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Spiroborate esters in the borane-mediated asymmetric synthesis of pyridyl and related heterocyclic alcohols

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Abstract—The effectiveness of several spiroborate ester catalysts was investigated in the asymmetric borane reduction of 2-, 3-, and 4-acetylpyridines under different reaction conditions. Highly enantiomerically enriched 1-(2-, 3-, and 4-pyridyl)ethanols and 1-(heterocyclic)ethanols were obtained using 1–10% catalytic loads of the spiroborate **5** derived from diphenylprolinol and ethylene glycol.

1. Introduction

Enantiopure secondary alcohols are key intermediaries in the synthesis of a large number of pharmaceutical products.[1,2] In particular, non-racemic alcohols (or their derived amines) containing heterocyclic fragments are known for their biological activity.[3–5] The borane-mediated reduction of prochiral ketones catalyzed by organoboranes, specifically the well-known 1,3,2-oxazaborolidines,[6–8] have become the preferred approach to obtain non-racemic alcohols due to their high enantioselectivity, predictable absolute stereochemistry, ease of handling and operation, and low environmental impact. However, ketones containing a heteroatom can form borane complexes that not only decrease the borane source but also compete with the enantioselective carbonyl reduction.[5] Acetylpyridines were reduced with borane employing 20 mol % of *B*-Me CBS catalyst, but the process resulted in a low selectivity (<52% ee). A stoichiometric amount of catalyst increased the % ee only modestly.[9] Masui[10] introduced a more reactive oxazaborolidine system generated in situ from 10% diphenyl prolinol and trimethylborate and successfully reduced 3- and 4-acetyl heteroaryl ketones with high to excellent enantioselectivity. However, to achieve good selectivity for the 2-acetyl analogues, a stoichiometric amount of the aminoalcohol was required. In related work, protection of the pyridine nitrogen by a methyl or allylic group significantly increased the enantioselectivity of non-enolizable diaryl- or pyridylaryl ketones.[11]

Recently, we reported the synthesis of a series of stable spiroborate esters derived from non-racemic 1,2-aminoalcohols and ethylene glycol. These compounds, shown in Figure 1, were fully characterized by ^{1}H, ^{13}C, and ^{11}B NMR, HRMS, IR, specific rotation, and mp.[12] All exhibited high efficiency and enantioselectivity as catalysts for the borane-mediated asymmetric reduction of acetophenone.

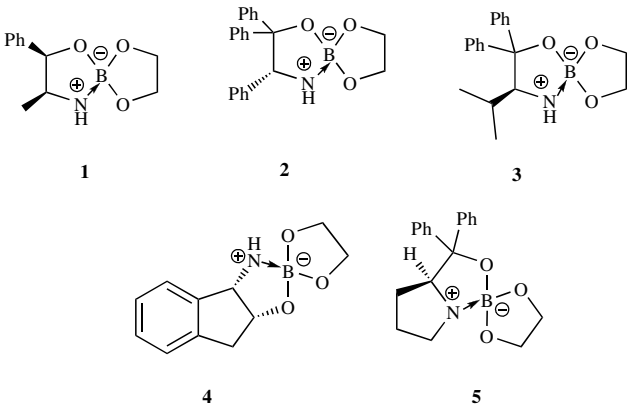

Figure 1. Chiral spiroborates derived from non-racemic 1,2-aminoalcohols.

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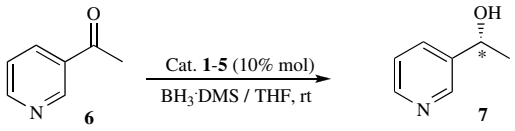
Herein, we report a systematic study of the asymmetric borane-mediated reduction of acetylpyridines and related heterocyclic ketones using the spiroborate esters **1**–**5** as catalysts. These spiroborates are crystalline compounds that can be stored for long periods of time (>1 y). Moreover, spiroborate **5** was exposed to moist air at 25 °C for over 24 h, without significant hydrolysis or decomposition being observed by ^{1}H, ^{13}C, and ^{11}B NMR analysis.

2. Results and discussion

Initially, we studied the asymmetric reduction of 3-acetylpyridine **6** using spiroborates **1**–**5**. The reduction was carried out with BH_3–SMe_2 (1.6 equiv) and 10 mol % of the catalyst at room temperature. The enantiopure 1-(3-pyridyl)ethanol **7** was isolated after the reaction mixture was quenched with methanol at 0 °C, left overnight at reflux temperature, concentrated under vacuum, and purified by column chromatography on deactivated aluminum oxide (method a). The results are summarized in Table 1.

Although catalysts **1**–**4** (entries 1–4) provided good enantioselectivities (i.e., >90% ee), spiroborate **5** was particularly effective, (99% ee) for the reduction of **6** (entry 5).

Table 1. Reduction of 3-acetylpyridine with spiroborate esters **1**–**5** as catalysts in THF at 25 °C using BH_3–SMe_2



Entry	Cat.	mol %	Yield (%)	ee[a] (%)	Conf.
1	**1**	10	89	91	(*R*)-(+)
2	**2**	10	85	96[b]	(*S*)-(−)
3	**3**	10	94	96[c]	(*R*)-(+)
4	**4**	10	88	92	(*S*)-(−)
5	**5**	10	80	99	(*R*)-(+)

[a] By GC of *O*-acetyl derivatives on a CP-Chiralsil-DexCB column.
[b] By GC on a chiral column.
[c] By ^{31}P NMR of phosphonate (CDA).[14]

Several studies were carried out to determine the minimum effective catalyst loading, the best reaction temperature and solvent, as well as borane source. For these studies, we chose to employ 3-acetylpyridine and spiroborate **1**, which is derived from the inexpensive and commercially available, norephedrine. The optimal amount of **1** was determined through the reduction of 3-acetylpyridine with BH_3–SMe_2 (1.6 equiv) by varying the amount of catalyst from 0.1 to 20 mol % at 25 °C. The results are shown in Table 2. The reduction of 3-acetylpyridine with 20 mol % of catalyst **1** afforded the corresponding alcohol in 91% ee and 84% isolated yield (entry 1). Decreasing the catalyst to 1 mol % slightly decreased the selectivity to 87% ee (entry 5). When smaller amounts of catalyst (>1 mol %) were used, the isolation process was more convenient by vacuum distillation in a Kugelrohr apparatus (method b), usually increasing the chemical yield.

Table 2. Studies on the reduction of 3-acetylpyridine employing different catalytic loads of **1**

Entry	Catalyst **1** (mol %)	Yield (%)	ee[c] (%)
1	20	84[a]	91
2	10	89[a]	91
3	5	94[a]	90
4	2.5	95[a]	89
5	1	93[b]	87
6	0.5	93[b]	84
7	0.25	96[b]	81
8	0.1	91[b]	65

[a] Purified by column chromatography.
[b] Purified by distillation.
[c] By GC of *O*-acetyl derivative on a CP-Chiralsil-DexCB column.

To illustrate the cut-off effect for catalyst **1**, the correlation curve between the amount of catalyst and the enantiopurity of 1-(3-pyridyl)ethanol is presented in Figure 2.

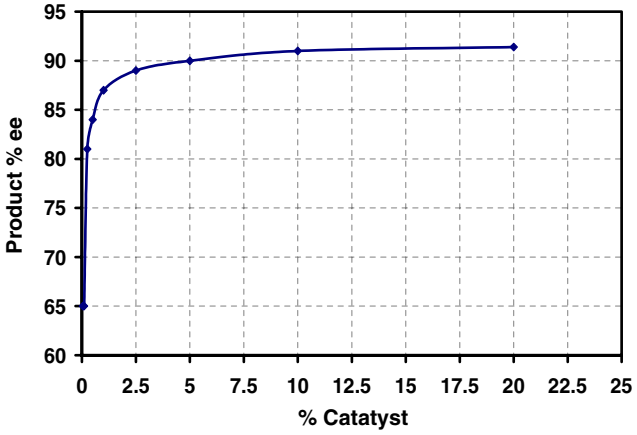


Figure 2. Amount of catalyst **1** versus % ee of 1-(3-pyridyl)ethanol.

Solvents play a key role in the degree of enantioselectivity achieved by the oxazaborolidine catalyzed borane-mediated reductions.[6,7] Therefore, we studied the 3-acetylpyridine reduction in different solvents using only 1 mol % of spiroborate ester **1** to enhance the differences in enantioselectivity. As shown in Table 3 (entry 1), THF was the most effective solvent in terms of chemical yield and enantioselectivity. Less polar solvents such as dichloromethane and toluene led to a decrease in the enantioselectivity of the reaction.

Table 3. Solvent effects on the reduction of 3-acetylpyridine with 1 mol % of catalyst **1**

Entry	Solvent	Yield[a] (%)	ee[b] (%)
1	THF	93	87
2	Dioxane	87	84
3	*t*-Butylmethylether	93	71
4	CH_2Cl_2	89	63
5	Toluene	65	61

[a] Isolated yield.
[b] By GC of *O*-acetyl derivative on a CP-Chiralsil-DexCB column.

Temperature and a differing borane source are also critical factors in the enantioselectivity of carbonyl and oxime reductions.[6,12,13] To amplify these changes, the reduction of

Table 4. Effect of temperature and different borane sources on the reduction of 3-acetylpyridine in THF with 0.5 mol % of catalyst **1**

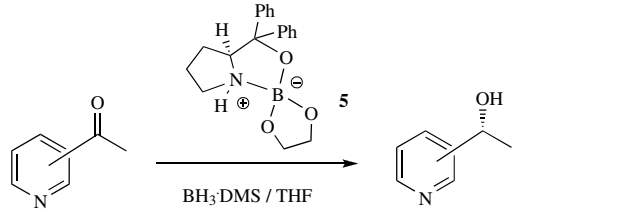
Entry	Reaction conditions	ee[a] (%)
1	BH_3–SMe_2, 0 °C	61
2	BH_3–SMe_2, 50 °C	71
3	BH_3–SMe_2, 25 °C	84
4	BH_3–THF,[b] 25 °C	15
5	BH_3–THF,[c] 25 °C	65
6	BH_3–DEA, 25 °C	65

[a] Determined by GC of *O*-acetyl derivatives.
[b] Borane was stabilized with 0.005 M $NaBH_4$.
[c] Borane was stabilized with <0.005 M *N*-isopropyl *N*-methyl-*tert*-butyl amine.

3-acetylpyridine was performed with 0.5 mol % spiroborate **1** in THF. The results are summarized in Table 4. Optimal selectivity was achieved at 25 °C in THF using BH_3–SMe_2 (entry 3, 84% ee). The use of BH_3–THF stabilized with $NaBH_4$ (entries 4) resulted in a dramatic decrease in the enantioselectivity.[7,15]

Further studies were extended to the reduction of the 2-, 3-, and 4-acetylpyridines with catalyst **5**. The results for the 3, and 4-acetylpyridines are shown in Table 5. Initially, the solvent dilution effect on the degree of selectivity was determined for the reduction of 3-acetylpyridine with 1 mol % of spiroborate ester **5**. When the catalyst was diluted ten times, the enantiomeric excess dropped from 98% to 82% ee.

Table 5. Enantioselective reduction of 3- and 4-acetylpyridine with catalyst **5**



(*R*)-1-(3-pyridyl)ethanol **7**
(*R*)-1-(4-pyridyl)ethanol **8**

Entry	Cat. **5** (mol %)	Pyridine	Yield (%)	ee[a] (%)
1	10	3-Acetyl	80	99
2	5	3-Acetyl	93	99
3	2.5	3-Acetyl	91	98
4	1.0	3-Acetyl	96	98
5	0.5	3-Acetyl	93	94
6	10	4-Acetyl	88	99
7	2.5	4-Acetyl	95	99
8	1	4-Acetyl	92	99

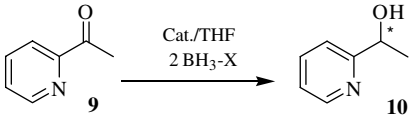
[a] By GC of *O*-acetyl derivatives on a chiral column.

The reduction of 3-, and 4-acetylpyridines with spiroborate **5** was successfully performed with less than 5 mol % providing the enantiopure pyridyl ethanols (>98% ee, Table 5, entries 4 and 8) in excellent yield. Remarkably, the reduction of 4-acetyl pyridine at 25 °C in THF using BH_3–SMe_2 afforded 99% ee even with 1 mol % of catalyst. In addition, using 10% catalyst **3** for the reduction of 3-, and 4-acetylpyridine, afforded also high enantioselectivity: 97.2% ee and 96.4% ee, respectively, determined by ^{31}P NMR analysis of the phosphonate derivatives, which were prepared by the Alexakis method.[14]

The asymmetric borane reduction of 2-substituted heteroaryl ketones is more challenging since borane complexed to the pyridyl nitrogen can reduce the carbonyl group through an intramolecular process, thereby decreasing the enantioselectivity of the reaction. Initially, 2-acetylpyridine **9** was reduced with 0.1 equiv of catalyst **1** and 2 equiv of borane–SMe_2 in THF at room temperature.

Quenching the reaction mixture with methanol (procedure a) for the isolation of 1-(2-pyridyl) ethanol **10** was not effective, perhaps, due to the formation of the stable alkoxyborane complexes. The product was successfully obtained after acid hydrolysis and continuous extraction from the aqueous phase for 3 days with diethyl ether. Nevertheless, the isolated yield was modest. The selectivity was also low, even when 1 equiv of spiroborate **1** was used (Table 6, entries 1–3). Several electrophiles, such as TMSCl, BF_3, $B(OMe)_3$, and BEt_3, were employed to protect the pyridyl nitrogen. The enantioselectivity, however, was not improved and other side products were observed. The reduction of 2-acetyl pyridine with 1 equiv of catalyst **5** and 2 equiv of borane–SMe_2 achieved 93% ee (entry 7). An attempt was made to use the catalyst **5** more efficiently by adding a second load of 2-acetylpyridine after the initial asymmetric reduction was performed, before quenching the reaction. Unfortunately, the enantioselectivity dropped from an initial 93% ee to 58% ee. Borane–DEA and catalyst **5** afforded 78% ee (entry 8). Surprisingly, when the reducing reagent was BH_3–DEA, the absolute configuration of the product was (*S*), the opposite compared to that obtained with borane–SMe_2. Since alcohol **10** is water-soluble, the chemical yield was improved by its isolation as its acetyl ester (entries 6 and 7).

Table 6. Enantioselective reduction of 2-acetylpyridine using spiroborates **1** and **5** as catalysts



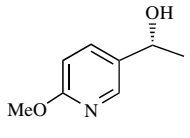
9 **10**

Entry	Catalyst	mol % catalyst	Reagent	Yield (%)	% ee[a], (conf.)
1	**1**	10	BH_3–SMe_2	59	8 (*R*)
2	**1**	25	BH_3–SMe_2	54	16 (*R*)
3	**1**	100	BH_3–SMe_2	58	40 (*R*)
4	**5**	10	BH_3–SMe_2	—	10 (*R*)
5	**5**	50	BH_3–SMe_2	56	58 (*R*)
6	**5**	100	BH_3–SMe_2	82[b]	93 (*R*)
7	**5**	100	BH_3–DEA	79[b]	78 (*S*)

[a] By GC on a chiral column (CP-Chiralsil-DexCB) of *O*-acetate.
[b] The product was isolated as an *O*-acetate derivative.

Other important heteroaryl ketones were reduced with borane employing the spiroborate **5** catalyst to expand the scope of the reaction. The results are presented in Table 7. The 5-acetyl-2-methoxypyridine was effectively reduced with only 1 mol % of catalyst **5** (98% ee, entry 1). The

Table 7. Enantioselective reduction of other heterocyclic ketones using spiroborates **3** and **5** as catalysts



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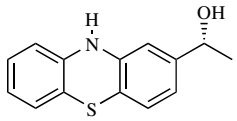

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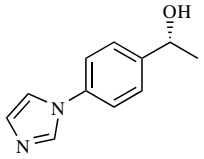

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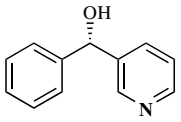

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Entry	Substrate	Catalyst	Prod	mol %	Yield (%)	ee[a] (%)
1	5-Acetyl-2-methoxy pyridine	**5**	**11**	1	77	98[b]
2	2-Acetylphenothiazine	**5**	**12**	1	94	94
3	2-Acetylphenothiazine	**5**	**12**	10	97	>99
4	2-Acetylphenothiazine	**3**	**12**	10	95	>99
5	4′-(Imidazol-1-yl)acetophenone	**5**	**13**	1	85	90
6	4′-(Imidazol-1-yl)acetophenone	**5**	**13**	10	76	92
7	3-Benzoylpyridine	**5**	**14**	10	83	83

[a] By ^{31}P NMR of phosphonate (CDA) derivative.[14]
[b] By GC of *O*-acetyl derivatives on a chiral column.

initial reduction of 2-acetylphenothiazine using 1 mol % of catalyst **5** afforded 94% ee, but with 10 mol % of catalyst provided highly enantiopure alcohol **12** (>99% ee). Interestingly, spiroborate ester **3** derived from (*S*)-diphenyl valinol also provided **12** with similarly high selectivity. In the reduction of 4′-(imidazol-1-yl) acetophenone with 10 mol % of catalyst **5**, the enantiomeric excess of alcohol **13** increased slightly to 92%. The solubilities of these large heterocyclic compounds play a crucial role since they require more dilute solutions which affects the effectiveness of the catalyst. The reduction of 3-benzoylpyridine with 10 mol % of **5** produced (*R*)-phenyl pyridyl methanol **14** in good yield with 83% ee (entry 7).

3. Conclusion

Prochiral ketones containing heteroaromatic fragments undergo asymmetric reduction with a high degree of enantioselectivity using the novel spiroborates derived from non-racemic 1,2-amino alcohols. This work demonstrates that these crystalline spiroborates can be successfully used as highly efficient chiral transfer reagents employing only 1 mol % of the catalyst in some cases. The synthesis of important enantiopure alcohols with heterocyclic groups was also achieved in high chemical yield by a rapid and practical procedure for small and potentially large-scale industrial use.

4. Experimental

All reactions were performed in oven-dried glassware (120 °C) under an N_2 atmosphere. Air- and moisture sensitive reagents and solvents were transferred via syringe. All reagents were obtained commercially unless otherwise noted. Common solvents were dried and distilled by standard procedures. Anhydrous borane reagents were purchased from Aldrich and used directly from the sealed bottle. Chromatographic purification of products was accomplished using flash chromatography on a Merck Silica Gel, Si 60® (200–400 mesh) or Fisher, Activity I, 60–325 mesh acid alumina oxide deactivated by 3% of water, 25–30 g; hexane–AcOEt 100:1 to 1:1 using HPLC grade solvents. Thin layer chromatography (TLC) was performed on Merck Silica Gel plates. Spots were made visible with a UV lamp and/or I_2 vapors. Infrared analyses were performed in a Termo Nicolet 670 FT-IR. ^{1}H, ^{13}C, and ^{11}B NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer with standard pulse sequences operating at 400.152 MHz, 100.627 MHz, 128.384 MHz, and 161.992 MHz for ^{1}H, ^{13}C, ^{11}B, and ^{31}P, respectively, in $CDCl_3$. Chiral gas chromatography analysis was processed on a Hewlett Packard GC 5890 equipped with a Chrompack Chiralsil-Dex-CB column (30 m × 0.25 mm × 0.25 μm). GC–MS analysis was processed on a Finnigan Trace GC/Polaris Q Mass detector using a Restek RTX-5MS column. A Perking Elmer Polarimeter Model 341 was used for optical rotation analysis.

4.1. (±)-1-(6-Methoxypyridin-3-yl)-ethanol 11

To 1-(6-methoxypyridin-3-yl)ethanone (151 mg, 1 mmol) in THF (5 mL) and MeOH (1 mL) was added solid sodium borohydride (38 mg, 1 mmol) at 25 °C. After the reaction mixture was stirred for 1 h, the solvents were evaporated and the residue dissolved in water (10 mL). Solid NaCl was added, followed by ammonia hydroxide solution

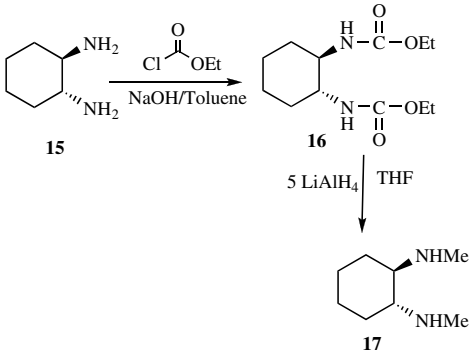
(30% in water, 1 mL). The product was extracted with ether (5×10 mL) and dried over Na_2SO_4. The solvents were removed under vacuum; the residue was distilled in a Kugelrohr apparatus under vacuum to give the final product as a colorless oil (133 mg, 87%).

4.2. General preparation of *O*-acetyl derivatives for GC-analysis of pyridyl ethanols

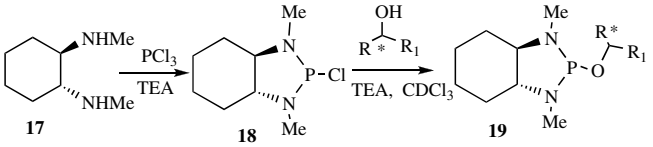
To a solution of the racemic or enantio-enriched alcohol (20 mg, 0.16 mmol) in dry dichloromethane (1 mL,) in a 2 mL vial was added neat triethylamine (0.1 mL, 0.72 mmol), acetic anhydride (0.1 mL, 1.06 mmol), and a small crystal of DMAP (5 mg, 0.04 mmol). The mixture was left at 25 °C for 5 min. After the reaction was complete (followed by TLC, hexane/AcOEt, 1:1), the mixture was transferred to a second 10 mL vial with H_2O (2.5 mL) and shaken for 5 min. Solid Na_2CO_3 (2 g) was carefully added by small portions and left for 5 min, shaking from time to time. Extreme evolution of gas was observed. The *O*-acetyl derivative was extracted with diethyl ether (4 mL) and the organic phase was transferred with a Pasteur pipette to another vial and analyzed by chiral GC.

4.3. Synthesis of chiral derivatizing agent (CDA) 18 for enantiomeric analysis of alcohols by ^{31}P NMR[14]

4.3.1. Dicarbamate 16. In a 250 mL round flask, a solution of (*R*,*R*)-(−)-cyclohexane-1,2-diamine **15** (10 g, 88 mmol) in toluene (130 mL) was stirred and cooled to 0 °C. Ethyl chloroformate (18.1 mL, 190 mmol) and NaOH (7.6 g, 190 mmol) in water (8.3 mL) were added simultaneously. The temperature should not reach more than 10 °C during the addition. The mixture was then stirred overnight and the precipitate was filtered and rinsed with CH_2Cl_2. The solid was continuously extracted in a Soxhlet system overnight with CH_2Cl_2 (150 mL). The solutions were then mixed, dried over $MgSO_4$, and concentrated under vacuum. The dicarbamate **17** was obtained as a white solid (89% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (m, CH_3); 1.72 (d, CH_2); 2.0 (d, CH_2); 3.33 (m, CH_2), 4.09 (m, CH), 4.97 (N–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6 (OCH_2CH_3), 24.8, 32.9, 55.4 (N*C*H), 60.7 (OCH_2CH_3), and 157.0 (*C*=O).



4.3.2. (*R*,*R*)-*N*,*N*′-Dimethyl-cyclohexane-1,2-diamine 17. To a solution of $LiAlH_4$ (14.89 g, 392.5 mmol) in dry THF (300 mL) was slowly added compound **16** (20.29 g, 78.5 mmol) in dry THF (50 mL) at 25 °C. The mixture was stirred for 18 h at reflux temperature and cooled to 0 °C. Ethylenediamine (20 mL) was slowly added to the mixture, followed by a 15% NaOH aqueous solution (20 mL) over 1 h. The precipitate was removed through a Celite pad, and the filtrate was concentrated under vacuum. The Celite was then extracted overnight with ethyl ether using a Soxhlet apparatus. The ether solutions were combined, dried over K_2CO_3, filtered, and concentrated. After vacuum distillation through a 10 cm Vigreux column, the colorless diamine **17** was obtained in a 61% yield. Bp 83 °C (20 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (m, 1H, CH); 1.25 (m, 1H, CH); 1.51 (s, 1H, N–H); 1.75 (m, 1H, CH); 2.04 (m, 1H, CH); 2.12 (m, 1H, CH); 2.42 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.0 (NH*C*H$_3$), 30.8, 33.6, 63.2 (NH*C*H).



4.3.3. Chloro-1,3-dimethyl-octahydro-benzo[1,3,2]diazaphosphole CDA 18. To a solution of chiral diamine **17** (0.50 g, 3.50 mmol) in CH_2Cl_2 (10 mL) in 25 mL flask was added triethylamine (2.44 mL, 17.5 mmol), followed by the addition of PCl_3 (1.22 mL, 14.0 mmol). The mixture was concentrated under vacuum to eliminate the excess of PCl_3. The CDA **18** in $CDCl_3$ (10 mL) was prepared as a standard solution (0.35 M) for further diastereoisomeric analyses.

4.3.3.1. CDA 18 preparation in a NMR tube. In a dried NMR tube were placed the chiral alcohol (0.02 g, 0.141 mmol) and $CDCl_3$ (0.4 mL). The tube was shaken until complete dissolution. Et_3N (0.1 mL, 0.717 mmol) was added with a micro syringe, followed by the addition of PCl_3 (0.05 mL, 0.573 mmol). The NMR tube was carefully shaken as an exothermic reaction takes place. The mixture was concentrated under vacuum. The same amounts of $CDCl_3$ and triethylamine were added again to the NMR tube. The in situ solution of CDA **18** was immediately used. A ^{31}P NMR spectrum was recorded to check the reagent; ^{31}P NMR (161.992 MHz, $CDCl_3$); δ 182.

4.3.4. General procedure for derivatization for ^{31}P NMR analysis. To the CDA **18** (0.141 mmol) in a NMR tube was added triethylamine (0.1 mL) and diamine **17** (8–10 μL). The solution was shaken and the ^{31}P NMR spectrum was recorded and analyzed. The conversion of **19** to the corresponding thiophosphoramidates with sulfur (S_8) powder was carried out in the same NMR tube for a second ^{31}P NMR determination in cases where the signals were not resolved. A racemic sample of each alcohol was used to identify the relevant signals before each non-racemic derivative was analyzed. This was also necessary to ensure that the alcohol enantiomers react at the same rate with the CDA. ^{31}P NMR (161.992 MHz, $CDCl_3$); δ (ppm) derivative of (±)-1-(4-pyridyl)ethanol **8**, 141.23 and 140.13 ($\Delta\delta = 1.10$); (±)-1-(3-pyridyl)ethanol **7**, 141.58 and 140.32

($\Delta\delta = 1.26$); (±)-1-(2-pyridyl)ethanol **10**, 141.11 and 138.23 ($\Delta\delta = 2.88$).

4.4. (*R*)-(+)-1-(3-Pyridyl)-ethanol 7 using 1 mol % of catalyst 5

A borane–SMe_2 complex (10 M, 1.6 mL, 16.0 mmol) was added to a solution of (*S*)-2-[(1,3,2-dioxaborolan-2-yloxy)diphenylmethyl]pyrrolidine **5**[12] (32 mg, 0.10 mmol) in dry THF (5 mL) at 25 °C and the mixture was stirred for 1 h. A solution of 3-acetylpyridine (1.21 g, 10.0 mmol) in THF (5 mL) was added for 5 h using an infusion pump. The reaction mixture was stirred at rt over 1 h, then cooled at 0 °C and quenched with methanol (10 mL). After refluxing for 12 h, the solvents were removed under vacuum; the residue was distilled in a Kugelrohr apparatus under vacuum to give the final product as colorless oil (1.18 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47 (d, $J =$ 6.5 Hz, 3H, Me), 4.88 (q, $J = 6.5$ Hz, *CH*Me), 6.02 (br s, 1H, OH), 7.22 (m, 1H, CH_{Ar}), 8.29 (m, 1H, CH_{Ar}), 8.41 (m, 1H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.3, 67.1, 123.6, 133.7, 142.2, 146.9, 147.6. Chiral GC of *O*-acetyl derivative (t_R 12.05 min) indicated 98.2% ee. $[\alpha]_D^{23} = +41.1$ (*c* 3.6, $CHCl_3$). Lit.[16] $[\alpha]_D^{20} = +52.4$ (*c* 1.40, $CHCl_3$) for >95% ee.

4.5. (*R*)-(+)-1-(4-Pyridyl)-ethanol 8 using 1 mol % of catalyst 5

Borane–SMe_2 complex (10 M, 1.6 mL, 16.0 mmol) was added to a solution of (*S*)-2-[(1,3,2-dioxaborolan-2-yloxy)diphenylmethyl]-pyrrolidine **5**[12] (32 mg, 0.10 mmol) in dry THF (5 mL) at 25 °C. A solution of 4-acetylpyridine (1.21 g, 10.0 mmol) in THF (5 mL) was added for 5 h using an infusion pump. The reaction mixture was stirred at 25 °C for 1 h, cooled at 0 °C and quenched with methanol (10 mL). After refluxing for 4 h, the mixture was analyzed by ^{11}B NMR and the N–BH_3 complex signal was observed at −13.28 ppm. More MeOH (10 mL) was added and refluxed for 12 h. The solvents were removed under vacuum and the residue was distilled in a Kugelrohr apparatus under vacuum to give pure (*R*)-1-(4-pyridyl)ethanol as a white crystalline material (1.13 g, 92%); (mp: 55–58 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (d, $J = 6.4$ Hz, 3H); 4.80 (q, $J = 6.4$ Hz, 1H); 5.1 (s, 1H); 7.22 (d, $J = 6.0$ Hz, 2H); 8.31 (d, $J = 5.6$Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.0 (CH_3); 68.2 (*C*–H(OH)); 120.6 (CH_{Ar}); 149.0 (CH_{Ar}); 156.0. Chiral GC of *O*-acetyl derivative (t_R 12.39 min) indicated 99% ee. $[\alpha]_D^{23} = +49.0$ (*c* 2.5, $CHCl_3$). Lit.[16] $[\alpha]_D^{20} = +42.5$ (*c* 1.04, MeOH) for >95% ee.

4.6. (*R*)-(+)-1-(2-Pyridyl)-ethanol 10 using 100 mol % catalyst 5

Borane–SMe_2 complex (10 M, 0.5 mL, 5.00 mmol) was added to a solution of (*S*)-2-((1,3,2-dioxaborolan-2-yloxy)diphenylmethyl)pyrrolidine **5**[12] (808 mg, 2.50 mmol) in dry THF (5 mL) at rt for 4 h. A solution of 2-acetylpyridine (303 mg, 2.50 mmol) in THF (2 mL) was added for 1 h using an infusion pump. The reaction mixture was stirred for 1 h at 25 °C, cooled to 0 °C, quenched with methanol (5 mL), and refluxed for 12 h. The solvents were removed under vacuum and the residue dissolved in CH_2Cl_2 (10 mL). Acetic anhydride (2 mL) and triethylamine (2 mL) were added followed by DMAP (5 mg). After stirring at 25 °C for 1 h, the reaction mixture was added to water (15 mL) and quenched with solid Na_2CO_3 (10 g). The organic phase was separated and the product was extracted with ethyl ether (5×10 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated in vacuum. The product was purified by column chromatography (Al_2O_3 deactivated by 3% of water, 35 g; hexane and hexane–AcOEt 100:1 to 10:1). The main fractions were concentrated under vacuum and the residue was distilled in Kugelrohr apparatus under vacuum to give the final product as a colorless oil (338 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.61 (d, $J = 6.8$ Hz, 3H, CH*Me*), 2.13 (s, 3H, OAc), 5.91 (q, $J = 6.8$ Hz, 1H, *CH*Me), 7.20 (m, 1H, CH_{Ar}), 7.33 (d, $J =$ 8Hz, 1H, CH_{Ar}), 7.68 (m, 1H, CH_{Ar}), 8.58 (m, 1H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.7, 21.3, 73.1, 120.5, 122.7, 136.7, 149.4, 160.3, 170.3. Chiral GC of *O*-acetyl derivative indicated 92.9% ee. $[\alpha]_D^{23} = +90.1$ (*c* 2.5, $CHCl_3$). Lit.[16] $[\alpha]_D^{20} = +102.3$ (*c* 1.27, $CHCl_3$) for >95% ee.

4.7. (*R*)-(+)-1-(6-Methoxy-pyridin-3-yl)-ethanol 11[17] using 1 mol % of catalyst 5

Borane–SMe_2 complex (10 M, 0.99 mL, 9.9 mmol) was added to a solution of (*S*)-2-[(1,3,2-dioxaborolan-2-yloxy)diphenylmethyl]pyrrolidine **5**[12] (19.9 mg, 0.06 mmol) in dry THF (3 mL) at rt and the mixture was stirred for 1 h. A solution of 1-(6-methoxypyridin-3-yl)ethanone (930 mg, 6.16 mmol) in THF (5 mL) was added for 5 h using an infusion pump. The reaction mixture was stirred at 25 °C over 1 h, then cooled to 0 °C and quenched with methanol (5 mL). After refluxing for 12 h, the solvents were removed under vacuum and the product was purified by column chromatography (Al_2O_3 deactivated by 3% of water, 25 g; hexane–AcOEt 100:1 to 1:1). The main fractions were concentrated under vacuum and the residue was distilled in a Kugelrohr apparatus (oven temperature 210 °C) under vacuum (1 mmHg) to give the final product as a colorless oil (726 mg, 77%). IR (CaF_2, film, cm^{-1}): 3355 (br, OH), 2974, 2948, 1609, 1496, 1325, 1286, 1253, 1094, 1029. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (d, $J = 6.5$ Hz, 3H, CH*Me*), 3.16 (br s, 1H, OH), 3.89 (s, 3H, OMe), 4.81 (q, $J = 6.5$, 1H, *CH*Me), 6.70 (d, $J = 8.6$ Hz, 1H, CH_{Ar}), 7.60 (m, 1H, CH_{Ar}), 8.01 (m, 1H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.8, 53.5, 67.6, 110.8, 133.7, 136.5, 144.1, 163.7. Chiral GC of *O*-acetyl derivative indicated 98.0% ee. $[\alpha]_D^{23} = +33.7$ (*c* 2.7, $CHCl_3$).

4.8. (*R*)-(+)-1-(10*H*-Phenothiazin-2-yl)-ethanol 12 using 10 mol % catalyst 5

A borane–SMe_2 complex (10.0 M, 2.0 mL, 20 mmol) was added to a solution of spiroborate **5** (0.323 g, 1.0 mmol) in dry THF (30 mL) at 25 °C and the mixture was stirred for about 15 min. A solution of 2-acetyl-1-phenothiazine (2.413 g, 10.0 mmol) in dry THF (40 mL) was added to the reaction mixture during for 1 h using an infusion pump. The mixture was allowed to react overnight. The reaction was cooled to 0 °C, quenched with MeOH (20 mL), and

heated at reflux for 2 h. The solvents were removed in vacuo. The crude product was purified by washing the solid 1-(10*H*-phenothiazin-3-yl)ethanol with dichloromethane (50 mL) several times to remove traces of impurities and dried overnight under high vacuum obtaining pure (*R*)-1-(10*H*-phenothiazin-2-yl)-ethanol (2.375 g, 97.6% yield). Mp 134–136 °C.[18] IR (cm^{-1}): 3396 (NH), 3314 (OH), 1091 (C–O). ^1H NMR (400 MHz, (DMSO)): δ 1.27 (d, $J = 6.4$ Hz, 3H, CH_3); 4.57 (m, 1H, C–HOH); 5.10 (d, $J = 4.0$ Hz 1H, –OH); 6.7–7.0 (m, 7H, Ar); 8.55 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO): δ 26.2, 68.1, 112.0, 114.6, 114.9, 117.0, 119.4, 122.1, 126.2, 126.7, 127.9, 142.4, 142.7, 147.6. ^{31}P NMR (162 MHz, $CDCl_3$): (racemic derivative): δ (ppm) 141.02 and 137.91 ($\Delta\delta = 3.11$). (chiral alcohol): δ (ppm) 137.91 (>99% ee). $[\alpha]_D^{23} = +24.0$ (*c* 1.0, MeOH).

4.9. (*R*)-(+)-4′-(Imidozol-1-yl)-phenyl ethanol 13 using 10 mol % catalyst 5

A borane–SMe_2 complex (10 M, 2.0 mL, 20.0 mmol) was added to catalyst **5** (323 mg, 1.0 mmol) in dry THF (20 mL) at rt. A solution of 4′-(imidazol-1-yl) acetophenone (1.86 g, 10.0 mmol) in THF (20 mL) was added for 5 h using an infusion pump. The reaction mixture was stirred at 25 °C overnight and then cooled to 0 °C and quenched with methanol (10 mL). After refluxing overnight, the solvents were removed under vacuum. The crude product was purified by flash column chromatography on a silica column (40 g) using ethyl acetate to give pure **13** as a white crystalline material (1.40 g, 76%), mp: 118–120 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 1.53 (d, $J = 6.4$Hz, 3H), 3.7 (br s, 1H), 4.96 (q, $J = 6.4$ Hz, 1H), 7.14 (s, 1H); 7.24 (s, 1H), 7.32 (d, $J = 8.4$ Hz, 2H), 7.8 (d, $J = 8.4$ Hz, 2H), 7.69 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.5 (CH_3); 69.3 (*C*–H(OH)), 118.3, 121.4, 127.0 (CH_{Ar}), 130.0, 135.5, 136.2 (CH_{Ar}), 146.0. The product was analyzed by ^{31}P NMR with a small amount of sulfur; the diastereomers signals at 86.1 ppm (3.5%) and 85.8 ppm (96%) provided 92.5% ee. $[\alpha]_D^{23} = +31.7$ (*c* 0.40, $CHCl_3$). Lit.[19] $[\alpha]_D^{17} = -33$ (*c* 0.48, $CHCl_3$) for >98% (by HPLC) for (*S*) enantiomer.

4.10. (*S*)-(+)-Phenyl(pyridin-3-yl)methanol 14 with 10 mol % catalyst 5

Borane–SMe_2 complex (10.0 M, 1.0 mL, 10 mmol) was added to a solution of spiroborate **5** (0.323 g, 1.0 mmol) in dry THF (30 mL) at 25 °C and the mixture was stirred for about 15 min. A solution of 3-benzoylpyridine (1.832 g, 10.0 mmol) in dry THF (10 mL) was added to the reaction mixture during 1 h. The mixture was allowed to react overnight. The reaction mixture was cooled to 0 °C, then MeOH (20 mL) was added and the mixture was heated at reflux for 8 h. Decomposition of N–BH_3 complex was confirmed by ^{11}B NMR and the mixture was concentrated to colorless oil. The residue was distilled under high vacuum in the Kugelrohr oven (140 °C/0.7 mmHg) obtaining pure phenyl (pyridin-3-yl)methanol (1.53 g, 83% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 4.20 (s, 1H, OH); 5.84 (s, 1H, C–H); 7.23 (m, 1H, C–H), 7.27–7.38 (m, 5H); 7.71 (m, $J = 7.6$ Hz, 1H); 8.36 (dd, $J = 4.4$ Hz, 1H); 8.50 (d, $J = 2.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 73.9, 123.5, 126.6, 127.9, 128.7, 134.4, 139.7, 143.2, 148.0, 148.3. Using the in situ CDA solution a diastereomeric sample was prepared and analyzed by ^{31}P NMR (161.992 MHz, $CDCl_3$); the enantiopurity was 83% ee. $[\alpha]_D^{23} = +12.0$ (*c* 1.6, $CHCl_3$). Lit.[20] $[\alpha]_D^{20} = -19.0$ (*c* 1.20, $CHCl_3$) for 75% ee (by HPLC).

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