Chiral Borate Esters in Asymmetric Synthesis

Part 2

Asymmetric Borane Reduction of Prochiral Ketones in the Presence of a Chiral Spiroborate Ester

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Asymmetric catalytic activity of the chiral spiroborate esters **1**–**9** with a O_3BN framework (see *Fig. 1*) toward borane reduction of prochiral ketones was examined. In the presence of 0.1 equiv. of a chiral spiroborate ester, prochiral ketones were reduced by 0.6 equiv. of borane in THF to give (*R*)-secondary alcohols in up to 92% ee and 98% isolated yields (*Scheme 1*). The stereoselectivity of the reductions depends on the constituents of the chiral spiroborate ester (*Table 2*) and the structure of the prochiral ketones (*Table 1*). The configuration of the products is independent of the chirality of the diol-derived parts of the catalysts. A mechanism for the catalytic behavior of the chiral spiroborate esters (*R*,*S*)-**2** and (*S*,*S*)-**2** during the reduction is also suggested.

1. Introduction. – Although numerous asymmetric reactions mediated by tricoordinated chiral boron compounds have been reported, asymmetric syntheses catalyzed by tetracoordinated boron compounds have seldom been investigated. *Yamamoto* and coworkers reported asymmetric syntheses catalyzed by a *Brønsted* acid derived from enantiomerically pure [1,1′-binaphthalene]-2,2′-diol and boron compounds [1]. In 2002, *Kanth* and *Brown* reported asymmetric borane reduction in the presence of chiral β-amino alcohol derivatives of 9-borabicyclo[3.3.1]nonane (9-BBN) with a OC_2BN framework [2]. In 2002, we observed that chiral spiroborate esters with three B–O bonds and a N→B coordination bond (*i.e.*, with a O_3BN framework) showed asymmetric catalytic activity in borane reductions of prochiral ketones, imines, oximes, and alkylation of aldehydes [3]. Recently, we disclosed the borane reduction of acetophenone catalyzed by the chiral spiroborate esters (=spiroanhydrides) **1** formed from boric acid (*R*)- or (*S*)-[1,1′-binaphthalene]-2,2′-diyl ester and L-proline [4]. In the present paper, we report asymmetric borane reductions of various prochiral ketones in the presence of the chiral spiroborate esters **1**–**9** (*Fig. 1*).

2. Results and Discussion. – 2.1. *Preamble.* In our preceding paper [4], we have shown that acetophenone was reduced by borane to give (1*R*)-1-phenylethanol in up to 76% ee in the presence of chiral spiroborate esters (*R*,*S*)- or (*S*,*S*)-**1** as catalysts. To examine extensively the asymmetric catalytic activity of chiral spiroborate esters with a O_3BN framework and reveal the law governing the asymmetric catalysis by this class of boron compound, a series of chiral spiroborate esters with a O_3BN framework have been synthesized [5], of which eleven representatives (*Fig. 1*) were used to examine catalysis during borane reduction of prochiral ketones. We found that the stereo-

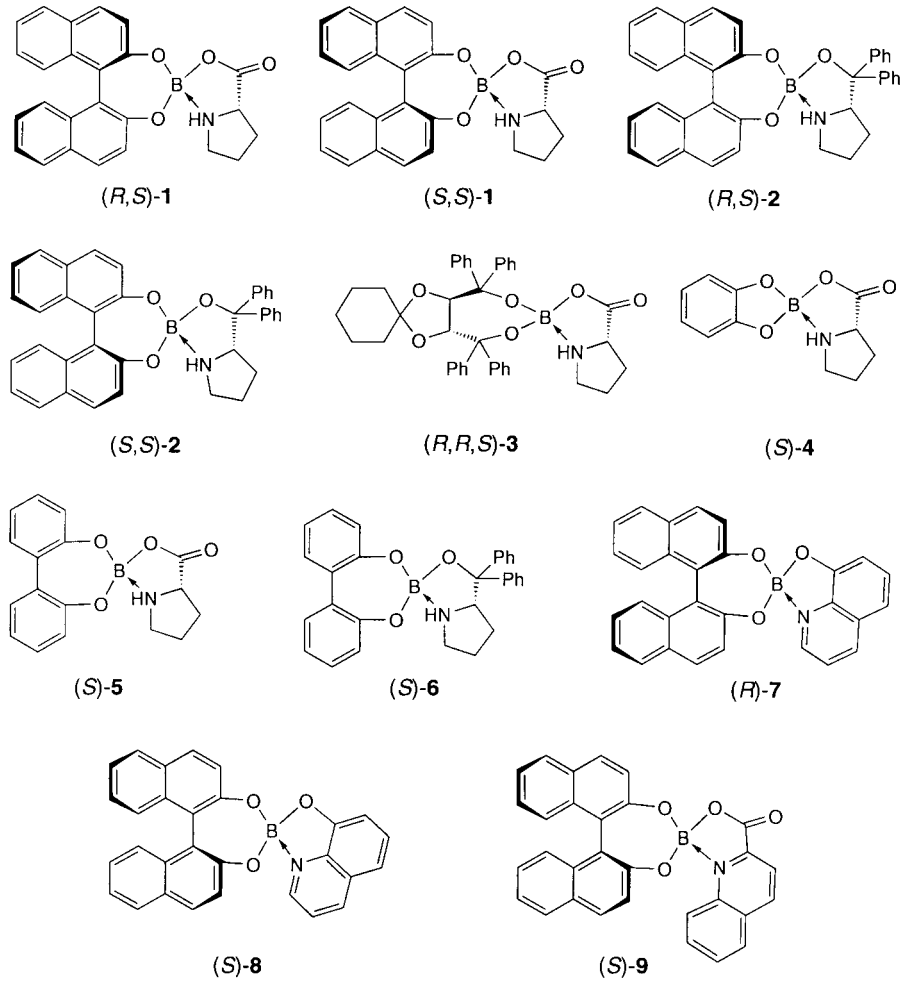
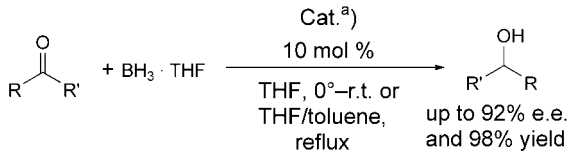


Fig. 1. *Examined chiral spiroborate esters with a O_3BN framework*

selectivity of the reduction was highly dependent on the constituents of the spiroborate esters and the type of prochiral ketones; under appropriate conditions, (*R*)-secondary alcohols in up to 92% ee and 98% yield were obtained (*Scheme 1*).

2.2. *Influence of the Type of Prochiral Ketones on the Stereoselectivity of the Reduction*. Borane reductions of seven prochiral ketones, *i.e.* of pentan-2-one, 4-methylpentan-2-one, 3-methylbutan-2-one, 3,3-dimethylbutan-2-one, acetophenone (=1-phenylethanone), propiophenone (=1-phenylpropan-1-one) and 1-(pyridin-4-yl)ethanone, were examined in the presence of (*R*,*S*)-**1**, (*S*,*S*)-**1**, (*R*,*S*)-**2**, or (*S*,*S*)-**2**. Because the previous investigation indicated better conditions for borane reductions of acetophenone [4], all reductions were performed under the same conditions as for acetophenone. When a prochiral ketone was added to a solution formed from the reaction of 0.1 equiv. of a spiroborate ester and 0.6 equiv. of borane in THF and then

Scheme 1. *Asymmetric Borane Reduction of Prochiral Ketones Catalyzed by Chiral Spiroborate Esters with a O_3BN Framework*

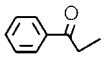
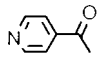


R= Me, R' = Pr, i-Bu, i-Pr, *t*-Bu
R= Ph, R' = Me, Et
R= Me, R' = 4-Py

[a]) For catalysts, see *Fig.* 1.

stirred at 0–5° for 2 h (exception: 20 h for 1-(pyridin-4-yl)ethanone, a secondary alcohol with (*R*)-configuration was obtained in all cases (*Table 1*). This indicated that the configuration of the products is independent of the chirality of the constituents of the catalysts.

Table 1. *Enantiomer Excess* (% ee) *of* (R)*-Secondary Alcohols Obtained from Asymmetric Borane Reduction of Prochiral Ketones Catalyzed by* (R,S)-**1**, (S,S)-**1**, (R,S)-**2**, *and* (S,S)-**2**[a])

							
(*R*,*S*)-**2**	47	50	66	68	92	81	59
(*S*,*S*)-**2**	6	14	32	....	68	31	3
(*R*,*S*)-**1**	53	....	64	....	76	53	3
(*S*,*S*)-**1**	23	42	64	....	60	49	11

[a]) All reductions were performed in a ketone/borane/catalyst molar ratio of 1 : 0.6 : 0.1 in THF at 0–5° for 2 h; exception: 20 h for 1-(pyridin-4-yl)ethanone and gave (*R*)-secondary alcohols in high yield. The ee of (*R*)-secondary alcohols were obtained by comparison with the maximum of specific rotations (see [6–12], resp.) and analysis of the ^{1}H-NMR spectra of diastereoisomeric phosphite esters formed with the phosphorochloridite of (4*R*,5*R*)-*trans*-2,2-dimethyl-$\alpha,\alpha,\alpha',\alpha'$-tetraphenyl-1,3-dioxolane-4,5-dimethanol as a chiral derivatizing agent [3][13].

In the case of borane reduction of aliphatic ketones, the stereoselectivity increased with increasing size of the alkyl group; in contrast, in the case of borane reduction of phenyl-substituted ketones, the stereoselectivity descreased with increasing size of the alkyl group (*Table 1*). The borane reduction of 1-(pyridin-4-yl)ethanone mostly showed very low asymmetric induction, which can be explained by a B-coordination competition between the O-atom of the ethanone moiety and the N-atom of the pyridine ring, the latter being more efficient. Thus, the carbonyl group of 1-(pyridin-4-yl)ethanone was reduced by borane in a relatively free state, *i.e.*, usually there was no dependence on the chirality of the catalyst, and 1-(pyridin-4-yl)ethanol was obtained in low ee.

2.3. *Influence of the Constituents of the Chiral Spiroborate Esters on the Stereoselectivity of the Reduction*. Acetophenone and propiophenone were selected as

substrates to study the influence of the constituents of the chiral spiroborate esters on the stereoselectivity of the borane reduction. The results obtained in the presence of different chiral spiroborate esters (*Table 2*) established that all the chiral spiroborate esters containing a chiral chelating agent showed asymmetric catalytic activity toward borane reduction of prochiral ketones whether the diol-derived constituents of the spiroborate esters were chiral or achiral; but lower ee of the (*R*)-secondary alcohols were obtained when these diol-derived parts were achiral. For the spiro[6.4] type of chiral spiroborate esters in which the diol-derived part and chelating agent were both chiral, the enantiomerically pure [1,1′-binaphthalene]-2,2′-diol derivatives **1** and **2** yielded higher ee than the (2*R*,3*R*)-α,α,α',α'-tetraphenyl-1,4-dioxaspiro[4.5]decane-2,3-dimethanol (*R*,*R*,*S*)-**3**, whereas, for the chiral spiroborate esters containing the [1,1′-biphenyl]-2,2′-diyl and pyrrolidine moieties, the asymmetric catalytic activity of (L)-proline derivative (*S*)-**5** was higher than that of (2*S*)-α,α-diphenylpyrrolidine-2-methanol derivative (*S*)-**6**. For the chiral spiroborate esters containing the [1,1′-binaphthalene]-2,2′-diyl and pyrrolidine moieties, asymmetric catalytic activity of (2*S*)-α,α-diphenylpyrrolidine-2-methanol derivatives **2** was higher than that of L-proline derivatives **1** and the derivatives (*R*,*S*)-**1** and (*R*,*S*)-**2** of (1*R*)-[1,1′-binaphthalene]-2,2′-diol showed stronger chiral induction than those of (1*S*)-[1,1′-binaphthalene]-2,2′-diol. It was also observed that the chiral spiroborate esters **7**–**9**, formed from a chiral diol and a chelating agent containing a quinoline (pyridine) ring, hardly showed catalytic activity toward the borane reductions. It is obvious that this is due to π-electron transfer of the heterocycle to the B-atom in those molecules. Thus, it appears that asymmetric catalytic activity of the chiral spiroborate esters is mainly determined by the chirality of the chelating-ring moiety, and an appropriate chiral diol-derived constituent enhances the asymmetric catalytic ability of the chiral spiroborate esters.

Table 2. *Enantiomer Excess* (% ee) *of* (R)*-Secondary Alcohols Obtained from Asymmetric Borane Reduction of Acetophenone and Propiophenone in the Presence of Different Chiral Spiroborate Ester Catalysts*[a])

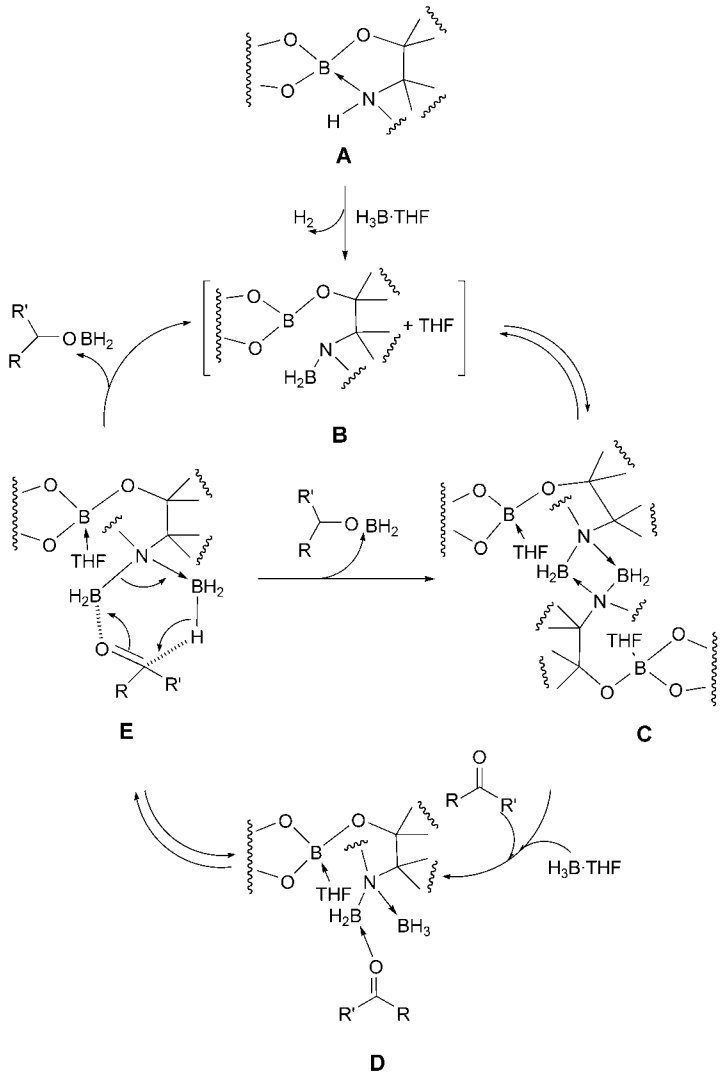
	(*R*,*S*)-**1**	(*S*,*S*)-**1**	(*R*,*S*)-**2**	(*S*,*S*)-**2**	(*R*,*R*,*S*)-**3**	(*S*)-**4**	(*S*)-**5**	(*S*)-**6**	(*R*)-**7**	(*S*)-**8**	(*S*)-**9**
	76	60	92	68	56	33	49	26	0.3	0.5	0.3
	53	49	81	31	....	....	52	31	0	0	0

[a]) For the exper. conditions and ee determination, see *Footnote a* in *Table 1*. The (*R*)-secondary alcohols were obtained in high yield, except for the reactions mediated by chiral spiroborate esters containing a quinoline ring.

2.4. *Mechanism of Borane Reduction Catalyzed by Chiral Spiroborate Esters* (R,S)-**2** *and* (S,S)-**2**. The spiroborate esters in the presence of borane in THF formed a homogeneous solution, and 1 equiv. of H_2 gas evolved when a $BH_3 \cdot THF$ solution was added to (*R*,*S*)-**2** or (*S*,*S*)-**2**. Obviously, H_2 is generated from the reaction of borane and the H-atom at the N-atom of the pyrrolidine ring (see *Scheme 2*), implying that the N–H bond of (*R*,*S*)-**2** or (*S*,*S*)-**2** is activated due to formation of an inner N→B coordination bond. The ^{11}B-NMR spectra ($CDCl_3$) of (*S*,*S*)- and (*R*,*S*)-**2** (*Fig. 2*) showed a single peak at δ(B) +8.62 and 8.37, respectively, which is characteristic of boron compounds with a O_3BN framework (see **A** in *Scheme 2*). On addition of a THF

solution of $BH_3 \cdot THF$ to the above $CDCl_3$ solutions, 2-*s* at δ(B) 17.62 and 8.86 for (*S*,*S*)-**2** and at δ(B) 17.72 and 8.60 for (*R*,*S*)-**2** appeared, respectively. The signal at δ(B) 17.67 ± 0.05 could be attributed to a common borate ester **B** with a O_3B framework, indicating that the B ← N bond of (*S*,*S*)-**2** or (*R*,*S*)-**2** has been broken (*Scheme 2*). However, the signal at δ(B) *ca.* 8.73 ± 0.13 indicates that the borate ester with a O_3B framework was in a new tetracoordinated environment, and in this boron complex, electron donation of the new ligand is lower than that of the pyrrolidine ring; this suggests that the signal is due to the complex **C** of the borate ester (with a O_3B

Scheme 2. *Possible Mechanism of Asymmetric Borane Reduction of Prochiral Ketones Catalyzed by (*R,S*)-***2*** and (*S,S*)-***2***



framework) with THF. It seems that there is an equilibrium between the tricoordinated borate ester **B** and the tetracoordinated boron complex **C**. Moreover, a *m* was observed in the region of δ 0 to −2.65, which is attributed to an aminoborane dimer with a $(NBH_2)_2$ framework (see **C**); but no signal for an amine·borane (with a $N \rightarrow BH_3$ framework) was observed (at *ca.* −20 ppm), indicating that the presence of excess borane cannot decompose the aminoborane dimer. When a prochiral ketone is added to the system, the concomitant action of the ketone and borane decomposes the dimer (→ **D**), and a six-membered cyclic transition state **E** is formed. In the sequential step, elimination of resulting chiral (alkyloxy)borane occurs, and the catalytic cycle is completed. It appears that, in the mechanism of the asymmetric catalytic borane reduction of prochiral ketones, the chiral spiroborate esters (*S*,*S*)-**2** and (*R*,*S*)-**2** with a O_3BN framework not only behave quite differently from those with a C_2OBN framework, but there is also a remarkable difference between (*S*,*S*)-**1** and (*R*,*S*)-**1**, which have the same framework.

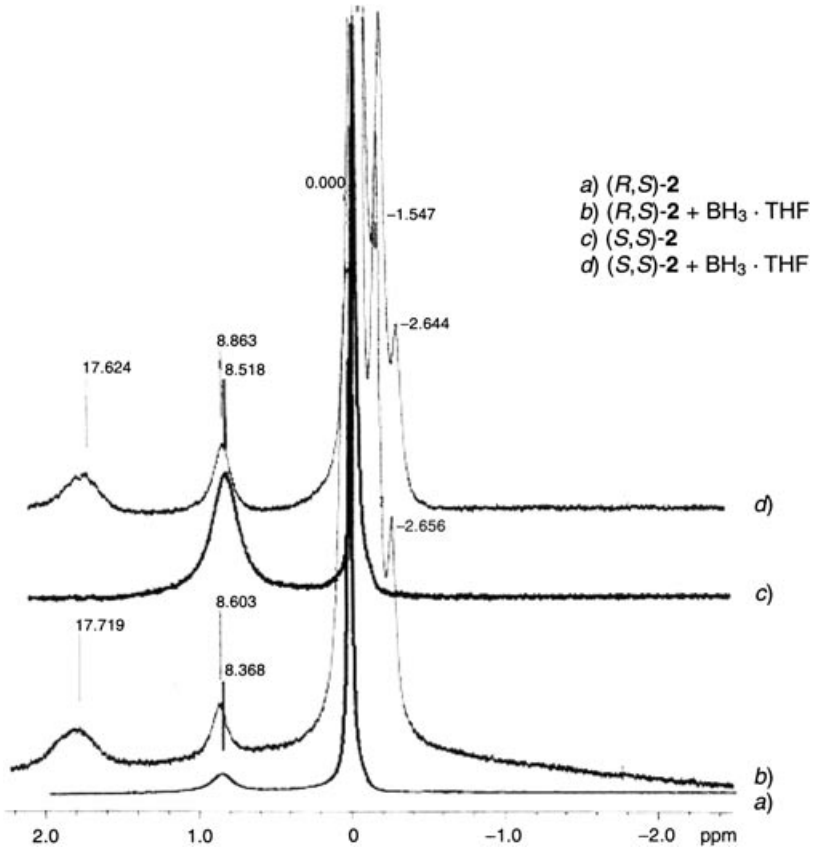


Fig. 2. *^{11}B-NMR Spectra* ($CDCl_3$, 300 MHz) *of* (S,S)-**2** *and* (R,S)-**2** *and of their mixture with a THF solution of borane*

3. Conclusions. – A new class of chiral catalyst for borane reduction of prochiral ketones was found. In the presence of 0.1 equiv. of a chiral spiroborate ester with a O_3BN framework, prochiral ketones were reduced by 0.6 equiv. of borane in THF to give chiral secondary alcohols in up to 92% ee and 98% isolated yields. The asymmetric catalytic activity of the chiral spiroborate esters depended heavily on their constituents. All the reductions gave products with the (*R*) configuration, regardless of the chirality of the diol-derived parts in the catalysts. The structures of the prochiral ketones influenced considerably the stereoselectivity of the reduction.

Chiral spiroborate esters, with a O_3BN framework are very stable to hydrolysis and oxidation, in contrast to tricoordinated oxazaborolidine derivatives and ordinary borate esters, which generally are susceptible to moisture in air. Therefore, it is quite convenient to use chiral spiroborate esters with a O_3BN framework as a catalyst for asymmetric borane reductions of prochiral ketones.

Financial support of the *National Natural Science Foundation of China* (Projects 29972033 and 20372053) is greatly appreciated.

Experimental Part

General. The chiral spiroborate esters were prepared according to [5]. The (2*S*)-α,α-diphenylpyrrolidine-2-methanol [14], (2*R*,3*R*)-α,α,α′,α′-tetraphenyl-1,4-dioxaspiro[4.5]decane-2,3-dimethanol [15], and the THF soln. of $BH_3 \cdot THF$ [16] were prepared according to the literature. All the selected prochiral ketones were commercially available, except for 3,3-dimethylbutan-2-one, which was prepared according to [17]; they were purified by distillation over CaH_2 and then dried over 4 Å molecular sieve. Other reagents were purchased. M.P.: *VEB-Wagetechnik-Rapio-PHMK05* instrument; not corrected. Optical rotatioins: *PE-341* polarimeter; for the determination of ee, see *Table 1*. IR Spectra: *Testscan Shimadzu FTIR 8000*; in KBr; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{11}B-NMR Spectra: *Varian Mercury VX 300*; δ values in ppm rel. to Me_4Si and $BF_3 \cdot OEt_2$, resp., *J* in Hz.

Asymmetric Borane Reduction of Prochiral Ketones: Representative Procedure. Under Ar, 0.81M $BH_3 \cdot THF$ in THF (4.5 ml, 3.6 mmol) was added by syringe to (*R*,*S*)-**2** (0.328 g, 0.6 mmol) at r.t., and the mixture was stirred for 20 min. Then the mixture was cooled to 0–5°, acetophenone (6 mmol, 0.7 ml) was added *via* syringe with stirring, and the mixture was kept for 2 h at 0–5°. After evaporation of THF, 2M HCl (20 ml) and Et_2O (20 ml) were added to the residue. The mixture was stirred and the solid filtered off: recovered (2*S*)-α,α-diphenylpyrrolidine-2-methanol hydrochloride. The aq. phase of the mother liquor was extracted with Et_2O (15 ml × 3) and the combined org. phase washed with 2M NaOH to remove (1*R*)-[1,1′-binaphthalene]-2,2′-diol. The Et_2O soln. was then washed successively with sat. NH_4Cl soln., sat. NaCl soln., and H_2O, dried (Na_2SO_4), and evaporated and the oil distilled under reduced pressure: *(1R)-1-phenylethanol* (0.68 g, 93%). $[\alpha]_D^{20} = +48.2$ ($c = 2.65$, in CH_2Cl_2); 92% ee ([10]: $[\alpha]_D^{23} = -52.5$ ($c = 2.52$, CH_2Cl_2). IR: 3363*s* (v.br., OH). ^{1}H-NMR (300 MHz, $CDCl_3$, 25°): 1.65 (*d*, *J* = 9.0, Me); 4.22 (*s*, OH); 4.98 (*q*, *J* = 9.0, H–C(1)); 7.54 (*s*, 5 arom. H).

Under similar conditions, reductions of other prochiral ketones catalyzed by chiral spiroborate esters (*R*,*S*)-**1**, (*S*,*S*)-**1**, (*S*,*S*)-**2**, (*R*,*R*,*S*)-**3**, (*S*)-**4**, (*S*)-**5**, or (*S*)-**6** gave (*R*)-secondary alcohols in high yield. For ee, see *Tables 1* and *2*.

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Received February 18, 2004