

4-Hydroxyphenylglycine-Based Oxazaborolidines for Enantioselective Reductions of Ketones

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Abstract: Amino alcohols **6** featuring the diphenylhydroxymethyl group are prepared from the commercial amino acid (*R*)-4-hydroxyphenylglycine **3**. Oxazaborolidines generated *in situ* from the amino alcohols **6** and borane-dimethyl sulfide serve as catalysts in enantioselective reductions of acetophenone. The *para*-substituents of the phenyl ring at the stereogenic carbon atom have a substantial influence

on the enantioselectivity. When mediated by the nonaflate **6d**, the reduction of ketones **7**, **9**, **11**, and **13** leads to the carbinols **8**, **10**, **12**, and **14** in 90 to 96 % *ee*.

Keywords: amino alcohols; asymmetric catalysis; boron; substituent effects; synthetic methods

Introduction

Oxazaborolidines that are derived from chiral 2-amino alcohols have proven themselves to be highly efficient catalysts for the reduction of carbonyl compounds and other enantioselective transformations.^[1] After early attempts using the diphenylvalinol backbone,^[2] the proline-based oxazaborolidines developed by Corey's group, the so-called CBS catalysts **1** (Scheme 1) distinctly helped the enantioselective reduction by borane on the road to success.^[3] In addition, oxazaborolidines derived from other amino alcohols have been developed,^[1] most of them featuring the diarylhydroxymethyl group.^[4] Thus, boronate **2a** generated from 2-amino-1,1,2-triphenylethanol has been used for the enantioselective reduction of ketones,^[5,6] whereas the reaction mediated by the corresponding borane **2b** was reported to occur with moderate enantioselectivity only.^[7] With respect to the application of enantioselective catalysts, the latter should be readily available as both enantiomers. As

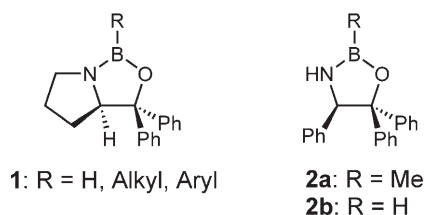
far as α -amino acids, the raw materials of most oxazaborolidines, are concerned, that postulate is in general fulfilled by non-proteinogenic, synthetic rather than natural amino acids.

The (*R*)-enantiomer of 4-hydroxyphenylglycine (**3**) is produced on a scale of more than 1000 tons per annum and serves as a building block for amoxicillin and other antibiotics.^[8] In addition, the (*S*)-enantiomer is commercially available as well. In this article, we describe the conversion of 4-hydroxyphenylglycine into the novel amino alcohol **5**, the phenolic moiety of which permits us to synthesize a series of *para*-substituted derivatives. After their incorporation in oxazaborolidines, they shall be tested in the borane reduction of ketones in order to find out the influence of the substituents on the enantioselectivity.

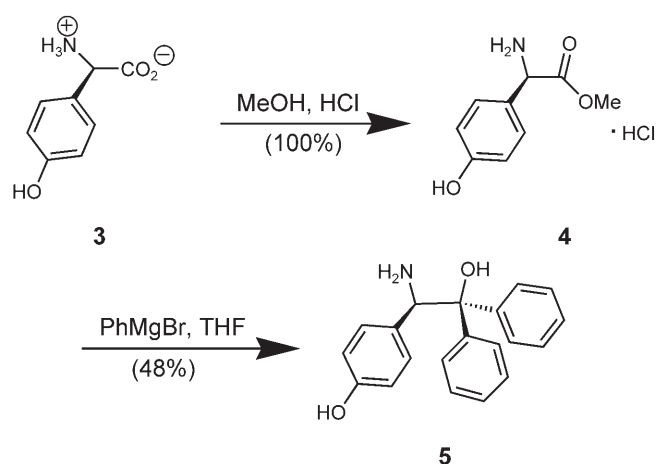
Results and Discussion

A straightforward route (Scheme 2) was elaborated that permitted us to convert (*R*)-hydroxyphenylglycine **3** into the amino alcohol **5** in two steps. Thus, the amino acid **3** was first esterified by treatment with hydrogen chloride in methanol.^[9] The salt **4** thus obtained was allowed to react with an excess of phenylmagnesium bromide to give aminoethanol **5** in 48 % overall yield.

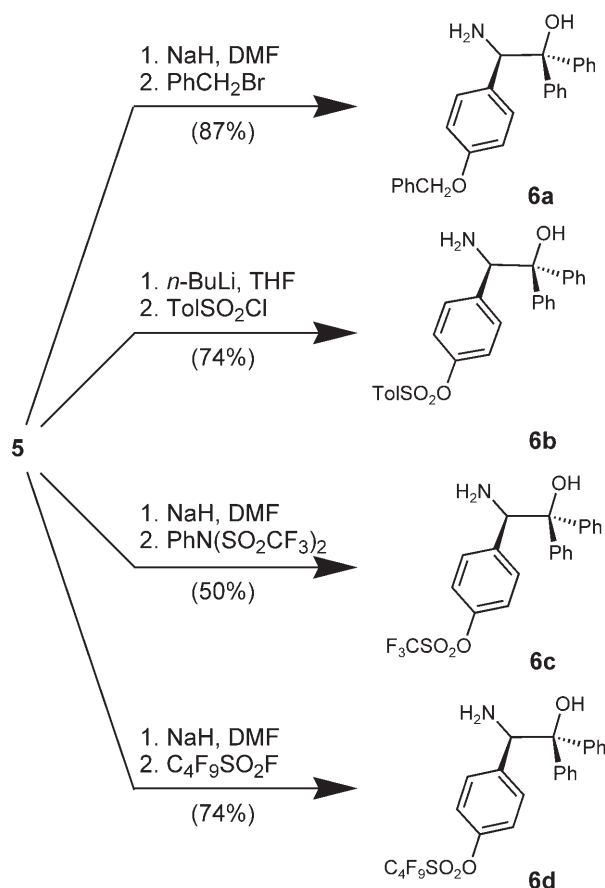
The free phenolic group then served for the introduction of different substituents in the phenyl group at the stereogenic center (Scheme 3), in order to find out how their electronic properties will influence the



Scheme 1. Oxazaborolidines derived from 2-(diphenylhydroxymethyl)pyrrolidine and 2-amino-1,1,2-triphenylethanol.



Scheme 2. Synthesis of amino alcohol **5** from 4-hydroxyphenylglycine **3**.



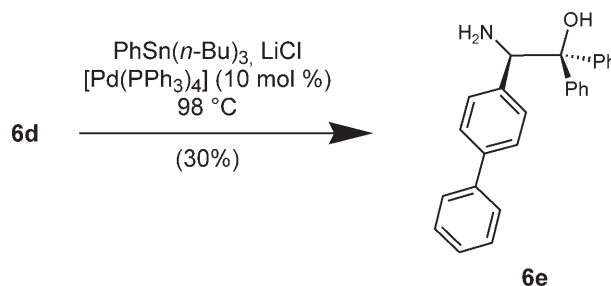
Scheme 3. Conversion of phenolic amino alcohol **5** into derivatives **6a–d**.

enantioselectivity in the reduction of ketones. Thus, the benzyl ether **6a** was easily obtained by protection of the phenolic hydroxy group, which, due to its acidity, was selectively deprotonated with sodium hydride. As a consequence, the phenolic benzyl ether **6a** re-

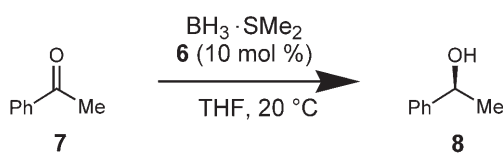
sulted as the single product from the Williamson reaction. In a similar way, the sodium phenolate of **5** was generated and treated subsequently with *N*-phenylbis(trifluoromethane)sulfonimide or nonafluorobutanesulfonyl fluoride to give the triflate **6c** and the nonaflate **6d**, respectively.^[10] Selective deprotonation of the amino alcohol **4** also occurred with butyllithium so that the subsequent treatment with toluenesulfonyl chloride led to the sulfonate **6b**.

With respect to a study of the influence on the enantioselectivity, not only hetero but also carbon substituents in the *para* position of the phenyl residue at the stereogenic center might be relevant. Therefore, the triflate **6c** and the nonaflate **6d** were considered as suitable substrates for aryl–aryl coupling reactions. However, various attempts to react the triflate **6c** with phenylboronic acid or phenylzinc chloride in the presence of tetrakis(triphenylphosphino)palladium failed completely. In contrast with these approaches, the Stille-type coupling was successful, in particular, when the nonaflate **6d** was used as the substrate. Thus, coupling with tributylphenylstannane mediated with tetrakis(triphenylphosphino)palladium led to the formation of biphenyl-substituted amino alcohol **6e** (Scheme 4).

Acetophenone **7** was chosen as a prochiral ketone in order to test the performance of amino alcohols **6** in the reduction with borane. In all cases, the corresponding oxazaborolidine was generated *in situ* from the corresponding aminoethanol **6** and borane–dimethyl sulfide complex. Thereafter, the ketone was added within 90 min, what turned out to provide higher enantioselectivity than the addition in one portion. Following this protocol, the non-catalyzed reduction by the borane could be widely suppressed. The resulting phenylethanol **8** was found to be (*S*) configured in all the reductions performed with (*R*)-aminoethanols **6**. The absolute configuration was assigned by comparison of the optical rotation with the data of authentic samples.^[11] After purification of the product by column chromatography and subsequent distillation, the enantiomeric excess was determined based on the optical rotation and GC on a chiral column. The results of the reductions are outlined in Table 1.



Scheme 4. Conversion of nonaflate **6d** into biphenyl-substituted amino alcohol **6e**.

Table 1. Enantioselective reduction of acetophenone **7** mediated by oxazaborolidines-derived amino alcohols **6a–e**.

Entry	Amino alcohol 6	ee [%]
1	6a	85
2	6b	14
3	6c	95
4	6d	96
5	6e	97

As the amino alcohol **6a** bearing the electron-donating benzyloxy group gave an enantiomeric excess of 85% for the product **8** (entry 1), it was an obvious idea to try to improve the selectivity by introducing electron-demanding substituents. However, the enantioselectivity vanished almost completely with the toluenesulfonyl-substituted amino alcohol **6b** (entry 2). Quite surprisingly, the oxazaborolidines originating from triflate **6c** and nonaflate **6d**, both catalysts with electron-withdrawing substituents, gave high enantioselectivities of 95 and 96% *ee*, respectively (entries 3 and 4). Again, it is remarkable that the phenyl substituent, exhibiting only a marginal electronic effect, leads to a high enantioselectivity (97% *ee*) as well (entry 5).

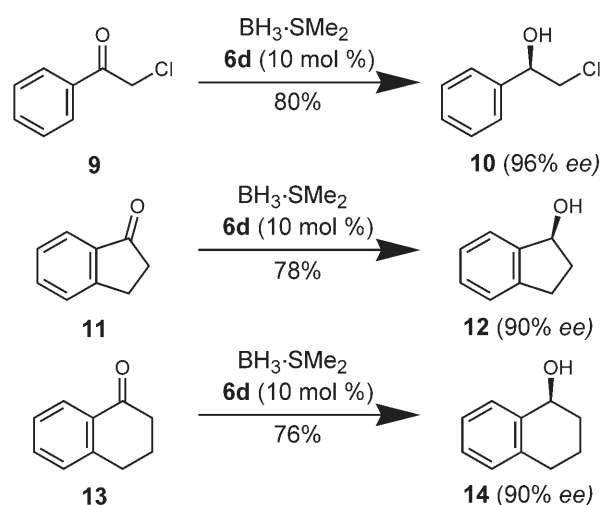
The conclusion to be drawn from the results given in Table 1 is clearly that the electronic character of the *para* substituent is not the selectivity determining parameter. Neither the good performance of oxazaborolidines with electronically very different substituents (entry 1 *versus* entries 3 and 4) nor the very different selectivity obtained with electronically similar substituents (entry 2 *versus* entries 3 and 4) suggest any linear effect of the substituents in compounds **6**.^[12] An explanation for the non-uniform enantioselectivity is offered by the ability of the substituent to act as a donor that might coordinate to the borane, thus competing with the 2-amino alcohol moiety. This seems to be the case for the benzyl ether **6a** and the sulfonate **6b**. As the borane might be bound at this site of the molecule, far away from the “chiral site”, the transfer of the hydride to the ketone is expected to be rather unselective. This could be the case to a smaller extent for the benzyl ether **6a**, but to a considerable degree for the sulfonate **6b**. Obviously, the biphenyl derivative **6e** does not offer an undesired binding site to the borane thus avoiding an unselective hy-

dride transfer to the ketone. Concerning the triflate **6c** and the nonaflate **6d**, one can assume that the strong electron-withdrawing effect of the trifluoromethyl and the nonafluorobutyl groups prevents the oxygen atoms in these substituents from acting as donors that could coordinate to the borane.

As, for practical reasons, the readily available nonaflate **6d** is the most suitable one for applications, the protocol was applied to the reduction of the ketones **9**, **11**, and **13** to give the secondary alcohols **10**, **12**, and **14**, respectively, upon reduction with borane-dimethyl sulfide complex (Scheme 5). Here again, remarkable enantioselectivity was obtained. The optical purity and the absolute configuration of the alcohols **10**, **12** and **14** was determined by the comparison of their optical rotations with those of authentic samples.^[11] In addition, the enantiomeric excesses were confirmed by NMR spectroscopy of the Mosher's esters^[13] of the carbinols **12** and **14**.

Conclusions

In summary, it has been shown that 4-hydroxyphenylglycine-derived amino alcohols **6** can be used for efficient borane reductions of ketones provided that they are suitably substituted in *para*-position of the phenyl residue at the stereogenic carbon atom. Thus nonaflate **6d**, readily accessible from 4-hydroxyphenylglycine in three steps, efficiently catalyzes the reduction of several ketones, so that the corresponding secondary alcohols are obtained in up to 96% *ee*. In contrast to known protocols using phenylglycine-derived boronates, the catalytically active oxazaborolidine is generated *in situ* so that its isolation and purification can be avoided.

**Scheme 5.** Enantioselective reduction of aryl alkyl ketones **9**, **11**, and **13**.

Experimental Section

General Remarks

Melting points (uncorrected) were determined with a Büchi melting point apparatus 540. Specific rotations were determined with a Perkin–Elmer 341 polarimeter. IR spectra: Bruker Vector 22. Mass spectra: Varian MAT 311 A. NMR spectra: Vairan VXR 200, VXR 300, and DRX 500. The spectra were recorded in CDCl₃ with TMS as internal standard. TLC: Silica gel 60 F₂₅₄ (Merck). Column chromatography: Macherey–Nagel Kieselgel 60 and Merck Kieselgel 60, mesh size 0.04–0.063. Reactions at temperatures below –20 °C were monitored by a thermocouple connected to a resistance thermometer (Ebro). General remarks concerning the handling of moisture-sensitive compounds are given in ref.^[14]

(R)-4-Hydroxyphenylglycine methyl ester hydrochloride (4) was prepared from **3** in quantitative yield as described in ref.^[9]

(R)-2-Amino-2-(4-hydroxyphenyl)-1,1-diphenylethanol (**5**)

A 500-mL three-necked flask was equipped with a pressure-equalizing dropping funnel, a reflux condenser with a connection to the combined nitrogen/vacuum line and a magnetic stirrer. The flask was charged with magnesium turnings (14.6 g, 0.60 mol) and a few crystals of iodine and closed with a septum. The air in the flask was replaced by nitrogen, anhydrous THF (50 mL) was added in a countercurrent of nitrogen, and the mixture was stirred until the color had disappeared. Bromobenzene (2 mL) was added through the dropping funnel and the magnesium turnings were heated by a heat gun to start the reaction. A solution of bromobenzene (91.2 g, 61.2 mL, 0.58 mol) in anhydrous THF (200 mL) was added through the dropping funnel at such a rate that the solution kept boiling gently. Thereafter, the mixture was refluxed for 1 h and cooled to 0 °C. Under a countercurrent of nitrogen, **4** (10.0 g, 60.0 mmol) was added in one portion. The suspension was stirred for 20 h at 0 °C and allowed to warm up to room temperature. Then, the mixture was poured into ice (400 g) and the precipitate was dissolved by the addition of 18 % hydrochloric acid (80 mL). The organic solvent was removed in a rotary evaporator and the hydrochloride of **5**, precipitating thereby, was filtered and washed with diethyl ether (100 mL). The precipitate was suspended in 150 mL of a 2 M solution of NaOH in methanol. After filtration, water (200 mL) was added to the filtrate. Under vigorous stirring, the solution was brought to pH 7 by careful addition of 4 M hydrochloric acid. Methanol was removed in a rotary evaporator, the precipitate formed thereby was filtered and recrystallized from a mixture of ethanol, ethyl acetate, and water (3:2:1). The product was dried in an oil-pump vacuum to give colorless **5**; yield: 6.9 g (48 %); mp 195–196 °C; [α]_D²⁰: +214 (*c* 1, THF); IR (KBr): ν = 3510, 3060, 3054, 2582, 1614, 1517, 1449, 1249, 1177, 1033, 836, 748, 700 cm^{–1}; ¹H NMR (500 MHz, THF-*d*₈): δ = 2.65 (s, 2H, NH₂), 4.95 (s, 1H, OH), 5.04 (s, 1H, 2-H), 6.42 (d, *J* = 8.5 Hz, 2H, aromatic H), 6.90–7.98 (m, 5H, aromatic H), 7.20–7.31 (m, 5H, aromatic H), 7.75 (d, *J* = 7.3 Hz, 2H, aromatic H), 7.92 (s, 1H, phenolic OH); ¹³C NMR

(125 MHz, THF-*d*₈): δ = 51.5 (C-2), 63.8 (C-1), 116.2–134.3 (aromatic C), 142.7–144.4 (aromatic *ipso* C), 159.0 (phenolic C); MS (FAB, NBA): *m/z* (%) = 306 (33) [M+1]⁺, 305 (6) [M]⁺, 212 (21), 195 (25), 167 (22), 120 (35), 107 (78), 89 (93), 77 (100); anal. calcd. for C₂₀H₁₉NO₂: C 78.60, H 6.47, N 4.54; found: C 78.66, H 6.27, N 4.59.

(R)-2-Amino-2-(4-benzyloxyphenyl)-1,1-diphenylethanol (**6a**)

A 10-mL two-necked flask was equipped with a connection to the combined nitrogen/vacuum line and a magnetic stirrer and charged with **5** (2.0 g, 6.6 mmol). The flask was closed with a septum, the air in the flask was replaced by nitrogen, and 10 mL of anhydrous DMF were injected by syringe. A 95 % suspension of sodium hydride in mineral oil (0.158 g, 6.6 mmol) was added under vigorous stirring in a countercurrent of nitrogen. The mixture was stirred at room temperature until the sodium hydride had completely disappeared and a bright yellow solution had formed (about 1 h). Benzyl bromide (0.78 mL, 6.6 mmol) was injected and the mixture was stirred at room temperature for 5 h. After addition of water (100 mL), the mixture was extracted three times with chloroform (50 mL portions). The combined organic layers were dried with magnesium sulfate, and the solvent was removed in a rotary evaporator. The residual viscous yellow liquid crystallized upon addition of water (25 mL). The solid was recrystallized from ethanol and dried in an oil pump vacuum to give **6a**; yield: 2.3 g (87 %); mp 158–159 °C; [α]_D²⁰: +205 (*c* 1, chloroform). IR (KBr): ν = 3380, 3059, 3031, 2887, 1612, 1514, 1254, 1178, 748, 700 cm^{–1}; ¹H NMR (500 MHz, CDCl₃): δ = 1.58 (s, 2H, NH₂), 4.65 (s, 1H, OH), 5.00 (s, 1H, 2-H), 5.01 (s, 2H, PhCHO), 6.75 (d, *J* = 7.9 Hz, 1H, aromatic H), 7.08–7.45 (m, 15H, aromatic H), 7.76 (d, *J* = 7.3 Hz, 2H, aromatic H); ¹³C NMR (125 MHz, CDCl₃): δ = 70.3 (C-1), 72.1 (PhCH₂O), 103.7 (C-2), 114.2–130.0 (aromatic C), 137.4, 148.1, 149.4 (aromatic *ipso* C), 158.3 (aromatic *ipso* C); MS (FAB, NBA): *m/z* (%) = 397 (5) [M+1]⁺, 396 (11) [M]⁺, 379 (50), 303 (28), 212 (45), 195 (33), 167 (26), 105 (39), 91 (100), 77 (52); anal. calcd. for C₂₇H₂₅NO₂: C 82.00, H 6.37, N 3.54; found: C 81.89, H 6.27, N 3.60.

(R)-2-Amino-2-[4-(toluene-4-sulfonyloxy)phenyl]-1,1-diphenylethanol (**6b**)

A 100-mL two-necked flask was connected to the combined nitrogen/vacuum line, equipped with a magnetic stirrer, charged with **5** (0.62 g, 2.0 mmol), and closed with a septum. The air in the flask was replaced by nitrogen and anhydrous THF (25 mL) was injected. After cooling to –70 °C, a 1.6 M solution of *n*-butyllithium in hexane (1.28 mL, 2.0 mmol) was added. The solution, which turned dark blue, was warmed to –25 °C. A solution of 4-toluenesulfonyl chloride (0.40 g, 2.0 mmol) in anhydrous THF (10 mL) was added slowly by syringe so that the temperature did not exceed –18 °C. In the course of this, the solution turned to yellow. Stirring was continued at –20 °C for 1 h and at 0 °C for 12 h. After the addition of water (45 mL) the mixture was extracted with three 30 mL portions of diethyl ether. The combined organic layers were dried with magnesium sulfate and the solvent was removed in a rotary evaporator. The residual

colorless solid was purified by column chromatography to give **6b**; yield: 0.68 g (74%); mp 163–165°C; R_f =0.35 (*n*-hexane/ethyl acetate, 3:2); $[\alpha]_D^{20}$: +176 (*c* 1, chloroform); ^1H NMR (500 MHz, DMSO- d_6): δ =2.44 (s, 3H, CH₃), 4.96 (s, 1H, 2-H), 5.64 (1H, s, OH), 6.64 (d, J =8.5 Hz, 2H, aromatic H), 6.98–7.36 (m, 10H, aromatic H), 7.45 (d, J =8.2 Hz, 2H, aromatic H), 7.58 (d, J =8.5 Hz, 2H, aromatic H), 7.69 (d, J =7.25 Hz, 2H, aromatic H); ^{13}C NMR (125 MHz, DMSO- d_6): δ =21.6 (CH₃), 60.9 (C-2), 80.3 (C-1), 112.8–130.4 (aromatic C), 145.9 (aromatic C), 147.3–147.6 (aromatic C); MS (FAB, NBA): m/z (%)=482 (7) [M^+ +Na], 460 (29) [$\text{M}+1$]⁺, 443 (30), 329 (13), 307 (39), 289 (27), 276 (100); anal. calcd. for C₂₇H₂₅NO₄S: C 70.57, H 5.48, N 3.05; found: C 70.40, H 5.61, N 3.09.

(*R*)-2-Amino-2-[4-(trifluoromethanesulfonyloxy)phenyl]-1,1-diphenylethanol (**6c**)

A 50-mL two-necked flask was equipped with a magnetic stirrer, connected to the combined nitrogen/vacuum line, charged with an 80% suspension of sodium hydride in mineral oil (0.29 g, 9.5 mmol), and closed with a septum. The air in the flask was replaced by nitrogen, and anhydrous DMF (20 mL) was injected by syringe. The mixture was cooled in an ice bath and a solution of **5** (1.53 g, 5.0 mmol) in anhydrous DMF (25 mL) was slowly added under stirring so that the temperature did not exceed 5°C. Stirring was continued in an ice bath for 3 h. In a counter current of nitrogen, *N*-phenylbis(trifluoromethanesulfonamide) (2.32 g, 6.5 mmol) was added in one portion. The ice bath was removed, and the mixture was stirred at room temperature overnight. The mixture was poured into a saturated solution of sodium carbonate (8 mL) and extracted three times with ethyl ether (50 mL portions). The combined organic layers were dried with magnesium sulfate and the solvent was removed under reduced pressure. The residue was purified by column chromatography to give colorless, solid **6c**; yield: 1.09 g (50%); mp 125–127°C; R_f =0.39 (*n*-hexane/ethyl acetate, 2:1); $[\alpha]_D^{20}$: +188 (*c* 1, chloroform); ^1H NMR (500 MHz, DMSO- d_6): δ =1.97 (s, 2H, NH₂), 5.07 (s, 1H, OH), 5.75 (s, 1H, 2-H), 6.97–7.06 (m, 3H, aromatic H), 7.15–7.38 (m, 9H, aromatic H), 7.71 (d, J =7.9 Hz, 2H, aromatic H); ^{13}C NMR (125 MHz, CDCl₃): δ =61.2 (C-2), 79.5 (C-1), 120 (CF₃), 120.1 (aromatic C), 125.8–130.3 (aromatic C), 140.6, 143.2, 145.8, 148.6 (aromatic *ipso* C); ^{19}F NMR (470 MHz, CDCl₃): δ =−73 (CF₃); MS (FAB, NBA): m/z (%)=438 (68) [$\text{M}+1$]⁺, 420 (90), 343 (10), 307 (38), 289 (26), 254 (100); anal. calcd. for C₂₁H₁₈F₃NO₄S: C 57.67, H 4.51, N 3.20; found: C 57.59, H 4.15, N 3.26.

(*R*)-2-Amino-2-[4-(nonafluorobutanesulfonyloxy)phenyl]-1,1-diphenylethanol (**6d**)

A 50-mL two-necked flask was equipped with a magnetic stirrer, connected to the combined nitrogen/vacuum line, charged with an 80% suspension of sodium hydride in mineral oil (0.23 g, 7.6 mmol), and closed with a septum. The air in the flask was replaced by nitrogen, and anhydrous DMF (40 mL) was added by syringe. The mixture was cooled in an ice-bath, and a solution of **5** (1.22 g, 4.0 mmol) in anhydrous DMF (40 mL) was injected at such a rate that the temperature was kept below 5°C. Stirring was continued at

0°C for 3 h. Then, nonafluorobutanesulfonyl fluoride (1.56 g, 0.94 mL, 5.17 mmol) was added in a countercurrent of nitrogen. The mixture was stirred at room temperature overnight, poured into a saturated solution of sodium carbonate and extracted with three 50 mL portions of diethyl ether. The combined organic layers were dried with magnesium sulfate and the solvent was removed in a rotary evaporator. The residue was purified by column chromatography to give colorless solid **6d**; yield: 1.74 g (74%); mp 113–115°C, R_f =0.47 (*n*-hexane/ethyl acetate, 2:1); $[\alpha]_D^{20}$: +131 (*c* 1, chloroform); ^1H NMR (500 MHz, DMSO- d_6): δ =1.97 (s, 2H, NH₂), 5.07 (s, 1H, OH), 5.74 (s, 1H, 2-H), 6.96–7.05 (m, 3H, aromatic H), 7.14–7.39 (m, 9H, aromatic H), 7.71 (d, J =7.9 Hz, 2H, aromatic H); ^{13}C NMR (125 MHz, DMSO- d_6): δ =61.6 (C-2), 79.9 (C-1), 123.9, 127.0, 130.7 (CF₂), 123 (CF₃), 120.5 (aromatic C), 126.2–130.7 (aromatic C), 140.9, 143.7, 146.2, 149.3 (aromatic *ipso* C); ^{19}F NMR (470 MHz, CDCl₃): δ =−81.1 (CF₃), −109.3, −121.3, −126.3 (CF₂); MS (FAB, NBA): m/z (%)=588 (18) [$\text{M}+1$]⁺, 404 (27), 183 (17), 154 (100), 77 (58); anal. calcd. for C₂₄H₁₈F₉NO₄: C 49.07, H 3.09, N 2.38; found: C 49.12, H 3.17, N 2.34.

(*R*)-2-Amino-2-(biphenyl-4-yl)-1,1-diphenylethanol (**6e**)

Under nitrogen, a mixture containing **6d** (0.88 g, 1.5 mmol), tributylphenylstannane (0.49 mL, 0.55 g, 1.5 mmol), lithium chloride (0.19 g, 4.5 mmol), tetrakis(triphenyl)phosphane (0.045 g, 0.039 mmol), 10 mL of freshly distilled 1,4-dioxane, and a few crystals of 2,6-di-*tert*-butyl-4-methylphenol was heated under stirring at 98–100°C for 23 h. After cooling to room temperature, a 10% solution of ammonium hydroxide (20 mL) was added. The mixture was diluted with diethyl ether and filtered through celite. The filtrate was washed with water and with brine, dried with magnesium sulfate and concentrated under vacuum. The residue was purified by column chromatography to give colorless solid **6e**; mp 193–195°C; R_f =0.4 (*n*-hexane/ethyl acetate, 1:1); $[\alpha]_D^{20}$: +242 (*c* 1, chloroform); ^1H NMR (500 MHz, DMSO- d_6): δ =1.89 (s, 2H, NH₂), 5.08 (s, 1H, OH), 5.68 (s, 1H, 2-H), 6.92–7.08 (m, 3H, aromatic H), 7.21–7.43 (m, 12H, aromatic H), 7.58 (d, J =7.25 Hz, 2H, aromatic H), 7.75 (d, J =7.25 Hz, 2H, aromatic H); ^{13}C NMR (125 MHz, DMSO- d_6): δ =61.9 (C-2), 80.0 (C-1), 126.5–129.5 (aromatic C), 139.6–141.2 (aromatic *ipso* C), 144.2 (aromatic *ipso* C); MS (FAB, NBA): m/z (%)=366 (10) [$\text{M}+1$]⁺; anal. calcd. for C₂₆H₂₃NO: C 85.44, H 6.34, N 3.83; found: C 85.50, H 6.58, N 3.83.

General Procedure for the Enantioselective Reduction of Ketones **7**, **9**, **11** or **13** with Borane-Dimethyl Sulfide in the Presence of Amino Alcohol **6d**

A 25-mL two-necked flask was charged with amino alcohol **6d** (0.059 g, 0.10 mmol), equipped with a magnetic stirrer and a connection to the combined nitrogen/vacuum line and closed with a septum. The air in the flask was replaced by nitrogen. The amino alcohol **6** was dissolved in THF (6 mL) under stirring and a 2M solution of the borane-dimethyl sulfide complex in THF (0.66 mL, 1.32 mmol) was added by syringe. After stirring at room temperature for 24 h, the fresh-

ly distilled ketone (1.00 mmol) was added within 90 min by means of a micro syringe. After stirring for 24 h at room temperature, methanol (2 mL) was added and the solvent was removed in a rotary evaporator. The residue was purified by column chromatography (*n*-hexane/ethyl acetate, 2 : 1 or 1 : 1) and subsequently distilled in a microdistillation apparatus, the receiving flask being cooled in a bath of liquid nitrogen.

According to this protocol, the following alcohols were obtained. Their spectroscopic data are in accordance with those of authentic samples.

(S)-1-Phenylethanol (8): $[\alpha]_{\text{D}}^{20}$: -40.5 (*c* 1.25, methanol); *ee*: 96 % according to GC on a FS-Lipodex A column (Macherey–Nagel; 50 m, 0.25 mm; 90°); (S)-8: t_{R} : 108.8 min; (R)-8: t_{R} : 112.3 min.

(R)-2-Chloro-1-phenylethanol (10): $[\alpha]_{\text{D}}^{20}$: -46 (*c* 1, cyclohexane); authentic sample: -48 .

(S)-1-Indanol (12): $[\alpha]_{\text{D}}^{20}$: -28 (*c* 1, chloroform); authentic sample: -31 ; MTPA ester: $^1\text{H NMR}$: major product: $\delta = 6.38$ (dd, $J = 6.7$ Hz, $J = 3.3$ Hz); minor product: $\delta = 6.35$.

(S)-1,2,3,4-Tetrahydro-1-naphthol (14): $[\alpha]_{\text{D}}^{20}$: -30 (*c* 1, chloroform); authentic sample: -33 ; MTPA ester: $^1\text{H NMR}$: major product: $\delta = 6.17$ (t, $J = 4.1$ Hz); minor product: $\delta = 6.14$.

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