Titanocene-Catalyzed Reduction of Esters Using Polymethylhydrosiloxane as the Stoichiometric Reductant

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Introduction

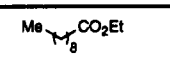
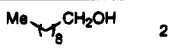
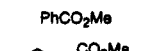
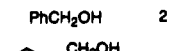
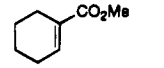
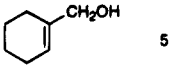
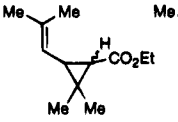
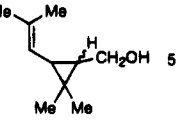
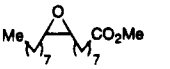
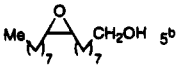
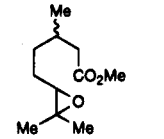
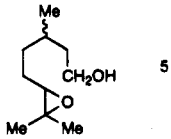
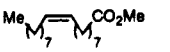
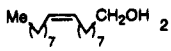
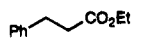
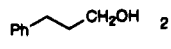
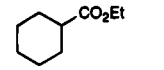
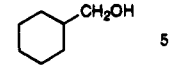
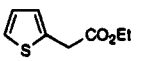
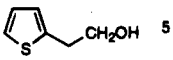
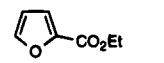
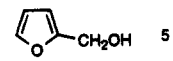
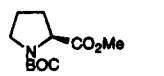
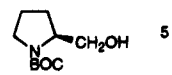
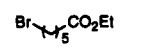
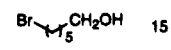
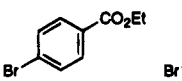
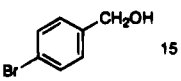
We have recently reported a titanocene-based catalytic system for the conversion of esters to primary alcohols[2] which employed $(EtO)_3SiH$ as the stoichiometric reductant (Scheme 1). Catalyst generation was effected by the addition of 2 equiv of *n*-BuLi to 5 mol % of Cp_2TiCl_2. Questions of cost and, more importantly, of safety[3] involved with the use of $(EtO)_3SiH$ and *n*-BuLi, especially on a large scale, prompted us to seek more synthetically useful reagents. To this end, we have directed our efforts toward the development of two modifications of our original experimental procedure: (a) the use of poly(methylhydrosiloxane) (PMHS),[4] an inexpensive siloxane polymer, as the stoichiometric reductant and (b) the use of EtMgBr in place of *n*-BuLi to generate an active catalyst system. We now detail our efforts to achieve these goals.

Results and Discussion

In our initial communication,[2a] we noted that use of Cp_2TiCl_2/2 *n*-BuLi with PMHS as the stoichiometric reductant allowed for the high-yield conversion of **1** to **2**. This combination was examined in greater detail and shown to be generally quite effective. As can be seen from Table 1, conversion of esters to the corresponding alcohols was accomplished in good to excellent yield. Most products were isolated in greater than 95% purity (by GC and ^1H NMR analysis) after simple extractive workup. In the case of the reduction of methyl cyclohexenecarboxylate (Table 1, entry 3), where chromatographic purification of the product was necessary, we believe that the lower yield observed is due in part to the volatility of the product alcohol. Less than 1% of competitive 1,4-reduction to cyclohexylmethanol was observed in this reaction.

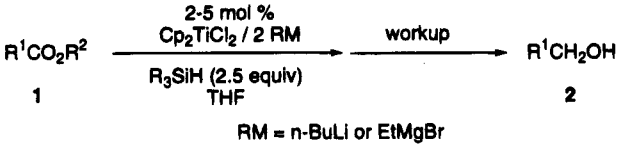
The secondary epoxide ester[5] (entry 5) was reduced in 64% yield when using the hindered titanocene precatalyst ethylene-1,2-bis(tetrahydroindenyl)titanium dichloride ((EBTHI)$TiCl_2$).[2a,6] Tertiary epoxide ester **3** (entry 6) was

Table 1. Results of the Application of Revised Reaction Conditions to the Reduction of Esters and Comparison with Results Obtained Previously[2a]

Entry	Ester	Product	% Cat	RM	Time (h)	Yield (%)[a]
1			2	EtMgBr	1.5	85
2			2	EtMgBr	1.5	94 (93)
3			5	*n*-BuLi	1	65 (71)
4			5	*n*-BuLi	1	91 (83)
5			5[b]	*n*-BuLi	1	64
6			5	*n*-BuLi	2	44[c]
7			2	EtMgBr	1.5	82 (90)
8			2	EtMgBr	1.5	94 (82)
9			5	EtMgBr	5	88
10			5	EtMgBr	17.5	92 (88)
11			5	EtMgBr	17.5	75 (75)
12			5	EtMgBr	23	70[d]
13			15	EtMgBr	3	53[e] (78)
14			15	EtMgBr	3	40[e]

[a] Numbers in parentheses refer to yields obtained using the original experimental conditions (see ref 2a). [b] (EBTHI)$TiCl_2$ was used in place of Cp_2TiCl_2. [c] A 28% yield of epoxide-reduction product **5** was also isolated. [d] The reaction was heated to 45 °C. [e] Crude ^1H NMR and GC analysis indicated a 9:1 ratio of product to debrominated material in the case of 6-bromohexanol and a 4.5:1 ratio in the case of 4-bromobenzyl alcohol.

Scheme 1



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(2) (a) Berk, S. C.; Kreutzer, K. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 5093. (b) Berk, S. C.; Buchwald, S. L. *J. Org. Chem.* **1992**, *57*, 3751 and *Ibid.* **1993**, *58*, 3221.

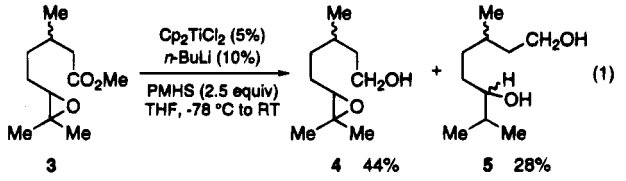
(3) Alkoxysilanes are known to disproportionate to form the highly pyrophoric silane gas (SiH_4). Refer to caution statements which appear in previous reports from our research group[2] for more details concerning this and other hazards associated with the use of silanes. See also: Xin, S.; Aikten, C.; Harrod, J. F.; Mu, Y.; Samuel, E. *Can. J. Chem.* **1990**, *68*, 471.

(4) For general reviews of PMHS chemistry see (a) Ojima, I. In *The Chemistry of Organic Silicon Compounds*; Patai, S.; Rappoport, Z., Eds.; John Wiley and Sons: New York, 1989. (b) Larson, G. L. In *Silicon Compounds. Register and Review*, 5th ed.; Anderson, R.; Larson, G. L.; Smith, C., Eds.; Hüls America: Piscataway, 1991; pp 8–23, 258. For specific examples of the application of PMHS for the reduction of carbonyl functional groups see (c) Nitzsche, S.; Wick, M. *Angew. Chem.* **1957**, *69*, 96. (d) Nitzsche, S.; Wick, M. U.S. Patent *3,061,424*, 1962. (e) Grady, G. L.; Kuivila, H. G. *J. Org. Chem.* **1969**, *34*, 2014. (f) Lipowitz, J.; Bownan, S. A. *Aldrichim. Acta* **1973**, *6*, 1. (g) Corriu, R. J. P.; Perz, R.; Réyé, C. *Tetrahedron* **1983**, *39*, 999. (h) Coumbe, T.; Lawrence, N. J.; Muhammad, F. *Tetrahedron Lett.* **1994**, *35*, 625.

(5) Rigorous purification of the substrate was necessary to remove trace amounts of an impurity, derived from the *m*-chloroperoxybenzoic acid used in the epoxidation of the corresponding alkenes, which was responsible for loss of catalytic activity.

0022-3263/94/1959-4323$04.50/0

reduced by the simple Cp_2TiCl_2-derived catalyst, although epoxy alcohol **4** was obtained in only 44% yield (eq 1). In addition to **4**, diol **5**, derived from reduction of the epoxide moiety, was obtained in 28% yield. This result was not unprecedented, as titanocene hydride reagents have been reported to reduce epoxides.[7] The regiochemistry observed is in agreement with that found previously.[7a]



An additional modification which we sought to employ was the use of EtMgBr in place of *n*-BuLi. In initial experiments, reactions employing 2–5 mol % Cp_2TiCl_2 and 2 equiv of EtMgBr failed to go to completion. We hypothesized that the magnesium salts present in the reaction mixture might be exerting a deleterious effect on the reaction. In accord with this view, the reaction proceeded to completion when dioxane or N-methylmorpholine (1–2 equiv per equiv of EtMgBr) was included to complex the salts. Subsequently, it was found that simply using a slight excess of EtMgBr (2.5 equiv per equiv of Cp_2TiCl_2) allowed for complete conversion of the ester substrate. A reaction protocol employing this stoichiometry was therefore utilized. The most generally applicable set of reaction conditions involved dissolving 2–5 mol % Cp_2TiCl_2 in a minimal amount of THF. The resulting solution was then cooled to 0 °C and 2.5 equiv of EtMgBr in ether was added. After 5 min, PMHS (2.5 equiv per equiv of substrate) was added, followed by stirring for an additional 5 min. The substrate was then added, and the reaction mixture was warmed to room temperature. The progress of the reaction was monitored by GC analysis. Once the reduction was complete, the reaction mixture was diluted with a small quantity of THF and then treated with 1 M NaOH and allowed to stir for at least 2 h. Extractive workup provided the alcohol, which, unless otherwise indicated, was estimated to be ≥95% pure by GC and ^{1}H-NMR analysis.

For the simplest substrates (entries 1, 2, 7, and 8), GC analysis indicated that the reactions using 2 mol % catalyst were complete within 90 min. Each of the products was isolated by extraction with no further purification required. With most of the remaining substrates, complete conversion within a reasonable period of time was only possible when 5 mol % catalyst was used. It appears that the active catalyst may decompose over time and that substrates for which the reduction proceeds more slowly experience a decrease in reaction rate which eventually precludes complete conversion. Thus, using 5 mol % catalyst, the reduction of ethyl cyclohexanecarboxylate (entry 9) reached completion within 5 h, while the heteroaromatic substrates, ethyl thiophene-2-ylacetate (entry 10) and ethyl 2-furoate (entry 11) required nearly 18 h. The proline carbamate methyl ester (entry 12) did not appear (by GC analysis) to undergo reduction at room temperature. However, warming to 45 °C for 23 h provided the protected prolinol in 70% yield.[8] The product alcohol was isolated in >95% ee as determined by analysis of the corresponding Mosher's esters.[9]

Attempts to reduce ester substrates containing a bromide substituent proved to be difficult. This was not unexpected, as many hydride transfer reagents reduce alkyl bromides[10] and PMHS has been shown to reduce halocarbons.[4f] In addition, titanocene hydrides have been shown to reduce alkyl and aryl bromides.[11] These dehalogenation reactions require stoichiometric amounts of the titanium reagent and thus would result in competitive catalyst deactivation. Initial attempts to reduce the ester moieties of ethyl 6-bromohexanoate (entry 13) and ethyl 4-bromobenzoate (entry 14) resulted in incomplete reactions. However, nearly complete (>98%) consumption of the starting esters was realized when 15 mol % catalyst and 5 equiv of PMHS are used. Also, evidence of hexanol and benzyl alcohol, the products resulting from debromination of the starting esters, can be found by ^{1}H NMR and GC analysis of the crude reaction mixtures (see Table 1, footnote d).

In conclusion, we have demonstrated that poly(methylhydrosiloxane) is an effective substitute for $(EtO)_3SiH$ as the stoichiometric reductant in our titanocene-catalyzed ester reduction reaction. We have also shown that an active catalyst system, similar in scope and reactivity to the original,[2a] can be generated by replacing *n*-BuLi with EtMgBr. Aside from cost considerations, these modifications are particularly important when safety concerns preclude the use of the more hazardous $(EtO)_3SiH$ and *n*-BuLi reagents, especially for large-scale preparations.

Experimental Section

All reactions were conducted under an argon or nitrogen atmosphere. Cp_2TiCl_2 was purchased from Boulder Scientific Inc., Mead, CO. Ethyl 6-bromohexanoate and ethyl 4-bromobenzoate were available from commercial sources and were purified just prior to use by passage through a short column of neutral alumina. Ethyl cyclohexanecarboxylate was available from commercial sources and was purified prior to use by distillation. Poly(methylhydrosiloxane) (mol weight 2270 g/mol) was available from Aldrich Chemical Co., Milwaukee, WI. Ethylene-1,2-bis(tetrahydroindenyl)titanocene dichloride ((EBTHI)$TiCl_2$)[6] was provided by Chris Willoughby, MIT, Cambridge, MA. Tetrahydrofuran was dried and deoxygenated by continuous refluxing over sodium/benzophenone ketyl followed by distillation. Dichloromethane was dried by continuous reflux over CaH_2 followed by distillation. Unless otherwise noted, all other reagents were prepared according to published procedures or were available from commercial sources and used without further purification. Preparative flash chromatography was performed on E. M. Science Kieselgel 60 (230–400 mesh). Yields, unless otherwise stated, refer to isolated yields of compounds of ≥95% purity as estimated by capillary GC and/or ^{1}H NMR analysis. The major impurities in these cases are small amounts of methylsiloxanes. Spectral data for commercially available compounds are not reported.[15]

Nuclear magnetic resonance (NMR) spectra were recorded on a Varian XL-300, Varian Unity 300, Varian VXR 500, or Bruker-250 Fourier transform spectrometer. All ^{19}F NMR spectra are

(6) (a) Wild, F. W. R. P.; Zsolnai, L.; Huttner, G.; Brintzinger, H. H. *J. Organomet. Chem.* **1982**, *232*, 233. (b) Collins, S.; Kuntz, B. A.; Taylor, N. J.; Wand, D. G. *J. Organomet. Chem.* **1988**, *342*, 21.

(7) (a) RajanBabu, T. V.; Nugent, W. A.; Beattie, M. S. *J. Am. Chem. Soc.* **1990**, *113*, 6408. (b) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1988**, *110*, 8561.

(8) Use of material which had been carefully purified by distillation was necessary to avoid incomplete conversion due to catalyst deactivation by trace impurities.

(9) Dale, J. A.; Dull. D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(10) Carruthers, W. *Some Modern Methods of Organic Synthesis*, 3rd ed.; Cambridge University: Cambridge, 1986; pp 457–491.

(11) Colomer, E.; Corriu, R. *J. Organomet. Chem.* **1974**, *82*, 367.

reported in ppm relative to the 0 ppm signal for fluorotrichloromethane. Infrared (IR) spectra were recorded on a Mattson Cygnus Starlab 100 or Perkin-Elmer 1600 Series Fourier transform spectrometer. Gas chromatography analyses were performed on Hewlett-Packard Model 5890 GC with a 3392A integrator and FID detector using a 25 m capillary column with cross-linked SE-30 as a stationary phase. Electron impact mass spectra and high resolution mass determinations (HRMS) were recorded on a Finnegan MAT System 8200. Melting points were measured on a Haake Buchler Melting Point Apparatus and are uncorrected. Optical rotations were recorded at an ambient temperature of 23 °C on a Perkin-Elmer 421 Polarimeter as the average of ten consecutive readings.

General Procedures for the Reduction of Esters. Procedure A. To a solution of Cp_2TiCl_2 (0.0149 g, 0.0600 mmol) in THF (2 mL) at 0 °C was added ethylmagnesium bromide (0.13 mL of a 1.14 M solution in ether, 0.15 mmol). After 5 min, the reaction mixture was treated with PMHS (0.43 mL, 0.45 g, 7.5 mmol hydride equiv), allowed to stir for 3 min, and treated with the ester to be reduced (3.0 mmol). The reaction flask was removed from the cooling bath and allowed to warm to room temperature. After GC analysis[16] indicated the absence of starting ester, the reaction mixture was diluted with THF (5 mL) and treated with 1 M aqueous NaOH (15 mL). After 10–20 h, the reaction mixture was diluted with ether (50 mL). The organic phase was washed with 1 M aqueous NaOH (2 × 30 mL) and then washed with saturated aqueous sodium chloride (30 mL). The aqueous extracts were back-extracted with ether (6 × 20 mL), and the combined organic portions were dried ($MgSO_4$) and concentrated *in vacuo* to provide the product.

Procedure B. To a slurry of Cp_2TiCl_2 (74 mg, 0.3 mmol) in THF (4 mL) at −78 °C (dry ice/acetone) was added *n*-butyllithium (564 μL of a 1.65 M hexane solution, 0.6 mmol). After stirring for 15 min, PMHS (930 μL, 15 mmol hydride equiv) was added, and the reaction mixture was allowed to warm to room temperature. The solution was then recooled to −78 °C, the ester to be reduced (6 mmol) was added slowly, and the reaction mixture was allowed to warm to room temperature. After 1–2 h, GC analysis of an aliquot taken from the reaction mixture showed complete disappearance of the starting material. The catalyst was deactivated by exposure to air until the color of the reaction mixture changed from dark brown to orange. The solution was transferred to a 100 mL round-bottom flask with THF (10 mL). Then, 1 M NaOH (30 mL) was added SLOWLY (to avoid bubbling over). The mixture bubbled vigorously and was stirred for 1.5 h. The reaction mixture was then added to a water/ether mixture (~50 mL each). The aqueous layer was extracted with ether (2 × 40 mL), and the combined organic extracts were washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$, and brine (40 mL each). The organic layer was then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the crude product.

Decanol (Table 1, entry 1). Procedure A was used to reduce ethyl decanoate (0.70 mL, 3.0 mmol). The reaction was complete after 90 min, and standard workup provided the product as a pale yellow oil (0.409 g, 84% yield).

Benzyl Alcohol (Table 1, entry 2). Procedure A was used to reduce methyl benzoate (0.38 mL, 3.0 mmol). The reaction was complete after 90 min, and standard work-up provided the product as a pale yellow oil (0.276 g, 92% yield).

Cyclohex-1-ene-1-methanol (Table 1, entry 3). Procedure B was used to reduce methyl cyclohex-1-ene-1-carboxylate (0.82 mL, 6 mmol). The reaction was complete after 1 h. Standard workup provided the crude product, which was purified by flash chromatography (ether:hexane = 1:3) to afford a pale yellow oil (446 mg, 66% yield).

Chrysanthemumyl Alcohol (Table 1, entry 4). Procedure B was used to reduce ethyl chrysanthemumate (0.65 mL, 3.0 mmol). The reaction was complete after 1 h, and standard workup provided a pale yellow oil (413 mg, 90% yield) which was a mixture of *cis* and *trans* isomers in a ratio identical to that of the starting material.

Oleyl Alcohol Oxide (Table 1, entry 5).[2b] Procedure B was folowed using ethylene-1,2-bis(tetrahydroindenyl)titanium dichloride ((EBTHI)$TiCl_2$) (0.0383 g, 0.100 mmol) in place of Cp_2TiCl_2 to reduce methyl oleate oxide[12] (0.63 mL, 2.0 mmol). After 1 h, GC analysis indicated that the reaction had ceased with >87% conversion, based on comparison to an internal standard (mesitylene, 2%). Standard workup provided a colorless solid (0.528 g, 65% product and 29% starting ester by GC analysis). Flash chromatography (hexane:ether:triethylamine = 55:40:5) afforded an orange oil shown to be starting ester (0.021 g, 2.3% yield) in addition to the desired product as a white solid (0.368 g, 65% yield, 66% yield based on recovered starting ester): mp 53 °C [lit.[2b] 52–53 °C]; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 6.7 Hz, 3 H), 1.22–1.63 (m, 29 H), 2.91 (m, 2 H), 3.63 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.6, 25.7, 26.6, 27.8, 29.2, 29.3, 29.5, 31.8, 32.8, 54.9, 57.2, 63.0, five peaks obscured by others; IR (KBr) 486, 638, 719, 846, 908, 938, 996, 1075, 1120, 1406, 1462, 2851, 2918, 3277 cm^{-1}; HRMS exact mass calcd for $C_{18}H_{36}O_2$ (M^+) 284.2715 amu, found 284.2733 amu.

(±)-Citronellol Oxide (Table 1, entry 6) and (±)-Diol Derivative. Procedure B was used to reduce (±)-methyl citronellate oxide[13] (0.40 mL, 2.0 mmol). After 2 h, GC analysis indicated that the reaction had ceased with >95% conversion, based on comparison to an internal standard (mesitylene, 2%). Standard workup afforded an amber oil (0.299 g, 44% epoxy alcohol and 19% diol by GC analysis). Flash chromatography (hexane:ether = 15:85 to 5:95) provided the desired product as a colorless oil shown to be a mixture of diastereomers (0.154 g, 45% yield) and a colorless oil, believed to be the diol, as a mixture of diastereomers (0.096 g, 99% pure by GC analysis). **Epoxy alcohol:** ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, J = 6.3 Hz, 3 H), 1.1–1.8 (m, 13 H), 2.10 (s, 1 H), 2.71 (t, J = 5.9 Hz, 1 H), 3.70 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.5, 18.6, 19.4, 19.3, 24.8 (two overlapping peaks), 26.1, 26.3, 29.1, 29.3, 33.6 (two overlapping peaks), 39.4, 39.6, 58.3, 58.4, 60.4 (two overlapping peaks), 64.5, 64.6; IR (neat) 678, 794, 870, 891, 962, 1059, 1120, 1250, 1326, 1379, 1461, 1649, 2872, 2926, 3422 cm^{-1}; HRMS exact mass calcd for $C_{10}H_{20}O_2$ (M^+) 172.1463 amu, found 172.1464 amu. **Diol:** ^1H NMR (300 MHz, $CDCl_3$) δ 0.75–1.05 (m, 9 H), 1.05–1.75 (m, 8 H), 2.40 (s, 1 H), 2.8 (s, 1 H), 3.30 (m, 1 H), 3.6–3.75 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.0, 17.3, 18.8 (two overlapping peaks), 19.6, 19.8, 29.1, 29.8, 31.0, 31.4, 32.8, 33.2, 33.4, 33.5, 39.6, 39.8, 60.64 (two overlapping peaks), 76.48 (two overlapping pekas); IR (neat) 734, 845, 907, 1008, 1206, 1106, 1180, 1380, 1463, 2954, 3100–3600 cm^{-1}; HRMS exact mass calcd for $C_{10}H_{22}O_2$ ($M - OH^+$) 157.1592 amu, found 157.1593 amu.

Oleyl Alcohol (Table 1, entry 7). Procedure A was used to reduce methyl oleate (1.02 mL, 3.0 mmol). The reaction was complete after 90 min, and standard workup provided the product as a pale yellow oil (0.701 g, 85% yield).

3-Phenylpropanol (Table 1, entry 8). Procedure A was used to reduce ethyl hydrocinnamate (0.53 mL, 3.0 mmol). The reaction was complete after 90 min, and standard workup provided the product as a pale yellow oil (0.397 g, 96% yield).

Cyclohexylmethyl Alcohol (Table 1, entry 9). Procedure A was used to reduce ethyl cyclohexanecarboxylate (0.51 mL, 3.0 mmol). The reaction was complete after 5 h, and standard workup provided the product as a pale amber oil (0.312 g, 93% yield).

2-(2-Thienyl)ethanol (Table 1, entry 10). Procedure A was used to reduce ethyl thiophene-2-ylacetate (0.46 mL, 3.0 mmol). The reaction was complete after 17.5 h, and standard workup provided the product as a pale amber oil (0.345 g, 89% yield).

Furfuryl Alcohol (Table 1, entry 11). Procedure A was used to reduce ethyl 2-furoate (0.42 g, 3.0 mmol). The reaction was complete after 17.5 h, and standard workup provided the product as a pale amber oil (0.345 g, 89% yield).

(2*S*)-*N*-(*tert*-Butoxycarbonyl)prolinol (Table 1, entry 12).[14] Procedure A was used to reduce (2*S*)-*N*-(*tert*-butoxycar-

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(14) (a) Jones, K.; Woo, K.-C. *Tetrahedron* **1991**, *47*, 7179. (b) Harris, B. D.; Bhat, K. L.; Joullié, M. M. *Heterocycles* **1986**, *24*, 1045.

(15) (a) For ^1H NMR data see: *The Aldrich Library of NMR Spectra*, 2nd ed.; Pouchert, C. J., Ed.; Aldrich Chemical: Milwaukee, 1983; Vol. 1. (b) For IR spectral data see: *The Aldrich Library of IR Spectra*, 1st ed.; Pouchert, C. J., Ed.; Aldrich Chemical: Milwaukee, 1985; Vol. 3.

(16) An aliquot was removed and partitioned between ether and water. The ether phase was dried ($MgSO_4$) and was then used directly for GC analysis.

bonyl)proline methyl ester[14] (0.61 mL, 3.0 mmol), except that the reaction mixture was heated to 45 °C. The reaction was complete after 23 h, and standard workup provided the product as a colorless solid (0.460 g, 75% yield): mp 57–58 °C [lit.[14] 57–58 °C]; $[\alpha]^{23}_D = -44.0°$ (*c* 0.91, CH_2Cl_2) [lit.[14] $[\alpha]^{25}_D = -47.2°$ (*c* 0.91, CH_2Cl_2) reported as >97% ee]; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 9 H), 1.60 (m, 1 H), 1.70–2.08 (m, 3 H), 3.32 (m, 1 H), 3.42 (m, 1 H), 3.61 (m, 2 H), 3.92 (m, 1 H), 4.87 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) (signals listed in parentheses indicates low intensity peak attributed to minor conformer) δ 23.9, (23.0), 28.4, (28.5), 47.4, (46.5), 59.9, (58.5) 67.0, (64.3), 79.9, (79.7), 156.6, (154.5); IR (neat) 773, 864, 908, 1053, 1107, 1169, 1254, 1403, 1668, 1694, 2878, 2974, 3426 cm^{-1}. Synthesis of the corresponding Mosher's ester[9] from the product alcohol and (*S*)-(+) MTPA, followed by analysis by ^{19}F NMR, indicated >95%[17] de of the ester and therefore >95% ee of the product alcohol. ^{19}F NMR (300 MHz, $CDCl_3$) δ −71.94, −72.18 (conformers). Independent synthesis of the diastereomeric Mosher's ester[9] from the product alcohol and (R)(−) MTPA, followed by analysis by ^{19}F NMR, indicated >95%[17] de of the ester and therefore >95% ee of the product alcohol. ^{19}F NMR (300 MHz, $CDCl_3$) δ −72.06, −72.12 (conformers).

6-Bromohexanol (Table 1, entry 13). Procedure A was used to reduce ethyl 6-bromohexanoate (0.54 mL, 3.0 mmol). The reaction was complete after 3 h, and standard workup provided a cloudy oil (0.694 g, ^1H NMR analysis indicates an 8:1 mixture of product:hexanol). Flash chromatography (hexane:ethyl acetate = 75:25) provided the desired product as a clear oil (0.298 g, 53% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 1.22–1.52 (m, 6 H), 1.75 (m, 2 H), 2.67 (s, 1 H), 3.31 (t, *J* = 6.8 Hz, 2 H), 3.49 (t, *J* = 6.6 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 27.9, 32.3, 32.6, 33.8, 62.3; IR (neat) 644, 728, 769, 894, 952, 1053, 1132, 1238, 1260, 1437, 1460, 2859, 2043, 3331 cm^{-1}.

(17) In the case where (*R*)(−) MTPA was used for ester formation, none of the minor diastereomer was observed by 282-MHz or 470-MHz ^{19}F NMR. When the (*S*)(+) isomer of MTPA was used, a baseline impurity which might be attributed to one conformer of the minor diastereomer was detected at δ −72.21 ppm. As such, integration of the signals indicated that the ester was >97% one diastereomer. However, since no corresponding peak was seen for the other conformer, it is unlikely that the observed conformer is due to the minor diastereomer.

4-Bromobenzyl Alcohol (Table 1, entry 14). Procedure A was used to reduce ethyl 4-bromobenzoate (0.54 mL, 3.0 mmol). The reaction was complete after 3 h, and standard workup provided a solid (0.629 g, ^1H NMR analysis indicated a 4:1 mixture of product:benzyl alcohol). Flash chromatography (hexane:ethyl acetate = 60:40) followed by concentration *in vacuo* of the appropriate fractions provided a clear oil (0.329 g, shown by ^1H NMR analysis to be 75% desired product, 15% benzyl alcohol, and 10% silyl derivatives, estimated yield: 44%). Subsequent recrystallization from ether/pentane provided the desired product as a white powder (0.218 g, 37% yield): mp 76 °C [lit.[15] 75–77 °C].

NOTE: For the each of the substrates in Table 1, a general protocol which included the use of mesitylene as an internal standard (1–3 mol % relative to the amount of substrate) was employed in order to ascertain, by GC analysis, the degree to which the reaction had proceeded. In cases where the reduction product was isolated without further purification, a trace (<3%) of residual mesitylene (δ 2.27 (s), 6.79 (s)) was often observed by ^1H NMR analysis. Yields of products isolated from these experiments were comparable to yields found in experiments where an internal standard was not used, except for entries 9–12, where an internal standard was used in all trials.

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Supplementary Material Available: ^1H and ^{13}C spectra for compounds **4** and **5** (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.