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Free Radical-Mediated Ring Expansion and Related Annulations

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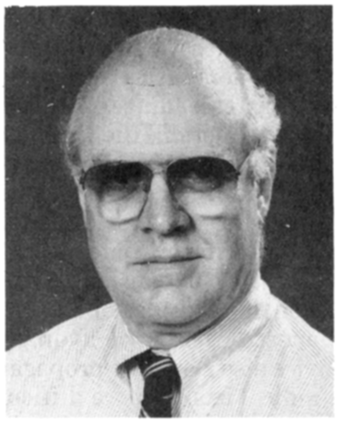
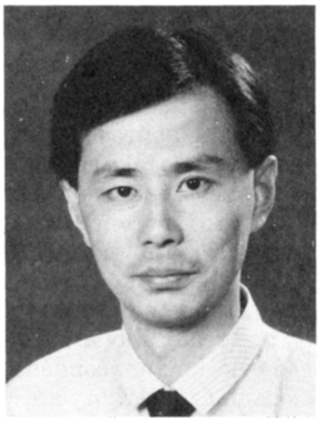


Paul Dowd is a native of Massachusetts. He received his A.B. degree in chemistry from Harvard College in 1958 and, in 1962, his Ph.D. from Columbia University. In 1970, he joined the faculty of the University of Pittsburgh. His current research includes the pursuit of old and new diradicals of the non-Kekulé class, the delineation of the mechanism of action of vitamin K and of vitamin B_{12}, and the development, with Wei Zhang, of new, free radical-based, synthetic methods.



Wei Zhang was born in Jiangsu in the People's Republic of China. He received his B.S. degree in chemistry from Nanjing University in 1982. After working as an analytical chemist at the Jiangsu Pesticide Research Institute for a few years, he enrolled as a graduate student in the Department of Chemistry at Pittsburgh in 1989. His research has been focused on the development of cyclobutanone-based ring expansion and annulation reactions. He is currently completing his Ph.D. thesis in this area and will be a Research Assistant Professor associated with Paul Dowd's group in the fall.

I. Introduction

During the development of organic chemistry, five- and six-membered rings received the major share of systematic synthetic attention, and justifiably so. However, many organic substances of interest contain larger rings, and it has become important to explore and develop new avenues of approach to appropriately functionalized medium and large rings.

Three general methods leading to the synthesis of medium rings have been outlined by Hesse in his outstanding recent monograph.[1a] This review will emphasize two approaches: chain insertion (eq 1) and ring annulation (eq 2), both with bond cleavage. The focus of this review will be on recently developed free radical methods for ring expansion and related annulations. Ionic methods have an essential place in ring expansion, and they have been well reviewed earlier by Gutsche[2a] and, more recently, by Hesse,[1] Haufe and Mann,[2b] and Wovkulich.[2c]

The advantages of free radicals in synthesis[3] have been enumerated on many occasions and include ease of execution, compatibility with a wide range of functional groups, as well as capability of specific generation at designated sites. The negative side of the picture should also be considered. In many free

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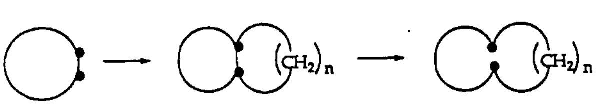


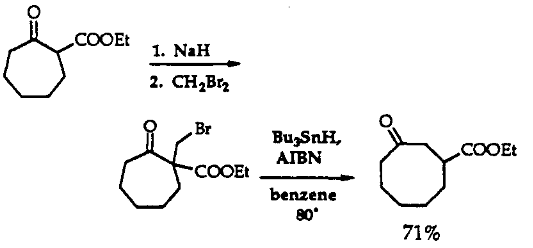
(2)

radical reactions, the desired outcome is one among several possible competing paths. It is the task of the experimenter to devise reaction conditions favoring the desired path at the expense of undesirable ones. The most common occurrence, when tri-*n*-butyltin hydride is used as the radical-generating reagent, is competitive hydrogen atom transfer leading to direct reduction. To circumvent direct reduction, the tin hydride reaction is often conducted under high dilution conditions by slow, syringe pump addition of the reagent. The chain transfer step involving tin hydride is then retarded, allowing time for the intermediate radicals to undergo rearrangement or ring expansion. Other strategies involve the use of the hydrides of silicon[4] and germanium,[5] which have stronger metal–hydrogen bonds than tin, but this device also slows the propagation step and can make the radical chains more difficult to sustain. Atom transfer[6] provides another potential solution to this problem and carries the advantage that radical-promoted transformations can be carried out in the absence of reducing agent. However, atom transfer can be quite sensitive to substitution, often requiring activating groups in the starting radical. Thiohydroxamates (Barton method) have also been used in the free radical reactions.[7]

II. Ring Expansion of β-Keto Esters

A. One-Carbon Ring Expansion

An attractive way to approach the synthesis of medium and large rings is to take advantage of existing ring structures. It is also important to devise methods of sufficient generality so that functional groups needed for subsequent transformations can be incorporated into the method. In their first approach to the ring expansion problem, Dowd and Choi[8,9] took advantage of the availability and ready alkylation of β-keto esters derived from the Dieckmann condensation. Thus, methyl 1-oxocycloheptane-2-carboxylate is readily alkylated with methylene dibromide (eq 3). The adduct is then treated in refluxing benzene with tri-*n*-butyltin hydride whereupon ring expansion to the eight-membered ring occurs smoothly and in good yield.

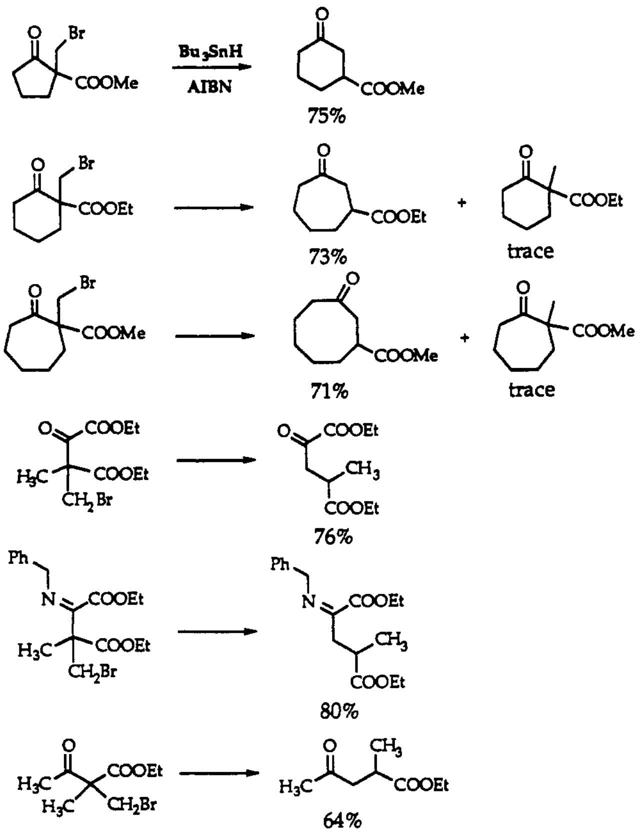


(3)

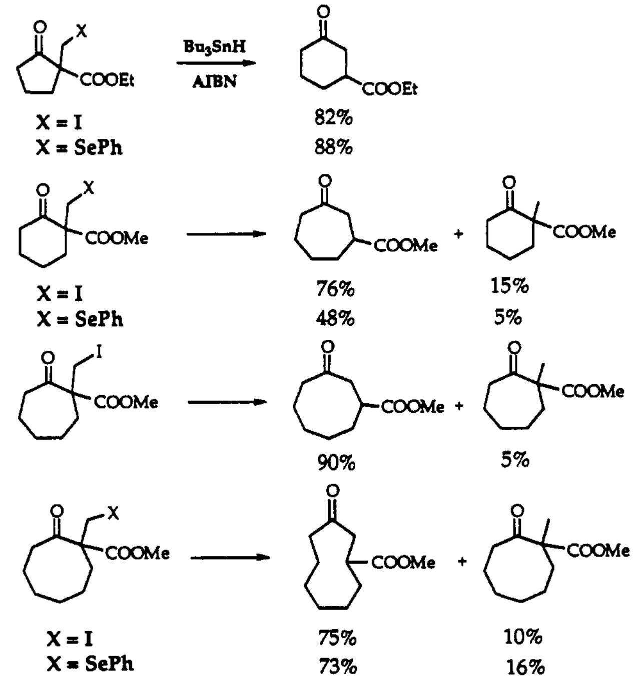
One-carbon ring expansion of β-keto esters is a straightforward, broadly based procedure with many potential applications. Several additional examples, including chain extension reactions, are shown in Table 1, part A.

Table 1. One-Carbon Ring Expansion

A. Bromomethyl Derivatives



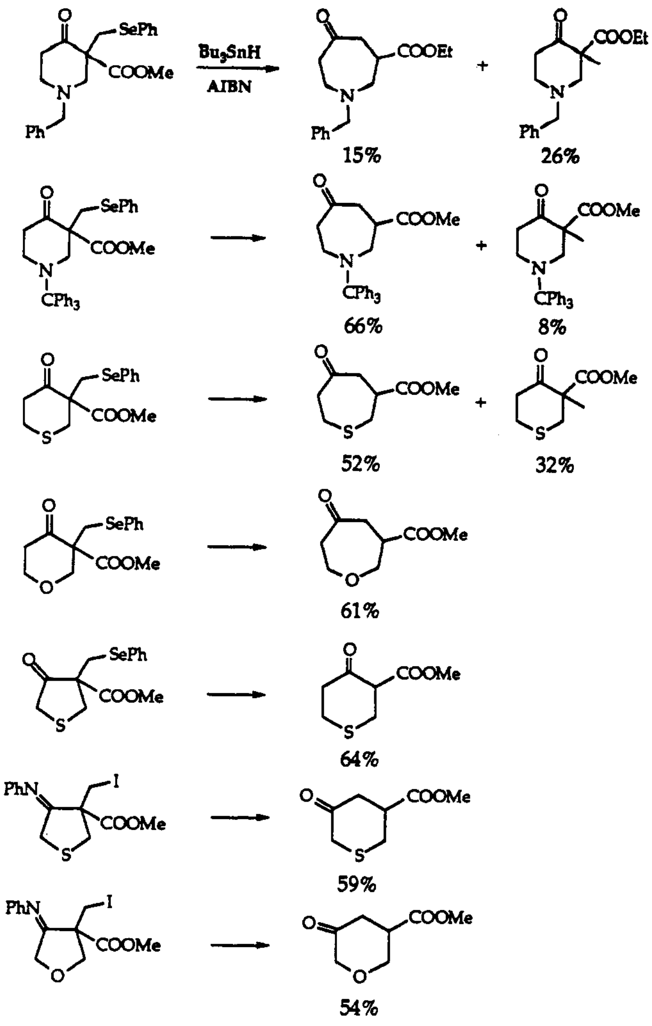
B. Iodomethyl and Selenophenylmethyl Derivatives



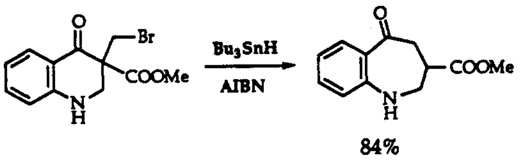
The corresponding iodides and selenides also undergo ring expansion. Thus, concurrently with our work, Beckwith reported an analogous series of rearrangements starting from the iodomethyl and (selenophenyl)-methyl derivatives (Table 1, part B).[10]

Use of the selenophenyl group is of special value in the one-carbon expansion of heterocyclic rings.[11] When a heteroatom is present, the use of the halomethyl group can create difficulty arising from internal alkylation.

Table 2. Ring Expansion of Heterocycles



In this context, the phenyl selenide is a most useful radical precursor, as shown for many of the examples in Table 2. However, the iodomethyl group was successfully employed in the tetrahydrofuran and tetrahydrothiophene series (Table 2), while the bromomethyl precursor proved to be useful in the benzazepine[12] and indole[13a] series (eqs 4 and 5).



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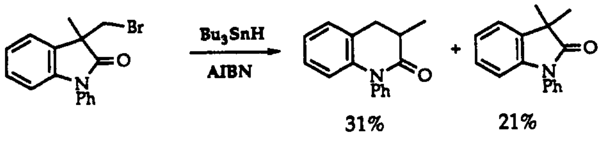


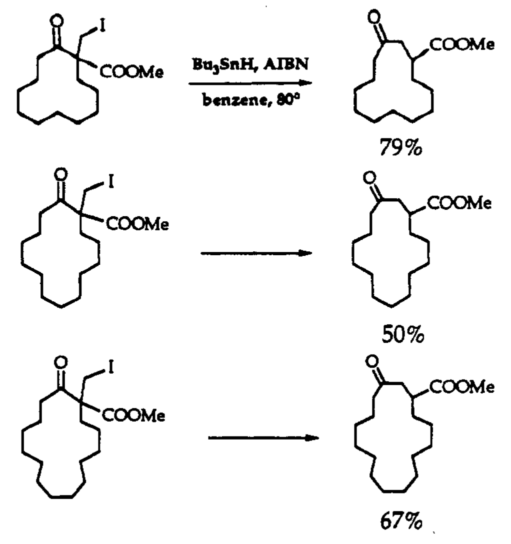
(5)

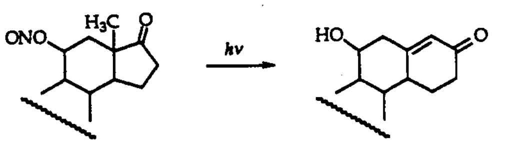
Application of the ring expansion technique to large rings[14] is a straightforward extension of the method and is illustrated by the examples in Table 3.

B. Other Examples

An early one-carbon ring expansion was reported by Barton and his co-workers.[15] The Barton nitrite ester photolysis was employed to abstract a hydrogen atom from the steroid 18-methyl group, generating the 18-methylene radical, which then inserted into the adjacent 17-ketone (eq 6). Barton also synthesized a tropone from a cyclohexadienone by tri-*n*-butyltin hydride initiated free radical reaction (eq 7).[16]

Table 3. One-Carbon Ring Expansion of Large Rings





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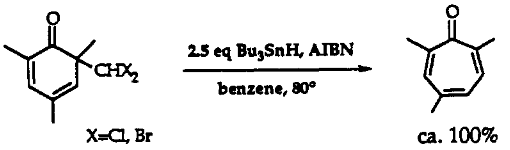
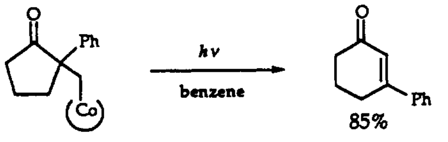


(7)

Examples of ring expansion have also been reported by the Tada group[17] during studies of 1,2-acyl migration of alicyclic 2-alkyl-2-(bromomethyl)alkanones using organocobaloximes (eqs 8 and 9). Radical cleavage of the carbon–cobalt bond of the organocobalt complexes was confirmed by reaction of the corresponding bromide with tri-*n*-butyltin hydride (eq 10). Recently, Murakami[18] and Torii[19] reported analogous ring expansions mediated by vitamin B_{12} and organocobalt complexes (Table 4).



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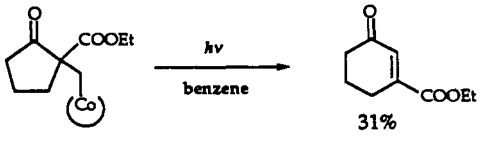

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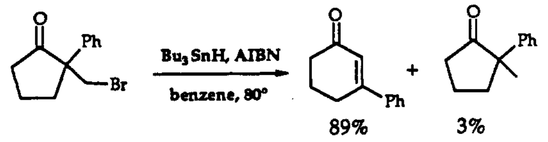

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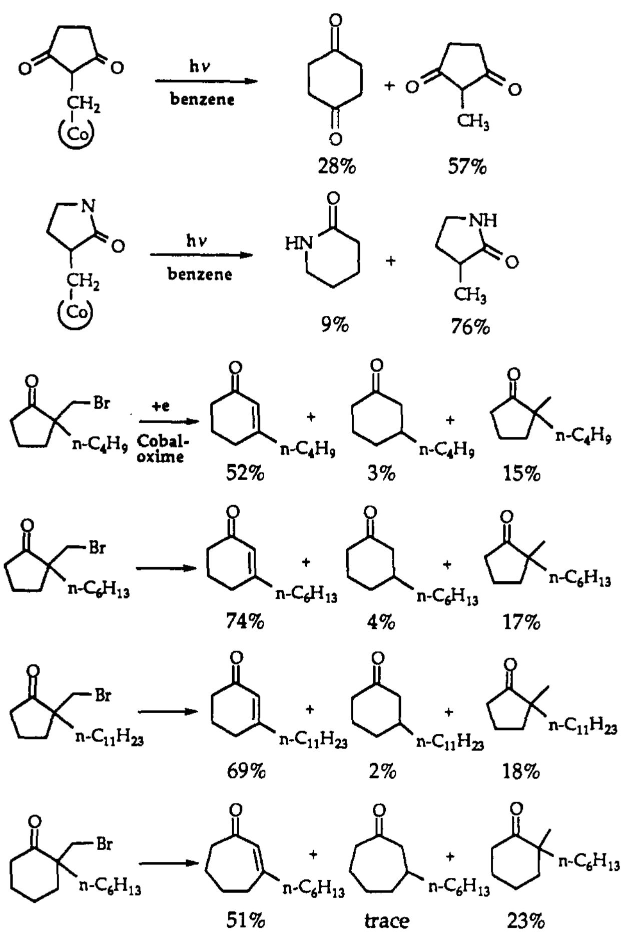
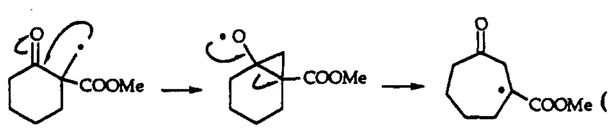
Table 4. One-Carbon Ring Expansion Using Vitamin B_{12} or Organocobalt Complexes



C. Mechanism

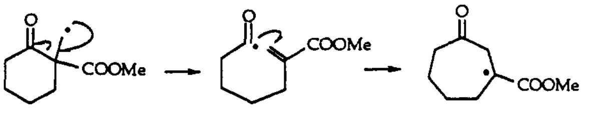
In the one-carbon ring expansion, it seems reasonable to suggest that formation of the primary radical is followed by attack on the ketone carbonyl, yielding the intermediate cyclopropyloxy radical (eq 11), which then



(11)

undergoes cleavage to the ring expanded product. In this reaction sequence, the ester group plays several roles. It facilitates the alkylation and it assists in the ring opening at the oxy radical stage. The ester group may also serve to activate the carbonyl group toward attack by the nucleophilic carbon radical.

It is also possible to write a fragmentation mechanism in which ring opening to an α-substituted acrylate is followed by β-addition of the acyl radical to the double bond (eq 12). In the one-carbon ring expansion, it is

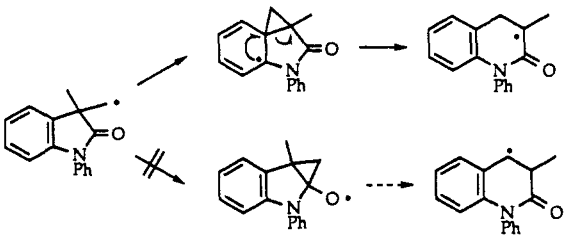


(12)

difficult to differentiate between the cyclopropyloxy and fragmentation mechanisms. In the acyclic chain extension reactions, a crossover experiment might differentiate the two radical paths.

Barton suggested a fragmentation–reclosure mechanism for his ring expansion.[15] We incline to the cyclopropyloxy radical mechanism, but only because of indirect evidence from the results of three- and four-carbon ring expansion experiments to be discussed in the next section.

Equation 5 shows a ring expansion yielding the product assigned the structure with the methyl group α to the carbonyl rather than the alternative product with the β-methyl.[13a] This result suggests that radical cyclization onto the arene (eq 13a)[13b] is more highly favored than that onto the amide carbonyl (eq 13b).

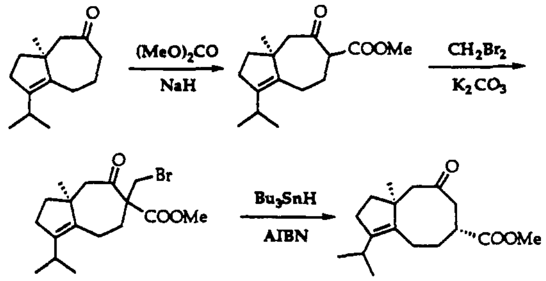


(13a)

(13b)

D. Further Applications

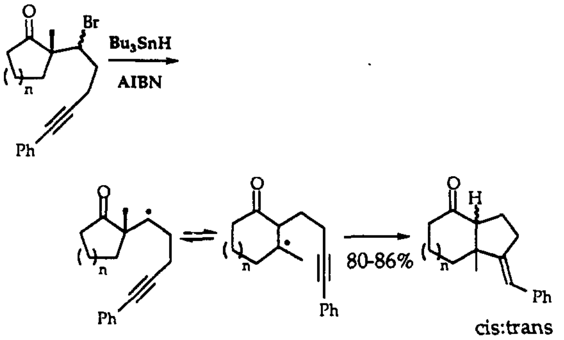
The recent literature contains a number of ingenious extensions of the free radical ring expansion strategy. Mehta required access to 5,8-fused ring systems[20] leading among others to fusicoplagin D and 7,8-epoxy-4-basmen-6-one. After unsuccessful efforts with more conventional protocols, the desired ring expansion from a seven- to an eight-membered ring was effected by the free radical method (eq 14).



(14)

Shono *et al.* have introduced a useful electroreductive variant on the free radical ring expansion method (Table 5).[21] In some instances, the reaction may proceed through a two-electron process.

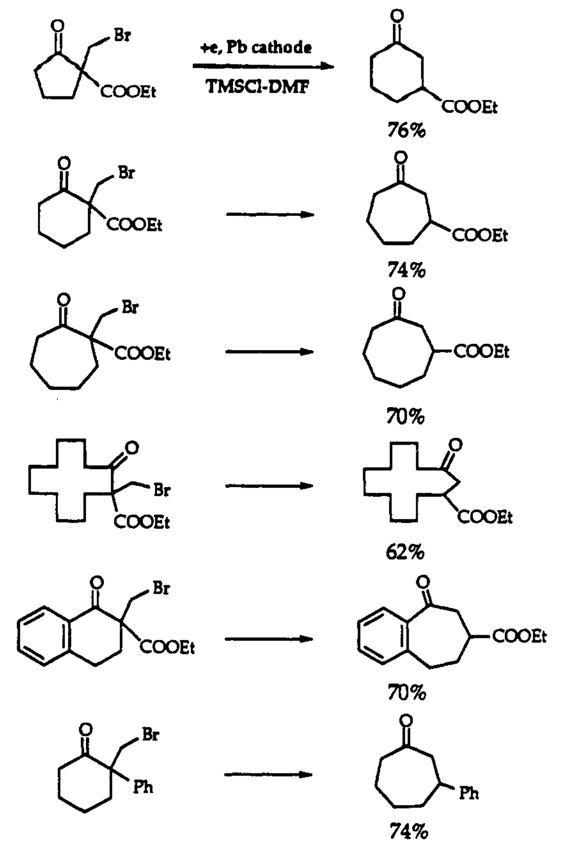
Boger provided an elegant example of one-carbon ring expansion tandem to cyclization (eq 15).[22] Thus,



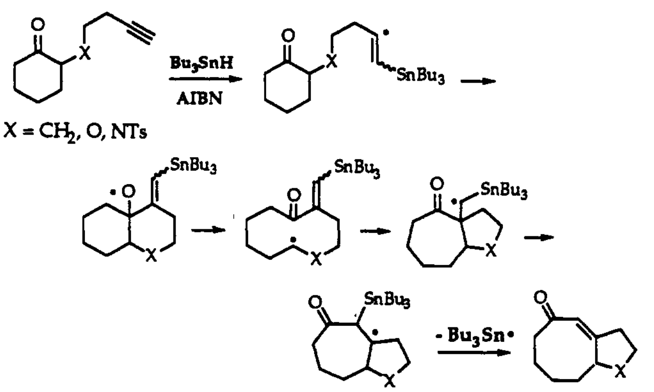
(15)

cis:trans
n=1, >97:3
n=2, 44:56
n=3, 42:58

Table 5. Electroreductive One-Carbon Ring Expansion



Scheme 1



tin hydride-induced ring expansion is followed by intramolecular trapping of the intermediate radical by the pendant alkyne chain.

Nishida *et al.* have recently added a marvelous sequence that begins with a four-atom ring expansion (*vide infra*), segues to a ring closure, and reaches a spectacular climax with a vinyl radical cyclization to the carbonyl, ring-cleavage, *exo*-1,5-addition, one-carbon ring expansion and loss of tri-*n*-butyltin radical yielding a fused, unsaturated eight-membered ring (Scheme 1).[23] More examples from the work of the Nishida group are shown in Table 6.

Bowman and Westlake have extended the one-carbon ring expansion method to include benzannelated examples (Table 7).[13a] Tri-*n*-butyltin adducts have also been employed in a modification of the ring expansion method leading to olefinic products[13c–f] and in a reaction of penams to cephams.[13g]

Table 6. Tandem Ring Expansion

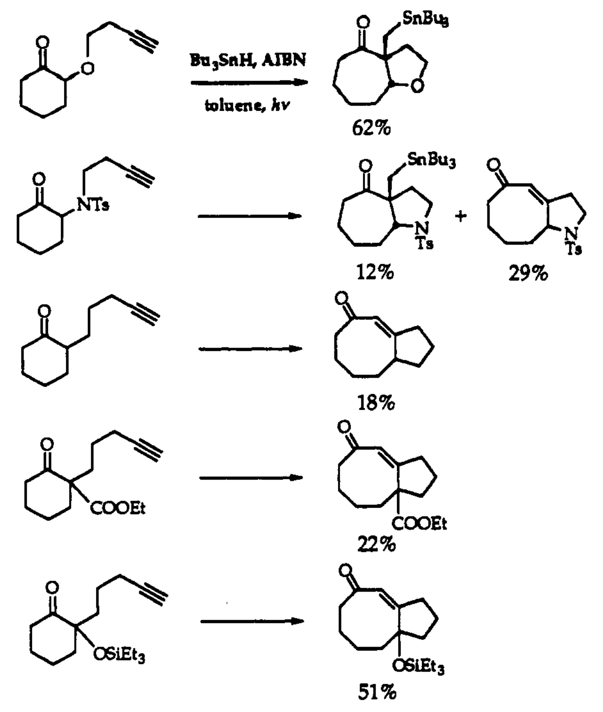
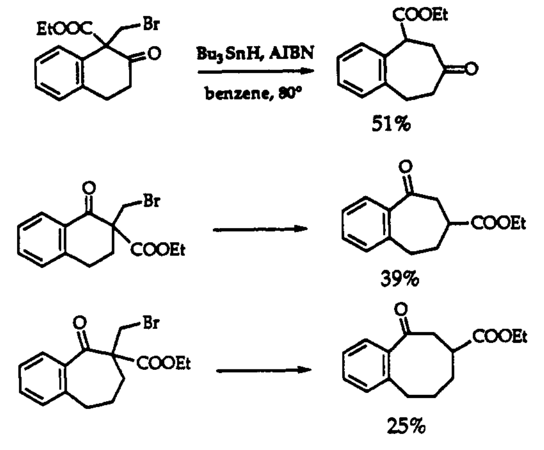
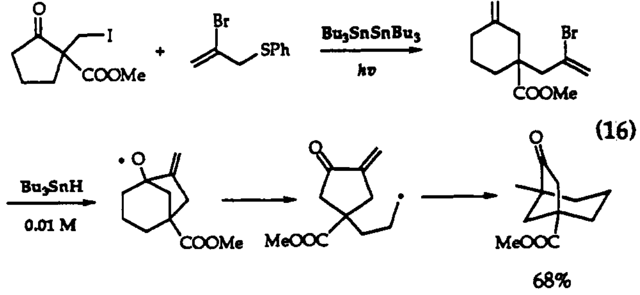


Table 7. One-Carbon Ring Expansion of Aromatic Systems



Curran and Yoo have discovered a fascinating sequence of "double" β-scission of alkoxy radicals leading to the formation of ring-expanded bicyclic ketones (eq 16).[24]



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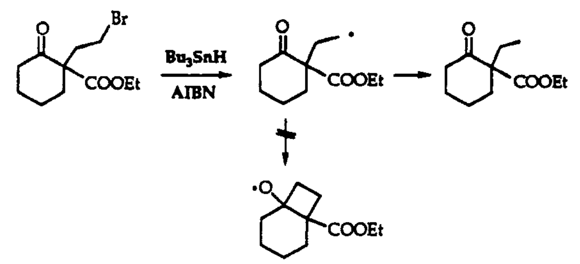
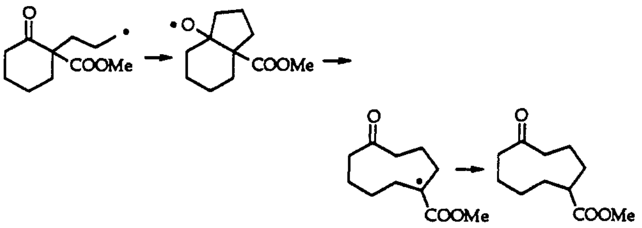
E. Three- and Four-Carbon Ring Expansions

Following the successful experiments in the one-carbon ring expansion series, we were encouraged to

Scheme 2



Scheme 3



explore ring expansions in larger increments. The radical precursors in this series are readily prepared by straightforward alkylation of the five-, six- and seven-membered β-keto ester Dieckmann condensation products.

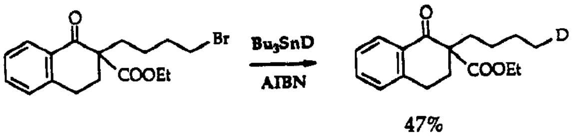
We were not sanguine about the prospects for two-carbon ring expansion. Thus, treatment of ethyl 2-(bromoethyl)-1-oxo-cyclohexan-2-carboxylate with tri-*n*-butyltin hydride (Scheme 2) yielded only the corresponding ethyl derivative, the product of direct reduction. None of the eight-membered ring expansion product was observed. Apparently, formation of the four-membered ring intermediate required for ring expansion is not competitive with chain transfer tin hydride reduction of the initially formed radical. Experiments with silane and germane hydrides were also not successful.

By contrast, ring expansion by three- and four-carbon increments was very successful as outlined in Table 8.[9,25]

In the multicarbon ring expansions, the mechanistic choice is clear. There is no possibility of fragmentation–ring enlargement; the ring expansion must proceed by radical addition to the carbonyl group, followed by bond cleavage of the intermediate alkoxy radical leading to the enlarged ring (Scheme 3). This sequence encourages the view that the one-carbon ring expansion also proceeds by ring-forming addition to the carbonyl group followed by oxy radical-induced fragmentation.

The experiments in this series require slow input of tin hydride to minimize the amount of direct reduction product. The major product in most of the examples in Table 9 is the ring expansion product. Use of the iodide instead of the bromide gives better yields in several instances, in accord with Porter's generalization.[26]

Bowman also explored the three-carbon ring expansion of benzocyclic ketones.[8] When the ketone is conjugated, only non-ring-expanded reduction product was obtained, even under syringe pump conditions (eq 17). However, the nonconjugated ketone gave a 23% yield of ring expansion product (eq 18), promoted by the intermediacy of the benzyl radical.



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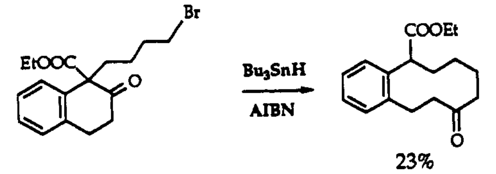
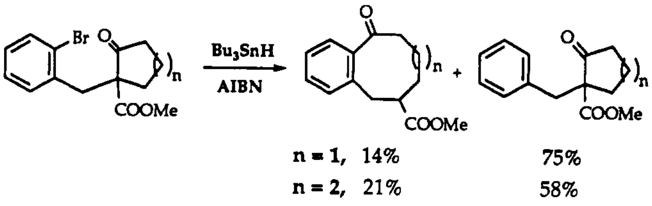


(18)

Shono's electroreductive method has also been extended to include three-carbon ring expansions (Table 9).[21]

Other multicarbon ring expansions, developed by Beckwith, involve reactive phenyl and vinyl radicals (eqs 19 and 20).[10]



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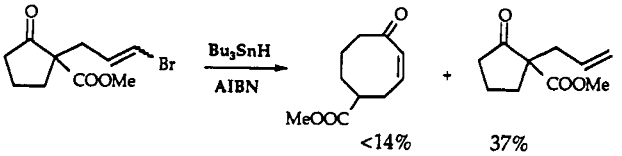
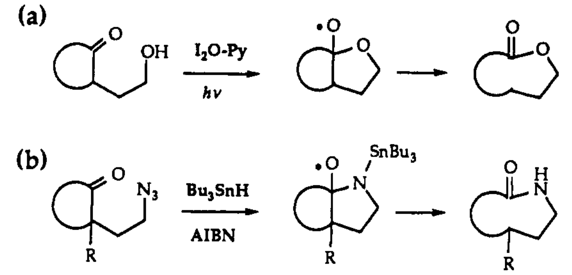


(20)

Suginome used an alkoxy radical to initiate ring expansion for the generation of lactones (Scheme 4, part a).[74d] Quite recently, Kim reported the use of azido groups as aminyl radical precursors to produce ring-expanded lactams (Scheme 4, part b).[27] Examples are listed in Table 10.

Scheme 4



III. Rearrangement of Fused-Cyclobutanones

A. Ring Expansion in the *Exo* Series

In extending the free radical ring expansion to the other synthetic areas, Dowd and Zhang observed a free radical-based ring expansion of cyclobutanones[28] that promises to open new synthetic doors. Questions of mechanistic interest are also posed. In the key finding, we discovered that intramolecular attack of the side chain free radical on a ring-fused cyclobutanone leads to ring expansion as the main reaction course (eq 21).

We had anticipated that ring opening of the oxy radical intermediate (eq 22) would result in cleavage of

Table 8. Ring Expansion by Three and Four Carbons

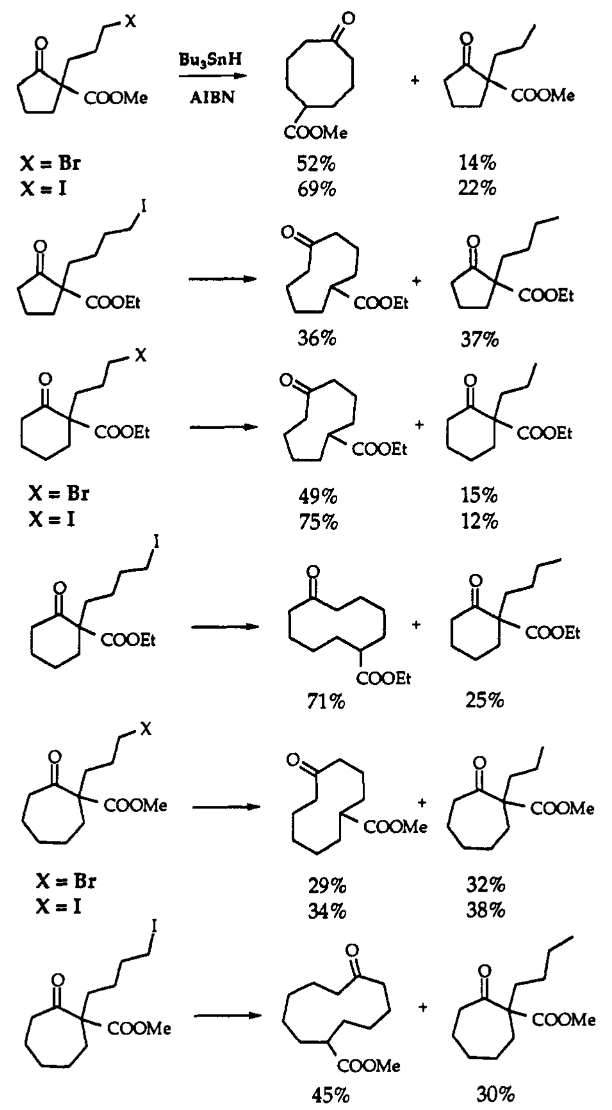


Table 9. Electroreductive Ring Expansion by Three Carbons

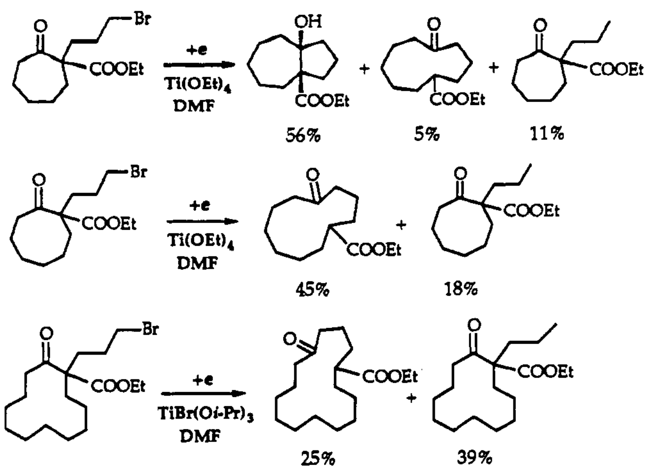
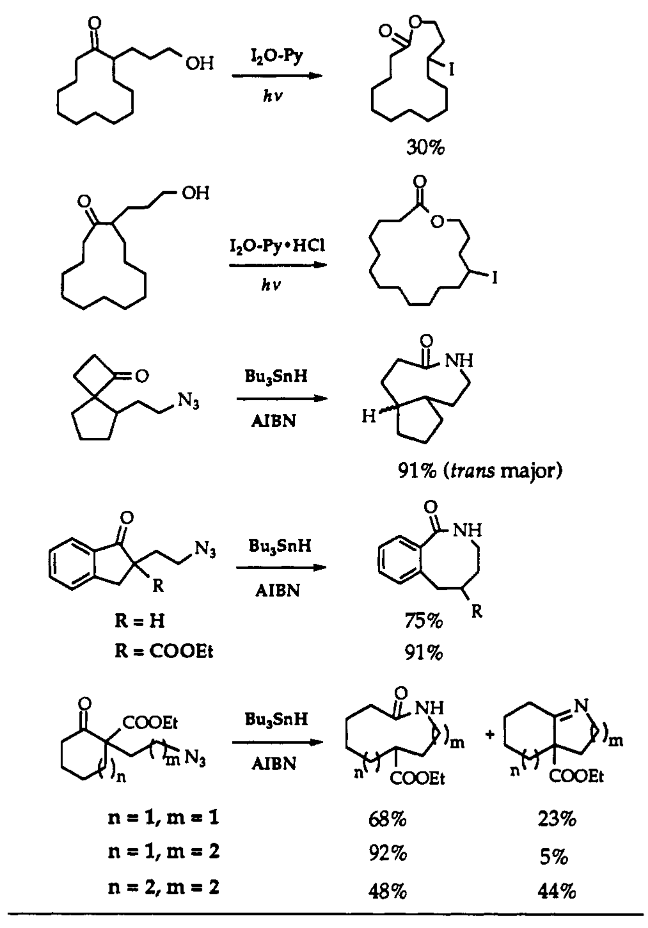
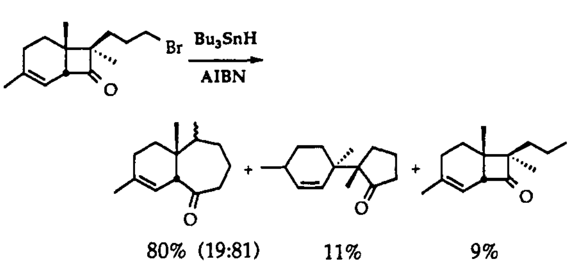


Table 10. Formation of Lactams by Ring Expansion





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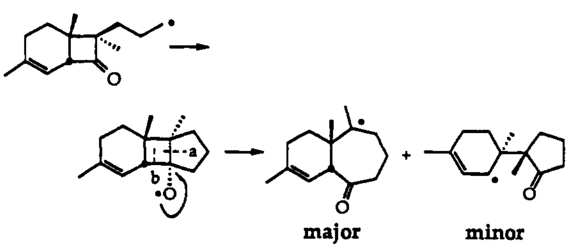


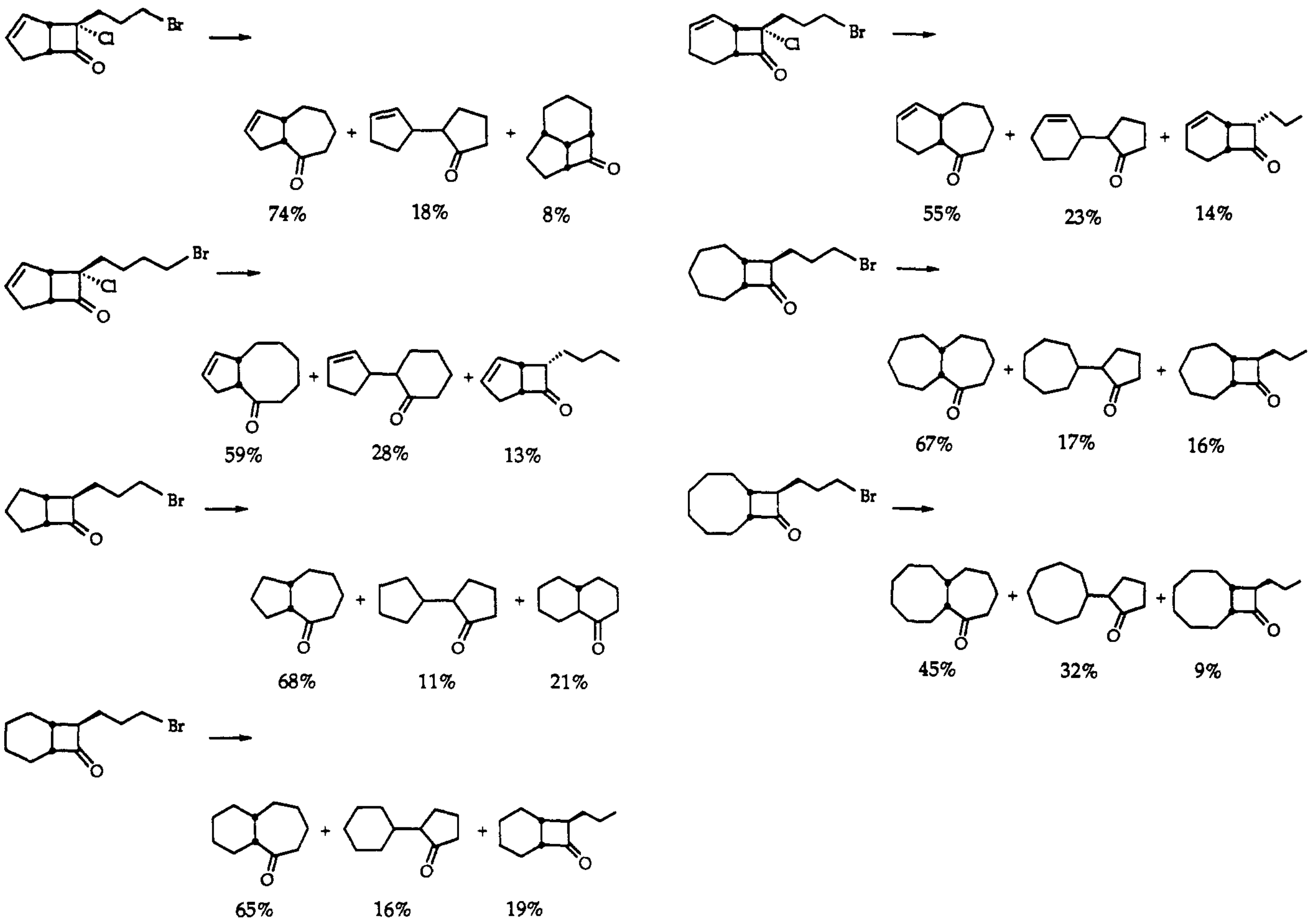
(22)

bond b, the allylic carbon–carbon bond. The stereoelectronic situation for cleavage of bond b does not appear to be unfavorable, and an MM2 calculation reveals that there is little thermodynamic bias, the major and minor products are about equally strained. Accordingly, the observation of preferential cleavage of bond a, the non-allylic bond, is intriguing; it may stem from an early transition state for bond cleavage.

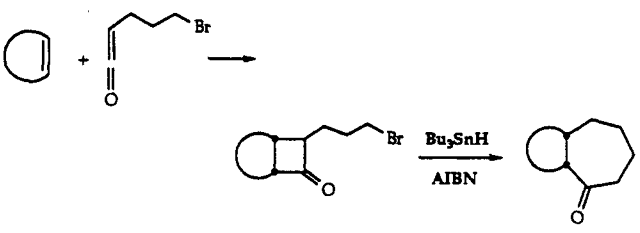
We can take advantage of this new method for preparing fused seven- and eight-membered rings, and it has the especially attractive feature that there are good ways to prepare fused cyclobutanone rings by cycloaddition of ketenes and keteniminium salts to alkenes. Accordingly, we have devised a new series of ketenes with bromoalkyl side chains to explore the method.

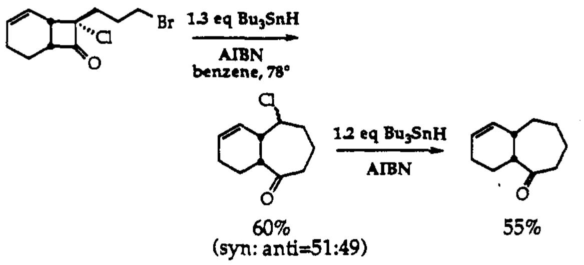
ω-Bromoalkyl ketenes are generated from the appropriate ω-bromo acids and in the presence of alkenes form cyclobutanones by [2 + 2] cycloaddition. Free

Table 11. Ring Expansion of Cyclobutanones (Relative Yields)



Scheme 5





(23)

radical reaction of the cyclobutanone adduct yields the ring-expanded annulation product (Scheme 5). The reaction sequence yielding the fused ring is stereospecific; the *cis* stereochemistry is enforced by the requirements of the four-membered ring and is transposed to the product of ring annulation.[29,30]

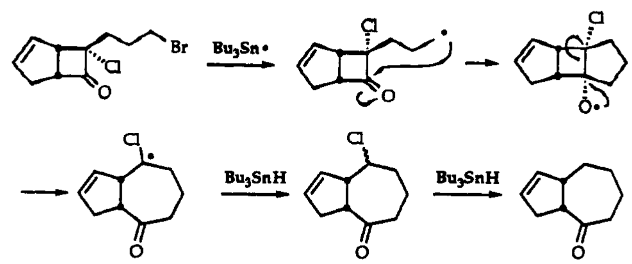
In the ketene cycloaddition, a mixture of *exo* and *endo* products is formed. The *exo* products undergo smooth ring expansion (Table 11). The *endo* products ordinarily undergo direct reduction as a consequence of steric hindrance to ring closure. However, we will later describe internal alkene additions in the *endo* series, one of which leads to an unusual rearrangement product.

For the *exo* series, an example from the Table 11 will illustrate the method. The *exo* adduct of 1,3-cyclohexadiene and (bromopropyl)chloroketene was treated with 2.5 equiv of tri-*n*-butyltin hydride and a catalytic amount of AIBN in refluxing benzene. The major product was the ring expanded bicyclo[5.4.0]undec-8-ene-2-one (eq 23). The four-membered cyclobutanone is transformed to the fused seven-membered ketone. If 1.3 equiv of tin hydride is employed, the corresponding chloroketone is isolated in 60% yield (eq 23). The structure of the *anti* product was established by X-ray crystallography. The chlorine atom improves the yield of the ketene cycloaddition reaction, assists in the free radical opening of the cyclobutanone, and has the potential to be a useful synthetic handle for further elaboration and ring expansion.

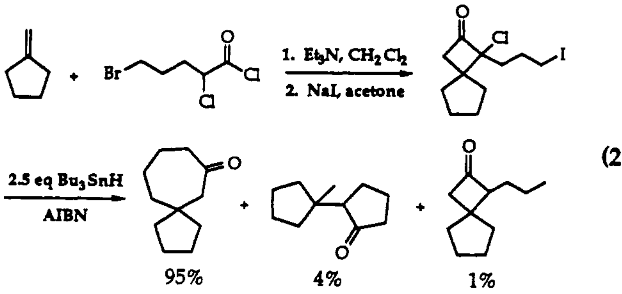
In this series of experiments[30] we proceeded on the premise that, following addition of the primary radical to the carbonyl group (Scheme 6), the cyclobutanone ring would open by bond cleavage of the intermediate oxy radical. A preponderance of internal bond cleavage leading to ring enlargement is observed, and this is the most desirable turn of events.

This method is particularly useful for the synthesis of spiro fused rings.[31] Thus, regiospecific cycloaddition of (ω-bromoalkyl)chloroketenes to methylenecycloal-

Scheme 6



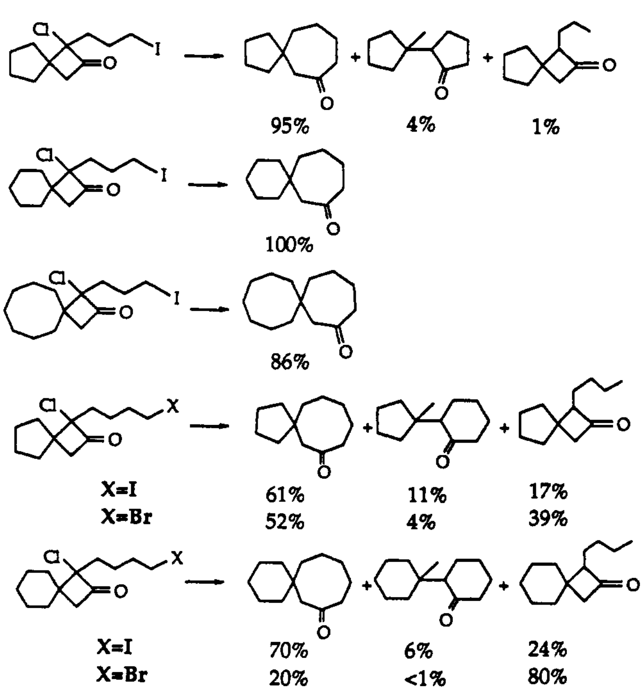
kanes leads to the corresponding spirocyclobutan-2-ones. Finkelstein reaction produces the corresponding iodide, which is then treated with tri-*n*-butyltin hydride under the standard conditions yielding the spirocycloheptanone product in excellent yield (eq 24).



(24)

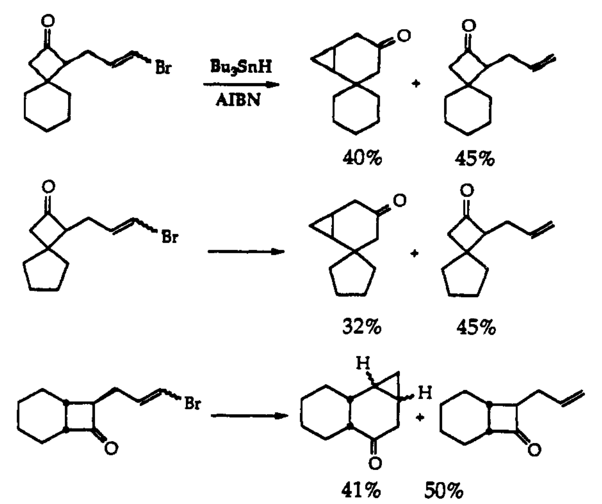
Other examples of spiroannulation are shown in Table 12. These examples also demonstrate, once again, the advantage of using the iodide in the ring expansion step.[26]

Table 12. Ring Expansion of Spirocyclobutanones (Relative Yields)

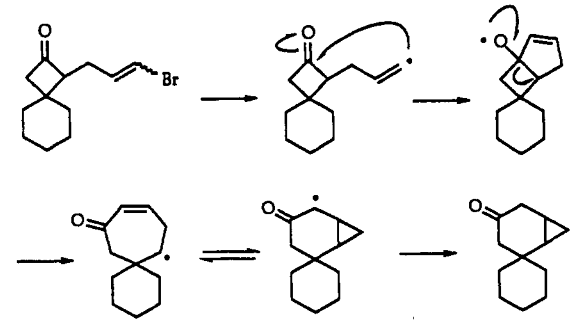


An interesting and unusual variation on the spiroannulation is observed when a vinyl halide is used in the ring expansion step. Thus, alkylation of the spirocyclobutanone with 1,3-dibromopropene yields the propenyl bromide adduct. Treatment with tri-*n*-butyltin hydride leads to a novel rearrangement product containing a cyclopropane ring (Table 13).[32]

Table 13. Formation of Cyclopropanes Following Ring Expansion



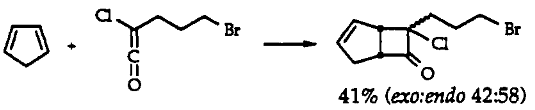
Scheme 7



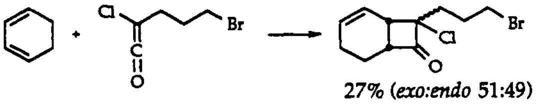
The proposed mechanism for ring expansion of fused cyclobutanones is readily extended to the spiroannulation method and is especially appropriate for the cyclopropane-forming reactions in Table 13. Thus, addition of the vinyl radical to the carbonyl group yields the oxy radical (Scheme 7). Ring cleavage leads to the seven-membered ring enone radical that is in equilibrium with the cyclopropyl radical. Stabilization of the radical center by overlap with the carbonyl group dominates the equilibrium, so the cyclopropane is the major product following chain transfer with tin hydride (Scheme 7).

B. Ring Annulation in the *Endo* Series

As described in section III.A, the (bromoalkyl)-chloroketenes react with 1,3-dienes yielding a mixture of *exo* and *endo* adducts (eqs 25 and 26), where the *exo* and *endo* designations refer to the relationship of the side chain to the ring junction. As noted above, the *exo* isomers undergo smooth ring expansion upon treatment with tri-*n*-butyltin hydride (Table 11).

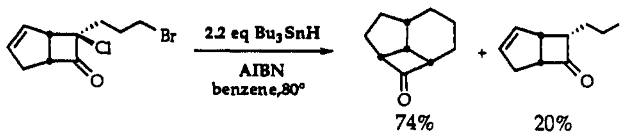


(25)



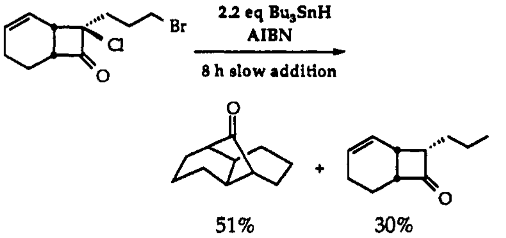
(26)

The *endo* isomers represent a different kind of ring expansion opportunity. We envisioned intramolecular free radical addition to the double bond,[30] that might be followed in a second step by modification or opening of the four-membered ring. In the event, tin hydride-promoted free radical cyclization to the fused cyclopentene ring proceeded smoothly yielding the expected tricyclo[5.2.1.0^{3,10}]decan-3-one in 74% yield (eq 27).



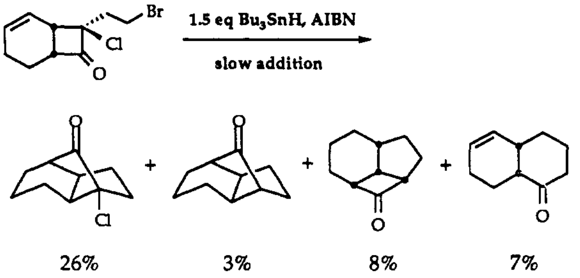
(27)

When the analogous reaction was attempted on the cyclohexyl-fused system, it was immediately clear that an unusual rearrangement had taken place (eq 28).[33] The major product from the reaction showed a carbonyl band at 1741 cm^{-1}. The product clearly contained a cyclopentanone, not a cyclobutanone carbonyl. Likewise the ^{13}C NMR spectrum showed six lines instead of the seven lines to be expected of the product of straightforward radical addition to the double bond. Following these revelations, the structure was demonstrated to be the tricyclo[4.4.1.0^{2,6}]undecan-11-one. When the tricyclic ketone was reduced with LiAlH$_4$ (eq 29), the ^{13}C NMR spectrum of the resulting alcohol showed eleven lines. A similar rearrangement was observed starting with the 8-(2-bromoethyl)bicyclo[4.2.0]oct-2-ene (eq 30). The mechanism of this unusual transformation is under active investigation.



(28)

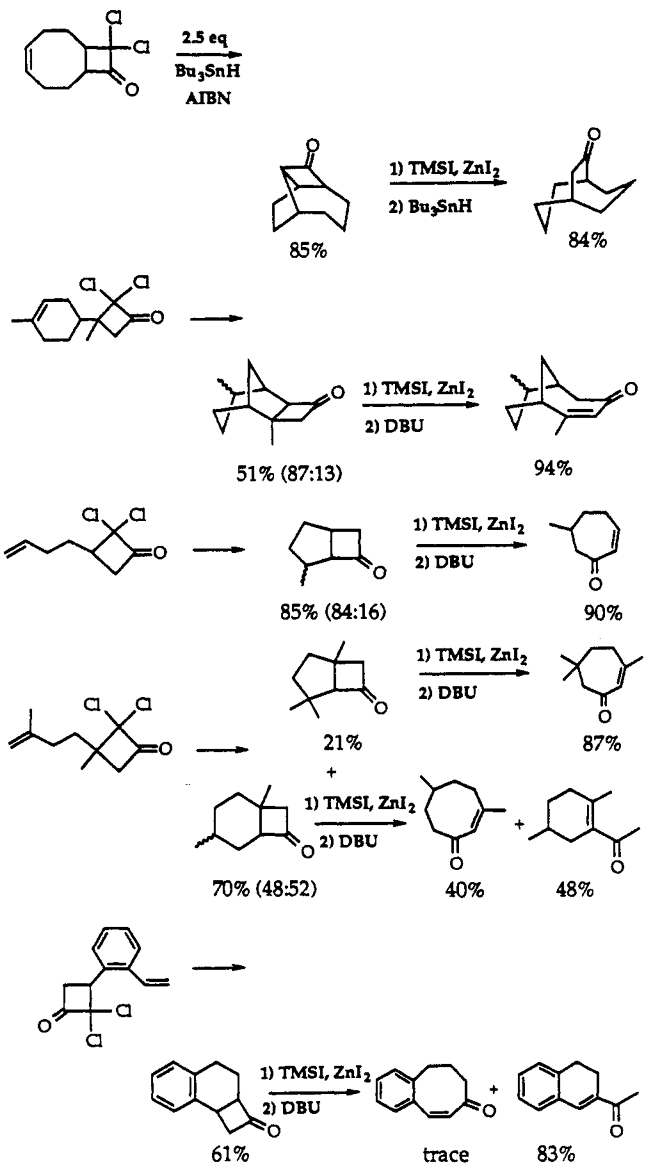
(29)



(30)

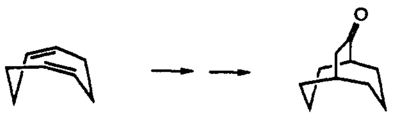
IV. Annulation Using Dichlorocyclobutanones

Table 14. Free Radical Annulation through Dichlorocyclobutanones[a]

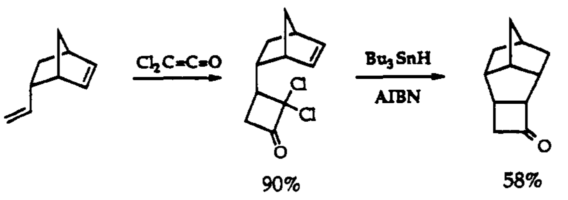


[a] Values in parentheses are ratios of the diastereomers.

In the course of exploring free radical chemistry in the cyclobutanone series, Dowd and Zhang discovered a new reaction sequence that provides a novel approach to the synthesis of polycyclic bridged ring systems.[34] The essence of the method: the elements of ketene are inserted across a 1,5-diene and two new carbon–carbon bonds are formed. For example, 1,5-cyclooctadiene can be transformed to bicyclo[3.3.2]decan-9-one by this means (eq 31). The dichlorocyclobutanone route provides flexible entry to a variety of bridged polycyclic structures. To explore a second example: dichloroketene was added to *endo*-5-vinylbicyclo[2.2.1]hept-2-ene, yielding an adduct dichlorocyclobutanone (eq 32). As anticipated, the reaction is both regio- and chemoselective, the dichlorocyclobutanone is formed with the carbonyl adjacent to the terminal methylene of the vinyl group (eq 32). Treatment of the adduct with tri-*n*-butyltin hydride results in ring-closure to



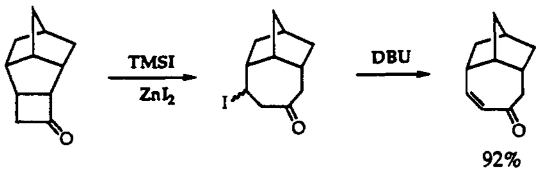
(31)



(32)

the tetracyclic ketone. If 1 equiv of tin hydride is used, the chlorine-containing product is obtained; with 2.2 equiv of tin hydride reductive removal of the second chlorine atom occurs (eq 32).

The tetracyclic ketone reacts with trimethylsilyl iodide (TMSI) and ZnI_2 yielding the open 2-iodotricyclo-[6.2.1.0^{6,10}]undecanone system (eq 33). When this product is treated with DBU, HI is eliminated yielding the enone with the new seven-membered ring incorporated into the system (eq 33). The iodide can also be removed reductively with tin hydride. Additional examples are shown in Table 14.



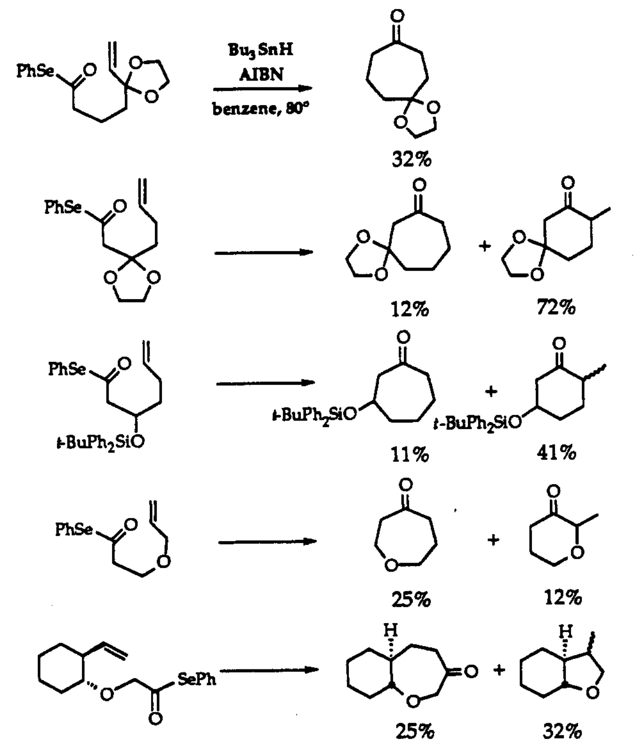
(33)

V. Endo versus Exo Cyclization of Acyl and Vinyl Radicals

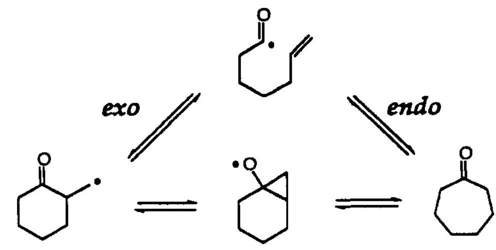
A. Cyclization of Acyl Radicals

Intramolecular addition of acyl radicals to terminal alkenes favors cyclization in the *exo* mode.[35] However, several apparent *endo* cyclization examples have been reported (Table 15).[36] While in some instances these might simply be *endo* additions, this mode of closure can also be explained if a one-carbon ring expansion follows the initial *exo* cyclization (Scheme 8).[36b]

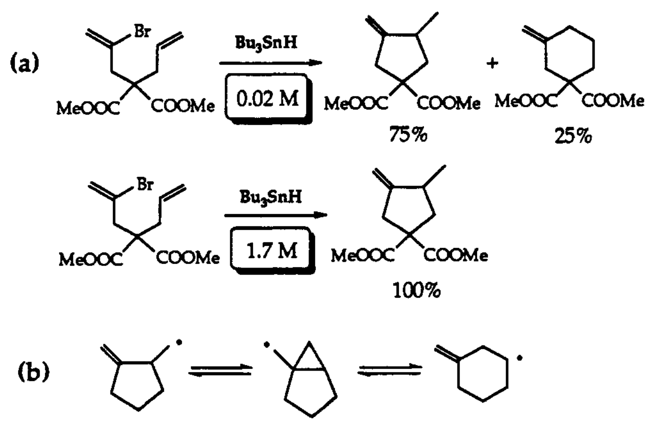
Table 15. Endo versus Exo Cyclization of Acyl Radicals



Scheme 8



Scheme 9



Boger and Mathvink used acyl radical addition to trisubstituted olefins to produce 6-*endo*/5-*exo* or 6-*endo*/6-*exo* tandem cyclization products (eqs 34 and 35).[22] Batty and Crich have developed a 7-*endo*/5-*exo* tandem cyclization based on disubstituted olefins (eq 36).[36c] The latter is formulated as a 6-*exo* addition/rearrangement with ring expansion/5-*exo* cyclization.

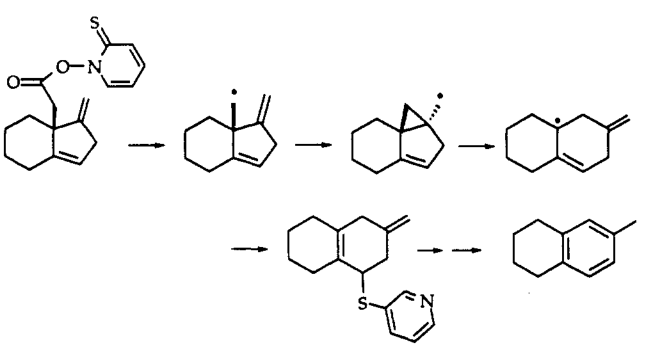
B. Cyclization of Vinyl and Aryl Radicals

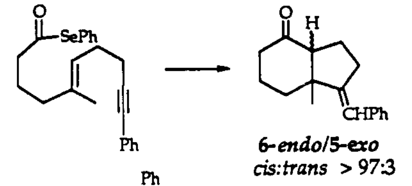
Cyclization of vinyl and aryl radicals follows a path parallel to that of acyl radicals. Early mechanistic studies have been carried out by Beckwith[37] and Stork.[38] At low Bu_3SnH concentration (0.02 M) reduction of the vinyl bromide gave a 3:1 mixture of 5-*exo* and 6-*endo* products. However, at high Bu_3SnH concentration (1.7 M) the 5-*exo* product was formed exclusively (Scheme 9a). At the lower Bu_3SnH concentration the radical resulting from 5-*exo* cyclization undergoes rearrangement by one-carbon ring expansion to the thermodynamically more favorable 6-*endo* radical (Scheme 9b).[38a]

A recent example supports the mechanism in which a one-carbon ring expansion takes place by way of a cyclopropane intermediate (Scheme 10).[39] In the course of a biomimetic study of the biogenesis of ring D aromatic steroids, a carbon radical was generated using the Barton decarboxylation method. Free radical ring expansion led to the isolation of the aromatic product.

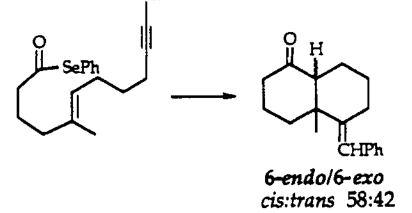
Shibasaki carried out experiments in which the reaction temperature was varied.[40] Under high-temperature conditions (120 °C), only the 6-*endo* cyclization product was observed (eq 37). Lowering the reaction temperature to −50 °C resulted in the formation of a mixture of 5-*exo* product (33%) together with an

Scheme 10

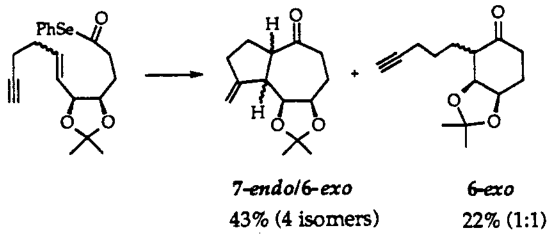




(34)

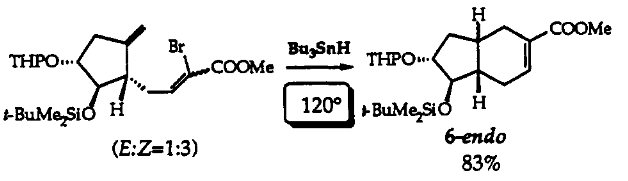


(35)

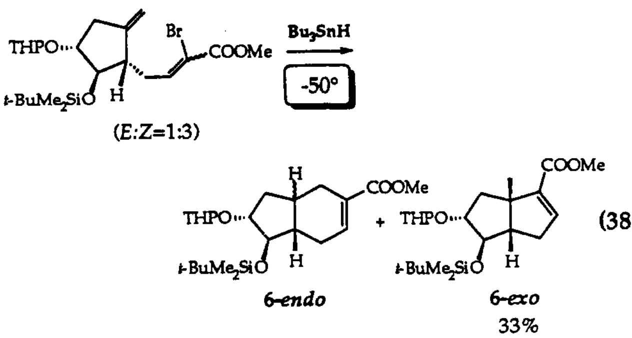


(36)

unspecified yield of the 6-*endo* cyclization product (eq 38). This result is consistent with thermodynamic control at elevated temperatures leading to the 6-*endo* product.



(37)



(38)

Cyclization of aryl radicals[41-43] occurs in a fashion analogous to that of vinyl radicals. Examples are presented in Table 16.

Table 16. *Endo* versus *Exo* Cyclization of Vinyl and Aryl Radicals

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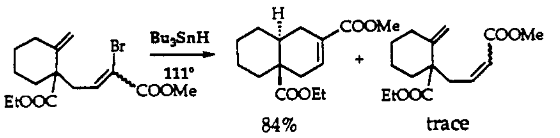
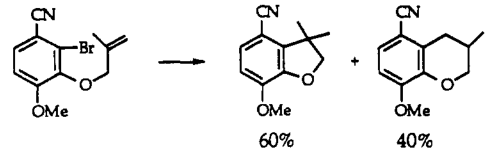
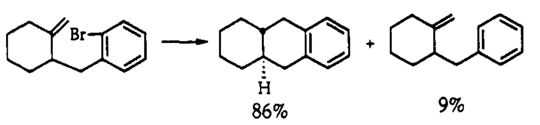
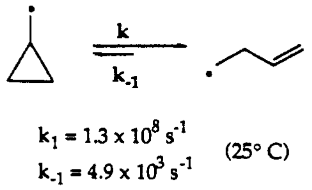
	40b
	42
	42
	43

VI. Fragmentation of Cyclopropylcarbinyl Radicals

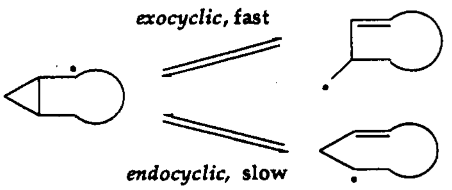
A. Ring Expansion of Cyclopropylcarbinyl Radicals

Ring opening of the cyclopropylcarbinyl radical[44] has also proved to be a useful strategy for ring expansion because of the ease with which cleavage of the three-membered ring takes place (Scheme 11). The literature on bicyclo[n.1.0] radicals reveals a preference for stereoelectronically controlled exocyclic radical ring opening as opposed to thermodynamically favored endocyclic ring opening (Scheme 12).[45] Early examples of endocyclic versus exocyclic ring opening are shown in Table 17.

Scheme 11

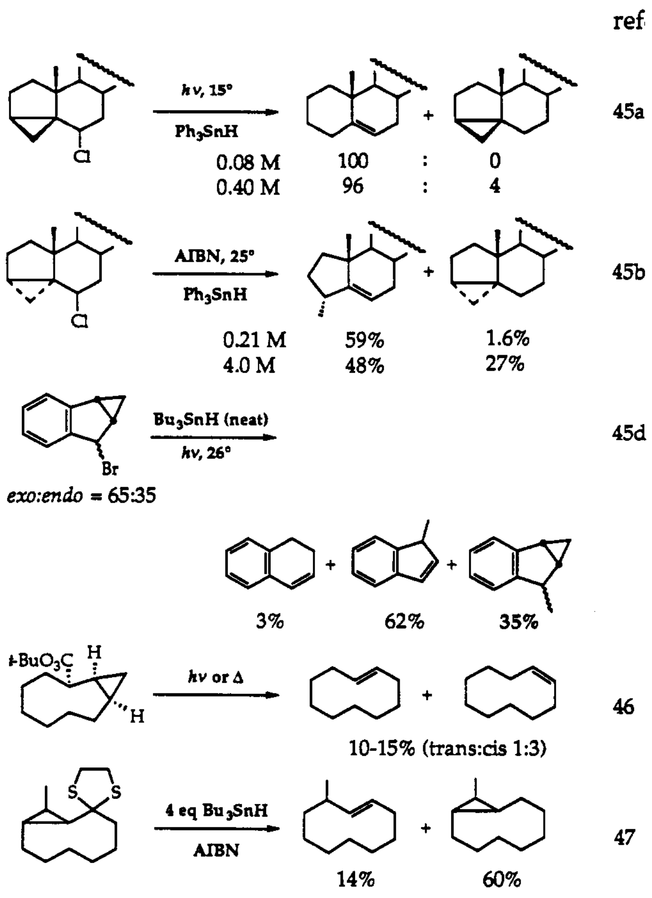


Scheme 12

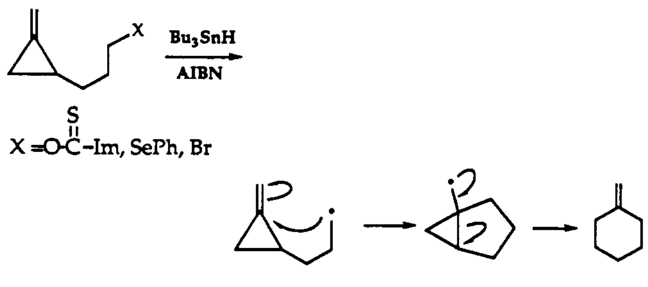


In an interesting recent extension, Destable and Kilburn described the ring expansion of a 1-(3-bromopropyl)-2-methylenecyclopropane (Scheme 13).[46a] Thus, tin hydride treatment resulted in 1,5-addition of the radical to the exocyclic double bond. This was followed by ring opening of the cyclopropylcarbinyl

Table 17. Ring Opening of Cyclopropylcarbinyl Radicals



Scheme 13

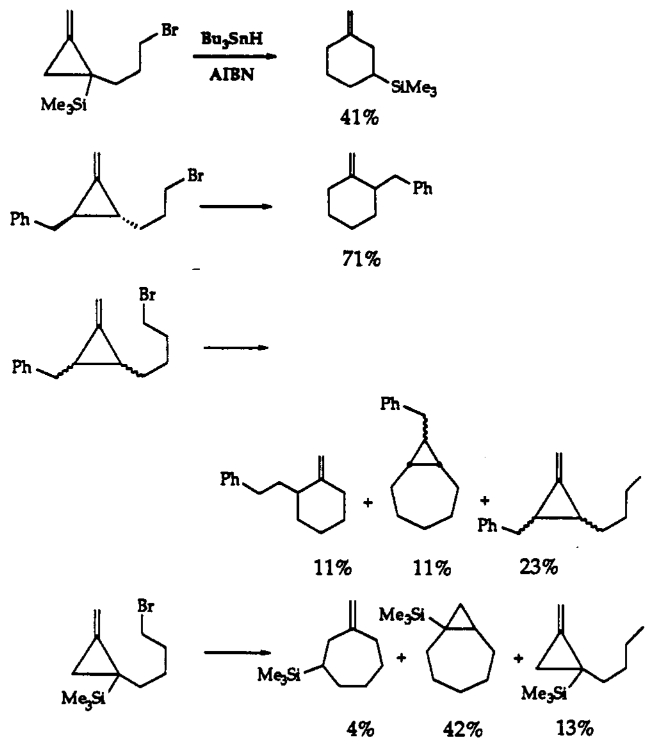


radical, yielding the desired methylenecyclohexane. Further studies of methylenecyclopropane derivatives showed that (methylenecyclopropyl)propyl radicals underwent exclusive 5-*exo* cyclization while (methylenecyclopropyl)butyl radicals afforded a mixture of 6-*exo* and 7-*endo* cyclization products (Table 18).[48]

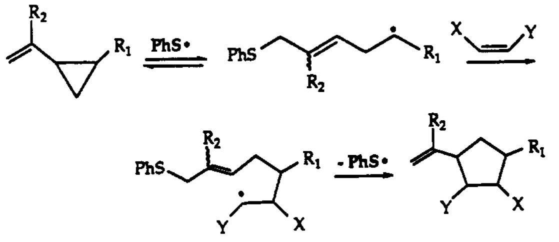
B. Intermolecular [3 + 2] Additions

Feldman[49] and Oshima[50] have developed an intermolecular [3 + 2] ring expansion strategy for the synthesis of functionalized cyclopentane rings starting with vinyl cyclopropanes. Thiophenyl radical-induced ring opening leads to an allylcarbinyl radical that can be trapped by an electron-rich alkene or alkyne. Cyclization of the adduct radical then leads to vinyl cyclopentane or vinyl cyclopentene products as the thiophenyl radical is regenerated (Scheme 14). Large excesses of olefins (15–50 equiv) are generally needed to conduct the reactions. The stereochemical outcome of the addition is determined during closure of the substituted 5-hexenyl or 5-hexadienyl radical. Results from this approach are shown in Table 19.

Table 18. Radical Cyclizations of Methylenecyclopropane Derivatives



Scheme 14



In a nice extension of this method, Singleton found a new thiyl radical-catalyzed [3 + 2] expansion of methylenecyclopropanes (Scheme 15),[51a] that overcomes the requirement of using olefins activated with electron-withdrawing groups. Moreover, in Singleton's method, a large excess of the olefin is not needed (Table 20).[51a,b] A *cis*/*trans* mixture of products is formed that, to some degree, is influenced by the steric bulk of the radical catalyst (Table 21).[51c]

Scheme 15

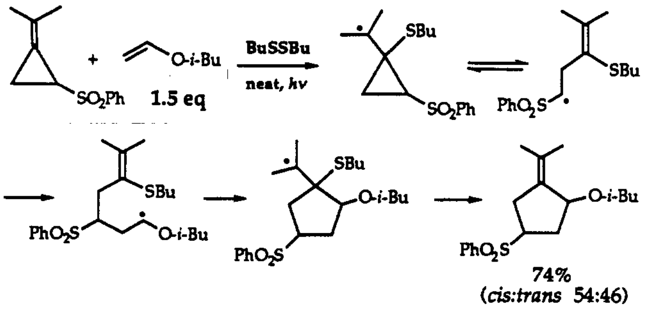
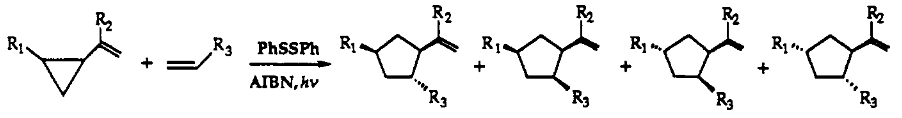
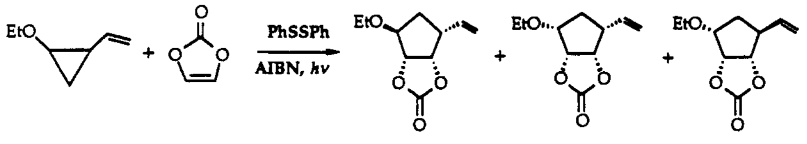
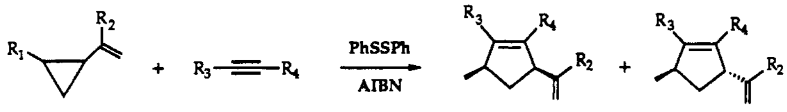
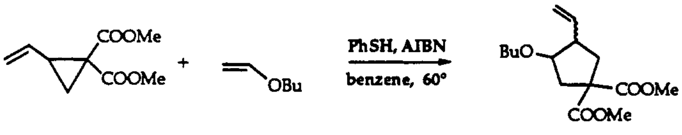
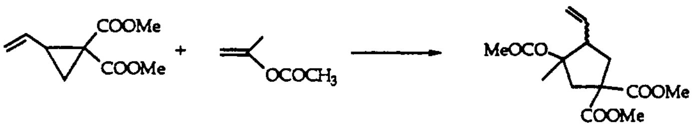
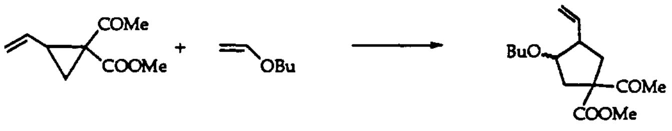


Table 19. [3 + 2] Addition of Vinylcyclopropanes[a]

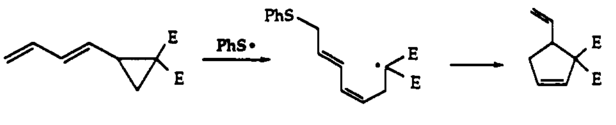
	reference
 R_1=CO$_2$-t-Bu, R_2=H, R_3=CO$_2$-t-Bu 27% 12% 7% 6% R_1=CO$_2$-t-Bu, R_2=CH$_3$, R_3=CO$_2$-t-Bu 19% 15% 5% 5%	49b
 21% 17% 4%	49b
 R_1=CO$_2$-t-Bu; R_2=H; R_3=H; R_4=CO$_2$Me 30% 9% R_1=CO$_2$-t-Bu; R_2= H; R_3=H; R_4=SO$_2$Ph 33% 17% R_1=CO$_2$-t-Bu; R_2= CH$_3$; R_3=H; R_4=CO$_2$Me 42% 11%	49c
 82% (65:35)	50
 74% (80:20)	50
 77%	50

[a] Values in parentheses are ratios of diastereomers.

C. Intramolecular [3 + 2] Additions

Oshima extended the [3 + 2] addition strategy to include an intramolecular version using 2-(1,3-butadienyl)cyclopropane-1,1-dicarboxylate as free radical precursor (Scheme 16).[52] Thus, thiophenyl radical-promoted cyclopropane ring opening leads to the butadienyl carbinyl radical that cyclizes to the vinyl cyclopentane product (Table 22). If the cyclopropyl diene is part of a bicyclo[3.1.0] system, expeditious entry to the bicyclo[3.3.0] series (Table 22) is possible.

Scheme 16



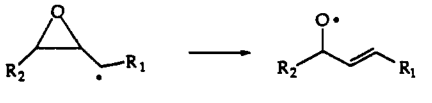
Motherwell used the intramolecular [3 + 2] addition to control the regio- and stereochemical generation of spirocyclic quaternary centers (Table 23).[53] This strategy has also been used for construction of bicyclic and tricyclic skeletons (Table 23).

Samarium(II) iodide proved to be particularly useful in preparing spiro and fused bicyclic systems in the corresponding ketone series (Table 24).[54]

VII. Fragmentation of Epoxides

A. Carbon–Oxygen Bond Cleavage

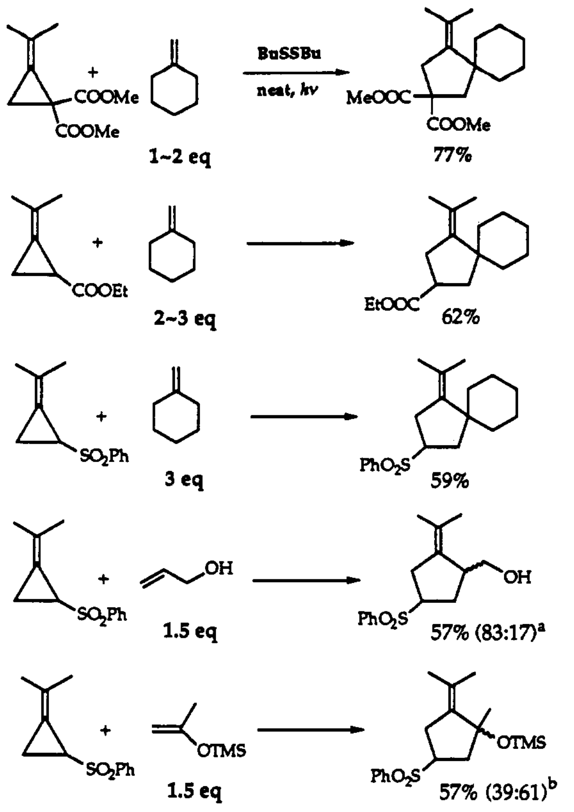
Epoxide ring opening by an adjacent carbon-centered radical constitutes another useful annulation strategy. In this series, carbon–oxygen bond cleavage generally predominates to give the alkoxy radical (eq 39), which then undergoes further rearrangement by cyclization, β-scission, or hydrogen transfer (see section IX.A).



(39)

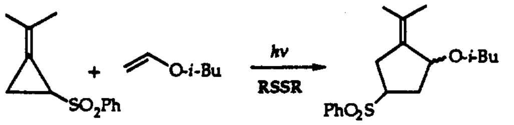
R_2 ≠ vinyl or aryl

Table 20. [3 + 2] Addition of Methylenecyclopropanes



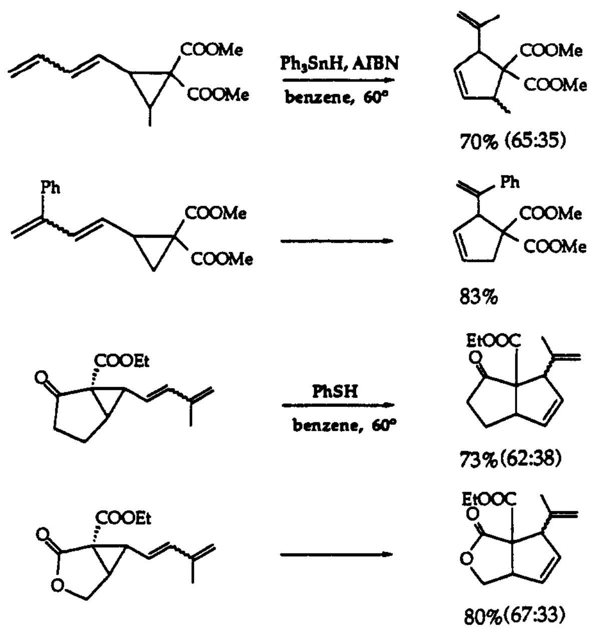
[a] Cis/trans product ratio. [b] Stereochemistry not yet assigned.

Table 21. Effect of the Steric Bulk of the Radical Catalyst on the [3 + 2] Addition



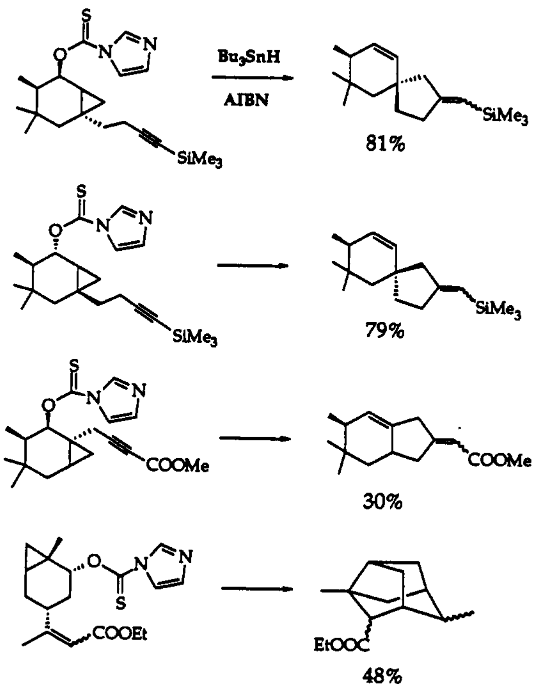
RSSR	*cis:trans*
none	44:56
1 eq $(n\text{-BuS})_2$	67:33
$(t\text{-BuS})_2$	35:65

Table 22. Intramolecular [3 + 2] Additions[a]



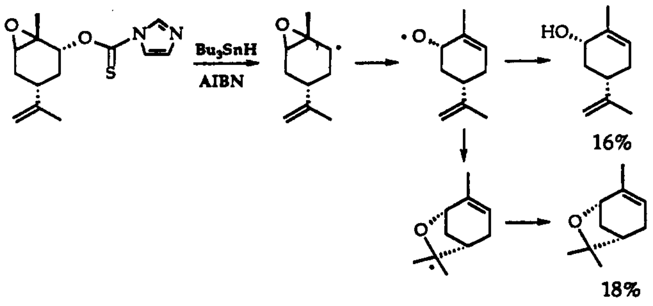
[b] Values in parentheses are *cis*/*trans* product ratios.

Table 23. Formation of Spirocyclic Bicyclic and Tricyclic Systems



Barton reported the first example of tetrahydrofuran ring formation by the cyclization of an alkoxy radical.[55] Thus, generation of the oxiranylcarbinyl radical is followed by ring opening to the oxy radical, which can undergo cyclization to the remote double bond in the 5-*exo* sense, yielding the tetrahydrofuran ring (Scheme 17). This method has been further developed by Murphy[56a] and Walton[56b] for the tandem cyclization to produce bicyclic products with bridged oxygen (Scheme 18, parts a,b).

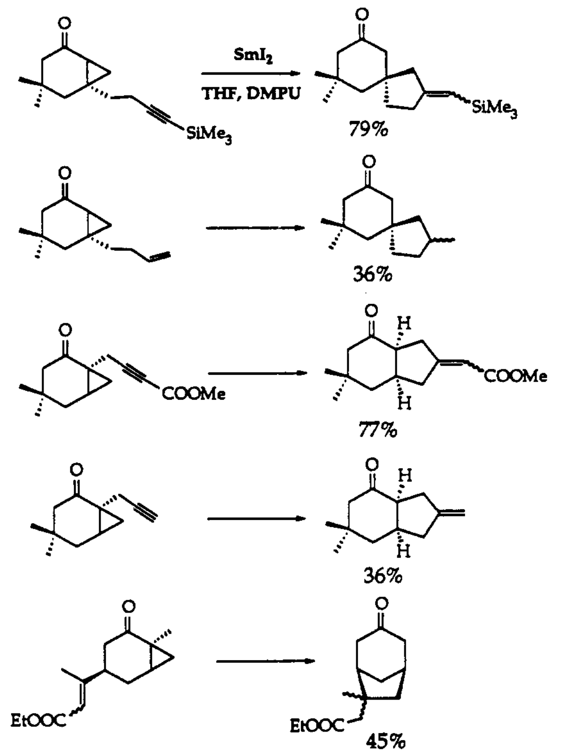
Scheme 17



Kim devised a ring expansion method based on the *β*-scission of alkoxy radicals arising from carbon–oxygen bond cleavage of oxiranylcarbinyl radicals (Scheme 19).[57] Reaction is initiated by tri-*n*-butyltin radical addition to the vinyl epoxide, with epoxide fragmentation leading to the alkoxy radical. Bond scission of the alkoxy radical then yields an alkyl radical, which cyclizes to the olefin to provide 6-*endo* or 5-*exo* cyclization products (Table 25).

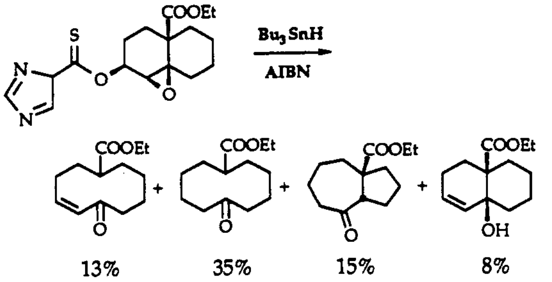
Other examples of alkoxy radical *β*-scission have been reported by Marples.[58] Treatment of epoxydecalin

Table 24. Formation of Spiro and Fused Systems Using SmI$_2$/DMPU[a]

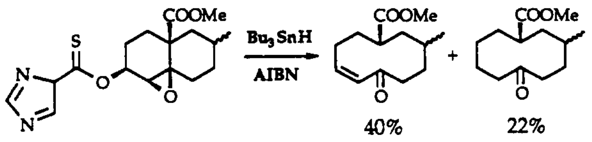


[a] DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone.

thiocarbonylimidazolides with tri-*n*-butyltin hydride induces cleavage of the epoxide. The resulting alkoxy radicals then undergo β-scission of the fused carbon–carbon bond to produce 10-membered carbocycles among other products (eqs 40 and 41).



(40)

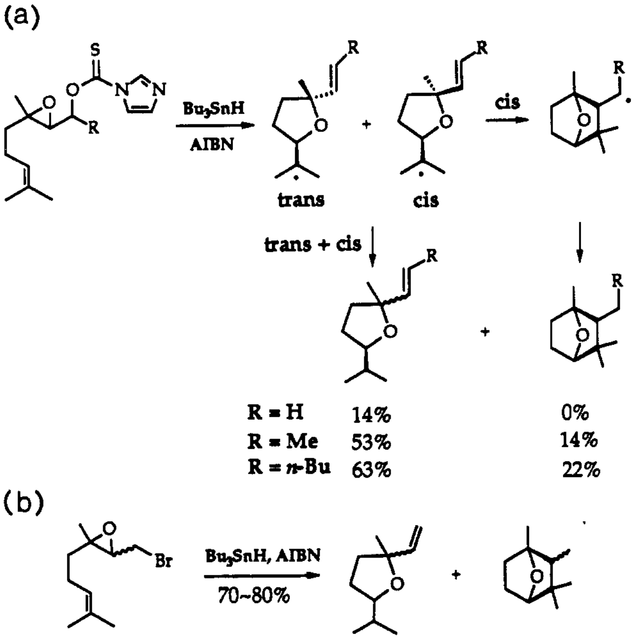


(41)

Nugent and RajanBabu explored transition metal-initiated, homolytic carbon–oxygen bond cleavage of epoxides.[59] The resulting hexenyl radical undergoes intramolecular trapping by the pendant olefin and leads to annulated products (Table 26).

Very recently, Galatsis reported a ring expansion strategy making use of iodo spiroepoxides (Scheme 20).[60] Thus, epoxide ring opening is followed by β-scission of the alkoxy radical yielding a primary radical, which then undergoes *endo* or *exo* cyclization to the olefin to yield two-carbon or one-carbon ring expansion products, respectively. Further examples are listed in Table 27.

Scheme 18



Scheme 19

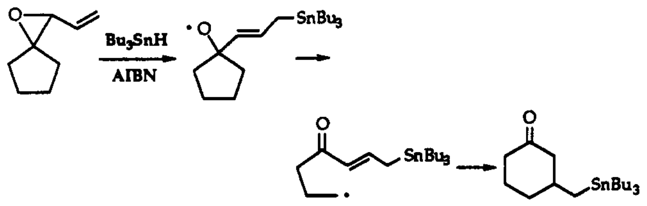
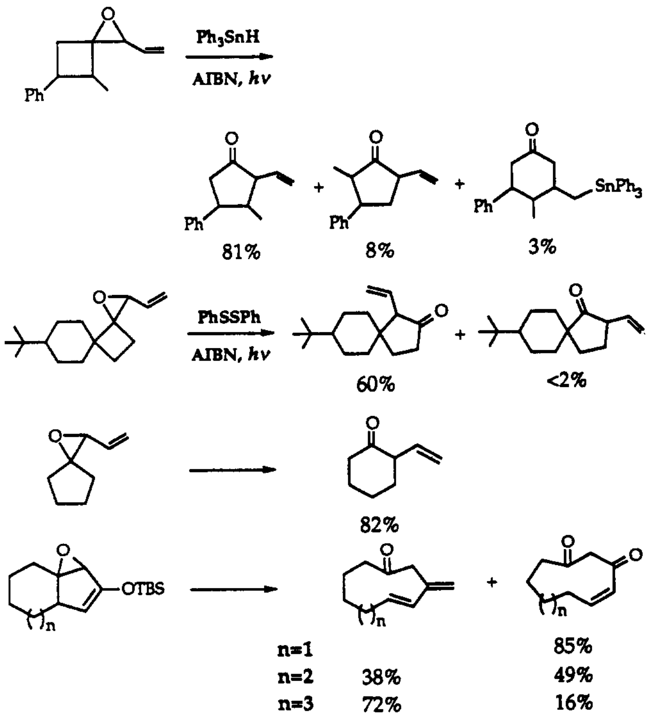


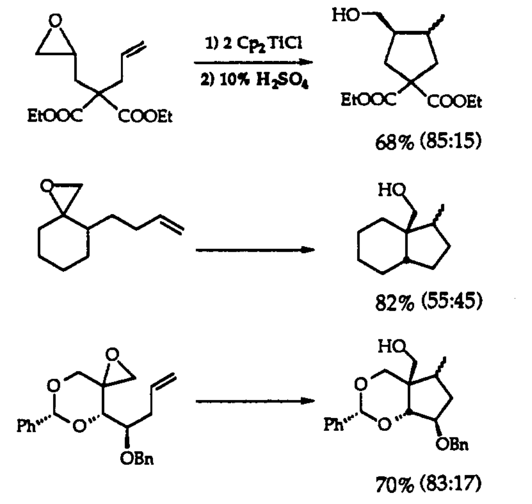
Table 25. Vinyl Epoxide Fragmentations



B. Carbon–Carbon Bond Cleavage

When the epoxide bears vinyl or aryl groups, carbon–carbon bond cleavage is often the main course of oxiranylcarbinyl radical ring opening (eq 42).[61a] A recent example of ring expansion in a ring-fused epoxide

Table 26. Transition Metal-Initiated Epoxide Fragmentation[a]



[a] Values in parentheses are *cis/trans* or *endo/exo* product ratios.

Scheme 20

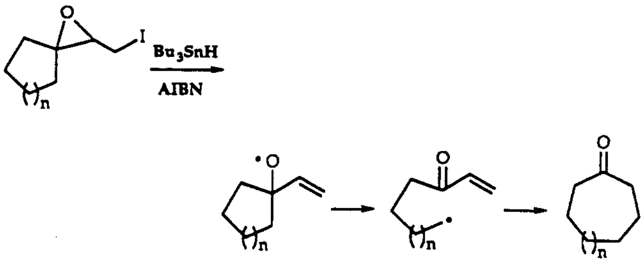
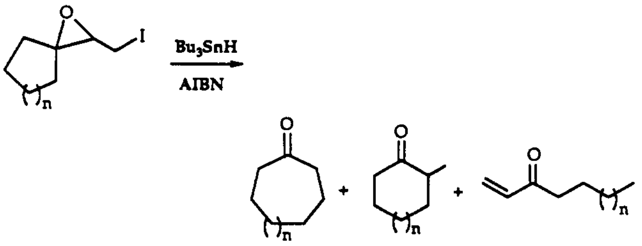
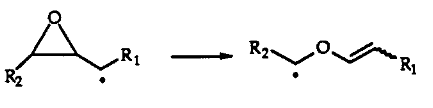


Table 27. Ring Expansion of Spiroepoxide



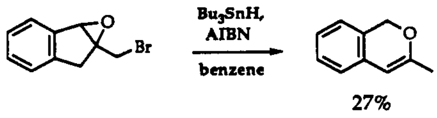
n = 1	9%	20%	
n = 2	23%		5%
n = 3	20%		16%
n = 8	47%		15%



(42)

R_2 = vinyl or aryl

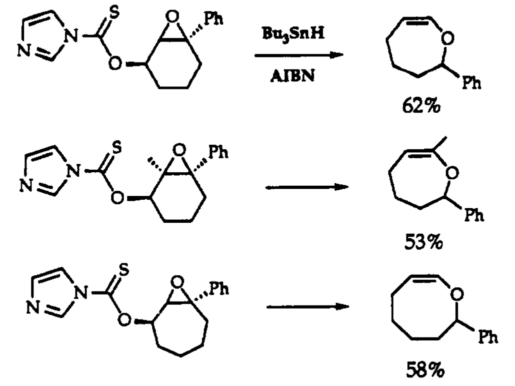
is showed in eq 43.[61b]

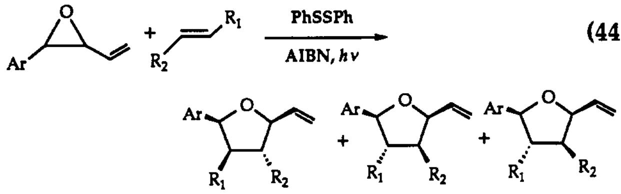


(43)

Feldman developed a radical-induced [3 + 2] ring expansion of vinyl epoxides leading to tetrahydrofurans (eq 44).[62] An analogous method has been developed for the synthesis of seven- and eight-membered oxygen heterocycles (Table 28)[58a] starting from the imidizolethioate esters.

Table 28. Formation of Oxygen Heterocycles





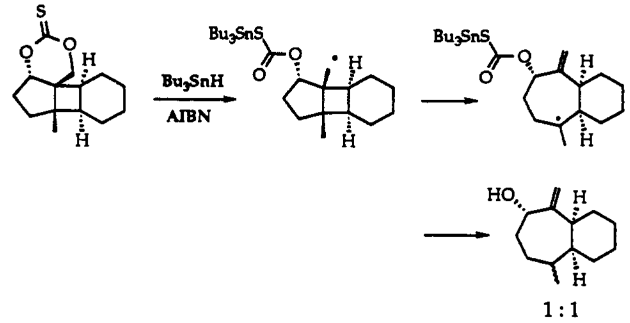
(44)

Ar=Ph; R_1=H; R_2=CO_2Me	36%	20%	
Ar=2-furanyl; R_1=H; R_2=CO_2Me	26%	12%	
Ar=Ph; R_1=CH_3; R_2=CO_2Me	31%	21%	5%

VIII. Fragmentation of Cyclobutylcarbinyl Radicals

Beckwith, Walton, and Ingold studied the stereoelectronic requirements for irreversible fragmentation of the parent cyclobutylcarbinyl radical.[63] Rapid ring opening of cyclobutylcarbinyl radicals provides another approach to ring expansion. For example, Ziegler reported the fragmentation of a cyclobutylcarbinyl radical leading to a bicyclic product (Scheme 21).[64]

Scheme 21



Noteworthy is the cleavage of the thiocarbonyl derivative at the primary carbon–oxygen bond. The resulting primary radical underwent exclusive ring opening at the more substituted cyclobutane bond to yield a 1:1 diastereomeric mixture of ring expansion products.

Crimmins has recently observed an interesting ring expansion in his triquinane subergorgic acid studies (Scheme 22).[65] Thus, radical-induced cleavage of the thiocarbonate leads to the cyclobutylcarbinyl radical. Carbon–carbon bond cleavage opens the cyclobutanone ring and releases the primary radical. Addition of the

Scheme 22

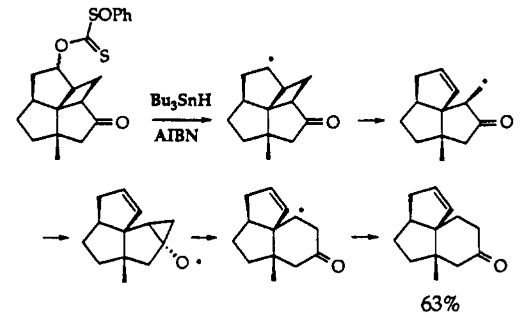
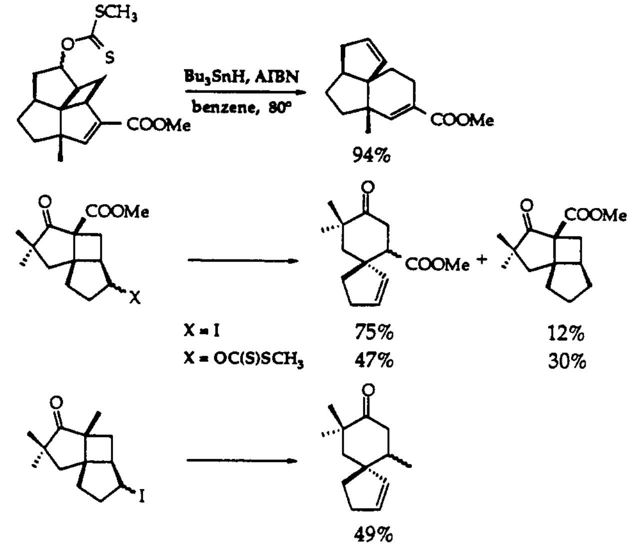


Table 29. *Exo* Fragmentation of Cyclobutylcarbinyl Radicals Accompanied by Ring Expansion



latter to the adjacent carbonyl then leads through the familiar cyclopropyloxy radical to the ring expanded product.

There are two distinct rearrangements in this series. In the first case, *exo* fragmentation of a cyclobutylcarbinyl radical is followed by one-carbon ring expansion (Table 29). In the other case *endo* fragmentation of cyclobutylcarbinyl radicals leads directly to the ring expansion products without further rearrangement (Table 30). Subtle substituent effects appear to be at work here.

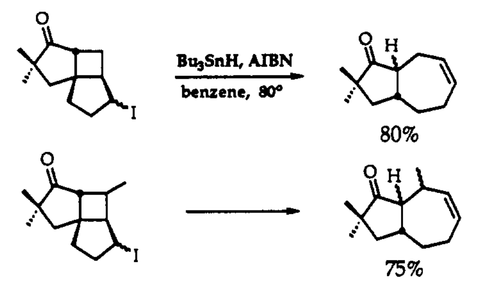
IX. Hydrogen Transfer in Ring Expansion

A. Ring Expansion Promoted by 1,5-Hydrogen Transfer

Intramolecular hydrogen transfer is an important process in free radical rearrangements. Rawal has introduced a new method which combines fragmentation with intramolecular hydrogen abstraction (Scheme 23).[66] Thus, the reactive alkoxy radical arising from epoxide fragmentation undergoes 1,5-hydrogen atom transfer to give the more stable radical adjacent to the ester. That radical is then positioned for cyclization to the double bond leading to the bicyclic product. More examples are listed in Table 31.

An analogous epoxide-opening strategy has been reported by Kim (Scheme 24).[67a] In this instance, fragmentation of the epoxide is initiated by tributyltin radical addition to the methylene group; sequential 1,5-hydrogen transfer then yields the product bicyclic alcohol (eqs 45 and 46).

Table 30. *Endo* Fragmentation of Cyclobutylcarbinyl Radicals



Scheme 23

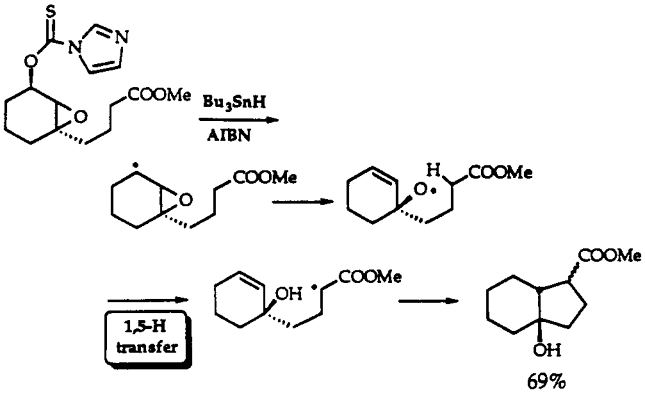
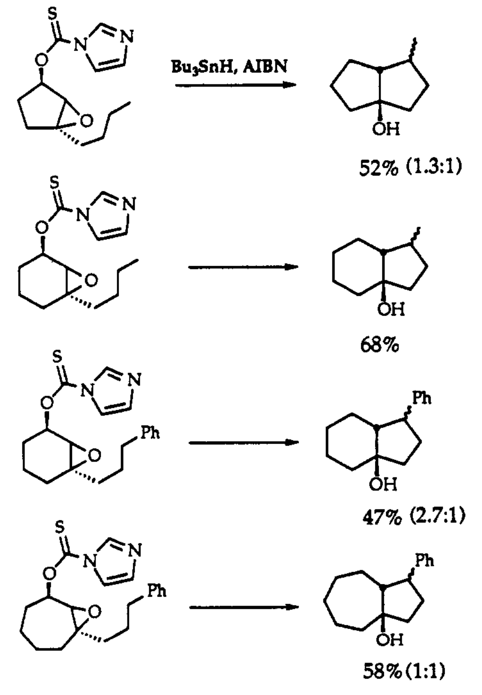


Table 31. Formation of Bicyclic Alcohols[a]



[a] Values in parentheses are ratios of diastereomers.

This strategy has been further developed to include acetoxyalkenyl epoxides (Table 32),[68a] epoxy silyl enol ethers (Table 33),[69] and epoxy ketones (Table 34).[67b,68b]

Kim reported an elegant ring-forming radical reaction of vinyl epoxides based on a 1,5-shift of a tributyltin group (Scheme 25)[67a] as a variation on the 1,5-hydrogen

Scheme 24

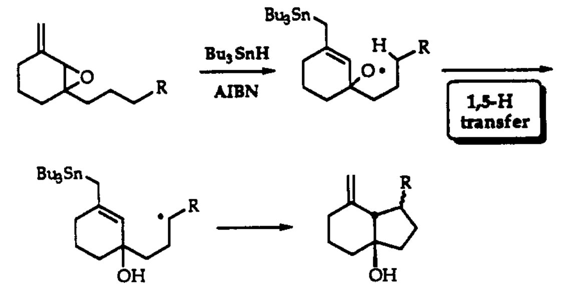
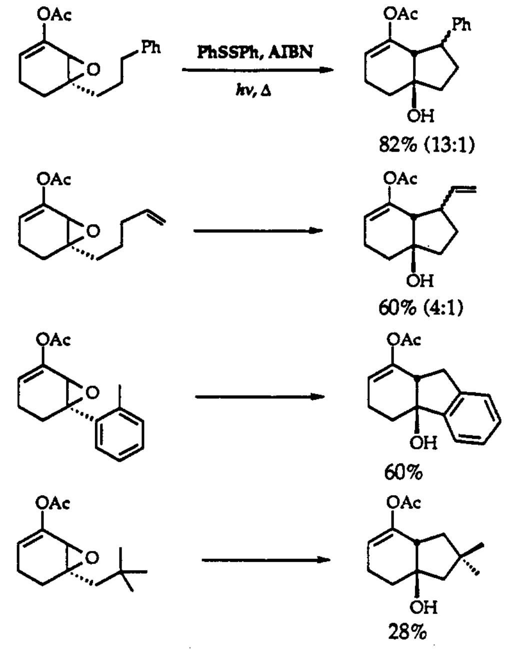
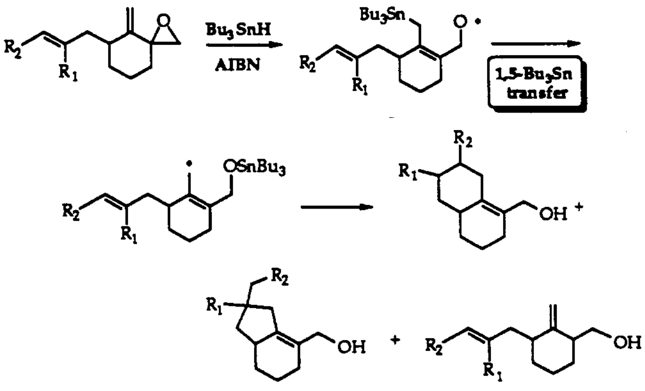


Table 32. Fragmentation of Acetoxyalkenyl Epoxides[a]



[a] Values in parentheses are the *exo*/*endo* product ratios.

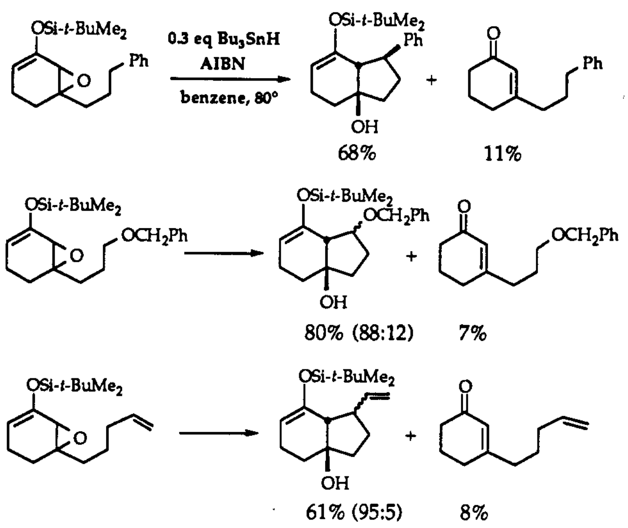
Scheme 25



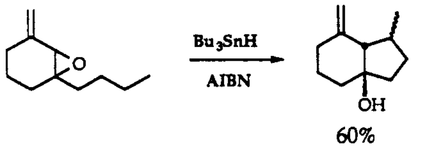
transfer strategy. The reaction is initiated by addition of the tri-*n*-butyltin radical to the vinyl epoxide and is followed by epoxide fragmentation to form the alkoxy radical. Tri-*n*-butyltin transfer to the alkoxy radical yields an alkyl radical that adds to the olefin to form the annulated product. Table 35 shows several more examples.

B. Ring Expansion Precluded by 1,5-Hydrogen Transfer

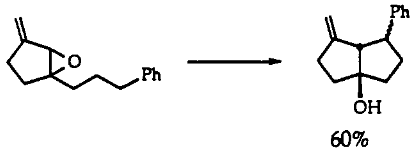
Table 33. Fragmentation of Epoxy Silyl Enol Ethers[a]



[a] Values in parentheses are the *exo*/*endo* product ratios.

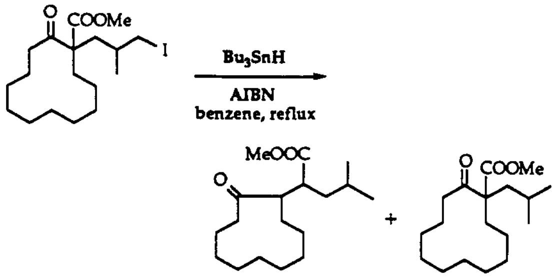


(45)



(46)

Although intramolecular hydrogen transfer has been successfully used for ring expansion, examples of ring expansion by 1,5-hydrogen transfer have also been reported. During an exploration of the direct synthesis of muscone,[14] we studied a three-carbon ring expansion of a 12-membered β-keto ester, the outcome was ring contraction, rather than the intended ring expansion (eq 47). The transformation can be formulated in terms of an internal hydrogen abstraction (Scheme 26).

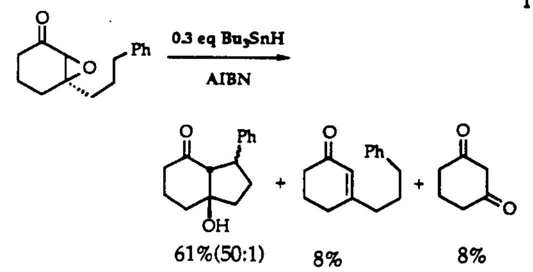
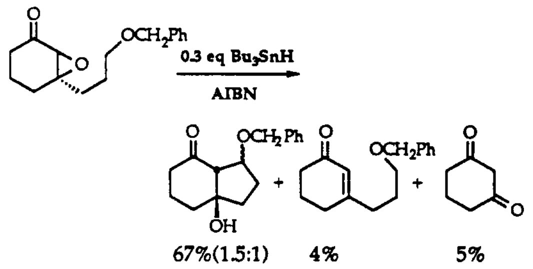
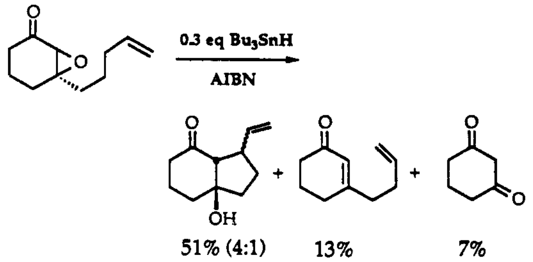
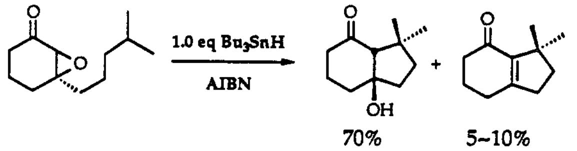
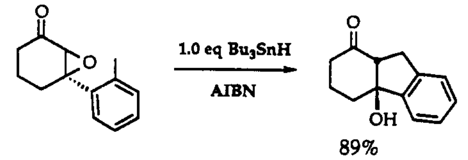
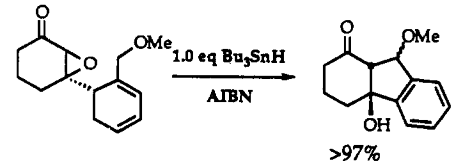


(47)

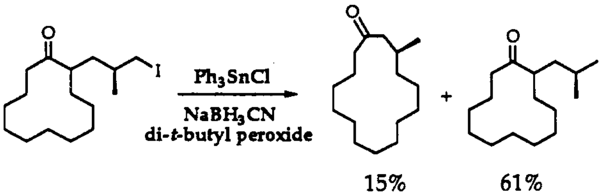
As noted earlier, the ester plays a useful role in facilitating alkylation and possibly providing inductive activation of the ketone, but the ester group is not indispensable in the three-carbon ring expansion. Removal of the ester group led to the desired ring expansion, albeit in only 15% yield because of competing direct reduction. Nonetheless, this made possible an expeditious synthesis of (*R*)-(−)-muscone (eq 48).

An interesting example of ring expansion accompanied by ring contraction and initiated by 1,5-hydrogen abstraction in the same reaction sequence is shown in Scheme 27.[10b]

Table 34. Fragmentation of Epoxy Ketones[a]

	reference
	67b
	67b
	67b
	68b
	68b
	68b

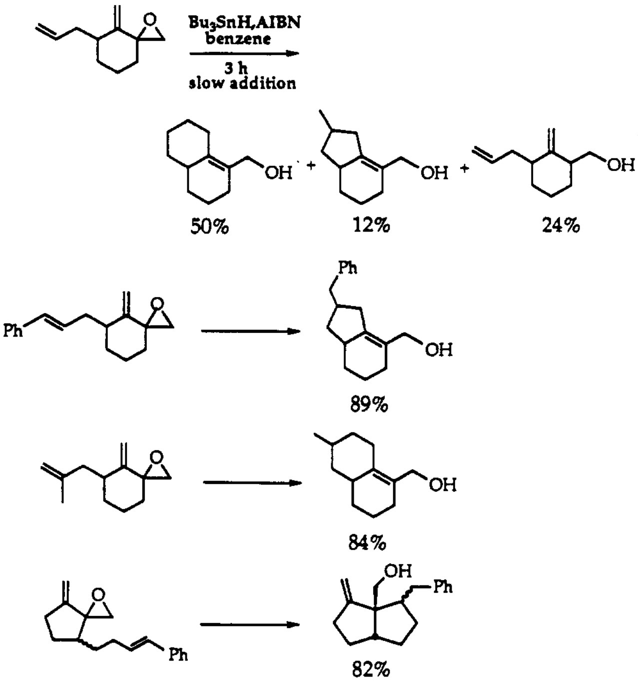
[a] Values in parentheses are the *endo/exo* product ratios.



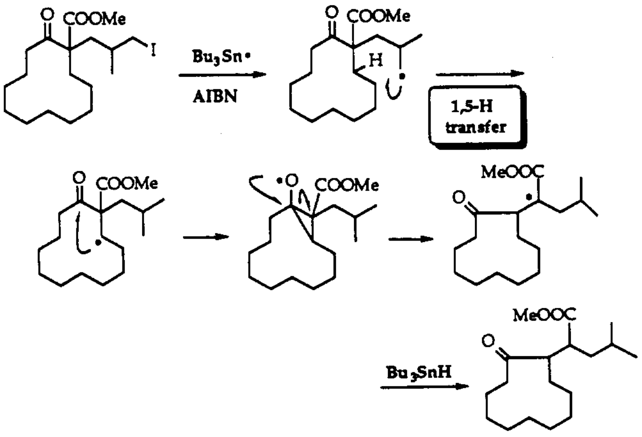
(48)

(R)-(-)-muscone

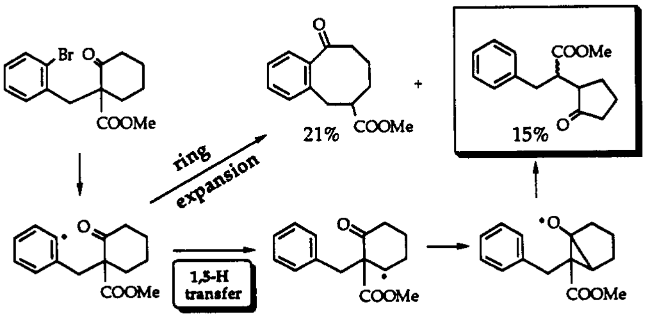
Table 35. 1,5-Bu₃Sn Transfer Vinyl Epoxide Reactions



Scheme 26



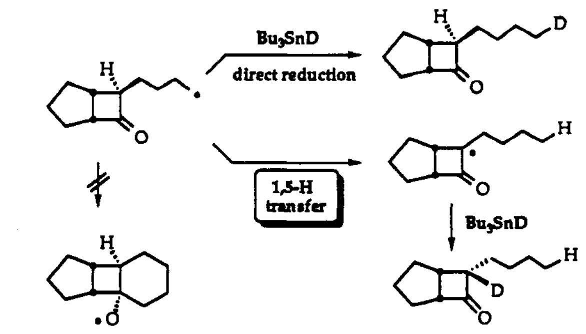
Scheme 27



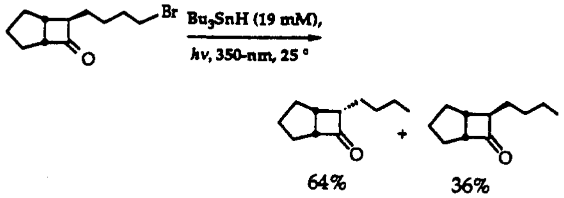
In the four-carbon ring expansion of fused cyclobutanones, a substituent group at the 5-position is essential to forestall internal hydrogen abstraction.[29,30] Free radical reaction of (4-halobutyl)cyclobutanones, unsubstituted at the 5-position, leads to an *exo/endo* mixture of direct reduction products. It can be demonstrated that 1,5-hydrogen transfer precludes ring expansion and that the initial primary radical is quenched by internal hydrogen transfer as shown in Scheme 28.[30]

There is competition between 1,5-hydrogen transfer and direct reduction. With the *exo*-bromide, 1,5-hydrogen abstraction by the initial, primary, side chain radical yields the cyclobutyl radical. Approach of tin hydride from the least hindered side then results in a preponderance of *endo* product (Scheme 28). Accordingly, the ratio of *exo* to *endo* products provides a measure of the extent of 1,5-hydrogen transfer. At relatively high concentrations of Bu_3SnH (19 mM), the

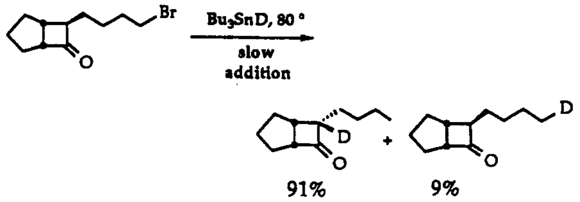
Scheme 28



ratio of 1,5-hydrogen transfer to direct reduction product is 64:36 (eq 49). Slow addition will favor 1,5-hydrogen abstraction, and under these conditions, treatment with Bu_3SnD leads to a 91:9 ratio of ring versus side chain deuteration (eq 50).



(49)



(50)

Recently, Batty and Crich designed a multiple radical cyclization fragmentation sequence leading to the formation of a 10-membered ring. Their aim was not achieved because a 1,5-hydrogen transfer process intervened.[70] Scheme 29 shows that the acyl radical generated from 7-cyclopropyl-7-(phenylseleno)heptenoate undergoes smooth cyclization to the olefin, followed by fragmentation of the cyclopropylcarbinyl radical to give a 1:2 mixture of *E* and *Z* isomers. The *E* isomer is reduced without further rearrangement, while the *Z* isomer undergoes intramolecular 1,5-hydrogen transfer to give a stabilized radical intermediate that is quenched selectively at its exocyclic terminus.

X. β-Scission of Alkyloxy and Iminyl Radicals

Ring expansion can be effected by cleavage of alkoxy radicals, as illustrated by many of the examples above. Highly reactive alkoxy radicals can be generated by numerous other methods including hypohalite thermolysis and/or photolysis,[71-74] oxidation of alcohols with heavy metal salts,[75] peroxide reduction,[76] nitrite ester photolysis,[77] and *N*-alkoxypyridinethione decomposition.[78] Recently, (diacetoxyiodo)benzene (DIB)[79,80] has been developed as an efficient reagent for the generation of alkoxy radicals. These methods have been employed in the ring expansions shown in Table 36.

Particularly noteworthy is the pioneering work of Beckwith[72] and McDonald[73] in the examination of ring opening reactions of decalinoxy radicals. Beckwith demonstrated that ring opening occurs preferentially toward the secondary and primary radicals depending upon temperature. As part of this series of experiments, attempts were made to observe cyclization of the radical from 2-butycyclohexanone but these experiments yielded only direct reduction products with no other identified products (eq 51). This result highlights the activating effect of the ester and the necessity of preventing hydrogen abstraction from the α position. The presence of the ester made possible the successful carbon radical ring expansions discovered subsequently (Table 8).[10b,25]

Scheme 29

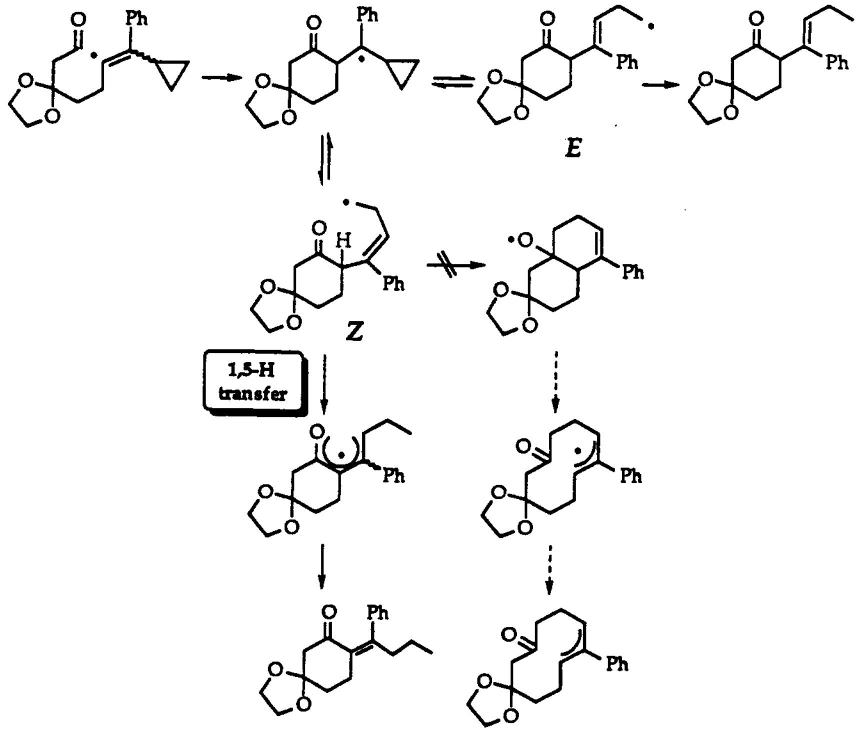
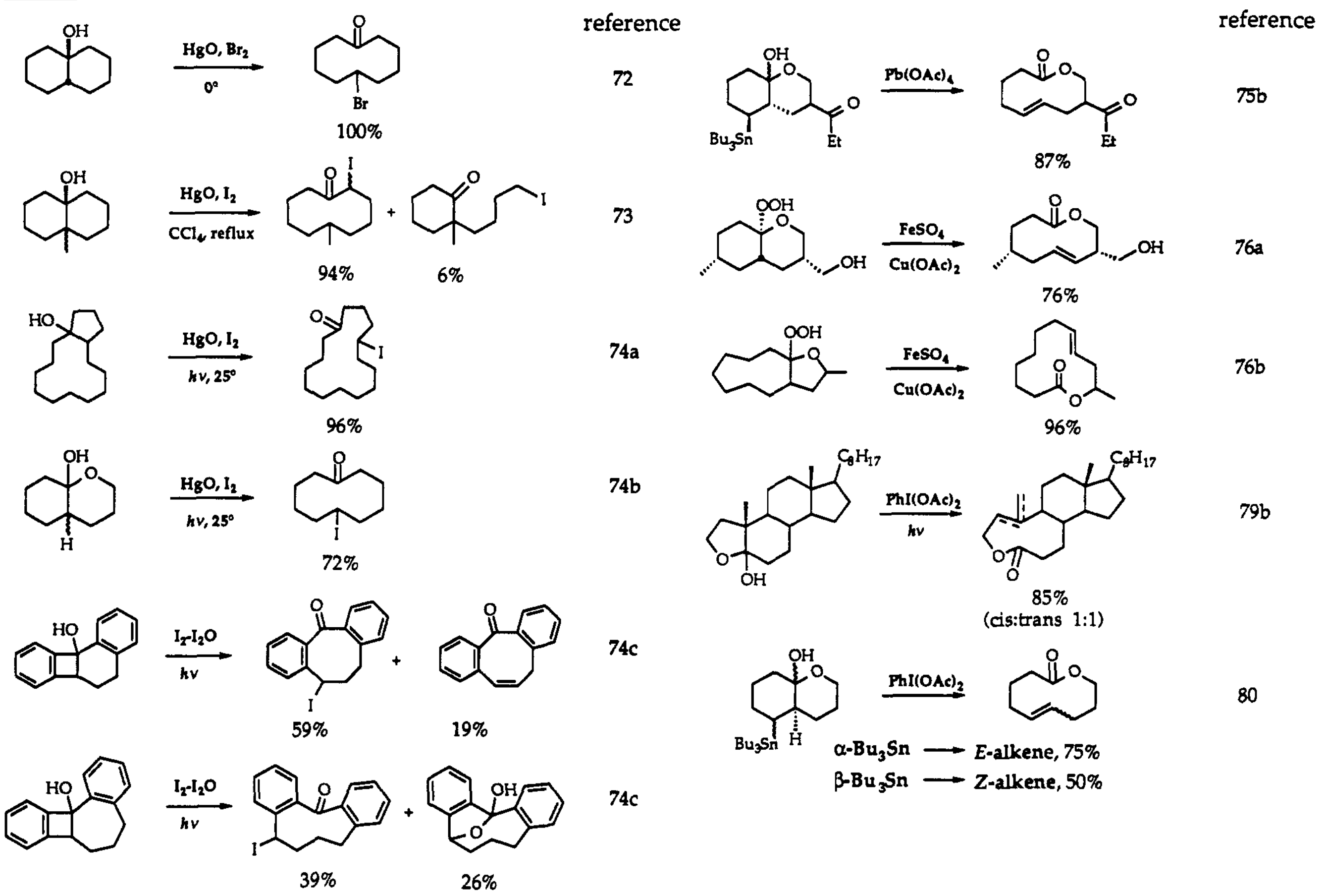
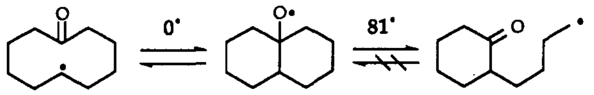


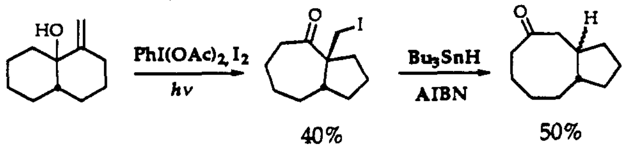
Table 36. Ring Expansion by β-Scission of Oxy Radicals



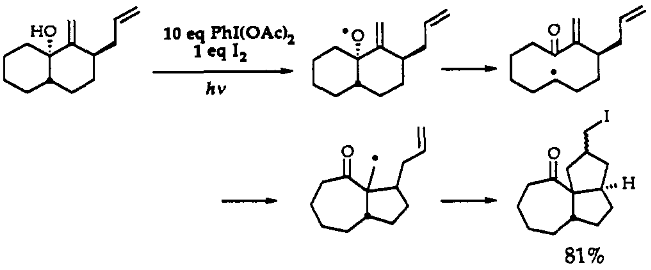


(51)

Pattenden employed an alkoxy radical fragmentation with transannular radical addition and subsequent tin hydride ring expansion to produce a bicyclic ketone (eq 52).[81a] A further refinement of the tandem fragmentation–transannular addition made use of a subsequent cyclization to afford tricyclic ketone (eq 53).[81b]



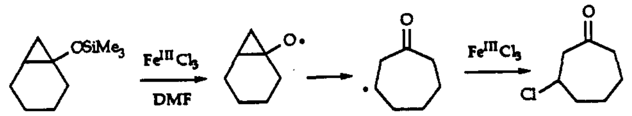
(52)



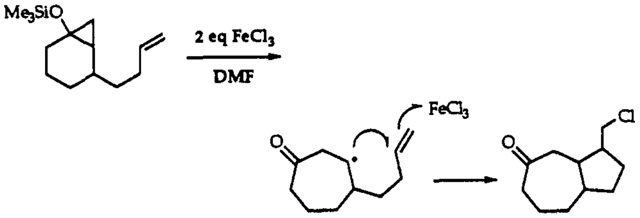
(53)

Reaction of [(trimethylsilyl)oxy]bicyclo[n.1.0]alkanes with Fe^{III}Cl$_3$ has been used to prepare one-carbon ring-expanded ketones by Saegusa (Table 37).[82a] An alkoxy radical mechanism was suggested for this sequence (Scheme 30). This strategy has been further developed for cyclodiones (eqs 54 and 55)[82a] and for macrocyclic tetraketones (eq 56).[82b]

Scheme 30

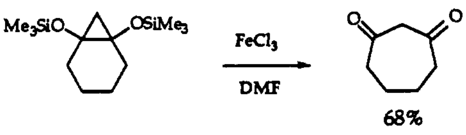


Scheme 31

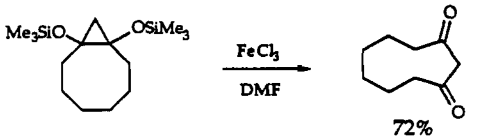


Recently, a tandem ring expansion–cyclization reaction was reported by Booker-Milburn (Scheme 31).[83] Treatment of the cyclopropyl silyl ether with ferric chloride produced 5,7-bicyclic chloro ketones by β-scission of the alkoxy radical and sequential cyclization (Table 38).

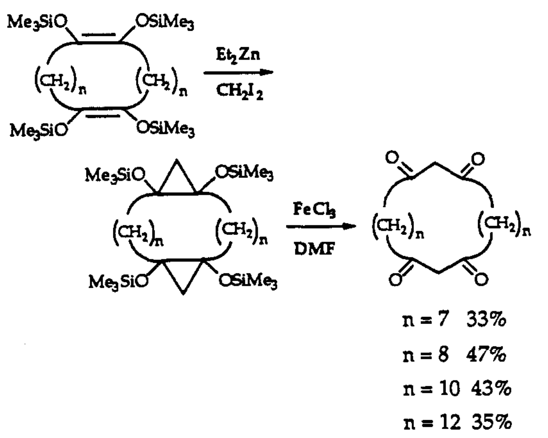
Narasaka reported the generation of β-keto radicals from cyclopropanol derivatives using manganese(III) tris(2-pyridinecarboxylate) (Mn(pic)$_3$). β-Keto radicals can either be trapped by olefins intermolcularly[84a] to give functionalized ring expansion products, or first trapped by olefins intramolecularly[84b] and then added



(54)



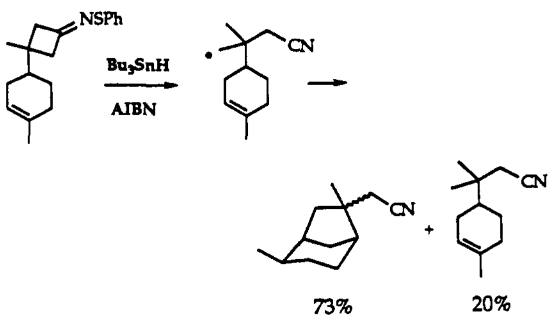
(55)



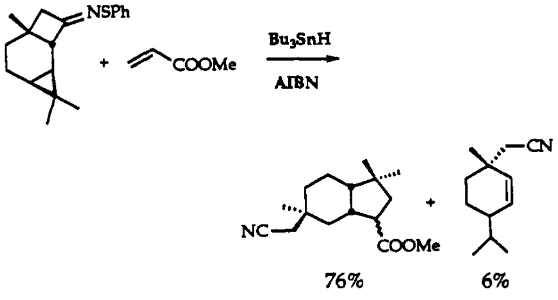
(56)

to a second olefin intermolecularly to give ring expansion–annulation products (Table 39).

Iminyl radicals have not been exploited as fully as alkoxy radicals because of the difficulty of generating such species. Recently, Zard described a general method for producing iminyl radicals from *S*-arylsulfenylimines using tri-*n*-butyltin hydride[85a,b] and used this technique to induce β-scission of cyclobutylimino radicals.[85c] The ring-opened radicals have been trapped by olefins intramolecularly to produce a bridged bicyclic product (eq 57) or intermolecularly to afford a [3 + 2] adduct (eq 58).[85c]



(57)



(58)

Table 37. Synthesis of 2-Cycloalkenones

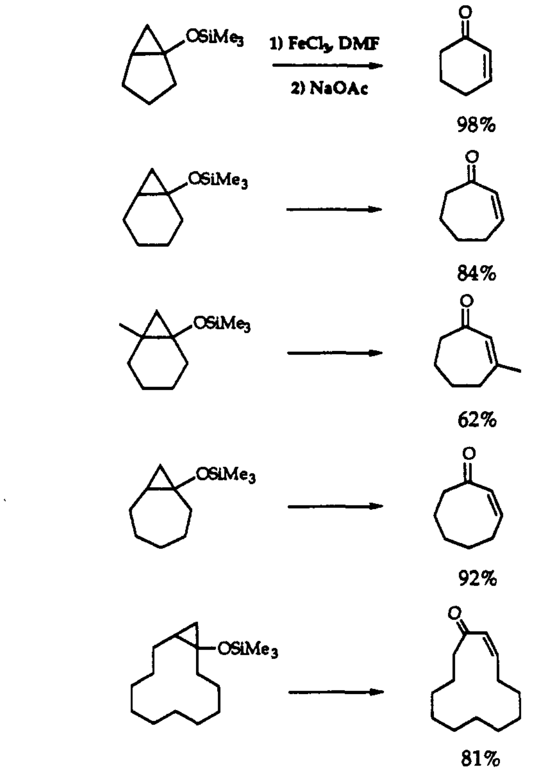
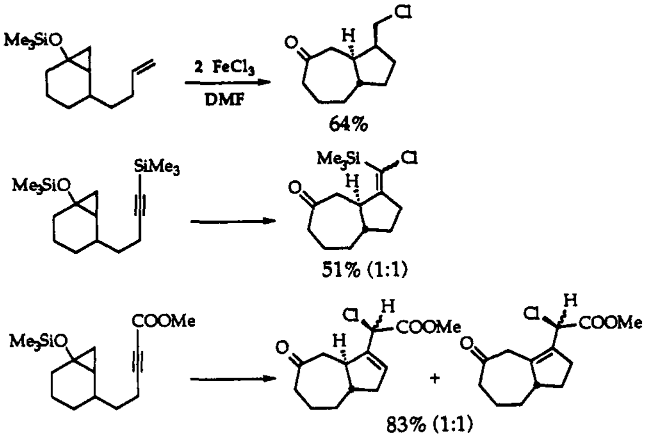


Table 38. Ring Expansion of Cyclopropyl Silyl Ethers[a]



[a] Values in parentheses are ratios of isomers.

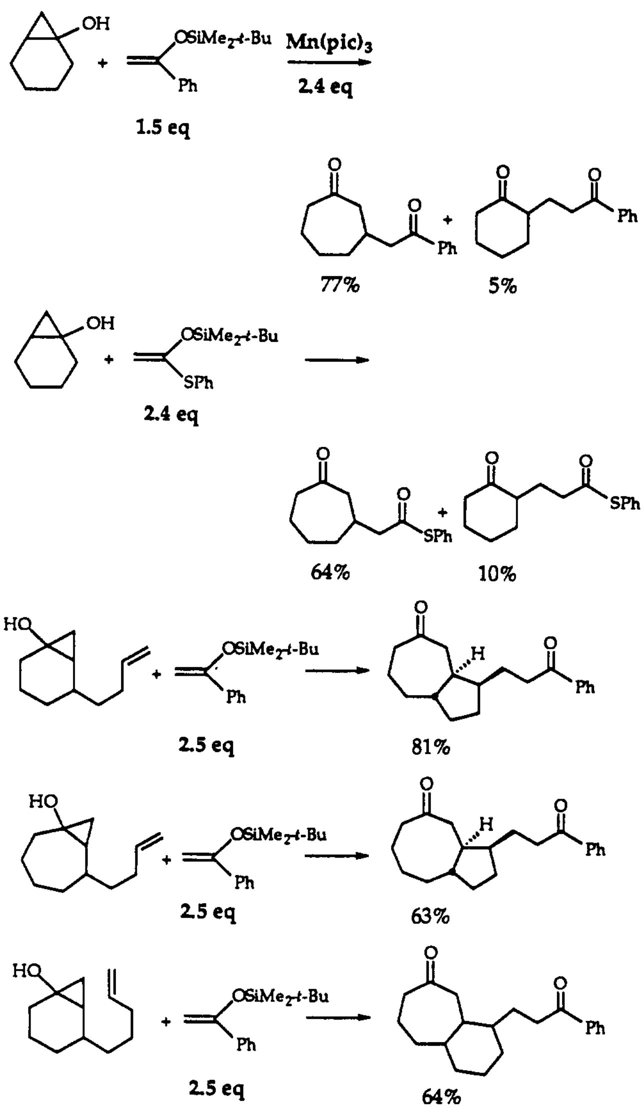
XI. Ring Contractions

Several examples of ring contraction have been reported as byproducts of the explorations of free radical expansion (see section IX.B). 1,5-Hydrogen transfer is involved in this kind of ring contraction. Another interesting ring contraction sequence has been observed by Lee as an offshoot of studies of the 8-endo cyclization of (alkoxycarbonyl)methyl radicals (Scheme 32).[86] A plausible mechanistic pathway for the formation of the bicyclic lactone is shown in Scheme 32. β-Scission of the alkoxy radical, formed from the addition of alkyl radical to the carbonyl, plays a key role in this transformation.

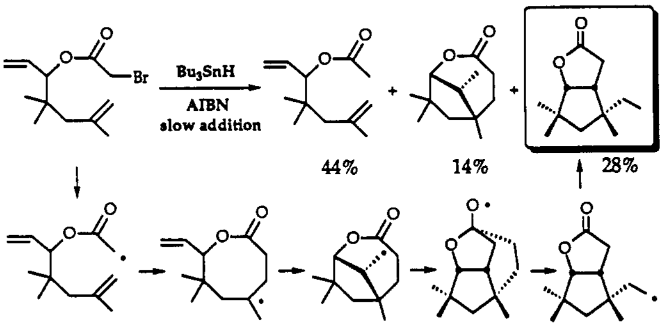
XII. Summary

In this review we have surveyed the relatively young field of free radical ring expansion and annulations.

Table 39. Ring Expansion of Cyclopropanols



Scheme 32



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