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Free radical chemistry of three-membered heterocycles

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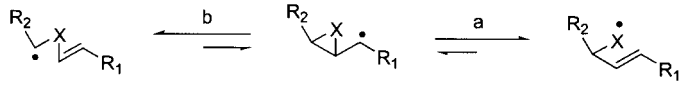
Contents

1. Introduction

A century has gone by since Gomberg reported the first stable free radical, the triphenylmethyl radical, in 1900. Since then, tremendous progress has been made by both physical and synthetic organic chemists in the free radical arena over the last hundred years. Especially during the last two decades, radical chemistry has evolved into a major field in a rather short period of time. Several books[1–4] and many review articles[5–12] have appeared covering the advancement of this field. Despite the phenomenal development and utility of radical chemistry in organic synthesis, it has not found many applications in the synthesis of pharmaceuticals. The greatest detriment arises from the use of toxic organotin reagents. However, many innocuous surrogates now have been discovered to replace organotin reagents. It is a matter of certainty that radical chemistry will find its way to medicinal and combinatorial chemistry.[13]

Three-membered heterocycles, including epoxides, aziridines, and oxaziridines as versatile building blocks, are prone to ring-opening because of the high-level ring strain resident therein. Under the radical ring-opening conditions, the weaker C–X bond fragments more easily (pathway a in Scheme 1) when R_2 is a hydrogen or an alkyl group. On the other hand, C–C bond cleavage (pathway b) is also possible when R_2 is a vinyl-, aryl-, or acyl group. Although the equilibrium favors the ring-opening process, syntheses of epoxides and aziridines have been achieved via the radical pathway with the right substrate setup.



Scheme 1.

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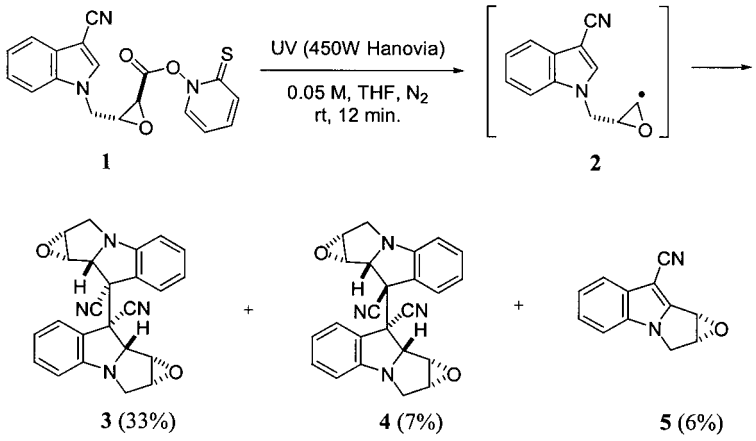


Scheme 2.

2. Oxiranyl radicals

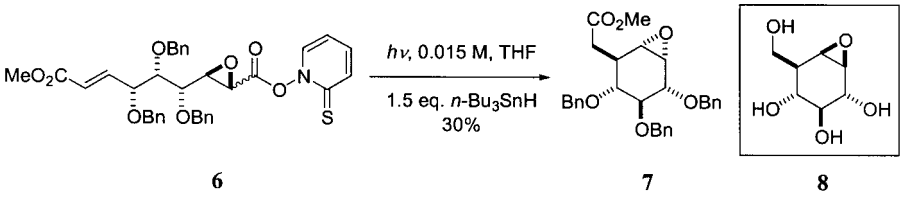
With the advent of modern synthetic method have come many practical asymmetric epoxidation methods. Today, asymmetric epoxidation of allylic alcohols (Sharpless asymmetric epoxidation),[14] (*Z*)-olefins (Jacobsen epoxidations),[15] and (*E*)-olefins (Shi epoxidations)[16] can be routinely carried out with high yields and high enantiomeric excesses (*ee*'s). While epoxides as electrophiles react with organometallic reagents to furnish a variety of useful ring-opening products, radical-initiated ring-opening processes can be run under neutral conditions, providing a unique opportunity for further manipulations of epoxides without the incompatibility problem one often encounters with organometallic reagents. This holds particular relevance during total synthesis of complex natural products bearing many functional groups.

Although the intermediacy of the oxiranyl radical was recognized in the early 1960s,[17] Ziegler was the first to demonstrate its synthetic utility via the oxiranyl radical cyclization in 1993.[18] As shown in Scheme 2, UV irradiation of thiohydroxamate ester **1**, readily accessible from the corresponding acid, led to symmetrical bis-indoline **3**, unsymmetrical bis-indoline **4**, and epoxyindole **5**. The initially generated *trans*-oxiranyl radical **2** underwent a rapid interconversion to its *cis*-counterpart, which then cyclized before rearrangement.

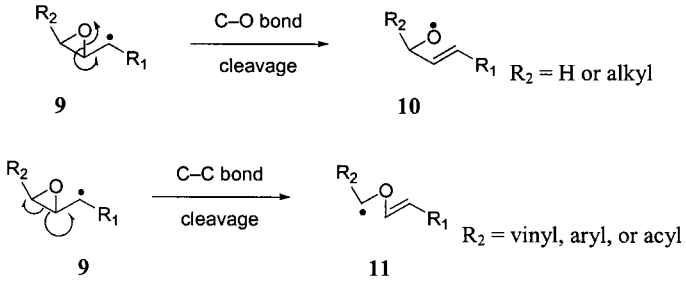
Based on the success of their intra- and intermolecular C–C bond formation reactions of oxiranyl radicals with olefins,[19] Ziegler's group attempted to apply the method to the total synthesis of (+)-cyclopellitol (**8**, Scheme 3).[20,21] Regardless of the stereochemistry of the thiohydroxamate ester in **6**, UV irradiation gave the 6-*exo-trig* intramolecular radical cyclization product **7**, which would lead to *epi*-cyclophellitol. The yield of the oxiranyl radical cyclization was moderate and the stereochemical outcome was not applicable to the synthesis of (+)-cyclopellitol (**8**). However, Ziegler demonstrated the utility of the oxiranyl radical as a novel venue for incorporating epoxides into synthetic targets either inter- or intramolecularly.

3. Oxiranylcarbinyl radicals

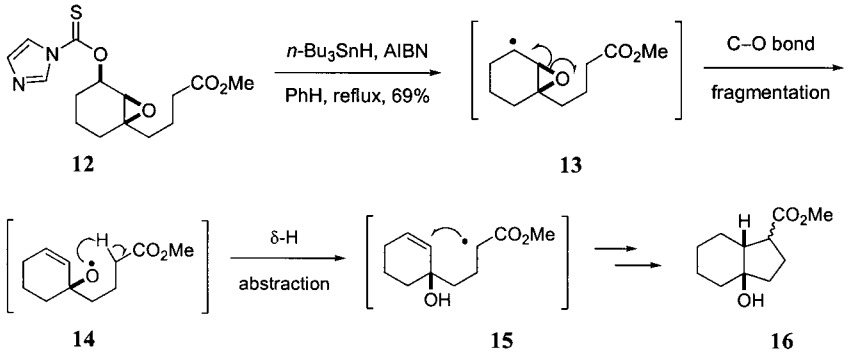
In contrast to the scarcity of precedence on oxiranyl



Scheme 3.



Scheme 4.



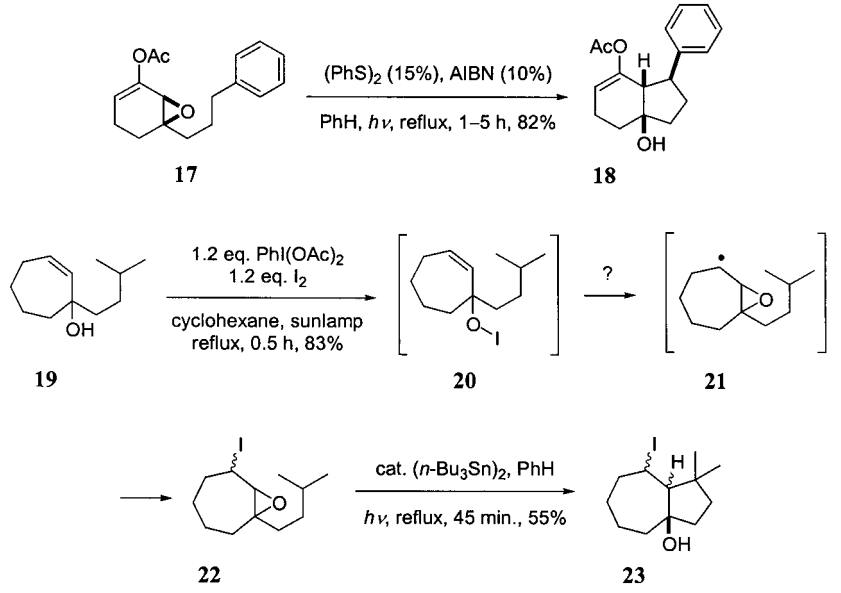
Scheme 5.

radicals, the literature is replete with studies of oxiranylcarbinyl radicals in both physical and synthetic organic chemistry.[22] Depending upon the nature of substituent R_2, the ring-opening of oxiranylcarbinyl radical **9** may proceed via either a C–O bond cleavage to give alkoxy radical **10**, or via a C–C bond cleavage to afford enol ether radical **11** (Scheme 4). When R_2 is a simple alkyl substituent or hydrogen, the C–O bond cleavage is predominant,[23] whereas when R_2 is a vinyl-, aryl-, or acyl group, the C–C bond cleavage is the major pathway to give stabilized radical **11**.[24] Oxiranylcarbinyl radicals, in turn, can be generated from α-hydroxyepoxides,[25–32] α-haloepoxides,[33–40] α-vinyl epoxides,[41–49] and α-ketoepoxides.[50–60]

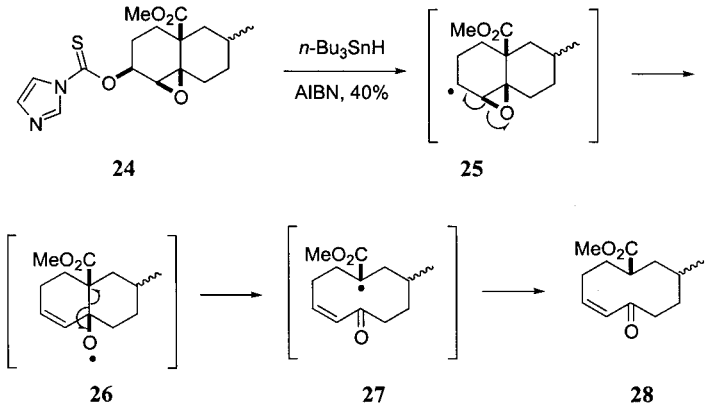
3.1. From α-hydroxyepoxides

Asymmetric synthesis of α-hydroxyepoxides can be readily achieved from allylic alcohols using the Sharpless asymmetric epoxidation.[14] The abundance of chiral α-hydroxy epoxides makes these species ideal substrates in organic synthesis. Rawal and coworkers designed a tandem C–O bond fragmentation, radical translocation, and cyclization sequence to assemble 5-membered carbocyclic rings from α-hydroxyepoxides.[25] As illustrated in Scheme 5, treatment of thiocarbonylimidazolide **12** under standard radical generation conditions gave *cis*-fused bicyclic octahydroindene **16** as a 2.7:1 mixture of diastereomers. Mechanistically, the C–O bond (weaker bond) in oxiranylcarbinyl radical **13** cleaved to give allyloxy radical **14**, which translocated to allylic alcohol **15** by abstracting an H· at the δ-position via a six-membered ring transition state. A 5-*exo-trig* cyclization of **15** was followed by a hydrogen abstraction from *n*-Bu_3SnH to afford **16**.

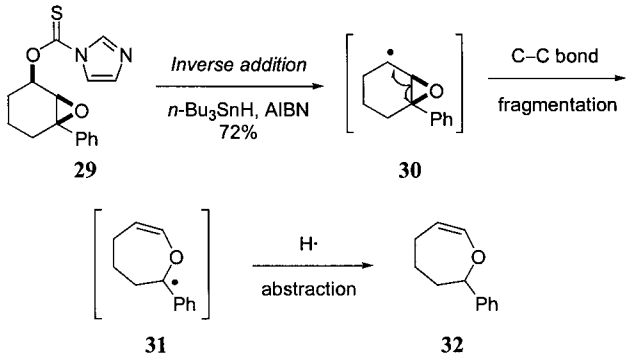
In order to further functionalize the bicyclic carbocycles such as **16**, Rawal et al. devised two strategies[26,27] based on their aforementioned tandem epoxide fragmentation, radical translocation, and cyclization sequence. In one case, the tandem radical sequence was triggered by generation of phenylthiyl radical, transforming acetoxyalkenyl epoxide **17** to acetoxyalkenyl cyclopentanol **18** (Scheme 6).[26] Kim later reported a similar stereoselective radical cyclization strategy using epoxysilyl ethers, giving rise to cyclopentanols.[28] In another case, *atom transfer cyclization* of iodoepoxide **22** led to iodocyclopentanol **23**.[27] Interestingly, iodoepoxide **22** was obtained from treatment of allylic alcohol **19** with $PhI(OAc)_2$ and I_2 under sunlamp irradiation, possibly via a putative hypoiodite intermediate **20** and subsequently oxiranylcarbinyl radical **21**.



Scheme 6.



Scheme 7.



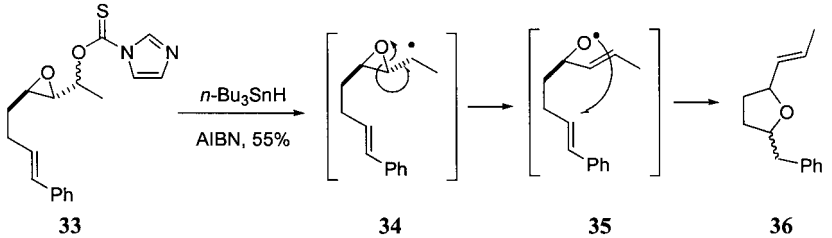
Scheme 8.

Another tandem radical reaction was crucial to Marples' synthesis of medium-size rings.[29] As depicted in Scheme 7, ten-membered carbocycle **28** was obtained from epoxydecalin thiocarbonylimidazolide **24**. Presumably, oxiranylcarbinyl radical **25** underwent a C–O bond fragmentation to give alkoxy radical **26**. Ring expansion of **26** was achieved via a C–C bond scission to furnish radical **27** which was stabilized by the ester group. Radical **27** then abstracted a hydrogen from *n*-Bu_3SnH to afford **28**. A similar result was reported by the Rawal group.[30]

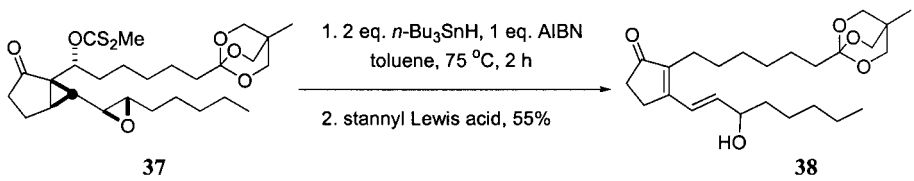
As discussed earlier, the C–C bond fragmentation prevails when there is a phenyl-, vinyl-, or acyl substituent on the oxiranylcarbinyl radical as illustrated by **9→11**. Indeed, when epoxy thiocarbonylimidazolide **29** and AIBN were added to the solution of *n*-Bu_3SnH (*reverse addition*), the ring-expansion product enol ether **32** was obtained, presumably from benzyl radical **31** via direct C–C bond cleavage of oxiranylcarbinyl radical **30** (Scheme 8).[29] The driving force for this pathway was that the resultant radical **31** was stabilized as a benzylic radical.

A major utility of α-hydroxyepoxides is their transformation to tetrahydrofurans via the intermediacy of oxiranylcarbinyl radicals. Murphy and associates prepared tetrahydrofuran **36** (*trans*:*cis*=3:1) from epoxy thiocarbonylimidazolide **33** (Scheme 9).[31] In this case, the oxiranylcarbinyl radical **34** underwent a C–O bond fragmentation to furnish allyloxy radical **35**, which then cyclized to **36** in a 5-*exo*-*trig* manner. An application of this method resulted in a synthesis of lilac alcohol.[31]

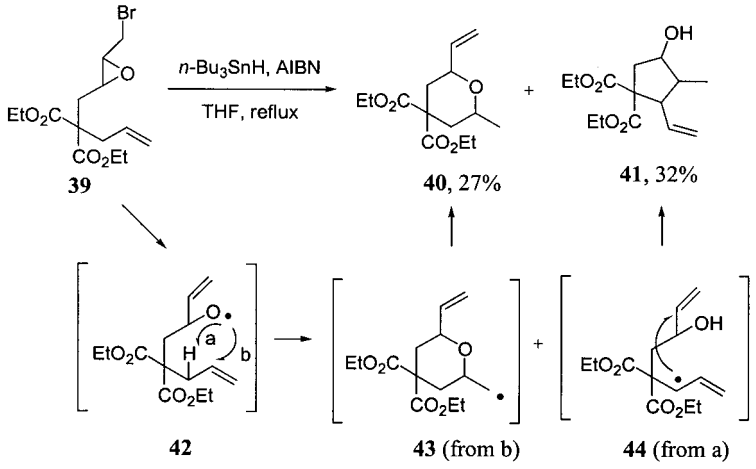
Another prominent application of the oxiranylcarbinyl radical, although not directly generated from an α-hydroxy epoxide, was the synthesis of prostaglandin B_1 orthoester **38** (Scheme 10). Xanthate **37** underwent an intricate radical cascade involving a Barton–McCombie reduction,



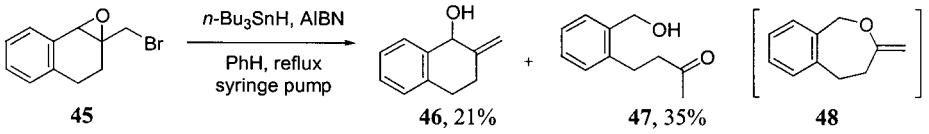
Scheme 9.



Scheme 10.



Scheme 11.



Scheme 12.

cyclopropylcarbinyl radical and oxiranylcarbinyl radical rearrangement to give a (*Z*)-allylic alcohol, which was isomerized to PGB_1 orthoester **38** under the influence of a stannyl Lewis acid.[32]

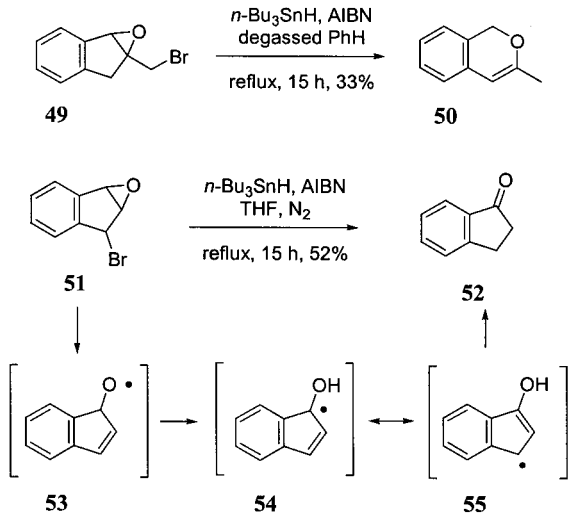
3.2. From α-haloepoxides

Analogous to transformation **33→36**, α-haloepoxides have been used in radical cascade reactions as well.[31] As illustrated in Scheme 11, when α-bromoepoxide **39** was subjected to the radical generation conditions, both the six-membered ring tetrahydropyran **40** and five-membered ring cyclopentanol **41** were formed in about equal amounts.[33] The C–O bond fragmentation intermediate, allyloxy radical **42**, had two competing pathways. One pathway formed radical **43** via 6-*exo-trig* intramolecular radical cyclization (pathway b). The other route was the competing Barton-type δ-abstraction (1,5-hydrogen abstraction, pathway a) to give translocated radical **44**, which rapidly cyclized to cyclopentanol **41**.

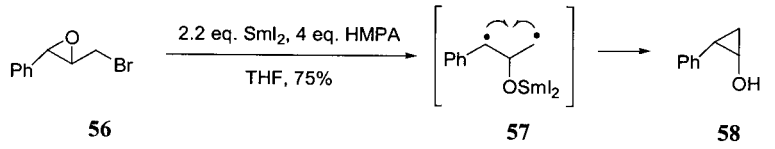
As discussed at the beginning of this section, C–C bond rupture becomes important when one substituent on the epoxide ring is a vinyl-, aryl-, or acyl group. Murphy explored the C–C bond fragmentation of ring-fused α-haloepoxides.[34,35] Treatment of tetrahydronaphthalene derivative **45** with *n*-Bu_3SnH and AIBN in benzene heated at reflux led to two products—allylic alcohol **46** from the C–O bond cleavage; and 4-[2-hydroymethyl)phenyl]butan-2-one (**47**), arising from hydration (on silica gel) of the C–C scission product, oxepane **48** (Scheme 12).

The oxiranylcarbinyl radical generated from substrate **45** underwent competitive rearrangement between C–C and C–O bond scissions. The product distribution was a reflection of the relative bond strength of the C–C and C–O bonds of the respective substrates. In Scheme 13, the oxiranylcarbinyl radical from bromoepoxide **49** gave the C–C bond rupture product, 3-methyl-1*H*-2-benzopyran (**50**), as the sole product. In contrast, the C–O bond cleavage product, indan-1-one (**52**), was obtained exclusively when 3-bromoindene 1,2-oxide (**51**) was subjected to similar conditions.[34,35] During transformation **51→52**, homoallyloxy radical **53** abstracted the α-hydrogen to isomerize to the more stable **54**, a resonance form of **55** as the precursor to **52**.

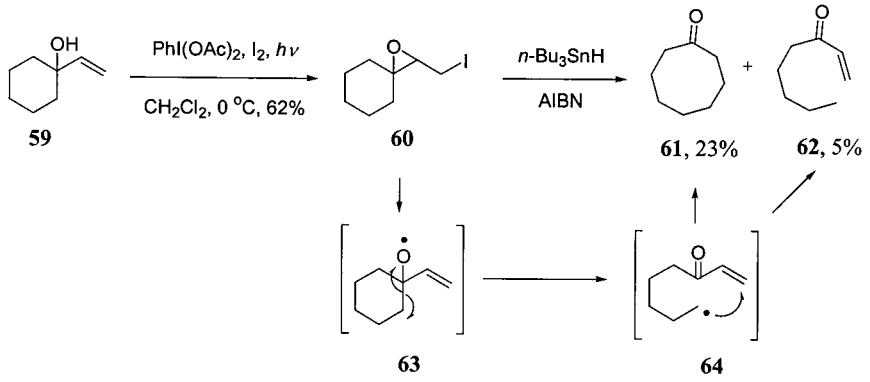
Interestingly, when bromoepoxide **56** was allowed to react with SmI_2, cyclopropanol **58** was obtained (Scheme 14).[36] Although the authors postulated the reaction proceeded via a



Scheme 13.



Scheme 14.



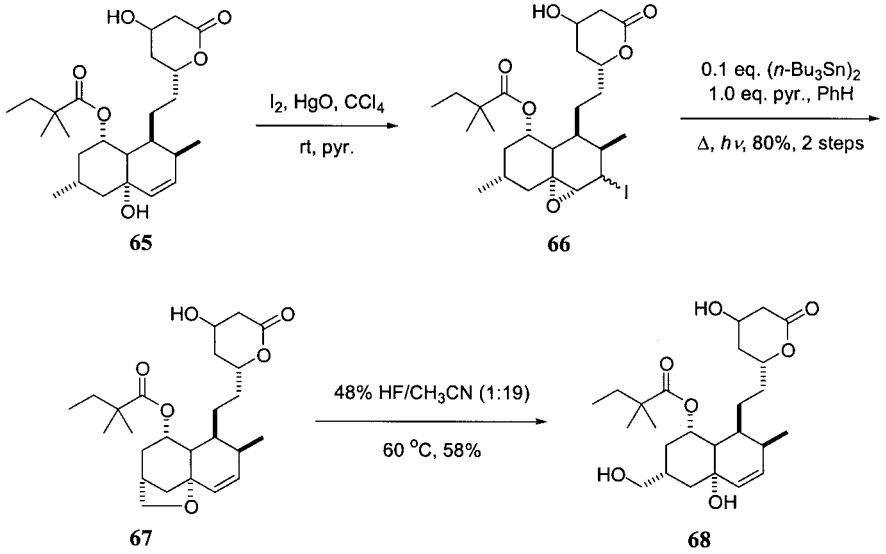
Scheme 15.

putative diradical intermediate **57**, it is unlikely that diradical **57** could be generated and existed in such a reducing medium.

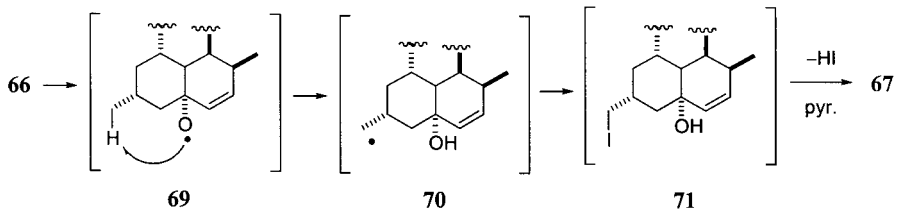
Galatsis prepared α-iodoepoxide **60** by exposure of tertiary allylic alcohol **59** to $PhI(OAc)_2$ and I_2 under photochemical conditions, probably via a radical pathway (Scheme 15).[37] A novel two-carbon ring expansion product **61** was isolated as the major product when **60** was treated with *n*-Bu_3SnH and AIBN in benzene heated at reflux.[38] Enone **62** was a minor product. Both products arose from the C–O bond fragmentation of the oxiranylcarbinyl radical to provide allyloxy radical **63**. Subsequent β-scission of **63** furnished enone radical **64**, which underwent an 8-*endo-trig* cyclization to deliver cyclooctanone (**61**). This was the first example of radical cyclization to make medium-sized carbocycles. Recently, Watson's group described a similar strategy for two-carbon cycloalkanone ring expansion using di-*tert*-butyl peroxide as the initiator.[39]

A Merck group synthesized oxygenated metabolite **68** of simvastatin using iodoepoxide **66** as the key intermediate (Scheme 16).[40] Initial attempts to make cyclic ether **67** by treatment of **65** with I_2 and HgO via radical mechanism failed. Instead, the major product was iodoepoxide **66**, which upon submission to the photolysis conditions in the presence of hexabutylditin and pyridine did indeed give the desired cyclic ether **67**. Acidic cleavage of the allylic cyclic ether **67** using 48% HF secured the 6α-hydroxymethyl metabolite **68**. This case exemplifies the power of radical chemistry in the synthesis of complex molecules with great functional group compatibility.

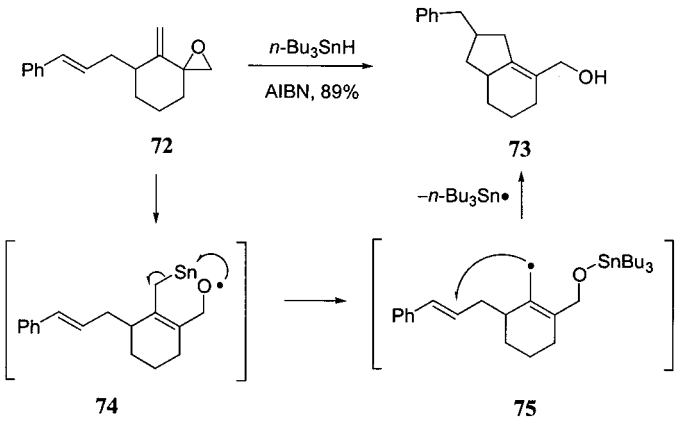
The mechanism for transformation **66→67** is delineated in



Scheme 16.



Scheme 17.



Scheme 18.

Scheme 17. The C–O scission of the originally formed oxiranylcarbinyl radical furnished allyloxy radical **69**, which translocated to allylic alcohol **70** by abstracting an H· from the methyl group at the δ-position via a six-membered ring transition state. An atom transfer of **70** provided methyl iodide **71**, which then cyclized to **67** with the aid of pyridine.

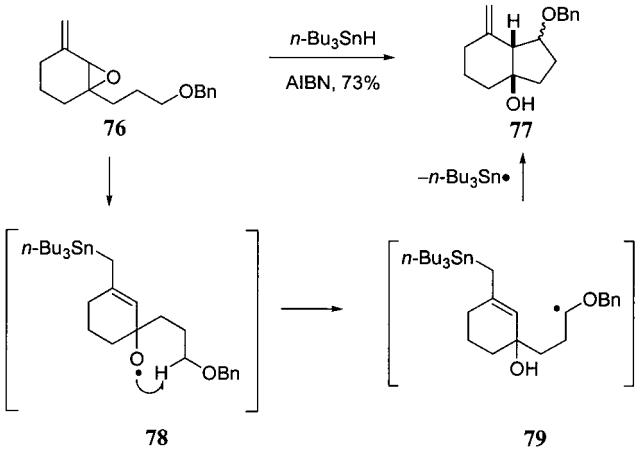
3.3. From α-vinyl epoxides

In 1970, Stogryn and Gianni obtained vinyl ethers by allowing vinyl epoxides bearing a phenyl or a vinyl substituent to react with the methylthiyl radical via a C–C bond homolysis.[24a] In 1991, Kim reported radical reactions of vinyl epoxides via radical translocation by a novel 1,5-*n*-Bu_3Sn group transfer.[41,42] As depicted in Scheme 18, the transformation from vinyl *exo*-epoxide **72** bearing a pendant cinnamyl substituent to bicyclic carbocycle **73** proceeded via alkoxy radical **74**, formed by the addition of *n*-Bu_3Sn· to the double bond followed by C–O bond rupture. A novel 1,5-*n*-Bu_3Sn group transfer in **74** then furnished allylic radical **75**, which cyclized in a 5-*exo-trig* mode to **73**.

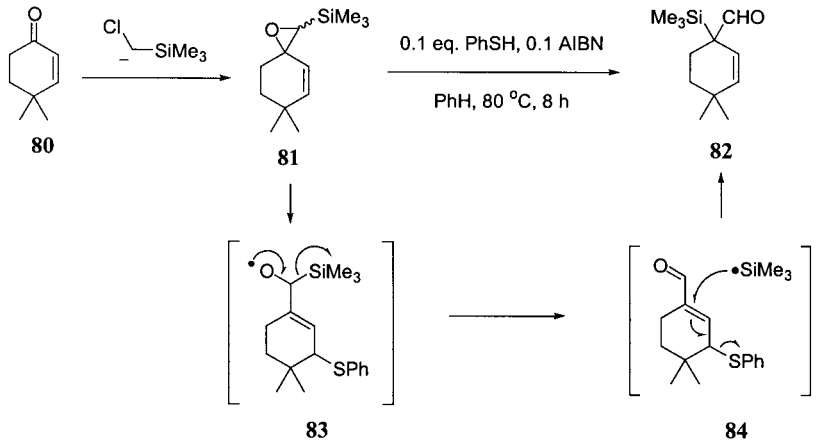
Analogously, treatment of the vinyl *endo*-epoxide **76** with *n*-Bu_3SnH and AIBN in benzene heated at reflux afforded bicyclic carbocycle **77** in 73% yield (Scheme 19).[41,42] Initially, *n*-Bu_3Sn· added to **76** in a manner similar to an S_N2' to give allyloxy radical **78**, which translocated to radical **79** by abstracting a hydrogen at the δ-position. Cyclization of **79** in a 5-*exo-trig* fashion then gave **77**.

Using Magnus' chloromethyltrimethylsilyl carbanion method,[43] Robertson et al. prepared vinyl epoxide **81** from enone **80** (Scheme 20).[44] A stable α-trimethylsilyl aldehyde **82** was obtained when **81** was subjected to radical generation conditions. Rather than a *homolytic Brook rearrangement* that would have provided a siloxyl enol ether, the authors proposed an ejection of a silyl radical in alkoxy radical **83** to give enal **84**. A re-addition of Me_3Si· to **84** subsequently afforded α-trimethylsilyl aldehyde **82**.

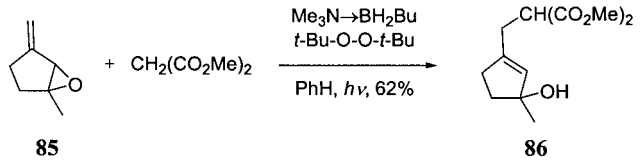
An Et_3B-induced radical from $C_6F_{13}I$, PhSH, or Ph_3GeH added to vinyl epoxides to afford the oxiranylcarbinyl radical, whose C–O bond then fragmented to furnish the corresponding allylic alcohol.[45] Using amine-boranes as polarity reversal catalysts, Roberts and collaborators synthesized α-carbonyl epoxides from allylic *tert*-butyl peroxides.[46] Furthermore, as illustrated in Scheme 21, treatment of vinyl epoxide **85** with dimethyl malonate in the presence of an amine-borane catalyst and di-*tert*-butyl peroxide gave allylic alcohol **86**.[47,48] Mechanistically, the nucleophilic amine-boryl radical ($Me_3N{\rightarrow}{\cdot}BHBu$),



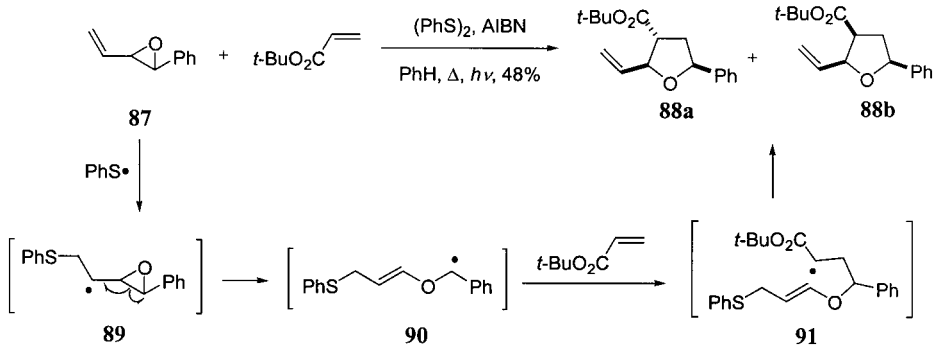
Scheme 19.



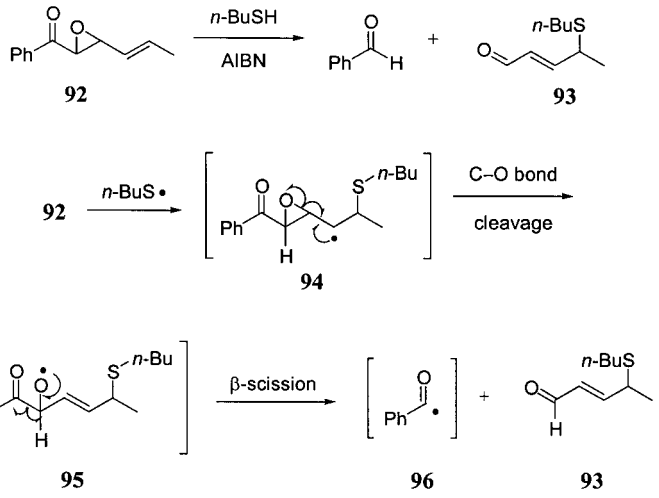
Scheme 20.



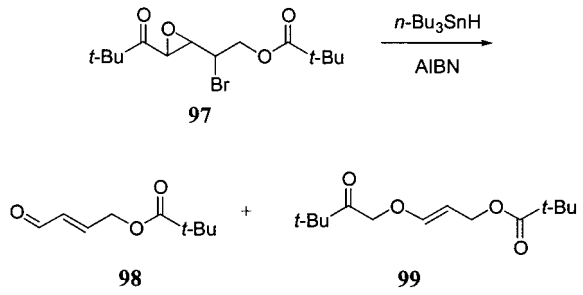
Scheme 21.



Scheme 22.



Scheme 23.



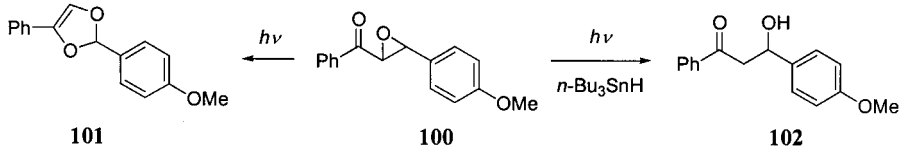
Scheme 24.

generated from the reaction of $Me_3N{\rightarrow}BH_2Bu$ and *tert*-butyloxy radical, abstracted a hydrogen regioselectively at the electron-deficient α-C–H bond of the malonate. Addition of this malonyl radical to the double bond of **85** was followed by a C–O bond fragmentation of the resulting oxiranylcarbinyl radical to give the allyloxy radical and subsequently allylic alcohol **86**. However, although the reaction worked well for rigid vinyl epoxides, the yields for more flexible vinyl epoxides were low.

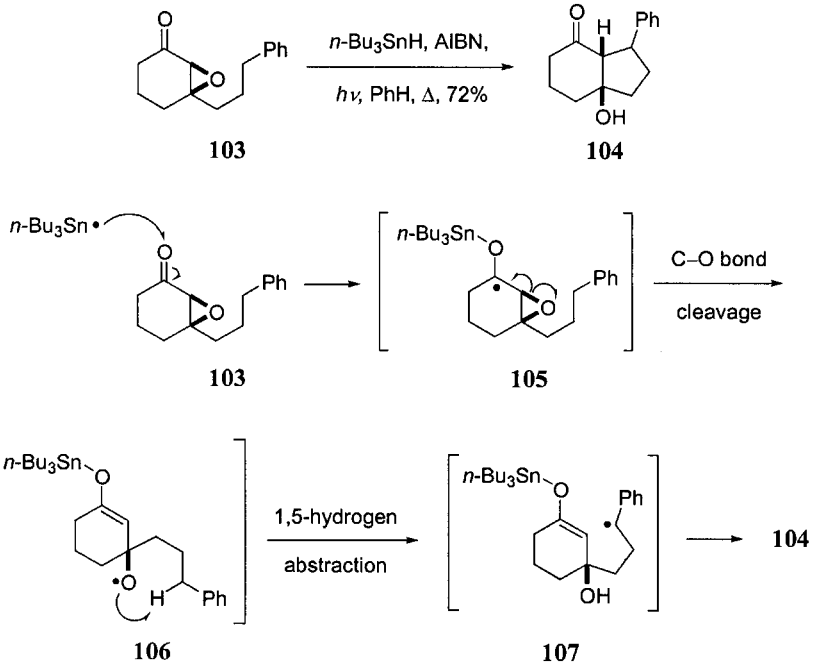
Polysubstituted tetrahydrofurans have been prepared by Feldman and Fisher using a free radical-mediated ('3+2') addition between aryl vinyl epoxides and alkenes.[49] A sense of asymmetric induction was achieved where *cis*-2,5-substitution was the major product as exemplified by tetrahydrofuran **88** from the reaction of phenyl vinyl epoxide **87** and *tert*-butyl acrylate (Scheme 22). As expected, oxiranylcarbinyl radical **89**, from addition of phenylthiyl radical to **87**, underwent a C–C bond scission to give enol ether radical **90**, which added to the acrylate from the less hindered site to furnish **91**. A 5-*exo-trig* cyclization of **91** was followed by a loss of phenylthiyl radical to deliver **88** (**88a**:**88b**=3:1).

3.4. From α-ketoepoxides

In the presence of tributyltin hydride, ketoepoxides are prone to be reduced to the ketone or α-hydroxyepoxide.[50] In the literature, both C–O and C–C bond cleavages have been recorded for radical-induced fragmentation of ketoepoxides.[51–53] Upon treatment of ketoepoxide **92** with *n*-butanethiyl radical, prepared from the reaction of *n*-butylthiol and AIBN, Murphy and coworkers observed only benzaldehyde and α,β-unsaturated aldehyde (Scheme 23).[51] Apparently, oxiranylcarbinyl radical **94** underwent a C–O bond cleavage to give alkoxyl radical **95**, which proceeded with a β-scission to furnish radical **96** as well as α,β-unsaturated aldehyde **93**. However, later experimental results[52] (vide infra) led the authors believe that it was possible that C–C bond cleavage may have also occurred and that the corresponding product decomposed simultaneously.



Scheme 25.



Scheme 26.

Scheme 27.

On the other hand, the Murphy group isolated both C–O bond cleavage product **98** (37% yield) and C–C bond cleavage product **99** (22% yield) when they treated keto-epoxide **97** with tributylstannyl radical (Scheme 24). They also used this example to model the vinyl ether formation in rifamycin S.[52]

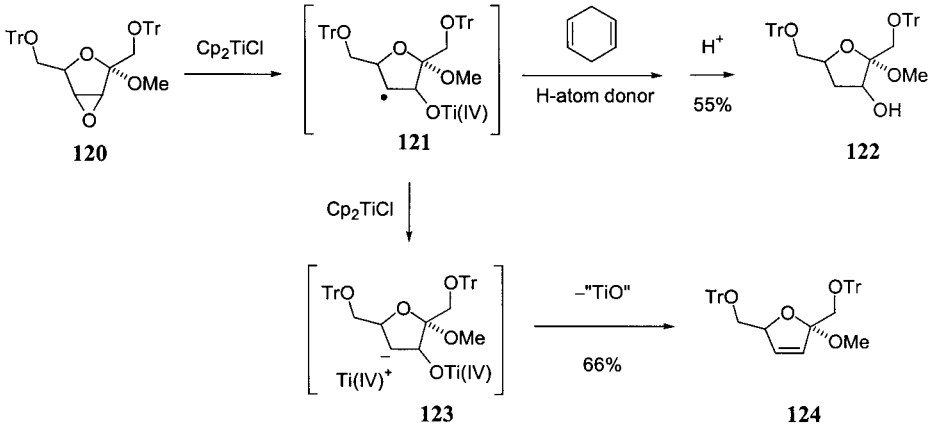
Contrary to a simple oxiranylcarbinyl radical with an aryl- or a vinyl substituent that undergoes C–C bond cleavage preferentially, C–O bond cleavage dominates for keto-epoxides with aryl substituents. As shown in Scheme 25, although photolysis of ketoepoxide **100** afforded 1,3-dioxole **101**, resulting from C–C bond cleavage,[54] irradiation in the presence of tributyltin hydride led to the C–O bond cleavage product as the 'aldol-adduct-like' β-hydroxyketone **102**.[55–57] The same results have also been observed by Ferreina and coworkers.[58,59]

Rawal took advantage of the radical intermediates generated from ketoepoxides to devise a tandem radical cyclization for the construction of carbocycles.[60] One example is shown in Scheme 26. The ketyl-like oxiranylcarbinyl radical **105** underwent a C–O bond fragmentation to give alkoxyl radical **106**. 1,5-Hydrogen abstraction of **106** resulted in benzyl radical **107**, which subsequently cyclized to secure bicyclic carbocycle **104** as *a single diastereomer*.

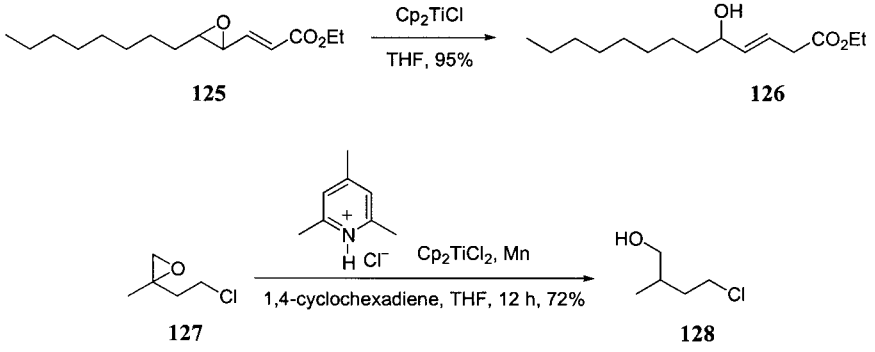
4. Radical reactions of epoxides mediated by Cp_2TiCl

In 1968, the Andrews' group observed the deoxygenation of epoxides by Cr(II) reagents.[61] Carbon-centered radicals were assumed to be the putative intermediates. During the last decade, titanium has emerged as an important transition metal in radical reactions. Elemental Ti has four 3*d* electrons, whereas Ti(III) and Ti(IV) have one and zero 3*d* electrons, respectively. Inspired by the analogy to the facile rearrangement of cyclopropanemethyl radical to homoallylic radical, Rajanbabu and Nugent generated radicals by treatment of epoxides with Cp_2TiCl, a paramagnetic Ti(III) species.[62–65] In Scheme 27, the σ-complex **108**, having a half-filled d orbital, represents an electronic analog of the cyclopropanemethyl radical. The C–O bond scission of **108** resulted in **109** from homolytic bond cleavage. This novel concept resulted in several synthetically useful transformations including selective reduction and deoxygenation of epoxides, as well as intra- and intermolecular C–C bond formation reactions.

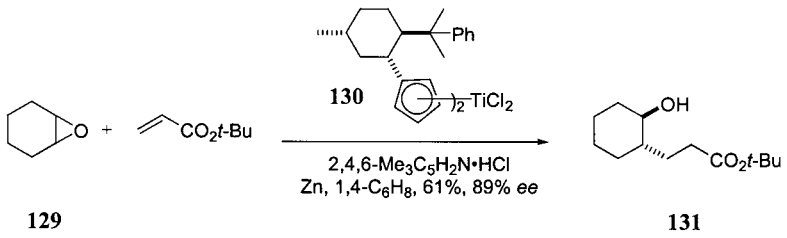
Free radical-mediated reduction and deoxygenation of epoxides may be exemplified by the reaction of methyl furanoside **120** and Cp_2TiCl in Scheme 28.[64,65] Treatment of epoxide **120** with one equivalent of Cp_2TiCl and 1,4-



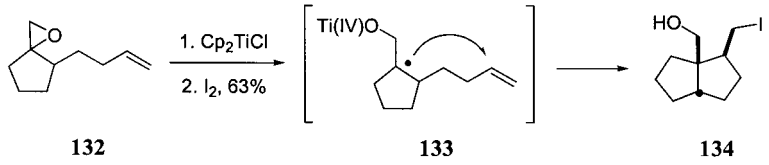
Scheme 28.



Scheme 29.



Scheme 30.

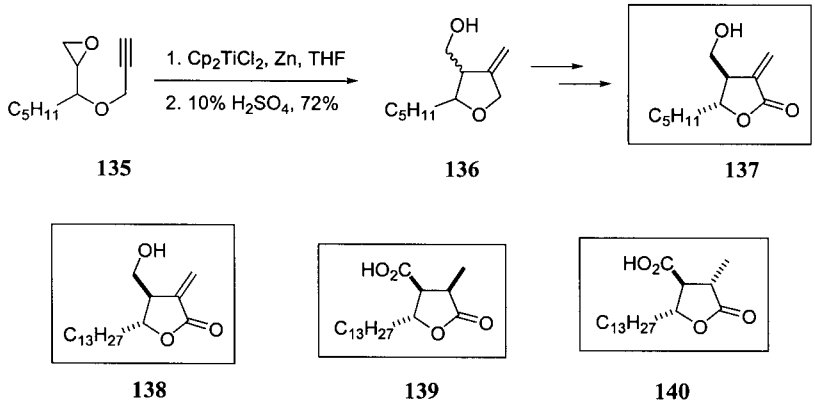


Scheme 31.

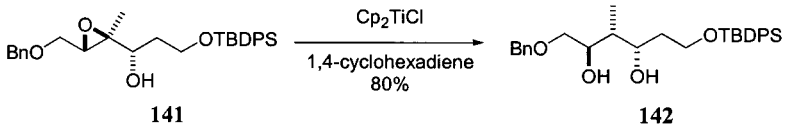
cyclohexadiene led to the reduction product **122**. 1,4-Cyclohexadiene served as a hydrogen atom donor to trap the radical intermediate **121**. On the other hand, deoxygenation product **124** was the major product when epoxide **120** was allowed to react with Cp_2TiCl in the absence of a hydrogen atom donor. Under this circumstance, anion **123**, derived from radical **121** by accepting an additional electron from Cp_2TiCl, expelled a putative 'TiO' unit to provide olefin **124**.

Many applications of radical reduction and deoxygenation of epoxides using titanocene reagents ensued. Epoxides **125** and **127** respectively, were reduced to the corresponding alcohols **126** and **128** with good yields and remarkable regioselectivity and functional group tolerance (Scheme 29).[66–69] At this point, transformation **127→128** is a good example to address the regiochemical issue of such reductions. Normally, the S_N2 reduction of an epoxide places the alcohol moiety on the more substituted site as the hydride added at the less hindered site. The radical-mediated reduction of epoxide **127** using Cp_2TiCl, on the other hand, gave alcohol **128** with the opposite regiochemistry as the S_N2 reduction due to a more stable radical intermediate on the highly substituted site. This is a particularly useful synthetic maneuver, offering additional opportunities for functionalizing epoxides.

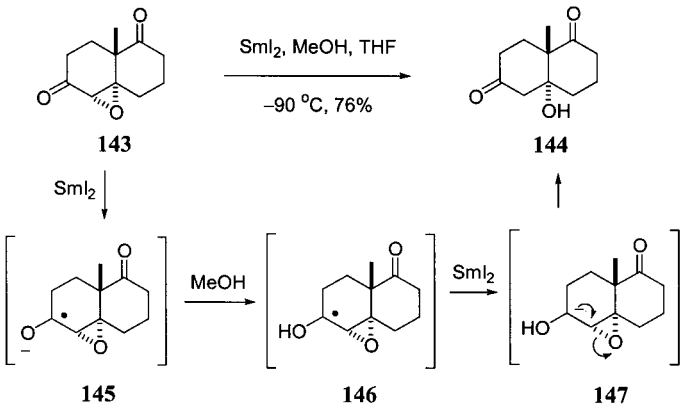
Utilizing chiral titanocene **130**, Gansäuer extended his epoxide reduction in **127→128** to an asymmetric process.[70] A range of 80–90% *ee* was obtained for the resultant alcohols from simple di-*sym*-substituted epoxides. More interestingly, trapping the radical anion intermediate with acrylates resulted in addition products. Epoxide **129** was coupled with *tert*-butyl acrylate to afford adduct **131** in 89% *ee* (Scheme 30). The corresponding epoxides with 5- and 7-membered



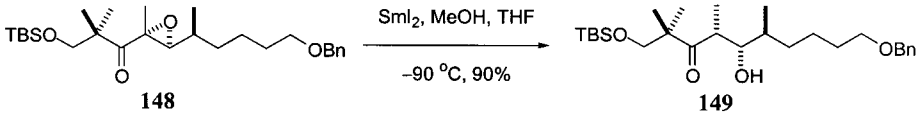
Scheme 32.



Scheme 33.



Scheme 34.



Scheme 35.

rings gave the desired adducts in 74 and 89% *ee*'s, respectively, reflecting the fitness of the substrates to the chiral pocket of the catalyst.

Logically, advantage has been taken of the radical intermediates such as **121** for further functionalization. In addition to the intermolecular coupling reactions described above,[70] many intramolecular coupling reactions have been reported to make bicyclic carbocycles. As shown in Scheme 31, Rajanbabu synthesized iodoalcohol **134** by treating vinyl epoxide **132** with Cp_2TiCl followed by I_2 quench,[63,65] presumably via the radical intermediate **133**.

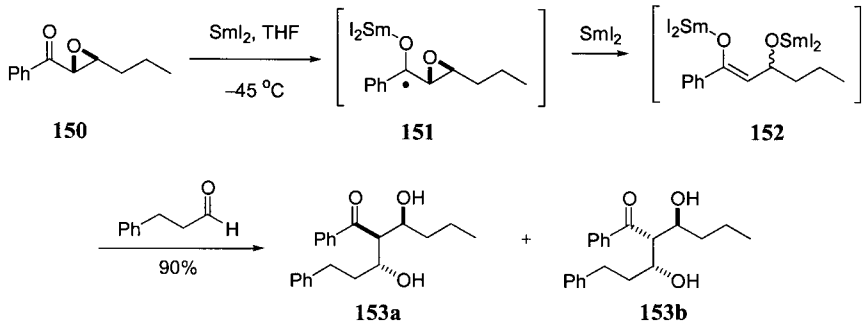
Roy et al. have accomplished the total syntheses of several polysubstituted tetrahydrofuran natural products utilizing the Ti(III)-mediated radical cyclizations of vinyl- or alkynylepoxides.[71–73] In Scheme 32, a Cp_2TiCl-mediated cyclization of alkynylepoxide **135** gave tetrahydrofuran **136** as a mixture of 5:1 *trans*:*cis* isomers.[71] Further manipulations of **136** then secured α-methylene-γ-butyrolactone **137**, (±)-methylenolactocin, an antibiotic isolated from *Penicillium sp*. (±)-Protolichesterinic acid (**138**), (±)-dihydroprotolichesterinic acid (**139**), and (±)-roccellaric acid (**140**) have also been synthesized in the same fashion.[72,73]

In addition, Cp_2TiCl has been found to be an efficient deoxygenation reagent for reducing α,β-epoxyketones to the corresponding enones.[74]

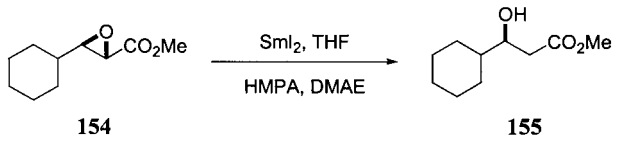
In the synthesis of the octenoic moiety of cryptophycins, Chakraborty and Das utilized Cp_2TiCl to conduct a diastereoselective ring opening of trisubstituted epoxy alcohols.[75,76] A 5:1 ratio of diastereomers of diol **142** was obtained upon treatment of hydroxyepoxide **141** with Cp_2TiCl and 1,4-cyclohexadiene (Scheme 33). The authors proposed a six-membered cyclic Ti(IV)-intermediate that governed the stereoselectivity. Apparently, this radical-mediated epoxide ring-opening here gave the opposite regiochemistry to an S_N2 hydride approach where the hydride attacks the sterically less hindered site. In addition, such a mild radical-mediated anti-Markovnikov ring opening provided an additional means of establishing chiral 1,3-diol substructures.

5. Radical reactions of epoxides mediated by SmI_2

Samarium falls into the category of lanthanide metals. Samarium(II) diiodide (SmI_2), as either a single or a double



Scheme 36.



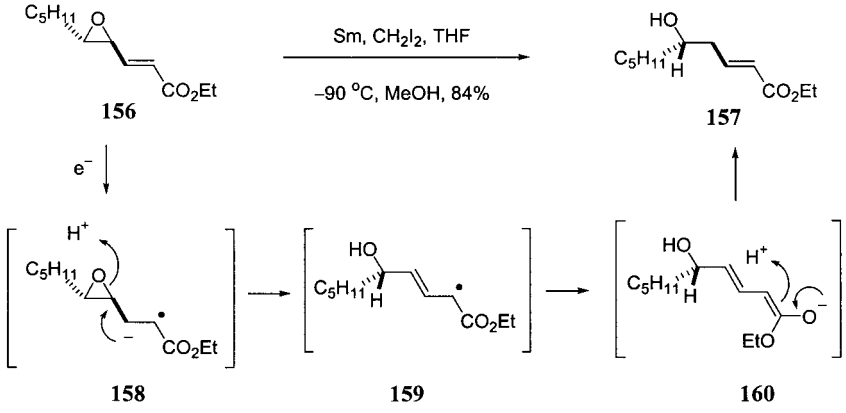
Scheme 37.

electron source, has emerged as an extremely useful reagent in organic synthesis, providing a rich repertoire of chemistry.[77] The oxophilicity of samarium(II) plays an important role in the outcome of radical reactions mediated by SmI_2. In 1980, deoxygenation of epoxides to olefins by SmI_2 was revealed by Kagan et al.[78] During the ensuing two decades, SmI_2 has proven to be a very versatile, exceedingly mild, and selective reagent in reduction and coupling reactions. For example, reduction of α-ketoepoxides using SmI_2 afforded β-ketoalcohols as exemplified by transformation **143→144** (Scheme 34).[79] The mechanism was assumed to be akin to that of a dissolving metal reduction. Thus, a single electron-transfer from SmI_2 to ketoepoxide **143** gave ketyl **145**, which was subsequently protonated by methanol to form radical **146**. An additional single electron-transfer from a second molecule of SmI_2 to **146** then afforded carbanion **147**, which readily underwent a facile ring opening, an enol tautomerization, and subsequent protonation to deliver β-ketoalcohol **144**.

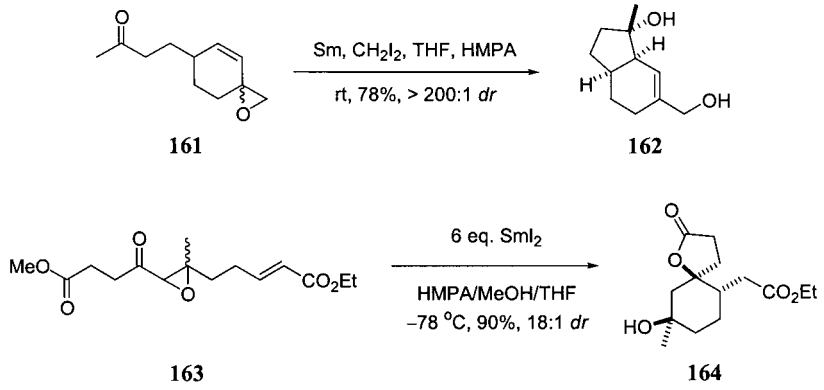
It is well established that SmI_2 opens α-ketoepoxides at the α-carbon. In Chakraborty's synthesis of C_1–C_{12} segment of epothilones,[75,80] Cp_2TiCl-mediated reduction of the corresponding hydroxyepoxide analog of **148** provided mostly the allylic alcohol over the desired anti-Markovnikov ring opening product (Scheme 35). However, SmI_2-induced radical opening of trisubstituted epoxide **148** secured alcohol **149** as the only diastereomer from the reduction of the ketoepoxide **148**.

Trapping the dianion intermediates generated from the reaction of ketoepoxides and SmI_2, Mukaiyama's group has synthesized 'bis-aldol' adducts.[81] Ketyl **151**, derived from α-ketoepoxide **150** and SmI_2, was transformed to samarium enolate **152** by reacting with another equivalent of SmI_2 (Scheme 36). The 'bis-aldol' adducts **153a** and **153b** were obtained in a 35:65 ratio from the reaction of **152** with hydrocinnamaldehyde. Again, the stereoselectivity arose from the steric bias as the result of a six-membered cyclic Sm(III)-intermediate.

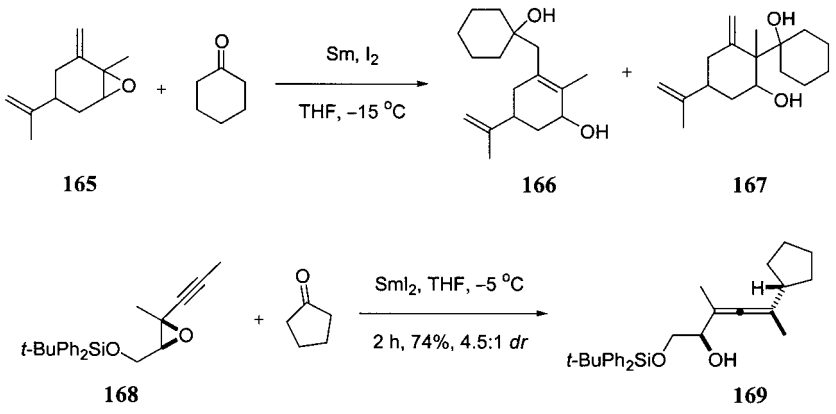
Reduction of α,β-epoxyesters using SmI_2 gave β-hydroxyesters in a highly regioselective fashion. The mechanism was very likely to resemble that of transformation **143→144**. As delineated in Scheme 37, Inanaga found that addition of *N*,*N*-dimethylaminoethanol (DMAE) as a proton source to the SmI_2-THF-HMPA system resulted in high regioselectivity for reductions such as **154→155**.[82] Since β-hydroxyester **155** may be also synthesized using appropriate aldol chemistry, SmI_2-induced reduction of



Scheme 38.

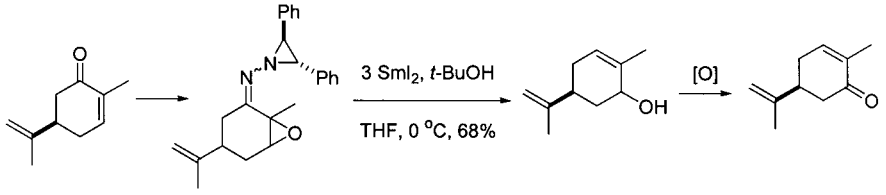


Scheme 39.



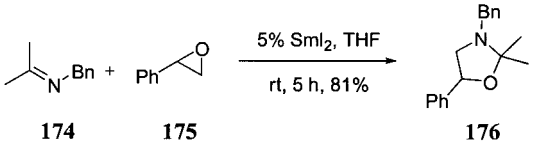
165 166 167 168 169

Scheme 40.



170 171 172 173

Scheme 41.



174 175 176

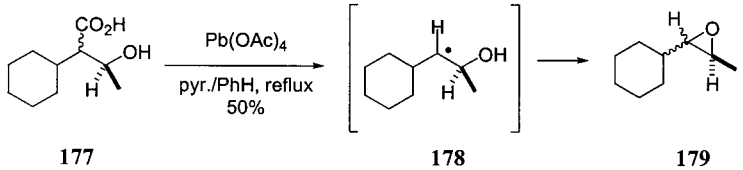
Scheme 42.

α,β-epoxyesters provided a mild alternative to the aldol condensation. Under similar reaction conditions, dialkyl-epoxides were deoxygenated to the corresponding dialkyl-olefins[83] in accord with Kagan's observation.[78]

The Molander group has made great strides in the applications of SmI_2 in organic synthesis including its reactions with a variety of epoxides. In addition to ketoepoxide **143**,[79] they also investigated the behavior of vinyl epoxides.[84–87] In transformation **156→157** in Scheme 38, a single electron transfer from SmI_2 to vinyl epoxide **156** led to radical anion **158**. The ring-opened product as allylic alcohol **159** then absorbed another electron to give enolate **160**, which was then protonated to provide **157**.

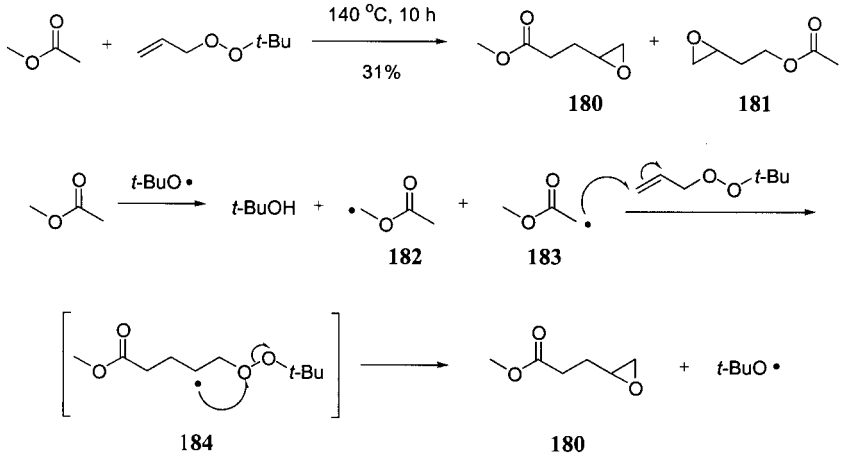
In addition, Molander and coworkers also investigated the chemistry of a variety of vinyl epoxides under the SmI_2-mediated conditions. Intramolecular ketyl–olefin cyclization of distal epoxy olefin **161** led to bicyclic diol **162** with excellent stereoselectivity as shown in Scheme 39.[85] The high diastereoselectivity was attributed to the oxophilicity of samarium ions that allowed chelation of HMPA to occur and thereby increased the steric bulk around the ketyl oxygen. Operating under a similar mechanism, sequential epoxide fragmentation/radical cyclization of substrates with multiple functional groups also gave carbocycles as in transformation **163→164**.[86,87] However, the diastereoselectivities of SmI_2-mediated reactions for epoxides bearing multiple functional groups are substrate-dependent, ranging from poor to excellent.

Aurrecoechea reported intermolecular coupling reactions between alkynyloxiranes and vinyloxiranes with ketones.[88,89] The coupling between vinyloxirane **165** and cyclohexanone furnished diol **166** and its isomer **167** with the isolated double bond kept intact,[88] whereas alkynyl-oxirane **168** coupled with cyclopentanone to afford

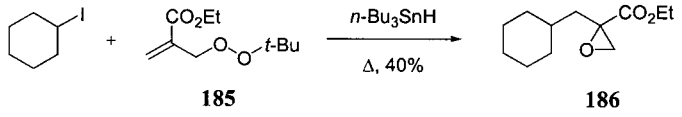


177 178 179

Scheme 43.



Scheme 44.



Scheme 45.

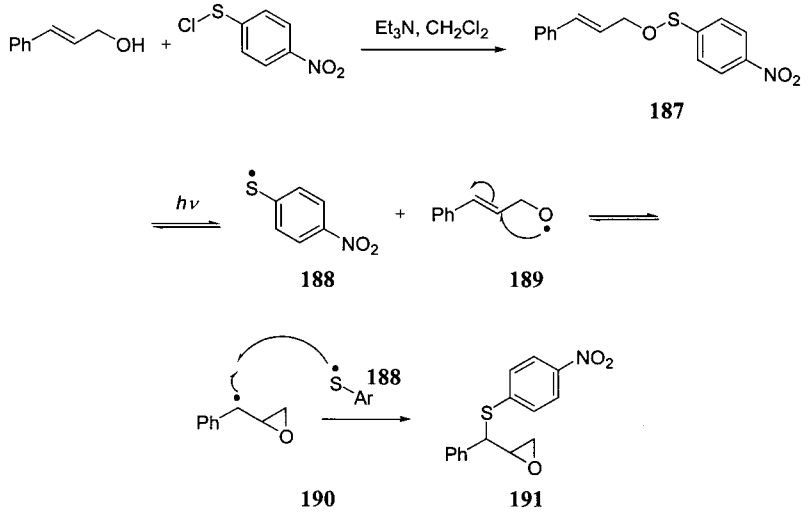
allenyldiol **169** (Scheme 40).[89] In both cases, the Sm(II)-bound ketyl radical/anion was the putative intermediate.

An unusual iodination reaction of 2,3-epoxycyclohexanone hydrazone using SmI_2 was observed by Kang and coworkers.[90] Reduction of epoxy hydrazone **171**, derived from (*R*)-(−)-carvone (**170**), prevailed when it was treated with SmI_2, giving rise to cyclohexenol **172** (Scheme 41). The oxygen transposition product (*S*)-(+)-carvone (**173**) was subsequently obtained after a Swern oxidation of alcohol **172**.

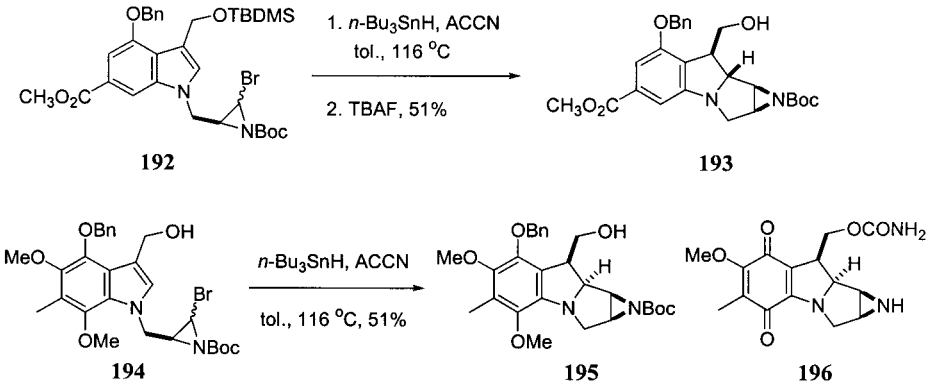
Recently, the Ishii group described a novel approach to 1,3-oxazolidines from imines and epoxides by samarium catalysis.[91] As shown in Scheme 42, using *catalytic* SmI_2, imine **174** reacted with terminal epoxide **175** to give 1,3-oxazolidine **176**. The method worked well for terminal epoxides, whereas internal epoxides gave low yields.

6. Epoxide formation via radical intermediates

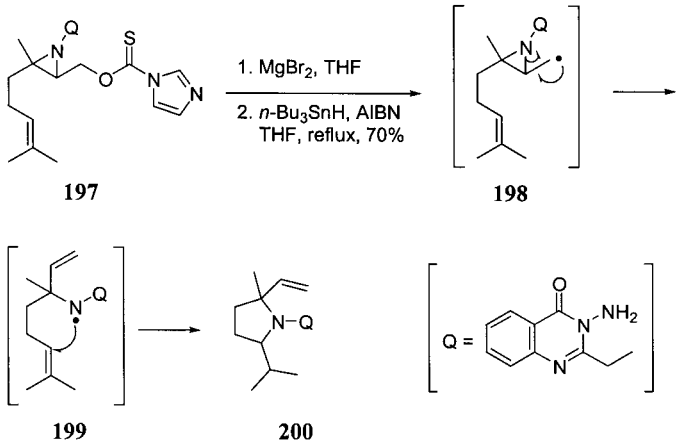
In 1963, Corey observed an epoxide formation from $Pb(OAc)_4$-mediated oxidative decarboxylation of a β-hydroxy acid.[92] In 1984, Walling recorded a similar observation using Cu(II).[93] In 1990, Snider and Kwon investigated epoxide formation from β-hydroxy radicals generated by the decarboxylation of a β-hydroxy acid with $Pb(OAc)_4$.[94] Secondary radical **178**, prepared from treatment of β-hydroxy acid **177** with $Pb(OAc)_4$, cyclized to afford **179** as a mixture of diastereomers in which the ratio of α-cyclohexyl isomer to β-cyclohexyl isomer was



Scheme 46.



Scheme 47.



Scheme 48.

14:1 (Scheme 43). The ratio was only 4:1 when the same reaction was carried out using $Cu(OAc)_2$ in place of $Pb(OAc)_4$.

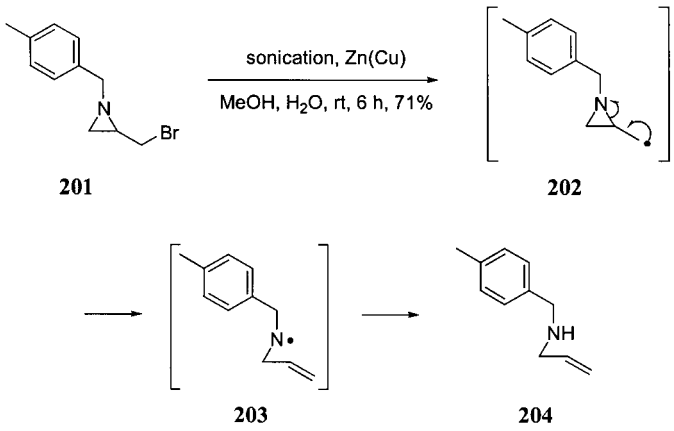
Montaudon and coworkers described an epoxide formation from allylic *tert*-butylperoxide via the radical pathway.[95,96] Thermolysis of allyl *tert*-butylperoxide in methyl acetate as the solvent led to epoxides **180** and **181**, reflecting the low selectivity with which the *tert*-butyloxyl radical abstracted from both electron-deficient and electron-rich α-C–H groups on AcOMe (Scheme 44). Mechanistically, hydrogen abstraction of AcOMe by *tert*-butyloxyl radical gave intermediates **182** and **183**. Addition of radical **183** to allyl *tert*-butylperoxide yielded adduct **184**, which rapidly underwent an epoxide cyclization to deliver epoxide **180**. Meanwhile, epoxide **181** was generated in the same fashion.

The chemoselectivity for the aforementioned reaction was greatly improved using amine-boranes as polarity reversal catalysts. Roberts' group synthesized α-carbonyl epoxides as the *only* products from allylic *tert*-butyl peroxide using $Me_3N{\rightarrow}BH_2Bu$ as the catalyst.[97,98] In comparison to the alkoxyl radical-initiated reactions, not only do the amine-borane catalysts preferentially abstract the electron-deficient α-C–H (α to the carbonyl), these polarity reversal catalysts also allow the reactions to be run at low temperature. In 1995, another variant of this kind of epoxide formation appeared in which epoxide **186** was obtained from the reaction of cyclohexyl iodide and ethyl *tert*-butylperoxyethylpropenoate **185** in the presence of n-Bu_3SnH (Scheme 45).[99]

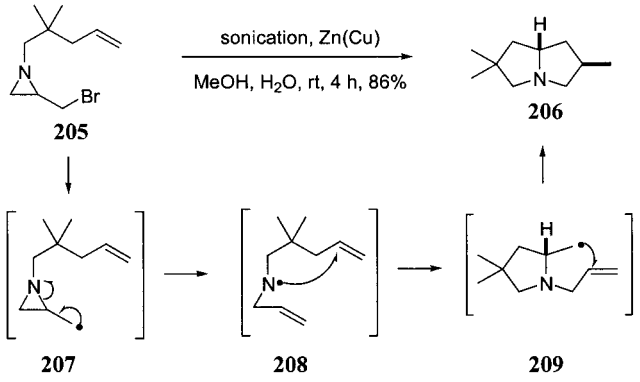
Recently, Wiest reported an epoxide formation by ring closure of the cinnamyl radical.[100] As shown in Scheme 46, under photolysis conditions, 4-nitrobenzenesulfenate **187**, derived from cinnamyl alcohol and 4-nitrobenzenesulfenyl chloride, underwent a homolytic C–O bond cleavage to give 4-nitrobenzenethiyl radical **188** and cinnamyloxy radical **189**. Oxiranyl benzyl radical **190**, derived from cyclization of **189**, subsequently coupled with thiyl radical **188** to give epoxide **191**. In this case, the 4-nitrobenzene motif performed a dual role–serving as a chromophore as well as stabilizing the thiyl radical via the electron-withdrawing properties.

7. Aziridinyl radicals

Carbon-centered aziridinyl radicals first became known in the 1970s.[101] In 1994, Ziegler reported an intramolecular radical cyclization of chiral aziridinyl radicals onto indole rings.[102] The results were reminiscent of those of its oxiranyl radical counterpart (cf. transformation **1**→**3**+**4**+**5**). In addition, the method has been successfully applied to the synthesis of mitomycin-like antitumor agents.[103,104] Cyclization of bromoaziridine **192** under the influence of tri-*n*-butyltin



Scheme 49.

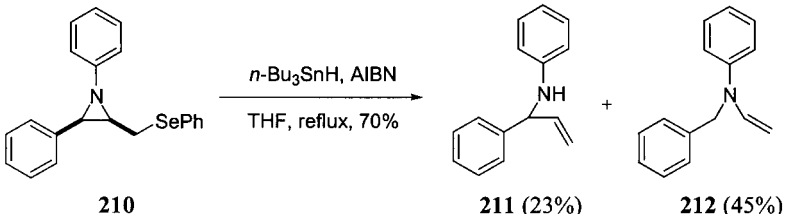


Scheme 50.

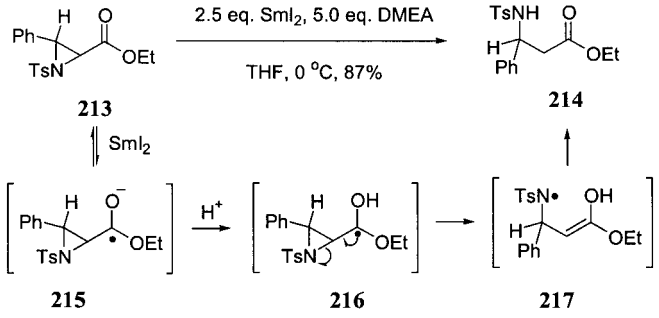
hydride and 1,1′-azobis(cyclohexylcarbonitrile) (ACCN) furnished indoline **193** in 51% yield after desilylation (Scheme 47).[103] An electron-withdrawing group at the C(3) position of the starting material indole was not necessary. Further oxidation of **193** provided an entry to the core nucleus of FR-900482. In a similar fashion, the aziridinyl radical generated from bromoaziridine **194** led to indoline **195**, which was manipulated further to provide (+)-9a-desmethoxymitomycin A in an additional seven steps.[104]

8. Aziridinylcarbinyl radicals

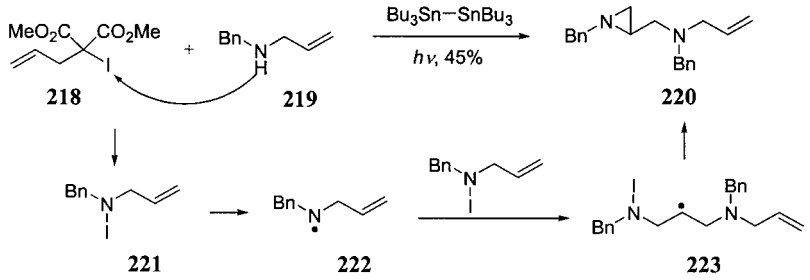
Early observations by the Stamm group indicated that the aziridinylcarbinyl radicals generated from *N*-acyl aziridines suffered C–N bond cleavage preferentially.[105,106] In Murphy's studies, it was also found that the C–N bond cleavage was predominant for the aziridinylcarbinyl radicals generated from xanthates.[107,108] As shown in Scheme 48, geraniol-aziridine-xanthate **197**, prepared from the reaction of geraniol and 3-amino-ethyl-4(3*H*)-quinazolinone (Q) followed by treatment with thiocarbonyldiimidazole, was transformed to pyrrolidine **200** in 70% yield under the radical-mediated conditions. Magnesium bromide was believed to stabilize the aminyl radical anion



Scheme 51.



Scheme 52.



Scheme 53.

199, a product of the C–N bond scission of the aziridinylcarbinyl radical **198**.

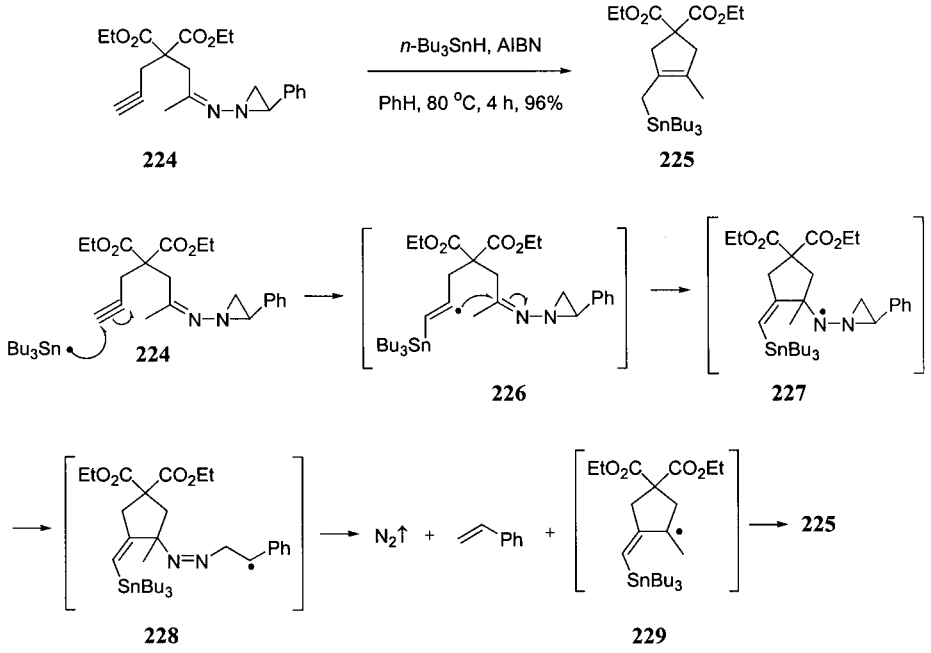
De Kimpe et al. synthesized a stable precursor to an aziridinylcarbinyl radical, 2-bromomethylaziridine **201** (Scheme 49).[109] Radical **202**, derived from sonication of **201** in the presence of a zinc–copper couple, broke the C–N bond preferentially, giving rise to aminyl radical **203** and then allylamine **204**. They also observed a similar outcome for the radical-induced ring opening of 2-phenylselenylmethylaziridine.[110]

Taking advantage of the intermediacy of the aminyl radical, De Kimpe et al. devised a radical cascade to synthesize pyrrolizidine **206** from 2-bromomethylaziridine **205** with a pendant terminal olefin (Scheme 50).[111] Apparently, aminyl radical **208** underwent a 5-*exo-trig* cyclization to afford **209**, which subsequently cyclized to furnish pyrrolizidine **206**, also in a 5-*exo-trig* fashion.

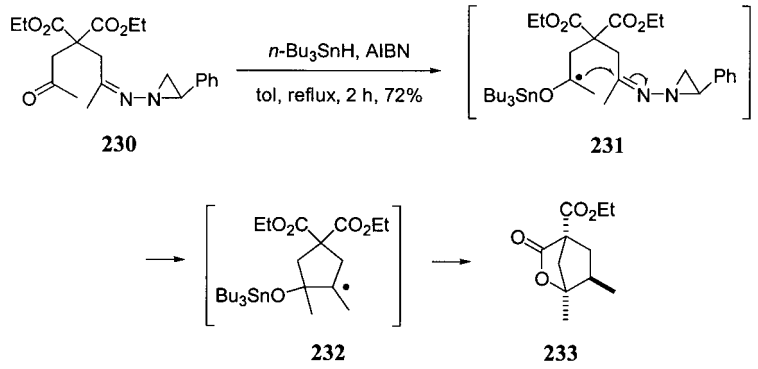
In accord with the aforementioned examples, Marples reported an exclusive C–N bond cleavage of the aziridinylcarbinyl radical.[112] However, when there was an aryl substituent on the aziridine, C–C bond cleavage occurred as illustrated by Schwan and Refvik.[113] The aziridinylcarbinyl radical generated from **210** gave both C–N bond cleavage product **211** and the C–C bond cleavage product **212** (Scheme 51).

As depicted in Scheme 52, Molander and Stengel investigated the reduction of 2-acylaziridines by SmI_2.[114] β-Aminoester **214** was obtained when aziridinyl ester **213** was treated with SmI_2 in the presence of *N*,*N*-dimethylethanolamine (DMEA). The product resulted from a C–N bond cleavage of the aziridinylcarbinyl radical **216**. No C–C bond cleavage product was detected in spite of the presence of a phenyl substituent. Similar results were observed for the corresponding aziridinyl ketones and amides.

A rare example of aziridine synthesis via the radical pathway was serendipitously discovered by Flynn and Zabrowski.[115] In an effort to prepare the azabicycles by treating iodomalonate **218** with *N*-benzylallylamine (**219**) in the presence of hexabutylditin, aziridine **220** was the only product isolated instead of the desired azabicycle (Scheme 53). In this case, **218** served as an iodinium source, which reacted with **219** to afford *N*-iodo species **221**.



Scheme 54.



Scheme 55.

Homolytic cleavage of **221** led to aminyl radical **222**. The combination of **221** and **222** gave rise to radical **223**, which subsequently cylized to aziridine **220**.

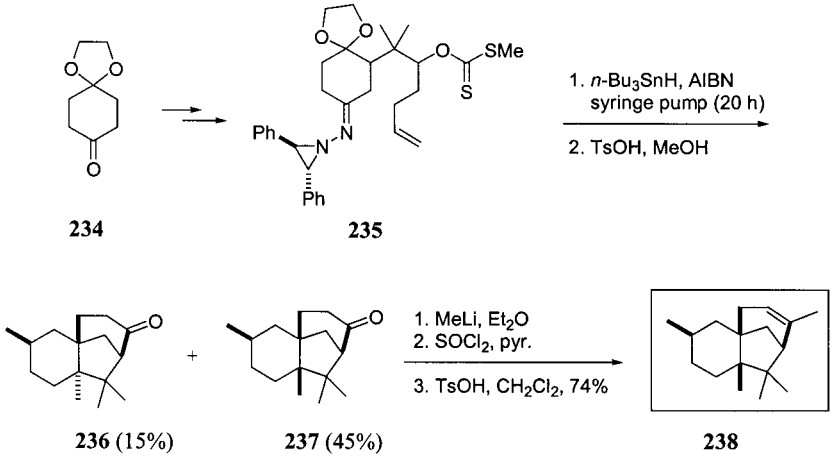
9. *N*-Aziridinyl imines in radical chemistry

Kim pioneered the application of *N*-aziridinyl imines in radical chemistry by taking advantage of the ease with which aziridine rings tend to ring-open to release the ring strain.[116,117] *N*-Aziridinyl imines are very unique in radical chemistry because they serve as *radical acceptors as well as radical donors* as illustrated by transformation **224→225** in Scheme 54. Aziridinyl aminyl radical **227**, formed from the 5-*exo-trig* cyclization of the initially generated vinyl radical **226** (here *N*-aziridinyl imine was a radical acceptor), underwent a β-fragmentation via the C–N bond cleavage to give radical **228**. Releasing a nitrogen molecule from **228** was thermodynamically favored, giving rise to a molecule of styrene and radical **229** as a radical donor, which further isomerized and abstracted a hydrogen to deliver **225**.

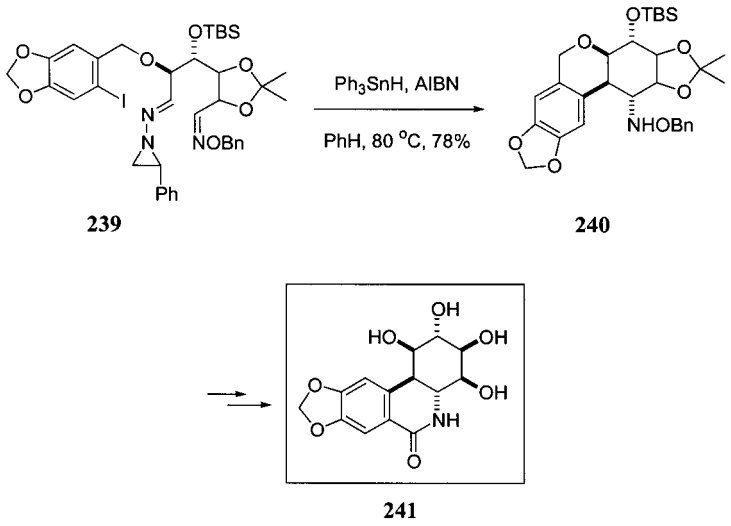
In addition to alkynes such as the one in **224**, carbonyl groups including both aldehyde and ketone can also form radical precursors using *N*-aziridinyl imines as radical acceptors.[118] As illustrated in Scheme 55, treatment of keto-*N*-aziridinyl imine **230** with Bu_3SnH-AIBN led to lactone **233**, presumably via radical **231** and subsequently **232**. It is worth noting that the alkyne moiety is more reactive when a substrate has both alkyne and carbonyl groups.

The aforementioned method has found applications in the synthesis of several natural products. In the total synthesis of α-cedrene **238** (Scheme 56),[119] the tandem radical cyclization precursor **235** was prepared from mono-protected cyclohexanedione **234**. Under high dilution conditions, stereoselective cyclization of *N*-diphenylaziridinylimine **235** furnished two diastereomers **236** and **237** after acidic hydrolysis. The pivotal cyclization step was remarkably efficient as four stereogenic centers including a quaternary carbon were established in a single step. To this end, the major diastereomer **237** was transformed to the natural product **238** via conventional methods. Furthermore, syntheses of *dl*-modhephene,[120] zizaene,[121] and *dl*-pentalenene have also been accomplished via the cascade radical cyclization of *N*-aziridinyl imine substrates.[122]

The remarkable property of *N*-aziridinyl imines as both radical acceptors and radical donors was elegantly showcased in Keck's total synthesis of (+)-7-deoxypancratistatin **241** (Scheme 57).[123] Using the triphenyltin hydride protocol, the tandem 6-*endo-trig*/6-*endo-trig* radical cyclization of substrate **239** proceeded cleanly to afford **240** as *a single diastereomer*, which was converted to (+)-7-deoxypancratistatin **241** using conventional transformations.



Scheme 56.

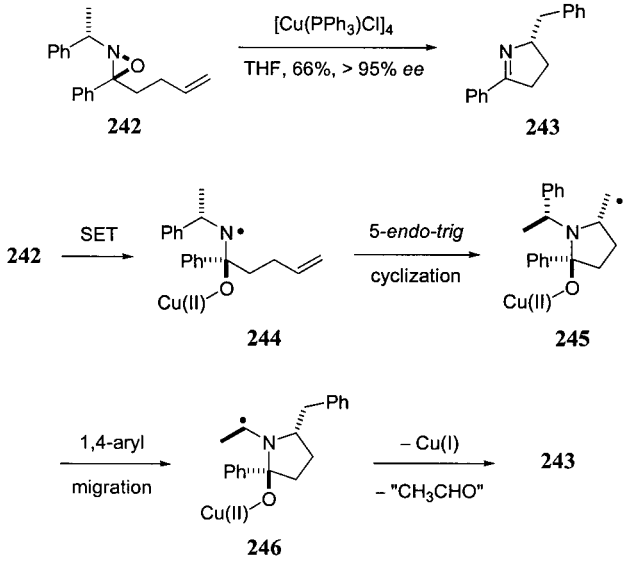


Scheme 57.

Due to the success of these examples, it is expected that the *N*-aziridinyl imine method in radical chemistry will find more applications in the synthesis of complex natural products.

10. Radical chemistry of oxaziridines, thiiranes, and dioxiranes

The last two decades have witnessed a proliferation in the utilization of oxaziridines as oxidants (e.g. in asymmetric hydroxylation[124]). In contrast, there are limited reports on their synthetic utilities in radical chemistry. Early studies revealed that iron(II) salts react with oxaziridines to give aminyl radicals,[125,126] whereas alkoxyl radicals were generated using photochemistry.[127,128] The Hudson group detected *N*-centered oxaziridinyl free radicals using E.S.R. by treatment of 3,3-disubstituted oxaziridines with PbO_2 in CCl_4.[129] More interestingly, Aubé's group demonstrated new Cu(I)-catalyzed reactions of oxaziridines via *N*-centered radicals.[130,131] They synthesized pyrroline (*S*)-**243** in 66% yield and greater than 95% ee by treatment of 3-butenyloxaziridine **242** with $[Cu(PPh_3)Cl]_4$ in THF heated at reflux (Scheme 58). Mechanistically, single-electron transfer from the Cu(I) salt fragmented **242** to afford *N*-centered radical/alkoxide pair **244**, a radical anion, which subsequently diastereoselectively cyclized to carbon-centered radical **245**. The next step, 1,4-aryl migration, was thermodynamically favored because the adjacent nitrogen stabilized the resulting radical **246**. Finally, formal loss of Cu(I) and acetaldehyde then led to pyrroline (*S*)-**243**.



Scheme 58.

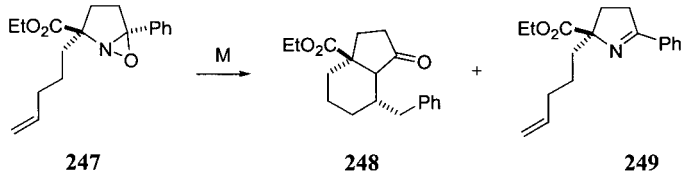
Radical cyclization of alkenyl oxaziridine **247** to bicyclic lactam **248** and pyrroline **249** followed analogous pathways (Scheme 59).[132] The product distribution depended on the nature of the transition metal catalyst—M=Fe, Sn, or Cu.

Many desulfurization processes of thiiranes involve radical intermediates. Kamata prepared aryl-substituted olefins via desulfurization of thiiranes catalyzed by aminium radical salts such as $(p\text{-}BrC_6H_4)_3N^+\cdot SbCl_6^-$.[133,134] Treatment of thiirane **250** with tributyltin hydride in the presence of AIBN led to the desulfurization product **252** (Scheme 60).[135] Presumably, addition of the tributyltin radical triggered the C–S bond cleavage, giving rise to β-thioalkyl radical **251**. Subsequent elimination of thiyl radical from the unstable radical **251** then afforded olefin **252**. In addition, desulfurization of thiiranes using a tributyltin hydride-triethylborane system was the key operation in Uenishi's transformation from geraniol to (+)- and (−)-linalool.[136]

Finally, despite the wide use of dioxiranes in oxidation processes, especially in epoxidation reactions, the mechanisms are not well understood. Nonetheless, it is generally believed that alkoxyl radical intermediates are involved in these oxidation reactions.[137,138]

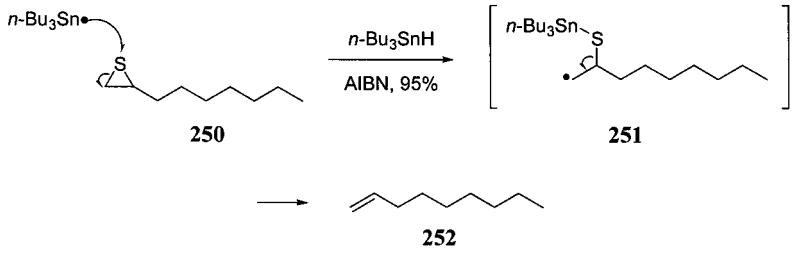
11. Concluding remarks

Three-membered heterocycles are unique in radical chemistry because of the ease of ring-opening to release



247 248 249

Scheme 59.



250 251

252

Scheme 60.

the ring-strain. With the advancement of organic chemistry has come a great collection of methods to synthesize epoxides and aziridines in an asymmetric fashion. These chiral substrates are practical precursors for further manipulations using radical chemistry in which the oxiranylcarbinyl radical has seen the most abundant applications. In addition to the advantage of tolerating a variety of functional groups, radical cascade reactions are routinely done to achieve good atom economy. Furthermore, radical chemistry mediated by transition metals such as Cp_2TiCl and SmI_2 have proven to be very powerful tools in synthesis without the use of toxic tin reagents. It is expected that radical chemistry will find its way to medicinal and combinatorial chemistry.

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Biographical Sketch

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