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A Protocol for NMR Analysis of the Enantiomeric Excess of Chiral Diols Using an Achiral Diboronic Acid Template

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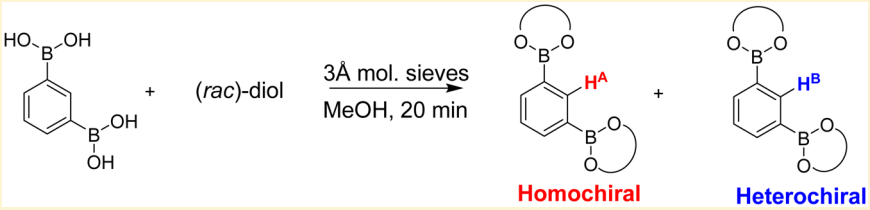
Supporting Information



ABSTRACT: A practically simple derivatization protocol for determining the enantiopurity of chiral diols by ^{1}H NMR spectroscopic analysis is described. Diols were treated with 0.5 equiv of 1,3-phenyldiboronic acid to afford mixtures of diastereomeric boronate esters whose homochiral/heterochiral ratios are an accurate reflection of the diol's enantiopurity.

NMR spectroscopic analysis has proven itself to be an effective technique for determining the enantiomeric excess (*ee*) of chiral substrates, with a wide range of chiral solvating agents and chiral derivatization agents having been developed for this purpose.[1−3] The Horeau concept of statistical amplification has also been employed to develop efficient dimerization protocols that enable the *ee* of chiral substrates to be determined by NMR spectroscopy.[4,5] In this approach the enantiomers of a chiral substrate react with 0.5 equiv of an *achiral* bifunctional substrate. This affords a mixture of diastereomeric homochiral and heterochiral (*meso*) dimers, whose diastereomeric excess (*de*) is then determined by NMR spectroscopic analysis. As long as no kinetic resolution occurs in the derivatization process, then the measured *de* can be used to calculate the enantiopurity of the parent diol. (All values reported are absolute *ee* values. Using this method it is not possible to define which enantiomer is in excess.) A range of different achiral bifunctional templates have been developed that enable the *ee* of chiral alcohols,[4−8] thiols,[7−9] amines,[10,11] amino esters,[12] phosphiranes,[12] and carboxylic acids[13−15] to be accurately determined. Further to these reports, we now describe a new Horeau based NMR protocol that employs an achiral *bis*-boronic acid template to determine the *ee* of chiral diols.

We have recently reported effective three-component chiral derivatization protocols to determine the *ee* of chiral diols, amines, amino alcohols, diamines, and hydroxylamines.[16−26] These approaches rely on the efficient formation of diastereomeric boronate esters from a three-component reaction of a chiral analyte with 2-formyl-phenyl boronic acid templates and a chiral auxiliary.[16−26] Inspired by the efficiency of these complexation reactions, we were intrigued to determine whether an achiral *bis*-boronic acid could be used as an achiral template to develop a Horeau based dimerization protocol to determine the *ee* of chiral diols. In this approach, we envisaged that reaction of a chiral diol with 0.5 equiv of a *bis*-boronic acid template would afford a mixture of homochiral and heterochiral *bis*-boronate esters whose diastereomeric ratio could then be determined by ^{1}H NMR spectroscopy. Provided no kinetic resolution occurs, then this diastereomeric ratio could then be used to calculate the *ee* of the parent diol.

Dimethyl-DL-tartrate **1a** (1.0 equiv) was first reacted with 1,3-phenyldiboronic acid (0.5 equiv) in methanol in the presence of 3 Å molecular sieves. This derivatization reaction was complete after 20 min, with ^{1}H NMR spectroscopic analysis in $CDCl_3$ revealing clean formation of a pair of diastereomeric heterochiral and homochiral *bis*-boronate esters in a statistical 50:50 ratio (Scheme 1).

This was confirmed by the presence of two singlet resonances in the 500 MHz ^{1}H NMR spectrum at δ 8.50 ppm and δ 8.48 ppm corresponding to the H^A and H^B aryl ring protons of the homochiral and heterochiral boronate esters respectively (Figure 1A). A pair of baseline resolved singlet resonances centered at δ 3.91 ppm ($OCH^C{}_3$ and $OCH^D{}_3$) were also present, corresponding to the methoxy ester protons of the homochiral and heterochiral boronate esters. These assignments were confirmed by repeating the derivatization reaction using enantiopure dimethyl-L-tartrate which gave a clean ^{1}H NMR spectrum exhibiting singlet resonances at δ 8.50 ppm (H^A) and δ 3.91 ppm ($OCH^C{}_3$) that were assigned to the homochiral boronate ester complex (Figure 1B).

In order to determine the scope and limitations of this new Horeau dimerization protocol, a series of racemic chiral diols were derivatized with 1,3-phenyldiboronic acid in the presence of 3 Å molecular sieves in methanol. Derivatization of (*rac*)-diols **1b−e** with 1,3-phenyldiboronic acid gave 50:50 mixtures of their corresponding homochiral and heterochiral boronate

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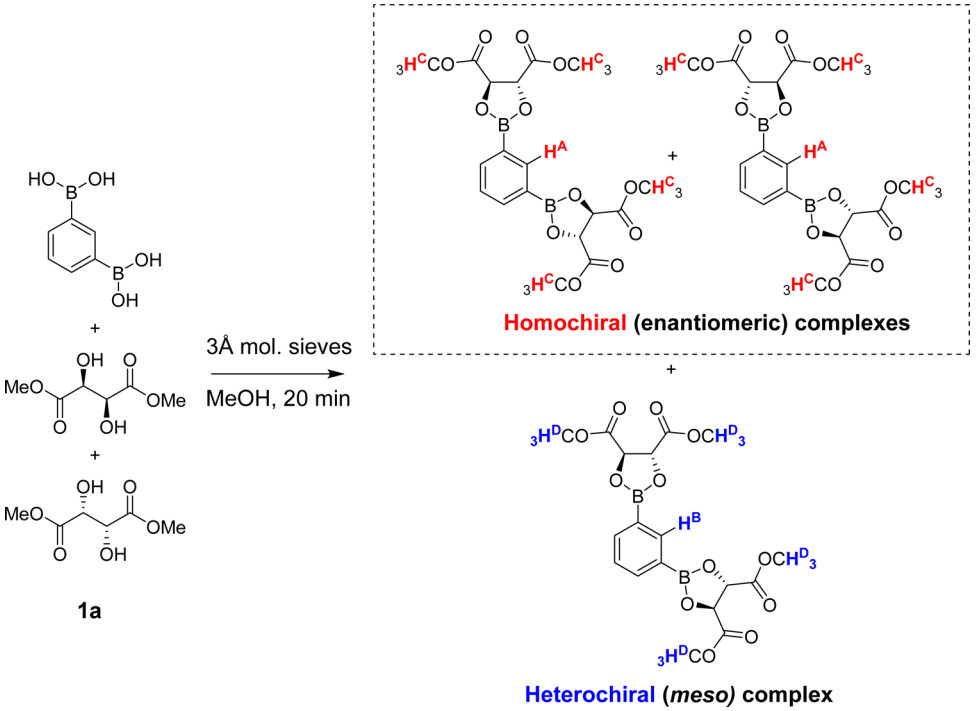
Scheme 1. Reaction of Dimethyl-DL-tartrate 1a with 1,3-Phenyldiboronic Acid Affords a 50:50 Mixture of Diastereomeric Homochiral and Heterochiral *bis*-Boronate Esters



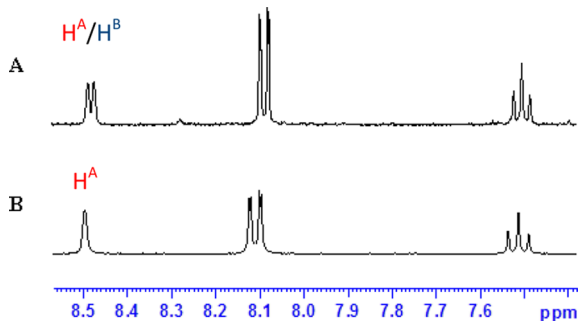


Figure 1. (A) Expansion of the 500 MHz ^{1}H NMR spectrum of the mixture of diastereomeric products formed from dimethyl-DL-tartrate **1a** and 1,3-phenyldiboronic acid. (B) Expansion of the 500 MHz ^{1}H NMR spectrum of the homochiral boronate ester product formed from reaction of enantiopure dimethyl-L-tartrate and 1,3-phenyldiboronic acid.

esters in quantitative yield (Table 1). 500 MHz ^{1}H NMR spectroscopic analysis of these mixtures revealed that the resonances for the aryl protons H^A and H^B of each pair of homochiral and heterochiral complexes were baseline resolved in each case.

Examination of the ^{1}H NMR spectrum of the 50:50 mixture of homochiral and heterochiral boronate esters derived from dibenzyl-DL-tartrate **1f** revealed partial overlap of the diagnostic singlets for their H^A and H^B protons at δ 8.46 ppm (Figure 2A). It was reasoned that the broadness of these singlets might be due to long-range coupling with aryl protons, and as a consequence, we decided to carry out a proton decoupled (^{1}H{^{1}H}) experiment in an attempt to eliminate these coupling effects.[27] It was found that selective irradiation of the aryl resonances centered at δ 8.05 ppm using a low power pulse during acquisition and Gaussian enhancement removed these long-range couplings. This resulted in significant sharpening of the diastereomeric H^A and H^B proton singlets that enabled baseline resolution of these resonances to be achieved (Figure 2B).

In order to determine the accuracy of this new Horeau protocol for determining *ee*, scalemic samples of methyl-2,3-dihydroxy-3-phenylpropionate **1b** of 95%, 80%, and 60% *ee* were derivatized with 1,3-phenyldiboronic acid in methanol in the presence of 3 Å molecular sieves. Analysis of the resultant ^{1}H NMR spectra revealed that the integrals of the diastereomeric H^A and H^B resonances of the homochiral and heterochiral complexes at δ 8.59 ppm and δ 8.57 ppm could be used to accurately measure the *de* of the heterochiral complex (Figure 3). In contrast to conventional ^{1}H NMR chiral derivatization protocols, the *de*'s measured using a Horeau-type derivatization protocol do not correlate directly to the *ee*'s of the chiral analyte. Instead, the *ee* must be calculated using a curve (see Supporting Information, Graph 1) which takes into account the quadratic relationship that exists between the *de* of the homochiral/heterochiral complexes and the *ee* of the chiral analyte. Therefore, the *de*'s of 88%, 61%, and 32% measured for the integral ratios of the homochiral/heterochiral complexes were shown to correlate to calculated values of 94%, 78%, and 58% *ee* respectively. These measured *ee* values are in excellent agreement with the known enantiopurities of the starting diols of 95%, 80%, and 60% *ee* respectively, indicating that no kinetic resolution occurs during the diol derivatization process. These values are within the 5% error limit normally accepted for determining *ee* using ^{1}H NMR spectroscopy, thus demonstrating that this Horeau derivatization protocol is effective for determining the *ee* of diols.

It should be noted that while this Horeau derivatization approach can be used to determine *ee*, it cannot be used to determine which enantiomer is present in excess within a scalemic sample. However, this information is easily obtainable from comparison of the sign of the optical rotation of the

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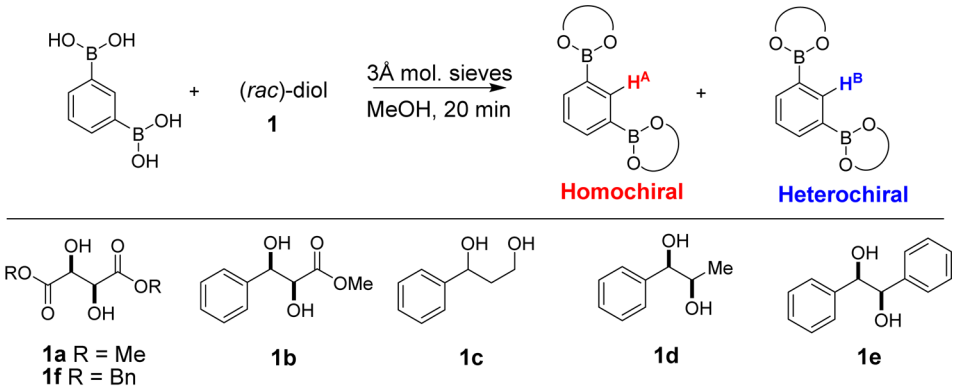
Table 1. Reaction of 1,3-Phenyldiboronic Acid with a Range of Chiral Diols 1a–f



*Derivatization of diols **1a-e** with 1,3-phenyldiboronic acid affords 50:50 mixtures of diastereomeric homochiral and heterochiral bis-boronate esters whose H^A and H^B resonances are baseline resolved in their ^1H NMR spectra*

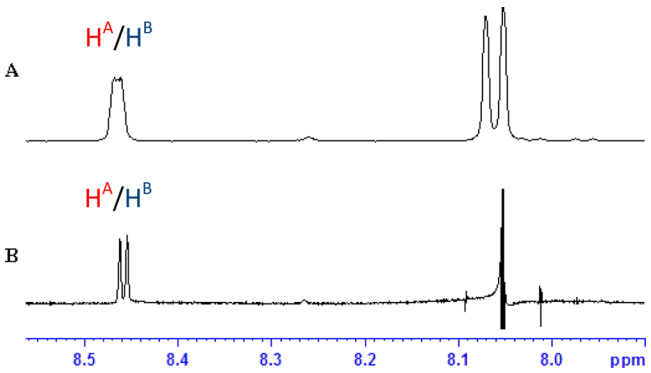


Figure 2. Expansion of the aryl region of the 500 MHz ^1H NMR spectrum of the 50:50 mixture of homochiral/heterochiral diastereomers formed from reaction of racemic dibenzyl-DL-tartrate **1f** with 1,3-phenyldiboronic acid. (A) Poor resolution observed for H^A/H^B resonances using standard ^1H NMR processing techniques. (B) Baseline resolution observed for H^A/H^B resonances using Gaussian enhancement of a $^1H\{^1H\}$ decoupling experiment.

scalemic diol with known literature values of its specific rotation.

Energy minimization and equilibrium geometry calculations were carried out using a semiempirical (PM3) method to calculate the lowest energy conformations of the heterochiral and homochiral boronate esters derived from 1-phenyl-1,3-propanediol **1c**. It can be seen for the heterochiral complex that the aryl rings of both diol fragments are directed toward the H^B proton that is flanked by both boronate ester functionalities (Figure 4A). The shielding effects of both these phenyl rings combine to result in a relative shift of the H^B resonance to a lower δ value in the ^1H NMR spectrum. In contrast, the homochiral model has one of its aryl rings pointing away from the aryl H^A proton, and as a consequence, the shielding it experiences is less than that for the heterochiral system, potentially resulting in a higher chemical shift value for H^A (Figure 4B).

In conclusion, a new Horeau protocol has been developed to determine the *ee* of chiral diols involving their reaction with 0.5 equiv of an achiral bifunctional boronic acid template to afford a mixture of heterochiral and homochiral diastereomers whose ratio can be accurately determined by ^1H NMR spectroscopic analysis. This diastereomeric ratio may then be used to calculate the *ee* of the parent diol. The simplicity of this approach, and the inexpensive achiral *bis*-boronic acid template employed, means it represents a versatile approach for determining the *ee* of chiral diols produced in asymmetric reactions.

EXPERIMENTAL SECTION

All racemic diols **1** were commercially available, except for **1d** which was prepared using the Sharpless dihydroxylation protocol described below.

Synthesis of (*rac*)-1-Phenylpropane-1,2-diol 1d.[28] AD-mix-α (0.70 g) and AD-mix-β (0.70 g) were dissolved in 1:1 *tert*-butanol/water (10 mL) and stirred at room temperature to produce two clear phases. Methanesulfonamide (95 mg, 1.00 mmol) was then added, and the mixture was cooled to 0 °C. *trans*-β-Methylstyrene (1.00 mmol) was then added, and the reaction was stirred vigorously at 0 °C for 24 h. Sodium sulfite was added, and the reaction was allowed to warm to room temperature and stirred for a further hour. The reaction mixture was extracted with dichloromethane (3 × 10 mL), and the combined organic layers were washed with 2 M potassium hydroxide solution. The combined organic layers were dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The crude product was purified by silica gel flash column chromatography (ethyl acetate/hexane) to afford the desired racemic diol **1d** as a white solid (128 mg, 84%). Mp 54–55 °C; IR (film/cm^{-1}) ν = 3340 cm^{-1} (OH); ^1H NMR (300 MHz; $CDCl_3$): δ_H = 7.42–7.32 (5H, m), 4.39 (1H, d, J = 7.3 Hz), 3.89 (1H, quin, J = 6.7 Hz), 2.72 (1H, br s), 2.56 (1H, br s), 1.09 (3H, d, J = 6.4 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ_C = 141.0, 128.5, 128.2, 126.9, 79.5, 72.3, 18.8; HRMS (ES): m/z calculated for $C_9H_{11}O_2$ $[M - H]^-$: 151.0759; found: 151.0773.

General Horeau Derivatization Protocol for Determining the Enantiomeric Excess of Chiral Diols. A chiral diol (0.24 mmol) was added to a solution of 1,3-phenyldiboronic acid (20 mg, 0.12 mmol) suspended in MeOH in the presence of 3 Å molecular sieves, and the suspension was stirred for 20 min at room temperature, before filtering and evaporation of the solvent under reduced pressure. The resultant mixture of heterochiral and homochiral diol products was then dissolved in $CDCl_3$ before acquiring a 500 MHz ^1H NMR spectrum.

50:50 Mixture of Homochiral and Heterochiral 2,2′-(1,3-Phenylene)bis(1,3,2-dioxaborolane-4,5-dicarboxylates). The title compounds were prepared according to the general Horeau derivatization procedure using racemic diol **1a** to afford a 50:50 mixture of homochiral and heterochiral diboronate esters as a white solid. ^1H NMR (500 MHz; $CDCl_3$): δ_H = 8.50 and 8.48 (1H, app d, $\Delta\delta$ = 0.020 ppm, BCC*H*CB), 8.09 (2H, d, J = 7.4 Hz), 7.51 (1H, t, J = 7.5 Hz), 5.16 (4H, s), 3.92 and 3.91 (12H, app d, $\Delta\delta$ = 0.010 ppm);

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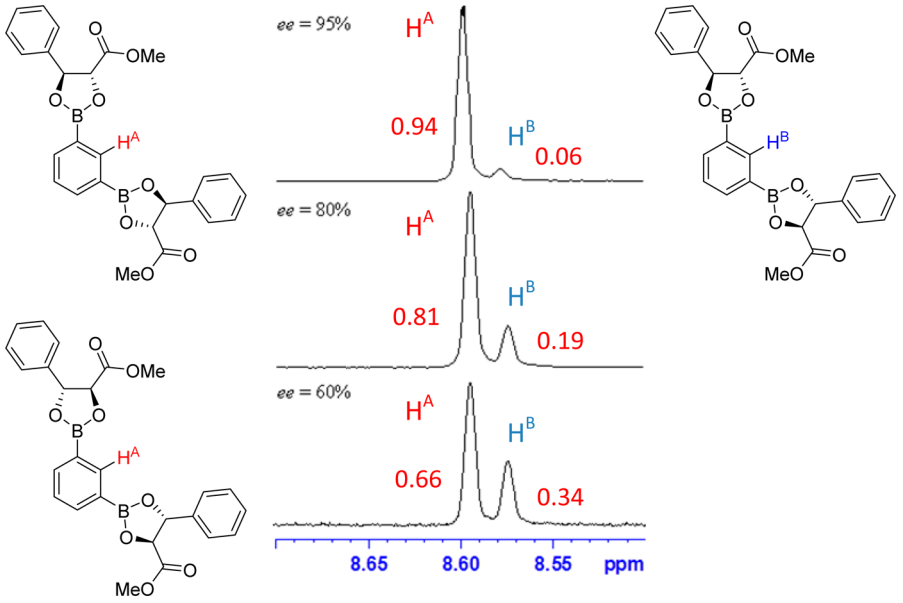

Figure 3. Expansion of the 500 MHz ^{1}H NMR spectra of the diastereomeric aryl resonances centered at δ 8.58 ppm formed from derivatization of scalemic **1b** with 1,3-phenyldiboronic acid. Expansions of ^{1}H NMR spectra shown for derivatization of scalemic samples of diol **1b** of 95%, 80%, and 60% *ee* respectively. Values in red refer to measured homochiral/heterochiral diastereomeric integral ratios.

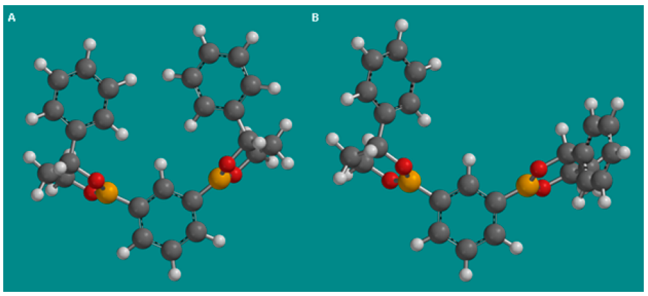

Figure 4. (A) Lowest energy conformation of the (*meso*)-heterochiral complex of diol **1c**; (B) lowest energy conformation of the (*R*,*R*)-homochiral complex of diol **1c**.

^{11}B NMR (96 MHz; $CDCl_3$): δ_B = 31.8; ^{13}C NMR (125 MHz; $CDCl_3$): δ_C = 169.8, 142.5, 142.4, 139.0, 127.5, 77.9, 53.1.

50:50 Mixture of Homochiral and Heterochiral Dimethyl 2,2′-(1,3-Phenylene)bis(5-phenyl-1,3,2-dioxaborolane-4-carboxylates). The title compounds were prepared according to the general Horeau derivatization protocol using racemic diol **1b** to afford a 50:50 mixture of homochiral and heterochiral diboronate esters as a white solid. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H = 8.59 and 8.57 (1H, app d, $\Delta\delta$ = 0.020 ppm), 8.14 (2H, d, J = 7.4 Hz), 7.53 (1H, t, J = 7.5 Hz), 7.47−7.40 (8H, m), 7.40−7.37 (2H, m), 5.65 (2H, dd, J_1 = 2.9 Hz, J_2 = 6.1 Hz), 4.90 (2H, d, J = 6.1 Hz), 3.90 (6H, s); ^{11}B NMR (96 MHz; $CDCl_3$): δ_B = 30.7; ^{13}C NMR (125 MHz; $CDCl_3$): δ_C = 171.0, 142.4, 140.3, 138.8, 128.9, 128.6, 127.6, 125.4, 125.3, 82.6, 81.9, 52.8; HRMS (ES): m/z calculated for $C_{26}H_{24}B_2O_8Na$ $[M + Na]^+$: 509.1554; found: 509.1540.

50:50 Mixture of Homochiral and Heterochiral 1,3-Bis(4-phenyl-1,3,2-dioxaborinan-2-yl)benzenes. The title compounds were prepared according to the general Horeau derivatization protocol using racemic diol **1c** to afford a 50:50 mixture of homochiral and heterochiral diboronate esters as a white solid. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H = 8.47 and 8.45 (1H, app d, $\Delta\delta$ = 0.020 ppm), 8.03 (2H, d, J = 7.3 Hz), 7.47−7.41 (9H, m), 7.37−7.33 (2H, m), 5.33 (2H, app dd, J_1 = 9.2 Hz, J_2 = 3.1 Hz), 4.30−4.24 (2H, m), 4.23−4.17 (2H, m), 2.36 (2H, dq, J_1 = 14.2 Hz, J_2 = 4.1 Hz), 2.13−2.05 (2H, m); ^{11}B NMR (96 MHz; $CDCl_3$): δ_B = 30.5; ^{13}C NMR (125 MHz; $CDCl_3$): δ_C = 142.7, 142.6, 139.7, 139.6, 136.4, 128.5, 127.5, 127.0, 125.3, 72.8, 61.0, 60.9, 35.4; HRMS (ES): m/z calculated for $C_{24}H_{24}B_2O_4Na$ $[M + Na]^+$: 421.1758; found: 421.1764.

50:50 Mixture of Homochiral and Heterochiral 1,3-Bis(4-methyl-5-phenyl-1,3,2-dioxaborolan-2-yl)benzenes. The title compounds were prepared according to the general Horeau derivatization protocol using racemic diol **1d** to afford a 50:50 mixture of homochiral and heterochiral diboronate esters as a white solid. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H = 8.51 and 8.50 (1H, app d, $\Delta\delta$ = 0.012 ppm), 8.07 (2H, d, J = 7.4 Hz), 7.49 (1H, t, J = 7.5 Hz), 7.42−7.40 (8H, m), 7.38−7.35 (2H, m), 5.07 (2H, d, J = 7.5 Hz), 4.50 (2H, quin, J = 6.2 Hz), 1.57 (6H, d, J = 6.2 Hz); ^{11}B NMR (160 MHz; $CDCl_3$): δ_B = 30.6; ^{13}C NMR (125 MHz; $CDCl_3$): δ_C = 142.0, 141.9, 140.6, 140.5, 138.1, 128.7, 128.3, 127.4, 125.7, 125.6, 86.1, 81.7, 21.2.

50:50 Mixture of Homochiral and Heterochiral 1,3-Bis(4,5-diphenyl-1,3,2-dioxaborolan-2-yl)benzenes. The title compounds were prepared according to the general Horeau derivatization protocol using racemic diol **1e** to afford a 50:50 mixture of homochiral and heterochiral diboronate esters as a white solid. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H = 8.65 and 8.63 (1H, app d, $\Delta\delta$ = 0.024 ppm), 8.16 (2H, d, J = 7.5 Hz), 7.53 (1H, t, J = 7.3 Hz), 7.42−7.34 (20H, m), 5.36 (4H, s, C*H*); ^{11}B NMR (96 MHz; $CDCl_3$): δ_B = 30.2; ^{13}C NMR (125 MHz; $CDCl_3$): δ_C = 141.5, 140.3, 138.6, 128.8, 128.4, 125.9, 125.8, 87.0.

50:50 Mixture of Homochiral and Heterochiral Tetrabenzyl 2,2′-(1,3-Phenylene)bis(1,3,2-dioxaborolane-4,5-dicarboxylates). The title compounds were prepared according to the general Horeau derivatization protocol using racemic diol **1f** to afford a 50:50 mixture of homochiral and heterochiral diboronate esters as a white solid. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H = 8.46 (1H, br s), 8.06 (2H, d, J = 8.8 Hz), 7.46 (1H, t, J = 9.4 Hz), 7.43−7.39 (20H, m), 5.32−5.26 (8H, m) 5.15 (4H, s); ^{11}B NMR (96 MHz; $CDCl_3$): δ_B = 32.0; ^{13}C NMR (125 MHz; $CDCl_3$): δ_C = 171.4, 169.1, 142.5, 142.4, 139.1, 134.9, 128.7, 128.6, 128.4, 128.3, 78.0, 72.1, 68.1, 67.7.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01005.

Output files from energy minimization and equilibrium geometry calculations using a semiempirical (PM3) method to calculate the lowest energy conformations

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of the heterochiral (meso) and homochiral boronate esters (*RR* and *SS*) derived from 1-phenyl-1,3-propanediol **1c** (ZIP)

^{1}H and ^{13}C NMR spectra of *bis*-boronate complexes formed from reaction of diols **1a−f** with 1,3-phenyldiboronic acid as well as a graphical representation and discussion of the quadratic relationship seen between the enantiomeric excess of the chiral diol and diastereomeric excess (homochiral−heterochiral) of the corresponding *bis*-boronate complex (PDF)

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Notes

The authors declare no competing financial interest.

All data created during this research (including NMR and MS data) are openly available from the University of Bath data archive at http://doi.org/10.15125/BATH-00211.

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