A Practical Process for the Preparation of Tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*]-[1,3,2]oxazaborole–Borane. A Highly Enantioselective Stoichiometric and Catalytic Reducing Agent

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A practical, large-scale process for the preparation of tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo-[1,2-*c*][1,3,2]oxazaborole–borane is reported. The title compound is a stable, free-flowing crystalline solid useful either stoichiometrically or catalytically for the enantioselective reduction of prochiral ketones. When used stoichiometrically to reduce acetophenone the enantioselectivity is ≥99.8% ee.

Introduction

We previously reported a practical enantioselective synthesis of α,α-diphenyl-2-pyrrolidinemethanol (diphenylprolinol, 1) and the corresponding *B*-methyloxazaborolidine 2 as a pure compound.[1] Chiral oxazaborolidines have been used as enantioselective catalysts for the reduction of prochiral ketones,[2–12]imines,[13] and oximes,[2c] the reduction of 2-pyranones to afford chiral biaryls,[14] the addition of diethylzinc to aldehydes,[15] asymmetric hydroboration,[16] the Diels–Alder reaction,[17–19] and the aldol reaction.[20,21] Corey proposed that the borane complex of the oxazaborolidine 3 is an important intermediate responsible for the enantioselectivity of ketone reductions and provided ^{11}B NMR evidence for its existence in solution.[4b] We subsequently discovered that borane complex 3 can be isolated as a stable, free-flowing crystalline solid[1b,g] and reported its single-crystal X-ray structure.[1c–e] After our disclosure, Corey also reported a preparation and single-crystal X-ray structure of borane complex 3.[22] We now report a practical, large-scale process for its preparation, information concerning its physiochemical properties, and our observations concerning the use of borane complex 3 as a reagent or catalyst for the enantioselective reduction of prochiral ketones.

Results and Discussion

Preparation of Oxazaborolidine–Borane Complex 3. We originally prepared borane complex 3[1b] by adding neat borane–dimethyl sulfide complex (BMS, 2–3 equiv)

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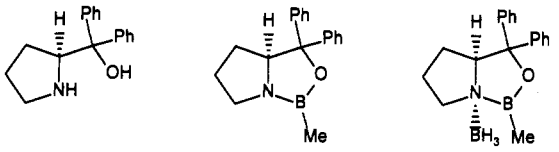

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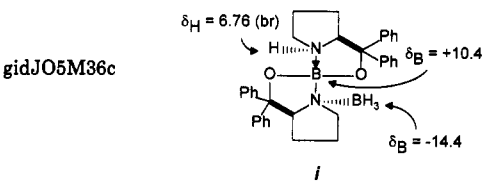
to a solution of oxazaborolidine 2[1a] in toluene (eq 1). The amount of borane complex 3 present in solution is a function of the relative amount of BMS (Figure 1). The reaction vessel was swept with nitrogen to remove dimethyl sulfide, driving the equilibrium to the right and eventually resulting in crystallization of the product. The mixture was filtered and the product dried in vacuo in an enclosed Schlenk filter. The isolated yield of crystalline 3 ranged from 80 to 90%. Although this procedure worked well on a small scale (1–50 g), the preparation of larger batches required more time to remove the malodorous dimethyl sulfide. An additional concern was the use of excess BMS, and the potential loss of free borane (as B_2H_6), making accurate charging of this reagent difficult.

$$2 + Me_2S\text{-}BH_3 \rightleftharpoons 3 + Me_2S \quad (1)$$

To avoid these problems we developed a modified procedure to prepare borane complex 3. In this case crystallization of the product rather than removal of dimethyl sulfide is used to drive the equilibrium. Thus, to a solution of oxazaborolidine 2 (2.0 M) in toluene (or xylene) is added BMS (1.2 equiv). The mixture is aged for 0.5–1.0 h at 20–25 °C and borane complex 3 then crystallized by the addition of dry hexane (4 vol). After the mixture is cooled to −10 °C, the product is isolated as above. The overall yield of crystalline borane complex 3 (from diphenylprolinol) for the revised procedure is 88–92%. The material remaining in the mother liquors is predominantly borane complex 3, which can be either isolated as a second crop or used "as is" as an effective source of the enantioselective catalyst. We have prepared several kilograms of borane complex 3 using this process. The procedure described in the Experimental Section will afford >250 g of the catalyst using equipment available in a typical synthetic organic laboratory. Using the same procedure we also prepared the enantiomeric (*R*)-borane complex 3 from (*R*)-diphenylprolinol (1) in 90% overall yield.[23]

Physiochemical Properties. Borane complex 3 is a colorless, free-flowing crystalline solid. Unlike oxazaborolidine 2,[1a] borane complex 3 is remarkably stable. We have stored samples of the material for over 3 years at room temperature under an atmosphere of nitrogen without noticeable degradation. The solid thermally decomposes with loss of gas (B_2H_6) at 124–126 °C. For comparison, free oxazaborolidine 2 melts at 79–81 °C.[1a]



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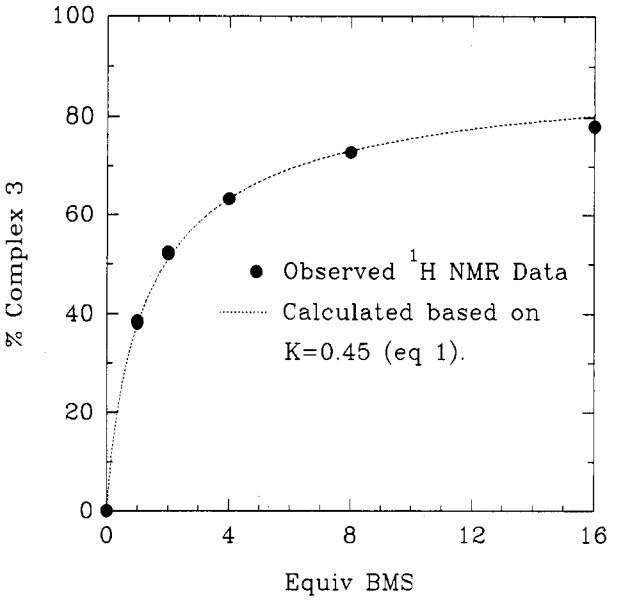

Figure 1. Plot of percent borane complex 3 versus equiv of BMS. Experimental data points based on integration of ^{1}H NMR spectra. Dashed line calculated using a fitted equilibrium constant (Mathcad and TableCurve) assuming that the BMS contained 5 mol % excess Me_2S.

The structure of borane complex 3 (at room temperature) was confirmed by single-crystal X-ray analysis on a crystal grown in benzene.[1c–e,24] The BH_3 is coordinated to the oxazaborolidine nitrogen. The length of the BH_3 B–N bond is 1.621 Å. Although shorter than the 1.718 Å calculated for borane complexed to a simple oxazaborolidine model,[25a] the data from the X-ray structure still indicate significant ionic character for this bond. For comparison the oxazaborolidine nucleus B–N and B–O bond lengths are 1.488 and 1.348 Å, respectively, vs calculated lengths of 1.485 and 1.336 Å. The structure is consistent with previous proposals by Corey.[4b,22]

Borane complex 3 is soluble in a variety of aprotic organic solvents such as benzene, dichloromethane, chloroform, or toluene. Although the solubility is lower in nonpolar solvents, as would be expected for a zwitterionic compound, the complex is quite soluble in dichloromethane (at least 0.8 M at −78 °C). When the complex is dissolved in noncoordinating solvents, an equilibrium exists between borane complex 3 and free oxazaborolidine 2 plus diborane (eq 2). As a result of this equilibrium, we always see a

$$3 \rightleftharpoons 2 + 0.5B_2H_6 \quad (2)$$

$$3 + THF \rightleftharpoons 2 + THF\text{-}BH_3 \quad (3)$$

small amount of free oxazaborolidine 2, which is not concentration dependent (but is temperature dependent), in the ^{1}H NMR spectrum of borane complex 3 dissolved in C_6D_6, CD_2Cl_2, $CDCl_3$, or C_7D_8 (Figure 2).[26] At room temperature approximately 10% of the material exists as free oxazaborolidine 2 and diborane. Indeed, bubbles of

(23) We have also prepared the borane complex from a variety of other oxazaborolidines. In many cases the products are also stable crystalline solids. Interestingly, we were not able to prepare the corresponding borane complex of the parent B–H oxazaborolidine, instead we obtained dimer i.

(24) (a) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. (b) A projection view of borane complex 3 is included in the supplementary material.

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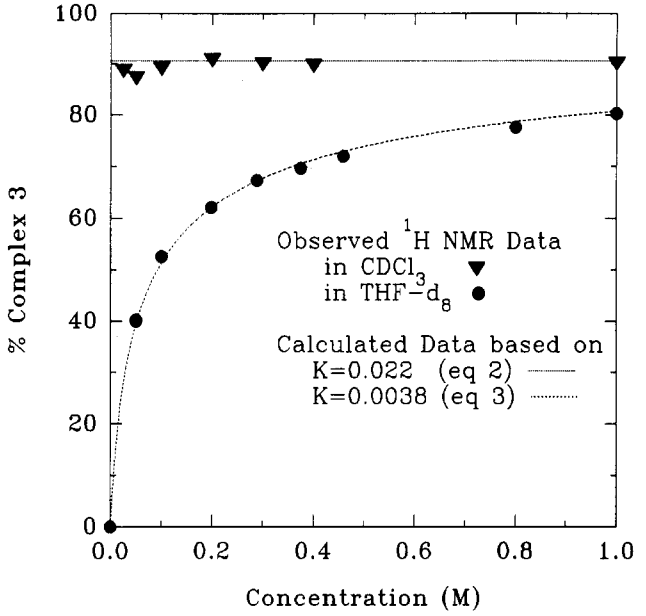


Figure 2. Plot of percent borane complex **3** at 25 °C versus concentration in $CDCl_3$ and THF-d_8. Experimental data points based on intergration of ^{1}H NMR spectra. Dashed lines calculated using a fitted equilibrium constant (Mathcad and TableCurve).

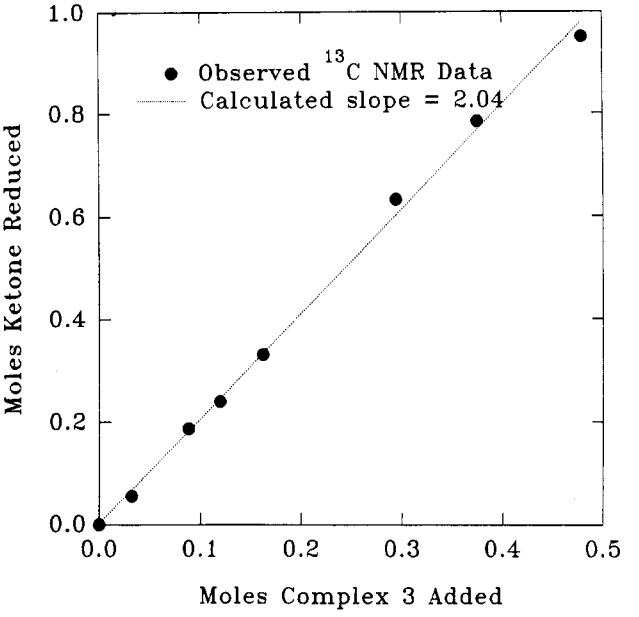
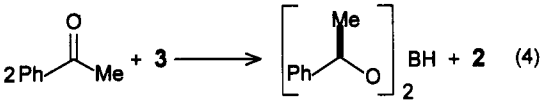


Figure 3. Plot of the amount of acetophenone reduced versus borane complex **3** added. Experimental data points based on integration of ^{13}C NMR spectra.

diborane are observed upon dissolution of the crystalline borane complex in noncoordinating solvents at room temperature. The situation is more complex with tetrahydrofuran (THF) and other aprotic, Lewis basic solvents. Herein, an additional equilibrium exists whereby the BH_3 forms a complex with the solvent (eq 3), and thus the percentage of borane complex **3** present in solution is concentration dependent (Figure 2). Since borane–THF will reduce prochiral ketones to racemic alcohol, this concentration dependent equilibrium is an important factor to consider during the optimization of oxazaborolidine catalyzed enantioselective ketone reductions performed in THF.

Use of Borane Complex 3 as an Enantioselective Reducing Agent. The stoichiometric reaction of prochiral ketones with borane complex **3** resulted in very high levels of enantioselection. We initially examined the stoichiometric reaction of acetophenone with borane complex **3** spectroscopically using ^{13}C and ^{11}B NMR (eq 4). Small



(4)

increments of **3** (weighed by difference) were added to a solution of acetophenone (0.60 mmol) in $CDCl_3$ (0.5 mL, previously treated with 4-Å molecular sieves and Na_2CO_3). ^{13}C NMR spectra were recorded after each addition. The intensities of methyl- and proton-bearing aromatic carbons were integrated for evaluation of the percentage conversion calculation. A total of about 0.35 mmol of borane complex **3** was added, and all additions were made using ice–methanol cooling of the NMR solution. For the ^{11}B NMR study, a separate preparation was made using 0.62 mmol of acetophenone to which four increments of 0.1 mmol of borane complex **3** was added. To obtain the sharpest possible ^{11}B NMR spectra, another model study used 0.68 mmol of acetone and 0.33 mmol of **3**.

Table I. ^{11}B NMR Properties of $(RO)_2BH$ Compounds[a]

R	*i*-Pr[b]	Me	Et	*n*-Pr	*n*-Bu	*i*-Bu	*s*-Bu	*t*-Bu
$\delta(^{11}B)$	27.3	26.1	26.1	27.5	27.2	27.0	26.8	25.8
J(BH)	157	141	141	165	160	168	168	166

[a] Reference 27. [b] This study.

A plot of acetophenone reduced vs the relative moles of borane complex **3** added is presented in Figure 3. The slope of almost exactly 2.0 implies a stoichiometry of 2 mol of ketone reduced per mol of **3**. ^{13}C intensities from the crowded aromatic region were used since the methyl groups hadmarked differences in relaxation rates. An acetophenone line at 128.4 ppm (C[*o*] or C[*m*]) and a product signal at 125.2 ppm (C[*o*]) were chosen. The latter had nearby features, some barely resolved, which could cause some inaccuracy. We have ascribed most of these weaker signals to disproportionation, indicated in aged solutions by both ^{13}C and ^{11}B NMR spectra, and included them in producing Figure 3. The enantioselection for this incremental addition experiment was high: >98% ee.

A crucial observation confirming the 2:1 stoichiometry of the borane complex is the ^{11}B NMR spectrum just at the point where 0.5 mol of the catalyst was added to a solution of acetone. A strong new signal at 27.3 ppm was split to a doublet of 157 Hz by a single directly attached hydrogen in a proton-coupled spectrum. Acetophenone produced a similar but broader line at 27.8 ppm; observation of proton splitting was not attempted there. Literature ^{11}B data for several $(RO)_2BH$ compounds span a narrow shift range of 26–28 ppm and spin couplings fall between 141 and 168 Hz (Table I).[27] A reported lack of ^{11}B spectral perturbation of trialkoxyboranes by a primary

(26) At first we were concerned that the crystalline material only contained ca. 90% of the borane complex based on the ^{1}H NMR spectra that were recorded at room temperature. Later, we found that by taking special precautions, i.e., dissolving the sample and recording the spectra at lower temperatures (−20 to −80 °C), we observe predominantly (>98%) a single compound by ^{1}H NMR. Also, microanalysis showed the crystalline product to be analytically pure.

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Table II. Enantioselectivity and Stoichiometry of Acetophenone Reductions

reactants		solvent					
		dichloromethane		THF		toluene	
3 (mmol)	ketone (mmol)	reaction[a] %	ee[a] %	reaction[a] %	ee[a] %	reaction[a] %	ee[a] %
10	5	100	99.0	100	99.0	100	98.6
10	10	100	98.8	100	98.4	100	98.6
10	15	100	98.6	100	96.2	100	95.2
10	20	100	98.0	98	96.0	95	94.2
10	25	86	96.8	84	95.6	78	94.0
10	30	72	95.6	70	94.6	65	93.8

[a] Percent reaction and enantiomeric purity determined by capillary GC (see Experimental Section for details).

amine[28] suggests that we may ignore potential effects of free oxazaborolidine here and compare shifts directly.

Aging of reaction solutions produced slow changes we ascribe to disproportionation of the initially formed dialkoxyborane. The acetone reaction gave a clear picture, where perceptible growth of ^{11}B signals at 30.7, 17.5, and −14.5 ppm occurred in just 0.5 h at 20 °C. After 2 days at room temperature the 17.5 ppm peak dominated with considerable decrease at 27.3 ppm. The borane complex accounts for the −14.5 ppm line; a broad peak at 34.5 ppm is due to overlap of the oxazaborolidine ^{11}B nucleus from both the free and borane-complexed species. On the basis of literature comparisons,[27] the 17.5 ppm signal is readily assigned to tris(isopropyloxy)borane. The nature of the species responsible for the 30.7 ppm signal (unsplit by H) is unknown. We note, however, the almost identical ^{11}B chemical shifts of several $(RO)_2B–B(OR)_2$ compounds[29] and wonder if oxidation to such occurs here.

We then examined the effect of stoichiometry and solvent on the reaction of borane complex **3** with acetophenone (eq 4). The reactions were performed by adding a solution of the ketone (1.0 M) to a solution (or a suspension in the case of toluene) of the catalyst (0.4–0.8 M) at −20 °C over a 10–60-min period. The solvent and ketone were dried over molecular sieves (water content ≤20 μg/mL by Karl Fischer titration) to ensure maximum enantioselectivity.[8a] To minimize the loss of borane from the reaction mixture, the solution of catalyst was quickly cooled to −20 °C upon dissolution and the reactions run in a minimum volume vessel under a static atmosphere of nitrogen. Reactions run in toluene became homogenous during the addition. The reactions were aged an additional 0.5 h at −20 °C and then quenched by the rapid addition to excess precooled (−20 °C) methanol. The extent of reaction and enantiomeric excess was determined directly by capillary GC. The minimum amount of the minor enantiomer detectable is ≤0.1%. The results are summarized in Table II. In all three solvents, the reaction goes to completion for a catalyst to ketone ratio up to 1:2.[30] Beyond this point, there is only partial reaction. This also indicates that two of the three hydrides are readily available for reaction. The enantioselection decreases slightly as the ratio of ketone to catalyst increases.[31] The highest level of enantioselection is observed in dichloromethane. At 20 °C and a concentration of 0.2 M the amount of borane complexed to the oxazaborolidine is ca. 90% in toluene or dichloromethane and 60% in THF (Figure 2).

As expected, the level of enantioselection increases by decreasing the reaction temperature (Table III, entries 1–4).[32] For the reduction of acetophenone with borane complex **3** this corresponds to a $\Delta\Delta G^{\ddagger}$ of ca. 2.7 kcal/mol. The rate of reduction decreases as the reaction temperature is reduced. Reactions at 25 and 0 °C were complete almost instantaneously, limited only by the rate of addition and external cooling required to maintain the reaction temperature (±5 °C). At −20 °C the ketone was added over a 0.5–1.0-h period and then aged an additional 0.5 h, whereas at −78 °C the ketone was added over 1–6 h and then aged an additional 2–6 h to ensure complete reaction. The ≥99.8% enantioselectivity obtained at −78 °C is the highest reported for an oxazaborolidine catalyzed reduction of acetophenone.[2,4–6,8a,11d]

We then investigated the reduction of other prochiral ketones, containing a variety of functional groups, with borane complex **3**. The reactions were run both stoichiometrically (1:1 or 2:1.1 ketone/borane complex) to determine the maximum enantioselectivity and catalytically using 5 mol % of borane complex **3**. The results are summarized in Table III. Unless otherwise noted, the reactions were performed in dichloromethane at −20 °C. Stoichiometric reactions were run using the procedure previously described for acetophenone—adding a solution of the ketone (1.0 M) to borane complex **3** over a 0.5–1.0-h period followed by an additional 1.0–3.0-h age. Catalytic reactions used BMS (0.5–1.0 mol equiv) as the borane source. The enantioselectivity was slightly higher when using 1.0 equiv of BMS. For these reactions, the ketone was added neat (or for solid ketones as a concentrated solution in dichloromethane) to a solution of BMS and borane complex **3** in dichloromethane over a 4–6-h period followed by an additional 2–4-h age. As noted before, the ketones and solvents for all of the reactions were dried over molecular sieves (water content <20 μg/mL by Karl Fisher titration) prior to use to ensure maximum enantioselectivity.[8a] By running the ketone reductions at −20 °C competing side reactions (i.e., nitrile reduction, hydroboration) were minimized.

The reactions were quenched by rapid addition to excess precooled (−20 °C) methanol (Caution: hydrogen evolution). The mixture was warmed to room temperature,

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(29) Wrackmeyer, B. *Ann. Rep. NMR Spectrosc.* **1988**, *20*, 61–203; see p 115.

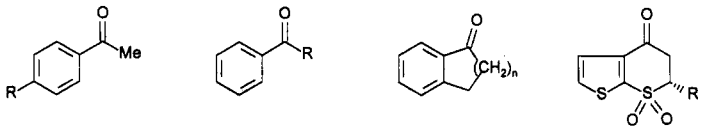
(30) If the vessel is swept with N_2, the reaction only goes to 85–90% completion for a catalyst to ketone ratio of 1:2 due to loss of borane.

(31) The lower apparent enantioselectivity observed for the second hydride transfer may be the result of competitive nonoxazaborolidine-catalyzed reduction (free diborane or borane–THF) or an alternate catalytic cycle whereby the alkoxy-BH_2 generated during the first hydride transfer remains coordinated to the oxazaborolidine, which then transfers the second hydride (with a different degree of enantioselectivity). We are currently investigating this question.

(32) This is in contrast to a previous report that indicated that oxazaborolidine-catalyzed reduction "loses stereoselectivity at lower temperatures"; see ref 4d.

(33) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549. The enantiomeric purity of the (*R*)-MTPA used to prepare the acid chloride was determined to be 99.4%; see ref 1a.

Table III. Enantioselection of Borane Complex 3 Catalyzed Reduction of Prochiral Ketones[a]



4 5 6 7

			stoichiometric[b]		stoichiometric[c]		catalytic[d]	
entry	ketone	temp (°C)	ee[e] %	yield[f] %	ee[e] %	yield[f] %	ee[e] %	yield[f] %
1	**4a** (R = H)	25	97.0	94				
2	**4a** (R = H)	0	98.2	95				
3	**4a** (R = H)	−20	98.8	95	98.0	95	97.6	95
4	**4a** (R = H)	−78	>99.8	95				
5	**4b** (R = F)	−20	98.8	95	98.0	95	97.0	94
6	**4c** (R = Cl)	−20	99.4	94	97.8	98		
7	**4d** (R = Br)	−20	99.3	96	95.3	98		
8	**4e** (R = Me)	−20	99.8	95				
9	**4f** (R = CF_3)	−20	98.7	92	95.0	98		
10	**4g** (R = CN)	−20	98.2	83	93.1	96		
11	**4h** (R = CO_2Et)	−20	99.3	94	96.6	96		
12	**4i** (R = OMe)	−20	99.6	90	97.2	92	99.2	96
13	**4j** (R = NO_2)	−20	98.7	92	94.4	97		
14	**4k** (R = $N(CH_2)_5$)	−20	>99.4[g]	88	97.6[g]	91		
15	**5a** (R = Et)	−20	99.0	95				
16	**5b** (R = $CH_2CH{=}CH_2$)	−20			96.0[g]	90		
17	**5c** (R = CH_2Ph)	−20	98.6[g]	95			97.2[g]	92
18	**6a** (*n* = 1)	−20	99.0[h]	99	96.5[h]		97.8[h]	98
19	**6b** (*n* = 2)	−20	99.2[h]	95	98.8[h]	96	99.0[h]	99
20	**6c** (*n* = 3)	−20	99.4[h]	92	98.3[h]	96	99.2[h]	96
21	**7a** (R = H)	−20	98.8[g]	94			98.0[g]	94
22	**7b** (R = Me)	−20	>99.4[i]	96			98.2[i]	96
23	**7b** (R = Me)[j]	−20	76.0[k]	92				

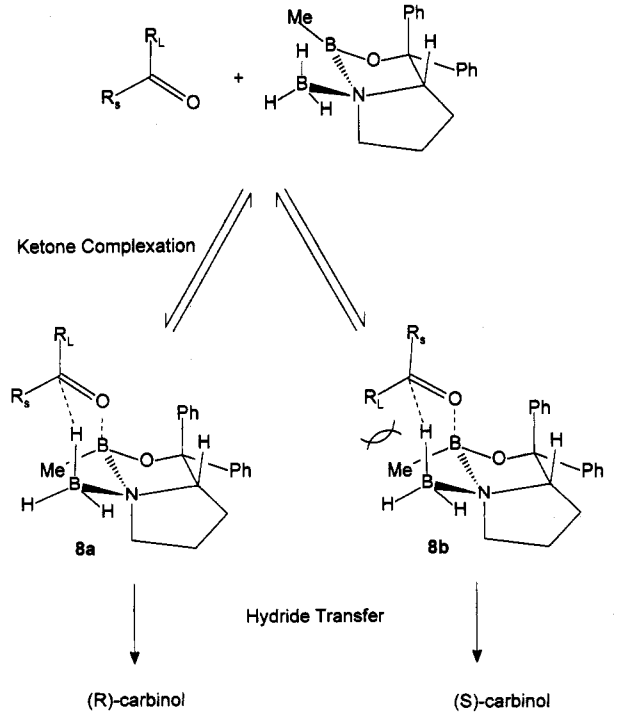
[a] Reactions run in CH_2Cl_2; see the Experimental Section for general procedures. [b] Ketone/catalyst ratio 1:1. [c] Ketone/catalyst ratio 2.0:1.1. [d] Ketone/catalyst/BMS ratio 20:1:20. [e] Unless otherwise noted, enantiomeric purity determined by capillary GC of the nonderivatized alcohol using a Cyclodex-B column (J&W Scientific). [f] Isolated yield of distilled product. [g] Enantiomeric purity determined by capillary GC or HPLC of the (*R*)-MTPA ester derivative (ref 33). [h] Enantiomeric purity determined before crystallization by chiral HPLC of the nonderivatized alcohol using a Chiralcel OB column (Diacel). [i] Diasteomeric purity (4*R*,6*S*-isomer) determined by normal-phase HPLC of the (*R*)-MTPA ester derivative. [j] Reaction run with (*R*)-borane complex **3**. [k] Diasteomeric purity (4*S*,6*S*-isomer) determined by normal-phase HPLC of the (*R*)-MTPA ester derivative.

concentrated in vacuo to remove the solvent (and dimethyl sulfide in the case of the BMS reactions), and then flushed twice with methanol (distillation at 1 atm) to remove trimethyl borate and dimethyl methylborate. To minimize the chance of racemization of acid labile benzylic alcohols, the resultant carbinols and diphenylprolinol were separated by eluting the mixtures in methanol through a column packed with Amberlyst 15 (NH_4^+).[8a] The methanol solutions containing the carbinols were then concentrated in vacuo and the products purified by molecular distillation and/or crystallization.

Recently, Liotta proposed an alternate "chair transition state assembly" to explain the origin of enantioselectivity observed in oxazaborolidine catalyzed reduction of prochiral ketones.[34] According to this model (Scheme I) the 1,3-diaxial interaction between the ketone R_L or R_S substituent and the oxazaborolidine methyl group differentiates the two diastereomeric transition states **8a** and **8b** leading the (*R*)-major and (*S*)-minor products.

Examination of the data obtained from the para-substituted acetophenone examples (Table III, entries 3 and 5–14) shows a slight decrease in enantioselectivity going from an electron-donating (MeO) to an electron-withdrawing substituent (NO_2). Presumably, electron-donating substituents stabilize the ternary ketone–oxazaborolidine–borane complex and, thus, increase the steric interactions responsible for enantioselectivity. The relative rates of reduction for the substituted acetophenones (MeO, 1.43; Me, 1.18; H, 1.00; F, 0.97; Cl, 0.93, Br, 0.93; CO_2Et, 0.87; CF_3, 0.94; CN, 1.07; NO_2, 1.36), deter-

Scheme I



(34) (a) Jones, D. K.; Liotta, D. C. Presented in part at the American Chemical Society National Meeting, Washington, D.C., Aug 1992. (b) Jones, D. K.; Liotta, D. C.; Shinkai, I.; Mathre, D. J. *J. Org. Chem.* **1993**, *58*, 799–801.

mined in competition experiments,[35] decrease slightly going from an electron-donating (MeO) to an electron-withdrawing substituent (CF_3). In the case of 4′-cyano- and 4′-nitroacetophenone the relative rate is greater than that of acetophenone. Presumably, the rate of hydride transfer is increased to a greater extent than the decrease in the ketone complexation equilibrium constants for these strongly electron-withdrawing substituents.

Increasing the size of the R_S ketone substituent from methyl to ethyl (Table III, entries 3 and 15) has a negligible effect on enantioselectivity, from 98.8 to 99.0% ee, respectively. In contrast, when the size of the oxazaborolidine boron substituent is increased from methyl to ethyl the enantioselectivity for the same two ketones is decreased to 96.6 and 95.6% ee, respectively. For the reduction of certain prochiral ketones, the *B*-phenyloxazaborolidine[1b] affords results as good as, if not better than, the corresponding *B*-methyloxazaborolidine.[7,8a] The conformation adopted by the phenyl group in these cases is presumably less sterically demanding than the space occupied by a methyl or larger alkyl group.

Reduction of ketosulfone **7a** (R = H), an intermediate in the synthesis of the carbonic anhydrase inhibitor MK-0417,[8a] with borane complex **3** provided the desired hydroxysulfone with an enantioselectivity of 98.8% ee. In the case of keto sulfone **7b** (R = Me), an intermediate in the synthesis of the related carbonic anhydrase inhibitor MK-0507,[36] reduction with (*S*)-borane complex **3** afforded predominantly the cis diastereomer (>99.7%). This is not surprising since reduction with BMS itself gives >95% of the cis diastereomer (hydride approaching from the side opposite the C6 methyl group). Reduction of ketosulfone **7b** (R = Me) with the enantiomeric (*R*)-borane complex **3** affords 88% of the trans diastereomer, showing that the oxazaborolidine is able to significantly override the effect of the C6 methyl group.

Summary

An efficient, practical large-scale process for the preparation of borane complex **3** has been described. Borane complex **3** is a stable, free-flowing crystalline solid. It is significantly more stable than the free oxazaborolidine and as such is the preferred form to store and use this important enantioselective catalyst. An investigation into the use of the borane complex showed that two of the three hydrides are effectively transferred, and that the enantioselectivity is higher for transfer of the first hydride. When used stoichiometrically very high levels of enantioselectivity were obtained.

Experimental Section

General. NMR spectra were recorded on a Bruker AM-250 (^1H, ^{13}C), WM-250 (^1H, ^{11}B, ^{13}C), or AM-400 (^1H, ^{13}C) spectrometer. ^1H chemical shifts are reported in ppm referenced to an internal standard of residual protic solvent. ^{11}B chemical shifts are reported in ppm from an external reference of boron trifluoride etherate (0.0 ppm). ^{13}C chemical shifts are reported in ppm referenced to the central peak of the solvent. Specific rotations were determined on a Perkin-Elmer 241 polarimeter. Analytical gas chromatography (GC) was carried out on a Hewlett-Packard 5890A gas chromatograph using the following capillary columns: DB-1, DB-23, or Cyclodex-B (J&W Scientific). Analytical high-performance liquid chromatography (HPLC) was carried out on a Hewlett-Packard 1090M diode-array HPLC using a Chiralcel-OB (Diacel) or Zorbax silica column. Combustion analyses were obtained in-house from our analytical Research Department.

Reactions were carried out under an atmosphere of dry N_2. As necessary, CH_2Cl_2, Et_3N, THF, toluene, and the ketones were dried over 3- or 4-Å molecular sieves. Residual water content was determined by Karl Fischer titration. Trimethylboroxine was obtained from Aldrich (neat, 94–96%), Callery Chemical Co. (45–50% w/w solution in THF), and Complex Chemical Corp. (15% w/w solution in THF). Neat (10 M) borane–dimethyl sulfide complex (BMS) was obtained from Aldrich and Callery Chemical Co.

(*S*)-Tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole–Borane (3). A mixture of (*S*)-diphenylprolinol hydrochloride [1 hydrochloride][37,38] (290 g, 1.00 mol), THF (1.0 L), and 2.0 M aqueous NaOH (1.0 L) was mechanically stirred at 20–25 °C until all of the solid dissolved (ca. 0.5 h). Toluene (2.5 L) was added and the mixture then filtered through a medium-frit, sintered-glass funnel. The mixture was warmed to 40–45 °C, and the layers were then separated. The upper (product) layer was washed with water (500 mL) and then concentrated by distillation (1 atm) to a volume of 500 mL. The solution was cooled to 20–25 °C, diluted to a volume of 2.0 L with dry toluene,[39] and then charged with trimethylboroxine (106 mL, 95.2 g, 0.758 mol).[40] The temperature of the mixture rose 10–15 °C as a white precipitate of the intermediate bis-methylboronic acid adduct was formed.[1a] The mixture was stirred for 0.5 h at 20–25 °C to ensure complete formation of the bis-adduct. The flask was fitted with a distillation head and wide-bore condenser. To convert the bis-adduct to the oxazaborolidine, the mixture was then heated and concentrated by distillation (1 atm) to a volume of 500 mL. During the initial stages of the distillation, the vessel was swept with N_2 to speed the removal of H_2O and $MeB(OH)_2$ and the condenser air-cooled to prevent the condenser from being plugged with $MeB(OH)_2$. The mixture was diluted to 2.0 L with dry toluene, concentrated by distillation (1 atm) to a volume of 500 mL, and then checked by ^1H NMR for completion. If necessary, additional trimethylboroxine (10.6 mL, 9.5 g, 0.076 mol) was added.[41] The mixture was diluted to 2.0 L with dry toluene and was then concentrated by distillation (1 atm) to a volume of 500 mL.[42] The solution of oxazaborolidine **2** (1.0 mol, ca. 2.0 M) was cooled to 20–25 °C and was then charged

(35) The competition experiment was performed in dichloromethane by adding a solution of the borane complex (2 mmol) to a mixture of the ketones (10 mmol total) at a rate to maintain the temperature at −20(±2) °C. The relative amounts of the ketones remaining and carbinols produced was determined by capillary GC using a DB-23 (J&W Scientific) column. Recently, Corey reported a larger difference in relative rates for *p*-nitro- (3.4) and *p*-methoxyacetophenone (1.8); see: Corey, E. J.; Link, J. O.; Bakshi, R. K. *Tetrahedron Lett.* **1992**, *33*, 7107–7110.

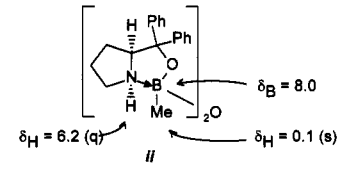
(36) Blacklock, T. J.; Sohar, P.; Butcher, J. W.; Lamanec, T.; Grabowski, E. J. J. *J. Org. Chem.* Accepted for publication.

(37) Recent batches of diphenylprolinol prepared via the procedure described in ref 1a were isolated as the hydrochloride rather than sulfate salt.

(38) For an alternate source of diphenylprolinol see: Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708–9710.

(39) The trimethylboroxine should not be added until after the solution has been diluted to a volume of 2.0 L with toluene. This avoids the problem of a highly exothermic reaction ($\Delta T > 50$ °C) and the formation of an unstirrable mixture of the crystalline bis-methylboronic acid adduct.

(40) Instead of neat trimethylboroxine we have also used commercially available solutions of trimethylboroxine in THF (15 or 50 wt %). When trimethylboroxine in THF was used we observed the generation of a new intermediate "anhydride" **ii** which presumably was formed because of the longer time required to heat the mixture to >110 °C. We found that temperatures >125 °C are required to convert anhydride **ii** to oxazaborolidine **2**. To overcome this problem, we removed all of the toluene and then heated the mixture at 150–170 °C for a period of ca. 0.5 h (until the ^1H NMR spectrum of a sample shows only oxazaborolidine **2**). Alternatively, the reaction can be run using xylenes (bp 137–145 °C).



ii

with BMS (10 M, 120 mL, 1.20 mol). The mixture was stirred for 0.5 h at 20–25 °C to ensure complete formation of the borane complex and was then slowly diluted to a volume of 2.5 L with dry hexane. During the addition the borane adduct began to crystallize.[43] After the addition was complete, the mixture was cooled to −10 °C, was stirred at this temperature for 1–4 h, and was then filtered in an enclosed Schlenk filter. The cake was washed with dry hexane (2 × 500 mL) and was then dried in vacuo (100 mBar, 20–25 °C) with a nitrogen sweep to constant weight (2–4 h), yield 263 g (90%) of borane complex **3** as a free-flowing crystalline solid: mp 124–126 °C (dec; ^{1}H NMR ($CDCl_3$) δ 7.6 (m, 2H, Ar-H), 7.15–7.40 (m, 8H, Ar-H), 4.65 (t, J = 7.9 Hz, 1H, C3a-H), 3.4 (m, 1H, C6-H), 3.2 (m, 1H, C6-H), 1.9 (m, 2H, C5-H_2), 1.7 (m, 1H, C4-H), 1.3 (m, 1H, C4-H), 2.1–0.8 (very br, 3H, BH_3), 0.78 (s, 3H, B-CH_3) [note: depending on sample preparation the spectrum contained resonances corresponding to the free oxazaborolidine[26]]; ^{11}B NMR ($CDCl_3$) δ 34.5 (oxazaborolidine nucleus), −14.5 (complexed-BH_3); ^{13}C NMR ($CDCl_3$) δ 144.6 (C1'), 143.5 (C1''), 128.3 (C3',C5'), 128.2 (C3'',C5''), 127.4 (C4'), 127.1 (C4''), 125.4 (C2',C6'), 125.0 (C2'',C6''), 90.6 (C3), 76.2 (C3a), 57.7 (C6), 31.4 (C4), 25.0 (C5), −3.9 (br, B-CH_3). Anal. Calcd for $C_{18}H_{23}NOB_2$: C, 74.29; H, 7.97; N, 4.81. Found: C, 74.34; H, 8.00; N, 4.69.

General Procedure A: Stoichiometric Reduction of Prochiral Ketones (1:1 Borane Complex/Ketone). Borane complex **3** (2.91 g, 10.0 mmol), under a static atmosphere of N_2, was dissolved in dry CH_2Cl_2 (10 mL, H_2O content <20 μg/mL), and the solution was cooled to −20 °C. A 1.00 M solution of the prochiral ketone in CH_2Cl_2 (10.0 mL, 10.0 mmol)[44] was added via syringe pump over a 30-min period while the internal temperature was maintained at −20 ± 5 °C. After the addition was complete, the mixture was stirred at −20 °C until GC analysis indicated the reaction to be complete (ca. 0.5–2.0 h). Without warming, the reaction mixture was poured *into* precooled (−20 °C) MeOH (100 mL). [Caution: H_2 evolution.] The solution was warmed to 25 °C, was stirred for 1 h until H_2 evolution ceased), and was then concentrated by distillation (1 atm) to a volume of 20 mL. MeOH (100 mL) was added and the distillation repeated to ensure complete removal of the $B(OMe)_3$ and $MeB(OMe)_2$. The remaining solution containing the product and diphenylprolinol was diluted to 80–100 mL with MeOH and was then loaded onto a 2.5 × 30 cm column packed with Amberlyst 15 (NH_4^+)[45] at 2.5 mL/min, collecting 40-mL fractions. The column was rinsed with MeOH until the product eluted (ca. 160–200 mL). The column was then rinsed with 1 M methanolic NH_4OH until the diphenylprolinol eluted (ca. 280–320 mL). The progress of the column was monitored by UV (260 nm), GC, and/or HPLC. Fractions containing the product were combined, concentrated in vacuo (40 °C, 100 mBar), and then purified by molecular (Kugelrohr) distillation. Fractions containing the diphenylprolinol were combined and concentrated in vacuo to a two-phase (H_2O + diphenylprolinol) mixture. *i*-PrOH (50 mL) was added and the solution concentrated in vacuo to remove the H_2O. The resultant oil was dissolved in hexane (5–10 mL) and the diphenylprolinol allowed to crystallize.

General Procedure B: Stoichiometric Reduction of Prochiral Ketones (1.1:2.0 Borane Complex/Ketone). Borane complex **3** (3.20 g, 11.0 mmol), under a static atmosphere of N_2, was dissolved in dry CH_2Cl_2 (10 mL, H_2O content <20 μg/mL), and the solution was cooled to −20 °C. A 1.00 M solution of the prochiral ketone in CH_2Cl_2 (20.0 mL, 20.0 mmol)[44] was added via syringe pump over a 1-h period while the internal temperature was maintained at −20 ± 5 °C. After the addition was complete, the mixture was stirred at −20 °C until GC analysis indicated the reaction to be complete (ca. 2–4 h). The reaction was quenched, and the product was isolated as described in general procedure A.

General Procedure C: Catalytic Reduction of Prochiral Ketones (1:20:20 Borane Complex/Ketone/BMS). Borane complex **3** (2.91 g, 10.0 mmol), under a static atmosphere of N_2, was dissolved in dry CH_2Cl_2 (10 mL, H_2O content <20 μg/mL). To the solution was added BMS (10 M, 20 mL, 200 mmol), and the mixture was then cooled to −20 °C. The prochiral ketone (200 mmol) either neat, or as a concentrated (ca. 50%) solution in CH_2Cl_2,[44] was added via syringe pump over a 5-h period while the internal temperature was maintained at −20 ± 5 °C. After the addition was complete, the mixture was stirred at −20 °C until GC analysis indicated the reaction to be complete (ca. 0.5–4.0 h). The reaction was quenched and the product isolated as described in general procedure A.

(*R*)-α-Methylbenzenemethanol. Acetophenone (1.0 M in CH_2Cl_2, 10.0 mL, 10.0 mmol) and borane complex **3** (2.91 g, 10.0 mmol) were reacted according to general procedure A. Kugelrohr distillation (75 °C, 40 μm) afforded 1.15 g (95%) of the title compound as a colorless oil: GC (Cyclodex-B, 15 lbs/in.^{2} He, 100–120 °C at 1 °C/min) acetophenone (t_R 5.96 min, <0.1%), (*R*)-carbinol (t_R 8.68 min, 99.4%), (*S*)-carbinol (t_R 9.38 min, 0.6%); $[\alpha]^{21}_{589}$ +43.6° (neat, d = 1.02) [lit.[46] $[\alpha]^{27}_{589}$ +42.8° (neat)]; ^{1}H NMR ($CDCl_3$) δ 7.45–7.2 (m, 5H, Ar-*H*), 4.9 (q, J = 7.2 Hz, 1H, C1-*H*), 2.1 (br s, 1H, O*H*), 1.5 (d, J = 7.2 Hz, 3H, Cα-H_3). In addition, 2.35 g (93%) of diphenylprolinol **1** was recovered as a white crystalline solid: mp 79.0–79.5 °C, identical to previously prepared material.[1a]

(*R*)-4-Fluoro-α-methylbenzenemethanol. 4'-Fluoroacetophenone (1.0 M in CH_2Cl_2, 20.0 mL, 20.0 mmol) and borane complex **3** (3.20 g, 20.0 mmol) were reacted according to general procedure B. Kugelrohr distillation (100 °C, 40 μm) afforded 2.66 g (95%) of the title compound as a colorless oil: GC (Cyclodex-B, 15 lbs/in.^{2} He, 100–120 °C at 1 °C/min) 4'-fluoroacetophenone (t_R 5.96 min, 0.2%), (*R*)-carbinol (t_R 10.29 min, 98.8%), (*S*)-carbinol (t_R 10.99 min, 1.0%); $[\alpha]^{21}_{589}$ +38.7° (c = 1.309, MeOH) [lit.[47] $[\alpha]^{20}_{589}$ +40.2° (c = 1.2 $CHCl_3$) reported for >97% ee]; ^{1}H NMR ($CDCl_3$) δ 7.45–7.3 (m, 2H, Ar-*H*), 7.1–6.95 (m, 2H, Ar-*H*), 4.9 (q, J = 6.5 Hz, 1H, C1-*H*), 2.0 (br s, 1H, O*H*), 1.5 (d, J = 6.5 Hz, 3H, Cα-H_3). In addition, 2.69 g (96%) of diphenylprolinol **1** was recovered as a white crystalline solid.

(*R*)-4-Chloro-α-methylbenzenemethanol. 4'-Chloroacetophenone (1.0 M in CH_2Cl_2, 20.0 mL, 20.0 mmol) and borane complex **3** (3.20 g, 20.0 mmol) were reacted according to general procedure B. Kugelrohr distillation (100 °C, 40 μm) afforded 3.08 g (98%) of the title compound as a colorless oil: GC (Cyclodex-B, 15 lbs/in.^{2} He, 100–130 °C at 1 °C/min) 4'-chloroacetophenone (t_R 14.0 min, <0.1%), (*R*)-carbinol (t_R 23.0 min, 98.9%), (*S*)-carbinol (t_R 24.6 min, 1.1%); $[\alpha]^{21}_{589}$ +39.8° (c = 1.064, MeOH) [lit.[48] $[\alpha]^{27}_{589}$ −54.0° (neat) reported for the enantiomer at 94% ee]; ^{1}H NMR ($CDCl_3$) δ 7.35–7.25 (m, 4H, Ar-*H*), 4.87 (q, J = 6.5 hz, 1H, C1-*H*), 2.0 (br s, 1H, O*H*), 1.45 (d, J = 6.5 Hz, 3H, Cα-H_3). In addition, 2.75 g (98%) of diphenylprolinol **1** was recovered as a white crystalline solid.

(*R*)-4-Bromo-α-methylbenzenemethanol. 4'-Bromoacetophenone (1.0 M in CH_2Cl_2, 10.0 mL, 10.0 mmol) and borane complex **3** (2.91 g, 10.0 mmol) were reacted according to general

(41) The second addition of trimethylboroxine and the subsequent toluene flushes are not always necessary. A sample of the reaction mixture (50 μL) is concentrated in vacuo (50 °C, <1 mBar, with scrupulous exclusion of adventitious moisture) and the residue examined by ^{1}H NMR using *dry* $CDCl_3$. The base line of the NMR spectrum should be clean, indicating the absence of diphenylprolinol δ 4.3 (t), trimethylboroxine δ 0.45 (s), the bis-methylboronic acid adduct δ 0.35 to −0.50 (multiple BCH_3 singlets), and the water adduct δ −0.25 (br s, BCH_3). If the NMR spectrum indicates the absence of these intermediates (see also ref 40) then the reaction can be continued at the preparation of the borane adduct (addition of BMS) stage.

(42) The combined distillate contains $MeB(OH)_2$, which crystallizes on standing (except when using THF solutions of trimethylboroxine as noted in ref 40). The $MeB(OH)_2$ can be recovered and recycled.

(43) Slow addition of hexane favors the formation of larger crystals, which tend to be more stable for long-term storage.

(44) A stock solution of 1.00 M acetophenone in CH_2Cl_2 was dried over 4-Å molecular sieves until the water content (KF) was <20 μg/mL.

(45) Amberlyst 15 (NH_4^+) column preparation: Amberlyst 15 (H+) (56 g, 100 mL dry) was suspended in an open beaker in methanol (100 mL). [Caution: the slurry exotherms to ca. 40 °C without external cooling and expands to ca. 1.5 times its initial volume.] The slurry was poured into a 2.5- × 30-cm column and eluted with 1 M methanolic ammonia (ca. 1 L) until a sample of the eluent diluted 1:1 with water was basic. The resin was then eluted with methanol (ca. 0.5 L) until a sample of the eluent diluted 1:1 with water was neutral.

(46) Dauben, H. J., Jr.; McCoy, L. L. *J. Am. Chem. Soc.* **1959**, *81*, 5404.

(47) Nieduzak, T. R.; Margolin, A. L. *Tetrahedron Asymmetry* **1991**, *2*, 113–122.

(48) Polavarapu, P. L.; Fontana, L. P.; Smith, H. F. *J. Am. Chem. Soc.* **1986**, *108*, 94–99.

procedure A. Kugelrohr distillation (100 °C, 30 μm) afforded 1.92 g (96%) of the title compound as a colorless oil: GC (Cyclodex-B, 15 lbs/in.^{2} He, 100–140 °C at 1 °C/min) 4′-bromoacetophenone (t_R 20.9 min, <0.1%), (*R*)-carbinol (t_R 31.4 min, 99.65%), (*S*)-carbinol (t_R 32.7 min, 0.35%); $[\alpha]^{21}_{589}$ +32.9° (*c* = 1.392, MeOH) [lit.[49] $[\alpha]^{25}_{589}$ −70.9° (neat) reported for the enantiomer at 91 ± 3% ee]; ^{1}H NMR ($CDCl_3$) δ 7.55–7.45 (m, 2H, Ar-*H*), 7.3–7.2 (m, 2 H, Ar-*H*), 4.87 (q, *J* = 6.5 Hz, 1H, C1-*H*), 1.9 (br s, 1H, O*H*), 1.48 (d, *J* = 6.5 Hz, 3H, Cα-H_3). In addition, 2.48 g (98%) of diphenylprolinol 1 was recovered as a white crystalline solid.

(*R*)-α,4-Dimethylbenzenemethanol. 4′-Methylacetophenone (1.0 M in CH_2Cl_2, 20.0 mL, 20.0 mmol) and borane complex **3** (3.20 g, 20.0 mmol) were reacted according to general procedure B. Kugelrohr distillation (75 °C, 40 μm) afforded 2.59 g (95%) of the title compound as a colorless oil: GC (Cyclodex-B, 15 lbs/in^2 He, 100–120 °C at 1 °C/min) 4′-methylacetophenone (t_R 10.28 min, <0.1%), (*R*)-carbinol (t_R 12.3 min, >99.8%), (*S*)-carbinol (t_R 13.8 min, <0.2%); $[\alpha]^{21}_{589}$ +43.8° (*c* = 0.914, MeOH) [lit.[49] $[\alpha]^{25}_{589}$ +42.4° (neat) reported for 92 ± 4% ee]; ^{1}H NMR ($CDCl_3$) δ 7.35–7.15 (m, 4H, Ar-*H*), 4.87 (q, *J* = 6.5 Hz, 1H, C1-*H*), 2.4 (s, 3H, 4′-CH_3), 2.0 (br s, 1H, O*H*), 1.5 (d, *J* = 6.5 Hz, 3H, Cα-H_3). In addition, 2.65 g (95%) of diphenylprolinol 1 was recovered as a white crystalline solid.

(*R*)-α-Methyl-4-(trifluoromethyl)benzenemethanol. 4′-(Trifluoromethyl)acetophenone (1.0 M in CH_2Cl_2, 10.0 mL, 10.0 mmol) and borane complex **3** (2.91 g, 10.0 mmol) were reacted according to general procedure A. Kugelrohr distillation (85 °C, 30 μm) afforded 1.77 g (93%) of the title compound as a colorless oil: GC (Cyclodex-B, 15 lbs/in.^{2} He, 100–120 °C at 1 °C/min) 4′-(trifluoromethyl)acetophenone (t_R 6.12 min, <0.1%), (*R*)-carbinol (t_R 12.83 min, 99.35%), (*S*)-carbinol (t_R 14.41 min, 0.65%); $[\alpha]^{21}_{589}$ +29.8° (*c* = 1.088, MeOH) [lit.[48] $[\alpha]^{25}_{589}$ −29.0° (*c* = 1.69, MeOH) reported for the enantiomer at 90% ee]; ^{1}H NMR ($CDCl_3$) δ 7.65 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 7.5 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 4.98 (q, *J* = 6.5 Hz, 1H, C1-*H*), 2.1 (br s, 1H, O*H*), 1.5 (d, *J* = 6.5 Hz, 3H, Cα-H_3). In addition, 2.48 g (98%) of diphenylprolinol 1 was recovered as a white crystalline solid.

(*R*)-4-(1-Hydroxyethyl)benzonitrile. 4-Acetylbenzonitrile (1.0 M in CH_2Cl_2, 10.0 mL, 10.0 mmol) and borane complex **3** (2.91 g, 10.0 mmol) were reacted according to general procedure A. Kugelrohr distillation (130 °C, 30 μm) afforded 1.20 g (82%) of the title compound as a colorless oil: GC (Cyclodex-B, 15 lbs/in.^{2} He, 100–160 °C at 1 °C/min) 4-acetylbenzonitrile (t_R 30.5 min, <0.1%), (*R*)-carbinol (t_R 47.8 min, 99.1%), (*S*)-carbinol (t_R 50.9 min, 0.9%); $[\alpha]^{21}_{589}$ +41.7° (*c* = 1.053, MeOH) [lit.[50] $[\alpha]^{21}_{589}$ +16.5° reported for 39% ee]; ^{1}H NMR ($CDCl_3$) δ 7.7–7.6 (m, 2H, Ar-*H*), 7.55–7.45 (m, 2H, Ar-*H*), 4.97 (q, *J* = 6.5 Hz, 1H, C1-*H*), 2.3 (br s, 1H, O*H*), 1.5 (d, *J* = 6.5 Hz, 3H, Cα-H_3). In addition, 2.79 g of diphenylprolinol 1 plus the over-reduction (nitrile to aminomethyl) byproduct was recovered as a white crystalline solid.

Ethyl (*R*)-4-(1-Hydroxyethyl)benzoate. Ethyl 4-acetylbenzoate (1.0 M in CH_2Cl_2, 10.0 mL, 10.0 mmol) and borane complex **3** (2.91 g, 10.0 mmol) were reacted according to general procedure A. Kugelrohr distillation (125 °C, 20 μm) afforded 1.84 g (95%) of the title compound as a colorless oil: GC (Cyclodex-B, 15 lbs/in.^{2} He, 100–170 °C at 1 °C/min) ethyl 4-acetylbenzoate (t_R 41.7 min, <0.1%), (*R*)-carbinol (t_R 53.5 min, 99.3%), (*S*)-carbinol (t_R 54.7 min, 0.7%); $[\alpha]^{21}_{589}$ +32.6° (*c* = 0.873, MeOH); ^{1}H NMR ($CDCl_3$) δ 8.0 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 7.42 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 4.96 (q, *J* = 6.5 Hz, 1H, C1-*H*), 4.36 (q, *J* = 7.4 Hz, 2H, OCH_2CH_3), 2.2 (br s, 1H, O*H*), 1.49 (d, *J* = 6.5 Hz, 3H, Cα-H_3), 1.39 (t, *J* = 7.4 Hz, 3H, OCH_2CH_3). In addition, 2.49 g (98%) of diphenylprolinol 1 was recovered as a white crystalline solid.

(*R*)-α-Methyl-4-nitrobenzenemethanol. 4′-Nitroacetophenone (1.0 M in CH_2Cl_2, 10.0 mL, 10.0 mmol) and borane complex **3** (2.91 g, 10.0 mmol) were reacted according to general procedure A. Kugelrohr distillation (125 °C, 30 μm) afforded 1.61 g (96%) of the title compound as a colorless oil: GC (Cyclodex-B, 15 lbs/in.^{2} He, 100–170 °C at 1 °C/min) 4′-nitroacetophenone (t_R 39.8 min, <0.1%), (*R*)-carbinol (t_R 58.9 min, 99.35%), (*S*)-carbinol (t_R 61.7 min, 0.35%); $[\alpha]^{21}_{589}$ +31.0° (*c* = 1.225, MeOH) [lit.[49] $[\alpha]^{25}_{589}$ +48.9° (neat) reported for 72% ee]; ^{1}H NMR ($CDCl_3$) δ 8.35–8.25 (m, 2H, Ar-*H*), 7.6–7.5 (m, 2H, Ar-*H*), 5.0 (q, *J* = 6.5 Hz, 1H, C1-*H*), 2.25 (br s, 1H, O*H*), 1.5 (d, *J* = 6.5 Hz, 3H, Cα-H_3). In addition, 2.46 g (97%) of diphenylprolinol 1 was recovered as a white crystalline solid.

(*R*)-α-Methyl-4-(piperidino)benzenemethanol. 4′-Piperidinoacetophenone (1.0 M in CH_2Cl_2, 10.0 mL, 10.0 mmol) and borane complex **3** (2.91 g, 10.0 mmol) were reacted according to general procedure A. In this case the product was purified by MPLC (4.8 × 30 cm EM-60 silica, 96.0:3.5:0.5 $MeCl_2$/*i*-PrOH/28% aqueous NH_4OH) to afford 0.16 g (8.5%) of the over-reduction (ketone to methylene) byproducts [R_f = 0.76 (EM-60 HPTLC, 96.0:3.5:0.5 $MeCl_2$/*i*-PrOH/28% aqueous NH_4OH); ^{1}H NMR ($CDCl_3$) δ 7.15 (m, 2H, Ar-*H*), 6.9 (m, 2H, Ar-*H*), 3.15 (m, 4H), 2.6 (q, *J* = 8.6 Hz, 2H, Ar-CH_2CH$_3$), 1.8–1.7 (m, 4H), 1.7–1.5 (m, 2H), 1.2 (t, *J* = 8.6 Hz, 3H, Ar-CH$_2$CH_3)] and 1.81 g (88%) of the title compound as an off-white crystalline solid: mp 79–81 °C; R_f = 0.30; $[\alpha]^{21}_{589}$ +37.6° (*c* = 1.434, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.25 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 6.95 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 4.82 (q, *J* = 6.5 Hz, 1H, C1-*H*), 3.25–3.05 (m, 4H), 2.0 (br s, 1H, O*H*), 1.8–1.65 (m, 4H), 1.65–1.55 (m, 2H), 1.47 (d, *J* = 6.5 Hz, 3H, Cα-H_3); ^{13}C NMR ($CDCl_3$) δ 151.7, 136.3, 126.2, 116.4, 70.0, 50.7, 25.8, 24.7, 24.3. Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 75.85; H, 9.06; N, 6.80. In addition, 2.41 g (95%) of diphenylprolinol (1) was recovered as a white crystalline solid.

(*R*)-4-Methoxy-α-methylbenzenemethanol. 4′-Methoxyacetophenone (1.0 M in CH_2Cl_2, 10.0 mL, 10.0 mmol) and borane complex **3** (2.91 g, 10.0 mmol) were reacted according to general procedure A. Kugelrohr distillation (100 °C, 60 μm) afforded 1.47 g (97%) of the title compound as a colorless oil: GC (Cyclodex-B, 15 lbs/in.^{2} He, 100–130 °C at 1 °C/min) 4′-methoxyacetophenone (t_R 23.9 min, <0.1%), (*R*)-carbinol (t_R 24.9 min, >99.9%), (*S*)-carbinol (t_R 25.6 min, <0.1%); $[\alpha]^{21}_{589}$ +41.0° (*c* = 1.069, MeOH) [lit.[51] $[\alpha]_{589}$ +45.2° (EtOH)]; ^{1}H NMR ($CDCl_3$) δ 7.35–7.25 (m, 2H, Ar-*H*), 7.95–7.85 (m, 2H, Ar-*H*), 4.85 (q, *J* = 6.5 Hz, 1H, C1-*H*), 3.82 (s, 3H, OCH_3), 1.9 (br s, 1H, O*H*), 1.5 (d, *J* = 6.5 Hz, 3H, Cα-H_3). In addition, 2.52 g (99%) of diphenylprolinol (1) was recovered as a white crystalline solid.

(*R*)-2,3-Dihydro-1*H*-inden-1-ol. 1-Indanone (26.4 g, 200 mmol), BMS (10 M, 20 mL, 200 mmol), and borane complex **3** (2.91 g, 10.0 mmol) were reacted according to general procedure C to afford after the Amberlyst 15 column 26.2 g (98%) of the title compound as a white crystalline solid: HPLC (Chiralcel-OB, 90:10 hexane/*i*-PrOH, 0.5 mL/min) 1-indanone (t_R 29.6 min, <0.1%), (*R*)-carbinol (t_R 10.3 min, 98.9%), (*S*)-carbinol (t_R 15.3 min, 1.1%). In addition, 2.42 g (99%) of diphenylprolinol (1) was recovered as a white crystalline solid.

A portion (23.0 g) of the crude 1-indanol was dissolved in hexane (230 mL) at 50–60 °C and the product allowed to crystallize as the mechanically stirred solution slowly cooled to room temperature (20–25 °C). The mixture was aged for 4 h at 22 °C and filtered and the cake washed with hexane (2 × 25 mL). The product was dried in vacuo (30 °C, 10 mBar) to afford 21.25 g (92%) of the title compound as a white crystalline solid (fine needles): mp 73.0–73.5 °C; HPLC (Chiralcel-OB) (*R*)-carbinol >99.9%, (*S*)-carbinol <0.1%; $[\alpha]^{21}_{589}$ −45.5° (*c* = 1.184, MeOH) [lit.[52] $[\alpha]_{589}$ +22.6° (*c* = 4.2, $CHCl_3$) reported for the enantiomer]; ^{1}H NMR ($CDCl_3$) δ 7.5–7.2 (m, 4H, Ar-*H*), 5.3–5.2 (m, 1H, C1-*H*), 3.15–3.0 (m, 1H, C3-*H*), 2.95–2.75 (m, 1H, C3-*H*), 2.6–2.4 (m, 1H, C2-*H*), 2.05–1.85 (m, 2 H, C2-H, O*H*). From the mother liquors was obtained an additional 1.75 g of 1-indanol of lower enantiomeric purity (HPLC: 85:15 *R*/*S*).

(*R*)-1,2,3,4-Tetrahydro-1-naphthol. 1-Tetralone (29.2 g, 200 mmol), BMS (10 M, 20 mL, 200 mmol), and borane complex **3** (2.91 g, 10.0 mmol) were reacted according to general procedure C to afford after the Amberlyst 15 column 29.5 g (99%) of the title compound as a pale yellow oil: HPLC (Chiralcel-OB, 90:10 hexane/*i*-PrOH, 0.75 mL/min) 1-tetralone (t_R 12.9 min, <0.1%),

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(*R*)-carbinol (t_R 6.3 min, 99.5%), (*S*)-carbinol (t_R 8.9 min, 0.5%). In addition, 2.30 g (91%) of diphenylprolinol (1) was recovered as a white crystalline solid.

The crude 1-tetralol (29.5 g) was dissolved in pentane (120 mL) at 30–35 °C and the product allowed to crystallize as the mechanically stirred solution was cooled to −20 °C. The mixture was aged for 12 h at −20 °C and filtered cold and the cake washed with precooled (−20 °C) pentane (2 × 25 mL). The product was dried in vacuo (20 °C, 10 mBar) to afford 24.9 g (84%) of the title compound as a white crystalline solid (fine needles): mp 39.5–40.0 °C; HPLC (Chiralcel-OB) (*R*)-carbinol >99.9%, (*S*)-carbinol <0.1%; $[\alpha]^{21}_{589}$ −24.6° (*c* = 1.287, MeOH) [lit.[52] $[\alpha]_{589}$ +26.8° (*c* = 2.3, $CHCl_3$) reported for the enantiomer]; ^{1}H NMR ($CDCl_3$) δ 7.5–7.05 (m, 4H, Ar-*H*), 4.35–4.25 (m, 1H, C1-*H*), 2.95–2.65 (m, 2H, C4-H_2), 2.1–1.7 (m, 5H, C2-H_2, C3-H_2, O*H*). From the mother liquors was obtained an additional 3.35 g of 1-tetralol of lower enantiomeric purity (HPLC: 96.7:3.3 *R*/*S*).

(*R*)-6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-5-ol. 1-Benzosuberone (1.0 M in CH_2Cl_2, 10.0 mL, 10.0 mmol) and borane complex **3** (2.91 g, 10.0 mmol) were reacted according to general procedure A. Kugelrohr distillation (125 °C, 30 μm) afforded 1.49 g (92%) of the title compound as a colorless oil that solidified on standing: mp 80.0–80.5 °C; HPLC (Chiralcel-OB, 99:1 hexane/*i*-PrOH, 0.50 mL/min) (*R*)-carbinol (t_R 29.4 min, 99.7%), (*S*)-carbinol (t_R 26.5 min, 0.3%); $[\alpha]^{21}_{589}$ +30.5° (*c* = 1.069, MeOH) [lit.[52] $[\alpha]^{25}_{589}$ −26.6° (*c* = 4, $CHCl_3$) reported for the enantiomer]; ^{1}H NMR ($CDCl_3$) δ 7.55–7.05 (m, 4H, Ar-*H*), 5.05–4.85 (m, 1H, C5-*H*), 3.05–2.65 (m, 2H, C9-H_2) 2.2–1.4 (m, 7H, C6-H_2, C7-H_2, C8-H_2, O*H*). In addition, 2.51 g (99%) of diphenylprolinol 1 was recovered as a white crystalline solid.

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Supplementary Material Available: Experimental details for determining the crystal structure of compound **3**, including a projection view and selected interatomic angles and distances, and ^{1}H NMR spectra for compounds **3**, **i**, and **ii** (7 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.