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Free-Radical Carbon-Carbon Bond Formation in Organic Synthesis

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Summary. Organic chemists have begun to use intra- and intermolecular free-radical addition reactions to develop useful synthetic transformations. Carbon-centered radicals can form bonds with electron-rich or electron-deficient alkenes, allenes, and acetylenes. Radical addition reactions can also be used to construct hindered carbon-carbon bonds. These characteristics, as well as the large number of functional groups that tolerate free-radical conditions contribute to the importance of such reactions in organic synthesis.

One of the most important problems in the synthesis of complex organic compounds is the construction of carbon-carbon bonds. This task is inherently difficult because of the character of the atoms involved in the bond. Thus, to construct a carbon-carbon bond it is necessary to perturb the electronic properties of the carbon atoms involved in a manner that encourages them to couple. In spite of this inherent problem, nature and man have become rather proficient at carbon-carbon bond construction. In the laboratory and in biosynthesis, carbon-carbon bond-forming reactions are dominated by polar processes in which nucleophiles and electrophiles couple to afford new bonds (*1*). Most polar coupling processes revolve around the chemistry of the carbonyl group. Less common in nature, but well known in the laboratory, are nonpolar coupling reactions which result in carbon-carbon bond formation. Nonpolar processes can be divided into several major categories. Two of these, for example, are pericyclic reactions (electrocyclizations, sigmatropic rearrangements, certain cycloadditions) and free radical addition reactions (*2*). Pericyclic reactions have been well developed and are now appreciated as tools for the construction of highly functionalized organic compounds (*3*). On the other hand, synthetic organic chemists have made only limited use of free radical carbon-carbon bond-forming addition reactions in the synthesis of polyfunctional molecules (*4*). In the last few years, however, free-radical addition reactions have gained popularity, and their use in the construction of complex organic compounds is being evaluated by a number of research groups. In this article, I focus on some of the recent advances in this rapidly developing area of synthesis.

An abbreviated mechanism for the free-radical chain addition of an addend (R-X) across a terminal double bond is shown in Eqs. 1 to 3. A large number of

Initiation

$$R\text{-}X + In\cdot \longrightarrow R\cdot + In\text{-}X \quad (1)$$

Addition

$$R\cdot + CH_2{=}CHR' \longrightarrow RCH_2\text{-}\dot{C}HR' \quad (2)$$

Chain Transfer

$$RCH_2\text{-}\dot{C}HR' + R\text{-}X \longrightarrow RCH_2CH(X)R' + R\cdot \quad (3)$$

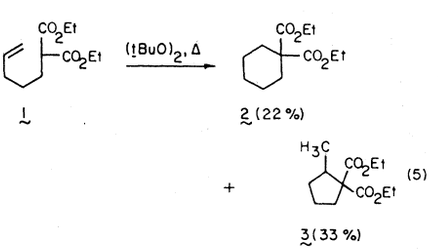
intermolecular additions of this type are known. For example, addition reactions of alkyl, aryl, acyl, α-halo, α-oxy, α-amino, and α-carbonyl radicals, among others, had all been reported by the end of the 1950's and the subject has been reviewed (*5–11*). The success of such reactions depends on a number of factors. First, site specific generation of R· is obviously important. Second, attack of the adduct radical $RCH_2\dot{C}HR'$ on the addend must occur at a rate faster than that of addition of $RCH_2\dot{C}HR'$ to the olefin. The later process leads to telomer and polymer formation, a major problem in radical addition reactions. Finally, the addition and chain transfer steps must compete favorably with chain-terminating reactions, such as certain hydrogen atom transfers (as in the allylic H-atom transfer) and radical combination reactions. In short, the success of a radical chain addition depends on a delicate balance of reaction rates that are sensitive to the structure of the initiator, addend, and unsaturated compounds involved.

A specific example of an intermolecular addition is shown in Eq. 4 (*12*). In this

$$CH_3(CH_2)_7CH{=}CH_2 + CH_2(CO_2Et)_2 \xrightarrow[75\%]{(CH_3)_3COOC(CH_3)_3} CH_3(CH_2)_9CH(CO_2Et)_2 \quad (4)$$

case, initial radical generation was accomplished by means of a hydrogen atom transfer between *t*-butoxy radicals and diethyl malonate and olefin telomerization was controlled by the use of a tenfold excess of the ester.

The intramolecular counterparts of a number of the reactions mentioned above are also known (*13–17*). For example, an intramolecular variant of the malonate addition (Eq. 4) is shown in Eq. 5 (*18*). By far the most studied intramolecular additions are those of 5-hexenyl radicals. Largely through the efforts of Walling, Ingold, Beckwith, and Julia, it has been shown that initial radical structure, steric effects resulting from olefin substitution patterns, and geometric constraints on the chain linking the olefin



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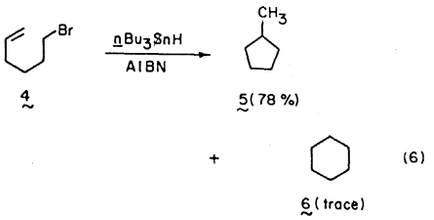
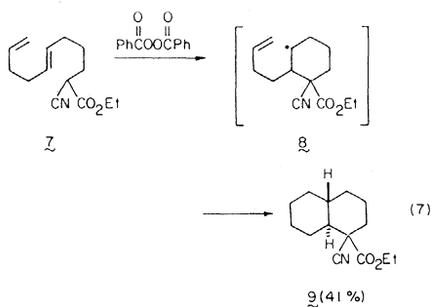
and radical are factors in governing cyclization regiochemistry (*19–27*). For example, the parent 5-hexenyl radical (Eq. 6), derived here from halogen atom abstraction by tri-*n*-butyltin radicals, gives



(6)

almost exclusively methylcyclopentane (*19, 28*). In contrast, the radical derived from **1** (Eq. 5) affords a mixture of five- and six-membered ring products, in part because of reversibility of the malonate cyclization (*29*). Finally, an attractive feature of the radical cyclization is that many of the rate problems associated with the slower intermolecular counterparts are eliminated.

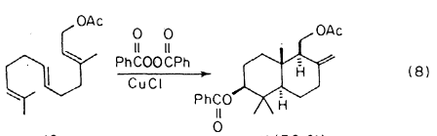
In view of the widespread occurrence of interesting carbocyclic and heterocyclic structures in nature, much research has focused on the development of free-radical cyclization reactions. The earliest contributions to this area emanated largely from the Julia laboratories (*23–26*). Among the numerous systems studied was the polycyclization shown in Eq. 7 (*29*). The conversion of **7** to **9** involved



(7)

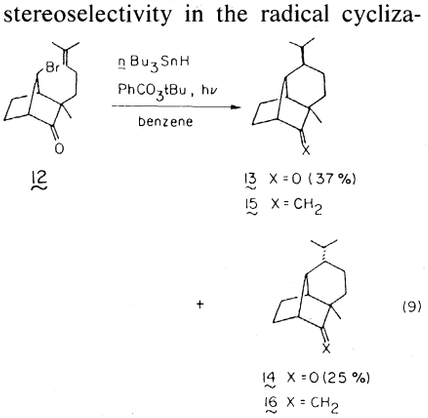
two sequential 5-hexenyl radical cyclizations, each affording cyclohexyl radicals. This early example illustrated the potential of radical cyclizations in carbocycle synthesis and, in retrospect, also showed that remote changes in substituents could profoundly influence the regiochemical course of cyclizations. For example, the cyclization of intermediate radical **8** to afford decalin **9** rather than a perhydroindane is still puzzling (*30*).

Another remarkable example of carbocycle synthesis via free-radical cyclizations is shown in Eq. 8 (*31*). The outstanding feature of this reaction is the degree of stereoselectivity.



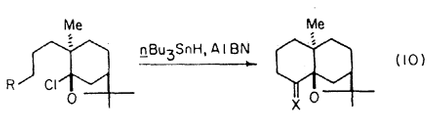
(8)

In spite of the promising work of Julia and co-workers, the use of free radical cyclizations in natural product synthesis design has only begun to surface. One conscious effort was the syntheses of the sesquiterpenes sativene (**15**) and capocamphene (**16**) (*32*). The crucial step involved cyclization of the 7-norbornyl radical derived from haloketone **12** to tricyclic ketones **13** and **14**. The major flaw in this synthesis was a lack of stereoselectivity in the radical cyclization. It is possible that uncertainty in directing the stereochemical course of radical reactions has served as a deterrent to their use in synthesis.



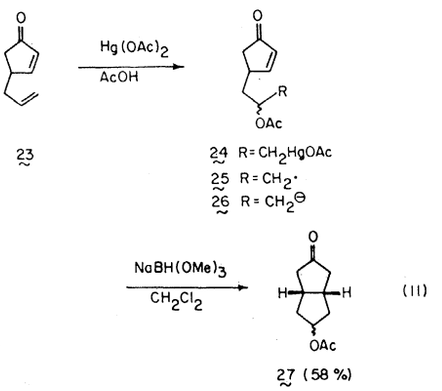
(9)

Similar stereochemical problems were encountered in a synthesis of dihydroagarofuran (**18**) (*33*). Cyclization of α-chloroether **17** gave a mixture of stereoisomers **18** (47 percent) and **19** (20 percent). When acetylene **20** was used as the cyclization substrate, however, a simple solution to the stereochemical problem was achieved. Cyclization of **20** gave vinylsilane **21** (72 percent) as a mixture of geometrical isomers. Protodesilylation of **21** and subsequent reduction of **22** with diimide gave dihydroagarofuran (**18**), contaminated with less than 5 percent of **19**. Thus, introduction of unsaturation permitted the control of stereochemistry by traditional means at a later stage of the synthesis.



(10)

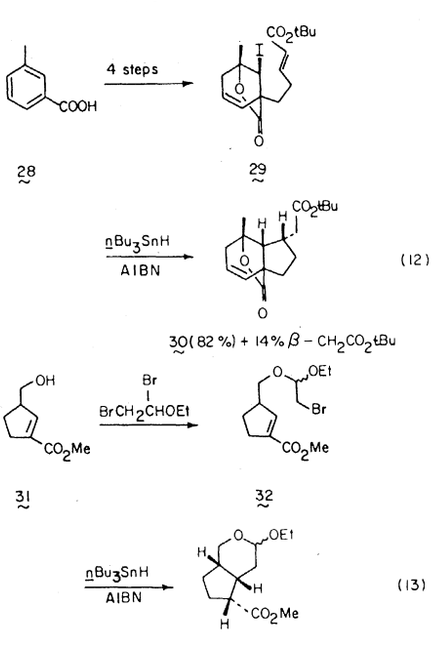
The most striking feature of the sesquiterpene syntheses outlined above is the unusual type of bond constructed in each radical cyclization. It is difficult to imagine efficient polar coupling reactions that would accomplish the same task, and therein lies the synthetic potential for many free-radical carbon-carbon bond-forming reactions. Another example of a bond construction that would be difficult to achieve by way of a polar coupling is shown in Eq. 11 (*34*). Reductive cyclization of the β-acetoxymercurial **24**, prepared by acetoxy-mercuration of dienone **23**, affords bicyclo[3.3.0]octane **27**, a substructure of a large number of natural products. This reaction presumably proceeds by cyclization of the intermediate β-acetoxy radical **25**, and a bond is formed between the radical center and an electrophilic fragment. Polar



(11)

construction of the same bond by hypothetical β-acetoxy carbanion **26** would be doomed because the nucleophilic component would undergo self destruction as a result of a β-elimination process (**26** → **23**). Thus, β-heteroatom substituted radicals can serve as surrogates for inaccessible or kinetically unstable nucleophiles.

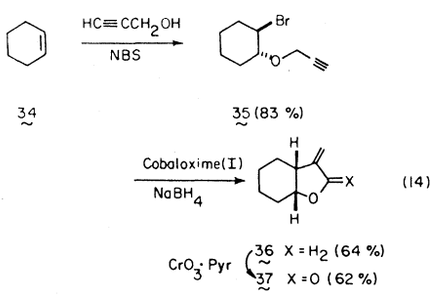
Two other potentially useful transformations also involve conjugate addition of radicals (Eqs. 12 and 13). In the conversion of **29** to the highly functionalized perhydroindane **30**, bond formation occurs at a sterically congested center and proceeds with good stereoselectivity (*35*). Although the exact reason for the



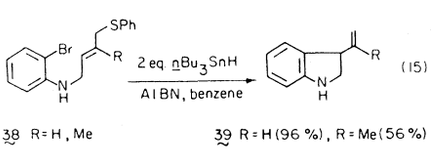
(12)
(13)

observed stereochemistry at C-7 in **30** is not clear, it is gratifying to find that the results in this relatively complex system are consistent with those reported for simpler carbocyclic systems (*36–38*). Stereoselectivity is also seen in the cyclization of bromoacetal **32** (*39*). Capture of the cyclized radical by tri-*n*-butyltin hydride from the convex face of the initially formed bicyclic system accounts for the observed stereoselectivity.

One important aspect of free-radical cyclizations is the question of maintaining functionality in the product. In all but one of the examples presented thus far, the cyclizations were terminated by hydrogen atom transfer. Although this may be desired in certain cases, reductive termination reduces the functionality in the product, sometimes rendering the initially unsaturated carbons inaccessible to further manipulation by oxidation or reduction techniques. One obvious ploy that has been used to increase the residual functionality is to increase the unsaturation in the starting material (for example, see Eq. 10) (*33*). Another interesting case, which results in annelation of an α-methylene lactone onto an olefin is shown in Eq. 14 (*40–42*). Here, a

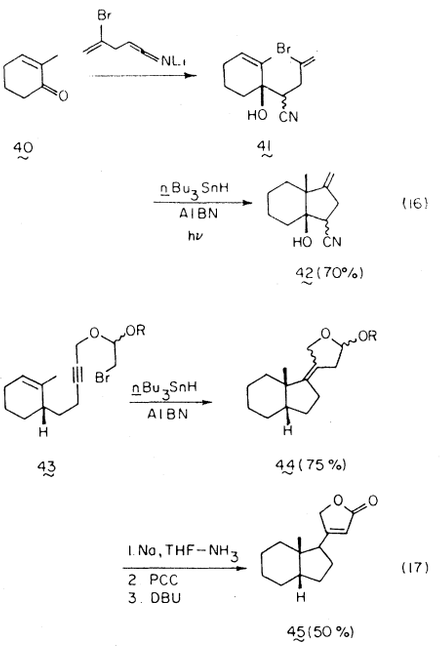


cobalt species, Co(I), serves as a catalyst for initial radical generation. Another tactic involves manipulation of the cyclized radical. Oxidation to a carbocation and subsequent deprotonation was used by Breslow *et al.* in the polycyclization shown in Eq. 8 (*31*). Cyclization termination by radical capture with halogen (*43*), sulfur (*44*), oxygen (*45*), cobalt (*46*), and even carbon (*47*) atoms has been reported although some of the examples are rather specialized and the generality of these methods is not secure. Another interesting method for producing residual functionality is



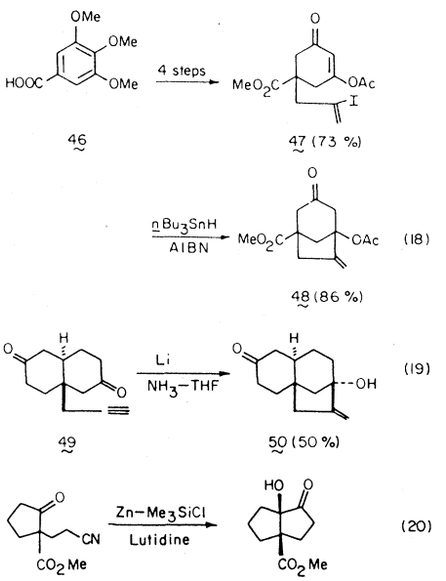
shown in Eq. 15 (*48*). In this reaction, an aryl radical cyclizes, and the resulting β-phenylthio radical fragments, yielding the dihydroindole **39** and phenylthiyl radicals. A second equivalent of tin hydride is needed to trap the phenylthiyl radical. Polymer supported tin hydrides have been used to initiate similar reactions and facilitate product isolation, an operational problem in many tin hydride initiated cyclizations (*49*). As will be seen, the radical addition-fragmentation strategy shows considerable potential for use in organic synthesis.

Recent interest in residual functionality has not been restricted to the unsaturated component of radical cyclizations. For example, Stork *et al.* have reported a number of vinyl radical cyclizations, two of which are shown in Eqs. 16 and 17

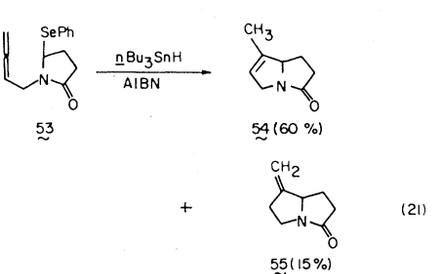


(*50–53*). These reactions, which serve as model studies for a synthetic approach to the cardiac aglycones, have several interesting features. Although radical addition reactions and cyclizations are sensitive to steric effects (*13, 54*), these cyclizations produce quaternary centers without complications. In addition, the vinylic fragments occupy predictable sites in the products and provide a handle for further manipulation. In Eq. 17, for example, tandem β-bromoacetal and vinyl radical cyclizations are followed by a few simple operations to afford butenolide **45**. The potential of vinyl radical cyclizations in synthesis is emphasized by the application outlined in Eq. 18 (*55*). Here, a bicyclo[3.2.1]octane related to gibberellic acid is assembled in a remarkably straightforward manner.

A similar bond to that constructed in Eq. 18 was prepared nearly 20 years earlier by reductive cyclization of ethynyl ketone **49** (Eq. 19) (*56*). Although the mechanism of the transformation was uncertain at the time, subsequent studies suggest that this reaction may involve cyclization of a radical anion derived from initial one electron reduction of the carbonyl group (*57, 58*). This cyclization strategy, which also leaves functionality at the initial radical site, has now been used to construct bonds between carbonyl carbons and acetylenes (*56–62*), olefins (*57–59, 62*), allenes (*61*), α,β-unsaturated esters (*62*), and nitriles (*62*). Important contributions have been the development of methods for ketyl generation that appear to be superior to those used in the initial studies. Thus, lithium naphthalenide (*57*), electrolytic reduction (*59, 61*), and zinc-chlorotrimethylsilane (*62*) appear to be useful for effecting certain cyclizations analogous to that shown in Eq. 19. Another example is shown in Eq. 20 (*62*).

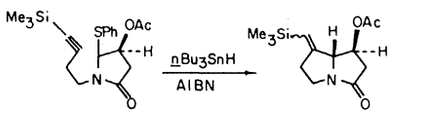


The application of radical cyclizations to the synthesis of natural products has not been limited to carbocycles and oxygen-containing heterocycles. For several years, my colleagues and I have focused on the development and use of α-acylamino radical cyclizations in alkaloid synthesis. Our early studies indicated that such cyclizations showed potential for the construction of pyrrolizidines and indolizidines, structural subunits of a large number of alkaloids (*63–65*). Two more recent examples are shown in Eqs. 21 and 22. Vinylsilane **57** has proved to be a useful intermediate in a synthesis of

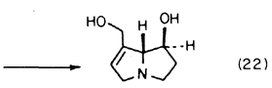


(−)-heliotridine (**58**) and several other pyrrolizidine alkaloids (*66*).

Independently, Bachi has studied α-acylamino radicals in the synthesis of β-lactam antibiotic analogs (*67–69*). The stability of the β-lactam nucleus and sensitive *N,O*-acetal in the example shown in Eq. 23 provides testimony to

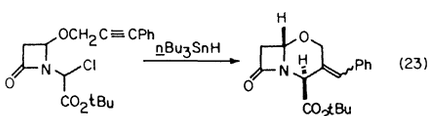


56 57 (68 %)



(22)

58

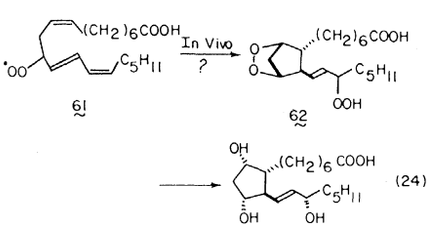


(23)

59 60 (64 %)

the mild nature of these cyclizations. In fact one of the outstanding features of free radical addition reactions is the array of functional groups which tolerate the reaction conditions.

Earlier in the article, it was noted that free radical carbon-carbon bond-forming reactions are rarely observed in biosynthesis. In closing this section, I note that carbocyclizations have been proposed to be involved in the biosynthesis of prostaglandins (Eq. 24) (*70*). Some evidence

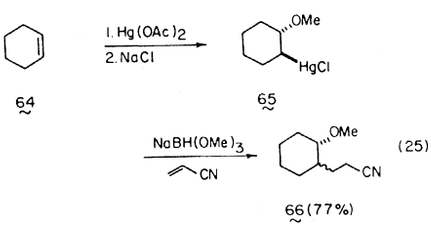


(24)

61 62 63 ($PGF_{1\alpha}$)

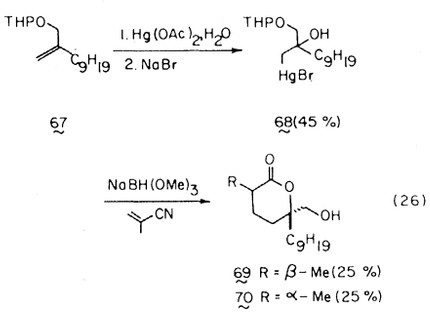
that supports the feasibility of this notion has been reported (*71–73*). Although a discussion of the pertinent studies on this topic is beyond the scope of this article, it is pleasing to see that free radical reactions, which show such promise in laboratory synthesis, may also be involved in the biosynthesis of this important class of molecules.

There has been less progress on the development of intramolecular addition reactions. This is due largely to the kinetic problems outlined earlier. Nonetheless, a few noteworthy contributions have appeared. Giese and his co-workers have reported several reactions in which *alkyl radicals*, generated by reduction of alkyl mercurials with sodium trimethoxyborohydride, were coupled with electron-deficient olefins (*74–76*). One simple example that has stimulated much interest is shown in Eq. 25 (*75*). In fact, it is this work which appears to have instigated the notion that radicals could serve as equivalents of inaccessible nucleophiles. Giese has also shown that γ-oxomercurials can serve as β-acylanion equivalents in the preparation of 1,6-dicarbonyl compounds (*76*). Ureidomercuration (*77*) and amidomercuration (*78*) have also been coupled with free radical additions to afford lactams, subunits of many alkaloids. A useful adaptation of this process involving hydroxymercuration has recently been developed within the context of a synthesis of the marine antibiotic malyngolide (**69**) (Eq. 26) (*79*). Alkyl iodides and selenides have also



64 65 66 (77 %)

(25)

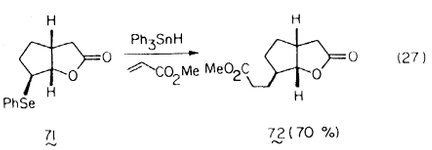


67 68 (45 %)

69 R = β-Me (25 %)
70 R = α-Me (25 %)

(26)

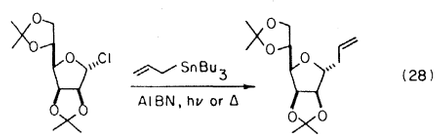
been used to generate radicals for use in intermolecular coupling with acrylates (*80*). An example which proceeds with clean stereochemistry is shown in Eq. 27.



71 72 (70 %)

(27)

One limitation of this group of intermolecular reactions is that the olefin must be used in large excess. As few as three, but more frequently 10 to 30 equivalents of olefin are needed. In addition, only a limited number of electron deficient alkenes work well. Recently, a promising strategy for dealing with the problem of stoichiometric coupling of radicals and alkenes has surfaced. Based on some early observations (*47, 81*), Keck and his co-workers have developed an efficient method for the allylation of a variety of carbon-centered radicals using allylstannanes (*82*). An impressive example appears in Eq. 28. In this reaction an initiation event affords an alkyl radical which adds to the terminus of the allylstannane. The resulting β-stannyl radical then fragments to give the allylated product and a chain-carrying tri-*n*-butyltin radical. Only two equivalents of allyl tri-*n*-butylstannane were required to achieve excellent yields of coupled products. In several examples, selenides and xanthates also served as initial radical precursors. This reaction has already been used in a synthesis of perhydrohistrionicotoxin which illustrates one way in which the pendant allyl group can be manipulated (*83*). Other applications in the areas of alkaloid synthesis (*84*) and in the preparation of the pseudomonic acid family of antibiotics (*82*) are under way.



72 73 (79 %)

(28)

Perhaps the most notable aspect of the allylstannane reaction is the exclusion of good hydrogen atom donors from the reaction system. In fact, reduction of the initially generated radical is a serious side reaction in a number of the inter- and intramolecular reactions that I have presented. It is likely that future advances in this area will focus on the development of other methods of radical generation in the absence of good hydrogen atom donors (*85*).

In this article I have tried to present examples which illustrate the recent explosion in the development and application of free-radical reactions to problems in organic synthesis. It is clear that this family of carbon-carbon bond-forming reactions has much to offer and I expect the field to flourish for some time. Finally, I recognize that I have neglected to mention a number of authors whose work laid the foundation for much current research in the area. To those and others whose work I may have overlooked I offer my apologies.

References and Notes

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