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Free Radicals in the Synthesis of Medium-Sized Rings

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Contents

1. Introduction

Free radical cyclization reactions are important tools for the construction of various types of cyclic compounds including biologically active natural products and pharmaceuticals.[1] The advantages these reactions offer to the synthetic organic chemist include mild reaction conditions with high levels of regio- and stereocontrol along with significant functional group

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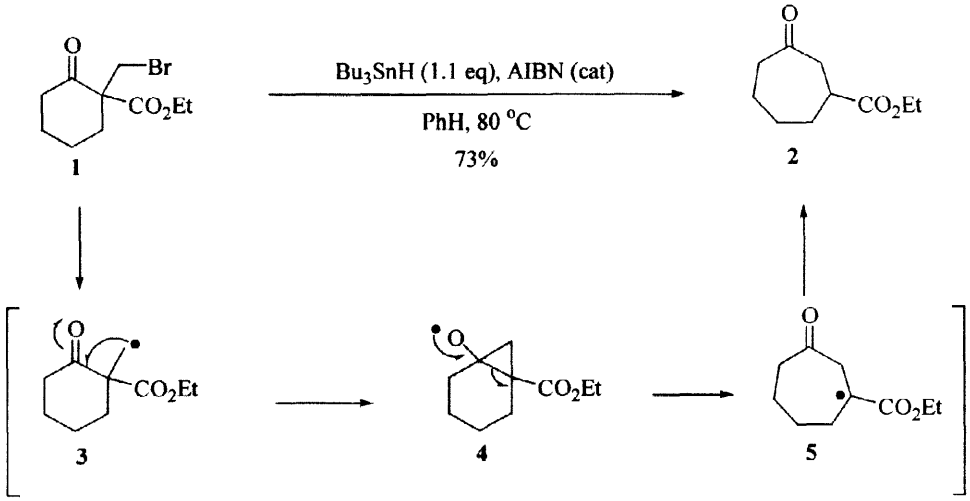
tolerance. Recent advances in radical chemistry have led to the development of some practical methods for the formation of seven-, eight-, and nine-membered rings via radical cyclization methods. In addition to formation of the usual five- and six-membered rings using carbon radicals, ring expansion via an oxy radical is increasingly becoming a useful tool in potential syntheses of medium- and large-sized rings.[2] This review discusses recent applications of radical chemistry to the syntheses of medium-sized (seven- to nine-membered) rings that have occurred from 1980 to end of 1998.

2. Alkoxy Radical Fragmentations

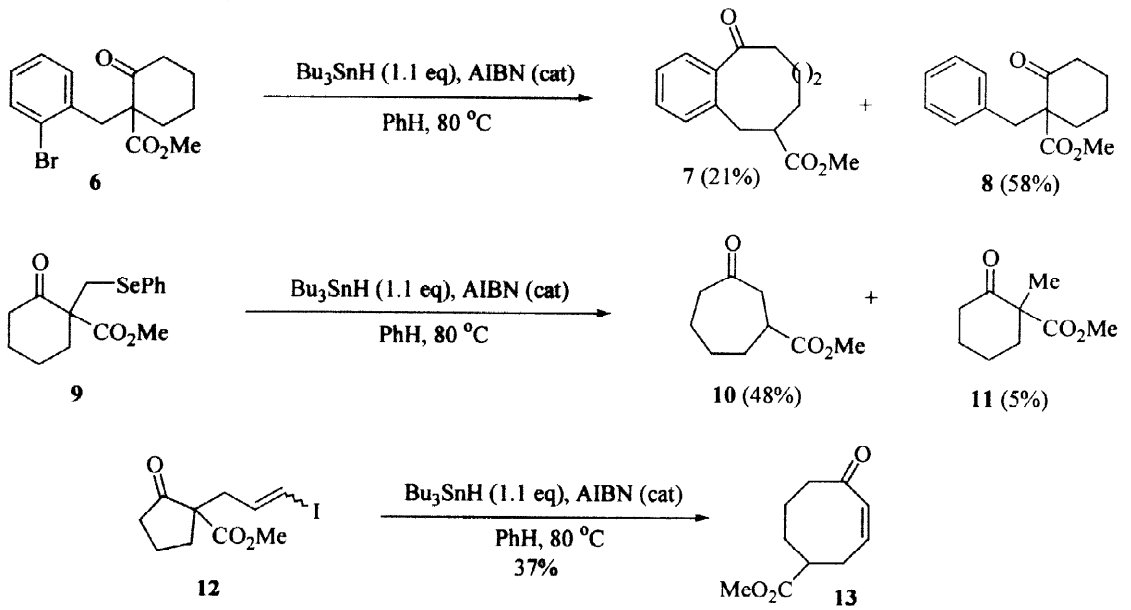
Radical cyclization reactions are not restricted to carbon-centered radical additions to carbon-carbon multiple bonds. Additions onto carbon-oxygen double bonds are permitted with aldehydes and ketones because ester and amide carbonyl groups are usually not reactive enough. In these alkoxy radical fragmentation process, it is generally thought of as an intramolecular process whereby the first step in the reaction is the formation of a reactive carbon radical tethered on a carbon chain attached to a five- or a six-membered ring. The carbon radical then is added to the carbonyl group to form the intermediate alkoxy radical. The alkoxy radical then reforms the carbonyl resulting in the fragmentation of a carbon-carbon bond to the ring-enlarged product. The fragmentation of the carbon-carbon bond is a facile process if the resulting radical is stabilized by groups such as a carboxylate ester, halogen, or an alkyl group. This method is suitable for ring expansions by one, three or four carbons but two carbons are more difficult because of the low rate of 4-*exo* closure. Alkoxy radicals can also be generated from alcohols.[3]

Dowd has demonstrated the utility of alkoxy radical rearrangements to medium-sized ring synthesis. The radical generated from bromomethyl β-keto ester **1** underwent ring expansion to keto ester **2** (Scheme 1).[4] Reaction of **1** proceeded through the tin hydride promoted production of primary radical **3** followed by attack of the latter on the neighboring carbonyl group. The resulting alkoxy radical **4** underwent ring opening to yield the stabilized radical **5** adjacent to the ester with subsequent reduction to **2**.



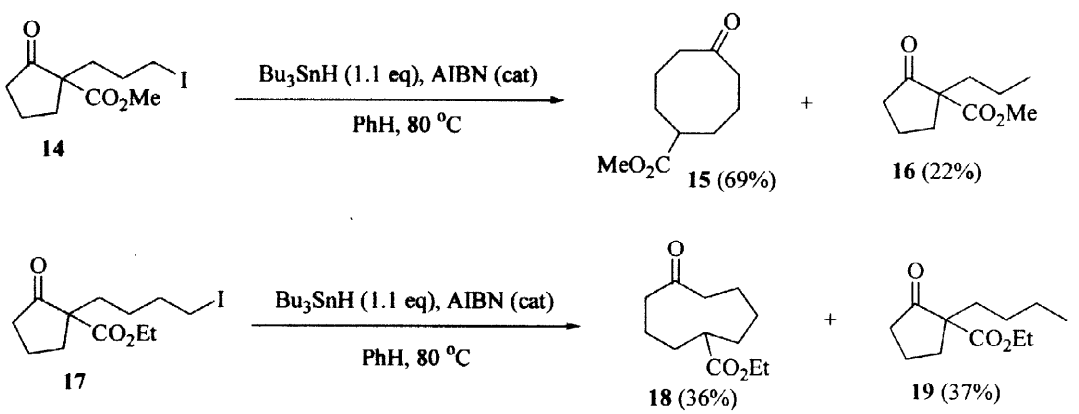
Scheme 1

Beckwith has examined the alkoxy radical fragmentation of various substrates. For example, aryl bromide **6** under radical conditions afforded benzononanone **7** in low yield with an appreciable amount of reduced product **8** (Scheme 2).[5] Selenide **9** gave cycloheptanone **10** with a smaller amount of reduced **11**. Iodo ester **12** furnished cyclooctenone **13** with no reduction product being observed.



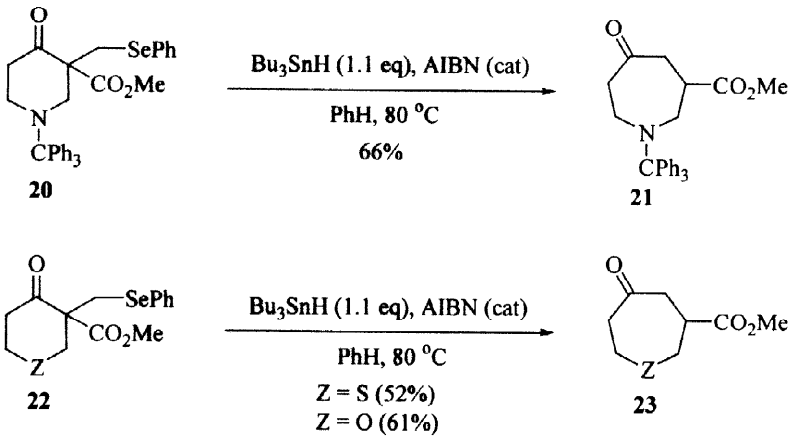
Scheme 2

Dowd further exploited the three- or four-carbon ring expansion of α-keto esters **14** and **17** to cyclooctanone **15** and cyclononanone **18**, respectively (Scheme 3).[6] Reduction products **16** and **19**, respectively, were also observed.

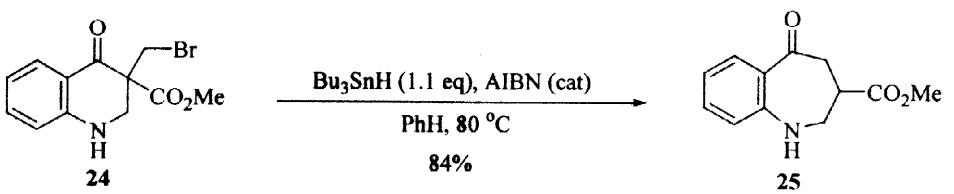


Scheme 3

Dowd has shown that six-membered piperidone **20** and sulfur/oxygen ketone **22** containing β-keto esters undergo alkoxy radical ring-expansion to the seven-membered azepine **21** and thiapane/oxepane **23**, respectively (Scheme 4).[7a] This application was extended to the benzo analogue **24** to give benzazepine **25** (Scheme 5).[7b,c]

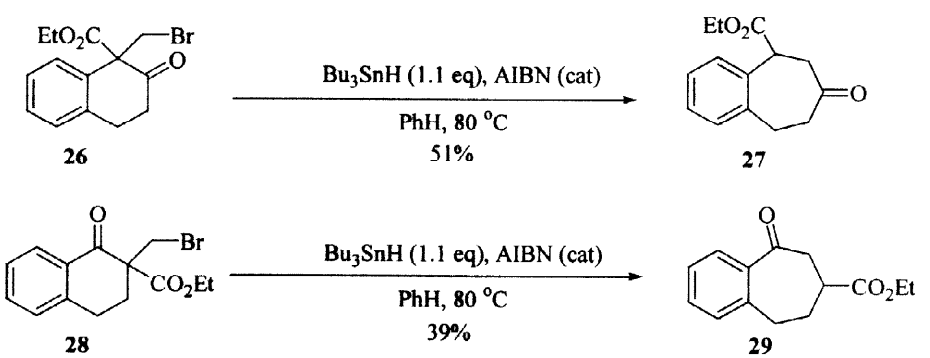


Scheme 4



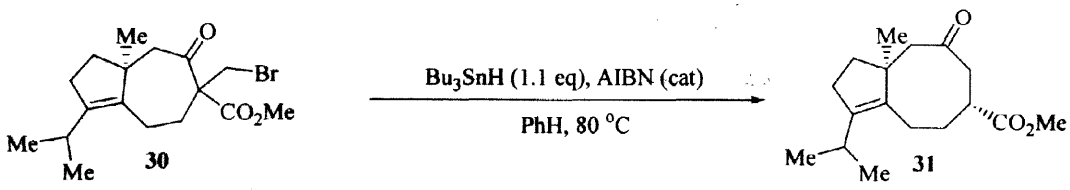
Scheme 5

Bowman has explored the one-carbon expansion to include benzannulated products. For example, bromomethyl β-keto esters **26** and **28** gave benzannulated ketones **27** and **29**, respectively (Scheme 6).[8]

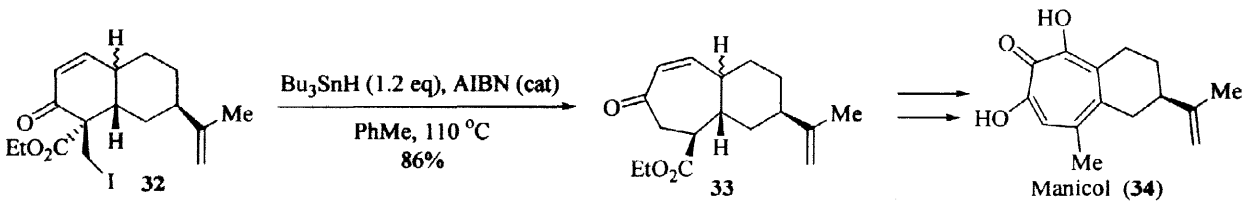


Scheme 6

Primary alkyl radicals derived from α-bromo- or α-iodo-methyl β-keto esters have become key intermediates in natural product synthesis. Mehta gained access to the 5,8-fused ring system of fusicoplagin D and 7,8-epoxy-4-basmen-6-one by free radical ring expansion of hydroazulene **30** to bicyclooctenone **31** (Scheme 7).[9] Beckwith-Dowd ring expansion of iodo ester **32** under radical conditions provided cycloheptenone **33** which embodies the full carbon skeleton of manicol (**34**, Scheme 8), a densely substituted troponoid nucleus with moderate activity against P-388 lymphocytic leukemia.[10]

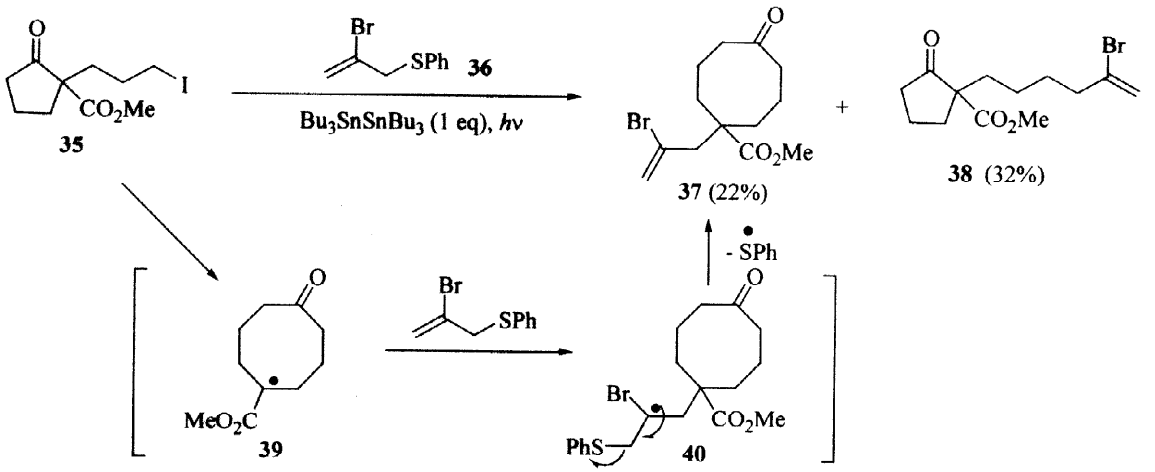


Scheme 7

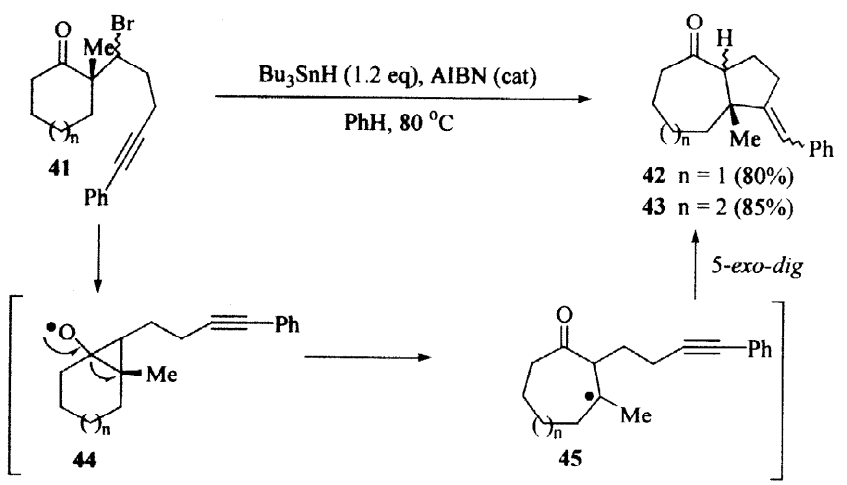


Scheme 8

Formation of the stabilized radical carboxylate or alkyl intermediates from these alkoxy fragmentations can undergo further intermolecular or intramolecular additions. For example, Curran and Yoo showed a sequential alkoxy radical ring expansion and allylation reaction using β-keto ester **35** under dibutyltin photochemical initiated conditions to give cyclooctenone **37** via ring expanded radical intermediate **39** which underwent intermolecular addition to 2-bromo-3-(phenylthio)propene (**36**) to give intermediate **40** (Scheme 9).[11] Simple addition product **38** was dominant from the initially formed radical of **35** and reaction with **36**. Boger has shown that bromo ketones **41** (n = 1, 2) underwent tandem free radical ring expansion via cyclopropyloxy radical **44** to cycloheptyl intermediate **45** followed by 5-*exo*-*dig* 5-hexynyl radical cyclization to provide hydroazulenone **42** and hydrocyclopentacycloctenone **43**, respectively, in excellent yields (Scheme 10).[12]

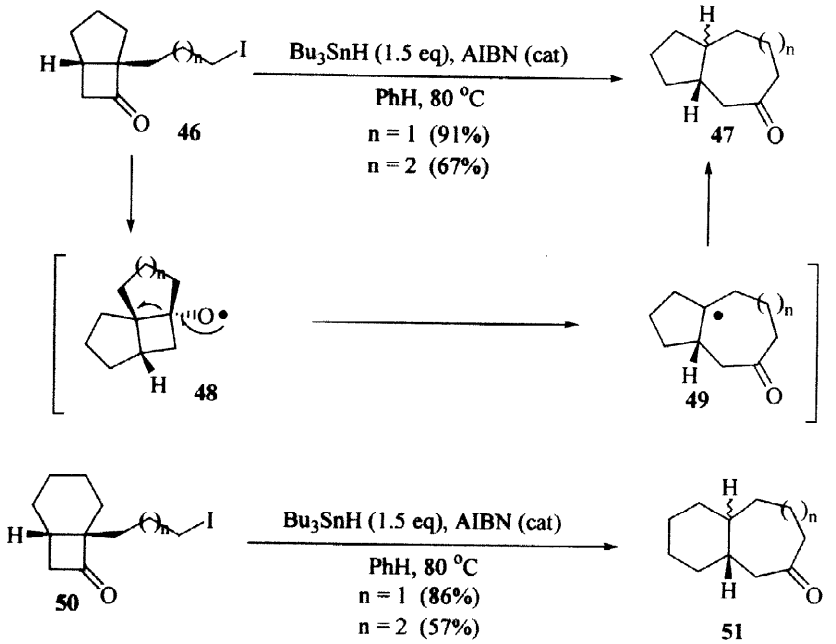


Scheme 9



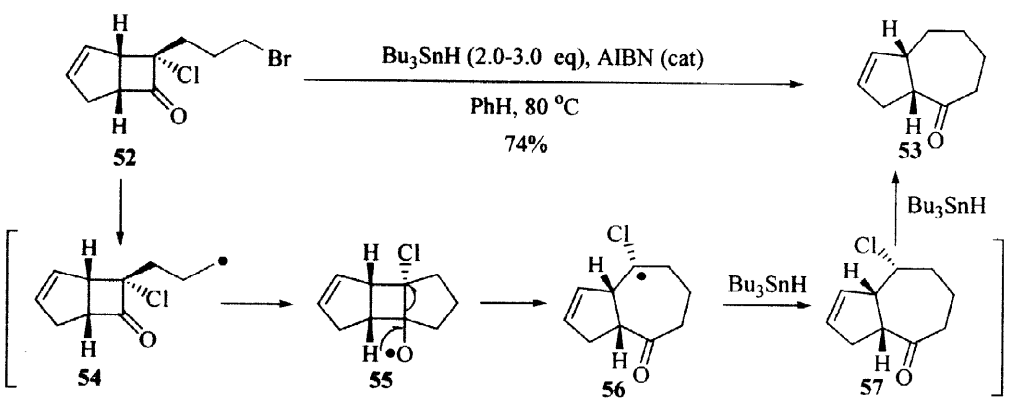
Scheme 10

Dowd also reported that free radical ring expansion of fused-cyclobutanones **46** and **50**, prepared by intramolecular [2 + 2] cycloaddition of ketenes or keteniminium salts to olefins, gave bicyclic ketones **47** and **51**, respectively (Scheme 11).[13] Addition of the primary radical generated from **46** gave alkoxy radical **48** which fragmented to stabilized tertiary radical **49** which was reduced to **47**.

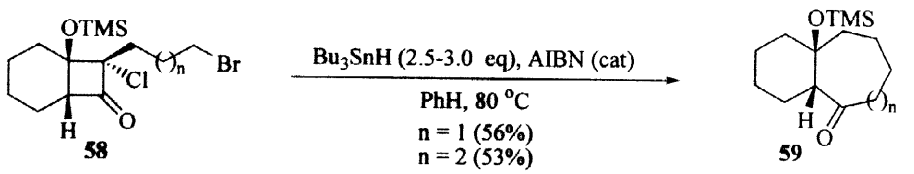


Scheme 11

Dowd demonstrated further the free radical ring expansion of fused cyclobutanone **52** to bicycloheptenone **53** (Scheme 12).[14] Radical **54** added to the carbonyl group to give alkoxy radical **55** which fragmented to give stabilized chloroketone radical **56** and reduction to **57**. Reaction of **57** with excess tin hydride gave reduced **53**. *Exo*-bromoalkyl cyclobutanones **58** underwent free radical ring expansion to *cis*-fused bicyclic ketones **59** under a similar mechanism (Scheme 13).[15]

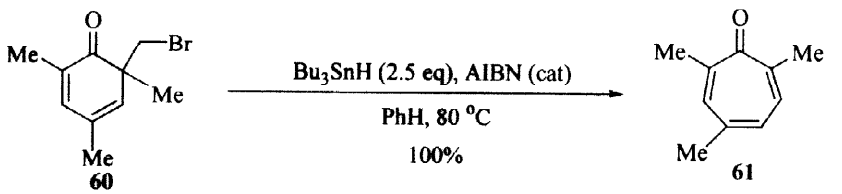


Scheme 12



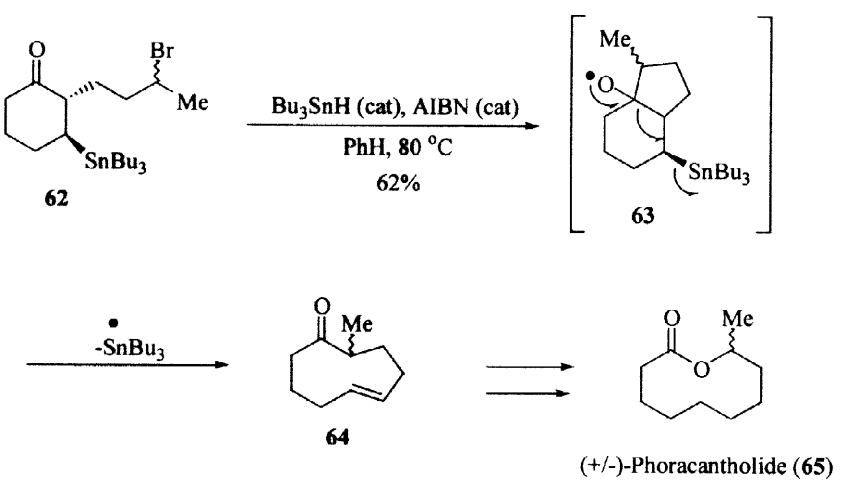
Scheme 13

Barton synthesized tropone derivative **61** from a tin hydride initiated one carbon ring expansion of cyclohexadienone **60** (Scheme 14).[16]

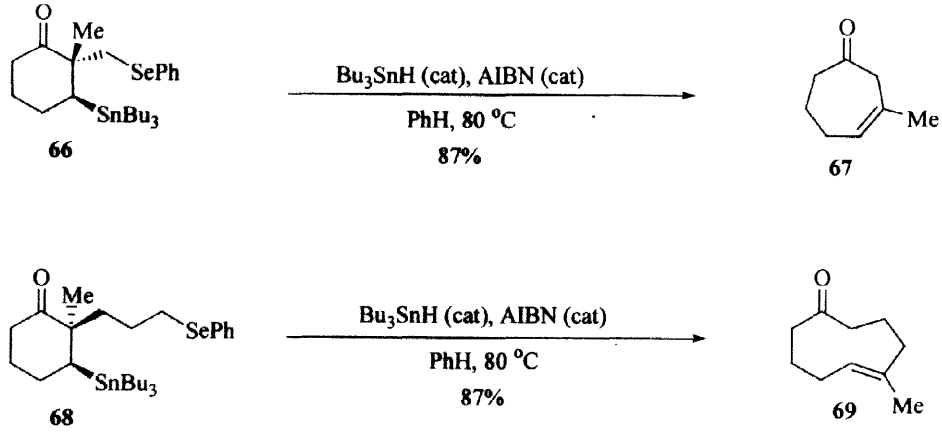


Scheme 14

Other pathways of generating alkoxy radicals other than radicals generated from α-alkyl β-keto esters have also been investigated. Baldwin has demonstrated the use of a free radical mediated ring expansion of *cis*- and *trans*-α-alkylated β-stannylcyclohexanone to provide efficient routes to *cis*- and *trans*-cyclononenones.[17] For example, bromo ketone **62** underwent free radical reaction to cyclopentyl alkoxy radical **63** which fragmented to β-alkyl radical and then eliminated a stannyl radical to form cyclononenone **64** which was further elaborated to (+/-)-phoracantholide (**65**, Scheme 15). Under similar mechanisms, selenyl ketones **66** and **68** provided cycloheptenone **67** and cyclononenone **69** respectively (Scheme 16).[18]

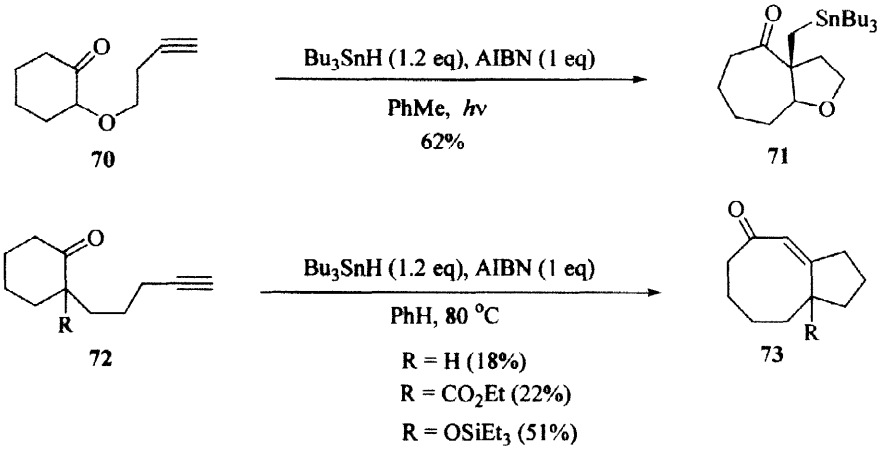


Scheme 15

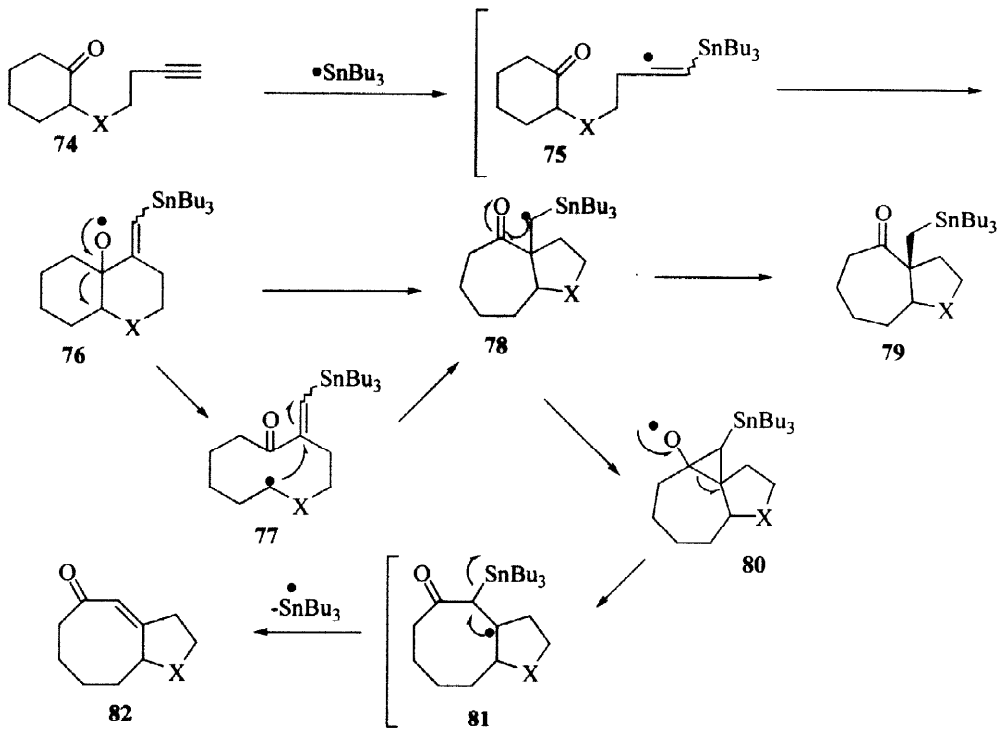


Scheme 16

Another unique alkoxy radical formation was shown by Nishida. Alkynyl ketones **70** and **72** under photochemical or thermal radical initiating conditions could lead to fused cycloheptanone **71** or cyclooctenone **73**, respectively (Scheme 17).[19] Mechanistically, addition of tributylstannyl radicals to alkyne **74** gives vinyl radicals **75** leading to alkoxy radical intermediate **76** which after β-cleavage provides final radical acceptor **77**. Intramolecular cyclization of **77** would afford **78**. Reduction of **78** gave cycloheptanone **79** (Scheme 18). However, radical **78** by the known cyclization/fragmentation sequence of **80** and **81** would give cyclooctenone **82**. The partitioning of the products between cycloheptanone **79** and cyclooctenone **82** would be governed by the relative rates for the cyclization of **78** to **80** versus reduction of **78** to **79**. If the concentration of the tin hydride is low, formation of cyclooctenone **82** will be favored.

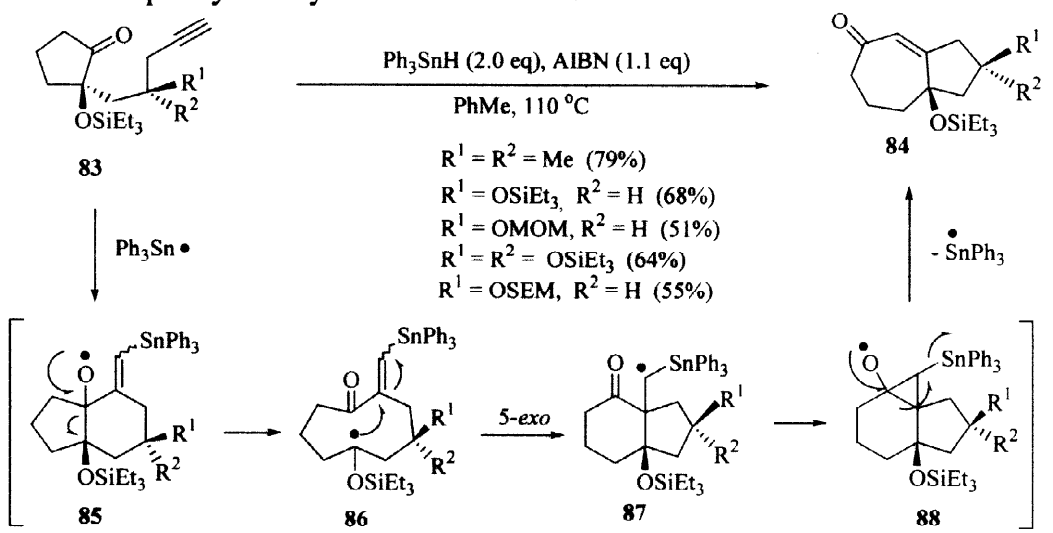


Scheme 17



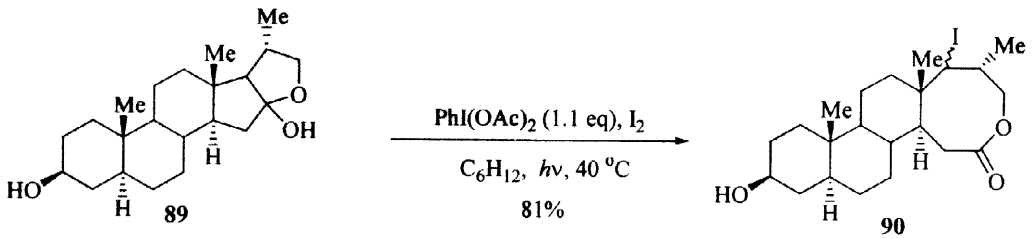
Scheme 18

2-(Pent-4-lynyl)cyclopentanones **83** underwent tandem radical cyclization to afford the hydroazulene skeleton **84**, a common structural component in some sesquiterpenes (Scheme 19).[20] Addition of triphenylstannyl radical to the alkyne of **83** followed by carbonyl attack provided alkoxy radical **85**. Fragmentation of **85** gave stabilized radical **86** which underwent 5-*exo* mode cyclization to **87** and further rearrangement to cyclopropyl alkoxy radical **88** followed by elimination of triphenylstannyl radical to afford **84**.



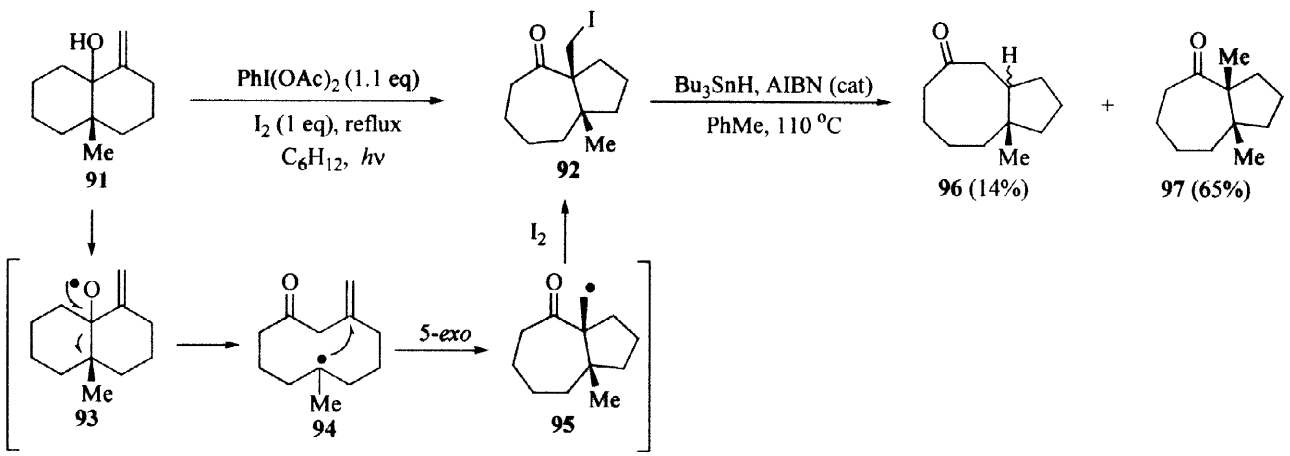
Scheme 19

Highly reactive alkoxy radicals can be generated from alcohols by various methods.[3] For example, the use of (diacetoxyiodo)benzene (DIB) has been developed as an efficient reagent for generation of alkoxy radicals. Suarez utilized this reagent in the synthesis of steroidal lactone **90** from alkoxy fragmentation of steroidal diol **89** (Scheme 20).[21]



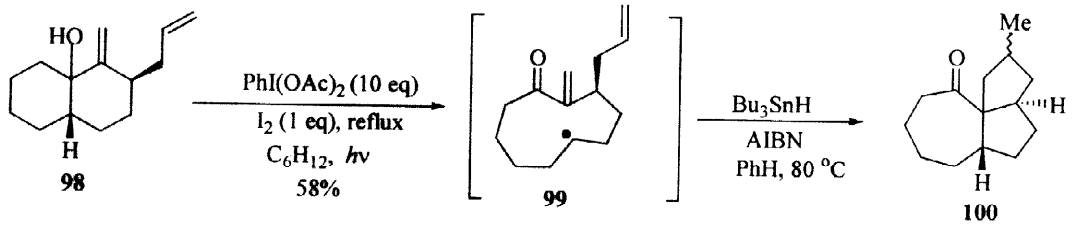
Scheme 20

Pattenden showed a sequential alkoxy radical fragmentation/transannular radical cyclization reaction with DIB. α-Methylene bicyclodecanol **91** was irradiated with (diacetoxyiodo)benzene in the presence of iodine to give hydroazulenone **92** via alkoxy fragmentation of **93** to tertiary radical **94** followed by 5-*exo* mode cyclization to radical **95** quenched by iodine (Scheme 21).[22] Tin hydride addition to iodo ketone **92** gave a mixture of bicyclooctanone **96** and reduced cycloheptanone **97**.



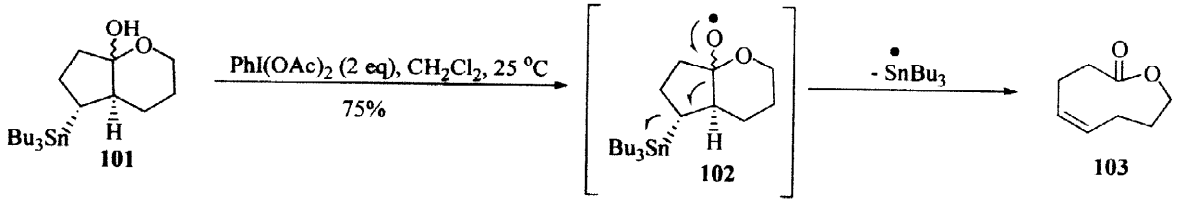
Scheme 21

As an extension of Scheme 21, Pattenden also took dienol **98** under identical conditions to provide angularly fused tricyclic ketone **100** via tandem ring closure of radical intermediate **99** (Scheme 22).[23]



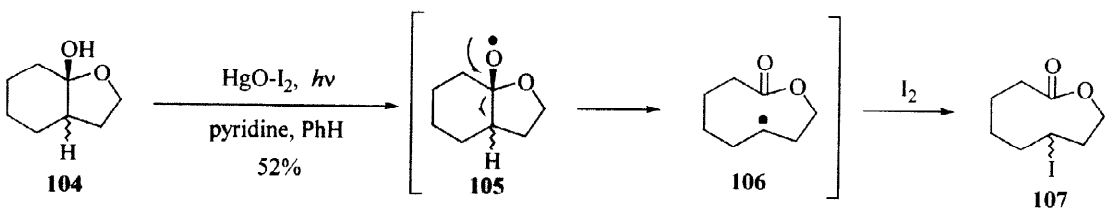
Scheme 22

Nagao has shown alkoxy radical **102**, generated from tributylstannyl lactol **101**, underwent fragmentation followed by elimination of the tributylstannyl radical to furnish lactone **103** in good yield (Scheme 23).[24]

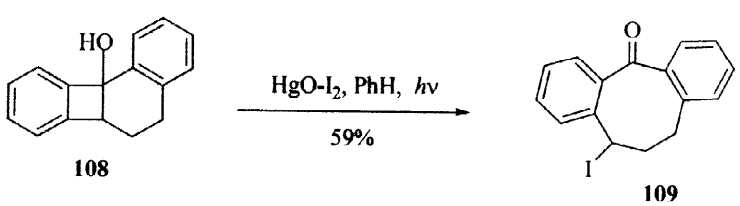


Scheme 23

Suginone used alkoxy radical **105**, generated photochemically from lactol **104**, to give radical **106** with subsequent iodine quenching to afford iodolactone **107** (Scheme 24).[25] He further exploited this methodology to benzocyclobutanol **108** to give dibenzoketone **109** (Scheme 25).[26]

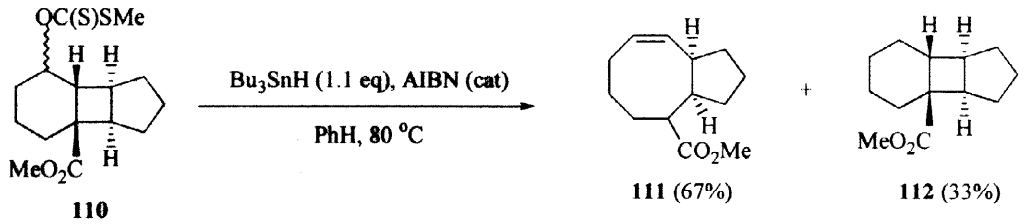


Scheme 24



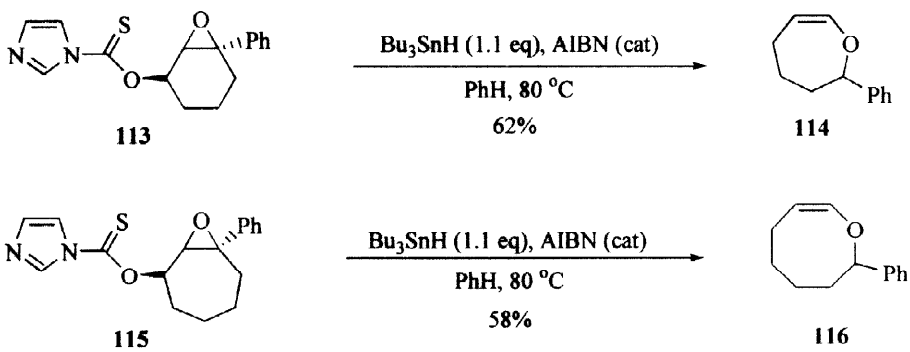
Scheme 25

Ranu has exploited a two-carbon ring expansion of cyclobutylcarbinyl radical fragmentation of tricyclic xanthate **110** to generate bicyclic ester **111** and reduced tricyclic ester **112** (Scheme 26).[27]



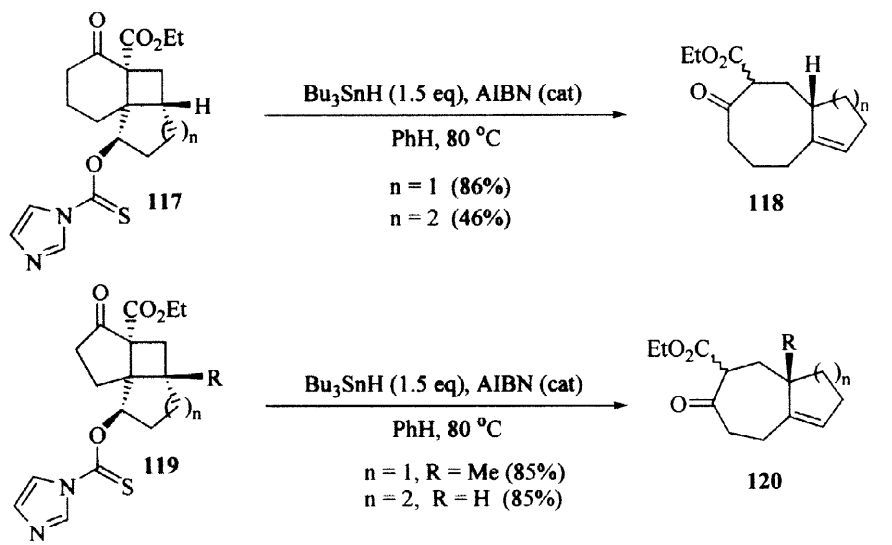
Scheme 26

An analogous method for the synthesis of seven- and eight-membered oxygen heterocycles **114** and **116** from imidazolethioate esters **113** and **115**, respectively, has been reported via alkoxy radical intermediates (Scheme 27).[28]



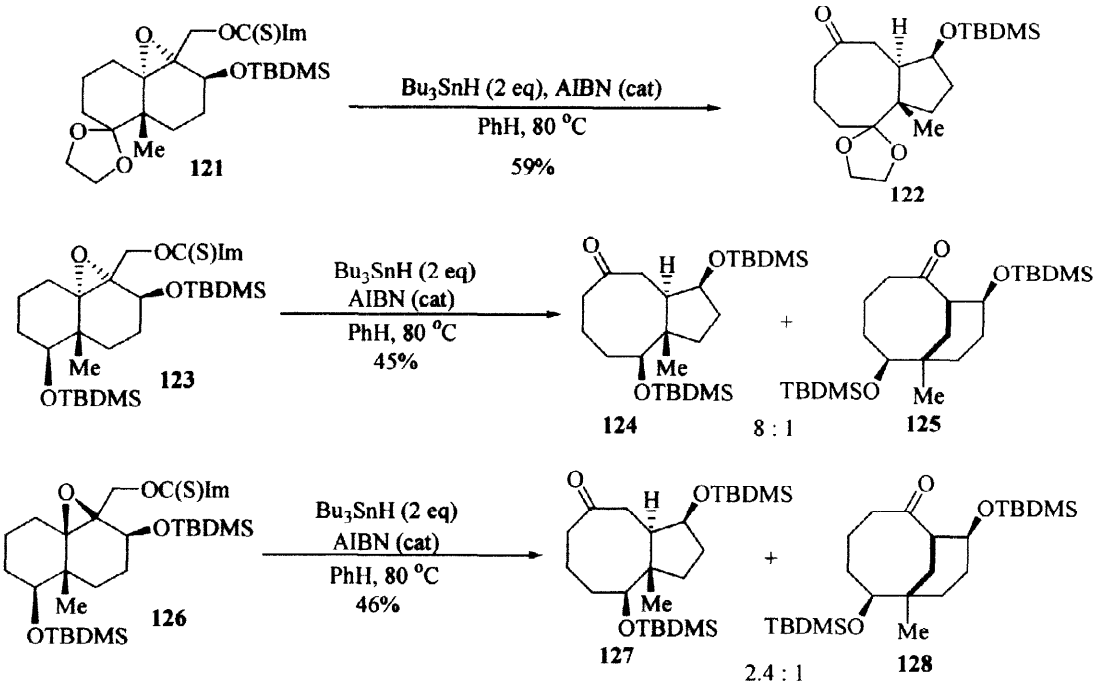
Scheme 27

Crimmins has shown that photoadducts **117** and **119** can undergo alkoxy radical fragmentation/elimination to yield medium ring-fused carbocycles **118** and **120**, respectively (Scheme 28).[29]

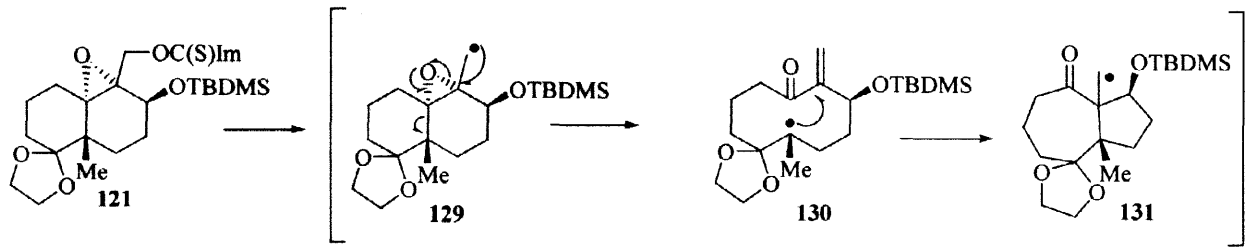


Scheme 28

Alkoxy radicals can also be obtained from α-β-epoxyalkyl radicals. The β-cleavage reaction of alkoxy radicals has recently been recognized as a useful method for the transposition of radical centers, sometimes occurring with skeletal rearrangement. Nishida reported a radical rearrangement using epoxydecalin thiocarbonylimidazolides.[30] Treatment of ketal **121** under standard radical conditions gave *trans*-fused bicyclooctanone **122**. *Trans* silyl ether **123** afforded bicyclooctanones **124** and **125** in a 8:1 ratio. *Cis*-bissilyl ether **126** gave a mixture of **127** and **128** in a 2.4:1 ratio (Scheme 29). Addition of tributylstannyl radical to **121** gave epoxyalkyl radical **129** which rearranges to alkoxy radical **130** which then continues similarly to give various products in different ratios (Scheme 30).

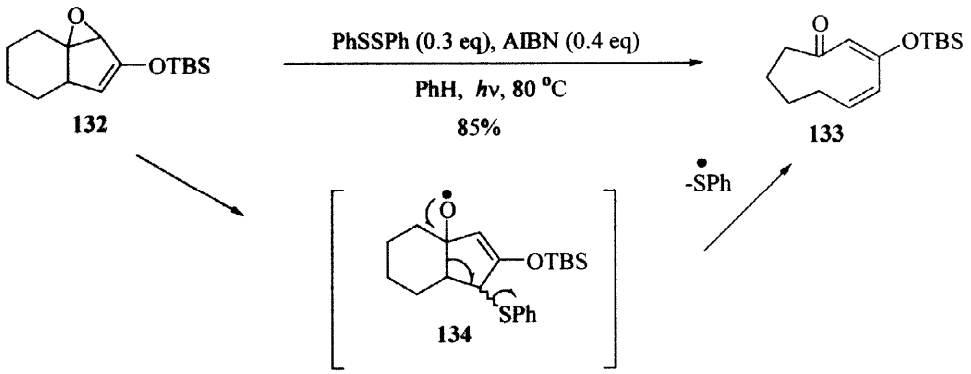


Scheme 29



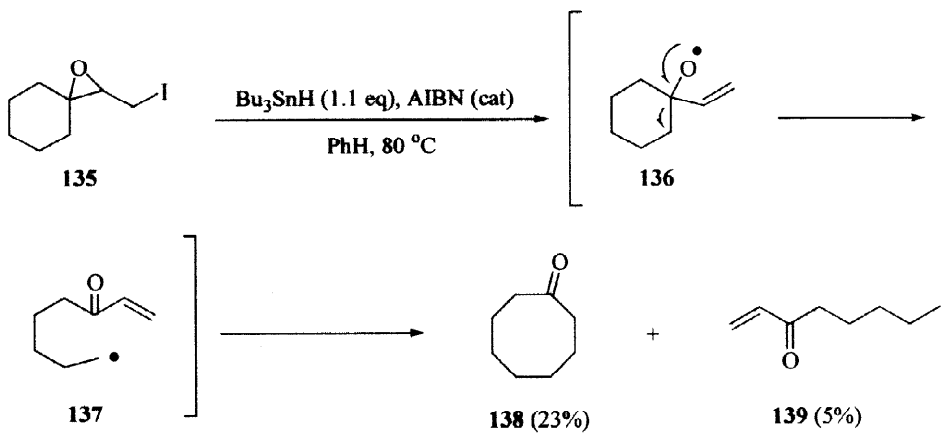
Scheme 30

Kim has shown that addition of phenylthio radical to epoxy enol silyl ether **132** occurs smoothly followed by β-cleavage of alkoxy radical **134** and elimination of phenylthio radical to afford ketone **133** (Scheme 31).[31]



Scheme 31

Galatsis reported a ring expansion strategy using iodo spiroepoxides.[32] Epoxide opening of iodo epoxide **135** gave alkoxy radical **136** which, after β-scission, yielded primary radical **137** which participated in an 8-*endo* cyclization to give cyclooctanone (**138**) or reduction to give enone **139** (Scheme 32).

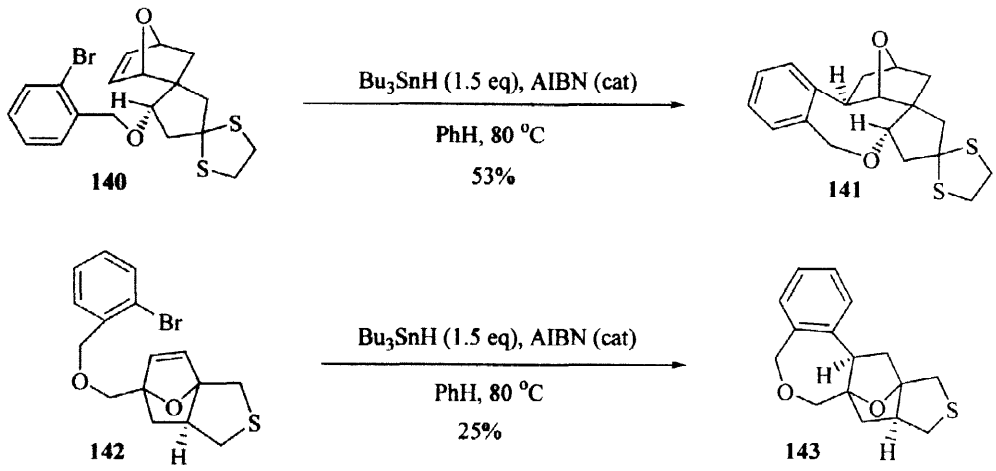


Scheme 32

3. Aromatic Radical Cyclizations

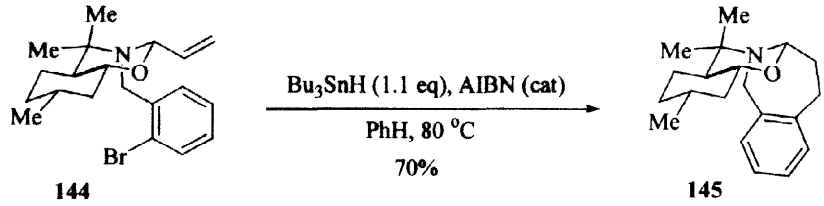
Aryl radicals, because they have not lost aromaticity during their formation, are very reactive σ-radicals that rapidly attack unsaturated neutral carbon atoms. Aryl radicals are widely employed for the formation of benzo-fused ring systems because of their high cyclization rates. Intramolecular cyclization to form medium-sized rings has been exploited by several groups in model studies and has been applied to syntheses of various natural products.

Hart described the first medium-sized ring examples of the aryl radical cyclization of aryl bromides **140** and **142** to give cyclized cyclooctyl ether **141** and cycloheptyl ether **143**, respectively (Scheme 33).[33]



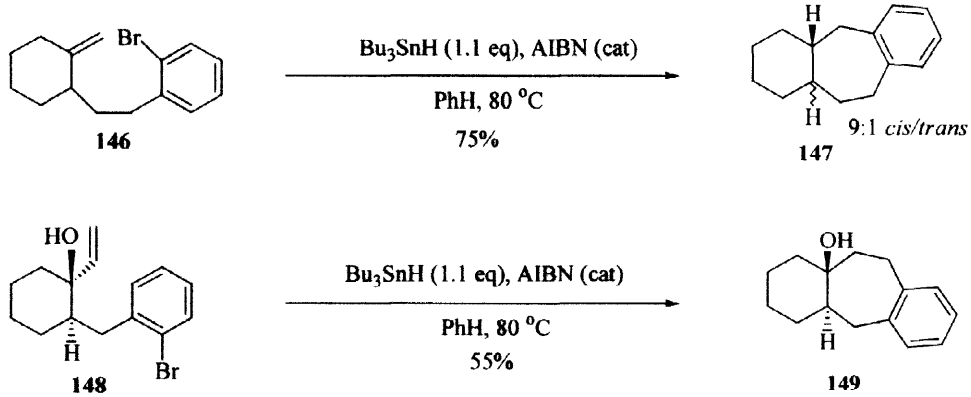
Scheme 33

Pedrosa has demonstrated an unexpected 7-*endo* aryl radical cyclization of chiral perhydro-1,3-benzoxazine **144** to benzazepine derivative **145** (Scheme 34).[34] No product from 6-*exo* radical cyclization was observed.

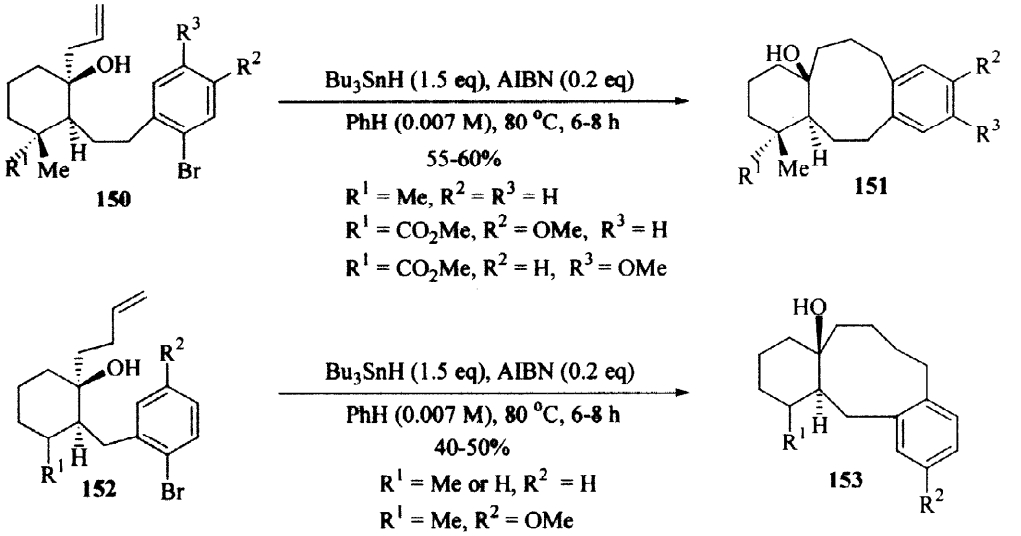


Scheme 34

Chatak explored the 7-*endo-trig* aryl radical cyclization of alkene **146** and vinyl alcohol **148** to give 6,7,6-tricyclic system **147** and tricyclic alcohol **149**, respectively (Scheme 35).[35] Similarly, allyl cyclohexanols **150** and butenyl cyclohexanols **152** cyclized in a 9-*endo*-trig aryl radical cyclization to afford benzocyclononanols **151** and **153**, respectively in moderate yields (Scheme 36).[36]

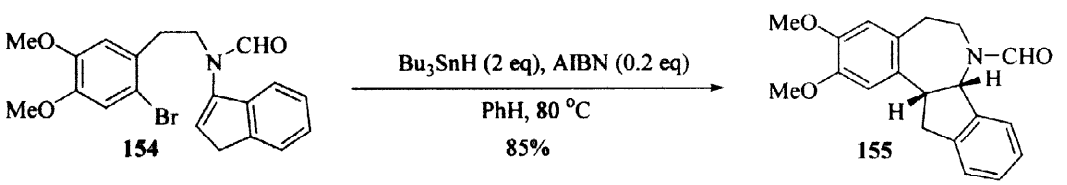


Scheme 35

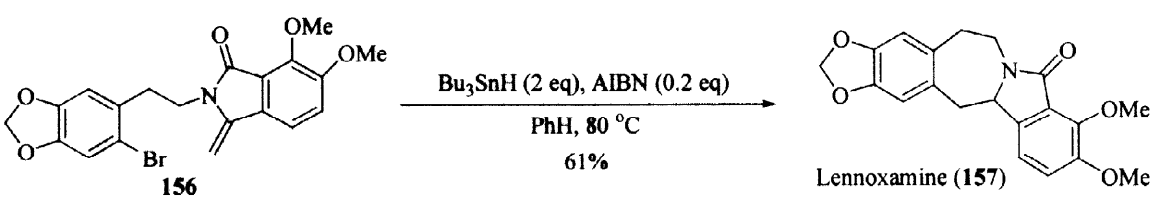


Scheme 36

Domínguez reported the regioselective intramolecular 7-*endo* aryl radical cyclization of aryl bromide **154** onto an enamide double bond to give benzazepine **155** (Scheme 37).[37] He further utilized this method for aryl radical cyclization of aryl bromide **156** as the last step to afford alkaloid lennoxamine (**157**, Scheme 38).[38]

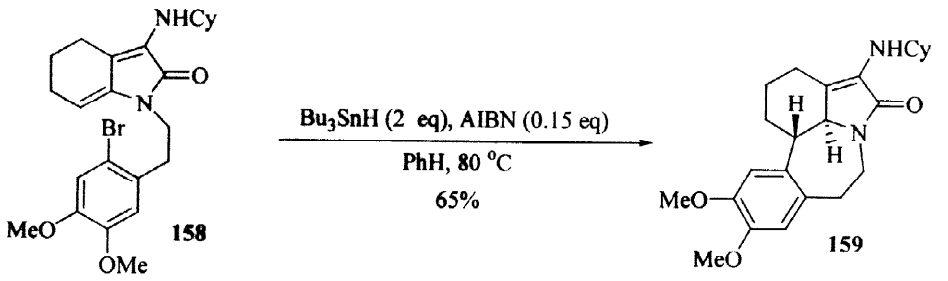


Scheme 37



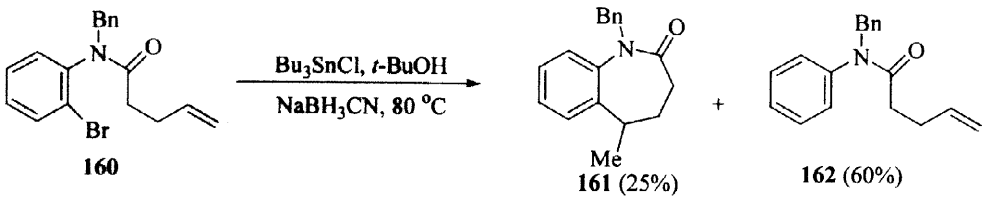
Scheme 38

Rigby has shown that *N*-alkylated lactam **158** proceeded in a 7-*endo* aryl radical cyclization to provide hydroapoerysopine derivative **159** in a stereoselective manner (Scheme 39).[39] None of the corresponding product derived from a 6-*exo* pathway was detected, a predominant pathway in spirocyclic oxindole formation. This could have been due to the bridgehead being more sterically encumbered. It is also interesting to note that numerous palladium-mediated cyclization conditions failed in this exact reaction.



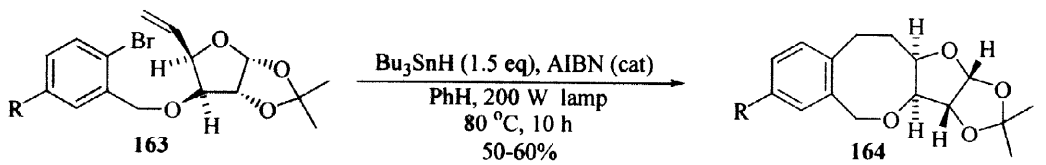
Scheme 39

Jones explored the 7-*exo* aryl radical cyclization of aryl bromide **160** onto an unactivated olefin to afford tetrahydro-1-benzazepin-2-one **161** in low yield along with appreciable reduction product **162** (Scheme 40).[40]



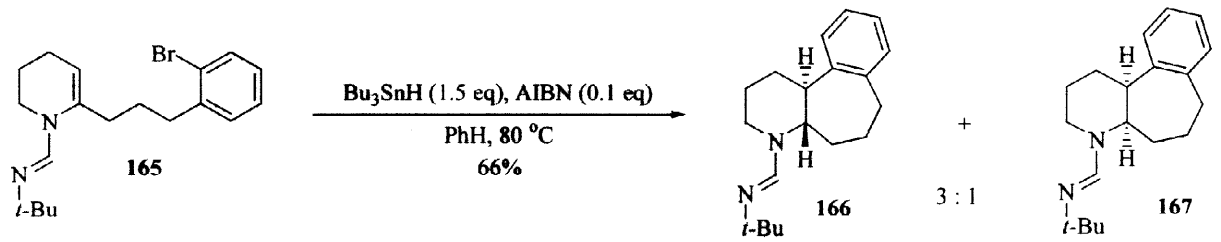
Scheme 40

A regioselective 8-*endo*-trig aryl cyclization of 5,6-deoxy-D-*xylo*-5-enofuranosides **163** with tributyltin hydride provided the chiral furo[3,2-*c*][2]benzoxocines **164** in good yields (Scheme 41).[41]



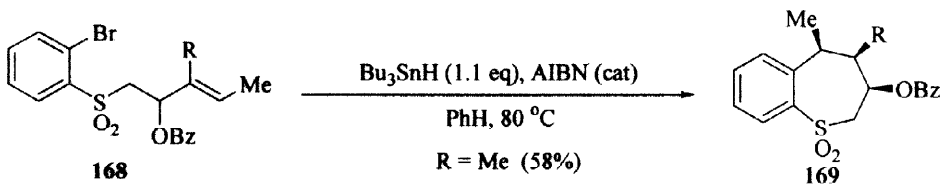
Scheme 41

Recently, Hallberg showed that enamide **165** participated in a 7-*endo* aryl radical cyclization to give *trans*-**166** and *cis*-**167** fused octahydrobenzo[*f*]quinolines (Scheme 42).[42]



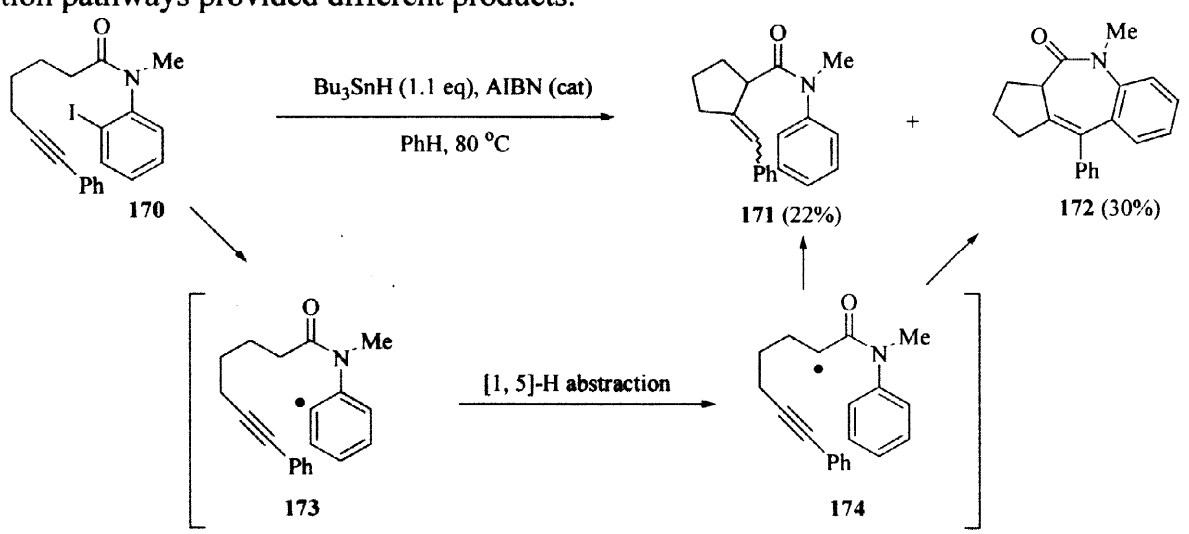
Scheme 42

Simpkins has demonstrated that radicals generated from bromoaryl sulfone **168** participated in a 7-*endo* cyclization to provide benzo-fused sulfone **169** stereoselectively (Scheme 43).[43] Although the formation of 7-*endo* products is well-documented, such reactions involving unactivated alkenes are rare (see examples above in this section). When R = H, only the 6-*exo* product was observed.



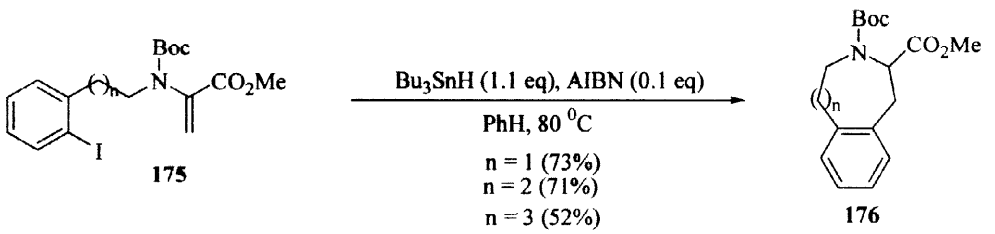
Scheme 43

Curran showed a unique cyclization using an aromatic radical method. *o*-Iodoanilide **170** underwent free radical cyclization to give methylenecyclopentanone **171** and tricyclic amide **172** (Scheme 44).[44] The operative mechanism is formation of aryl radical **173** followed by a [1,5]-hydrogen abstraction to form a radical α to the carbonyl group as in **174**. Subsequent reaction pathways provided different products.



Scheme 44

Gibson has explored the complimentary radical cyclization approach of aryl iodides **175** (n = 1-3) in the syntheses of conformationally constrained amino acids **176** (n = 1-3) outlined in Scheme 45.[45] The yields compared favorably with the palladium catalyzed Heck couplings of **175** to **176.**

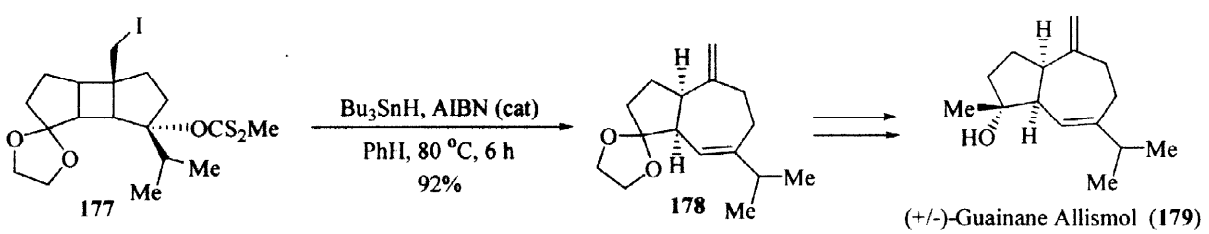


Scheme 45

4. Cyclobutylcarbinyl Radical Ring Expansions

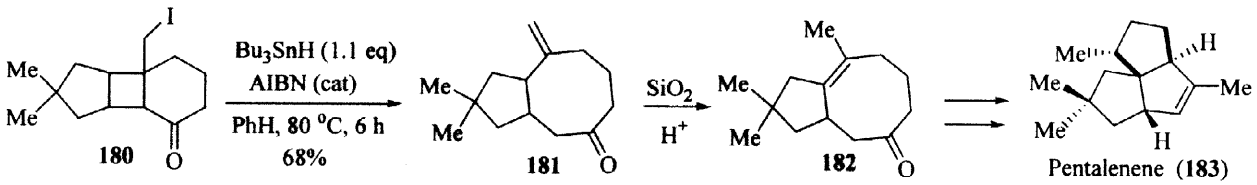
Polycyclic compounds containing cyclobutane units are versatile intermediates in organic synthesis and are easily obtained from [2 + 2] photochemical or thermal cycloadditions.[46] Radical ring expansions based on cyclobutane subunits have provided access to medium-sized rings found in many natural products.

Lange showed iodo xanthate **177** in a radical fragmentation/elimination sequence led to diene **178**, an intermediate in the first total synthesis of (+/-)-guainane allismol (**179**, Scheme 46).[47] Abstraction of the iodide initiated the fragmentation and the xanthate served as the leaving group. Xanthates, halides, SPh, SOPh, SO_2Ph, and SePh have been shown to be effective radical leaving groups.[48]



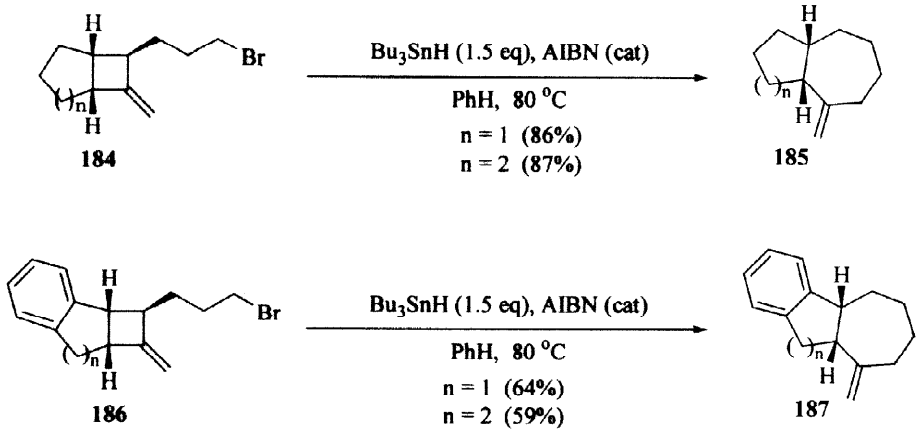
Scheme 46

Under similar conditions, Lange demonstrated that iodoketone **180** underwent radical fragmentation to provide bicyclooctenone **182** constituting a formal total synthesis of the angular triquinane sesquiterpenoid pentalenene (**183**, Scheme 47).[49]



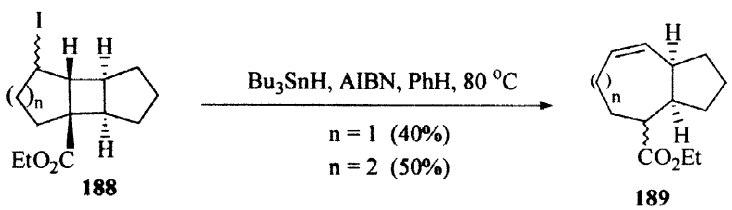
Scheme 47

Dowd showed that fused methylenecyclobutanes **184** and **186** under radical initiating conditions led to *cis*-fused methylenecycloheptanes **185** and **187**, respectively (Scheme 48).[50]



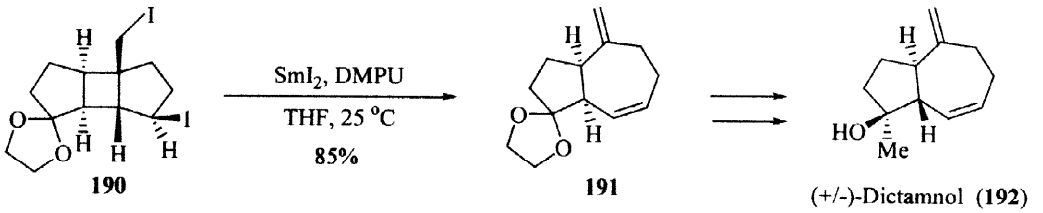
Scheme 48

Ranu has investigated the fragmentation of cyclobutylcarbinyl radicals in suitably substituted cyclobutane derivatives leading to functionalized seven- and eight-membered ring systems by way of two-carbon ring expansions.[51] Photoadduct **188** under radical conditions gave bicyclic esters **189** in moderate yields (Scheme 49).



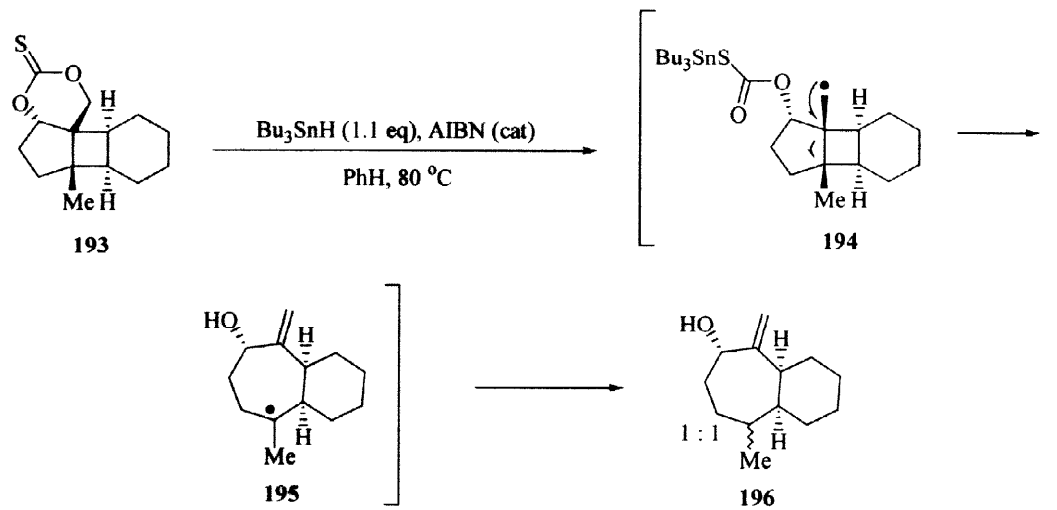
Scheme 49

Radical-mediated fragmentations of strained cyclobutane systems derived from photoadducts have been exploited in the preparation of a variety of bicyclic ketones. For instance, diiodide **190** underwent a samarium(II) diiodide mediated fragmentation/elimination sequence to yield *cis*-fused 5,7 bicyclic diene **191** which was further elaborated to (+/-)-dictamnol (**192**, Scheme 50).[52]



Scheme 50

Ziegler exploited the fragmentation of cyclobutylcarbinyl radical **194**, generated from thiocarbonyl **193**, to bicycloheptyl radical **195** which on reduction gave bicycloheptenol **196** (Scheme 51).[53]

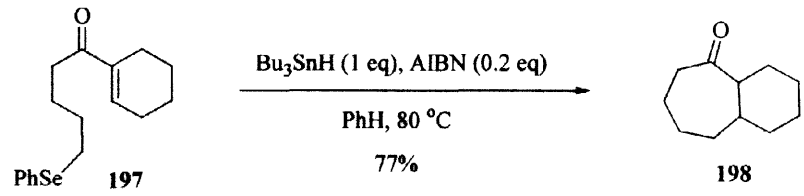


Scheme 51

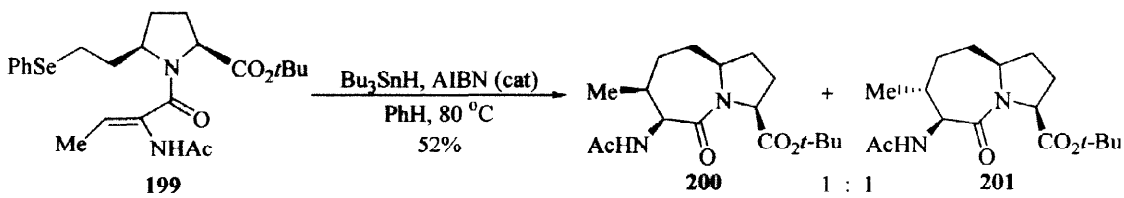
5. Intramolecular Michael Additions

Some examples of radicals derived from alkyl, acyl, and vinyl groups have been exploited in intramolecular Michael additions to gain access to medium-sized rings.

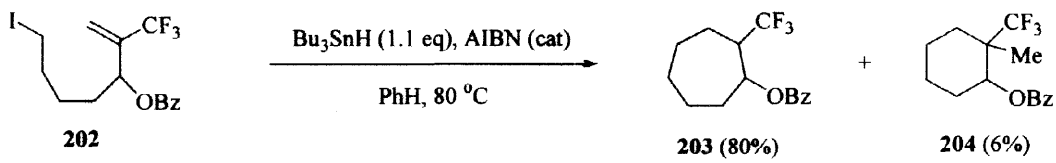
Examples of alkyl-derived radicals participating in this mode of cyclization are shown below. Yamakawa presented a novel annulation method that included an intramolecular Michael addition of the radical derived from selenide **197** to give bicycloheptanone **198** in excellent yield (Scheme 52).[54] Colombo demonstrated that α-N-acetyl acrylamide **199** in a 7-*endo* radical cyclization afforded 5,7-fused bicyclic lactams **200** and **201** in a 1:1 ratio, which were used as substrates for conformationally restricted peptide mimics (Scheme 53).[55] Kobayashi has reported that iodo olefin **202** participated in an intramolecular 7-*endo* Michael addition with a trifluoro olefin as the π-acceptor to yield trifluorocycloheptane **203** in excellent yield with some cyclohexane **204** from 6-*exo* mode of cyclization (Scheme 54).[56]



Scheme 52

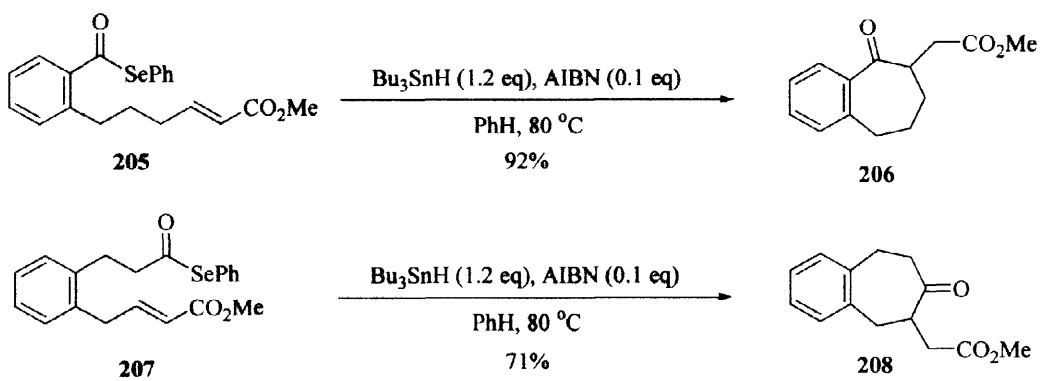


Scheme 53



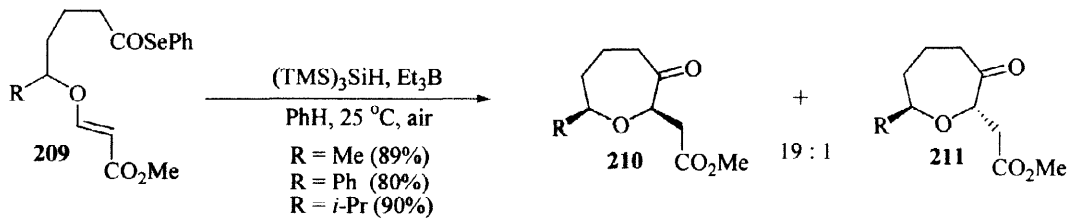
Scheme 54

Acyl selenides have been shown to be useful radical precursors. Boger has reported the acyl radicals derived from acyl selenides **205** and **207** reacted in a 7-*exo* rather than in an 8-*endo* mode in an intramolecular Michael addition to give benzocycloheptanone esters **206** and **208**, respectively (Scheme 55).[57]



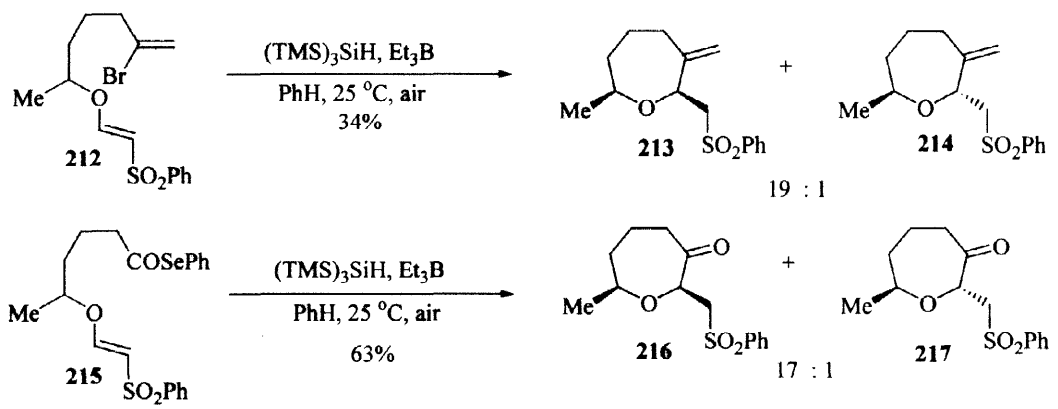
Scheme 55

Evans reported the first example of the intramolecular Michael addition of an acyl radical to a vinylogous ester for the efficient and stereoselective construction of seven-membered cyclic ethers.[58] Treatment of acyl selenides **209** with a combination of *tris*(trimethylsilyl)silane and triethylborane in the presence of air at room temperature afforded *cis*- and *trans*-2,7-disubstituted oxepan-3-ones **210** and **211** in excellent yields (Scheme 56). Decarbonylation was suppressed at room temperature as when the experiment was performed at higher temperatures six-membered cyclic ethers were formed from competitive decarbonylation.



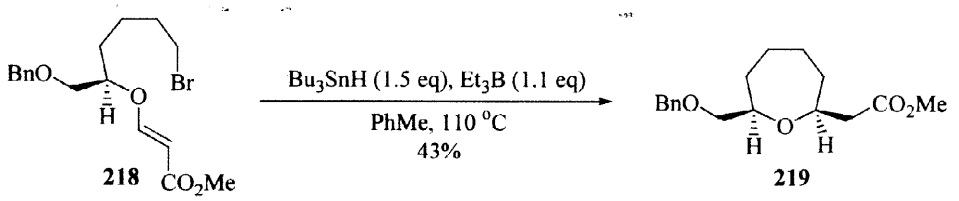
Scheme 56

Radicals from vinyl bromides have also been used. Evans extended this work to vinyl sulfones to give cyclic ethers.[59] Vinyl bromide **212** and acyl selenide **215** under similar conditions afforded 2,7-disubstituted oxepines **213**, **216** (*cis*) and **214**, **217** (*trans*), respectively, with very good diastereoselectivities (Scheme 57). The modest yields suggest that the vinylogous sulfonate is not as efficient a Michael acceptor as the vinylogous ester.



Scheme 57

Shibuya applied the Michael addition methodology to the synthesis of 2,7-disubstituted oxepane ring systems. Alkoxyacrylate **218** was treated with tributyltin hydride in the presence of triethylborane as the radical initiator in refluxing toluene to give oxepane **219** in modest yield (Scheme 58).[60] When the same reaction was done in the presence of the Lewis acid Et_2AlCl, which lowered the LUMO energy, a 61% yield was obtained with 3.6:1 diastereoselectivity.

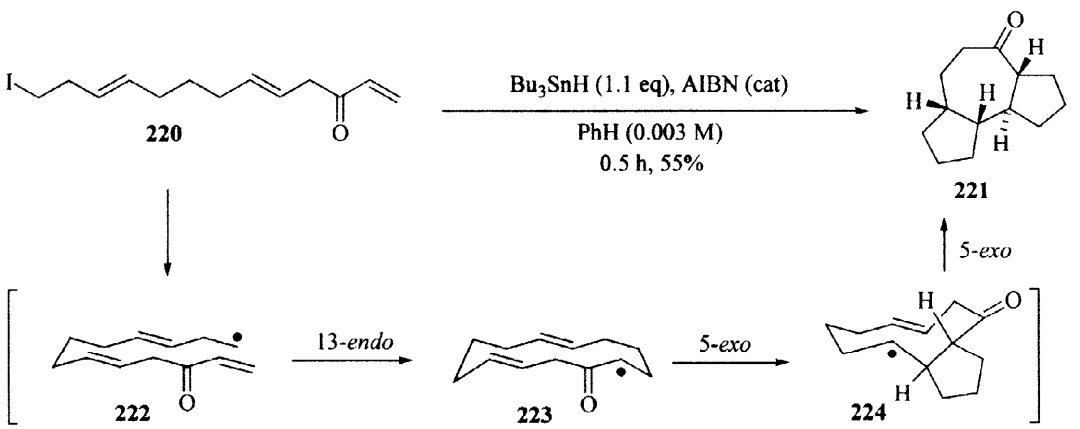


Scheme 58

6. Tandem Radical Cyclizations

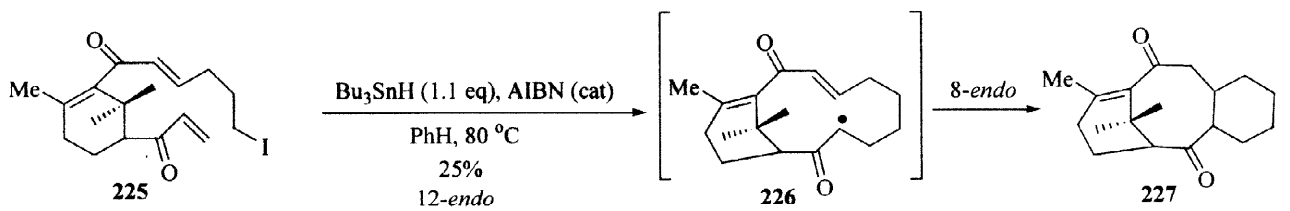
A valuable method for the construction of bi- and polycyclic systems involves tandem reaction sequences in which two or more consecutive radical cyclizations are connected in a reaction series.[61]

Pattenden was the first to extensively exploit the capability of radicals to undergo tandem cyclization in a useful synthetic sequence.[62] He showed that treatment of iodotrienone **220** with tributyltin hydride resulted in the formation of the angular 5,7,5-ring fused tricycle **221** by way of a novel sequential 13-*endo*-trig macrocyclization of **222** to **223** followed by two successive 5-*exo*-trig transannulation processes of **223** and **224** intermediates (Scheme 59).



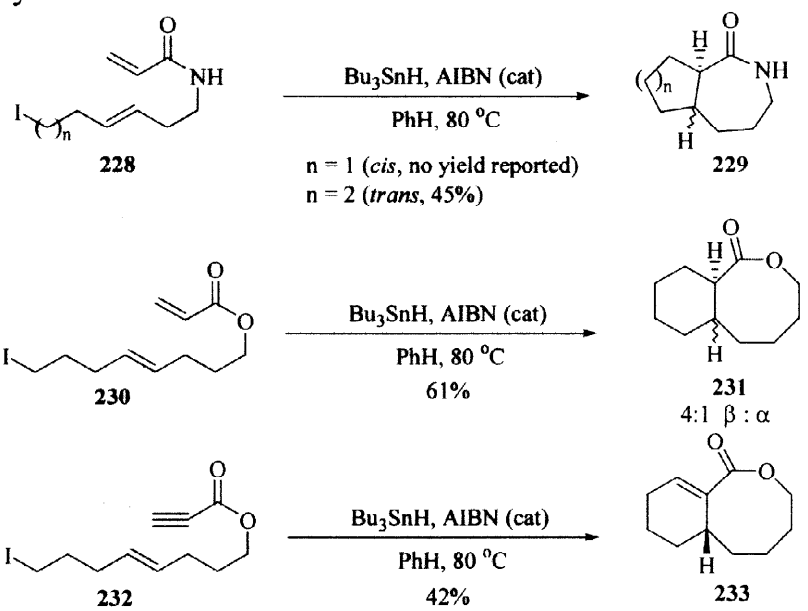
Scheme 59

Furthermore, Pattenden described a novel radical macrocyclization-transannulation strategy toward the tricyclo[9.3.1]pentadecane ring system in the taxanes.[63] Iodide **225** reacted in a 12-*endo* cyclization to yield radical **226** with sequential 8-*endo* cyclization to tricyclic diketone **227** (Scheme 60).



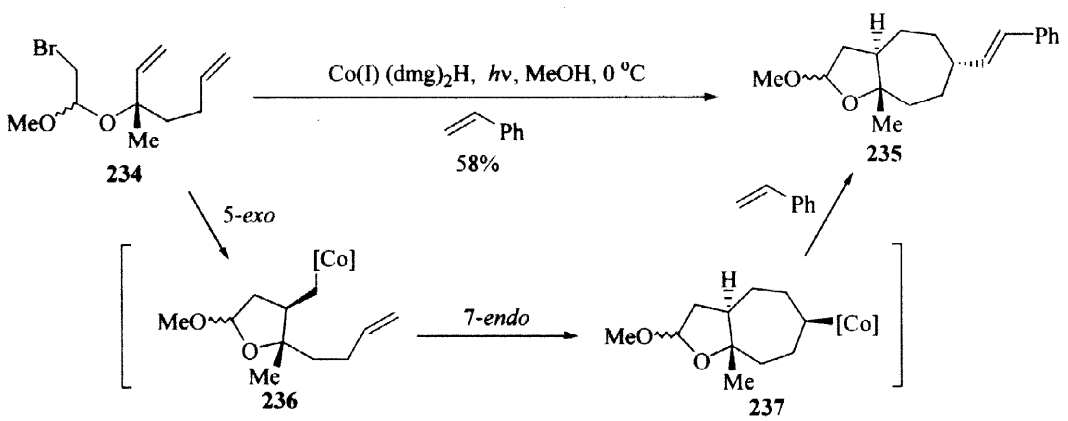
Scheme 60

Pattenden has also reported a novel radical-mediated cascade macrocyclization-transannular cyclization of a range of alkenyl acrylates and acrylamides resulting in concise syntheses of stereodefined 5,7- and 6,8- bicyclic lactones and lactams.[64] Treatment of amide **228** (n = 1) with tributyltin hydride led to 5,7- fused bicyclic lactam **229** (n = 1) via a consecutive 10-*endo*, 5-*exo* trig radical cyclization process (Scheme 61). Similarly, acrylamide **228** (n = 2) gave 6,7- fused lactam **229** (n = 2) as a result from 12-*endo*, 6-*exo*- trig transannulation. Alkenyl acrylate **230** and alkenyl ynoate **232** afforded bicyclic lactones **231** and **233**, respectively.



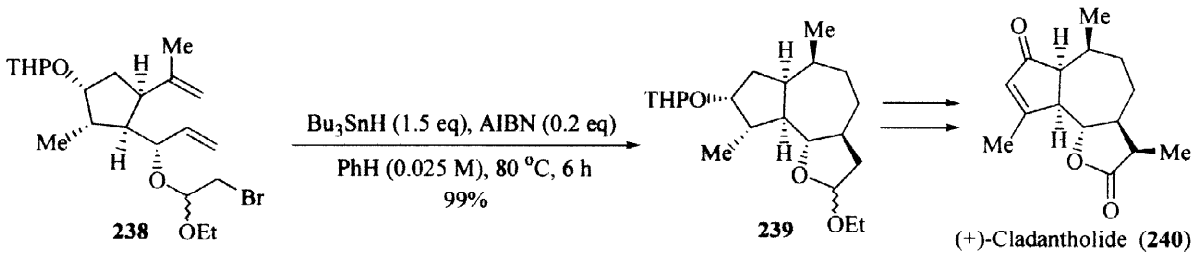
Scheme 61

Pattenden has exploited the use of cobalt-mediated initiating radical cascade reactions leading to bicyclic systems.[65] Bromoacetal **234** was irradiated in the presence of cobalt(I) dimethylglyoxime and styrene to give bicyclic ether **235** (Scheme 62). Bromoacetal **234** reacted with cobalt complex in a 5-*exo* mode to cobaloxime **236**. Subsequent 7-*endo* cyclization of **236** to bicyclic intermediate **237** and interception by styrene gave **235**.

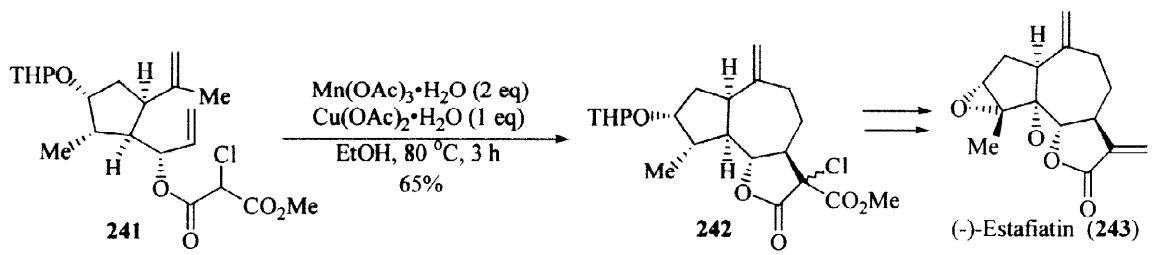


Scheme 62

A remarkable, 5-*exo*, 7-*endo* tandem radical cyclization approach was successfully employed for the formation of the *cis*-fused hydroazulenic ring system present in many guaianolides. Cyclopentyl bromoacetal **238**, under tin hydride conditions, gave hydroazulenic acetal **239**, a useful precursor to (+)-cladantholide (**240**, Scheme 63).[66] Chloromalonate **241**, under oxidative radical conditions employing manganese(III) acetate[67] and copper(II) acetate, furnished lactone **242**, a precursor to (-)-estafiatin (**243**, Scheme 64).[67]



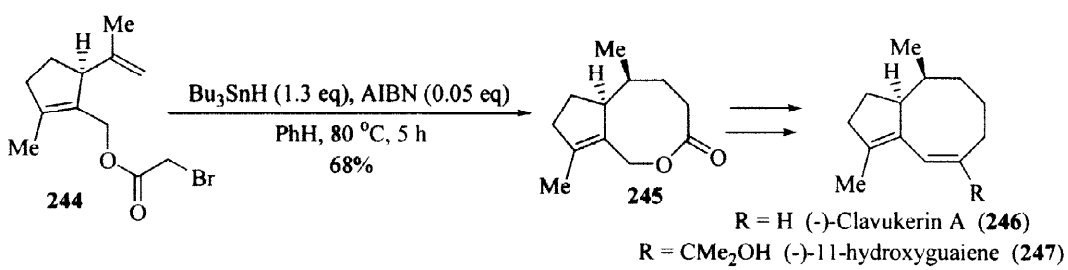
Scheme 63



Scheme 64

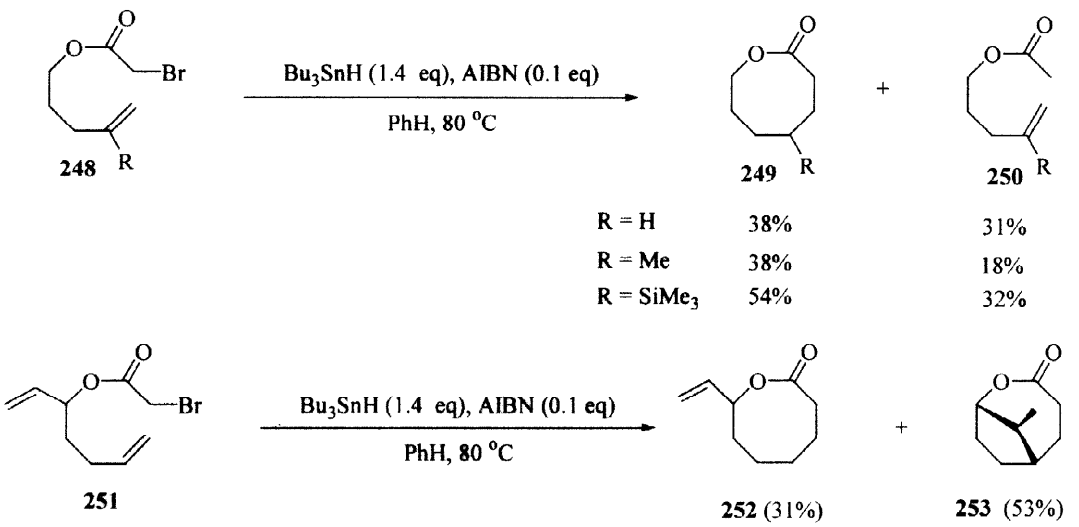
7. Cyclizations via α-Acyl Radicals

α-Acyl radicals have not been heavily exploited in medium-sized ring synthesis but have been valuable in forming eight-membered lactones and amides. Bromoacetate **244** reacted via 8-*endo* radical cyclization under standard high dilution conditions with tributyltin hydride to give lactone **245**, a precursor to (-)-clavukerin A (**246**) and (-)-11-hydroxyguaiene (**247**, Scheme 65).[68]



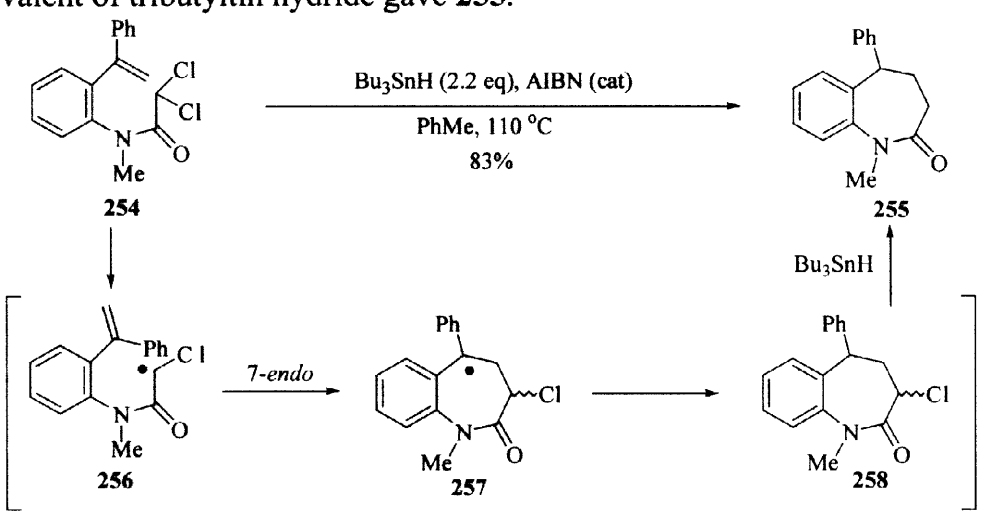
Scheme 65

Lee has reported the preferential formation of eight-membered lactones **249** via 8-*endo* cyclization of reaction of an (alkoxycarbonyl)methyl radical derived from bromocetate **248** accompanied by reduction product **250** (Scheme 66).[69] Lee also demonstrated that 8-*endo* cyclization is much faster than 5-*exo* cyclization for (alkoxycarbonyl)methyl radicals. For example, bromoacetate **251**, under standard conditions, gave lactone **252** and bicyclic lactone **253**, resulting from 8-*endo* cyclization and 8-*endo*/5-*exo* tandem radical cyclization, respectively. Simple 5-*exo* cyclization products were not found.



Scheme 66

Ikeda showed that dichloroacetamide **254**, in the presence of excess tin hydride, formed benzazepinone **255** in excellent yield (Scheme 67).[70] Formation of radical **256** in a 7-*endo* cyclization gave tertiary radical **257** which was transformed to **258**. Reduction of **259** with the second equivalent of tributyltin hydride gave **255**.

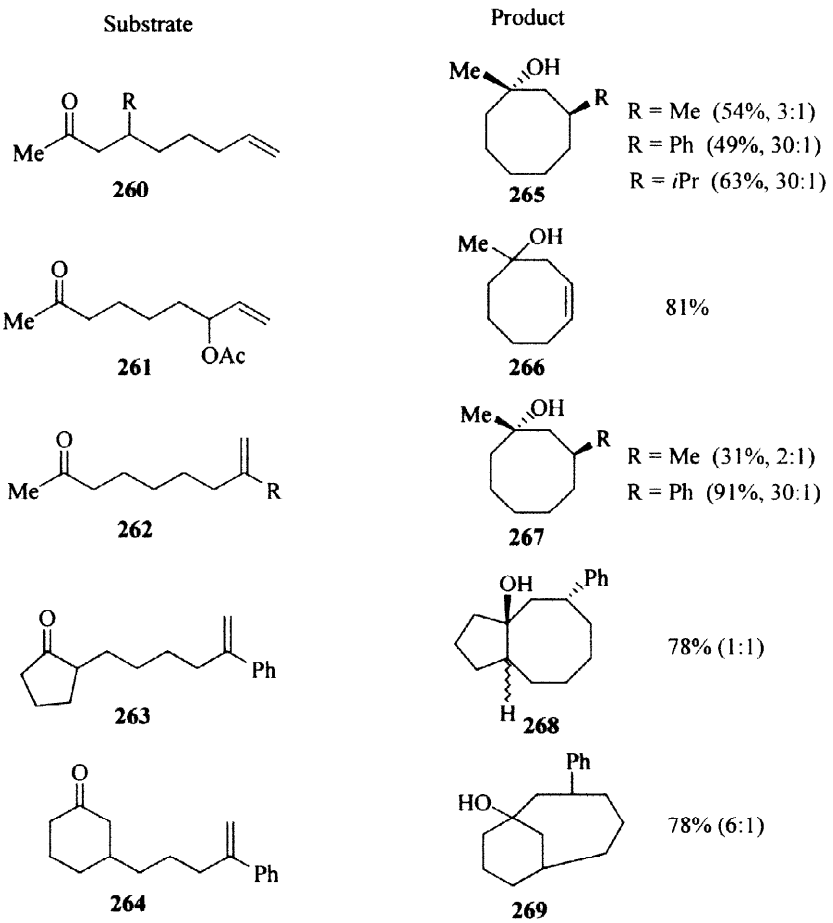


Scheme 67

8. Metal-Promoted Free Radical Cyclizations

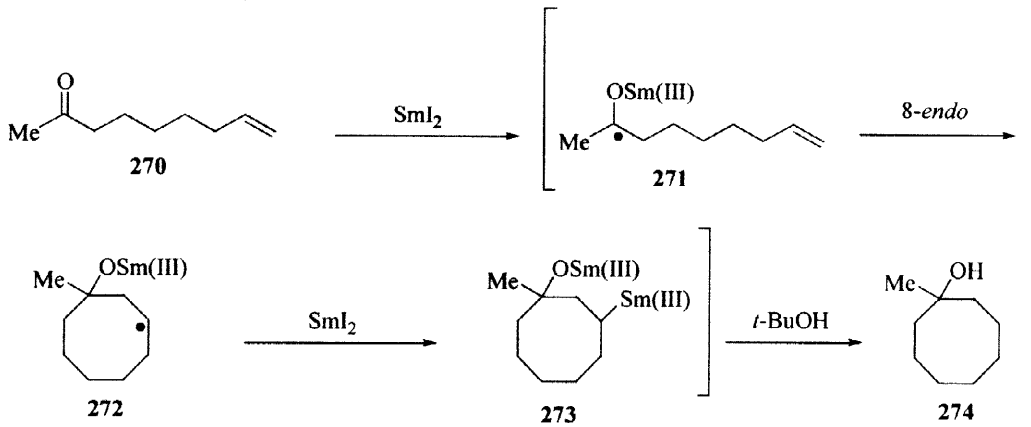
Metal-promoted oxidative free radical cyclizations have found useful applications to medium-sized rings in the last decade. Samarium, manganese, and iron have been the metals of choice in these reactions and examples are shown below.

Samarium(II) diiodide in the presence of HMPA has been employed to promote an efficient 8-*endo* radical cyclization of a variety of substituted olefinic ketones **260-264** (Scheme 68).[71] Molander showed that various substituted monocyclic **265-267**, fused bicyclic **268**, and bridged bicyclic cyclooctanols **269** have been synthesized in fair to excellent yields. Samarium(II) diiodide adds to ketone **270** to form ketyl radical **271** which undergoes 8-*endo* cyclization to unstabilized radical intermediate **272** (Scheme 69). Intermediate **272** is trapped by another equivalent of samarium(II) diiodide to **273** which is quenched to **274** by *tert*-butanol, an efficient hydrogen donor source in these types of cyclizations.



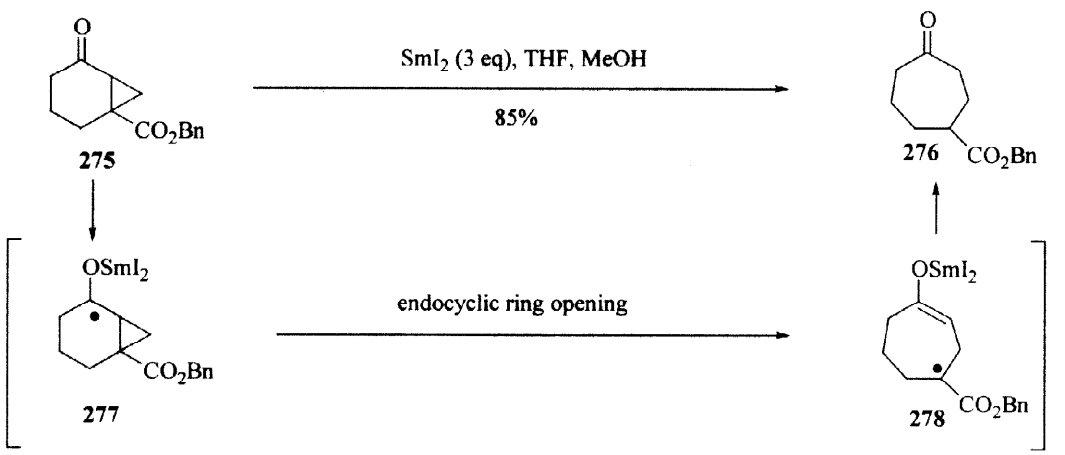
Conditions: SmI_2 (2.2 eq), HMPA (8 eq), *t*-BuOH (2 eq), THF, 25 °C

Scheme 68



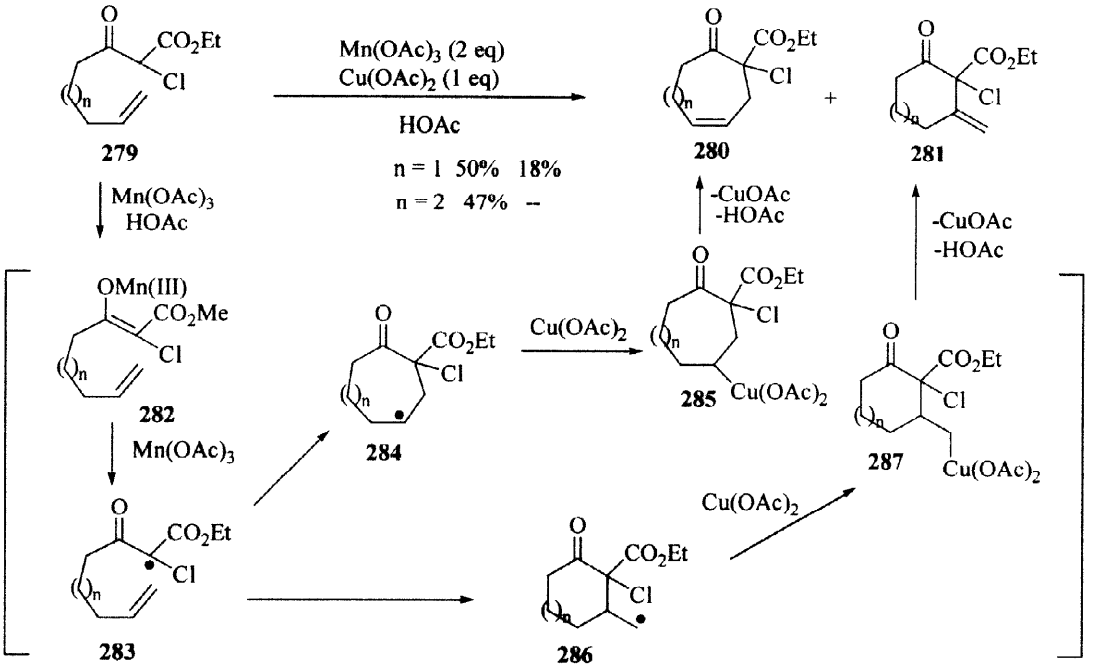
Scheme 69

Lee has reported that samarium(II) diiodide induced single electron transfer cleavage of 5-oxobicyclo[4.1.0]heptane-1-carboxylate **275** to 4-oxocycloheptanecarboxylate **276** occurs in excellent yield via ketyl **277** followed by endocyclic ring opening to **278** with methanol as an effective proton source (Scheme 70).[72]

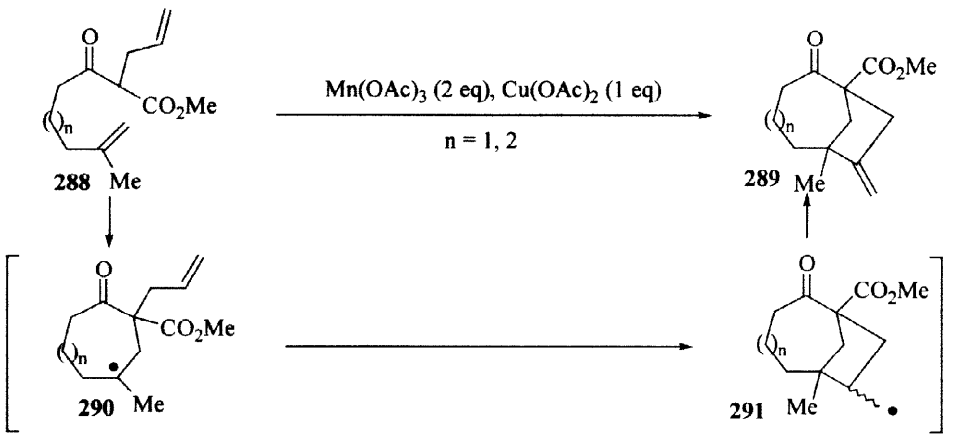


Scheme 70

Radicals derived from β–keto esters by oxidative methods are especially useful for the formation of medium-sized rings due to increased rate of *endo* cyclization of α-carbonyl substituted radicals. Snider has demonstrated that Mn(III)-based oxidative free radical cyclizations can be used to prepare both cycloheptanes and cyclooctanes.[73] For example, acetoacetate **279** reacted with manganese(III) acetate and copper(II) acetate in acetic acid to give a mixture of β-cyclic ketoesters **280** and methylenecyclohexanones **281** proceeding through intermediates **282** to **287** (Scheme 71). This method was also applied in a tandem cyclization of β–ketoester **288** to bicycloalkenones **289** in good yields through intermediates **290** and **291** (Scheme 72).[73] Other minor products were observed.

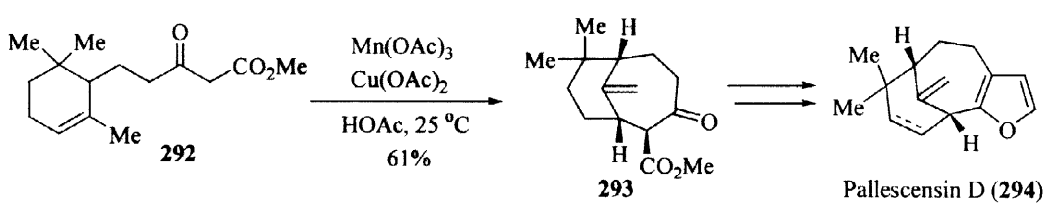


Scheme 71



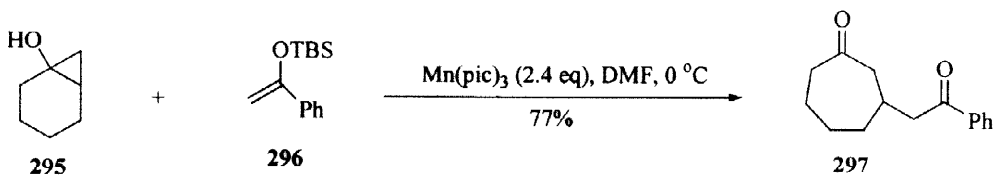
Scheme 72

Utilizing the above methodology, White showed that exposure of β-keto ester **292** to manganese(III) acetate and copper(II) acetate (1:1 ratio) gave bicyclo[4.3.1]decanone **293** which was further elaborated to provide pallescensin D (**294**), a furanosesquiterpene (Scheme 73).[74]



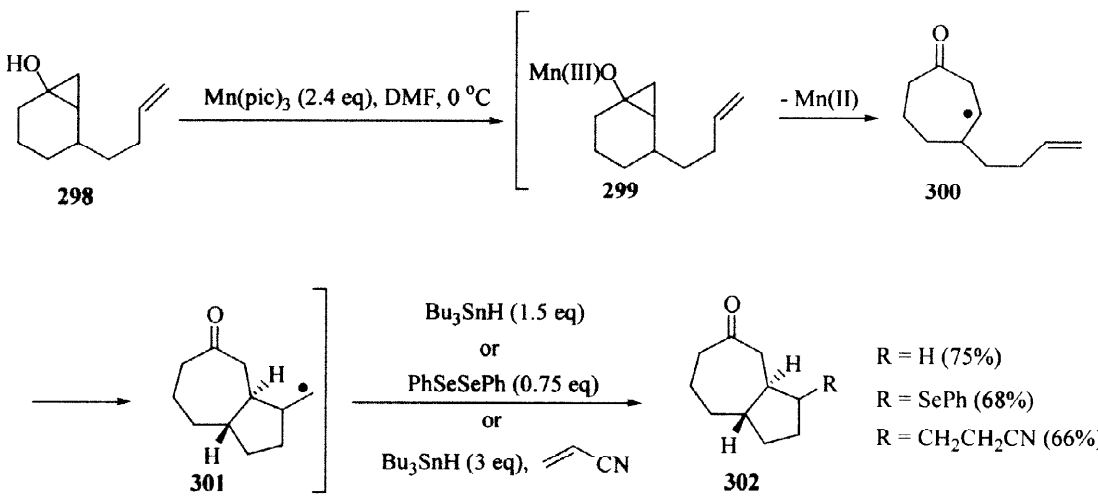
Scheme 73

Iwasawa showed that treatment of cyclopropanol **295** with manganese(III) tris(2-pyridinecarboxylate) generates β-keto radicals which added intermolecularly to enol silyl ether **296** to give ring-expanded cycloheptanone **297** in good yields (Scheme 74).[75] This method was further exploited in the synthesis of a bicyclic framework skeleton. Intramolecular cyclization of cyclopropanol **298** to radical intermediates **299** to **301** and trapping of **301** with various acceptors gave bicyclic ketones **302** stereoselectively (Scheme 75).[76]



295 296 297

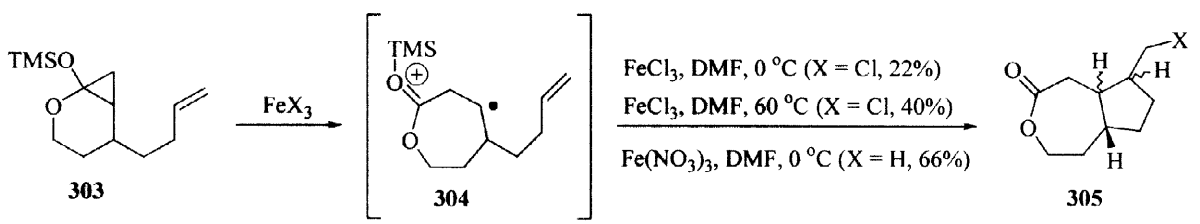
Scheme 74



298 299 300 301 302

Scheme 75

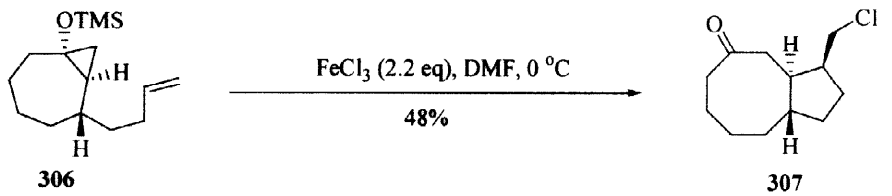
Booker-Milburn studied the Fe(III)-mediated oxidative radical cyclization of cyclopropanone acetal **303** via ring-expanded intermediate **304** with subsequent atom transfer cyclization to give cycloheptyl lactone **305** (Scheme 76).[77]



303 304 305

Scheme 76

Booker-Milburn also showed that ring expansion cyclization of cyclopropyl ether **306** proceeded uneventfully to give 5,8-bicyclic chloroketone **307** as a single diastereomer (Scheme 77).[78]

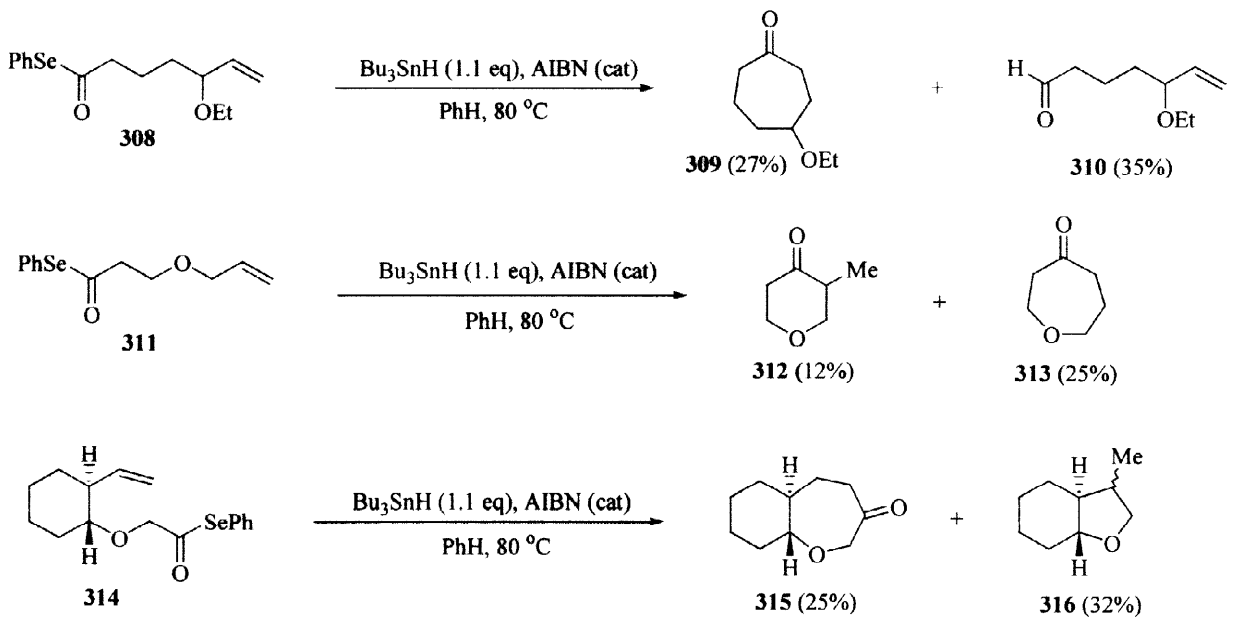


Scheme 77

9. Cyclizations via Acyl Radicals

Acyl radicals, especially generated from acyl selenides, have been a useful method for the synthesis of cyclic systems. A serious side reaction in these types of reactions is decarbonylation of the intermediate acyl radical prior to cyclization. Decarbonylation is disfavored if the formed alkyl radical is stabilized.

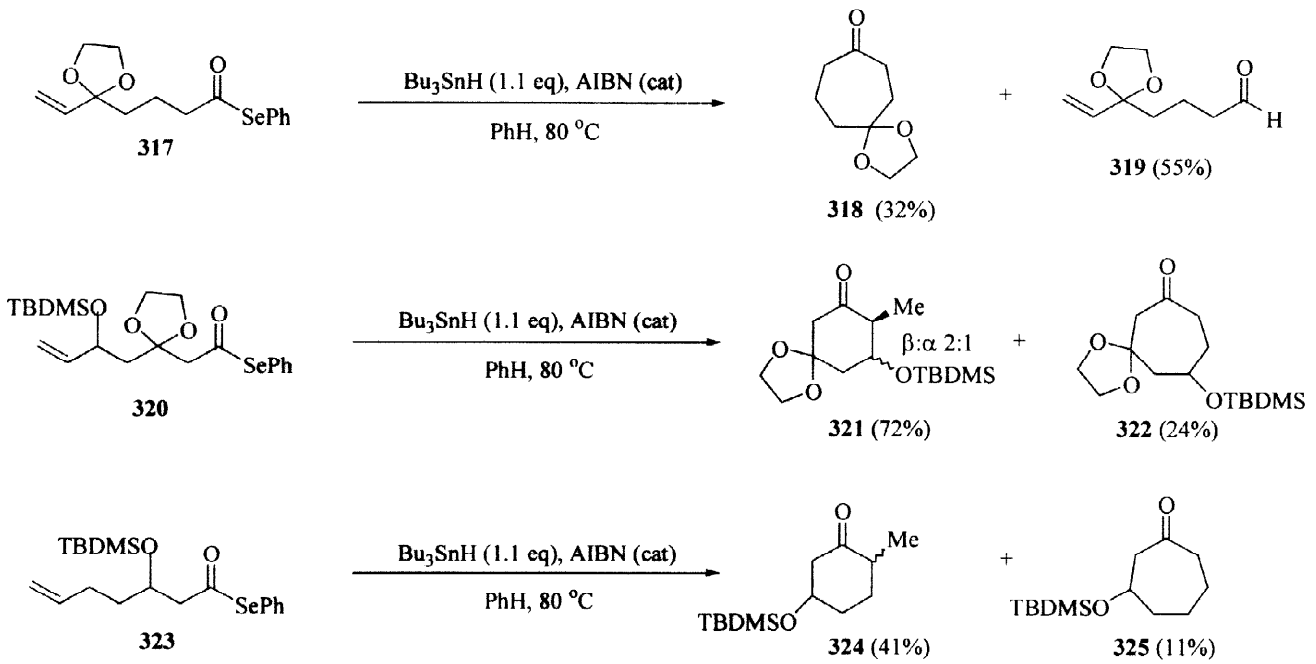
Crich reported some of the first studies of acyl radical cyclization with reactive acyl selenides of 6,7-unsaturated carbonyl compounds.[79] For example, selenoester **308**, under standard conditions, provided cycloheptanone **309** in low yield along with reduced aldehyde **310** (Scheme 78). Selenoester **311** gave a mixture of heterocycles **312** and **313**. Selenoester **314** provided bicycloheptanone **315** and bicyclic ether **316**, a product of decarbonylation followed by 5-*exo-trig* cyclization. No evidence for the 6-*exo-trig* mode was observed.



Scheme 78

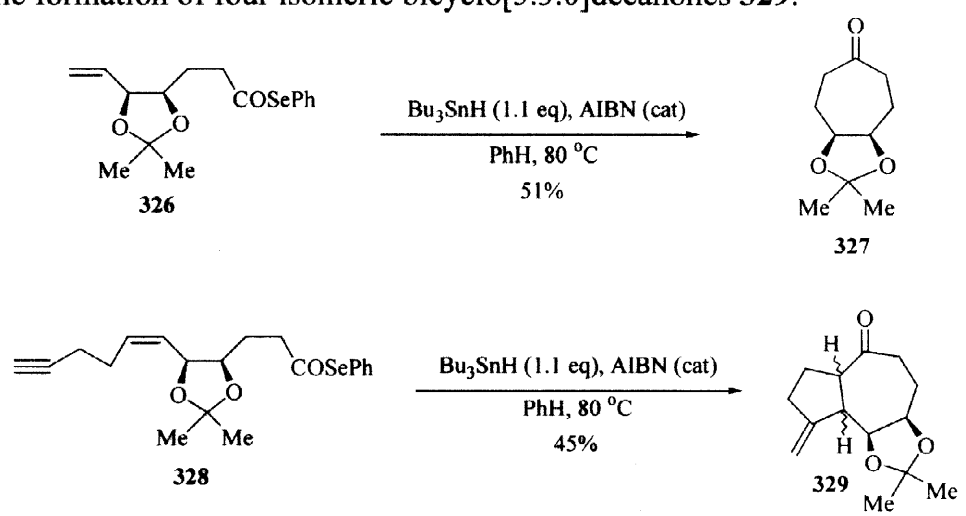
Crich has found that substituent effects play a role in the mode and efficiency of cyclization of 6-heptenoyl radicals.[80] Selenoester **317** with 5-oxygenation substitution gave cycloheptanone **318** and reduced aldehyde **319** (Scheme 79). With 3-oxygenation substitution,

6-*exo* cyclization was the dominant product in the reactions of selenoesters **320** and **323** to give cyclohexanones **321** and **324**, respectively, with some cycloheptanones **322** and **325** in lower yields.



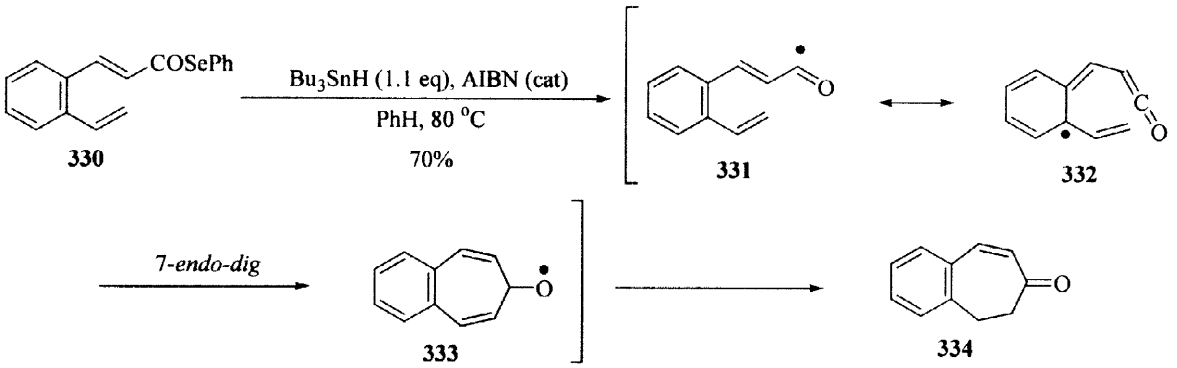
Scheme 79

Crich also demonstrated that selenoester **326**, under radical initiating conditions, furnished *meso*-cycloheptanone **327** in a 7-*endo* radical fashion (Scheme 80).[81] He also reported seleno ester **328**, in an acyl radical initiated tandem 7-*endo*/5-*exo* radical cyclization, resulted in the formation of four isomeric bicyclo[5.3.0]decanones **329**.[82]

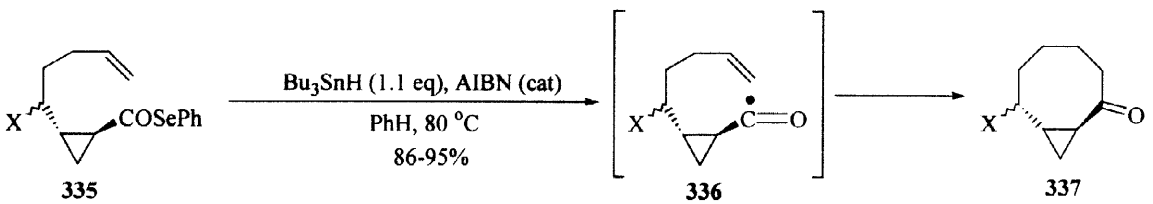


Scheme 80

Pattenden has shown that α,β-unsaturated acyl radical intermediates can take part in a variety of synthetically useful ring forming reactions via α-ketenyl radicals.[83] For example, cinnamyl selenoester **330** was converted to unsaturated ketone **334** via acyl radical **331** to ketenyl radical **332** followed by 7-*endo-dig* cyclization to **333** (Scheme 81). Cyclopropane selenoester **335** under the usual conditions led to the unusual *trans*-cyclopropane ring-fused eight-membered ring ketone **337** from a straightforward 8-*endo-trig* cyclization of acyl radical intermediate **336** (Scheme 82).[83]

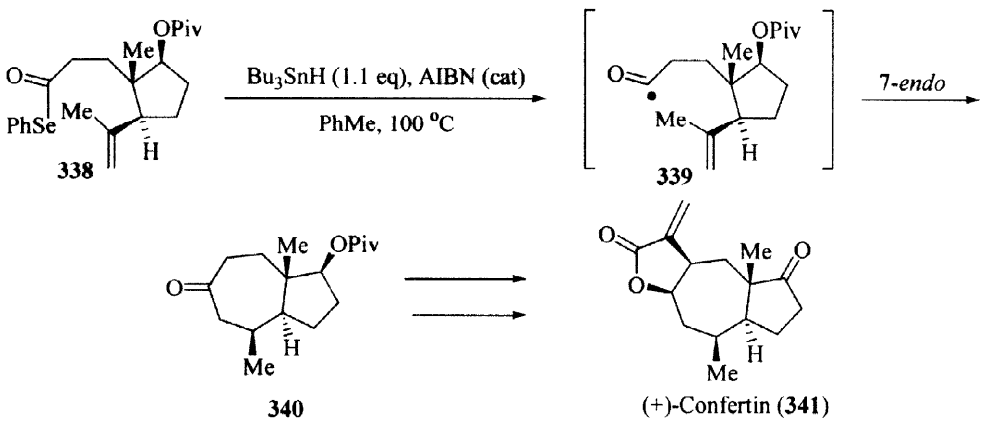


Scheme 81



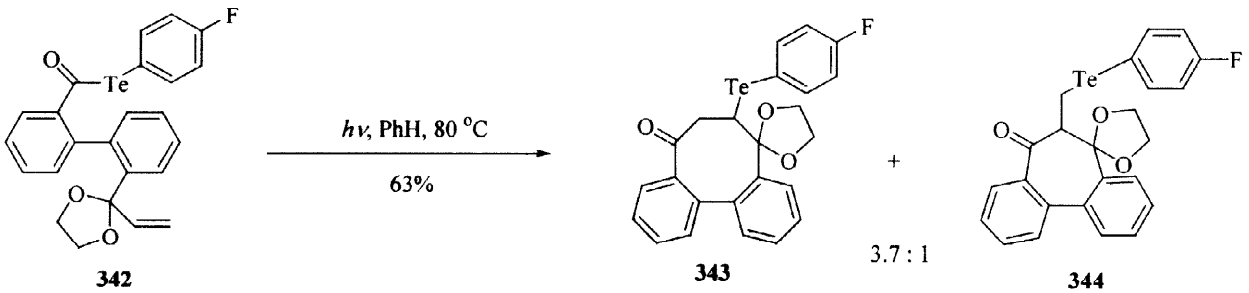
Scheme 82

Shishido has demonstrated that selenoester **338** can be cyclized to bicycloheptanone **340** as a single product via acyl radical-mediated 7-*endo-trig* cyclization of intermediate **339** in a formal total synthesis of (+)-confertin (**341**, Scheme 83).[84]



Scheme 83

Crich has examined the radical cyclizations of acyl tellurides. Bisaryl acyl telluride **342** underwent cyclization in the presence of white light in refluxing benzene to cyclooctanone **343** and cycloheptanone **344** in a 3.7:1 ratio, resulting from an 8-*endo* and 7-*exo* mode with atom transfer (Scheme 84).[85]



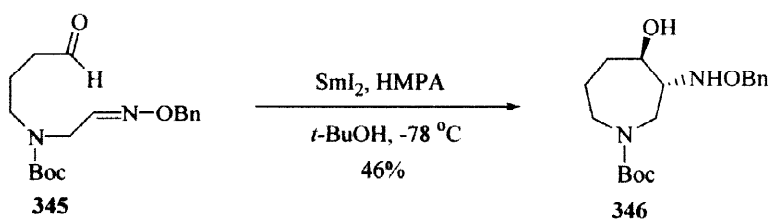
342 343 344

Scheme 84

10. Radical Cyclizations Involving Nitrogen

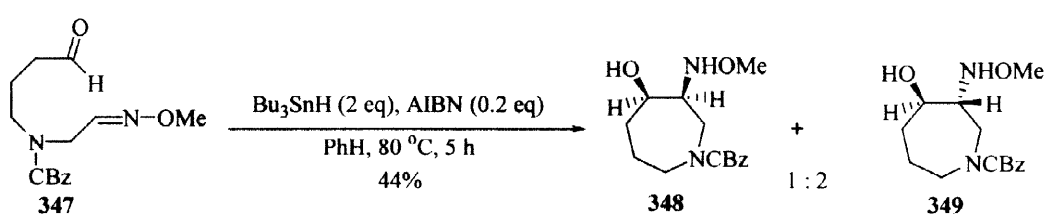
In general, radical cyclization reactions are not restricted to additions to carbon-carbon multiple bonds but additions to carbon-nitrogen multiple bonds are possible.[86] These reactions are irreversible and occur in the *exo*-mode with attack at the carbon atom exclusively.

A free radical cyclization of oxime ethers tethered to an aldehyde has been reported. Naito prepared the enantiomerically pure *trans* amino alcohol hexahydroazepine fragment **346** of (-)-balanol from the samarium(II) diiodide promoted radical cyclization of oxime ether **345** (Scheme 85).[87] Tin hydride addition to **347** gave *cis* **348** and *trans* **349** amino alcohols in a 1:2 ratio (Scheme 86).[88]



345 346

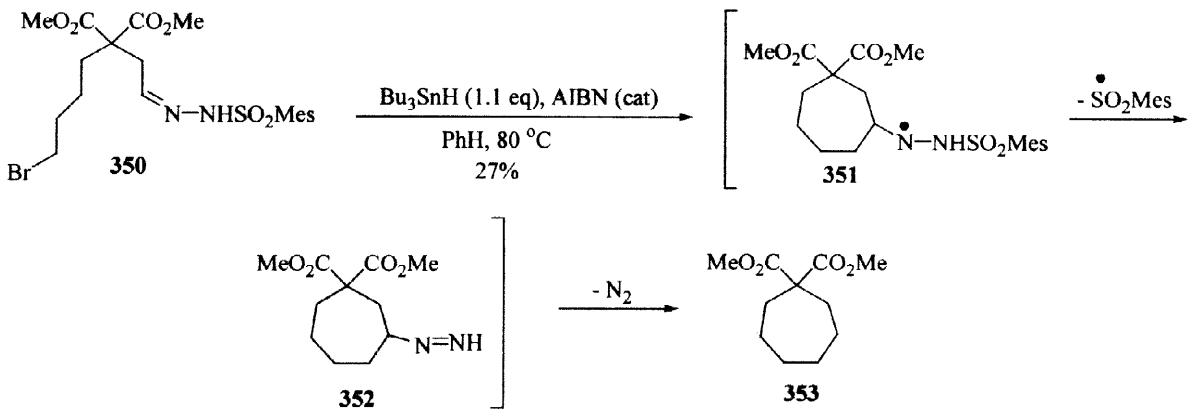
Scheme 85



347 348 349

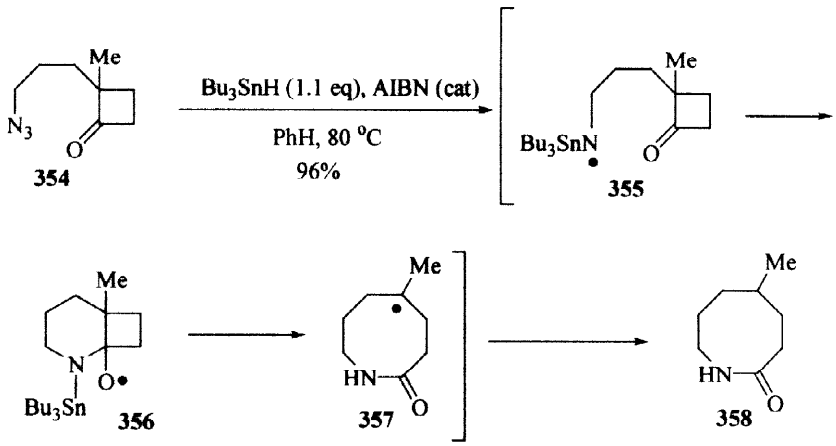
Scheme 86

Kim examined the use of arenesulfonylhydrazones as radical acceptors. Mesitylenesulfonylhydrazone **350** under radical conditions reacted to afford radical intermediate **351** decomposing to azo **352** followed by elimination of nitrogen to give cycloheptane diester **353** (Scheme 87).[89]



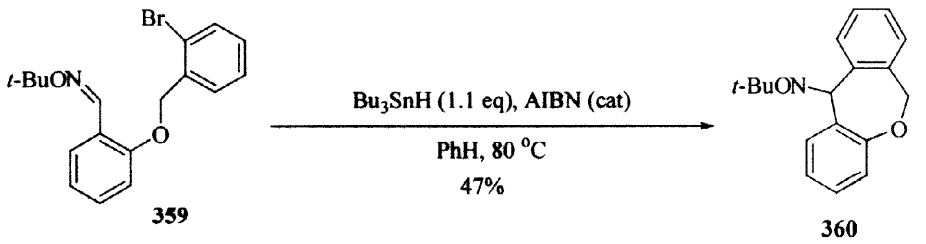
Scheme 87

Kim has also developed an intramolecular addition of aminyl radicals to carbonyl groups to form amides in excellent yields after rearrangement of the initial oxygen radical intermediate.[90] Treatment of azide **354** with tin hydride afforded aminyl radical **355** which after addition to the carbonyl group gave alkoxy radical **356** (Scheme 88). Ring cleavage of **356** gave tertiary radical **357** which was reduced to lactam **358**.



Scheme 88

Jenkins reported an intramolecular aryl radical addition onto an oxime ether acceptor for the general synthesis of heterocyclic rings.[91] For example, reaction of aryl bromide **359** under radical initiating conditions gave cyclic ether **360** in modest yield (Scheme 89).

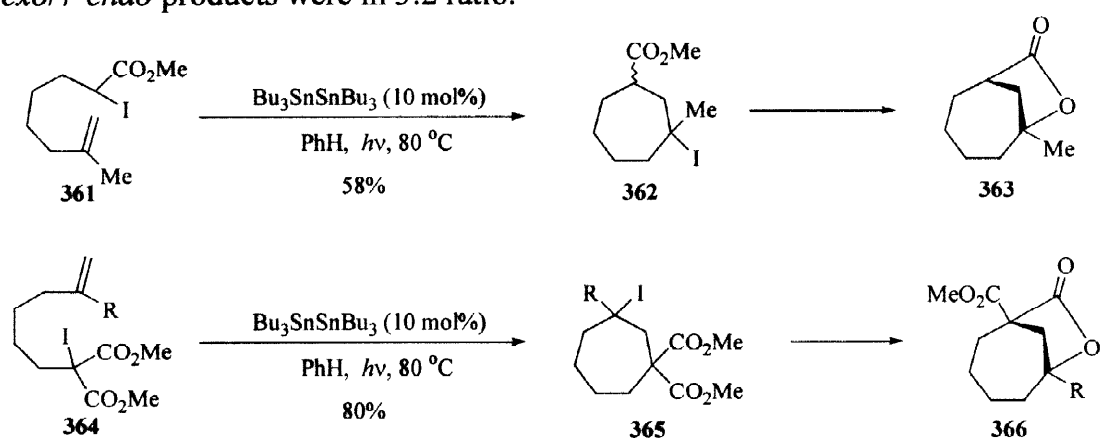


Scheme 89

11. Atom Transfer Methods

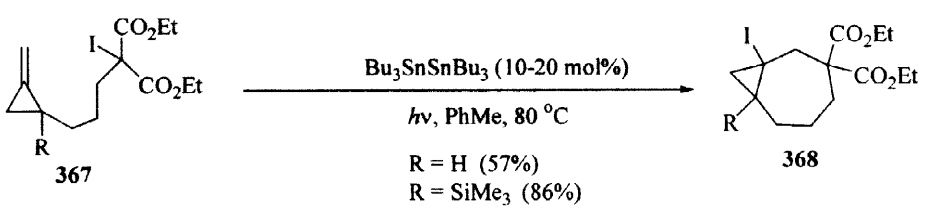
Atom transfer methods have been of synthetic use during the last decade.[92] The atom transfer of a C-X (where X is a monovalent atom) across a double bond is a fundamental reaction of organic free radicals. This method is suitable for radical cyclization when there is no fast radical trap like tin hydride in the reaction medium.

Curran has explored atom transfer cyclization reactions of various substrates.[93] α-Iodo ester **361** under photochemical distannane conditions gave intermediate iodo ester **362** which spontaneously cyclized to lactone **363** (Scheme 90). Similarly, α-iodo malonate **364** (R = Me) gave bridgehead lactone **366** via 7-*endo* cyclization. No 6-exo product was observed. When R = H, 6-*exo*/7-*endo* products were in 3:2 ratio.



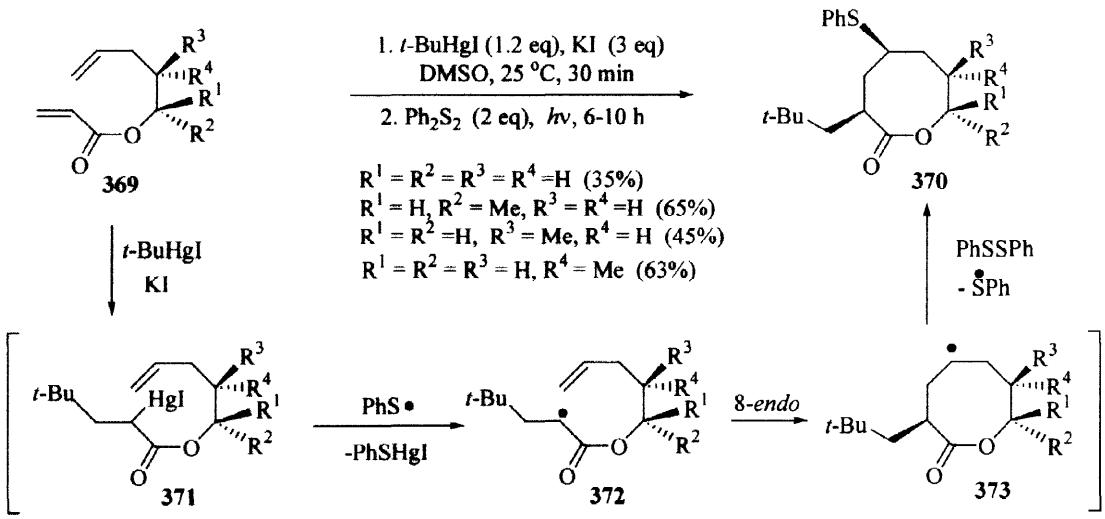
Scheme 90

Kilburn has studied the malonate radical cyclization of methylenecyclopropane derivatives.[94] Radicals derived from malonate **367** participated in a 7-*endo* cyclization to give bicyclo[1.5.0]octane derivatives **368** (Scheme 91).



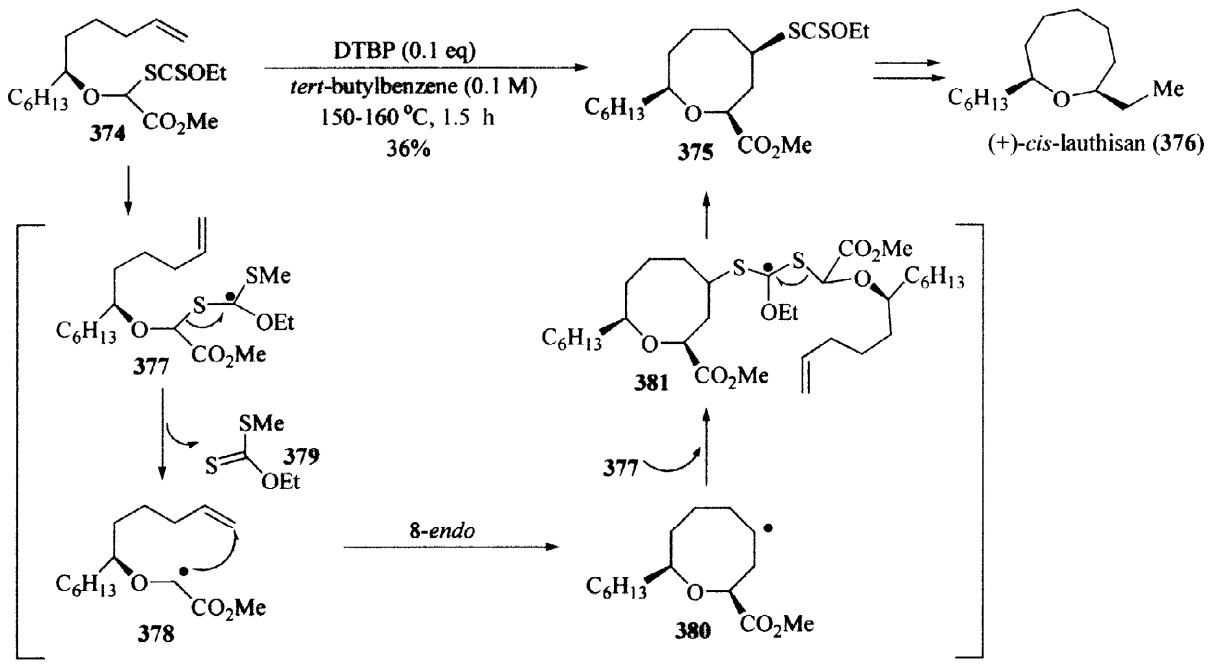
Scheme 91

Free radical addition of *t*-BuHgI/KI to 1-vinyl-4-pentenyl acrylates **369** in dimethyl sulfoxide followed by photolysis with diphenyl disulfide led to eight-membered lactone **370** by 8-*endo* cyclization (Scheme 92).[95] Addition of *t*-BuHg/KI to acrylate **369** gave mercuric intermediate **371** which is transformed to α-acyl radical **372**. 8-*Endo* cyclization of **372** followed by trapping with diphenyl disulfide of radical intermediate **373** under photochemical conditions gave lactone **370**. Diphenyl disulfide is an excellent chain propagator because of its low reactivity towards electrophilic radicals but high reactivity towards nucleophilic radicals.



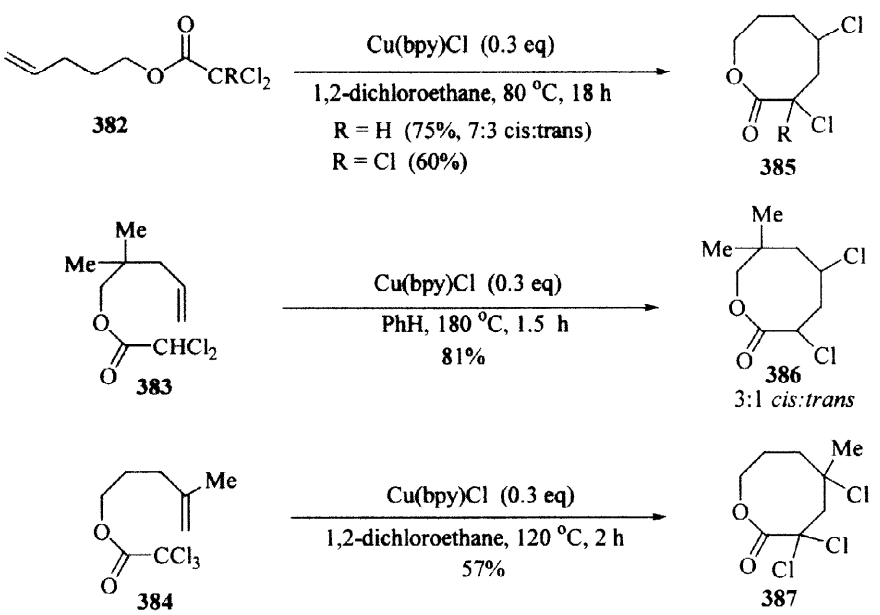
Scheme 92

α-Alkoxy-α-ester **374** participated in a 8-*endo* xanthate radical transfer cyclization with di-*tert*-butylperoxide (DTBP) in *tert*-butylbenzene, a high boiling solvent, to form *cis*-2,8-disubstituted oxocane **375** which was transformed to lauthisan (**376**, Scheme 93).[96] Mechanistically, initiation of the chain occurs after generation of the methyl radicals by thermal decomposition of DTBP. Addition of the methyl radical to the thiocarbonyl group of **374** gives the carbon-centered radical **377** which fragments to give stabilized ester radical **378** and thioester **379**. Cyclization of **378** in a 8-*endo* mode lead to the secondary, nonstabilized alkyl radical **380**. Addition of xanthate **377** gives radical **381** which fragments to oxocane **375** and radical **378** in which propagation of the chain continues.

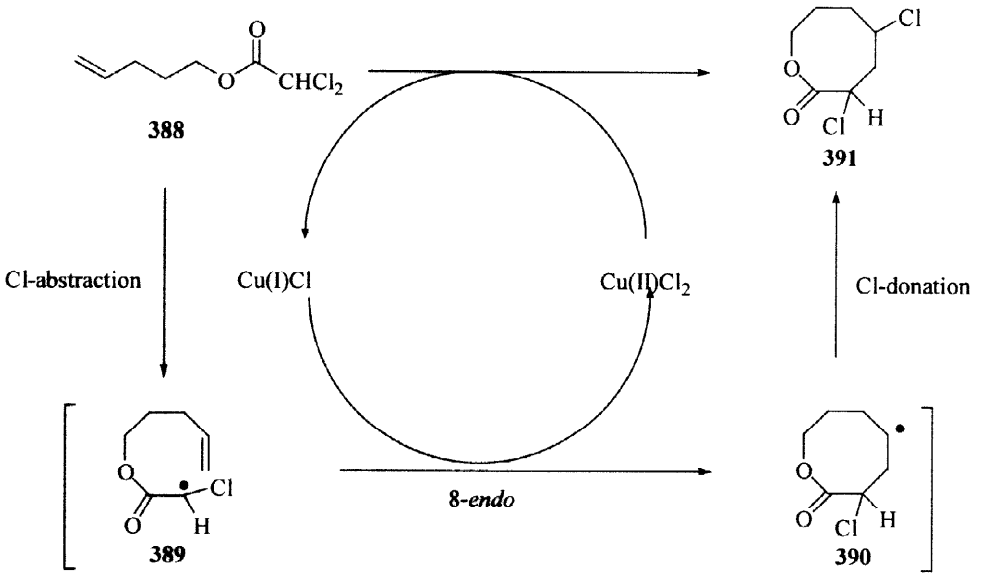


Scheme 93

Speckamp has employed the use of di- and trichloracetates **382-384** in a copper catalyzed chlorine radical transfer in an 8-*endo* cyclization to yield eight-membered lactones **385-387** in good yields (Scheme 94).[97] Mechanistically, the copper(I) catalyst abstracts a chlorine atom from **388** to furnish carbon radical **389** and a copper(II) species. Carbon radical **389** reacts in a 8-*endo* cyclization to unstabilized lactone **390** which abstracts a chlorine atom from the previously formed copper(II) complex to give **391** and the cycle is regenerated (Scheme 95).

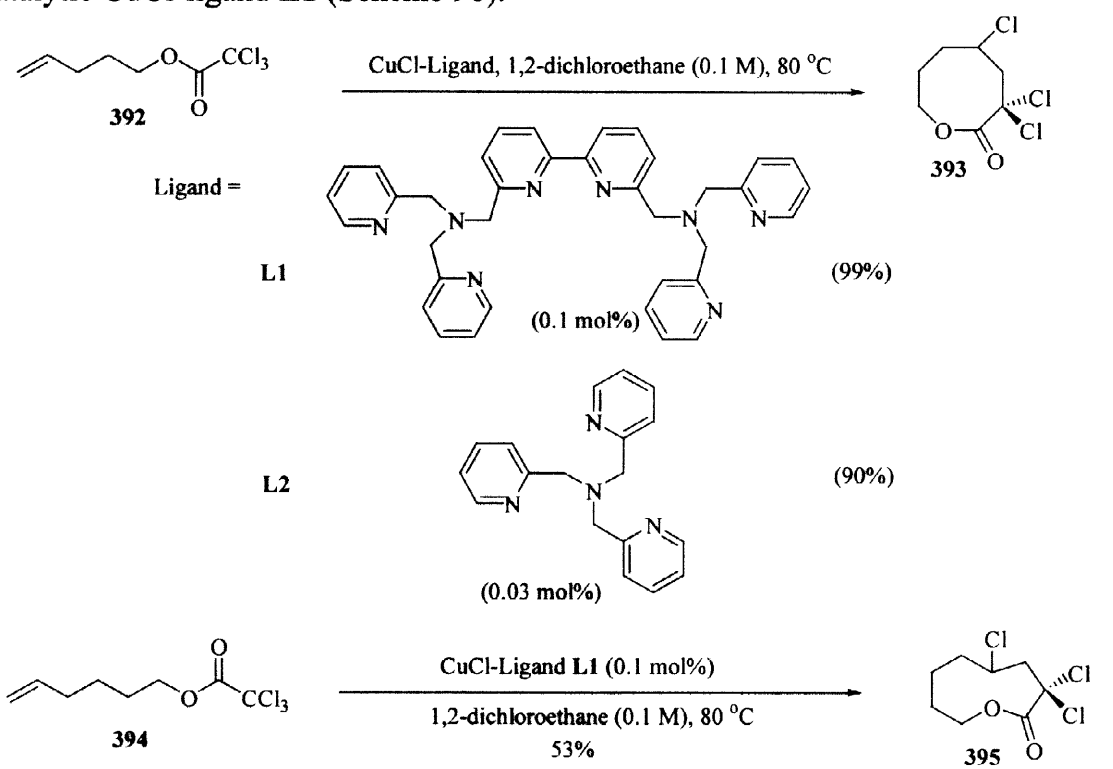


Scheme 94



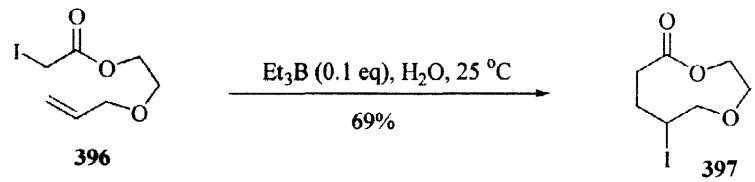
Scheme 95

Verlhac has shown that pent-4-enyl trichloroacetate **392** can be converted to trichlorolactone **393** in an atom transfer radical addition reactions using copper(I) chloride and ligands **L1** or **L2**.[98] Similarly, hex-5-enyl trichloroacetate **394** furnished trichlorolactone **395** using catalytic CuCl-ligand **L1** (Scheme 96).



Scheme 96

Oshima examined the triethylborane-mediated atom transfer radical cyclization of α-iodoester **396** to nine-membered lactone **397** (Scheme 97).[99] Water as reaction solvent accelerated the reaction rate whereas organic solvents such as hexane or benzene gave a much lower yield. Triethylborane has proven to be an efficient radical initiator which could take place at low temperatures such as –78 °C in the presence of trace amount of oxygen. Various solvents such as alcohol or water could be used because of stability of triethylborane in aqueous media.

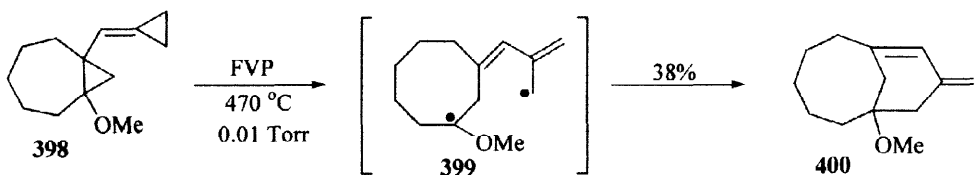


396 397

Scheme 97

12. Medium-Sized Rings from Biradicals

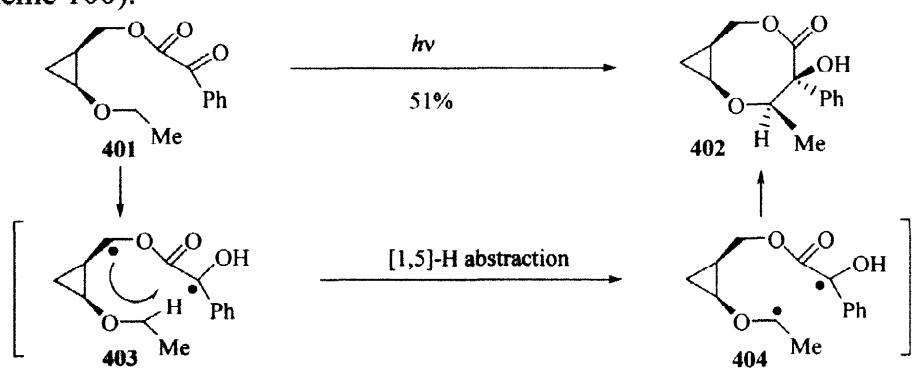
Medium-sized rings can also be formed from diradical intermediates generated by high thermal or photochemical methods. Cohen has applied flash vacuum pyrolysis (FVP) to cyclopropylalkylidenecyclopropane **398** via diradical intermediate **399** to gain entry to the bicyclo[5.3.1]undecane skeleton **400** of the AB ring system of taxanes (Scheme 98).[100]



398 399 400

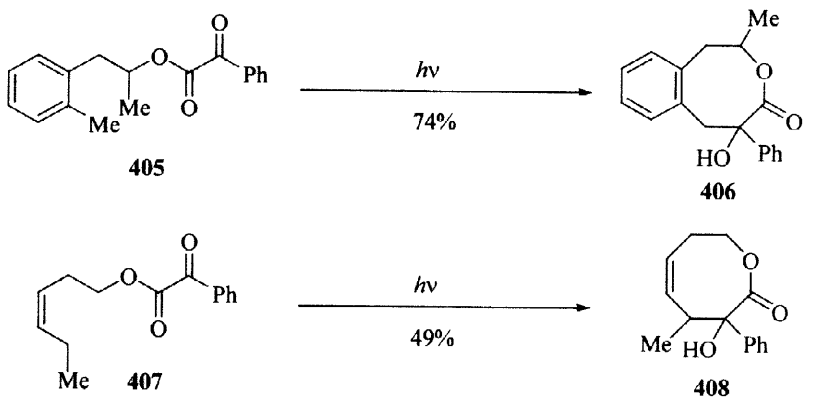
Scheme 98

Kraus demonstrated that photolysis of α-keto ester **401** gave diradical **403** which underwent 1,5-hydrogen abstraction to diradical **404** with subsequent recombination to lactone **402** (Scheme 99).[101] Furthermore, α-keto esters **405** and **407** gave lactones **406** and **408**, respectively (Scheme 100).



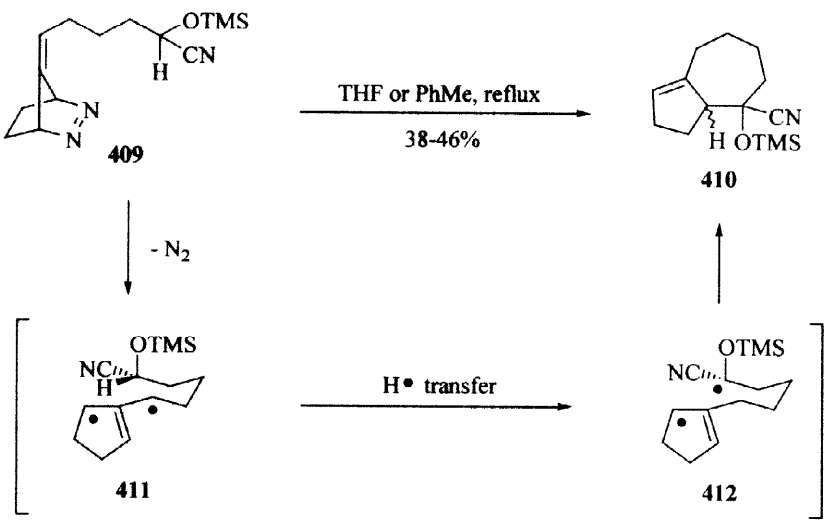
401 402 403 404

Scheme 99

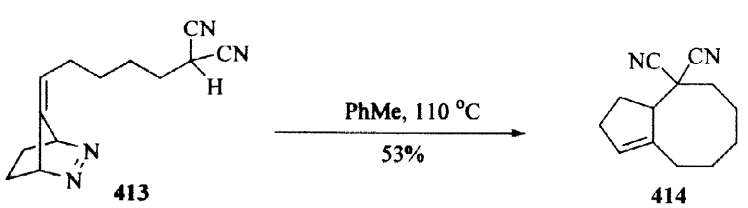


Scheme 100

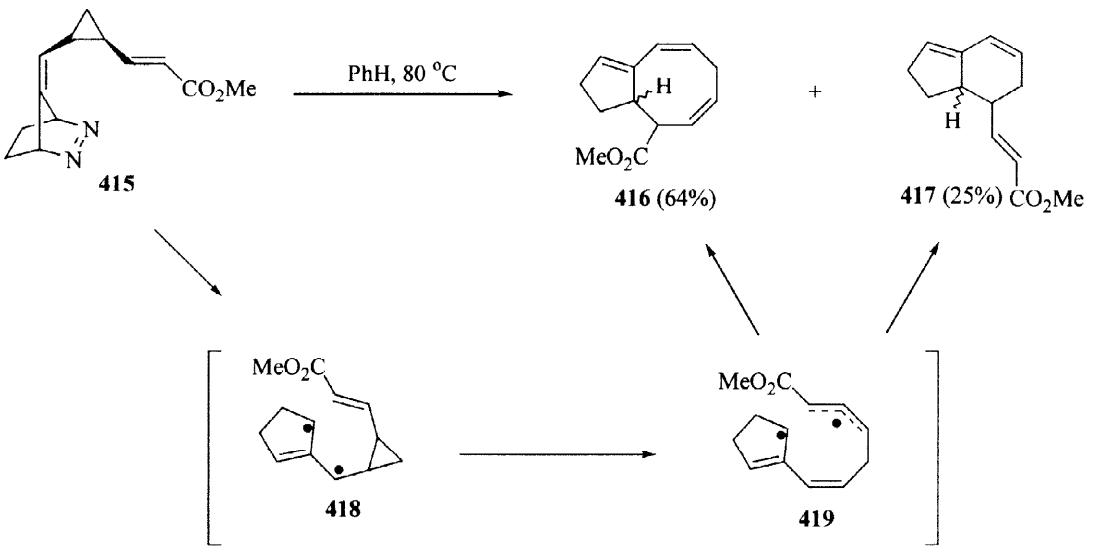
Little has demonstrated that tetramethylenemethane-like diradicals (TMM diyls) can be exploited in a variety of synthetically useful reactions.[102] For example, diazene precursor **409** under thermal conditions provided bicycloheptene **410** (Scheme 101).[103] Expulsion of nitrogen gave diradical **411** which underwent 1,6-hydrogen transfer to **412**. Diradical recombination of **412** afforded **410**. Similarly, diazene **413** gave bicyclooctene **414** (Scheme 102). More recently, he has expanded this methodology to include diazene **415** to give bicyclotriene **416** as the major product with some byproduct **417** arising from diyl **418** to allylic distonic diyl **419** (Scheme 103).[104]



Scheme 101



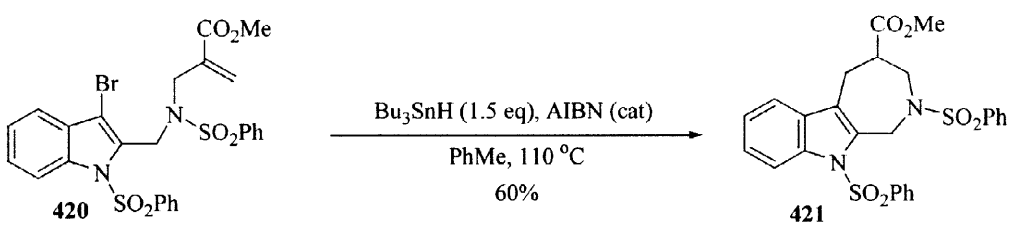
Scheme 102



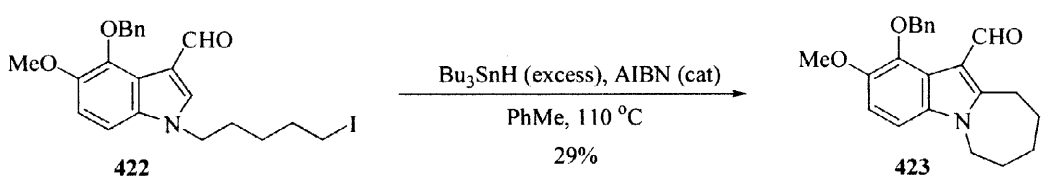
Scheme 103

13. Heterocyclic Synthesis via Radicals

Indole structures have been shown to participate in radical cyclization reactions to give synthetically useful heterocycles. For example, Srinivasan showed the radical cyclization of indole-3-bromide **420** to give β-carboline **421** (Scheme 104).[105] Intramolecular Heck cyclization of **420** gave the six-membered methylene product. Traditionally, β-carboline alkaloids are synthesized from tryptamine derivatives using Pictet-Spengler reactions. Moody reported radical cyclization with oxidation of iodo indole **422** to give 1,2-fused indoles **423** (Scheme 105).[106]

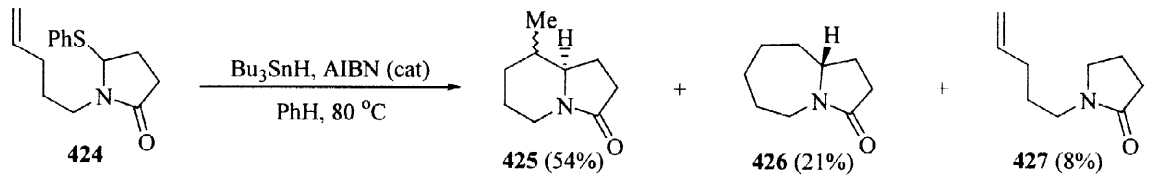


Scheme 104



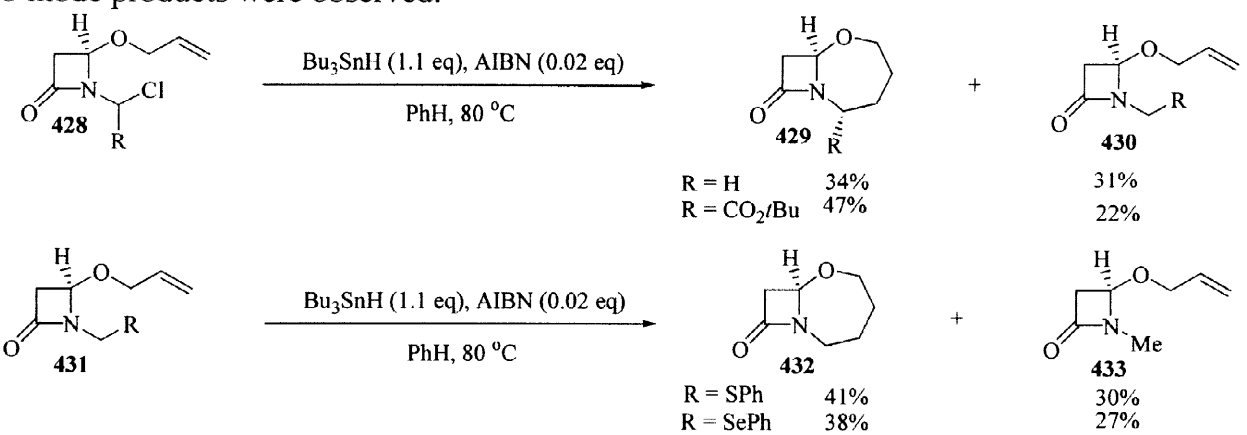
Scheme 105

Hart has shown that α-acylamino radicals generated from phenylthio lactam **424** underwent cyclization to indolizidine **425** and bicyclic lactam **426** via 6-*exo* and 7-*endo* modes, respectively, along with a small amount of reduction product **427** (Scheme 106).[107]



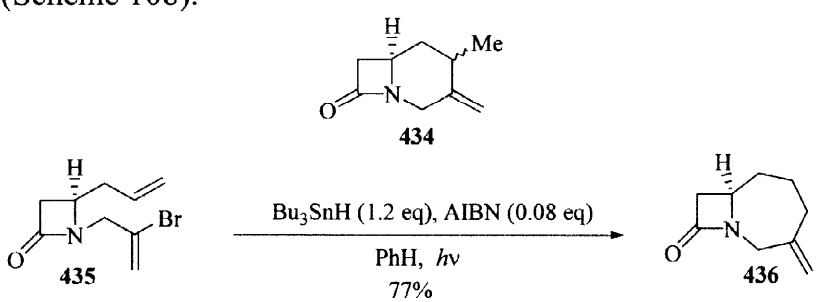
Scheme 106

Bachi demonstrated that *N*-chloromethyl β-lactams **428** under radical conditions provided fused bicyclic β-lactams **429** via 7-*endo* radical annelation and reduction products **430** (Scheme 107).[108] Furthermore, phenylthio and phenylselenyl substrates **431** provided bicyclic lactams **432** and reduction products **433** in basically the same ratios as the chloro derivative.[109] No 6-*exo* mode products were observed.



Scheme 107

Parsons investigated the radical cyclization of β-lactam **435** in hope of producing carbacepham **434** via 6-*exo* mode but instead β-lactam **436** was obtained by a 7-*endo* cyclization mode (Scheme 108).[110]

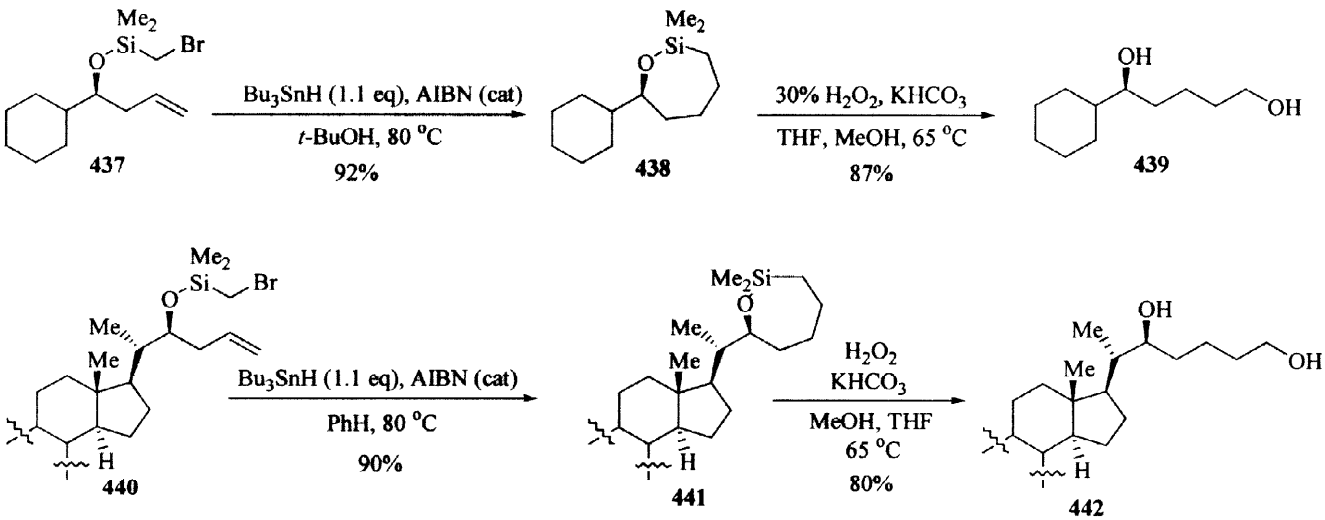


Scheme 108

14. Silacarbocycle Radical Intermediates

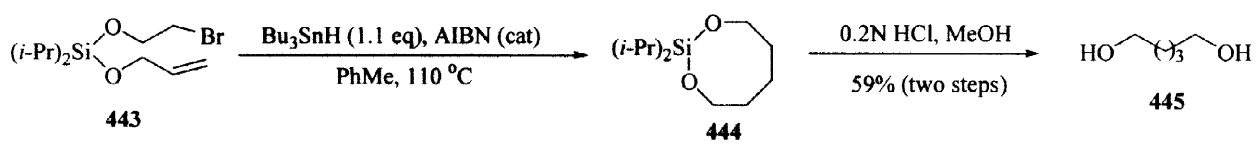
In recent years, there has been increasing interest in the use of silicon as a tether for the intramolecular radical cyclization reaction.[111] A silicon tether allows a radical generated on one ligand to react with a proximinal radical acceptor on a second ligand providing a degree of regio- and stereochemical control.

Koreeda showed that radicals generated from (bromomethyl)silyl ether **437** underwent a regioselective 7-*endo* cyclization to give siloxane **438** which was oxidized to diol **439** (Scheme 109).[112] However, substituents at the olefin terminus gave products of 6-*exo* mode cyclization with *cis*-stereochemistry. This was further applied for the regio- and stereocontrolled synthesis of steroid chains. For instance, (bromomethyl)silyl ether **440** under free radical conditions gave cyclic siloxane **441** as the only cyclization product which was oxidatively cleaved to diol **442**.



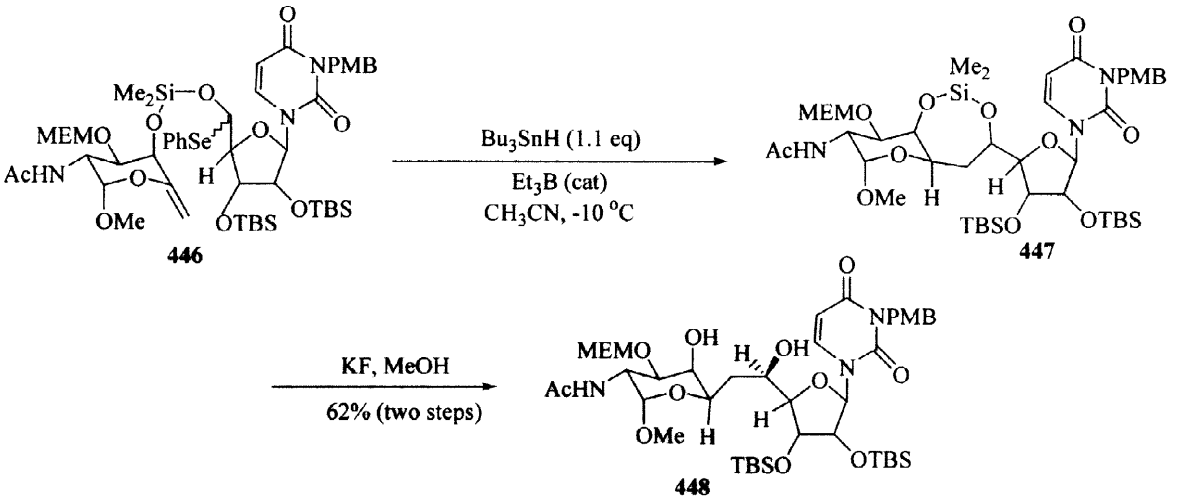
Scheme 109

Hutchinson also showed that intramolecular radical cyclization of diisopropylsilyl ether **443** reacted in a preferential 8-*endo* mode to siloxane **444** which was cleaved to 1,5-pentanediol (**445**) under acidic conditions (Scheme 110).[113]



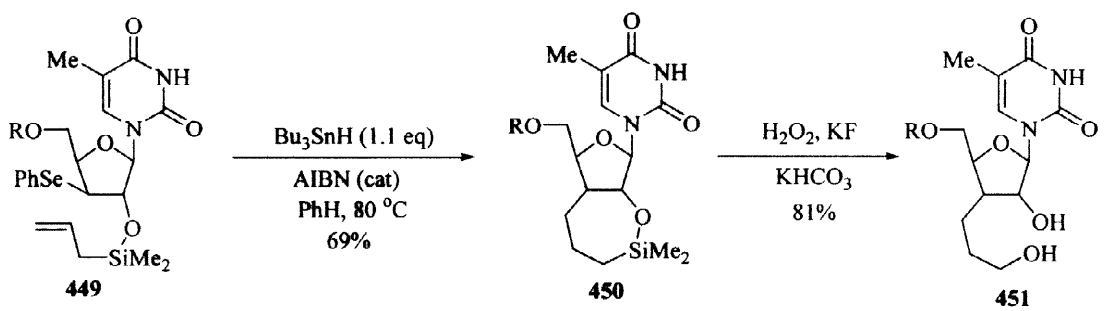
Scheme 110

Myers applied this methodology to the synthesis of natural products.[114] Silyl diether **446** reacted under triethylborane initiated low temperature radical conditions to give siloxane **447** which after basic hydrolysis gave diol **448** with good diastereoselectivity, an advanced intermediate towards tunicaminyluracil (Scheme 111).



Scheme 111

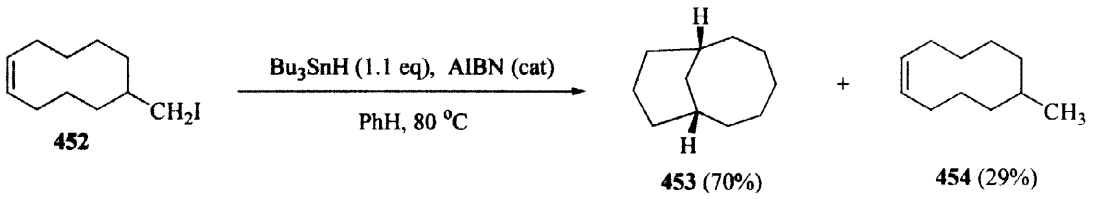
Chattopadhyaya demonstrated successful intramolecular trapping of nucleoside radicals using a tethered allyl siloxane.[115] Treatment of the allyl siloxane derivative of selenium nucleoside **449** under radical conditions gave cyclic siloxane **450** stereospecifically which was cleaved oxidatively to diol **451** (Scheme 112).



Scheme 112

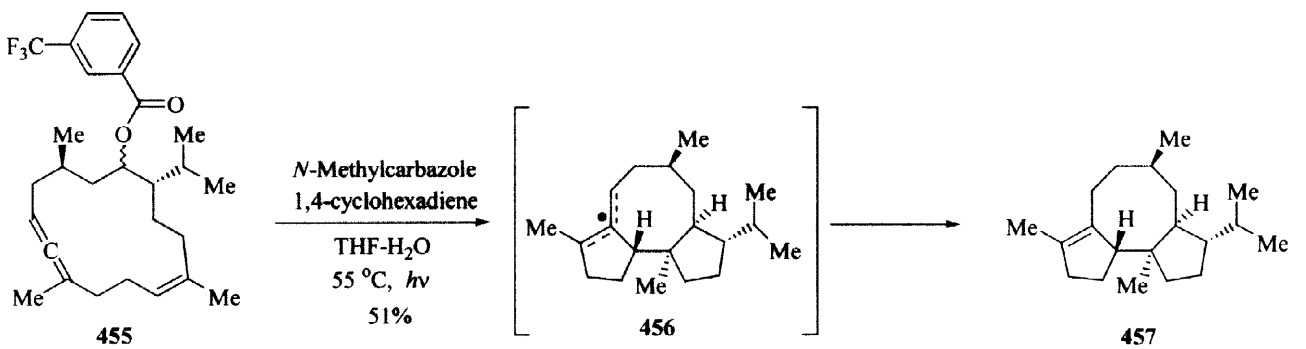
15. Medium-Sized Rings From Macrocycles

Winkler has demonstrated that the radical derived from *cis*-iodomethylcyclodecene **452** underwent transannular cyclization with regio- and stereoselectivity to give *cis*-bicyclo[5.3.1]undecane **453**, an important structural feature of taxane diterpenes, along with reduced product **454** (Scheme 113).[116]



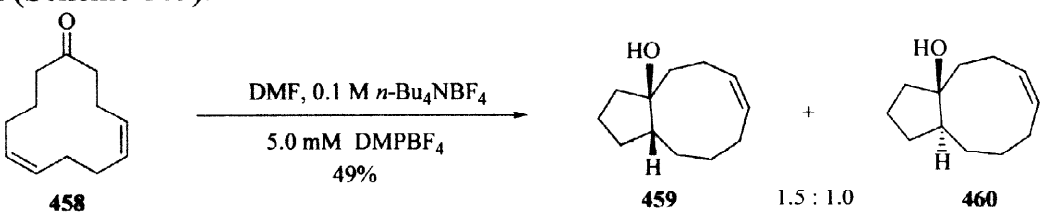
Scheme 113

Myers has reported the photochemical transannular cyclization of the radical derived from benzoyl allene **455** to give transient radical **456** which was reduced to tricyclic alkene **457**, an advanced intermediate to (+/-)-7,8-epoxy-4-basmen-6-one (Scheme 114).[117]



Scheme 114

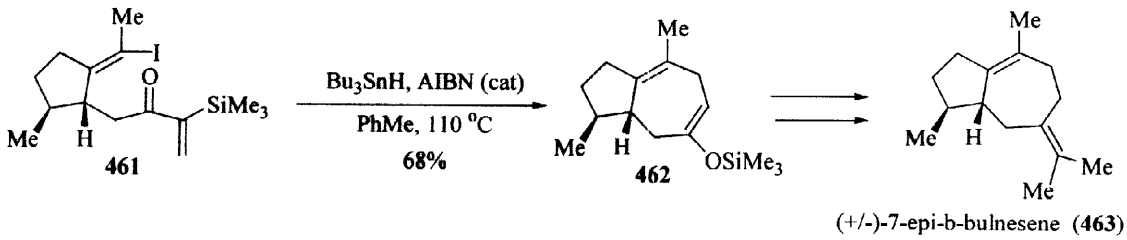
Kariv-Miller studied the cathodic reduction of (Z)-4,8-cyclododecadien-1-one (**458**) to give bicyclic alcohols **459** and **460** in a 1.5:1.0 ratio using tetrabutylammonium tetrafluoroborate as the supporting electrolyte and *N, N*-dimethylpyrrolidinium tetrafluoroborate ($DMPBF_4$) as the other electrolyte via a ketyl radical anion intramolecular cyclization mechanism (Scheme 115).[118]



Scheme 115

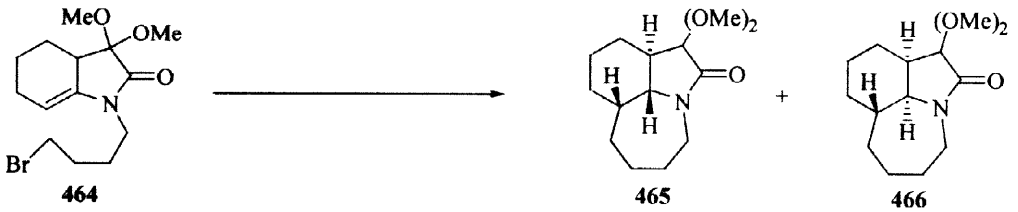
16. Miscellaneous Methods

Negishi has utilized alkenyl iodide **461** under radical initiating protocol to give hydroazulene **462** which was carried on to (+/-)-7-epi-β-bulnesene **463** (Scheme 116).[119]



Scheme 116

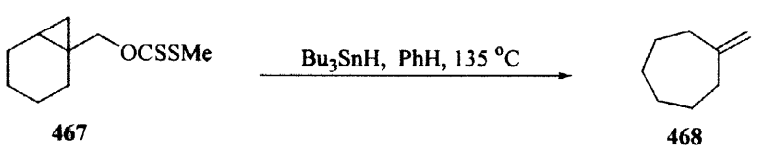
Rigby explored the 7-*endo* intramolecular radical cyclization of hydroindolone **464** under a variety of conditions to give various mixtures of isomeric azepinoindoles **465** and **466** with the best yield and product ratio obtained using triphenyltin hydride in studies directed toward the tricyclic core of the *Stemona* alkaloids (Scheme 117).[120]



$(TMS)_3SiH$ (1.2 eq), AIBN (20 mol%), PhH, 80 °C	2 : 1 (49%)
$NaBH_4$, cat. Bu_3SnCl, *t*-BuOH, 80 °C	3 : 1 (50%)
Ph_3SnH (1.2 eq), AIBN (20 mol%), PhH, 80 °C	5 : 1 (85%)

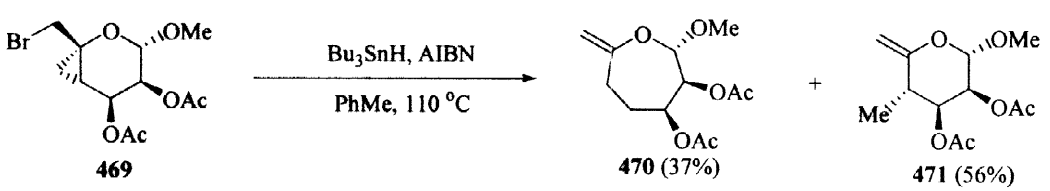
Scheme 117

Kurth has examined the cyclopropylcarbinyl radical-mediated ring expansion of cyclopropyl xanthate **467** to methylenecycloheptane (**468**) with tributyltin hydride in a benzene heated sealed tube (Scheme 118).[121]



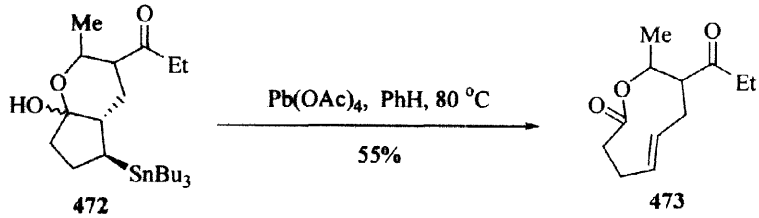
Scheme 118

Gurjar observed radical ring expansion when cyclopropanated sugar **469** gave methylene oxepane **470** and sugar **471** under usual radical conditions (Scheme 119).[122]



Scheme 119

Posner has demonstrated that lactol **472** could be converted to lactone **473** via an alkoxy fragmentation/tributylstannyl radical elimination sequence (Scheme 120).[3f]



472 473

Scheme 120

17. Conclusions

The study and use of free radicals in synthetic organic chemistry will no doubt continue. This review has shown that the application of free radicals in medium-sized ring synthesis complements other available existing methods.

18. References

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Biographical sketch

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