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TIN(IV) ENOLATES FROM ALLYLIC O-STANNYL KETYLS: REACTIONS WITH ALKYL HALIDES AND HMPA

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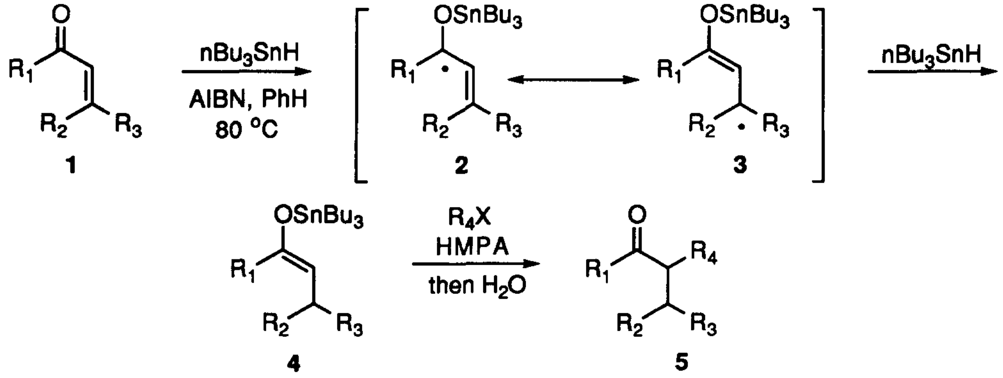
Abstract: The mild free radical reaction of an α,β-unsaturated ketone and tributyltin radical produced a resonance-stabilized allylic O-stannyl ketyl intermediate. A subsequent hydrogen atom transfer produced a tin(IV) enolate which reacts readily with activated alkyl halides and HMPA to provide a useful and mild alternative to analogous Li-NH$_3$ alkylations.

Tin(IV) enolates have been demonstrated to have potential utility in organic synthesis.[1] Although intrinsically less reactive than lithium enolates, yet more reactive than silyl enol ethers, their direct alkylation with organohalides is sluggish, or in many cases, no reaction occurs.[1,2] Few alkylations of unactivated tin(IV) enolates have been successful to date; usually these required high temperatures (up to 140°C) or prolonged reaction times (up to 60 h).[1-3] In the past, tin(IV) enolates were obtained from transmetallation of a more reactive enolate or by transesterification of enol acetates.[1-2] We have recently initiated a new program on the study and preparation of tin(IV) enolates from O-stannyl ketyls by neutral and mild free radical conditions.[4]

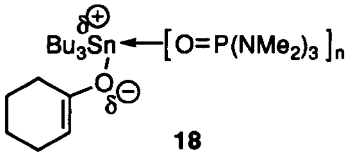
The reaction of α,β-unsaturated carbonyl group **1** with tributytin radical produces an electronically-rich and resonance stabilized allylic O-stannyl ketyl intermediate [**2** ↔ **3**] which has significant potential to become a synthetically useful tool.[5-9] This intermediate subsequently leads to tin enolate **4** by hydrogen atom transfer from nBu$_3$SnH to the β-position of **3**, rather than the radical site in ketyl **2**.[4(a)] Although no literature precedent existed, it was hoped that direct alkylation of **4** with an organohalide would lead to **5** directly from the nucleophilic tin(IV) enolate in the same pot. In order for the alkylation reaction to be successfully mediated by free radical precursors, the alkyl halide had to be added later to the reaction at a point where the tin hydride was totally consumed by the α,β-unsaturated ketone. Careful stoichiometry should play an important role here because the rate of a nBu$_3$Sn• reaction with an alkyl halides is faster than the unsaturated ketone.[10]



This Letter describes the first examples of tin(IV) enolate alkylations from α,β-unsaturated ketones and alkyl halides promoted by tributyltin hydride. In addition, there are two concepts particularly worth noting in the reaction sequence. First, the radical reaction discussed herein results in a direct contrast to how an α,β-unsaturated ketone classically undergoes additions in free radical reactions with an alkyl halide.[12] The normal attack of the alkyl radical, which forms from the alkyl halide, occurs at the β-position in a 1,4-manner as it does with essentially all one- and two-electron donors. By simply delaying the addition of the alkyl halide reagent, the tin(IV) enolate forms first, and α-alkylation follows. Greater flexibility is now possible in both types of reactions because both use similar starting materials. Secondly, the reaction provides a very mild and regioselective alternative to classical metal enolate formation by avoiding strong bases such as LDA or alkylations from Li-NH_3 reductions of unsaturated ketones. The conditions we use, in contrast, are neutral and free radical-based.

Several examples of the alkylation sequence described above have been collected in the Table.[15] The first attempted tin(IV) enolate alkylation was performed in a manner similar to a previous tin(IV) aldol condensation.[4(b)] Benzyl bromide or allyl bromide were added in large excess (4 equiv) even in refluxing toluene, but achieved only modest yields. Thus, the tin(IV) enolate was simply not reactive enough to be alkylated in high yields.

Additional activation of the tin-oxygen bond in the enolate was next pursued.[14] Alkylation of the enolate was greatly facilitated by coordination with ligands to hexamethylphosphoramide (HMPA). This additive considerably increased the nucleophilic capacity of the tin(IV) enolate in these reactions. The high coordination ability of HMPA allows it to act as a Lewis base and increase the polarity of the tin(IV) enolate. This was found to improve alkylation yields significantly, however, the amount of HMPA caused a variation in the yield, presumably due to an optimal coordination number around the tributyltin moiety. Several experiments were performed on Table entry 1, which should have tin(IV) enolate **18** as an intermediate, by varying the equivalents of HMPA, shown below. When 5.0 equivalents of HMPA was added prior to the alkyl halide, yields improved by 50%. When over 5.0 equivalents of HMPA was used, the alkylated product formed in better yield than without using HMPA, but not as good as using 5.0 equivalents. Similar results were observed in entries 2 and 3. Cyclic unsaturated ketones generally seemed to function better here than the acyclic unsaturated ketone in entry 4.

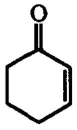
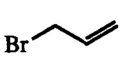
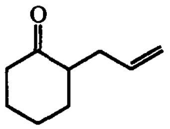
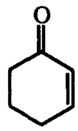
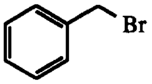
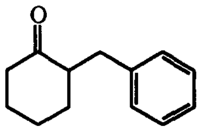
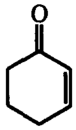
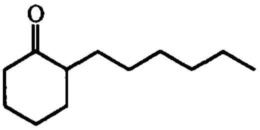
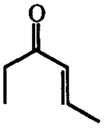
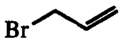
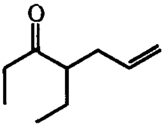
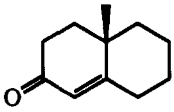
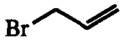
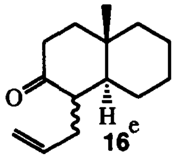
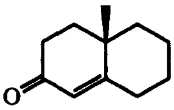
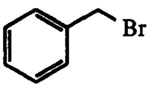
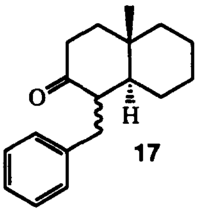


18

Number of Equivalents of HMPA (n)	Yield (%)
0.0	21
5.0	71
8.0	60

General Procedure for Tin(IV) Enolate Alkylation: An unsaturated ketone (1 equiv), tributyltin hydride (1.1 equiv) and azobisisobutyronitrile (0.2 equiv) were dissolved in benzene (1.0 M). The solution was degassed for 0.3 h with a steady stream of argon. The reaction mixture was then refluxed until starting ketone was consumed by TLC (ca. 4 h). After the reaction vessel was allowed to cool to room temperature, HMPA (5 equiv) was added and the reaction mixture stirred 3 min. The appropriate alkyl halide was added next, and the reaction was refluxed for 12-14 h. The reaction mixture was then cooled to room temperature, diluted to 3

Table. Alkylation Reactions Via Allylic O-Stannyl Ketyls

Entry	Unsaturated Ketone	Alkyl Halide	Product	Yield (%)[a]
1	 **6**	 **7**	 **8**[d]	71
2	 **6**	 **9**	 **10**[d]	69
3	 **6**	Hexyl Iodide **11**	 **12**[d]	61
4	 **13**	 **7**	 **14**	48
5	 **15**[d]	 **7**	 **16**[e]	76[b]
6	 **15**	 **9**	 **17**	65[c]

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[a] Yields refer to chromatographically homogeneous material with spectral data consistent with the structure shown.[15] [b] Ratio determined to be 4 : 1, β : α by capillary GC. [c] Ratio determined to be 1 : 1, β : α by capillary GC. [d] The preparation of compounds **15**,[11] **8**,[16] **10**,[17] **12**,[18] have been described previously. [e] Epimerization of **16** with DBU (4.0 equiv) in THF led to a 1 : 2, β : α mixture by capillary GC.

volumes with diethyl ether, and washed with 4 volumes of brine to remove HMPA. To the organic layer was added DBU (1,8-diazobicylco[5.4.0]undec-7-ene) (1.2 equiv) and 2-3 drops of water; an ethereal solution of iodine was added dropwise until the iodine color persisted.[13] Rapid suction filtration through silica gel was performed, and the solution was concentrated and subjected to careful flash column chromatography to afford the alkylated product.

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