Organotin Hydride-Catalyzed Conjugate Reduction of α,*β*-Unsaturated Ketones

David S. Hays, Matthias Scholl, and Gregory C. Fu*

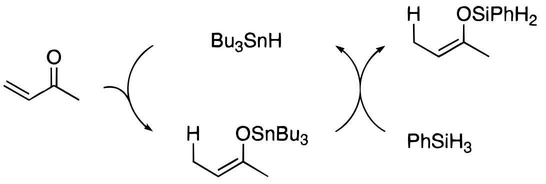
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received May 7, 1996

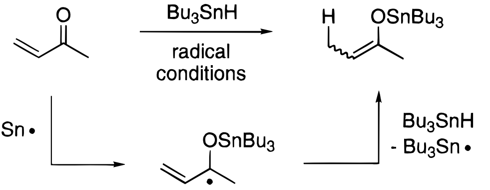
Organotin reagents have become standard tools in organic synthesis,[1] with applications of radical processes mediated by Bu_3SnH being particularly widespread.[2,3] One drawback associated with the use of Bu_3SnH is the toxicity of certain triorganotin species,[4] and the development of non-tin-based alternatives has therefore been the focus of considerable attention. The pioneering studies of Chatgilialoglu and Barton have established that tris(trimethylsilyl)silane[5] and dimethyl phosphite[6] may serve as useful substitutes for Bu_3SnH in many synthetic applications. However, silicon, phosphorus, and tin radicals are distinct chemical entities, and they can therefore display disparate behavior, both in terms of reactivity toward a given functional group[7] and in terms of stereoselectivity.[8]

Rather than seeking substitutes for organotin reagents, we are developing tin-*catalyzed* variants of processes that are known to be accomplished by a stoichiometric quantity of an organotin compound.[9] In one version of this approach the tin catalyst effects the key transformation of the substrate, and then an otherwise inert organosilicon species regenerates the tin catalyst from the initial reaction product.[10,11] This strategy allows us to exploit the relatively well-understood, sometimes unique, chemistry of tin, while greatly reducing the amount of organotin reagent that is required. We describe herein the successful application of this approach to the radical-mediated conjugate reduction of α,*β*-unsaturated ketones.[12]

Scheme 1. Proposed Catalytic Cycle for Bu_3SnH-Catalyzed Conjugate Reduction of Enones

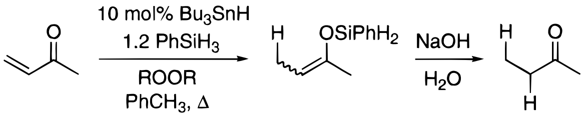


The 1,4-addition of Bu_3SnH to an enone via a radical chain process (eq 1) was first reported by Pereyre and Valade in 1965.[13−15] Two years later, the same group noted that a tin enolate can react with a silicon hydride to generate a tin hydride and a silyl enol ether.[16] We have established that these two observations form the basis for a new catalytic process, the Bu_3SnH-catalyzed, $PhSiH_3$-mediated conjugate reduction of an α,*β*-unsaturated ketone (Scheme 1[17]). Treatment of a wide array of enones with 10 mol % of Bu_3SnH and 1.2 equiv of $PhSiH_3$[18] in refluxing toluene (di-*tert*-butyl peroxide as initiator), followed by basic hydrolysis, provides the saturated ketones in good yields (eq 2; Table 1).



(1)

Hindered *β*,*β*-disubstituted enones are cleanly reduced (Table 1, entries 3 and 4), and dienones undergo selective monoaddition (Table 1, entries 5 and 6[19]). Control experiments for each substrate establish that little (0−



(2)

---

[1] Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: Boston, 1987.

[2] For reviews of the chemistry of Bu_3SnH, see: (a) Neumann, W. P. *Synthesis* **1987**, 665−683. (b) RajanBabu, T. V. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995.

[3] For leading references to radical chemistry, see: (a) Hart, D. J. *Science* **1984**, *223*, 883−887. (b) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon: New York, 1986. (c) Curran, D. P. *Synthesis* **1988**, 417−439, 489−513. (d) Regitz, M.; Giese, B. *Houben-Weyl, Methoden der Organischen Chemie*; Georg Thieme Verlag: Stuttgart, 1989. (e) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic: New York, 1992. (f) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: New York, 1996.

[4] Boyer, I. J. *Toxicology* **1989**, *55*, 253−298.

[5] (a) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188−194. (b) Giese, B.; Dickhaut, J. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995.

[6] Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *J. Org. Chem.* **1993**, *58*, 6838−6842.

[7] For example, see: Ballestri, M.; Chatgilialoglu, C.; Lucarini, M.; Pedulli, G. F. *J. Org. Chem.* **1992**, *57*, 948−952. See also ref 5a.

[8] For example, see: (a) Apeloig, Y.; Nakash, M. *J. Am. Chem. Soc.* **1994**, *116*, 10781−10782. (b) Lee, E.; Park, C. M.; Yun, J. S. *J. Am. Chem. Soc.* **1995**, *117*, 8017−8018.

[9] For seminal work on Bu_3SnH-catalyzed radical processes, see: (a) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1975**, *40*, 2554−2555. (b) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303−304.

[10] For applications of this approach to polar chemistry, see: (a) Tin hydride: Lipowitz, J.; Bowman, S. A. *J. Org. Chem.* **1973**, *38*, 162−165. Vedejs, E.; Duncan, S. M.; Haight, A. R. *J. Org. Chem.* **1993**, *58*, 3046−3050. (b) Tin cyanide: Scholl, M.; Fu, G. C. *J. Org. Chem.* **1994**, *59*, 7178−7179. Scholl, M.; Lim, C.-K.; Fu, G. C. *J. Org. Chem.* **1995**, *60*, 6229−6231.

[11] (a) For a suggestion that radical-mediated reactions might be susceptible to this strategy, see: Lipowitz, J.; Bowman, S. A. *Aldrichim. Acta* **1973**, *6*, 1−6. (b) For an application of this approach to radical chemistry, see: Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 4−5.

[12] For other methods for effecting the conjugate reduction of enones, see: (a) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989; pp 9−12. (b) Parkes, K. E. B.; Richardson, S. K. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon: New York, 1995; Vol. 3, pp 127−128. (c) Keinan, E.; Greenspoon, N. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 8, Chapter 3.5.

[13] (a) Pereyre, M.; Valade, J. *Compt. Rend.* **1965**, *260*, 581−584. (b) Pereyre, M.; Valade, J. *Bull. Soc. Chim. Fr.* **1967**, 1928−1936. For an overview, see ref 1.

[14] For an application of this process in natural products chemistry, see: Laurent, H.; Esperling, P.; Baude, G. *Liebigs Ann. Chem.* **1983**, 1996−1999.

[15] Tin enolates exist as a mixture of interconverting tautomers in which the tin is bound either to oxygen or to carbon. For simplicity, we have illustrated the oxygen-bound tautomer in eq 1 and Scheme 1. See: (a) Pereyre, M.; Bellegarde, B.; Mendelsohn, J.; Valade, J. *J. Organomet. Chem.* **1968**, *11*, 97−110. (b) Lutsenko, I. F.; Baukov, Y. I.; Belavin, I. Y. *J. Organomet. Chem.* **1970**, *24*, 359−369.

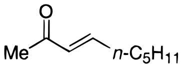
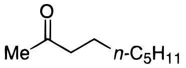
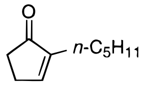
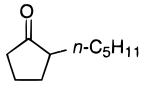
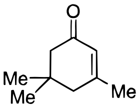
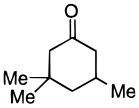
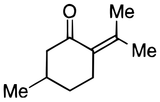
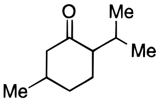
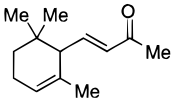
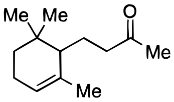
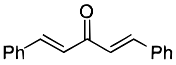
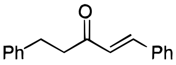
[16] (a) Bellegarde, B.; Pereyre, M.; Valade, J. *Bull. Soc. Chim. Fr.* **1967**, 746−747. (b) Bellegarde, B.; Pereyre, M.; Valade, J. *Bull. Soc. Chim. Fr.* **1967**, 3082−3083.

[17] A mixture of silyl enol ethers (bearing zero to two hydrogens on silicon) is probably formed.

[18] Lower yields are observed when polymethylhydrosiloxane is employed as the stoichiometric reductant.

S0022-3263(96)00846-8 CCC: $12.00

Table 1. Bu_3SnH-Catalyzed Conjugate Reduction of Enones (eq 2)

Entry	Substrate	Product	Time (h)	Yield (%)
1			12	82
2			24	74
3			24	80
4			12	85[a]
5			24	80
6			2	76

[a] 1.8:1 mixture of diastereomers.

8%) reduction is observed in the absence of Bu_3SnH under otherwise identical conditions.

In conclusion, we have developed an organotin hydride-catalyzed, silicon hydride-mediated method for effecting the conjugate reduction of α,β-unsaturated ketones. This catalytic process is mechanistically distinct from other silane-based procedures for accomplishing this transformation, all of which rely upon catalysis by a transition metal.[20]

Experimental Section

General Methods. All substrates were obtained from Aldrich, with the exception of (*R*)-(+)-pulegone, which was purchased from Eastman Kodak. Each substrate was purified by distillation immediately prior to use, except for (*R*)-(+)-pulegone and *trans,trans*-dibenzylideneacetone, which were purified by flash chromatography. Bu_3SnH (Gelest) and $PhSiH_3$ (Fluka) were distilled, and di-*tert*-butyl peroxide (Aldrich) was used as received. Toluene was distilled from sodium.

Analytical thin layer chromatography was accomplished using EM Reagents 0.25 mm silica gel 60 plates. Flash chromatography was performed on EM Reagents silica gel 60 (230−400 mesh).

All reactions were carried out in oven-dried, sealed Schlenk tubes under an atmosphere of argon with magnetic stirring. All yields reported in Table 1 are the average of two runs. Reaction products for entries 1−5 (Table 1) were identical by ^1H and ^{13}C NMR with authentic reduction products that were either commercially available or prepared independently.

Representative Procedure: Conjugate Reduction of 3-Nonen-2-one (Table 1, Entry 1). $PhSiH_3$ (130 mg, 1.2 mmol), Bu_3SnH (29.1 mg, 0.1 mmol), and di-*tert*-butyl peroxide (29.2 mg, 0.2 mmol) were added to a Schlenk tube containing a colorless solution of 3-nonen-2-one (140 mg, 1.0 mmol) in 0.2 mL of toluene. The resulting homogeneous reaction mixture was placed in a 120 °C oil bath and stirred for 12 h, at which time GC showed the reaction to be complete. The mixture was diluted with acetone (10 mL), and then 4 N NaOH (10 mL) was added dropwise, leading to vigorous bubbling. The resulting orange solution was stirred for 30 min, and then the product was isolated by extraction (EtOAc). The organic layer was dried ($MgSO_4$) and concentrated, providing an orange oil. Flash chromatography (10% EtOAc/hexanes) afforded 112 mg (80%) of nonan-2-one, a colorless oil.

The conjugate reduction of 3-nonen-2-one on a 5 mmol scale provided a 72% yield of nonan-2-one (average of two runs).

(*E*)-1,5-Diphenyl-1-penten-3-one: white solid; ^1H NMR (300 MHz, C_6D_6) 7.50 (d, 1H, $J = 16.1$ Hz), 7.30−7.10 (m, 10H), 6.62 (d, 1H, $J = 16.2$ Hz), 3.06 (t, 2H, $J = 7.7$ Hz), 2.68 (t, 2H, $J = 7.6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 199.1, 142.5, 141.1, 134.3, 130.3, 128.8, 128.4, 128.3, 128.1, 126.0, 42.3, 30.0; IR 3028, 2919, 1685, 1613, 1496, 1449, 999, 748, 696 cm^{-1}; HRMS calcd for $C_{17}H_{16}O$ 236.1201, found 236.1202; mp 54.0−54.5 °C.

Acknowledgment. Support has been provided by the MIT Undergraduate Research Opportunities Program (partial support for M.S.), the National Science Foundation (predoctoral fellowship to D.S.H.; Young Investigator Award to G.C.F., with funding from Hoechst Celanese, Merck, Pfizer, Procter & Gamble, Rohm & Haas, and Upjohn), the American Cancer Society (Junior Faculty Research Award to G.C.F.), and the Camille and Henry Dreyfus Foundation (New Faculty Award in Chemistry to G.C.F.). Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

Supporting Information Available: ^1H and ^{13}C NMR spectra of all reaction products (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO960846E

---

[19] Because the enone product illustrated in entry 6 (Table 1) is not revealed until hydrolysis of the initially formed silyl enol ether occurs (Scheme 1), only one of the two carbon−carbon double bonds of *trans,trans*-dibenzylideneacetone is reduced.

[20] (a) Ojima, I.; Kogure, T.; Nagai, Y. *Tetrahedron Lett.* **1972**, 5035−5088. (b) Reference 12.