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

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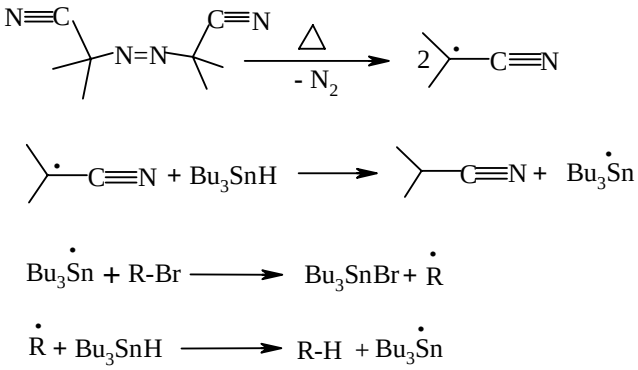
Abstract - This brief review describes the syntheses of different five- and six-membered heterocyclic rings in various compounds by radical cyclization.

Until few years ago radicals were still a domain for mechanistically oriented research; a wealth of experimental data has led to a deeper understanding of their chemistry. Nowadays radical reactions are increasingly employed in synthesis, wherein the product is formed through reactions of radicals either with other radicals or with molecules whose electron spins are paired. In radical-radical reactions, the radicals must be continuously generated, so that an equivalent amount of radical initiator is required.

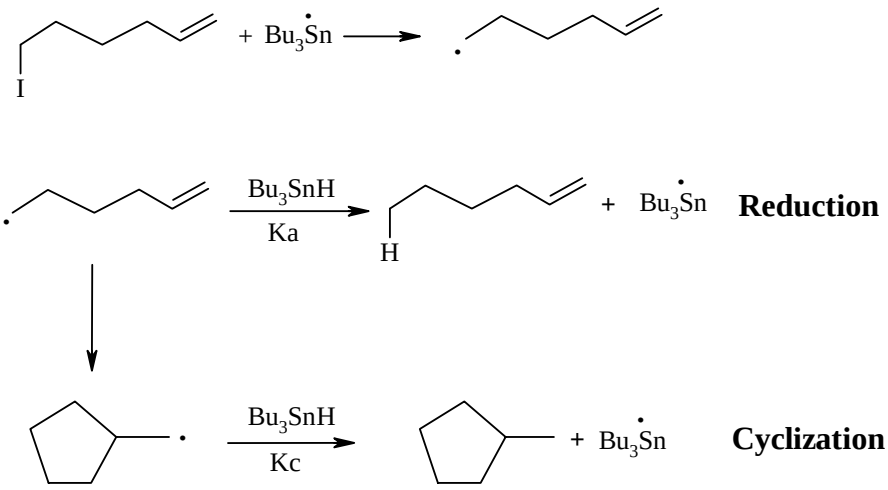
The use of radical cyclization for the synthesis of heterocycles continues to grow and many new methodologies have been published in addition to the use of tributyltin hydride (Bu_3SnH) or related triorganostannanes. The bulk of radical cyclizations in heterocyclic chemistry is still carried out by using Bu_3SnH. The reaction conditions are generally to use an excess of Bu_3SnH with a smaller equivalent (10-25 mol %) of a radical initiator, most commonly azobisisobutyronitrile (AIBN). The reactions are generally refluxed in benzene or toluene for 1-10 h. The purification of the product is a real problem but this problem can partially be reduced by using catalytic amount of Bu_3SnH. Syringe pump technique for addition of tin hydride can minimize the concentration of this reagent and offer a valuable alternative when slow cyclizations are involved. This can bypass the need for large solvent volumes. In this methodology Bu_3SnCl is reduced *in situ* with sodium cyanoborohydride or sodium borohydride[1-5] thereby producing small amounts of Bu_3SnH which is continually used up generating more Bu_3SnX (X = Br, I) in a cycle.[6,7]

This process was initially developed for the reduction of alkyl halides, and it remains an excellent synthetic method for that purpose. One equivalent of Bu_3SnH is required to reduce one equivalent of alkyl halide. Each step in the sequence is energetically favored, so side reactions are minimized. Tributyltin radical does not abstract hydrogen from the alkyl, it only attacks the halide (Br or I).

Likewise, the carbon radical abstracts the hydrogen from tin much more readily than it does other C-H hydrogens. From the mechanistic point of view the process is clean and consequently results in clean reduction products.



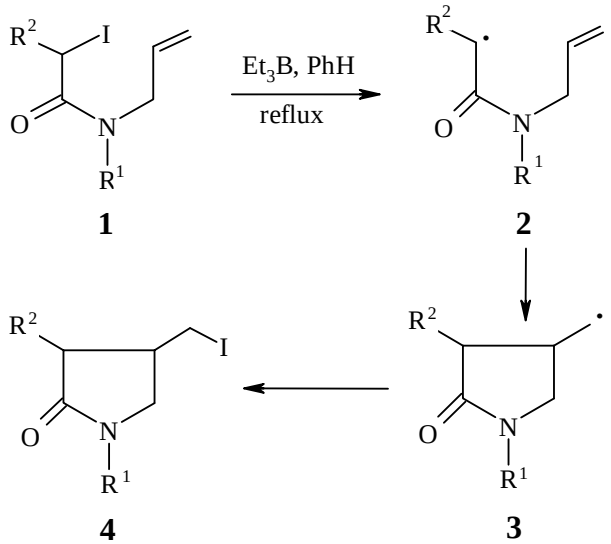
If this application of free radical generation method is extended to an unsaturated alkyl halide, there are two pathways available. It can abstract a hydrogen from tributyltin hydride and give a reduced product, as mentioned earlier. Alternatively, it can cyclize to give a new cyclic radical. This radical can abstract hydrogen from tributyltin hydride to give a cyclized product. These competing propagation steps are shown in the following:



The ratio of products obtained from these two processes depends on their competing rates. The rate of reduction of the radical is given by k_a [R˙] [Bu_3SnH] while the rate of cyclization is given by k_c [R˙]. It has been observed that k_c is sufficiently large so that cyclization is often the major process. However, reduction is always possible. Since rate of reduction is a second order process and it depends on the concentration of both the radical R˙ and tributyltin hydride; the rate of reduction can be lowered by simply running the reaction under dilute conditions. As the concentration goes down, the rate of

reduction goes down much faster than the rate of cyclization, and cyclization is favored. When a good donor-acceptor relationship is present, the cyclization of free radicals is quite fast, and in such cases high dilution techniques are irrelevant.

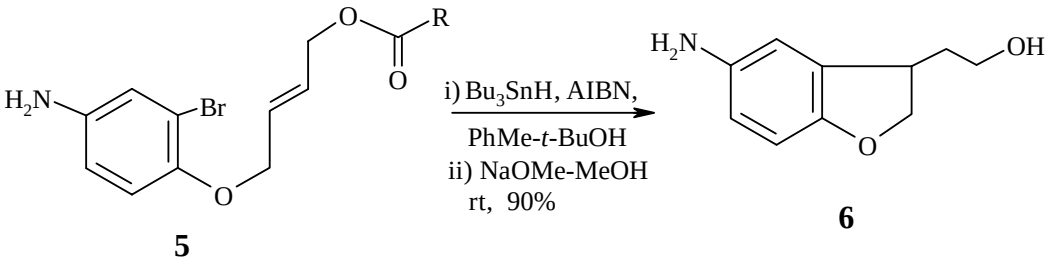
In addition to Bu_3SnH there are several other reagents used for the purpose of radical cyclization. One such reagent is tributylgermanium hydride (Bu_3GeH). It is much less toxic and reacts slightly slower thereby facilitating improved cyclization yield over use of Bu_3SnH but is very expensive. This is examplified by its use in the cyclization of perfluoroalkenyl radicals.[8] Tris(trimethylsilyl)silane [$(Me_3Si)_3SiH$] is also less toxic and easier to work up than Bu_3SnH but is also expensive.[9-11] While AIBN is the most commonly used radical initiator, 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 participate in radical reactions. It is also lower boiling than toluene.[12,13] The use of triethylborane and oxygen as an initiator is useful because it allows reactions to be carried out at low or room temperature.[14-17] Triethylborane can also be utilized for initiating iodine atom transfer reactions. A large number of radical reactions using cyclization of radicals, β to the nitrogen atom, onto β-alkenes have been used for the synthesis of a wide range of pyrrolidines. For instance, γ-lactams have been prepared by several methods.[18,19] 2-Iodo-*N*-(prop-2-enyl)acetamides upon treatment with triethylborane in boiling benzene undergo iodine atom transfer cyclization to afford the 4-iodomethylpyrrolidin-2-ones in high yield.[18] Triethylborane and oxygen were used to initiate the reaction thus providing a synthetic route which doesn't require Bu_3SnH. In the iodine abstraction mechanism, the cyclized radical (**3**) abstracts iodine from the starting material (**1**) to yield the product iodide (**4**) and intermediate radical (**2**). The methodology was also extended to the synthesis of γ-lactones. γ-Lactams (pyroglutamates) have been synthesized from dehydroalanines which contain



1 **2** **3** **4**

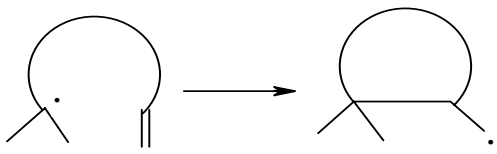
chiral ester auxiliaries *via* "*5-endo*" radical cyclizations using Bu_3SnH.[19] The use of triethylborane as the initiator failed to produce any improvement in the cyclization.

The use of solid phase organic synthesis is an important advancement in radical reactions.[20, 21] The beauty of the solid phase synthesis is that the radical precursor is attached to the resin and the Bu_3SnH used in the reaction can be washed off when the radical cyclization is complete, thereby eliminating purification problems and lowering problems of toxicity. An example of the use of solid phase synthesis for 2,3-dihydrobenzofurans is shown below. In this preparation the precursor (**5**) is attached to Tenta Gel resin beads and after radical cyclization the product heterocycle (**6**) is removed by standard methods. Solid phase synthesis has also been used for the radical synthesis of 2,3-dihydrobenzofurans using samarium diiodide.[21]



5 **6**

Cyclization involves the intramolecular addition of a free radical to a double bond, and for this the free radical center and the π-bond, come within bonding distance of one another.



7 **8**

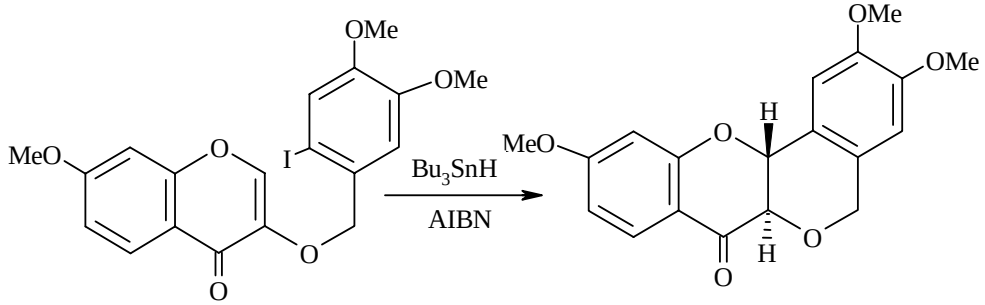
Most radical cyclizations used for the synthesis of heterocycles proceed by *5-exo-trig* regioselectivity. There are three good reasons for this:

i) Formation of 5-membered rings by the method of radical cyclization are faster than for any other ring size. The simple 5-hexenyl radical cyclizes 20 times faster than does the 6-heptenyl radical.[22, 23] Five membered ring-forming reactions are thus least subject to competitive formation of reduced, uncyclized by-products.

ii) The regioselectivity for *5-exo* cyclizations is often outstanding.[22-24]For the parent 5-hexenyl radical, *5-exo* cyclization is 50 times faster than *6-endo* cyclization. Substituted examples often show higher selectivities.

iii) Radical cyclizations giving 5-membered rings can be highly stereoselective.[22, 23, 25, 26] The major product in a *5-exo* radical cyclization can generally be predicted by using the Beckwith transition state model.[25] According to this model, the early transition state of a *5-exo* radical cyclization resembles a cyclohexane ring, prefers the chair over the boat form, and prefers that substituents be pseudoequatorial rather than pseudoaxial.[22, 23, 25] Simple model studies show that substitution at C-1 or C-3 of the 5-hexenyl radical gives primarily *cis*-disubstituted cyclopentanes, whereas substitution at C-2 or C-4 gives primarily *trans*-disubstituted cyclopentanes. Stereoselectivity is highest for C-1 and C-4 substituted systems.

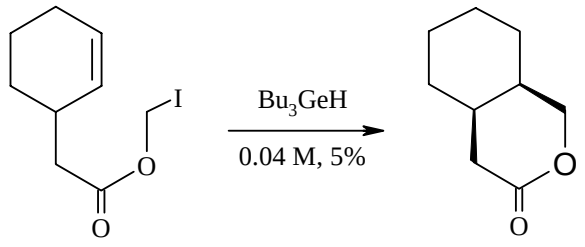
From the above discussion it is clear that radical cyclizations leading to 6-membered rings are less general than cyclizations leading to 5-membered rings; however they still have an important place in synthesis. Because, 6-membered ring forming reactions are slower, they are more subject to competitive formation of reduced, uncyclized by-products. Many 6-heptenyl radicals are also subject to intramolecular 1,5-hydrogen atom transfer. Such 1,5-hydrogen transfers are usually exothermic, (because they form allylic radicals), and they can sometimes be very fast. Simple *6-exo* radical cyclizations are also less regioselective than are *5-exo* cyclizations. For the 5-hexenyl radical, *5-exo* cyclization is 50 times faster than *6-endo* cyclization, but for the 7-heptenyl radical, *6-exo* cyclization is only 6 times faster than *7-endo* cyclization.[22, 23] In addition to diminished reactivity, diminished chemoselectivity and diminished regioselectivity, known 6-heptenyl radical cyclizations also show diminished stereoselectivity relative to 5-hexenyl radical cyclizations. Despite these limitations, radical cyclizations using the tin hydride method can often be successfully applied to the synthesis of 6-membered rings. Six-membered rings have occasionally been made by *6-endo* cyclizations of appropriately substituted 5-hexenyl radicals. The high *5-exo* regioselectivity of 5-hexenyl-radical cyclization is suppressed by substitution at the 5-position. For example, *5-exo* cyclization of the 5-methyl-5-hexenyl radical is 25 times slower than that of the parent 5-hexenyl radical, and the regioselectivity reverses from 50:1 to 1:2.[22, 23] When the 5-position is substituted, conformational or electronic bias is usually required for regioselective formation of either 5- or 6-membered rings. An example of a useful *6-endo* cyclization is the following, where the carbonyl substituent in **9** favors



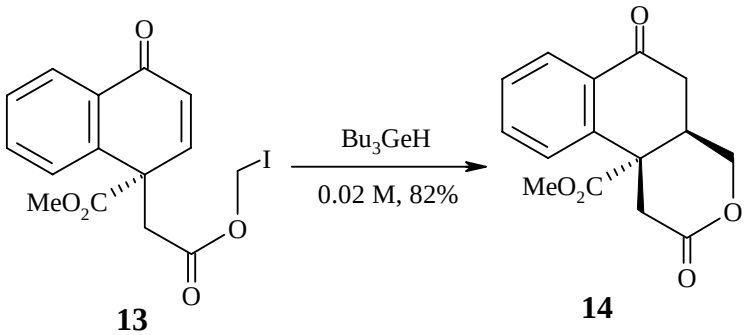
9 **10**

6-endo cyclization.[27] Cyclization occurred in 42% yield. Only a trace amount of the *cis* stereoisomer was observed.

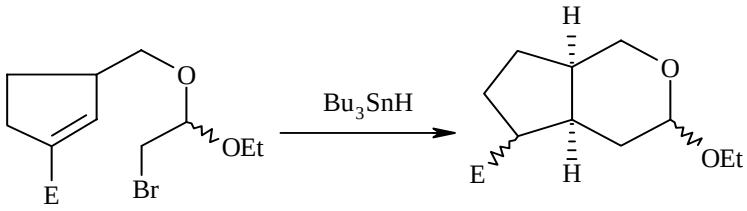
Despite several difficulties, the formation of six-membered rings can be accomplished by appropriate design of cyclization precursors. One route is the removal of all appropriately located allylic hydrogens. Even in the presence of allylic hydrogens, the introduction of activating groups on the alkene acceptor provides a practical method to conduct *6-exo* cyclizations.[28] Some recent examples of this technique are shown below.



11 **12**



13 **14**

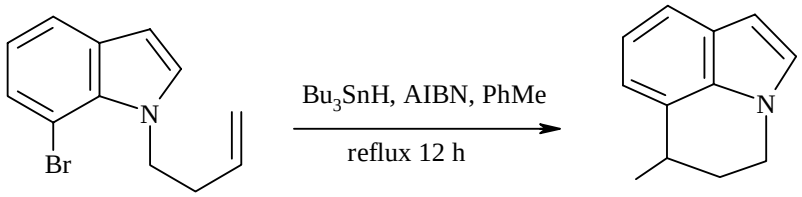


15 **16**

E= H, 51%
E= CO_2Me, 90%

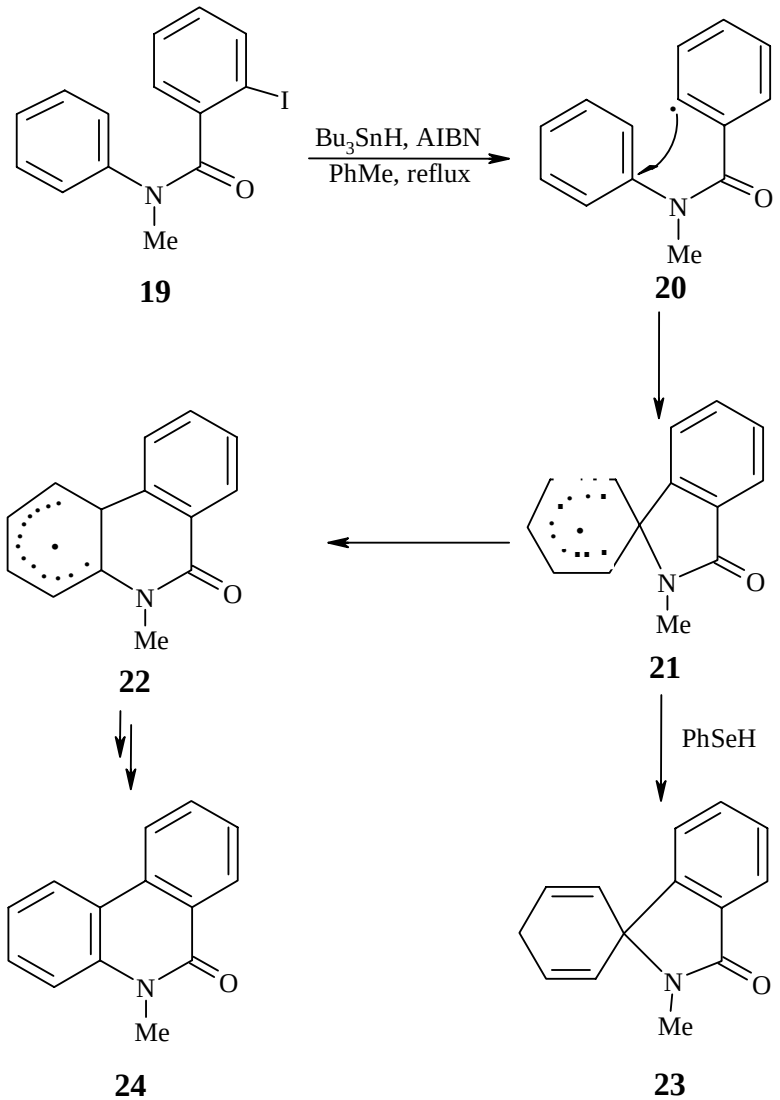
The cyclization of radicals obtained from *N*-substituted 7-bromoindoles for the synthesis of tricyclic indole analogues was reported.[29, 30] The tricyclic indole (**18**) was produced by the "*6-exo*" cyclizations of the butenyl derivative (**17**). The analogous *N*-allyl-7-bromoindole undergoes "*6-endo*" rather than "*5-exo*" cyclization because the geometry of the iodole ring enforces to do so. *N*-(*ω*-Alkenyl)-2-bromoindoles react to yield intermediate indol-2-yl radicals which undergo "*5-exo*" or "*6-exo*" cyclization onto the pendant alkene to yield [1,2-*a*]-fused pyrroles. Indolines was reported[31] to be

prepared by cyclization of aryl radicals generated from *o*-halogeno *N*-alkenyl anilines. Indolines have also been synthesized using lithium tributylmanganate.[31]



17 **18**

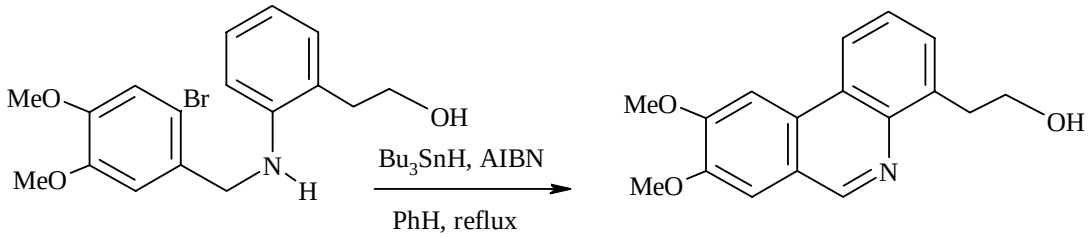
It was also reported[32] that the *o*-iodobenzamide (**19**) underwent radical cyclization in presence of Bu_3SnH and AIBN in refluxing toluene to produce phenanthridone (**24**). The exact reason why the "*6-endo*" cyclization product is exclusive in the system (**19**) is not clear at present, but the formation of product (**24**) from **19** may be explained by the generation of an aryl radical (**20**) and subsequent "*5-exo*" cyclization may give spirohetrocyclic radical (**21**) followed by neophyl rearrangement to give **22** or by a "*6-endo*" route directly to intermediate radical (**22**). This unknown aspect of the mechanism of these reactions had been solved by trapping with benzeneselanol (PhSeH), which is an extremely fast



19 **20** **21** **22** **23** **24**

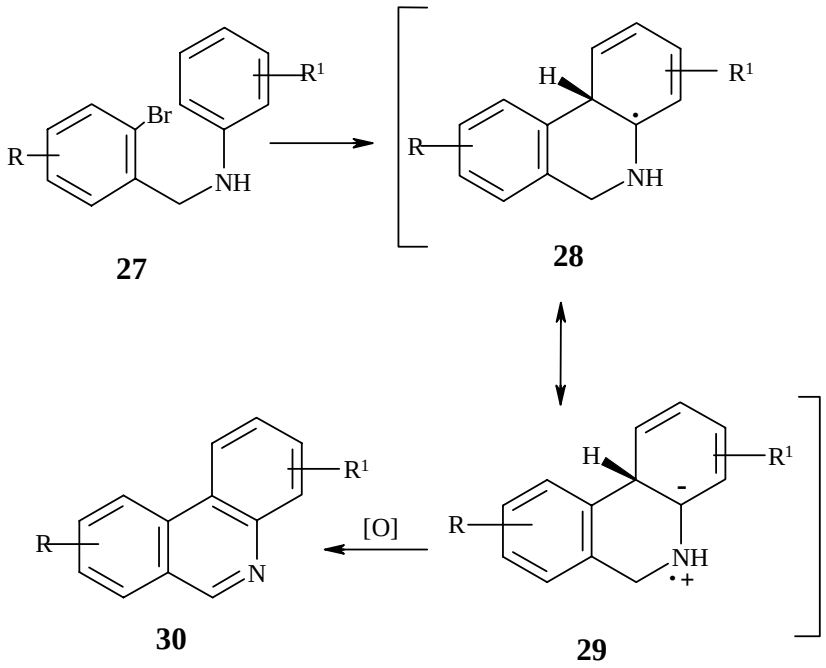
hydrogen donor. Radical (**21**) was trapped with PhSeH to yield the spirocyclohexadiene (**23**) to provide strong evidence for "*5-exo*" cyclization. The intermediate radical (**22**) rearomatised to yield the phenanthridone (**24**) by an unknown mechanism, which was useful for this synthetic sequence, *i.e.* an oxidation step in a Bu_3SnH mediated cyclization.[33]

Rosa *et al*. observed[33] that *N*-(2-bromo-4,5-dimethoxybenzyl)-2-(*β*-hydroxyethyl)aniline (**25**) under normal radical cyclization condition furnished 4-(*β*-hydroxyethyl)-8,9-methylenedioxyphenanthridine (**26**).



25 **26**

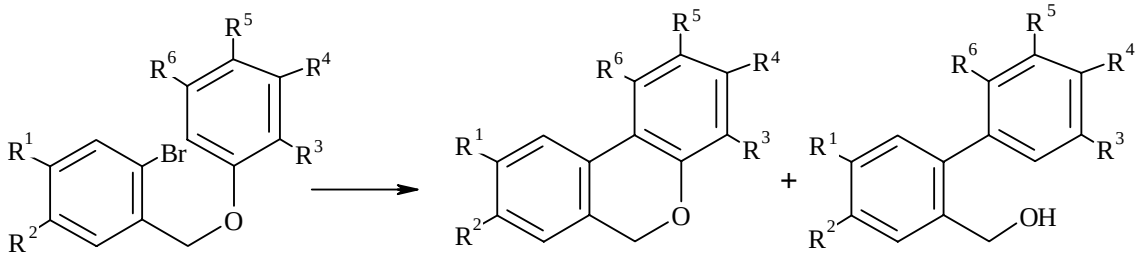
Rosa *et al*. reported[34] that *N*-*o*-bromobenzylanilines (**27**) on treatment with tri-*n*-butyltin hydride and AIBN furnished phenanthridines (**30**) in good yield. In this approach radical cyclization was utilized as the key step in the establishment of C_{aryl}-C_{aryl} bond.



27 **28** **30** **29**

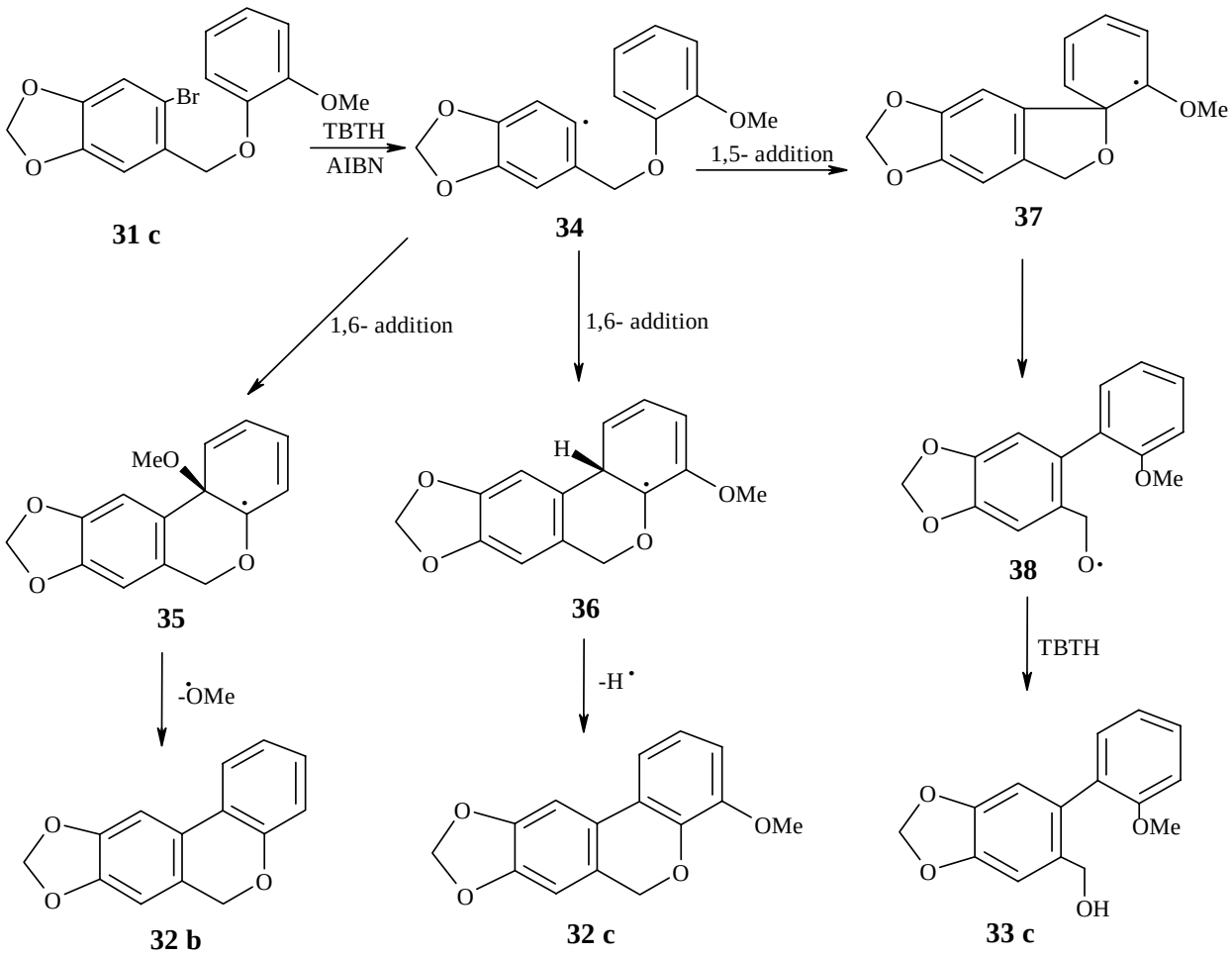
Rosa *et al*. also reported[35] that (*o*-bromobenzyl)phenylethers (**31**) was converted to 6*H*-dibenzo[*b*,*d*]pyrans (**32**) and a range of precursors with various methoxy and methylenedioxy substituents. Treatment of *o*-bromobenzyl phenyl ethers and a two-fold excess of tri-*n*-butyltin hydride (TBTH) with 0.5 to 0.6 mol. equiv. of AIBN induced an inefficient C_{aryl}-C_{aryl} bond formation. The

structures of the products resulting from 1,5- and / or 1,6- additions were found to be largely determined by the presence or absence of the substituent and its position in the phenyl ring. Compounds (**31a**) and (**31b**), carrying no substituent in the phenoxy ring, when treated under normal radical cyclization condition, afforded the corresponding pyran derivatives (**32a**) and (**32b**), respectively in modest yield (*ca*. 45%). Introduction of a OMe group in the 2-position of the phenoxy ring, as in (**31c**), furnished a



31 **32** **33**

a) $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = H$
b) $R^1, R^2 = OCH_2O, R^3 = R^4 = R^5 = R^6 = H$
c) $R^1, R^2 = OCH_2O, R^3 = OMe, R^4 = R^5 = R^6 = H$
d) $R^1, R^2 = OCH_2O, R^4 = OMe, R^3 = R^5 = R^6 = H$
e) $R^1, R^2 = OCH_2O, R^5 = OMe, R^3 = R^4 = R^6 = H$
f) $R^1, R^2 = OCH_2O, R^3 = R^4 = OMe, R^5 = R^6 = H$



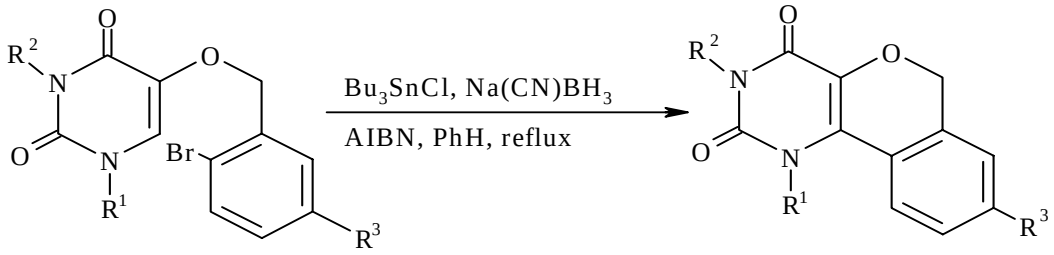
31 c **34** **37**

35 **36** **38**

32 b **32 c** **33 c**

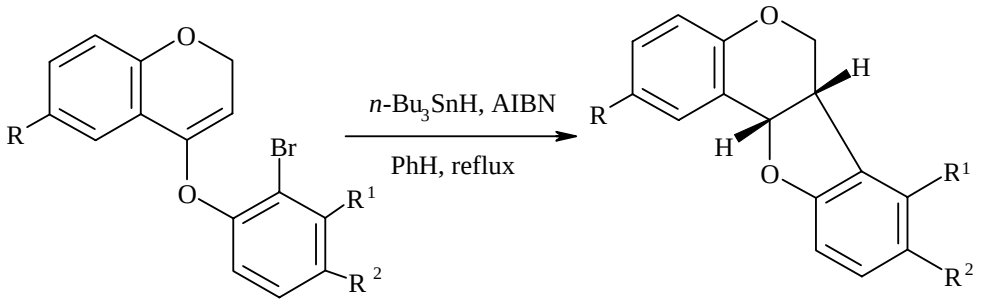
mixture of compounds from which the methoxypyran (**32c**) (*ca*. 5%), the demethoxylated compound (**32b**) (*ca*. 7%) and the biphenyl alcohol (**33c**) (18%) were isolated. The placement of the same substituent in the 4-position, *e.g*. (**31e**), also gave the pyran (**32e**) (22%) and the alcohol (**33e**) (*ca*. 7%). However, the 3-methoxy isomer (**31d**) produced the pyran (**32d**) (20%) as the only isolable product. It is thus became apparent that the position of the methoxy group dictates the nature of various possible reactions that occur, namely cyclizations with or without loss of substituent and / or the cleavage of the C-O bond. Referring to the reaction of **31c**, the various radical intermediates that could be formed on the homolysis of the C-Br bond, is shown above.

Recently we reported[36] the regioselective synthesis of 1*H*,3*H*,6*H*-[2]benzopyrano[4,3-*d*]pyrimidine 2,4-diones (**40**) in 80-85 % yield by refluxing a number of 5-(2′-bromobenzyloxy)pyrimidine2,4-diones (**39**) in boiling benzene with tri-*n*-butyltin chloride and sodium cyanoborohydride in the presence of a catalytic amount of azobisisobutyronitrile (AIBN).



39 **40**

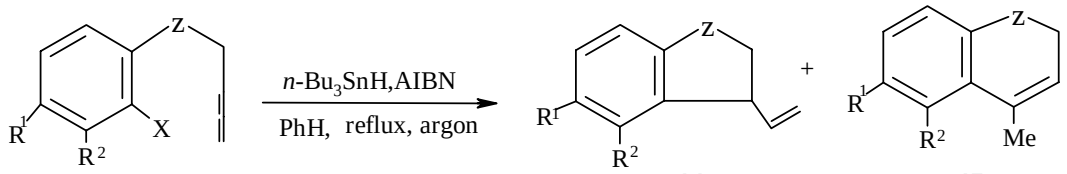
Balasubramanian *et al*. reported[37] the radical cyclization of 4-(*o*-bromophenoxy)-2*H*[1]benzopyrans (**41**) to synthesize pterocarpan derivatives (**42**). The reaction was carried out by refluxing a 0.02 M solution of (**41**) in benzene with 1.1 equivalent of *n*-Bu_3SnH in the presence of catalytic amount of azobisisobutyronitrile to furnish 6*a*,11*a*-dihydro-6*H*-benzofuro[3,2-*c*]benzopyran (**42**) in 90 % yield.



41 **42**

Balasubramanian *et al*. reported[38] that *o*-haloaryl allenyl ethers (**43a-c**) upon treatment with tri-*n*-butyltin hydride and AIBN in refluxing benzene underwent a *5-exo-trig* free radical cyclization to give 3-ethenyl-

2,3-dihydrobenzofurans (**44a-c**) in good yield. The nitrogen analogues (**43d,e**) afforded the corresponding 3-ethenyl-2,3-dihydroindoles (**44d,e**) in good yield under radical cyclization condition.



43 **44** **45**

When, X= Br, Z= O

Z= O

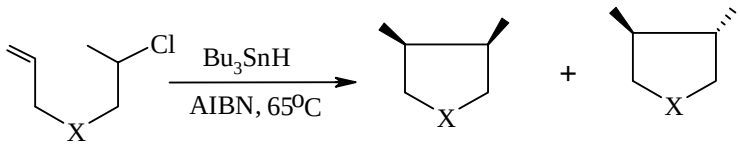
a) R^1 = Cl, R^2 = H
b) R^1 = Me, R^2 = H
c) R^1 = Ph, R^2 = H

When, X= I, Z= N (*p*-$MeC_6H_4SO_2$)

Z= N (*p*-$MeC_6H_4SO_2$)

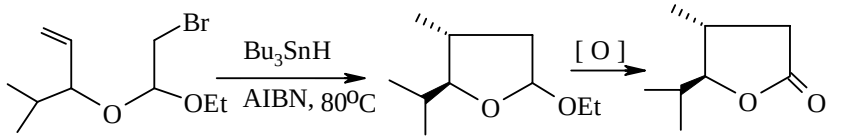
d) R^1 = Cl, R^2 = H
e) R^1 = Me, R^2 = H

It is quite interesting for the five membered-ring radical cyclizations that the annelation to cyclic alkenes gives *cis* products for steric reasons. Beckwith *et al*. observed[39] that the cyclization of open-chain 5-hexenyl radicals substituted in positions 1 or 3 gave preferentially *cis*-disubstituted cyclopentanes (**46**) to (**47**). This *cis* cyclization was interpreted in terms of attractive interactions between the methyl group and the π-bond, which could occur in the very early transition states of radical addition to alkenes. In contrast, with 2- or 4- substituted "5-hexenyl radicals" the *trans*-disubstituted products were

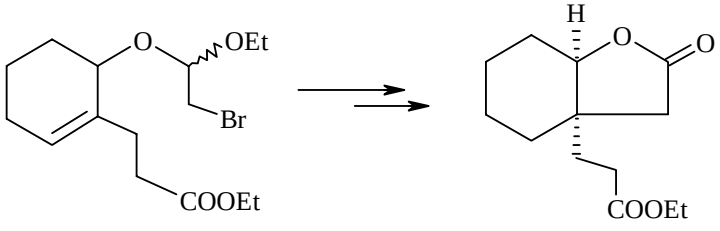


46 **47** **48**

X= CH_2, O (70 : 30)



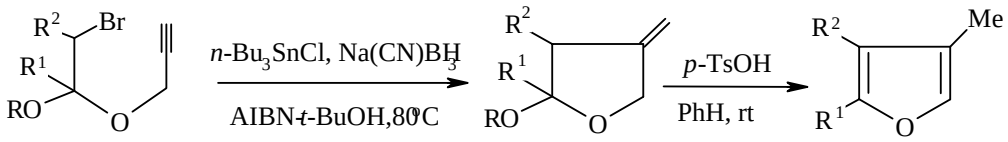
49 **50** 81% **51** 97-98%



52 **53**

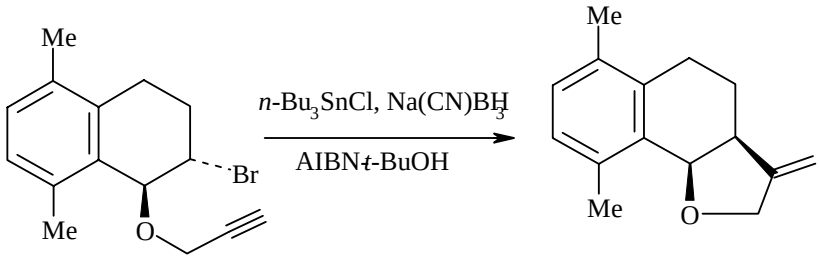
preferentially formed, as seen in the formation of **50** from **49**.[40] The formation of heterocycles by tin hydride mediated radical cyclization is often practical.[41, 42] Both Stork[40, 43, 44] and Ueno[45-47] have developed a general route to γ-lactones, which has been increasingly applied in synthesis.[48-50] The following examples illustrated some of the salient features of the method. Reduction of **49** with tin hydride produced a mixture of anomers (**50**) in 81% yield. Jones oxidation gave lactone (**51**), which was 97-98% *trans* isomer. This bromoacetal method was developed because direct cyclization of the α-bromo ester is a very unfavorable process. The location of the oxygen atom in the chain is of importance, since it significantly accelerates the "*5-exo*"-cyclization. This is manifested in the conversion of **52** to the "*5-exo*"-product (**53**).

Srikrishna *et al*. observed[51] that tri-*n*-butyltin hydride mediated radical cyclization of the bromo acetal (**54**) furnished 2-alkoxy-4-methylenetetrahydrofuran (**55**). The cyclized products (**55**) were found to be too labile and were aromatized directly to furans (**56**), without purification using a catalytic amount of *p*-toluenesulfonic acid in benzene at room temperature.



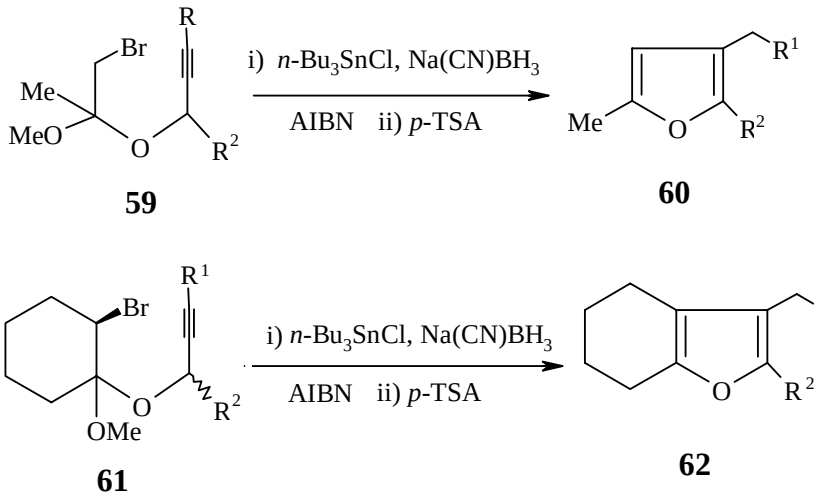
54 **55** **56**

Srikrishna[52] applied this methodology for the radical cyclization of bromo ether (**57**) to produce **58** in 85 % yield.

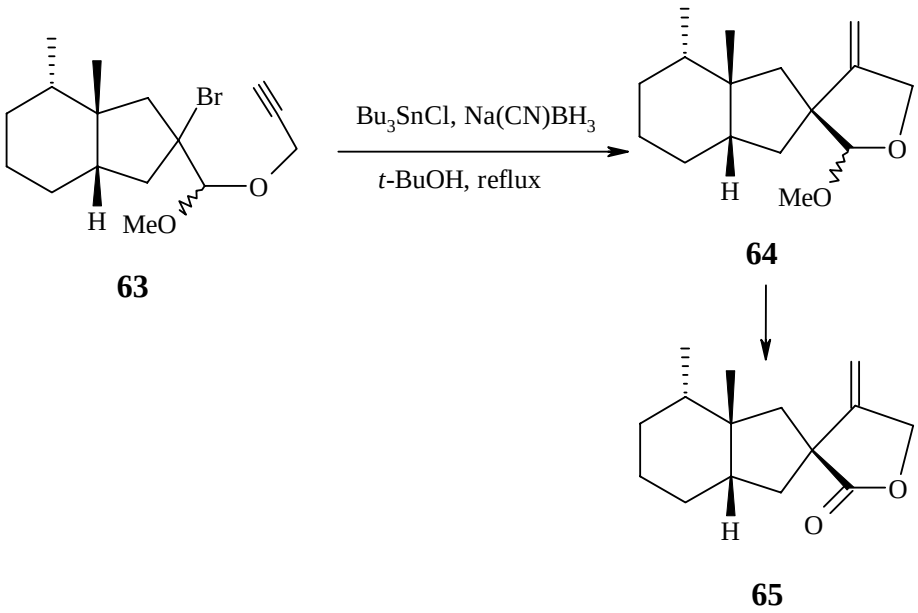


57 **58**

Srikrishna *et al*. also extended the methodology, to establish the versatility of the sequence, to polysubstituted furans and they described[53] the syntheses of 2,3,5-tri- and 2,3,4,5-tetrasubstituted furans. Radical cyclization of the bromo acetal (**59**) followed by aromatization produced 2,3,5-trisubstituted furans (**60**). Analogously, the bromo acetal (**61**) furnished the tetrasubstituted furans (**62**).

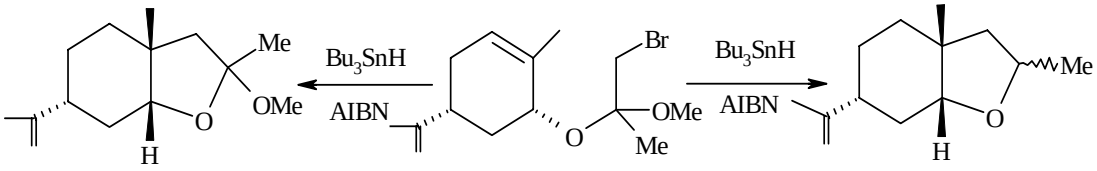


The masked ester (**63**) is used for carrying out the central spirocyclization step to produce **64** which was hydrolyzed to give the butyrolactone ring present in the product (**65**).[54]



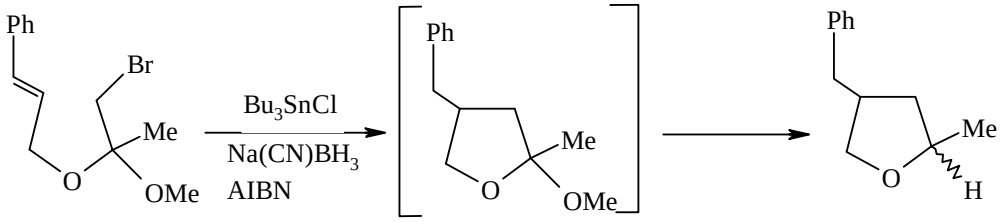
63 **64** **65**

Srikrishna *et al*. also observed[55] that the bromo ketal (**66**) with tri-*n*-butyltin hydride in the presence of a catalytic amount of AIBN under standard conditions furnished the *5-exo-trig*-cyclized product (**67**).[54] In contrast, by using a combination of a catalytic amount of tri-*n*-butyltin chloride and sodium cyanoborohydride for the *in situ* generation of tri-*n*-butyltin hydride[56, 57] generated the demethoxylated product (**68**). The formation of the product (**68**) can be explained as follows: at first the ketal (**67**) was produced *via 5-exo-trig*-radical cyclization of the bromo ketal (**66**) by *in situ* generated catalytic tri-*n*-butyltin hydride. This was followed by tri-*n*-butyltin bromide (by-product formed in the reaction) catalyzed reductive demethoxylation of the ketal by the excess sodium cyanoborohydride present in the medium.



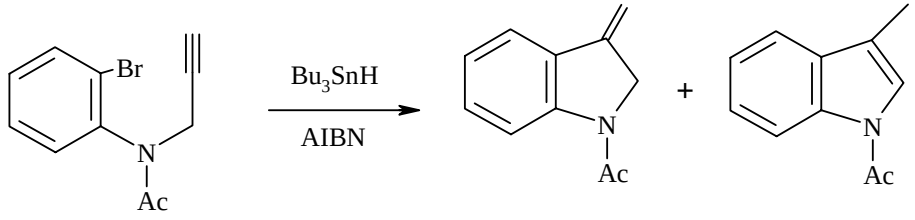
67 **66** **68**

Srikrishna *et al*. also reported[58] a regioselective reductive demethoxylation of dimethyl and mixed ketals, using sodium cyanoborohydride in the presence of a catalytic amount of tributyltin chloride as Lewis acid in refluxing *tert*-butanol. In the *5-exo-trig*-radical cyclization reaction of bromo ketals, *e.g.* (**69**), he observed that tributyltin chloride acts as a Lewis acid in the sodium cyanoborohydride mediated reductive demethoxylation of ketals to the corresponding ethers. The formation of the ether (**71**) from the bromo ketals (**69**) can be explained as follows: The ketal (**70**) was produced *via* the *5-exo-trig*-radical cyclized product and tributyltin chloride formed in the reaction acts as a Lewis acid and the excess sodium cyanoborohydride present in the medium reductively cleaves[59] the ketal (**70**) similar to ionic hydrogenation reactions[59] to give the product (**71**). It is very interesting to note that no reductive demethoxylation was found by using a catalytic amount of tributyltin hydride.



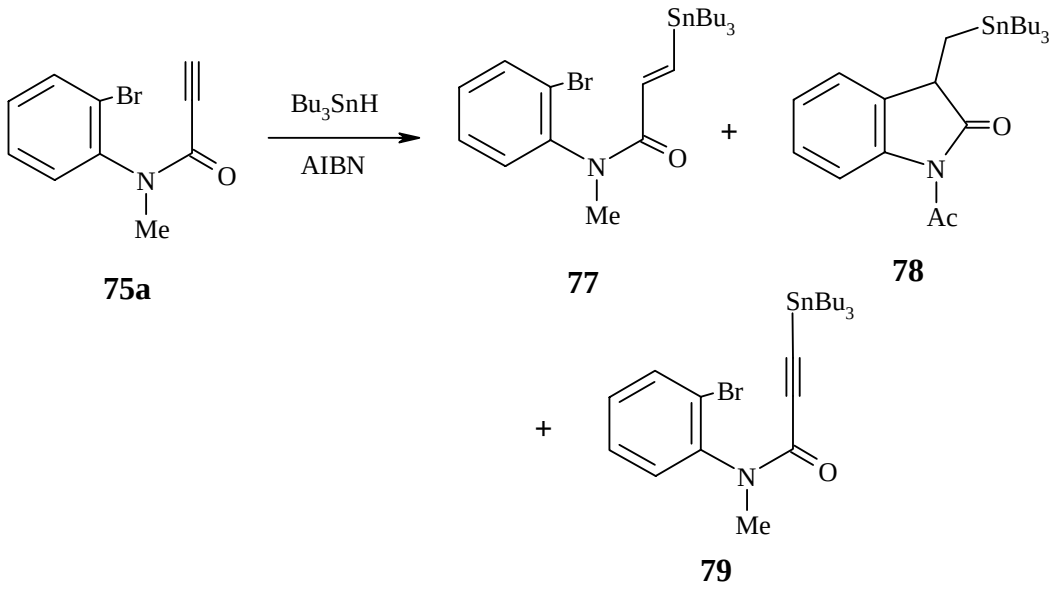
69 **70** **71**

Although *5-exo-trig* cyclizations of aryl radicals[60] are very common, *5-exo-dig* cyclizations are also found in some cases. Boger and Coleman[61] utilized such cyclizations in the total synthesis of the antitumour antibiotic CC-1065. This reaction was used to prepare a number of dihydroindoles[62] from the corresponding alkynyl amides as in the cyclization of **72** to give the indole derivative (**73**) which aromatised to give a 99% yield of a mixture of **73** and **74**.



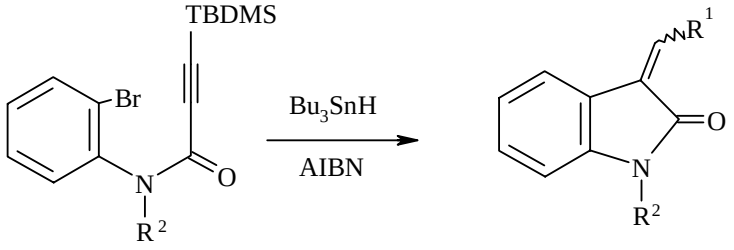
72 **73** **74**

The reaction of the alkyne with tributyltin hydride was a real problem. For further study of such a reaction, a range of amides (**75**) and (**76**) were synthesized.[63] *N*-(2′-Bromophenyl)-*N*-methylpropynamide (**75a**) under standard radical cyclization condition incorporated a mixture of three products (**77**), (**78**) and (**79**) in 42% yield in which **79** was the major product.



75a **77** **78** **79**

In order to slow down the various unwanted reaction products, a substituent was introduced onto the terminus of the alkyne. Generally a removable group was used on the terminus of the alkyne and for this a silyl group was chosen.[64] Initial studies were carried out by using trimethylsilyl group, but it was unsuccessful at the radical cyclization stage. Therefore bulkier *tert*-butyldimethylsilyl group was introduced. In addition, an *N*-allyl group was also introduced into the cyclization precursors. The intermediate aryl radical generated from **76** undergoes *5-exo-dig* cyclization to yield mixtures of E- and Z-isomers of the desired methylene oxindoles (**80**).[63] Various factors control the balance between '*5-exo*'



76

a) $R^2 = CH_3$
b) R^2 = allyl

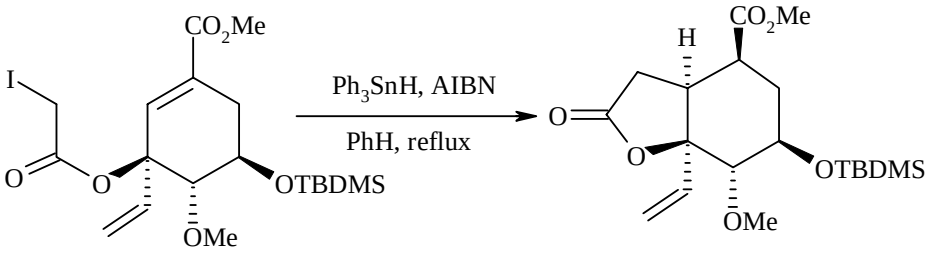
80

a) R^1 = TBDMS, $R^2 = CH_3$
b) R^1 = TBDMS, R^2 = allyl
c) $R^1 = CH_3$, $R^2 = CH_3$

(TBDMS = *tert*-Butyldimethylsilyl)

and '*6-endo*' cyclization for cyclization of aryl radical onto side chain α-β-unsaturated amides to give oxindoles and dihydroquinolones respectively.[65]

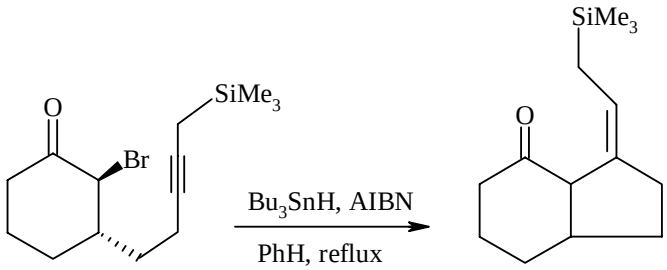
It is a general technique to synthesize lactones by the application of radical cyclization procedure. The bicyclic lactone (**82**) was produced in 73% yield by the reaction between the α-iodoester (**81**) and Ph_3SnH.[66]



81 **82**

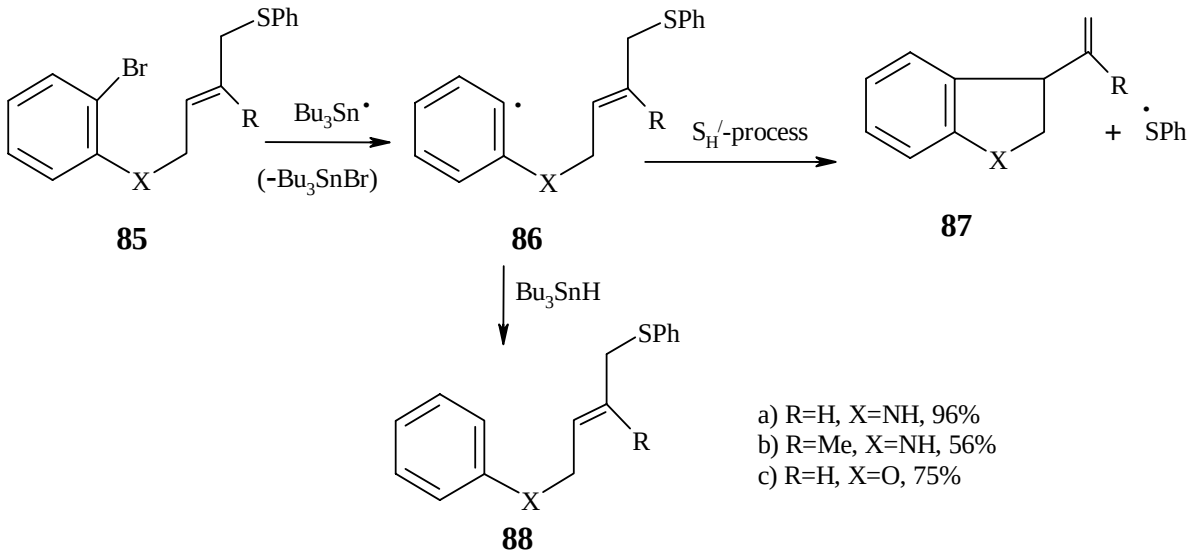
(TBDMS = *tert*-Butyldimethylsilyl)

Schinzer *et al*. carried out[67] the radical cyclization of various propargylic silanes under normal radical cyclization condition. Ring closure of carbocycles and also of 5- and 6- membered *o*-heterocyclic rings was achieved in high yield. One such representative example is the conversion of **83** to **84**.



83 **84**

Ueno *et al*. reported[68] that *N*-(4-phenylthio-2-butenyl)-*o*-bromoaniline (**85**) reacted with tri-*n*-butyltin hydride to give 3-vinyl-2,3-dihydroindole (**87a**) in 96% yield *via* hitherto unknown intramolecular $S_H^/$

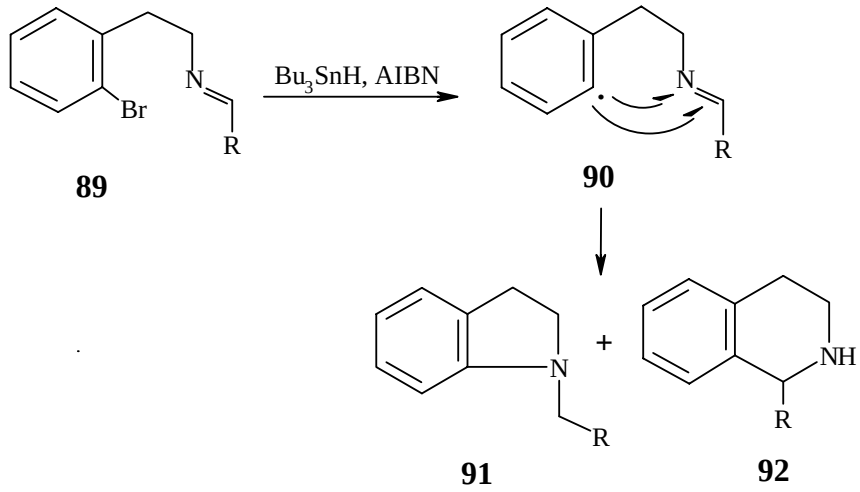


85 **86** **87**

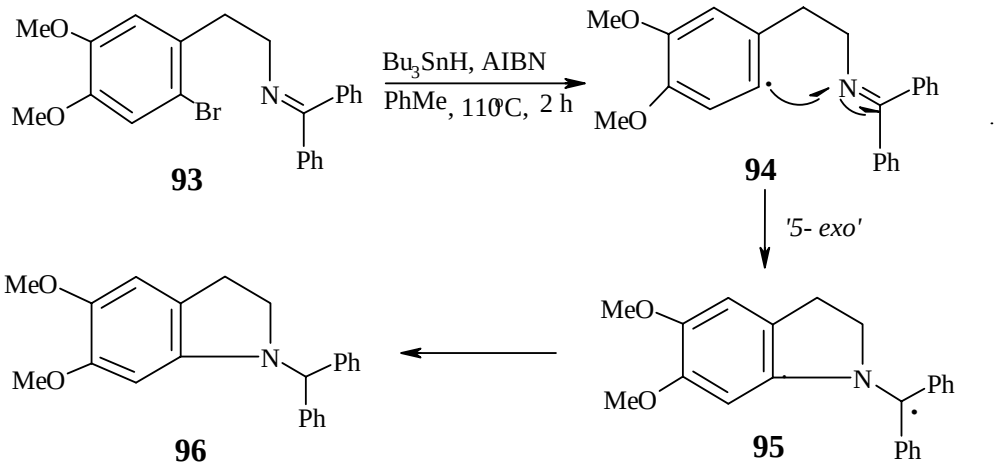
88

process.[69] Similarly, dihydroindole (**87b**) or benzofuran (**87c**) was obtained in 56% or 75% yield respectively. When the same reaction was carried out at higher concentration of Bu_3SnH simple reduction product (**88**) was also obtained in addition to **86**.

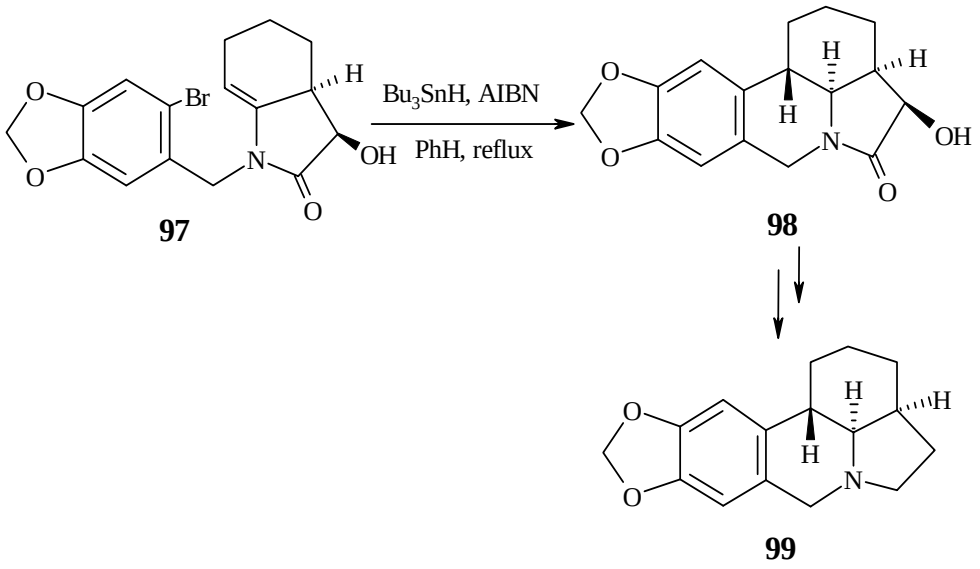
It was observed that the synthesis of indolines by cyclization of aryl radicals onto side chain imines[70, 71] normally gave *6-endo* cyclization, *e.g.* the imine (**89)** produced a mixture of tetrahydroisoquinoline product (**92)** as the major product through *6-endo* route and a very little of the indoline product (**91**) (*5-exo* route*) via* aryl radical (**90**).



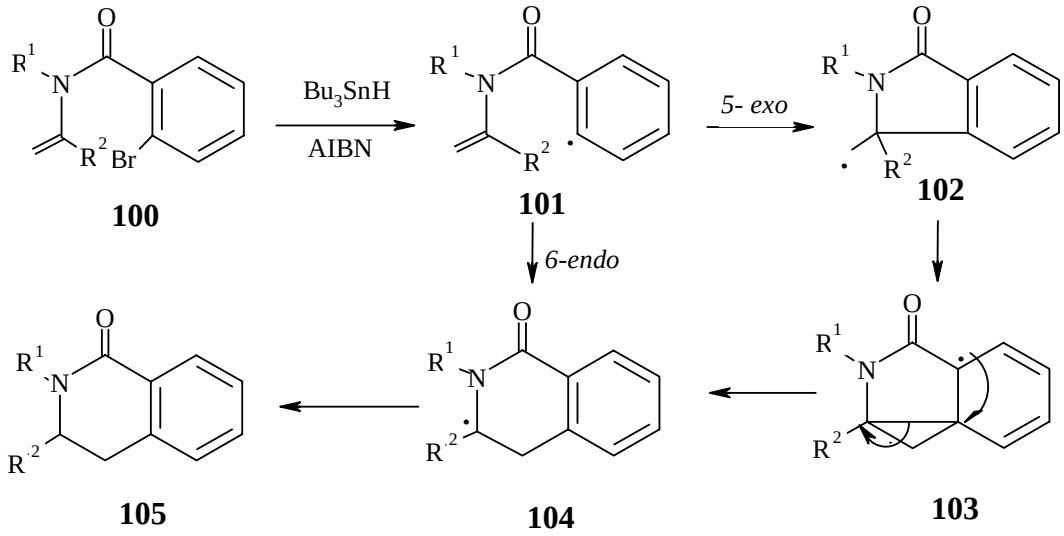
However, when groups are attached to stabilize the radical resulting from *5-exo*-cyclization onto the nitrogen atom of the imine, *e.g.* phenyl, *5-exo*-cyclization became more favorable. The radical (**94**), resulting from bromine abstraction from the *o*-bromophenyl imine (**93**), proceeded by selective *5-exo*-cyclization to give the stable diphenylmethyl radical (**95**).[71] The indoline (**96**) is the only product, but when alkyl groups in place of aryl groups are present the cyclization was selective to *6-endo*-cyclization.[70, 71]



The use of aryl radical cyclization to form benzoheterocycles is now a well known radical procedure and it is illustrated in the following synthesis.[72] The key step involved a "*6-endo*"-cyclization in the intermediate aryl radical, generated from starting material (**97**), onto the β-position of an enamide using the standard Bu_3SnH procedure. The cyclized product (**98**) was obtained in 79% yield as a single diastereomer.

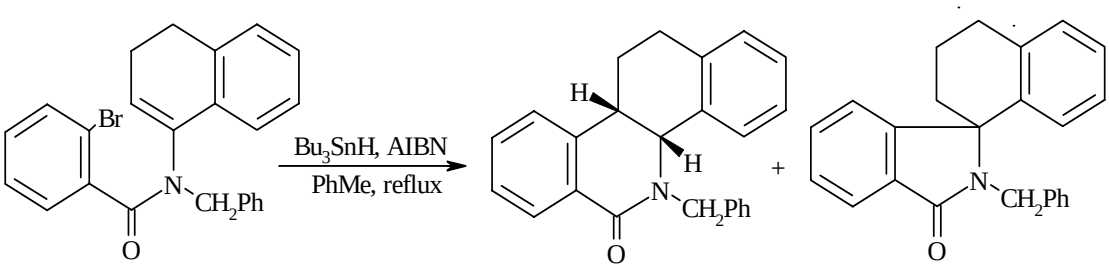


Bu_3SnH mediated aryl radical cyclizations are now widely used in organic synthesis for the construction of fused aromatic compounds. From the study of various literature it is clear that although enamide having a simple alkenic bond at the 5-position relative to the aryl radical center gives five-membered lactam (**126a** to **127a**), enamides having a substituent at the 5-position usually cyclize in a "*6-endo*" manner exclusively or predominantly to give six-membered lactams. The corresponding *N*-vinylic benzamide systems (**100**) have been reported[73-78] to cyclize in a *6-endo-trig* manner exclusively or predominantly, leading to the isoquinolones (**105**). The exact reason why the *6-endo*-cyclization



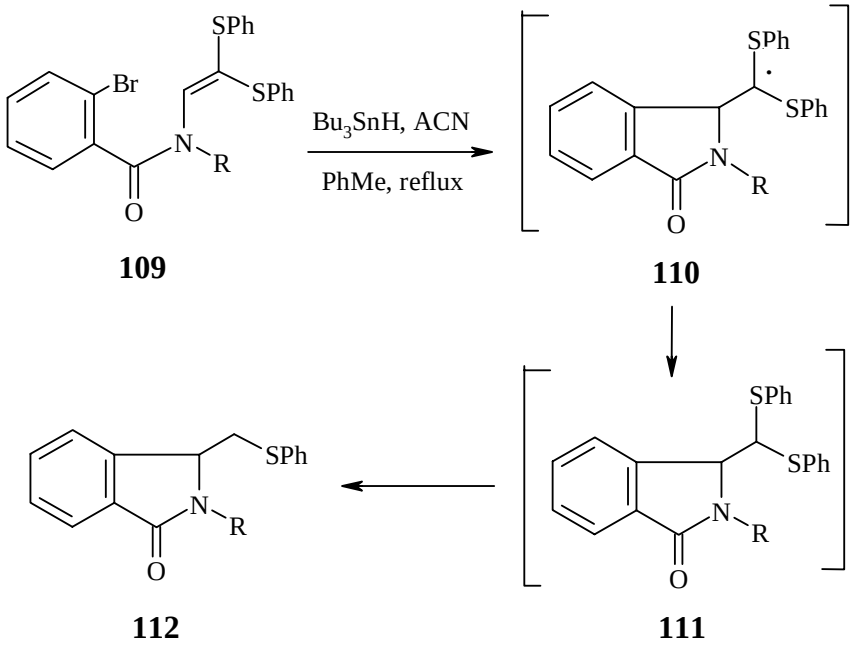
predominates in the systems (**100**) is not clear at present, but one possible explanation involves an assumption that the initially formed aryl radical cyclize in the usual "*5-exo*" manner to give radical (**102**), which then undergo a neophyl rearrangement[79, 80] through the intermediate (**103**) to give more stable radical (**104**).

Takano *et al*. found[73] that when the enamide substrate (**106**) bearing *endo* olefin moiety was treated under the standard radical cyclization condition competitive 1,6- and 1,5- cyclization occurred to give the *6-endo*-cyclization product (**107**) as the major product (38% yield) accompanied by the *5-exo*-cyclization product (**108**) (27% yield).



106 **107** **108**

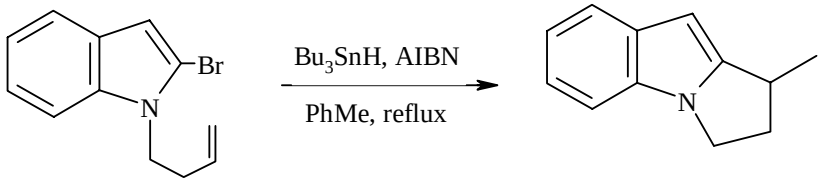
Recently it was also reported[81] that the Bu_3SnH-induced aryl radical cyclization of the enamides (**109**) having two phenylsulfanyl groups at the terminus of the *N*-vinylic bond provided exclusively the isoindolone (**111**). Because aryl radicals are very reactive species with very early transition states their products are not generally determined by the product radical stability.



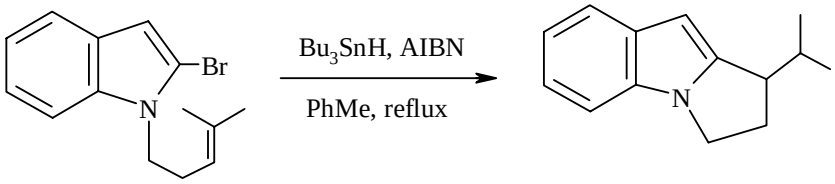
109 **110**

112 **111**

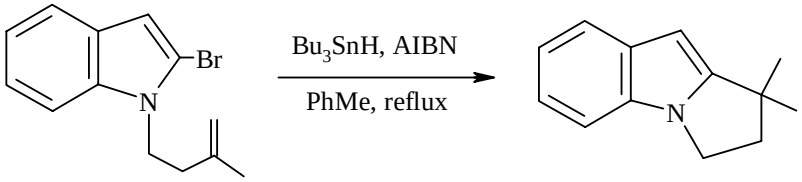
It was found[82] that 2-bromoindole carrying an unsaturated *N*-alkyl group underwent normal radical cyclization reaction. When "*5-exo*" reactions were possible, 5-membered ring products were formed exclusively, irrespective of the substituents on the carbon chain and around the double bond. In the case of the simple 5-hexenyl radical, substitution at C-5 leads to formation of a mixture of cyclopentane (*via 5-exo*-cyclization) and cyclohexane (*via 6-endo*-cyclization). However in case of compounds (**113**), (**115**), (**117**) only the product of *5-exo*-cyclization was detected. This may be caused by the bond angles involved in the 5-membered ring of the indole. When the chain length was extended to a *N*-pentenyl chain, a mixture of *6-exo*-cyclized product and reduction product was observed (as in the case of **119**) with the cyclized product being the major one; no seven membered ring formation was observed.



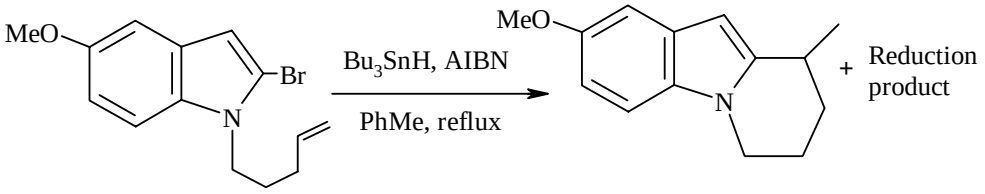
113 **114** (79%)



115 **116** (71%)



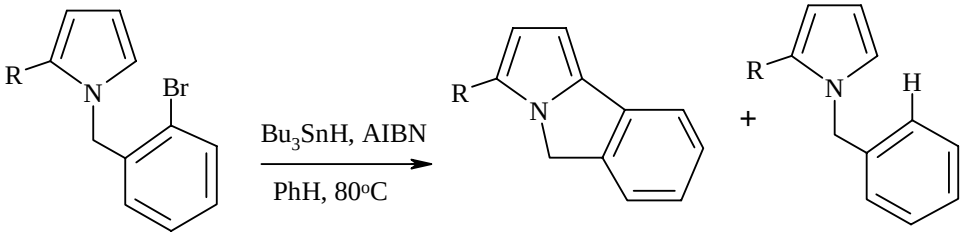
117 **118** (73%)



119 **120** (96%)

Both an inter- and intra- molecular addition of aryl radicals to benzenoid aromatic rings was reported by Hey *et al.*[83] Toga observed that the quinolones were produced[84] in high yield where the two benzene rings are linked by an amide. The mechanism of such reactions is controversial. Especially the rearomatization of the ring undergoing addition is a matter of much debate from the mechanistic point of

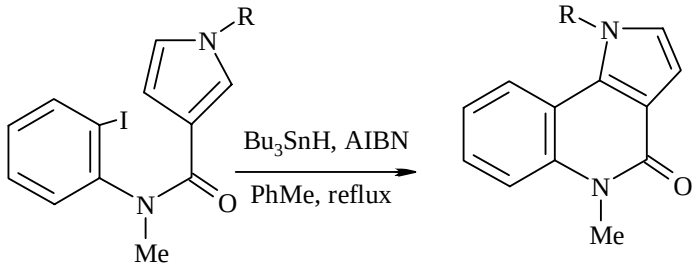
view. Bowman[85] explained such reactions in terms of $S_{RN}^{/}$ mechanism. However, very little work has been published[86] regarding the radical addition to the pyrrole nucleus. The addition of electrophilic carbon radicals to the unsubstituted α-position of pyrroles under oxidative conditions was shown by Muchowski[87] and Baciocchi.[88] Aryl radical addition to pyrroles under reductive conditions was offered by Muchowski.[89] Electron-withdrawing group at the C-2 position of the pyrrole is the necessary requirement for the cyclization to be observed. It is very interesting to note that similar reactions involving indole was found to produce dihydroindoles.[90]



121 **122** **123**

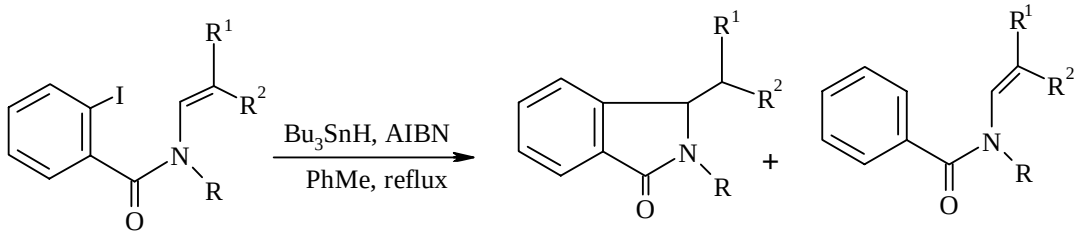
a) R = H (0%) (70%)
b) R = CHO (43%) (<10%)

N-(2′-Iodophenyl)pyrrole-3-carboxamides (**124**) under standard reductive radical cyclization conditions (tributyltin hydride in refluxing toluene with AIBN catalyst) furnished the tricylic pyrrolo[3,2-*c*]quinolone ring system (**125**).[91]



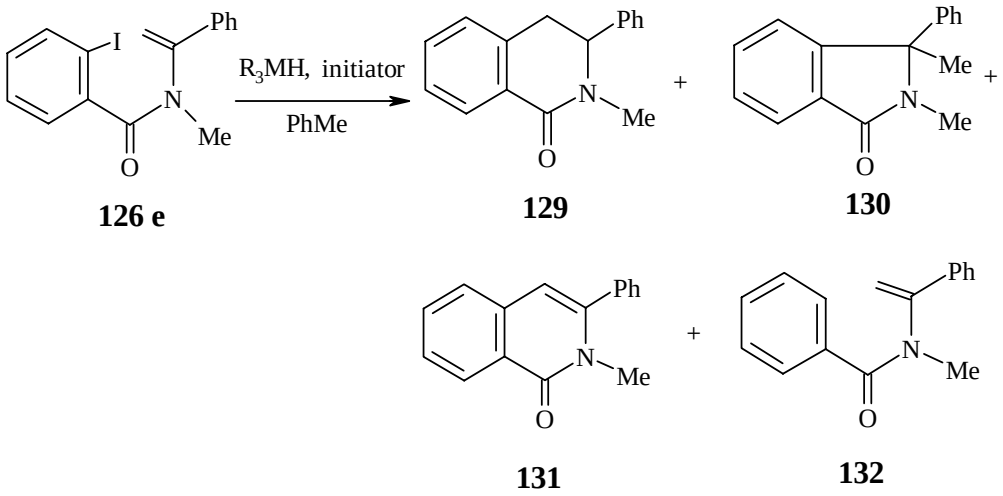
124 **125**

Ishibashi *et al*. recently reported[92] that *N*-vinylic-*o*-iodobenzamides (**126a-d**) gave exclusively the '*5-exo*'-cyclization product (**127a-d)**, along with the reduction product (**128a-d**). The enamide (**126e**)



126 a-d **127 a-d** **128 a-d**

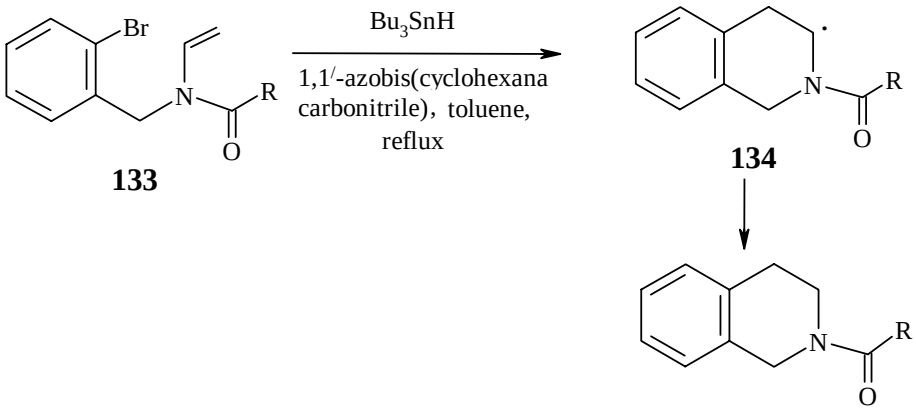
a) $R^1 = R^2 = H$
b) $R^1 = Ph$, $R^2 = H$
c) $R^1 = R^2 = Ph$
d) $R^1 = R^2 = COOEt$



126 e **129** **130** **131** **132**

having a phenyl substituent on the vinyl carbon atom α to the nitrogen atom gave predominantly the '*6-endo*' cyclization products (**129**) together with the five-membered lactam (**130**), the unsaturated six-membered lactam (**131**) and the reduction product (**132**).

Aryl radical cyclization has recently emerged as a valuable tool for organic synthesis.[3, 93, 94] The generation and subsequent reactions of radicals formed from aryl halides using tri-*n*-butyltin hydride and azobisisobutyronitrile (AIBN) is now well established[3, 93, 94] and a wide range of natural product synthesis based on aryl radical cyclizations have been reported.[79, 95-97] Literature shows only a few examples of heteroaryl radicals. Several examples, by Snieckus[95, 96, 98] and Harowven,[99, 100] involve pyridine and pyridyl radicals. One reported example of an indonyl radical was offered by Sundberg,[101] in the synthesis of Iboga alkaloids.[34] Aryl radical cyclization normally has a high *exo* : *endo* ratio indicating a stronger preference for "*exo*" cyclization than alkyl radicals. However, this preference is found to be reversed by cyclization to stabilised radicals.[102-104] This is examplified by the radical cyclization of *N*-(*o*-bromobenzyl)enamide precursors (**133**) which exclusively undergoes *6-endo-trig* cyclization to stable α-aminoalkyl radical intermediate (**134**).[104] The only cyclized products were the tetrahydroisoquinoline derivative (**135**) and no *5-exo*-cyclization was observed but some reduced

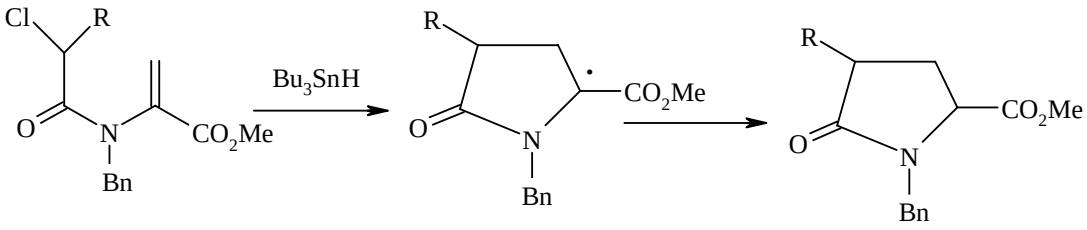


133 **134**

a) R=Et, 80% **135**
b) R=H, 43%

uncyclized products were also obtained. The mode of cyclization can be shifted to a *5-exo-trig* manner by introducing a phenylthio group at the terminus of the *N*-vinylic bond.

N-(*α*-Chloroacetamido)dehydroalanine derivatives (**136**) undergoes an unusual *5-endo*-cyclization to produce proline analogues (**138**).[105] The *α*-acetamido radical cyclized onto the dehydroalanine to furnish stable captodative *α*-amido ester radicals (**137**). These stable cyclized radicals may be the driving force for the unusual *5-endo*-cyclization, or a SET mechanism may be considered. A similar protocol involving *5-endo*-cyclization onto α-acetamidostyrenes was also reported.[106]



136 **137** **138**

R = H, Me, Ph

In presence of radical stabilizing substituents such as methyl, phenyl, phenylthio, dimethyl or dichloro group γ-lactam is formed exclusively via *5-endo-trig* cyclization from a range of 2-halo-*N*-(3,4-dihydro-2-napthyl)acetamides.[107] This was observed in relation to a study of the regioselectivity in Bu_3SnH mediated radical cyclization. The product formation was found to be dependent on various factors such as substituents on the radical center and on the nitrogen atom as well as the reaction temperature.

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 the aspects. Therefore, only the introduction, mechanism and representative examples are given. Application of the radical cyclization for the formation of the pyran and furan rings in heterocycles is included. In recent years there has been considerable study of the cyclization of radicals on heterocyclic compounds, a reaction that had previously been ignored.

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