Experimental Section

3az: All experiments including chromatography were performed at 0 °C under nitrogen. A stirred 15 mM solution of **2az** in wet ether was treated with 1.8 equiv of $NaBH_4$. After 1 min, the reaction mixture was filtered through a short pad of silica gel (diethyl ether), and the solvent removed in vacuo. Chromatographic purification (silica gel, Et_2O/pentane, 1/9) afforded **3az** ($R_f = 0.61$, EtOAc/hexane, 1/2) in 81 % yield as a white solid. ^1H NMR (400 MHz, $CDCl_3$, 20 °C): $\delta = 1.19$ (t, $J = 6.85$ Hz, 3 H, CH_2CH_3), 2.62 (q, $J = 6.85$ Hz, 2 H, CH_2CH_3), 7.25 (s, ^2J(Hg,H) = 120.3 Hz, 1 H, C=CH Hg), 7.34, 8.30 (d, $J = 8.80$ Hz, Ph), 13.14 (s, ^1J(Hg,H) = 3218.0 Hz, 1 H, HgH); ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): $\delta = 13.7$ (CH_2CH_3), 28.9 (CH_2CH_3), 122.6, 125.2, 145.4, 149.2 (Ph), 155.7 (C=CHg), 172.9 (C=O), 181.8 (C=CHg); IR (KBr): $\tilde{\nu} = 1983\ cm^{-1}$(Hg–H).

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[6] Thermolysis reactions were carried out in a vacuum-sealed Pyrex NMR tube previously washed with HNO_3, NH_4OH, and bis(trimethylsilyl)acetamide (14 h). The reaction mixture was thoroughly degassed by several freeze/thaw cycles. The hydrides are rather sensitive to acidic impurity, which generates 2-ethylacrylate by protonolysis of the Hg–H bonds (for example, the deuteride **3D-ay** reacts with CF_3COOH at 50 °C to quantitatively afford the protonolysis product **11** in 20 min). Thus, the rate measurements are always slightly dependent on reaction conditions. This is probably the reason why analytically pure samples have not yet been made.

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[15] A referee pointed out that the estimated activation energy of CH_3HgH decomposition (ca. 23 kcal mol^{-1}) is much lower than the calculated BDE (70–71 kcal mol^{-1}). We suggest that decomposition of CH_3HgH proceeds by a radical chain reaction involving bimolecular hydrogen abstraction (for instance, by $CH_3^{\bullet}$). Hence, the activation energy of CH_3HgH decomposition is related to but not the same as the BDE, which is a measure of the stability of a single isolated molecule.

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New Ligands for the Titanium(IV)-Induced Asymmetric Reduction of Ketones with Catecholborane[**]

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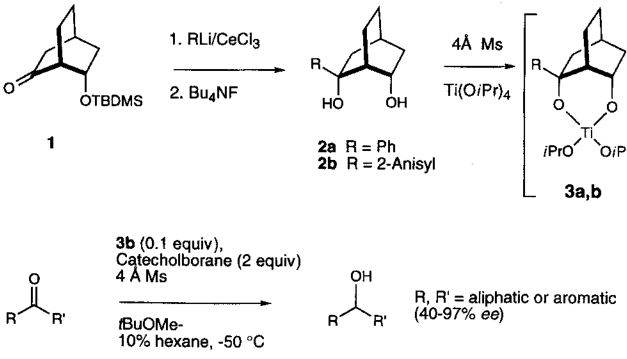
Enantioselective reduction of ketones[1] is an important reaction because the resulting optically active alcohols may be used in many syntheses of complex target molecules. Particularly attractive reduction methods are those that can be performed at ambient conditions and that require only catalytic amounts of the chiral inductor, such as borane reductions either in the presence of oxazaborolidines[2–9] or titanium TADDOLates.[10, 11] During work with optically active bicyclo[2.2.2]octane derivatives, we became interested in the development of these compounds into new, chiral bidentate ligands. Herein, we report on our results with (1*R*, 2*R*, 4*S*, 6*S*)-2-phenylbicyclo[2.2.2]octane-2,6-diol (**2a**) and (1*R*, 2*R*, 4*S*, 6*S*)-2-(2-anisyl)bicyclo[2.2.2]octane-2,5-diol (**2b**) in the Ti^{IV}-catalyzed reduction of ketones with catecholborane. We also suggest that diols based on the bicyclo[2.2.2]octane framework are named BODOLs (*b*icyclo[2.2.2]*o*ctane*diol*s).

BODOLs **2a** and **2b** (Scheme 1) of high enantiomeric purity (≥98%) were synthesized simply by addition of the corresponding $RLi/CeCl_3$ reagent[12, 13] to the O-TBDMS protected (TBDMS = *tert*-butyldimethylsilyl) optically active hydroxy ketone **1**,[14] followed by deprotection. The catalysts **3a** and **3b** were then prepared by mixing the BODOLs with $Ti(OiPr)_4$ in a 1.2:1 ratio in the presence of molecular sieves (Union Carbide Type A, 4 Å) at 0 °C, and then keeping the mixture at room temperature overnight. A small excess of the BODOLs was used to consume all $Ti(OiPr)_4$, thus avoiding reduction by complexation of the ketones with this achiral Lewis acid. In order to make this ligand exchange effective it was important to activate the powdered molecular sieves at 400 °C for 5–7 h. Very extended times at this temperature resulted in inactive molecular sieves, and heating at lower temperatures (100–300 °C) was not sufficient. We recommend that the amount of the molecular sieves be



Scheme 1. Synthesis of the Ti-BODOL complexes **3a** and **3b** and their application in the reduction of ketones with catecholborane. Ms = molecular sieves.

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maintained at a certain level (11 to 36 g per mmol of the BODOL).

Recently, Lindsley and DiMare demonstrated that a titanium TADDOLate based on tartrate was effective as a catalyst (0.05 equiv) in the asymmetric reduction of acetophenone with $BH_3 \cdot THF$ (24% *ee*).[10] Higher enantiomeric excesses (up to 84%) were later obtained by Giffels et al. by using catecholborane and a titanium TADDOLate based on a bicyclic framework.[11] Thus, it seemed appropriate to test our catalysts **3a** and **3b** in this type of reaction, as exemplified in Scheme 1. Our results are summarized in Table 1. The absolute configuration of the alcohols produced was checked in the reductions of acetophenone and hept-6-yn-2-one. Thus, the (+)-forms of the BODOLs both gave the corresponding alcohols with *R* configuration (entries 1, 2, 7, and 8). The highest enantiomeric excess (97%) was reached in the reduction of acetophenone in the presence of **3b** (entry 2), but perhaps more interesting are the fairly high enantiomeric excesses (75–83%) obtained with the linear methyl ketones with catalyst **3b** (entries 8, 10, 12). These values are among the highest hitherto recorded for this type of ketones. In comparison, the use of the titanium TADDOLates gave only 34% *ee* in the reduction of 2-octanone. [11] Propiophenone gave a low enantiomeric excess with catalyst **3a** but reached a much higher level with **3b**, although in both cases the chemical yields were only moderate (entries 3 and 4). Also the enantiomeric excesses in the reductions of octan-3-one (entries 5 and 6) are low, but the increase from 23 to 40% *ee* in going from **3a** to **3b** indicates that the ligand system may be adjusted to bring these values up to useful levels. It is encouraging that the chemical yield obtained in this case by using **3b** is 81%. Although the reduction of 2-methylcyclohexanone (entries 13 and 14) was not particularly diastereoselective, the excess of the *cis* isomer (the racemate was prepared according to ref. [15]) was fairly high (74%) when **3b** was used as the catalyst (entry 14). In all cases tested catalyst **3a** gave lower enantiomeric excesses than **3b**. In the absence of a Lewis acid the ketones were not reduced at the low temperatures applied.

Table 1. Asymmetric reduction of ketones with catecholborane in the presence of about 0.1 equiv of **3a** or **3b** [a].

Entry	Starting material	Catalyst	Yield of alcohol [%]	*ee* [%]	Reaction time [h]
1	acetophenone	**3a**	47	89 (*R*)	7.5
2		**3b**	>97	97 (*R*)	4.5
3	propiophenone	**3a**	<40	<15	5
4		**3b**	48	76	10
5	octan-3-one	**3a**	46	23	7.5
6		**3b**	81	40	5
7	hept-6-yn-2-one	**3a**	97	60 (*R*)	7.5
8		**3b**	>98	83 (*R*)	5
9	octan-2-one	**3a**	>97	62–75	2.5–5
10		**3b**	>98	79	5
11	hexan-2-one	**3a**	>98	66	4
12		**3b**	>98	75	4.5
13	2-methylcyclohexanone	**3a**	67/28 [b]	25; 35 [c]	3
14		**3b**	63/37 [b]	45; 74 [c]	9.5

[a] Yields and enantiomeric excesses (*ee*) were determined by chiral phase GC analysis. [b] *trans*/*cis* ratio. [c] *ee* of the *trans* or *cis* isomer.

The structures of **3a** and **3b** have not yet been determined, and the formula shown in Scheme 1 only indicates the approximate stoichiometry. The exact nature of the active catalyst is difficult to assess with certainty, as has been experienced for other similar systems. [10, 16–18] However, **2a** and **2b**, as bidentate ligands, must form six-membered rings with titanium, in contrast to the seven-membered titanium TADDOLates, and also **3a** and **3b** are C_1 symmetric, while the TADDOLates used by Lindsley and DiMare[10] as well as by Giffels et al.[11] are C_2 symmetric.

Experimental Section

2a: A solution of ketone **1** [14] (1.00 g, 3.94 mmol) in THF (2.5 mL) was added dropwise to a mixture of phenyllithium (10.1 mmol) and $CeCl_3$ (13.1 mmol) [13] in THF (30 mL) at −78 °C. The reaction mixture was allowed to warm to room temperature overnight and then quenched with saturated NH_4Cl solution at 0 °C. After standard workup, including filtration through a short pad of silica gel, the crude half-protected diol was deprotected at 0 °C by using tetrabutyl ammonium fluoride (1 M in THF, 6 mL, 6 mmol) in THF (65 mL). Crystalline **2a** (817 mg, 95%) was obtained after chromatography (SiO_2, heptane/ethyl acetate 2:1, $R_f = 0.19$); m.p. 84–87 °C; $[\alpha]_D^{22} = +71$ ($c = 2.2$ in $CHCl_3$); IR (KBr): $\tilde{\nu} = 3100-3500, 2940, 2860, 1490, 1450, 1060\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.55$ (m, 2H), 7.37 (m, 2H), 7.28 (m, 1H), 3.98 (m, 1H), 3.90 (d, $J = 8.7$ Hz, 1H), 3.32 (s, 1H), 2.45 (dm, $J = 14.3$ Hz, 1H), 2.22 (m, 1H), 2.06 (m, 1H), 2.00 (m, 1H), 1.95 (dm, $J = 14.3$ Hz, 1H), 1.68 (dm, $J = 13.6$ Hz, 1H), 1.23-1.38 (m, 4H); anal. calcd. for $C_{14}H_{18}O_2$: C 77.03; H 8.31, found: C 77.3; H 8.3.

2b: The preparation was analogous to that for **2a** but with 2-anisyllithium [19] instead of phenyllithium. Yield 90%; m.p. 74–78 °C; $[\alpha]_D^{22} = +46$ ($c = 0.68$ in $CHCl_3$); IR (KBr): $\tilde{\nu} = 3555, 3500, 3070, 2935, 1595, 1580, 760\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.27$ (m, 2H), 6.97 (m, 2H), 4.59 (s, 1H), 4.36 (d, $J = 9.8$ Hz, 1H), 3.92 (s, 3H), 3.92 (m, 1H), 2.45 (m, 1H), 2.17 2.26 (m, 3H), 1.93 (m, 1H), 1.72 (dm, $J = 13.5$ Hz, 1H), 1.28–1.49(m, 4H); HRMS: calcd. for $C_{15}H_{20}O_3$ 248.1412, found 248.1414.

General procedure for the reduction of the ketones:
$Ti(OiPr)_4$ (0.18 mL, 0.064 M in *t*BuOMe, 0.012 mmol) was added to a mixture of diol (0.014 mmol) and powdered molecular sieves (500 mg, 4 Å) in *t*BuOMe (2.6 mL) at 0 °C. The resultant slurry was kept at room temperature overnight, whereafter the ketone (0.115 mmol) and hexane (0.29 mL) were added. After 30 min at room temperature this mixture was cooled to −50 °C (−40 °C for propiophenone), followed by addition of catecholborane (0.23 mL, 1 M in THF, 0.23 mmol). The progress of the reaction was monitored by GC analysis (Supelco SPB-5), and after consumption of all of the starting material 1 M HCl (2 mL) was added. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were washed with 1 M NaOH and dried. Normal phase (Supelco SPB-5) and chiral phase (ALPHA-DEX 120) GC analyses were done on these extracts. The results are summarized in Table 1.

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