Free Radical Approach to Directed Aldol-Type Reactions Promoted by Allylic *O*-Stannyl Ketyls

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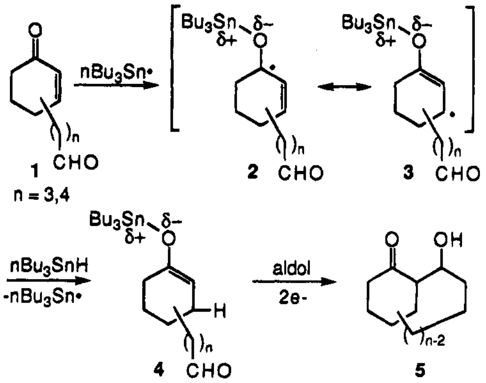
Organic synthesis has greatly benefited from free radical reactions as is evidenced by their powerful applications to cyclization methodologies.[1] Electronically-rich radicals such as ketyl radical anions are not as well-understood, and in particular, their inherent nucleophilic character remains unexploited.[2] Synthetic reactions leading to ketyl radical anion intermediates by partial reduction or one-electron transfer to an aldehyde or ketone have been promoted photochemically, electrochemically, and by metals.[3] Allylic *O*-stannyl ketyls, a resonance-stabilized radical anion species, are produced under mild free radical conditions by the reaction of a conjugated aldehyde or ketone with tributyltin radical (nBu$_3$Sn$^\bullet$).[4−6]

Precursors used to form *O*-stannyl ketyls generally have only one aldehyde or ketone to react with nBu$_3$Sn$^\bullet$. Compound **1**, however, bears a choice of two potentially reactive carbonyls. Previous studies and steric arguments might favor attack at the aldehyde leading to *O*-stannyl ketyl addition to the β-olefin site or direct reduction to an alcohol.[5a] Alternatively, nBu$_3$Sn$^\bullet$ attack at the cyclohexenone moiety in **1** affords resonance-stabilized allylic *O*-stannyl ketyl **2** ↔ **3** (Scheme 1). If hydrogen atom transfer occurs regioselectively at the β-position of **3**, a tin enolate **4** would be prepared by a novel approach. The resulting enolate can now undergo an intramolecular aldol with the tethered aldehyde to prepare the bicylic structure **5**. The interesting combination of free radical and enolate chemistry required in this reaction exemplifies a new rapidly-emerging class of sequential one- and two-electron reactions.[7]

Scheme 1



Herein we describe preliminary results for this new cyclization protocol where the annulation is the result of a directed tin aldol based on a two-electron mode of reactivity. These studies also introduce a mild alternative to current enolate chemistry which avoids NaH, LDA, LHMDS, or other strongly reductive conditions such as dissolving metal media. To test this hypothesis, cyclohexenones were constructed bearing suitably tethered aldehydes as electrophiles, and their tin enolate cyclizations were then examined. To the best of our knowledge, neutral free radical approaches to aldol chemistry using nBu$_3$SnH have not been examined.

Aldol precursor **8**, bearing an aldehyde tether in the C$_3$-position on a cyclohexanone ring, was readily prepared from Grignard reagent **7** derived from 4-chlorobutanol[8] in a reaction with 3-ethoxy-2-cyclohexanone (**6**), followed by a standard Swern oxidation.[9] The tin enolate cyclization was promoted by treatment of **8** with tributyltin hydride under free radical conditions[10] which afforded the *cis*-decalone alcohol **9** in 81% yield (Scheme 2). Interestingly, three new stereocenters resulted from the cyclization, one bearing the alcohol and two arising from the *cis*-decalin ring fusion. Only a single product could be isolated (>50:1), and other diastereomers could not be detected by NMR or chromatographic methods. To unambiguously ensure that the structure and stereochemistry were correct, a single crystal X-ray determination was obtained.[11] Spiro-cyclization of the β-carbon-centered radical of **8** with the tethered aldehyde may have been particularly blocked due to the formation of a

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(10) General procedure: A solution of the ketoaldehyde (1.0 mmol) in benzene (4.0 mL) with AIBN (0.10 mmol) and nBu$_3$SnH (2.0 mmol) was degassed with a stream of Ar for 15 min and heated to 80 °C for 12 h. The reaction was quenched with water (10 mL), extracted with ether (3 × 20 mL), dried over Na$_2$SO$_4$, and concentrated to an oil. Flash chromatography with ether−hexane over silica gel gave the desired bicyclic products.

(11) Compound **9** had to be converted into its *p*-bromobenzoate ester prior to stereochemical confirmation by X-ray studies. This not only gave better quality crystals but also incorporated a heavy atom (Br) into the structure.

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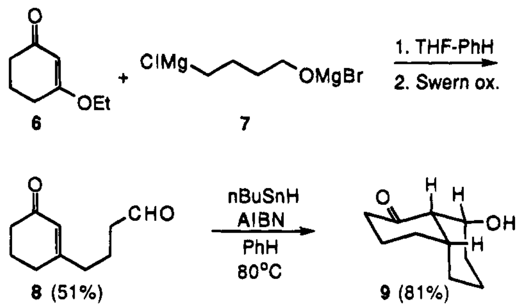
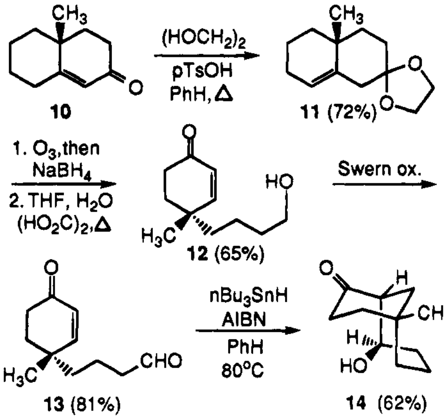
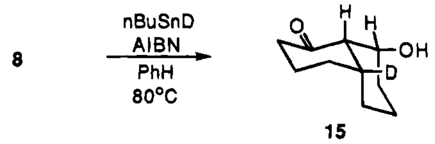
Scheme 2



Scheme 3



Scheme 4

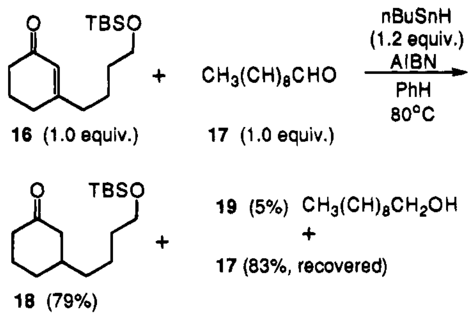


hindered quaternary center; thus, a second example where this was not possible was examined next.

Aldehyde **13** bears a different pattern of substitution on the cyclohexenone and was constructed by adapting the general protocol of Becker.[12] It was prepared from the Robinson-annulated product **10**[13] which was protected with concomitant olefin migration to afford **11** (Scheme 3).[12] Introduction of a four-carbon alcohol appendage by ozonolysis, reduction, and deprotection gave ketone **12**.[12] Aldehyde **13**, the *O*-stannyl enolate precursor, was prepared by Swern oxidation.[9] We were pleased in this case to find that the tin hydride-mediated cyclization gave a seven-membered annulated ring, constructing bicyclic alcohol **14** in 62% yield. As with the example above, no other diastereomers were present by GC, TLC, or NMR; however, some unreacted **13** remained (ca. 17%) in this case. Single crystal X-ray studies confirmed the stereochemistry of **14**, in which the sterically congested hydroxyl was endo in the bicyclo[4.3.1]nonane skeleton.

Two chemical studies, shown in Schemes 4 and 5, were conducted which support the aldol cyclization by the allylic *O*-stannyl ketyl mechanism (Scheme 1). Compound **8** was reacted with tributyltin deuteride and formed only deuterated compound **15** after the reaction was stopped at ca. 30% completion, as shown in Scheme 4. This confirmed the regiochemically favored location of radical at the ring juncture in the annulation reaction; however, it does not rule out the *O*-stannyl ketyl formation at the aldehyde.

Scheme 5



Thus, an alternative explanation for the cyclization is that the tin ketyl forms at the aldehyde carbonyl site and cyclization occurs by attack at the α-position of the enone. This possibility cannot be ruled out, but seems unlikely, because an *O*-stannyl ketyl is a nucleophilic radical and intramolecular attack at the electrophilic β-position of the alkene should be favored.[5a,b] Had this occurred in the case of **13**, a six-membered ring, rather than the observed seven-membered ring, would have prevailed.

A study to distinguish between the ketyls of the aldehyde and the 2-cyclohexenone compared **16** and decanal (**17**) in a simple competition experiment, shown in Scheme 5. As predicted, **18** was formed more rapidly than **19**, which suggests a preference for the resonance stabilized allylic *O*-stannyl ketyl of the 2-cyclohexenone over the *O*-stannyl ketyl of the aldehyde. The small amount of decyl alcohol (**19**) formed due to the dilution of the reaction mixture or from the slight excess (1.2 equiv) of tin hydride used.[14] On the basis of these observations, we propose that free radicals are not involved in the cyclization step, but rather it proceeds via the tin enolate (Scheme 1).

In conclusion, a new free radical method for the construction of carbon–carbon bonds from allylic *O*-stannylketyls has been developed. A directed aldol-type carbonyl addition promoted by nBu_3SnH led to annulated cycloalkanols, where up to three new stereocenters resulted in a highly stereoselective manner. These studies provide a neutral method to prepare tin enolates which may have future applications to intermolecular aldol-type reactions.[14]

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Supplementary Material Available: Spectral data for compounds **9**, **13**, **14**, **16**, and **18** (2 pages).

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(14) Earlier studies have shown that either moiety can be reduced with tin hydride.[4] Low concentrations were employed to separate reactive partners and prevent a bimolecular aldol. This allowed the tin enolate to remain unreacted until workup.