# HETEROATOM RADICAL ADDITION-CYCLIZATION AND ITS SYNTHETIC APPLICATION

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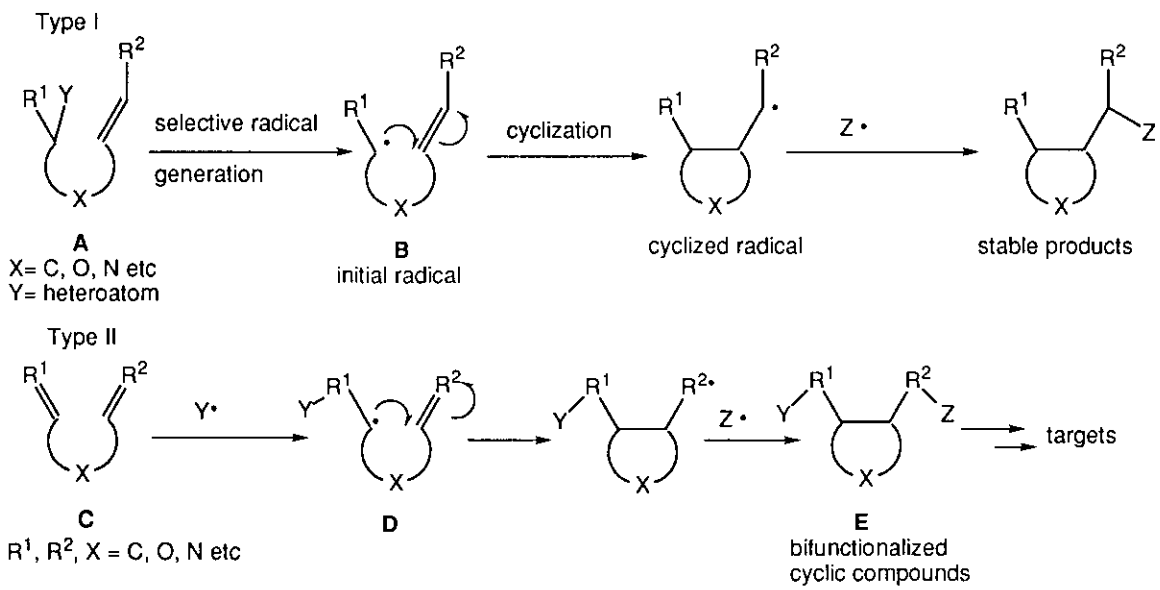
**Abstract**- Heteroatom radical and heteroatom-mediated addition-cyclizations of the substrates including various types of multiple bonds are reviewed from a synthetic point of view.

Contents

## 1. INTRODUCTION

Strategies involving radical reactions have become preeminent tools in organic synthesis.[1] Free radical-mediated cyclization has particularly developed as a powerful method for preparing various type of cyclic compounds *via* carbon-carbon bond forming processes. The advantages of radical cyclization for the synthetic chemists include high functional group tolerance, mild reaction conditions and high levels of regio- and stereoselectivities. Generally, radical cyclization reactions comprise three basic steps: selective radical generation, radical cyclization, and conversion of the cyclized radical to the final stable product. For the generation of the initial radical, two types of procedure can be employed (Scheme 1). Therefore, radical cyclizations can be classified into two types, based on the structures of the radical initiators.[2] Type I radical cyclizations proceed through the formation of a carbon centered radical (**B**) by the homolytic cleavage of a carbon-heteroatom bond in **A**, such as C-X, C-S, C-Se, and so on. One drawback in the type I cyclization is loss of the inherent functional groups. Alternatively, type II radical cyclization is designated as radical addition-cyclization and defined as one in which the carbon centered radical (**D**) is generated by the addition of a radical Y to a multiple bond such as alkene, alkyne, carbonyl, imino and cyano groups. Type II cyclizations have at least three advantages over the type I counterparts: (a) the starting substrates (**C**), which possess two multiple bonds, are relatively readily available and/or prepared; (b) the radical source (Y) and the radical trapping agent (Z) are also readily available and chosen depending upon the structure of target molecules, and (c) the cyclized products (**E**) are bifunctionalized and thus regarded as useful key intermediates for the further target molecules.




**Scheme 1**

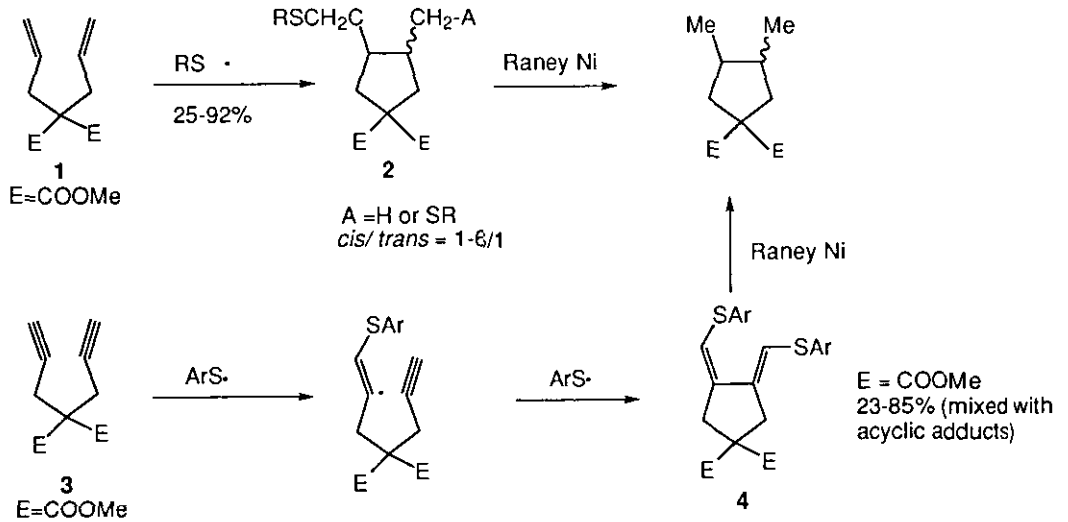
This review concentrates on heteroatom radical addition-cyclization of the appropriate substrates in which two multiple bonds are incorporated generally at the terminal positions. Multiple bonds are carbon-carbon double and triple bonds, carbon-heteroatom double and triple bonds, and other related functional groups

such as allene, isothiocyanate and so on. However, space limitations have prevented description of the addition-cyclizations involving thiocarbonates, thiocarbamates, thioxanthates, and thiohydroxamates in addition to tandem radical addition-cyclizations of two and more substrates. As a related heteroatom addition-cyclization, several examples of samarium-mediated addition-cyclizations are summarized. In order to avoid large Figures and Tables, most representative examples have been selected from original papers. The interested readers can accumulate the important features by reading structures and approach to the original papers for more details. Many excellent review articles and books dealing with radical cyclizations are available.[1,3]

## 2. Thiyl Radical Addition-Cyclization

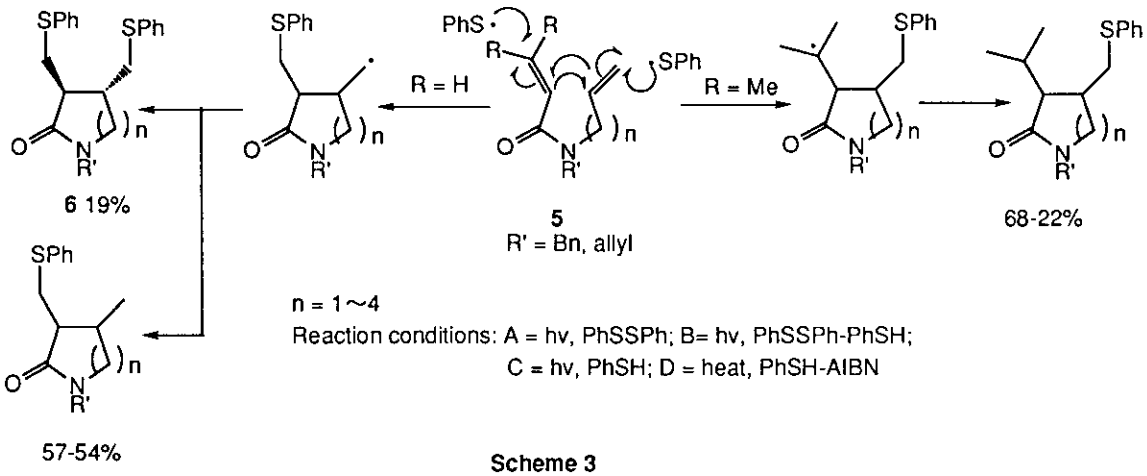
### 2-1. Thiyl Radical Addition-Cyclization of Carbon-Carbon Multiple Bonds

Kuehne[4] has explored the thiyl radical induced cyclization of dienes (Scheme 2). Thus, diallylmalonate (**1**) was subjected to the radical reaction in the presence of either ethanethiol, dimethyl disulfide, or bis(trifluoromethyl) disulfide under either thermal or photochemical condition to give good yields of *cis*- and *trans*-disubstituted cyclopentanes (**2**) (6:1). The same reaction was extended to the synthesis of natural dienylterpenes such as $\alpha$-acoradiene, $\alpha$-bulnesene, and geranyl acetate, of which the former two terpenes were effectively converted into the the corresponding terpene derivatives. Thiyl radical cyclization of dienes proceeds when unstrained cyclopentanes can be formed. Cyclization yields decrease in favor of the formation of acyclic adducts when cyclizations are forced towards energetically less favored, strained or six-membered ring closure. No significant cyclization arises from attack on an aromatic ring. The same group[5] has also reported the first example of thiyl radical addition-cyclization of 1,6-diyne (**3**) under photochemical condition which however proceeds not cleanly to give a mixture of acyclic adducts as precursors for the cyclized products. The alkylthiomethyl and arylthiomethylene groups of cyclized products (**2**, **4**) were reductively desulfurizated to the methyl group.



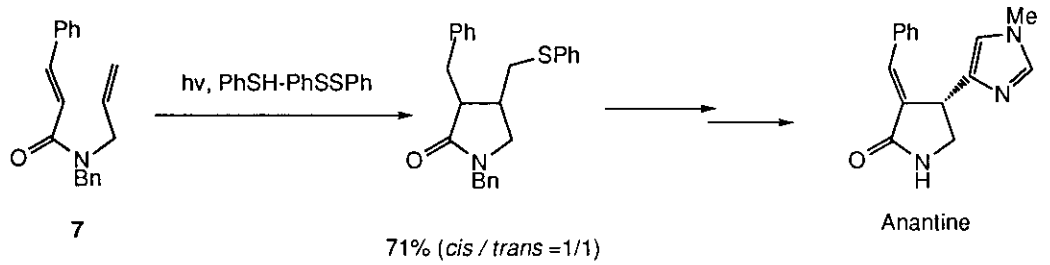

Scheme 2

Naito[6] has systematically investigated thiyl radical addition-cyclization of dienyl amides (**5**) under four different conditions and established a novel synthetic method for bifunctionalized cyclic heterocycles (**6**) (Scheme 3). Employing the dienes with two different double bonds, one that is in conjugation with the amide group and the other that is isolated, his group[2] established a new method for the synthesis of five- to eight-membered lactams in which the preferential formation of the *trans*-cyclized lactams was observed.



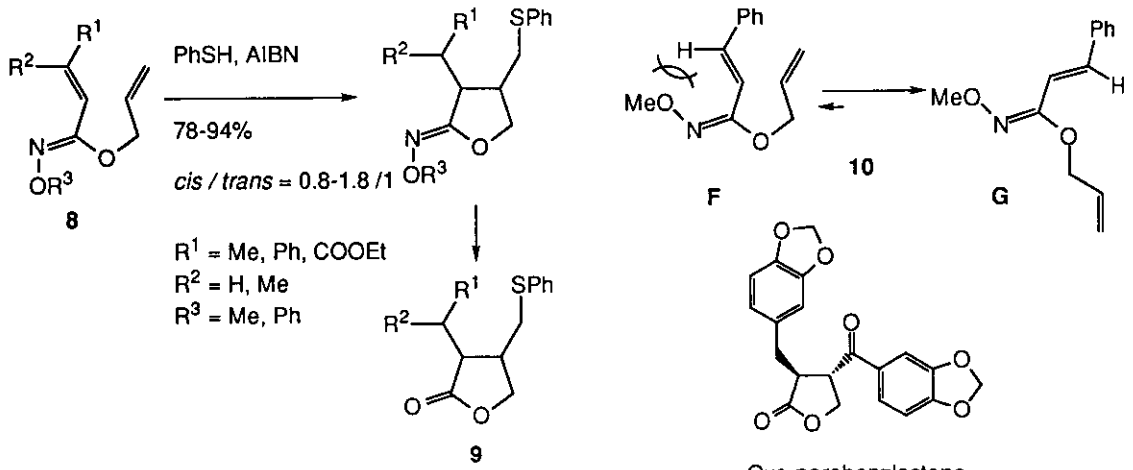

**Scheme 3**

The thiyl radical addition-cyclization was successfully applied to the synthesis of biologically active compounds such as alkaloids,[7] lignans,[8] and amino acids.[9] Anantine and the related alkaloids having the similar structure to pilocarpine which is used as a muscarinic agonist for the symptomatic treatment of Alzheimer's disease are stereoselectively synthesized *via* thiyl radical addition-cyclization of dienyl amide (**7**) (Scheme 4).



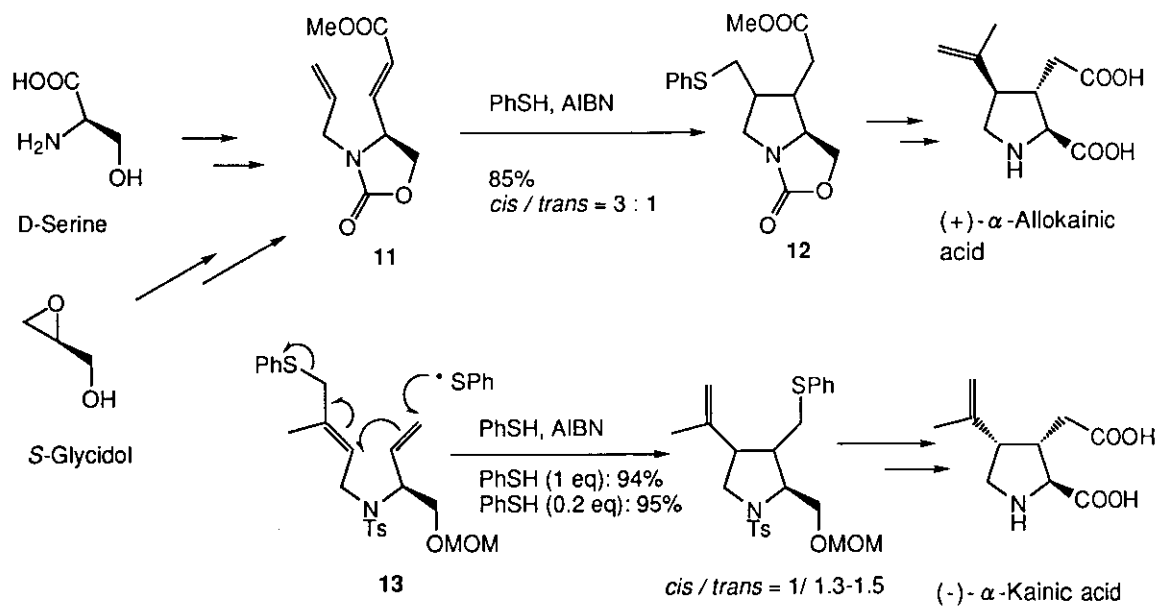

**Scheme 4**

Thiyl radical addition-cyclization of the diene (**8**) tethered with *Z*-hydroximate which is *N*-alkoxy imidate and an ester analog was employed as a key reaction for the novel synthesis of 3,4-disubstituted lactones (**9**) (Scheme 5).[8a] Unsuccessful cyclization of *E*-hydroximate (**10**) was reasonably explained by the disfavorable conformation (**G**) for cyclization. The strategy proved to be very useful for the stereoselective synthesis of a lignan, oxo-parabenzlactone.[8b]



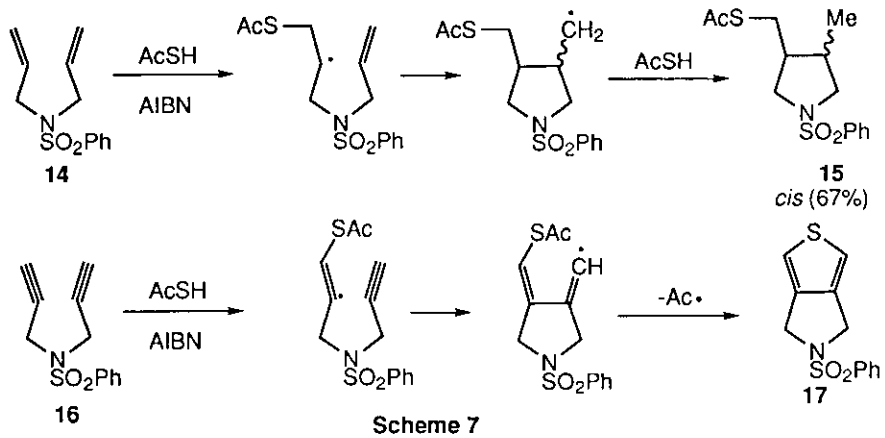

Scheme 5

Kainoids, principally neuroexcitatory agents were also synthesized[9] *via* thiyl radical addition-cyclization of optically active diene (**11**), readily available from natural sources (Scheme 6). D-Serine and *S*-glycidol were easily converted into dienyloxazolone (**11**) which was subjected to thiyl radical addition-cyclization to afford bifunctionalized product (**12**). Conversion of the resulting phenylthiomethyl group into the isopropenyl group accomplished the chiral synthesis of (+)-$\alpha$-allokainic acid.[9a] Naito[9b] has improved the radical reaction to thiyl radical addition-cyclization-elimination of diene (**13**) which issubstituted with the phenylthio moiety at allylic position. Furthermore, he succeeded in the thiyl radicaladdition-cyclization-elimination to a catalytic version which was used as a key reaction for an enantioselective synthesis of (-)-$\alpha$-kainic acid.[9b]



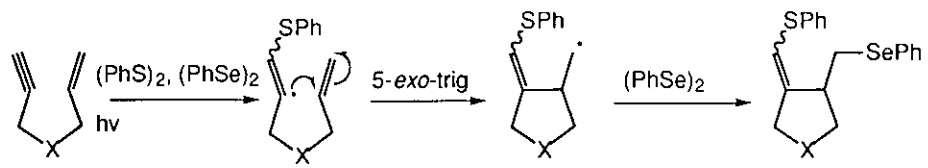

Scheme 6

Padwa[10] has studied the radical addition-cyclization of diallylsulfonamide (**14**) using thiolacetic acid which gave a mixture of *cis*- and *trans*-disubstituted cyclic pyrrolidines (**15**). The preferential formation of the *cis*-isomer is explained by the effects of orbital symmetry. *N*,*N*-Bis(2-propynyl)benzenesulfonamide (**16**) gave bicyclic product (**17**) as a result of the addition of the thiolacetyl radical onto the triple bond followed by internal 1,5-cyclization (Scheme 7).




Scheme 7

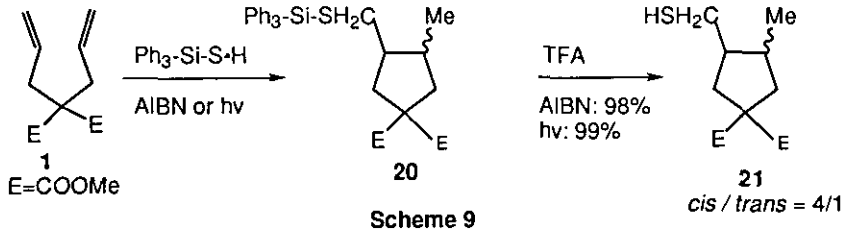
Based on the relative reactivities between the thio and seleno radicals and between disulfide and diselenide, Sonoda[11] has found that two different chalcogeno-groups can be introduced simultaneously into carbon-carbon triple bonds with excellent selectivity. As an extension to the intramolecular systems, his group demonstrated thiyl radical addition-cyclization of enynes (**18**) using $(PhS)_2$-$(PhSe)_2$ binary system under photochemical condition. The product (**19**) bears phenylthio and phenylseleno groups at both terminal positions regioselectively (Scheme 8).




Scheme 8

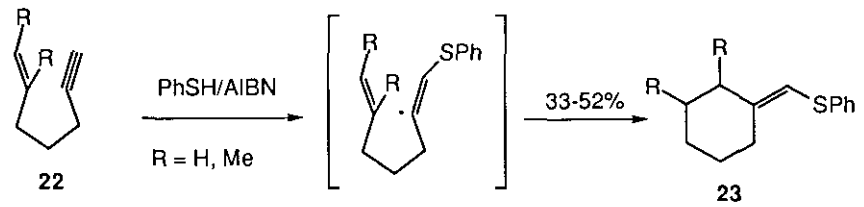
Gareau[12] has reported the addition-cyclization of the diene (**1**) using triphenylsilanethiol as a $H_2S$ equivalent under thermal and photochemical conditions. The reagent ($Ph_3SiSH$) is easily prepared in one step from triphenylsilane and molecular sulfur. Initially formed cyclized product (**20**) was readily hydrolyzed with TFA to give cyclized thiol product (**21**) in excellent yields (Scheme 9).

Broka[13] has reported the addition-cyclization of the enynes (**22**) using thiophenol which proceeded regioselectively to give cyclohexylidene thioethers (**23**). However, this reaction depends upon the



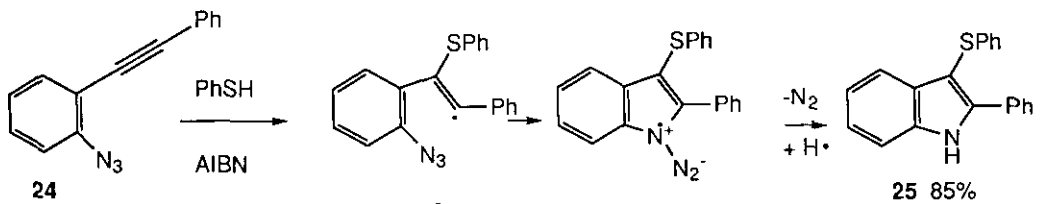

**Scheme 9**

reaction conditions, thus the protocol of slowly adding the thiol (over 16 h) to a refluxing solution of the substrate (**22**) and AIBN. Thus, the concentration of thiophenol as a hydrogen atom donor could be maintained at a low level allowing the vinyl radical every chance to cyclize though the reaction could not tolerate a longer connecting side chain leading to the formation of only uncyclized adduct in 1-octen-7-yne (Scheme 10).




**Scheme 10**

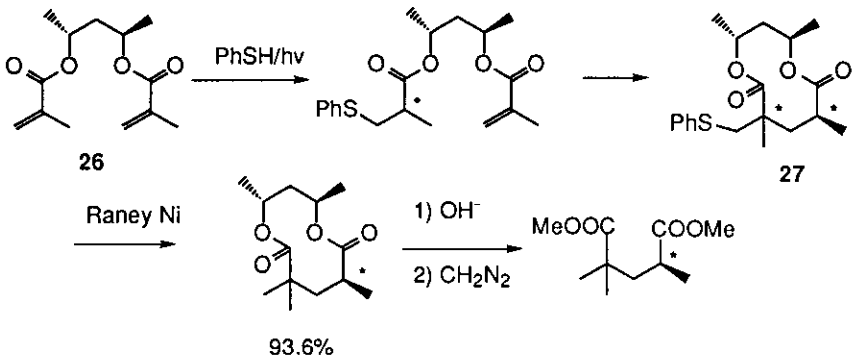
Thiyl radical addition-cyclization of 2-azidodiphenylacetylene (**24**) was also found to give indole compounds (**25**) as a result of radical addition to triple bond followed by cyclization of the resulting vinyl radical onto the aromatic azide group (Scheme 11).[14]




**Scheme 11**

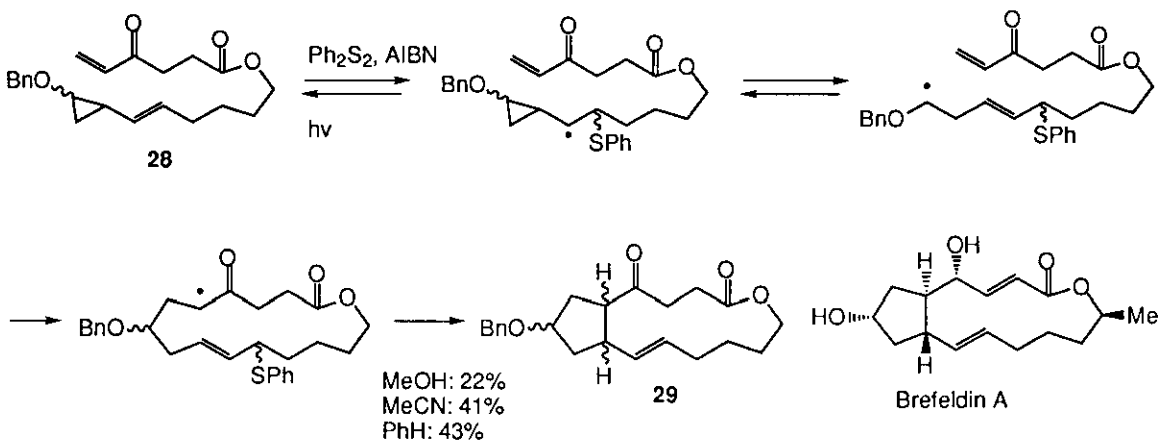
Sugimura[15a] has established the diastereoselective thiyl radical addition-cyclization of $C_2$-symmetrical methacrylate (**26**) of (2*R*,4*R*)-2,4-pentanediol under photochemical condition to give dimer type product (**27**) which was eventually converted into (4*S*)-2,2,4-trimethylglutarate. The excellent yield of dimer type product (**27**) is noteworthy because the intramolecular radical addition step is the entropically unfavorable construction of ten-membered ring (Scheme 12). Pattenden[15b] has developed the thiyl radical addition-cyclization of undeca-1,4,8-triene hydrocarbon humulene leading to the formation of substituted bicyclo[6.3.0]undecene.

Feldman[16] has applied thiyl radical addition-cyclization to the total synthesis of natural products, rocaglamide and brefeldin families. Following by the synthesis of the tricyclic cyclopenta[*b*]benzofuran framework of rocaglamide,[16a] he[16b] has demonstrated that thiyl radical-addition-cyclization-elimination of



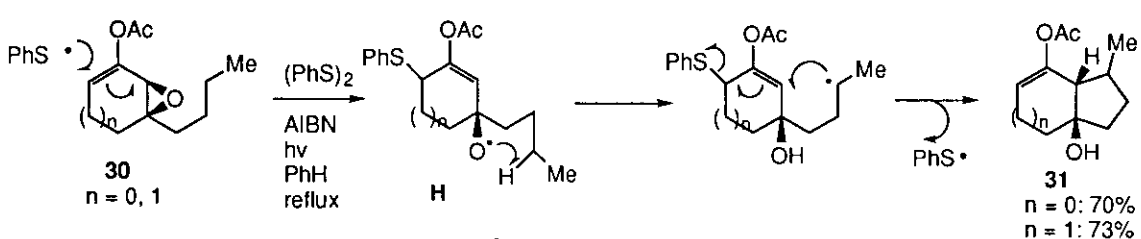

**Scheme 12**

substituted vinylcyclopropanes (**28**) with activated alkenes proceeds in good yield to provide bicyclic products (**29**) featuring an 13-membered ring appended onto the core vinylcyclopropane unit which is coincident with the skeleton of the brefeldin family of naturally occurring antibiotics (Scheme 13).



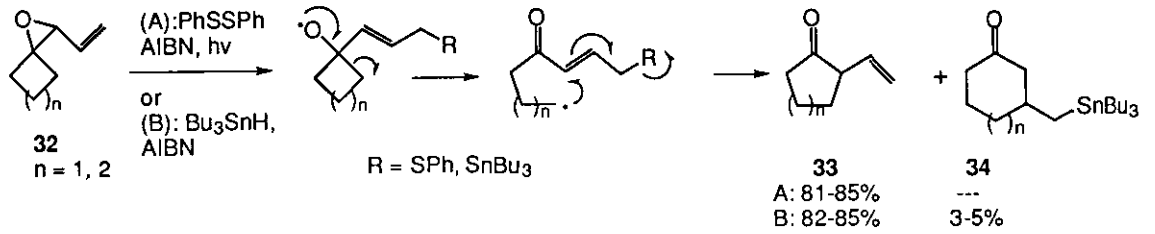

**Scheme 13**

Rawal[17] has developed the thiyl radical addition-fragmentation-cyclization of acetoxyalkenyl epoxides (**30**) to give acetoxyalkenyl cyclopentanols (**31**). The reaction proceeds under photochemical condition as follows. Addition of a thiyl radical to a suitably protected epoxy ketone enolate (**30**) generated the requisite oxyranyl carbinyl radical (**H**) which went through the tandem sequence involving 1,5-hydrogen abstraction and elimination-cyclization of phenylthiyl radical (Scheme 14).



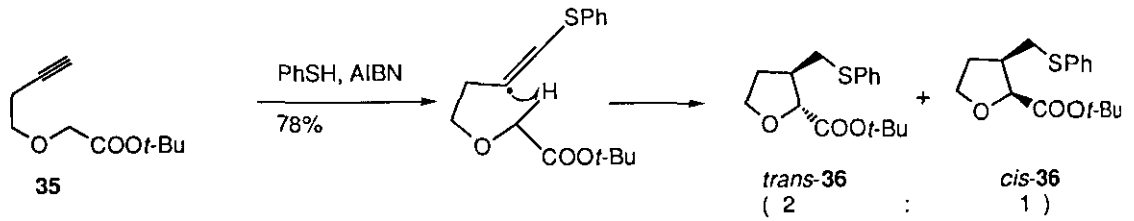

**Scheme 14**

Kim[18] has established a novel reaction sequence involving the thiyl radical addition-fragmentation-cyclization-elimination of vinyl spiro epoxides (**32**) under photochemical condition employing diphenyl disulfide and AIBN. The reaction is useful for the synthesis of cyclopentanone (**33**) and cyclohexanone derivatives (**34**) *via* the feasible ring expansion of alkoxy radical (Scheme 15).




**Scheme 15**

Burke[19] has developed the thiyl radical addition-cyclization of alkynes (**35**) in which the second cyclization reaction step involves 1,5-hydrogen atom transfer to afford 2,3-disubstituted tetrahydrofurans (**36**) (Scheme 16).

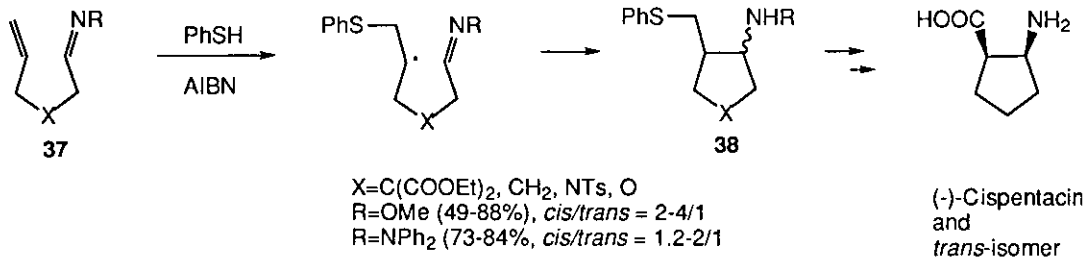



**Scheme 16**

## 2-2. Thiyl Radical Addition-Cyclization of Carbon-Heteroatom Multiple Bonds

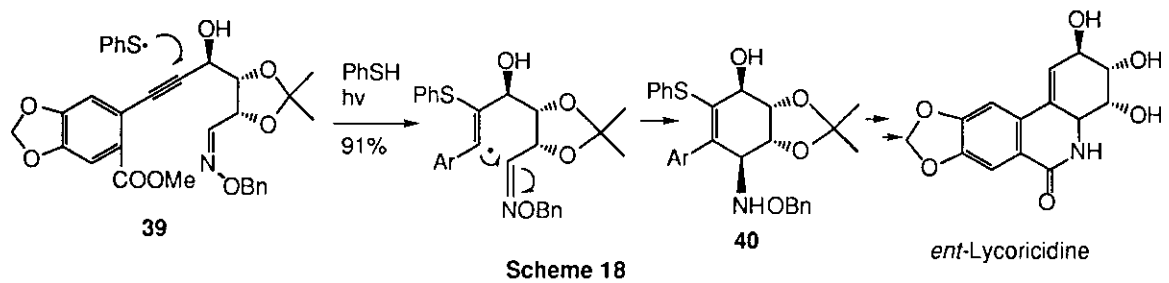
Carbon-heteroatom multiple bonds have been also used as potential radical acceptors in thiyl radical addition-cyclizations. They can be classified into two groups, one is that carbon-heteroatom multiple bond plays as a thiyl radical acceptor in the first step and the other is that carbon-heteroatom multiple bond plays as a radical acceptor of the resulting carbon radical which is formed by addition of thiyl radical as a first step. Two groups[20,21] reported independently the thiyl radical addition-cyclizations of the alkenyl tethered oxime ethers and related hydrazones. Since both oxime ethers and hydrazones are well known to be effective radical acceptors, Naito[20] has investigated the thiyl radical addition-cyclization of the alkenyl tethered oxime ethers and hydrazones (**37**) and found that the radical cyclization is powerful method for construction of the disubstituted five-membered cyclic compounds (**38**) which were also effectively converted into cyclic $\beta$-amino acids including (-)-cispentacin (Scheme 17). At the almost same time, Kaim[21] has reported the same type of thiyl radical addition-cyclization of hydrazones and oxime ethers tethered with alkene and alkyne.

Keck[22] has succeeded in total synthesis of *ent*-lycoricidine through the thiyl radical addition-cyclization of oxime ether tethered with alkyne as a key reaction (Scheme 18). Though the attempted stannyl radical



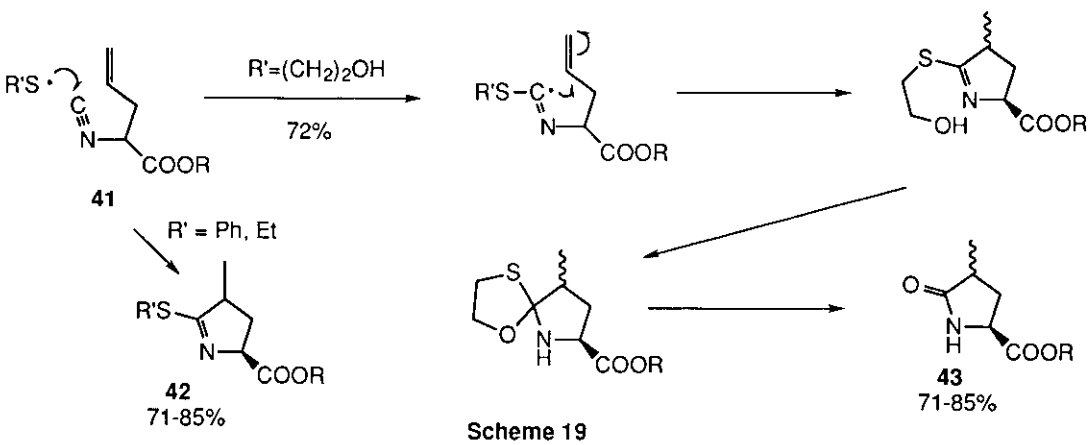

**Scheme 17**

addition-cyclization of the alkynyl oxime ether (**39**) was unsuccessful, the thiyl radical addition-cyclization proceeded smoothly under photochemical condition to give the desired product (**40**) which was readily converted into *ent*-lycoricidine *via* three operations involving $SmI_2$ procedure.




**Scheme 18**

Another example is the thiyl radical addition-cyclization of alkenyl and alkyl isocyanides reported by Bachi[23] (Scheme 19). Considering Saegusa's finding[24] on radical reaction of isocyanides with thiols, he has found that upon treatment with thiols such as benzenethiol and ethanethiol in the presence of AIBN, isocyanides (**41**) gave the corresponding 2-arylthio- or 2-alkylthio-1-pyrrolines and related compounds (**42**). Interestingly when mercaptoethanol was used as a thiol, pyroglutamates (**43**) were obtained in one step.

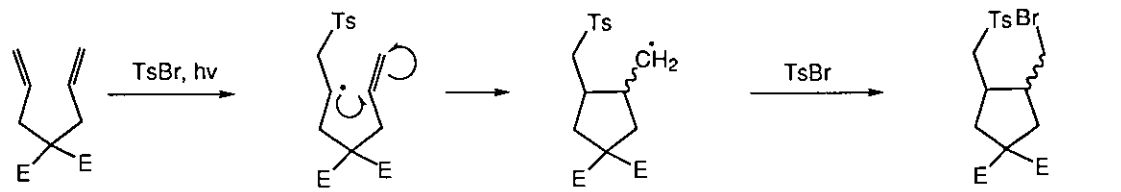



**Scheme 19**

## 3. Sulfonyl Radical Addition-Cyclization

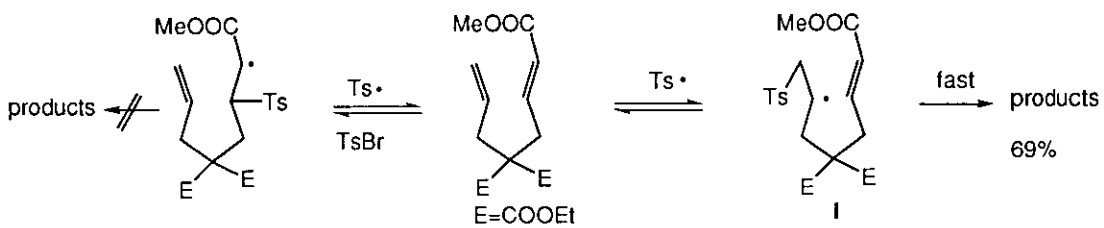
### 3-1. Sulfonyl Radical Addition-Cyclization Using Arylsulfonyl Halides

Bertrand[25] and Chuang[26] groups have independently studied the sulfonyl radical addition-cyclization of substrates having multiple bonds. Based on his discovery of the radical addition of sulfonyl halides to nonconjugated dienes leading to the formation of bifunctional carbocycles and heterocycles, Bertrand[25] has investigated systematically sulfonyl radical addition to nonconjugated dienes, particularly on the view of regio- and stereoselectivities including theoretical force-field calculations. The reactions were performed either by irradiating acetonitrile solution of dienes (**1**) in the presence of tosyl halide with a high-pressure mercury lamp, or in cholorobenzene under reflux. Generally, *cis*-**44** predominates though the *cis*/*trans* ratios are depending upon the number and nature of the substituents in position 3 with respect to the radical center and the reaction temperature employed (Scheme 20).




**Scheme 20**

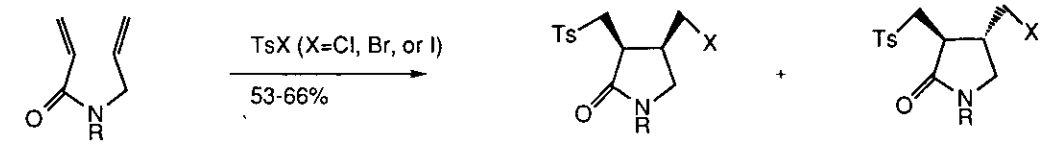
Most stereoselective example is the radical addition of tosyl bromide to dialkyl esters of diallylmalonic acid at room temperature leading to the formation in a 93 to 7 *cis*:*trans* proportion. This result was explained by the Beckwith stereoelectronic model of a chair-like transition state and corroborated by theoretical force-field calculations.[25c] The systematic studies on sulfonyl radical addition-cyclization of unsymmetrical 1,6-dienes bearing both a nucleophilic and an electrophilic double bond clearly indicated that highly chemo-, regio-, and stereoselective sulfonyl radical addition-cyclization is not related to the generally accepted electrophilic nature of tosyl radical but the reversibility of the first step, *i.e.* tosyl radical addition to the double bond, which favors the formation of the adducts resulting from the one intermediate radical (**I**) that cyclizes faster (Scheme 21).[25d]




**Scheme 21**

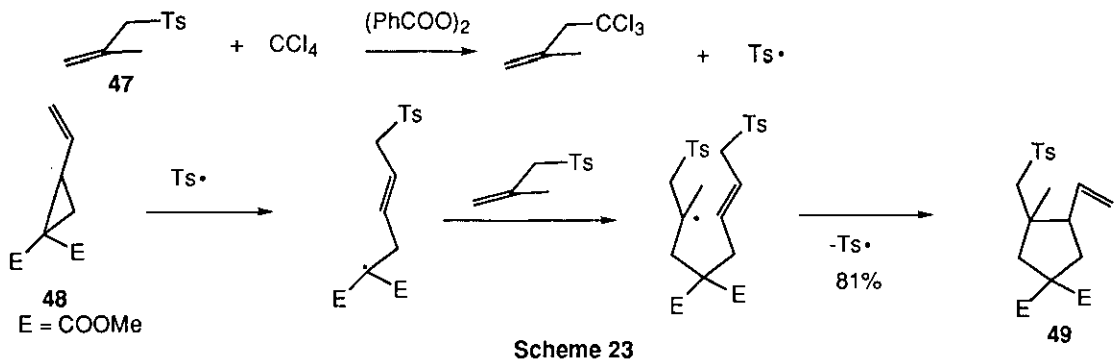
The radical addition[25d] of tosyl halide to the acrylamides (**45**) led mainly to diastereomeric pyrrolidones (**46**) in favor of *trans*-isomer by chemoselective addition to the electron-poor double bond. Though the

preference for the *trans*-isomer seems to be unusual in the field of 5-*exo* radical cyclization, the same results were observed in the radical cyclization using thiyl and tin radicals and classical stereoelectronic model of "chair-like" and "boat-like" transition states may not apply to $\alpha$-carbamoyl radicals involving a rather rigid amide moiety (Scheme 22). MM force field calculations recently performed on other $\alpha$-carbamoyl-5-hexenyl radicals conclude that the most stable transition state leads to the *trans* cyclized product, which therefore, must be the kinetic product.



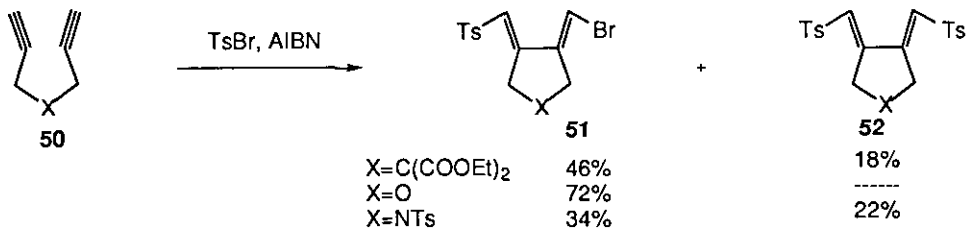

**Scheme 22**

Furthermore, sulfonyl radical addition-cyclization of 1,6-diene was applied to the synthesis of kainoids[25e] and pyranoside.[25f] Chuang[26] extended the sulfonyl radical addition-cyclization reaction to three components coupling reaction. For example, the sulfonyl radical addition-cyclization of vinylcyclopropane (**48**) by using allyl sulfone (**47**) as a sulfonyl radical precursor and an acceptor provided a useful route to functionalized cyclopentanes (**49**) (Scheme 23).[26a]




**Scheme 23**

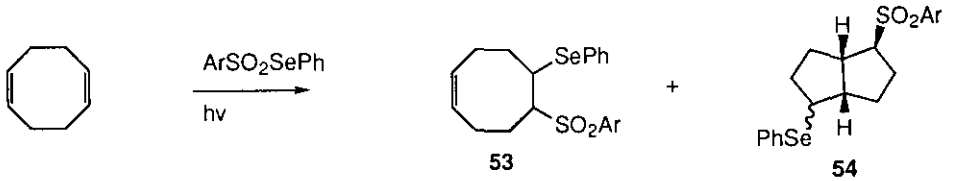
Correa[27] has investigated sulfonyl radical addition-cyclization of several diallylic compounds such as diallyl sulfides, diallyl sulfones, simple hexa-1,5-diene, and allyl methacrylate and found that the cyclization occurs in some cases but the yields are quite low. Caddick[28] has postulated that sulfonyl radical addition-cyclization would lead to an electron deficient $\pi$-system; further addition would be disfavored due to the electrophilic nature of sulfonyl radicals. Based on his proposal, treatment of diyne (**50**) with TsBr in the presence of AIBN in refluxing benzene gave five- and six-membered carbocycles and heterocycles containing vinyl sulfone (**52**) and vinyl halide groups (**51**) (Scheme 24). The reaction has a clear advantage over related tin based transformations.




Scheme 24

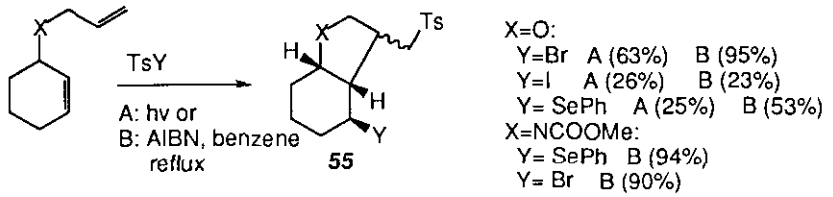
### 3-2. Sulfonyl Radical Addition-Cyclization Using Arylselenosulfonate

In 1984, Kice[29] reported that arylselenosulfonates undergo facile but non-selective sulfonyl radical addition-cyclization of 1,5-cyclooctadiene to give bicyclic product (**54**) as a mixture of 1,2-adduct (**53**) (Scheme 25).



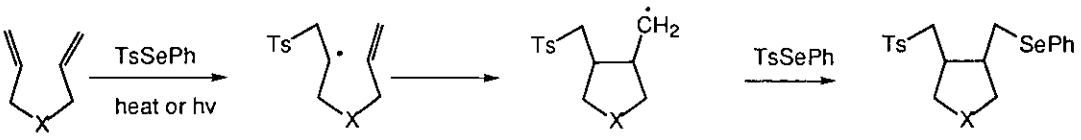

Scheme 25

Simpkins[30] has compared the efficiency of sulfonyl radical addition-cyclization using TsX with analogous reaction using TsSePh which displays many features in common with the corresponding TsX reactions and may be limited to substrates capable of rapid 5-*exo*-cyclization. However, the reaction gives cyclized alkyl sulfones (**55**) containing the synthetically useful phenylselenyl or halogeno functionality (Scheme 26).




Scheme 26

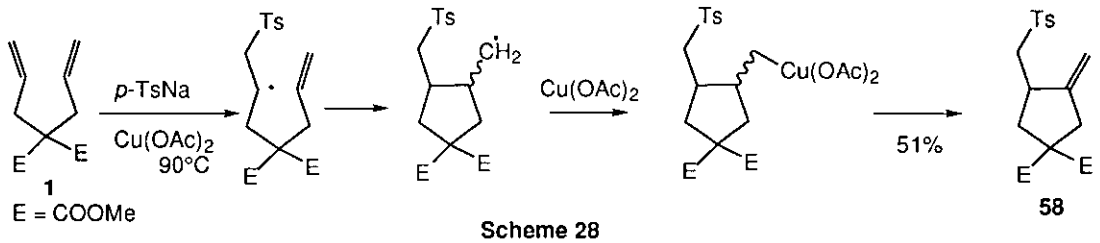
The sulfonyl radical addition-cyclization employing arylselenosulfonate has reported by Chuang[31] who established the regio- and stereoselective radical addition-cyclization of 1,6-diene (**56**) under both photochemical and thermal conditions leading to the formation of functionalized cyclopentane systems (**57**) (Scheme 27). Nitrogen quaternization of the dienylamines as a substrate is found to lead a 20% increase in the diastereoselectivity of the sulfonyl radical addition-cyclization using TsSePh probably due to the triple contribution of polar effect, enthalpic effect, and *gem*-dimethyl effect.[32]




Scheme 27

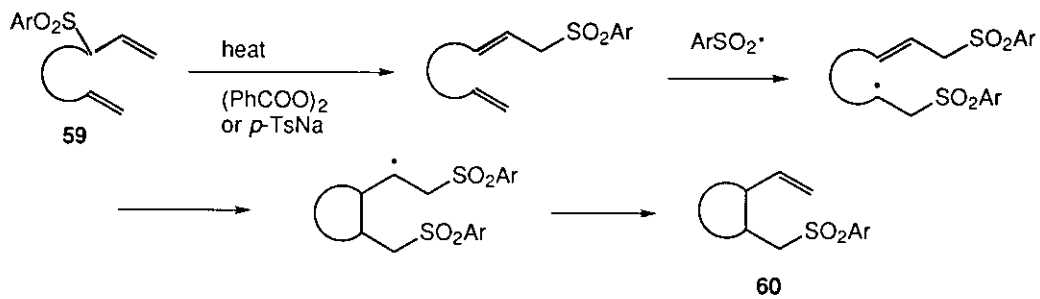
## 3-3. Sulfonyl Radical Addition-Cyclization Using Arylsulfonyl Cyanide and Sodium Arylsulfinate

Since *p*-toluenesulfonyl cyanide (TsCN) has been successfully utilized in many synthetic aspects, Fang[33] applied the sulfonyl radical addition-cyclization using TsCN to norbornadiene, pinene, and 1,5-cyclooctadiene which gave effectively cyclic compounds containing the cyano and sulfonyl groups. Chuang[34] has further studied the sulfonyl radical addition-cyclization under the conditions by using sodium *p*-toluenesulfinate/copper (II) acetate which afforded cyclic compounds (**58**) bearing *p*-toluenesulfonyl group (Scheme 28).




Scheme 28

Whitham[35] has also the investigated sulfonyl radical addition-cyclization-elimination reaction of unsaturated allylic sulfones under the condition in the presence of either benzoyl peroxide or sodium *p*-toluenesulfinate in aqueous acetic acid. Treatment of readily available unsaturated sulfone (**59**) with $ArSO_2Na$ in aq. AcOH at 100 ℃ gave a stereoisomeric mixture of the vinylcyclopentylmethyl sulfones (**60**) in 95% yield (Scheme 29).[35]



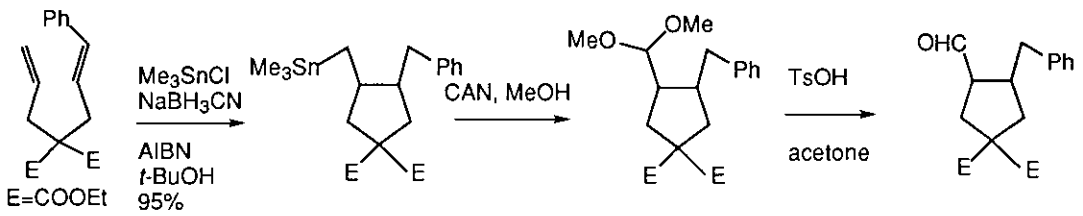

Scheme 29

## 4. Stannyl Radical Addition-Cyclization

There have been so many examples of stannyl radical addition-cyclization. In this Chapter they are classified by the type of multiple bonds in the substrates in which multiple bonds are either/both carbon-carbon or/and carbon-heteroatom bonds.

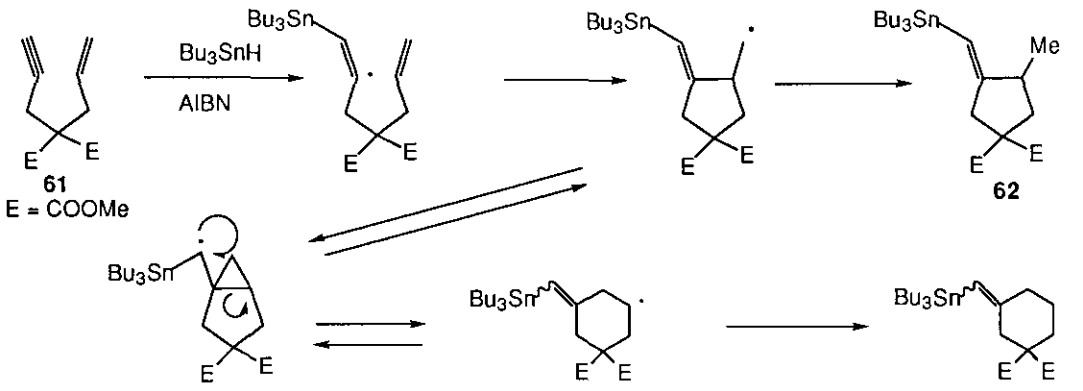
### 4-1. Stannyl Radical Addition-Cyclization of Carbon-Carbon Multiple Bonds

Hanessian[36] has reported that stannyl radical addition-cyclization of a variety of activated and unactivated dienes proceeds smoothly to afford monocyclic, bicyclic, and polycyclic compounds containing a vicinally substituted stannylmethyl group and an appropriate branch (Scheme 30). His group[36a] also established oxidative cleavage of the carbon-stannyl bond to give the corresponding aldehydes using ceric ammonium nitrate in methanol. The synthesis of natural antitumor lignan, burseran, was accomplished by applying the stannyl radical addition-cyclization of dienyl ether.[36b]




Scheme 30

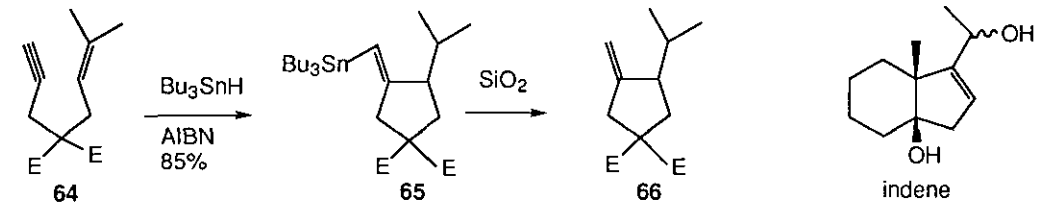
Stannyl radical addition-cyclization of vinyl acetylenes (**61**) is reported by Stork[37a] who established that the ratio of methylenecyclopentane (**62**) to methylenecyclohexane (**63**) increases with the concentration of substrate and tin hydride proposing that radical cyclizations are under thermodynamic control at low concentrations (Scheme 31).




| Molar concentration of $Bu_3SnH$ : Enyne | Product ratio |
|---|---|
| **61** | **62 : 63** |
| 0.02 : 0.02 | 1 : 4 |
| 0.3 : 0.25 | 4 : 1 |
| 2.2 : 1.9 | 100 : 1 |

Scheme 31

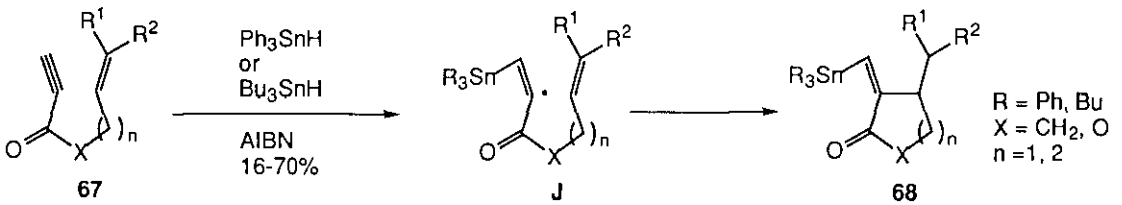
His group[37b] has also developed regioselective stannyl radical addition-cyclization of enyne (**64**) to give the tin-substituted methylenecyclopentane (**65**) in which the tin substituent was readily removed without effecting other structural changes: simple stirring with dry silica gel in methylene chloride caused protiodestannylation to **66**. A particularly striking example of regiocontrol in acetylenic olefins is also shown in indene synthesis (Scheme 32).




**64** E = COOMe **65** **66** indene

**Scheme 32**

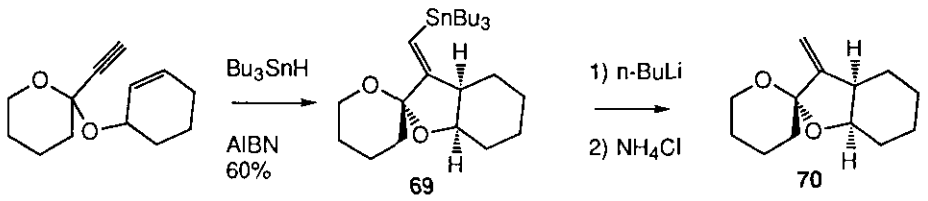
Lee[38] has investigated the stannyl radical addition-cyclization of enynes (**67**) in which triple bonds are conjugated with ketone or ester group. In each case, $\alpha$-methylene-$\gamma$-butyro- and valerolactones or $\alpha$-methylenecyclopenta- and cyclohexanones are obtained in good yields and the former $\gamma$-butyrolactone synthesis was successfully applied to the synthesis of lignans.[38c] In these cyclizations, *Z*-stannylvinyl radicals (**J**) are expected to show greater tendency to cyclize and acyclic products tend to be *Z*-isomers[38d] (Scheme 33).




**67** **J** **68**

**Scheme 33**

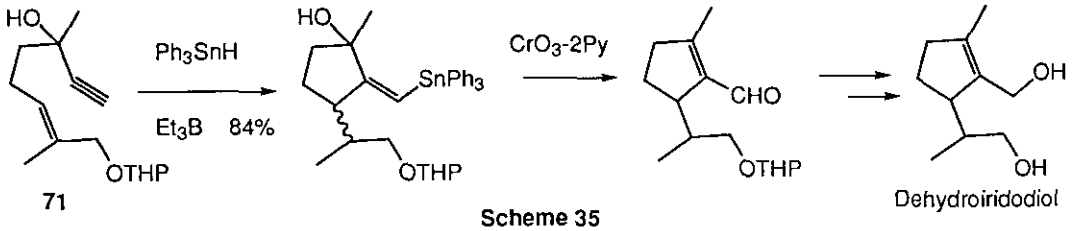
Ever since Stork's reports,[37] there have been so many examples of the application to natural product synthesis (Scheme 34). Parsons[39] has provided a new route to spiroacetals (**69**) and the construction of a model compound (**70**) for phyllanthocin synthesis by the combination of stannyl radical addition-cyclization and destannylation with BuLi.




**69** **70**

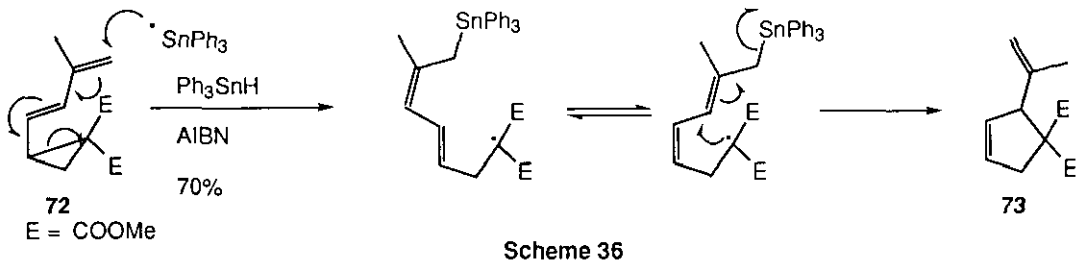
**Scheme 34**

Chapleur,[40] Thomas,[41] and Clive[42] applied effectively the stannyl radical addition-cyclization to the syntheses of carbohydrates, bryostatin 1, and triquinane system, respectively. Utimoto[43] has established triethylborane-induced stannyl radical addition-cyclization of enyne (**71**) by using a catalytic amount of $Et_3B$ and triphenylstannane in toluene and successfully applied the reaction to the synthesis of dehydroiridodiol and the related terpenes (Scheme 35).



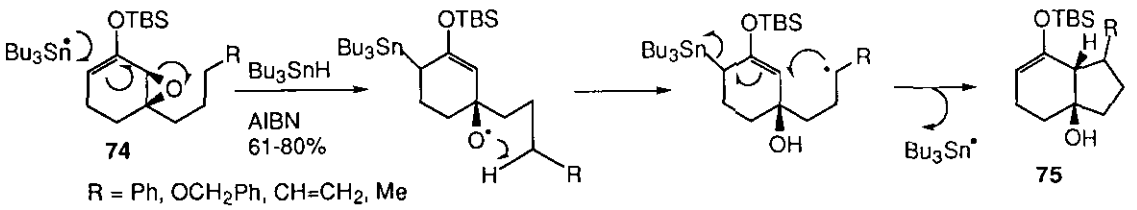

**Scheme 35**

As a further extension,[44] stannyl radical addition-cyclization was successfully extended to more complicated substrates (**72**) having dienylcyclopropane moiety which gave the substituted cyclopentanes (**73**) in good yields (Scheme 36). The use of triphenylgermyl hydride or benzenethiol instead of triphenyltin hydride also undertook the same type of radical addition-cyclizations to give the identical products.[44]




**Scheme 36**

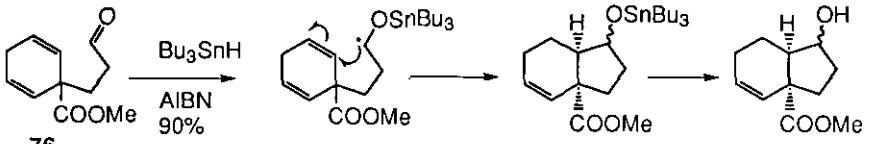
Tandem radical reaction *via* five steps has been reported by Kim[45] who showed that stannyl radical reaction of epoxy silyl enol ethers (**74**) provided a useful method for the synthesis of highly stereocontrolled *cis*-fused bicyclic compounds (**75**) (Scheme 37). His approach relied on stannyl radical addition to olefins, epoxide fragmentation to the alkoxy radical, 1,5-hydrogen transfer to generate carbon radical, cyclization, and elimination of stannyl radical to form the bicyclic compounds. Examples[17] of the related thiyl radical addition-cyclization of analogous substrates have been already described in Scheme 14.




**Scheme 37**

## 4-2. Stannyl Radical Addition-Cyclization of Carbon-Carbon Multiple Bonds and Carbonyl Compounds

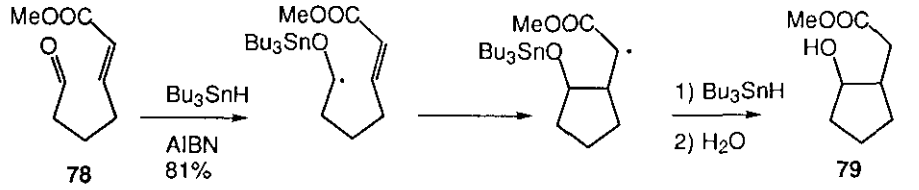
Stannyl radical addition-cyclization of either aldehyde or ketone connected with olefinic system has been reported by Beckwith[46] who observed that upon heating with tributylstannane the aldehyde (**76**) is converted into cyclized tin alkoxide (**77**) in 90% yield which was readily hydrolyzed to the corresponding alcohol (Scheme 38).




**76** **77**

**Scheme 38**

Enholm[47] reported the stannyl radical addition-cyclization of carbonyl compounds (**78**) tethered to the substituted olefinic system which provided a mild and regiocontrolled method to construct substituted cyclopentanols (**79**) and $\gamma$-lactones (Scheme 39). His group has also proposed the reaction pathway as follows: stannyl radical addition to the aldehyde carbonyl group to form *O*-stannyl ketyl radical which cyclizes by addition to another olefinic system to produce carbon-centered radical. The carbon radical is stabilized by the neighboring groups such as phenyl or ester group and then hydrogenated by tributyltin hydride to render the cyclized products and tributyltin radical which repeats the process.

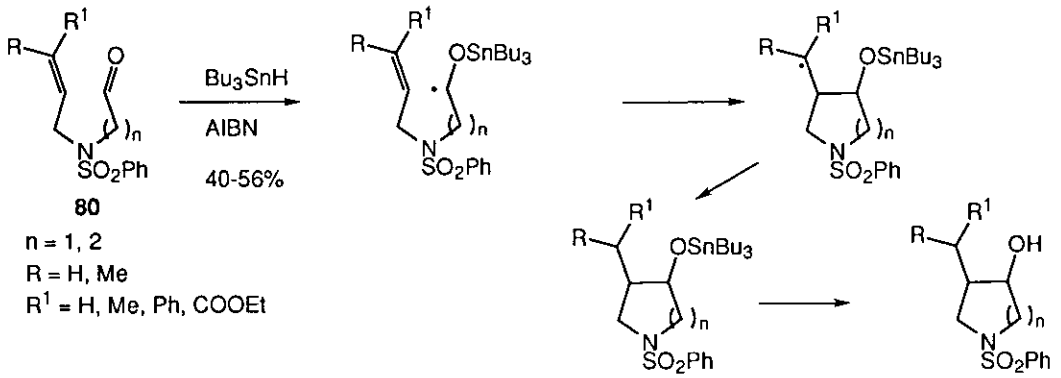



**78** **79**

**Scheme 39**

*trans* / *cis* = 58 / 42

Parsons[48] has investigated the stannyl radical addition-cyclization of a variety of $\alpha$- and $\beta$-amino aldehydes (**80**) to form substituted pyrrolidines and piperidines (**81**) under mild and neutral reaction condition (Scheme 40). The addition-cyclization using a variety of electron poor or rich carbon-carbon double bonds proceeded smoothly to afford hydroxy-pyrrolidines or -piperidines (**81**) after work-up. Related cyclizations using an alkyne or $\alpha,\beta$-unsaturated amide as a radical acceptor are problematic and low yielding. Lee[49] has also investigated almost same study on $\beta$-alkoxyacrylates tethered to terminal formyl group which gave oxacyclic ring products with secondary hydroxyl group.



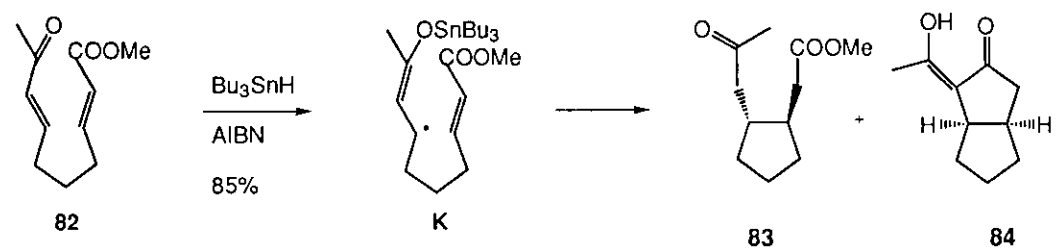

80

n = 1, 2
R = H, Me
$R^1$ = H, Me, Ph, COOEt

81

Scheme 40

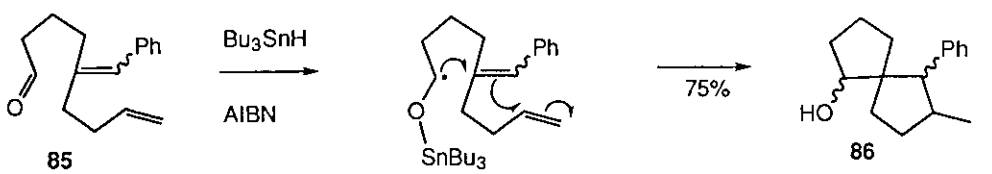
Considering that an allylic *O*-stannyl kety radical (**K**), produced by the reaction of enone (**82**) with a trialkyltin radical, would be resonance stabilized by the adjacent olefin moiety, Enholm[50a] has investigated the stannyl radical addition-cyclization of unsaturated ketone precursors which formed substituted cyclopentane rings (**83**) and bicyclo[3.3.0]ring systems (**84**) (Scheme 41).




82 K 83 ( 2.1 : 84 1 )

Scheme 41

Enholm[50b] has extended the stannyl radical addition-cyclization to tandem cyclization using various free radical precursors such as aldehydes and ketones. An example shown below is the formation of a spiro[4.4]nonane (**86**) by the radical addition-cyclization of dienyl aldehyde (**85**) (Scheme 42).

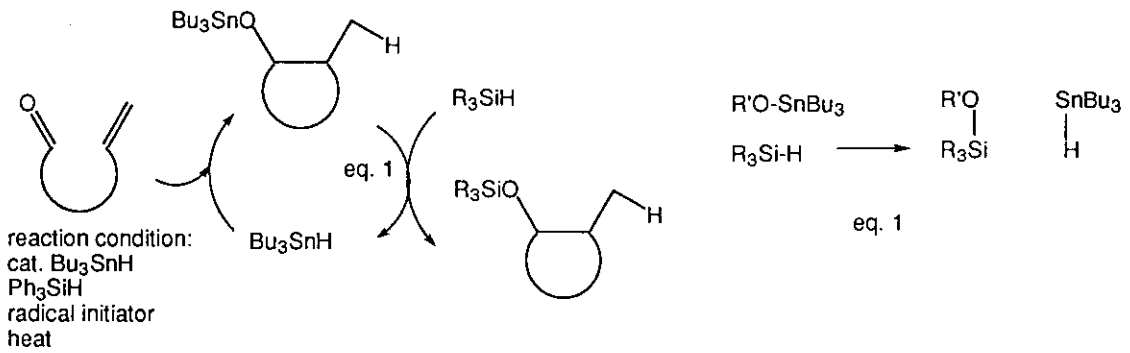



85 86

isomer ratio
2.5 : 2.5 : 3.0 : 1.0

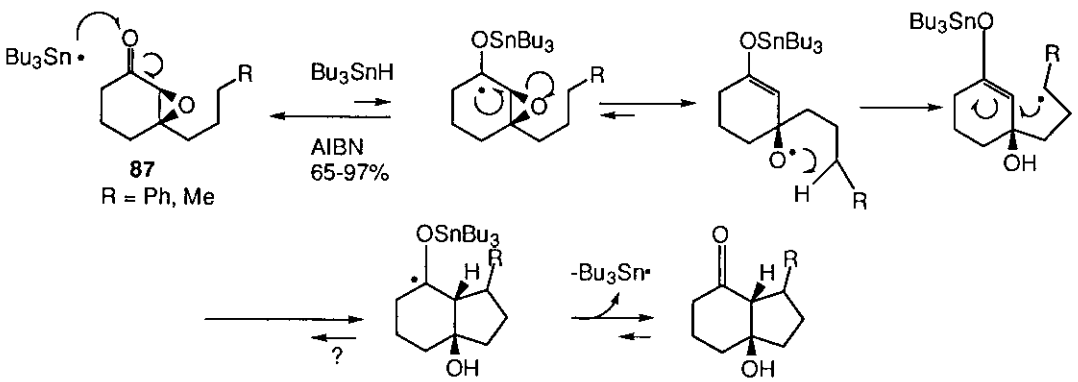
Scheme 42

Motivated both by an awareness of the toxicity of triorganotin species as well as by an interest in asymmetric catalyst, Fu[51] has reported the development of a tributyltin hydride-catalyzed, triphenylsilyl hydride-mediated radical addition-cyclization in which organotin hydride is used as a catalyst rather than as a stoichiometric reagent (Scheme 43).




Scheme 43

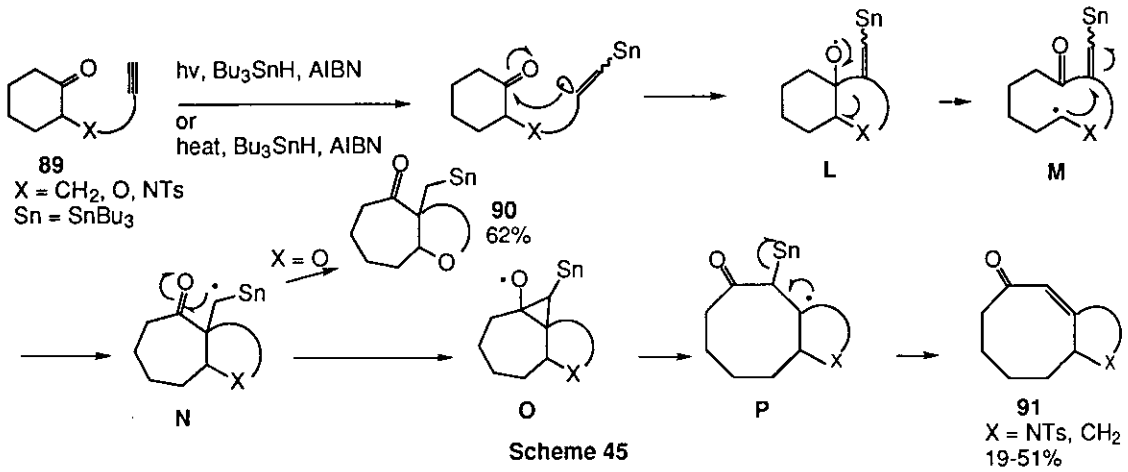
Rawal[52] has extended the radical addition-cyclization to epoxy ketones (**87**) which underwent stannyl radical addition to ketone moiety, concomitant epoxide fragmentation, hydrogen radical abstraction and final cyclization to give the bicyclic hydroxy ketones (**88**) (Scheme 44).




Scheme 44

Nishida[53] has developed a new radical reaction of acetylenic ketone (**89**) involving stannyl radical addition-cyclization followed by alkoxy radical fragmentation (**L**→**M**; **O**→**P**) and subsequent radical-olefin recyclization processes (**M**→**N**) which provided a unique entry for the preparation of complex seven- (**90**) and eight-membered carbocyclic skeletons (**91**) (Scheme 45).

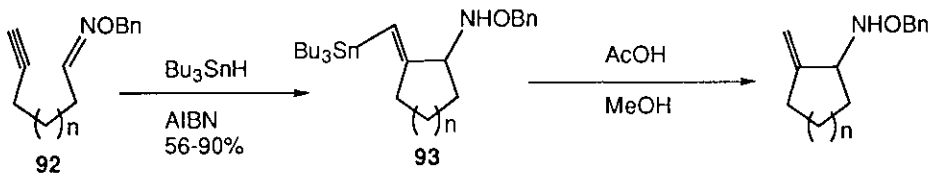
There have been several examples of the synthesis of natural products and the related compounds by applying the stannyl radical addition-cyclization of carbonyl compounds connected with olefins. Ueda[54] has showed the synthesis of carbon-bridged carbonucleoside and Shibuya[55] completed the enantioselective synthesis of natural amino acid, cyclic (+)-bulgecinine. Another example[56] is the synthesis of bicyclic southern sub-unit of avermectin *via* the route involving the stannyl radical addition-cyclization of acetylenic ketones.




Scheme 45

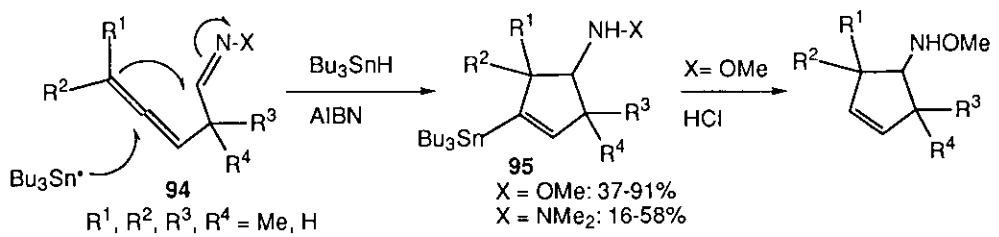
## 4-3. Stannyl Radical Addition-Cyclization of Carbon-Carbon Multiple Bonds and Carbon-Nitrogen Multiple Bonds

Stannyl radical addition-cyclization between carbon-nitrogen multiple bonds and carbon-carbon multiple bonds has been extensively studied for the preparation of cyclic amine derivatives. Enholm[57] has developed the stannyl radical addition-cyclization of benzyl oxime ethers (**92**) tethered to a terminal alkyne group which afforded five- and six-membered rings (**93**) bearing a protected amino and vinylstannane functionalities (Scheme 46). The cyclized products (**93**) were subsequently protiodestannylated to prepare the unsubstituted exo-methylene compounds.



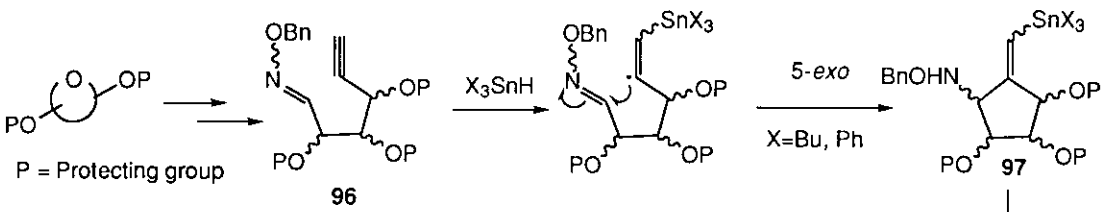

Scheme 46

Hatem has extended his studies[58a] on $\beta$-allenic oxime ether to allenic hydrazones[58b,c] and found that allenic substrates (**94**) undergo stannyl radical addition-cyclization to afford cyclopentene derivatives.[59] His group[58b] also reported the first example of asymmetric radical addition-cyclization using SAMP allenic hydrazones (Scheme 47).



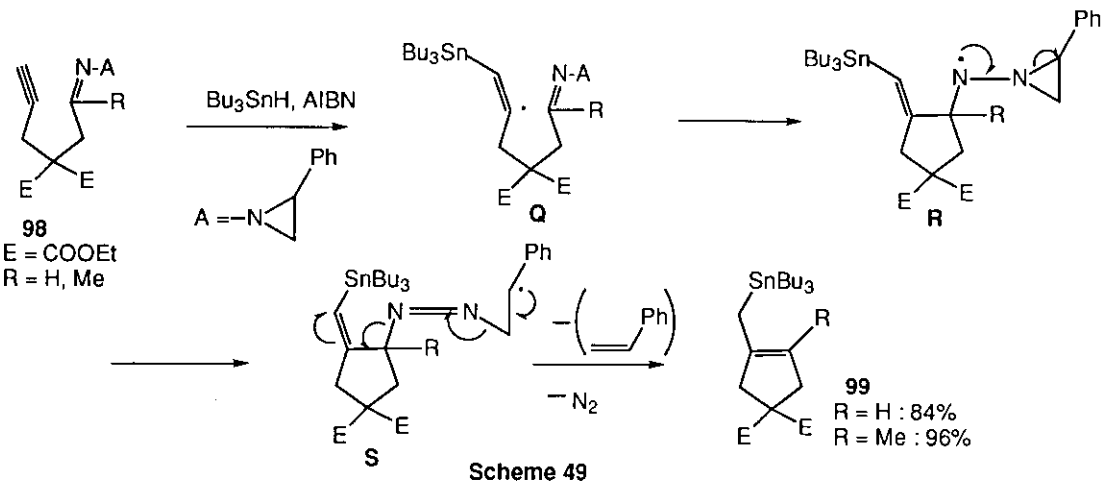

Scheme 47

M.-Contelles[59a] has reported the first application of stannyl radical addition-cyclization of enantiomerically pure alkyne-tethered oxime ethers (**96**) to asymmetric synthesis of aminocyclopentitols (Scheme 48). The oxime ethers (**96**) were readily prepared from the commercially available sugars. Radical addition-cyclization was carried out in the presence of either tributyl or triphenyltin hydride plus triethylborane to yield a mixture of *Z*- and *E*-vinyltin isomers (**97**), but with excellent diastereoselection at the new stereocenter formed during the ring closure. Thus, M.-Contelles[59] and Hatem[58] have shown that stannyl radical addition-cyclization of allene- or alkyne-tethered oxime ethers or hydrazones is a convenient method for the preparation of (vinylstannyl)cyclopentylamine derivatives in terms of simplicity and chemical yields. M.-Contelles[59b] has recently published an excellent review entitled carbocycles from carbohydrates *via* free radical cyclizations of oxime ethers and the related compounds.



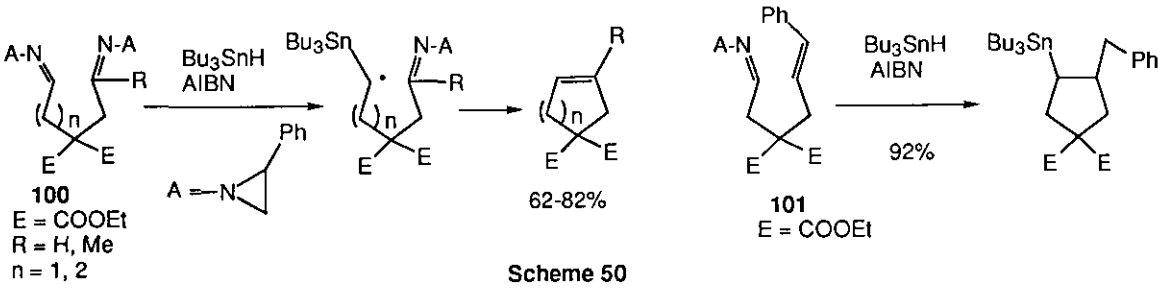

Scheme 48

Kim[60] has developed a novel radical cyclization of *N*-aziridinylimines (**98**) in which alkyne-tethered hydrazones and dihydrazones underwent stannyl radical addition-cyclization to give cyclic compounds (**99**) in good yields (Scheme 49). Latter half step is based on three factors along with the original Eschenmoser reaction,[61] first, alkyl radical (**Q**) adds to hydrazones, second, $\beta$-fragmentation of three-membered rings (**R**), and third, consecutive $\beta$-fragmentation (**S** → **99**) *via* ejection of styrene and nitrogen.



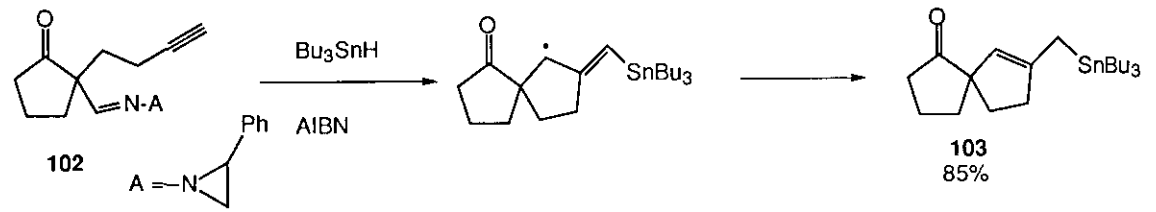

Scheme 49

Additional interesting examples are the cases of dihydrazones (**100**) and olefinic hydrazone (**101**)[60] (Scheme 50).



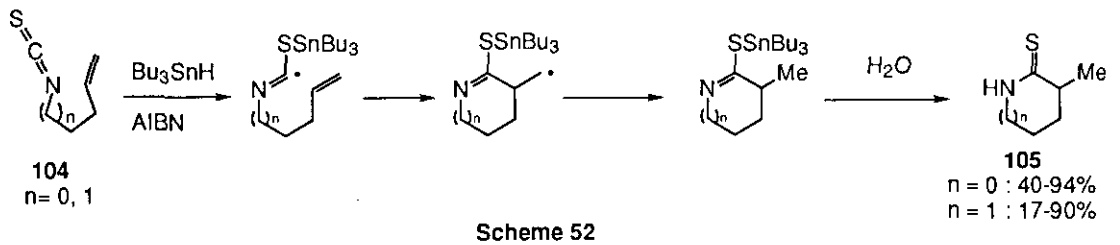

**Scheme 50**

Competition reaction between a keto and an imino group in **102** showed preferential attack of a vinyl radical to the imino group to afford the spiro ketone (**103**) in good yield[62] (Scheme 51). Zard[63] has reported multiple stannyl radical addition-cyclization starting with iminyl radical derived from sulphenylimines.



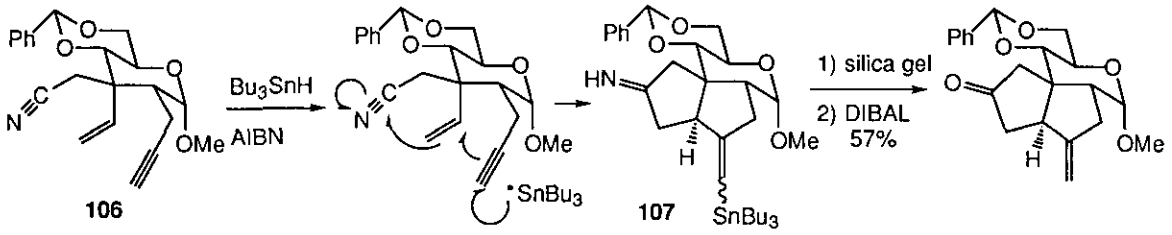

**Scheme 51**

Bachi[64] has developed the stannyl radical addition-cyclization of olefin-tethered isothiocyanates (**104**) which underwent *exo* cyclization to give, after hydrolysis, the corresponding $\gamma$ - or $\delta$-thiolactams (**105**) in good to excellent yields (Scheme 52).




**Scheme 52**

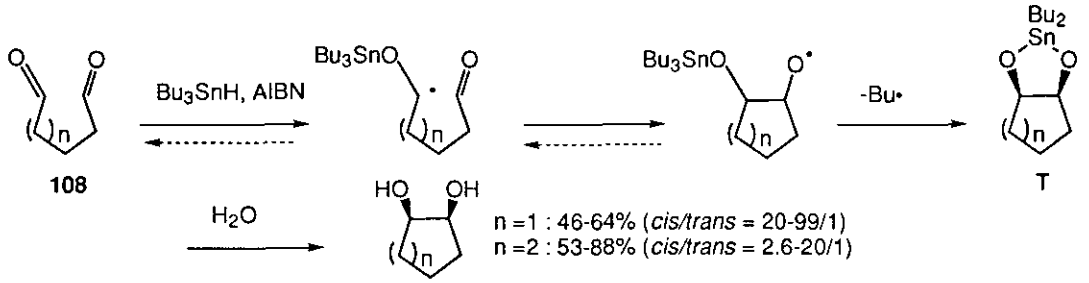
Fraser-Reid[65] has reported serial stannyl radical addition-cyclization of suitably functionalized appendages (alkyne, alkene, and cyano groups at $C_2$- and $C_3$-positions) of sugar skeletons (**106**) which afforded multiply substituted pyranoside diquinanes (**107**) (Scheme 53). His group has succeeded in the total synthesis of (-)- $\alpha$ -pipitzol by applying the stannyl radical addition-cyclization.[65a]




Scheme 53

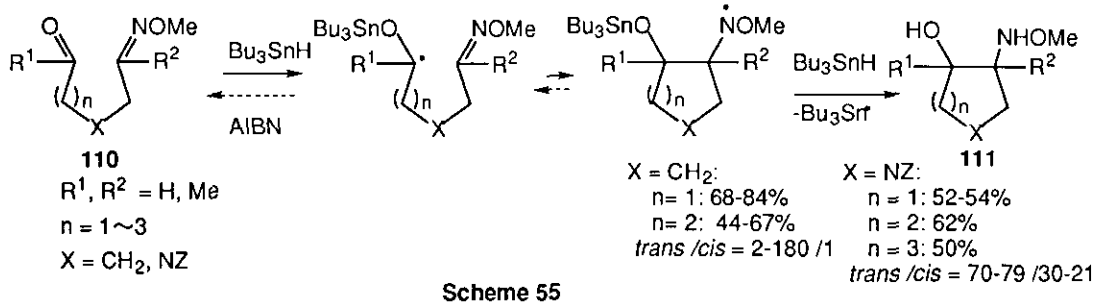
## 4-4. Stannyl Radical Addition-Cyclization of Bis(Carbon-Heteroatom Multiple Bonds)

Stannyl radical addition-cyclization of dicarbonyl groups belongs to the pinacol coupling reaction which was developed by Fu[66] group. Both 1,5- and 1,6-dialdehydes (**108**) undergo cyclization, as do 1,5- and 1,6-keto aldehydes giving *cis*-cyclopentane-1,2-diols (**109**) stereoselectively *via* 1,3,2-dioxastannolane (**T**) as a cyclic intermediate (Scheme 54).




Scheme 54

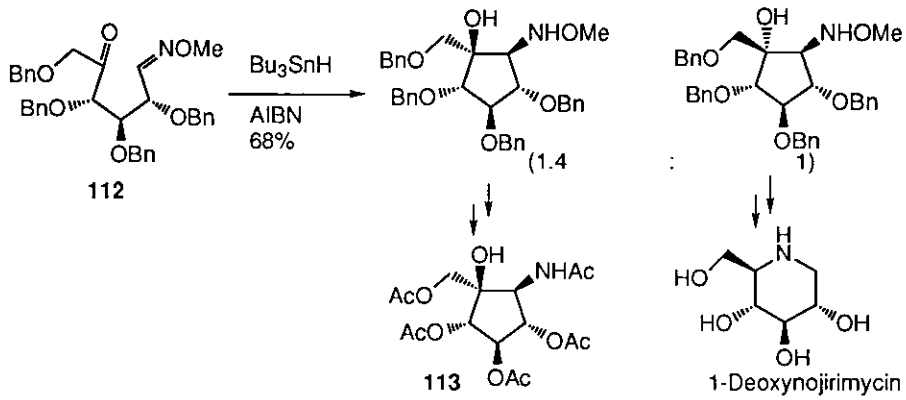
Just before radical addition-cyclization of dicarbonyl compounds has been published,[66] Naito[67] has reported the first example of stannyl radical addition-cyclization of oxime ethers (**110**) tethered with the carbonyl group which provides a new entry to five- to seven-membered heterocyclic amino alcohols (**111**) widely found in biologically active natural products (Scheme 55). Among two stereoisomers, *trans*-amino alcohols are generally obtained as major products which would be formed *via* an intermediate with less electron-repulsion between stannyloxy group and the neighboring aminyl radical. Later, Fu[68] has studied



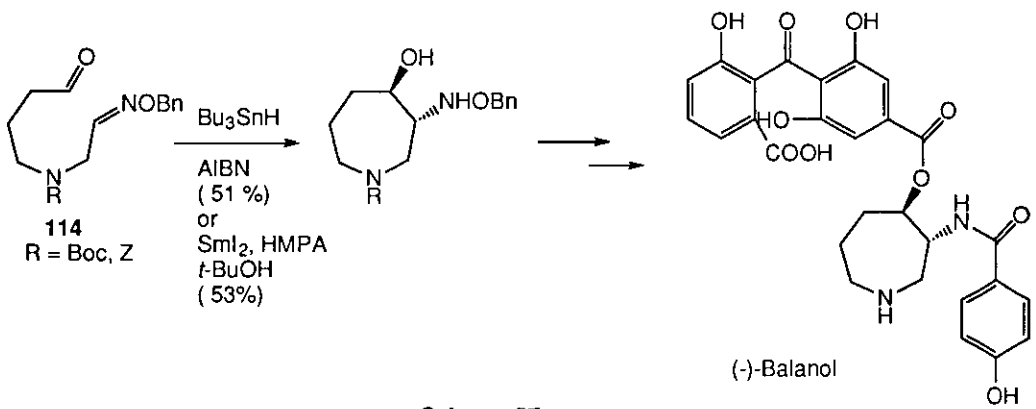

Scheme 55

the stannyl radical addition-cyclization of carbonyl-oxime ethers to generate carbocyclic amino alcohols of which *trans*-isomers were obtained with moderate to excellent stereoselectivity.

Stannyl radical addition-cyclization of oxime ethers (**112, 114**) tethered with the carbonyl group was successfully applied to the synthesis of biologically active natural products such as aminocyclitols (**113**) [69] with glycosidase inhibitory activity (Scheme 56) and balanol[70] with potent protein kinase C inhibitory activity (Scheme 57).

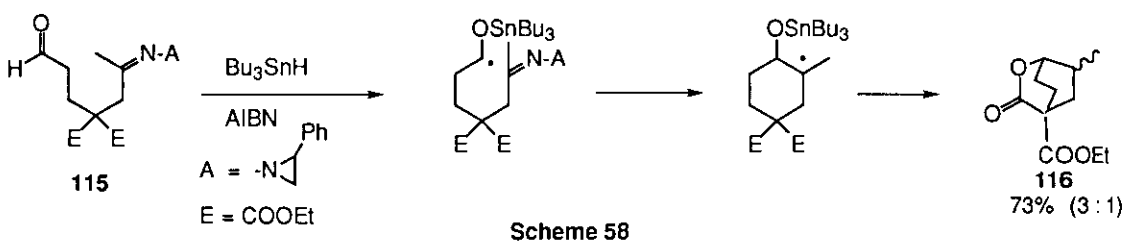



**Scheme 56**




**Scheme 57**

Kim[62] has extended the radical addition-cyclization to *N*-aziridinyl imine type of hydrazone (**115**) tethered with the carbonyl group which undergoes three sequential reactions involving stannyl radical addition to the

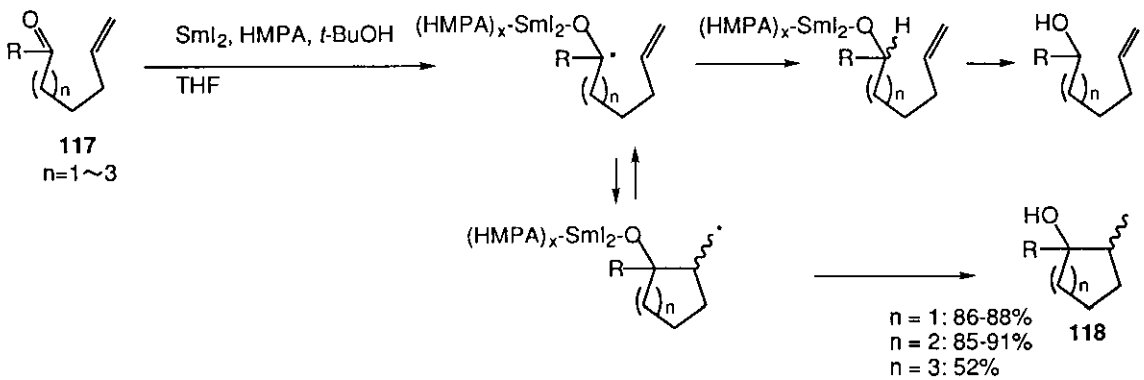



**Scheme 58**

carbonyl group, addition of the resulting carbon radical to hydrazone, and finally fragmentation of *N*-aziridinyl imine to yield six-membered carbocycles (**116**) (Scheme 58).

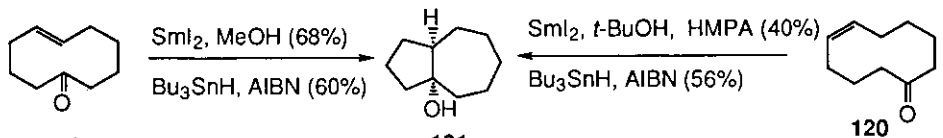
## 5. Samarium-mediated Addition-Cyclization

Samarium-mediated ketyl radical addition-cyclizations are relatively new and have many advantages compared to simple radical cyclizations. Therefore, this review describes several examples of the addition-cyclization though the first step of samarium addition to the carbonyl group is mechanistically non-radical character. There have been excellent reviews[1c] on samarium-mediated reactions including those by Molander[71a] and Skrydstrup.[71b] Since samarium(II) iodide is found to evolve as a unique single electron reducing agent, Molander[71] has developed the samarium addition-cyclization of unactivated olefinic ketones (**117**) which is quite general for the formation of carbocycles (**118**) (Scheme 59). In addition to delineating the synthetic potential of the cyclization by extension to sequential radical cyclization-nucleophilic addition-substitution reaction in the presence of an electrophile, he refined the role played by HMPA in enhancing $SmI_2$ reactivity.




**Scheme 59**

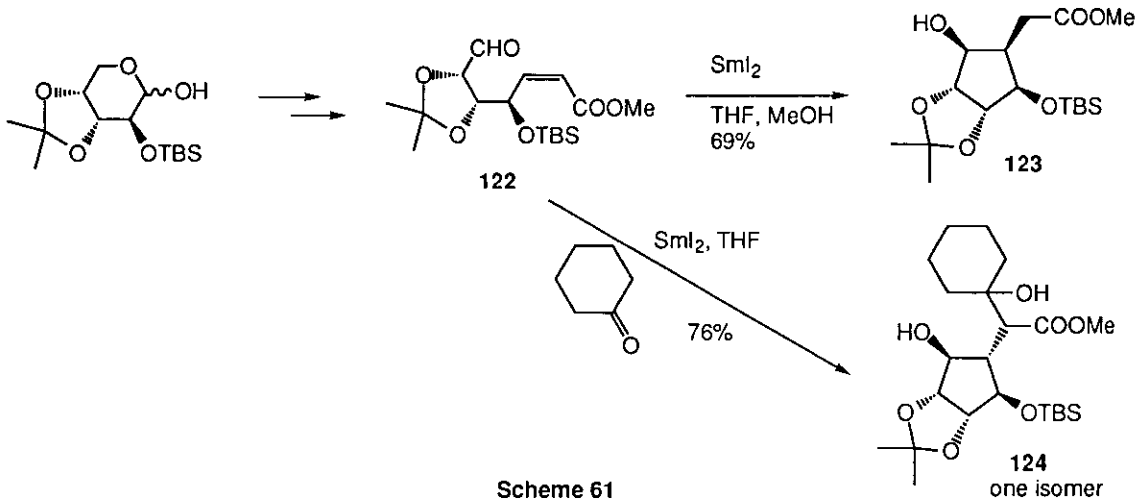
Comparing electrophilic transannular cyclization with radical versions using identical substrates, White[72] has reported that both stannyl radical addition-cyclization and samarium addition-cyclization of *E*-5-cyclodecenone (**119**) and *Z*-**120** gave identical hydroazulene (**121**) in moderate yields (Scheme 60).




**Scheme 60**

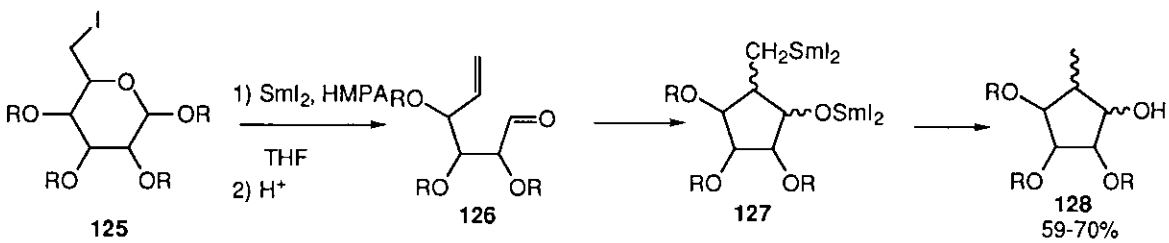
The application of samarium addition-cyclization to carbohydrate template (**122**) was reported by Enholm group[73] who provided a novel method for the stereoselective preparation of polyhydroxylated carbocycles (**123**) and demonstrated a surprising reversal in the diastereoselectivity in the products depending on whether the olefin geometry of the starting carbohydrate is *cis* or *trans* [73b] (Scheme 61). A successful

application to the synthesis of C ring of natural product anguidine was accomplished.[73a] Enholm[73c] has also explored a new reaction sequence in which the tetrahydropyran ring is deoxygenated and cyclized to afford an elaborated cyclopentane rings (**124**) *via* tandem key steps, $SmI_2$-promoted a sequential one-electron radical cyclization of aldehyde (**122**) followed by a two-electron intermolecular carbonyl addition reaction.



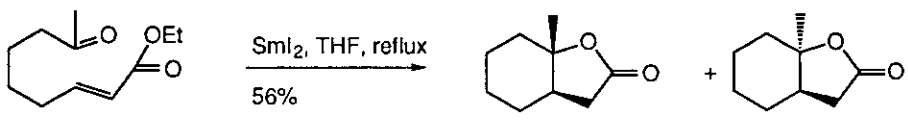

Scheme 61

Chiara[74] has developed cascade reaction promoted by samarium diiodide including four SET steps which consists of 1) reductive dealkoxyhalogenation of 6-deoxy-6-iodohexopyranosides (**125**), 2) samarium addition-cyclization of the resulting olefinic aldehyde (**126**), 3) intermolecular trapping of the organosamarium (**127**) with proton to produce finally branched cyclopentitols (**128**) (Scheme 62). The process represents a new and simple method for the one-pot preparation of highly functionalized and enatiomerically pure cyclopentanes from readily accessible carbohydrates.



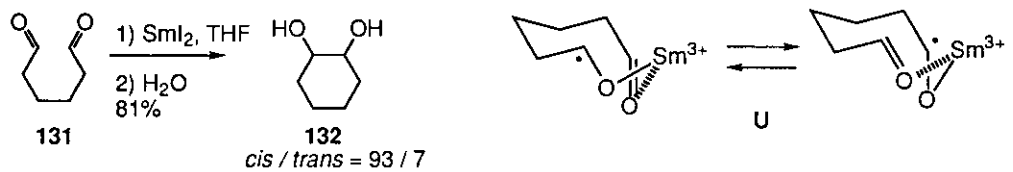

Scheme 62

As an extension of samarium diiodide-induced reductive coupling of $\alpha,\beta$-unsaturated esters with carbonyl compounds, Fukuzawa[75a] has investigated the intramolecular reaction of $\alpha,\beta$-unsaturated keto ester (**129**) which was treated with 2 mole equiv. of $SmI_2$ in refluxing THF to afford a 56% yield of the bicyclic $\gamma$-lactone (**130**) as a mixture of *cis*- and *trans*-isomers in the ratio of *trans* : *cis* = 7 : 3 recovering a 30% of the starting material (Scheme 63). Related works have been reported by Matsuda[75b] and Little[75c] groups.



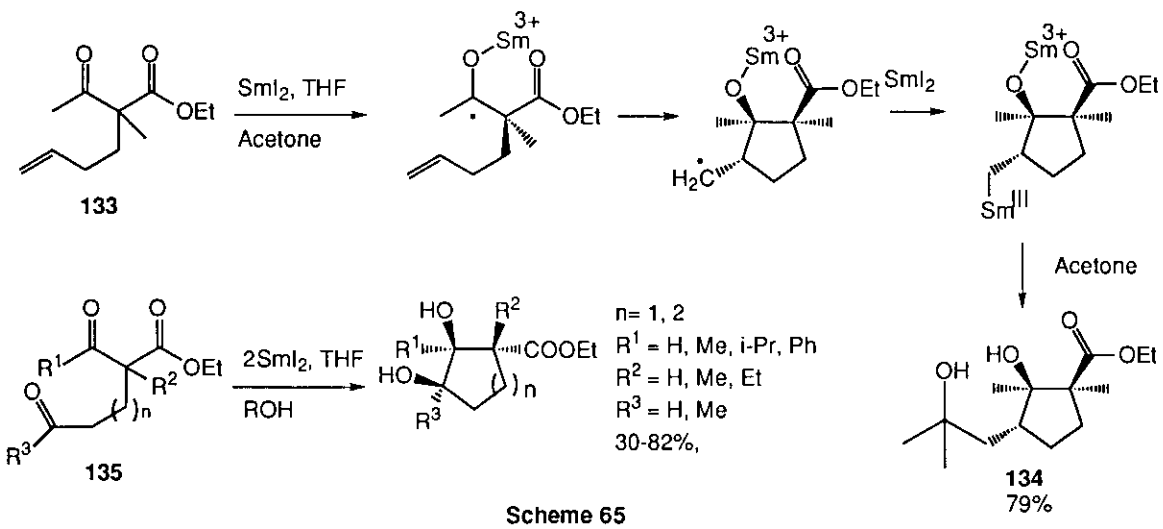

Scheme 63

Based on the successful result of intermolecular radical coupling reaction of two carbonyl compounds,[76a] Hanessian[76b] has successfully applied the reaction to the intramolecular addition-cyclization of dialdehyde (**131**) (Scheme 64). Nine-membered transition state (**U**) is proposed for the preferable formation of *cis*-glycol (**132**). Its synthetic applications to carbohydrate field were reported by Iadonisi group[76cd] who succeeded in an efficient synthesis of highly functionalized cyclopentanes containing a quaternary chiral center.




Scheme 64

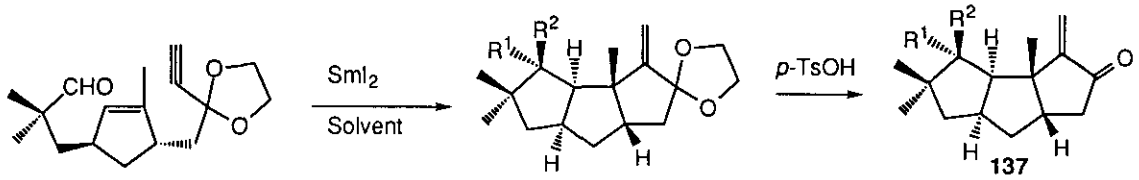
Molander[77] has developed sequential radical cyclization-intermolecular carbonyl addition reaction of dicarbonyl olefin (**133**) initiated by $SmI_2$ which undergoes two new carbon-carbon bonds formation in a one-pot process leading to the formation of complex carbocycles (**134**) having three contiguous stereocenters (Scheme 65). Encouraged by the sequential radical cyclization-intermolecular carbonyl addition reaction initiated by $SmI_2$, his group[77c] has also investigated intramolecular pinacol coupling reactions of tricarbonyl- (**135**) and dicarbonyl-nitrile compounds including chiral substrates.




Scheme 65

Factors controlling the stereochemical outcome of these reaction and mechanistic consideration were also discussed. Sequential epoxide fragmentation-radical cyclizations mediated by samarium(II) iodide was recently reported by Molander.[77e]

Curran[78] has succeeded in the total synthesis of triquinane sesquiterpenes, (±)-hypnophilin and the formal total synthesis of (±)-coriolin *via* the route involving samarium addition-cyclization of ethynyl olefinic aldehyde (**136**) which constructs the two outer rings of a triquinane about a central, preformed cyclopentene ring (Scheme 66). Samarium addition-cyclization of **136** in the presence of either HMPA or DMPU proceeded smoothly to give tricyclic compound (**137**) after deketalization of the crude material with *p*-TsOH. Some examples of the related sequential samarium addition-cyclization of more complex substrates having three-membered ring such as cyclopropane and epoxide were reported by Motherwell[79a] and Molander.[77d] Samarium addition-cyclization of the keto-alkynes was recently used as the key step in an approach to a natural product, erigerol.[79b]

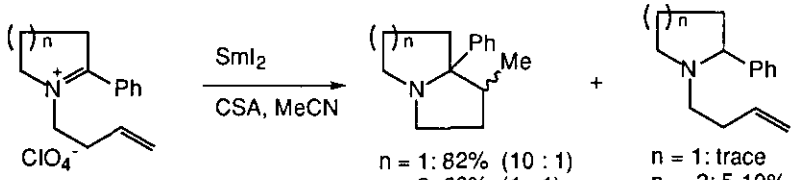



136

THF / HMPA = 20 /1: $R^1$ = OH, $R^2$ = H: 91%
THF / DMPU = 20 /1: $R^1$ = OH, $R^2$ = H: 87%
$R^1$ = H, $R^2$ = OH: 9%

**Scheme 66**

Martin[80] has reported the samarium addition-cyclization of ω-unsaturated iminium salts (**138**) in the presence of camphorsulfonic acid which proceeds *via* reduction of the iminium moiety to form α-amino radical and its facile 5-*exo*-trig cyclization leading to heterocyclic products (Scheme 67). Some of the related *N*-alkenyl substituted iminium salts have revealed several limitations in this addition-cyclization depending upon the structure of the substrates.




138

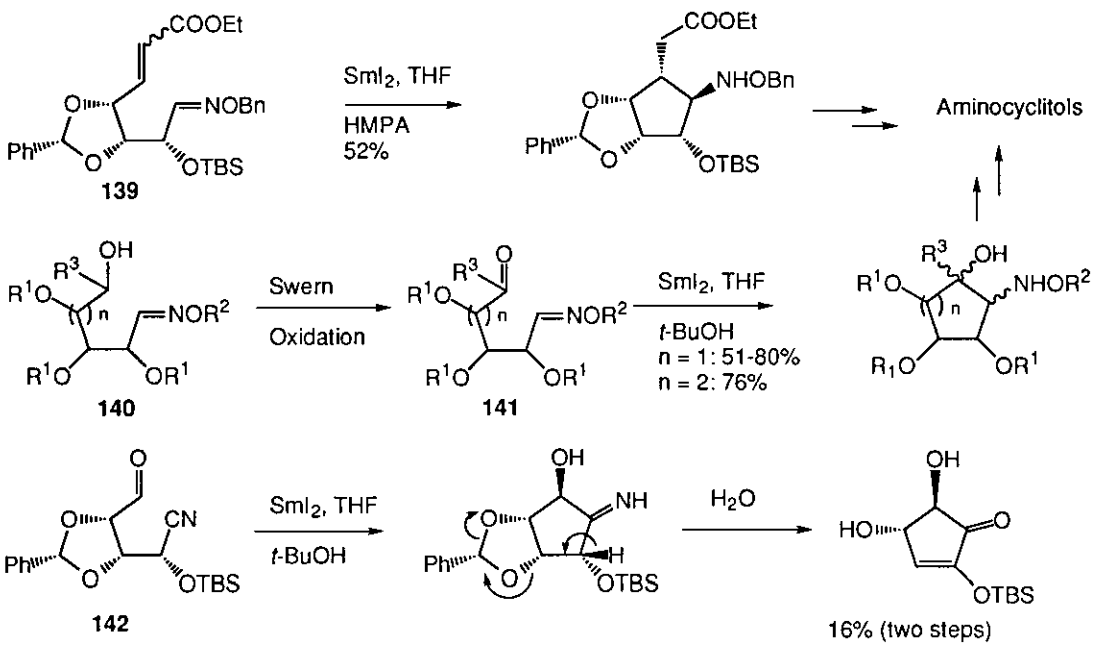
n = 1: 82% (10 : 1)
n = 2: 60% (1 : 1)

n = 1: trace
n = 2: 5-10%

**Scheme 67**

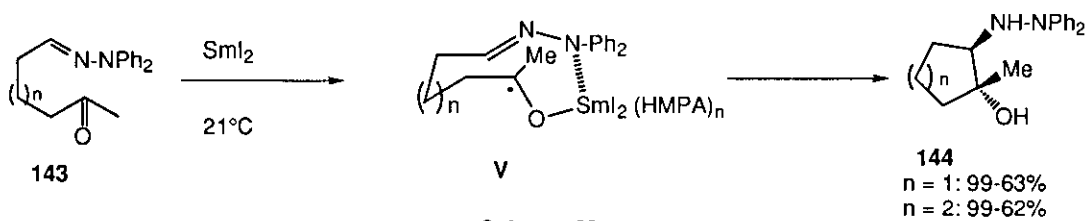
M.-Contelles[81a] has systematically investigated samarium addition-cyclization of a series of simple or polyoxygenated oxime ethers (**139, 141**) δ- or ε-functionalized with α,β-unsaturated ester, aldehyde, or ketone group and found that the addition-cyclization proceeds under mild conditions, in good chemical yields and with high stereoselectivity (Scheme 68). Particularly when applied to highly functionalized substrates derived from carbohydrates, this approach provides a selective entry to enantiomerically pure

aminocyclitols of varying regio- and stereoselectivity. The samarium addition-cyclization of carbonyl-tethered oxime ethers proceeded in a one-pot sequence, following a Swern oxidation step, allowing the direct transformation of hydroxyl-tethered oxime ethers (**140**) into the corresponding aminocyclitols. Moreover, the resulting *O*-benzylhydroxylamine products of these cyclizations can be further reduced *in situ* with excess $SmI_2$, in the presence of water, to the corresponding amino alcohols in excellent yields. Synthesis of nucleoside analogues is an recent example[81b] of the successful application of the addition-cyclization. The addition-cyclization of nitrile-tethered aldehyde (**142**) was also studied.[81a]




**Scheme 68**

Fallis[82] has established that *N,N*-diphenylhydrazones (**143**) are excellent radical acceptors and effectively used in samarium addition-cyclization in the preparation of nitrogen functionalized cyclopentanes and cyclohexanes (**144**) (Scheme 69). Contrary to the inseparable *syn-anti* mixture that usually results from oxime ethers, hydrazones can be prepared as *E*-hydrazones exclusively. Additionally, the radical addition-cyclization of hydrazones provided *trans*-cyclic hydrazino alcohols. This high level of selectivity was achieved when the reaction was conducted at room temperature. Fallis[82a] proposes a transition state (**V**)



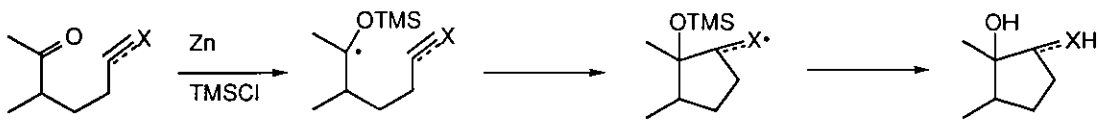

**Scheme 69**

which allows the large *N,N*-diphenylamino substituent to adopt a pseudoequatorial orientation, and the axial oxygen helps reduce the gauche interactions on route to the observed products. Synthetic utility of the addition-cyclization is further enhanced by conversion of the cyclic hydrazines into amines. Recently, Molander[83] has published an excellent review on sequential reactions with samarium(II) iodide involving both radical and anionic processes.

## 6. Miscellaneous Heteroatoms (Si, Se, O, P) Radical Addition-Cyclization

### 6-1. Silicon-mediated Addition-Cyclization

Corey[84] has reported a new method for ring formation leading to cyclopentanol systems (**146**) *via* the action of zinc-TMSCl on the ketones (**145**). Electron transfer from zinc followed by silylation forms an $\alpha$-trimethylsilyloxy radical which adds to the $\delta,\varepsilon$-multiple bond (Scheme 70). This reaction involves basically a silicon atom addition-cyclization in which either carbon-carbon, carbon-oxygen, or carbon-nitrogen multiple bond was used as a radical acceptor. The synthetic application for stemodin diterpenoids has reported by Mann's group.[85]

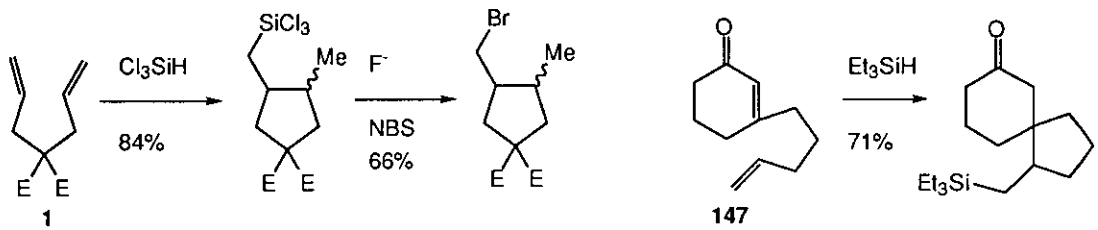



**145**
X = C, N, O

**146**
65-84%

**Scheme 70**

In view of the propensity of organosilicon reagents to form silicon-oxygen bonds, Kraus[86] has reported the examples of silicon radical addition-cyclization of dienes (**1**) and olefinic ketones (**147**) (Scheme 71). Trichlorosilyl radicals attack both alkenes and the carbonyl oxygen atom while triethylsilyl radicals preferentially attack alkenes.

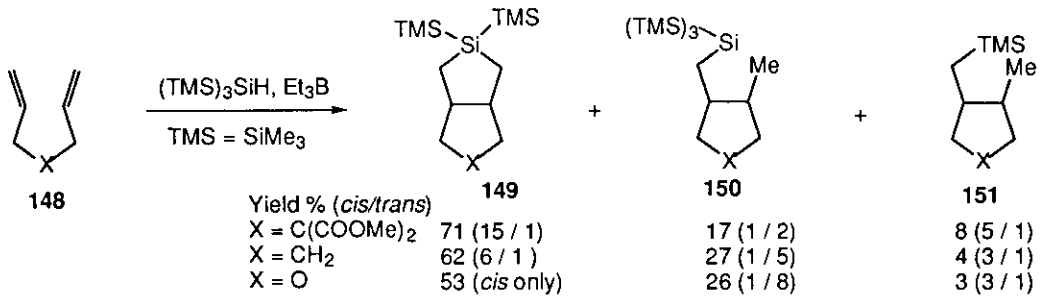



**1**
E = COOMe

**147**

**Scheme 71**

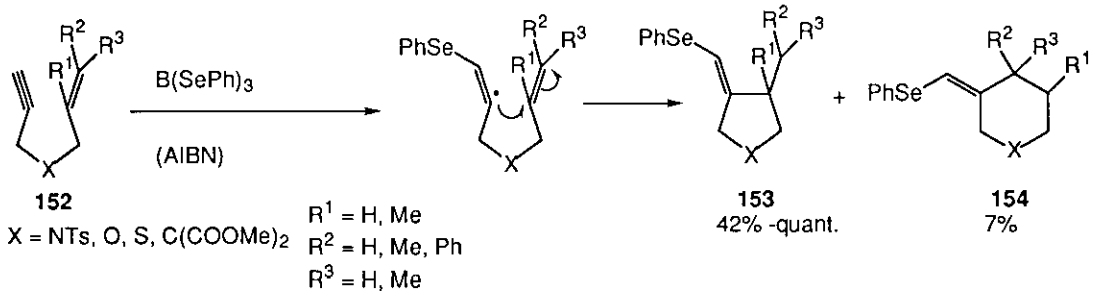
Utimoto[87] and Giese[88] have independently developed tris(trimethylsilyl)silyl radical addition-cyclization of 1,6-dienes (**148**) which gave 3,3-bis(trimethylsilyl)-3-silabicylo[3.3.0]octanes (**149**) as a result of initial attack of silyl radical to terminal olefinic carbon (Scheme 72). Utimoto[87] has also reported the similar addition-cyclization of 1,6-enynes. Ojima[89] has established silylcarbocyclization reaction catalyzed by Rh and Rh-Co complexes as a related reaction. Pattenden[90] has reported cascade silicon-mediated radical cyclization-fragmentation-transannular ring expansion reactions of alkynyl oxime ethers.




Scheme 72

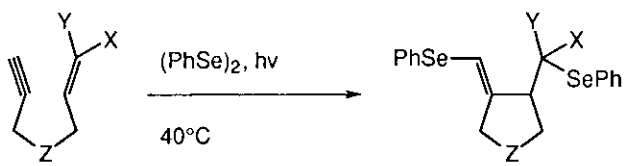
## 6-2. Seleno Radical Addition-Cyclization

Kataoka[91] has found that tris(methylseleno)- and tris(phenylseleno)boranes are new reagents for generation of alkyl selenyl radical and cause the seleno radical addition-cyclization of enynes (**152**) to form vinyl selenide-substituted 5- and 6-membered carbocycles and heterocycles (**153, 154**) (Scheme 73). The novel seleno radical addition-cyclization was successfully applied to the synthesis of α-kainioid derivatives.[91b]




Scheme 73

Sonoda[92] has reported that seleno radical addition-cyclization of enynes (**155**) proceeds smoothly under the photochemical condition to give the vinyl selenide-substituted 5-membered carbocycles and heterocycles (**156**) (Scheme 74).

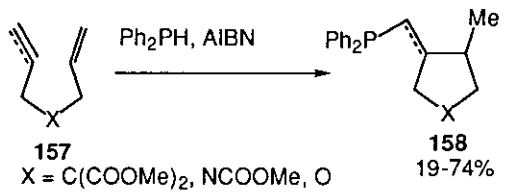



Scheme 74

## 6-3. Phosphorus, Oxygen, and Iodo Radical Addition-Cyclization

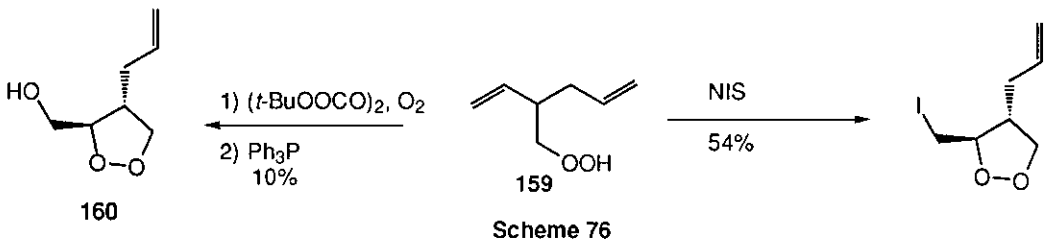
Phosphorus, oxygen, and iodine atoms are known as a heteroatom related to this review though there have been not so many examples. Simpkins[93] has developed phosphorus radical addition-cyclization of 1,6-

dienes and enynes (**157**) which gave carbocycles and heterocycles (**158**) substituted with phosphine or vinylphosphines (Scheme 75).




**Scheme 75**

Oxygen radical addition-cyclization was reported by Bloodworth[94] who investigated 1,2-dioxolane *versus* 1,2-dioxane formation in the cyclization of α,ω-diene hydroperoxide (**159**) and found regioselective radical addition-cyclization at the C-1,C-2 double bond leading to the formation of 1,2-dioxolanes (**160**) (Scheme 76). His group[94] has also reported iodo radical addition-cyclization of identical diene (**159**) in the same paper.




**Scheme 76**

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