Reactions of Tin(IV) Enolates and Radicals Derived from the Tin Hydride Scission of Cyclopropyl Ketones

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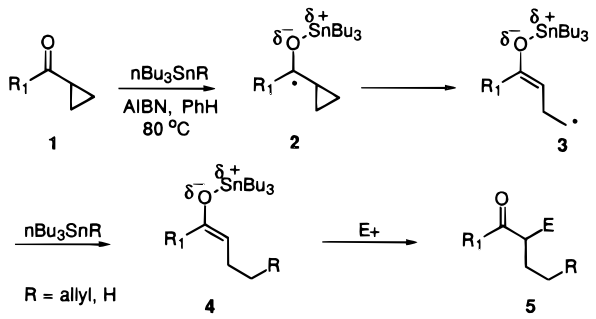
Tin(IV) enolates have been used for a variety of useful synthetic transformations because these intermediates can function as a more stable version of the lithium enolate.[1] Likewise, carbon-centered free radicals have seen intensive growth as a neutral intermediate for the construction of complex organic substrates.[2] An *O*-stannyl ketyl, obtained from the reaction of tributyltin hydride and an enone precursor, is an intermediate with both species delocalized by resonance within the same π-system.[3−5] It is possible, however, to separate the reactivity of the tin(IV) enolate and radical intermediate by a single methylene unit via a fragmentation reaction. The release of strain energy in a three-membered ring can function as the driving force of such a reaction, leading to a sequestration of each species and new synthetic avenues to explore in independent reactions of either moiety.

One reaction that has the capacity to isolate the enolate and radical reactive intermediates is the tributyltin radical cleavage of a cyclopropyl ketone, as shown in the synthetic sequence of **1** → **5** (Scheme 1). Initial formation of the *O*-stannyl ketyl **2**, followed by ring scission **3**, prepares the tin(IV) enolate **4** after transfer of the R group.[6,7] It is worth noting that the new tin(IV) enolate is prepared under very mild and neutral conditions and the radical center in **3** also has untapped synthetic potential because it can be trapped by an unsaturated radicophilic acceptor.

Scheme 1



We have recently initiated a new program on the study and preparation of tin(IV) enolates from tin hydride under free-radical conditions in the absence of a base.[5] Using the tributyltin radical cleavage of cyclopropyl ketones, this work demonstrates useful methods to capture the resulting tin(IV) enolates and radicals within the framework of new bimolecular carbon−carbon bond-forming reactions. The enolates were reacted with aldehyde or alkyl halide electrophiles (E^+), as in the transformation of **4** → **5**, to examine the scope and stereochemical consequences of the reaction sequence. The one-pot process provides a useful one-electron alternative to the classical methods of ketone enolate alkylation performed with hindered bases such as LDA. Radical reactions with allyltributylstannane, as in the transformation of **3** → **4**, were also examined. These transformations take advantage of the radical character in the bifunctional intermediate **3**.

The studies were initiated by examining two strained-ring precursors and subsequent attempts to trap the tin(IV) enolate in a ketocyclopropane fragmentation−aldol reaction. Thus, commercially available cyclopropyl ketone **6** was subjected to standard free-radical conditions involving treatment with tributyltin hydride (1.5 equiv) in benzene (0.3 M) with AIBN at reflux for 2 h. Thin-layer chromatography confirmed the ring scission had occurred. The reaction mixture was cooled to room temperature, cyclohexanecarboxaldehyde (3.0 equiv) was added, and the resulting mixture was stirred overnight (12 h). Curran's procedure for tin removal in the workup and subsequent flash chromatography produced the desired *erythro*-**7** and *threo*-**8** aldol products (92%) in an excellent diastereomeric ratio of 20:1, respectively.[8,10]

The fragmentation−aldol reaction of ketocyclopropane **9** with cyclohexanecarboxaldehyde was next examined. The precursor was prepared from commercial *trans*-chalcone using a sulfur ylide in 78% yield.[9] The free-radical transformation of **9**, followed by the aldol reaction of the enolate, produced *erythro*-**10** and *threo*-**11** products (92%) as an 8:1 mixture of diastereomers, respectively, as shown in Scheme 3. As in Scheme 2, the erythro product predominated here as well.[10]

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(10) The stereochemical assignment of the major product as erythro was made by ^{1}H NMR, using the $J_{threo} > J_{erythro}$ relationship.[11] The assignment was also further confirmed by Heathcock's ^{13}C NMR studies of the carbinol resonance of β-(hydroxycarbonyl) compounds.[12]

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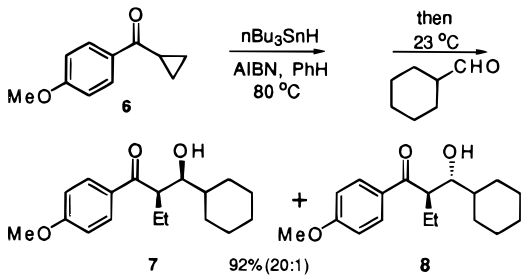
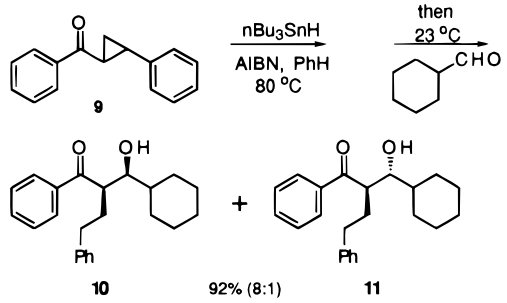
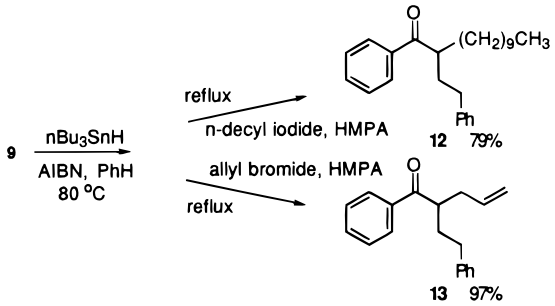
Scheme 2



Scheme 3



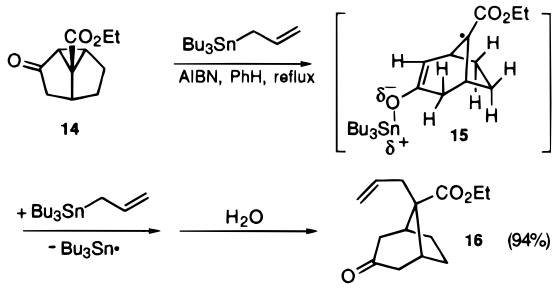
Scheme 4



Two interesting aspects of this reaction deserve comment. First, due to the poor chelating abilities of the bulky tributyltin enolate with an aldehyde, especially at ambient temperatures, a Zimmerman−Traxler transition state for the aldol is unlikely. Instead, an extended acyclic transition state leading to the erythro diastereomer appears more plausible.[1] Secondly, selective cleavage of only one cyclopropane bond in **9** was achieved during the *O*-stannyl ketyl scission process. This fragmentation leads to the more stable benzylic radical intermediate, which has been observed in several previous studies of α-radical cleavage of three-membered rings.[2,6]

Alkylation reactions were also studied using the tin(IV) enolate of **9**, as shown in Scheme 4. Because tin(IV) enolates are slow to react with alkyl halides, HMPA (5 equiv) was added at room temperature to facilitate the reaction by coordination to the tin atom.[1,5j] Either *n*-decyl iodide or allyl bromide was next added, and the mixture was refluxed for 12 h, constructing **12** or **13**, respectively, in good yield.

Scheme 5



In order to expand the utility of these intermediates into the radical domain, allyltributyltin was next used in the cyclopropane fragmentation studies.[7c] It was hoped that a second type of carbon−carbon bond might be readily obtained at the γ-position, relative to the carbonyl. To examine the fragmentation−allylation reaction, ketone **14** was refluxed with allyltributyltin and AIBN in benzene, as shown in Scheme 5. The desired allylation product **16** was isolated as a single diastereomer (>50:1) in 94% yield.

Three interesting aspects of this reaction are worth noting. First, selective cleavage of the cyclopropane bond leading to the ester-stabilized radical center was observed, likely as a result of thermodynamic control.[5f] Even though there is better orbital overlap with the ketyl carbon, the kinetically controlled cleavage of the other cyclopropane bond did not predominate, and no allyl transfer from this alternate mode of cyclopropane cleavage was observed. Secondly, the high diastereoselectivity in **16** might be rationalized by the steric differences between the faces of the radical center in intermediate **15** for approaching allyltributyltin molecule. The face bearing the tin(IV) enolate is less hindered due to the presence of two sp^2 carbons. Thirdly, this free-radical method of forming a carbon−carbon bond from allyltributyltin and a cyclopropyl ketone has not been observed before, to the best of our knowledge.

In a summary, tin(IV) enolates and radicals generated from the reactions of cyclopropyl ketones with trialkyltin reagents are synthetically useful and appear to function well in both two- and one-electron modes of reactivity. Diastereoselectivity up to 20:1 in aldol reactions and related alkylation products was readily obtained. The new radical-mediated allyltributyltin fragmentation holds synthetic promise via the introduction of a three-carbon unit.

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Supporting Information Available: General procedures and spectral data for compounds **7**, **10**, **12**, **13**, and **16** (7 pages).

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