Organotin Hydride Catalyzed Carbon−Carbon Bond Formation: Radical-Mediated Reductive Cyclization of Enals and Enones

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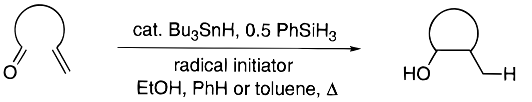
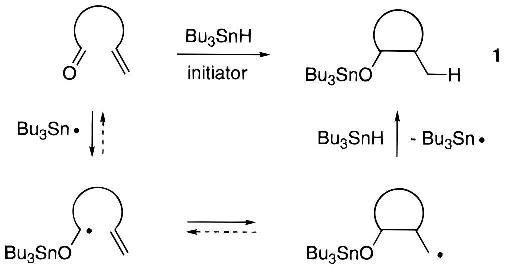
Radical reactions are now employed routinely by synthetic organic chemists.[1] Many of these transformations are mediated by a stoichiometric quantity of Bu_3SnH. Motivated both by an awareness of the toxicity of triorganotin species[2] as well as by an interest in asymmetric catalysis,[3] we have initiated a program focused on the design of new processes in which organotin hydrides are used as catalysts rather than as stoichiometric reagents. In this paper, we report the development of a Bu_3SnH-catalyzed, $PhSiH_3$-mediated carbon−carbon bond-forming reaction, the reductive cyclization of enals and enones (eq 1).



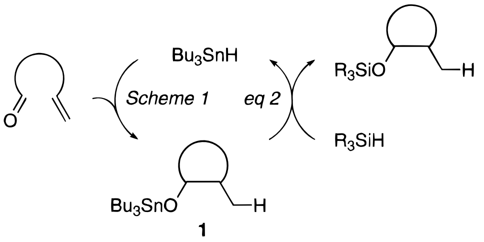
(1)

Several groups have reported that enals and enones undergo reductive cyclization[4] by a free radical chain process upon treatment with a stoichiometric quantity of Bu_3SnH (Scheme 1).[5,6] In the first step, a tributyltin radical adds to the carbonyl group to produce a tin ketyl. Addition of this ketyl to the pendant olefin affords a new radical, which abstracts a hydrogen atom from Bu_3SnH to generate the reductive cyclization product (**1**).

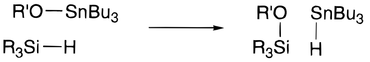
Scheme 1. Reductive Cyclization with Stoichiometric Bu_3SnH



Scheme 2. Proposed Catalytic Cycle for Tin Hydride-Catalyzed, Silicon Hydride-Mediated Reductive Cyclization



Employing Bu_3SnH as a *catalyst* for this transformation requires the use of a stoichiometric amount of a second metal hydride capable of regenerating Bu_3SnH from tributyltin alkoxide **1**.[7,8] Several workers have independently reported that silicon hydrides react with tin alkoxides to afford tin hydrides and silyl ethers (eq 2).[9,10] Two known reactions, run in sequence, thus provide the basis for a new catalytic process (Scheme 2).[11]



$$\begin{matrix} R'O-SnBu_3 \\ R_3Si-H \end{matrix} \longrightarrow \begin{matrix} R'O & SnBu_3 \\ | & | \\ R_3Si & H \end{matrix} \qquad (2)$$

As illustrated in Table 1, we have established that Bu_3SnH does indeed effectively catalyze the silicon hydride-mediated reductive cyclization of enals and of enones. Thus, treatment of unsaturated aldehydes or ketones with 5−15 mol % of $(Bu_3Sn)_2O$[12−14] and 0.5 equiv of $PhSiH_3$[15] (radical initiator, 2 equiv of EtOH,[16] refluxing benzene or toluene) affords the desired cyclic products in good yields.[17]

This new catalytic carbon−carbon bond-forming process efficiently generates both five- (Table 1, entries 1−4) and six-membered rings (entries 5 and 6).[18] Cyclization proceeds more readily when the remote position of the

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(1) For leading references, 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.

(2) For leading references, see: Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: Boston, 1987; Chapter 1.

(3) (a) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.

(4) Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821−2824. For a review, see: Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237−1286.

(5) Early work: (a) Beckwith, A. L. J.; Roberts, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 5893−5901. (b) Ardisson, J.; Ferezou, J. P.; Julia, M.; Pancrazi, A. *Tetrahedron Lett.* **1987**, *28*, 2001−2004. (c) Sugawara, T.; Otter, B. A.; Ueda, T. *Tetrahedron Lett.* **1988**, *29*, 75−78.

(6) Enholm was the first to systematically explore the scope of this reaction: (a) Enholm, E. J.; Prasad, G. *Tetrahedron Lett.* **1989**, *30*, 4939−4942. (b) Enholm, E. J.; Burroff, J. A. *Tetrahedron Lett.* **1992**, *33*, 1835−1838.

(7) A polar variant of this strategy (catalytic tin hydride, stoichiometric silicon hydride) has been applied to the reduction of carbonyl groups. For an early report, see: Nitzsche, S.; Wick, M. *Angew. Chem.* **1957**, *69*, 96. For a suggestion that radical-mediated reactions might be susceptible to this approach, see: Lipowitz, J.; Bowman, S. A. *Aldrichim. Acta* **1973**, *6*, 1−6.

(8) For Bu_3SnH-catalyzed, borohydride-mediated radical dehalogenation processes, see: (a) $NaBH_4$: Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1975**, *40*, 2554−2555. (b) $NaBH_3CN$: Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303−304 (carbon−carbon bond-forming reactions).

(9) (a) Reference 7. (b) Itoi, K. Fr. Patent 1,368,522, 1964. Itoi, K.; Kumano, S. *Kogyo Kagaku Zasshi* **1967**, *70*, 82−86. (c) Hayashi, K.; Iyoda, J.; Shiihara, I. *J. Organomet. Chem.* **1967**, *10*, 81−94. (d) Bellegarde, B.; Pereyre, M.; Valade, J. *Bull. Soc. Chim. Fr.* **1967**, 3082−3083.

(10) For a mechanistic study, see: Pijselman, J.; Pereyre, M. *J. Organomet. Chem.* **1973**, *63*, 139−157.

(11) For *titanium*-catalyzed reductive cyclization of δ,ε-unsaturated enals and enones to cyclopentanols: (a) Kablaoui, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 6785−6786. (b) Crowe, W. E.; Rachita, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 6787−6788.

(12) For all of the substrates illustrated in Table 1, very little (<3%) reductive cyclization is observed in the absence of $(Bu_3Sn)_2O$ under otherwise identical conditions.

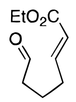
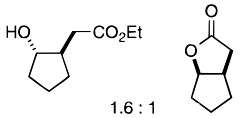
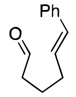
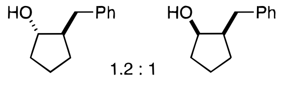
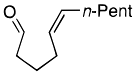
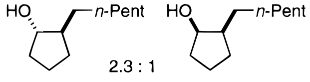
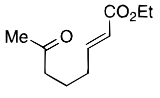
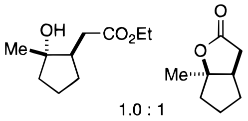
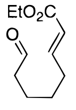
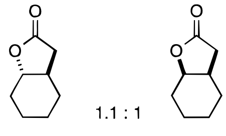
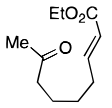
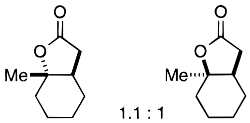
(13) $(Bu_3Sn)_2O$ serves as a convenient and inexpensive source of Bu_3SnH (treatment of $(Bu_3Sn)_2O$ with $PhSiH_3$/EtOH in benzene at room temperature results in clean formation of 2 equiv of Bu_3SnH). Reductive cyclizations in which catalytic amounts of Bu_3SnH are used in place of $(Bu_3Sn)_2O$ provide yields and stereoselectivities essentially identical to those reported in Table 1.

(14) Table 1, entries 1, 2, and 4: 5 mol % $(Bu_3Sn)_2O$; entry 6: 10 mol % $(Bu_3Sn)_2O$; entries 3 and 5: 15 mol % $(Bu_3Sn)_2O$.

(15) Preliminary efforts to employ polymethylhydrosiloxane (PMHS) as the stoichiometric reducing agent predominantly afforded uncyclized alcohol (1,2-reduction), along with small amounts (<25%) of the reductive cyclization product.

0022-3263/96/1961-0004$12.00/0

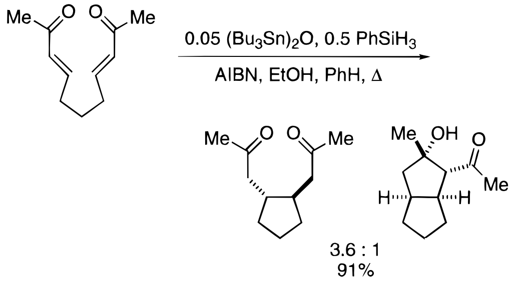
Table 1. Bu_3SnH-Catalyzed Reductive Cyclization of Enals and Enones

Entry	Substrate	Products[a]	Yield[b]
1		 1.6 : 1	71
2		 1.2 : 1	85
3		 2.3 : 1	67[c]
4		 1.0 : 1	75
5		 1.1 : 1	76
6		 1.1 : 1	66

[a] Product ratios are based on analysis by capillary gas chromatography and/or ^1H NMR. [b] Yields refer to isolated mixtures of the cis and trans products and are the average of two runs. [c] 29% 1,2-reduction is observed.

olefin bears a radical-stabilizing substituent (e.g., ester or phenyl, entries 1 and 2); otherwise, a significant quantity of uncyclized alcohol resulting from 1,2-reduction of the aldehyde is produced (29%; entry 3).[6a,19] We observe essentially the same diastereoselectivities when we conduct the reactions under the catalyzed conditions as when we run them with stoichiometric Bu_3SnH,[6a] a result consistent with the catalytic reaction proceeding by the pathway outlined in Scheme 2.

We have begun to explore the development of Bu_3SnH-catalyzed variants of related radical-based transformations.[20] For example, Enholm has reported that activated dienes undergo intramolecular coupling upon treatment with 3 equiv of tributyltin hydride.[21] We have found that this reaction can be effected with 5 mol % of $(Bu_3Sn)_2O$ and 0.5 equiv of $PhSiH_3$ in comparable yield and stereoselectivity (eq 3).



(3)

In summary, we have developed a new Bu_3SnH-catalyzed carbon–carbon bond-forming process, the radical-mediated reductive cyclization of enals and enones. Ongoing investigations include the following: further examination of the scope of this reaction,[6b] including application to the synthesis of heterocycles;[22] the pursuit of mechanistic studies; the development of Bu_3SnH-catalyzed variants of other tin ketyl-mediated processes; and the design and synthesis of chiral, nonracemic organotin hydride catalysts.

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Supporting Information Available: Experimental procedures and compound characterization data (16 pages).

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(16) In some of the reactions that we have explored, a somewhat lower yield of cyclic product is observed if EtOH is not present. The following data suggested to us that the addition of EtOH would facilitate the regeneration of Bu_3SnH, which might in turn improve the efficiency of the reductive cyclization: (1) exchange of alcohols with tin alkoxides is rapid at room temperature (ref 2, Chapters 2 and 11), and (2) primary tin alkoxides are more readily reduced by silanes than are secondary or tertiary tin alkoxides (ref 9b). Thus, we believe that, in the presence of EtOH, Bu_3SnH is regenerated through reduction of Bu_3SnOEt.

(17) Sample experimental details (Table 1, entry 5): To a solution of the enal (184 mg, 1.00 mmol) in benzene (2.0 mL) in a 10 mL sealable Schlenk tube was added $(Bu_3Sn)_2O$ (76 μL, 0.15 mmol), $PhSiH_3$ (62 μL, 0.50 mmol), ethanol (117 μL, 2.00 mmol), and AIBN (16 mg, 0.10 mmol in 200 μL of benzene) under an atmosphere of nitrogen. The container was sealed, shaken, and immersed in an 80 °C oil bath. After 6.5 h, TLC analysis indicated that no starting material remained. The reaction mixture was treated with TBAF (3.0 mL of a 1.0 M solution in THF; 1 h at rt) and then subjected to workup with 2 M HCl (15 mL) and ether. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to afford a crude mixture of *trans* hydroxy ester and *cis* lactone. The residue was dissolved in CH_2Cl_2 (10 mL), a catalytic quantity of TsOH was added, and the solution was stirred for 20 h at rt, at which time GC analysis indicated that all of the trans hydroxy ester had lactonized. The reaction mixture was concentrated and then purified by flash chromatography to afford 103 mg (74%) of an analytically pure mixture of cis and trans lactones as a colorless oil (1.1:1 trans:cis by ^1H NMR).

(18) We have not yet explored the generation of other ring sizes.

(19) We observe the formation of a similar quantity of 1,2-reduction product under the stoichiometric reductive cyclization conditions (1.2 equiv of Bu_3SnH, no $PhSiH_3$).

(20) For example, see: (a) Conjugate reduction of α,β-unsaturated carbonyls: Pereyre, M.; Valade, J. *Compt. Rend.* **1965**, *260*, 581–584. (b) Reductive cyclization of keto-oximes: Naito, T.; Tajiri, K.; Harimoto, T.; Ninomiya, I.; Kiguchi, T. *Tetrahedron Lett.* **1994**, *35*, 2205–2206. Kiguchi, T.; Tajiri, K.; Ninomiya, I.; Naito, T.; Hiramatsu, H. *Tetrahedron Lett.* **1995**, *36*, 253–256. (c) Conjugate reduction/intramolecular aldol: Enholm, E. J.; Xie, Y.; Abboud, K. A. *J. Org. Chem.* **1995**, *60*, 1112–1113.

(21) (a) Enholm, E. J.; Kinter, K. S. *J. Am. Chem. Soc.* **1991**, *113*, 7784–7785. (b) Enholm, E. J.; Kinter, K. S. *J. Org. Chem.* **1995**, *60*, 4850–4855.

(22) For example, see: Lee, E.; Tae, J. S.; Chong, Y. H.; Park, Y. C.; Yun, M.; Kim, S. *Tetrahedron Lett.* **1994**, *35*, 129–132.