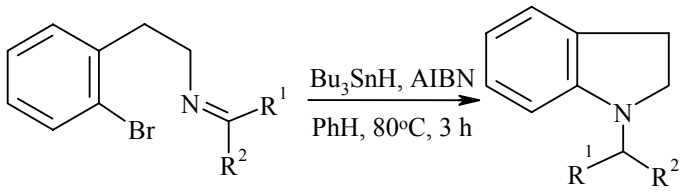
Scheme-3

Zard *et al*. reported[35] the radical reaction between an *N*-ethylsulfonylenamide (**14**) and an α-xanthyl ketone (**15**) in the presence of AIBN in a 5:1 mixture of heptane and chlorobenzene to give rise to an intermediate γ-keto imine (**16**) which spontaneously ring closes to the pyrrole (**17**) (**Scheme-4**).



Scheme-4

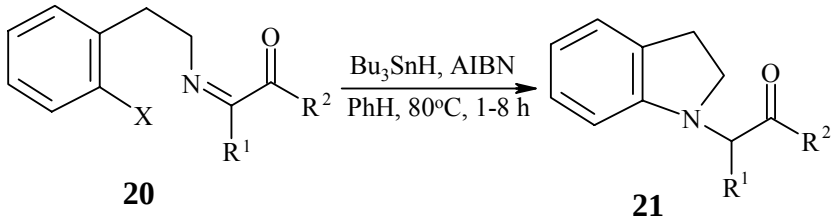
Recently tributyltin hydride mediated radical cyclization of various ketimines (**18**) was carried out to analyze the aryl radical additions to the nitrogen of azomethines.[36] Aryl, trifluoromethyl alkyl and α,β-unsaturated ketimines are engaged in regioselective aryl nitrogen bond formation *via* 5-*exo* cyclizations of an aryl radical to azomethine nitrogen. C-N bond formation is more selective than C-C bond and competes only with direct aryl radical reduction by stannane (**Scheme-5**).



a) R^1 = Ph, R^2 = Me (87%)
b) R^1 = R^2 = Ph (86%)
c) R^1 = 4-$Me_2NC_6H_4$, R^2 = Me (90%)
d) R^1 = 4-$CF_3C_6H_4$, R^2 = Me (72%)

Scheme-5

In case of α-ketoimines (**20**) no such competitive aryl radical reduction was observed. The reaction are performed under pH-neutral conditions and are therefore mildest methods available for amination of an aromatic ring (**Scheme-6**).

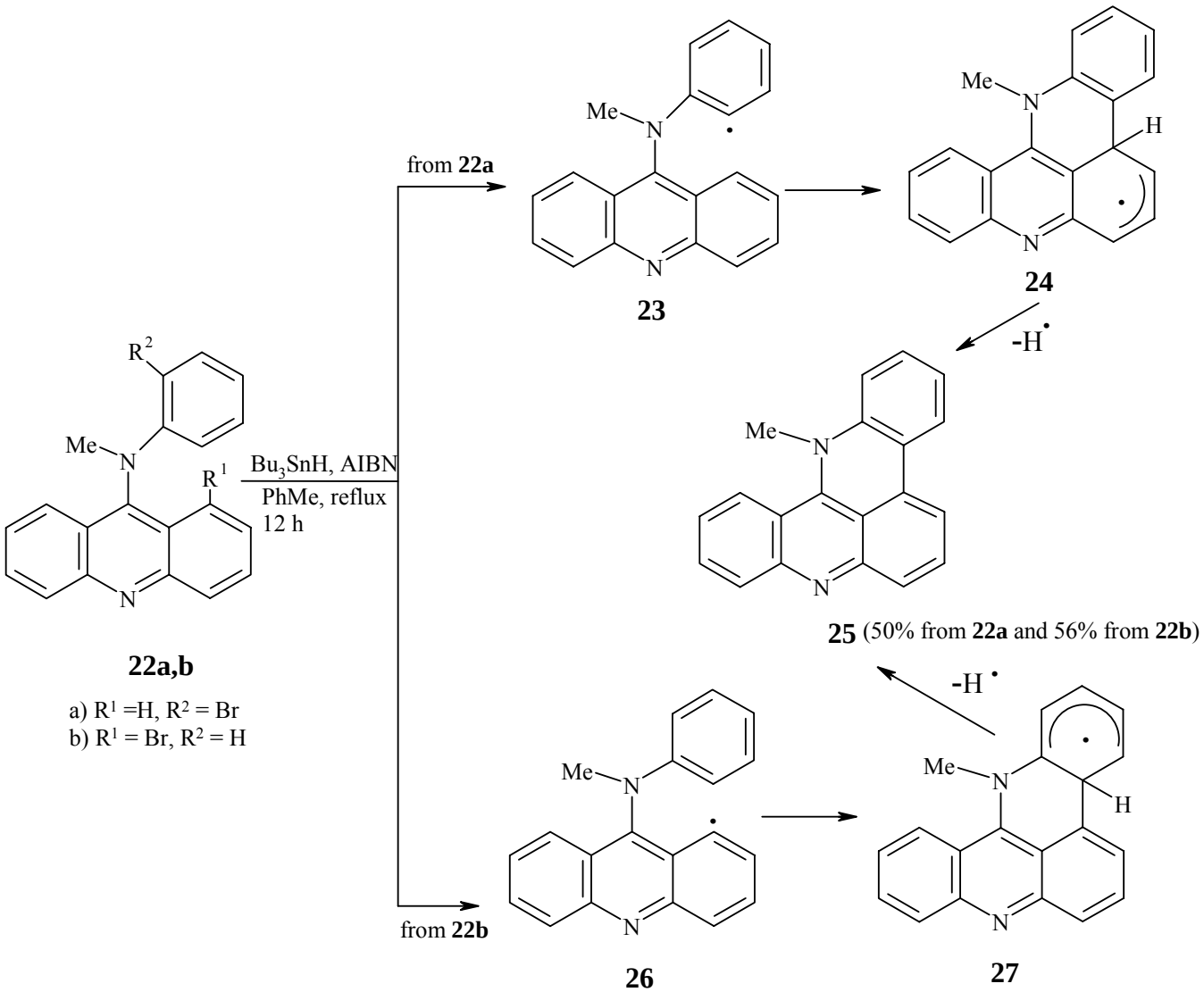


20 **21**

a) X = Br, $R^1 = R^2$ = Me (41%)
b) X = I, $R^1 = R^2$ = Me (44%)
c) X = I, $R^1 = R^2$ = Ph (65%)
d) X = I, R^1 = Me, R^2 = OMe (75%)

Scheme-6

9-(2-Bromo-*N*-methylanilino)acridine (**22a**) was cyclized[34] under normal radical cyclization condition *via* the intermediate radicals (**23**) and (**24**) to produce the 1,3-methylquinoacridine (**25**) as the major product (50%). Similarly 1-bromo-9-(*N*-methylanilino)acridine (**22b**) undergoes radical cyclization *via* the intermediate radicals (**26**) and (**27**) to furnish the same product (**25**) in 56% yield (**Scheme-7**).



22a,b

a) R^1 =H, R^2 = Br
b) R^1 = Br, R^2 = H

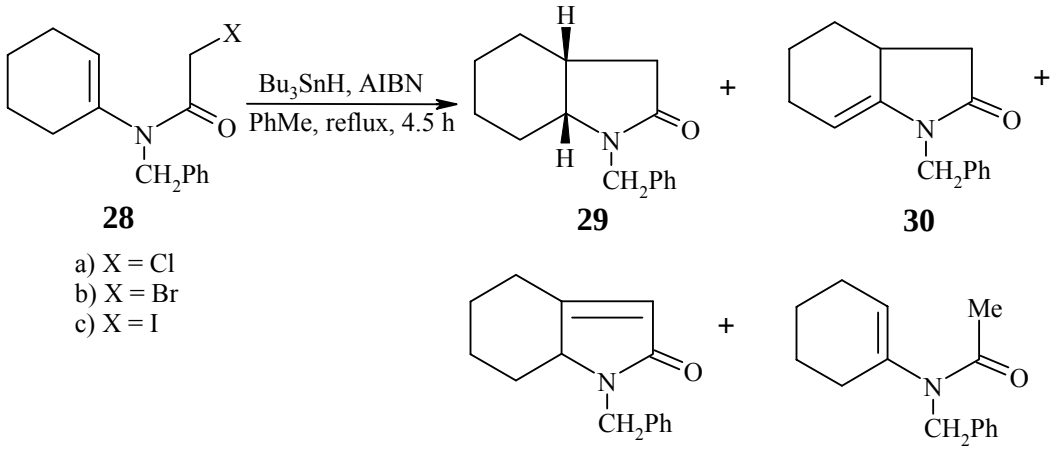
Scheme-7

Aryl radicals generated by the homolysis of Ar-Br bond by *n*-Bu_3SnH–AIBN have been used extensively as the key step in the establishment of C_{aryl}-C_{alkyl} bond. This method has been applied to construct a variety of system such as dihydroindoles,[37] benzofuran,[38] tetrahydro-*β*-naphthol[39] and oxindoles.[40] Rosa *et al*. have subjected[41] *N*-(*o*-bromobenzyl)anilines in the presence of tri-*n*-butyltin hydride and AIBN to obtain phenanthridine *via* dihydrophenanthridines, by intramolecular addition of aryl radicals to the *o*-position of the aryl ring bearing the nitrogen atom.

In the synthesis of pyrrolophenanthridine alkaloids, *N*-(2-bromo-4,5-dimethoxybenzyl)-*N*-(2′-*β*-hydroxyethylphenyl)amine was prepared[42] in one of the steps and then TBTH mediated radical cyclization reaction was carried out to obtain the phenanthridine alcohol as a colorless solid (27% yield).

Sato *et al*. found[43] that 2-chloro-*N*-(cyclohex-1-enyl)-*N*-methylacetamide in the presence of a catalytic amount of AIBN and 1.1 mol equiv. of Bu_3SnH furnished the *cis*-octahydroindol-2-one in 63% yield along with a very small amount of the reduction product. Treatment of the corresponding iodo congener under similar reaction condition, gave only simple reduction product with no cyclization product.

Tamura *et al*. have examined[44] the effect of a halogen atom in 5-*endo* radical cyclization of *α*-haloamides by employing *N*-benzylamides (**28a-c**). The cyclization ability decreased in the order of chloro to bromo to iodo amide (**28a→b→c)**. $(TMS)_3SiH$ annulated reactions have also exhibited the same tendency.



28

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

29 **30** **31** **32**

	29	**30**	**31**	**32** (Yield %)
a	92	0	0	0
b	55	11	11	0
c	0	13	11	68

Scheme-8

Compound (**28a**) under normal radical cyclization condition (Bu_3SnH in the presence of AIBN in boiling toluene) afforded cyclization product (**29**) in 92% yield, while compound (**28b**) gave a mixture of compound (**29**), enamide (**30**) and *α,β*-unsaturated products (**31**) in 55, 11 and 11% yields, respectively. The reaction of *α*-iodoamide (**28c**) furnished simple reduction product (**32**) in 68% yield along with very

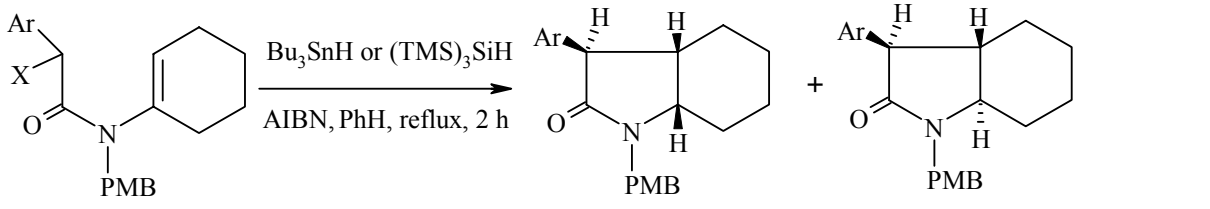
small amount of cyclization products (**30**) and (**31**). The effectiveness of the cyclization of α-iodoamides was restored by using Bu_3SnCl[45] or Bu_3SnF as additives (**Scheme-8**).

N-(α-Haloacetamido)dehydroalanine derivatives on treatment with tributyltin hydride in boiling benzene or toluene afforded pyroglutamates *via* disfavored 5-*endo-trig* manner.[46] The *N*-benzyl substituent was found to be essential for this type of cyclization because the corresponding *N-H* derivatives furnished no pyroglutamate.

Dichloro- and trichloroamides are found to be more efficient for the effective formation of pyroglutamate. The cyclization of the S-phenyl derivative also furnished the pyrrolidinone as a 2:1 mixture of diastereomers in only 28% yield. Parsons *et al*. also explored[47] the Bu_3SnH mediated radical cyclization of various *N*-acryloxy-2-amino-2-cyclohexanones to afford bicyclic lactams.

Influenced by the radical stabilizing substituents such as methyl, phenyl, phenylthio, dimethyl or dichloro group, γ-lactam is prepared exclusively *via* 5-*endo-trig* cyclization from a range of 2-halo-*N*-(3,4-dihydro-2-naphthyl)acetamides.[48] The *5-endo-trig* cyclization of carbamoylmethyl radicals has been applied to the synthesis of (±) cotinine.[49]

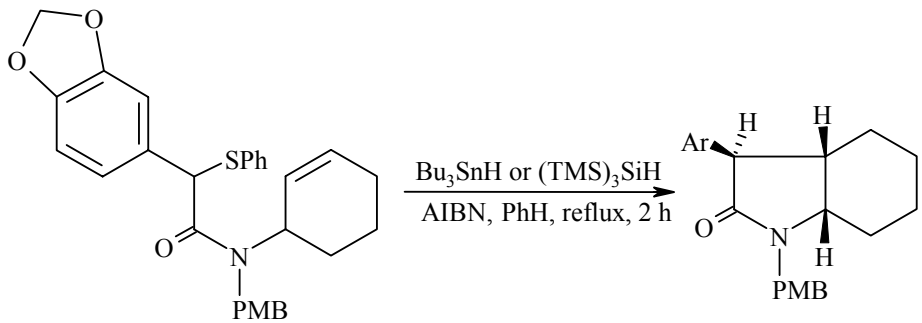
Ikeda *et al*. reported[50] the Bu_3SnH or $(TMS)_3SiH$ mediated 5-*endo-trig* radical cyclization of *N*-(cyclohex-1-enyl)-*N*-(4-methoxybenzyl)-2-(3,4-methylenedioxyphenyl)-2-(phenylseleno)acetamide (**33**) to give a mixture of *cis*-fused (3*R**, 3*aS**, 7*aS**)- and *trans*-fused (3*R**, 3*aS**, 7*aR**)-3-aryloctahydroindol-2-ones (**34**) and (**35**) respectively. On the other hand 5-*exo-trig* radical cyclization of *N*-cyclohex-2-enyl-*N*-(4-methoxybenzyl)-2-(3,4-methylenedioxyphenyl)-2-phenylthioacetamide (**36**) furnished compound (**34**) in a stereoselective manner (**Scheme-9**).



33 (X = SePh)
(Ar = 3,4-Methylenedioxyphenyl
PMB = *p*-Methoxybenzyl)

34
17%
39%

35
21% [using Bu_3SnH]
21% [using $(TMS)_3SiH$]

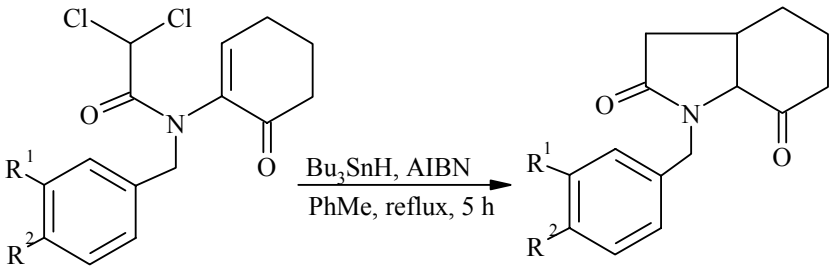


36

34
78% [using Bu_3SnH]
85% [using $(TMS)_3SiH$]

Scheme-9

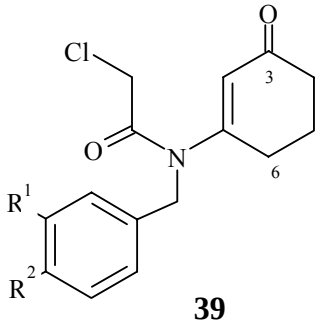
A new radical cyclization involving tributyltin hydride have been demonstrated[51] to form tri- and tetracyclic ring systems related to the Amaryllidaceae or Erythrina family of alkaloids. The radical cyclization of dichloroethanamides (**37a-d**) was reported to generate a 5,6-bicyclic ring system (**38a-d**).



37a-d **38a-d**

compound **37**	R^1	R^2	Bu_3SnH addition in h	Yield of **38**(%)	*cis*:*trans*
a	H	H	1	63	4.2:1
b	H	OMe	1	65	4.8:1
b	H	OMe	5	85	3.3:1
c	- OCH_2O-		5	74	5.1:1
d	F	H	5	71	4.6:1

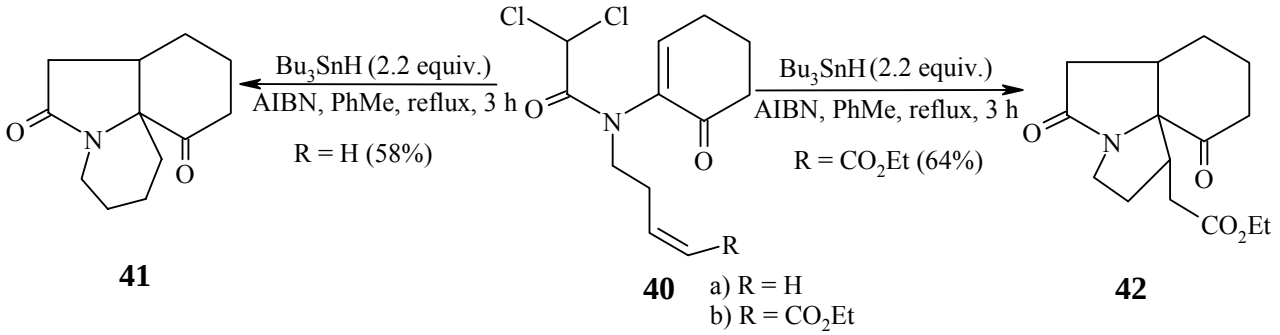
The chloroethanamide (**39**) having a ketone group at C-3 (instead of C-6) under tributyltin hydride mediated radical cyclization condition furnished very small amount (16%) of octahydroindolone.



39

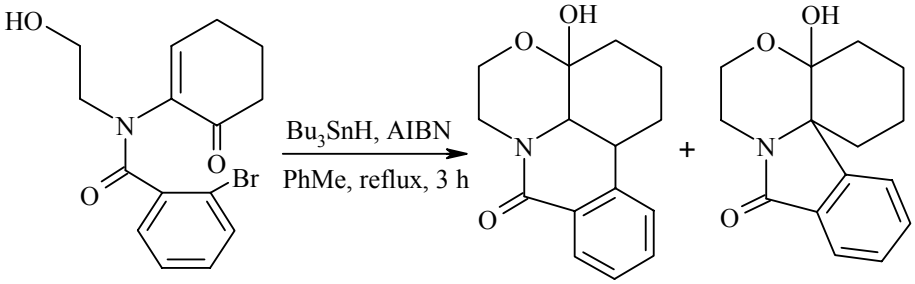
This clearly suggests that the efficiency of the 5-*endo* cyclization is influenced only when the ketone group is placed at C-6.

It was also reported[51] that Bu_3SnH mediated radical cyclization reaction of *N*-but-3-enyl dichloroethanamide (**40a**) and *N*-4-ethoxycarbonylbut-3-enyldichloroethanamide (**40b**) produced tricycles (**41**) and (**42**) in 58% and 64% yields, respectively. The exclusive formation of 5,6,6-tricycle (**41**) (as a single diastereomer) may be explained by a 5-*endo*/6-*endo* cyclization mechanism and the formation of the 6-membered ring is presumably due to the stability of the intermediate captodative radical and this promotes a reversible cyclization leading to the thermodynamic (6-membered) product. On the other hand **40b** undergoes 5-*endo*/5-*exo* tandem cyclization because the ester substituent is capable of stabilizing the radical produced on 5-*exo* cyclization and the second cyclization is no longer reversible and so the kinetic (5-membered) product (**42**) is formed as a 1:1 mixture of diastereomers (**Scheme-10**).



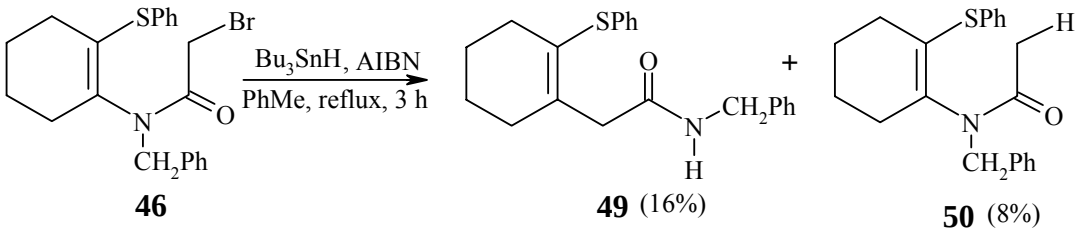
Scheme-10

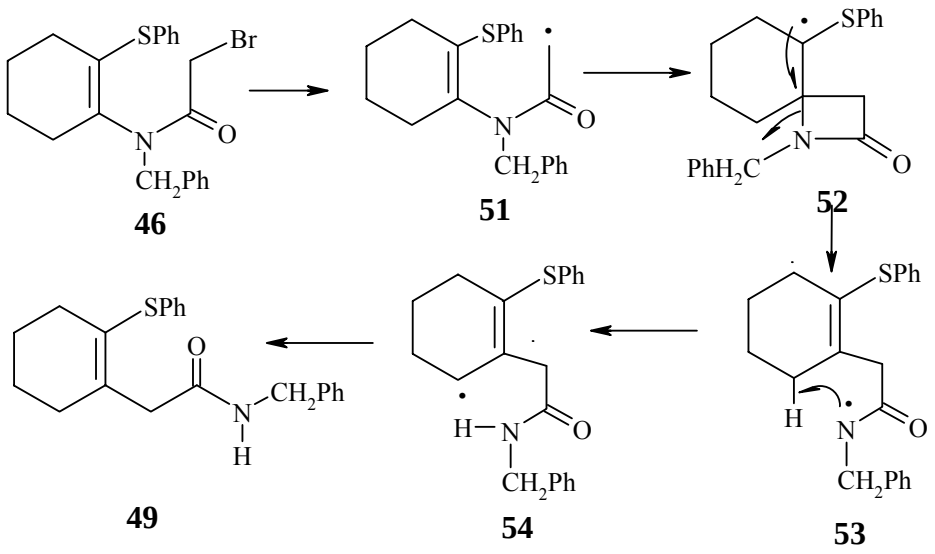
The predominance of 5-*exo*- over 6-*endo*- cyclization was found[51] in the radical cyclization of *N*- (2-hydroxyethyl)-*N*-(6-oxocyclohex-1-enyl)-2-bromobenzamide (**43**) to produce tetracycles (**44**) and (**45**) in 30% and 40% yield, respectively (as single diastereomers). The major product (**45**) is the result of 5-*exo* cyclization of the aryl radical whereas **44** is produced from a competitive 6-*endo* cyclization (**Scheme-11**).



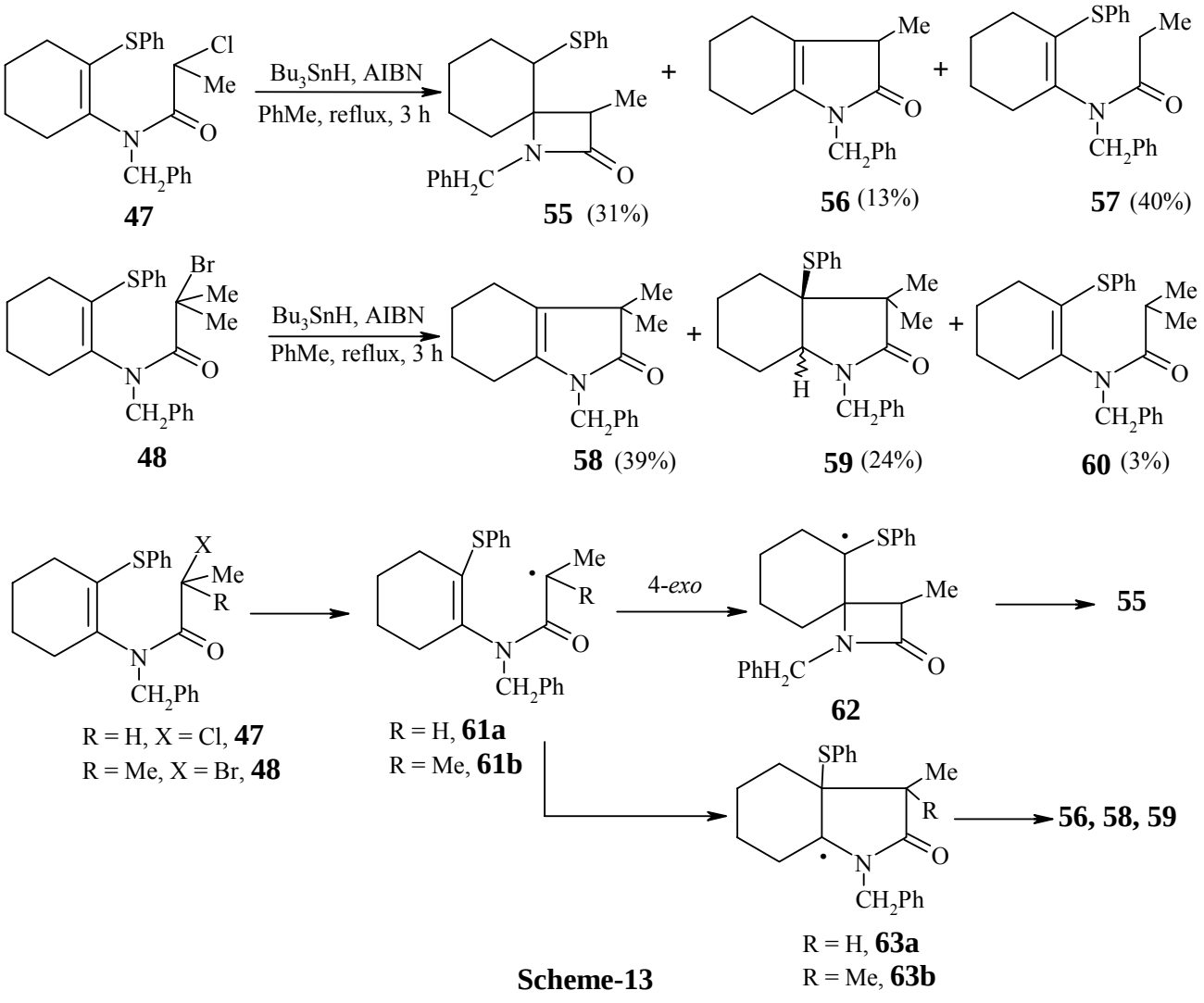
Scheme-11

Tributyltin hydride mediated radical cyclization of *N*-(2-phenylthiocyclohex-1-enyl)-*α*-haloamides was also reported.[52] Bromoacetamide (**46**) having no substituent *α* to the halogen atom cyclized exclusively in a 4-*exo*-*trig* manner, whereas the fully substituted haloamides (**47**) and (**48**) gave 5-*endo*-*trig* cyclization products. The carbamoylmethyl radical (**51**), formed from **46**, cyclized in a 4-*exo*-*trig* manner to give the sulfur stabilized radical (**52**) and this is then followed by a ring opening to give amidyl radical (**53**). A subsequent [1,5] hydrogen shift produces the allylic radical **(54**), which is then trapped by Bu_3SnH to give **49** (**Scheme-12**).





Scheme-12



Scheme-13

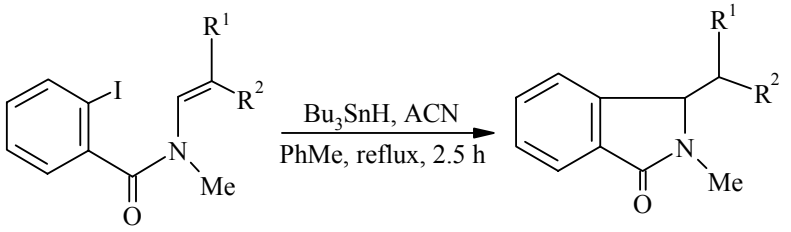
Formation of **55** from enamide (**47**) may be explained by the attack of Bu_3SnH on the sulfur–substituted intermediate radical (**62**) generated by a 4-*exo-trig* cyclization of carbamoylmethyl radical (**61a**). On the other hand the radical (**63a**) generated from 5-*endo-trig* cyclization of radical (**61a**) undergoes an

elimination of benzenethiyl radical to give **56**. Similarly the reactions of radical **63b**, generated from **48** *via* **61b** gives **58**. Compound (**59**) is produced by an attack of Bu_3SnH on the radical center of **63b** (**Scheme-13**).

The above results clearly indicate that the mode of cyclization is affected by the size of the substituents around the radical center.

Radical cyclizations attributing 5-membered rings are highly stereoselective.[53-56] Although, the formations of 6-membered rings *via* radical cyclizations are less common compared to the 5-membered rings, they still have an important role in the synthesis. Bu_3SnH mediated radical cyclization of *o*-iodobenzamide was reported to produce phenanthridone *via* 6-*endo* cyclization.[57]

Ishibashi *et al*.[58] reported that *N*-vinylic-*o*-iodobenzamide (**64**) upon treatment with Bu_3SnH-ACN gave mainly the 5-*exo* cyclization product (**65**) (**Scheme-14**). However, the enamide having a phenyl substituent on the vinyl carbon atom *α*- to the nitrogen atom gave predominantly the 6-*endo* cyclization product.

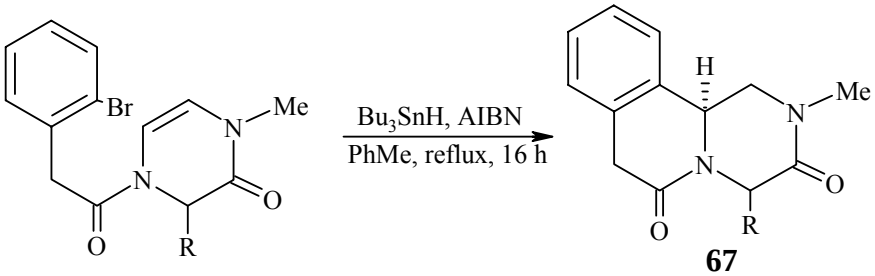


64a-d **65a-d**

a) $R^1 = R^2 = H$ (60%)
b) $R^1 = Ph$, $R^2 = H$ (53%)
c) $R^1 = R^2 = Ph$ (43%)
d) $R^1 = R^2 = COOEt$ (65%)

Scheme-14

Todd *et al*. encountered difficulty in developing a general synthesis of the fused-ring system *via* the acyliminium intermediate and therefore turned their attention to radical cyclization as an alternative approach. Influenced by the success of Rigby[59] and Ishibashi *et al*.[60] with the ring closure of aryl radicals onto acyclic enamides. Todd *et al*. used the similar protocol to the acyl pyrazinone intermediate (**66**).[61] Tri-*n*-butyltin hydride mediated radical cyclization of the bromophenyl dihydropyrazinone (**66**) furnished



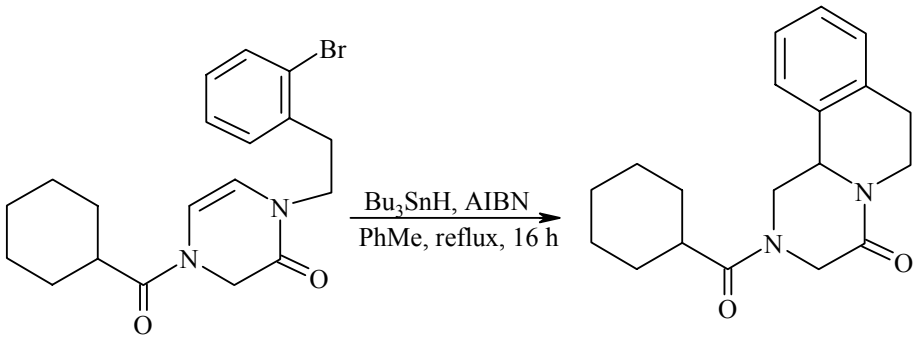
66 **67**

a) R = Bn (80%)
b) R = *i*-Pr (70%)
c) R = CH_3 (71%)

Scheme-15

the peptide mimics **67** in good yield *via* 6-*exo* selectivity (**Scheme-15**).

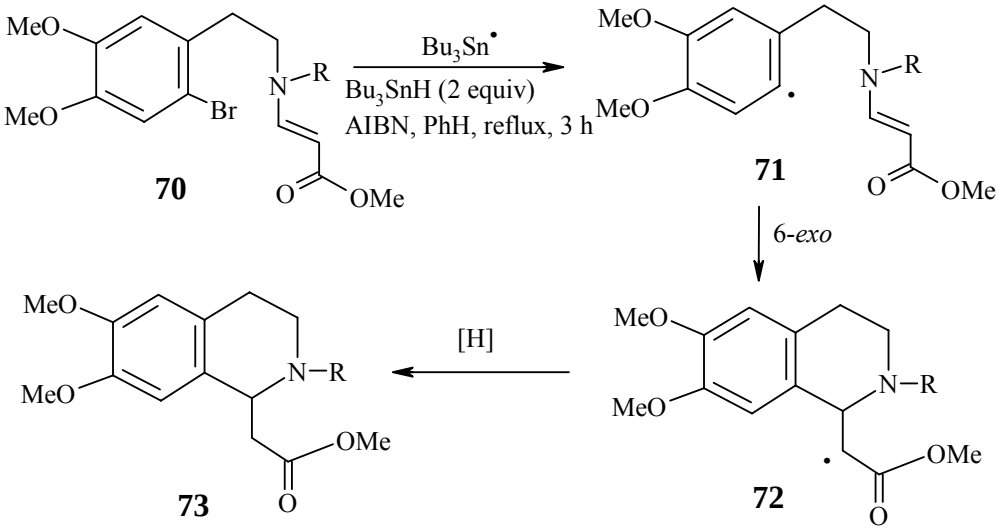
The anthelmentic drug praziquantel (**69**) has been synthesized[61] following the radical initiated cyclization of pyrazinone **68** (**Scheme-16**). Tetracyclic galanthan alkaloid ring system has also been prepared by Bu_3SnH mediated radical cyclization of aryl radicals.[62]



68 **69** (90%)

Scheme-16

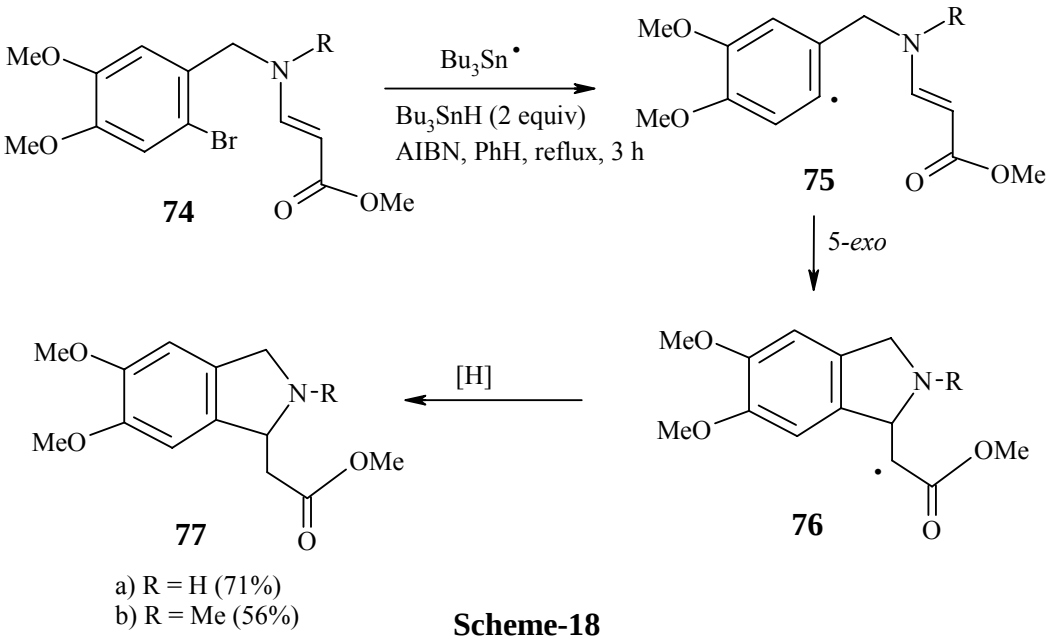
Radical cyclizations of highly reactive aryl radicals onto double and triple bonds are very useful to construct carbocycles and heterocycles[1,63] and especially aza- heterocycles[63] in particular. Various sizes of aza-heterocycles have been obtained by radical addition to *N*-vinylamides (enamides).[60,64,65] *N*-Vinyl unit containing compounds like enamines,[66] *N*-sulfonylenamines[67] and enaminones[68,69] are less common. Aryl radical cyclization in *N*-phenyl-, *N*-benzyl- and *N*-phenethylenaminone has been developed.[70] Tetrahydroisoquinolines (**73**) have been produced by the 6-*exo* cyclization onto *N*-phenethylenaminones (**70**) (**Scheme-17**) whereas 5-*exo* radical cyclization of *N*-benzylenaminones (**74**) afforded isoindoles (**77**) in good yield (**Scheme-18**). No cyclized product was obtained from *N*-phenyl enaminones.



70 **71** **72** **73**

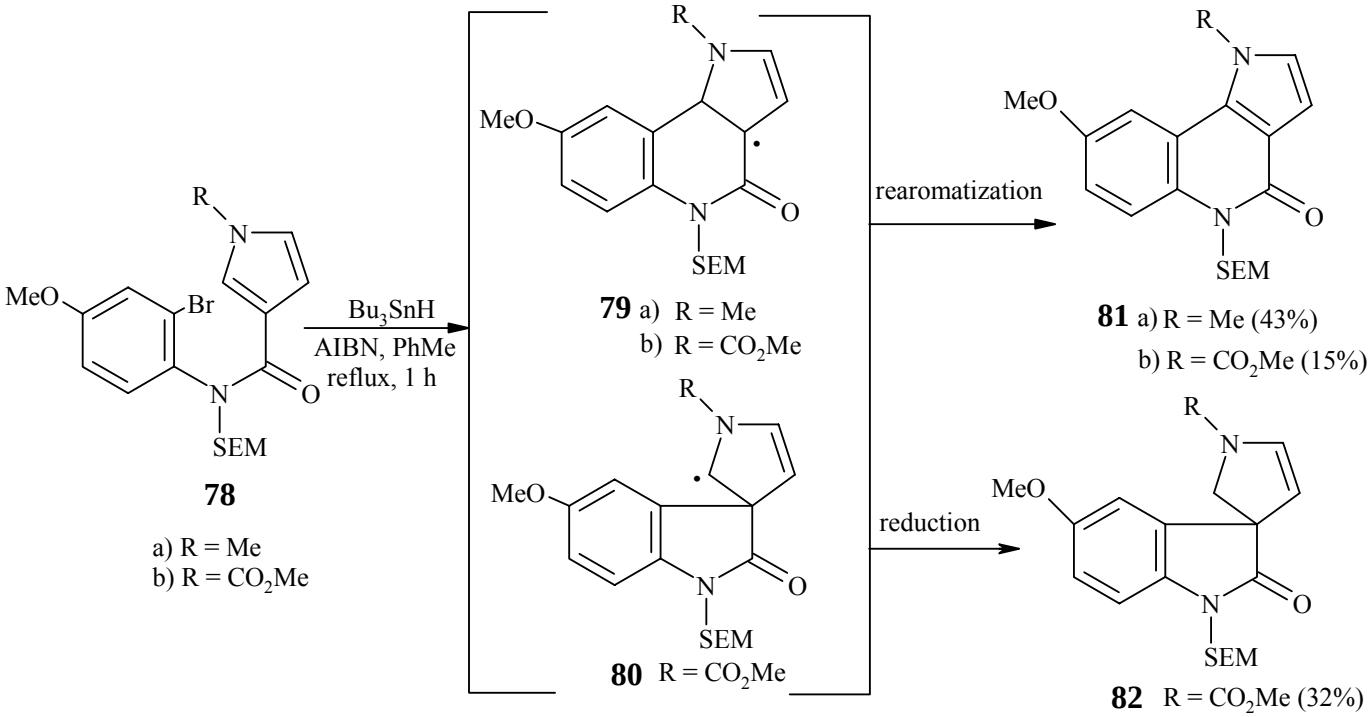
a) R = H (82%)
b) R = Me (51%)

Scheme-17



Scheme-18

Aryl radical cyclization has been proved to be very useful in the development of modern heterocyclic chemistry and also in the synthesis of natural products.[71] Jones *et al*. have reported[72] that the regiochemistry of cyclization of aryl radicals onto pyrroles attached through an amide at the C-3 position is influenced by the *N*-substituent on the pyrrole. Pyrroles substituted with an electon-donating group

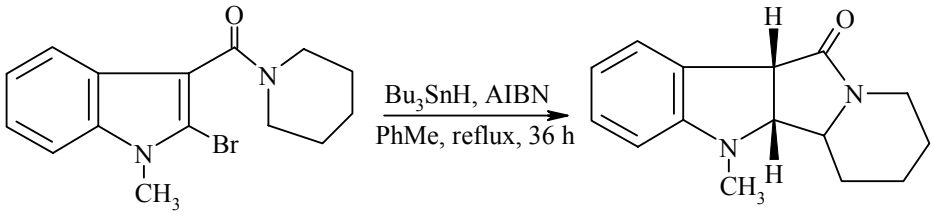


Scheme-19

(methyl) on nitrogen, **78a** gave exclusively 8-methoxy-1-methyl-5-(2-trimethylsilylethoxymethyl)-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinolin-4-one (**81a**) in 43% yield arising from 6-*endo* cyclization. No 5-*exo* or 6-*exo* cyclization product was isolated from the above reaction. On the other hand, pyrroles substituted

on nitrogen with an elecron-withdrawing group (carbamate) *e.g.* **78b** furnished the spiropyrrolodinyloxindole (**82**) as the major product (32% yield) *via* 5-*exo* cyclization along with a small amount of **81b** in 15% yield (**Scheme-19**). From the consideration of above results it can be concluded that the formation of either the spiropyrrolidinyloxindole or pyrrolo[3,2-*c*]quinoline nucleus from a common intermediate can be controlled by changing the substituent on the pyrrole, and the regiochemistry is not influenced by the substituents on the benzene ring.

2-Bromo-3-carboxamide (**83**) was found to attribute hexahydropyrrolo[3,4-*b*]indole (**84**),[73] when refluxed in toluene in the presence of Bu_3SnH and catalytic amount of AIBN. Some reduction product was also encountered from the reaction.



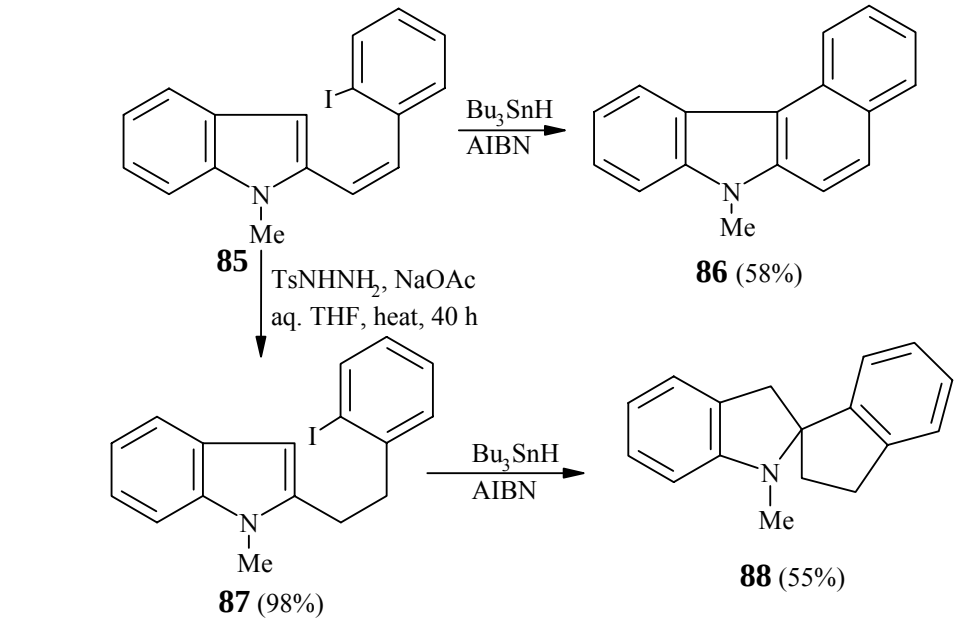
83 **84** (54%)

This reaction is believed to involve the generation of the expected C-2 radical followed by [1,5]-hydrogen atom abstraction to give the *α*-amidoyl radical and then 5-*endo-trig* cyclization to the indole double bond, followed by hydrogen abstraction to give indoline (**84**). Snieckus and Curran termed the first two steps in this process as 'radical translocation'. [74]

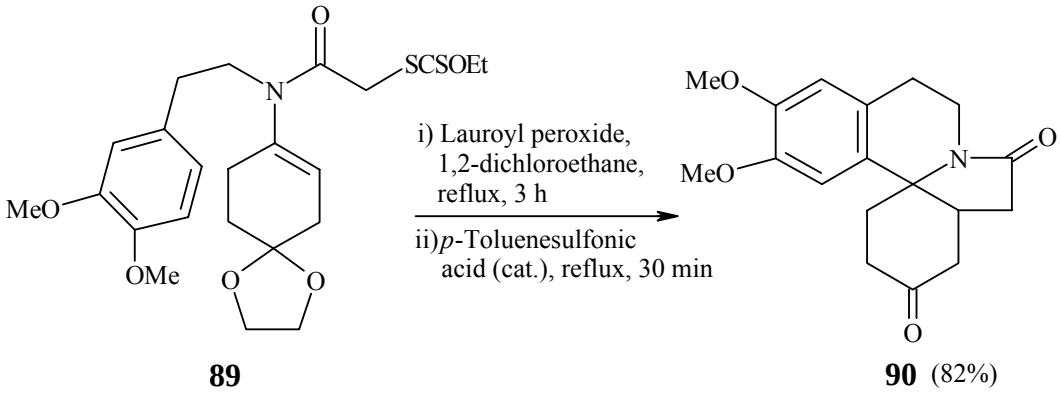
A few years ago the synthesis of 2-stannylindole was reported[75] by the radical cyclization of 2-alkenyl-phenylisonitrile. With this in view, Tokuyama *et al*. have synthesized[76] 2,3-disubstituted indoles by Bu_3SnH annulated radical cyclization of 2-alkenylthioanilides. The *cis*-isomer of 2-alkenylthioanilide on treatment with Bu_3SnH-AIBN in toluene at 80°C for 5 min furnished the expected 2-*n*-pentyl-3-acetoxymethylindole in 93% yield. The same product was also obtained within 5 min at room temperature by using Et_3B as the radical initiator.[77]

Recently it was observed[78] that the tributyltin hydride mediated radical cyclization of 2-styrylindole (**85**) took place at C-3 of the indole *via* 6-*endo-trig* pathway to produce benzo[*c*]carbazole (**86**) in 58% yield as the major product. On the other hand the radical cyclization of indole (**87**) generated the spirocycle (**88**) as the major product in 55% yield (**Scheme-20**).

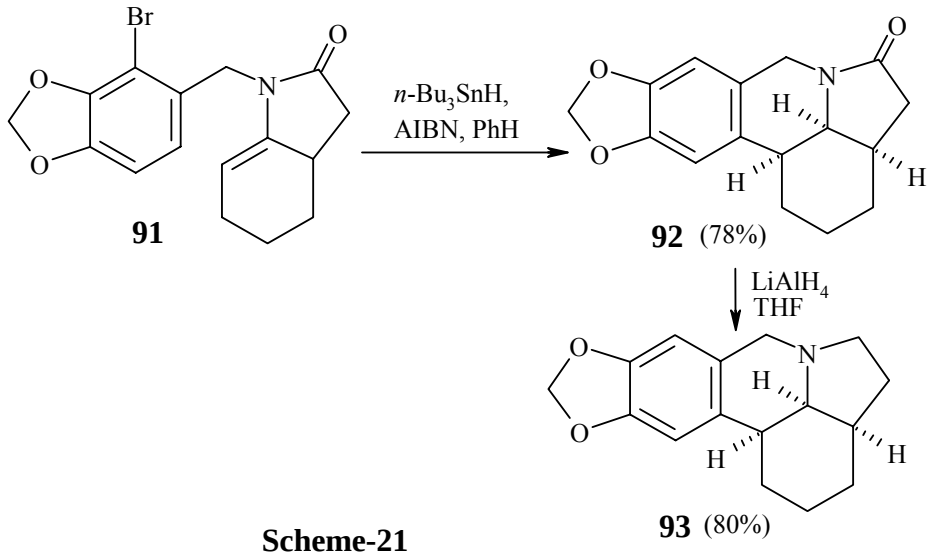
A short synthesis of (±)-*α*-lycoran and the erythrina ring system has been demonstrated by Zard *et al*.[79] For the synthesis of the erythrina system the corresponding xanthate (**89**) was refluxed in 1,2-dichloroethane with the stoichiometric addition of lauroyl peroxide; followed by addition of catalytic amount of *p*-toluenesulfonic acid to furnish compound (**90**) in 82% yield.



Scheme-20

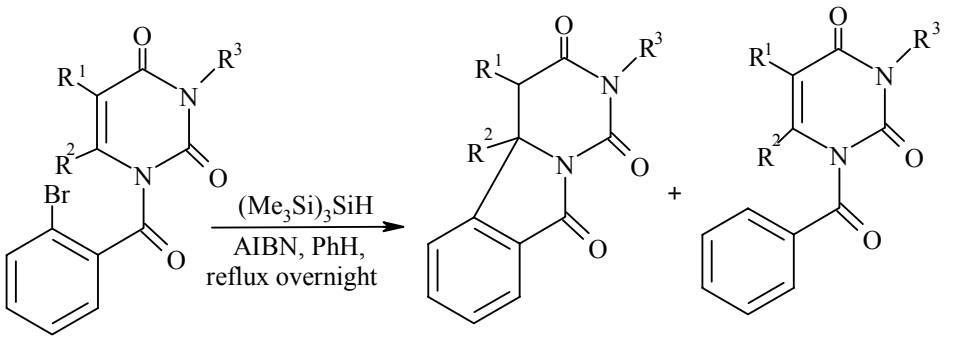


Similarly, tetrahydroindolones (**91**) on treatment with tributyltin hydride and AIBN in boiling benzene gave the tetracyclic compound (**92**) in 78% yield. Reduction of compound (**92**) with $LiAlH_4$ furnished (±)-*α*-lycoran (**93**) in 80% yield (**Scheme-21**).



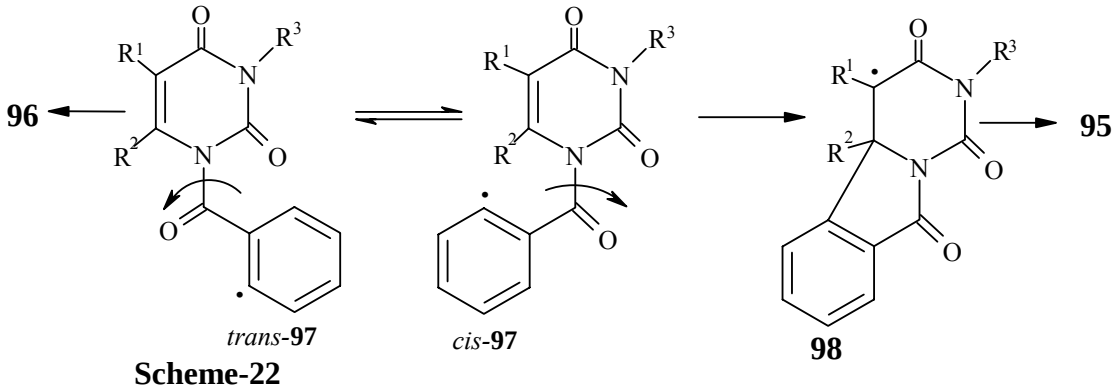
Scheme-21

Recently Zhang *et al.* described[80] a general method for constructing a variety of nitrogen heterocycles. They treated the *N*-acylated cyclic nitrogen compound (**94**) with $(TMS)_3SiH$ and AIBN to generate the tricyclic isoindolinones (**95**) as the major product along with some reduction product (**96**). In this case the initial radical (**97**) is generated from **94** and is equilibrated between the *cis*- and *trans*- amide conformation. Only the *cis*-amide conformation (*cis*-**97**) underwent the conjugate radical cyclization to give **95**. The *trans*- amide conformation (*trans*-**97**) gave the direct reduction product (**96**) (**Scheme-22**).



94a-d **95a-d** **96a-d**

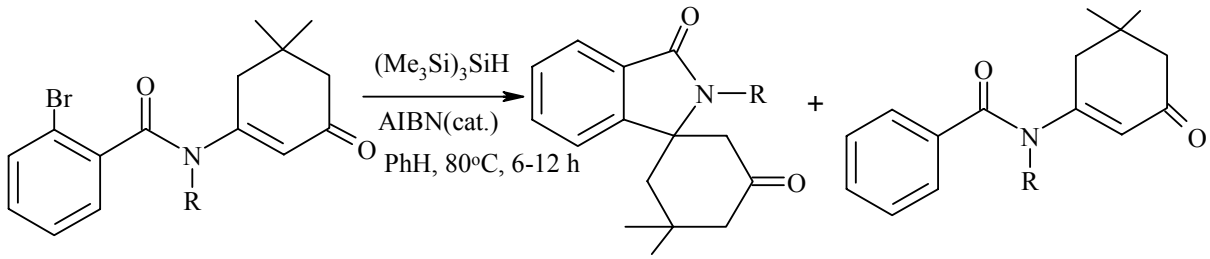
a) R^1 = H, R^2 = Me, R^3 = CH(Me)Et (50%) c) R^1 = Me, R^2 = R^3 = H (80%)
b) R^1 = R^2 = R^3 = H (59%) d) R^1 = CF_3, R^2 = R^3 = H (59%)



trans-**97** *cis*-**97** **98**

Scheme-22

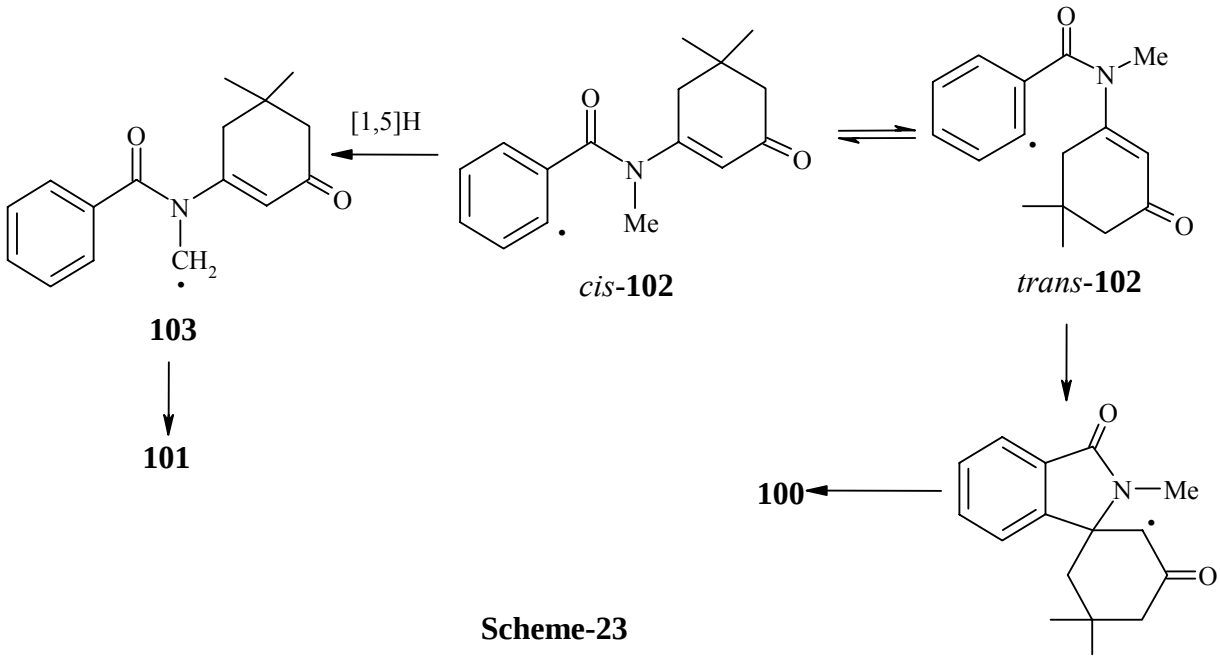
By the application of similar protocol[80] they prepared spiro isoindolinones (**100**). In this case the yield of the cyclization products were very low and significant amount of reduction products were obtained. It is proposed that the equilibrium between *cis*-**102** and *trans*-**102** favors the formation of *cis*-**102** and the relatively stable α- amidomethyl radical (**103**) is generated from *cis*-**102** by a [1,5]-hydrogen atom transfer (**Scheme-23**).



99 a) R = Me
b) R = CH_2CH_2Ph

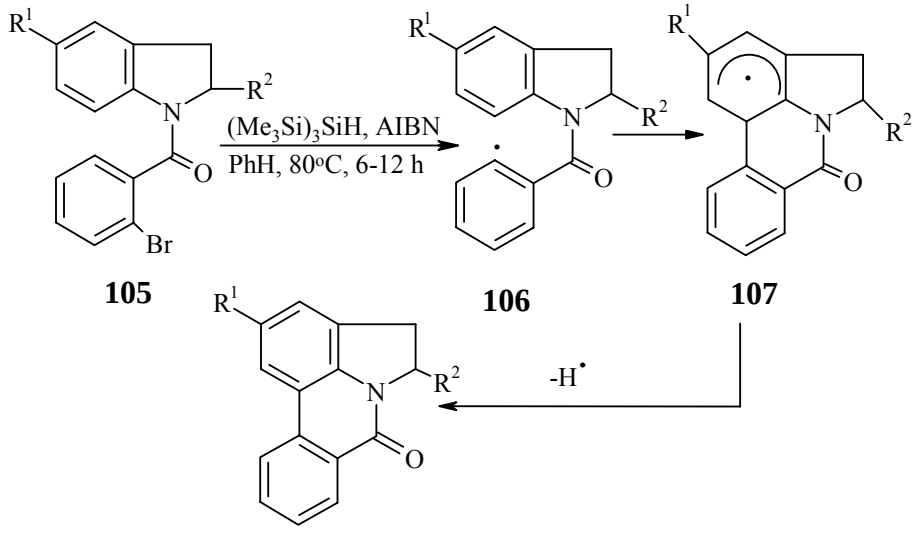
100 a) 35%
b) 41%

101 a) 61%
b) 52%



Scheme-23

Zhang *et al*. then extended their protocol toward the synthesis of various tetracyclic isoquinolinones.[80] One such reported case is depicted below (**Scheme-24**).

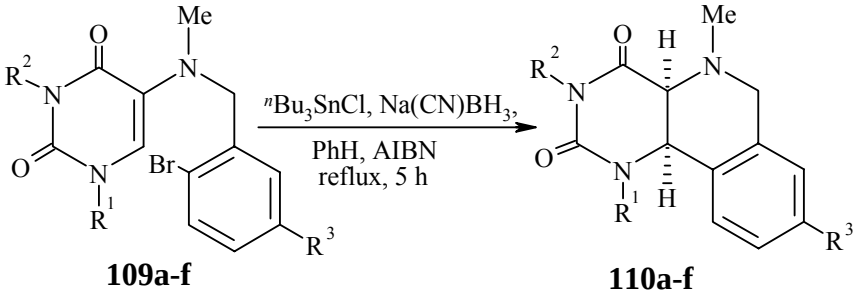


Scheme-24

Recently we have reported[81] the regioselective synthesis of a number of pyrimidino[3,2-*c*]tetrahydroisoquinolin-2,4-diones (**110a-f**) from 1,3-dialkyl-5-(*N*-2′-bromobenzyl, *N*-methyl)amino-pyrimidine-2,4-dione (**109a-f**) by intramolecular addition of aryl radical to the uracil ring bearing the amino nitrogen atom (**Scheme-25**).

The formation of six-membered heterocyclic ring in products (**110a-f**) from the substrates (**109a-f**) may be easily explained by the initial formation of the aryl radical (**111)** followed by a 6-*endo* ring closure to give a tertiary radical (**114**) which may then be reduced to afford the final products (**110a-f**). In an

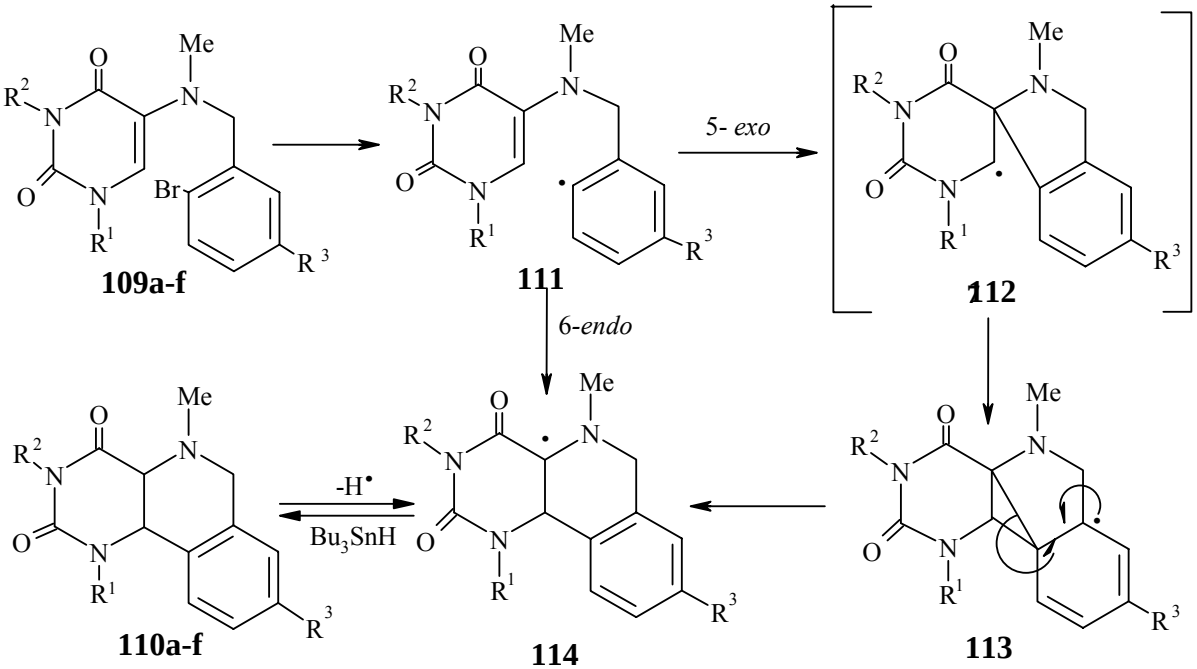
alternative route the aryl radical (**111**) may undergo a 5-*exo*-ring closure to generate a spiroheterocyclic radical[82] (**112**) which may be converted to the tertiary radical (**114**) *via* radical (**113**) by a neophyl rearrangement[83] (**Scheme-26**).



109a-f **110a-f**

a) R^1 =Et, R^2 = Me, R^3 = H (85%)
b) R^1 = Et, R^2 = Me, R^3 = OMe (80%)
c) R^1 = R^2 = Me, R^3 = H (83%)
d) R^1 = R^2 = Me, R^3 = OMe (84%)
e) R^1 = R^2 = Et, R^3 = H (84%)
f) R^1 = R^2 = Et, R^3 = OMe (85%)

Scheme-25



109a-f **111** **112** **113** **114** **110a-f**

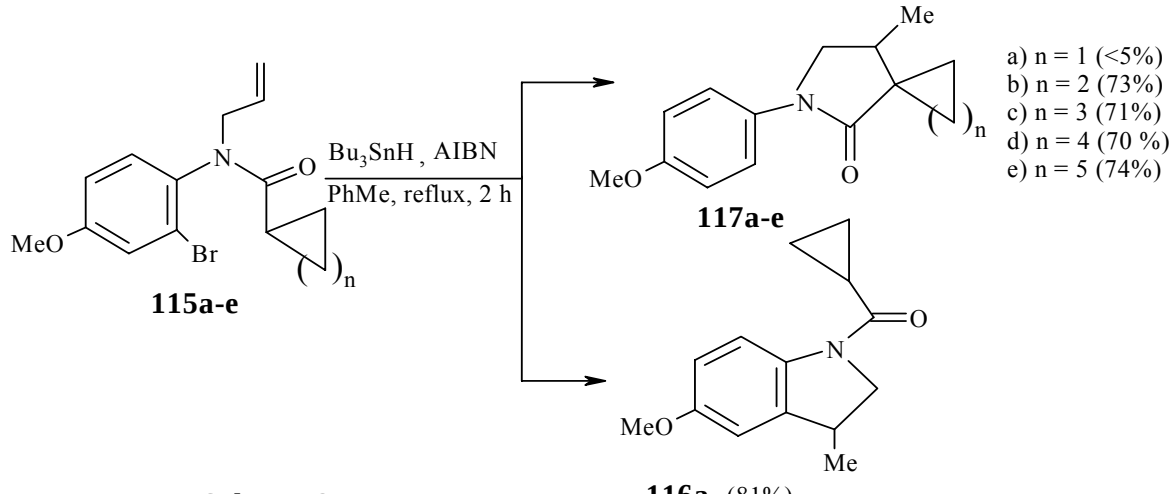
Scheme -26

One interesting feature of this reaction sequence is that the usual aerial oxidation in this type of cyclization with ^{n}Bu$_3$SnH is not observed and the dihydro compounds are isolated in excellent yield.

Several methods have been employed for the preparation of *γ*-lactams.[84,85] 2-Iodo-*N*-(prop-2-enyl)acetamides upon treatment with triethyl borane in boiling benzene afforded the 4-iodomethylpyrrolidin-2-ones in high yield through iodine atom transfer cyclization.[84] Formation of *γ*-lactam by the use of 5-*exo* or 5-*endo* cyclization of a carbamoylmethyl radical has received considerable attention by researchers and the interest continues to grow.[1,5,86] It is now well-established that in Bu$_3$SnH-

mediated radical cyclizations of ω-haloalkenes, iodine atom is a better leaving group than bromine or chlorine atom,[5] because of the lower C-I bond dissociation energy compared to C-Br or C-Cl bond.[5] Therefore, the result of using a chlorine atom as a leaving group for the radical cyclization of ω-haloalkenes is an increase in the amount of uncyclized reduction products. This trend was indicated in the Bu_3SnH-mediated 5-*exo* radical cyclization of *N*-cyclohex-2-enyl-α-haloacetamides.[88] The fact that an iodine atom is a better leaving group for Bu_3SnH mediated radical cyclization of ω-haloalkenes is not applicable to the 5-*endo-trig* cyclization of α-haloamides having an alkenic sp^2 carbon atom α to the amide nitrogen atom.

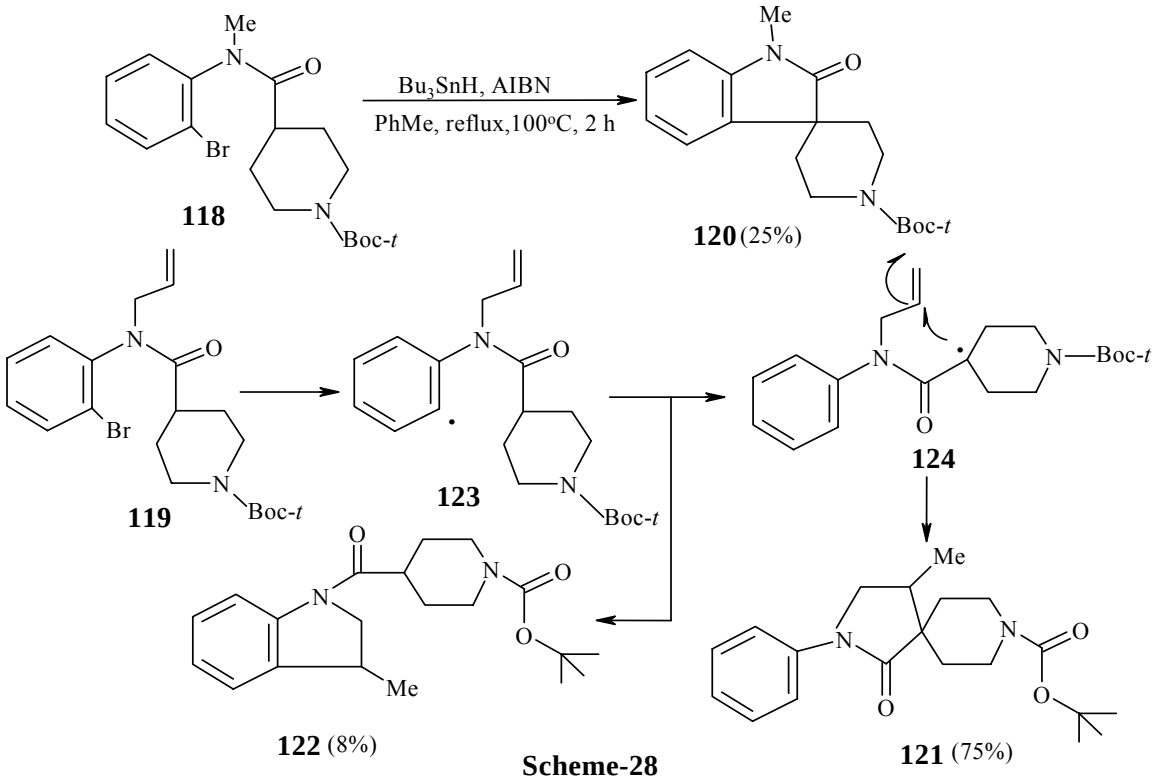
A novel synthesis of a series of spirocyclic pyrrolidin-2-ones was described by Storey.[89] Compounds (**115a-e**) were treated with tributyltin hydride under standard radical cyclization conditions and the spirocyclic pyrrolidin-2-ones (**117b-e**) were obtained in excellent yield. By examining the NMR spectrum of the crude cyclized products (**117b-e**) it was found that small amounts of product was also produced from direct cyclization of the aryl radical onto the allyl double bond. The major products (**117b-e**) were the result of [1,5]-hydrogen atom transfer followed by 5-*exo-trig* cyclization. The reaction of the cyclopropyl precursor (**115a**) gave <5% of the desired spirocyclic product (**117a**), and gave almost exclusively the dihydroindole (**116**) arising from direct cyclization of the aryl radical onto the allyl bond. This interesting observation is the result of the greater bond strength of a cyclopropyl C-H bond compared with the carbon-hydrogen bond strengths in the other substrates, which makes [1,5] hydrogen atom abstraction less efficient (**Scheme-27**).



Scheme-27

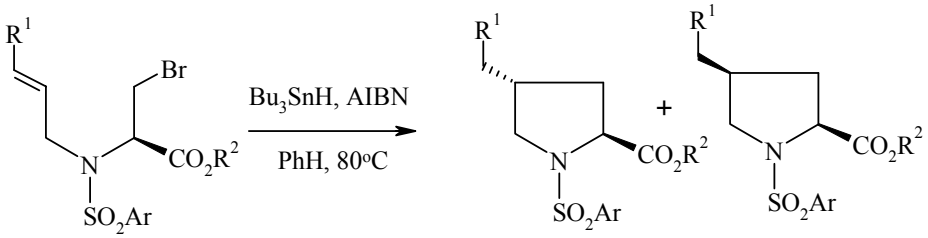
The reaction of compound (**118**) has been explored[90] in toluene solution with TBTH in the presence of AIBN at 100°C for 2 h to synthesize compound (**120**). The formation of compound (**120**) in the above case is difficult to rationalize, but there are several reported examples in the literature[91] relating to the formation of oxidation products during TBTH mediated reactions. Under similar reaction conditions compound (**119**) produced a mixture of two compounds (**121**) (75% yield) and (**122**) (8% yield). Reaction

of compound (**119**) to give **121** and **122** could be rationalized as follows. The initial radical (**123**) undergoes *exo*- cyclization followed by the abstraction of the newly formed radical by hydride to give **122**. Compound (**121**) on the other hand was formed by the rearrangement of **123** to the more stable radical (**124**) followed by *exo*- cyclization (**Scheme-28**).



Scheme-28

Basak *et al*. subjected[92] the *N*-arylsulphonyl-*N*-allyl-3-bromo-L-alanines (**125a-f**) to tributyltin hydride mediated radical cyclization to obtain enantiopure 4-substituted L-proline derivative **(126a-f**) and (**127a-f**) in good yield. The predominant product was the *trans* isomer (**126a-f**) and the reaction followed the



125a-f

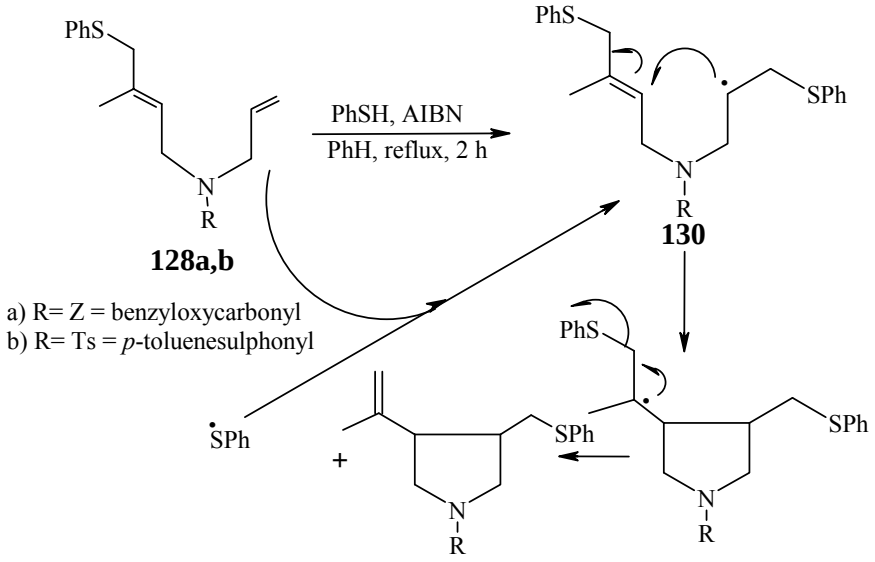
a) R^1 = H, R^2 = Bn, Ar = *p*-Tolyl
b) R^1 = H, R^2 = Bn, Ar = *p*-Nitrophenyl
c) R^1 = H, R^2 = Bn, Ar = *p*-Chlorophenyl
d) R^1 = H, R^2 = Bn, Ar = 2-Naphthyl
e) R^1 = H, R^2 = $CHPh_2$, Ar = *p*-Tolyl
f) R^1 = Ph, R^2 = Bn, Ar = *p*-Tolyl

126a-f	**127a-f**
126a:127a = 3:1	80%
126b:127b = 4:1	83%
126c:127c = 4:1	85%
126d:127d = 8:1	85%
126e:127e = 3:1	82%
126f:127f = 1.7:1	85%

Scheme-29

exclusive 5-*exo*-addition in all cases (**Scheme-29**).

The radical cyclization of the carbamate (**128a**) have been demonstrated[93] in the presence of 1 equiv. of thiophenol and 0.5 equiv. of AIBN in benzene under refluxing condition to produce a mixture of the *cis*- and *trans*-pyrrolidines (**129a)** having an isopropenyl group in 22% combined yield as an inseparable mixture. The same reaction with 2 equiv. of thiophenol furnished compound (**129a**) in 63% yield. The mechanism of the reaction is shown in (**Scheme-30**).



129. a) R = Z
b) R = Ts

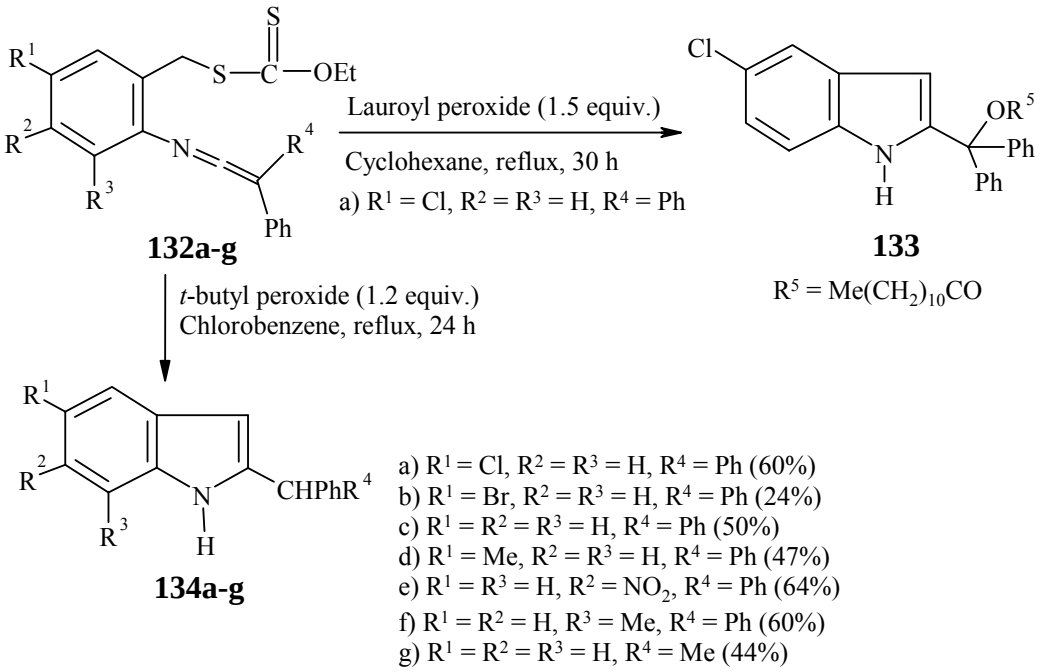
131

Substrate	PhSH (equiv.)	AIBN (equiv.)	Yield (%)
128a	1.0	0.5	22
128a	2.0	1.0	63
128a	0.2	0.2	16
128b	0.2	0.2	50

Scheme-30

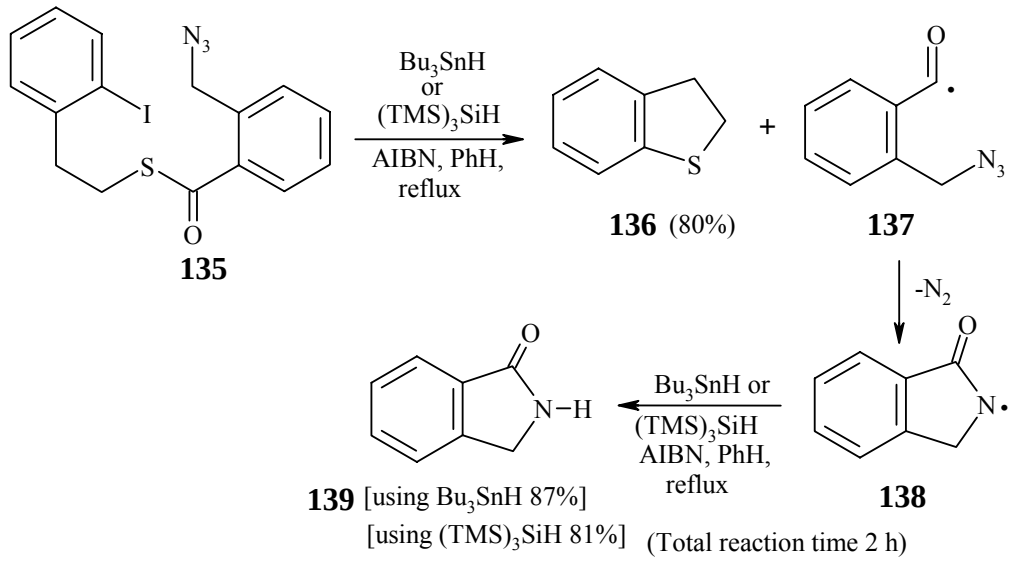
The first step of the reaction is the intermolecular addition of a phenylsulfanyl radical to the terminal olefin of **128**, producing thereby the carbon centered radical (**130**), and then ring closure to radical (**131**) followed by subsequent β-elimination leading to the isopropenylpyrrolidine (**129**) and sulfanyl radical which reacts with **128** to give back the radical (**130**).

A novel radical annulated synthesis of 2-alkylindoles based on the intramolecular addition of benzylic radicals onto the central carbon atom of ketenimine function following a 5-*exo-dig* cyclization was described very recently.[94] Here the radical cyclization of ketenimine (**132a**) was initiated by lauroyl peroxide in refluxing cyclohexane to furnish the indole containing lauroyloxy fragment (**133**) in 38% yield along with a small amount of 5-chloro-2-diphenylmethylindole (**134a**). On the other hand if the reactions of ketenimine (**132a**) was carried out in boiling chlorobenzene with stoichiometric amount of *t*-butyl peroxide, compound (**134a**) was obtained in 60% yield as the only product (**Scheme-31**).



Scheme-31

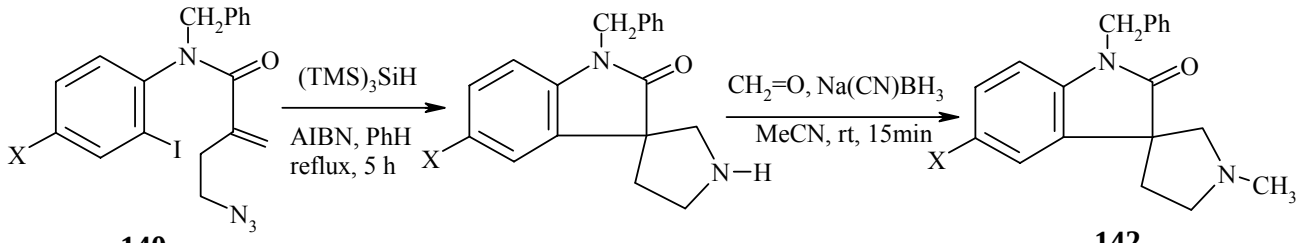
Benati *et al*. has shown[95] that aryl- and alkyl-derived azidoacyl radicals, generated from thiolesters by intramolecular homolytic substitution at the sulphur can undergo five- and six- membered cyclization onto the azido moiety to give the cyclized lactams. The thiolester (**135**) on treatment with Bu_3SnH or $(TMS)_3SiH$ and AIBN in refluxing benzene furnished the cyclized indolinone (**139**) in excellent yield. The formation of the product (**139**) may be explained by the generation of acyl radical (**137**) followed by intramolecular 5-*exo* cyclization onto the azido moiety producing the cyclized amidyl radical (**138**), which is then reduced by the tin hydride to give the product (**139**) (**Scheme-32**).



Scheme-32

The synthesis of spiropyrrolidinyloxindoles, horsfiline and coerulescine has been described[96] in which the key step was the tandem radical cyclization of iodoaryl alkenyl azides. The radical cyclization of 2-(2-azidoethyl)-*N*-benzyl-*N*-(2-iodo-4-methoxyphenyl)acrylamide (**140a**) by using $(TMS)_3SiH$ and AIBN in

refluxing benzene furnished 1-benzyl-5-methoxy-1*H*-spiro[indole-3,3′-pyrrolidin]-2-one (**141a**); and this was subjected to the *in situ* methylation to produce 1-benzyl-5-methoxy-1′-methyl-1*H*-spiro[indole-3,3′-pyrrolidin]-2-one (**142a**) in 60% yield. Similar protocol was also followed for the conversion of **140b** to**142b** (**Scheme-33**).



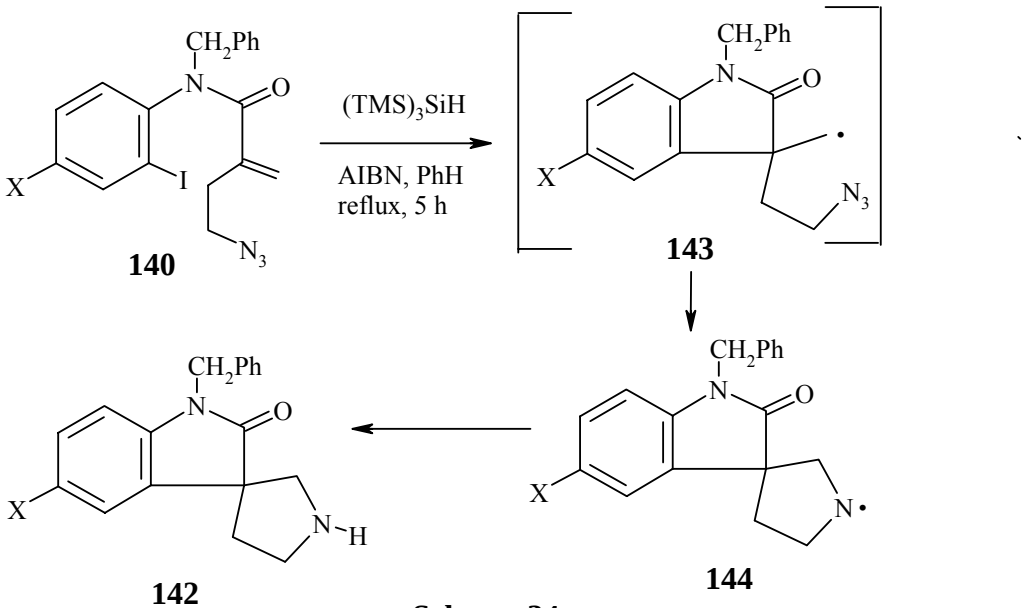
140 **141** **142**

a) X = OMe
b) X = H

a) X = OMe (60%)
b) X = H (63%)

Scheme-33

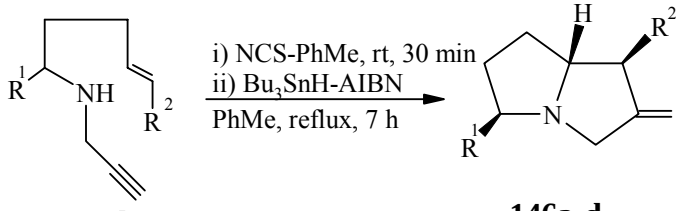
The mechanism for the conversion of **140** to **142** was depicted in (**Scheme-34**).



140 **143** **144** **142**

Scheme-34

Tandem cyclization of *N*-propargylaminyl radicals produced by *N*-chlorination of (*E*)-alk-4-enylamines (**145a-d**) followed by treatment with tributyltin radical in the presence of *n*-Bu_3SnH and catalytic AIBN, afforded 2-methylenepyrrolizidines[97] (**146a-d**) and the reaction is highly stereoselective (**Scheme-35**).



145a-d **146a-d**

a) R^1 = Me, R^2 = Pr (54%)
b) R^1 = Me, R^2 = Ph (63%)
c) R^1 = Ph, R^2 = Ph (43%)
d) R^1 = Me, R^2 = $Si(Et)_3$ (52%)

Scheme-35

Transition state (**A**) for the aminyl radical cyclization is found to be chair-like, in which R^1 possesses *pseudo-equatorial* position.[98] The first ring closure produces *trans*-2,5-disubstituted pyrrolidine intermediate (**B**), and this is then followed by 5-*exo* cyclization on to the C≡C bond efficiently to give pyrrolizidine intermediate (**C**) as a diastereomer. This then abstracts a hydrogen atom from tributyltin hydride to give the product **146** (**Figure 1**).

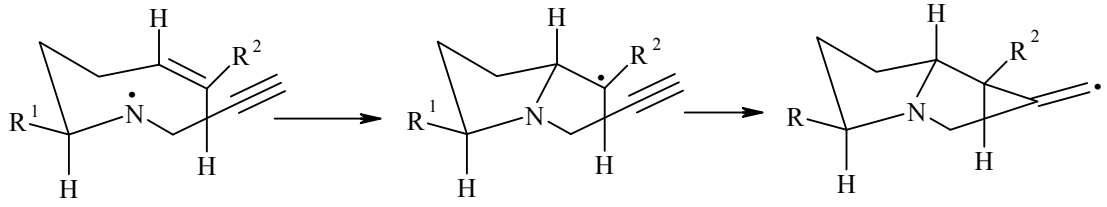
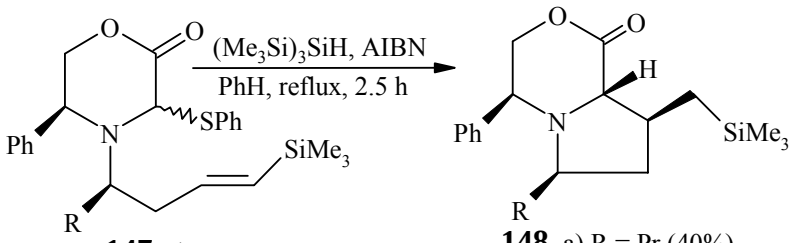


Figure 1

Recently Agami *et al*. carried out[99] the transformation of *β*–amino alcohols having a vinylsilane functionality **147** into bicyclic derivatives (**148**) *via* a diastereoselective 5-*exo-trig* radical cyclization. However the yield of **148c** may be increased to 40% by using triethylborane as initiator and tris(trimethylsilyl)silane as hydrogen donor in refluxing benzene (**Scheme-36**).

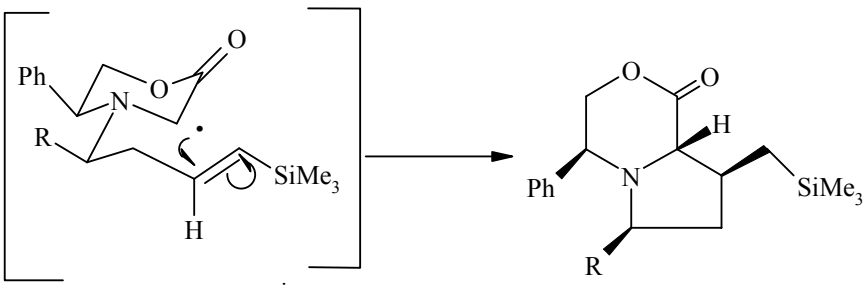


147 a) R = Pr
b) R = *i*-Pr
c) R = *t*-Bu

148 a) R = Pr (40%)
b) R = *i*-Pr (60%)
c) R = *t*-Bu (28%)

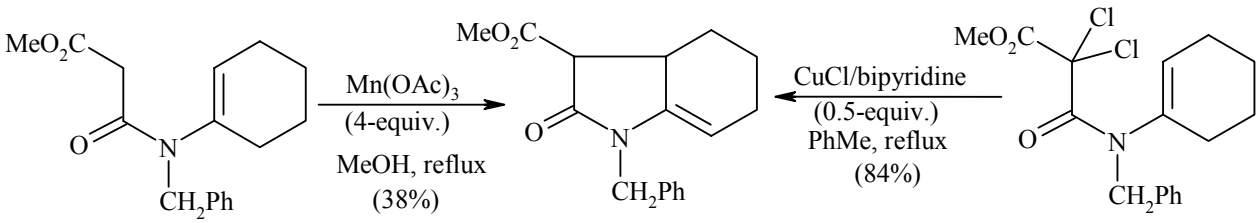
Scheme-36

It is important in this connection that two stereogenic centers are generated during these cyclizations. Here the radical reacts with the double bond of the vinyl silane moiety by assuming a chair-like transition state[100] according to an axial approach[101] in a relative *anti* position to both the phenyl group and the R substituent. The radical undergoes 5-*exo-trig* cyclization[102] and the chair-like transition state in which the vinyl silane adopts a pseudo equatorial position and this explains the absolute configuration of second center.



147 **148**

Radical cyclization of unsaturated organohalides[86,103] is very common for preparing 5-membered nitrogen heterocycles, and a variety of pyrrolidinones[104] have been prepared following favored 5-*exo-trig* pathway. Recently it was reported that the 5-*endo-trig* radical cyclization of haloenamides[105] also furnished pyrrolidinones. This cyclization is unusual in the sense that the initial carbamoylmethyl radical reacts to form a 5-membered rather than a 4-membered (or *β*-lactam) ring. The formation of *β*-lactam ring following the favored 4-*exo-trig* cyclization is generally observed when radical stabilizing (aromatic) groups are introduced on the enamide C=C bond.[106] Tributyltin hydride annulated 5-*endo* cyclizations have provided efficient approaches to substituted pyroglutamates.[46,107] It is very difficult to use tributyltin hydride as tin containing by-products are often difficult to remove and the cyclization leads to the reduction of C-halogen and C=C bonds. Under the circumstances Davies *et al*. have developed[108] a more straightforward and versatile approach in which the 5-*endo-trig* radical cyclization reaction of enamides with manganese(III) acetate or copper(I) chloride/bipyridine have been utilized to produce functionalized pyrrolidinones. Both of the reagents are cheaper, the metal by-products are more easily removed and a functional group (generally double bond or halogen atom) is introduced into the product after cyclization. The copper(I) mediated cyclizations are very efficient and bicyclic dienes can be isolated in >80% yield, while the corresponding manganese(III) reactions are generally more problematic, producing the dienes in lower yield (35–52%). One such reported example is shown in **Scheme-37**.



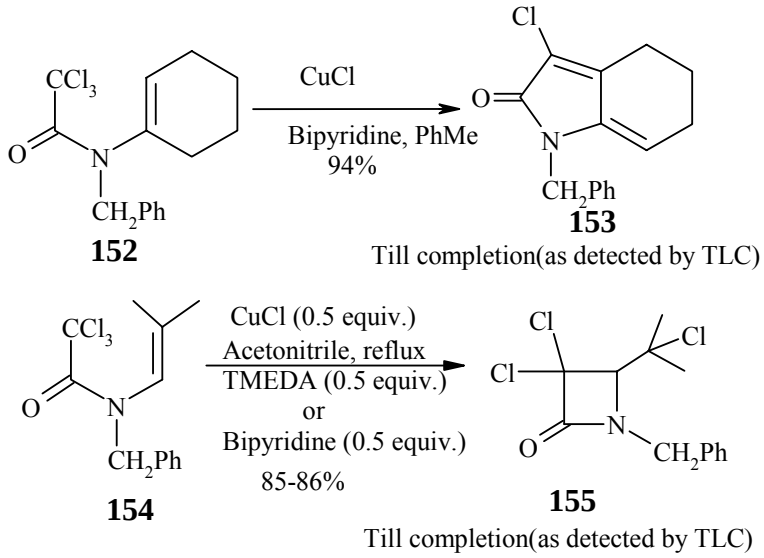
149 **151** **150**

Scheme-37

Bryans *et al*. carried out[109] the radical cyclization of a variety of haloenamides with copper(I) or ruthenium(II) complex. They observed that copper(I)/bipyridine reactions give predominantly *γ*-lactams *via* 5-*endo* route whereas *β*-lactams are mainly produced *via* 4-*exo* pathway by using dichlorotris-(triphenylphosphine)ruthenium(II) or copper(I)/TMEDA. Two such reported cases are shown in **Scheme-38**.

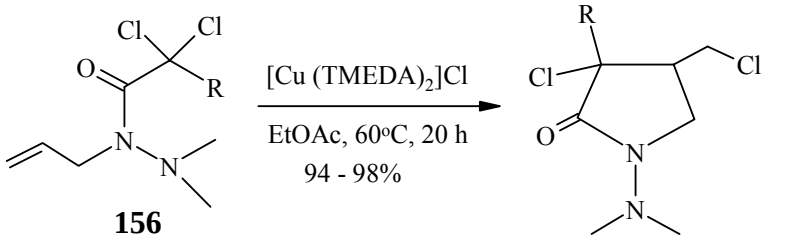
N-Allyl-*N,N*-dimethyl-2,2-dichlorohydrazides (**156a-f**) were found to react with CuCl/TMEDA in ethyl acetate to afford *N*-(dimethylamino)-2-pyrrolidinones (**157a-f**)[110] as a mixture of inseparable diastereomers (**Scheme-39**). The *trans* isomer for **157b** is formed preferentially. For **157a** and **157d-f** the *cis* isomers are predominant as the C-3 alkyl groups are bulkier compared to the chloro substituent at C-3.

Steric interactions are responsible for the C-3 chloro and C-4 chloromethyl groups to adopt a *cis* arrangement.



154

Scheme-38

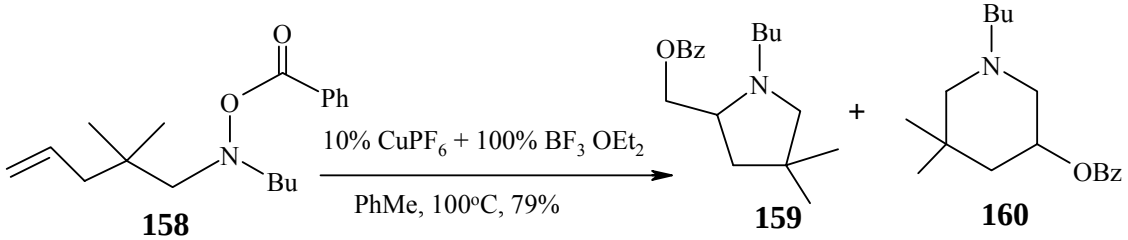


156

157 a) R = Me (97%)
b) R = H (17%)
c) R = Cl (94%)
d) R = Et (98%)
e) R = Pr (96%)
f) R = *i*-Pr (96%)

Scheme-39

Radical aminohydroxylation of double bonds has been developed to produce cyclic amino alcohols.[111] Benzoyloxyamine (**158**) in refluxing with 10% copper(I) acetate in THF furnished a mixture of 2-benzoyloxymethylpyrrolidine (**159**) and 3-benzoyloxypiperidine (**160**) in 3:1 ratio in 13% yield. However, the yield may be increased to 79% by using copper(I) hexafluorophosphate and 100% BF_3-etherate in toluene at 100°C (**Scheme-40**).



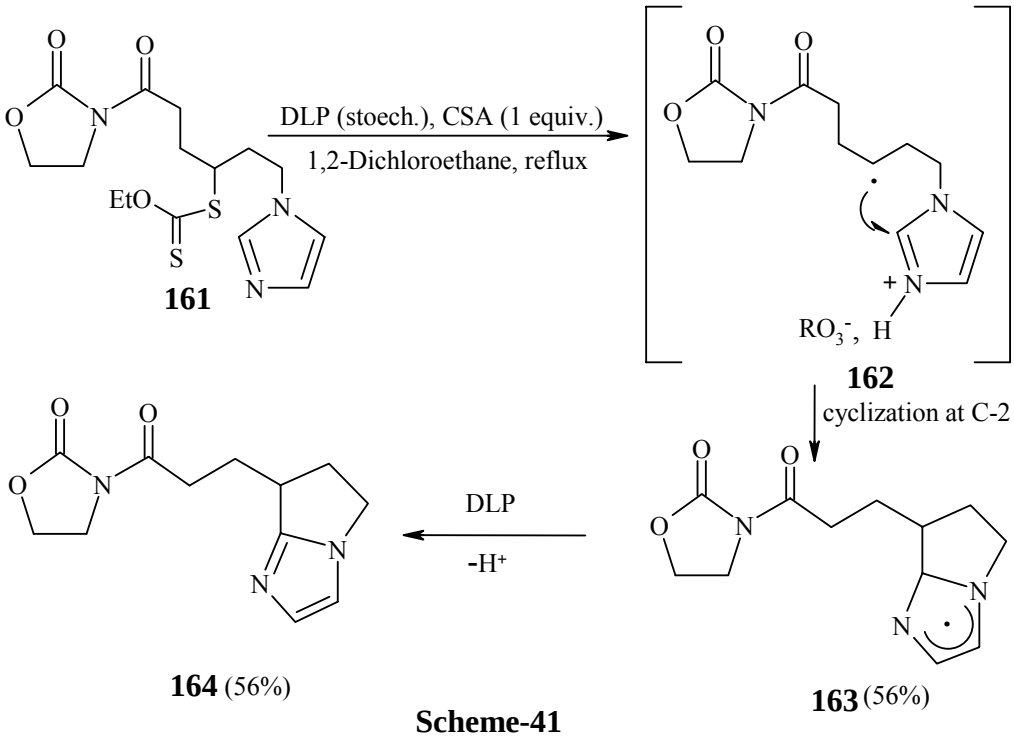
158 **159** **160**

(**159**:**160** = 3:1)

Scheme-40

Here the piperidine (**160**) must be formed *via* an unusual 6-*endo* radical cyclization. This surprising result might be related to the influence of the two-alkyl groups on the rotamer distribution in the substrate (*gem*-dialkyl effect)[112] or on the bond angles (Thorpe–Ingold effect).[113]

Zard *et al*. pointed out that the xanthate group in adduct (**161**) may be used to implement a radical cyclization on the imidazole ring.[114] When the xanthate adduct (**161**) was refluxed in 1,2-dichloroethane with 1 equivalent of camphorsulfonic acid (CSA) and followed by gradual addition of a stoichiometric amount of lauroyl peroxide, regioselective ring closure occurred at C-2 position of imidazole as shown in (**Scheme-41**). In the present instance, CSA played a double role by extremely activating and directing the cyclization to give pyrrolo[1,2-*a*]imidazole (**164**) in 56% yield.



Scheme-41

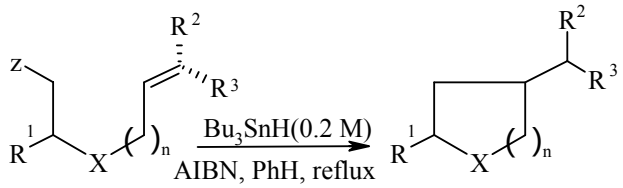
γ-Lactams have been prepared by several methods.[84,85] The formation of heterocycles by tinhydride mediated radical cyclization is often practical.[115,116] A general route to *γ*-lactones has been developed by Stork[117-119] and Ueno[120-122] and this has been increasingly applied in the synthesis.[123-125]

The synthesis of tetrahydrofurans by radical cyclization of bromoacetals and bromoketals is very common. Srikrishna *et al*. have utilized[126] the tributyltin hydride annulated radical cyclization reaction to produce 2-alkoxy-4-methylenetetrahydrofuran from the suitable bromo acetal. Srikrishna *et al*. also reported[127] the radical cyclization reaction of various bromo acetal followed by aromatization to produce 2,3,5-tri- and 2,3,4,5-tetrasubstituted furans respectively.

It was also observed[128] that the bromo ketal, 3-[(2-bromo-1-methoxy-1-phenyl)ethoxypropyne when treated with tri-*n*-butyltin chloride and $Na(CN)BH_3$ in the presence of catalytic amount of AIBN for 30 min furnished a mixture of the mixed ketal and 3-methylene-5-phenyltetrahydrofuran, in 87% yield.

Aromatization with *p*-TSA produced the furan (38%) and the tetrahydrofuran (47%). Radical cyclization reaction of bromoketal for a longer time (3 h) furnished the tetrahydrofuran in 83% yield. Tributylchlorostannane acts as a Lewis acid in the presence of sodium cyanoborohydride in the regioselective reductive demethoxylation of dimethyl and mixed ketals.[129] In this connection it is to be noted that only demethoxylated products were obtained in case of mixed ketals and no reductive cleavage was observed in case of cyclic ketals.

Beckwith *et al*. pointed out[130] the Bu_3SnH prompted radical cyclization of various acyclic bromoacetals (**165a-j**). It was observed that radicals obtained from **165a-e** underwent 1,5-*exo* cyclization to furnish *cis*-



165a-j **166a-j**

a) R^1 = OEt, R^2 = R^3 = H, n = 1, X = O, Z = Br
b) R^1 = OAc, R^2 = R^3 = H, n = 1, X = O, Z = Br
c) R^1 = OEt, R^2 = H, R^3 = CH_2OH, n = 1, X = O, Z = Br
d) R^1 = OEt, R^2 = H, R^3 = Ph, n = 1, X = O, Z = Br
e) R^1 = OEt, R^2 = R^3 = $CH_2(CH_2)_3CH_2$, n = 1, X = O, Z = Br
f) R^1 = OEt, R^2 = R^3 = H, n = 2, X = O, Z = Br
g) R^1 = CH_2OH, R^2 = R^3 = H, n = 1, X = O, Z = Br
h) R^1 = Me_3SiCH_2, R^2 = R^3 = H, n = 2, X = O, Z = Br
i) R^1 = *i*-Pr, R^2 = R^3 = H, n = 1, X = O, Z = SePh
j) R^1 = OEt, R^2 = R^3 = H, n = 1, X = CH_2, Z = HgCl

Reaction conditions:

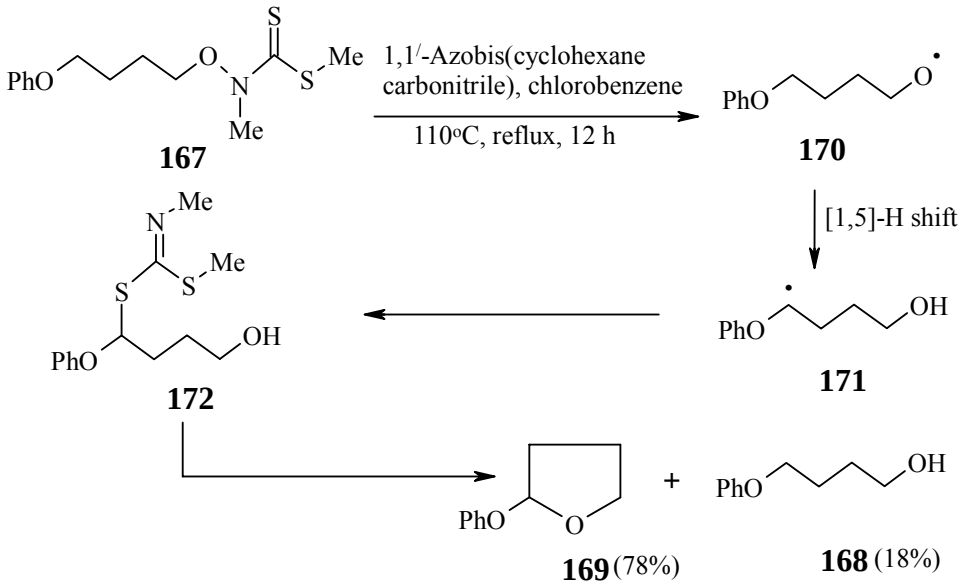
A : Bu_3SnH (0.2M), PhH, AIBN, reflux
B : Bu_3SnH (0.2M), pentane, $(Bu^tON)_2$
C : Bu_3SnH (syringe pump), PhH, AIBN, reflux
D : Bu_3SnH (0.2M), PhH, AIBN, photolysis
E : Bu_3SnH (0.07M), PhH, AIBN, reflux
F : Bu_3SnH (0.02M), PhH, AIBN, reflux
G : $Na(OMe)_3BH$, CH_2Cl_2

Precursor	Method	temp (°C)	Product	C*is/Trans*	Yield (%)
165a	A	80	166a	4.7	12
165a	B	40	166a	5.8	61
165b	B	40	166b	3.5	48
165b	C	80	166b	1.7	16
165c	A	80	166c	2.1	44
165c	D	ca. 20	166c	2.7	71
165d	A	80	166d	2.1	44
165d	B	40	166a	2.7	66
165e	A	80	166e	1.6	61
165f	E	80	166f	0.36	50
165g	B	40	166g	0.2	72
165h	B	40	166h	2.2	84
165i	F	80	166i	0.2	50
165J	G	20	166j	1.1	-

Scheme-42

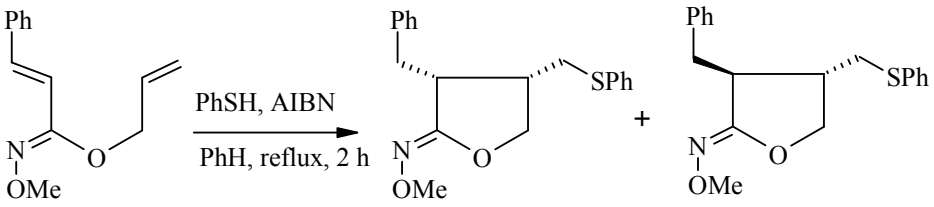
2,4-disubstituted tetrahydrofurans. From the stereochemical point of view these results are reverse to the usual steric rules for cyclization of substituted acyclic alkenyl radicals.[102,98,131,132] However, these results were in good agreement with stabilization of transition state stereochemistry by anomeric effects. The preferential formation of the *trans* product by 1,6-*exo* cyclization of the radical obtained from **165f** was contrary to the expectation. The radicals generated from **165g-j** in which no anomeric interactions are possible follow the usual steric guidelines[102,98,131,132] (**Scheme-42**).

One of the methods for the synthesis of tetrahydrofurans by radical cyclization is 5-*exo* cyclization of alkoxy radicals. A novel method for the generation of alkoxy radicals has been introduced[133] from *N*-alkoxydithiocarbamates (**167**) by employing different conditions. Radical reaction of compound (**167**) with Bu_3SnH/AIBN in refluxing benzene for 3 h furnished 4-phenoxy-1-butanol (**168**) in 95% yield. Alkoxy radical was also generated under tin free condition[134,135] using PhSH as a radical mediator in the presence of AIBN in refluxing benzene and under this condition the alcohol (**168**) was obtained in 55% yield along with the unreacted starting material (**167**) in 43% yield. However, the reaction of **167** with 1,1/-azobis(cyclohexanecarbonitrile) (0.1equiv.) as an initiator in refluxing chlorobenzene for 12 h resulted the compound (**169**) in 78% yield along with the direct reduction product (**168**) in 18% yield (**Scheme-43**).



Scheme-43

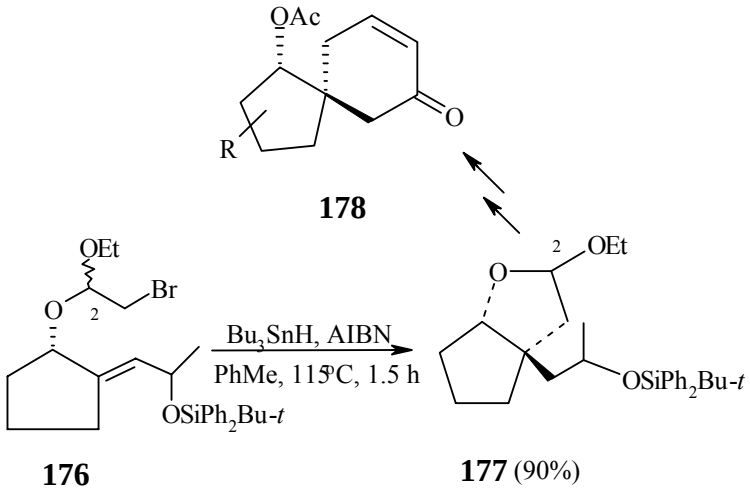
A combination of sulfanyl radical addition–cyclization of dienes connected with hydroximates followed by conversion of the resulting cyclic hydroximate to the lactone was proved to be an unique method for the construction of α,β-disubstituted γ-lactones.[136] The radical cyclization of Z-hydroximates (**173**) in the presence of thiophenol and AIBN furnished a mixture of cyclized *cis*- and *trans*-products (**174**) and (**175**) respectively in 82% combined yield. However no such cyclized product was obtained from the corresponding (*E*)-hydroximates (**Scheme-44**).



173 (Z) **174** (*cis*) **175** (*trans*)

Scheme-44

Clive *et al*. have described[137] a method for making spiro enones of the type (**178**), from bromoacetals (**176**), in such a way that the stereochemistry at the spiro center is controlled by the stereochemistry of an adjacent hydroxyl group. In this case the bromoacetals (**176**) were cyclized by rapid heating (115°C) with a mixture of Bu_3SnH and AIBN in PhMe to furnish the cyclized product (**177**) following 5-*exo*-*trig* pathway (**Scheme-45**).

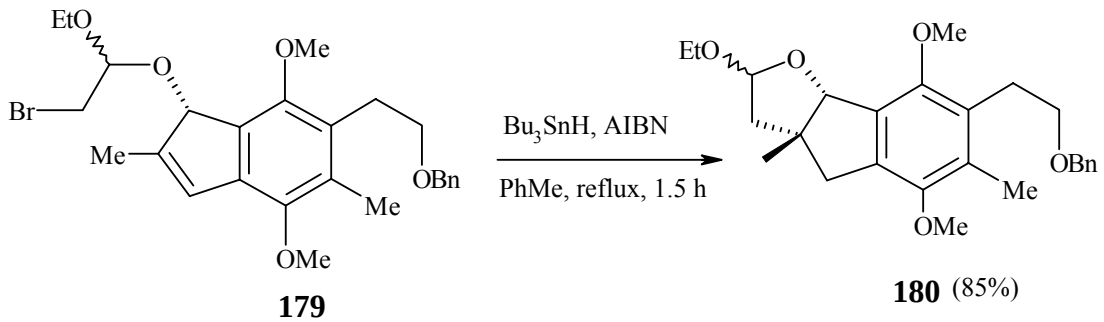


178

176 **177** (90%)

Scheme-45

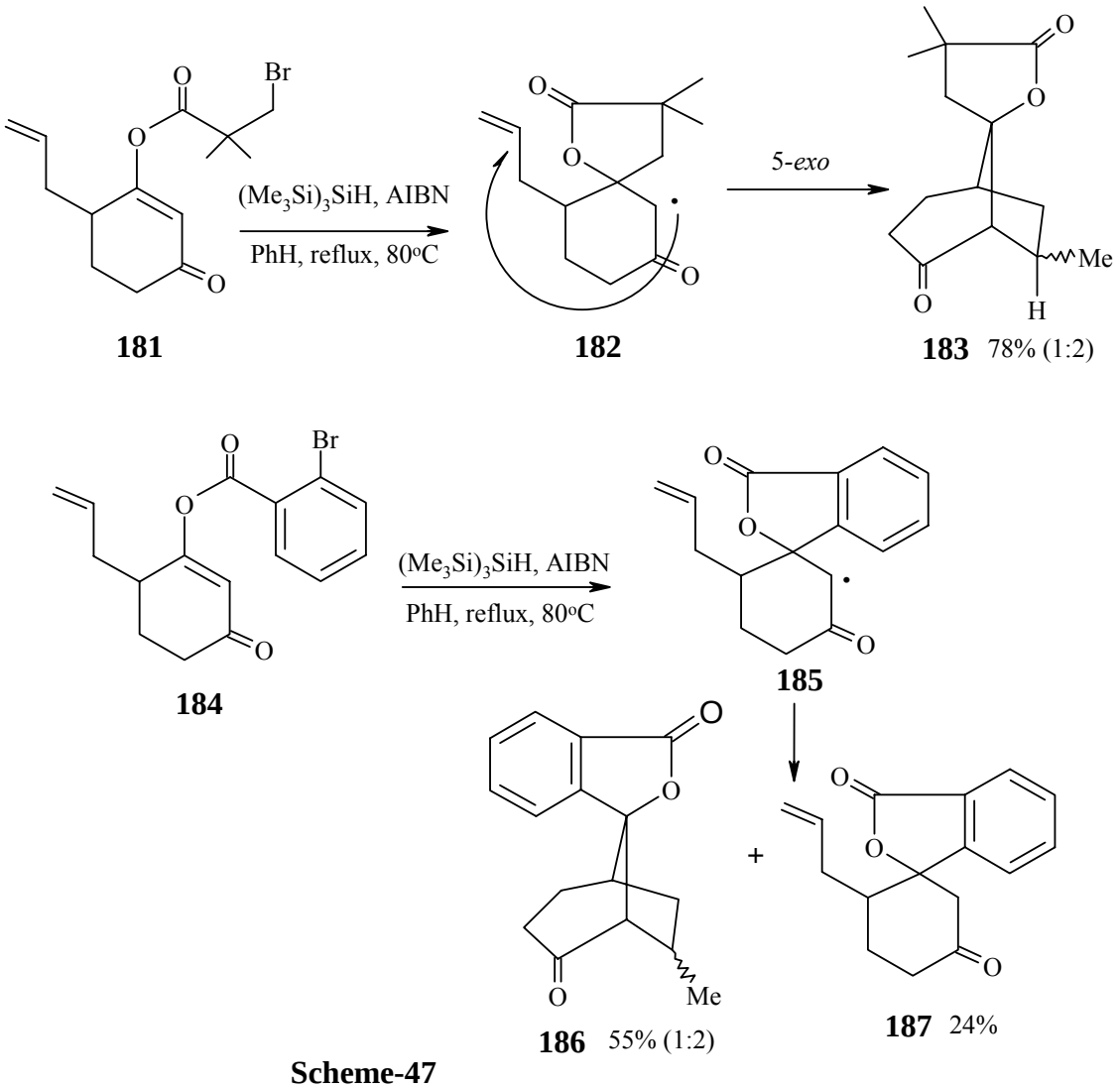
Clive *et al*. have devised[138] a synthetic route for the synthesis of (+)-puraquinonic acid, in which one of the steps involved the radical cyclization of Stork bromoacetals (**179**) in the presence of Bu_3SnH and AIBN in refluxing toluene to afford compound (**180**). Best results (85%) were obtained when the stannane and the initiator were added in one portion. It is important to note that the cyclization must occur with *cis* ring fusion[139] (**Scheme-46**).



179 **180** (85%)

Scheme-46

Several new bridged spiro lactones can be prepared by tandem radical cyclizations of α,β-unsaturated cyclohexanone derivatives bearing an appropriate allyl side chain *via* double radical cyclization of enol ester radical.[140] In case of $(Me_3Si)_3SiH$ mediated radical cyclization of enol esters (**181**) and (**184**) the initial radicals undergo double cyclizations, first by intramolecular Michael addition to form stabilized intermediate radicals (**182**) and (**185**), followed by 5-*exo* cyclization onto the alkene to give bridged spiro lactones (**183**) and (**186**). Reaction of compound (**181**) produces **183** as a mixture of two diastereomers, while the reaction of **184** furnishes dicyclization product (**186**) along with monocyclization product **187** (**Scheme-47**).

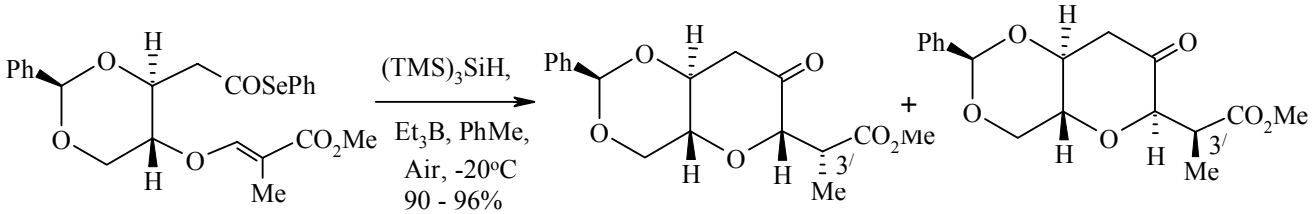


Scheme-47

Acyl radicals participate in a wide range of inter and intramolecular reactions and hence they are very useful synthetic intermediates.[141] Few years ago Evans *et al*. observed[142] that treatment of the acyl selenide (**188**) furnished the cyclic ethers (**189/190**) in 90–96% yield, with 33:1 diastereoselectivity (by HPLC) at C-3′ favoring **189** (**Scheme-48**).

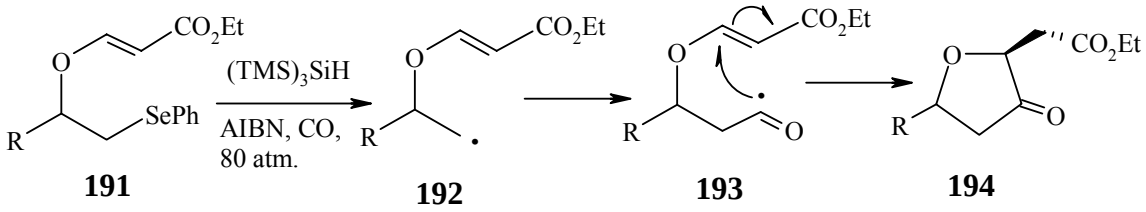
Acyl radicals have also been used in the synthesis of 5-, 6- and 7-membered oxygen heterocycles. Substituted tetrahydrofuran-3-ones can be easily prepared[143] from *o*-vinylated β-hydroxyalkylphenyl

chalcogenides *via* carbonylation or reductive cyclization. The initially formed alkyl radical (**192**) is carbonylated using high pressure CO to give an acyl radical (**193**), which facilitates 5-*exo-trig* cyclizations onto vinyl ethers with electron-withdrawing groups (**Scheme-49**).



188 **189** **190**

Scheme-48

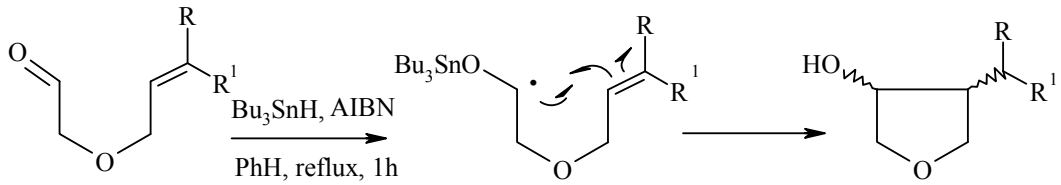


191 **192** **193** **194**

a) R = Bn (88%, dr 9:1)
b) R = $BnOCH_2$ (42%, dr 7:1)
c) R = Ph (64%, dr 8:1)

Scheme-49

Recently Bu_3SnH mediated radical cyclization of unsaturated organohalides has attracted considerable interest to synthetic organic chemists.[86,103,144] Under mild, neutral reaction conditions a large number of 5- and 6-membered rings may be prepared by employing this methodology. Exposure of the aldehyde (**195a,b**) under normal radical cyclization condition leads to the formation of hydroxy tetrahydrofurans (**197a,b**)[145] in 59–64% yield. These reactions are expected to proceed *via* 5-*exo-trig* cyclization of the intermediate *o*-stannylketyls (**196a,b**) followed by hydrogen atom transfer from tributyltin hydride and hydrolysis of the tributyltin alkoxide on aqueous work up (**Scheme-50**).



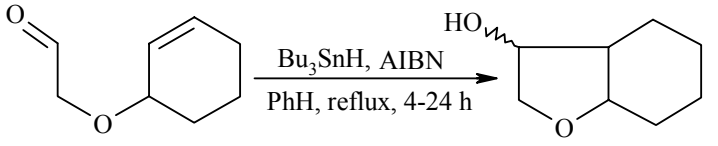
195 a) R = Ph, R^1 = H
b) R = R^1 = Me

196a, b

197 a) 59%
b) 64%

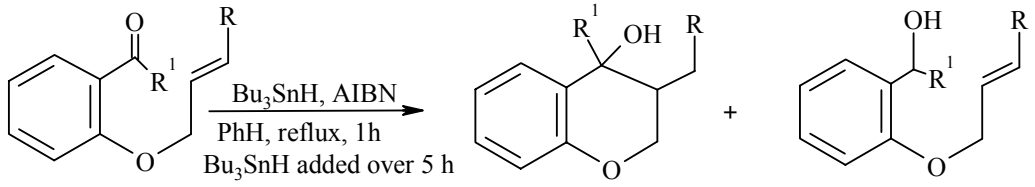
Scheme-50

The radical cyclization of cyclohexenyl aldehyde **(198**) afforded octahydrobenzofuran (**199**)[145] in 73% yield.



198 **199** (73%)

The cyclization of the benzaldehyde derivative (**200a**) furnished chromanol (**201a**), as a 5.5:1 mixture of separable *trans-cis* isomers in 78% yield. The formation of a more stable *o*-stannyl ketyl radical is the result of the introduction of a benzene ring and it has a marked effect on both the efficiency and stereoselectivity of the 6-*exo-trig* cyclization. This explains the predominance of the thermodynamically more stable *trans*- isomer of **201a** (**Scheme-51**).



200 **201** **202**

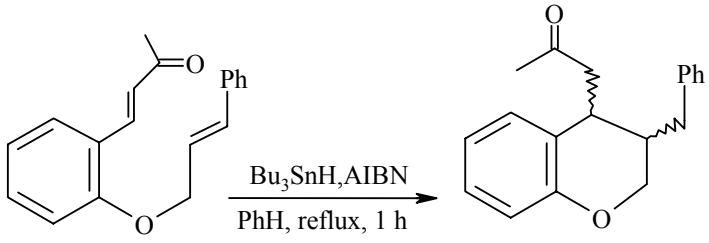
200 a) R = Ph, R¹ = H
b) R = R¹ = H
c) R = Ph, R¹ = Me

201 a) 78% (*trans:cis* = 5.5:1)
b) 24% (*trans:cis* = 5:1)
c) 82% (*trans:cis* = 4.2:1)

202 a) 0%
b) 62%
c) 0%

Scheme-51

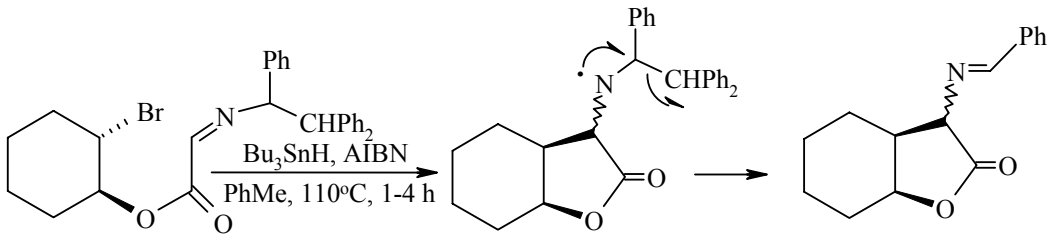
The use of an allylic *o*-stannyl ketyl radical cyclization to form chroman (**204**) as a 2:3:1 mixture of diastereomers by the 6-*exo-trig* cyclization of the diene (**203**) was also reported[146] (**Scheme-52**).



203 **204** (50%)

Scheme-52

Clive *et al*. reported[147] the Bu_3SnH mediated radical cyclization reaction of *trans*-2-bromocyclohexyl-[*N*-(1,2,2-triphenylethyl)formimidoyl]formate (**205**). The imino ester (**205**) was so constituted that the initial radical cyclization product (**206**) could lead directly to an imine (**206**→ **207**), (**Scheme-53**).

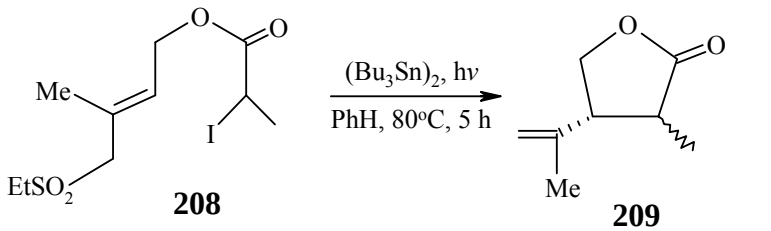


205 **206** **207**

Scheme-53

Recently three different routes have been investigated for the stereoselective synthesis of botryodiplodin.[148] The intramolecular allylation of acetals was found to be unsatisfactory due to unstable intermediates and poor stereocontrol. Zard intramolecular radical allylation of a 2-iodopropionate

derivative allows the development of an expeditious synthesis of racemic botryodiplodin. The iodide (**208**) was irradiated with a sun lamp in the presence of a catalytic amount of hexabutylditin. The cyclization became efficient at 80 ^{o}C and lactone (**209**) was isolated in 63% yield as a *trans* / *cis* (60:40) mixture of isomers (**Scheme-54**).

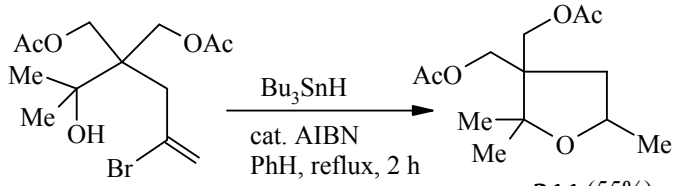


208 **209**

63% (*trans*/*cis* = 60:40)

Scheme-54

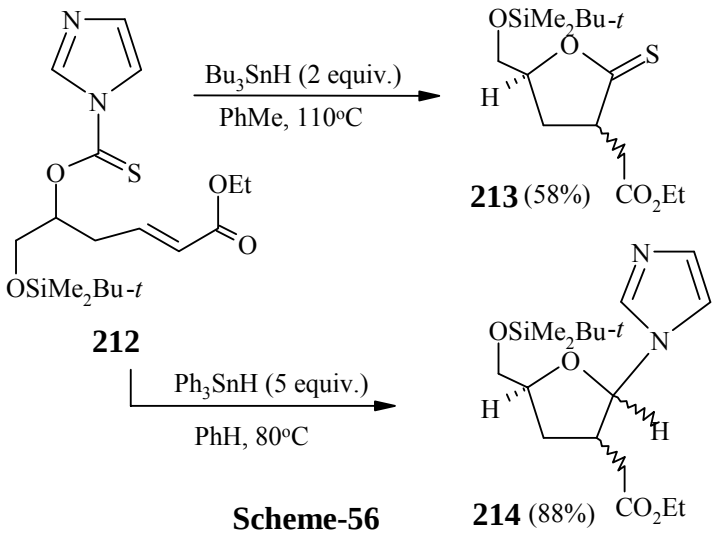
Recently, Yokota *et al*. has achieved[149] the tri-*n*-butyltin hydride mediated radical cyclization of hydroxy-vinyl bromide (**210**) *via* 5-*exo*-*trig* cyclization of alkoxy radical and it is thought to be produced by unusual [1,5]-hydrogen shift from hydroxyl group to vinyl radical to generate an unusual furan (**211**) in 55% yield as the major product (**Scheme-55**). Similar results were also obtained by using primary and secondary alcohols as substrates. The conformation of the carbon chain is controlled by the presence of the quaternary carbon center at the *β*–position to hydroxyl group.



210 **211** (55%)

Scheme-55

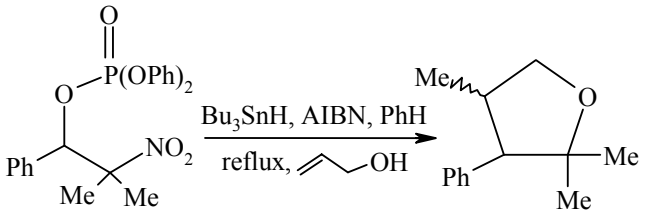
Thiolactone (**213**) (*cis*:*trans* = 2.1:1.0) was produced[150] in 58% yield by Bu_3SnH mediated radical cyclization reaction of a simple carbohydrate derived imidazole thioate (**212**). However, when a dilute solution of the substrate (**212**) in benzene was added to an excess of Ph_3SnH at 80^{o}C (reverse addition), the immediate result was the formation of an imidazole glycoside (**214**) in 88% yield (**Scheme-56**).



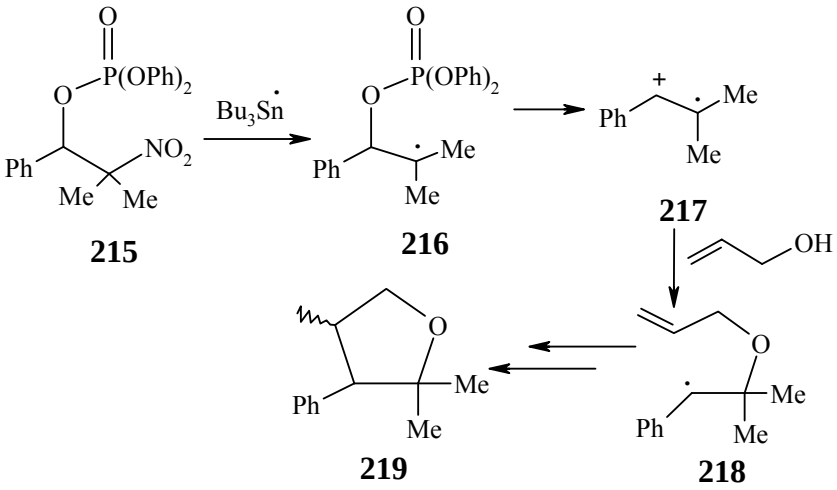
212 **213** (58%) **214** (88%)

Scheme-56

The diphenyl phosphate of the type (**215**) was synthesized[151] and then it was subjected to reflux with tributyltin hydride in 3:1 mixture of benzene and allyl alcohol. The immediate result was the formation of (1:10) *trans*: *cis* mixture of 2,2,4-trimethyl-3-phenyltetrahydrofuran (**219**). The reaction sequence is depicted in **Scheme-57**.

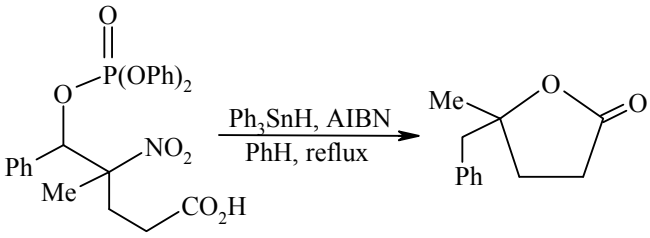


215 **219** (90%)
(*trans*:*cis* = 1:10)



Scheme-57

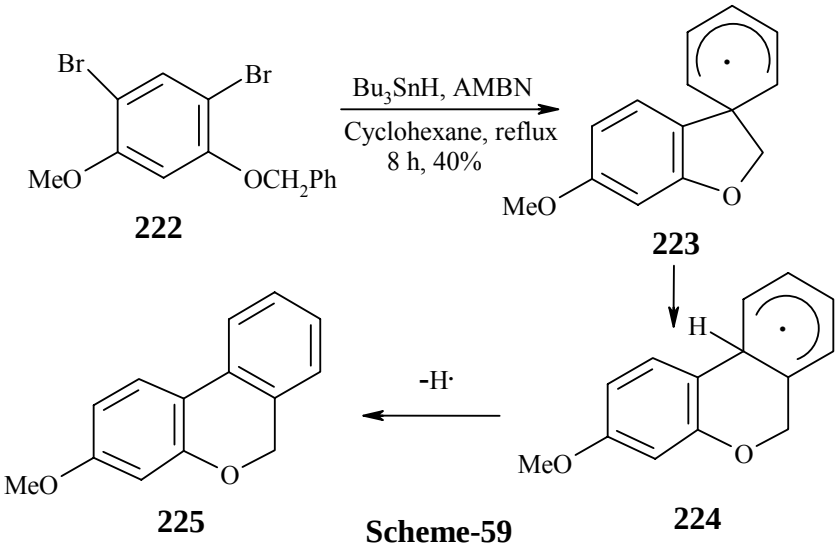
The formation of γ-lactone (**221**) was also achieved in 90% yield by refluxing the phosphorylated nitro acid (**220**) with triphenyltin hydride and AIBN in benzene[151] (**Scheme-58**).



220 **221** (90%)

Scheme-58

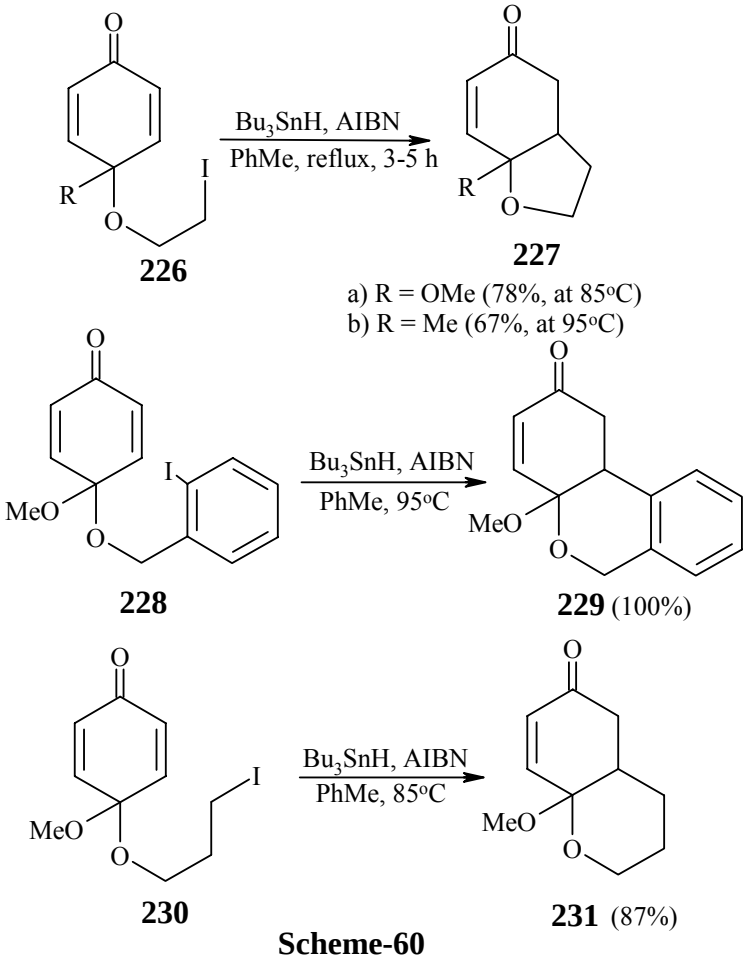
Cyclization of aryl radicals onto a second ring is commonly used and this protocol has been used for the synthesis of benzochromene (**225**).[152]The cyclization of aryl radical obtained from **222** produces the spiro intermediate (**223**) *via* a 5-*exo* cyclization and this then undergoes neophyl rearrangement to give the 6-*endo* product (**224**). The lost hydrogen atom is abstracted by a species derived from the initiator AMBN [azo-bis(methylisobutyronitrile)] to afford the cyclized benzochromene (**225**) (**Scheme-59**).



222 **223** **224** **225**

Scheme-59

Recently, Clive *et al*. have utilized[153] radical cyclization reaction in some of the cross-conjugated dienones, which are readily available from phenols. Here some reported cases are shown below (**Scheme-60**).



226 **227**

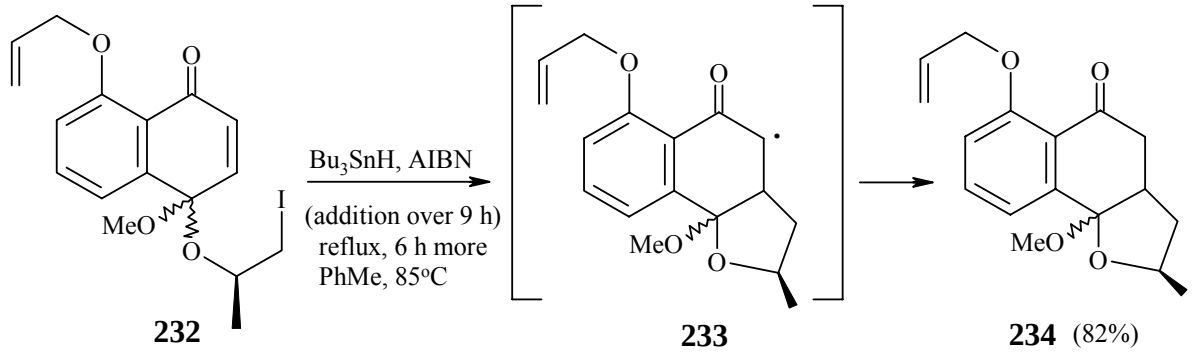
a) R = OMe (78%, at 85°C)
b) R = Me (67%, at 95°C)

228 **229** (100%)

230 **231** (87%)

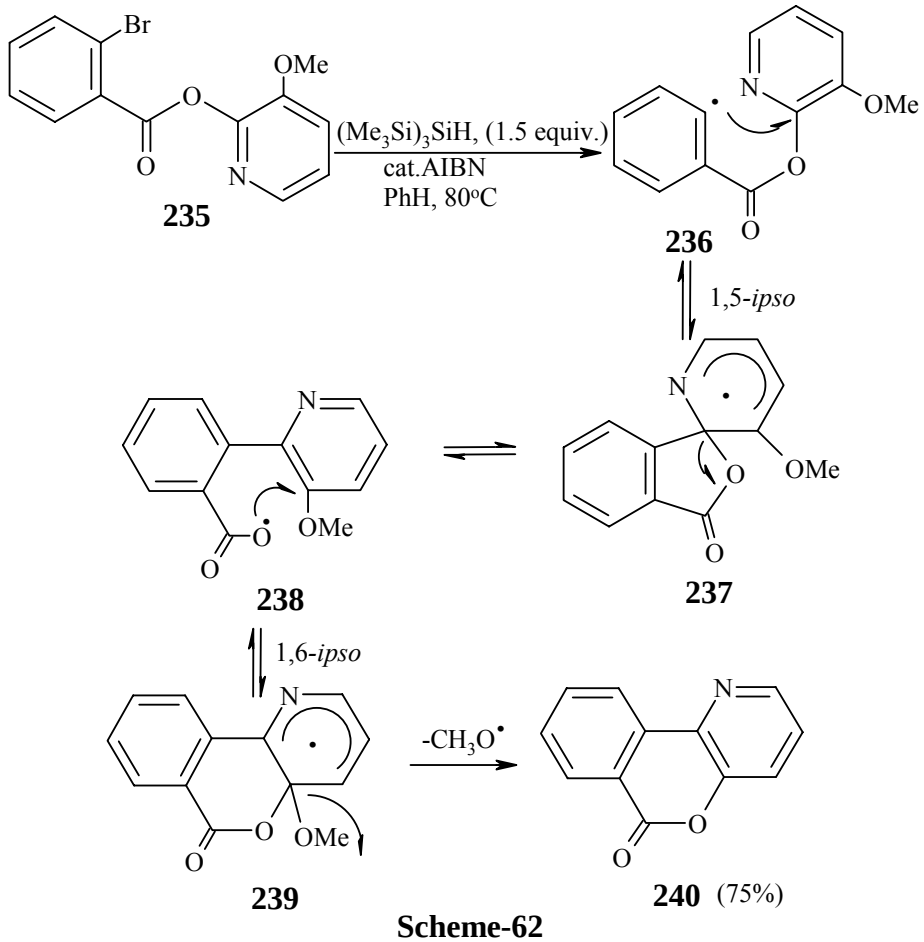
Scheme-60

Clive *et al*. have demonstrated[154] the synthesis of (+)-nocardione A, in which the key step was the radical cyclization of the enone (**232**) under standard condition to furnish the diastereomeric furans (**234**) in 82% yield *via* intermediate radicals (**233**) (**Scheme-61**).



Scheme-61

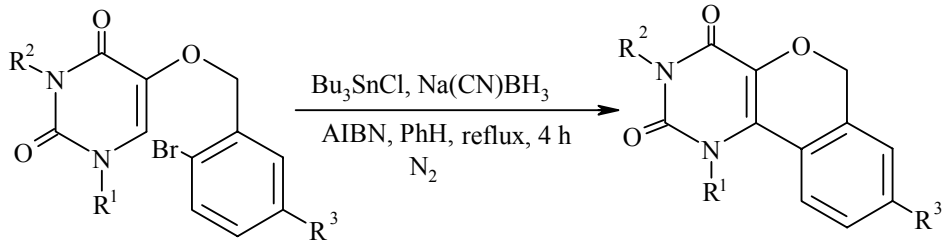
Intramolecular homolytic *ipso* substitution have already been used for the preparation of benzo-fused ring systems like phenanthridinones[57,91] and benzochromenes.[152,155] Here Zhang *et al*. achieved a novel double *ipso* substitution process for the synthesis of azabenzoisocoumarins.[80] In this case the initial radical (**236**) generated from the radical precursor (**235**) underwent 1,5-*ipso* substitution by the radical attack at 2-position of the pyridine ring to produce the carbonyloxy radical (**238**). This then underwent a second 1,6-*ipso* substitution to displace the methoxy group to furnish 10-oxa-4-azaphenanthren-9-one (**240**). The yield of the rearrangement product (**240**) was decreased to <10% in absence of the methoxy group and this suggests the important role of methoxy group in the promotion of the double *ipso* rearrangement (**Scheme-62**).



Scheme-62

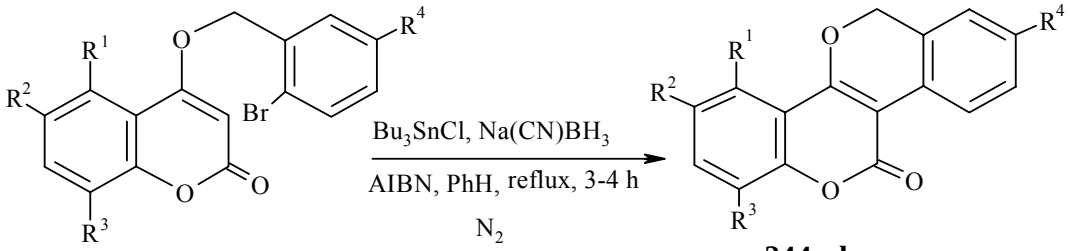
It is important to note that the oxime ethers connected with either an aldehyde or a ketone *via* a nitrogen atom smoothly underwent[156] stannyl radical addition-cyclization in the presence of tributyltin hydride and AIBN to give five and seven membered *cis*- and *trans*- heterocyclic amino alcohols of which the *trans* isomers were major products.

Recently we have reported[157] the regioselective synthesis of 1*H*,3*H*,6*H*[2]benzopyrano[4,3-*d*]pyrimidin-2,4-diones (**242a-f**) (75-85%) and 12*H*-benzopyrano[3,2-*c*][1]benzopyran-5-ones (**244a-h**) (70-85%) respectively by radical cyclization reactions. The starting materials 5-(2′-bromobenzyloxy)-pyrimidin-2,4-diones (**241a-f**) or 4-(2′-bromobenzyloxy)benzopyran-7-ones (**243a-h**) were separately refluxed in benzene under nitrogen atmosphere with tri-*n*-butyltin chloride and sodium cyanoborohydride in the presence of a catalytic amount of azobisisobutyronitrile (AIBN) for 3-4 h to give cyclic product (**242a-f**) or (**244a-h**) respectively (**Scheme-63**).



241a-f **242a-f**

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

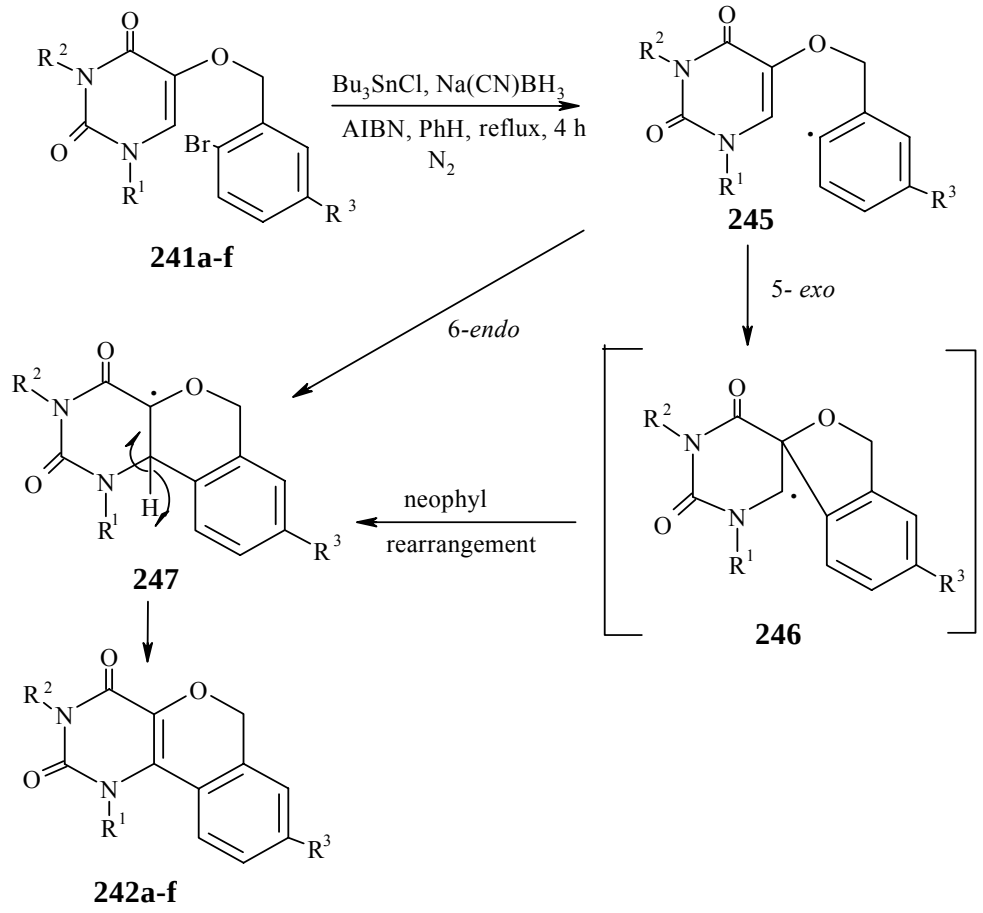


243a-h **244a-h**

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

Scheme-63

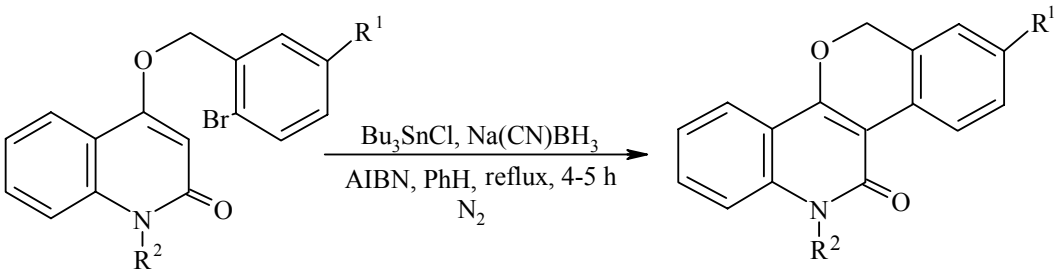
The exact reason why the 6-*endo* cyclization product is exclusively formed is not clear at present. But the formation of products (**242a-f**) from **241a-f** may be explained by the generation of an aryl radical (**245**). Subsequent 5-*exo* cyclization may give spiroheterocyclic radical[82] (**246**) (not isolated) followed by neophyl rearrangement[83] to give the more stable intermediate radical (**247**) (benzylic radical) or by a 6-*endo* route directly to give the intermediate radical (**247**) which then rearomatises to yield the products (**242a-f**) by an unknown mechanism which is usual for this type of synthetic sequence, *i.e*. an oxidation step in *n*-Bu_3SnH mediated cyclizations.[42,86b,158] Similar mechanism is also operative for the formation of products (**244a-h**) from **243a-h** (**Scheme-64**).



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

Scheme-64

Recently we also extended our efforts[159] in the regioselective synthesis of 2*H*-benzopyrano[3,2-*c*]quinolin-7(8*H*)-ones (**249a-f**) by Bu_3SnH mediated radical cyclization of 4-(2′-bromobenzyloxy)quinolin-2-(1*H*)-one derivatives (**248a-f**) (**Scheme-65**).



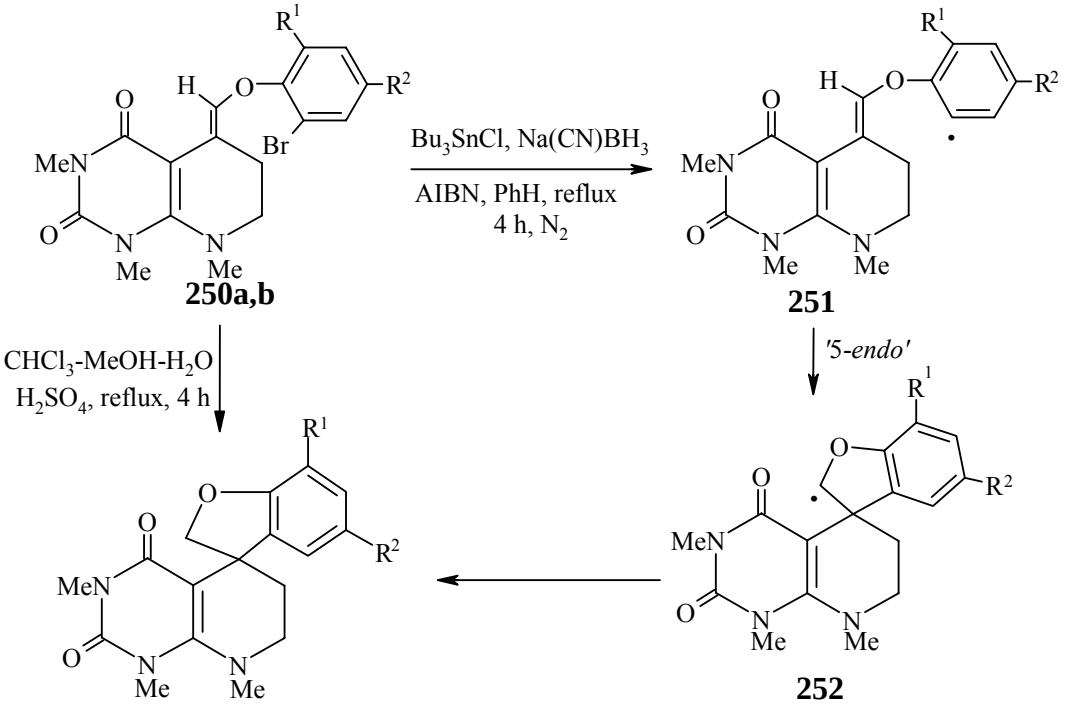
248a-f **249a-f**

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

Scheme-65

Recently we have synthesized[160] various spiroheterocycles (**253a,b**) by tri-*n*-butyltin hydride induced radical cyclization of 5-(*o*-bromoaryloxymethylene)-6,7,8-trihydropyrido[2,3-*d*]pyrimidines-2,4(1*H*,3*H*) diones (**250a,b**). These heterocycles[160] can also be obtained under acid-catalyzed enol-ether cleavage condition.

The formation of the products (**253a,b**) from **250a,b** may be explained by the formation of aryl radical (**251**) followed by 5-*endo-trig* cyclization to give spirocyclic radical (**252**), which may then give the final spiroheterocycles (**253a,b**) (**Scheme-66**).



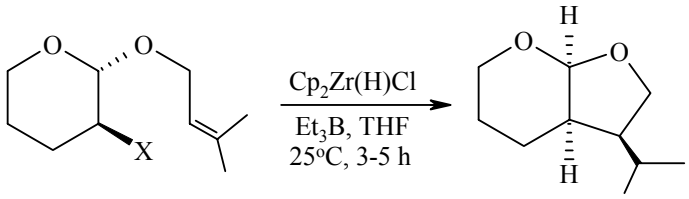
250a,b **251** **252** **253a,b**

a) R^1 = R^2 = H (52%)
b) R^1 = R^2 = Me (55%)

Scheme-66

Reduction of halides with bis(cyclopentadienyl)zirconium chloride hydride [$Cp_2Zr(H)Cl$, Schwartz reagent] proceeded smoothly *via* a radical processs, which is similar to the reduction with *n*-Bu_3SnH, in

the presence of triethyl borane as an initiator.[161] It was reported[162] that the haloacetals (**254**)[117,121] on treatment with $Cp_2Zr(H)Cl$ in the presence of Et_3B in THF at 25°C for 3 h furnished the cyclized product (**255**) in excellent yield. The reduction of **254** with *n*-Bu_3SnH, instead of $Cp_2Zr(H)Cl$, afforded **255** with the same selectivity. The stereochemical outcome of **255** was quite similar to the previous report of EtMgBr in THF mediated radical cyclization reaction.[163] Therefore, the structure of the transition state of radical cyclization would be the same in all of these reactions (**Scheme-67**).



254

a) X = Br

b) X = I

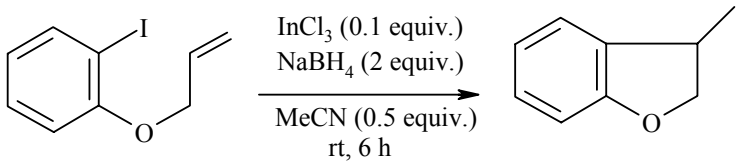
255

a) 92 %

b) 89 %

Scheme-67

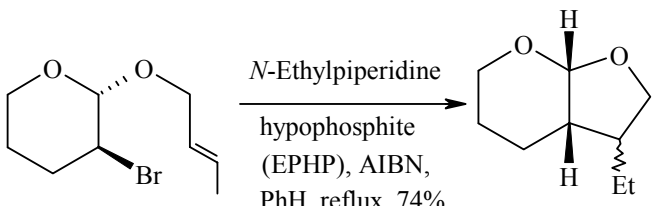
Baba *et al*. have described[164] a novel reducing system $NaBH_4$ / $InCl_3$ for the synthesis of 3-methyl-2,3-dihydrobenzofuran (**257**) from aryl iodide such as 1-allyloxy-2-iodobenzene (**256**). Here indium hydride acts as a reducing agent and it is generated by transmetalation between $InCl_3$ and $NaBH_4$ (**Scheme-68**).



256 **257** (62%)

Scheme-68

Hypophosphorous acid (H_3PO_2), and the corresponding, 1-ethylpiperidine salt, *N*-ethylpiperidine hypophosphite (EPHP) are now well established for the generation of radical in both aqueous and organic media.[165,166] This method has the good potential to replace the toxic Bu_3SnH.[152] The conversion of **258** to the bicyclic heterocycle (**259**) in moderate yield is one such reported[166]example of this method (**Scheme-69**).

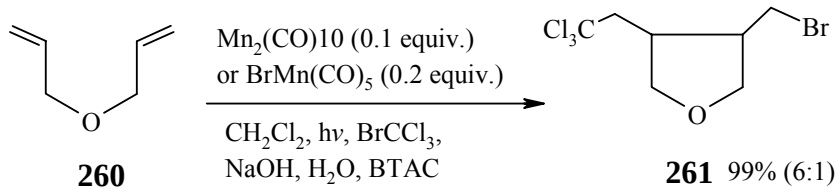


258 **259**

Scheme-69

Parsons *et al*. have shown[167] that manganese carbonyl- mediated C-C bond forming reactions can be carried out in biphasic conditions. Reaction of bromotrichloromethane with diene (**260**) and $Mn_2(CO)_{10}$ (0.1 equiv. with respect to $BrCCl_3$ or 0.3 equiv. with respect to diene **260**) or $BrMn(CO)_5$ (0.2 equiv. with

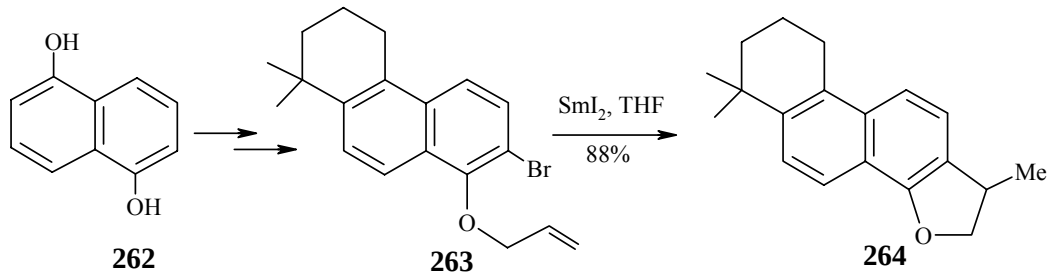
respect to $BrCCl_3$) furnished tetrahydrofuran (**261**) in essentially quantitative yield. The reagent $BrMn(CO)_5$ is an important in the sense that it has been reported for the first time to initiate radical cyclization reactions. The use of an aqueous alkaline solution and a phase transfer catalyst effectively removes $BrMn(CO)_5$ from organic products, which are retained in the dichloromethane layer. Here, $BrMn(CO)_5$ can be used in place of $Mn_2(CO)_{10}$ in coupling and cyclization reactions (**Scheme-70**).



260 **261** 99% (6:1)

Scheme-70

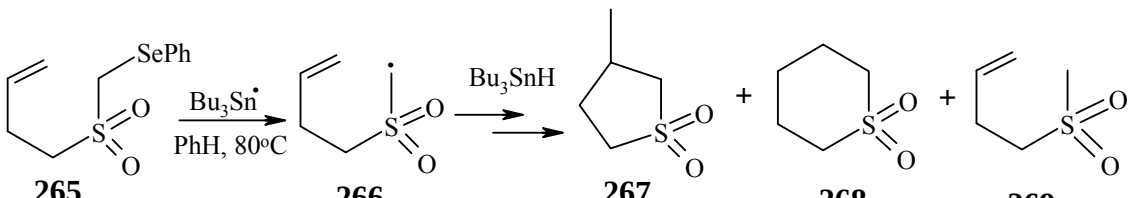
Samarium diiodide induced reductive radical cyclization of various haloalkenes has been developed.[168] Jiang *et al*. have synthesized[169] (±)-cryptotanshinone and tanshinone IIA from readily available 1,5-naphthalenediol (**262**) in which the key step was the SmI_2 promoted intramolecular radical cyclization of compound (**263**) to produce cyclic product (**264**) in 88% yield.[170] Compound (**264**) was found to serve as a suitable precursor to cryptotanshinone and tanshinone IIA (**Scheme-71**).



262 **263** **264**

Scheme-71

Della *et al*. explored[171] that the reductive cyclization of the 2-sulfonyl-5-hexenyl radical (**266**) with tributyltin hydride in benzene at 80°C afforded a 73:23 mixtures of the sulfones (**267**) and (**268**) (combined GC yield 96%) derived from 5-*exo* and 6-*endo*-ring closure along with a small quantity (4%) of the reduced material (**269**). Under similar conditions, the 2-thia-5-hexenyl radical gave a 70:13:17 mixture of the corresponding sulfides (**Scheme-72**).



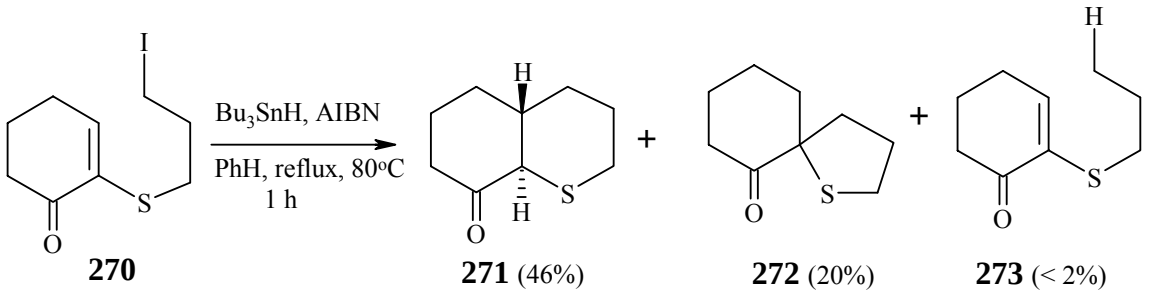
265 **266** **267** **268** **269**

Scheme-72

267:**268** (73:23 mixtures)
(combined GC yield 96%)

A few years ago, Ponaras *et al*. reported the Bu_3SnH mediated radical cyclization of diosphenol-ω-haloalkyl ethers to produce spiro- and fused bicycloalkanones was reported.[172] Influenced by this result the

same workers extended this methodology to the sulphur containing system 2-(ω-haloalkylthio)enones to produce predominantly fused thiapolycycloalkanones.[173] Some reported cases are shown in (**Scheme-73**).

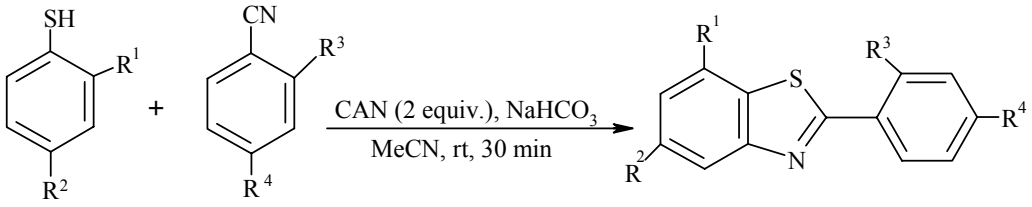


270 **271** (46%) **272** (20%) **273** (< 2%)

Scheme-73

Acyl and aryl selenides are often the precursors of choice for acyl radicals due to their capability to take part in chain sequences with tri-*n*-butylstannane and tris(trimethylsilyl)silane.[174-176] The replacement of acyl selenides by thiol esters are normally very poor sources of acyl radicals[174] and this lack of reactivity may be increased by the inclusion of an additional propagation step in which an aryl radical brings about an intramolecular homolytic substitution at sulphur.

Tale observed[177] that the thiophenols (**274a-j**) on treatment with aromatic nitriles (**275a-j**) in the presence of ceric ammonium nitrate (CAN) proceeded smoothly to afford the corresponding 2-arylbenzothiazoles (**276a-j**) in excellent yield (**Scheme-74**). The benzothiazole nucleus is very useful in medicinal chemistry. In this connection it is very important to note that 2-(4-aminophenyl)benzothiazoles represent a class of potent and selective antitumor agents.[178]



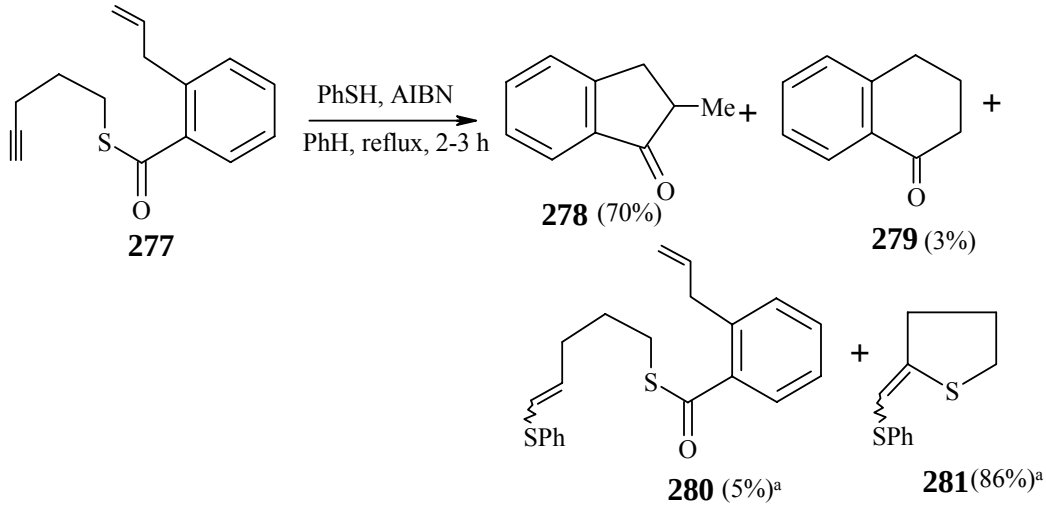
274a-j **275a-j** **276a-j**

a) $R^1 = R^2 = R^3 = R^4 = H$ (95%)
b) $R^1 = R^2 = R^3 = H$, $R^4 = OMe$ (95%)
c) $R^1 = R^3 = H$, $R^2 = R^4 = Me$ (90%)
d) $R^1 = H$, $R^2 = Me$, $R^3 = R^4 = OMe$ (89%)
e) $R^1 = Me$, $R^2 = R^3 = H$, $R^4 = NO_2$ (85%)
f) $R^1 = F$, $R^2 = R^4 = H$, $R^3 = Cl$ (87%)
g) $R^1 = R^2 = R^4 = Cl$, $R^3 = H$ (87%)
h) $R^1 = R^3 = H$, $R^2 = CF_3$, $R^4 = Br$ (78%)
i) $R^1 = R^4 = H$, $R^2 = CF_3$, $R^3 = I$ (80%)
j) $R^1 = Br$, $R^2 = R^3 = H$, $R^4 = CN$ (96%)

Scheme-74

The radical reactions of some thiol esters are carried out[179] by adding a benzene solution of PhSH and AIBN under refluxing condition. The thiol ester (**277**) led to the isolation of cyclized indanone (**278**) and tetralone(**279**) in *ca*. 96:4 ratio (overall 73% yield) along with comparable amounts of (*E*)- and (*Z*)-

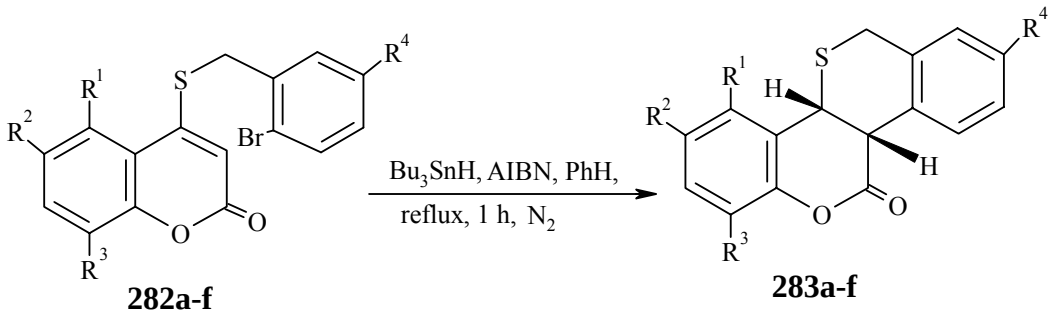
dihydrothiophenes (**281**). Small amounts of (*E*)- and (*Z*)- vinyl sulfide adducts (**280**) were the additional products (**Scheme-75**).



277 **278** (70%) **279** (3%) **280** (5%)[a] **281**(86%)[a]

Scheme-75 a = mixture of (E)- and (z)-isomer

Recently, we have also described[180] a simple convergent synthesis of *cis*-benzothiopyrano[3,2-*c*]benzopyran-7(2*H*)-ones (**283a-f**) (70-75%) through implementation of a regioselective 6-*endo-trig* aryl radical cyclization of the respective 4-(2′-bromobenzyl)thiobenzopyran-7-ones (**282a-f**) with tributyltin hydride in the presence of a catalytic amount of radical initiator AIBN (**Scheme-76**).



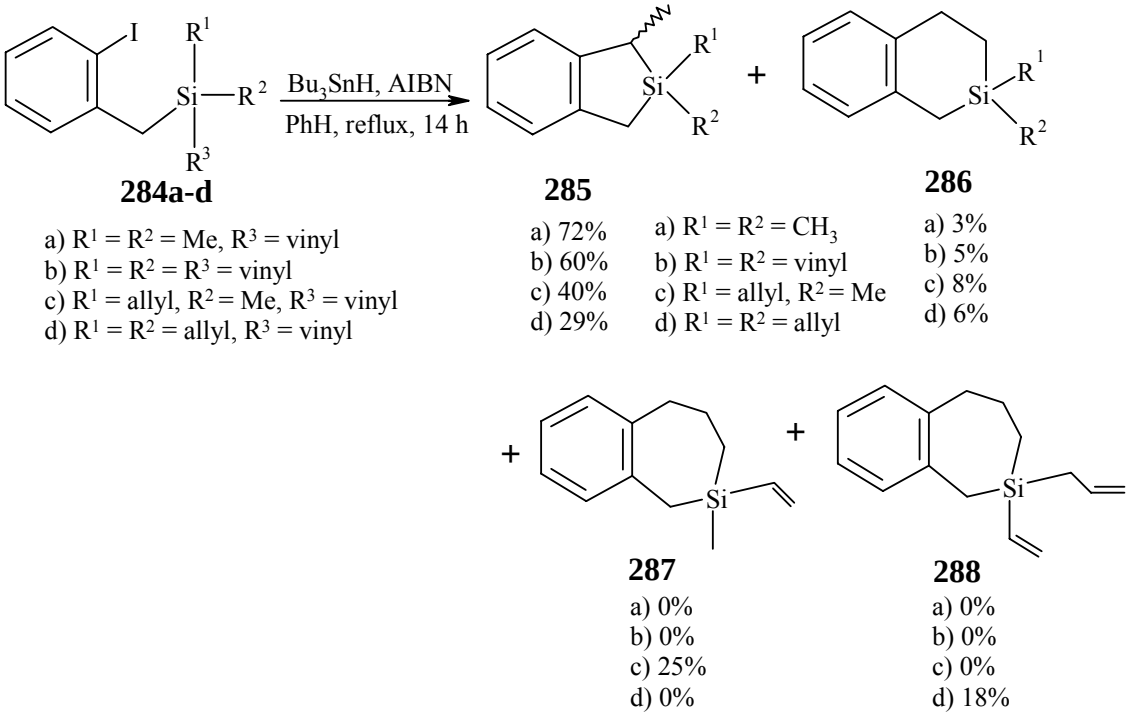
282a-f **283a-f**

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

Scheme-76

Intramolecular free-radical mediated formation of C-C bonds has been studied for a long time and is one of the most important methods for the synthesis of carbocyclic compounds.[103] Tributyltin radical induced intramolecular radical reactions of *ortho*-substituted phenyl halides have been explored for the preparation of indanes, dihydroindoles, dihydrobenzofurans and tetrahydrobenzopyrans.[170, 181-185] It was reported[186] that when *o*-iodobenzyldimethylvinylsilane (**284a**) was treated with tributyltin hydride and AIBN, the siloles (**285a**) and (**286a**) were obtained in 72% and 3% yield respectively, *i.e*. the 5-*exo-trig* cyclized product was exclusive. Similar result was also obtained in the cyclization of compound (**284b**).

Treatment of the *o*-iodobenzylallylvinylmethylsilane (**284c**) under the radical cyclization condition furnished products (**285c**) (mixture of diastereomers) and (**286c**) as well as (**287**) in 40%, 8% and 25% yields respectively. In this case the 7-*endo* cyclization is competitive with 5-*exo* cyclization, while the 6-*endo* reaction seems to be rather slow. The compound (**284d**) under similar reaction condition furnished the siloles (**285d**) and (**286d**) *via* a 5-*exo* and 6-*endo* cyclization in 29% and 6% yields respectively. In case of **284d**, compound (**288d**) was additionally formed in 18% yield *via* 7-*endo* cyclization. The results with **284c,d** is the indicative of the fact that the vinyl group reacts in preference to the allyl group (**Scheme-77**).



284a-d

a) $R^1 = R^2 = Me$, $R^3 = vinyl$
b) $R^1 = R^2 = R^3 = vinyl$
c) $R^1 = allyl$, $R^2 = Me$, $R^3 = vinyl$
d) $R^1 = R^2 = allyl$, $R^3 = vinyl$

285

a) 72% a) $R^1 = R^2 = CH_3$
b) 60% b) $R^1 = R^2 = vinyl$
c) 40% c) $R^1 = allyl$, $R^2 = Me$
d) 29% d) $R^1 = R^2 = allyl$

286

a) 3%
b) 5%
c) 8%
d) 6%

287

a) 0%
b) 0%
c) 25%
d) 0%

288

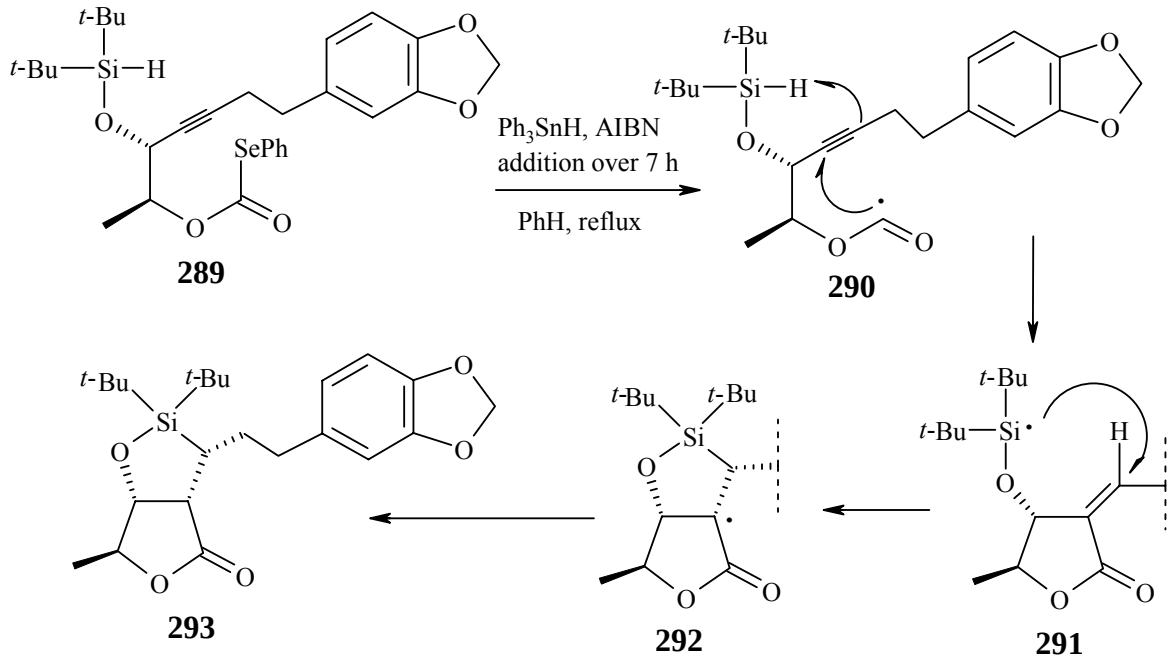
a) 0%
b) 0%
c) 0%
d) 18%

Scheme-77

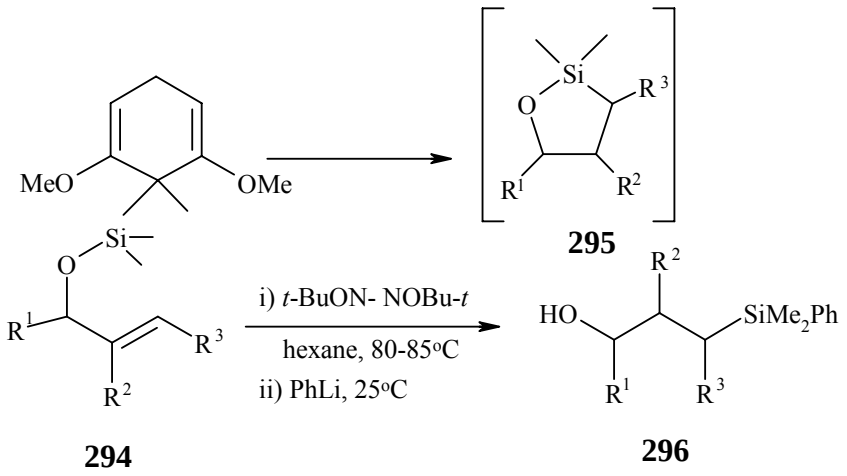
It was observed[187] that phenylselenocarbonate (**289**) on refluxing with Ph_3SnH and AIBN in benzene afforded compound (**293**) in 79% yield following 5-*exo-dig* radical cyclization, intramolecular hydrogen transfer and then 5-*endo-trig* cyclization (**290**→ **291**→ **292**) respectively (**Scheme-78**).

Intramolecular hydrosilylation of allyloxy- or allenyloxysilanes using transition metal catalysis is well documented.[188] Intramolecular radical hydrosilylations using allyloxy and propargyloxycyclohexadienylsilanes comprising 5-*endo-trig* as well as 5-*endo-dig* processes were described by Studer *et al*.[189] The intramolecular hydrosilylation of silyl ether (**294a**) in hexane using di-*tert*-butyl hyponitrite as initiator (0.3 equivalent) in hexane at 80-85^oC (sealed tube, 0.25 M) afforded the desired 5-*endo*-cyclization product (**295**). AIBN was unsuitable as initiator in the intramolecular hydrosilylation. It turned out that alkoxysilane (**295**) is prone towards hydrolysis and is difficult to isolate. Hence, the crude reaction mixture was treated with an excess of phenyllithium (PhLi) to produce alcohol (**296a**) in 47% isolated yield. The secondary alcohol (**296b**) was obtained in 43% yield starting from silyl ether (**294b**).

The hydrosilylation ring-opening product (**296c**) was obtained in 20% yield as a 2:1 mixture of diastereomers (**Scheme-79**).



Scheme-78



a) $R^1 = R^2 = R^3 = H$ (47%)
b) $R^1 = Me$, $R^2 = R^3 = H$ (43%)
c) $R^1 = R^3 = Me$, $R^2 = H$ (20%)
d) $R^1 = R^2 = Me$, $R^3 = H$ (14%)

Scheme-79

CONCLUSIONS

As stated, the literature on the synthesis of heterocycles by radical cyclization is vast and it is beyond the scope of this brief review to include all aspects. Therefore, only the introduction, mechanism and recent representative examples have been included. Application of the radical cyclization for the formation of the pyran and furan rings in heterocycles is incorporated. Mechanistic aspects of various radical

cyclization reactions have been studied in detail. In recent years there has been considerable study of the cyclization of radicals on heterocyclic compounds, a reaction that had previously been ignored. However, radical cyclization reactions, still offer enormous challenges to synthetic organic chemists.

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REFERENCES

1. S. M. Allin, W. R. S. Barton, W. R. Bowman, and T. Mclnally, *Tetrahedron Lett*., 2002, **43**, 4191; R. Suero, J. M. Gorgojo, and J. M. Aurrecoechea, *Tetrahedron*, 2002, **58**, 6211; P. A. Evans and T.Manangan, *Tetrahedron Lett*., 2001, **42**, 6637; W. R. Bowman, M. J. Broadhurst, D. R. Coghlan, And K. A. Lewis, *Tetrahedron Lett*., 1997, **38**, 6301.
2. D. L. J. Clive, M. Sannigrahi, and S. Hisaindee, *J. Org. Chem*., 2001, **66**, 954.
3. K. C. Nicolaou, A. J. Roecker, R. Hughes, R. V. Summeren, J. A. Pfefferkorn, and N. Winssinger, *Bioorg. and Med. Chem*., 2003, **11**, 465.
4. A. J. Mc Carroll and J. C. Walton, *J. Chem. Soc*., *Perkin Trans. I*, 2001, 3215.
5. J. Robertson, J. Pillai, and R. K. Lush, *Chem. Soc. Rev*., 2001, **30**, 94.
6. J. J. Li, *Tetrahedron*, 2001, **57**, 1.
7. B. Giese, Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds, Pergamon Press, Oxford, 1986; W. B. Motherwell and D. Crich, Free Radical Chain Reactions in Organic Synthesis, Academic Press, London, 1992; J. E. Leffler, An Introduction to Free Radicals, Wiley-Interscience, New York, 1993; J. Fossey, D. Lefort, and J. Sorba, Free Radicals in Organic Chemistry, John Wiley & Sons, Chichester, New York, Brisbane, Toronto, Singapore, 1995; T. Linker and M. Schmittel, Radikale and Radikalionen in der Organischen Chemie, Wiley–VCH: Weinheim, 1998; Radicals in Organic Synthesis, Vol. 1, ed. by P. Renaud and M. P. Sibi, Wiley–VCH, Weinheim, 2001, Radicals in Organic Synthesis, Vol. 2, ed. by P. Renaud and M. P. Sibi, Wiley–VCH, Weinheim, 2001.
8. D. P. Curran, In Comprehensive Organic Synthesis, Vol. 4, ed. by B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, 715; D. P. Curran, N. A. Porter, and B. Giese, Stereochemistry of Radical Reactions, VCH, Weinheim, 1995.
9. C. P. Jasperse, D. P. Curran, and T. L. Felvig, *Chem. Rev*., 1991, **91**, 1237; M. Malacria, *Chem. Rev*., 1996, **96**, 289.
10. A. L. J. Beckwith and D. M. O'Shea, *Tetrahedron Lett*., 1986, **27**, 4525.
11. G. Stork and R. Jr. Mook, *Tetrahedron Lett*., 1986, **27**, 4529.

12. D. Crich, J. T. Hwang, and H. Liu, *Tetrahedron Lett*., 1996, **37**, 3105.
13. I. Ryu, H. Fukushima, T. Okuda, K. Matsu, N. Kambe, N. Sonoda, and M. Komatsu, *Synlett*, 1997, 1265; C. Chatgilialoglu, C. Ferreri, M. Lucarini, A. Venturini, and A. A. Zavitsas, *Chem*. *Eur*. *J*. ,1997, **3**, 376.
14. W. P. Neumann, *Synthesis*, 1987, 665; M. Pereyre, J. –P. Quintard and A. Rahm, Tin in Organic Synthesis, Butterworths, Toronto, 1987; T. V. Rajanbabu, In Encyclopedia of reagents for Organic Synthesis, Vol. 7, ed. by L. Paquette, Wiley, New York, 1995, 5016; A. G. Davies, Organotin Chemistry, Wiley – VCH, Weinheim, 1997.
15. R. K. Ingham, S. D. Rosenberg, and H. Gilman, *Chem*. *Rev*., 1960, **60**, 459; I. J. Boyer, Toxicology, 1989, **55**, 253.
16. J. E. Leibner and J. Jacobus, *J*. *Org*. *Chem*., 1979, **44**, 449.
17. D. L. J. Clive and J. Wang, *J*. *Org*. *Chem*., 2002, **67**, 1192.
18. P. A. Baguley and J. C. Walton, *Angew*. *Chem*., *Int*. *Ed*., 1998, **37**, 3072; *Angew*. *Chem*., 1998, **110**, 3272.
19. G. E. Keck, T. T. Wager, and S. F. McHardy, *J*. *Org*. *Chem*.,1998, **63**, 9164.
20. S. Berlin and L. Engman, *Tetrahedron Lett*., 2000, **41**, 3701.
21. J. H. Rigby, D. M. Danca, and J. H. Horner, *Tetrahedron Lett*., 1998, **39**, 8413.
22. B. Quiclet-Sire, S. Seguin and S. Z. Zard, *Angew*. *Chem*., *Int*. *Ed*., 1998, **37**, 2864.
23. R. A. Batey and D. V. Smil, *Tetrahedron Lett*., 1999, **40**, 9183.
24. J. Quirante, C. Escolano, and J. Bonjoch, *Synlett*, 1997, 179.
25. J. Quirante, C. Escolano, L. Costeja, and J. Bonjoch, *Tetrahedron Lett*., 1997, **38**, 6901; J. Quirante, C. Escolano, M. Massot, and J. Bonjoch, *Tetrahedron*, 1997, **53**, 1391.
26. J. Quirante, C. Escolano, A. Merino and J. Banjoch, *J*. *Org*. *Chem*.,1998, **63**, 968.
27. C. Chatgilialoglu, *Acc*. *Chem*. *Res*., 1992, **25**, 188; C. Chatgilialoglu, C. Ferreri, and T. Gimisis, In The Chemistry of Organic Silicon Compounds, Vol. 2, ed. by S. Rappoport and Y. Apeloig, Wiley, London, 1998, 1539; C. Chatgilialoglu and C. H. Schiesser, In The Chemistry of Organic Silicon Compounds, Vol. 3, ed. by S. Rappoport and Y. Apeloig, Wiley, London, 2001, 341.
28. W. R. Dolbier, Jr., X. X. Rong, B. E. Smart, and Z. –Y. Yang, *J*. *Org*. *Chem*., 1996, **61**, 4824.
29. T. Nakamura, H. Yorimitsu, H. Shinokubo, and K. Oshima, *Bull*. *Chem*. *Soc*. *Jpn*., 2001, **74**, 747.
30. H. Nambu, G. Anilkumar, M. Matsugi, and Y. Kita, *Tetrahedron*, 2003, **59**, 77.
31. W. R. Bowmann, P. T. Stephenson, N. K. Terrett, and A. R. Young, *Tetrahedron*, 1995, **51**, 7959.
32. I. Ryu, K. Matsu, S. Minakata, and M. Komatsu, *J*. *Am*. *Chem*. *Soc*., 1998, **120**, 5838.
33. I. Ryu, Shin-ichi. Ogura, S. Minakata, and M. Komatsu, *Tetrahedron Lett*., 1999, **40**, 1515.
34. M. J. Ellis and M. F. G. Stevens, *J*. *Chem*. *Soc*., *Perkin Trans*. *I*, 2001, 3180.
35. B. Quiclet-Sire, F. Wendeborn, and S. Z. Zard, *Chem*. *Commun*., 2002, 2214.

36. R. Viswanathan, E. N. Prabhakaran, M. A. Plotkin, and J. N. Johnston, *J. Am. Chem. Soc*., 2003, **125**, 163.
37. J. P. Dittami and H. Ramanathan, *Tetrahedron Lett*., 1988, **29**, 45.
38. K. Shankaran, C. P. Sloan, and V. Snieckus, *Tetrahedron Lett*., 1985, **26**, 6001.
39. H. Urabe and I. Kuwajima, *Tetrahedron Lett*., 1986, **27**, 1355.
40. W. R. Bowman, H. Heaney, and B. M. Jordon, *Tetrahedron Lett*., 1988, **29**, 6657.
41. A. M. Rosa, S. Prabhakar, and A. M. Lobo, *Tetrahedron Lett*., 1990, **31**, 1881.
42. A. M. Rosa, A. M. Lobo, P. S. Branco, S. Prabhakar, and M. Sa-da-Costa, *Tetrahedron*, 1997, **53**, 299.
43. T. Sato, N. Nakamura, K. Ikeda, M. Okada, H. Ishibashi, and M. Ikeda, *J. Chem. Soc*., *Perkin Trans. I*, 1992, 2399.
44. O. Tamura, H. Matsukida, A. Toyao, Y. Takeda, and H. Ishibashi, *J. Org. Chem*., 2002, **67**, 5537.
45. H. Ishibashi, H. Matsukida, A. Toyao, O. Tamura, and Y. Takeda, *Synlett*, 2000, 1497.
46. K. Goodall and A. F. Parsons, *Tetrahedron*, 1996, **52**, 6739.
47. A. F. Parsons and D. A. J. Williams, *Tetrahedron*, 1998, **54**, 13405.
48. M. Ikeda, S. Ohtani, T. Yamamoto, T. Sato, and H. Ishibashi, *J. Chem. Soc*, *Perkin Trans. I*, 1998, 1763.
49. T. Sato, N. Machigashire, H. Ishibashi, and M. Ikeda, *Heterocycles*, 1992, **33**, 139; T. Sato, N. Chono, H. Ishibashi and M. Ikeda, *J. Chem. Soc*., *Perkin Trans. I*, 1995, 1115.
50. M. Ikeda, M. Hamada, T. Yamashita, K. Matsui, T. Sato, and H. Ishibashi. *J. Chem. Soc., Perkin Trans. I*, 1999, 1949.
51. A. F. Parsons and D. A. J. Williams, *Tetrahedron*, 2000, **56**, 7217.
52. H. Ishibashi, K. Kodama, M. Higuchi, O. Muraoka, G. Tanabe, and Y. Takeda, *Tetrahedron*, 2001, **57**, 7629.
53. K. N. Houk, M. N. Paddon-Row, D. C. Spellmeyer, N. G. Rondan, and S. Nagase, *J. Org. Chem*., 1986, **51**, 2874; D. C. Spellmeyer and K. N. Houk, *J. Org. Chem*., 1987, **52**, 959.
54. A. L. J. Beckwith and C. H. Schiesser, *Tetrahedron Lett*., 1985, **26**, 373; A. L. J. Beckwith and C. H. Schiesser, *Tetrahedron,* 1985, **41**, 3925.
55. A. L. J. Beckwith, C. J. Easton, T. Lawrence, and A. K. Serelis, *Aust. J. Chem*., 1983, **36**, 545.
56. T. V. Rajanbabu, *J. Am. Chem. Soc*., 1987, **109**, 609; T. V. Rajanbabu, *J. Org. Chem*., 1988, **53**, 4522; T. V. Rajanbabu and T. Fukanga, *J. Am. Chem. Soc*., 1989, **111**, 296; T. V. Rajanbabu, T. Fukanga, and, G. S. Reddy, *J. Am. Chem. Soc*., 1989, **111**, 1759.
57. D. Crich and J. –T. Hwang, *J. Org. Chem*., 1998, **63**, 2765.
58. H. Ishibashi, K. Ohata, M. Niihara, T. Sato, and M. Ikeda, *J. Chem. Soc*, *Perkin Trans. I*, 2000, 547; K. C. Majumdar and P. K. Basu, *Heterocycles*, 2002, **57**, 2413.

59. J. H. Rigby and M. N. Qabar, *J. Org. Chem*., 1993, **58**, 4473.
60. H. Ishibashi, I. Kato, Y. Takeda, M. Kogure, and O. Tamura, *Chem. Commun*., 2000, 1527; H. Ishibashi, K. Ohata, M. Niihara, T. Sato, and M Ikeda, *J. Chem. Soc*., *Perkin Trans. I*, 2000, 547.
61. M. H. Todd, C. Ndubaku, and P. A. Bartlett, *J. Org. Chem*., 2002, **67**, 3985.
62. I. Jabin and P. Netchitailo, *Tetrahedron Lett*., 2001, **42**, 7823.
63. D. P. Curran, *Synthesis*, 1988, 417; D. P. Curran, *Synthesis*, 1988, 489; D. P. Curran, In Comprehensive Organic Synthesis, Vol. 4, ed. by B. M. Trost and I.. Fleming, Pergamon Press, New York, 1991, 779.
64. A. D'Annibale, D. Nanni, C. Trogolo, and F. Umani, *Org. Lett*., 2000, **2**, 401; D. T. Davies, N. Kapur, and A. F. Parsons, *Tetrahedron Lett*., 1999, **40**, 8615; A. J. Clark, C. P. Dell, J. M. Ellard, N. A. Hunt, and J. P. McDonagh, *Tetrahedron Lett*., 1999, **40**, 8619; S. R. Baker, K. I. Burton, A. F. Parsons, J. F. Pons, and M. Wilson, *J. Chem. Soc*., *Perkin Trans. I*, 1999, 427; H. Ishibashi, M. Inomata, M. Ohba, and M. Ikeda, *Tetrahedron Lett*., 1999, **40**, 1149.
65. J. Fidalgo, L. Castedo, and D. Dominguez, *Tetrahedron Lett*., 1993, **34**, 7317; G. Rodriguez, M. M. Cid, C. Saa, L. Castedo, and D. Dominguez, *J. Org. Chem*., 1996, **61**, 2780; M. M. Cid, D. Dominguez, L. Castedo, and E. Vazquez-Lopez, *Tetrahedron*, 1999, **55**, 5599.
66. S. A. Glover and J. Warkentin, *J. Org. Chem*., 1993, **58**, 2115.
67. J. Ahman and P. Somfai, *J. Chem. Soc*., *Perkin Trans. I*, 1994, 1079.
68. D. S. Middleton, N. S. Simpkins, and N. K. Terret, *Tetrahedron Lett*., 1989, **30**, 3865.
69. S. Berteina and A. De Mesmaeker, *Synlett*, 1998, 1227.
70. A. Navarro-Vazquez, A. Garcia, and D. Dominguez, *J. Org. Chem*., 2002, **67**, 3213.
71. B. K. Banik, *Curr. Org. Chem*., 1999, **3**, 469.
72. C. Escolano and K. Jones, *Tetrahedron Lett*., 2000, **41**, 8951; C. Escolano and K. Jones, *Tetrahedron*, 2002, **58**, 1453.
73. G. W. Gribble, H. L. Fraser, and J. C. Badenock, *Chem. Commun*., 2001, 805.
74. V. Snieckus, J. –C. Cuevas, C. P. Sloan, H. Liu, and D. P. Curran, *J. Am. Chem. Soc.*, 1990, **112**, 896.
75. T. Fukuyama, X. Chen, and G. Peng, *J. Am. Chem. Soc*., 1994, **116**, 3127; Y. Kobayashi and T. Fukuyama, *J. Heterocycl. Chem*., 1998, **35**, 1043.
76. H. Tokuyama, T. Yamashita, M. T. Reding, Y. Kaburagi, and T. Fukuyama, *J. Am. Chem. Soc*, 1999, **121**, 3791.
77. K. Nozaki, K. Oshima, and K.Utimoto, *Tetrahedron*, 1989, **45**, 923.
78. S. R. Flanagan, D. C. Harrowven, and M. Bradley, *Tetrahedron Lett*., 2003, **44**, 1795.
79. L. D. Miranda and S. Z. Zard, *Org. Lett*., 2002, **4,** 1135.
80. W. Zhang and G. Pugh, *Tetrahedron*, 2003, **59***,* 3009.
81. K. C. Majumdar and P. P. Mukhopadhyay, *Synthesis*, 2003, 920.

82. H. Ishibashi, H. Kawanami, H. Nakagawa, and M. Ikeda, *J. Chem. Soc., Perkin Trans. I,* 1997, 2291.
83. A. N. Abeywickrema, A. L. J. Beckwith, and S. Gerba, *J. Org. Chem.,* 1987, **52**, 4072.
84. M. Ikeda, H. Teranishi, K. Nozaki, and H. Ishibashi, *J. Chem. Soc.*, *Perkin Trans. I.*, 1998, 1691.
85. K. Goodall and A. F. Pearsons, *Tetrahedron Lett*., 1997, **38**, 491.
86. W. R. Bowman, C. F. Bridge, and P. Brookes, *J. Chem. Soc., Perkin Trans. I*, 2000, 1; W. R. Bowman, M. O. Cloonan, and S. L. Krintel, *J. Chem. Soc., Perkin Trans. I*, 2001, 2885; H. Ishibashi, T. Sato, and M. Ikeda, *Synthesis*, 2002, 695.
87. R. S. Jolly and T. Livinghouse, *J. Am. Chem. Soc*., 1988, **110**, 7536.
88. D. P. Curran and J. Tamine, *J. Org. Chem*., 1991, **56**, 2746.
89. J. M. D. Storey, *Tetrahedron Lett*., 2000, **41**, 8173.
90. A. K. Ganguly, C. H. Wang, M. David, P. Bartner, and T. M. Chan, *Tetrahedron Lett*., 2002, **43**, 6865.
91. W. R. Bowman, H. Heaney, and B. M. Jordan, *Tetrahedron*, 1991, **47**, 10119.
92. A. Basak, S. S. Bag, K. R. Rudra, J. Barman, and S. Dutta, *Chem. Lett*., 2002, 710.
93. O. Miyata, Y. Ozawa, I. Ninomiya, and T. Naito, *Tetrahedron*, 2000, **56**, 6199.
94. M. Alajarin, A. Vidal, and M. –M. Ortin, *Tetrahedron Lett*., 2003, **44**, 3027.
95. L. Benati, R. Leardini, M. Minozzi, D. Nanni, P. Spagnolo, S. Strazzari, and G. Zanardi, *Org. Lett*., 2002, **4**, 3079.
96. D. E. Lizos and J. A. Murphy, *Org. Biomol. Chem*., 2003, **1**, 117.
97. H. Hasegawa, H. Senboku, Y. Kajizuka, K. Orito, and M. Tokuda, *Tetrahedron*, 2003, **59**, 827.
98. A. L. J. Beckwith, *Tetrahedron*, 1981, **37**, 3073.
99. C. Agami, S. Comesse, S. Guesne, C. Kadouri- Puchot, and L. Martinon, *Synlett*, 2003, 1058.
100. J. E. Baldwin, *J. Chem. Soc*., *Chem. Commun*., 1976, 734.
101. M. L. Harwood and I. A. Lilley, *Tetrahedron Lett*., 1993, **34**, 537.
102. A. L. J. Beckwith, C. E. Easton, and A. K. Serelis, *J. Chem. Soc*., *Chem. Commun*., 1980, 482; A. L. J. Beckwith, T. Lawrence, and A. K. Serelis, *J. Chem. Soc*., *Chem. Commun*., 1980, 484.
103. B. Giese, B. Kopping, T. Gobel, J. Dickhaut, G. Thoma, K. J. Kulicke, and F. Trach, Organic Reactions, 1996, **48**, 301; F. Aldabbagh and W. R. Bowman, *Contemp. Org. Synth*., 1997, 261.
104. J. S. Bryans, J. M. Large, and A. F. Parsons, *J. Chem. Soc., Perkin Trans. I.*, 1999, 2897; J. S. Bryans, J. M. Large, and A. F. Parsons, *J. Chem. Soc., Perkin Trans. I*, 1999, 2905; H. Ishibashi, T. S. So, K. Okochi, T. Sato, N. Nakamura, H. Nakatani, and M. Ikeda, *J. Org. Chem*.,1991, **56**, 95; S. Ozaki, H. Matsushita, and H. Ohmori, *J. Chem. Soc., Perkin Trans. I*, 1993, 2399; B. Cardillo, R. Galeazzi, G. Mobbili, M. Orena, and M. Rossetti, *Heterocycles*, 1994, **38**, 2663; G. Stork and R. Mah, *Heterocycles*, 1989, **28**, 723.
105. S. R. Baker, K. I. Burton, A. F. Parsons, J. –F. Pons, and M. Wilson, *J. Chem. Soc., Perkin Trans. I*, 1999, 427; H. Ishibashi, M. Higuchi, M. Ohba, and M. Ikeda, *Tetrahedron Lett*., 1998, **39**, 75; M.

Ikeda, S. Ohtani, T. Yamamoto, T. Sato, and H. Ishibashi, *J. Chem. Soc., Perkin Trans. I*, 1998, 1763.

106. A. D'Annibale, S. Resta, and C. Trogolo, *Tetrahedron Lett*., 1995, **36**, 9039.
107. K. Goodall and A. F. Parsons, *J. Chem. Soc., Perkin Trans. I*, 1994, 3257.
108. D. T. Davies, N. Kapur, and A. F. Parsons, *Tetrahedron*, 2000, **56**, 3941.
109. J. S. Bryans, N. E. A. Chessum, A. F. Parsons, and F. Ghelfi, *Tetrahedron Lett*., 2001, **42**, 2901.
110. F. Ghelfi, *J. Org. Chem*., 2000, **65**, 6249.
111. M. Noack and R. Gottlich, *Chem. Commun*., 2002, 536.
112. M. F. Jung, *Synlett*, 1999, 843.
113. R. M. Beesley, C. K. Ingold, and J. F. Thorpe, *J. Chem. Soc.,* 1915, 1080.
114. F. Gagosz and S. Z. Zard, *Org. Lett*., 2002, **4**, 4345.
115. O. Moriya, Y. Urata, Y. Ikeda, Y. Ueno, and T. Endo, *J. Org. Chem*., 1986, **51**, 4708.
116. J. P. Dulcere, J. Rodriguez, M. Santelli, and J. P. Zohra, *Tetrahedron Lett*., 1987, **28**, 2009.
117. G. Stork, R. Jr. Mook, S. A. Biller, and S. D. Rychnovsky, *J. Am. Chem. Soc.*, 1983, **105**, 3741.
118. G. Stork, In Current Trends in Organic Synthesis, ed. by H. Nozaki, Pergamon Press, Oxford, 1983, 359.
119. G. Stork, In selectivity–A Goal For Synthetic Efficiency, ed. by W. Bartmann and B. M. Trost, *VCH*, Weinheim, 1984, p. 281.
120. Y. Ueno, O. Moriya, K. Chino, M. Watanabe, and M. Okawara, *J. Chem. Soc*., *Perkin Trans. I*, 1986, 1351.
121. Y. Ueno, K. Chino, M. Watanabe, O. Moriya, and M. Okawara, *J. Am. Chem. Soc*., 1982, **104**, 5564.
122. O. Moriya, M. Okawara, and Y. Ueno, *Chem. Lett*., 1984, 1437.
123. M. Ladlow and G. Pattenden, *Tetrahedron Lett*., 1984, **25**, 4317.
124. J. H. Hutchinson, G. Pattenden, and P. L. Myers, *Tetrahedron Lett*., 1987, **28**, 1313.
125. M. Ihara, N. Taniguchi, K. Fukumoto, and T. Kametani, *J. Chem. Soc.*, *Chem. Commun*.,1987, 1438.
126. A. Srikrishna and K. C. Pullaiah, *Tetrahedron Lett*., 1987, **28**, 5203.
127. A. Srikrishna and G. Sundarababu, *Tetrahedron*, 1990, **46**, 7901.
128. A. Srikrishna, R. Viswajanani, and C. V. Yelamaggad, *Tetrahedron*, 1997, **53**, 10479.
129. A. Srikrishna and R. Viswajanani, *Synlett*.,1995, 95.
130. A. L. J. Beckwith and D. M. Page, *J. Org. Chem*., 1998, **63**, 5144.
131. A. L. J. Beckwith and K. U. Ingold, In Rearrangement in Ground and Excited states, ed. by P. de Mayo, Academic Press, New York, 1980, 161.
132. A. L. J. Beckwith, *Chem. Soc. Rev*. 1993, **22**, 143.
133. S. Kim, C. J. Lim, S. –E. Song, and H. –Y. Kang, *Synlett*, 2001, 688.

134. D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Am. Chem. Soc*., 1961, **83**, 4076; G. D. Vite and B. Fraser-Reid, *Synth. Commun*., 1988, **18**, 1339; S. Kim and T. A. Lee, *Synlett*, 1997, 950; S. Kim, T. A. Lee and Y. Song, *Synlett*, 1998, 471.
135. A. L. J. Beckwith, B. P. Hay, and G. M. Williams, *Chem. Commun*., 1989, 1202; D. J. Pasto and G. L'Hermine, *J. Org. Chem*., 1990, **55**, 5815; D. J. Pasto and F. Cottard, *Tetrahedron Lett*., 1994, **35**, 4303.
136. O. Miyata, A. Nishiguchi, I. Ninomiya, K. Aoe, K. Okamura, and T. Naito, *J. Org. Chem*., 2000, **65**, 6922.
137. D. L. J. Clive and X. Huang, *Tetrahedron*, 2001, **57**, 3845.
138. D. L. J. Clive and M. Yu, *Chem. Commun*., 2002, 2380.
139. G. Stork and M. Kahn, *J. Am. Chem. Soc*., 1985, **107**, 500; D. L. J. Clive, D. R. Cheshire, and L. Set, *J. Chem. Soc., Chem. Commun*., 1987, 353.
140. W. Zhang and G. Pugh, *Tetrahedron Lett*., 2001, **42***,* 5617.
141. D. L. Boger and R. J. Mathvink, *J. Am. Chem. Soc*., 1990, **112**, 4003; D. L. Boger and R. J. Mathvink, *J. Am. Chem. Soc*., 1990, **112**, 4008; D. L. Boger and R. J. Mathvink, *J. Org. Chem*., 1992, **57**, 1429; D. Crich, C. Chen, J. –T. Hwang, H. Yuan, A. Papadatos, and R. I. Walter, *J. Am. Chem. Soc*., 1994, **116**, 8937; D. Crich and Q. Yao, *J. Org. Chem*., 1996, **61**, 3566; D. Crich and X. Hao, *J. Org. Chem*., 1997, **62**, 5982; L. Chen, G. B. Gill, G. Pattenden, and H. Simonian, *J. Chem. Soc*., *Perkin Trans. I*, 1996, 31; A. Batsanov, L. Chen, G. B. Gill, and G. Pattenden, *J. Chem. Soc*., *Perkin Trans. I*, 1996, 45; G. Pattenden, L. Roberts, and A. J. Blake, *J. Chem. Soc*., *Perkin Trans. I*, 1998, 863.
142. P. A. Evans, S. Raina, and K. Ahsan, *Chem. Commun*., 2001, 2504.
143. S. Berlin, C. Ericsson, and L. Engman, *Org. Lett*., 2002, **4**, 3.
144. A. F. Parsons, An Introduction to Free radical Chemistry, Blackwell Science, Oxford, 2000, p. 105.
145. D. Bebbington, J. Bentley, P. A. Nilsson, and A. F. Parsons, *Tetrahedron Lett*., 2000, **41***,* 8941.
146. J. Bentley, P. A. Nilsson, and A. F. Parsons, *J. Chem. Soc*., *Perkin Trans. I*, 2002, 1461.
147. D. L. J. Clive, J. Zhang, R. Subedi, V. Bouetard, S. Hiebert, and R. Ewanuk, *J. Org. Chem*., 2001, **66**, 1233.
148. R. Nouguier, S. Gastaldi, D. Stien, M. Bertrand, F. Villar, O. Andrey, and P. Renaud, *Tetrahedron Assymetry*, 2003, **14***,* 3005.
149. M. Yokota, M. Toyota, and M. Ihara, *Chem. Commun*., 2003, 422.
150. J. U. Rhee, B. I. Bliss, and T. V. Rajanbabu, *J. Am. Chem. Soc*., 2003, **125**, 1492.
151. D. Crich, K. Ranganathan, S. Neelamkavil, and X. Huang, *J. Am. Chem. Soc*., 2003, **125**, 7942.
152. W. R. Bowman, E. Mann, and J. Parr, *J. Chem. Soc., Perkin Trans. I*, 2000, 2991.
153. D. L. J. Clive, S. P. Fletcher, and M. Zhu, *Chem. Commun*., 2003, 526.

154. D. L. J. Clive and S. P. Fletcher, *Chem. Commun*., 2003, 2464.
155. D. C. Harrowven, M. I. T. Nunn, N. A. Newman, and D. R. Fenwick, *Tetrahedron Lett*., 2001, **42**, 961.
156. T. Naito, K. Nakagawa, T. Nakamura, A. Kasei, I. Ninomiya, and T. Kiguchi, *J. Org. Chem*., 1999, **64**, 2003.
157. K. C. Majumdar, P. K. Basu, P. P. Mukhopadhyay, S. Sarkar, S. K. Ghosh, and P. Biswas, *Tetrahedron,* 2003, **59**, 2151.
158. F. Aldabbagh and W. R. Bowman, *Tetrahedron Lett*., 1997, **38**, 3793; D. P. Curran, S. –B. Ko, and, H. Josien, *Angew. Chem*., *Int. Ed. Engl*., 1995, **34**, 2683.
159. K. C. Majumdar and P. P. Mukhopadhyay, *Synthesis*, 2003, 97.
160. K. C. Majumdar, S. Sarkar, and T. Bhattacharrya, *Tetrahedron*, 2003, **59**, 4309; K. C. Majumdar, and T. Bhattacharrya, *Synthesis*, 2001, 1568.
161. K. Nozaki, K. Oshima, and K. Utimoto, *J. Am. Chem. Soc.*, 1987, **109**, 2547.
162. K. Fujita, T. Nakamura, H. Yorimitsu, and K. Oshima, *J. Am. Chem. Soc.*, 2001, **123**, 3137.
163. A. Inoue, H. Shinokubo, and K. Oshima, *Org. Lett*., 2000, **2**, 651.
164. K. Inoue, A. Sawada, I. Shibata, and A. Baba, *J. Am. Chem. Soc.*, 2002, **124**, 906.
165. S. R. Graham, J. A. Murphy, and D. Coates, *Tetrahedron Lett*., 1999, **40**, 2415.
166. R. McCague, R. G. Pritchard, R. J. Stoodley, and D. S. Williamson, *Chem. Commun*., 1998, 2691.
167. N. Huther, P. T. McGrail, and A. F. Parsons, *Tetrahedron Lett*., 2002, **43***,* 2535.
168. G. A. Molander and L. S. Harring, *J. Org. Chem.,* 1990, **55**, 6171.
169. Y. –Y. Jiang, Q. Li, W. Lu, and J. –C. Cai, *Tetrahedron Lett*., 2003, **44**, 2073.
170. J. Inanaga, O. Ujikawa, and M.Yamaguchi, *Tetrahedron Lett*., 1991, **32**, 1737.
171. E. W. Della and S. D. Graney, *Tetrahedron Lett*., 2000, **41***,* 7987.
172. A. A. Ponaras and O. Zaim, *Tetrahedron Lett*., 1993, **34**, 2879.
173. A. A. Ponaras and O. Zaim, *Tetrahedron Lett*., 2000, **41**, 2279.
174. C. Chatgilialoglu, D. Crich, M. Komatsu, and I. Ryu, *Chem. Rev*., 1999, **99**, 1991.
175. S. M. Allin, W. R. S. Barton, W. R. Bowman, and T. McInally, *Tetrahedron Lett*., 2001, **42**, 7887; M. –L. Bennasar, T. Roca, R. Griera and J. Bosch, *Org. Lett*., 2001, **3**, 1697; M. –L. Bennasar, T. Roca, R. Griera, M. Bassa, and J. Bosch, *J. Org. Chem.,* 2002, **67**, 6268.
176. R. Braslau, M. O. Anderson, F. Rivera, A. Jimenez, T. Haddad, and J. R. Axon, *Tetrahedron*, 2002, **58**, 5513; S. Bath, N. M. Laso, H. Lopez-Ruiz, B. Quiclet-Sire, and S. Z. Zard, *Chem. Commun*., 2003, 204.
177. R. H. Tale, *Org. Lett*., 2002, **4**, 1641.
178. T. D. Bradshaw, S. Wrigley, D. F. Shi, R. J. Schulz, K. D. Paull and M. F. G. Stevens, *Br. J. Cancer*, 1998, **77**, 745.

179. L. Benati, G. Calestani, R. Leardini, M. Minozzi, D. Nanni, P. Spagnolo, and S. Strazzari, *Org. Lett.*, 2003, **5**, 1313.
180. K. C. Majumdar, A. Biswas, and P. P. Mukhopadhyay, *Synthesis*, 2003, 2385.
181. K. Miura, Y. Ichinose, K. Nozaki, K. Fugami, K. Oshima, and K. Utimoto, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 143.
182. H. Togo and O. Kikuchi, *Heterocycles*, 1989, **28**, 373.
183. P. Rigollier, J. R. Young, L. A. Fowley, and J. R. Stille, *J. Am. Chem. Soc.*, 1990, **112**, 9441.
184. L. J. Beckwith and S. Gebra, *Aust. J. Chem.*, 1992, **45**, 289.
185. K. Jones and J. M. D. Storey, *J. Chem. Soc., Chem. Commun.*, 1992, 1766.
186. B. Ding, Z. Teng, and R. Keese, *J. Org. Chem.,* 2002, **67**, 8906.
187. D. L. J. Clive and E-S. Ardelean, *J. Org. Chem.,* 2001, **66**, 4841.
188. K. Tamao, T. Tanka, T. Nakajima, R. Sumiya, H. Arai, and Y. Ito, *Tetrahedron Lett.*, 1986, **27**, 3377; K. Tamao, T. Nakajima, R. Sumiya, H. Arai, N. Higuchi, and Y. Ito, *J. Am. Chem. Soc.*, 1986, **108**, 6090; K. Tamao, T. Yamauchi, and Y. Ito, *Chem. Lett.*, 1987, 171; S. H. Bergens, P. Noheda, J. Whelan, and B. Bosnich, *J. Am. Chem. Soc.*, 1992, **114**, 2121; S. H. Bergens, P. Noheda, J. Whelan, and B. Bosnich, *J. Am. Chem. Soc.*, 1992, **114**, 2128.
189. S. Amrein and A. Studer, *Chem. Commun.*, 2002, 1592.