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Chiral spiroaminoborate ester as a highly enantioselective and efficient catalyst for the borane reduction of furyl, thiophene, chroman and thiochroman containing ketones

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Abstract

Prochiral heteroaryl ketones containing furan, thiophene, chroman and thiochroman moieties were successfully reduced in the presence of 1 – 10 mol % of spiroaminoborate ester **1** with different borane sources to afford non-racemic alcohols in up to 99% ee. In addition, modest enantioselectivity, around 80% ee, was achieved in the reduction of linear α,β -unsaturated heteroaryl ketones.

1. Introduction

Heterocyclic fragments containing oxygen or sulfur in the ring are important cores found in natural and synthetic products used in the flavor, fragrance and pharmaceutical industry.¹ Recently, enantiomerically pure (*R*)-2-furanyl-2-ethanol was used as a building block by O'Doherty and et al. to introduce chirality in the synthesis of the anthrax tetrasaccharide produced by *Bacillus anthracis*.^{2a} Other furfuryl enantiopure alcohols were used by the same group to obtain iminosugar natural products.^{2b} Benzofuran carbinols are important units found in chiral drugs such as bufuralols, potent nonselective β -blocker antagonists. 2d,e In addition, sulfur heterocycles are important intermediates in the synthesis of chiral biologically active compounds such as the antidepressant Duloxetine **2** (Cymbalta),³ and the carbonic anhydrase inhibitor, MK-0417 **3**.⁴ used for the treatment of glaucoma (Figure 1). Zileuton **4** from Abbott and other related furan, thiophene and benzofuran 5-lipoxygenase inhibitors have been developed for the treatment of asthma and other inflammatory diseases.⁵ In addition, chroman and thiochroman carbinols are found in many drugs, such as 4-hydroxy tertalolol **5**, which is employed in the treatment of high blood pressure.

Consequently, the synthesis of single isomeric heteroaryl carbinols is currently a vast area of research. Although conventional chemical resolutions of racemic drug precursors are still being used to obtain enantiopure products, more efficient bioenzymatic resolution methods are being developed.⁷ For example, the kinetic resolution of racemic heterocyclic alcohols by lipases has been demonstrated to be a useful tool since it provides high enantiopure heteroaryl ethanol. 7a,b Nevertheless, the maximum yield is still 50% of the desired non-racemic alcohols. To

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overcome this limitation, the quantitative chemoenzymatic reduction of ketones has also been widely studied.⁸ Baker's yeast reduction has been applied effectively to obtain (*S*)-1-heteroarylethanol in high enantiopurity, however, the opposite enantiomer required a chemical transformation.^{8c} Other limitations of biocatalysts are the lack of generality and difficulties encountered in scaling-up the methods for pharmaceutical production.⁸ The Noyori asymmetric transfer hydrogenation method, which uses ruthenium diamino complexes, has been successfully applied to the synthesis of heterocyclic enantiopure secondary alcohols.^{2,9}

Asymmetric addition of boron, aluminum and silicon hydrides to the carbonyl group of prochiral ketones is an area of major interest since these methods provide a less expensive, efficient and suitable access to a great variety of non-racemic alcohols with predictable stereochemistry.¹⁰ Oxazaborolidines have been the most widely used boron catalysts for the borane reduction of heteroaryl ketones.^{11,12} However, the oxazaborolidine reduction of ketones containing oxygen, sulfur and nitrogen, have been observed in some substrates, to provide inferior enantioselectivity, particularly at the 2-position, possibly due to a competitive intramolecular reduction by the heterocyclic-borane complex.^{12a}

Recently, a series of novel stable aminoborate esters with oxazaborolidine-like enantioselectivity were synthesized and characterized by our group. The structure of some of these aminoborate esters was established by X-ray analysis.^{13c,e} The highly crystalline and stable spiroaminoborate complex **1**, derived from diphenylprolinol (Scheme 1) and ethylene glycol, was found to be highly enantioselective and a convenient catalysts for the asymmetric borane reduction of prochiral ketones.^{13a–e} As part of our interest in the enantioselective synthesis of biological active precursors, we decided to apply our spiroaminoborate methodology for the asymmetric reduction of heteroaryl compounds containing oxygen or sulfur.

2. Results and Discussion

In previous work, we have studied the borane-mediated reduction of aryl and pyridyl ketones using different aminoborate catalysts, and the process was optimized using different solvents, borane sources, temperatures and amount of catalysts.^{13a–c} To assess the catalytic performance of **1**, a curve of catalytic load vs. enantiomeric excess was established using the acetophenone reduction with boranedimethyl sulfide in THF at 25 °C, as a model. The maximum enantioselectivity (99% ee) was attained with 10 molar % of aminoborate **1**, and the catalytic cut-off was 0.5 mol % obtaining 98% ee.^{13c} Additionally, we have carried out similar studies with the 3- and 4-acetyl pyridines observing excellent enantioselectivities, 98% ee and 99% ee, respectively, with 1 mol % of catalyst.^{13d}

Derivatives of 2-acetylfuran are important synthons for the preparation of α -hydroxy and other α -functionalized acids by ozonolysis of the furan ring.¹⁴ The reduction of 2-acetylfuran in the presence of 10 mol % of **1** gave (+)-(*R*)-1-(furan-2-yl)ethanol in 95% ee. When 1% mol of catalyst was used, the selectivity was still high, 95% ee. The yield was moderate probably due to the high volatility of the alcohol causing product loss during distillation in the purification process (Table 1, entry 1 and 2). Other commercially available substrates with a furanyl fragment were studied (entry 3–6). Unexpectedly, 2-acetyl-5-methylfuran provided the corresponding alcohol with significantly lower selectivity with 1% of catalyst, but with 10 mol %, the enantiopurity of the corresponding alcohol increased to 91% ee (entry 3). The enantioselectivity for the 2-acetyl benzofuran reduction was 96% ee using 1% and 10% of **1**, in good yield (entries 5 and 6).

The unstable and enolizable benzofuran-3(2*H*)-one afforded the corresponding alcohol with good selectivity (92%) using 10% and 5% of catalyst (entry 7 and 8 in Table 1). However, a

lower level of asymmetric induction was observed with 1% of catalyst, obtaining the dihydrobenzofuranol with less than 50% ee and in low yield (33%). However, remarkable enantioselectivity was achieved for the 4-chromanone reduction with 10 mol % of catalyst **1**, providing the chromanol in >99% ee (entry 9).

Our study was then extended to the synthesis of representative sulfur containing heteroaryl alcohols. Prochiral thiophenyl ketones and thiochromanones were, in general, successfully reduced to the corresponding alcohols with 10 and even 1 mol % of catalyst **1** (Table 2). Outstanding enantioselectivities (>96% ee) were attained in most instances even with a low catalytic load, and the reactions were completed in less than an hour. The products were easily isolated in high yield and purified, usually, by a simple distillation. In addition, we studied the reduction of some sulfur heterocyclic ketone using borane diethylaniline (DEA) as a more stable borane sources.¹⁵ In general, for the selected thiophene compounds, we observed high enantioselectivity, up to 99% ee with 10% catalyst **1** (as shown in parenthesis in Table 2). However the yields were modest, possibly due to the more laborious DEA extraction process during the work-up.

Chiral allylic alcohols are very important synthons in organic synthesis and can be prepared by asymmetric reduction of the corresponding unsaturated ketones.¹⁶ For reduction of heteroaryl α,β -unsaturated ketones, we investigated the reaction of (*E*)-4-phenylbut-3-en-2-one **6** using different amount of catalyst **1** and a variety of borane reagents (Table 3, entries 1–6). The optimal enantiomeric excess (80%) was achieved using borane-DMS with 10% of **1**. The reaction was conducted in THF at 0 °C, and no reduction of the double bond was observed. The reduction of commercially available enones containing thiophenyl and furyl substituents **7** and **8** was studied with different catalytic loads of **1** using a borane-DMS complex under the previous conditions. Similarly, using 10% mol of catalyst **1** provided the optimal selectivity affording (*R,Z*)-4-(furan-3-yl)but-3-en-1-ol and (*R,E*)-4-(thiophen-3-yl)but-3-en-2-ol (entries 8 and 11) in 80 and 83% ee, respectively. The absolute configuration of the products was assigned based on the comparison with the literature specific rotation values and by the predicted stereochemistry outcome produced by catalyst **1**.

3. Conclusions

In general, the asymmetric borane reduction of prochiral furyl, chroman, thiochromanyl, and thiophenyl ketones was successfully achieved with high enantioselectivity using only 1% mol of spiroborate ester **1** as a catalyst and under very mild and convenient conditions, offering an efficient synthetic tool for the preparation of enantiopure secondary alcohols. Although only moderate selectivity was achieved in the reduction of linear α,β -unsaturated aromatic ketones, it is a facile method and further studies will be considered to improve the enantiomeric purity.

4. Experimental part

All reactions were preformed in oven-dried glassware under an N₂ atmosphere. Air- and moisture sensitive reagents and solvents were transferred via syringe. All reagents were obtained commercially from Aldrich unless otherwise noted. Common solvents were dried and distilled by standard procedures.

Chromatographic purification of products was accomplished using flash chromatography on Merck silica gel, 200–400 mesh, as eluent, hexane-AcOEt 100:1 to 1:1 using HPLC grade solvents. Thin layer chromatography (TLC) was performed on Merck silica plates. The spots were visible with an UV lamp. Infrared analyses were performed in a Perkin Elmer Spectrum 100 FT-IR with ATR. ¹H, ¹³C NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer with standard pulse sequences operating at 400.152 MHz and 100.627 MHz in CDCl₃. Chiral gas chromatography analysis was processed on a Hewlett Packard GC 5890

equipped with a Chrompack Chiralsil-Dex-CB column (30 m $\times$ 0.25 mm $\times$ 0.25 μ m). GC-MS analysis was processed on a Finnegan 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 General procedure for the preparation of racemic alcohols

To a solution of the ketone (1 mmol) in THF (3 mL) and MeOH (3 mL), solid sodium borohydride (37 mg, 1 mmol) was added at 0 °C. After the reaction mixture was stirred at 25 °C over 1 h, the solvents were evaporated. The residue was dissolved in dichloromethane (DCM) (10 mL) and added into water (15 mL) in a separatory funnel and extracted. The aqueous phase was extracted with DCM (2 $\times$ 10 mL) and dried over Na₂SO₄. The solvents were removed under vacuum. The crude product was used for the preparation of the *O*-acetyl derivative for the enantiopurity determination by GC-analysis.

4.2 General procedure for the preparation of *O*-acetyl derivatives for GC-analysis of alcohols

To a solution of the racemic or enantio-enriched alcohol (0.5 mmol) in dry ethyl ether (3 mL,) in a 10 mL vial, neat triethylamine (0.5 mL, 3.60 mmol), acetic anhydride (0.5 mL, 5.30 mmol) and a small crystal of DMAP (2 mg, 0.02 mmol) were added. The mixture was left at 25 °C for 5 min, then H₂O (3 mL) and the mixture were shaken for 5 min. Solid Na₂CO₃ (3 g) was carefully added a 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 additional diethyl ether (2 mL) and the organic phase was transferred with a Pasteur pipette to another vial. Chiral gas chromatography analysis was processed on a Hewlett Packard GC 5890 equipped with a Chrompack Chiralsil-Dex-CB column (30 m $\times$ 0.25 mm $\times$ 0.25 μ m).

4.3 General optimized method for the asymmetric reduction of ketones using 1 mol% of spiroborate 1

Borane-SMe₂ complex (10 M, 0.7 mL, 7.0 mmol) was added to a solution of (*S*)-2-[(1,3,2-dioxaborolan-2-yloxy)diphenylmethyl]pyrrolidine **1** (32 mg, 0.10 mmol) in dry THF (5 mL) at 25 °C and the mixture was stirred for 1h. A solution of ketone (10.0 mmol) in THF (5 mL) was added for 1 h using an infusion pump. The reaction mixture was stirred at 25 °C over 1 h, then cooled at 0 °C and quenched with methanol (5 mL), concentrated. The residue was dissolved in methanol (10 mL) and refluxed over 3 h, concentrated, re-dissolved in methanol (5 mL) and concentrated again. The residue was distilled in a Kugelrohr apparatus under vacuum to give the final product.

Reduction of 2-acetylfuran using 1 mol% of spiroborate—A solution of freshly redistilled 1-(furan-2-yl)ethanone (1.10 g, 10.0 mmol) in THF (5 mL) was added to the reaction flask. After following the general procedure, (+)-(*R*)-1-(furan-2-yl)ethanol was obtained as colorless oil (730 mg, 65%). Bp: 150 °C/1 mmHg. IR (cm⁻¹): 3335, 2981, 1505, 1148, 1066, 1008. MS *m/z* (relative intensity, ion): 112.0 (28, M), 97.1 (46, M-CH₃), 95.1 (100, M-OH, -H), 69.2 (32, M-CHOHCH₃). ¹H NMR (400 MHz, CDCl₃): δ 1.48 (d, *J* = 6.6 Hz, 3H, Me), 3.08 (br. s, 1H, OH), 4.81 (q, *J* = 6.6 Hz, CHMe), 6.19 (dt, *J* = 3.3, 0.7 Hz, 1H, C₃'H), 6.29 (dd, *J* = 3.2, 1.8 Hz, 1H, C₄'H), 7.33 (dd, *J* = 1.8, 0.8 Hz, 1H, C₅'H); ¹³C NMR (100 MHz, CDCl₃): δ 21.3, 66.4, 105.1, 110.1, 141.8, 157.8. Chiral GC of *O*-acetyl derivative at T₁ = 70 °C (10 min), gradient = 4 °C/min, T₂ = 190 °C (35 min): Rt_R 19.2 min; Rt_S 17.4 min, indicated 95% ee. [α]_D²² = +21 (c 1.45, CHCl₃). Lit^{7d} (*R*): [α]_D = +22 (c 2.7, CHCl₃), 95% ee.

Reduction of 1-(5-methylfuran-2-yl)ethanone using 10 mol % of spiroborate—A solution of freshly redistilled 1-(5-methylfuran-2-yl)ethanone (0.62 g, 5.00 mmol) in THF (5 mL) was added to the reducing mixture for 1 h using an infusion pump. After the usual work-

up, the crude product was distilled in a Kugelrohr apparatus under vacuum to give the final product, (+)-(*R*)-1-(5-methylfuran-2-yl)ethanol, as a colorless oil (468 mg, 74%). Bp: 150 °C/1 mmHg. The reaction was repeated to improve the yield and the crude product was purified by column chromatography with silica gel 60 Å and hexane/EtOAc gradients to give 0.546 g (87%). ¹H NMR (400 MHz, CDCl₃): δ 1.49 (d, *J* = 6.6 Hz, 3H, CHMe), 2.26 (d, *J* = 0.8 Hz, 3H, C₅Me), 2.45 (br. s, 1H, OH), 4.79 (q, *J* = 6.6 Hz, CHMe), 5.87–5.88 (m, 1H, C₄H), 6.07 (d, *J* = 3.0 Hz, 1H, C₃H); ¹³C NMR (100 MHz, CDCl₃): δ 13.5, 21.2, 63.5, 105.9, 106.0, 151.6, 155.9. GC/MS *m/z* (relative intensity) 126 M⁺ (16%), 110 (32%), 109 (100%), 95 (52%), 81 (12%). Chiral GC of *O*-acetyl derivative at T₁ = 70 °C (10 min), gradient = 4 °C/min, T₂ = 190 °C (35 min): Rt_R 21.3 min, Rt_S 16.9 min, indicated 91% ee, determined from crude derivative. [α]_D²³ = +7.2 (c 1.25, CHCl₃). Lit.^{7d} (*R*): [α]_D = +8.5 (c 2.2, CHCl₃), 95% ee.

Reduction of 2-acetylbenzofuran using 1 mol% of spiroborate 1—A solution of freshly redistilled 2-acetylbenzofuran (1.60 g, 10.0 mmol) in THF (5 mL) was added for 1 h using an infusion pump. After usual work-up, the crude residue was distilled in a Kugelrohr apparatus under vacuum to give the final (+)-(*R*)-1-(benzofuran-2-yl)ethanol as a colorless oil (1.54 g, 95%). Bp: 220 °C/0.5 mmHg ¹H NMR (400 MHz, CDCl₃): δ 1.57 (d, *J* = 6.6 Hz, 3H, Me), 2.88 (br. s, 1H, OH), 4.94 (q, *J* = 6.4 Hz, CHMe), 6.53 (s, 1H, C₃H), 7.18–7.27 (m, 2H, C₅H and C₆H), 7.44 (dd, *J* = 8.0, 0.6 Hz, C₄H), 7.51 (d, *J* = 6.0 Hz, 1H, C₇H); ¹³C NMR (100 MHz, CDCl₃): δ 21.4, 66.0, 101.7, 111.2, 121.0, 122.7, 124.1, 128.2, 154.7, 160.3. Chiral GC of *O*-acetyl derivative at T₁ = 90 °C (10 min), gradient = 1 °C/min, T₂ = 150 °C (35 min): Rt_R 47.2 min; Rt_S 46.2 min, indicated 96% ee. [α]_D²³ = +18 (c 3, CHCl₃). Lit.^{7a} (*S*) [α]_D²⁰ = −16.6 (c 1.0, CHCl₃), 98.6% ee.

Reduction of benzofuran-3(2*H*)-one using 10 mol % of borate ester 1—To a dry 25 mL round flask under a nitrogen flow, spiroborate **1** (0.097 g, 0.3 mmol), was added and then, dry THF (5 mL) was added to make a clear solution. Borane dimethyl sulfide complex (0.21 mL, 10.0 M, 2.1 mmol) was added to the solution and the mixture was stirred during 1 h. The initial cloudy mixture changed to a colorless solution. Benzofuran-3(2*H*)-one (0.402 g, 3.0 mmol) in dry THF (5.0 mL) was added to the solution over 1 h using an infusion pump, and the mixture was allowed to stir for an additional 1 h. The reaction was then monitored by TLC using a silica plate and hexane as eluent to confirm the substrate consumption. The reaction was quenched with MeOH (2 mL) and the mixture was stirred overnight. The solvents were removed in the rotovaporator at 60 °C at approximately 20 mmHg and finally concentrated to afford a yellow oil. The crude product was treated with H₂O (10 mL), extracted with methylene chloride (3 × 10 mL), dried over sodium sulfate, filtered and concentrated in the rotovaporator at 60 °C under vacuum. The crude product was purified by column chromatography using silica gel 60 Å Mesh 70–130 and hexane/EtOAc 1:1 as eluent to give (+)-(*S*)-2,3-dihydrobenzofuran-3-ol as a yellow solid, m.p. 48–50. (0.349 g, 86% yield). ¹H-NMR (400 MHz, CDCl₃) δ ppm: 2.24 (s, 1H, OH); 4.45 (dd, *J*₁ = 2.6 Hz, *J*₂ = 10.6 Hz, 1H, CH₂); 4.56 (m, 1H, CH₂); 5.36 (d, *J* = 4.8 Hz, 1H, HO-C-H); 6.99 (td, *J*₁ = 0.8 Hz, *J*₂ = 7.4 Hz, 1H, Ar); 7.31 (td, *J*₁ = 0.8 Hz, *J*₂ = 8.0 Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ ppm: 72.2, 78.2, 110.6, 121.1, 125.5, 128.3, 130.8, 160.2. Chiral GC of *O*-acetyl derivative at T₁ = 70 °C (10 min), gradient = 4 °C/min, T₂ = 190 °C (35 min): Rt_R 21.3 min; Rt_S 19.9 min, indicated 92% ee. [α]_D²² = +13 (c 2.2, CHCl₃). With 5% it was afforded 78% chemical yield, 92% ee and similar specific rotation: [α]_D²² = +61 (c 1.8, CHCl₃). Lit.^{7e} (*R*): [α]_D = +67 (c 0.63, CHCl₃), >98% ee.

Reduction of chroman-4-one using 10 mol% of spiroborate 1—To a 100 mL, one neck round bottom flask, previously dried and under nitrogen was placed (*S*)-2-[(1,3,2-dioxaborolan-2-yloxy)diphenylmethyl]pyrrolidine (**1**) (0.323 g, 1.0 mmol) and dissolved in dry THF (40 mL). Borane-SMe₂ complex (10 M, 2.0 mL, 20 mmol) was added via an infusion

pump during 30 min, and the mixture was stirred at 25 °C for 1 h. A solution of chroman-4-one (1.48 g, 10 mmol) in THF (5 mL) was added for 1 h using an infusion pump. The reaction mixture was stirred at 25 °C over 3 h, then cooled at 0 °C and quenched with methanol (5 mL) and left stirring overnight at room temperature. After the mixture was concentrated in the rotoevaporator at 70 °C, the residue was dissolved in methanol (10 mL) and concentrated again. The residue was treated with NH₄Cl (20 mL), and extracted with diethyl ether (4 × 15 mL) and water (3 × 10 mL). The organic phases were collected and the organic phase was dried with K₂CO₃. After concentration at 30 °C in the rotoevaporator, the crude product was purified by flash column chromatography on silica gel (45 g): ethyl acetate: hexane 1:5, obtaining the (+)-(*R*)-4-chroman-4-ol as a white solid (1.23 g, 82 % yield). ¹H-NMR (400 MHz, CDCl₃): δ 1.8 (s, 1H, OH), 2.5 (m, 2H, CH₂), 4.3 (m, 2H, CH₂), 4.83 (m, 1H, CH-OH), 6.86 (d, *J* = 6.40, 1H, Ar), 6.95 (t, *J* = 7.60, 1H, Ar), 7.24 (m, 1H, Ar), 7.35 (m, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃-d): δ 63.5, 30.5, 62, 154.5, 116.8, 129, 120.5, 130.1, 124; FT-IR ν (cm⁻¹): 3434 (O-H), 3054, 2987, 1062 (C-O, OH). GC Rt 6.97 min/MS *m/z*: 150 M⁺ (50%), 131 (100%), 95 (20%), 121 (80%). The alcohol was derivatized with the CDA Alexakis reagent¹⁵ for ³¹P-NMR (161.992 MHz, CDCl₃): δ 146 provide >99.8% ee. [α]_D²⁰ = +61 (c 0.045, CHCl₃). Lit.^{9a} (*S*): [α]_D²⁵ = -60.5 (c 2.55, EtOH), 95% ee.

Reduction of 2-acetylthiophene using 1 mol% of borate ester 1—A solution of freshly redistilled 2-acetylthiophene (1.26 g, 10.0 mmol) in THF (5 mL) was added for 1 h using an infusion pump. After the usual work-up, the crude product was distilled in a Kugelrohr apparatus under vacuum to give the final product (+)-(*R*)-1-(thiophen-2-yl)ethanol as a colorless oil (1.109 g, 87%). Bp: 200 °C/1 mmHg; IR (cm⁻¹) 3342 (OH), 2974 (CH₃), 1435 (CH), 1370 (CH), 1066 (C-O), 849 (C-S); ¹H NMR (400 MHz, CDCl₃): δ 1.53 (d, *J* = 6.4 Hz, 3H, Me), 2.91 (br. s, 1H, OH), 5.04 (q, *J* = 6.4 Hz, Me), 6.91–6.93 (m, 2H, C₃'H and C₄'H), 7.17–7.19 (m, 1H, C₅'H); ¹³C NMR (100 MHz, CDCl₃): δ 25.2, 66.0, 123.1, 124.3, 126.6, 150.0. GC/MS *m/z* 128 M⁺ (10%), 113 (32%), 95 (20%), 85 (100%). Chiral GC of *O*-acetyl derivative at T₁ = 90 °C (10 min), gradient = 1 °C/min, T₂ = 150 °C (35 min): Rt_R 20.2 min; Rt_S 17.4 min, indicated 96% ee. [α]_D²³ = +27 (c 2.5, CHCl₃). With 10% of **1**, it was obtained 92% yield and 98% ee [α]_D²³ = +26 (c 2.0, CHCl₃). Lit.^{7d}: [α]_D = +24.2 (c 5, CHCl₃), 100% ee.

Reduction of 1-(5-chlorothiophen-2-yl)ethanone using 1 mol% of spiroborate 1—A solution of freshly redistilled 1-(5-chlorothiophen-2-yl)ethanone (1.61 g, 10.0 mmol) in THF (5 mL) was added for 1h using an infusion pump. The crude product was distilled to give the (+)-(*R*)-1-(5-chlorothiophen-2-yl)ethanol as a white solid (1.49 g, 91%). Bp: 250 °C/1 mmHg. ¹H NMR (400 MHz, CDCl₃): δ 1.53 (d, *J* = 6.4 Hz, 3H, Me), 2.46 (br. s, 1H, OH), 4.97 (q, *J* = 6.4 Hz, Me), 6.70 (dd, *J* = 3.8, 0.8 Hz, 1H, C₃'H), 6.74 (d, *J* = 3.8 Hz, C₄'H); ¹³C NMR (100 MHz, CDCl₃): δ 25.0, 66.4, 122.4, 125.6, 129.0, 148.6. Chiral GC of *O*-acetyl derivative at T₁ = 70 °C (10 min), gradient = 4 °C/min, T₂ = 190 °C (35 min): Rt_R 28.8 min; Rt_S 28.0 min, indicated 98% ee. [α]_D²³ = -27.4 (c 1.8, CHCl₃). Lit.^{10e}: [α]_D²⁵ = -29.2 (c 2.1, CHCl₃), 54% ee.

Reduction of 3-acetylthiophene using 1 mol% of spiroborate 1—A solution of freshly redistilled 3-acetylthiophene (630 mg, 5.00 mmol) in THF (5 mL) was added for 1h using an infusion pump. After the usual work-up, the crude was distilled to give (+)-(*R*)-1-(thiophen-3-yl)ethanol as a colorless oil (550 mg, 86%). Bp: 200 °C/1 mmHg. ¹H NMR (400 MHz, CDCl₃): δ 1.45 (d, *J* = 6.5 Hz, 3H, Me), 2.82 (br. s, 1H, OH), 4.86 (q, *J* = 6.4 Hz, CHMe), 7.04 (dd, *J* = 5.0, 1.2 Hz, 1H, C₄'H), 7.10–7.12 (m, 1H, C₂'H), 7.24 (dd, *J* = 5.0, 3.0 Hz, 1H, C₅'H); ¹³C NMR (100 MHz, CDCl₃): δ 24.4, 66.3, 120.1, 125.7, 126.0, 147.3. Chiral GC of *O*-acetyl derivative at T₁ = 120 °C (10 min), gradient = 5 °C/min, T₂ = 185 °C (3 min):

R_{T} 5.4 min; R_{T} 5.15 min, indicated 98.4 % ee. $[\alpha]_{\text{D}}^{23} = +27^{\circ}$ (c 1.5, CHCl_3). Lit.^{9b} $[\alpha]_{\text{D}}^{24} = +33.8$ (c 0.43, EtOH), 91% ee and Lit.^{9c} $[\alpha]_{\text{D}}^{25} = +44.7$ (c 1.00, EtOH), 99.8% ee

Reduction of 2,5-dimethyl-3-acetylthiophene using 1 mol% of spiroborate 1.^{7d}

—A solution of freshly redistilled 2,5-dimethyl-3-acetylthiophene (1.54 g, 10.00 mmol) in THF (5 mL) was added to the reducing solution for 1 h using an infusion pump. After the work-up, the crude was distilled to give (+)-(R)-1-2,5-dimethyl-3-yl)ethanol as a white solid (1.395 g, 89%). Bp: 152 °C/9 mmHg; mp 83–84 °C. ^1H NMR (400 MHz, CDCl_3): δ 1.41 (d, $J = 6.4$ Hz, 3H, CHMe), 2.02 (br. s, 1H, OH), 2.33 (s, 3H, Me), 2.38 (s, 3H, Me), 4.86 (q, $J = 6.6$ Hz, 1H, CHMe), 6.66 (s 1H, C_4H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.6, 15.1, 23.9, 64.4, 123.6, 131.5, 136.0, 141.3. Chiral GC of *O*-acetyl derivative at $T_1 = 70$ °C (10 min), gradient = 4 °C/min, $T_2 = 190$ °C (35 min): R_{T} 27.4 min; R_{T} 27.2 min, indicated 95.6% ee. $[\alpha]_{\text{D}}^{23} = +18$ (c 3.5, CHCl_3). Lit.^{9c}: $[\alpha]_{\text{D}}^{21} = +7.0$ (c 0.45, CHCl_3), 97% ee.

Reduction of 2,5-dichloro-3-acetylthiophene using 1 mol% of spiroborate 1—A

solution of freshly redistilled 2,5-dichloro-3-acetylthiophene (1.95 g, 10.00 mmol) in THF (5 mL) was added for 1 h using an infusion pump. After the work-up, the crude was distilled to give (+)-(R)-1-(5-chlorothiophen-2-yl)ethanol as a white solid (1.795 g, 91%). Bp: 143 °C/8 mmHg; mp 66–68 °C. ^1H NMR (400 MHz, CDCl_3): δ 1.42 (d, $J = 6.5$ Hz, 3H, CHMe), 2.25 (br. s, 1H, OH), (q, $J = 6.5$ Hz, 1H, CHMe), 6.87 (s 1H, C_4H); ^{13}C NMR (100 MHz, CDCl_3): δ 23.2, 64.1, 121.4, 124.4, 126.9, 142.5. Chiral GC of *O*-acetyl derivative at $T_1 = 90$ °C (10 min), gradient = 4 °C/min, $T_2 = 190$ °C (35 min): R_{T} 12.6 min; R_{T} 12.4 min, indicated **98.6% ee**. $[\alpha]_{\text{D}}^{23} = +24^{\circ}$ (c 3.8, CHCl_3). For 99.8% ee: $[\alpha]_{\text{D}}^{20} = +30^{\circ}$ (c 0.011, CHCl_3). Lit.^{9b} $[\alpha]_{\text{D}}^{21} = +6.75$ (c 0.2, CHCl_3), 92.1% ee.

Reduction of 6,7-dihydrobenzo[b]thiophen-4(5H)-one using 1 mol% of spiroborate 1—A

solution of freshly redistilled 3-acetylthiophene (760 mg, 5.00 mmol) in THF (5 mL) was added for 1 h using an infusion pump. After the work-up, the residue was under vacuum to give (+)-(R)-4,5,6,7-tetrahydrobenzo[b]thiophen-4-ol as a white solid (716 mg, 93%). Bp: 152 °C/6 mmHg; mp 57–59 °C. ^1H NMR (400 MHz, CDCl_3): δ 1.1.75–2.10 (m, 5H, C_5H , C_6H and OH), 2.67–2.84 (m, 2H, C_7H), 4.76 (br s, 1H, C_4H), 7.01 (d, $J = 5.2$ Hz, C_3H), 7.08 (d, $J = 5.2$ Hz, C_2H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.9, 25.0, 32.3, 65.4, 122.7, 122.6, 138.0, 138.7. Chiral GC of *O*-acetyl derivative at $T_1 = 110$ °C (10 min), gradient₁ = 1 °C/min, $T_2 = 120$ °C (10 min), gradient₂ = 0.5 °C/min, $T_3 = 130$ °C (20 min), gradient₃ = 10 °C/min, $T_4 = 150$ °C/min (20 min): R_{T} 43.4; R_{T} 43.8 min, indicated 94% ee. $[\alpha]_{\text{D}}^{23} = -7^{\circ}$ (c 1, CHCl_3).

Reduction of thiochroman-4-one using 1 mol% of spiroborate 1—A

solution of freshly redistilled thiochroman-4-one (1.64 g, 10.0 mmol) in THF (5 mL) was added for 1 h using an infusion pump. After the usual work-up, the residue was distilled under vacuum to give (+)-(R)-thiochroman-4-ol as a white solid (1.53 g, 92%). Bp: 155 °C/4 mmHg; mp 78–80 °C. ^1H NMR (400 MHz, CDCl_3): δ 1.96–2.04 (m, 1H, C_3H), 2.21 (br s, 1H, OH), 2.24–2.31 (m, 1H, C_3H), 2.79–2.84 (m, 1H, C_2H), 3.22–3.30 (m, 1H, C_2H), 4.72 (br tr, $J = 3.9$ Hz, 1H, C_4H), 7.01–7.05 (m, 1H, C_8H), 7.07–7.16 (m, 2H, C_7H and C_6H), 7.24–7.28 (m, 1H, C_5H); ^{13}C NMR (100 MHz, CDCl_3): δ 21.5, 30.0, 66.5, 124.2, 126.7, 128.4, 129.7, 120.4, 133.2, 134.6; Chiral GC of *O*-acetyl derivative at $T_1 = 150$ °C gradient = 1 °C/min, $T_2 = 185$ °C: R_{T} 14.97 min; R_{T} 15.5 min, indicated 98.7% ee. $[\alpha]_{\text{D}}^{23} = +134$ (c 1.9, CHCl_3). Lit.^{9a} (S): $[\alpha]_{\text{D}}^{25} = -113.1$ (c 0.46, CHCl_3), 90% ee.

4.4.12 Reduction of 6-chlorothiochroman-4-one using 1 mol% of spiroborate 1

—A solution of freshly redistilled 6-chlorothiochroman-4-one (995 mg, 5.00 mmol) in THF (5 mL) was added for 1 h using an infusion pump. After the work-up, the residue was distilled

under vacuum to give (+)-(*R*)-6-chlorothiochroman-4-ol as a white solid (920 g, 92%). Mp 102–104 °C. ¹H NMR (400 MHz, CDCl₃): δ 2.02–2.10 (m, 1H, C₃H), 2.24–2.30 (m, 1H, C₃H), 2.59 (br. s, 1H, OH), 2.87–2.93 (m, 1H, C₂H), 3.22–3.28 (m, 1H, C₂H), 4.71 (dd, *J* = 4.9, 3.1 Hz, 1H, C₄H), 7.07 (d, *J* = 8.4 Hz, 1H, C₈H), 7.15 (dd, *J* = 8.4, 2.1 Hz, 1H, C₇H), 7.35 (d, *J* = 1.8 Hz, 1H, C₅H); ¹³C NMR (100 MHz, CDCl₃): δ 21.8, 30.0, 66.4, 127.9, 128.5, 129.7, 129.9, 131.8, 136.3; Chiral GC of *O*-acetyl derivative at T₁ = 150 °C gradient = 1 °C/min, T₂ = 185 °C: Rt_R 25.6 min; Rt_S 26.7 min, indicated 98.7% ee. [α]_D²³ = +79 (*c* 2.2, CHCl₃).

Reduction of (*E*)-4-phenylbut-3-en-2-one using 10% of spiroborate 1—A solution of (*E*)-4-phenylbut-3-en-2-one (730 g, 5.0 mmol) in THF (5 mL) was added at 0 °C for 1 h using an infusion pump. The reaction mixture was stirred at 25 °C over 30 min, then cooled at 0 °C and quenched with methanol (5 mL), concentrated. The residue was dissolved in methanol (10 mL) and refluxed over 5 h, concentrated, re-dissolved in methanol (10 mL) and concentrated again. The residue was distilled in a Kugelrohr apparatus under vacuum to give (+)-(*R,E*)-4-phenylbut-3-en-2-ol as a pale yellow oil (543 mg, 73%). Chiral GC of *O*-acetyl derivative at T₁ = 90 °C gradient = 4 °C/min, T₂ = 190 °C (35 min: Rt_R 37.4 min; Rt_S 36.5 min, indicated 80% ee. [α]_D²³ = +25.6 (*c* 4, CHCl₃). Lit.^{10g} [α]_D = +27 (*c* 0.5, CHCl₃) 84% ee, Lit.^{10f} (*S*) [α]_D = −32.2 (*c* 5, CHCl₃) 81% ee.

Reduction of (*Z*)-4-(furan-3-yl)but-3-en-2-one using 10% of spiroborate 1—A solution of (*Z*)-4-(furan-2-yl)but-3-en-2-one (1.36 g, 10.0 mmol) in THF (5 mL) was added to the reducing solution at 0 °C for 1 h using an infusion pump. After the usual work-up, the crude was distilled in a Kugelrohr apparatus under vacuum to give (*R,Z*)-4-(furan-2-yl)but-3-en-2-ol as a yellow oil (1.14 g, 83%). ¹H NMR (400 MHz, CDCl₃): δ 1.32 (d, *J* = 6.4 Hz, 1H), 2.26 (br. s, 1H, OH), 4.39–4.45 (m, 1H), 6.15–6.23 (m, 2H), 6.32–6.41 (m, 2H), 7.32 (d, *J* = 1.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 23.4, 68.3, 107.9, 111.3, 117.6, 132.4, 141.9, 152.5; Chiral GC of *O*-acetyl derivative at T₁ = 90 °C gradient = 4 °C/min, T₂ = 190 °C: Rt_R 8.5 min; Rt_S 7.7 min, indicated 83% ee. [α]_D²³ = +24 (*c* 2.5, CHCl₃).

Reduction of (*E*)-4-(thiophen-3-yl)but-3-en-2-one using 10% of spiroborate 1—A solution of (*Z*)-4-(thiophen-2-yl)but-3-en-2-one (1.52 g, 10.0 mmol) in THF (5 mL) was added at 0 °C for 1 h using an infusion pump. After the work-up, the residue was distilled in a Kugelrohr apparatus under vacuum to give the (*R,E*)-4-(thiophen-2-yl)but-3-en-2-ol as a yellow oil (1.14 g, 83%). ¹H NMR (400 MHz, CDCl₃): δ 1.32 (d, *J* = 6.4 Hz, 1H), 2.26 (br. s, 1H, OH), 4.36–4.43 (m, 1H), 6.07 (dd, *J* = 15.8, 6.4 Hz), 6.65 (d, *J* = 15.8 Hz, 1H), 6.90–6.94 (m, 2H), 7.11–7.12 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 23.3, 68.4, 122.5, 124.2, 125.7, 127.3, 141.8; Chiral GC of *O*-acetyl derivative at T₁ = 110 °C gradient = 1 °C/min, T₂ = 140 °C: Rt_R 25.3 min; Rt_S 24.2 min, indicated 80% ee. [α]_D²³ = +18.2 (*c* 2.3, CHCl₃). Lit.^{9c} [α]_D²⁵ = +41.3 (*c* 0.49, CHCl₃), 91% ee.

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Figure 1.
Biologically active heterocyclic compounds containing sulfur.

Scheme 1.

Table 1Reduction of ketones containing the furanyl ring and using spiroborate ester **1** in 10 and 1 mol %^a

Entry	Substrate	Cat. 1 (%)	Yield ^d (%)
1	2-Acetylfuran	10	63
2		1	65
3	2-Acetyl-5-methylfuran	10	87 ^d
4		1	91

Entry	Substrate	Cat. 1 (%)	Yield ^d (%)
5		10	88 ^d
6		1	95
1-(benzofuran-2-yl)ethanone			
7	benzofuran-3(2H)-one	10	86 ^d
8		5	78 ^d
9	Chroman-4-one	10	82

^aThe reaction was carried out using 0.7 equiv of borane DMS in THF at room temperature.

^bYield after distillation in a Kugelrohr apparatus.

^cDetermined by GC of the acetate on a CP-Chirasil-Dex CB column.

^dYield after column chromatography.

^aDetermined by ³¹P NMR of a phosphonate (CDA) derivative.¹⁵

Table 2Reduction of heteroaryl ketones containing sulfur using 1 and 10 mol % of spiroaminoborate ester **1**.^a

Entry	Substrate	Cat. 1 (%)	Yield (%)
1	2-acetylthiophene	10	
2		1	
3	2-acetyl-5-chlorothiophene	10	91
4		1	
5	3-acetylthiophene	10	
6		1	86
7	3-acetyl-2,5-dimethylthiophene	10	90
8		1	
9	3-acetyl-2,5-dichlorothiophene	10	92
10		1	

Entry	Substrate	Cat. 1 (%)	Yield (%)
11		10	92
12		1	

6,7-Dihydro-5H-benzo[b]thiophen-4-one

Entry	Substrate	Cat. 1 (%)	Yield (%)
13		10	8
14		1	
<h1>Thiochroman-4-one</h1>			
15		10	8
16		1	
6-chlorothiochroman-4-one			

^aThe reaction was carried out using 0.7 equiv of borane DMS in THF at room temperature.

^bIsolated yield after distillation in a Kugelrohr apparatus.

^cDetermined by GC of the acetate on chiral column.

^dThe reaction was carried out using BH₃-DEA

Table 3

Studies on the reduction of unsaturated ketones using spiroborate ester **1**.^a

6: *E*, R = Ph
7: *E*, R = 2-thiophenyl
8: *Z*, R = 2-furyl

Entry	Substrate	Cat. (%)	Borane	Yield ^b (%)	Ee ^c (%)
1		25	BH_3 -DMS	87 ^g	79
2		10	BH_3 -DMS	73	80
3		1	BH_3 -DMS	73	70
4		10	BH_3 -DEA	^d	67
5		10	BH_3 -THF ^e	^d	72
6		10	BH_3 -THF ^f	^d	74

(*E*)-4-phenylbut-3-

6: *E*, R = Ph

7: *E*, R = 2-thiophenyl

8: *Z*, R = 2-furyl

Entry	Substrate	Cat. (%)	Borane	Yield ^b (%)	Ee ^c (%)
7	 (<i>E</i>)-4-(thiophen-2-yl)but-3-en-2-one 7	25	BH ₃ -DMS	55 ^g	72
8		10	BH ₃ -DMS	83	80
9		1	BH ₃ -DMS	87	62
10	 (<i>Z</i>)-4-(furan-2-yl)but-3-en-2-one 8	25	BH ₃ -DMS	73 ^g	81
11		10	BH ₃ -DMS	83	83
12		1	BH ₃ -DMS	88	65

^aThe reaction was carried out using 0.6 equiv of borane reagent in THF at 0 °C.

^bYield after distillation in a Kugelrohr apparatus.

^cDetermined by GC of the acetate on a chiral column.

^dThe product was not isolated.

^eBorane-THF complex was stabilized by < 0.005M of NaBH₄.

^fBorane-THF complex was stabilized by < 0.005M of *N-tert*-butyl-*N*-isopropyl-*N*-methylamine.

^gYield after column chromatography.