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A Mild, Convenient, and Inexpensive Method for Converting Imines into Amines: Tin-Catalyzed Reduction with Polymethylhydrosiloxane (PMHS)

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Abstract: We have developed a mild, convenient, and inexpensive protocol for reducing imines to amines. Thus, treatment of any of a wide array of imines with catalytic *n*-butyltris(2-ethylhexanoate)tin and stoichioimetric polymethylhydrosiloxane (PMHS) in ethanol at room temperature cleanly affords the desired secondary amine product. Alkyl bromides, alkynes, epoxides, esters, nitriles, and olefins are inert toward these reduction conditions, whereas aldehydes, ketones, and nitro compounds are not.
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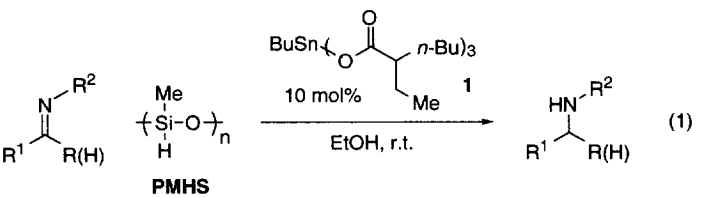
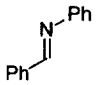
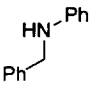
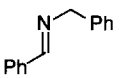
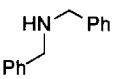
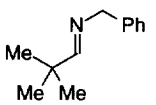
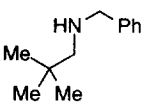
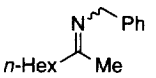
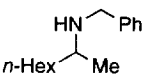
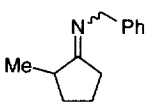
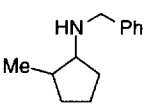
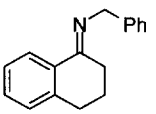
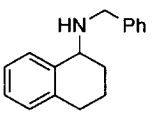
Because organotin compounds mediate an array of important transformations, they are widely used in synthetic organic chemistry, usually as stoichiometric reagents.[1] Motivated in part by the knowledge that difficulties in purification[2] and issues of toxicity[3] plague many stoichiometric applications of organotin compounds, we have undertaken a program directed at the development of processes *catalyzed* by organotin species. To date, we have focused our attention largely on reactions of the carbonyl group.[4] In this report, we describe work in the area of imine chemistry, specifically, a mild and convenient method for converting imines to amines that uses *n*-butyltris(2-ethylhexanoate)tin (**1**) as the catalyst and polymethylhydrosiloxane (PMHS) as the stoichiometric reductant (eq 1).[5,6,7]



(1)

Treatment of an imine with catalyst **1** and PMHS in ethanol at room temperature cleanly furnishes the reduction product, a secondary amine (Table 1). Imines derived from aldehydes (entries 1-3) as well as from ketones (entries 4-6) undergo reaction, including those that are sterically hindered at the imine carbon (entry 3). The *N*-substituent may be either an aryl (entry 1) or an alkyl (entries 2-6) group.

Table 1. Tin-Catalyzed Reduction of Imines with PMHS (eq 1)

Entry	Substrate	Product	Yield (%)[a]
1			82
2			76
3			75
4			81
5			84
6			82

[a]Average of two runs.

Organotin compounds other than **1**, such as Bu_2SnCl_2, also serve as catalysts for the reduction of imines, but **1** is particularly appealing due to its low cost ($42/mol[8]) and low toxicity.[9] Similarly, the low cost ($6/mol of hydride[10]) and low toxicity of PMHS render it a more attractive stoichiometric reducing agent than alternative silicon hydrides like $PhSiH_3$.

Alkyl bromides, alkynes, epoxides, esters, nitriles, and olefins are inert toward the **1**/PMHS reduction conditions, whereas aldehydes, ketones, and nitro compounds are not. This protocol for imine reduction seems to be tolerant of air, moisture, and impurities--reactions run open to the atmosphere with unpurified reagents cleanly furnish the desired secondary amine. The reaction yield is not a strong function of scale, as reductions run on 1 mmol and on 10 mmol of substrate proceed with comparable efficiency. None of the imines illustrated in Table 1 are reduced by PMHS in the absence of catalyst **1** (<5% conversion).

In conclusion, we have developed a mild, convenient, and inexpensive procedure for reducing imines to amines. Studies relevant to the mechanism of this reaction are underway.

EXPERIMENTAL

General. ^{1}H nuclear magnetic resonance spectra were recorded on a Varian XL-300 or a Varian Unity 300 at ambient temperature in $CDCl_3$ and are referenced to residual solvent downfield from tetramethylsilane (δ 7.27 for $CHCl_3$). ^{1}H NMR data are reported as follows: chemical shift (δ scale), multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constant (Hz), and integration.

All ^{13}C NMR spectra were obtained in $CDCl_3$ with complete proton decoupling on a Varian XL-300 NMR spectrometer at 75 MHz and are referenced to residual solvent downfield from tetramethylsilane (δ 77.23 for $CHCl_3$).

Infrared spectra were obtained on a Perkin-Elmer 1600 FT-IR spectrometer (cm^{-1}). High resolution mass spectra were recorded on a Finnigan System 8200 mass spectrometer.

All reactions were set up under an atmosphere of nitrogen in oven-dried glassware inside a Vacuum Atmospheres glove box.

Gas chromatographic analysis was carried out on a Hewlett Packard 5890 Series II instrument using a DB-1 capillary column (J & W Scientific; 30 m length, 0.25 mm inner diameter, 40 mL/min of nitrogen flow rate).

Toluene was dried by refluxing over and distilling from sodium metal under argon, and ethanol was dried according to the method of Lund and Bjerrum.[11] *N*-Benzylideneaniline (Aldrich) was recrystallized from 85% ethanol,[12] and *N*-benzylidenebenzylamine (Aldrich) was used as received. *n*-Butyltris(2-ethylhexanoate)tin (Gelest) and PMHS (Aldrich) were degassed under vacuum.

Flash chromatography was performed on EM Reagents silica gel 60 (230-400 mesh). Yields refer to isolated yields of compounds >95% pure, as assessed by ^{1}H NMR.

General procedure for the preparation of imines. The carbonyl compound (1.0 equiv) and benzylamine (1.1 equiv) were dissolved in dry toluene (50-100 mL) under argon in a round-bottom flask equipped with a reflux condenser and a Dean-Stark trap. The mixture was heated to reflux for 24-48 hours. The solvent was then removed, and the imine product was purified by distillation.

The reagents required for the imine preparations are commercially available and were used as received.

***N*-(2,2-Dimethylpropylidene)benzylamine.** The general procedure was followed using pivaldehyde (4.0 g, 46 mmol). The imine was purified by vacuum distillation (40-45 °C, 300 mtorr), which afforded 5.5 g (68%) of the desired product. ^{1}H NMR: δ 7.67 (s, 1H), 7.40-7.20 (m, 5H), 4.60 (s, 2H), 1.14 (s, 9H); ^{13}C NMR: δ 172.7, 139.6, 128.1, 127.4, 126.5, 64.3, 36.1, 26.8; IR (neat): 2959, 2814, 1666, 1496, 1453, 1364, 1298, 1206, 1051, 1030, 914, 733, 696. The spectroscopic data are consistent with the literature data.[13]

***N*-(2-*n*-Octylidene)benzylamine.** The general procedure was followed using 2-octanone (5.0 g, 39 mmol). The imine was purified by vacuum distillation (90-95 °C, 300 mtorr), which afforded 4.9 g (58%) of the desired product as a 2.8 : 1 mixture of geometric isomers. ^{1}H NMR: major isomer δ 7.35-7.15 (m, 5H), 4.44 (s, 2H), 2.28 (t, J = 7.8, 2H), 1.86 (s, 3H), 1.60-1.50 (m, 2H), 1.35-1.20 (m, 6H), 0.90-0.80 (m, 3H); minor isomer δ 4.47 (s, 2H), 2.03 (s, 3H), some resonances of the minor isomer are obscured; ^{13}C NMR: δ 170.2, 140.2, 127.7, 127.2, 125.9, 54.5, 42.3, 31.2, 28.6, 26.0, 22.2, 16.9, 13.6; IR (neat): 2934, 2849, 1714, 1660, 1495, 1454, 1367, 1029, 731, 697, 556, 491; HRMS (EI) calcd for $C_{15}H_{23}N$ (M^+) 217.1830; found 217.1830.

***N*-[(2-Methyl)cyclopentylidene)]benzylamine.** The general procedure was followed using 2-methylcyclopentanone (4.6 g, 47 mmol). The imine was purified by vacuum distillation (80 °C, 250 mtorr), which afforded 3.5 g (40%) of the desired product as a 10 : 1 mixture of geometric isomers. ^{1}H NMR: major isomer δ 7.30-7.10 (m, 5H), 4.47 (s, 2H), 2.45-2.30 (m, 2H), 2.25-2.15 (m, 1H), 2.10-2.00 (m, 1H), 1.95-1.85 (m, 1H), 1.75-1.65 (m, 1H), 1.40-1.30 (m, 1H), 1.18 (d, J = 14.2, 3H); minor isomer δ 2.90-2.80 (m, 1H), 1.11 (d, J = 14.4, 3H), some resonances of the minor isomer are obscured; ^{13}C NMR: major isomer δ 182.7, 140.9, 127.9, 127.1, 126.0, 56.6, 41.1, 32.8, 28.8, 22.1, 16.7; minor isomer δ 56.3, 35.3, 33.8, 33.2, 20.9, some resonances of the minor isomer are obscured; IR (neat): 2956, 2860, 1681, 1494, 1453, 1351, 1300, 1177, 1029, 736; HRMS (EI) calcd for $C_{13}H_{17}N$ (M^+) 187.1361; found 187.1361.

***N*-(2,3,4-Trihydro-1-naphthylidene)benzylamine.** The general procedure was followed using α-tetralone (5.0 g, 34 mmol). The imine was purified by vacuum distillation (140 °C, 300 mtorr), which afforded 3.2 g (40%) of the desired product. ^{1}H NMR: δ 8.30 (d, J = 7.8, 1H), 7.45-7.15 (m, 8H), 4.71 (s, 2H), 2.83 (t, J = 6.7, 2H), 2.66 (t, J = 6.1, 2H), 2.00 (pentet, J = 6.2, 2H); ^{13}C NMR: δ 165.5, 141.1, 140.7, 134.9, 129.9, 128.5, 127.8, 126.6, 126.5, 126.1, 54.6, 30.0, 28.4, 22.8; IR(neat): 3036, 2922, 1943, 1860, 1803, 1621, 1455, 1294, 1155, 1117, 1028, 767, 690, 649. The spectroscopic data are consistent with the literature data.[14]

GENERAL PROCEDURE FOR THE REDUCTION OF IMINES. *n*-Butyltris(2-ethylhexanoate)tin (60 mg, 0.10 mmol) and PMHS (180 mg, 3.00 mmol) were added to a solution of imine (1.00 mmol) in EtOH (234 μL, 4.00 mmol) in a 10 mL sealable Schlenk tube. The mixture was allowed to stir at room temperature for the specified time (vide infra). The solution was then transferred to a round-bottom flask, and the EtOH was removed. The residue was taken up in Et_2O and stirred with 1 M HCl (3 mL) for 10 minutes. The layers were separated, and the Et_2O layer was extracted with 1 M HCl (3 x 10 mL). The aqueous layers were combined, made basic with solid KOH, and extracted with Et_2O (4 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The amine was then purified by flash chromatography on silica gel.

***N*-Phenylbenzylamine** (Table 1, entry 1). *N*-Benzylideneaniline (181 mg, 1.00 mmol) was reduced in 7 hours, following the general procedure. The amine was purified by flash chromatography (hexanes → 92 : 8 hexanes/EtOAc), which afforded 150 mg (82%) of product. ^{1}H NMR: δ 7.17 (m, 6H), 6.62 (t, J = 7.4, 1H), 6.54 (d, J = 8.0, 1H), 4.23 (s, 2H), 3.94 (br, 1H); ^{13}C NMR: δ 148.3, 139.6, 129.5, 128.8, 127.7, 127.4, 117.7, 113.0, 48.5. The spectroscopic data are consistent with the literature data.[15]

Dibenzylamine (Table 1, entry 2). *N*-Benzylidenebenzylamine (197 mg, 1.00 mmol) was reduced in 10 hours (a trace of starting material remained), following the general procedure. The amine was purified by flash chromatography (hexanes→ 85 : 15 hexanes/EtOAc), which afforded 157 mg (79%) of product. The spectroscopic data are consistent with the literature data (*The Aldrich Library of NMR Spectra*).

***N*-Benzylneopentylamine** (Table 1, entry 3). *N*-(2,2-Dimethylpropylidene)benzylamine (175 mg, 1.00 mmol) was reduced in 20 hours (a trace of starting material remained), following the general procedure. The amine was purified by flash chromatography (hexanes → 70 : 30 hexanes/EtOAc), which afforded 128 mg

(72%) of product. ^{1}H NMR: δ 7.30-7.15 (m, 5H), 3.75 (s, 2H), 2.29 (s, 2H), 1.19 (br s, 1H), 0.85 (s, 9H); ^{13}C NMR: δ 141.2, 128.4, 128.1, 126.9, 61.8, 54.9, 31.7, 28.0; IR (neat) 3353, 2952, 2860, 2802, 2361, 1454, 1362, 1118, 1028, 734; HRMS (FAB, *m/e*) calcd for $C_{12}H_{20}N$ (M+H) 178.1596; found 178.1596.

Benzyl(2-octyl)amine (Table 1, entry 4). *N*-(2-*n*-Octylidene)benzylamine (217 mg, 1.00 mmol) was reduced in 6 hours, following the general procedure. The amine was purified by flash chromatography (hexanes → 90 : 10 hexanes/EtOAc), which afforded 182 mg (83%) of product. ^{1}H NMR: δ 7.35-7.15 (m, 5H), 3.79 (d, J = 13.0, 1H), 3.69 (d, J = 13.0, 1H), 2.70-2.60 (m, 1H), 1.50-1.40 (m, 1H), 1.40-1.20 (m, 9H), 1.03 (d, J = 6.3, 3H), 0.84 (t, J = 6.4, 3H); ^{13}C NMR: δ 141.1, 128.5, 128.2, 126.9, 52.6, 51.6, 37.3, 32.0, 29.6, 26.1, 22.8, 20.5, 14.2; IR (neat): 3307, 3085, 3062, 3026, 2918, 2855, 1603, 1494, 1453, 1374, 1554, 1072, 1028, 906, 728, 697; HRMS (FAB, *m/e*) calcd for $C_{15}H_{26}N$ (M+H) 220.2065; found 220.2067.

Benzyl-[(2-methyl)-cyclopentenyl]amine (Table 1, entry 5). *N*-[(2-Methyl)cyclopentylidene)]-benzylamine (187 mg, 1.00 mmol) was reduced in 9 hours, following the general procedure. The amine was purified by flash chromatography (hexanes → 90 : 10 hexanes/EtOAc), which afforded 150 mg (80%) of the desired compound as a 1.8/1 mixture of diastereomers. ^{1}H NMR: major isomer δ 7.30-7.15 (m, 5H), 3.73 (d, J = 14.3, 1H), 3.66 (d, J = 14.3, 1H), 2.94 (dd, J = 13.2, 6.6, 1H), 2.10-1.20 (m, 7H), 0.84 (d, J = 7.5, 3H); minor isomer δ 2.51 (dd, J = 14.0, 6.5, 1H), 0.93 (d, J = 6.9, 3H) some resonances of the minor isomer are obscured; ^{13}C NMR: both isomers δ 141.1, 128.5, 128.2, 128.2, 126.9. Major isomer 61.7, 52.6, 36.0, 31.9, 30.4, 21.3, 13.9. Minor isomer 66.4, 52.9, 40.9, 33.2, 32.8, 22.6, 19.2; IR (neat): 3324, 2950, 2857, 1604, 1495, 1453, 1377, 1345, 1125, 1073, 1028, 735, 697; HRMS (FAB, *m/e*) calcd for $C_{13}H_{20}N$ (M+H) 190.1596; found 190.1595.

***N*-(2,3,4-Trihydro-1-naphthyl)benzylamine** (Table 1, entry 6). *N*-(2,3,4-Trihydro-1-naphthyl-idene)benzylamine (235 mg, 1.00 mmol) was reduced in 10 hours, following the general procedure. The amine was purified by flash chromatography (hexanes → 90 : 10 hexanes/EtOAc), which afforded 196 mg (83%) of product. ^{1}H NMR: δ 7.40-7.00 (m, 9H), 3.91 (d, J = 14.0, 1H), 3.81 (d, J = 13.2, 1H), 3.80-3.70 (m, 1H), 2.85-2.60 (m, 2H), 2.05-1.85 (m, 3H), 1.80-1.65 (m, 1H), 1.40 (br s, 1H); ^{13}C NMR: δ 141.2, 139.6, 137.7, 129.2, 129.0, 128.5, 128.3, 127.0, 126.8, 125.9, 54.8, 51.4, 29.6, 28.4, 19.2; IR (neat): 3331, 3061, 3024, 2931, 2858, 1682, 1602, 1488, 1453, 1102, 1028, 909, 734, 698; HRMS (FAB, *m/e*) calcd for $C_{17}H_{20}N$ (M+H) 238.1596; found 238.1595.

Competition experiments. *p*-Methoxybenzaldehyde, α-tetralone, 2-octanone, ethyl decanoate, 5-bromo-1-pentene, 1-bromooctane, cyclododecane epoxide, pentadecanenitrile, 1-heptyne, 1-dodecene, and nitrocyclohexane were used in the competition experiments. **General procedure**: PMHS (180 mg, 3.00 mmol), heptadecane (31 μL, 0.10 mmol; internal standard), and *n*-butyltris(2-ethylhexanoate)tin (60 mg, 0.10 mmol) were added to a solution of *N*-benzylideneaniline (181 mg, 1.00 mmol) and the substrate (1.00 mmol) in EtOH (234 μL, 4.00 mmol) in a sealable Schlenk tube. The vessel was closed, and the mixture was allowed to stir at room temperature. Aliquots were removed at different intervals and treated with a solution of 1 M NaOH for 3 hours, then extracted with Et_2O and analyzed by GC. In those reactions in which substrate reduction was observed (*p*-methoxybenzaldehyde, α-tetralone, and 2-octanone), the identity of the products was established by comparison with authentic samples (*p*-methoxybenzylalcohol, 1,2,3,4-tetrahydro-1-naphthol, and 2-octanol).

The competition experiment with nitrocyclohexane afforded a mixture of products in which nitrosocyclohexane was the main product.

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REFERENCES AND NOTES

1. Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: Boston, 1987.
2. Leading references: Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 7200-7201.
3. Boyer, I. J. *Toxicology* **1989**, *55*, 253-298.
4. (a) Scholl, M.; Fu, G. C. *J. Org. Chem.* **1994**, *59*, 7178-7179. (b) Scholl, M.; Lim, C.-K.; Fu, G. C. *J. Org. Chem.* **1995**, *60*, 6229-6231. (c) Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 4-5. (d) Hays, D. S.; Scholl, M.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 6751-6752.
5. Other methods for reducing imines to amines: (a) Hutchins, R. O.; Hutchins, M. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 8, Chapter 1.2. (b) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989.
6. Earlier studies of imine reduction by silicon hydrides: (a) Frainnet, E.; Bazouin, A.; Calas, R. *Compt. Rend.* **1963**, *257*, 1304-1306. (b) Loim, N. M. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1968**, 1345. (c) Ojima, I.; Kogure, T.; Nagai, Y. *Tetrahedron Lett.* **1973**, 2475-2478. (d) Langlois, N.; Dang, T.-P.; Kagan, H. B. *Tetrahedron Lett.* **1973**, 4865-4868.
7. Early studies of tin-catalyzed, PMHS-mediated reduction of carbonyl groups: (a) Nitzsche, S.; Wick, M. *Angew. Chem.* **1957**, *69*, 96. (b) Lipowitz, J.; Bowman, S. A. *J. Org. Chem.* **1973**, *38*, 162-165.
8. Gelest, Inc. (Tullytown, PA).
9. Among organotin compounds, the highest toxicity is generally observed for triorganotin species (e.g., see: *Tributyltin: Case Study of an Environmental Contaminant*; de Mora, S. J., Ed.; Cambridge University Press: Cambridge, UK, 1996.); diorganotin and monoorganotin compounds display successively lower toxicity (Blunden, S. J.; Cusack, P. A.; Hill, R. *The Industrial Uses of Tin Chemicals*; Royal Society of Chemistry: London, 1985.). The U.S. Food and Drug Administration has approved the use of **1** as a catalyst for the preparation of polyester materials that come in indirect contact with food: *Federal Register*, **54**, 48857-48859 (November 28, 1989).
10. Aldrich Chemical Company (Milwaukee, WI).
11. *Vogel's Textbook of Practical Organic Chemistry*; Longman Scientific and Technical: London, 1991; pp 401-402.
12. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon Press: London, 1988; p 97.
13. Guthrie, R. D.; Burdon, L. G.; Lovell, F. L. *J. Org. Chem.* **1973**, *38*, 3114-3119.
14. Martin, G.; Guitian, E.; Castedo, L.; Saa, J. M. *J. Org. Chem.* **1992**, *57*, 5907-5911.
15. Kawakami, T.; Sugimoto, T.; Shibata, I.; Baba, A.; Matsuda, H.; Sonoda, N. *J. Org. Chem.* **1995**, *60*, 2677-2682.

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