Supporting Information

Aldol reactions mediated by a tetrahedral boronate

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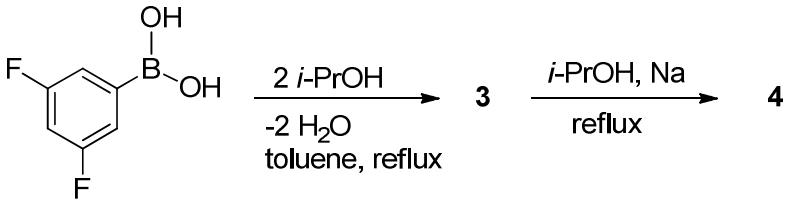
Materials and Methods

Experiments were performed with commercially available chemicals. Dry toluene and 2-propanol were used to synthesize the catalyst. 3Å molecular sieves were purchased from Metrohm and was used for the isolation of the products. The aldehydes were freshly distilled or crystallized prior use in the reaction. Aldol reactions where performed at two temperatures, 30 and 5 °C, under N_2-atmosphere. Separation of **7e** and **8e** was done by column chromatography, using silica-gel (Fluka, particle size 0.06 – 0.2 nm) and dichloromethane with 1% methanol and 1% triethyl amine as eluent. TLC was performed with Silica gel 60 F254 (Merck) and analysed at 254 and 365 nm. When required, the product was visualized with Iodine on the TLC-plate. NMR spectra were recorded with either Bruker Avance-400 or Varian-Inova-300 spectrometer operating at 400, 128, and 100 MHz (^{1}H, ^{11}B and ^{13}C NMR) or 300, 96, 75 MHz respectively. The NMR chemicals shifts are reported in ppm, referencing either to 0.1M solution of boric acid (^{11}B NMR) or to the residual solvent peak. A Hololab series 5000 Raman spectroscopy (Kaiser Optical System, Inc.) facilitated the recording of Raman spectra of solids and solutions. The Raman spectra were recorded by excitation radiation at 785 nm using a NIR probe.

Synthesis of boron-based mediators



Scheme S1 Synthesis of the trigonal (**3**) and tetrahedral (**4**) phenyl boronic acid ester.

Diisopropyl 3,5-difluorophenylboronic acid ester (3). 4.74 g (30 mmol) 3,5-difluorophenylboronic acid and 12 g (15 mL, 200 mmol) 2-propanol were dissolved in 15 mL toluene. The Dean-Stark trap was filled with 11 g molecular sieves (3Å), 5 mL 2-propanol and 5 mL toluene. The reaction mixture was stirred for 24 h under reflux. Solvent was removed and the product was distilled (6.5×10^{-2} mbar, 50 °C). 4.1 g (16.9 mmol) of a colourless liquid was obtained (isolated yield: 56 %). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.25 (d, 12H, 4×CH_3, *J* = 6.4 Hz); 4.58 (sept, 2H, 2×CHOB, *J* = 6.6 Hz); 6.81 (m, 1H,

HAr); 7.06 (m, 2H, 2×HAr). **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 7.6. **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 24.6; 66.7; 104.7 (t, *J* = 25.2 Hz); 115.1 (m); 138.5 (s); 163.0 (dd, *J* = 11.2 Hz; *J* = 249.7 Hz).

Sodium triisopropoxy(3,5-difluorophenyl)boronate (4). The reaction was carried out in a N_2-atmosphere. 345 mg (15 mmol) sodium was dissolved in 60 mL 2-propanol. The solution was stirred for 1 h under reflux and then cooled to 30 °C. 3.63 g (15 mmol) diisopropyl 3,5-difluorophenylboronic acid ester **(3)** was dissolved in 8 mL 2-propanol and added dropwise over 30 min. The mixture was stirred for 16 h at 30 °C. The solvent was removed under vacuum. 5.12 g of a white powder was obtained (3.828 g boronate; 11.8 mmol; Yield: 79 %). **^{1}H NMR** (300 MHz, 2-propanol-d_8): δ = 1.11 (d, 18H, 6×CH_3, *J* = 6 Hz); 3.9 (sept, 3H, CHOB, *J* = 6 Hz); 6.54 – 7.04 (m, 3H, 3×HAr). **^{11}B NMR** (128 MHz, 2-propanol-d_8); δ = -15.5. **^{13}C NMR** (75 MHz, 2-propanol-d_8): δ = 25.3; 63.6; 99.3 (m); 115.3 (m); 162.6 (dd, *J* = 10.3 Hz; *J* = 245.8 Hz); 162.9 (dd, *J* = 10.4 Hz; *J* = 246.5 Hz).

General procedures for the aldol reactions with 4

Aldol reaction in the flask: 130 mg (0.4 mmol) sodium triisopropoxy(3,5-difluorophenyl)boronate **(4)** and 2 mmol of an aldehyde were dissolved in 1.161 g (20 mmol) acetone. The reaction mixture was stirred at 30 °C for a given amount of time. Acetone was removed and the residue was dissolved in 3 mL water. The product was extracted with 3×5 mL ethyl acetate. The organic layers were combined, dried with $MgSO_4$, filtered and solvent was removed. The crude product was purified with column chromatography.

Aldol reaction in the NMR tube: 66 mg (0.2 mmol) sodium triisopropoxy(3,5-difluorophenyl)boronate **(4)**, 1 mmol of an aldehyde 68 mg (0.4 mmol) 1,3,5-trimethoxybenzene were dissolved in 640 mg (10 mmol) acetone. 50 µL of benzene-d_6 was added to lock the signal. The conversion was followed by ^{1}H-NMR at 30 or 5 °C. The ^{1}H NMR peak of the latter (6.1 ppm) was integrated and used to calculate the amount of formed aldol (i.e. aldol product of benzaldehyde at δ = 5.16 ppm).

Aldol reaction with sodium 2-propanolate (Table 1, entries 1 - 4): benzaldehyde **(5a)** 213 mg (2 mmol) was dissolved in 1.161 g (20 mmol) acetone and a given amount of sodium 2-propanolate (2 mol% up to 20 mol%) was added to the solution. The reaction mixture was stirred at 30 °C for 20 min. Small samples (25µl) were dissolved in $CDCl_3$ and conversion was determined by ^{1}H NMR.

NMR data of isolated products 7 and 8

4-hydroxy-4-phenylbutan-2-one (7a)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.18 (s, 3H, CH_3); 2.77 – 2.92 (m, 2H, CH_2); 3.30 (s, 1H, OH); 5.16 (m, 1H, CHCOH); 7.28 – 7.36 (m, 5H, HAr). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.8; 52.1; 69.9; 125.7; 127.7; 128.6; 142.9; 209.1. (isolated yield: 34%).

(E)-4-phenylbut-3-en-2-one (8a)
^{1}H NMR (400 MHz, CDCl3): δ = 2.39 (s, 3H, CH_3); 6.72 (d, 1H, CHCO, *J* = 16.4 Hz); 7.33 – 7.56 (m, 6H, 5×HAr + CHCAr). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.6; 127.3; 128.4; 129.1; 130.6; 134.5; 143.6; 198.6. (11%).

4-hydroxy-4-(4-methoxyphenyl)butan-2-one (7b)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.17 (s, 3H, CH_3); 2.74 – 2.91 (m, 2H, CH_2); 3.37 (s, 1H, OH); 3.79 (s, 3H, OCH_3); 5.08 (d, 1H, CHOH); 6.87 (d, 2H, 2×HAr); 7.26 (d, 2H, 2×HAr). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.8; 52.0; 55.3; 69.5; 113.9; 127.0; 135.1; 159.1; 209.3. (27%).

(E)-4-(4-methoxyphenyl)but-3-en-2-one (8b)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3H, CH_3); 3.84 (s, 3H, OCH_3); 6.60 (d, 1H, CHCO, *J* = 16.2 Hz); 6.91 – 7.51 (m, 5H, 4×HAr + CHCAr). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.4; 55.4; 114.5; 127.1; 130.1; 132.0; 143.4; 161.7; 198.6. (7%).

(E)-4-hydroxy-6-phenylhex-5-en-2-one (7c)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.19 (s, 3H, CH_3); 2.75 (d, 2H, CH_2, *J* = 6.0 Hz); 3.23 (s, 1H, OH); 4.74 (dd, 1H, CHOH, *J* = 6.0 Hz and 6.0 Hz); 6.19 (dd, 1H, CArCH=CH, *J* = 6.0 Hz and 16.0 Hz); 6.63 (d, 1H, CArCH=CH, *J* = 16.0 Hz); 7.21 – 7.39 (m, 5H, 5×HAr). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.9; 50.1; 68.5; 126.6; 127.8; 128.7; 130.3; 130.5; 136.6; 209.0. (28%).

(3E,5E)-6-phenylhexa-3,5-dien-2-one (8c)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.31 (s, 3H, CH_3); 6.25 (d, 1H, CHCO, *J* = 15.6 Hz); 6.88 – 6.93 (m, 2H, CArCH=CH); 7.24 – 7.48 (m, 6H, 5×HAr + CH=CHCO). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.4; 126.7; 127.3; 128.9; 129.3; 130.6; 136.0; 141.4; 143.5; 198.5. (22%).

4-hydroxy-4-(4-nitrophenyl)butan-2-one (7d)*
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.21 (s, 3H, CH_3); 2.83 – 2.89 (m, 2H, CH_2); 3.66 (s, 1H, OH); 5.23 – 5.26 (m, 1H, CHOH); 7.52 (d, 2H, HAr, *J* = 8.64 Hz); 8.18 (d, 2H, HAr, *J* = 8.76 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.8; 51.6; 69.0; 123.9; 126.5; 147.4; 150.1; 208.7. (29%).
*52% aldol, 5% aldehyde was determined by internal standard and other by-products (42%) were obtained.

4-hydroxyoctan-2-one (7e)
1H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, 3H, CH_3, *J* = 6.9 Hz); 1.30 – 1.64 (m, 6 H, CH_2CH_2 CH_2); 2.17 (s, 3H, CH_3); 2.48 – 2.63 (m, 2H, CH_2CO); 4.03 (m, 1H, CHOH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1; 22.8; 27.8; 30.9; 36.2; 50.1; 67.7; 210.2. (49%).

4-(furan-2-yl)-4-hydroxybutan-2-one (7f)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.20 (s, 3H, CH_3); 2.90 (dd, 1H, CHH, *J* = 3.5 Hz and 17.4 Hz); 3.04 (dd, 1H, CHH, *J* = 8.9 Hz and 17.4 Hz); 3.61 (s, 1H, OH); 5.19 (m, 1H, CHOH); 6.26 – 6.32 (m, 2H, 2×H_{Furan}); 7.36 (m, 1H, H_{Furan}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.6; 48.2; 63.6; 106.2; 110.3; 142.1; 155.1; 208.3. (24%).

(E)-4-(furan-2-yl)but-3-en-2-one (8f)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.32 (s, 3H, CH_3); 6.49 (m, 1H, H_{Furan}); 6.61 (d, 1H, CH=CHCO, *J* = 16.0 Hz), 6.66 (m, 1H, H_{Furan}); 7.27 (d, 1H, CH=CHCO, *J* = 16.0 Hz); 7.50 (m, 1H, H_{Furan}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0; 112.6; 115.7; 124.4; 129.5; 145.1; 151.0; 197.9. (16%).

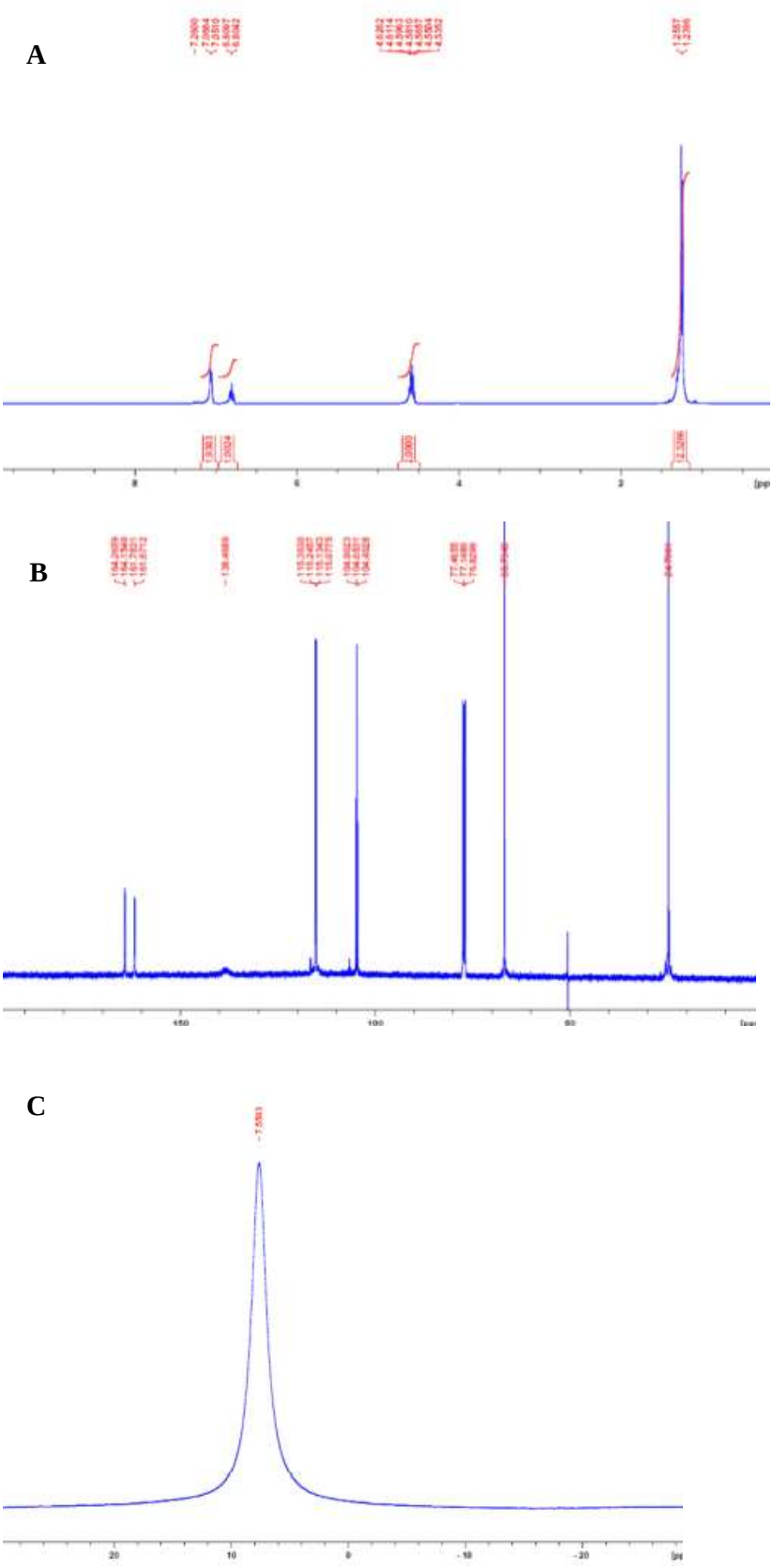


Fig. S1 NMR spectra of Diisopropyl 3,5-difluorophenylboronic acid ester (**3**): ^{1}H NMR (A) and ^{13}C NMR (B), and ^{11}B NMR (C).

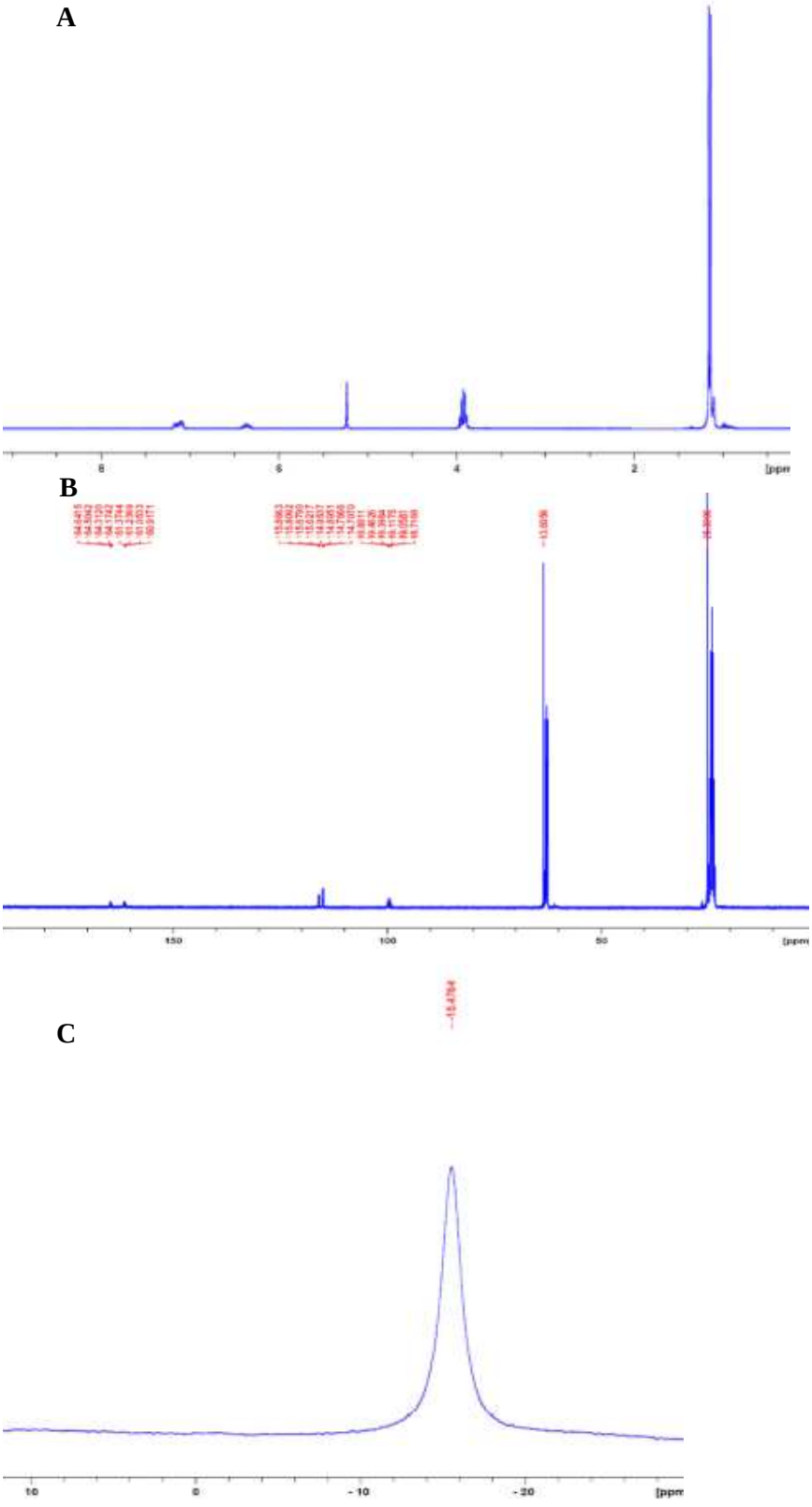


Fig. S2 NMR spectra of sodium triisopropoxy(3,5-difluorophenyl)boronate (**4**): ^{1}H NMR (A) and ^{13}C NMR (B), and ^{11}B NMR (C).

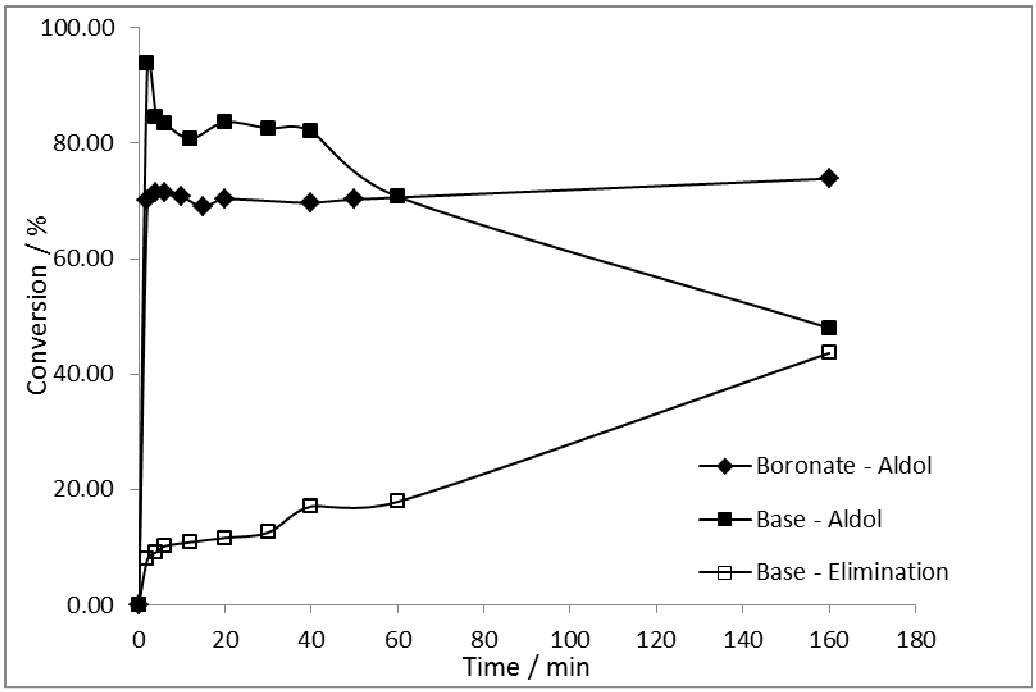


Fig. S3 Conversion of benzaldehyde in the presence of 10 mol% of boronate salt **4** or 10 mol% of NaOiPr at 5 ºC monitored by ^{1}H NMR. Formation of dimerization side-products during boronate catalysed reaction was detected by the MS, which explains the lower yield of the aldol; no elimination product was detected.

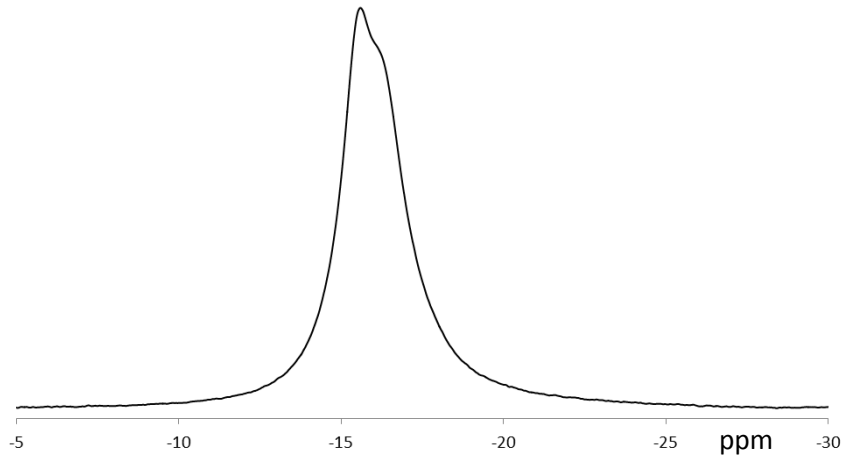


Fig. S4 ^{11}B NMR spectrum of boronate salt **4** and benzaldehyde in acetone.

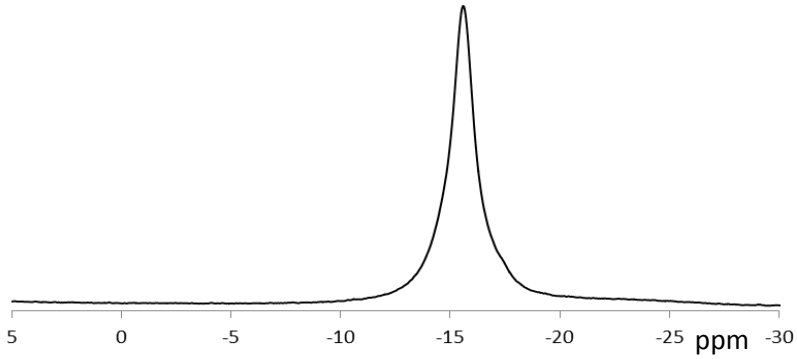


Fig. S5 ^{11}B NMR spectrum of boronate salt **4** and benzaldehyde in CD_2Cl_2.

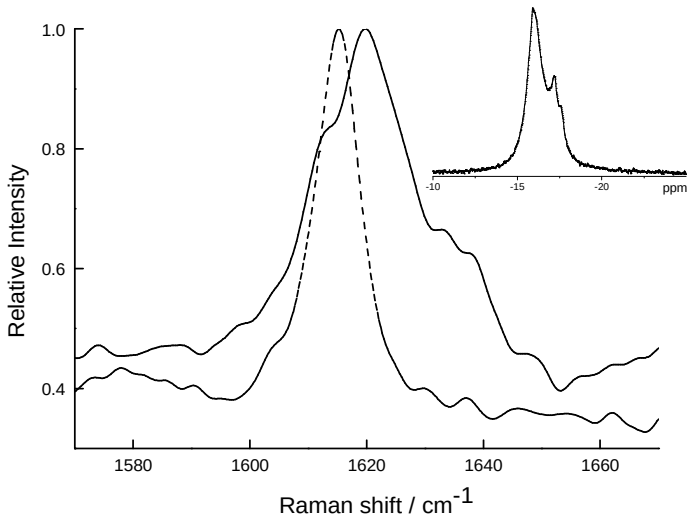


Fig. S6 Raman spectra of tetrahedral boronate salt **4** as a solid (dashed line) and as a solution in acetone (solid line). An additional boron ester peak corresponds to the conjugate of **4** with acetone through formation of enolate. The inset represents the ^{11}B NMR spectra of **4** interacting with acetone (related to H_3BO_3 (0.1M) at 0 ppm).

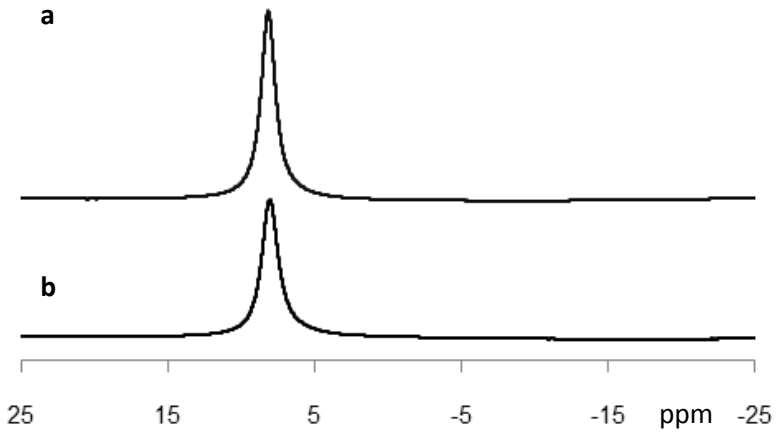


Fig. S7 ^{11}B NMR spectra of boron ester **3** mixed with a) acetone (**6**), b) acetone and benzaldehyde **(5a)**. Neither acetone nor benzaldehyde was coordinating to boron ester **3.** No tetrahedral boronate salt was formed, which excludes a six membered transition state as a possible mechanism. As a standard 0.1 M boric acid solution in D_2O at 0 ppm was used. No other solvent was added.