Development of Bu_3SnH-Catalyzed Processes: Efficient Reduction of Azides to Amines

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Taken together, the ever-increasing utility of tin chemistry[1] and the growing concern about tin toxicity[2] provide a powerful incentive to discover processes in which tin compounds are employed as catalysts, as opposed to stoichiometric reagents. We have initiated a program directed at the development of reactions wherein Bu_3SnH, one of the most synthetically useful organotin compounds,[3] is utilized as a catalyst, and a silicon hydride fills the role of stoichiometric reductant. To date, we have focused our attention largely on processes in which Bu_3SnH reacts with a substrate to produce an intermediate with a Sn−O bond, which the silicon hydride then reduces to regenerate Bu_3SnH.[4] We have now expanded the scope of our investigation to include processes that furnish an intermediate with a Sn−N bond. The radical-mediated reduction of azides to amines is an example of a Sn−N bond-forming process that currently requires stoichiometric Bu_3SnH (eq 1).[5,6] In this report, we describe a strategy for effecting Bu_3SnH-catalyzed reactions that permits this reduction to be accomplished with only 5 mol % Bu_3SnH (eq 2).

$$R{-}N_3 \xrightarrow[\text{AIBN, benzene, }\Delta]{Bu_3SnH\ (excess)} R{-}NH_2 \qquad (1)$$

via " R−N(H)−$SnBu_3$"

$$R{-}N_3 \xrightarrow[PhSiH_3 \text{ or PMHS, } n\text{-PrOH, AIBN, 80 °C}]{Bu_3SnH\ (5\%)} R{-}NH_2 \qquad (2)$$

On the basis of our recent observation that $PhSiH_3$ can cleanly reduce Bu_3SnNMe_2 to Bu_3SnH,[7] we anticipated that it might be possible to effect a Bu_3SnH-catalyzed, silicon hydride-mediated azide reduction process according to the pathway outlined in Figure 1. Initially, as in eq 1, Bu_3SnH would reduce RN_3 to $RNHSnBu_3$; then, in the turnover step, the stoichiometric reducing agent, $HSiR_3$, would react with $RNHSnBu_3$ to regenerate the catalyst, Bu_3SnH.

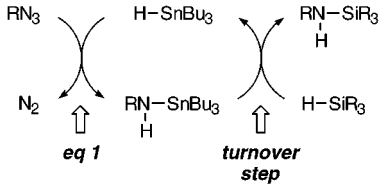

Figure 1. Bu_3SnH-catalyzed, silicon hydride-mediated reduction of azides: an initial approach.

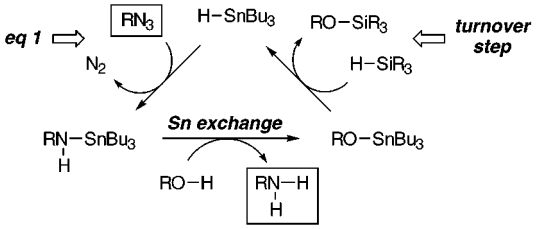

Figure 2. Bu_3SnH-catalyzed, silicon hydride-mediated reduction of azides: an alternate approach.

Unfortunately, this proposed catalytic process has not proved to be viable. Thus, treatment of 1-azidoadamantane with 10 mol % of Bu_3SnH and 0.5 equiv of $PhSiH_3$ (AIBN, refluxing benzene) affords 1-aminoadamantane in low yield (∼11%). Through NMR studies, we have determined that $RHNSnBu_3$ and $RN(SnBu_3)_2$, the major tin-containing products from the reaction of RN_3 with Bu_3SnH, are not readily reduced by $PhSiH_3$ to Bu_3SnH.

Rather than depending upon the reduction of Sn−N to Sn−H for our turnover step (Figure 1), we chose to pursue an alternate strategy that relies upon the reduction of Sn−O to Sn−H[8] (Figure 2). Thus, we anticipated that if we added an alcohol to the reaction, transfer of the $SnBu_3$ group from the nitrogen of the initially formed $RNHSnBu_3$ to the oxygen of the alcohol would occur (Figure 2, Sn exchange).[9] The resulting tin alkoxide could then be reduced by the silicon hydride to regenerate the catalyst, Bu_3SnH.

We chose a primary alcohol to be our additive, since the reduction of Sn−O to Sn−H by silicon hydrides has been shown to be sensitive to steric effects,[8a] and we found that

(1) (a) Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: Boston, 1987. (b) Davies, A. G. *Organotin Chemistry*; VCH: New York, 1997.

(2) (a) Boyer, I. J. *Toxicology* **1989**, *55*, 253−298. (b) De Mora, S. J. *Tributyltin: Case Study of an Environmental Contaminant*; Cambridge University Press: Cambridge, UK, 1996.

(3) 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.

(4) For Bu_3SnH-catalyzed reactions. (a) Reductive cyclization: Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 4−5. (b) Conjugate reduction of α,β-unsaturated ketones: Hays, D. S.; Scholl, M.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 6751−6752. (c) Barton−McCombie deoxygenation: Lopez, R. M.; Hays, D. S.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 6949−6950.

(5) (a) For the reduction of benzoyl azide with Bu_3SnH, see: Frankel, M.; Wagner, D.; Gertner, D.; Zilkha, A. *J. Organomet. Chem.* **1967**, *7*, 518−520. (b) For an application of Bu_3SnH-mediated azide reduction in natural product synthesis (*O*-methylorantine), see: Wasserman, H. H.; Brunner, R. K.; Buynak, J. D.; Carter, C. G.; Oku, T.; Robinson, R. P. *J. Am. Chem. Soc.* **1985**, *107*, 519−521. (c) Poopeiko, N. E.; Pricota, T. I.; Mikhailopulo, I. A. *Synlett* **1991**, 342. (d) Samano, M. C.; Robins, M. J. *Tetrahedron Lett.* **1991**, *32*, 6293−6296.

(6) (a) Larock, Richard C. *Comprehensive Organic Transformations*; VCH: New York, 1989; pp 409−410. (b) Gilchrist, T. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 8, Chapter 2.2. (c) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297−368.

(7) Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 7070−7071.

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

(9) (a) Amberger, E.; Kula, M.-R.; Lorberth, J. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 138. (b) Jones, K.; Lappert, M. F. *Proc. Chem. Soc.* **1964**, 22−23. (c) Lorberth, J.; Kula, M.-R. *Chem. Ber.* **1964**, *97*, 3444−3451.

(10) We use 2.5 mol % $(Bu_3Sn)_2O$ as our precatalyst in these reductions. Under the reaction conditions, it is converted to 5 mol % Bu_3SnH (for a discussion, see ref 4c). Relative to Bu_3SnH, $(Bu_3Sn)_2O$ has cost ($38 versus $250 per mol of tin) and stability advantages.

(11) **Typical Experimental Procedure.** $(Bu_3Sn)_2O$ (29.8 mg, 0.0500 mmol), $PhSiH_3$ (108−144 mg, 1.00−1.33 mmol), and *n*-PrOH (240 mg, 4.00 mmol) were added to a solution of the alkyl azide (2.00 mmol) and AIBN (16 mg, 0.10 mmol) in benzene (2.0 mL). The reaction was heated to reflux for 90−120 min in an oil bath maintained at 90 °C. After the mixture was cooled to rt, pentane (10 mL) was added, followed by anhydrous HCl (5−7 mL of a 1.0 M solution in Et_2O). The resulting white solid was collected by filtration and then dissolved in MeOH. Removal of the solvent afforded the product amine as a white hydrochloride salt. The ^1H and ^{13}C NMR spectra of the hydrochloride salt were identical to spectra for material prepared by protonation of the commercially available amine. Note: Reactions run on a 20 mmol scale provide comparable results.

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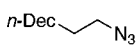
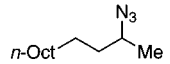
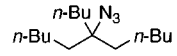
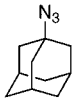
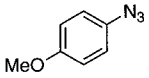
Table 1. Bu_3SnH-Catalyzed Reduction of Azides to Amines

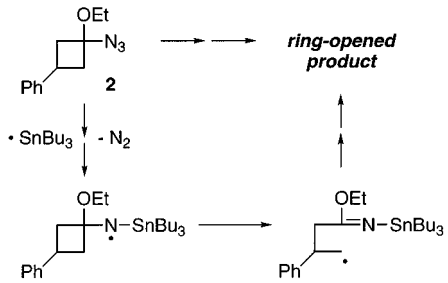
Entry	Substrate	Yield (%)[a] $PhSiH_3$[11]	Yield (%)[a] PMHS[14]
1		94[b]	95[b]
2		92[b]	94[b]
3		96	94
4		99[b]	96[b]
5		94	91

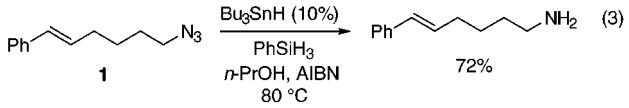
[a] Isolated yield, average of two runs.
[b] Isolated as the amine hydrochloride salt.

this modified catalytic process is indeed extremely efficient. Thus, treatment of a primary, secondary, tertiary, or aryl azide with Bu_3SnH (5 mol %)[10] and $PhSiH_3$ (0.6 equiv) in the presence of *n*-PrOH (2 equiv) in refluxing benzene provides the primary amine in excellent yield (92−99%; Table 1, $PhSiH_3$).[11,12] A ^{119}Sn NMR spectrum taken at the end of the reduction of 2-azidododecane reveals that Bu_3SnH is the only detectible tin-containing species, and GC analysis shows that 96% of the original Bu_3SnH still remains.

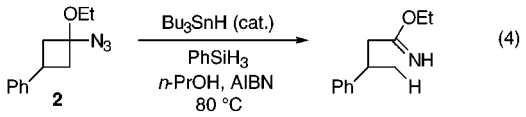
We have established that inexpensive PMHS (TMSO−$(SiHMeO)_n$−TMS)[13] can also be used as the stoichiometric reductant in this Bu_3SnH-catalyzed transformation. Reaction of an organic azide with Bu_3SnH (5 mol %), PMHS (3 equiv), and *n*-PrOH (2 equiv) at 80 °C affords the desired amine in uniformly high yield (91−96%; Table 1, PMHS).[14] With either set of reaction conditions (PMHS or $PhSiH_3$), little or no reduction of the azide (<10%) is observed in the absence of Bu_3SnH or of *n*-PrOH. Alkynes, esters, and alkyl chlorides are compatible with both of the reduction conditions, but aldehydes, ketones, nitro groups, and alkyl bromides are not.[15] For the reaction of azido olefin **1**, we obtained the unsaturated amine in lower-than-usual yield (eq 3; 72% yield by ^1H NMR); interestingly, this appears to be due to [3 + 2] cycloaddition of the substrate,[16] not cyclization of the intermediate nitrogen radical.[17,18]

Scheme 1





To provide evidence for radical-mediated N−N bond cleavage in these Bu_3SnH-catalyzed reductions, we examined the reaction of azide **2** (Scheme 1); as demonstrated by Kim, if the reduction of this substrate follows a radical pathway, then a ring-opened product should be observed.[19] We have established that under our Bu_3SnH-catalyzed azide reduction conditions ring opening does indeed occur to generate an acyclic imino ester (eq 4).



In conclusion, we have developed a new Bu_3SnH-catalyzed process, the reduction of azides to amines. Although we were not able to effect this transformation according to our original plan (Figure 1), we have established the viability of an alternate strategy for catalysis that is likely to be general for reactions that involve the formation of Sn−N bonds (Figure 2). The development of additional Bu_3SnH-catalyzed processes is underway.

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Supporting Information Available: Experimental procedures and compound characterization data (45 pages).

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(12) Under these reduction conditions, tertiary azides are slightly less reactive than secondary azides, which are slightly less reactive than primary azides.

(13) (a) Price per mole of hydride (Aldrich Chemical Co.): PMHS: $6; Bu_3SnH: $250. (b) Toxicity: LD50 of PMHS: 80 g/kg. Klyaschitskaya, A. L.; Krasovskii, G. N.; Fridlyand, S. A. *Gig. Sanit.* **1970**, *35*, 28−31; *Chem. Abstr.* **1970**, *72*, 124864r. (c) For a review of PMHS, see: Lipowitz, J.; Bowman, S. A. *Aldrichim. Acta* **1973**, *6*, 1−6.

(14) **Typical Experimental Procedure.** $(Bu_3Sn)_2O$ (29.8 mg, 0.0500 mmol), PMHS (360 mg, 6.00 mmol), and *n*-PrOH (240 mg, 4.00 mmol) were added to a mixture of the alkyl azide (2.00 mmol) and AIBN (16 mg, 0.10 mmol). The reaction was heated in an oil bath maintained at 80 °C. After 1−2 h, the residue was cooled to rt and treated with anhydrous HCl (5 mL of a 1.0 M solution in Et_2O). Hexane was added if needed to facilitate precipitation. The resulting white solid was collected by filtration and then dissolved in MeOH. If insoluble material appeared upon standing, the solution was filtered prior to concentrating, which afforded the amine as a white hydrochloride salt. The ^1H and ^{13}C NMR spectra of the hydrochloride salt were identical to spectra for material prepared by protonation of the commercially available amine. Note: Reactions run on a 20 mmol scale provide comparable results; a rapid exotherm may accompany large-scale reactions.

(15) The reductions were run individually in the presence of the following compounds: 1-dodecyne, ethyl caprate, chlorocyclohexane, octyl aldehyde, 2-octanone, nitrocyclohexane, and bromocyclohexane. In the presence of *trans*-2-heptene and *cis*-2-heptene, no isomerization was observed with $PhSiH_3$ as the stoichiometric reductant, but small amounts of olefin isomerization were observed with PMHS.

(16) Logothetis, A. L. *J. Am. Chem. Soc.* **1965**, *87*, 749−754.

(17) For the synthesis of 2-benzylpiperidine, see: Meyers, A. I.; Edwards, P. D.; Bailey, T. R.; Jagdmann, G. E., Jr. *J. Org. Chem.* **1985**, *50*, 1019−1026.

(18) For leading references to intramolecular additions of aminyl radicals to olefins, see: Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543−17594.

(19) Kim, S.; Joe, G. H.; Do, J. Y. *J. Am. Chem. Soc.* **1993**, *115*, 3328−3329.