

# Asymmetric organocatalytic diboration of alkenes

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## Instrumentation and chemicals

All reactions and manipulations were carried out under argon atmosphere, using Schlenk-type techniques. The solvents were distilled from dehydrating agents, and were deoxygenated before use. Bis(pinacolato)diboron was used as purchased from Allychem. Substrates, chiral alcohols were purchased from Sigma-Aldrich, and used as received, except for one. Chiral alcohol (1*S*,3*S*)-3-(butylamino)-1-phenylbutan-1-ol (**16**) was prepared in accordance with a previously described procedure.<sup>1</sup>

NMR spectra were obtained on either a Varian Goku 400 or a Varian Mercury 400 spectrometer. <sup>1</sup>H NMR and <sup>13</sup>C{<sup>1</sup>H} NMR chemical shifts are reported in ppm (δ) relative to tetramethylsilane, referenced to the chemical shifts of residual solvent resonances. <sup>11</sup>B{<sup>1</sup>H} NMR chemical shifts are reported in ppm (δ) relative to (CH<sub>3</sub>CH<sub>2</sub>)<sub>2</sub>O·BF<sub>3</sub>.

For GC analysis of the reaction mixtures a HP-5 column (L × I.D. 30 m × 0.25 mm, d<sub>f</sub> 0.25 μm) was used. For chiral chromatography the following columns were used. Chiral gas chromatography was carried out using a SUPELCO β-DEX 120 column (L × I.D. 30 m × 0.25 mm, d<sub>f</sub> 0.25 μm). Chiral HPLC experiments were carried out using either Chiracel OD-H or Chiracel OJ columns.

## General procedure to survey the substrate scope of the enantioselective metal free diboration reaction

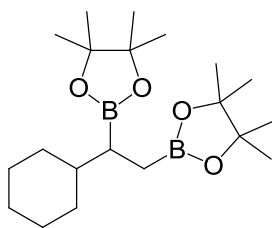
Cs<sub>2</sub>CO<sub>3</sub> (81.5 mg, 0.25 mmol) and bis(pinacolato)diboron (70 mg, 0.275 mmol) were transferred into an oven-dried Schlenk tube, provided with magnetic stir bar, under argon. DCM (1 ml) was added, and the mixture was stirred for a few minutes. After that, the substrate (0.25 mmol) and the chiral alcohol **14**, (*S*)-1-phenylpropan-1-ol, (69 μL, 68 mg, 0.5 mmol) were added, and the reaction mixture was stirred at 45 °C oil bath temperature for 16 hours. The reaction mixture was cooled to room temperature. An aliquot of 0.1 mL was taken from the solution. It was diluted with CH<sub>2</sub>Cl<sub>2</sub> (1 mL) and analyzed by GC/GC-MS to determine conversion and chemoselectivity. The aliquot was added to the reaction mixture and the entire sample was gently concentrated on a rotary evaporator. After all volatiles were evaporated, the sample was purified by silica-column.

## Oxidation Protocol

The 1,2-diborated product was treated with NaOH (2 mL, 3M) and H<sub>2</sub>O<sub>2</sub> (1 mL, 33%). The mixture was stirred for 4 hours. After this period of time, it was quenched with a saturated solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, and then extracted with AcOEt (3 x 20 mL). The organic phase was dried over MgSO<sub>4</sub>. The MgSO<sub>4</sub> was filtered off, and the solvents were evaporated in vacuum.

## Acetalisation Protocol

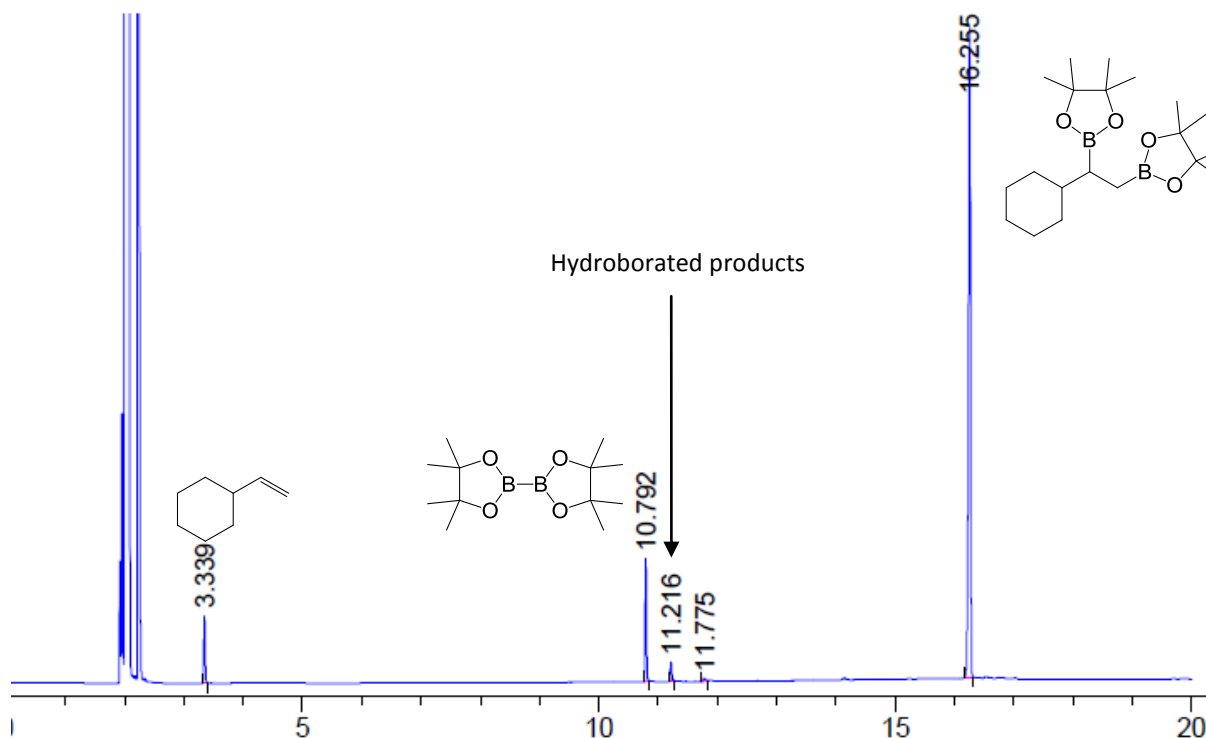
The 1,2-diol, obtained via the oxidation protocol, was treated with 1 mL of 2,2'-dimethoxypropane in the presence of catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was stirred for 30 min at 60 °C. The solution was gently concentrated on a rotary evaporator.



**2,2'-(1-cyclohexylethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane):**<sup>2</sup> The title compound was synthesized using the general procedure. The reaction was followed by TLC, and the conversion was determined by GC, and <sup>1</sup>H-NMR. The analytical samples were combined with the rest of the reaction mixture, all the volatiles were removed in vacuum, and the crude product was purified by column chromatography (silica, petroleum ether: EtOAc, 7:1). Colorless oil. Yield: 65 mg (72%). *R*<sub>f</sub> = 0.54 (silica TLC, petroleum ether : EtOAc, 7:1) <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ = 1.70-1.55 (m, 10H, C<sub>6</sub>H<sub>11</sub>), 1.31 (m, 1H, C<sub>6</sub>H<sub>11</sub>), 1.23 (s, 12H, B(pin)), 1.21 (s, 12H, B(pin)), 1.20-0.97 (m, 1H, CHB(pin)), 0.80 (dd, *J*<sub>1</sub> = 16, *J*<sub>2</sub> = 4 Hz, 1H, CH<sub>2</sub>B(pin)), 0.71 (dd, *J*<sub>1</sub> = 16, *J*<sub>2</sub> = 5.2 Hz, 1H, CH<sub>2</sub>B(pin)); <sup>13</sup>C{<sup>1</sup>H}NMR (CDCl<sub>3</sub>, 100 MHz): δ = 82.76, 82.72, 41.47, 32.08, 31.96, 26.87, 26.83, 26.71, 24.96, 24.93, 24.85, 24.68. <sup>11</sup>B{<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 128 MHz): δ = 34.76, 34.57. HRMS (ESI) *m/z* calculated for C<sub>20</sub>H<sub>38</sub>B<sub>2</sub>O<sub>4</sub> [*M*+*H*]<sup>+</sup> = 365.3043, found: 365.3019. The ee was determined via the analysis of the acetal derivative of the title compound by GC-MS equipped with a β-cyclodextrine chiral column (SUPELCO β-DEX 120).<sup>3</sup>

GC of the reaction mixture:

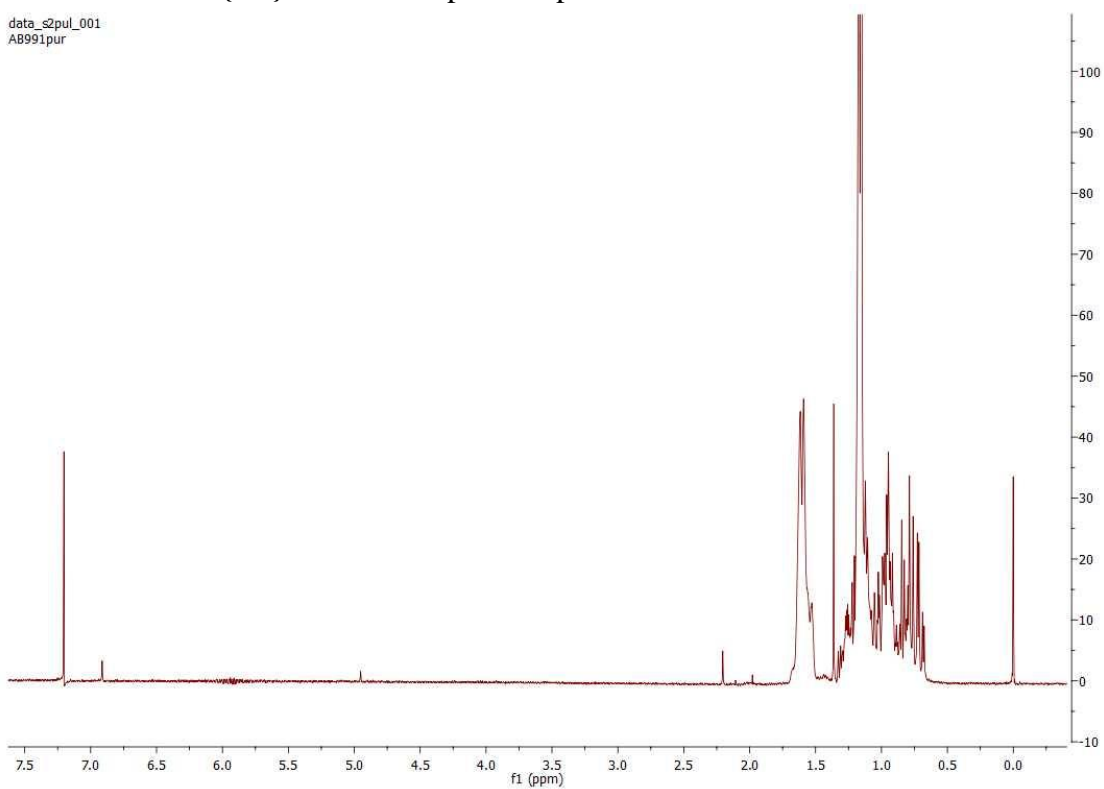
HID1 A, (AMA10VAB991.D)



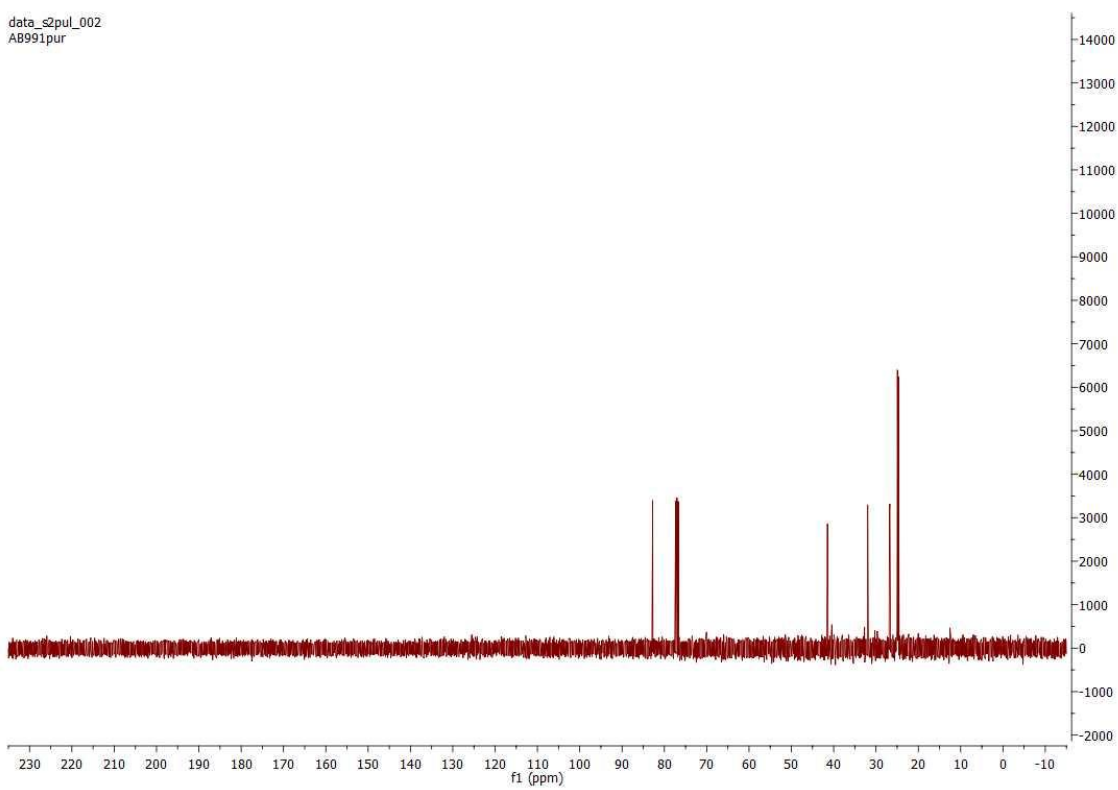
Injector temperature: 250 °C. Detector temperature: 275 °C. Pressure: 100 KPa.  
Initial oven temperature: 80 °C. Maintained for 3 min. Rate: 15 °C/min.  
Final oven temperature: 250 °C. Maintained for 5.67 min.

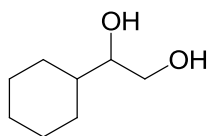
$^1\text{H}$ -NMR and  $^{13}\text{C}\{^1\text{H}\}$ NMR of the purified product:

data\_s2pul\_001  
AB991pur

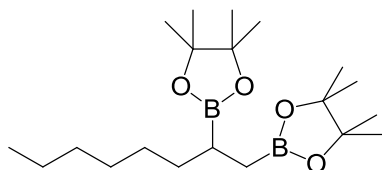


data\_s2pul\_002  
AB991pur



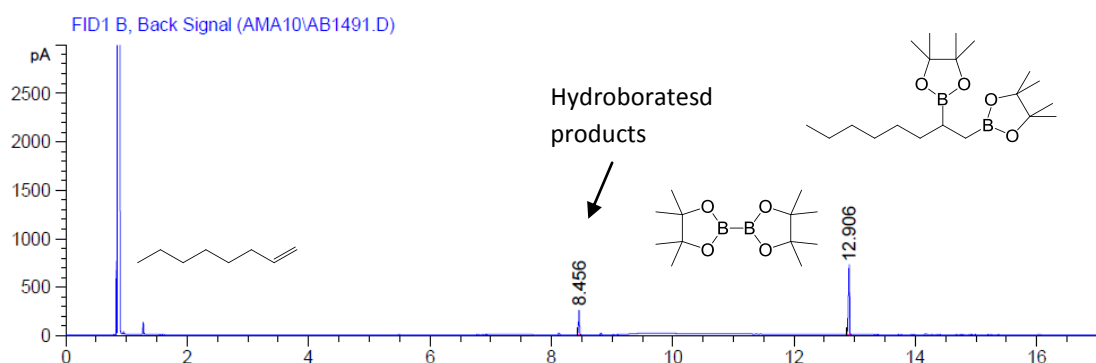


**1-cyclohexylethane-1,2-diol:**<sup>2</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): 3.69 (dd,  $J_1 = 10.8$ ,  $J_2 = 2.4$ , 1H), 3.51 (dd,  $J_1=10.8$ ,  $J_2 = 8$ , 1H), 3.42 (dt,  $J_1=6.8$ ,  $J_2 = 2.8$ , 1H), <sup>13</sup>C{<sup>1</sup>H}NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  76.4, 64.7, 40.7, 28.9, 28.6, 26.3, 26.0, 25.9.



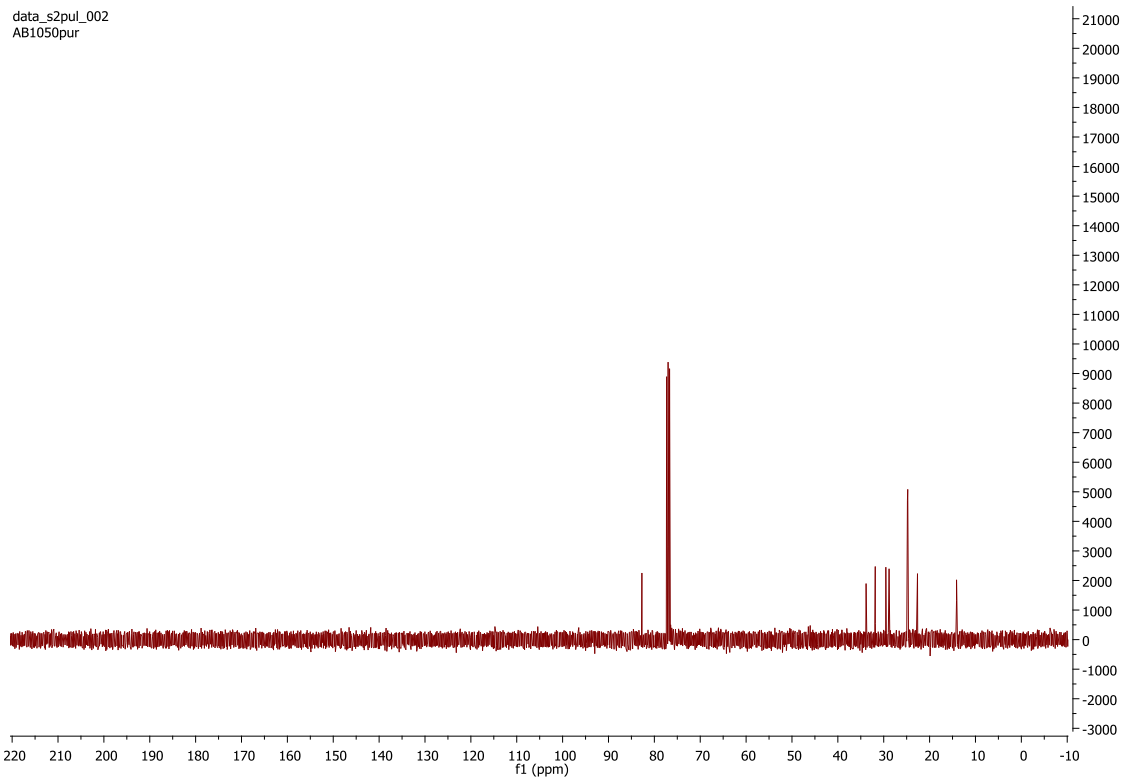
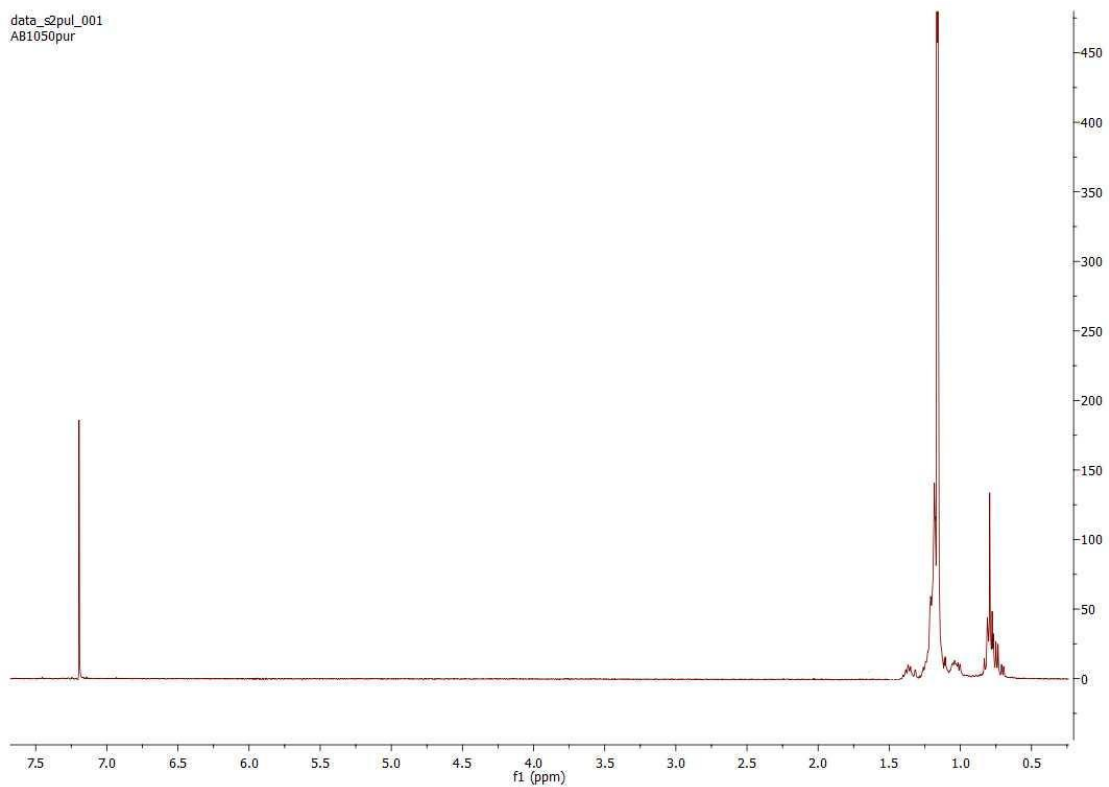
**2,2'-(octane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane):**<sup>2</sup> The title compound was synthesized using the general procedure. The reaction was followed by TLC, and the conversion was determined by GC, and <sup>1</sup>H-NMR. The analytical samples were combined with the rest of the reaction mixture, all the volatiles were removed in vacuum, and the crude product was purified by column chromatography (silica, from petroleum ether to petroleum ether: EtOAc, 5:1). Colorless oil. Yield: 111 mg (61%).  $R_f = 0.42$  (silica TLC, petroleum ether : EtOAc, 7:1). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta = 1.43$  (m, 1H), 1.27 (m, 8H), 1.23 (s, 12H), 1.22 (s, 12H), 1.11 (m, 2H), 0.86 (t, 3H,  $J=2.4$ ), 0.78 (dd, 3H,  $J=15.5$ ,  $J=6$ ). <sup>13</sup>C{<sup>1</sup>H}NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta = 82.8$ , 82.7, 33.9, 31.9, 29.5, 28.8, 24.9, 24.8, 24.7, 22.6, 14.1. <sup>11</sup>B NMR (CDCl<sub>3</sub>, 128 MHz):  $\delta = 35.0$ . HRMS (ESI)  $m/z$  calculated for C<sub>20</sub>H<sub>40</sub>B<sub>2</sub>O<sub>4</sub> [ $M+Na$ ]<sup>+</sup> = 389.3010, found: 389.3018. The ee was determined via the analysis of the acetal derivative of the title compound by GC-MS equipped with a  $\beta$ -cyclodextrine chiral column (SUPELCO  $\beta$ -DEX 120).<sup>3</sup>

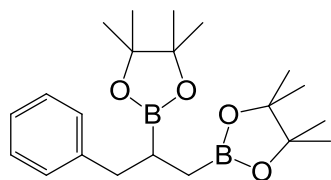
GC of the reaction mixture:



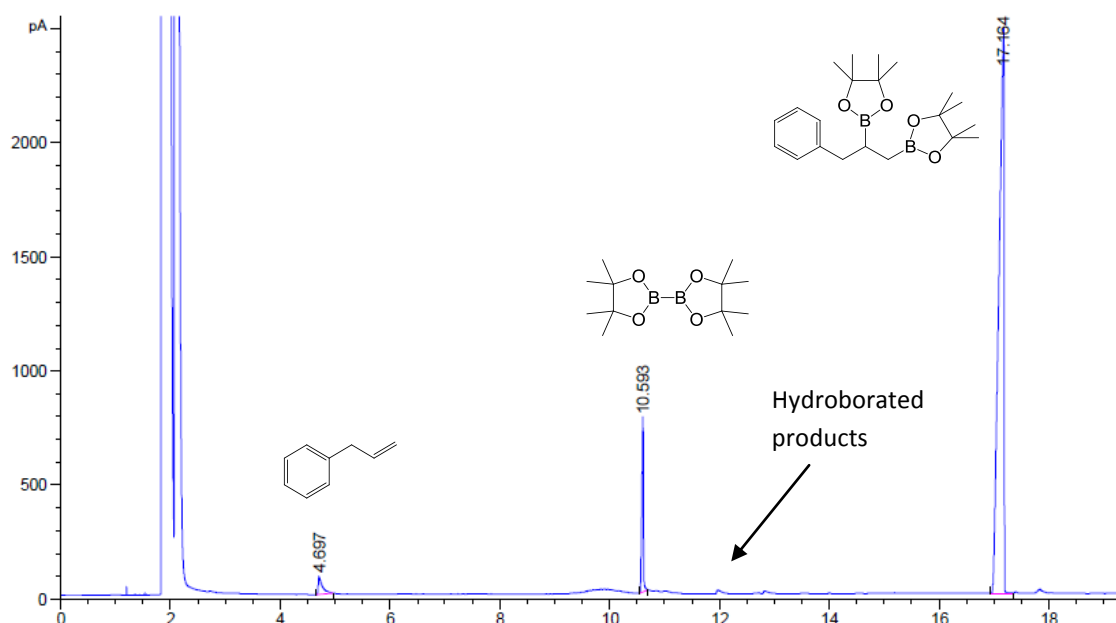
Injector temperature: 250 °C. Detector temperature: 275 °C. Pressure: 100 KPa.  
Initial oven temperature: 80 °C. Maintained for 3 min. Rate: 15 °C/min.  
Final oven temperature: 250 °C. Maintained for 5.67 min.

$^1\text{H}$ -NMR and  $^{13}\text{C}\{^1\text{H}\}$ NMR of the purified product:

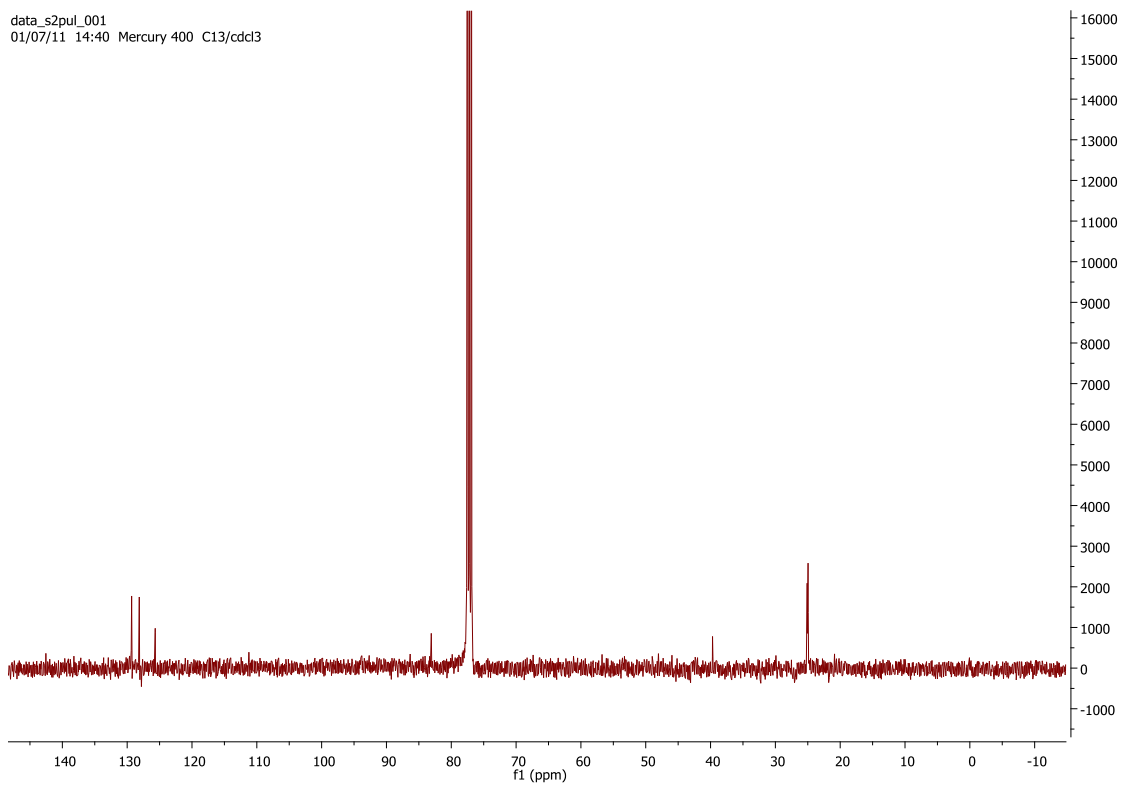
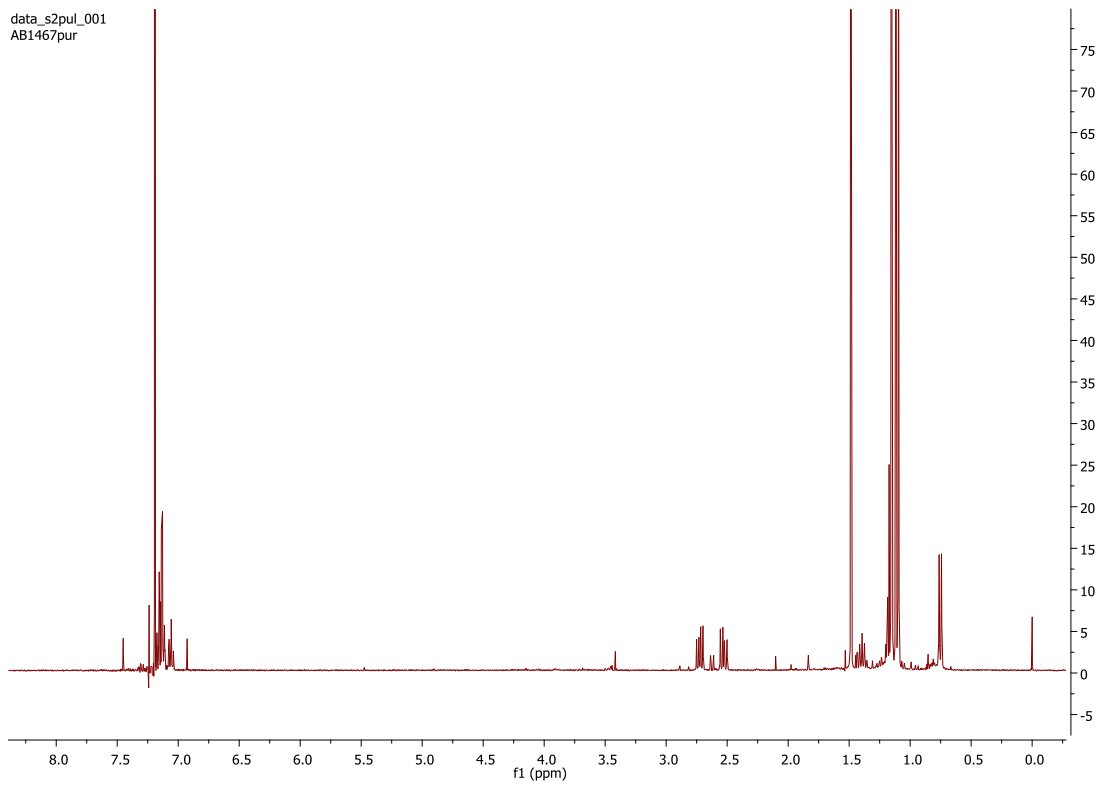




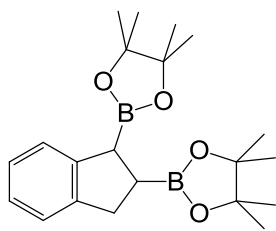
**4,4,5,5-tetramethyl-2-(4-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-yl)-1,3,2-dioxaborolane:**<sup>4</sup> The reaction was followed by TLC, and the conversion was determined by GC, and <sup>1</sup>H-NMR. The analytical samples were combined with the rest of the reaction mixture, all the volatiles were removed in vacuum, and the crude was purified by column chromatography (deactivated silica, from petroleum ether (with 10% NEt<sub>3</sub>) to petroleum ether (with 10% NEt<sub>3</sub>) : EtOAc 5:1). Colorless oil. Yield: 78 mg (84%) R<sub>f</sub> = 0.39 (silica TLC, petroleum ether : EtOAc, 9:1) <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 7.24-7.17 (4H, m, PhH), 7.13-7.09 (1H, m, PhH), 2.79 (1H, dd, *J* = 13.2, 7.6 Hz, CH<sub>2</sub>Ph), 2.59 (1H, dd, *J* = 13.2, 8.0 Hz, CH<sub>2</sub>Ph), 1.47-1.43 (1H, m, CHB(pin)), 1.21 (12H, s, B(pin)), 1.17 (6H, s, B(pin)), 1.15 (6H, s, B(pin)), 0.81 (2H, d, *J* = 7.6 Hz, CH<sub>2</sub>B(pin)); <sup>13</sup>C{<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 128 MHz): δ 142.4, 129.2, 128.0, 125.6, 83.0, 82.9, 39.6, 25.0, 24.9, 24.9, 24.8, 20.7, 12.4. The ee was determined via the analysis of the diol derivative of the title compound by HPLC-MS equipped with Chiralcel OD-H chiral column.



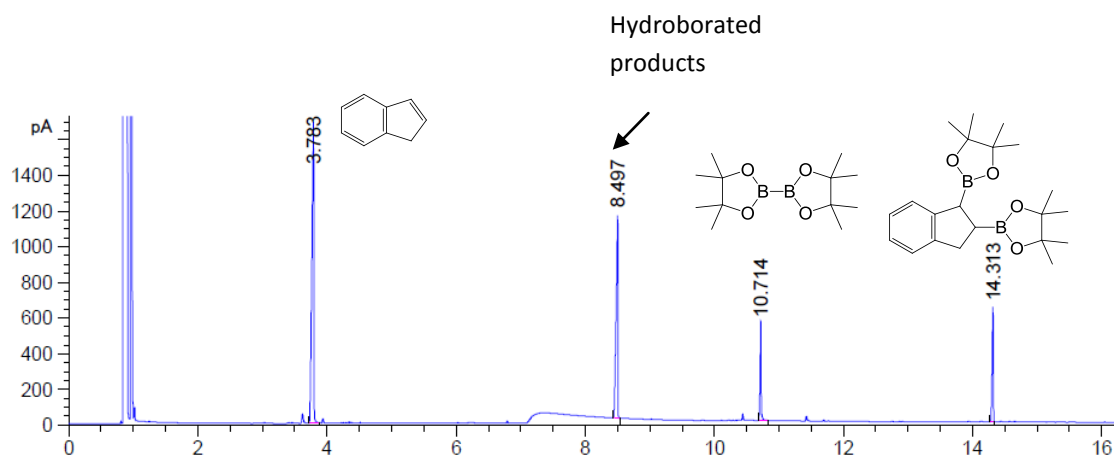
Injector temperature: 250 °C. Detector temperature: 275 °C. Pressure: 100 KPa.  
Initial oven temperature: 80 °C. Maintained for 3 min. Rate: 15 °C/min.  
Final oven temperature: 250 °C. Maintained for 5.67 min.







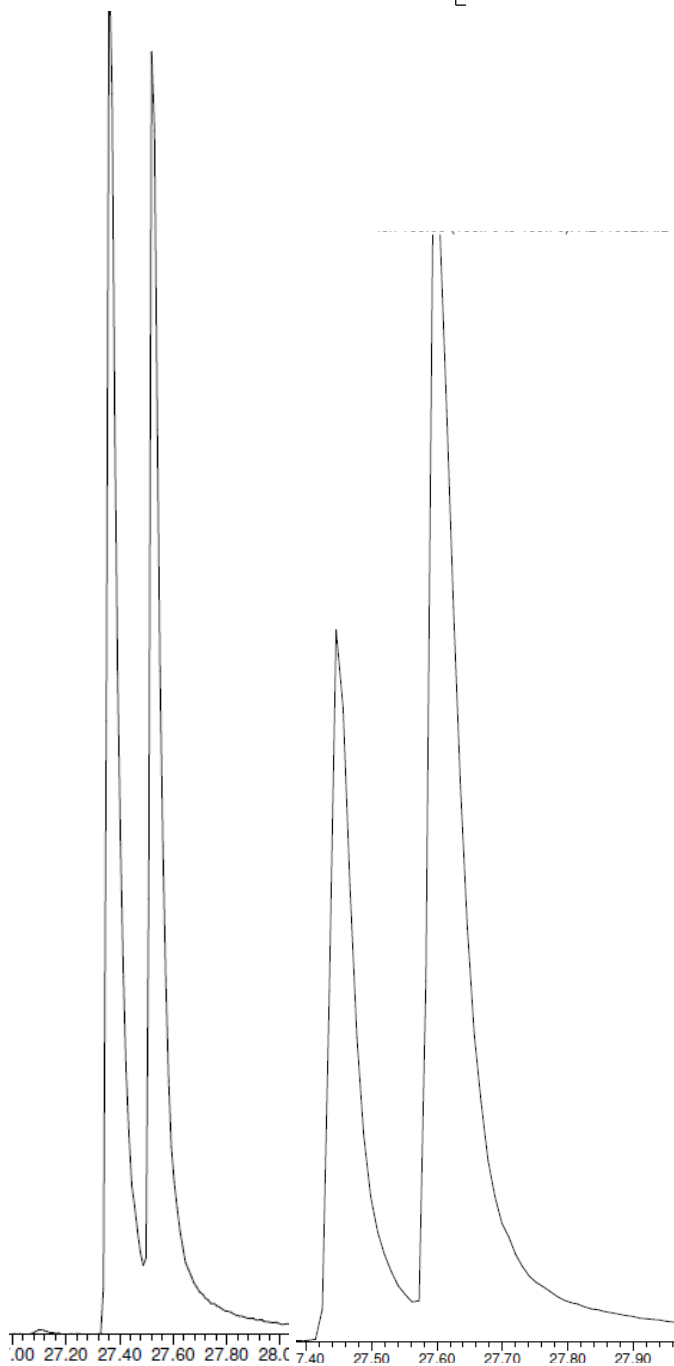
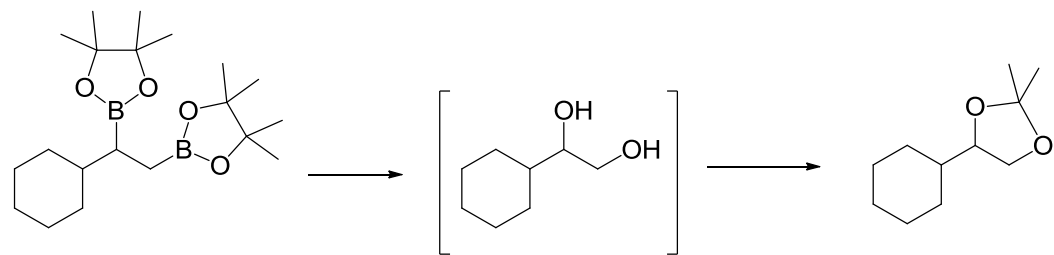
**2,2'-(2,3-dihydro-1H-indene-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane):**<sup>3</sup> The title compound was synthesized using the general procedure. Conversion and chemoselectivity were determined by GC-MS. The low GC yield did not allow the isolation of the diborated product. The ee was determined via the analysis of the diol derivative of the title compound by HPLC-MS equipped with Chiralcel OJ chiral column.



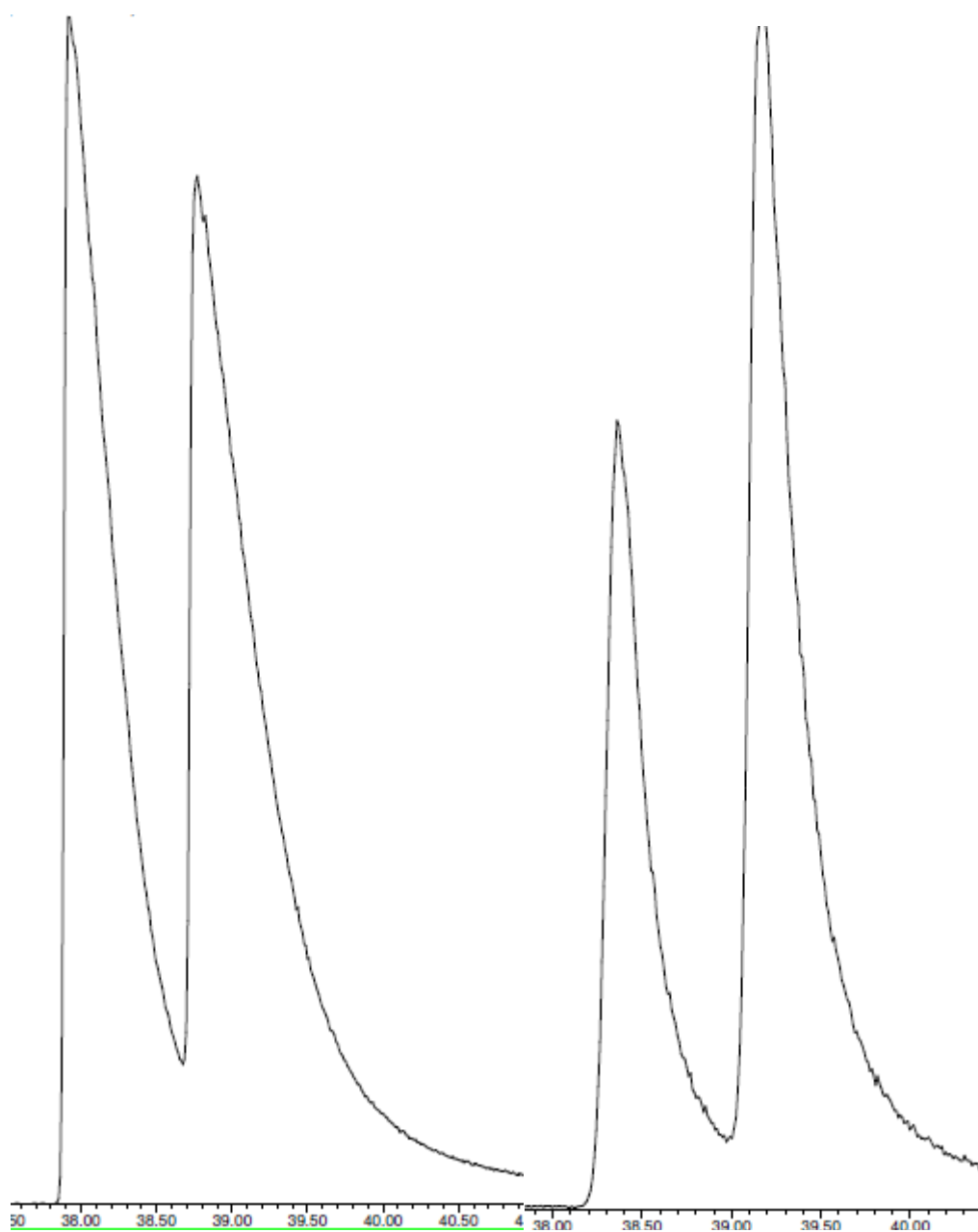
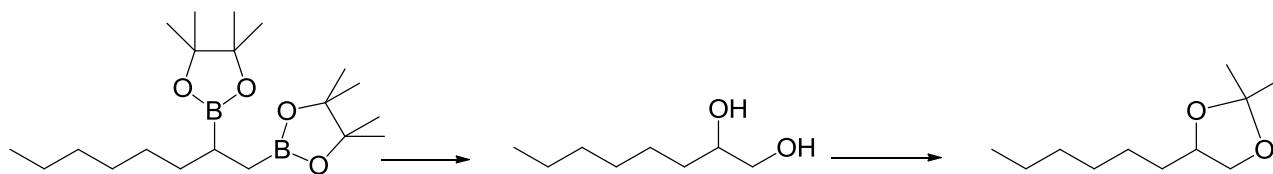
Injector temperature: 250 °C. Detector temperature: 275 °C. Pressure: 100 KPa.  
Initial oven temperature: 80 °C. Maintained for 3 min. Rate: 15 °C/min.  
Final oven temperature: 250 °C. Maintained for 5.67 min.

### **Chromatographic analysis of the enantiomeric excesses**

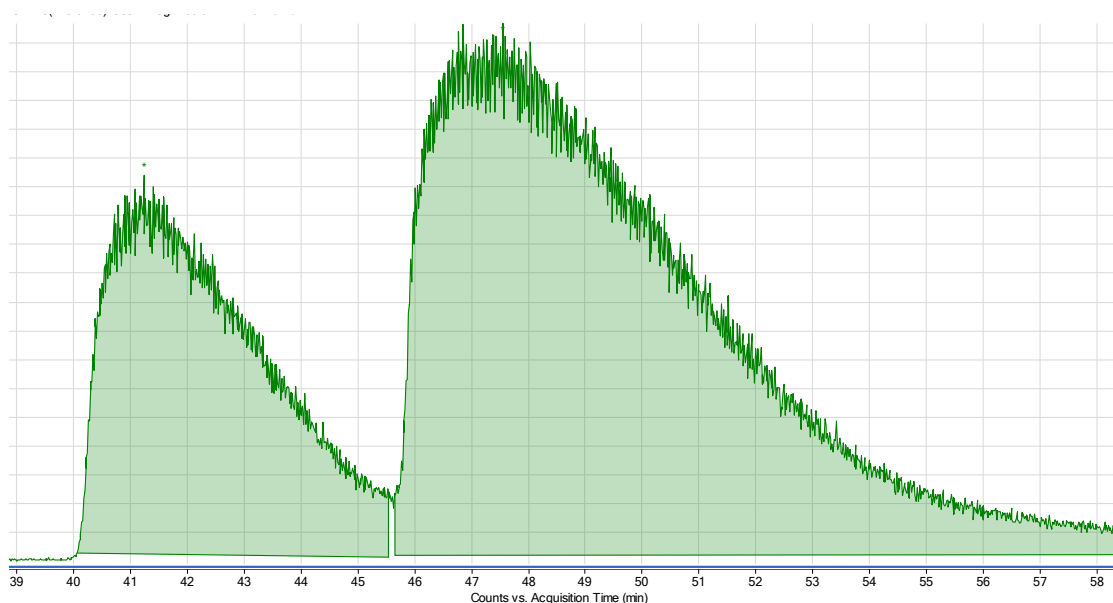
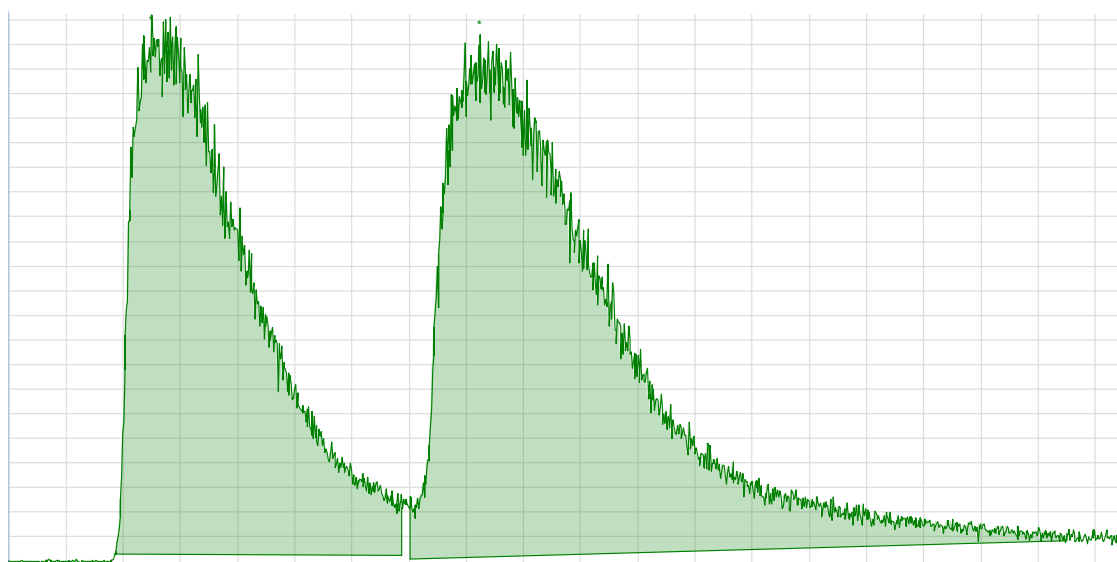
**2,2'-(1-cyclohexylethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)** was converted into **4-cyclohexyl-2,2-dimethyl-1,3-dioxolane** using the general oxidation and acetalisation procedures. The ee was determined via the analysis of the acetal derivative by GC-MS equipped with a  $\beta$ -cyclodextrine chiral column (SUPELCO  $\beta$ -DEX 120). Initial oven temperature: 70 °C. Maintained for 10 min. Rate 1 °C/min. Final oven temperature: 100 °C. Pressure: 150 KPa. Rt: 27.45 min (S), 27.65 min (R).



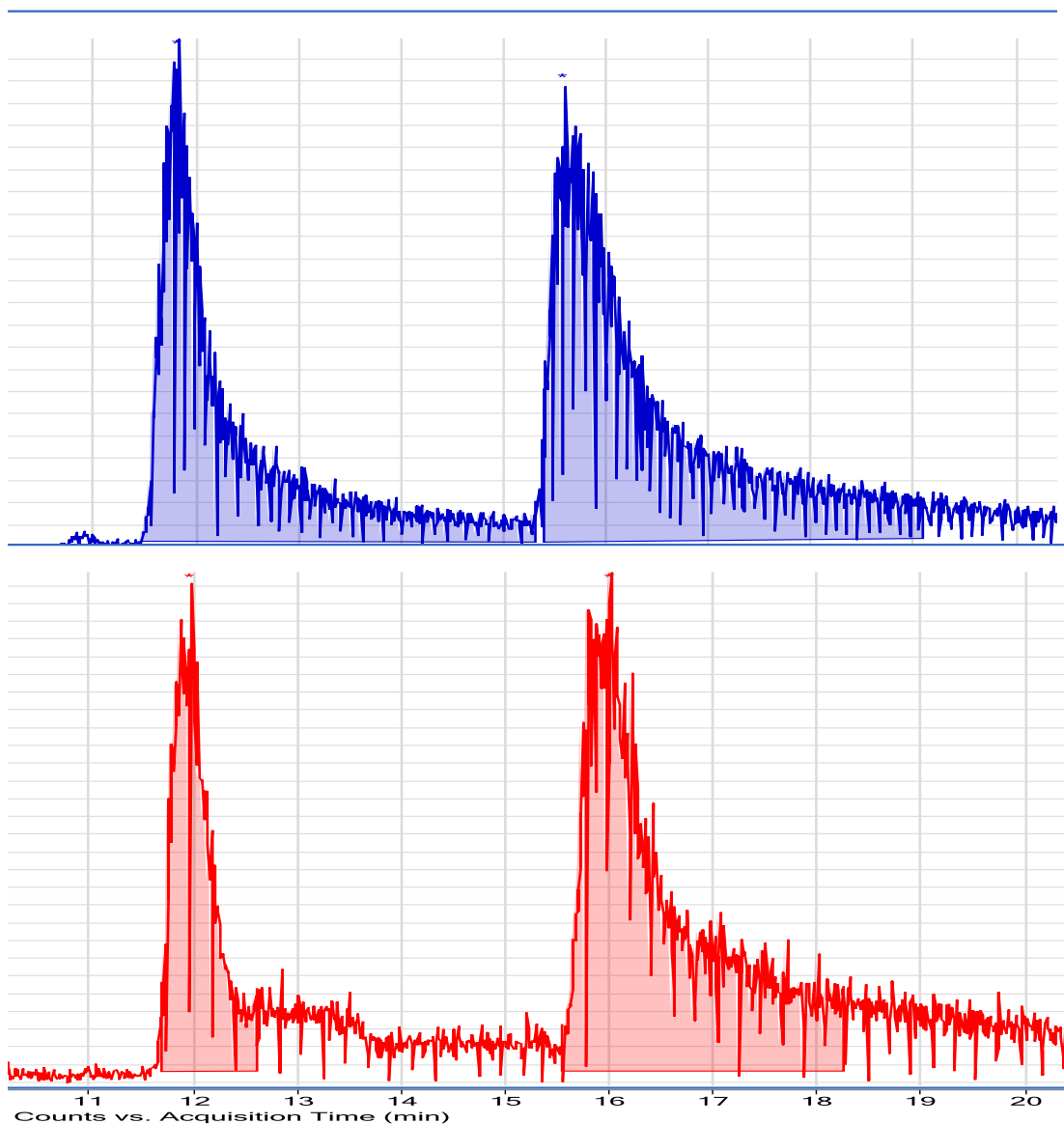
**2,2'-(octane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)** was converted into **4-hexyl-2,2-dimethyl-1,3-dioxolane** using the general oxidation and acetalisation procedures. The ee was determined via the analysis of the acetal derivative by GC-MS equipped with a  $\beta$ -cyclodextrine chiral column (SUPELCO  $\beta$ -DEX 120). Initial oven temperature: 70 °C. Maintained for 10 min. Rate 1 °C/min. Final oven temperature: 100 °C. Pressure: 150 KPa. Rt: 38.4 min (S), 39.4 min (R).



**4,4,5,5-tetramethyl-2-(4-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-yl)-1,3,2-dioxaborolane** was converted into **3-phenylpropane-1,2-diol** using the general oxidation procedure. The ee was determined via the analysis of the diol derivative by chiral HPLC. Column: Chiracel OD-H. Eluent: hexanes/*i*-PrOH 95/5. Rate: 1 mL/min. Rt: 41.2 min (*S*), 47.2 min (*R*).



**2,2'-(2,3-dihydro-1H-indene-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)** was converted into **2,3-dihydro-1H-indene-1,2-diol** using the general oxidation procedure. The ee was determined via the analysis of the diol derivative by chiral HPLC. Column: Chiracel OJ. Eluent: hexanes/*i*-PrOH 92.5/7.5. Rate: 1 mL/min. Rt: 11.8 min (*minor*), 47.2 min (*major*).



References:

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- <sup>1</sup> <sup>a</sup>C. Solé, A. Whiting, H. Gulyás, E. Fernández *Adv. Synth. Catal.* **2011**, *353*, 376 – 384; <sup>b</sup>C. Solé, A. Tatla, J. A. Mata, A. Whiting, H. Gulyás, E. Fernández *Chem. Eur. J.* **2011**, *17*, 14248 – 14257.
- <sup>2</sup> A. Bonet, C. Pubill-Ulldemolins, C. Bo, H. Gulyás, E. Fernández *Angew. Chem. Int. Ed.* **2011**, *50*, 7158.
- <sup>3</sup> Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 8702.
- <sup>4</sup> Y. Lee, H. Jang, A. Hoveyda *J. Am. Chem. Soc.*, **2009**, *131*, 18234.