Tandem Radical Reactions of Carbon Monoxide, Isonitriles, and Other Reagent Equivalents of the Geminal Radical Acceptor/Radical Precursor Synthon

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I. Introduction

In a period of just over a decade, tandem radical reactions have emerged as a very powerful group of synthetic transformations.[1] Indeed, radical reactions are ideally suited for sequencing for a very simple yet very fundamental reason—the product of every radical reaction with itself or with another closed shell molecule is a radical. This product radical then becomes the precursor for the subsequent step in a sequence of reactions. The challenge in designing tandem radical reactions is one of selectivity.[1b] The fate of each individual radical in a sequence must be strictly controlled, and the transiency of radicals makes this especially challenging since the sequential addition of reagents to a reaction is generally not possible.[2] All the intermediate radicals in the sequence are present in the mixture simultaneously, so all the components of the sequence must be present as well. Selectivity is imparted by various kinetic substituent effects or, more generally, by intramolecularity.

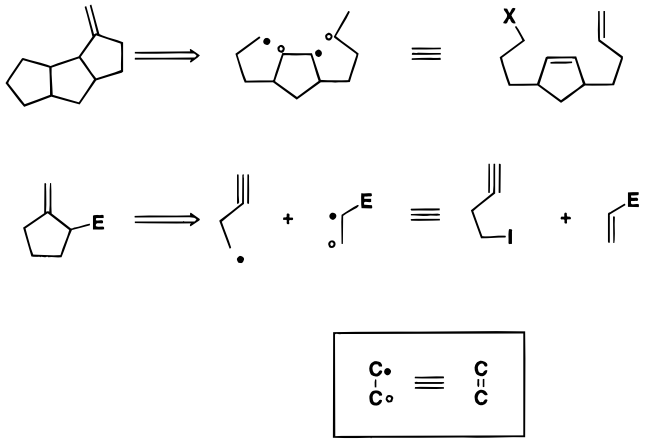

Figure 1. Alkenes as vicinal radical acceptor/radical precursor equivalents.

By far the most popular approach to tandem radical reactions has been to use alkenes, alkynes, or other multiple bonds as reagent equivalents of the "vicinal radical acceptor/radical precursor" synthon, as shown in Figure 1. The notation of the imaginary synthons[1a] uses "closed circles" to represent radical precursors and "open circles" to represent radical acceptors. This is analogous to the way that "plus" and "minus" signs are used to represent synthons for ionic bond-forming strategies. An alkene, or any other multiple bond for that matter, accepts a radical at one end, and the new radical then reacts at the other end. The availability of multiply bonded functional groups coupled with their diverse types of radical reactions has made the formation of vicinal bonds in radical sequences a popular and powerful method.

Figure 2 shows two specific examples of tandem radical reactions—a tandem radical cyclization[3] and a radical annulation[4]—that illustrate the strategies outlined in Figure 1. Considerably more sophisticated sequences now exist, and guidelines for planning and conducting such reactions have been laid out.[1a,b]

Methods to form nonvicinal bonds in tandem radical reactions have appeared more recently. In the

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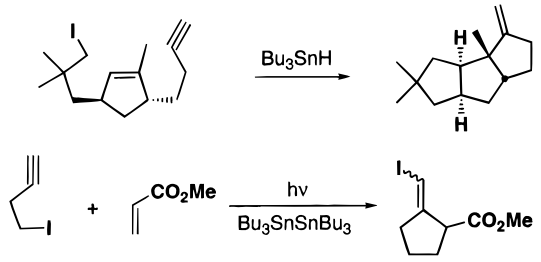

Figure 2. Examples of the strategies outlined in figure 1.

example shown in Figure 3, the principle of vinylogy is applied, and a diene placed in the middle of a tandem cyclization allows the formation of 1,4 (vinylogously vicinal) bonds.[5] Although it has rarely been exploited,[6] a more versatile approach uses a

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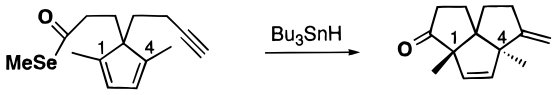


Figure 3. Tandem reaction that forms nonvicinal bonds.

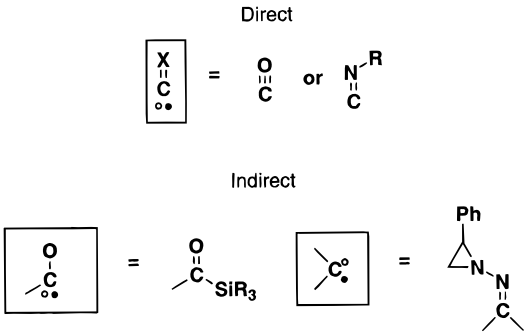


Figure 4. Reagent equivalents of the "geminal radical acceptor/radical precursor" synthon.

radical translocation reaction[7] to move a radical from one site to another in between two other reactions.

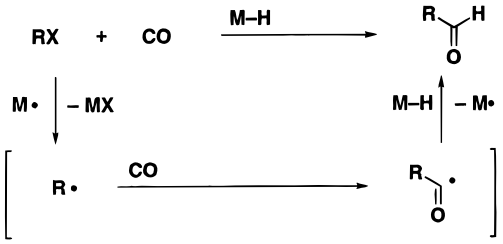
Over the past several years, a number of new methods have emerged to form geminal bonds in tandem radical reactions. These methods are the subject of this review. To form geminal carbon–carbon bonds by tandem radical reactions requires reagent equivalents of the "geminal radical acceptor/radical precursor" synthon shown in Figure 4. These reagents are grouped into two classes: "direct" reagents like carbon monoxide and isonitriles behave as radical acceptors, and the immediate products of the addition are radicals at the same site as the attack; "indirect" reagents like acylsilanes and *N*-aziridinyl imines also behave as radical acceptors, but the immediate products of the addition must further evolve to return the radical to the initial site

of attack. This evolution is a type of radical translocation.[7c]

II. Bimolecular Reactions of Radicals with CO

The potential of carbon monoxide as a C1 radical synthon has been recognized in recent years. The efficient trapping of CO by a variety of carbon radicals in a radical chain was demonstrated in 1990.[8] In this tin hydride mediated transformation (Scheme 1), an alkyl radical, generated from an alkyl bromide or iodide via abstraction of halogen by a tin radical, adds efficiently to CO to form an acyl radical. Subsequent hydrogen abstraction by the acyl radical from tin hydride produces an aldehyde and at the same time regenerates the tin radical (Scheme 1, MH = Bu_3SnH). Primary, secondary, and tertiary alkyl radicals can be efficiently carbonylated by the tin hydride/CO system to furnish one-carbon homologated aldehydes.

Scheme 1



These radical formylations are generally performed at substrate concentrations of 0.01−0.05 M with 70−90 atm of CO at 80 °C for 2−4 h. The reaction apparatus is an autoclave and AIBN is used as a radical initiator. Aromatic or vinylic iodides can also be formylated to give the corresponding aldehydes.[1b] Tris(trimethylsilyl)silane[9] (TTMSS) and triorganogermanes[10] can be used in place of tin hydride in the formylation reactions. These reagents are poorer hydrogen donors, so the formylation reaction proceeds at lower CO pressures.

To design tandem radical reactions involving carbon monoxide as a C1 radical acceptor/donor synthon, qualitative kinetic information accumulated during the tin hydride mediated free radical formylation studies is useful. It has been demonstrated that high CO pressures (concentrations) are necessary for efficient carbonylation to compete with premature reduction of carbon radicals by tin hydride prior to CO trapping and decarbonylation (back reaction) of acyl radicals. Known kinetic data help to explain the varied efficiency of carbon radicals toward carbonylation; this efficiency depends largely on the structure of the starting radicals. For example, compared to primary and secondary alkyl radicals, higher CO pressures are required for the carbonylation of sp^2 radicals such as phenyl and vinyl radicals. This is true even though the back reaction from the resulting acyl radicals is expected to be slow, judging from the strength of the newly formed sp^2 C−C σ bond and the instability of the sp^2 radicals. The need for higher CO pressures can be ascribed to the very rapid rate of hydrogen abstraction by sp^2 radicals.[11] The decarbonylation rate is in the order of primary acyl < secondary acyl < tertiary acyl < phenylacetyl.[12,13] This order explains why a primary radical can be carbonylated efficiently even at relatively low CO pressures[14] but carbonylation of benzyl radicals is difficult to achieve. In addition to benzyl radicals, carbon radicals substituted by other radical stabilizing groups (for example, cyano, carbonyl, vinyl, and alkoxy groups) do not add to CO to a synthetically meaningful extent. Although the absolute rate constants for decarbonylation reactions of acyl radicals to give these stable radicals are not always available, rapid decarbonylation is probably the dominant factor causing these unsuccessful carbonylations.

In designing efficient tandem radical reactions of CO, some useful guidelines can be put forth: (i) The key radicals capable of adding to CO should be alkyl, aryl, and vinyl. Alkyl radicals should not have an α-radical stabilizing substituent. (ii) The product acyl radicals should be rapidly trapped by a subsequent C−C bond-forming reaction to lead to more stable radicals that are not prone to carbonylation by another molecule of CO. (iii) The resulting carbon radicals can be terminated by hydrogen atom abstraction or can be incorporated into useful further C−C bond-forming reactions. (iv) It is also possible to use an S_H2 reaction that accompanies C−heteroatom bond formation or one-electron oxidation to form acyl cations. (v) In certain cases, acyl radicals can react to produce carbon radicals that are still reactive toward CO. This is the case for kinetically driven acyl radical cyclizations to give (3-oxocyclopentyl)-methyl radicals and for 3-oxo radicals in copolymerization of CO and ethylene.[15] In the former case, however, fine tuning of the reaction conditions may allow the design of useful double CO trapping reactions. This is discussed in detail in section V.

The following sections will emphasize recently developed multicomponent coupling reactions that incorporate CO as a reagent equivalent of the C1 radical acceptor/donor synthon.[16]

III. CO Trapping and Intermolecular C–C Bond Formation

A. Unsymmetrical Ketones

Direct attachment of two different carbon chains to carbon monoxide represents a strategy for preparing unsymmetrical ketones, in which CO operates as C1 radical acceptor/precursor synthon (Chart 1). In a radical formylation of alkyl halides to give aldehydes, both the trapping of the alkyl radical by CO and the subsequent abstraction of a hydrogen atom from tributyltin hydride by the product acyl radical take place efficiently.[8] If an alkene is also present in this system, at least two competing pathways can be envisioned: (i) the direct addition of the alkyl radical to the alkene and (ii) the trapping of the alkyl radical by CO to form an acyl radical followed by addition of that radical to the alkene. Fine tuning of the reaction conditions allows the carbonylation

Chart 1

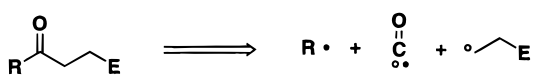
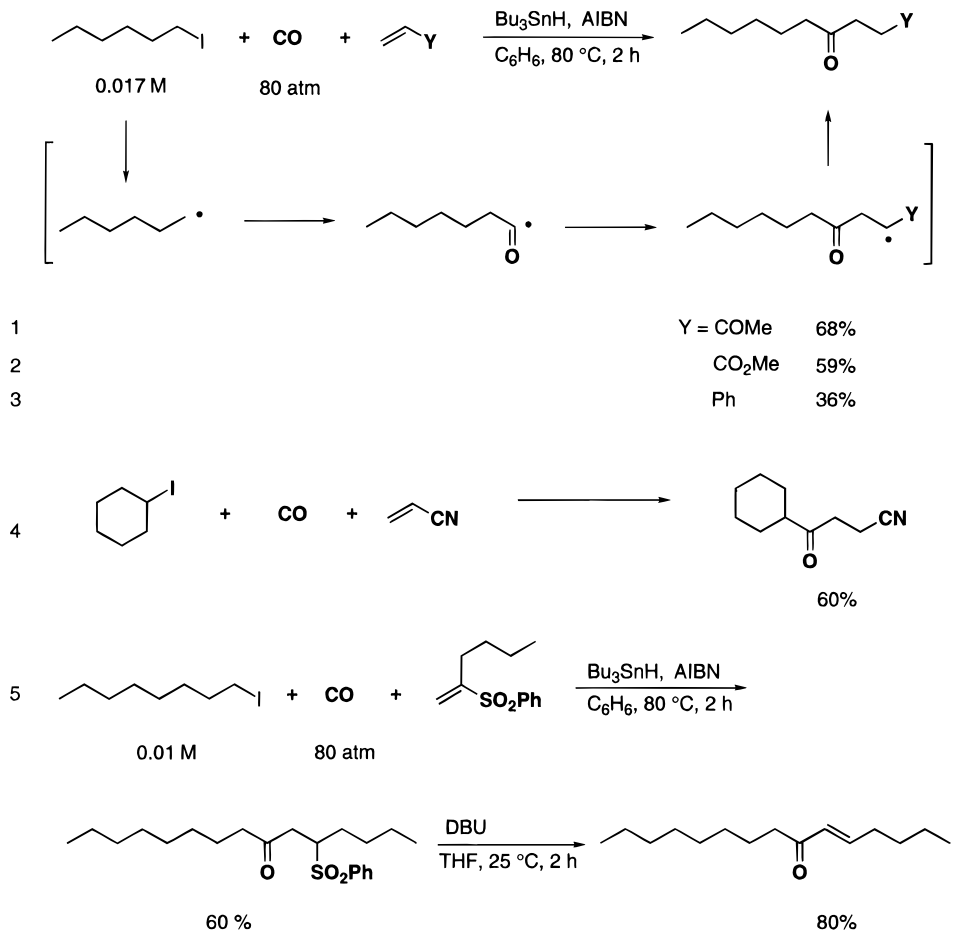


Table 1. Ketone Synthesis by Double Alkylation of CO



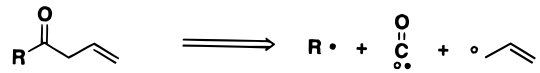
reaction to predominate over the direct addition, thereby providing a useful method for unsymmetrical ketone synthesis by a double alkylation of CO.[17]

For example, heating a benzene solution of hexyl iodide, Bu_3SnH, AIBN (catalytic), and methyl vinyl ketone in an autoclave under 80 atm of CO at 80 °C for 2 h yields 2,5-undecanedione together with 2-decanone (Table 1, entry 1). Performing this reaction under high dilution conditions is very effective for suppressing the direct addition pathway leading to 2-decanone. Alkyl bromides and iodides serve well as sources of the alkyl radicals, and acrylonitrile, methyl acrylate, and styrene serve as acceptor alkenes. TTMSS can also be used in place of tin hydride. This system has the merit of lower CO pressure. For example, the coupling of hexyl iodide, CO, and acrylonitrile can be effected smoothly at 20 atm of CO.[9]

β-Sulfonyl ketones are prepared in good yield starting from vinyl sulfones.[18] Since β-sulfonyl ketones can undergo dehydrosulfonylation to give enones upon treatment with a base such as DBU,[19] the overall process provides a synthesis of α,β-unsaturated ketones in which vinylic sulfones operate as an alkyne equivalent.

Allyltin is a particularly useful free-radical reagent because it serves as both the acceptor alkene and the tin radical source to ensure a free-radical chain.[20] The combination of allyltin-mediated radical reaction with a CO trapping sequence has proven eminently successful. The strategy for three-component coupling to synthesize β,γ-unsaturated ketones is shown in Chart 2.

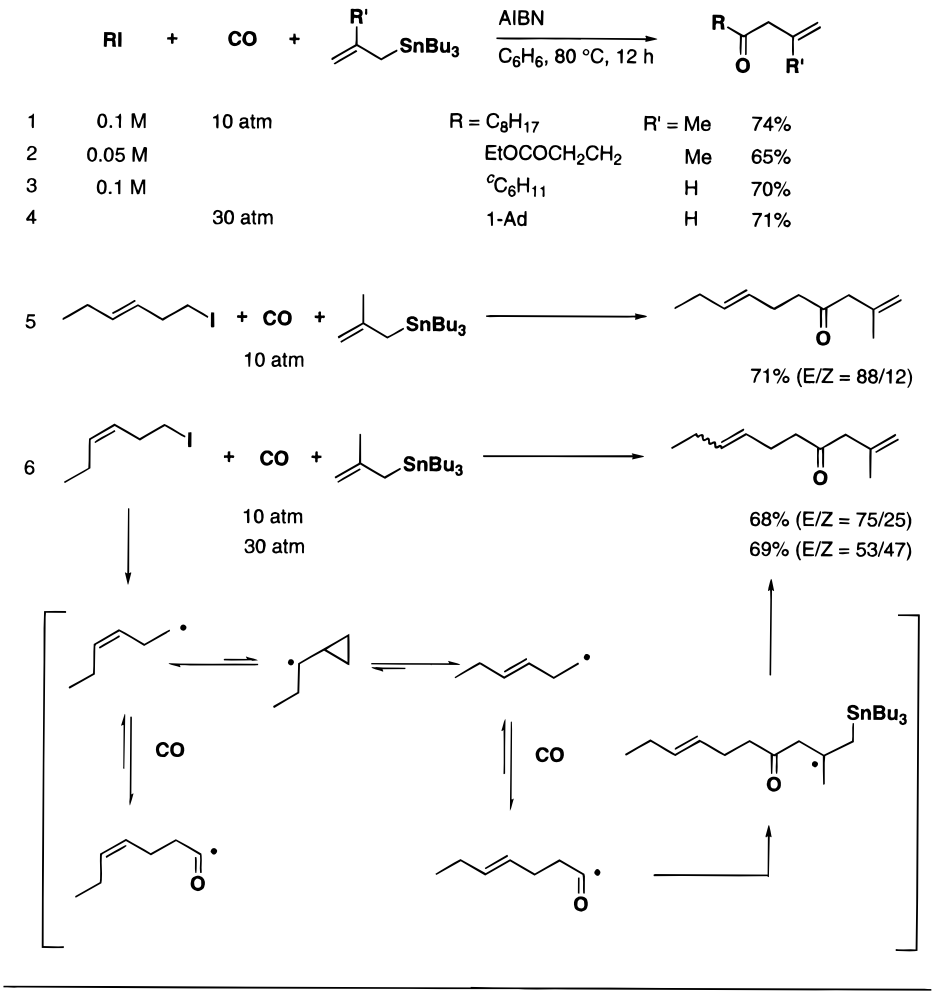
Chart 2



Heating a benzene solution of a primary alkyl iodide (0.1−0.05 M), tributylallyltin (2 equiv), and 0.2−0.4 equiv of AIBN in an autoclave under 2−20 atm of CO (80 °C, 12 h) yields an alkyl allyl ketone in good yield.[21] This reaction works similarly with secondary and tertiary alkyl iodides, but increased CO pressures (30−50 atm) are necessary for carbonylated products to predominate over allylated alkanes. A number of examples are shown in Table 2.

Compared to the tin hydride-mediated system, this allyltin-mediated three-component reaction can be conducted at lower CO pressures. Since addition of alkyl radicals to allyltin occurs at a relatively slow rate compared with hydrogen abstraction by alkyl radicals from tin hydride,[22] the lower CO pressure system is a reflection of the slower competing reaction. On the other hand, the slower S_H2' termination step demands a higher reaction concentration ([RX] = 0.1 M) to ensure an efficient free-radical chain.

Table 2. β,γ-Enone Synthesis

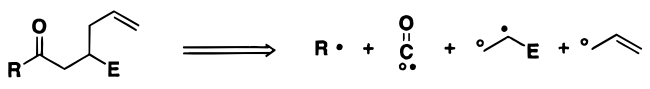


Unlike the tin hydride system,[8] both (*E*)- and (*Z*)-3-hexenyl iodides afford the same (*E*)-vinyl ketone with high selectivity (Table 2, entries 5 and 6). An equilibrium between (*E*)- and (*Z*)-3-hexenyl radicals via a cyclopropylmethyl radical appears to be permitted in this slow reaction system and this may also suggest that the addition of alkyl radical to CO is reversible.

B. β-Functionalized δ,ϵ-Unsaturated Ketones

The methodology coupling the four carbon units RX, carbon monoxide, an alkene, and allyltin has proven to be very useful (Chart 3).[23]

Chart 3

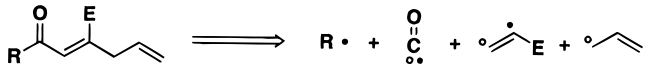


For example, 2-methyl-4-cyano-1-tetradecen-6-one is obtained in good yield from the reaction of octyl iodide (0.025M), acrylonitrile (1.2 equiv), methallyltin (2 equiv), and CO (10 atm). This result can be explained by the radical chain mechanism outlined in Table 3, entry 1. This chain propagation sequence appears to occur more smoothly than that in the β,γ-enone synthesis, judging from the fact that the reaction occurs cleanly at low substrate concentrations (generally 0.025 M). The lower SOMO energy of the radicals with electron deficient substituents compared to that of the acyl radical should be more suitable for the S_H2' termination with allyltin. It is important to use only stoichiometric quantities of reactive alkenes, as shown by the examples in Table 3, to minimize the undesirable three-component reaction without CO incorporation.[24]

This sequence is quite flexible in terms of the versatility of RX (R = primary, secondary, and tertiary alkyl, aryl, and vinyl) and the electron withdrawing substituent on the alkene (Y = CN, CHO, COMe, CO_2Me, SO_2Ph, etc.). Thus, the four-component methodology can provide a convenient synthesis of 3-cyano ketones, 4-oxo aldehydes, 1,4-diketones, 4-oxo esters, 3-sulfonyl ketones, etc., all bearing δ,ϵ-unsaturation, which can be further elaborated. The procedure is quite simple to carry out, since it only requires heating a benzene solution of the reactants and a catalytic amount of AIBN under CO pressure in an autoclave.

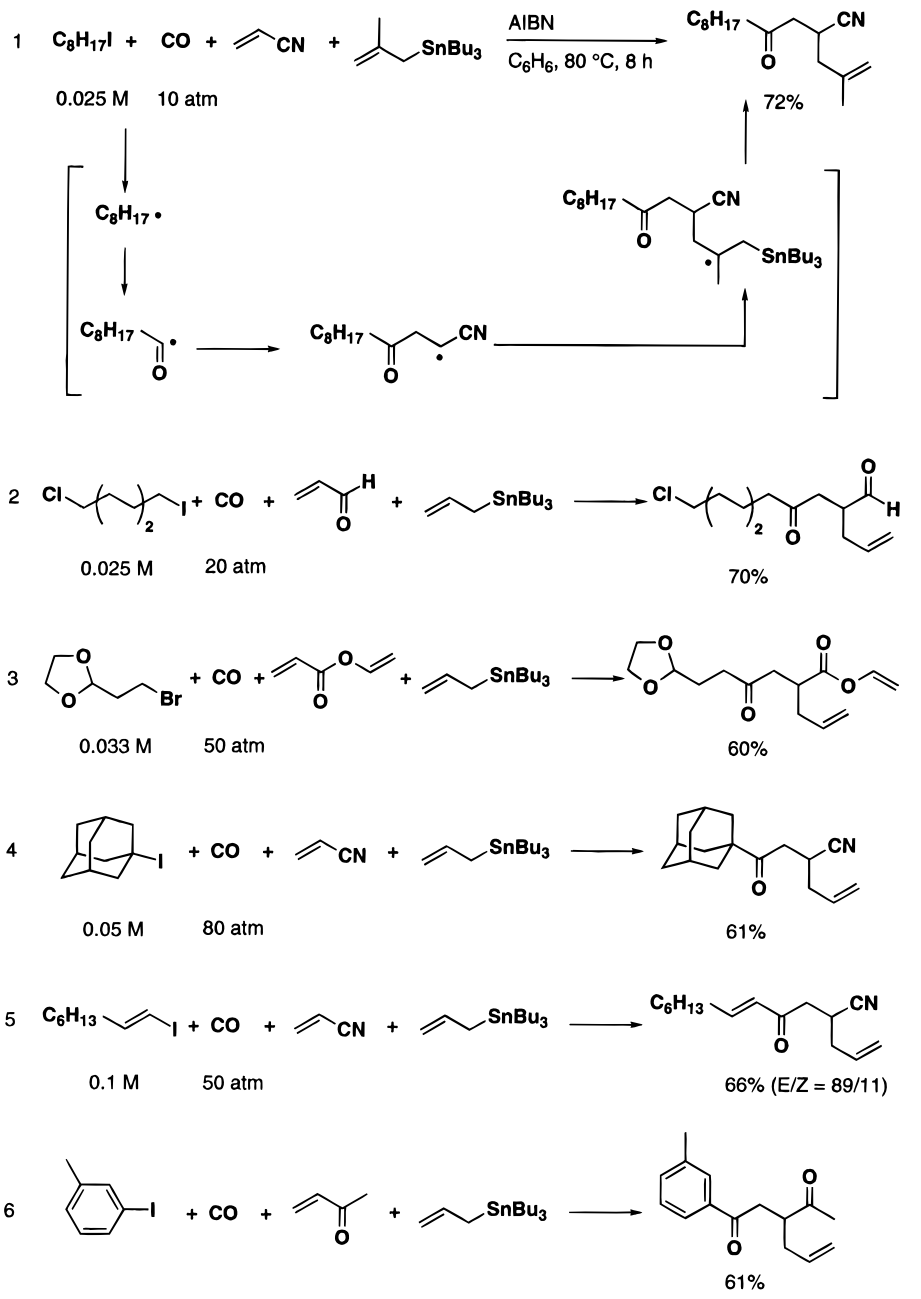
The concept of four-component methodology need not be restricted to alkenes but can also be applied to alkynes such as ethyl propiolate (Chart 4). A

Chart 4

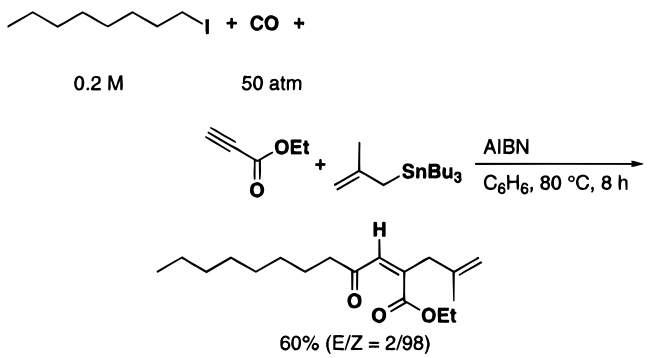


specific example is shown in Scheme 2. The observed

Table 3. Four-Component Coupling Reaction of RX, CO, Alkene, and Allyltin



Scheme 2



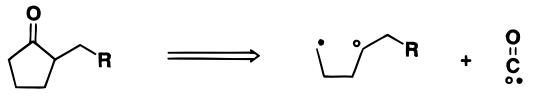
stereoselectivity with regard to allylation may be a result of the least hindered site attack on the rapidly inverting vinyl radical.[25]

IV. CO Trapping and Intramolecular C–C Bond Formation

A. Cyclopentanones

The propensity of 4-alkenyl radicals to resist 4-*exo* cyclization[26] allows a CO trapping/cyclization sequence that leads to cyclopentanone derivatives (Chart 5).[27] However, the problem to be circum-

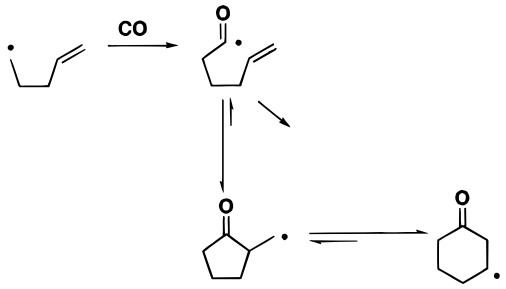
Chart 5



vented is product selectivity arising from isomerization of the (3-oxocyclopentyl)methyl radical (the

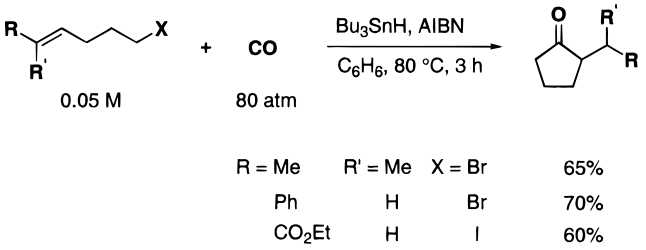
kinetic product of radical cyclization) into the more stable 3-oxocyclohexyl radical (Scheme 3). The isomerization mechanism had been controversial over the years since Ingold's report.[28]

Scheme 3



For example, the free-radical reaction of 1-bromo-4-hexene with tributyltin hydride and CO yielded a 2:1 mixture of 2-ethylcyclopentanone and 2-methylcyclohexanone. One easy solution to selectively obtain five-membered ring ketones is to substitute the cyclized radical with stabilizing α-substituents. Indeed, terminal dialkyl, phenyl, or ethoxycarbonyl substitution of 4-pentenyl bromide effected selective 5-*exo* cyclization leading to cyclopentanones (Scheme 4).[29] The efficient acyl radical trapping system with internal styryl attachment was applied successfully to evaluate the rate constant for CO trapping by a primary alkyl radical.[14a] In this experiment, a 5-hexenyl radical cyclization was employed as a radical clock.[30] The obtained rate constant for carbonylation of 6×10^5 M^{-1} s^{-1} (80 °C) is reasonably fast.

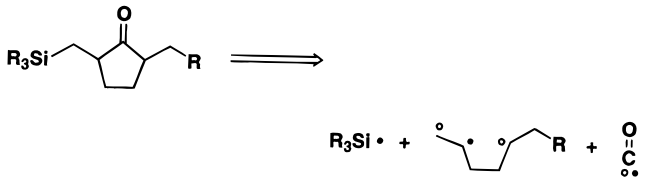
Scheme 4



R = Me	R' = Me	X = Br	65%
Ph	H	Br	70%
CO_2Et	H	I	60%

Silylcarbonylation of 1,5-dienes by tris(trimethylsilyl)silane and CO under free radical reaction conditions is also possible (Chart 6). Although silylcarbonylation of the parent 1,5-hexadiene gives a mixture of 2-(silylmethyl)cyclopentanone, 2-(silylmethyl)cyclohexanone, and other products, introduction of

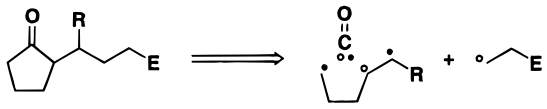
Chart 6



appropriate substituents at the diene terminus again leads to the selective formation of a 2-(silylmethyl)-cyclopentanone in high yield (Scheme 5).[31]

The tactic of using terminal substitution to selectively form the 5-*exo* cyclization product can be extended to the synthesis of cyclopentanones bearing diverse α-chains (Chart 7). In the presence of an alkene having an electron-withdrawing substituent, tertiary radicals arising from five-membered radical ring closure add efficiently. For example, the reaction of 2-iodo-6-methyl-5-heptene with CO in the presence of acrylonitrile yields the corresponding cyclopentanone derivative in good yield.[32] Interestingly, it was found that Luche's zinc system[33] can also be used for this transformation in place of tin hydride, although the yield is somewhat lower.

Chart 7



Allyltin can also serve as an acceptor alkene to yield δ,ϵ-unsaturated cyclopentanones (Chart 8 and

Chart 8

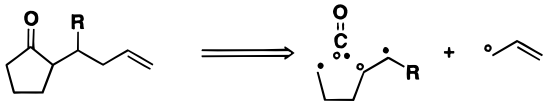


Table 4, entries 4 and 5). In particular, an ethoxycarbonyl substituent at the olefin terminus promotes a clean reaction, thereby giving a high yield of a 4-keto ester bearing an allyl group α to the ester carbonyl (Table 4, entry 5).[34] On the other hand, the reaction with the substrate having a styryl terminus was unsuccessful. It is likely that the low reactivity of the benzyl radical arising from carbonylation/cyclization with allyltin retards chain propagation.

Scheme 5

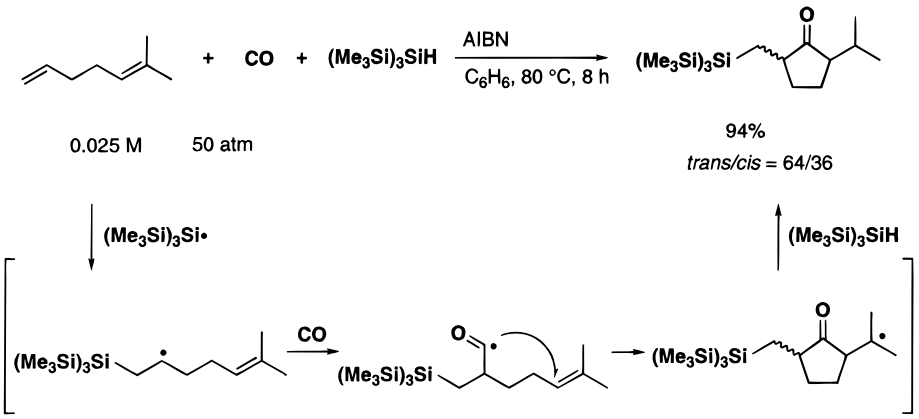
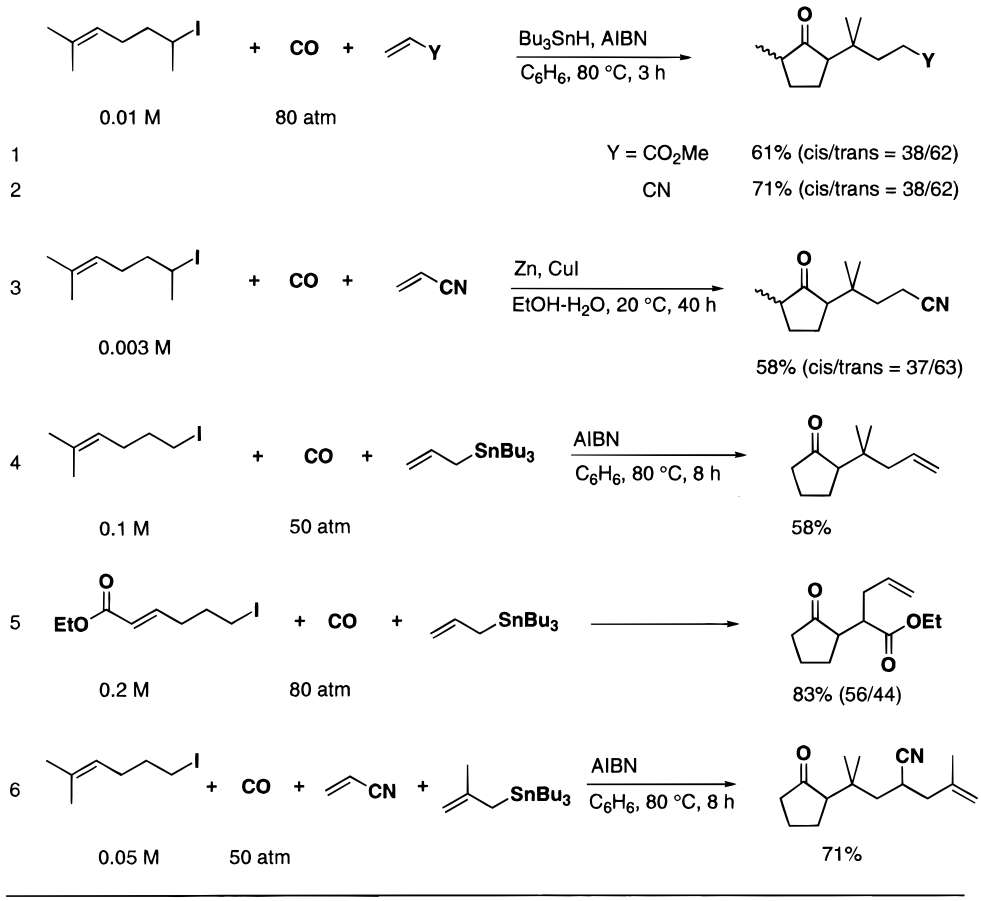
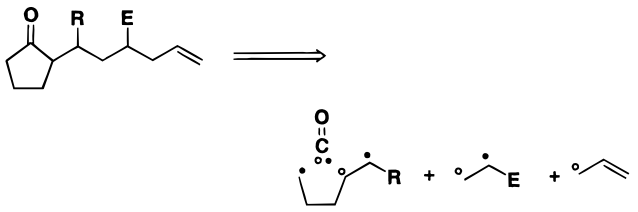


Table 4. Synthesis of Substituted Cyclopentanones



A four carbon component coupling reaction, which assembles 5-methyl-4-hexenyl iodide, CO, acrylonitrile and methallyltin, is also possible (Chart 9).

Chart 9

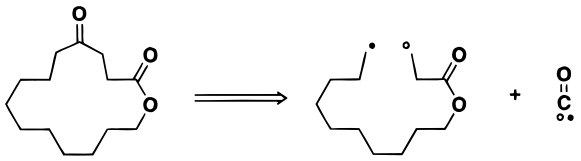


Thus, subjection of the iodide (Table 4, entry 6) to a mixed system of methallyltin and acrylonitrile afforded δ-cyano-δ-methallylcyclopentanone in 71% yield. Four C−C bonds are formed in this remarkable reaction.

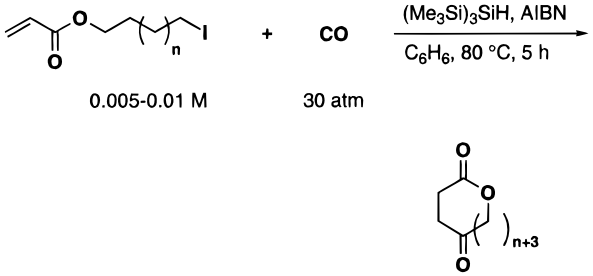
B. Macrocyclic Ketolactones

The biological importance of macrolides has led to extensive efforts to develop diverse synthetic methods of macrolide formation. Pioneering studies of Porter and co-workers have defined the steric and electronic requirements for successful alkyl radical macrocyclization reactions.[35] These studies suggested that applications of such a free radical macrocyclization methodology to include an acyl radical cyclization would be successful.[36] A free-radical-mediated $n + 1$ strategy for the synthesis of macrocyclic carbonyl compounds provides a useful tool for the synthesis of macrocyclic ketolactones (Chart 10 and Scheme 6).

Chart 10



Scheme 6



n = 2	28%	7	61%
3	68%	8	50%
5	70%	9	78%

The synthesis of 10−17-membered 4-oxolactones from CO, TTMSS (or tin hydride), and alkyl iodides bearing a terminal acryloxy group takes place cleanly in moderate to good yields under free-radical condi-

tions.[37] Low substrate concentrations (0.005−0.01 M) are favorable for both intermolecular trapping of CO and intramolecular acyl radical addition to the C−C double bond. The use of CO as the C1 unit for macrolide synthesis is rare in the field of metal-catalyzed carbonylations.

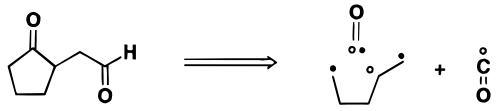
V. Double CO Trapping Reactions with Cyclization

A. 2-(Formylmethyl)cyclopentanones

The previous section provided examples of carbonylation/cyclization sequences in which selective five-membered ring formation relied upon substituents attached to the C−C double bond termini. In this section, another simple method of controlling the selectivity in favor of five-membered ring products is introduced. This method, based on kinetic trapping of a five-membered radical by the second molecule of CO, has proven to be a very convenient route to a variety of 1,4-dicarbonyl compounds.

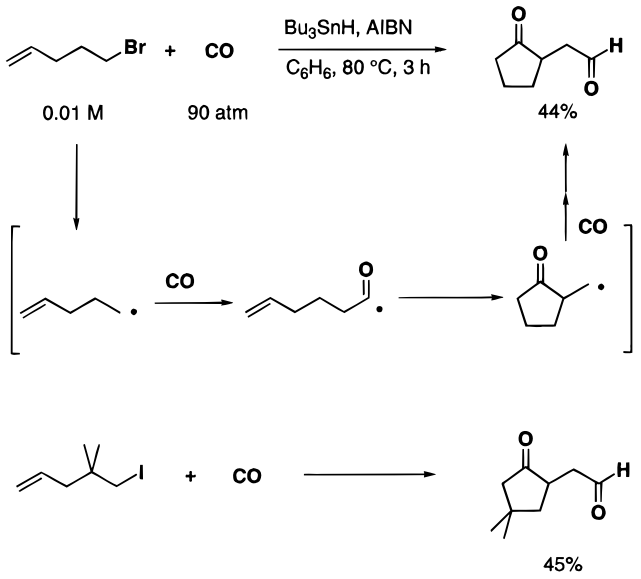
Trapping of the kinetically favored radical product by the second molecule of CO was first examined with the reaction of the 4-pentenyl radical with CO in the tin hydride-mediated system. The preparation of 4-keto aldehydes was envisioned according to Chart 11.

Chart 11



The AIBN-initiated reaction of 4-pentenyl bromide with tributyltin hydride and CO (85−90 atm) furnished the desired keto aldehyde, 2-(2-oxoethyl)-cyclopentanone, in 44% yield (Scheme 7).[38] Another example of this double CO trapping approach is also shown in Scheme 7. The use of tin hydride is indispensable for this keto aldehyde synthesis. If a hydrogermane is used instead of tin hydride, the doubly carbonylated 2-oxabicyclo[3.3.0]octan-3-one is formed as the major product (see below).

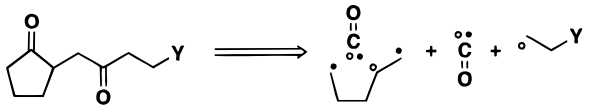
Scheme 7



B. 2-(Acylmethyl)cyclopentanones

The above CO trapping, cyclization, and the second CO trapping sequence can be followed by the addition of the resulting acyl radicals to alkenes present in the reaction system (Chart 12). When the reaction

Chart 12



of 4-pentenyl iodide with CO was carried out in the presence of acrylonitrile, a 6-cyano-1,4-diketone having a five-membered ring was the major product (Table 5, entry 1).[39] Similarly, the reaction with acrolein furnished the corresponding tricarbonyl product in acceptable yield (Table 5, entry 2).

Double CO trapping can work well when the 5-*exo* acyl radical cyclization gives rise to a primary alkyl radical. However, a similar attempt to obtain a "double carbonylated/five-membered ring" (five-double) product from the secondary 4-hexenyl radical was less fruitful. The reaction of 4-hexenyl iodide with allyltin and CO afforded a nearly 1:1 mixture of six-double and five-double carbonylated products. This may be ascribed to the general observation that the CO trapping reaction by secondary alkyl radicals is less effective than that by primary alkyl radicals.

As outlined in Chart 13, the double CO trapping sequence can be extended to a mixed alkene system where the alternating sequence of two carbonylations and one intermolecular and two bimolecular C−C bond-forming reactions must take place smoothly. Thus, when the reaction was conducted with a mixed system of acrylonitrile and tributylmethallyltin, the desired functionalized ketone was obtained in 62% yield as a 1:1 mixture of diastereomers.[39] This is a remarkable yield for a system that consecutively creates five C−C bonds (Table 5, entry 4). The overall process can be carried out in one operation and is experimentally simple.

Chart 13

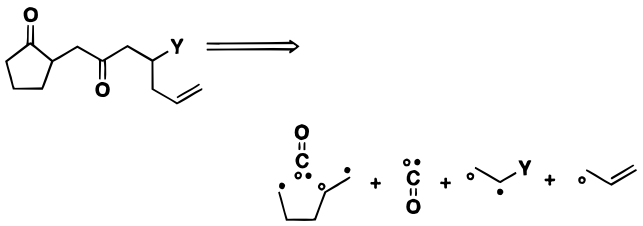
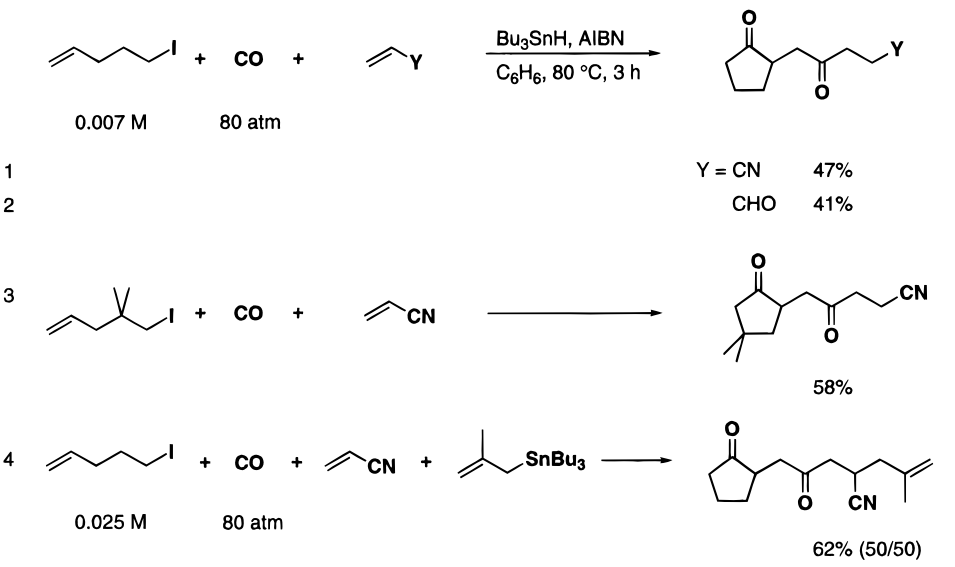


Table 5. 1,4-Diketone Synthesis by Double CO Trapping

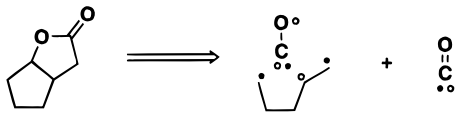


VI. CO Trapping and C–O or C–Se Bond Formation

A. γ-Lactones and δ-Lactones

In the course of exploring double CO trapping reactions of 4-pentenyl radicals, a unique reaction sequence that provides bicyclic γ-lactone rings was discovered (Chart 14).

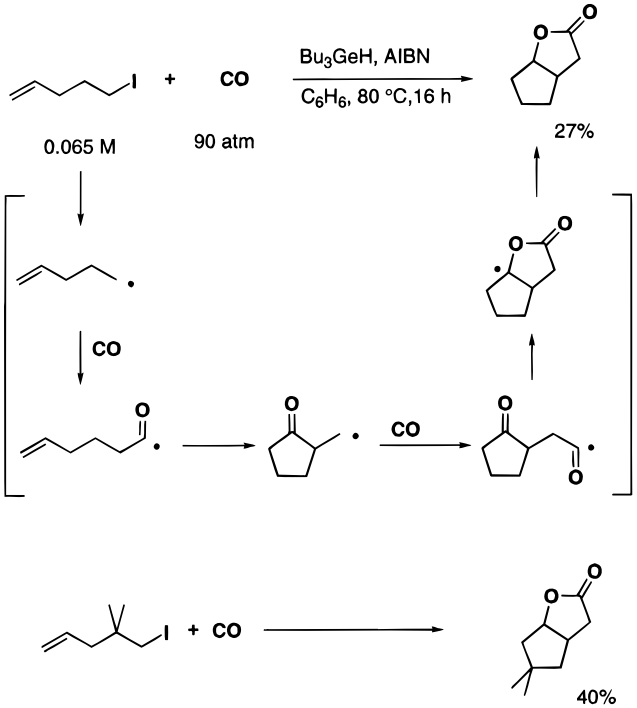
Chart 14



As shown in the preceding section (V.A.), free-radical reactions of 4-alkenyl halides under high pressure of CO (90 atm) in the presence of tin hydride yielded 2-(formylmethyl)cyclopentanones as the main products. When a similar reaction was examined with tributylgermane as a radical mediator, 2-oxabicyclo[3.3.0]octan-3-one was formed as the main product together with 2-(formylmethyl)cyclopentanone (Scheme 8).[38] A 5-*endo* cyclization of the acyl radical resulting from the second CO trapping to the internal ketone carbonyl probably accounts for the lactone ring formation. The slow-terminating H-transfer step with the hydrogermane[40] may allow such a rare cyclization to occur.[41] The yields of this reaction require improvement, but it is remarkable that three C−C bonds and one C−O bond are created in this transformation. The 5-*endo* cyclization product was also formed with TTMSS,[42] but the selectivity was inferior.

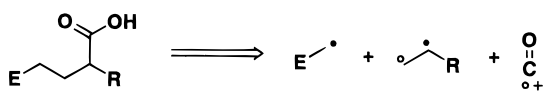
A CO trapping sequence by carbon radicals can be combined with the subsequent one-electron oxidation, which should lead to acyl cations.[43] Since acyl cations react with oxygen nucleophiles, the system can be applied to the synthesis of carboxylic acids and their derivatives. In such transformations, CO acts as a C1 radical/cation synthon.

Scheme 8

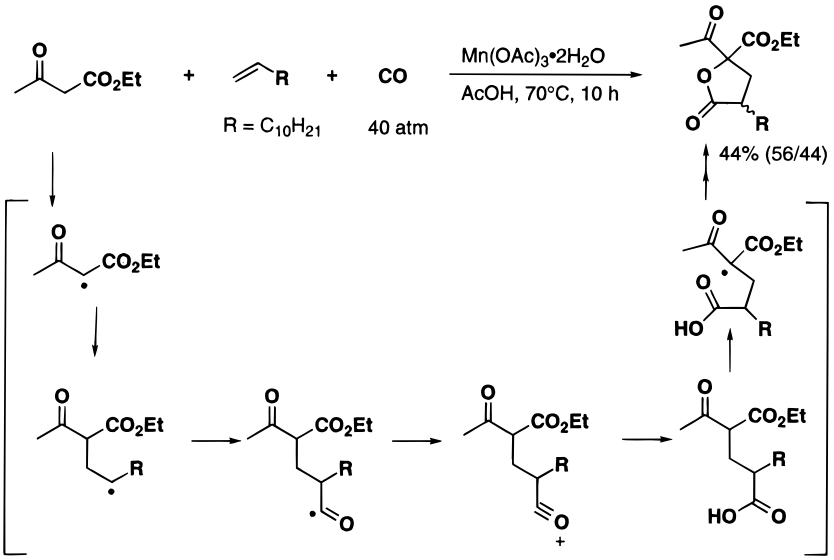


Alper and Ryu provided examples of this strategy, which is outlined in Chart 15. Thus, they demonstrated that carbon radicals α to the carbonyl, generated by the oxidation of 1,3-dicarbonyl compounds by Mn(III), undergo consecutive addition to alkenes and carbonylation to form acyl radicals. These are then oxidized and hydrolyzed to give carboxylic acids.[44] Oxidation of primary and secondary radicals by Mn(III)[45] is rather inefficient, and this leads to the frequent use of a cupric salt as a supplementary oxidizing reagent.[46] But such a slow oxidation pro-

Chart 15



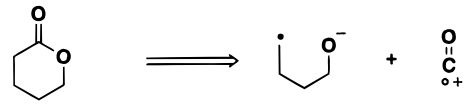
Scheme 9



cess is in turn favorable for CO trapping by the carbon radicals. An interesting γ-lactone formation was observed when a mixture of ethyl acetoacetate and 1-dodecene was treated with manganese triacetate (Scheme 9). The γ-lactone was produced by the second oxidative cyclization of the initially formed carboxylic acid.

Tsunoi, Ryu, and Sonoda have recently reported that saturated alcohols can be transformed to δ-lactones by the reaction with carbon monoxide in the presence of lead tetraacetate (LTA).[47a] This process also uses CO as a C1 radical/cation synthon, and the concept is shown in Chart 16.

Chart 16



This remote carbonylation reaction is suited for primary and secondary alcohols having primary or secondary δ-carbons. Radicals at the δ-carbon are generated by 1,5-hydrogen transfer reaction from carbon to oxygen.[48] The roles of LTA are to generate the alkoxy radical in the initial step[49] and to oxidize the acyl radical to an acyl cation in the final step. Table 6 illustrates selected examples of this δ-lactone synthesis, which includes an application to the short synthesis of the carpenter bee pheromone from commercially available (*R*)-(−)-2-hexanol and CO.

β-Scission of a cyclobutyloxy radical to lead to a γ-formylalkyl radical can be coupled with the subsequent CO trapping. Thus, carbonylation of cyclobutanol in the presence of LTA gives 5-acetoxy-δ-valerolactone.[47b] Addition of an acyl cation to the internal formyl group may account for the lactone ring formation.

B. Acyl Selenides

A novel S_H2 transformation of acyl radicals at selenium has recently been discovered. Certain organoselenium compounds are ideal group transfer reagents in bimolecular homolytic substitutions. Group transfer additions of chalcogen-containing compounds to alkenes are of current interest in view of their high efficiency and synthetic potential. Such reactions take advantage of the well-known capability of the radicals stabilized by an electron-withdrawing substituent to add efficiently to simple alkenes and the capability of chalcogen-containing compounds to deliver an organochalcogen group to the resulting carbon radicals. The recent independent work of Byers and Curran in this field[50] and kinetic work by Curran and Newcomb provides a basis for designing group transfer reactions that include free-radical carbonylation.[51]

Chart 17 summarizes a strategy for a three-component coupling reaction leading to acyl selenides. The key to success is whether the acyl radical resulting from the carbonylation can undergo smooth group transfer reactions with α-seleno carbonyl compounds with extrusion of α-carbonyl radicals. Ryu, Sonoda, and co-workers observed that the photoinduced three-component coupling reaction of methyl α-(phenylseleno)acetate, CO, and alkenes takes place efficiently.[52] It is important for the success of the reaction to choose slow group transfer systems in order to give carbon radicals a sufficient chance to capture CO in preference to a group transfer reaction. Indeed, α-(phenylseleno)acetate is superior to α-(phenylseleno)malonate. Thus, irradiation of a benzene solution of methyl α-(phenylseleno)-acetate (0.01 M) and 1-octene (20 equiv) using 500-W xenon lamp (>300 nm) for 20 h at 60 °C at 80 atm of CO gave the desired selenol ester in 55% isolated yield (Table 7, entry 1). Some other examples are given in Table 7 (entries 2−4). The mechanism of the reaction involves (1) the photoinduced homolysis of methyl α-(phenylseleno)acetate, (2) the addition of a (methoxycarbonyl)methyl radical to an alkene, (3) the trapping of the alkyl free radical so formed by CO, and (4) termination of the reaction by a phenylseleno group transfer from the starting selenide. A cyclization process accompanied by CO trapping is also successful.

Chart 17

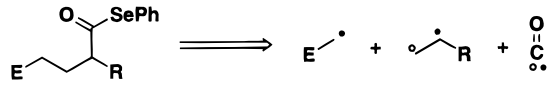
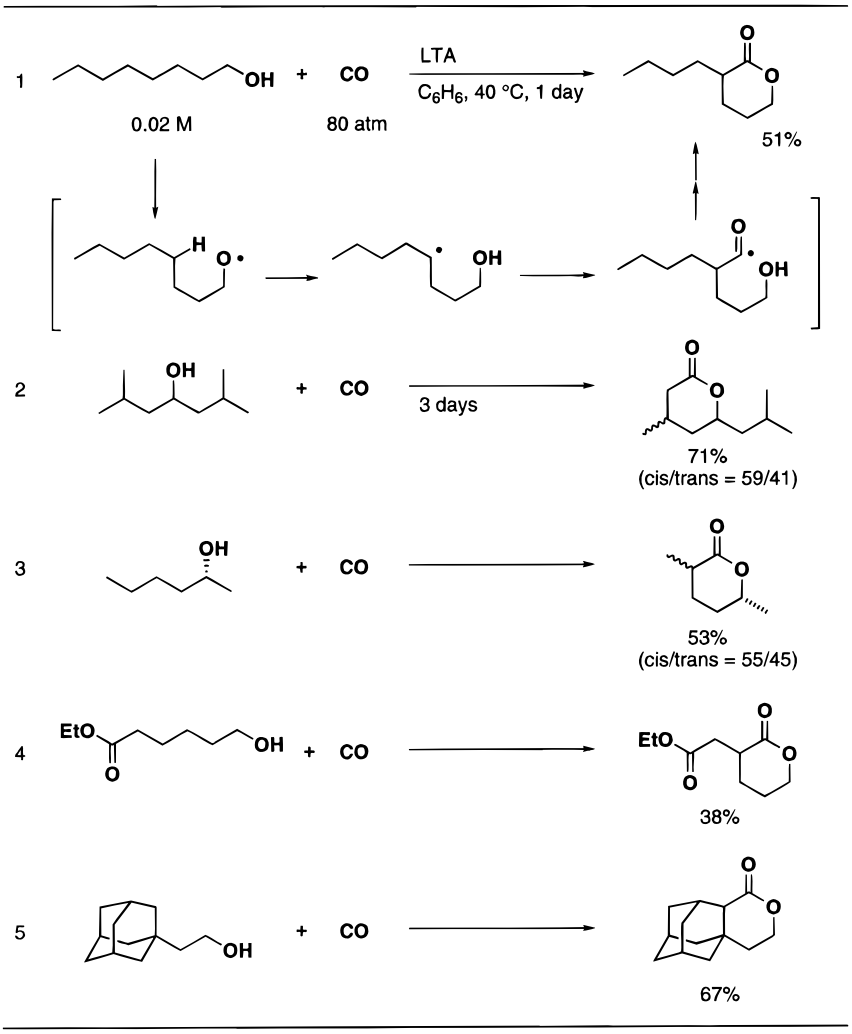


Table 6. Synthesis of δ-Lactones from Alcohols and CO in the Presence of LTA



The overall transformation achieved the consecutive insertions of an olefin and CO into a C−Se bond, and the products, selenol esters having γ-functionalities, are useful compounds for further elaborations in organic synthesis.

VII. Bimolecular Reactions of Radicals with Isonitriles

Isonitriles are isoelectronic with carbon monoxide, and they can likewise participate in radical addition reactions (Scheme 10).[53] Addition of a radical $R^1\bullet$ to an isonitrile provides an intermediate imidoyl radical, which is roughly analogous to an acyl radical formed on carbonylation with CO. However, there are two important differences between acyl radicals and imidoyl radicals: (1) imidoyl radicals are not as prone to cleavage by fragmentation of the α bond (the analog of decarbonylation), but (2) they are prone to fragmentation of the β bond to give nitriles. The β-fragmentation reaction is driven by the formation of the strong C−N triple bond, and typically occurs when the fragmenting radical ($R^2\bullet$) is stabilized. Bimolecular additions are frequently followed by a β-fragmentation reaction, as shown in the general equation and specific example in Scheme 10.[54] In this reaction, isonitriles are the reagent equivalents of the "nitrile radical acceptor" synthon shown in Chart 18.

Scheme 10

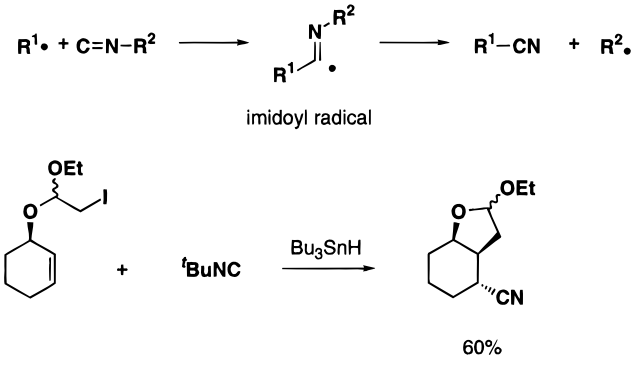
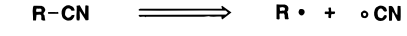
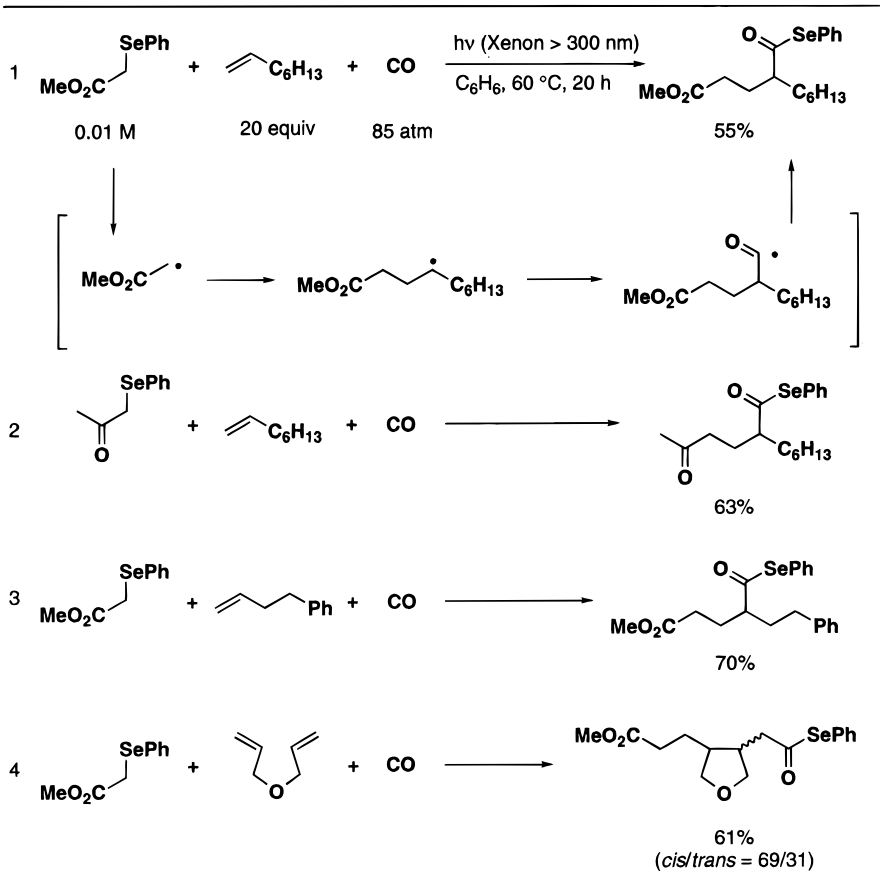


Chart 18

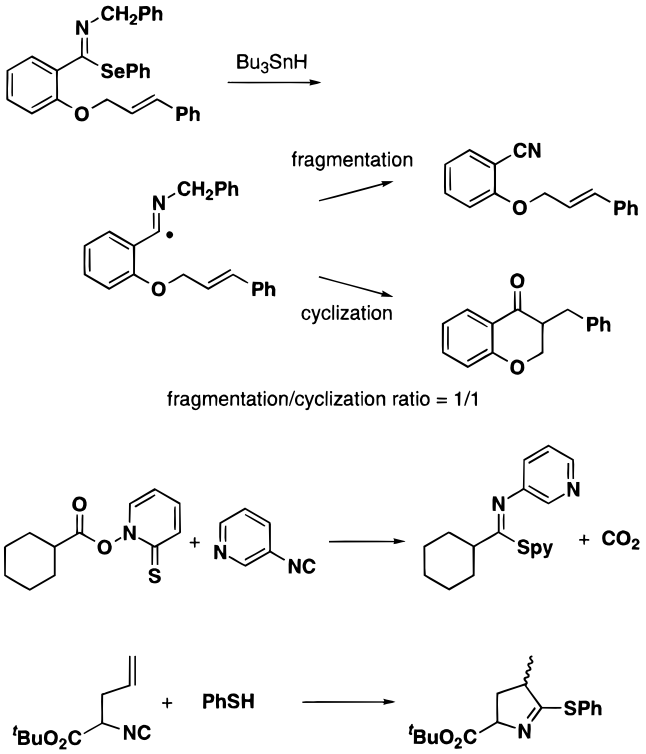


Imidoyl radicals generated by means other than addition to isonitriles can undergo reactions such as addition[55] and cyclization in competition with β-fragmentation. The first example in Scheme 11 shows that even a 6-*exo* cyclization can compete with the β-fragmentation to the stabilized benzyl radical.[56] In principle, an addition reaction to an isonitrile can be

Table 7. Group Transfer Carbonylation with α-Selenocarbonyl Compounds



Scheme 11



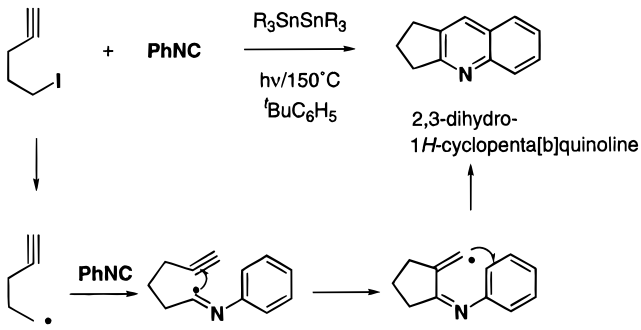
followed by another addition or cyclization reaction, thereby making the tandem chemistry of isonitriles very similar to that of CO. However, directly analogous reactions of isonitriles and CO have rarely been observed in practice. The second example in Scheme 11 shows an addition reaction to an isonitrile by the Barton thiohydroxamate method that is roughly analogous to the selenium transfer reactions shown in Chart 17 and Table 7.[57] The reaction uses a pyridyl isonitrile to prevent the β-fragmentation (an unstable aryl radical would be generated). This overall transformation is effectively a "decarboxylative carboxylation", so it has limited synthetic utility. But it does show that with appropriate selection of substituents, isonitriles may be able to function as CO surrogates in certain classes of tandem reactions. Since isonitriles are liquids or solids and high pressures are not required, such reactions are simple to set up and require no specialized apparatus.

The lower example in Scheme 11 shows the use of an isonitrile as a radical precursor for an imidoyl radical cyclization; related reactions based on tin radical additions have also been developed.[58] These reactions have no analogy in CO chemistry. Neither of the lower two examples in Scheme 11 are tandem radical reactions by the usual definition,[59] but they both illustrate the potential use of isonitriles in vicinal bond forming reactions.

VIII. Tandem Reactions of Radicals with Aryl Isonitriles

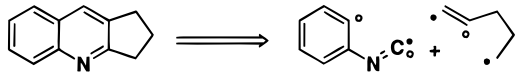
Most tandem reactions of aryl isonitriles directly involve the aryl ring, and as such they have no analogy in CO chemistry. The reaction of 1-iodopentyne with excess phenyl isonitrile at high temperature provides 2,3-dihydro-1*H*-cyclopenta[*b*]quinoline

Scheme 12



in yields over 60% (Scheme 13).[29a] Mechanistic studies suggest the sequence of radical addition, cyclization to the triple bond, and cyclization to the aromatic ring shown in Scheme 12. The last cyclization to the aryl ring must be quite rapid, since it overwhelms the expected[60] rapid bimolecular iodine transfer reaction of the vinyl radical with the starting iodopentyne. There are still some unresolved questions about this mechanism, including the nature of the oxidative rearomatization that must occur in the final step. This reaction accomplishes the unusual transformation shown in Chart 19.

Chart 19



A number of examples of this type of annulation/cyclization are shown in Table 8. Substituents on the terminal alkyne position are well-tolerated, but the presence of aryl substituents on the isonitrile provides mixtures of products. When a *para* substituent is present, two products—one "normal" and one "rearranged"—are formed in ratios ranging from 4/1 to about 10/1. When a *meta* substituent is

Scheme 13

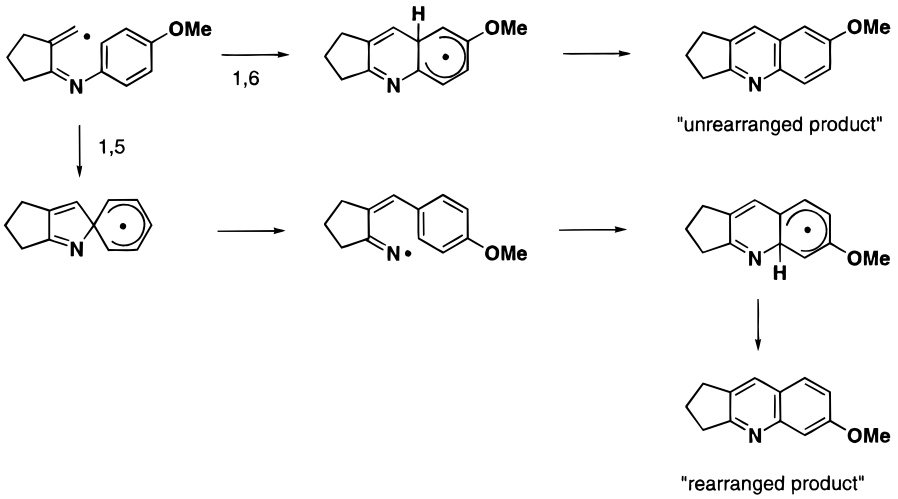


Table 8. Tandem Addition/Cyclization/Cyclization Reactions of Aryl Isonitriles

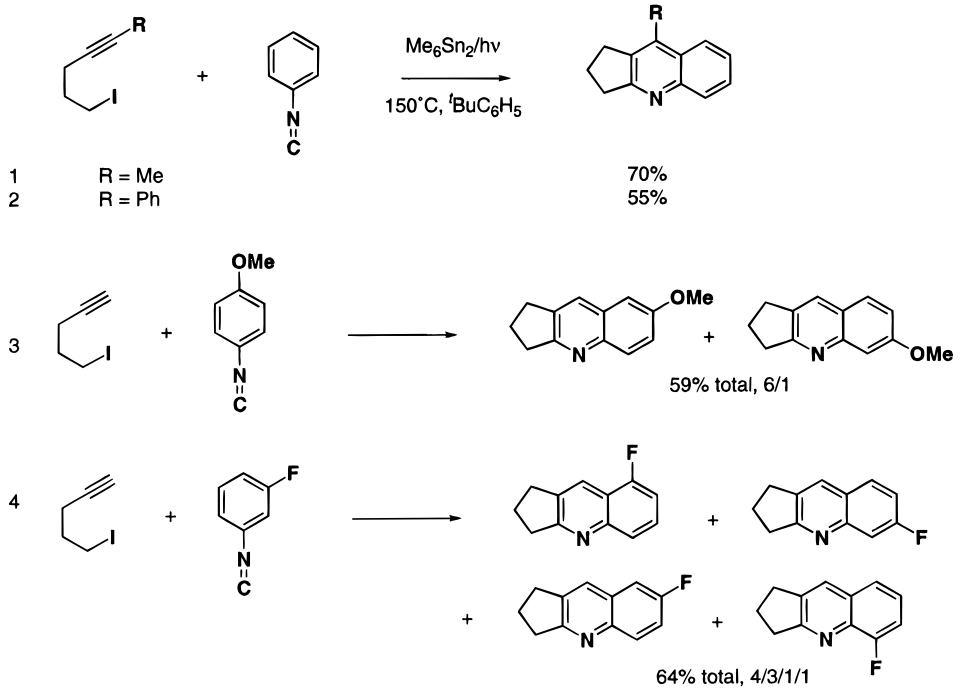
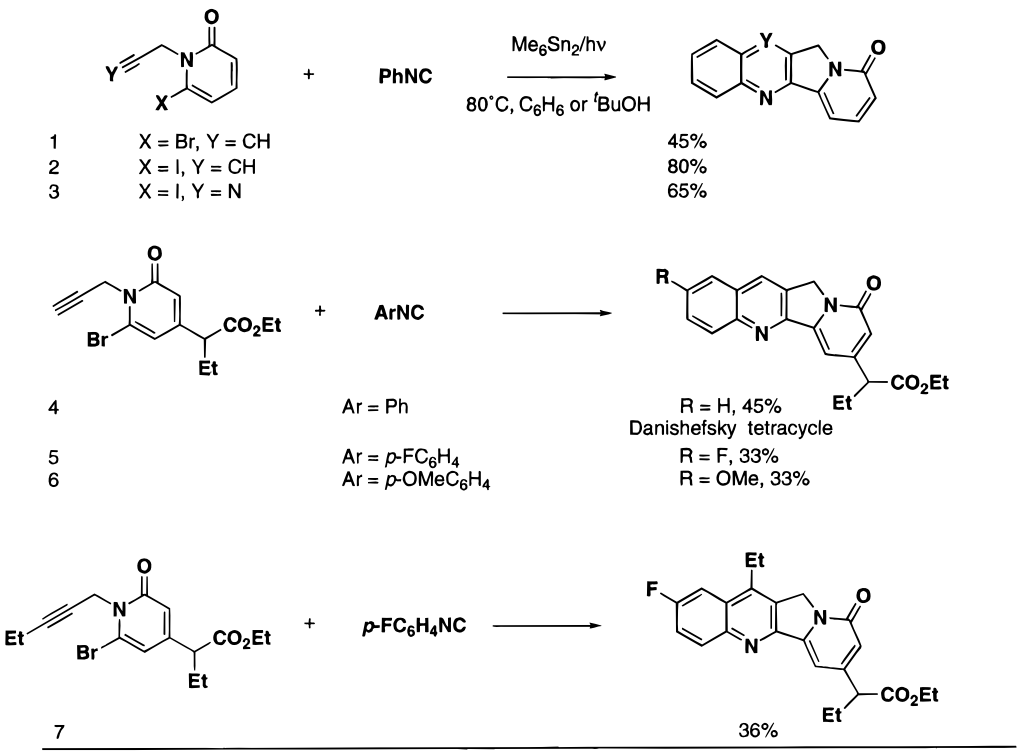


Table 9. Reactions of 6-Halopyridones with Aryl Isonitriles



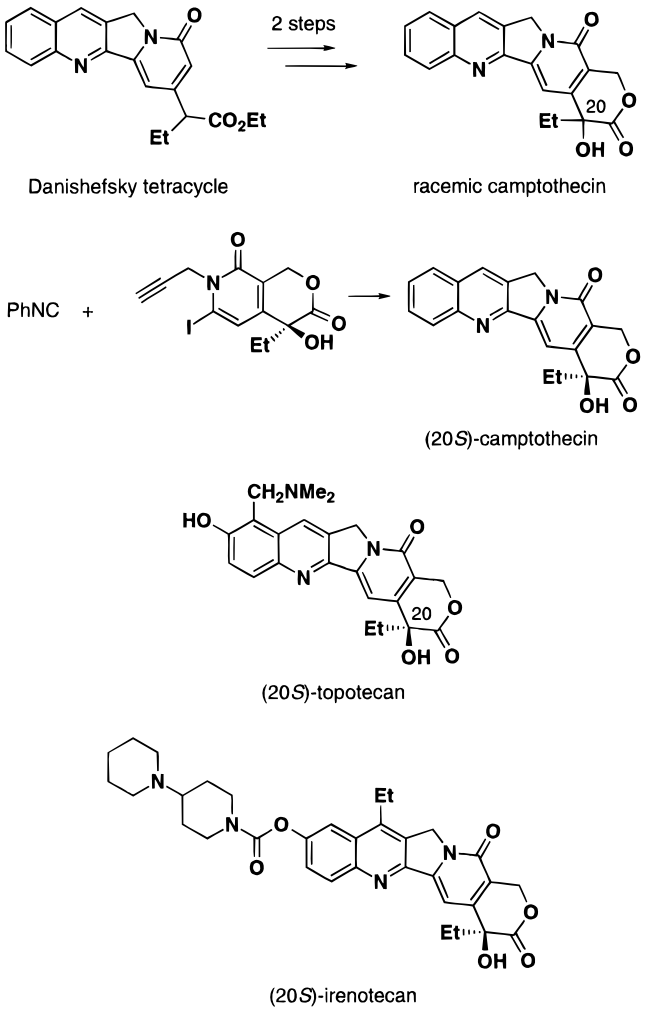
present, there are four products—two normal and two rearranged—in variable ratios.

A probable mechanism for the formation of the normal and rearranged products is shown in Scheme 13 for the *para*-substituted case. Cyclization of the intermediate vinyl radical can occur in a 1,6-fashion to ultimately provide the normal product or in a 1,5-fashion to ultimately provide the rearranged product. Several pathways for the rearrangement can be envisaged, but the indicated sequence of fragmentation of the C−N bond and recyclization of the iminyl radical in a 1,6-fashion is the most probable. In the case of *meta* substituents (not shown), there are two pathways for 1,6-cyclization (*ortho* or *para* to the substituent), so four products result.

This unique radical strategy for the synthesis of cyclopenta-fused quinolines holds considerable potential for the efficient synthesis of complex heterocycles. Reactions of halopyridones have been singled out for study because the tetracyclic products contain four of the five rings of the camptothecin family of anticancer agents.[61] Table 9 compiles several representative examples.[62] In these systems, substituents on both the radical precursor and the isonitrile are well-tolerated, and only normal products are observed. The *N*-propargyl pyridone linkage is apparently too rigid to allow the 1,5-cyclization to occur. The replacement of the C−C triple bond by a C−N triple bond results in the nuclear substitution of carbon by nitrogen in the product.

The product of entry 4 of Table 9 is the popular Danishefsky tetracycle,[63] which is now available from dimethyl acetone dicarboxylate in only six steps.[64] The Danishefsky tetracycle can be converted in two steps to racemic camptothecin (Scheme 14). Recently, an even more direct route to (20*S*)-camptothecin has been developed,[65] and this is summarized in the center of Scheme 14. Addition of a bicyclic iodopyridone to phenyl isonitrile gives camptothecin in 50−60% yield. The bromopyridone is prepared in

Scheme 14



optically active form by a catalytic asymmetric Sharpless dihydroxylation.[66] Analogous syntheses of important derivatives of camptothecin, including topotecan and irinotecan have also been completed.

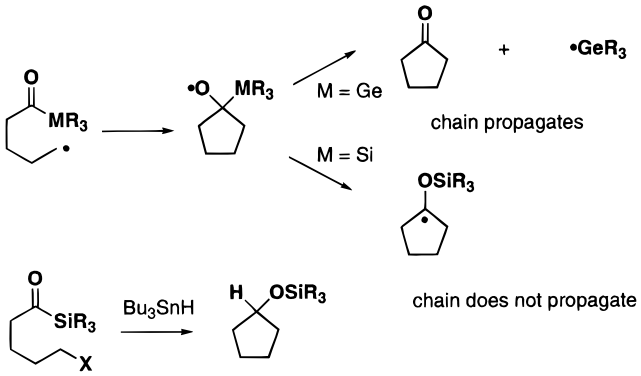
IX. "Indirect" Equivalents of the Geminal Radical Acceptor/Radical Precursor Synthon

Reagents can indirectly function as equivalents of a one-carbon radical acceptor/radical precursor synthon through the aegis of a radical translocation reaction. The product radical of the initial bond-forming reaction is not at the same atom as the attack, but it translocates back to that atom by a subsequent reaction or series of reactions. A second bond-forming reaction then occurs at the site of initial attack. Reagents in this class include acylsilanes and *N*-aziridinyl imides.

A. Acylsilanes

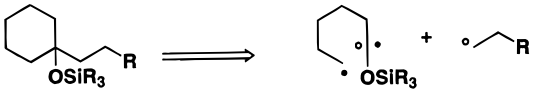
It has recently been shown that acylsilanes[67] and acylgermanes[68] are excellent radical acceptors (Scheme 15). Both 5-*exo* (shown) and 6-*exo* (not shown)

Scheme 15



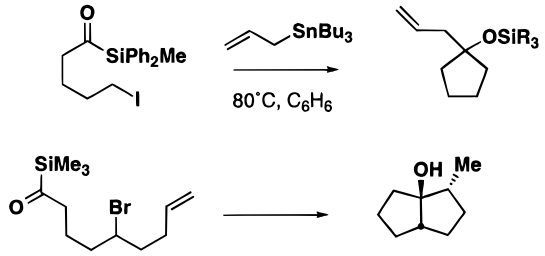
cyclizations can occur. However, after radical cyclization, these two related classes of molecules evolve quite differently. The intermediates from acylgermane cyclizations suffer rapid β-fragmentation of the germyl radical, and a chain reaction ensues. In contrast, the intermediates from acylsilane cyclizations apparently undergo a 1,2-silyl shift[69] (sometimes called a "radical Brook rearrangement") to give α-silyloxy radicals. Because of this shift, acylsilanes will generally not propagate radical chains on their own (the silyl radical is never released to abstract a halogen), but reductive chains can readily be propagated by adding a standard reagent like tributyltin hydride. The 1,2-silyl shift makes acylsilanes reagent equivalents of the "carbinyl radical acceptor/radical precursor" synthon, as shown in Chart 20.

Chart 20



Examples of tandem reactions of acylsilanes are shown in Scheme 16.[70] The initial reaction in the sequence is always a cyclization; acylsilanes have not yet been shown to serve as radical acceptors in

Scheme 16

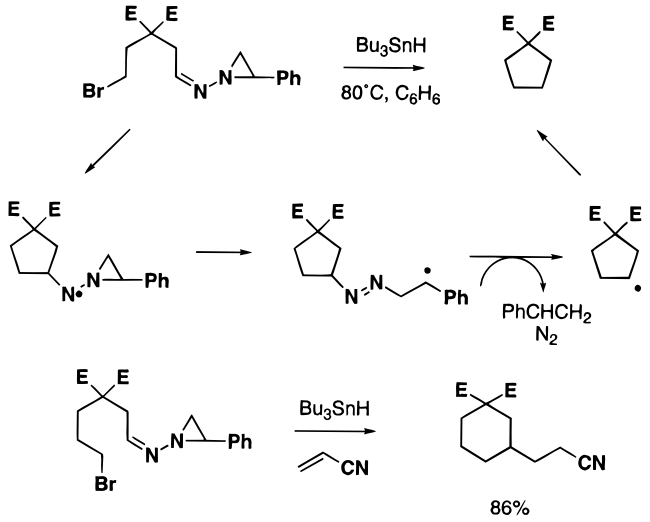


bimolecular reactions. Radical Brook rearrangement then translocates the radical back to the initial site of cyclization, and a second carbon−carbon bond-forming reaction occurs. This second reaction can be either inter- or intramolecular.

B. *N*-Aziridinyl Imines

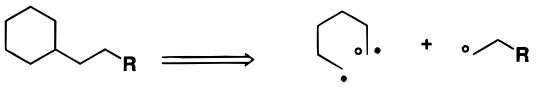
Kim and co-workers have shown that radical cyclizations to *N*-aziridinyl imines also evolve through an interesting radical translocation sequence to return the radical to the initial site of attack.[71] This sequence is shown in Scheme 17. Cyclization is

Scheme 17



followed by 3-*exo* opening of the aziridine and subsequent loss of styrene and dinitrogen to give the translocated radical. When only tin hydride is present, this translocated radical is reduced. These *N*-aziridinyl imines then become reagent equivalents of the parent (unfunctionalized) geminal radical acceptor/radical donor synthon, as shown in Chart 21. A tandem 6-*exo* cyclization/translocation/addition sequence is shown in the lower part of Scheme 17.

Chart 21



X. Conclusions

Synthetic sequences of radical reactions are no longer limited to forming vicinal bonds, and strategies that form geminal bonds are especially practical and useful. Direct sequences with carbon monoxide and isonitriles are now well-established, though it appears that considerably more room for develop-

ment exists. Indirect sequences involving acylsilanes and *N*-aziridinyl imines have been used less frequently, yet they show considerable promise for application in synthesis and they also suggest that the development of other indirect methods that would provide new geminal acceptor/donor synthon is warranted.

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