MIDA boronates are hydrolysed fast and slow by two different mechanisms

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I. General methods

Materials and Experimental Methods

Reactions which are specified in the text below as having been carried out under nitrogen were conducted using conventional Schlenk-line technique, purging three times with nitrogen vacuum cycles in oven- or flame-dried glassware. When anhydrous solvents were used (Et_2O, THF, DCM, PhMe, MeCN, EtOH), these were obtained from an M-Braun SPS system. H_2O was freshly distilled without further treatment unless except where specified.

Reagents and materials purchased from commercial suppliers were used without further purification except where specified.

Flash chromatography was carried out on columns packed with E. Merck silica gel (40-63 μm). Compounds were detected by UV (254 nm) or $KMnO_4$.

Stopped-Flow UV-vis Spectroscopy

UV spectra were recorded on an Ocean-Optics USB400 Miniature Fiber Optic Spectrometer fitted with a DH2000-BALUV lamp (deep-UV deuterium and tungsten halogen lamps), solarised resistant grade optical fibres. A Hi-Tech Scientific SFA-20 rapid kinetics stopped-flow accessory attached to a quartz 1.0 cm-path cuvette was used for rapid mixing. Reagents were load in two independent 2.5 mL syringes and then mixing induced by a pneumatic drive at constant air pressure (5 bar). UV-vis analysis were performed with a 200-600 nm spectral window. Data were analysed with 3.5 version of kinetic studio software (TgK Scientific).

NMR Spectroscopy

NMR spectra were acquired on JEOL Lambda 300, JEOL Eclipse Bruker and JEOL Eclipse 400 spectrometers at School of Chemistry, University of Bristol, and Bruker AVIII 400, AVIII 500 and AVIII 600 spectrometers with nitrogen or helium cryoprobes at School of Chemistry at the University of Edinburgh. Chemical shifts are quoted in parts per million (ppm) or parts per billion (ppb). ^1H and ^{13}C NMR spectra are referenced to residual protonated solvent.[1] ^2H spectra were externally referenced to neat $Si(CD_3)_4$, ^{10}B and ^{11}B

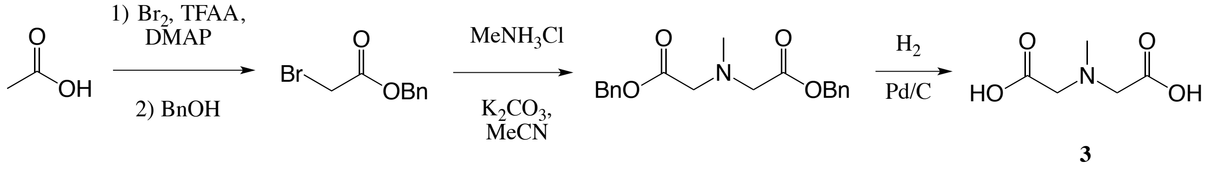
spectra to $BF_3{\cdot}OEt_2$ in $CDCl_3$, ^{15}N spectra to CH_3NO_2 in $CDCl_3$, and ^{19}F spectra to neat $CFCl_3$, ^{15}N spectra to CH_3NO_2 in $CDCl_3$. The following format is used to report data: chemical shift in ppm (multiplicity, J values (coupling constant(s)) in Hz, integral value). Multiplicities of peaks are reported as s (singlet), d (doublet), t (triplet), q (quartet).

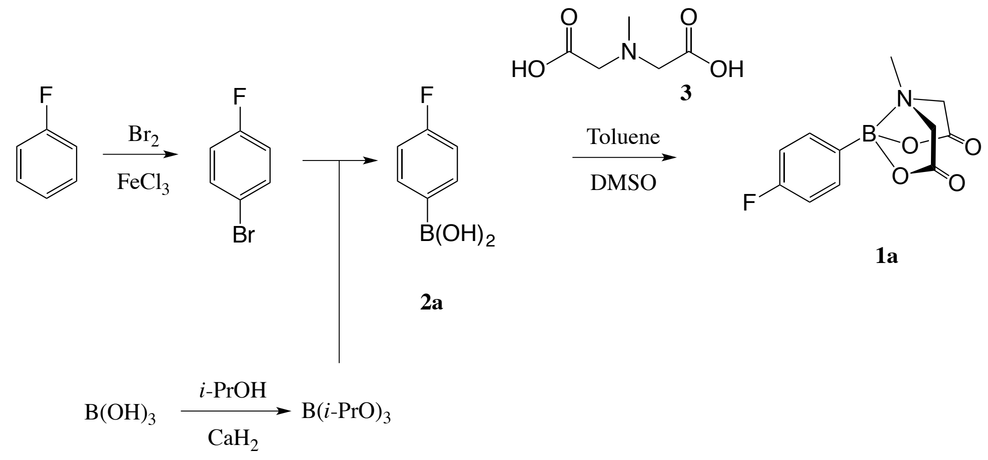
Mass spectrometry

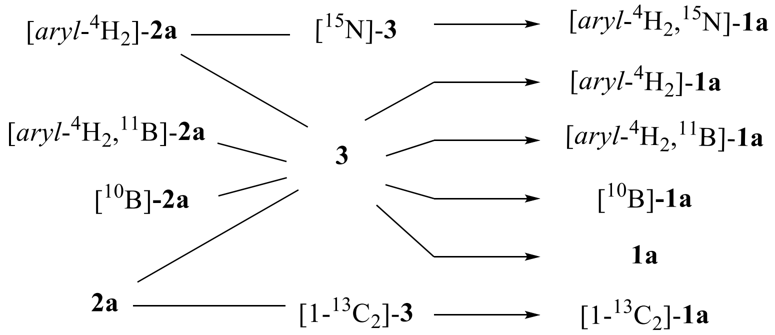
High resolution mass spectra were recorded on a Bruker microTOF II spectrometer by the mass spectrometry service at the University of Edinburgh.

II. Synthesis

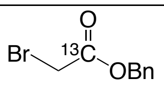
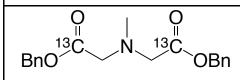
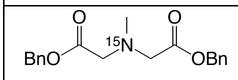
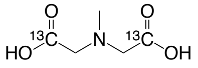
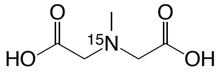
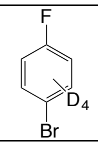
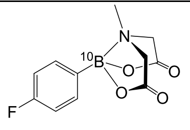
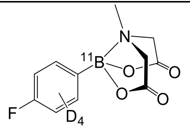
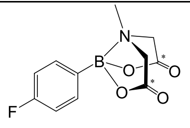
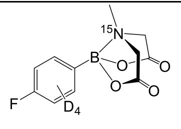
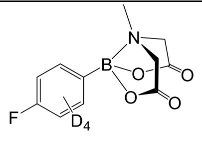
The general route used to install the isotopic labels (^{10}B, ^{11}B, ^{13}C, ^{15}N, ^{2}H) is outlined below.



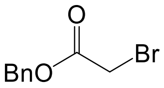




Isotopic enrichments

Compound	Isotope enrichment	Method
	>98.5 > ^{13}C	^{1}H NMR
	> 98.5 > ^{13}C$_2$	^{1}H NMR
	> 98.0 ^{15}N	MS
	> 95.0 % ^{13}C$_2$	MS
	> 97.0 ^{15}N	MS
	> 97.2 D$_4$	MS
 [^{10}B]-**1a**	> 98.7 ^{11}B	MS
 [*aryl*-^{2}H$_4$,^{11}B]-**1a**	> 97.1 > D$_4$ > 98.7 ^{11}B	^{19}F NMR MS
 [*aryl*-^{2}H$_4$,^{11}B]-**1a**	> 98.7 ^{13}C$_2$	MS
 [*aryl*-^{2}H$_4$,^{15}N]-**1a**	> 97.2 D$_4$ > 98.0 ^{15}N	^{19}F NMR MS
 [*aryl*-^{2}H$_4$]-**1a**	> 97.3 D$_4$	^{19}F NMR

Benzyl bromoacetate



A flame-dried, 50 mL, three neck round-bottomed flask equipped with a magnetic stirrer bar was charged with AcOH (1.0 g, 16.7 mmol, 1.0 equiv), TFAA (5.72 g, 27.2 mmol, 1.7 equiv), and DMAP (20.0 mg, 0.164 mmol, 0.010 equiv). The system was adapted with a thermometer, a dropping funnel with pressure compensation, and a condenser in reflux position before stirring and warming up at 60 °C for 10 min in an oil bath. Then Br_2 (2.75 g, 17.2 mmol, 1.0 equiv) was added dropwise over 90 min through the dropping funnel. The reaction was heated for an additional 90 min, and then cooled down to room temperature. A flow of N_2 was used to flush out the HBr produced and remaining Br_2, which were quenched with a gas trap. Then, BnOH (10.3 g, 95.2 mmol, 5.95 equiv) was added and the reaction mixture was stirred for 19 h at 60 °C. After cooling to room temperature, the reaction mixture was poured into a solution of $NaHCO_3$ (10 mL). Then, Et_2O (20 mL) was added to reaction mixture and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with saturated aqueous solution of $NaHCO_3$ (10 mL), saturated $Na_2S_2O_3$ (10 mL) and finally H_2O (10 mL). The organic layer was dried with $MgSO_4$ and the solvent was removed in *in vacuo*. The residue was purified on silica column (Hexanes/ AcOH 95:5) to afford benzyl bromoacetate as a pale yellow liquid (3.280 g, 14.3 mmol, yield 86 %). The ^1H and ^{13}C NMR data were consistent with the structure of this compound.**[2]**

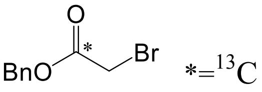
This material was carried forward into further reactions without additional purification.

R_f (Hex/AcOEt 6:1 v/v)= 0.50 (UV lamp).

^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm)= 7.40-7.34 (m, 5H), 5.21 (s, 2H), 3.88 (s,2H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ(ppm)= 167.2 (s), 135.1 (s), 128.81 (s), 128.75 (s), 128.5 (s), 68.1 (s), 25.9 (s).

Benzyl [1-^{13}C]-bromoacetate

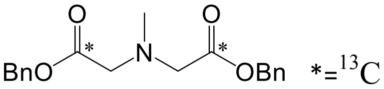


The general procedure was used with [1-^{13}C]-AcOH (3.0 g, 49.2 mmol, 1 equiv), DMAP (0.060 g, 0.49 mmol, 0.010 equiv), and TFAA (17.16 g, 81.7 mmol, 1.66 equiv). Br_2 (8.24g, 51.6 mmol, 1.05 equiv) was added dropwise over 90 min at 60 °C. Upon complete addition, the mixture was stirred for 90 min, BnOH (31.35 g, 290 mmol, 5.9 equiv) was added and heated at 60 °C for 18 h and subsequently quenched with saturated $NaHCO_3$ aqueous solution (10 mL). After addition of Et_2O (45 mL) and extraction of the aqueous layer with Et_2O (3 x 30 mL), the organic phase was dried with $MgSO_4$. The solvent was distilled of in *vacuo* to give a yellow liquid. The crude product that was purified on silica column (Hexanes/AcOH 95:5) to give benzyl [1-^{13}C]-bromoacetate as a pale yellow liquid (8.833 g, 38.4 mmol, yield 78%)

The ^{1}H and ^{13}C NMR data were consistent with the structure of this compound [3]
This material was carried forward into further reactions without additional purification.

R_f(Hex:AcOEt 6:1 v/v)= 0.5 (UV lamp).
^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm)= 7.40-7.33 (m, 5H), 5.21 (d, $^{3}J_{H\text{-}C}$= 3.2 Hz, 2H), 3.88 (d, $^{2}J_{H\text{-}C}$= 4.8 Hz, 2H).
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ(ppm)= 167.20 (s), 135.12 (d, $^{3}J_{C\text{-}C}$= 2.0 Hz), 128.81 (s), 128.76 (s), 128.5 (s), 68.1 (d, $^{2}J_{C\text{-}C}$= 2.4 Hz), 25.9 (d, $^{1}J_{C\text{-}C}$= 65.5 Hz).

Dibenzyl [1-^{13}C$_2$] *N*-methyliminodiacetate



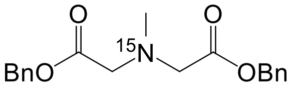
A flame-dried, 100 mL, two neck round-bottomed flask equipped with a magnetic stirrer bar was charged with $MeNH_2 \cdot HCl$ (0.911 g, 13.5 mmol, 1 equiv), K_2CO_3 (11.054 g, 80.0 mmol, 5.9 equiv). The flask was sealed with a rubber septum and subsequently purged three times via nitrogen / vacuum cycles. Then, dry MeCN (25 mL) was added to the flask before starting the stirring. Benzyl [1-^{13}C]-bromoacetate (5.674 g, 24.7 mmol, 1.83 equiv) was dissolved in dry MeCN in a septum-sealed vial and the solution transferred *via* cannula to the reaction mixture. The system was lowered into a 50 °C oil bath and stirred overnight for 20 h. After cooling down to room temperature, the mixture was vacuum filtered through celite and rinsed with AcOEt (3 x 10 mL). The filtrate was concentrated *in vacuo*. The residue was absorbed onto Celite and loaded onto a silica-gel column. Elution with hexanes/AcOEt (5:2) gave dibenzyl *N*-[1-$^{13}C_2$] methyliminodiacetate (3.567 g, 10.8 mmol, yield 88%) as a pale yellow liquid. The ^{1}H and ^{13}C NMR data were consistent with the structure of this compound. This material was carried forward into further reactions without additional purification.

R*f*(AcOEt)= 0.71(UV lamp).

^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm)= 7.38-7.31 (m, 10H), 5.15 (d, $^3J_{H\text{-}C}$= 3.1 Hz, 4H), 3.58 (d, $^2J_{H\text{-}C}$= 5.3 Hz, 4H), 2.56 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ(ppm)= 170.7 (s), 135.8 (d, $^3J_{C\text{-}C}$= 2 Hz), 128.7 (s), 128.50 (s), 128.48 (s), 66.5 (d, $^2J_{C\text{-}C}$= 2.4 Hz), 57.2 (dd, $^1J_{C\text{-}C}$= 59.7, $^2J_{C\text{-}C}$= 2.0 Hz), 42.3 (t, $^3J_{C\text{-}C}$= 1.4 Hz).

Dibenzyl [^{15}N]-*N*-methyliminodiacetate



The general procedure was used with benzyl bromoacetate (3.1058 g, 13.6 mmol, 2.47 equiv), K_2CO_3 (4.598g, 33.7 mmol, equiv 6.1 equiv), $CH_3{}^{15}NH_2{\cdot}HCl$ (0.380 g, 5.5 mmol, 1equiv) and MeCN (20 mL) to afford dibenzyl [^{15}N]-*N*-methyliminodiacetate (1.8016 g, 5.5 mmol, yield 94%) as a pale yellow liquid. The ^{1}H and ^{13}C NMR data were consistent with the structure of this compound. This material was carried forward into further reactions without additional purification.

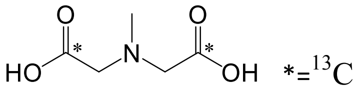
R*f*(AcOEt)= 0.69 (UV lamp).

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm)= 7.38-7.30 (m, 10H), 5.16 (s, 4H), 3.58 (s, 4H), 2.56 (s, 3H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ(ppm)= 170.7 (d, $^3J_{C\text{-}N}$= 2.5 Hz), 135.8 (s), 128.7 (s), 128.5 (s), 128.47 (s), 66.5 (s), 57.3 (d, $^1J_{C\text{-}N}$= 6.8 Hz), 42.3 (d, $^1J_{C\text{-}N}$= 5.9 Hz).

^{15}N NMR (126 MHz, $CDCl_3$): δ(ppm)= 171 (s).

[1-$^{13}C_2$]-*N*-methyliminodiacetic acid (3)



[1-$^{13}C_2$]-**3**: dibenzyl *N*-[1-$^{13}C_2$] methyliminodiacetate (2.762 g, 8.4 mmol, 1 equiv) and 50 mL of EtOH were charged to an oven-dried, 100 mL, round-bottomed flask with a magnetic stirrer and sealed with a rubber septum. N_2 was bubbled through the solution for 15 minutes via an needle, with a vent needle placed through the septum. 10% w/w Pd/C (0.315 g, 0.30 mmol, 0.026 equiv) was added quickly to the reaction mixture. With vigorous stirring, an H_2 balloon was used to bubble H_2 through the suspension with the needle immersed in the solution alongside the vent needle, for 10 minutes. The outlet needle was removed and the inlet needle was moved to a position above the mixture. The reaction was stirred for 24 hours at room temperature. The H_2 balloon was removed, and N_2 used to purge the remaining hydrogen from the suspension. The mixture was vacuum filtered, rinsing with EtOH (3x5 mL) and the solid was dissolved in 30 mL of H_2O. The solution was filtered to remove the Pd/C, and then concentrated in *vacuo* to approximately 3-5 mL. Then, 20 mL of acetone was added and the flask was cooled in a water-ice bath to precipitate a white solid. The solid was vacuum filtered and dried overnight to afford [1-$^{13}C_2$] *N*-methyliminodiacetic acid [1-$^{13}C_2$]-**3** (1.132 g, 7.59 mmol, yield 91%) as a white solid.

m.p.:213-215 ^{o}C (dec)

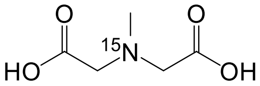
^{1}H NMR (500 MHz, D_2O): δ(ppm)= 4.02 (d, $^2J_{H\text{-}C}$= 5.4 Hz, 4H), 3.04 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, D_2O): δ(ppm)= 169.10 (s), 57.26 (d, $^1J_{C\text{-}C}$ = 55.3 Hz), 42.6 (s).

HRMS (m/z): $[M]^+$ calcd. for $C_3{}^{13}C_2H_9O_4N$, 149.05932; found, 149.06059

^{1}H and ^{13}C NMR shifts are consistent with those of the unlabelled compound.$^{\mathbf{4}}$

[^{15}N]-*N*-methyliminodiacetic acid



[^{15}N]-**3**: The general procedure was followed using dibenzyl [^{15}N]-*N*-methyliminodiacetate (1.295 g. 3.9 mmol, 1 equiv), 10 % w/w Pd/C (0.171 g, 0.16 mmol, 0.041 equiv), and EtOH (25 mL) to afford [^{15}N]-methyliminodiacetic acid] [^{15}N]-**3** (0.354 g, 2.4 mmol, 60 % yield).

m.p.: 213-215 ^{o}C (dec).

^{1}H NMR (500 MHz, D_2O): δ(ppm)= 4.00 (s, 4H), 3.02 (s, 3H).

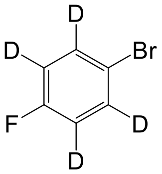
^{13}C{^{1}H} NMR (126 MHz, D_2O): δ(ppm)= 169.11 (s), 57.24 (d, $^{1}J_{C\text{-}N}$= 6.6 Hz), 42.5 (d, $^{1}J_{C\text{-}N}$= 5.6 Hz).

^{15}N NMR (500 MHz, D_2O): δ(ppm)= 43.5 (s).

HRMS (m/z): $[M]^+$ calcd. for $C_5H_9O_4{}^{15}N$, 148.04964; found, 148.05081.

^{1}H and ^{13}C NMR shifts are consistent with those of the unlabelled compound.$^{\mathbf{4}}$

[*aryl*-^{2}H$_4$]-*4*-bromofluorobenzene



Using a previously reported procedure,[5] 4-fluorobenzene-d$_5$ (2.620g, 25.9 mmol, 1 equiv) and $FeCl_3$ (0.125 g, 0.77 mmol, .030 equiv) in 2.5 mL of DCM was cooled to 10-14 ^{o}C, and Br_2 (4.34 g, 27.2 mmol, 1.05 equiv) in 3.5 mL of DCM added dropwise over 60 min with vigorous stirring. After 4 h, mixture was washed with water (3x6 mL), saturated aqueous $Na_2S_2O_3$ (3x6 mL), and water (3x6mL). The aqueous layer was extracted with DCM (3x10 mL) and the combined organic phases dried over $MgSO_4$. The solvent was removed *in vacuo* (760 mbar, 40 ^{o}C, 1 h.). The residue was distilled at 450-450 mbar, collecting the fraction at 60-67 ^{o}C to afford 4-[^{2}H$_4$]-bromofluorobenzene as a pale yellow liquid (3.450 g, 19.3 mmol, yield 74%). The ^{2}H, ^{19}F and ^{13}C NMR shifts are consistent with the structure of this compound.[5]

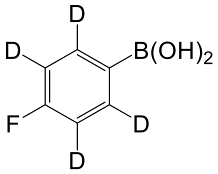
^{2}H NMR (61.4 MHz, $CDCl_3$): δ(ppm)= 7.52 (s, 2D), 7.04 (s, 2D).

^{13}C{^{1}H} NMR (101 MHz, , $CDCl_3$): δ(ppm)= 162.0 (d, $^{1}J_{C\text{-}F}$ = 246.7 Hz), 132.70 (td, $^{1}J_{C\text{-}D}$= 25.9 Hz, $^{3}J_{C\text{-}F}$ = 8.6 Hz), 117.01 (td, $^{1}J_{C\text{-}D}$= 25.9 Hz, $^{2}J_{C\text{-}F}$= 22.9 Hz), 116.4 (s).

^{19}F NMR (377 MHz, $CDCl_3$) δ(ppm)= -115.9 (s).

HRMS (m/z): $[M]^+$ calcd. for $C_6{}^{2}H_4{}^{79}BrF$, 177.97260; found, 177.97177.

4-[$^{2}H_4$]-fluorophenyl boronic acid



[$^{2}H_4$]-**2a:** Using a previously reported procedure,[5] 4-[$^{2}H_4$]-bromofluorobenzene (1.760 g, 9.8 mmol, 1 equiv), in 20 mL of toluene and 5mL of THF at -80 °C was treated with 6.5 mL of *n*-BuLi (1.6 M, 10.4 mmol, 1.06 equiv) over 30 minutes. The mixture was stirred for an additional 60 min. This solution was transferred to a solution of freshly distilled $B(O\text{-}i\text{Pr})_3$ (1.990 g, 10.6 mmol, 1.08 equiv) in 40 mL of Et_2O at -70 °C. The mixture was stirred for one hour and warmed to room temperature. 15 mL of HCl (2 M) was added, the organic phase separated and the aqueous layer extracted with Et_2O (3x20 mL). The combined organic layers were dried with $MgSO_4$, and the volatiles removed in *vacuo*. The solid was recrystallized from water and vacuum-dried to afford 4-[$^{2}H_4$]-fluorophenyl boronic acid [$^{2}H_4$]-**2a** (0.449 g, 3.1 mmol, 0.316g). The product also contains some boroxine. ^{2}H, ^{11}B, ^{19}F and ^{13}C NMR shifts are consistent with the structure of this compound.[5]

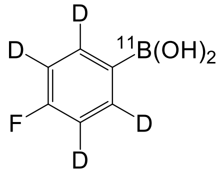
^{2}H-NMR (61.4 MHz, DMSO): δ(ppm)= 7.9 (s, 2D), 7.2 (s, 2D).

^{11}B-NMR (96 MHz, DMSO-d_6): δ(ppm)= 27.5 (s).

^{13}C{^{1}H,^{2}H}-NMR (101 MHz, DMSO-d_6): δ(ppm)= 164.2 (d, $^{1}J_{C\text{-}F}$=246.9 Hz), 136.6 (d, $^{3}J_{C\text{-}F}$= 8.0 Hz), 134.5 (s), 114.4 (d, $^{2}J_{C\text{-}F}$= 19.4 Hz).

^{19}F-NMR (377 MHz, DMSO-d_6): δ(ppm)= -111.4 (s).

4-[$^2H_4$, ^{11}B]-fluorophenylboronic acid



[$^2H_4$, ^{11}B]-**2a**: Using the above procedure with 4-[$^2H_4$]-bromofluorobenzene (1.096 g, 6.1 mmol) and $^{11}B(O\text{-}i\text{Pr})_3$ (1.260 g, 6.69 mmol, 1.08 equiv) gave [$^2H_4$, ^{11}B]-**2a** (0.7121 g, 5.7 mmol, 93 % yield). The ^2H, ^{11}B, ^{13}C and ^{19}F NMR shifts are consistent with that expected based on data for the same compound with natural abundance $^{10}B/^{11}B$ (20/80).[5] NB [^{10}B]-**2a** has been prepared previously by us,[5] and samples were used for the current study.

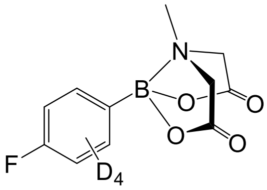
^2H NMR (61.4 MHz, DMSO): δ(ppm)= 7.9 (s, 2D), 7.2 (s, 2D).

^{11}B NMR (160 MHz, DMSO-d$_6$): δ(ppm)= 28.2 (s, 1B).

$^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d$_6$): δ(ppm)= 163.7 (d, $^1J_{C\text{-}F}$= 245.5 Hz), the other signals were broad.

^{19}F NMR (471 MHz, DMSO-d$_6$): δ (ppm)= -111.5 (s).

4-[*aryl*-$^2H_4$]-MIDA boronate



[*aryl*-$^2H_4$]-**1a:** As a general procedure, [*aryl*-$^2H_4$]-**2a** (0.274 g, 1.90 mmol, 1 equiv) and **3** (0.316 g, 2.1 mmol, 1.11 equiv) were placed in a 50 mL round-bottomed flask with a magnetic stirrer. Then, toluene (30 mL) and DMSO (3 mL) were added. A Dean-Stark apparatus was connected to the reaction flask alongside a condenser in reflux position and the mixture heated at 115-120 °C for approximately 16 h. The reaction was cooled to room temperature, the toluene removed *in vacuo*, and the residue added to cold water (10 mL, 5-10 °C). The solid that formed was collected by vacuum-filtration, dissolved in MeCN and then loaded onto silica-gel column. Elution with Et_2O/MeCN (4:1 v/v), after removal of the solvent the product was recrystallized from MeCN/$Et_2O$to afford [*aryl*-$^2H_4$]-**2a** as a crystalline white solid (0.419 g, 1.64 mmol, yield 86 %).

m.p.: 218-221 °C.

R*f*(AcOEt)= 0.33 (UV lamp).

^{1}H NMR (500 MHz, DMSO-d$_6$): δ(ppm)= 4.33 (d, $^2J_{H\text{-}H}$= 17.2 Hz, 2H), 4.11 (d, $^2J_{H\text{-}H}$= 17.2 Hz, 2H), signal of CH_3- is obscured by overlap with DMSO-d$_{6\text{-}n}$.

^{13}C{^{1}H} NMR (101 MHz, DMSO-d$_6$): δ(ppm)= 163.7 (d, $^1J_{C\text{-}F}$= 243 Hz), 134.4-134.(m), 114.4-113.9 (m), 61.78 (s), 47.54 (s), broad C-B signal not observed.

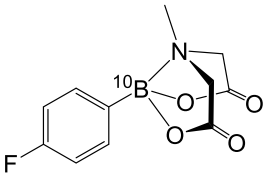
^{11}B NMR (160 MHz, DMSO-d$_6$): δ(ppm)= 11.1 (s).

^{15}N NMR (50.7 MHz, DMSO-d$_6$): δ(ppm)= 49.3 (s).

^{19}F NMR (471 MHz, DMSO-d$_6$): δ(ppm)= -113.6 (s).

HRMS (m/z): [M]$^+$ calcd for $C_{11}H_7{}^2H_4O_4N^{11}BF$, 255.10108; found, 255.10098.

[^{10}B]-MIDA boronate



[^{10}B]-**1a**: The general procedure was followed with [^{10}B]-**2a** (0.549 g, 3.95 mmol, 1 equiv), **3** (0.780 g, 5.30 mmol, 1.34 equiv), toluene (40 mL), and DMSO (4 mL). After purification, [^{10}B]-**1a** (0.807 g, 3.27 mmol, yield 83 %) was obtained as a white crystalline solid.

m.p.: 218-221 °C.

R*f*(AcOEt)= 0.33 (UV lamp).

^{1}H NMR (500 MHz, DMSO-d$_6$): δ(ppm)= 7.47 (dd, $^3J_{H-H}$= 8.6 Hz, $^4J_{H-F}$= 6.3 Hz, 2H), 7.17 (dd, $^3J_{H-F}$= 9.5 Hz, $^3J_{H-H}$= 8.6, 2H), 4.33 (d, $^2J_{H-H}$= 17.2 Hz, 2H), 4.11 (d, $^2J_{H-H}$= 17.2 Hz, 2H), the CH$_3$ signal is obscured by overlap with DMSO-d$_{6-n}$.

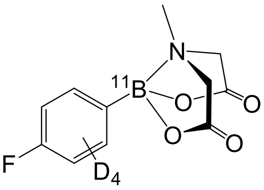
^{13}C{^{1}H} NMR (126 MHz, DMSO-d$_6$): δ(ppm)= 169.3 (s), 162.9 (d, $^1J_{C-F}$= 245.2 Hz), 134.6 (d, $^3J_{C-F}$= 7.8 Hz), 114.5 (d, $^2J_{C-F}$= 19.7 Hz), 61.8 (s), 47.6 (s), broad C-B signal not observed.

^{10}B-NMR (54 MHz, DMSO-d$_6$): δ(ppm)= 11.2 (s).

^{19}F NMR (471 MHz, DMSO-d$_6$): δ(ppm)= -113.0 (s).

HRMS (m/z): [M]$^+$ calcd. for $C_{11}H_{11}O_4N^{10}BF$, 250.07960; found, 250.07908.

4-[*aryl*-^{2}H$_4$, ^{11}B]-MIDA boronate



[*aryl*-^{2}H$_4$,^{11}B]-**1a**: The general procedure was followed with [*aryl*-^{2}H$_4$,^{11}B]-**2a** (0.517 g, 3.60 mmol, 1 equiv), **3** (0.703 g, 4.78 mmol, 1.33 equiv), toluene (40 mL), and DMSO (4 mL). After purification, [*aryl*-^{2}H$_4$,^{11}B]-**1a** (0.700 g, 2.74 mmol, yield 76 %) was obtained as a white crystalline solid.

m.p.: 218-221 °C.

R*f*(AcOEt)= 0.33 (UV lamp).

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ(ppm)= 4.34 (d, $^2J_{H-H}$= 17.2 Hz, 2H), 4.11(d, $^2J_{H-H}$= 17.2 Hz, 2H), signal of CH$_3$- is obscured by overlap with DMSO-d$_{6-n}$.

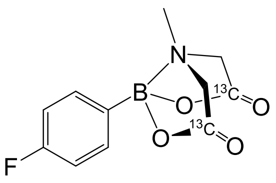
^{13}C{^{1}H}-NMR (126 MHz, DMSO-d$_6$): δ(ppm)= 169.3 (s), 162.9 (d, $^1J_{C-F}$=246.5 Hz), 134.4-134.0 (m), 114.5-113.8 (m), 61.8 (s), 47.5 (s), broad C-B signal not observed.

^{11}B-NMR (160 MHz, DMSO-d$_6$): δ(ppm)= 11.1 (s).

^{19}F-NMR (471 MHz, DMSO-d$_6$): δ(ppm)= -113.6 (s).

HRMS (m/z): [M]$^+$ calcd. for $C_{11}H_7{}^2H_4O_4N^{11}BF$, 255.10108; found, 255.10142.

[1-$^{13}C_2$]-MIDA boronate



[1-$^{13}C_2$]-**1a**: The general procedure was followed with **2a** (0.554 g, 3.90 mmol, 1.03 equiv), [1-$^{13}C_2$]-**3** (0.562 g, 3.77 mmol, 1.0 equiv), toluene (40 mL), and DMSO (4.5 mL). After purification, [1-$^{13}C_2$]-**1a** (0.692 g, 2.46 mmol, yield 63 %) was obtained as a white crystalline solid.

m.p.: 217-220 °C.

R*f*(AcOEt)= 0.35 (UV lamp).

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ(ppm)= 7.47 (dd, $^3J_{H-H}$= 8.3 Hz, $^4J_{H-F}$= 6.3 Hz, 2H), 7.17 (dd, $^3J_{H-F}$= 9.5 Hz, $^3J_{H-H}$= 8.6), 4.33 (dd, $^2J_{H-H}$= 17.2 Hz, $^2J_{H-C}$= 5.0 Hz, 2H), 4.11 (dd, $^2J_{H-H}$= 17.2 Hz, $^2J_{H-C}$= 5.0 Hz, 2H), signal of CH_3- is obscured by overlap with residual solvent.

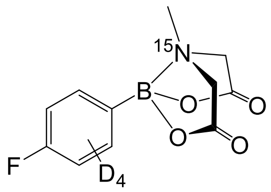
$^{13}C\{^1H\}$-NMR (126 MHz, DMSO-d$_6$): δ(ppm)= 169.3 (s), 163.0 (d, $^1J_{C-F}$= 245.2 Hz), 134.6 (d, $^3J_{C-F}$= 7.8 Hz), 114.5 (d, $^2J_{C-F}$= 20.0 Hz), 61.8 (d, $^1J_{C-C}$= 53.1 Hz), 47.6 (t, $^2J_{C-C}$= 1.9 Hz).

^{11}B-NMR (160 MHz, DMSO-d$_6$): δ(ppm)= 11.1 (s).

^{19}F-NMR (471 MHz, DMSO-d$_6$): δ(ppm) = -113.6 (s)

HRMS (m/z): $[M]^+$ calcd. for $C_9{}^{13}C_2H_{11}O_4N{}^{11}BF$, 253.08268; found, 253.08396.

[*aryl*-$^2H_4$,^{15}N]-MIDA boronate



[*aryl*-$^2H_4$,^{15}N]-**1a:** The general procedure was followed with [*aryl*-$^2H_4$]-**2a** (0.334 g, 2.32 mmol, 1.07 equiv), [^{15}N]-**3** (0.322 g, 2.17 mmol, 1.0 equiv), toluene (40 mL), and DMSO (4 mL). After purification, [*aryl*-$^2H_4$,^{15}N]-**1a** (0.419 g, 1.63 mmol, yield 75 %) was obtained as a white crystalline solid.

m.p.: 219-222 ^oC.

R$_f$(AcOEt) =0.36 (UV lamp).

^{1}H-NMR (500 MHz, DMSO-d$_6$) δ(ppm)= 4.33 (d, $^2J_{H\text{-}H}$= 17.5 Hz, 2H) 4.11(d, $^2J_{H\text{-}H}$= 17.5 Hz, 2H), signal of CH_3- is obscured by overlap with DMSO-d$_{6\text{-}n}$.

^{13}C{^{1}H,^{2}H}-NMR (101 MHz, DMSO-d$_6$): δ(ppm)= 169.3 (d,$^2J_{C\text{-}N}$=3.0 Hz), 162.9 (d, $^1J_{C\text{-}F}$= 245.0 Hz), 134.2 (d, $^3J_{C\text{-}F}$= 7.9 Hz), 114.2 (d, $^2J_{C\text{-}F}$=19.7 Hz), 61.8 (d, $^1J_{C\text{-}N}$= 5.8 Hz), 47.5 (d, $^1J_{C\text{-}N}$= 5.6 Hz), broad C-B signal not observed.

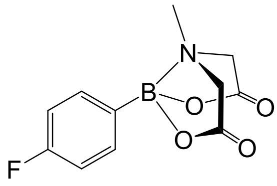
^{11}B-NMR (160 MHz, DMSO-d$_6$): δ(ppm)= 11.1 (s).

^{15}N-NMR (51 MHz, DMSO-d$_6$): δ(ppm)= 49.3 (s).

^{19}F-NMR (471 MHz, DMSO-d$_6$): δ(ppm)= -113.6 (s).

HRMS (m/z): $[M]^+$ calcd. for $C_{11}H_7{}^2H_4O_4{}^{15}N^{11}BF$, 256.09811; found, 256.09862.

Synthesis of 4-fluorophenylboronic MIDA boronate [*methylene*- $^2H_{1.6}$]-1a



[*methylene*-$^2H_{1.6}$]-**1a**

In a 50 mL round bottom flask with a magnetic stirrer, **1a** (1.50 g, 5.98 mmol) alongside THF (30 mL). Then a premade solution of K_2DPO_4 in D_2O (6 mL, pD=9.2) was added to the flask. The system was stirred for 20 minutes (500 rpm, 21^o C) and then HCl (2 M) was added until pD=7 (measured with pH paper). The system was saturated with NaCl until the phase splitting was observed. Organic and aqueous layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layer was dried over MgSO4, filtered and the solvent was distilled *in vacuo*.

The remaining solid was purified by column in silica gel using Et_2O/MeCN (1:1 v/v) as a eluent. The product was recrystallized from Et_2O/MeCN and vacuum filtrated and dried. The final product [*methylen*e-$^2H_{1.6}$]-**1a** (0.668 g, 44 % yield) was obtained and characterised.

R*f*(AcOEt) =0.36 (UV lamp).

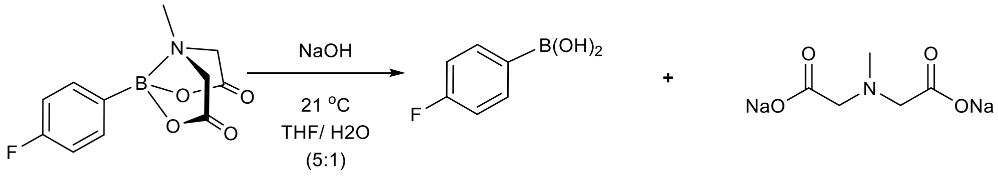
^{1}H-NMR (500 MHz, DMSO-d_6) δ(ppm)= 7.47 (dd, $^3J_{H\text{-}H}$= 8.7 Hz, $^4J_{H\text{-}F}$= 6.3 Hz, 2H), 7.17 (dd, $^3J_{H\text{-}F}$= 9.5 Hz, $^3J_{H\text{-}H}$= 8.7, 2H), 4.33 (m, 0.81H) 4.11(m, 1.6H), signal of CH_3- is obscured by overlap with DMSO-$d_{6\text{-}n}$.

^{13}C{^{1}H,^{2}H}-NMR (101 MHz, DMSO-d_6): δ(ppm)= 169.3 (s), 162.9 (d, $^1J_{C\text{-}F}$= 245.0 Hz), 134.64 (d, $^3J_{C\text{-}F}$= 7.9 Hz), 114.5 (d, $^2J_{C\text{-}F}$=19.7 Hz), 61.8 (m), 47.5 (s), broad C-B signal not observed.

^{11}B-NMR (160 MHz, DMSO-d_6): δ(ppm)= 11.2 (s).

^{19}F-NMR (471 MHz, DMSO-d_6): δ(ppm)= -113.0 (s).

III. NaOH titrations of 1a



1a **2a** **3**

For each sample, **1a** (0.012 g, approximately 4.8 x 10^{-2} mmol) was dissolved in THF (0.400 mL) in a J-Young valve NMR tube with vigorous shaking. An aqueous solution of NaOH (0.08 mL, *x* equiv; *x* = 0.02 to 1.6) was added slowly via micro-syringe with rapid shaking used to mix the solution as the NaOH was added. A capillary filled with DMSO-d_6 was placed in the tube. The sample was analysed by ^{19}F NMR, the first data point was acquired after approximately 9 min and then a spectrum was recorded every 2 h. The ^{19}F NMR signals corresponding to **1a** and **2a** were integrated (the product of oxidation of **2a** was also observed, <2 %) to calculate conversion. The results are displayed in Figure 1.

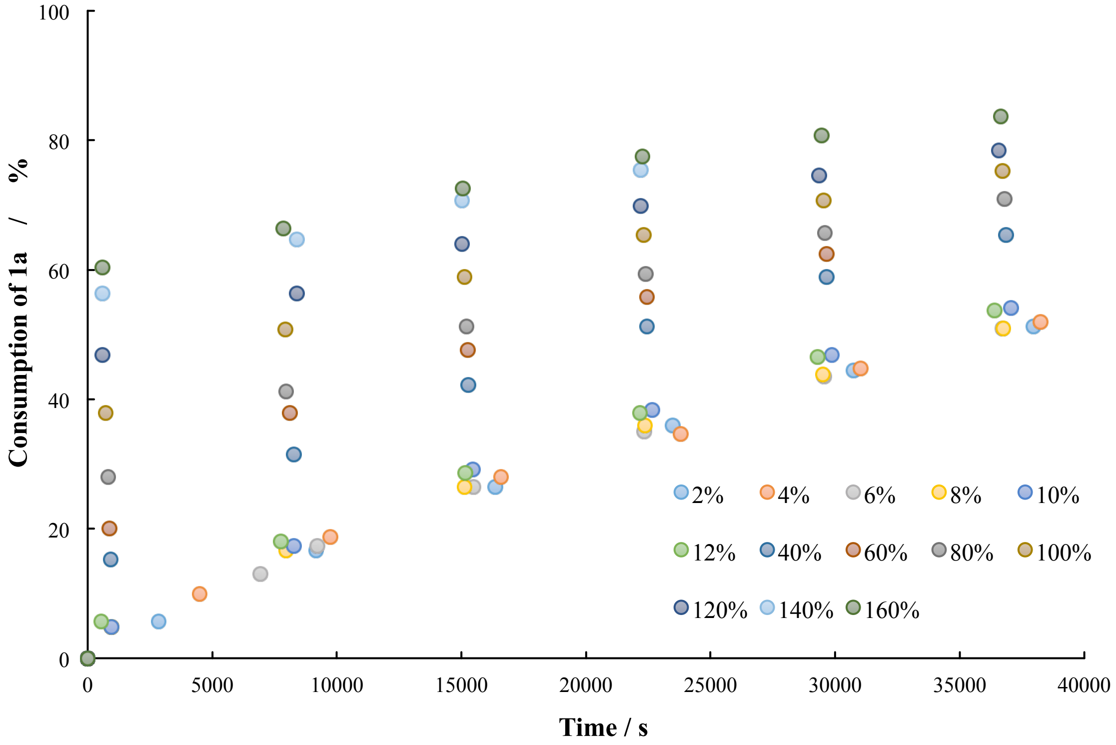
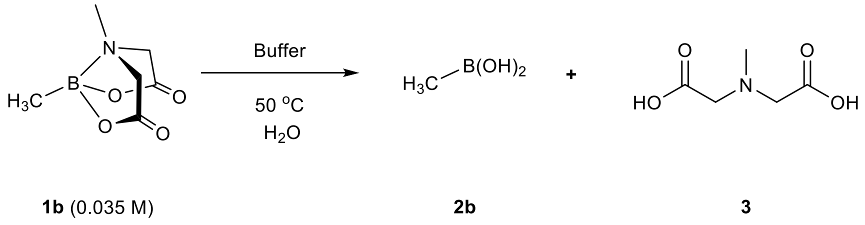


***Figure 1**. Titration of 4-fluorophenyl MIDA boronate **1a** in THF-H_2O with NaOH at room temperature.*

IV. pH rate profile for hydrolysis of Me- MIDA in Buffer



A sample of methyl MIDA boronate **1b** (27.75 mg, 1.62 x 10^{-4} mol) in distilled water (4.6 mL) was mixed in a 10 mL round-bottomed flask charged with a magnetic stirrer. The system was put in a water bath, preheated at 50 ºC, and stirred at 750 rpm. The pH was measured with a calibrated pH meter every 5 minutes over 140 min, data are presented in Figure 2.

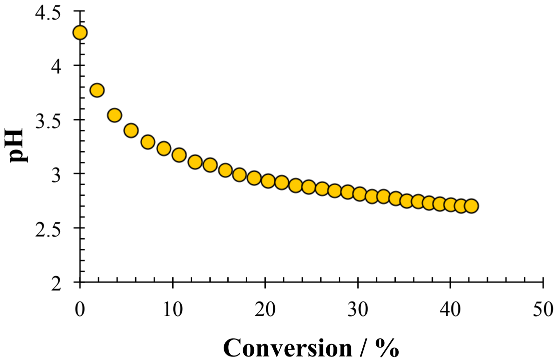


***Figure 2**. Change in pH due to hydrolysis of **1b** in aqueous solution at 50 °C. Conversion was calculated using a first order decay with k_{obs}=6.3 × 10-5 s^{-1}.*

Buffer preparation

0.5 M stock solutions of CH_3COOH, H_3PO_4, HCOOH, K_3PO_4, CH_3COOK, NH_3, NH_4^+Cl were used to make buffers at specific pH, as shown in Table 1.

The amount of each stock solution was calculated using the Henderson-Hasselbalch equation, the pH was measured with a pH meter. The pH was adjusted adding small amounts of the respective stock solution.

Entry	**pH**	k_{obs} /s^{-1}	log k_{obs}	**Buffer**
1	1	7.15 x 10^{-5}	-3.73	CF_3COOH/CF_3COO
2	1.5	9.33 x 10^{-5}	-4.03	
3	2.5	7.4 x 10^{-5}	-4.13	
4	3	5.01 x 10^{-5}	-4.3	CH_3COOH / CH_3COO^-
5	3.9	7.15 x 10^{-5}	-4.15	
6	4.0	7.01 x 10^{-5}	-4.15	
7	4.1	6.77 x 10^{-5}	-4.17	
8	4.2	6.28 x 10^{-5}	-4.20	
9	4.3	6.59 x 10^{-5}	-4.18	
10	4.4	6.65 x 10^{-5}	-4.18	
11	4.5	6.78 x 10^{-5}	-4.17	
12	5.0	7.75 x 10^{-5}	-4.11	
13	6.0	1.03 x 10^{-4}	-3.99	$H_2PO_4^-$ / HPO_4^{2-}
14	7.0	1.37 x 10^{-4}	-3.86	
15	7.5	2.03 x 10^{-4}	-3.69	
16	8.0	2.35 x 10^{-4}	-3.63	
17	8.5	1.98 x 10^{-4}	-3.70	NH_3/NH_4^+
18	9.0	6.53 x 10^{-4}	-3.19	
19	9.5	1.55 x 10^{-3}	-2.81	
20	10	2.07 x 10^{-3}	-2.68	HPO_4^{2-}/ PO_4^{3-}
21	10.5	4.20 x 10^{-3}	-2.38	
22	11	4.25 x 10^{-3}	-1.96	

***Table 1**. Pseudo-first order rate constants of hydrolysis of MeB(MIDA) **1b** at 50 °C in aqueous solution.*

pH-rate profile

Methyl MIDA boronate **1b** (2.4×10^{-5} mol) was added to a J-Young valve NMR tube in 0.6 mL of the buffer solution. The tube was briefly shaken and then placed in the NMR spectrometer at 50 °C. Each experiment was followed by ^{11}B NMR, 200 scans were recorded every 5 minutes for several hours until approximately 90 % conversion. Spectra were analysed manually and both baseline and phase were corrected. Integrations of **1b** and **2b** were used to calculate pseudo-first order rate constant, plotted in Figure 3. The dashed line is the best fit where k_{obs} values were calculated with the following equation:

$$k_{obs} = k_H[H^+] + k_0 + k_{OH}[OH^-] \qquad \text{(Eq 1)}$$

If pH > 4 then,

$$k_{obs} \approx k_0 + k_{OH}[OH^-] \qquad \text{(Eq 2)}$$

k_0 = uncatalyzed rate constant (7.08×10^{-5} s^{-1})
k_{OH} = base promoted rate constant (2.51 M^{-1} s^{-1}).
k_{H+} = acid promoted rate constant (8×10^{-4} M^{-1} s^{-1}).

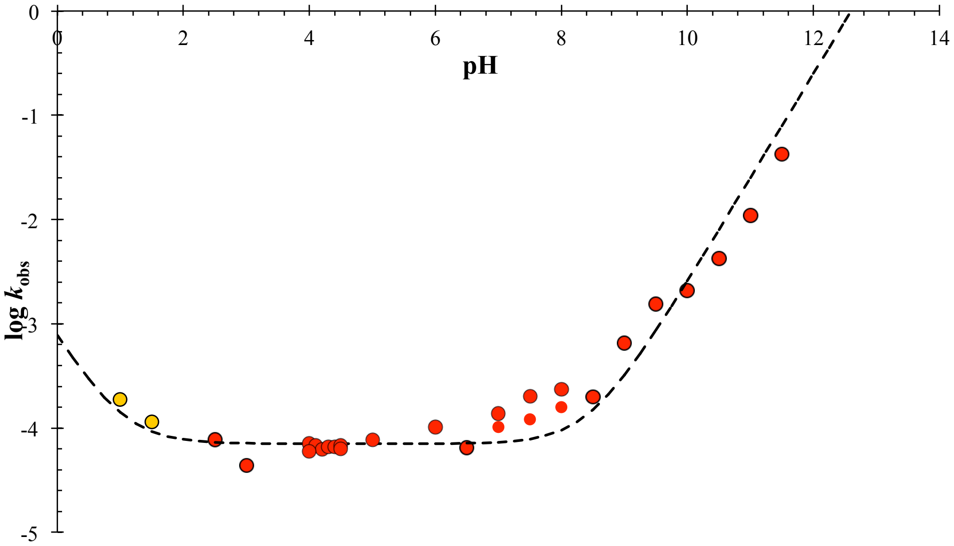
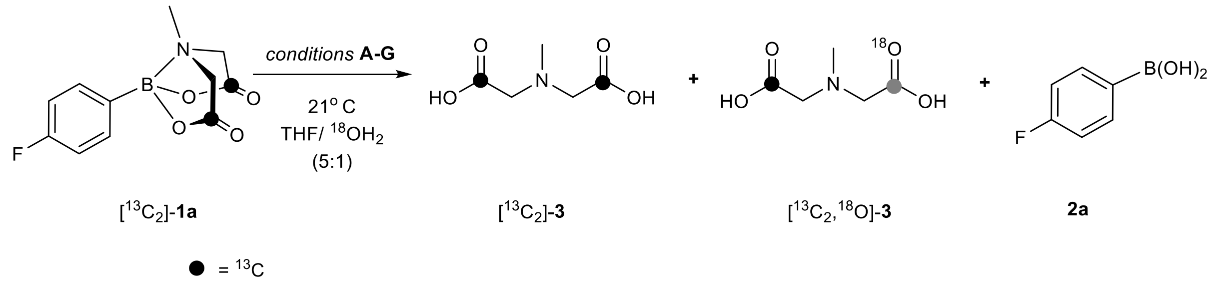


Figure 3. *Experimental and theoretical pH-rate profiles of hydrolysis of **1b** at 50 °C in aqueous buffer solutions.*

V. ^{18}O Incorporations under Conditions A-G



CONDITIONS A to G: In all cases, reactions were performed in a 2 mL glass vial at room temperature (21 °C) stirred with a magnetic bar. For each experiment a solution of [$^{13}C_2$]-**1a** (0.500 mL, 0.1 M) in dry THF was measured with a syringe and place in the vial. Consumption of starting material was confirmed by TLC (R_f= 0.3, EtOAc, UV lamp). The hydrolysis was conducted using $^{18}OH_2$ with isotope enrichment specified as 97.7 %.

*Experiment **A** (2.9 equiv, NaOH, 1000 rpm, 10 min)*

NaOH (5.8 mg, 0.145 mmol, 2.9 equiv) was dissolved $^{18}OH_2$ (0.1 mL) in a vial and then added over 20 seconds via fine-needle syringe to the solution of **1a**, being stirred at 1000 rpm. The mixture was stirred for an additional 10 min. The upper organic layer of the heterogeneous mixture was removed via syringe and transferred to a round-bottomed flask and the solvent removed *in vacuo*. Residual **1a** was analysed by $^{13}C\{^1H\}$ NMR. The plastic cap of the vial was replaced with a rubber cap, and N_2 flushed through for 40 minutes to evaporate any THF. The white solid thus obtained was dissolved in H_2O (0.400 mL) and transferred to a NMR tube. A capillary of D_2O was placed in the tube before running a $^{13}C\{^1H\}$ NMR spectrum of **3** (Na salt).

*Experiment **B** (3 equiv, NaOH, 1000 rpm, saturated NaCl, 24 h)*

In this case, a saturated solution of NaCl in $^{18}OH_2$ (0.05 mL) was added to the substrate solution. Then, a solution of NaOH in $^{18}OH_2$ (0.05 mL) was added to the reaction. The system was stirred at 1000 rpm for 24 h. The organic layer was removed by syringe, the remaining organic solvent was removed from the aqueous layer with nitrogen for 2 h. The white solid was dissolved in H_2O (0.4 mL), a capillary of D_2O added and the sample analysed by $^{13}C\{^1H\}$ NMR

*Experiment **C** (3 equiv, NaOH, 100 rpm, saturated NaCl, 24 h)*

Experiment C was run in parallel with experiment B, the only difference being the stirring rate (100 rpm).

*Experiment **D** (3 equiv K_3PO_4, 1000 rpm, 24 h)*

A solution of K_3PO_4 in $^{18}OH_2$ (0.5 mL, 2.5 M, 5 equiv) was added to the substrate solution. The vial was sealed with a plastic cap and stirred for 24 h at room temperature. After this time, no substrate was detected by TLC. The upper organic layer was removed from the vial via syringe, and nitrogen was used to flush out the remaining organic solvent over a period of 2 hours. The remaining white solid was dissolved in H_2O (0.4 mL) a capillary of D_2O added and the sample analysed by $^{13}C\{^1H\}$ NMR.

*Experiment **E** (3 equiv K_3PO_4, 100 rpm, 24 h)*

Experiment E was run in parallel with experiment D under same conditions, the only difference being the stirring rate (100 rpm).

*Experiment **F** (initially homogeneous, 1000 rpm, 24 h)*

$^{18}OH_2$ (0.1 mL) was added to the vial with the substrate (**1a)** in THF (0.5 ml). The vial was sealed with a plastic cap. The initially homogeneous solution was stirred at 1000 rpm for 24 h. The precipitated formed was removed by vacuum filtration, and washed with THF (1 mL) before being dissolved in H_2O (0.4 mL) transferred to a NMR tube, a capillary of D_2O added and analysed by $^{13}C\{^1H\}$ NMR.

*Experiment **G** (homogeneous throughout, 0 rpm in an NMR tube, 7 h)*

To prepare a concentrated HCl solution in $^{18}OH_2$, a two- necked round-bottomed flask (100 mL) was charged with $CaCl_2$ (30 g) and a magnetic stirrer. A dropping funnel with pressure compensation was added to the flask, on the second neck: a gas adaptor, a piece of tubing, and a glass Pasteur pipette were connected to bubble the HCl generated through a vial containing $^{18}OH_2$ (97 % enrichment). The dropping funnel was charged with HCl (20 mL, 36 % w/w) and the system was sealed with a rubber septum. The concentrated solution of acid was added slowly (over 3 h) to the $CaCl_2$, and the gas generated was circulated. A positive overpressure of N_2 was maintained throughout. The solution formed was titrated (3 times) against a standard solution of NaOH using phenolphthalein as indicator. The final concentration of HCl in $^{18}OH_2$ was found to be 12.3 M.

The hydrolysis experiment was conducted by dissolving [*carbonyl*-$^{13}C_2$]-**1a** (12.78 mg, 0.051 mmol) in THF-d_8 (0.5 mL) in a J-Young valve NMR tube and adding the 12.3 M HCl solution (0.1 mL) to give a 2M HCl solution (pH -0.3). The sample was vigorously shaken for 30 seconds and then inserted in the spectrometer. The reaction was followed via in situ $^{13}C\{^1H\}$ NMR at 21° C. Incorporation of $^{18}OH_2$ was calculated with the early conversion data since a fast equilibrium occurs before hydrolysis and a second exchange equilibrium was observed in the free ligand, [*carbonyl*-$^{13}C_2$]-**3**, under the reaction conditions.

In all cases the molar ratio of the ^{13}C-^{16}O and ^{13}C-^{18}O (Δδ=30 ppb) was calculated based on the integration of the respective peaks in the ^{13}C NMR spectra. The general ^{13}C NMR (101 MHz) experiment consisted of an inverse gated decoupled 10° pulse, 2 seconds of relaxation time, 32.55 seconds of acquisition time, and 10 ppm of spectral width. ^{13}C NMR spectra with the relative integration of the ^{13}C-^{16}O and ^{13}C-^{18}O are shown in Figure 4.

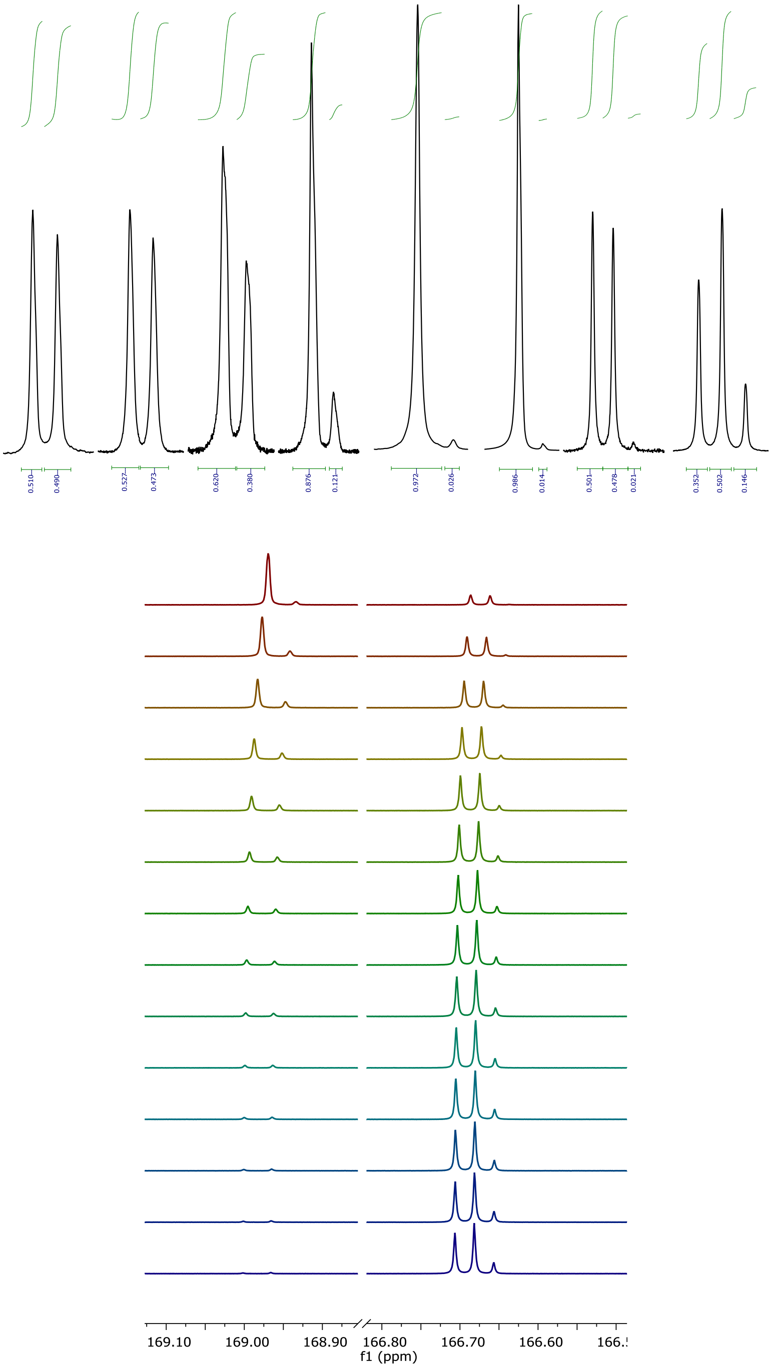


Figure 4. *Upper: ^{13}C{^{1}H}NMR spectra (carbonyl peaks) of ^{13}C$_2$-MIDA ligand **3** after hydrolysis of [^{13}C$_2$]-**1a** at room temperature in THF/^{18}OH$_2$ (5:1) mixtures. From left to right (experiments **A-G** - last two spectra are G at 25 % conversion and 98 % conversion). Lower: in situ ^{13}C{^{1}H} NMR spectra of conditions **G**; spectra (top to bottom) run every 20 minutes, showing ^{18}O-exchange into **1a** (169 ppM) but not **3** (167 ppm).*

Control experiments: Since N-methyliminodiacetic acid (**3**) is not soluble in THF/H_2O mixtures, tests for 16/18 oxygen exchange in **3** (0.0316 g, 0.215 mmol) were conducted in mixtures of D_2O (0.200 mL) and $^{18}OH_2$ (0.200 mL) in an NMR tube, analysing by $^{13}C\{^1H\}$ NMR. The sample was kept at room temperature (21 °C) and a signal for ^{13}C-^{18}O was observed after approximately 2 days (Fig 5-left). To confirm further exchange the sample was heated at 60 °C for 65 h and 89 h (Figs. 5-middle and 5-right respectively). This experiment suggests that the small amount of ^{18}O incorporation observed in [$^{13}C_2$]-**3** (*experiment* ***A***) is the result of the background exchange of **3** with the solvent. It also confirms that the peak at 169.12 ppm is due to ^{13}C-$^{16}O_2$ and not ^{13}C-$^{16}O_1{}^{18}O_1$.

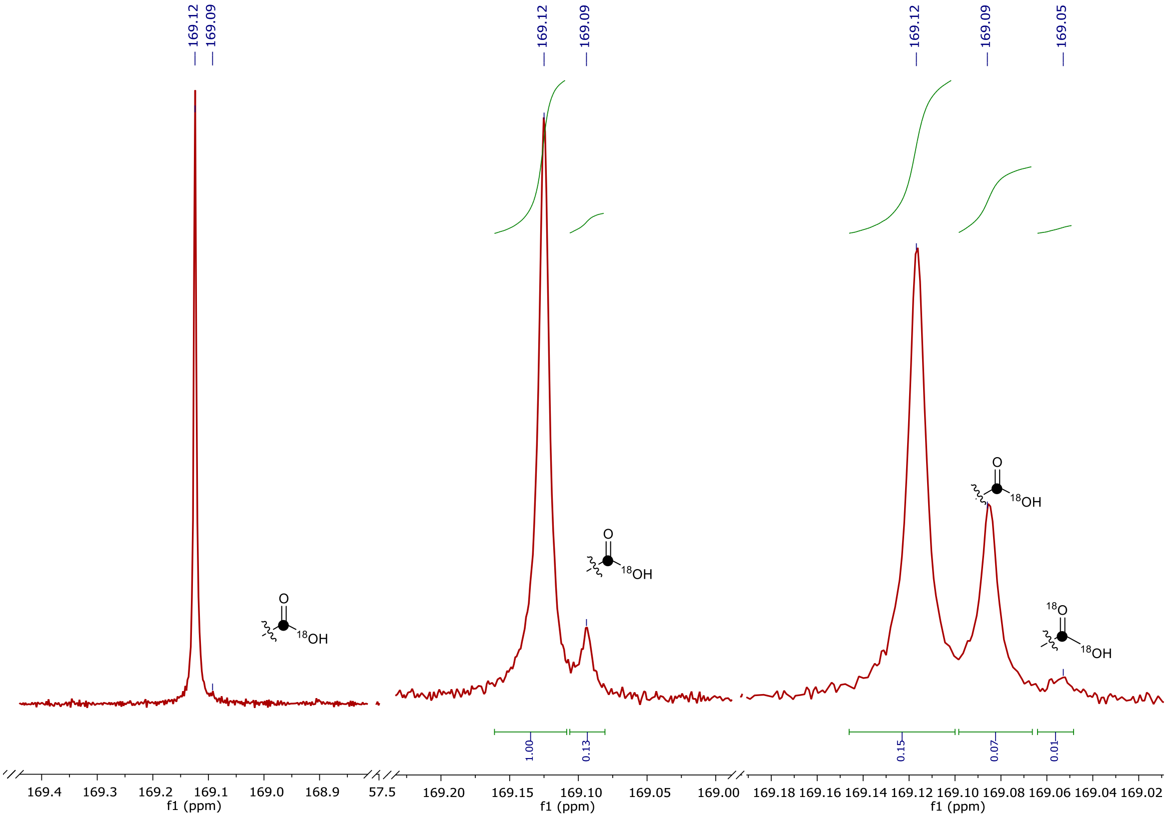


Figure 5 *$^{13}C\{^1H\}$NMR spectra (carbonyl peaks) of* ***3*** *after:*

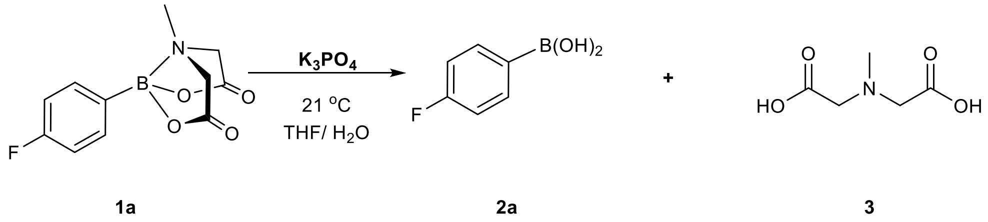
left hand side: sample after 2 days at 21 °C

middle: sample after 65 h at 60 °C

right hand side: sample after 89 h at 60 °C, under neutral conditions

VI. Neutral Hydrolysis Kinetics and KIEs

Effect of K_3PO_4



A 10.0 mL stock solution was made up with 4-fluorophenyl MIDA boronate (**1a**) (251.1 mg, 1.00 mmol), bis[4-(trifluoromethyl)phenyl] (13.3 mg, 0.0459 mmol) as internal standard, in THF. Aliquots of the solution (0.5 mL) were syringed into a J-Young valve NMR tube, 0.100 mL of an aqueous solution of K_3PO_4 (as shown in Table 2) added, and finally a capillary with DMSO-d_6. The tube was vigorously shaken before putting in the spectrometer. ^{19}F NMR spectra were recorded every 4 hours, the NMR tubes were kept at 21 °C between NMR measurements. Reactions were followed to approximately 90 % conversion. Concentrations of all species were calculated based on the integrations against the internal standard. For each experiment k_{obs} was calculated from the slope of ln{[**1a**]$_0$/[**1a**]$_t$} *vs* time. In all cases, $R^2 > 0.99$, pseudo-first order rate constants are displayed in Table 2 and plotted in Figure 6.

Entry	$Ar_FB(MIDA)$ / mmol	K_3PO_4 / mmol	Equivalents	k_{obs} / s^{-1}	R^2
1	0.050	0	0	1.75×10^{-5}	0.999
2	0.050	0.025	0.50	1.74×10^{-5}	0.999
3	0.050	0.050	1.0	1.74×10^{-5}	0.999
4	0.050	0.075	1.5	1.69×10^{-5}	0.999
5	0.050	0.10	2.0	1.68×10^{-5}	0.999
6	0.050	0.15	3.0	1.52×10^{-5}	0.999
7	0.050	0.20	4.0	1.37×10^{-5}	0.998
8	0.050	0.30	6.0	7.01×10^{-6}	0.997

***Table 2**. Pseudo-first order rate constants for hydrolysis of 4-fluorophenyl MIDA boronate (**1a**) at room temperature in THF-H_2O (5:1) at different nominal K_3PO_4 concentrations. These reactions undergo phase separation, the reaction monitored is that occurring in the upper aqueous-organic phase.*

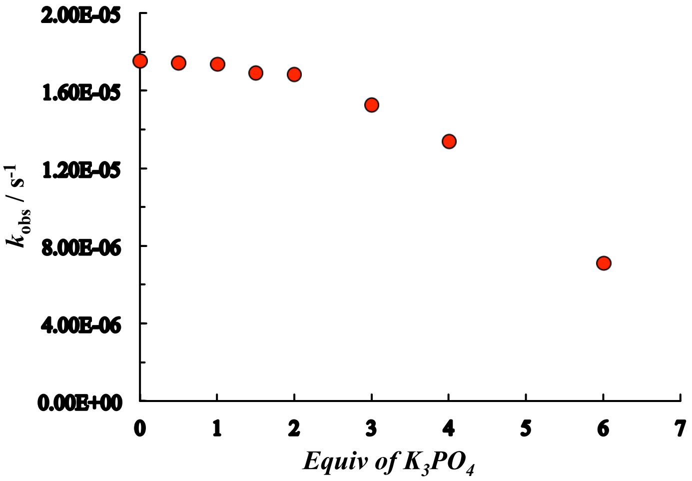


Figure 6. *Effect of K_3PO_4 on hydrolysis of 4-fluorophenyl MIDA boronate (**1a**) at room temperature in THF-H_2O (5:1).*

Effect of H_2O

Distilled degassed water was weighed into 10 mL volumetric flasks, then THF was added to complete the volume and the total weight of the solutions recorded (as shown in *Table 3*). 4-flurophenyl MIDA boronate (**1a**) (12.5 mg, 0.0498 mmol) and 0.500 mL of the THF-H_2O mixture were loaded in a J-Young valve NMR tube, the tube was shaken until the solid was fully dissolved. A capillary with DMSO-d_6 was place in the tube and then the first ^{19}F NMR spectrum was recorded. ^{19}F NMR spectra were recorded at 300 K every 3 hours, the NMR tubes were kept at 21 ^{o}C between NMR measurements. Reactions were followed up to 15-90% conversion. Concentrations of 4-fluorophenyl MIDA boronate (**1a**) and 4-fluorophenyl boronic acid (**2a**) were calculated based on molar ratio. For each experiment k_{obs} was calculated from ln{[**1a**]$_0$/[**1a**]$_t$} vs time. In all cases $R^2 > 0.99$, values are displayed in Table 3 and plotted in Figure 7.

Entry	$[H_2O]$ / M	% w/w (H_2O)	% w/w (THF)	mol fraction (H_2O)	mol fraction (THF)	k_{obs} / s^{-1}
1	0.000	0.00	0.00	0.000	1.000	0
2	0.528	1.08	98.9	0.042	0.958	8.29×10^{-7}
3	0.986	2.00	98.0	0.076	0.924	2.59×10^{-6}
4	2.00	4.05	96.0	0.144	0.856	8.98×10^{-6}
5	2.99	6.02	94.0	0.204	0.796	1.25×10^{-5}
6	3.02	6.07	93.9	0.206	0.794	1.33×10^{-5}
7	4.99	10.0	90.0	0.204	0.692	1.65×10^{-5}
8	7.05	14.1	86.0	0.396	0.604	1.69×10^{-5}
9	9.06	18.0	82.0	0.467	0.533	1.72×10^{-5}
10	11.0	21.7	78.3	0.525	0.475	1.69×10^{-5}
11	19.9	38.1	61.9	0.711	0.289	1.86×10^{-5}

***Table 3**. Pseudo-first order rate constants for hydrolysis of 4-fluorophenyl MIDA boronate (**1a**) at room temperature in THF-H_2O mixtures.*

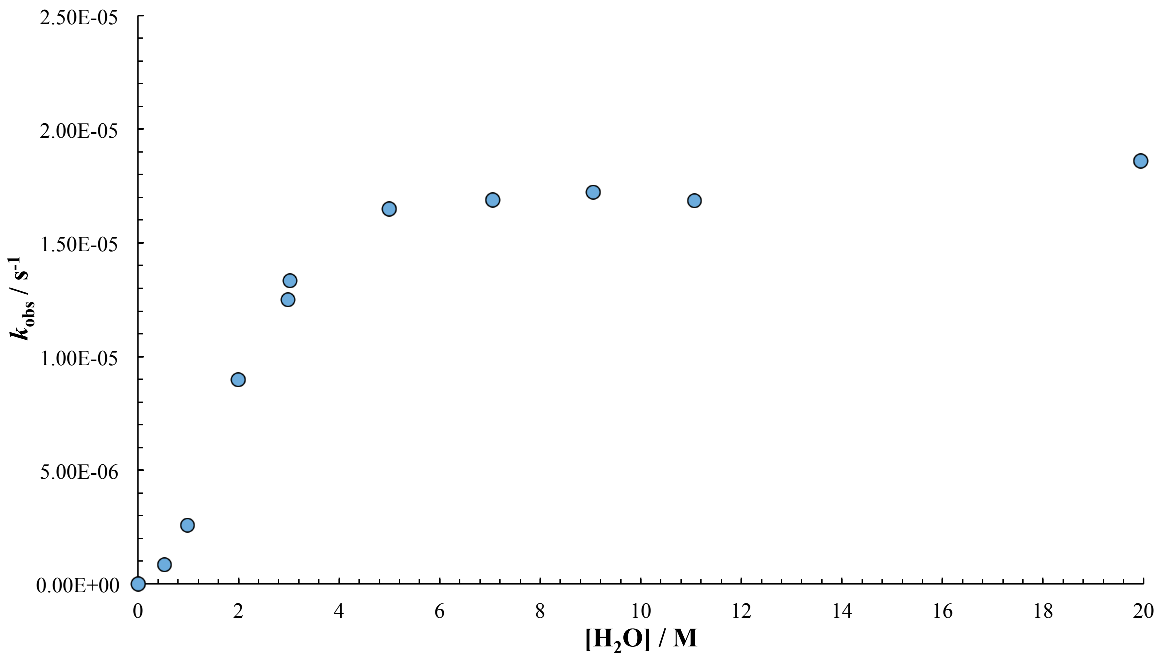


***Figure** 7. Effect of $[H_2O]$ on hydrolysis of 4-fluorophenyl MIDA boronate (**1a**) at room temperature.*

A polynomial (eq 3) was fitted to reported values for water activity in THF/H_2O. This equation was used with the experimental mol fraction of H_2O (X_{H_2O}) to calculate respective water activity (a_w). These values are displayed in Table 4

$$a_w = -3.1378x^6 + 23.635x^5 - 53.676x^4 + 56.232x^3 - 30.272x^2 + 8.2124x + 0.0068 \quad \text{(Eq. 3)}$$

Where x = H_2O mol fraction. This equation was obtained from the 6th order polynomial trend line of the data reported for water activity in mixtures with THF, shown in Figure 8.[6] A linear correlation between was obtained at plotting k_{obs} *vs* $a_w^{2.8}$, see Figure 9.

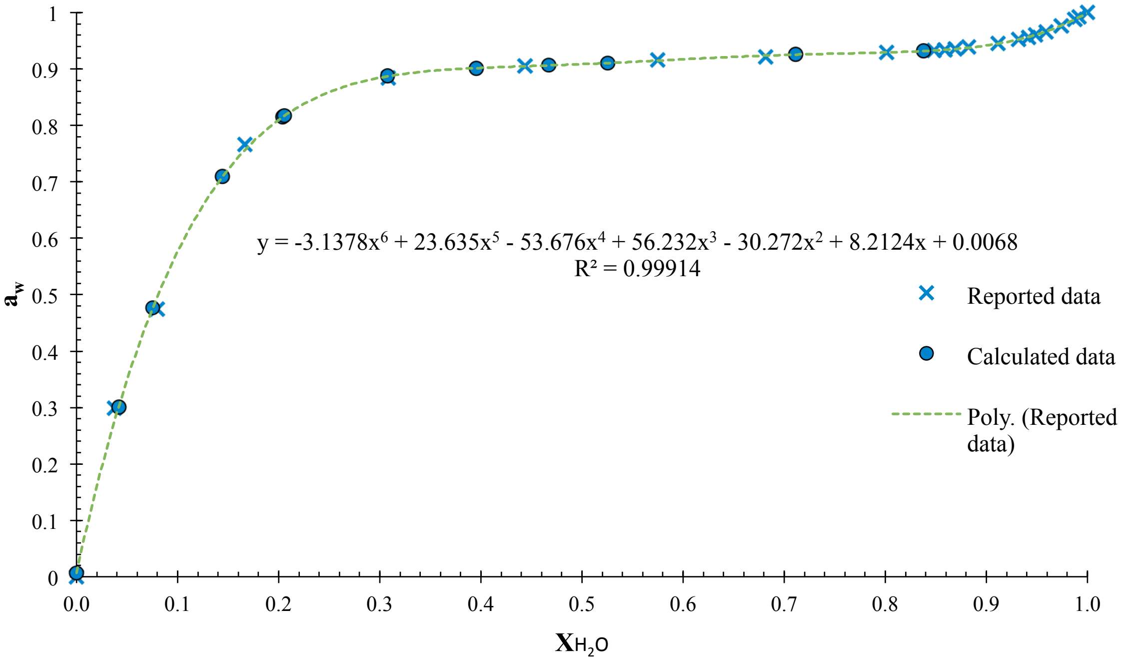


***Figure 8**. Water activity (a_w) as a function of water mol fraction in THF-H_2O mixtures.*

Entry	$[H_2O]$ / M	mol fraction (H_2O)	a_w	k_{obs} / s^{-1}
1	0.000	0.000	0.0	0
2	0.528	0.042	0.30	8.29×10^{-7}
3	0.986	0.076	0.48	2.59×10^{-6}
4	2.00	0.144	0.71	8.98×10^{-6}
5	2.99	0.204	0.81	1.25×10^{-5}
6	3.02	0.206	0.81	1.33×10^{-5}
7	4.99	0.204	0.89	1.65×10^{-5}
8	7.05	0.396	0.90	1.69×10^{-5}
9	9.06	0.467	0.91	1.72×10^{-5}
10	11.0	0.525	0.91	1.69×10^{-5}
11	19.9	0.711	0.91	1.86×10^{-5}

***Table 4**. Calculated values of water activity in THF/H_2O mixtures at room temperature.*

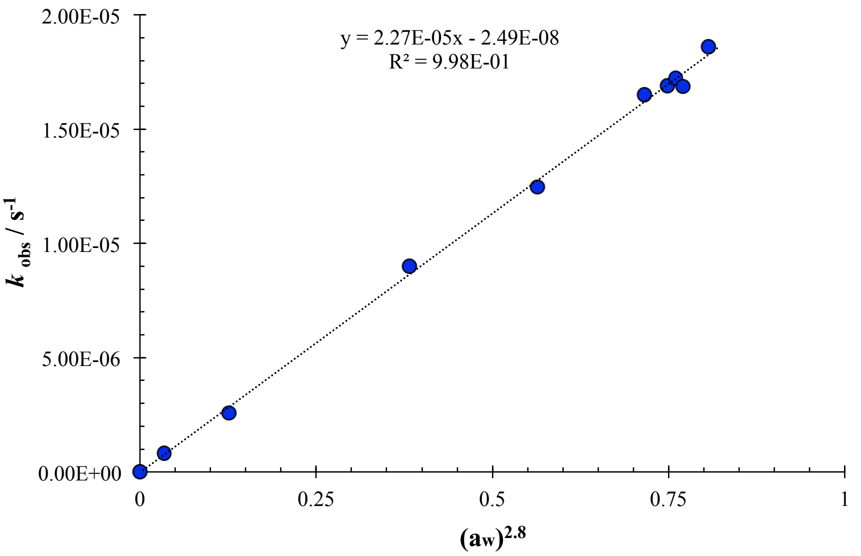


***Figure 9**. pseudo-first order rate constant as a function of a higher water activity term*

Thermodynamic Parameters

A stock solution of was made up with 5 mL of THF and 1 mL of H_2O. 4-fluorophenyl MIDA boronate (**1a**) (approximately 15.3 mg, 0.0601 mmol) was placed in a J-Young valve NMR tube. The temperature in the NMR probe was established for 30 minutes to ensure stability. Then 0.600 mL of the THF/H_2O solution and a capillary with DMSO-d_6 was added to the NMR tube, this was vigorously shaken before placing in the spectrometer. ^{19}F-NMR spectra were recorded every half hour, the NMR tubes were kept in the probe to keep the temperature constant. Reactions were followed up to 50-95 % conversion. A similar procedure was followed using a mixture containing 0.5 M water. For each experiment k_{obs} was calculated from ln{[**1a**]$_0$/[**1a**]$_t$} vs time. In all cases $R^2 > 0.99$, values are displayed in Table 5. Activation parameters were calculated using the following constants: k_B=1.38 x 10^{-23} J K^{-1}, h = 6.63 x10^{-34}, and R = 8.314 J mol K^{-1}, and the slope and y-intercept of the Eyring analysis, Figure 10.

Entry	Temp / K	T^{-1} / K^{-1}	k_{obs} /s^{-1} (9 M)	k_{obs} /s^{-1} (0.5 M)
1	294.15	0.00340	-	8.29×10^{-7}
2	298.15	0.00335	2.22×10^{-5}	
3	303.15	0.00330	4.08×10^{-5}	-
4	308.15	0.00325	6.92×10^{-5}	3.39×10^{-6}
5	313.15	0.00319	1.20×10^{-4}	5.39×10^{-6}
6	318.15	0.00314	1.86×10^{-4}	8.09×10^{-6}
7	323.15	0.00309	2.90 x10^{-4}	1.15 x10^{-5}

Table 5*. Pseudo-first order rate constants for hydrolysis of 4-fluorophenyl MIDA boronate (**1a**) in THF-H_2O (9.1 M and 0.5 M) at different temperatures.*

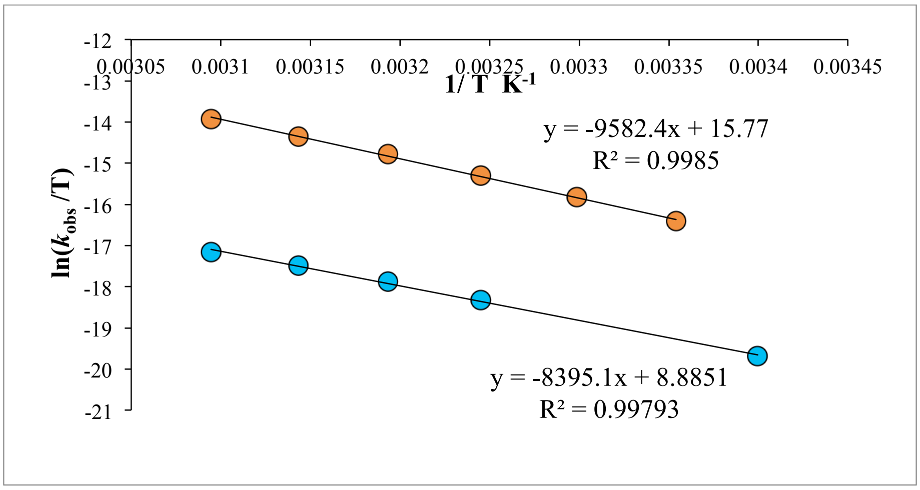


Figure 10*. Eyring plot for hydrolysis of 4-fluorophenyl MIDA boronate (**1a**) in THF-H_2O (9 M and 0.5 M)*

Proton inventory: Hydrolysis in L_2O : THF mixtures (L= H or D)

A 5 mL stock solution (A) was made up with distilled H_2O (812.0 mg, 45.1 mmol) and THF to give a 9.02 M solution. A second solution (B) was prepared with D_2O (903.5 mg, 45.1 mmol) and THF to give a total volume of 5 mL. Approximately 0.05 mmol of 4-fluorophenyl MIDA boronate (**1a)** was placed in a J-Young valve NMR tube along with 0.5 mL of a mixture of solutions A and B. The solid was completely dissolved and a capillary with DMSO-d_6 was put into the NMR tube. ^{19}F-NMR spectra were recorded at 300 K every 3 hours, the NMR tubes were kept at 20 ^{o}C between NMR measurements. Reactions were followed up to approximately 90 % conversion. For each experiment k_{obs} was calculated ln{[**1a**)]$_0$/[**1a**]$_t$} vs time. In all cases $R^2 > 0.99$. The solvent compositions are displayed in Table 6 and the $k_{obs}L/k_{obs}H$ ratios against mol fraction D_2O (X_{D_2O}) are plotted in Figure 11.

Entry	Solution A / mL	Solution B / mL	mol Fraction D_2O	$[L_2O]_T$ /M	k_{obs} ($\times 10^{-5}$) / s^{-1}
1	0	0.50	0	9.0	1.63
2	0.05	0.45	0.1	9.1	1.59
3	0.10	0.40	0.2	9.1	1.56
4	0.15	0.35	0.3	9.1	1.53
5	0.20	0.30	0.4	9.1	1.47
6	0.25	0.25	0.5	9.1	1.44
7	0.30	0.20	0.6	9.1	1.41
8	0.35	0.15	0.7	9.1	1.37
9	0.40	0.10	0.8	9.1	1.33
10	0.45	0.05	0.9	9.1	1.26
11	0.50	0.00	1.0	9.1	1.20

***Table 6**. Pseudo-first order rate constants for hydrolysis of 4-fluorophenyl MIDA boronate (**1a**) in THF-L_2O (9.1 M) at room temperature;* L=H/D.

The theoretical values of the $k_{obs}L/k_{obs}H$ were calculated with the equation:

$\frac{k_{obs\,L}}{k_{obs\,H}}=(1\text{-}X_{L_2O}+X_{L_2O}\emptyset_1)(1\text{-}X_{L_2O}+X_{L_2O}\emptyset_2)$ where X_{L_2O} is the mol fraction D_2O and $\emptyset_1/\emptyset_2$ are fractionation factors for deuterium at two sites.

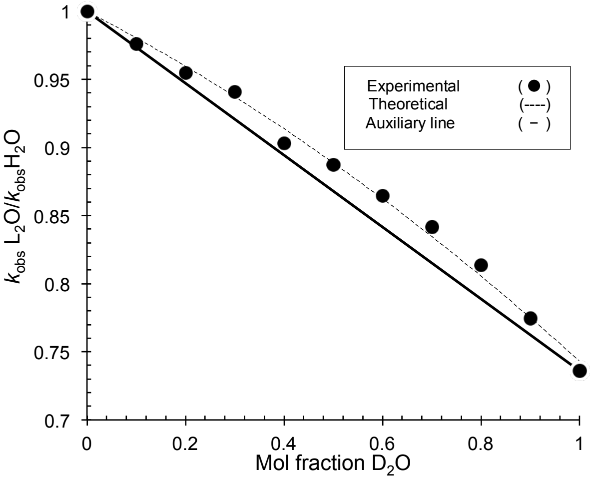
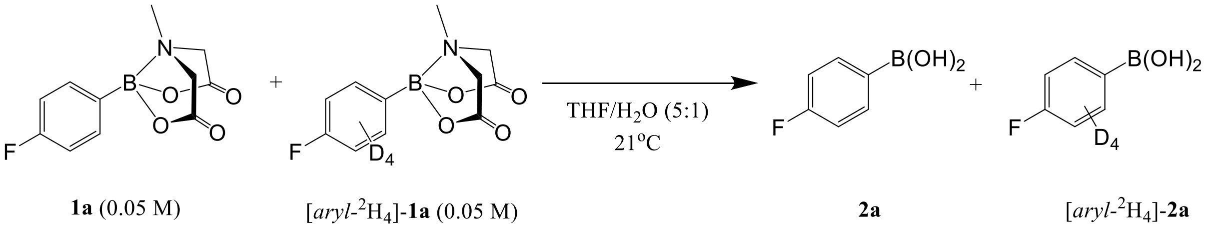


***Figure 11**. Proton inventory plot for hydrolysis of **1a** in THF-L_2O mixtures at room temperature; L=H/D.*

Kinetic Isotope Effect Measurements



1a (0.05 mmol), the respective labelled reagent [*aryl* $^2H_4$, ^nL]-**1a** (0.05 mmol), and 4-CF_3PhBr as an internal standard were put in a J-Young valve NMR tube. Then, a mixture of THF/H_2O (5:1) (0.5 mL) was added and the tube was vigorously shaken. A capillary with DMSO-d_6 was inserted and ^{19}F NMR spectra were recorded approximately every 3 h. The NMR spectra were phased and baseline corrected manually. The concentration of reagents and products was calculated based on the integration against the internal standard. The isotopologue ratio and fractional conversions were calculated at different conversions and the data were fitted using a pseudo-first order competition.

Entry	Reagents	KIE	Measured	Corrected
1	[^{10}B]-**1a** / [*aryl*-$^{2}H_4$,^{11}B]-**1a**	$^{10}B/^{11}B$	1.049	1.032
2	[1-$^{13}C_2$]-**1a** / [*aryl*-$^{2}H_4$]-**1a**	$^{12}C/^{13}C$	1.015	0.999
3	**1a** / [*aryl*-$^{2}H_4$,^{15}N]-**1a**	$^{14}N/^{15}N$	1.033	1.016
4	**1a** / [*aryl*-$^{2}H_4$]-**1a**	$^{1}H/^{2}H$	1.017	1.000

***Table** 7. KIE measurements in neutral conditions.*

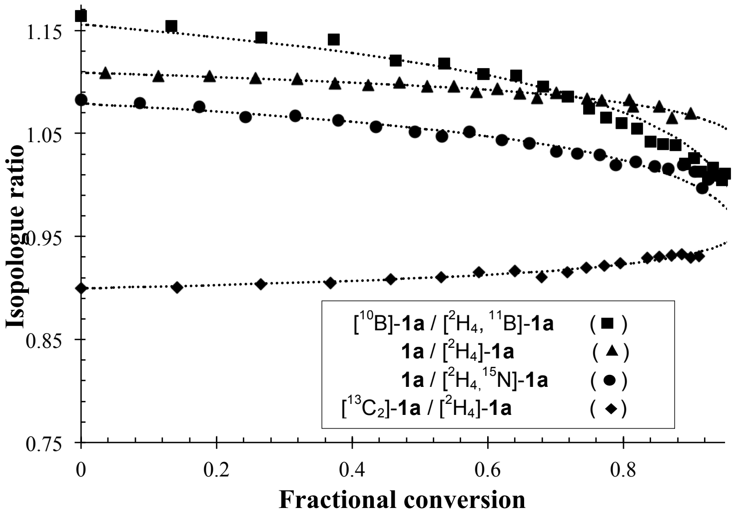
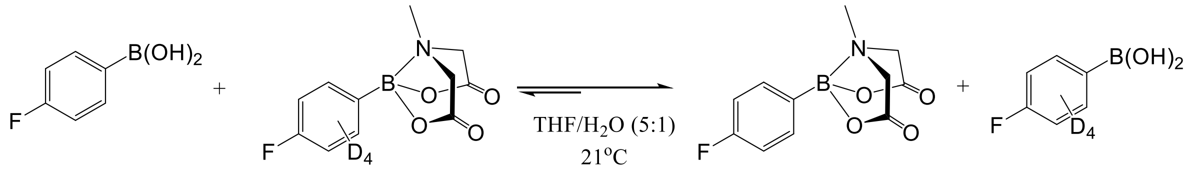


***Figure 12**. KIE determination in slow release conditions.*

Crossover experiment - control for MIDA ligand / isotope exchange at high conversions



2a [*aryl*-$^{2}H_4$]-**1a** **1a** [*aryl*-$^{2}H_4$]-**2a**

In a J-Young valve NMR tube: [*aryl*-$^{2}H_4$]-**1a** (0.0073 g, 0.0288 mmol, 1 equiv), **2a** (0.0041 g, 0.0297 mmol, 1.031 equiv), dry THF (0.5 mL), and H_2O (0.1 mL) were mixed. Then, a capillary with DMSO-d_6 was placed in the tube and a ^{19}F NMR spectrum was recorded periodically. The tube was kept at room temperature (21 °C) when this was outside of the probe. Hydrolysis of [*aryl*-$^{2}H_4$]-**1a** was observed after few minutes however, formation of **1a** was observed after 20 h, as shown in Figure 13. Due to the phase splitting in the system, only a small amount of the ligand **3** remains in the organic layer however, this is enough to produce **1a**.

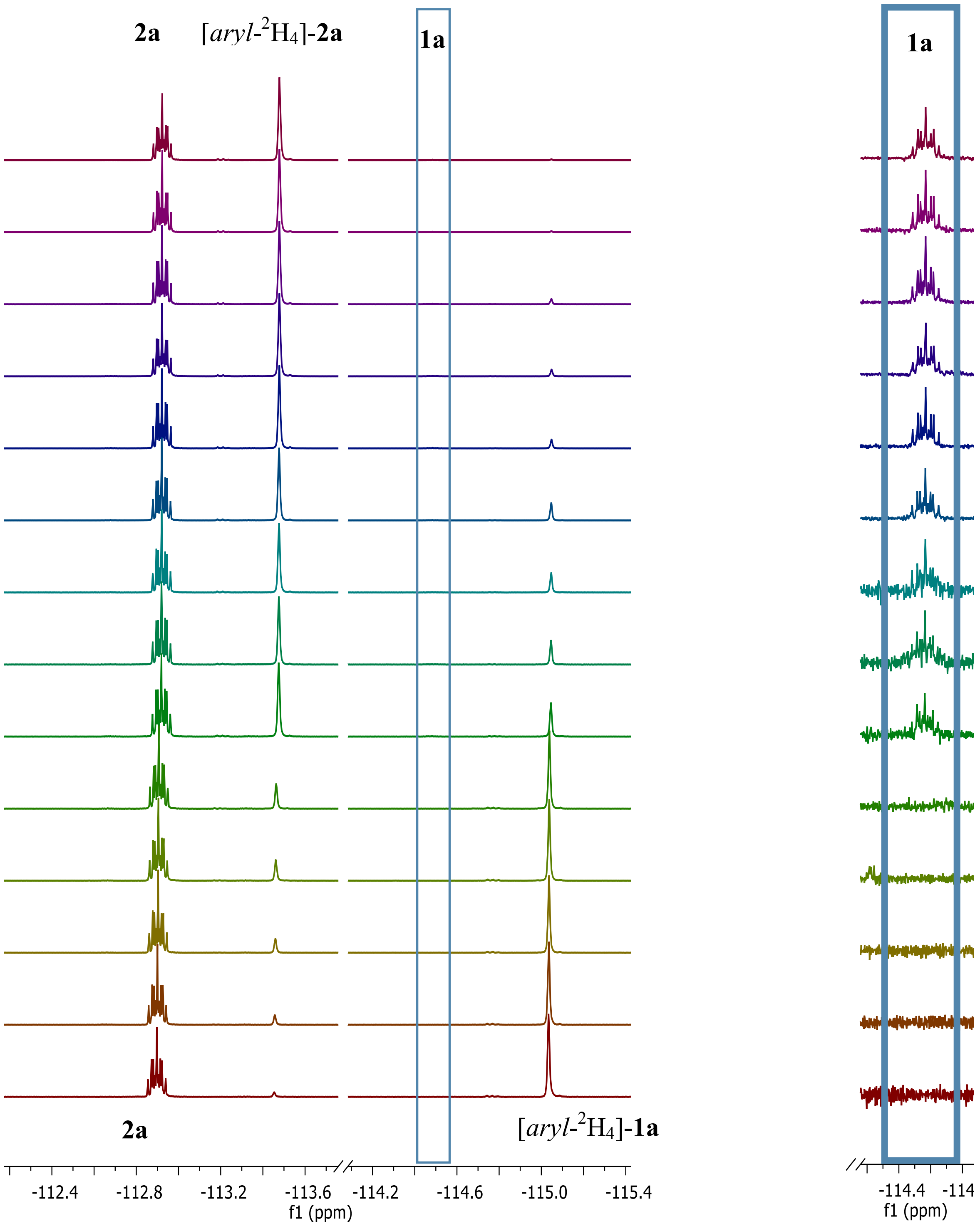
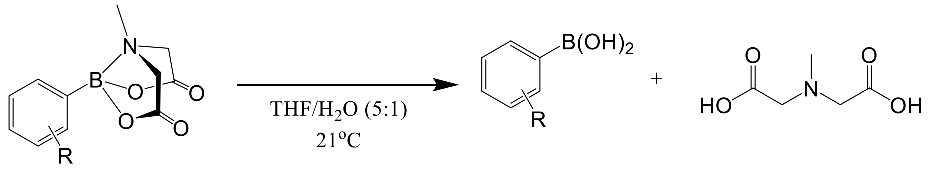


Figure 13. *Cross-over experiment between **2a** + **3** and [aryl-^{2}H$_4$]-**1a** at room temperature in THF/H$_2$O.*

Hammett Plots



1(a,c-h) (0.1 M) **2(a,c-h)** **3**

Approximately 5 x10^{-5} mol of the aryl MIDA **1(a,c-h)** was put in a J-Young valve NMR tube and then a mixture of fresh prepared THF/H$_2$O solution (5:1) (0.5 mL) was added. The tube was sealed and vigorously shaken for few seconds. A capillary with DMSO-d$_6$ was inserted and a ^{11}B NMR spectrum recorded immediately. Then, the sample was kept at 21 °C and the reaction was followed by ^{11}B NMR. Concentrations of the MIDA boronate and the respective boronic acid were calculated based on molar ratio. For each experiment k_{obs} was calculated by first order function and in all cases R^2 > 0.99. The rate constants and the k_{obs}X/k_{obs}H ratios against $\sigma_{\mathrm{Hammett}}$ values are shown in Table 8 and Figure 14.

Substrate	R-	$\sigma_{\mathrm{Hammett}}$	k_{obs} / s^{-1}	log (k_{obsX}/k_{obsH})
1c	4-CH$_3$O-	-0.29	6.57×10^{-6}	-0.37
1d	4-CH$_3$-	-0.14	1.11×10^{-5}	-0.14
1e	H-	0	1.53×10^{-5}	0
1a	4-F-	0.15	1.79×10^{-5}	0.069
1f	4-CF$_3$-	0.53	4.17×10^{-5}	0.44
1g	3-NO$_2$-	0.71	4.73×10^{-5}	0.49
1h	3,5-(CF$_3$)$_2$-	0.92	7.39×10^{-5}	0.69

Table 8. *Pseudo-first order rate constants for aryl MIDA boronate hydrolysis in THF/H$_2$O at 21°C.*

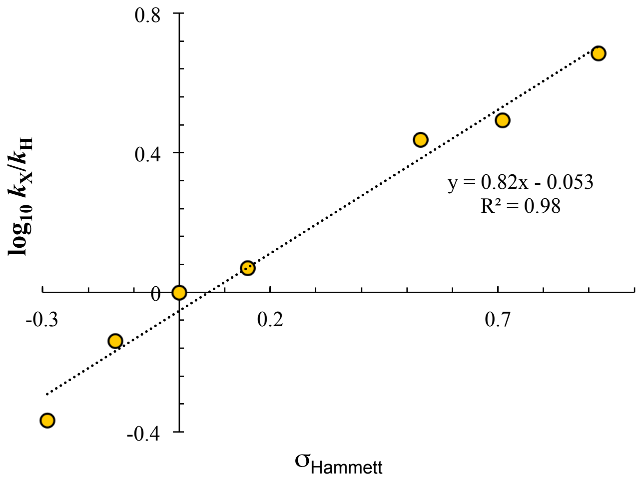


Figure 14*.Hammet plot of neutral hydrolysis at 21 °C (upper 9.1 M H2O; lower: [H2O])*

In additional experiments, the fluorinated aryl MIDA boronates: **1a** (3.0 × 10^{-5} mol), **1f** (1.0 × 10^{-6} mol) and **1h** (5 × 10^{-4} mol) were put in a J-Young valve NMR tube and dissolved in a mixture of THF/H_2O (0.5 mL). After insertion of a capillary of DMSO-d_6, ^{19}F NMR spectra were recorded every 3 h. k_{obs} for each substrate was calculated from the slope at plotting $\ln\{[Ar_FB(MIDA)]_0/[Ar_FB(MIDA)]\}$ vs time. The rate constants were used to calculate the gradient of a Hammett plot with three data points.

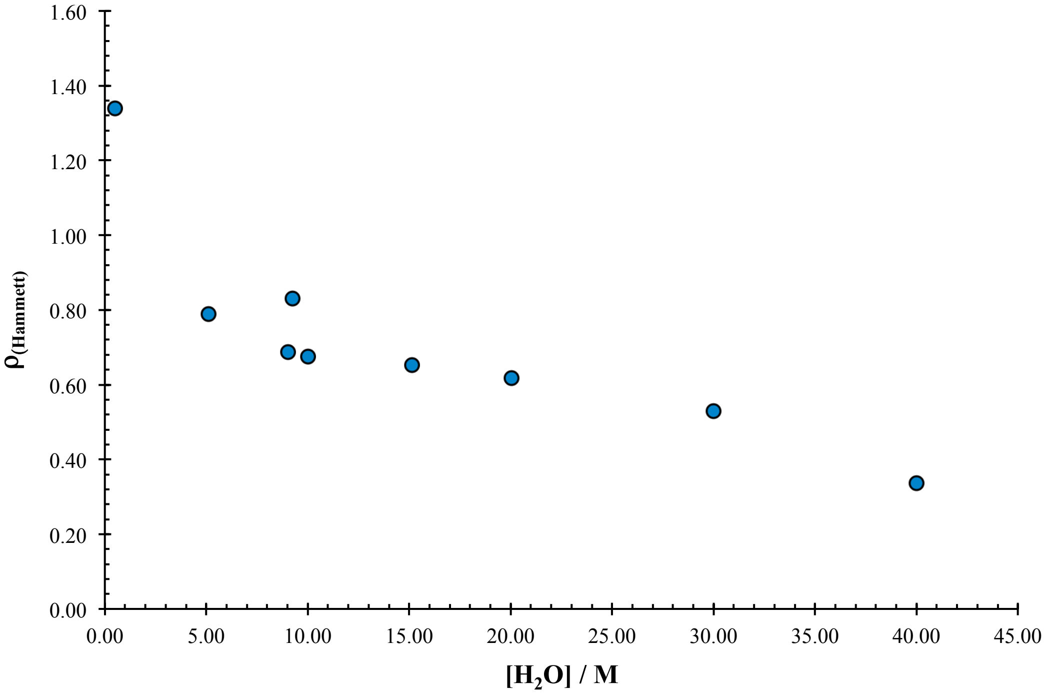
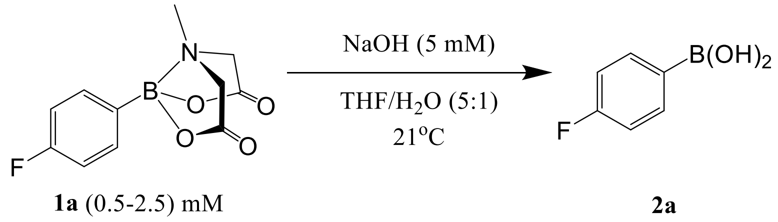


Figure 15*.Hammett ρ(rho) values in different THF/H_2O mixtures at 21 °C.*

VII. Base-Mediated Hydrolysis Kinetics and KIEs

Kinetic order in substrate



A 50 mL NaOH stock solution (10 mM) was prepared diluting aqueous NaOH (1.00 mL, 0.50 M) and topped up with THF/H_2O (5:1) A set of solutions at different substrate concentrations was prepared with 4-fluorophenyl MIDA boronate **1a** (1-5 mM, 10 mL) as shown in Table 9. Blank solvent, THF/H_2O (5:1), and the NaOH solution (10 mM) in THF/H2O (5:1) were loaded in the stopped flow reservoir syringes, then mixed to run the reference UV spectra and confirm the efficiency of the mixing at room temperature (21 °C). The blank solvent syringe was replaced with the freshly prepared substrate solution syringe (avoiding slow-release contribution), the system was purged 5 times with both solutions and then the absorbance was followed for the first five seconds, collecting 100 data points per second. Rate of absorbance change was plotted against base concentration as shown in Figure 16. Reaction order in substrate (**1a**) concentration

Entry	**Mass 1a / mg**	**Vtot / mL**	**[1a)] / mM**	**[NaOH] / mM**	**ΔA / s^{-1}**
1	2.66	10.00	0.50	5.0	7.94×10^{-3}
2	5.01	10.00	1.0	5.0	1.46×10^{-2}
3	7.51	10.00	1.5	5.0	2.23×10^{-2}
4	10.10	10.00	2.0	5.0	2.93×10^{-2}
5	12.61	10.00	2.5	5.0	3.43×10^{-2}

Table 9. *Effect of substrate concentration on hydrolysis rate.*

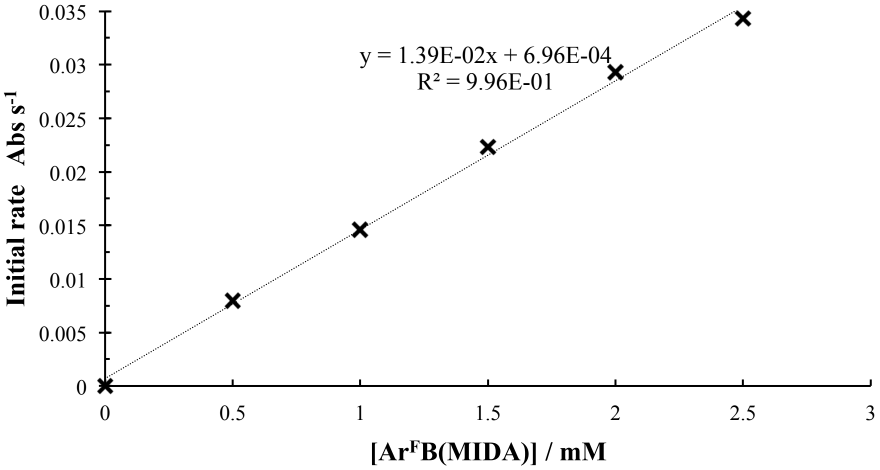


***Figure 16**. Reaction order in substrate (1a) concentration.*

Kinetic order in NaOH

A 50 mL stock solution was made up with 4-fluorophenyl MIDA boronate **1a** (25.4 mg, 0.101 mmol) and THF/H_2O (5:1). A second 50 mL stock solution was made up with NaOH (1.013 g, 25.3 mmol) and fresh distilled water, and from this solution, aliquots were diluted with H_2O and the same THF/H_2O (5:1) as shown in Table 10

Entry	**mL / NaOH**	**mL of H_2O**	**Final volume / mL**	**[NaOH] / mM**
1	0.250	1.250	25.0	5.0
2	0.375	1.375	25.0	7.5
3	0.500	1.000	25.0	10.0
4	0.625	0.875	25.0	12.5
5*	0.750	1.750	25.0	15.0

***Table 10**. Preparation of NaOH solution in THF/H_2O for fast release experiments.*

Blank solvent, THF/H_2O (5:1), and the respective base solution were loaded in the stopped flow reservoir syringes and mixed them to run the reference UV spectra and confirm the efficiency of the mixing at room temperature (21 °C). The blank solvent syringe was replaced with a substrate syringe, the stopped flow unit was purged 5 times with base and substrate solutions using single compressed air shots with a pressure of 80 psi. Once the system was purged, the absorbance was measured at different wavelength (250-450 nm) within the first 5 seconds using 5 ms for integration time (100 data points per second). Three experiments were recorded for each base concentration, and the average absorbance at 264 nm was used for kinetic analysis as well as the absorbance at 400 nm as a baseline correction. For each base concentration the absorbance was followed for 250 s to get the plateau (A_∞). The initial change in absorbance was calculated with kinetic studio software at different base concentrations. The gradient of the best fit line and the absorbance at infinite time, A_∞, were used to calculate the relative change in absorbance, as shown in Table 11.

Entry	[NaOH] / mM	Initial rate / Abs s^{-1}	Abs_∞	ΔAbs_{rel} s^{-1}
1	2.5	4.85×10^{-3}	0.333	1.45×10^{-2}
2	3.8	9.28×10^{-3}	0.373	2.49×10^{-2}
3	5.0	1.31×10^{-2}	0.399	3.28×10^{-2}
4	6.3	1.83×10^{-2}	0.440	4.16×10^{-2}
5*	7.5	2.37×10^{-2}	0.477	4.98×10^{-2}

Table 11 *Effect of base concentration on hydrolysis of 4-fluorophenyl MIDA boronate* ***1a*** *in fast release conditions*

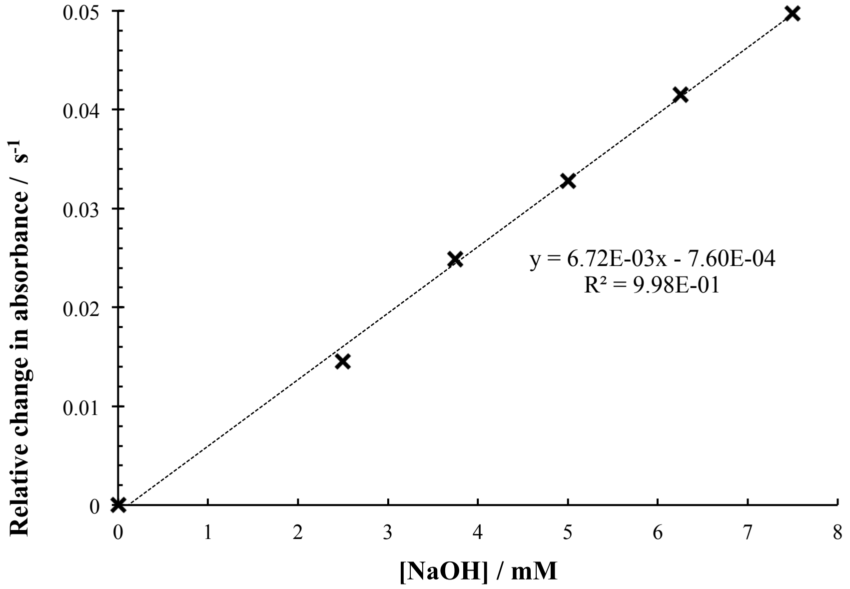
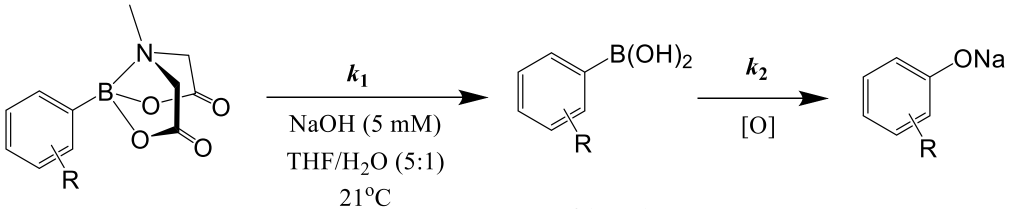


Figure 17. *Determination of order reaction on NaOH concentration for hydrolysis of 4-flurophenyl MIDA boronate* ***1a*** *in fast release conditions*

Hammett Correlation



1(a,c-h) (1 mM) **2(a,c-h)**

1 mM stock solutions were prepared with aryl MIDA boronates **1**(**a,c-h**) in THF/H_2O (5:1) at room temperature.* The same solvent mixture was used to make a 10 mM NaOH solution, the amount of hydroperoxides was below 50 mg/L at any time during the experiment to avoid extensive peroxide promoted oxidation of the boronic acid.

Reservoir syringes were charged, one with blank solvent and the other with the NaOH solution. The system was purged 5 times with base and substrate solutions using single compressed air shots with a pressure of 80 psi, after this the background spectrum was recorded. The blank solvent syringe was replaced by a substrate syringe; the system was purged again 5 times with base and substrate solutions. Then, the change in absorbance was measured from 0 – 250 s. The experiment was repeated three times and the average was used to calculate the pseudo-first order rate constant with kinetic studio software at the wavelength shown in Table 12. Relative rate constants were used to get a Hammett plot shown in Fig 18.

Entry	**Substrate**	**R**	ρ_{Hammett}	**λ / nm**	k_1 /s^{-1}	k_2 /s^{-1}	**log (k_{1X}/k_{1H})**
1	**1c**	CH_3O-	-0.29	243.1	1.17×10^{-2}	-	-0.33
2	**1d**	CH_3-	-0.14	302.8	1.74×10^{-2}	9.21×10^{-3}	-0.16
3	**1e**	H-	0	251.6	2.59×10^{-2}	6.08×10^{-3}	0.00
4	**1a**	4-F-	0.15	264.5	2.96×10^{-2}	-	0.073
5	**1f**	4-CF_3-	0.53	-	-	-	-
6	**1g**	3-NO_2-	0.71	307	5.88×10^{-2}	-	0.37
7	**1h**	3,5-$(CF_3)_2$-	0.92	262.3	5.31×10^{-2}	-	0.33

Table 12. *Relative pseudo-first order rate constants for aryl MIDA boronates in base-promoted hydrolysis. k1 is hydrolysis, k2 is oxidation to phenol(ate).*

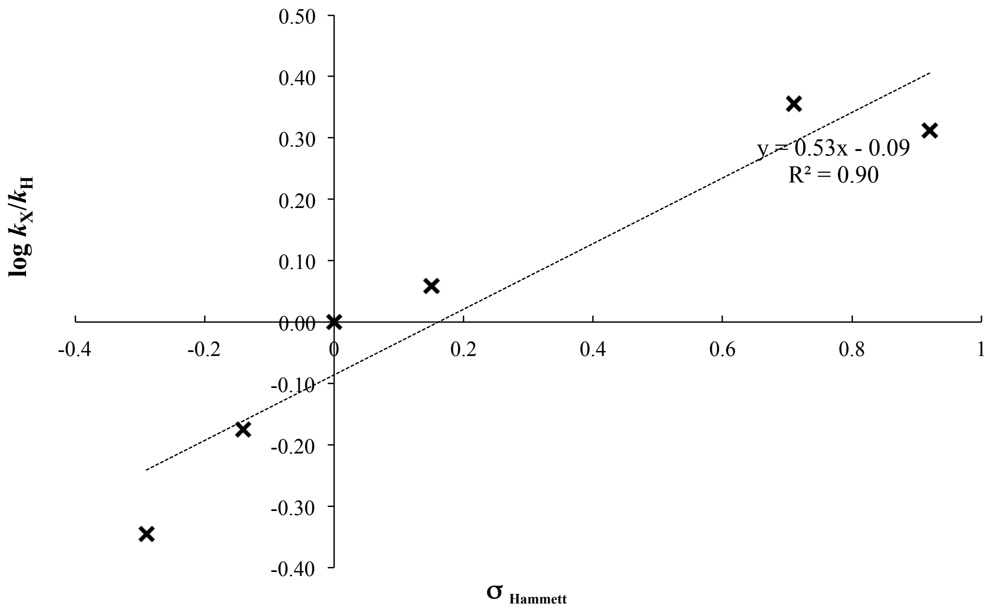


Figure 18. *Hammett plot of base-promoted hydrolysis at room temperature.*

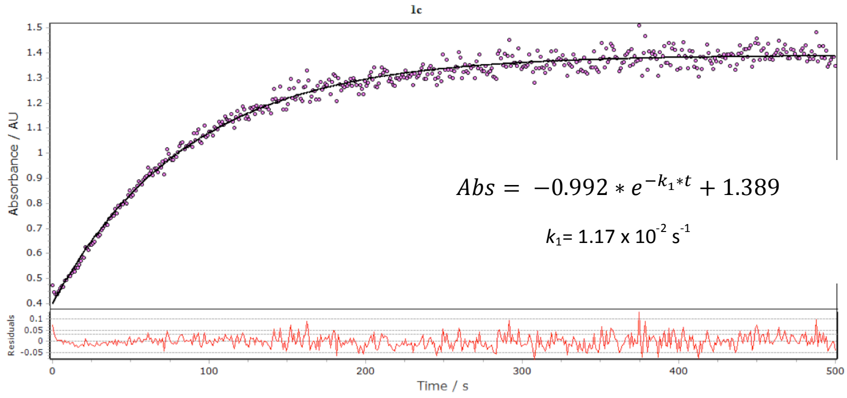


***Figure 19**. Experimental and fitted data for **1c** at 243.1 nm*

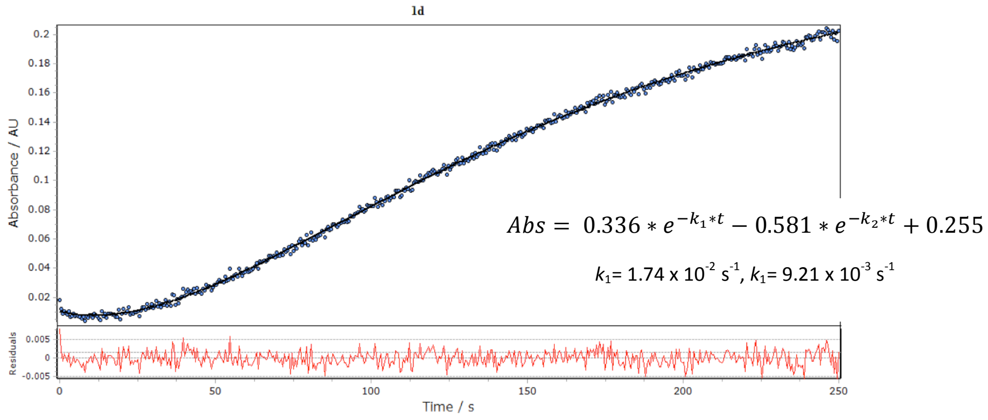


Figure 20. *Experimental and fitted data for **1d** at 302.8 nm.*

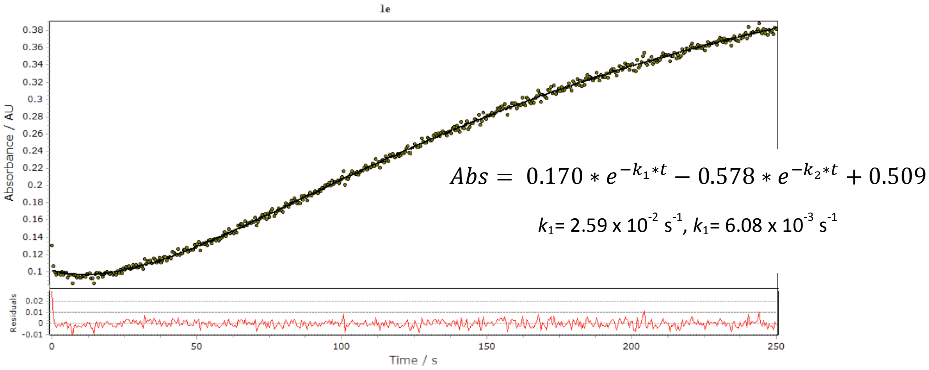


Figure 21. *Experimental and fitted data for* ***1e*** *at 251.6 nm.*

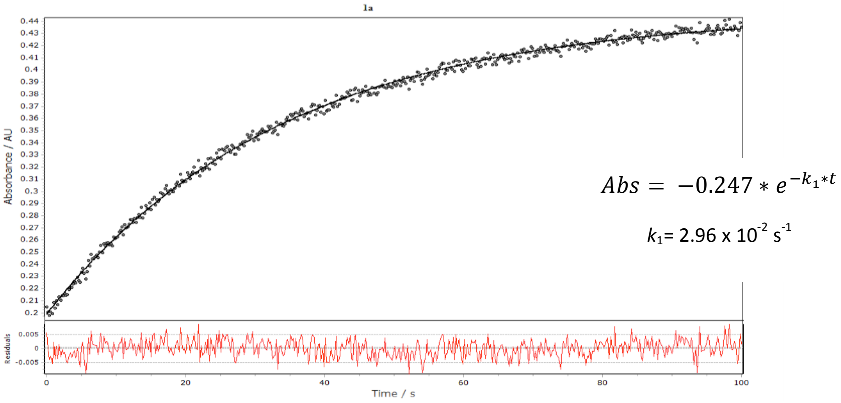


Figure 22. *Experimental and fitted data for* ***1a*** *at 264.5 nm.*

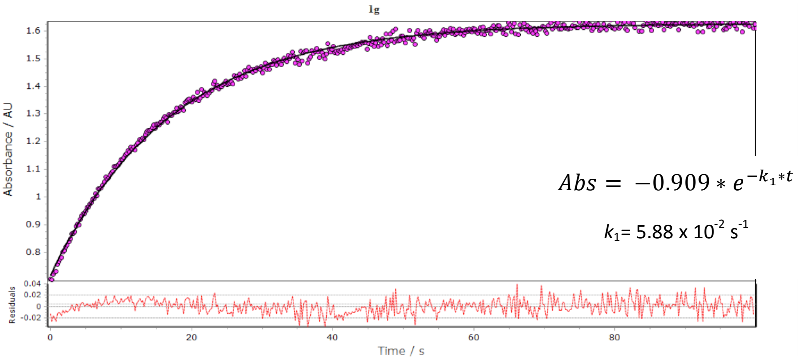


Figure 23*.* *Experimental and fitted data for* ***1d*** *at 307 nm.*

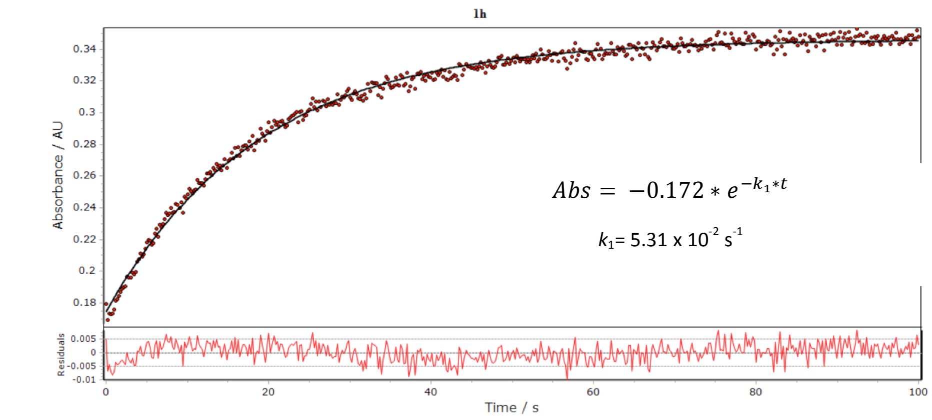
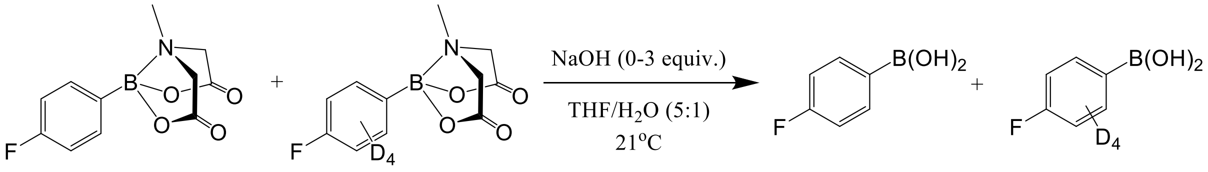


Figure 24. *Experimental and fitted data for* ***1d*** *at 262.3 nm.*

Kinetic isotope measurements



1a (5 mM) [*aryl*-$^2H_4$]-**1a** (5 mM) **2a** [*aryl*-$^2H_4$]-**2a**

General procedure

A 50.00 mL stock solution was made up with approximately **1a** (0.25 mmol), [*aryl*-$^2H_4$]-**1a** (0.25 mmol), and bis[(4-CF_3Ph)$_2$] (0.020 mmol) as internal standard in THF. Then, a 5.0 mL aliquot was transferred to a 10 mL round-bottomed flask previously charged with a magnetic stirrer. The system was put in a water bath at 21°C and stirred at 1000 rpm. A solution of NaOH (0-3 equiv., 1.0 mL) was loaded in a syringe adapted with a fine needle. The needle tip was collocated on the surface of the vortex generated due to the stirring. The aqueous hydroxide solution was added slowly with a syringe pump (0.2 mL min^{-1}). Once addition was completed, the system was put in an ice-water bath and then enough $MgSO_4$ was added to dry the solution. The solution was then filtered through a cotton wool plugged glass Pasteur pipette and received in a round-bottom flask. The solution was subsequently concentrated *in vacuo* (40°C, 150 mbar) to 0.5 mL. After transfer to an NMR tube, a capillary with DMSO-d_6 was added and the solution analysed by ^{19}F NMR.

The concentration of both products and reagents was calculated based on integrations and concentration against the internal standard. The above was repeated to obtain each data point. The isotopologue ratios were plotted against total fractional conversion, see Figure 25.

The kinetic isotope value was determined by non-linear regression minimising the square error between experimental and theoretical values. The model consisted of a standard first-order competition (k_{rel}) to correlate the change in isotopologue ratio, as a function of overall fractional conversion (0 to 1).

Entry	Reagents	KIE	Measured	Corrected
1	[^{10}B]-**1a** / [*aryl*-^{2}H$_4$,^{11}B]-**1a**	^{10}B/^{11}B	1.004	0.999
2	[1-^{13}C$_2$]-**1a** / [*aryl*-^{2}H$_4$]-**1a**	^{12}C/^{13}C	1.043	1.049
3	**1a** / [*aryl*-^{2}H$_4$,^{15}N]-**1a**	^{14}N/^{15}N	1.004	0.999
4	**1a** / [*aryl*-^{2}H$_4$]-**1a**	^{1}H/^{2}H	1.005	1.000

***Table 13**. KIE measurements in fast release conditions.*

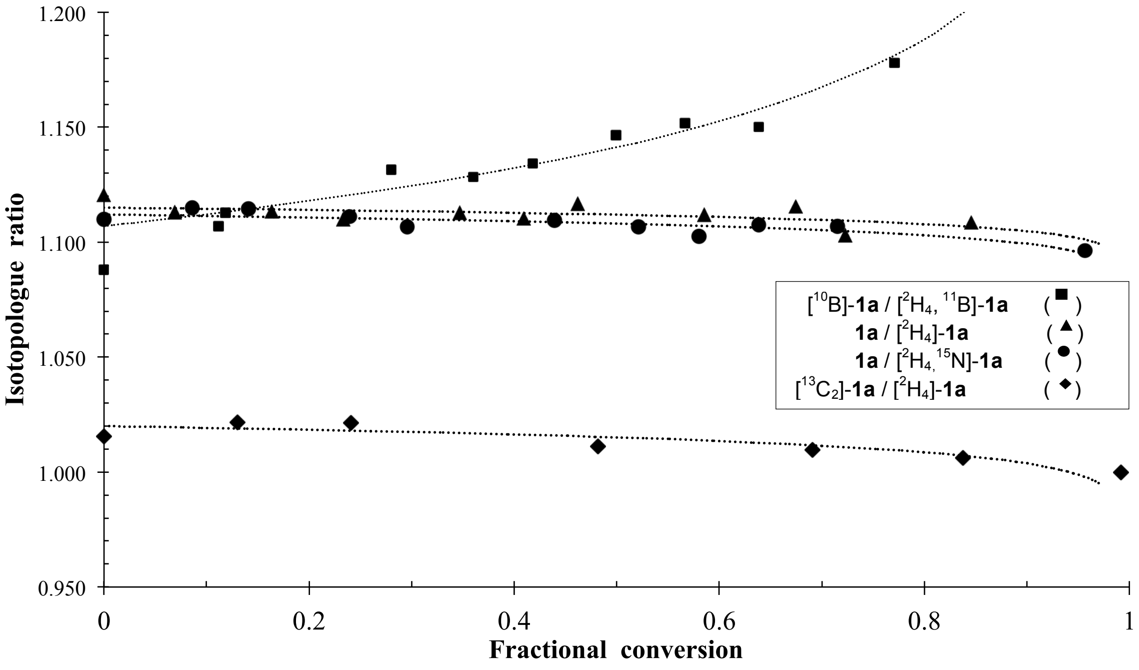


***Figure 25.** KIE determination in fast release conditions.*

VIII. Acid promoted hydrolysis

Order in acid

A 5 mL solution was prepared with **1a** (130.94 mg, 0.523 mmol), 4-trifluoromethylbromobenze (18.2 mg, 0.081 mmol) and THF. From this solution, aliquots (0.500 mL) were placed in NMR tubes. Then, an aqueous solution of HCl (0.3 – 6 M, 0.100 mL) was added to the system, the solution was vigorously shaken for 1 minute and a capillary full with DMSO-d_6 was inserted in the NMR tube.

An initial ^{19}F NMR experiment was run and subsequent experiments were recorded at different times. In all cases a pseudofirst order rate constant was calculated from the gradient at plotting plotting Ln{$[Ar_FB(MIDA)]_0/[ArB(MIDA)]$} vs time at different [HCl]. The k_{obs} values are summarized below.

Entry	[HCl]	k_{obs} / s^{-1}	R^2
1	0	1.76×10^{-5}	0.99
2	0.051	1.59×10^{-5}	0.99
3	0.102	1.73×10^{-5}	0.99
4	0.203	2.05×10^{-5}	0.99
5	0.407	3.30×10^{-5}	0.99
6	0.813	7.62×10^{-5}	0.99
7	1.017	9.38×10^{-5}	0.99

Table 14. *Pseudo-first order rate constants for hydrolysis of **1a** aryl MIDA boronates in THF/H_2O (5:1 v/v) at 21 °C in presence of HCl.*

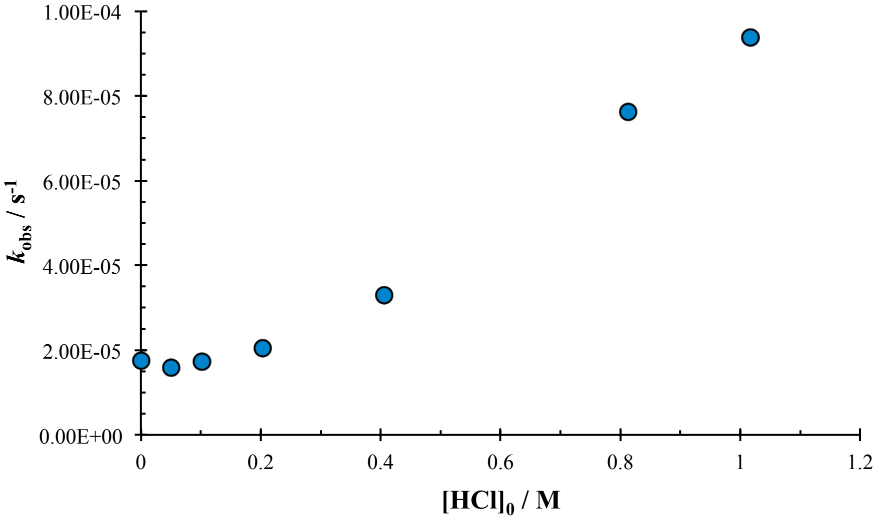
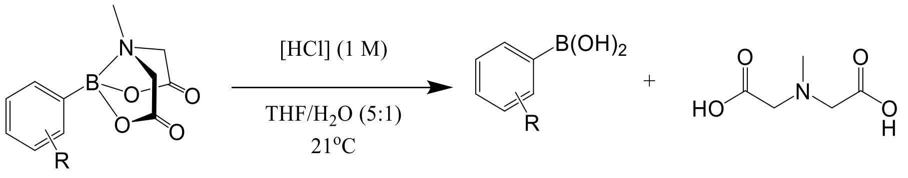


Figure 26 *Pseudo-first order rate constants for hydrolysis of **1a** aryl MIDA boronates in THF/H_2O (5:1 v/v) at 21 °C in presence of HCl.*

Hammett Plot



1(a,c-h) (0.083 M) **2(a,c-h)** **3**

The aryl MIDA boronate (0.05 mmol) was placed in a J-Young valve NMR tube with THF (0.5 mL). The sample was vigorously shaken and then an aqueous HCl solution (0.1 mL, 6 M) added and the tube shaken again for 30 seconds. A capillary with DMSO-d$_6$ was inserted in the tube and the hydrolysis reaction was followed by ^{11}B NMR. Experiments were recorded every hour up to 98 % of conversion for each substrate. Since the system was homogeneous, ^{11}B was used calculate the conversions. Pseudo-first order rate constants (k_{obs}) were calculated at plotting ln{[Ar$_F$B(MIDA)]$_0$/[Ar$_F$B(MIDA)]} vs time. The k_{obs} values are presented in Table 15. Due to the background reaction (H$_2$O promoted hydrolysis) a correction was applied (data Table 8) to obtain the rates of the acid promoted hydrolysis.

Substrate	**R-**	**$\sigma_{\mathrm{Hammett}}$**	**$k_0 + k_H$[HCl] /s^{-1}**	**k_0 / s^{-1}**	**k_H[HCl] / s^{-1}**	**log ($k_H$rel)**
1c	4-CH$_3$O-	-0.27	8.46 x10^{-5}	6.6 x10^{-6}	7.8 x10^{-5}	-0.016
1d	4-CH$_3$-	-0.14	1.17 x10^{-4}	1.2 x10^{-5}	1.1 x10^{-4}	0.12
1e	H-	0	9.63 x10^{-5}	1.5 x10^{-5}	8.1 x10^{-5}	0
1a	4-F-	0.15	1.18 x10^{-4}	1.8 x10^{-5}	1.0 x10^{-4}	0.10
1f	4-CF$_3$-	0.53	1.52 x10^{-4}	4.2 x10^{-5}	1.1 x10^{-4}	0.13
1g	3-NO$_2$-	0.71	1.39 x10^{-4}	4.7 x10^{-5}	9.2 x10^{-5}	0.05
1h	3-(CF$_3$)$_2$-	0.92	1.52 x10^{-4}	7.4 x10^{-5}	7.8 x10^{-5}	-0.02

Table 15 *Rate constants for aryl MIDA boronate hydrolysis in 6M HCl, THF/H$_2$O at 21^{o}C.*

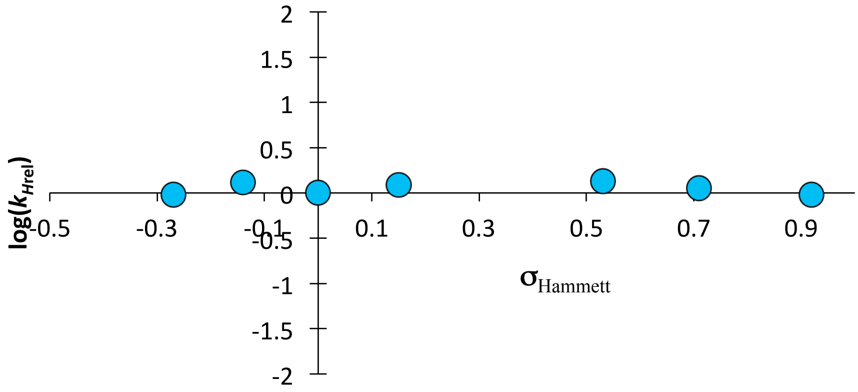


***Figure** 27.Hammet plot: acid hydrolysis (1 M HCl in THF/H$_2$O (5:1 v/v) at 21 ^{o}C)*

Kinetic isotope measurements

A 25 mL solution was made up with 4-CF_3PhBr (41.47 mg, 0.184 mmol) in degassed THF. Then a sample (0.50 mL) of the solvent solution was transferred to J-Young valve NMR tube containing a mixture of the isotopologues (approximately 0.024 mmol of each isotopologue). The sample was vigorously shaken and a capillary with DMSO-d_6 was placed in the tube before running the initial ^{19}F NMR experiment. An aqueous solution of HCl (0.10 mL, 6 M) was added to the solution in the NMR tube and shaken again for 30 seconds. The sample was inserted in the spectrometer at 21 °C and ^{19}F NMR spectra recorded every 15 minutes for 12 h. Spectra were processed, phased and baseline corrected. Integrations of the starting materials and products were compared against the internal to calculate isotopologue ratio and fractional conversion. Experimental KIEs were corrected for approximately 19 % contribution from H_2O promoted hydrolysis.

Entry	Reagents	KIE	Measured	Corrected
1	[^{10}B]-**1a** / [*aryl*-$^{2}H_4$,^{11}B]-**1a**	^{10}B/^{11}B	1.008	0.999
2	[1-$^{13}C_2$]-**1a** / [*aryl*-$^{2}H_4$]-**1a**	^{12}C/^{13}C	1.036	1.041
3	**1a** / [*aryl*-$^{2}H_4$,^{15}N]-**1a**	^{14}N/^{15}N	1.004	0.998
4	**1a** / [*aryl*-$^{2}H_4$]-**1a**	^{1}H/^{2}H	1.001	0.997

Table 16 KIE data for hydrolysis in HCl (1M); corrected for H_2O promoted hydrolysis.

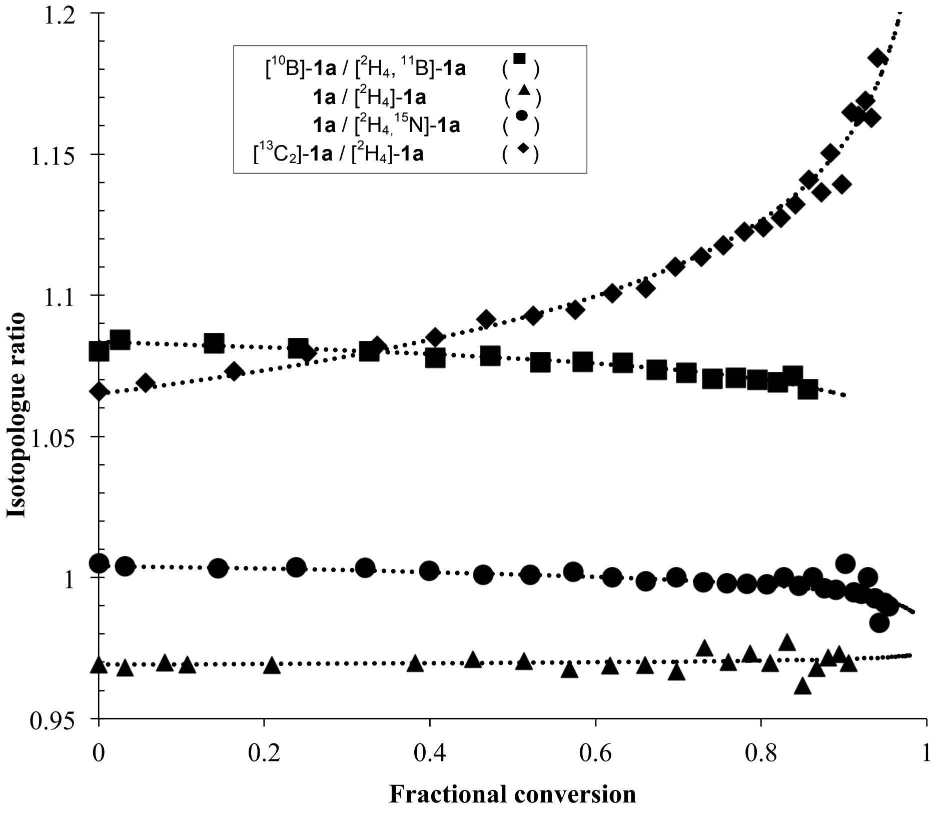
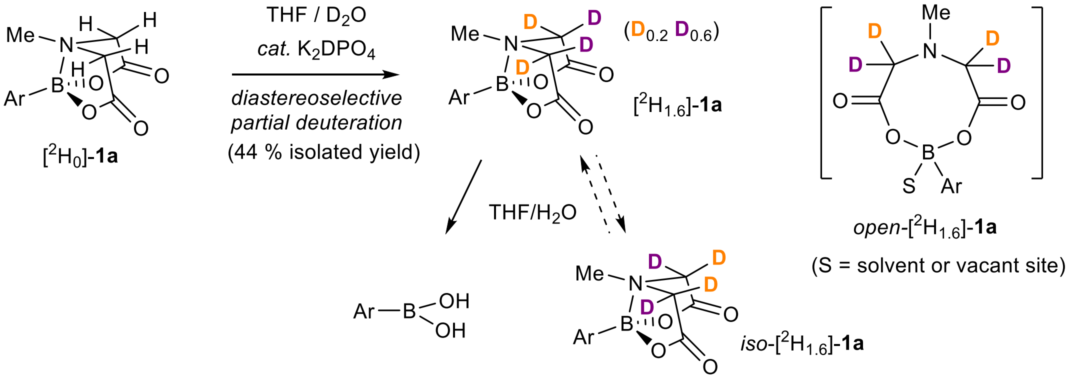


Figure 28 - Isotopologue ratio versus conversion for acidic hydrolysis (pH = 0).

IX. Tests for "open-1a"



Equilibrium vs hydrolysis

A 1 mL solvent stock solution was prepared with (4-$CF_3PH)_2$ (0.60 mg, 0.002 mmol), D_2O (10.98 mg, 0.549 mmol) and THF-d_8. Then [*methylene*-$^2H_{1.6}$]-**1a** (0.043 mmol) was placed in a J-Young valve NMR tube with the solvent solution (0.5 mL). The hydrolysis reaction was followed by ^1H NMR over a week, the sample being kept at 21° C. The spectra were analysed: the integration of the internal standard and the aromatic protons were used to monitor the hydrolysis reaction while the signal of the methylene protons was compared against the signal of the aromatic protons to calculate the equilibration with the diastereomer. A second experiment was run with (4-$CF_3Ph)_2$ (0.52 mg, 0.002 mmol), D_2O (184.43 mg, 9.22 mmol) and THF-d_8 to make up 1 mL stock solution. A similar analysis compares hydrolysis vs equilibration. The result are summarised below.

Conditions	***% of equilibration***	***% of hydrolysis***
0.55 M D_2O in THF	Less than 1%	52 %
9.22 D_2O in THF	Less than 1.5 %	77 %

Table 17. Comparison of hydrolysis and equilibrium of [$^2H_{1.6}$]-**1a** at room temperature.

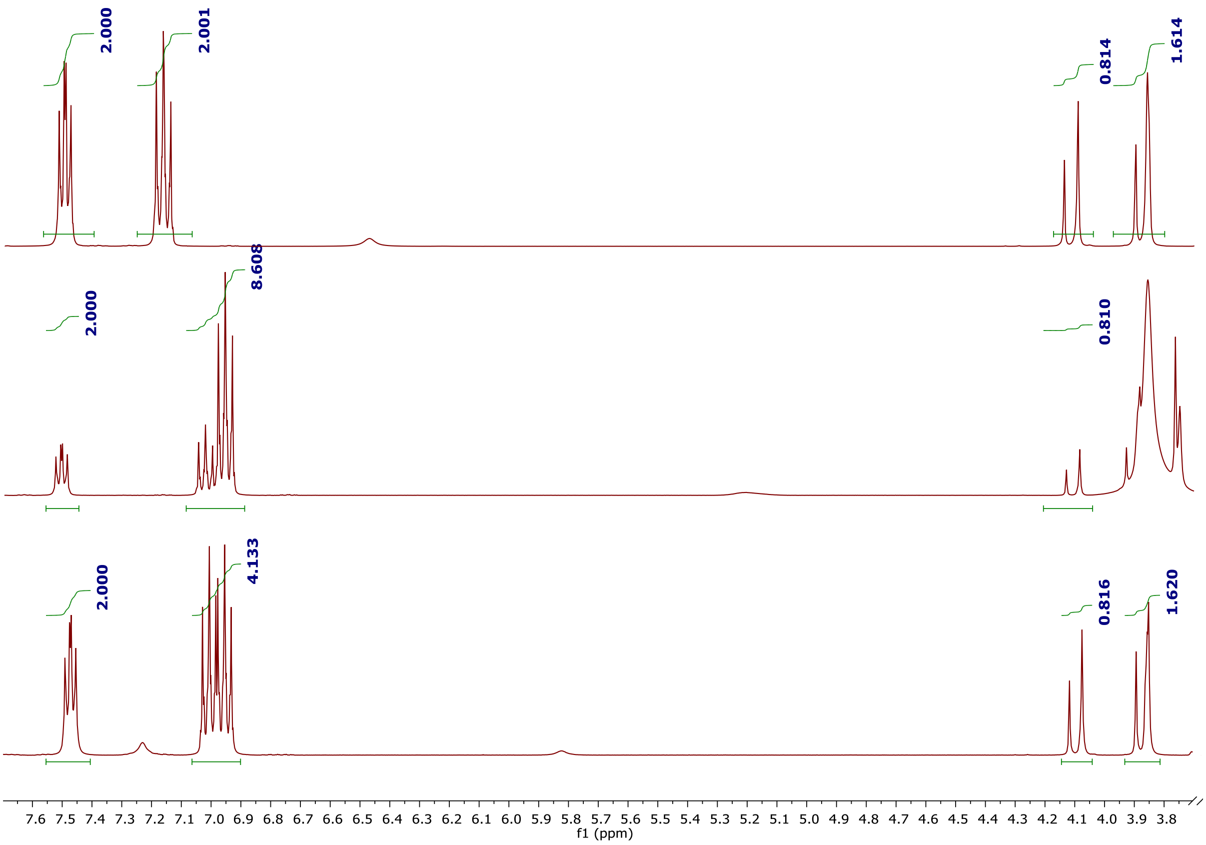
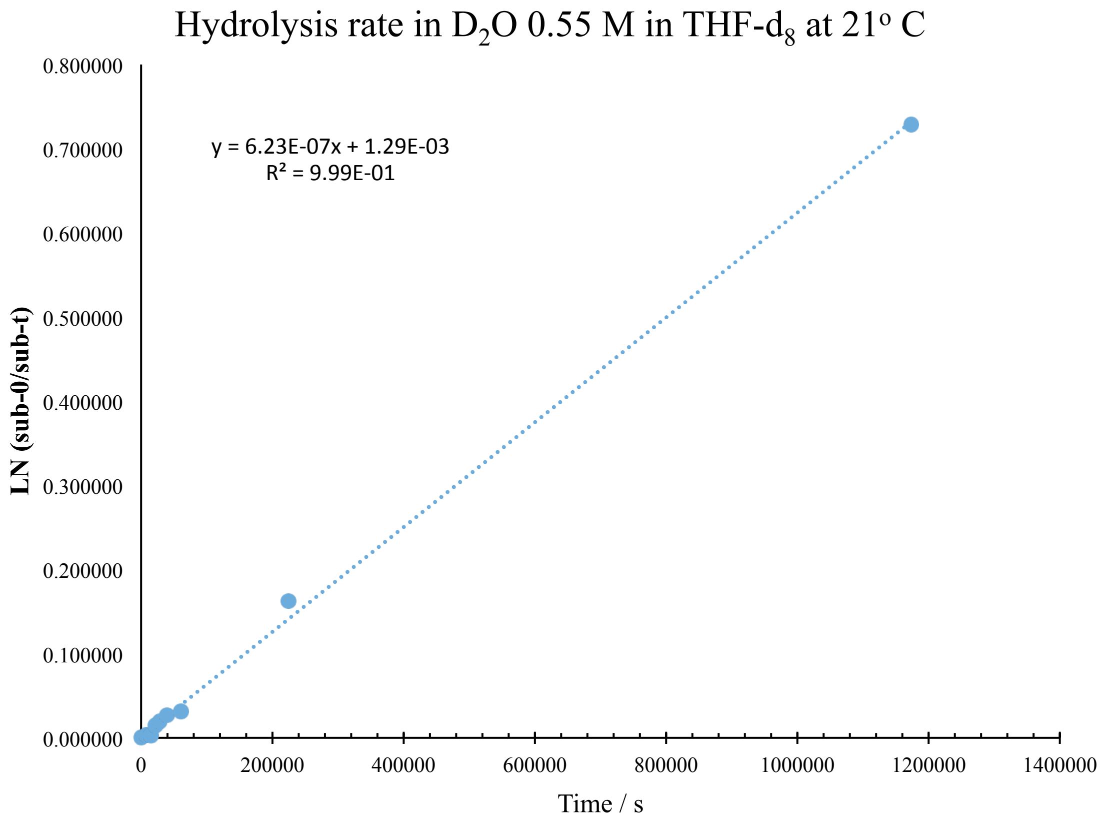


Fig 29. ^{1}H NMR spectra of the equilibration of [*methylene*-$^2H_{1.6}$]-**1a**, (aromatic protons were used as an internal standard) **a)** initial spectra in DMSO-d_6 **b**) Reaction in THF(d_8)/D_2O (9.2 M) after 77 % of hydrolysis. **c**) Reaction in THF(d_8)/D_2O (0.55 M) after 52 % hydrolysis.



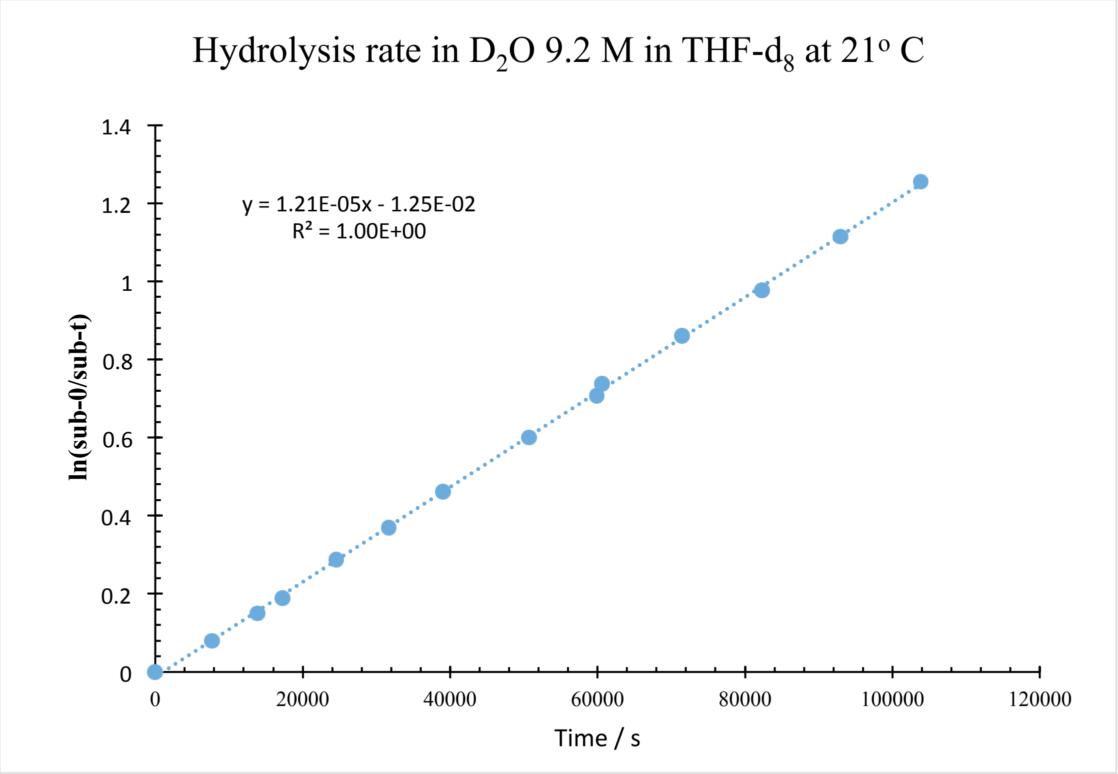
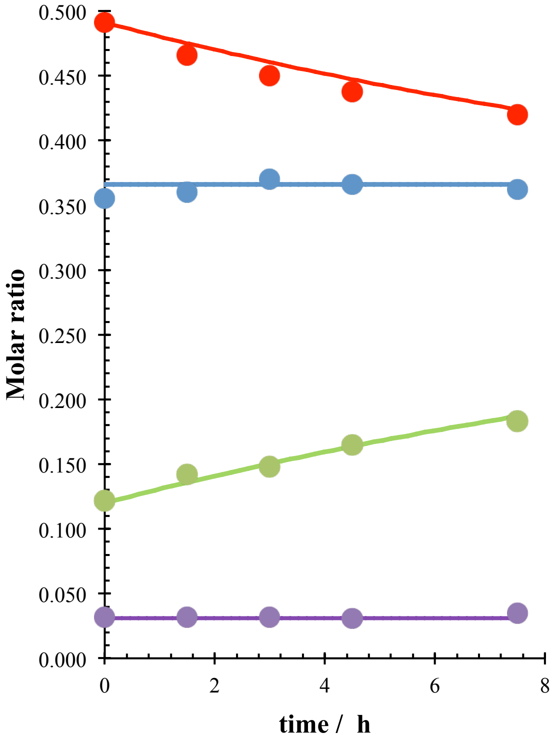


Figure 30 - Hydrolyses in D_2O/d8-THF; rates are affected by solvent kinetic isotope effects.

Thermal equilibration

In a J-Young valve NMR tube, [*methylene*-$^2H_{3.4}$]-**1a** (10.3 mg, 0.041 mmol) was dissolved in THF-d_8. A ^1H NMR experiment was run for this sample at room temperature. Then, the NMR tube was put in an oil bath (100° C), the sample was removed from the oil bath at specific times, cooled to room temperature and analysed approximately every 90 minutes by ^1H NMR. The spectra were processed, and the integration of the peaks was used to calculate the molar ratio of all species. Aromatic protons were used as an internal standard to quantify the change in integrations. The amount of hydrolysis was calculated based on the signals in the aromatic region in the ^1H NMR spectra. Data were fitted to calculate the rate constant of the thermal equilibration, the graph is shown in Fig 31.



S

Fig 31. Thermal equilibration of [*methylene*-$^2H_{3.4}$]-**1a** in THF-d_8 at 100° C. Hydrolysis was not detected. Blue and Purple data points are CH2 and CD2 signals and are constant, showing there to be no CH/D exchange. Red and green datapoints are CHD and CDH signals.

X. *T_1 Measurements and Quantitation*

A solution of **1a** (12.25 mg, 0.049 mmol) and [*aryl*-$^2H_4$]-**1a** (12.27 mg, 0.048 mmol) in THF (0.5 mL) was prepared in a NMR tube. Then a capillary with DMSO-d_6 was placed in the tube. The T_1 relaxation time was measured using an inversion recovery experiment. The experiment consists of the relaxation delay, an 180° inversion pulse, delay period τ, a 90° pulse and an acquisition time where the data is collected. The logarithmic decay of *z*-magnetisation against time is plotted in Figure 32. Once the experiment was finished, water was added to the sample (0.1 mL) and then a second inversion recovery experiment was conducted to measure T_1 under these conditions (THF/H2O 5:1 v/v) at 21 °C.

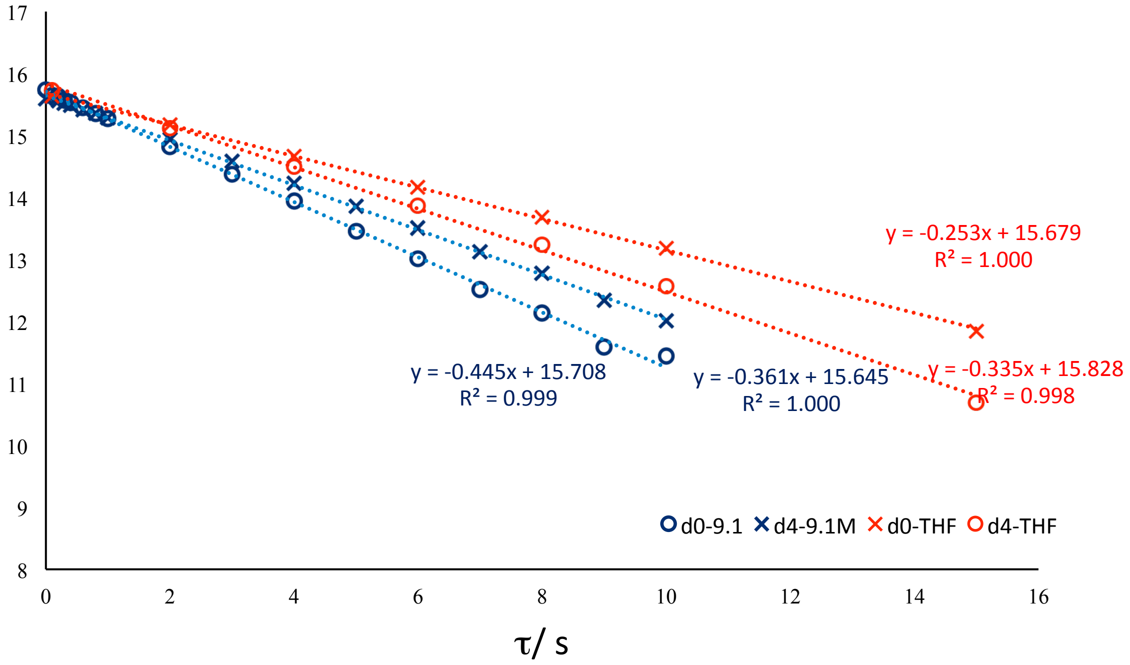


Fig 32 Inversion recovery experiments on 1a.

Calculations of T_1 and quantitation in NMR measurements of the species of interest are given below.

	T_1 in THF	T_1 in THF/H_2O
1a	3.00 s	2.18 s
[*aryl*-$^2H_4$]-**1a**	3.95 s	2.99 s

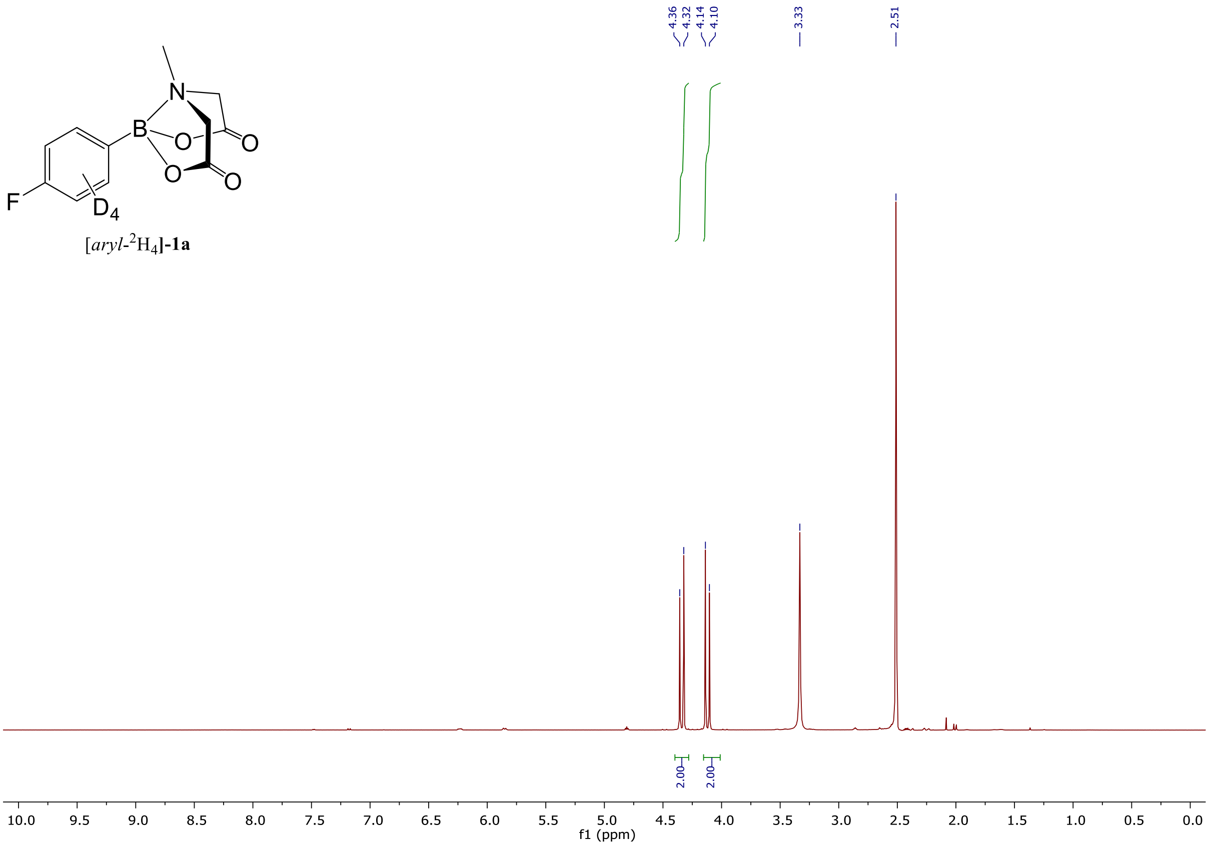
Table 18. T1 values calculated for **1a** and [*aryl*-$^2H_4$]-**1a**.

The standard ^{19}F NMR experiment employed for kinetics and KIEs etc. presented herein, consists of a 30° pulse (Ø) and a delay of 7.5 s (T_r), with these parameters and the T_1 measurements, the fraction of the population that is quantified (*f*) can be calculated with the following equation:

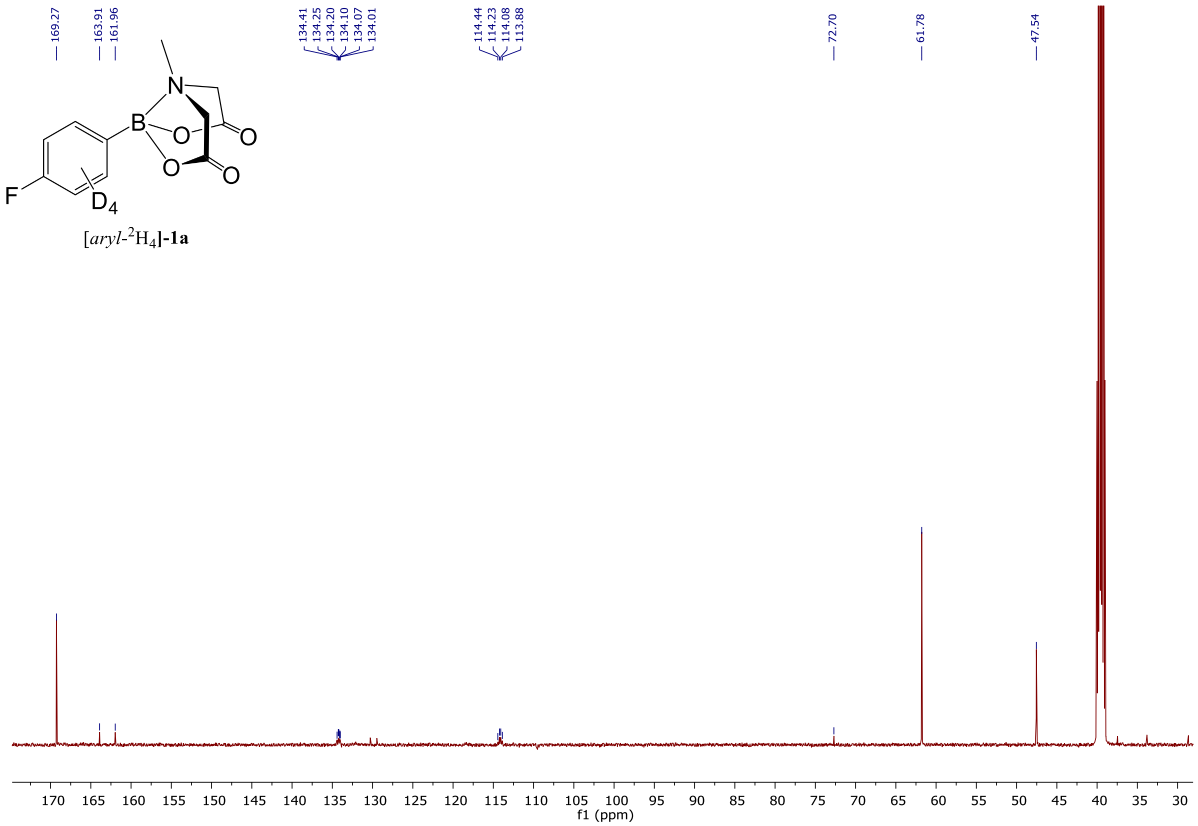
$$Ln\,\frac{(f-1)}{(\cos\emptyset-1)}=-\frac{T_r}{T_1}$$

	f in THF	*f* in THF/H_2O
1a	0.99	0.99
[*aryl*-$^2H_4$]-**1a**	0.98	0.99

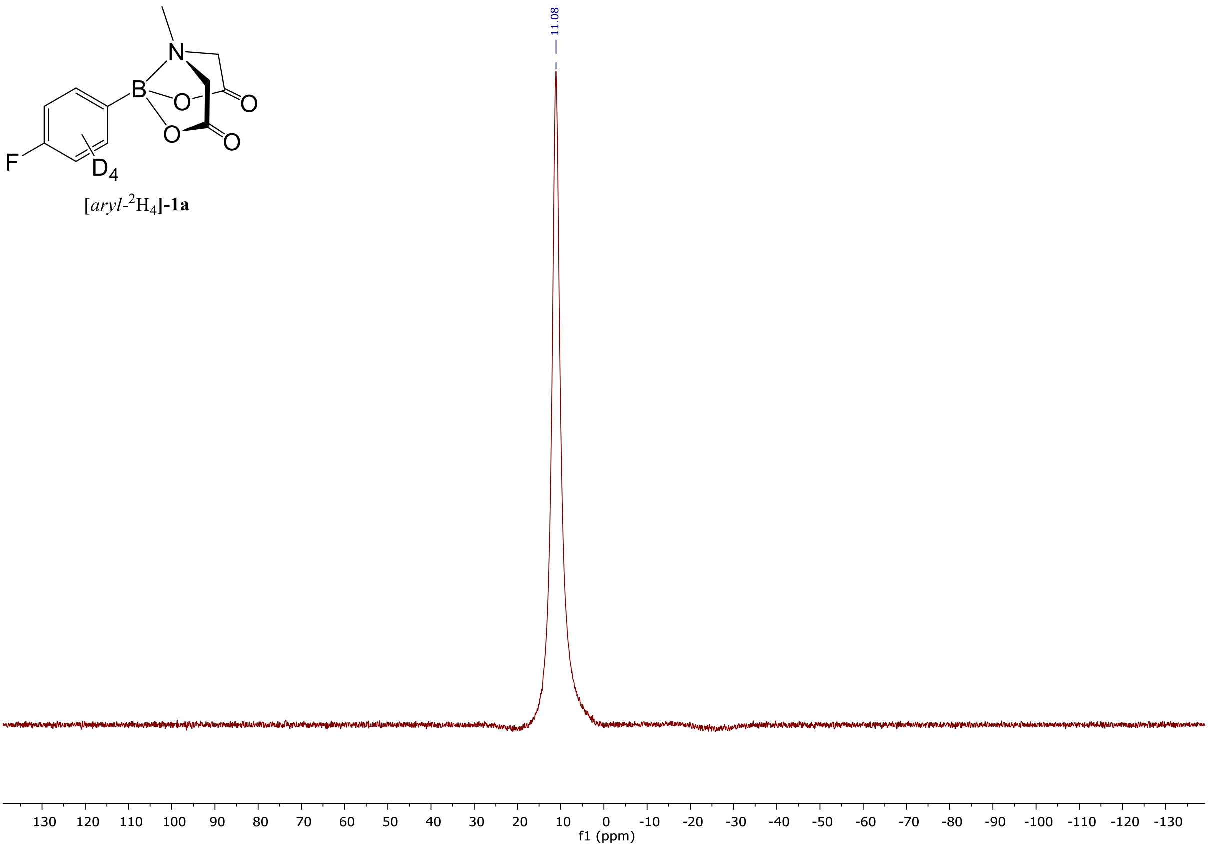
Table 19. Estimation of fractional quantitation of **1a** and [*aryl*-$^2H_4$]-**1a** by ^{19}F NMR.



^{1}H NMR (500 MHz, DMSO-d$_6$)

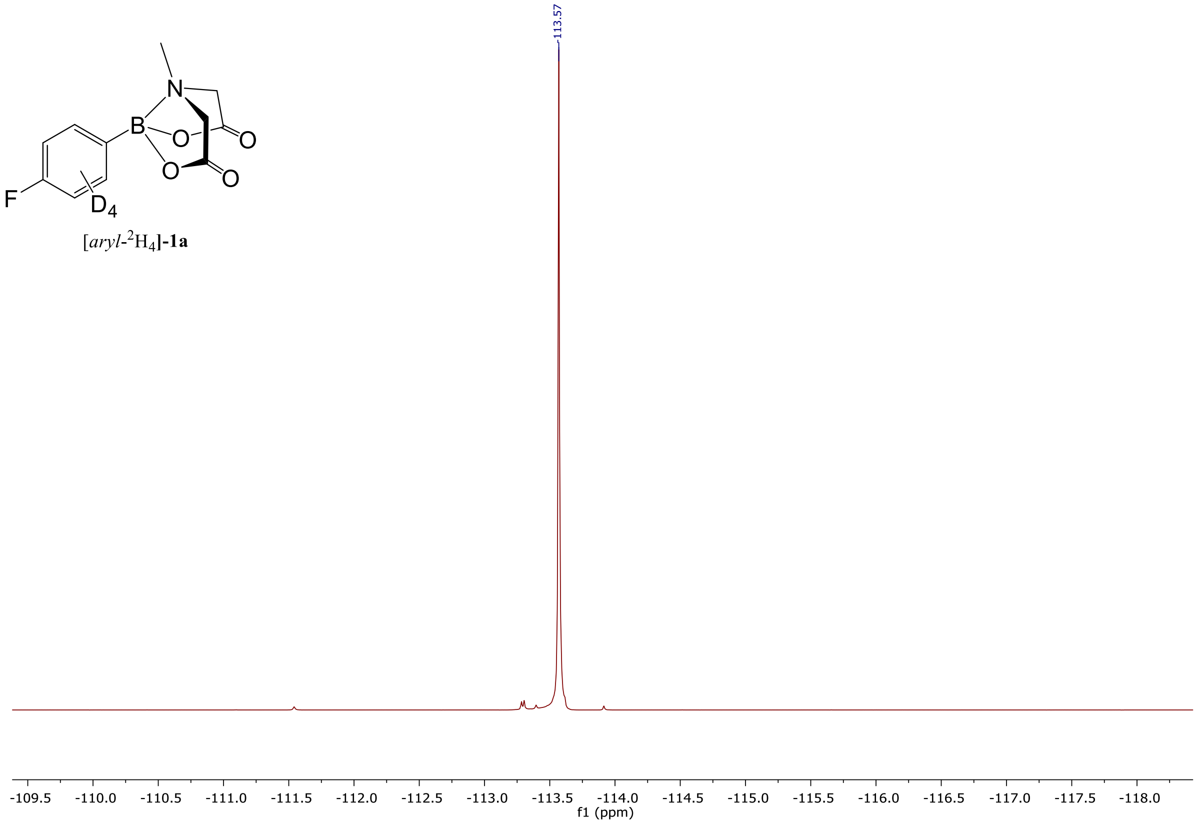


^{13}C{^{1}H} NMR (500 MHz, DMSO-d$_6$)



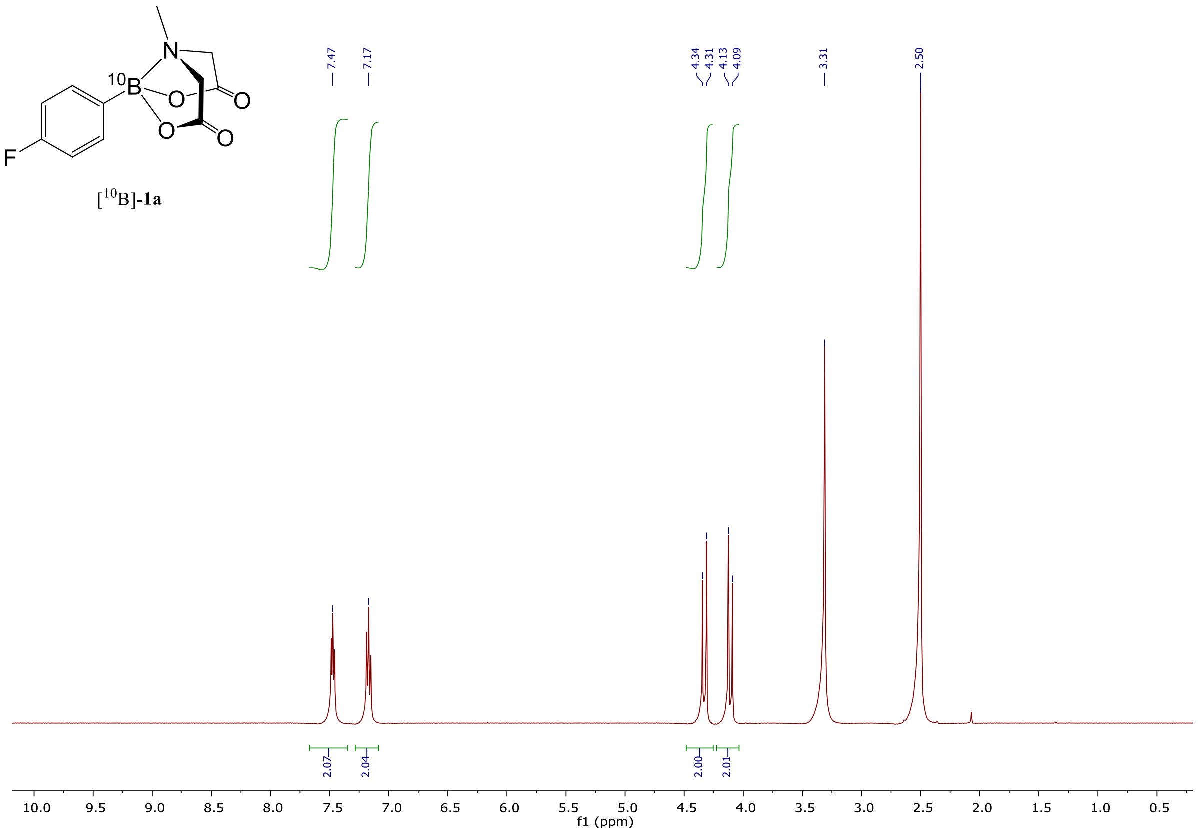
[*aryl*-^{2}H$_4$]-**1a**

^{11}B NMR (160 MHz, DMSO-d$_6$)



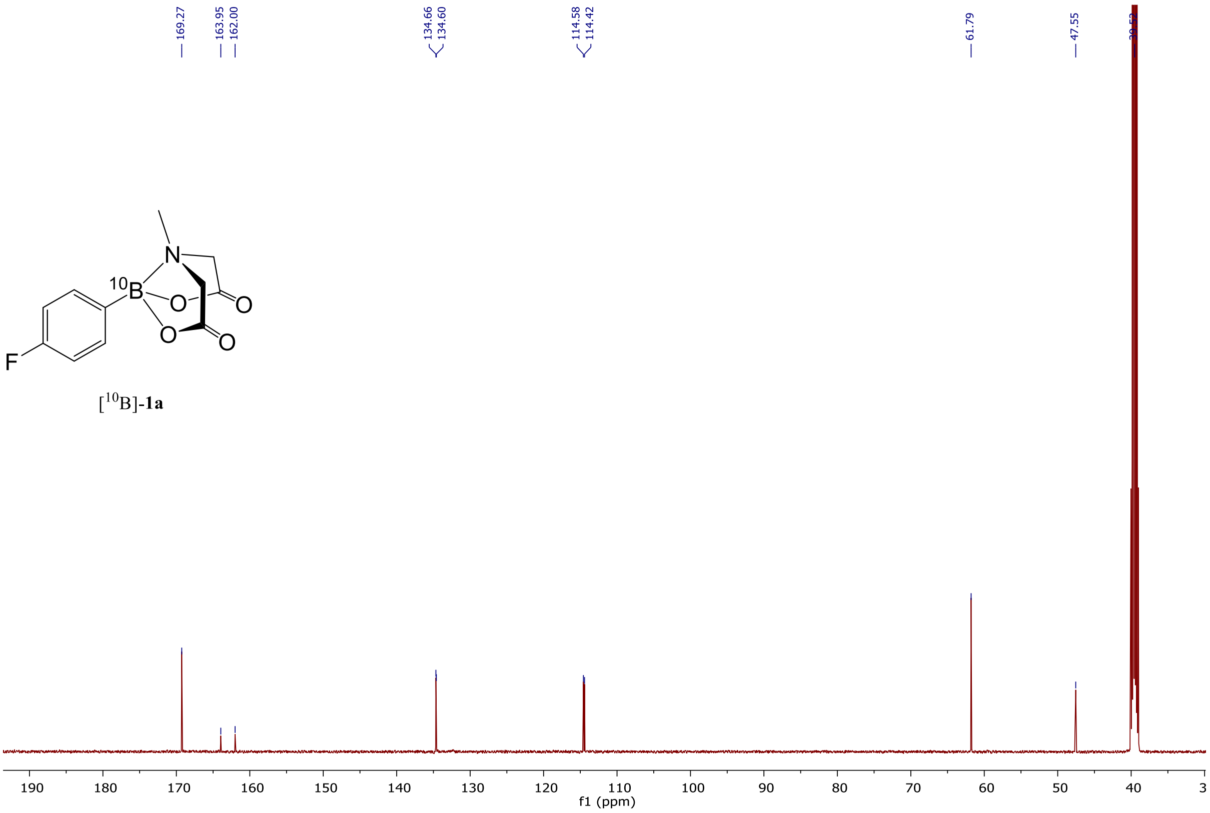
[*aryl*-^{2}H$_4$]-**1a**

^{19}F NMR (471 MHz, DMSO-d$_6$)



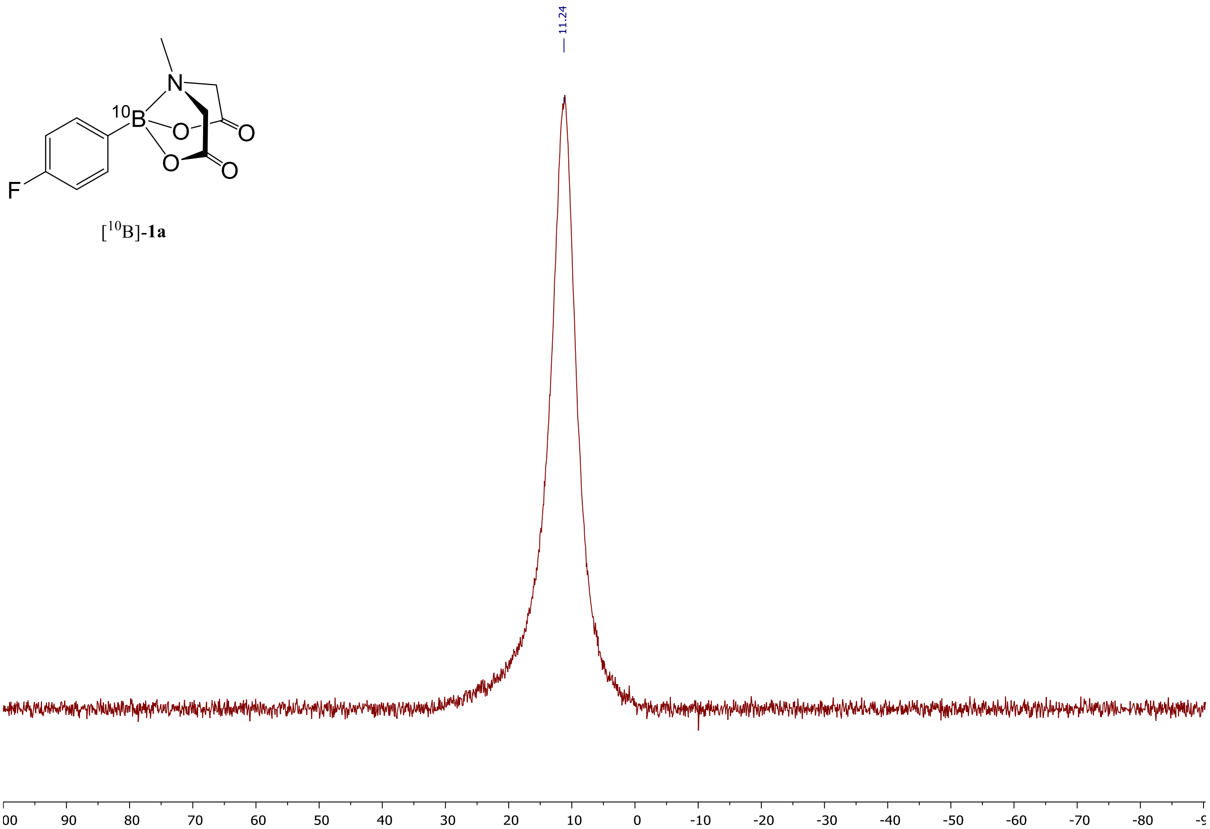
[^{10}B]-**1a**

^{1}H NMR (500 MHz, DMSO-d$_6$)



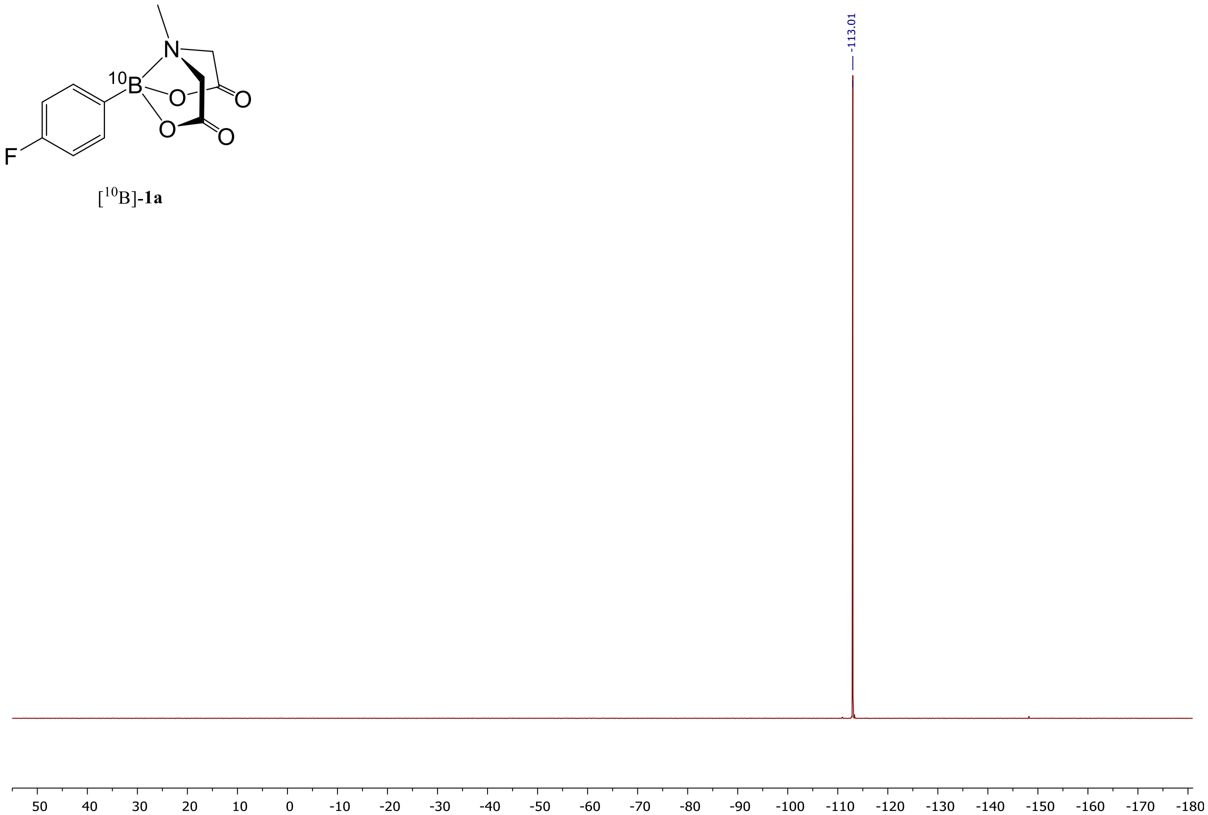
[^{10}B]-**1a**

^{13}C{^{1}H} NMR (126 MHz, DMSO-d$_6$)



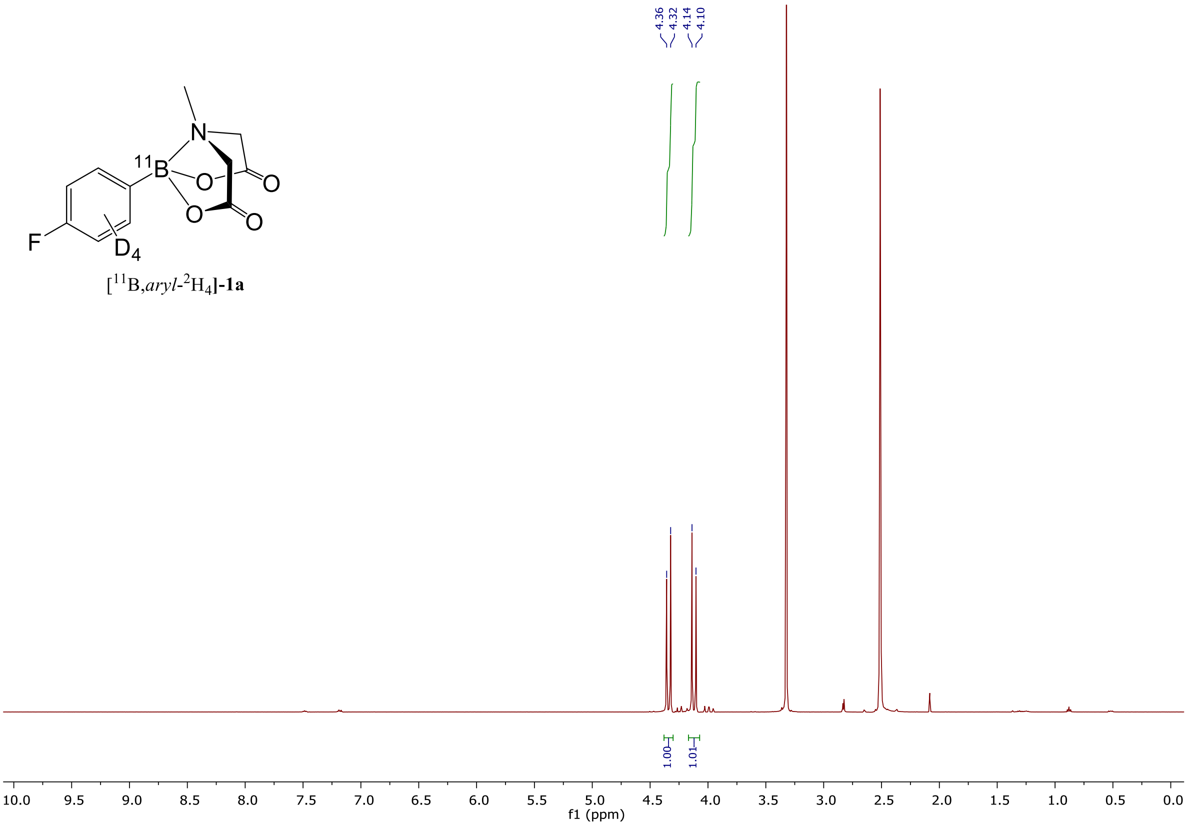
[^{10}B]-**1a**

^{10}B NMR (54 MHz, DMSO-d$_6$)



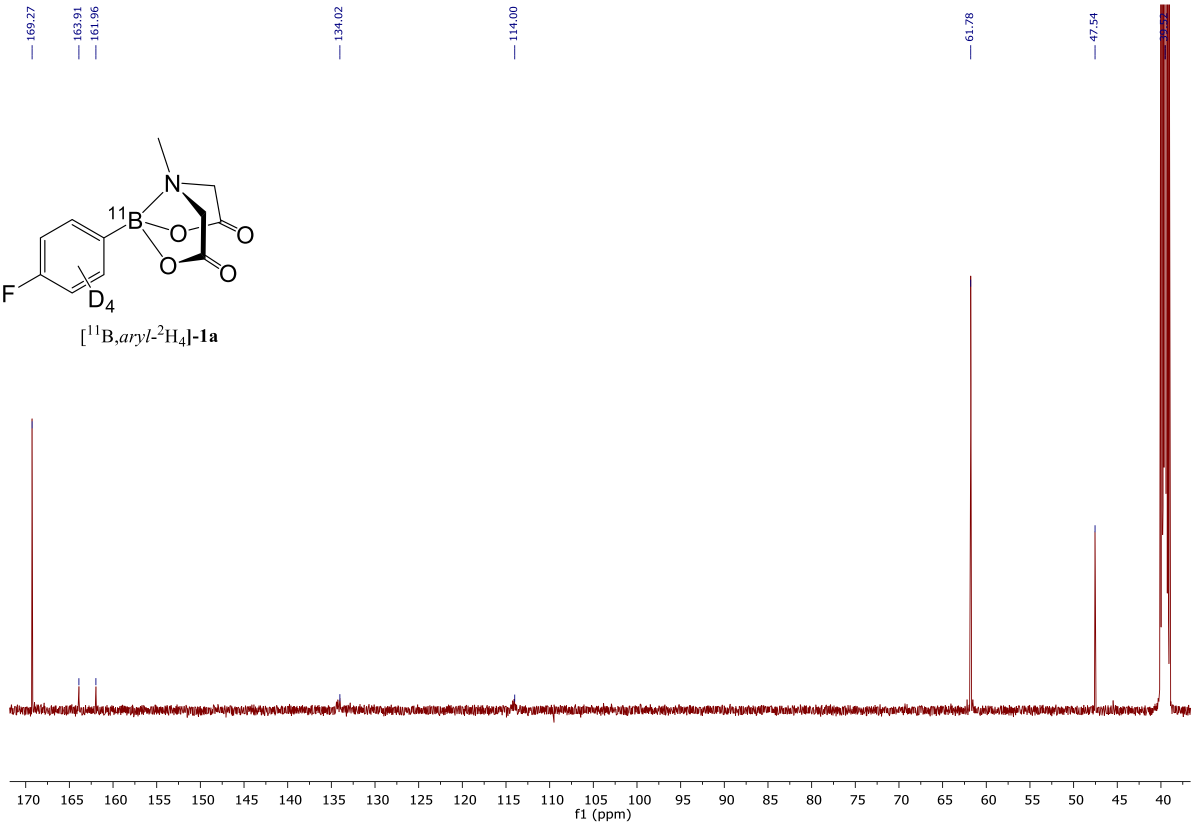
[^{10}B]-**1a**

^{19}F NMR (471 MHz, DMSO-d$_6$)



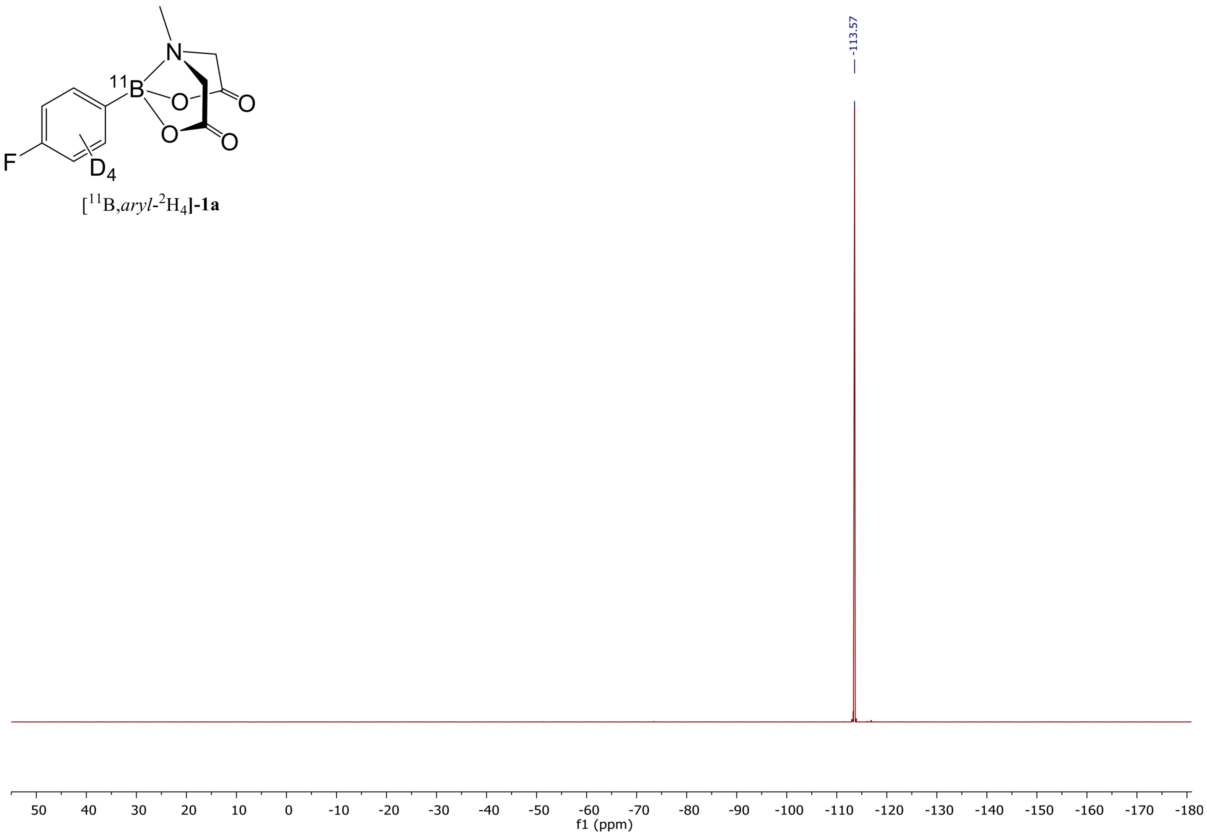
[^{11}B,*aryl*-^{2}H$_4$]-**1a**

^{1}H NMR (500 MHz, DMSO-d$_6$)

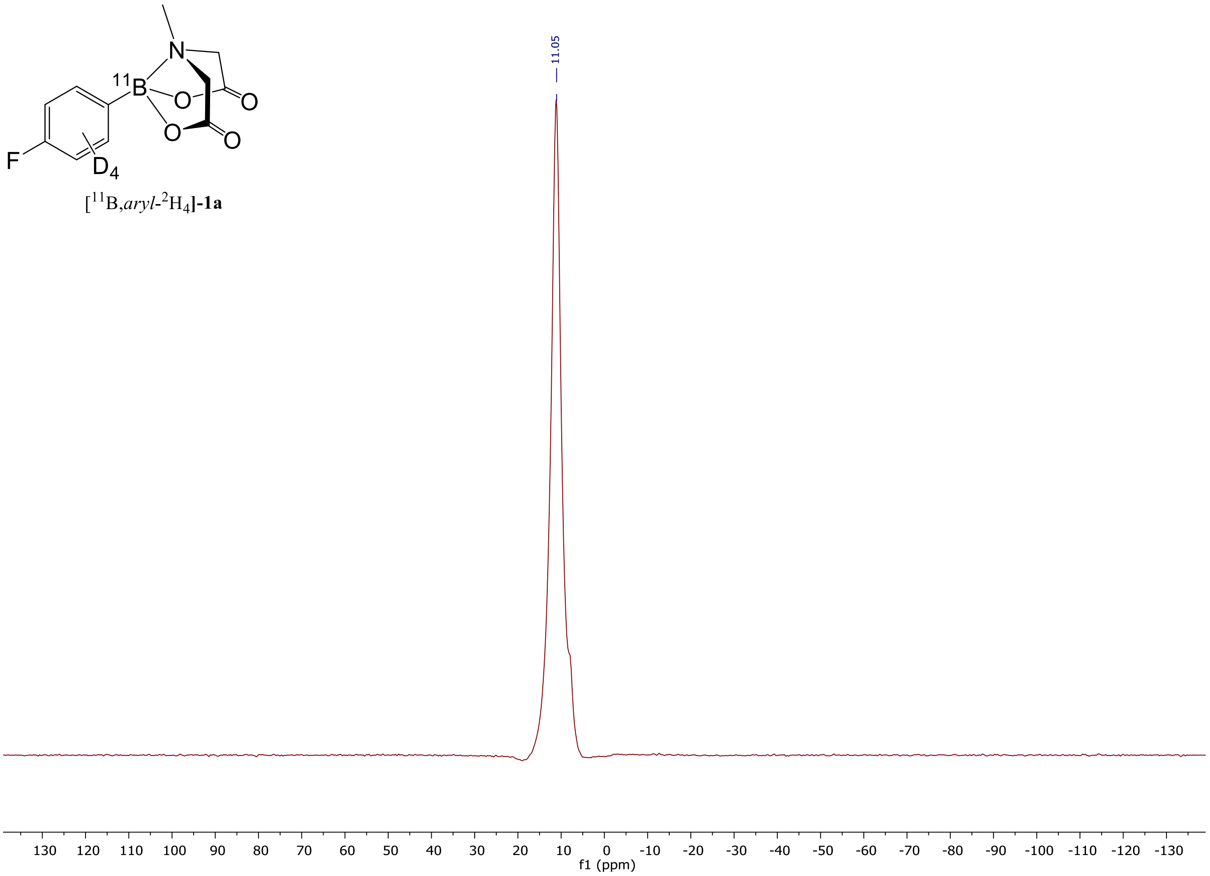


[^{11}B,*aryl*-^{2}H$_4$]-**1a**

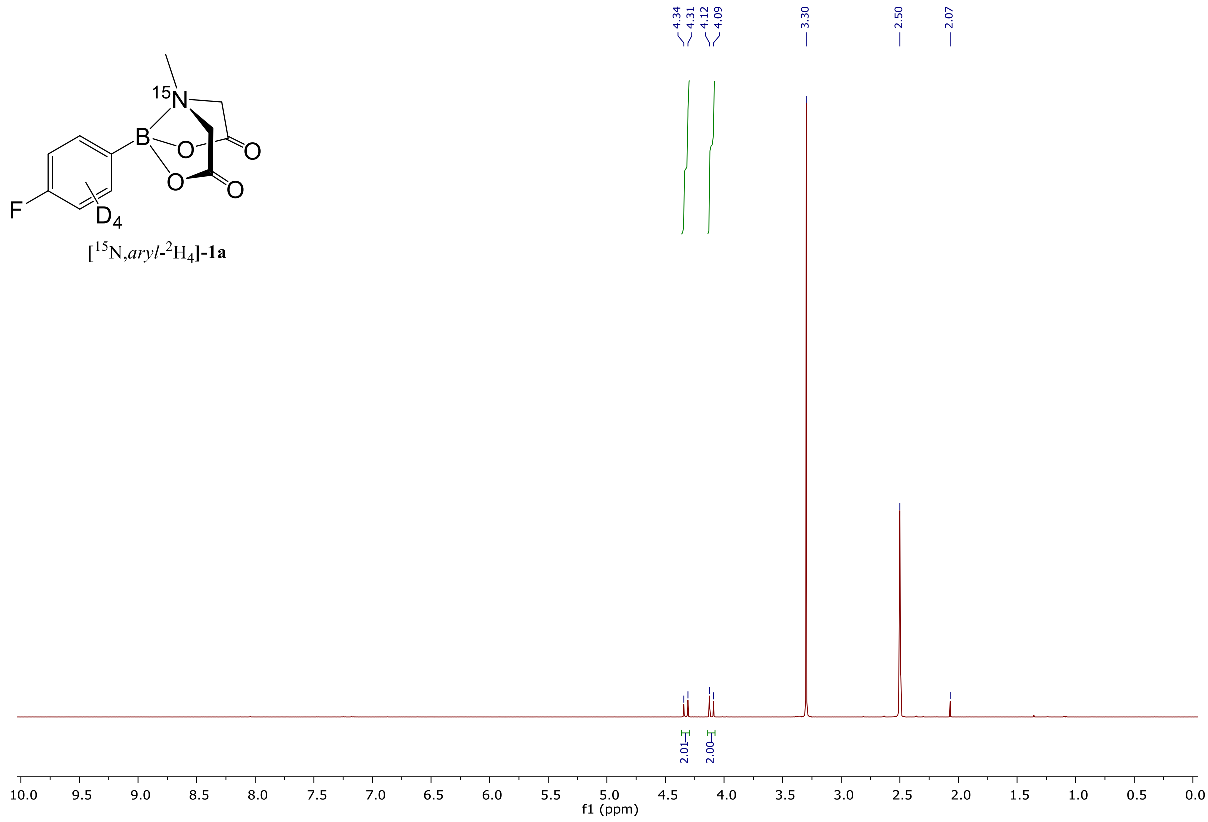
^{13}C{H} NMR (126 MHz, DMSO-d$_6$)



^{19}F NMR (471 MHz, DMSO-d$_6$)

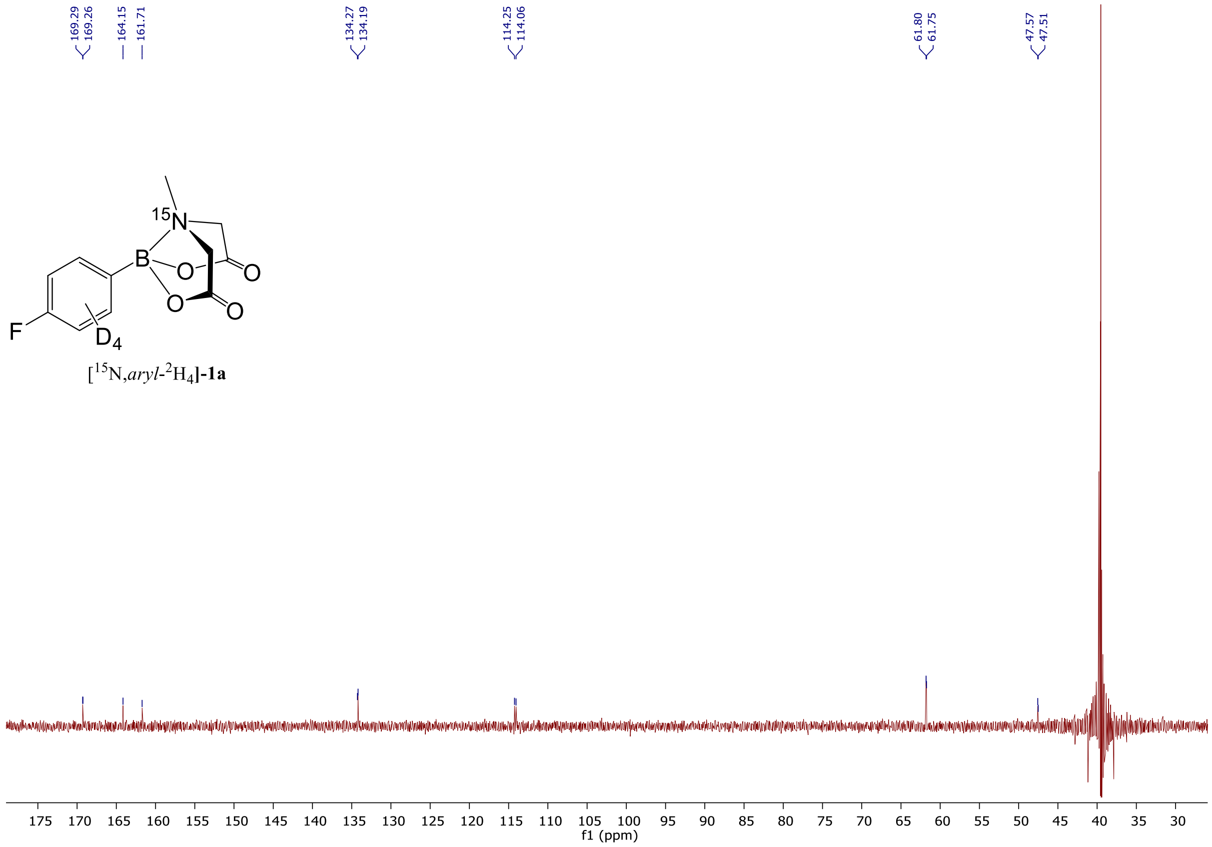


^{11}B NMR (160 MHz, DMSO-d$_6$)



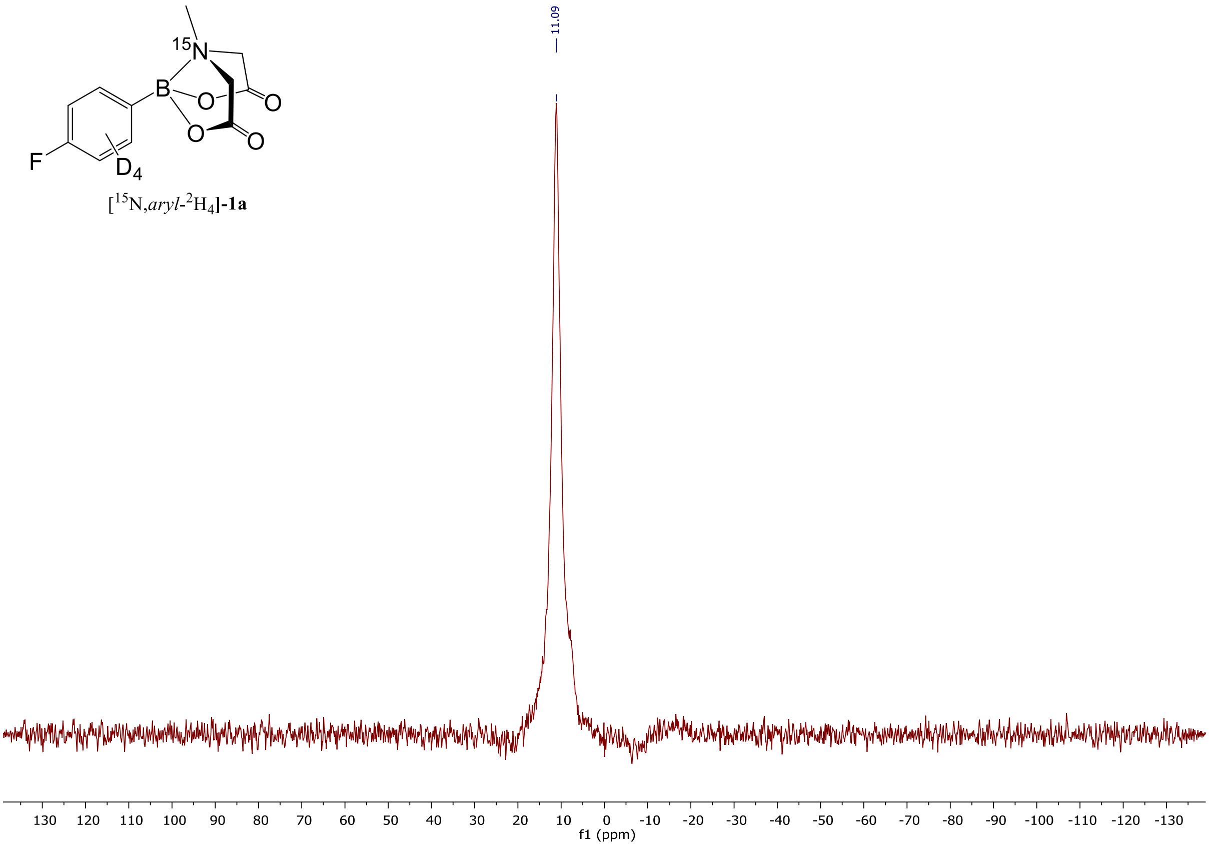
[^{15}N,*aryl*-^{2}H$_4$]**-1a**

^{1}H NMR (500 MHz, DMSO-d$_6$)



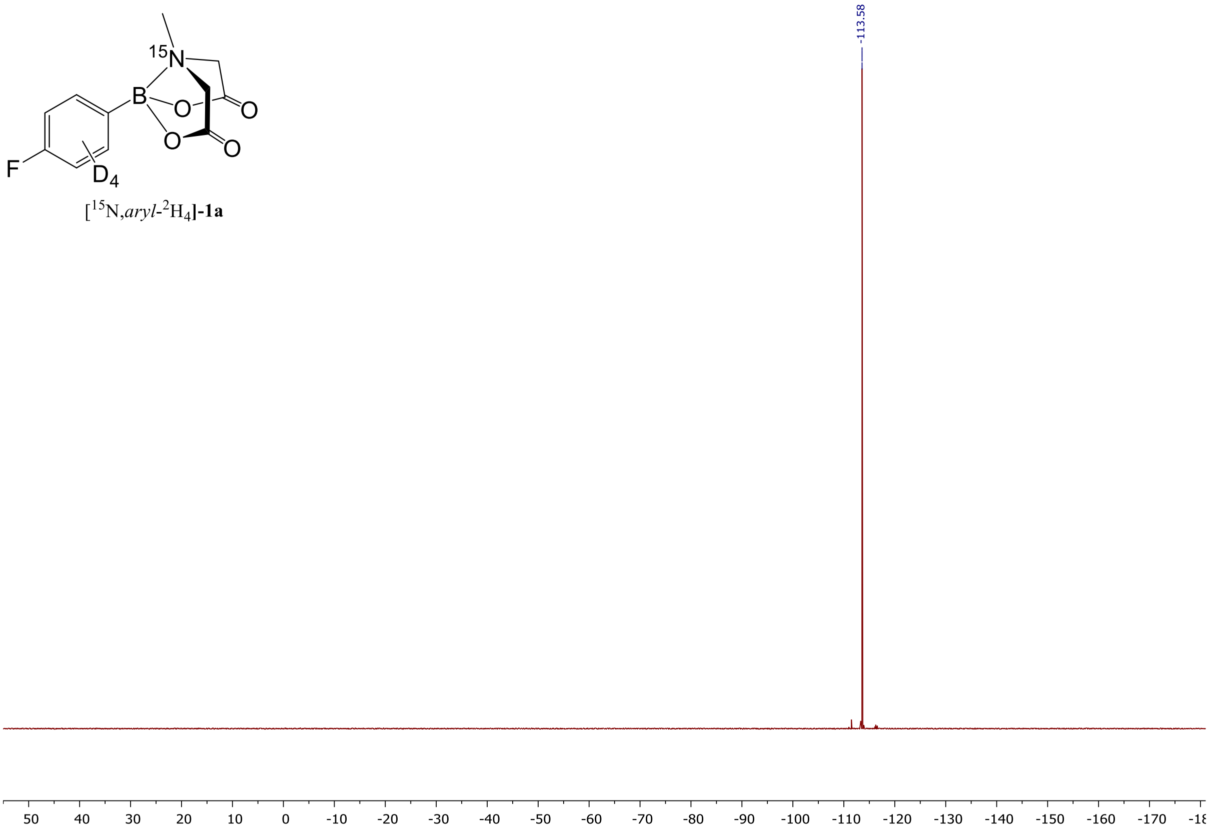
[^{15}N,*aryl*-^{2}H$_4$]**-1a**

^{13}C{^{1}H, ^{2}H} NMR (101 MHz, DMSO-d$_6$)



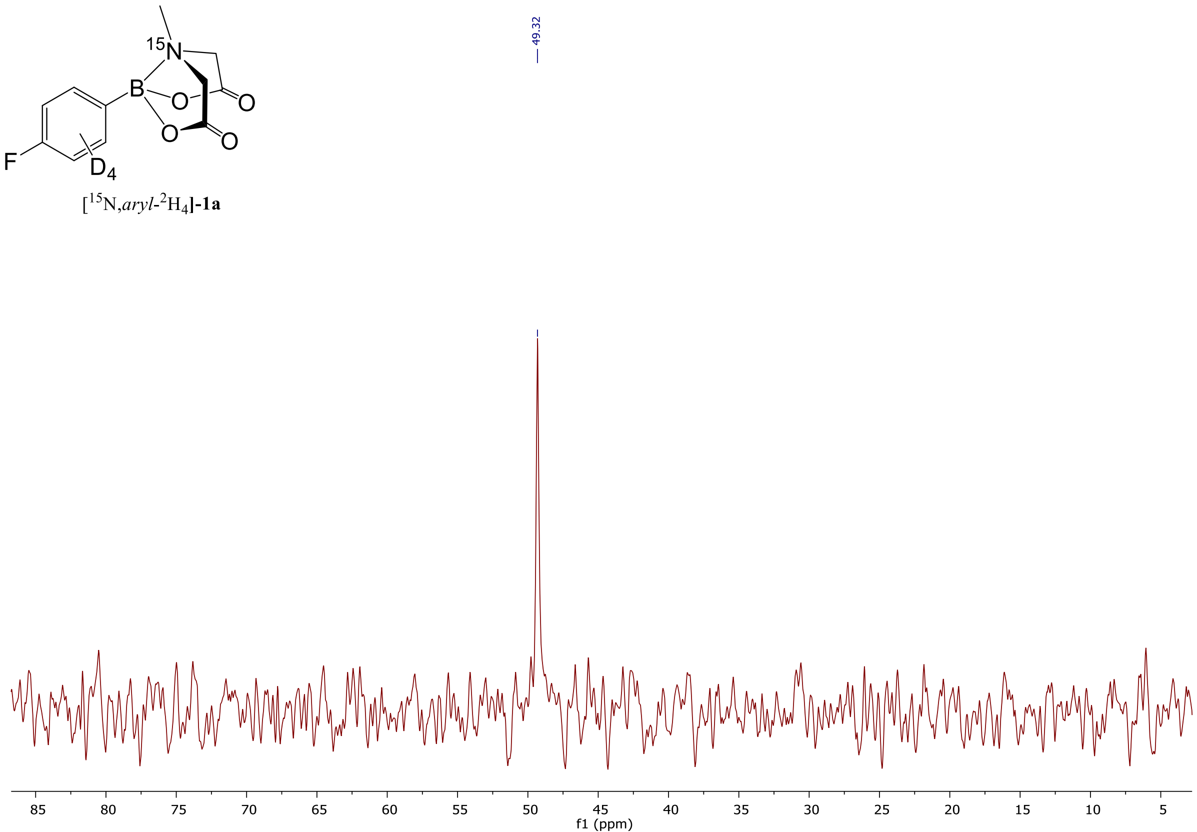
[^{15}N,*aryl*-^{2}H$_4$]-**1a**

^{11}B NMR (160 MHz, DMSO-d$_6$)



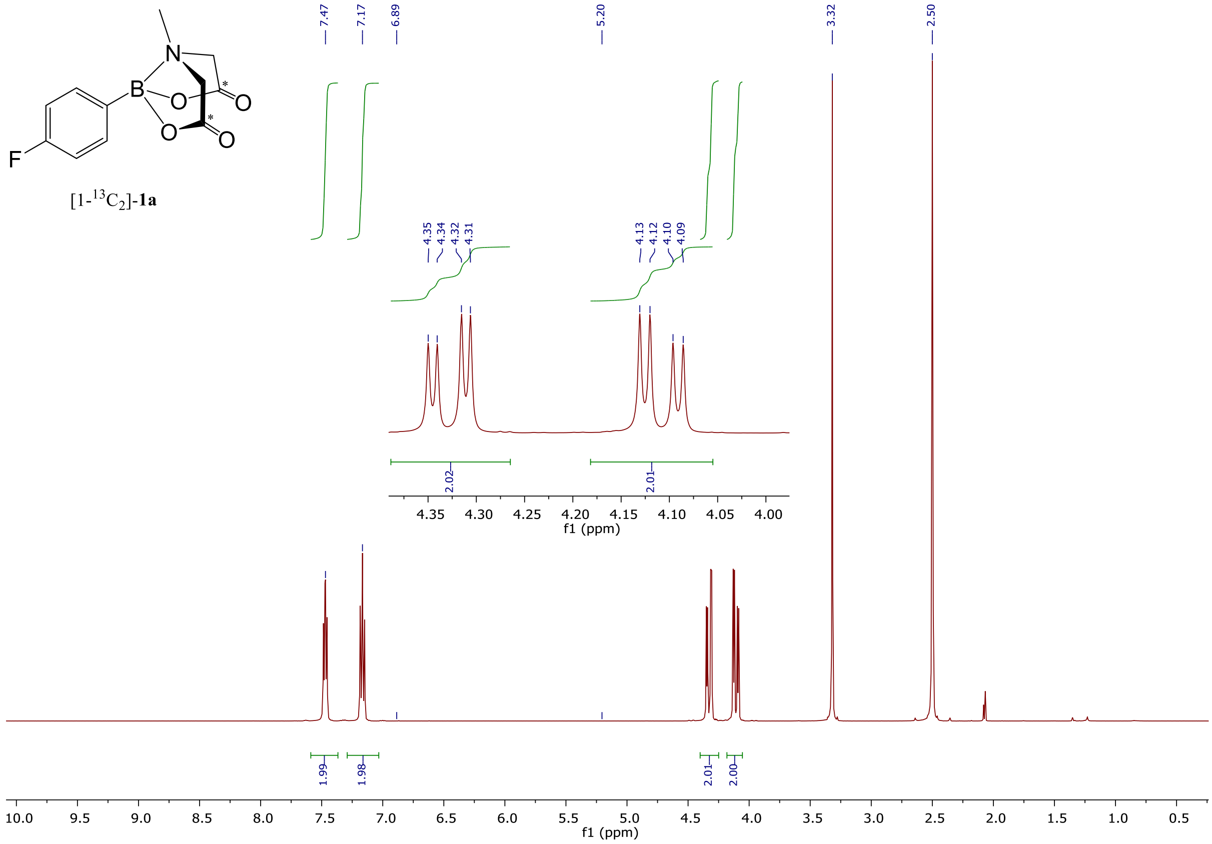
[^{15}N,*aryl*-^{2}H$_4$]-**1a**

^{19}F NMR (471 MHz, DMSO-d$_6$)



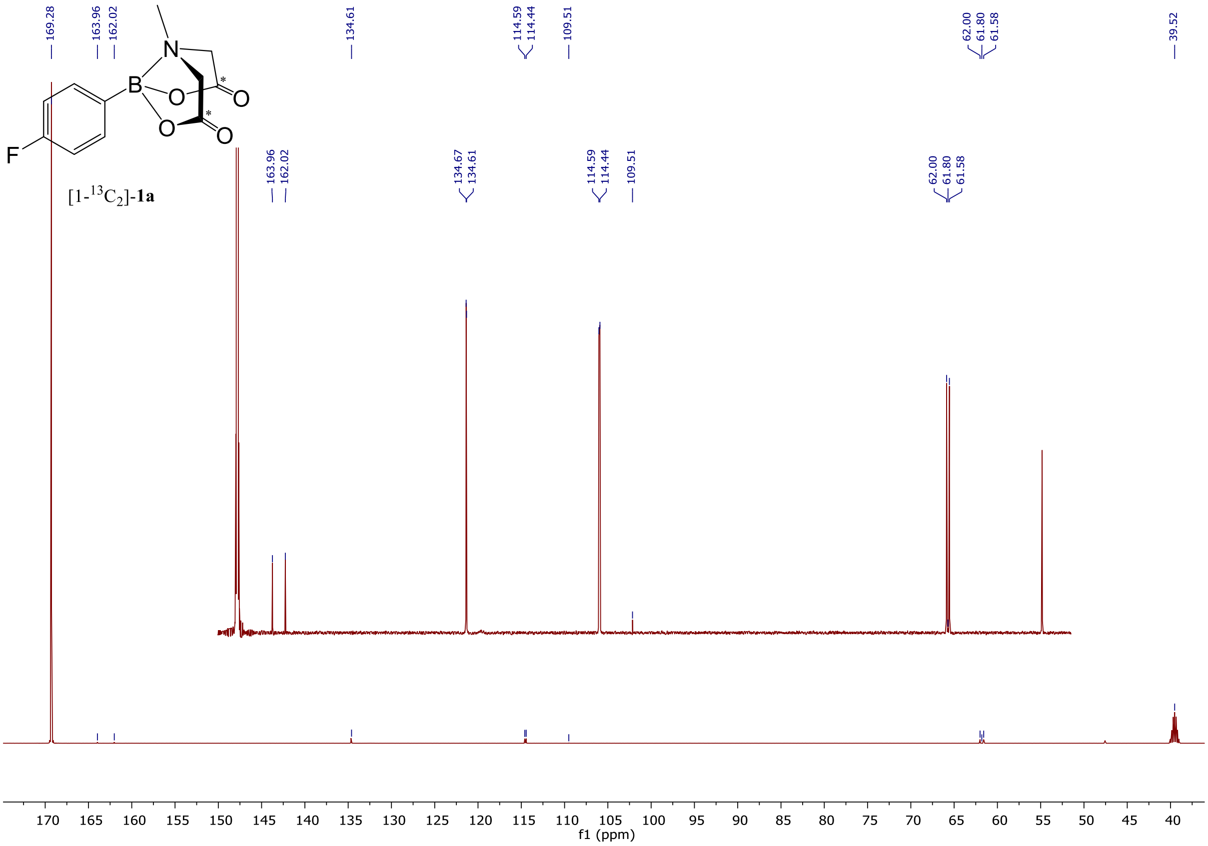
[^{15}N,*aryl*-^{2}H$_4$]-**1a**

^{15}N NMR (51 MHz, DMSO-d$_6$)

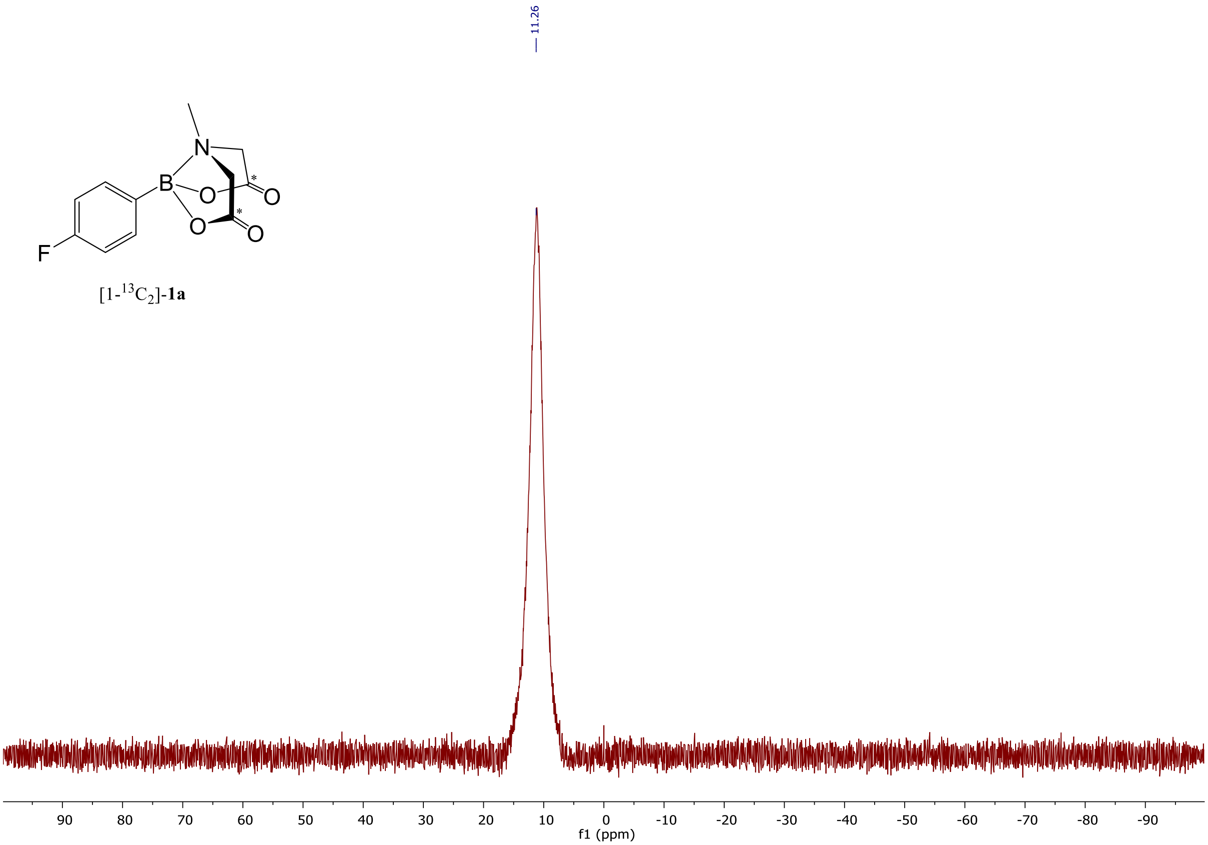


[1-^{13}C$_2$]-**1a**

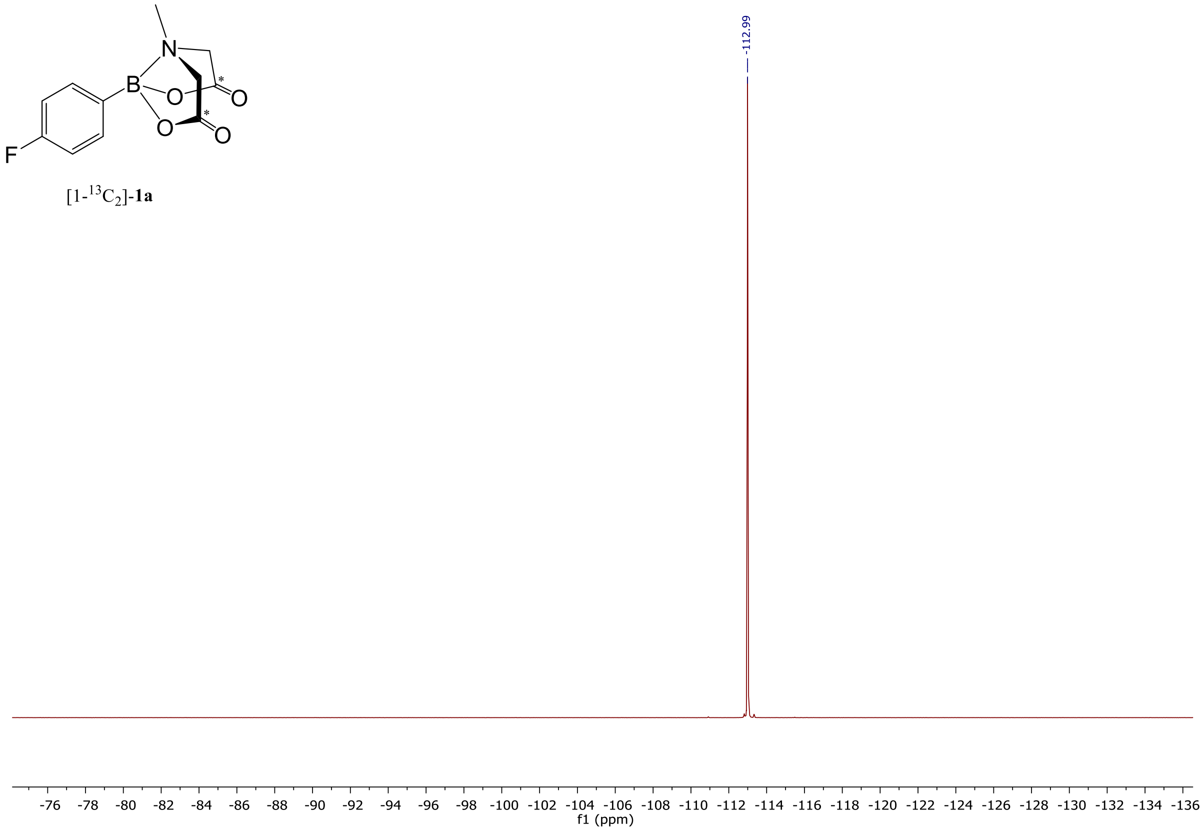
^{1}H NMR (500 MHz, DMSO-d$_6$)



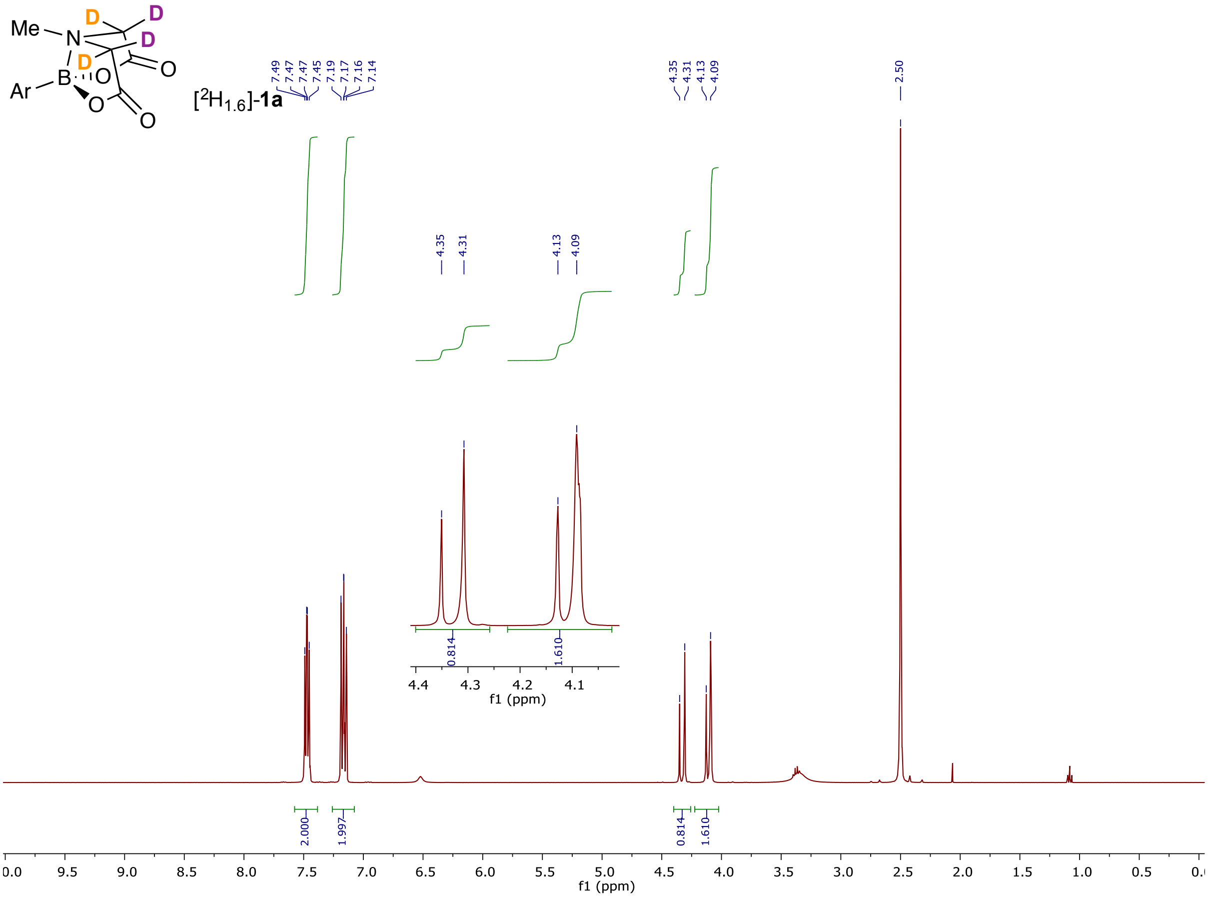
$^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d$_6$)



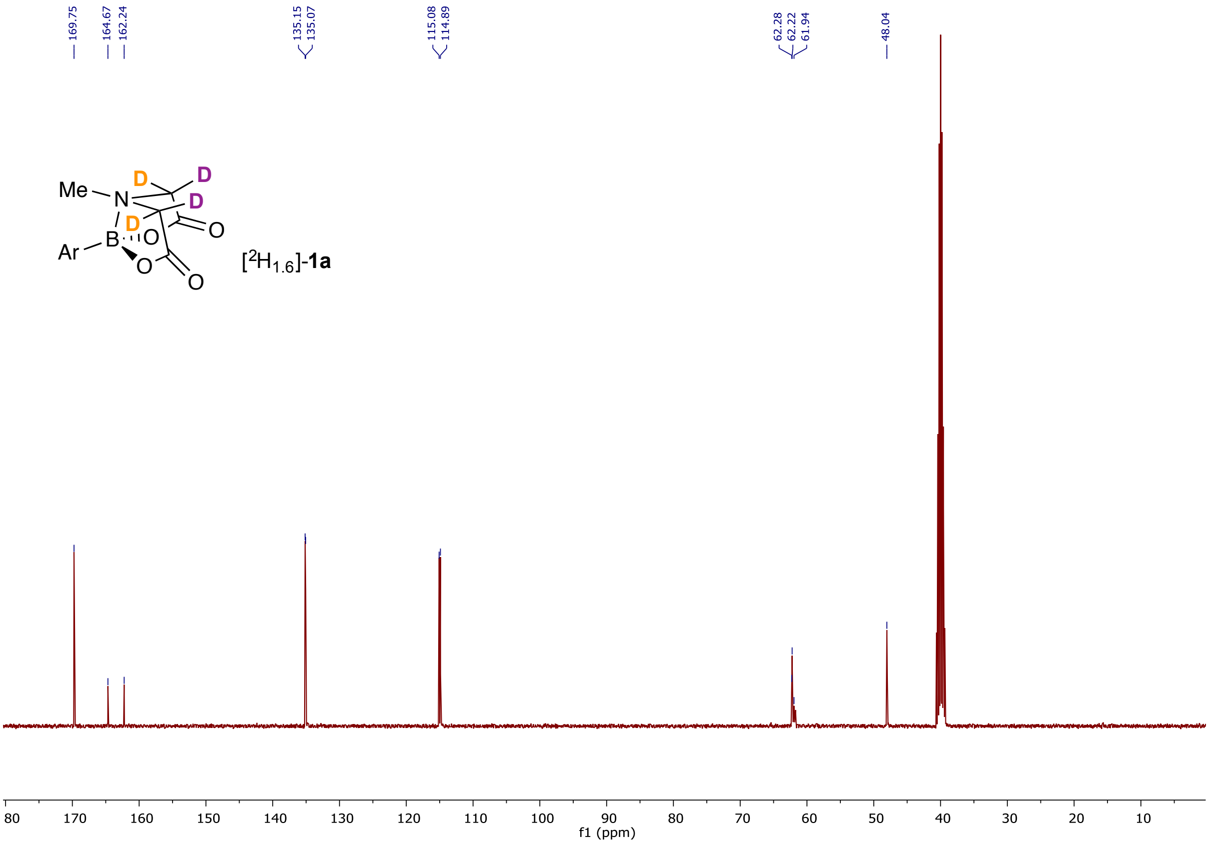
^{11}B NMR (160 MHz, DMSO-d$_6$)



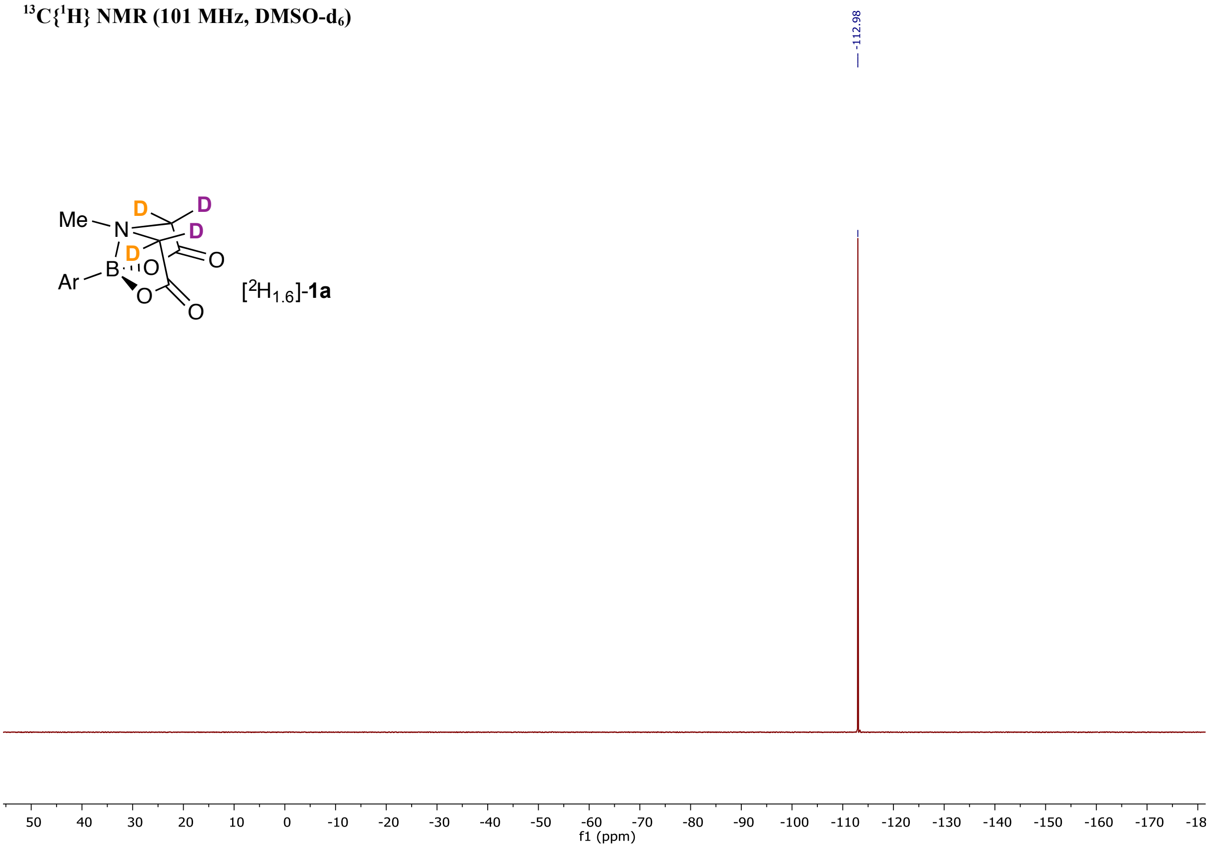
^{19}F NMR (471 MHz, DMSO-d$_6$)



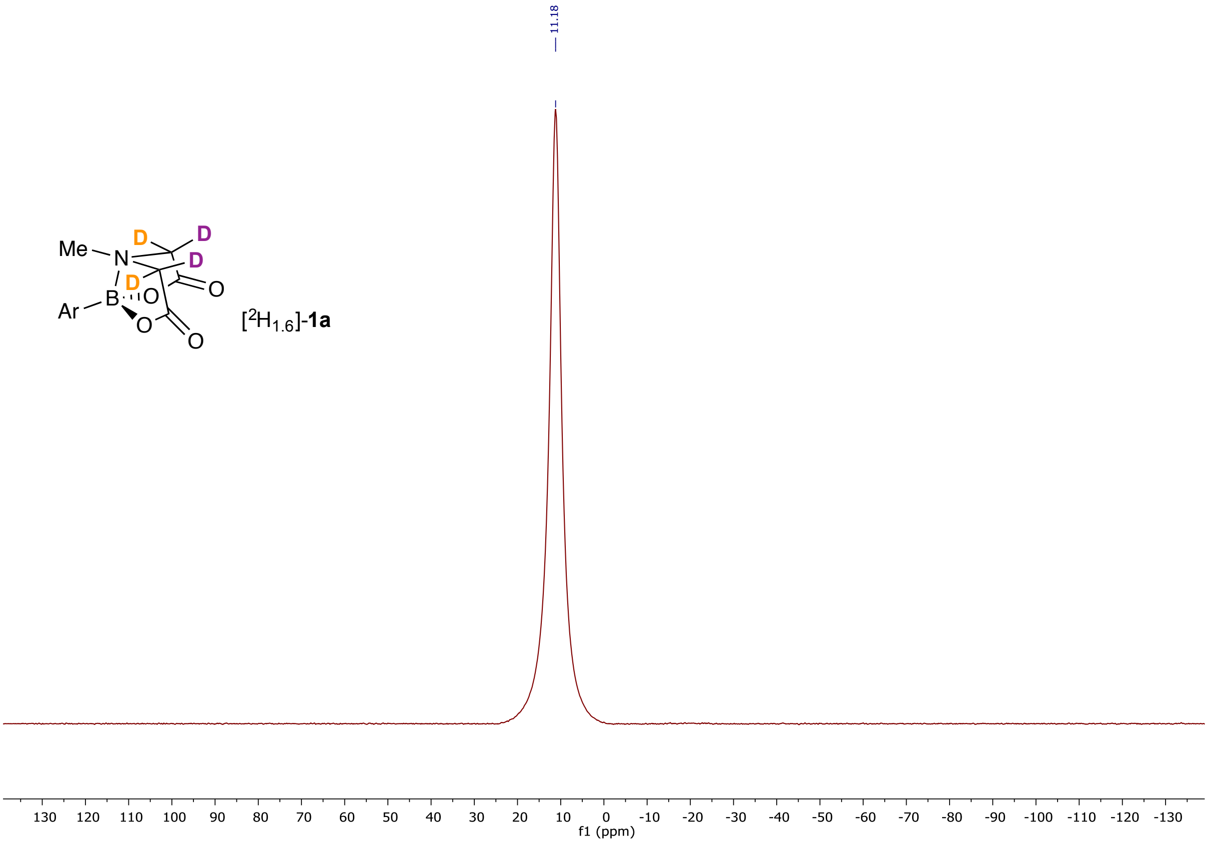
^{1}H NMR (400 MHz, DMSO-d$_6$)



^{13}C{^{1}H} NMR (101 MHz, DMSO-d$_6$)



^{19}F NMR (376 MHz, DMSO-d$_6$)



[$^{2}H_{1.6}$]-**1a**

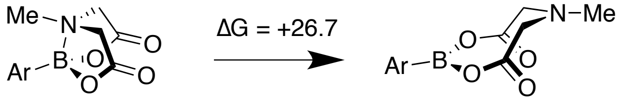
^{11}B NMR (128 MHz, DMSO-d$_6$)

VII. Computational Studies

1. Full Authorship of Gaussian 09

Gaussian 09 - Gaussian 09, Revision A.1, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, **2009**

*2. B-N Cleavage of MIDA Boronate **1a***



1

"open-**1a**"

Figure 33. *B-N cleavage of **1a** results in an open intermediate **"open" 1a** disfavored by 26.7 kcal/mol.*

Geometries, Energies, and Thermal Corrections

1a

```
------------------------------------------------------
---------------------
 Using  Gaussian 09:  AM64L-G09RevD.01 24-
Apr-2013
======================================
======================================
====
 # opt=maxcycle=250 freq=noraman 6-31g(d)
scrf=(solvent=thf,pcm)
 geom=connectivity density=current m062x
scf=(maxcycle=300,direct,tight)
 #N Geom=AllCheck Guess=TCheck
SCRF=Check GenChk RM062X/6-31G(d) Freq
------------------------------------------------------
---------------------
 Pointgroup= C1   Stoichiometry= C11H11BFNO4
C1[X(C11H11BFNO4)]  #Atoms= 29
 Charge = 0         Multiplicity = 1
------------------------------------------------------
---------------------
 SCF Energy= -905.937028796       Predicted
Change= -4.446002D-09
======================================
======================================
====
 Optimization completed.           {Found       2
times}
 Item      Max Val.    Criteria    Pass?      RMS Val.
Criteria    Pass?
 Force      0.00000 ||  0.00045    [ YES ]      0.00000
||  0.00030    [ YES ]
 Displ      0.00040 ||  0.00180    [ YES ]      0.00040 ||
0.00180    [ YES ]
------------------------------------------------------
---------------------
      Atomic                 Coordinates (Angstroms)
       Type              X                 Y              Z
------------------------------------------------------
---------------------
 N       -1.437453      0.027498       0.966851
 C       -0.728690     -0.589285       2.113599
 C       -2.696113     -0.705833       0.662403
 C       -2.348568     -1.671120      -0.468692
 O       -3.029703     -2.602646      -0.803643
 O       -1.196597     -1.324203      -1.034361
 B       -0.631582     -0.089951      -0.498799
 C        0.947558     -0.099845      -0.362520
 O       -1.179886      1.115880      -1.153321
 C       -1.685972      2.013426      -0.317733
 O       -2.097436      3.098811      -0.633108
 C       -1.644096      1.484279       1.116014
 C        1.652584     -1.302902      -0.218709
 C        3.033071     -1.324979      -0.044648
 C        3.709864     -0.114686      -0.014377
 C        3.061277      1.101905      -0.158475
 C        1.679865      1.094437      -0.335388
 H        0.228133     -0.086118       2.250736
 H       -0.549139     -1.642521       1.887115
 H       -1.341894     -0.500098       3.012867
 H       -3.459347     -0.010215       0.301703
 H       -3.081915     -1.229160       1.538431
 H       -2.548733      1.725229       1.676267
 H       -0.777869      1.915398       1.627120
 H        1.111764     -2.245527      -0.254181
 H        3.586293     -2.251941       0.061414
 H        3.635719      2.021730      -0.140008
 H        1.170124      2.045804      -0.471890
 F        5.043471     -0.122269       0.155899
------------------------------------------------------
---------------------
 Statistical Thermodynamic Analysis
 Temperature= 298.150 Kelvin       Pressure=
1.00000 Atm
======================================
======================================
====
 SCF Energy=     -905.937028796    Predicted
Change= -4.446002D-09
```

```
 Zero-point correction (ZPE)=              -905.7142
              0.22276

 Internal Energy (U)=                      -905.6996
              0.23740
 Enthalpy (H)=                             -905.6986
              0.23834
 Gibbs Free Energy (G)=                    -905.7565
              0.18043
------------------------------------------------------
---------------------
 Frequencies --     48.9865               52.9343
60.5363
```

“open” 1a

```
------------------------------------------------------
---------------------
 Using  Gaussian 09:  AM64L-G09RevD.01 24-
Apr-2013
======================================
======================================
====
 # opt=maxcycle=250 freq=noraman 6-31g(d)
scrf=(solvent=thf,pcm)
 geom=connectivity density=current m062x
scf=(maxcycle=300,direct,tight)
 #N Geom=AllCheck Guess=TCheck
SCRF=Check GenChk RM062X/6-31G(d) Freq
------------------------------------------------------
---------------------
 Pointgroup= C1   Stoichiometry= C11H11BFNO4
C1[X(C11H11BFNO4)]  #Atoms= 29
 Charge = 0          Multiplicity = 1
------------------------------------------------------
---------------------
 SCF Energy= -905.890547477       Predicted
Change= -1.263980D-08
======================================
======================================
====
 Optimization completed.           {Found       2
times}
 Item      Max Val.    Criteria    Pass?     RMS Val.
Criteria    Pass?
 Force      0.00000 ||  0.00045   [ YES ]      0.00000
||  0.00030   [ YES ]
 Displ      0.00160 ||  0.00180   [ YES ]      0.00160 ||
0.00180   [ YES ]
------------------------------------------------------
---------------------
      Atomic                 Coordinates (Angstroms)
       Type              X              Y            Z
------------------------------------------------------
---------------------
    N       3.527223     0.194494     0.070837
    C       4.505470    -0.608874    -0.656473
    C       2.672784     0.929227    -0.856613
    C       1.731008     1.816437    -0.059767
    O       2.021650     2.909707     0.331705
    O       0.494739     1.318819     0.218334
    B      -0.083132     0.069552     0.091189
    C      -1.630682     0.010136     0.031613
    O       0.592105    -1.132470     0.011818
    C       1.838550    -1.568599     0.350316
    O       2.170792    -2.674684     0.024936
    C       2.765540    -0.582677     1.045743
    C      -2.399596     1.183825     0.068837
    C      -3.786987     1.138224     0.010479
    C      -4.397958    -0.104545    -0.086258
    C      -3.680550    -1.292341    -0.125131
    C      -2.294344    -1.222683    -0.065562
    H       5.153015    -1.117918     0.061495
    H       5.119002     0.056645    -1.268963
    H       4.045121    -1.365054    -1.311427
    H       2.106145     0.275458    -1.542186
    H       3.303391     1.586538    -1.459012
    H       3.464522    -1.159893     1.653041
    H       2.208170     0.087909     1.706677
    H      -1.901723     2.145931     0.146985
    H      -4.396577     2.034524     0.036961
    H      -4.209446    -2.235831    -0.201720
    H      -1.713171    -2.139581    -0.097082
    F      -5.736340    -0.159744    -0.146001
------------------------------------------------------
---------------------
 Statistical Thermodynamic Analysis
 Temperature= 298.150 Kelvin       Pressure=
1.00000 Atm
======================================
======================================
====
 SCF Energy=     -905.890547477    Predicted
Change= -1.263980D-08
 Zero-point correction (ZPE)=              -905.6691
              0.22140
 Internal Energy (U)=                      -905.6535
              0.23695
 Enthalpy (H)=                             -905.6526
              0.23790
 Gibbs Free Energy (G)=                    -905.7141
              0.17643
------------------------------------------------------
---------------------
 Frequencies --     14.2117               45.1276
53.7393
```

3. NaOH Mediated Hydrolysis C-Attack First Pathway

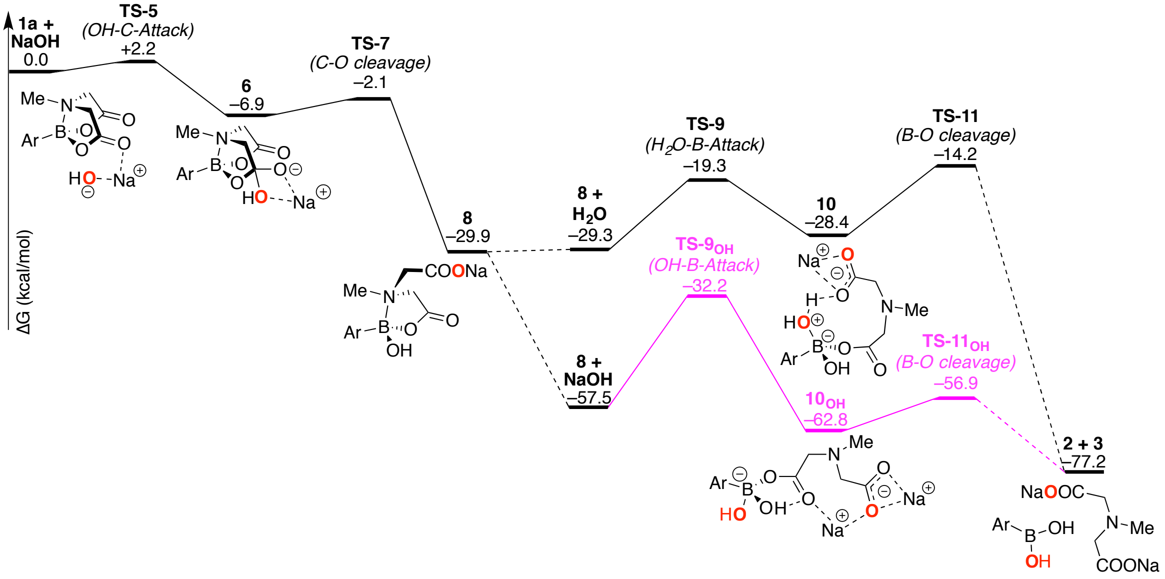


Figure 34. Minimum energy pathway for the NaOH-mediated hydrolysis of MIDA boronate **1a**.

Geometries, Energies, and Thermal Corrections

1a + NaOH

```
--------------------------------------------------------
 Using  Gaussian 09:  AM64L-G09RevD.01 24-
Apr-2013
========================================
 #M062X/6-31G(d)
scf=(maxcycle=300,direct,tight) density=current
 SCRF=(PCM,SOLVENT=THF)
opt=(maxcycle=250) freq=noraman
 #N Geom=AllCheck Guess=TCheck
SCRF=Check GenChk RM062X/6-31G(d) Freq
--------------------------------------------------------
 Pointgroup= C1   Stoichiometry=
C11H12BFNNaO5   C1[X(C11H12BFNNaO5)]
#Atoms= 32
 Charge = 0          Multiplicity = 1
--------------------------------------------------------
 SCF Energy= -1144.05117475       Predicted
Change= -1.124972D-07
========================================
 Optimization completed.          {Found        2
times}
```

```
 Item      Max Val.    Criteria    Pass?      RMS Val.
Criteria    Pass?
 Force      0.00010 ||  0.00045    [ YES ]      0.00001
||  0.00030    [ YES ]
 Displ      0.00161 ||  0.00180    [ YES ]      0.00161 ||
0.00180    [ YES ]
--------------------------------------------------------
     Atomic              Coordinates (Angstroms)
      Type            X              Y            Z
--------------------------------------------------------
       N       -1.100609      0.831855      0.965589
       C       -0.494270      0.138491      2.138925
       C       -2.439703      0.247571      0.662281
       C       -2.276398     -0.562370     -0.609481
       O       -3.137679     -1.291913     -1.060817
       O       -1.128109     -0.321267     -1.196579
       B       -0.284999      0.650263     -0.490292
       C        1.224058      0.187901     -0.351645
       O       -0.464843      1.998307     -1.065517
       C       -0.940798      2.907203     -0.229215
       O       -1.153159      4.059983     -0.506446
       C       -1.134506      2.300780      1.155152
       C        1.515994     -1.153456     -0.054961
```

```
C       2.828725    -1.590243     0.091423
C       3.853177    -0.666692    -0.066536
C       3.613879     0.665404    -0.361173
C       2.290179     1.080724    -0.501486
H       0.547012     0.448930     2.226930
H      -0.592579    -0.936741     1.946447
H      -1.052359     0.427928     3.033692
H      -3.175941     1.038179     0.494134
H      -2.767693    -0.409094     1.467322
H      -2.055045     2.639033     1.633007
H      -0.284348     2.595025     1.777561
H       0.685964    -1.846844     0.088428
H       3.072164    -2.621875     0.324538
H       4.448860     1.347871    -0.478863
H       2.088568     2.121414    -0.743709
O      -1.368096    -2.513185     0.955434
Na     -2.503413    -3.448547    -0.574659
H      -0.616724    -2.999398     1.323419
F       5.126888    -1.081333     0.074708
-------------------------------------------------------
 Statistical Thermodynamic Analysis
 Temperature= 298.150 Kelvin       Pressure=
1.00000 Atm
=====================================
 SCF Energy=     -1144.05117475    Predicted
Change= -1.124972D-07
 Zero-point correction (ZPE)=              -1143.8143
            0.23680
 Internal Energy (U)=                      -1143.7958
            0.25532
 Enthalpy (H)=                             -1143.7949
            0.25626
 Gibbs Free Energy (G)=                    -1143.8610
            0.19012
-------------------------------------------------------
 Frequencies --     46.0313              52.0689
62.4743
```

TS-5

```
-------------------------------------------------------
 Using  Gaussian 09:  AM64L-G09RevD.01 24-
Apr-2013
=====================================
 #M062X/6-31G(d)
scf=(maxcycle=300,direct,tight) density=current
 SCRF=(PCM,SOLVENT=THF)
opt=(maxcycle=250,ts,calcfc,noeigentest)
 freq=noraman
 #N Geom=AllCheck Guess=TCheck
SCRF=Check GenChk RM062X/6-31G(d) Freq
-------------------------------------------------------
 Pointgroup= C1   Stoichiometry=
C11H12BFNNaO5   C1[X(C11H12BFNNaO5)]
#Atoms= 32
 Charge = 0          Multiplicity = 1
-------------------------------------------------------
 SCF Energy= -1144.04647939       Predicted
Change= -2.087281D-09
=====================================
```

```
 Optimization completed.          {Found       2
times}
 Item      Max Val.    Criteria    Pass?      RMS Val.
Criteria    Pass?
 Force      0.00001 ||  0.00045   [ YES ]      0.00000
||  0.00030   [ YES ]
 Displ      0.00148 ||  0.00180   [ YES ]      0.00148 ||
0.00180   [ YES ]
-------------------------------------------------------
     Atomic             Coordinates (Angstroms)
      Type            X              Y           Z
-------------------------------------------------------
      N        -0.967497     0.898918     0.946093
      C        -0.420639     0.221099     2.154524
      C        -2.370577     0.470048     0.670888
      C        -2.302675    -0.515526    -0.486184
      O        -3.297799    -1.022367    -0.990304
      O        -1.140274    -0.399362    -1.131441
      B        -0.222453     0.539455    -0.513374
      C         1.271448     0.015412    -0.374690
      O        -0.310796     1.871316    -1.171059
      C        -0.653837     2.870193    -0.378067
      O        -0.767859     4.021359    -0.717936
      C        -0.837372     2.370061     1.049630
      C         1.577312    -1.346421    -0.483247
      C         2.876933    -1.822208    -0.325756
      C         3.880926    -0.907223    -0.050491
      C         3.634484     0.453363     0.057309
      C         2.327269     0.899808    -0.113537
      H         0.651111     0.415813     2.206624
      H        -0.638799    -0.843905     2.046262
      H        -0.920131     0.631902     3.036572
      H        -2.953575     1.336522     0.342007
      H        -2.829836     0.024972     1.551144
      H        -1.693927     2.829935     1.544998
      H         0.067185     2.607108     1.618172
      H         0.781795    -2.048611    -0.719427
      H         3.120958    -2.875340    -0.416164
      H         4.455285     1.132971     0.260168
      H         2.134474     1.969371    -0.051635
      O        -1.687043    -2.140344     0.872560
      Na       -3.273765    -3.135002    -0.201598
      H        -0.817731    -2.414298     0.546919
      F         5.141099    -1.351952     0.108814
-------------------------------------------------------
 Statistical Thermodynamic Analysis
 Temperature= 298.150 Kelvin       Pressure=
1.00000 Atm
=====================================
SCF Energy=      -1144.04647939     Predicted
Change= -2.087281D-09
 Zero-point correction (ZPE)=              -1143.8108
            0.23562
 Internal Energy (U)=                      -1143.7929
            0.25348
 Enthalpy (H)=                             -1143.7920
            0.25443
 Gibbs Free Energy (G)=                    -1143.8575
            0.18892
-------------------------------------------------------
```

```
 Frequencies --   -236.2815              24.5821
39.3362
```

6

```
-------------------------------------------------------
 Using  Gaussian 09:  AM64L-G09RevD.01 24-
Apr-2013
=======================================
 #M062X/6-31G(d)
scf=(maxcycle=300,direct,tight) density=current
 SCRF=(PCM,SOLVENT=THF)
opt=(maxcycle=250) freq=noraman
 #N Geom=AllCheck Guess=TCheck
SCRF=Check GenChk RM062X/6-31G(d) Freq
-------------------------------------------------------
Pointgroup= C1   Stoichiometry=
C11H12BFNNaO5   C1[X(C11H12BFNNaO5)]
#Atoms= 32
 Charge = 0         Multiplicity = 1
-------------------------------------------------------
 SCF Energy= -1144.06344097       Predicted
Change= -2.721340D-08
=======================================
 Optimization completed.           {Found       2
times}
 Item      Max Val.    Criteria    Pass?      RMS Val.
Criteria    Pass?
 Force      0.00005 ||  0.00045    [ YES ]      0.00000
||  0.00030    [ YES ]
 Displ      0.00123 ||  0.00180    [ YES ]      0.00123 ||
0.00180    [ YES ]
-------------------------------------------------------
      Atomic               Coordinates (Angstroms)
       Type              X               Y           Z
-------------------------------------------------------
       N      -0.780572     0.830996     1.011949
       C      -0.322449     0.043049     2.177287
       C      -2.232276     0.623597     0.736880
       C      -2.350329    -0.553916    -0.261999
       O      -3.411444    -0.534590    -0.995522
       O      -1.093900    -0.564203    -0.959492
       B      -0.147845     0.375866    -0.477325
       C       1.362529    -0.141466    -0.372130
       O      -0.221978     1.723819    -1.149510
       C      -0.327245     2.744723    -0.325490
       O      -0.318457     3.910019    -0.646556
       C      -0.431114     2.259032     1.119546
       C       1.635201    -1.501985    -0.176523
       C       2.933255    -1.983435    -0.030106
       C       3.977990    -1.073282    -0.082627
       C       3.768229     0.282218    -0.279695
       C       2.457253     0.732353    -0.424775
       H       0.762975     0.118008     2.252137
       H      -0.618567    -0.994965     2.026700
       H      -0.790720     0.433852     3.085033
       H      -2.619295     1.513927     0.237212
       H      -2.781970     0.451289     1.665294
       H      -1.164409     2.827992     1.694926
       H       0.550927     2.354929     1.594435
       H       0.807709    -2.206823    -0.145010
       H       3.146885    -3.036852     0.117292
       H       4.618021     0.955238    -0.323480
       H       2.291878     1.793476    -0.599422
       O      -2.286131    -1.801349     0.566185
       Na     -4.339150    -2.392711    -0.360443
       H      -1.600724    -2.337163     0.137121
       F       5.240019    -1.522699     0.058066
-------------------------------------------------------
 Statistical Thermodynamic Analysis
 Temperature= 298.150 Kelvin       Pressure=
1.00000 Atm
=======================================
 SCF Energy=     -1144.06344097    Predicted
Change= -2.721340D-08
 Zero-point correction (ZPE)=              -1143.8254
              0.23794
 Internal Energy (U)=                      -1143.8078
              0.25561
 Enthalpy (H)=                             -1143.8068
              0.25656
 Gibbs Free Energy (G)=                    -1143.8719
              0.19144
-------------------------------------------------------
 Frequencies --     30.7680              43.7501
46.1134
```

TS-7

```
-------------------------------------------------------
 Using  Gaussian 09:  AM64L-G09RevD.01 24-
Apr-2013
=======================================
 #M062X/6-31G(d)
scf=(maxcycle=300,direct,tight) density=current
 SCRF=(PCM,SOLVENT=THF)
opt=(maxcycle=250,ts,calcfc,noeigentest)
 freq=noraman
 #N Geom=AllCheck Guess=TCheck
SCRF=Check GenChk RM062X/6-31G(d) Freq
-------------------------------------------------------
 Pointgroup= C1   Stoichiometry=
C11H12BFNNaO5   C1[X(C11H12BFNNaO5)]
#Atoms= 32
 Charge = 0         Multiplicity = 1
-------------------------------------------------------
 SCF Energy= -1144.05503951       Predicted
Change= -1.068458D-08
=======================================
 Optimization completed.           {Found       1
times}
 Item      Max Val.    Criteria    Pass?      RMS Val.
Criteria    Pass?
 Force      0.00004 ||  0.00045    [ YES ]      0.00000
||  0.00030    [ YES ]
 Displ      0.00192 ||  0.00180    [ NO ]      0.00192 ||
0.00180    [ YES ]
-------------------------------------------------------
      Atomic               Coordinates (Angstroms)
       Type              X               Y           Z
```

```
--------------------------------------------------------
      N      -0.890817      0.293245      1.191978
      C      -0.238880     -0.558663      2.203271
      C      -2.343724      0.054160      1.107468
      C      -2.768537     -1.199407      0.356074
      O      -3.702120     -1.192589     -0.437719
      O      -1.054689     -0.913825     -1.054926
      B      -0.299984      0.045796     -0.516639
      C       1.305673     -0.095668     -0.409515
      O      -0.676552      1.505982     -0.930409
      C      -0.776191      2.382980      0.035165
      O      -0.950024      3.575977     -0.109128
      C      -0.640685      1.725509      1.410583
      C       1.855637     -1.384104     -0.329145
      C       3.225085     -1.602092     -0.204699
      C       4.063280     -0.497126     -0.168692
      C       3.580065      0.797674     -0.258562
      C       2.201889      0.981464     -0.378115
      H       0.822440     -0.309625      2.233019
      H      -0.354660     -1.602523      1.913258
      H      -0.687730     -0.393677      3.188926
      H      -2.805421      0.890810      0.580529
      H      -2.771564      0.005532      2.117771
      H      -1.320973      2.179027      2.137700
      H       0.387518      1.856123      1.762072
      H       1.180141     -2.235893     -0.370022
      H       3.650184     -2.598575     -0.139143
      H       4.274124      1.631607     -0.239243
      H       1.827679      2.000090     -0.464670
      O      -2.329245     -2.329727      0.923324
      Na     -2.669925     -0.291273     -2.343713
      H      -2.713338     -3.070511      0.421302
      F       5.392866     -0.691664     -0.048160
--------------------------------------------------------
 Statistical Thermodynamic Analysis
 Temperature= 298.150 Kelvin      Pressure=
1.00000 Atm
====================================
 SCF Energy=     -1144.05503951    Predicted
Change= -1.068458D-08
 Zero-point correction (ZPE)=              -1143.8182
            0.23680
 Internal Energy (U)=                      -1143.8003
            0.25467
 Enthalpy (H)=                             -1143.7994
            0.25561
 Gibbs Free Energy (G)=                    -1143.8644
            0.19062
--------------------------------------------------------
 Frequencies --   -130.4213              32.4692
53.3280
```

8

```
-----------------------------------------------------------------------
-----

 Using  Gaussian 09:  AM64L-G09RevD.01 24-Apr-2013

============================================
================================

 #M062X/6-31G(d) scf=(maxcycle=300,direct,tight)
density=current

 SCRF=(PCM,SOLVENT=THF) opt=(maxcycle=250)
freq=noraman

 #N Geom=AllCheck Guess=TCheck SCRF=Check
GenChk RM062X/6-31G(d) Freq

-----------------------------------------------------------------------
-----

 Pointgroup= C1   Stoichiometry= C11H12BFNNaO5
C1[X(C11H12BFNNaO5)]  #Atoms= 32

 Charge = 0    Multiplicity = 1

-----------------------------------------------------------------------
-----

 SCF Energy= -1144.10162423    Predicted Change= -
1.090056D-08

============================================
================================

 Optimization completed.         {Found      2
times}

 Item     Max Val.   Criteria   Pass?    RMS Val.
Criteria   Pass?

 Force    0.00001 ||  0.00045   [ YES ]     0.00000 ||
0.00030   [ YES ]

 Displ    0.00057 ||  0.00180   [ YES ]     0.00057 ||
0.00180   [ YES ]

-----------------------------------------------------------------------
-----

    Atomic      Coordinates (Angstroms)

     Type     X        Y     Z

-----------------------------------------------------------------------
-----

     N     -0.709753     -0.896068      0.982654

     C      0.209789     -1.794992      1.717098

     C     -2.005127     -1.626761      0.779126

     C     -3.013332     -0.778246     -0.023417

     O     -3.606913      0.130423      0.598613

     O     -0.392177     -1.308173     -1.541404
```

B	-0.078545	-0.382100	-0.546509
C	1.493416	-0.103969	-0.400057
O	-0.878231	0.912132	-0.602218
C	-1.194137	1.405028	0.584946
O	-1.665471	2.507360	0.750413
C	-0.908962	0.393814	1.685224
C	2.407676	-1.108963	-0.748859
C	3.782750	-0.929671	-0.630773
C	4.247527	0.287555	-0.154584
C	3.391109	1.318803	0.193626
C	2.018757	1.109327	0.063254
H	1.138314	-1.265017	1.927975
H	0.425173	-2.658053	1.083801
H	-0.256686	-2.124326	2.649613
H	-2.420203	-1.860709	1.763789
H	-1.765810	-2.544717	0.241811
H	-1.734667	0.360615	2.397563
H	0.016373	0.668258	2.199967
H	2.028546	-2.052999	-1.131963
H	4.491646	-1.704910	-0.902341
H	3.798690	2.259065	0.549381
H	1.353177	1.932596	0.316529
O	-3.095982	-0.989465	-1.264654
Na	-3.272481	1.381717	-1.381014
H	-1.362267	-1.348116	-1.675420
F	5.575488	0.474737	-0.032787

```
-------------------------------------------------------------------------
-----

 Statistical Thermodynamic Analysis

 Temperature= 298.150 Kelvin      Pressure= 1.00000
Atm

===========================================
===============================

 SCF Energy=    -1144.10162423 Predicted Change= -
1.090056D-08

 Zero-point correction (ZPE)=       -1143.8631  0.23849

 Internal Energy (U)=             -1143.8451  0.25647

 Enthalpy (H)=                 -1143.8442   0.25741

 Gibbs Free Energy (G)=          -1143.9086    0.19297

-------------------------------------------------------------------------
-----

 Frequencies --    48.0550             49.7249
67.3570
```

8 + H_2O

```
---------------------------------------------------------
---------------------
 Using  Gaussian 09:  AM64L-G09RevD.01 24-
Apr-2013
======================================
======================================
====
 #M062X/6-31G(d)
scf=(maxcycle=300,direct,tight) density=current
 SCRF=(PCM,SOLVENT=THF)
opt=(maxcycle=250) freq=noraman
 #N Geom=AllCheck Guess=TCheck
SCRF=Check GenChk RM062X/6-31G(d) Freq
---------------------------------------------------------
---------------------
 Pointgroup= C1   Stoichiometry=
C11H14BFNNaO6   C1[X(C11H14BFNNaO6)]
#Atoms= 35
 Charge = 0     Multiplicity = 1
---------------------------------------------------------
---------------------
 SCF Energy= -1220.49971357     Predicted
Change= -2.156260D-08
======================================
======================================
====
 Optimization completed.           {Found       1
times}
 Item      Max Val.    Criteria    Pass?     RMS Val.
Criteria    Pass?
 Force      0.00002 ||  0.00045   [ YES ]      0.00000
||  0.00030   [ YES ]
 Displ      0.00207 ||  0.00180   [ NO ]       0.00207 ||
0.00180   [ YES ]
---------------------------------------------------------
---------------------
     Atomic        Coordinates (Angstroms)
      Type      X          Y      Z
---------------------------------------------------------
---------------------
      N       -0.728651       1.053301       1.026673
```

```
C      0.300407     1.811224     1.791707
C     -1.210845    -0.064783     1.893706
C     -2.132232    -1.069461     1.174983
O     -3.180769    -0.603995     0.649980
O     -0.888537    -0.445919    -1.069784
B     -0.091052     0.596056    -0.493551
C      1.433546     0.156047    -0.354778
O     -0.282488     1.903682    -1.178076
C     -1.256102     2.642247    -0.664157
O     -1.667823     3.669710    -1.143086
C     -1.790496     2.007447     0.614324
C      1.767459    -1.081843     0.215432
C      3.091951    -1.483226     0.375004
C      4.093164    -0.624213    -0.052562
C      3.816476     0.607300    -0.624896
C      2.483102     0.986146    -0.766257
H      0.678975     2.626705     1.171809
H      1.124263     1.145063     2.044881
H     -0.153233     2.214753     2.700610
H     -1.734754     0.375244     2.749929
H     -0.324377    -0.590552     2.250964
H     -2.710370     1.451812     0.413022
H     -1.980429     2.760288     1.383071
H      0.977074    -1.747446     0.562414
H      3.356976    -2.435589     0.822210
H      4.634188     1.244431    -0.944903
H      2.253313     1.951456    -1.210421
O     -1.753217    -2.260349     1.162169
H     -1.829660    -0.210603    -1.122791
Na    -1.260924    -2.747618    -0.995713
O     -3.417783    -2.242719    -1.452609
H     -3.766729    -1.719713    -2.187241
F      5.377515    -0.998815     0.097169
H     -3.550541    -1.690690    -0.637979
---------------------------------------------------------
---------------------
 Statistical Thermodynamic Analysis
 Temperature= 298.150 Kelvin       Pressure=
1.00000 Atm
=====================================
=====================================
====
 SCF Energy=     -1220.49971357 Predicted
Change= -2.156260D-08
 Zero-point correction (ZPE)=       -1220.2358
0.26385
 Internal Energy (U)=             -1220.2153
0.28435
 Enthalpy (H)=                  -1220.2144   0.28529
 Gibbs Free Energy (G)=          -1220.2843
0.21534
---------------------------------------------------------
---------------------
 Frequencies --     35.3716              54.0300
58.2874
```

8 + NaOH

```
---------------------------------------------------------
 Using  Gaussian 09:  AM64L-G09RevD.01 24-
Apr-2013
=====================================
 #M062X/6-31G(d)
scf=(maxcycle=300,direct,tight) density=current
 SCRF=(PCM,SOLVENT=THF)
opt=(maxcycle=250) freq=noraman
 #N Geom=AllCheck Guess=TCheck
SCRF=Check GenChk RM062X/6-31G(d) Freq
---------------------------------------------------------
 Pointgroup= C1   Stoichiometry=
C11H13BFNNa2O6   C1[X(C11H13BFNNa2O6)]
#Atoms= 35
 Charge = 0         Multiplicity = 1
---------------------------------------------------------
 SCF Energy= -1382.24480054       Predicted
Change= -1.339447D-07
=====================================
 Optimization completed.          {Found       1
times}
 Item      Max Val.    Criteria    Pass?     RMS Val.
Criteria    Pass?
 Force     0.00003 ||  0.00045   [ YES ]      0.00000
||  0.00030   [ YES ]
 Displ     0.00413 ||  0.00180   [ NO ]      0.00413 ||
0.00180   [ YES ]
---------------------------------------------------------
     Atomic              Coordinates (Angstroms)
      Type             X              Y           Z
---------------------------------------------------------
      N      -0.298009    -0.658596    -1.406215
      C       0.768555    -0.593754    -2.436498
      C      -1.508164    -0.011849    -1.995090
      C      -2.727018     0.115804    -1.066320
      O      -2.944211    -0.821311    -0.260304
      O      -0.547381     1.348635     0.198500
      B       0.139343     0.141762     0.100472
      C       1.746185     0.211736     0.184349
      O      -0.391941    -0.914397     1.044369
      C      -0.798738    -2.041000     0.496731
      O      -1.299147    -2.947425     1.128738
      C      -0.538116    -2.064218    -0.995612
      C       2.410942     1.394537    -0.165521
      C       3.799372     1.501640    -0.131805
      C       4.532161     0.395162     0.269631
      C       3.928084    -0.796529     0.637572
      C       2.536701    -0.871820     0.591399
      H       1.668511    -1.079057    -2.060216
      H       0.993903     0.453517    -2.645814
      H       0.428390    -1.089172    -3.350789
      H      -1.799230    -0.587630    -2.883193
      H      -1.211125     0.987648    -2.309208
      H      -1.380258    -2.513980    -1.522194
      H       0.363913    -2.654142    -1.186557
      H       1.819299     2.256059    -0.465999
      H       4.316920     2.416434    -0.401611
      H       4.541697    -1.632903     0.955737
      H       2.061345    -1.803349     0.894453
      O      -3.426229     1.140722    -1.242010
      H      -1.190132     1.373748     1.053634
```

```
     Na     -2.624848      2.715987      0.110451
     O      -2.257768      1.549655      1.967556
     H      -1.889762      1.961565      2.760357
     Na     -2.665156     -0.608875      1.952073
     F       5.876616      0.483233      0.309663
 ---------------------------------------------------------
 Statistical Thermodynamic Analysis
 Temperature= 298.150 Kelvin      Pressure=
1.00000 Atm
 =======================================
 SCF Energy=    -1382.24480054    Predicted
Change= -1.339447D-07
 Zero-point correction (ZPE)=              -1381.9941
          0.25062
 Internal Energy (U)=                      -1381.9724
          0.27230
 Enthalpy (H)=                             -1381.9715
          0.27324
 Gibbs Free Energy (G)=                    -1382.0442
          0.20052
 ---------------------------------------------------------
 Frequencies --     36.9155              46.6536
57.2145
```

TS-9

```
 ---------------------------------------------------------
 ---------------------
 Using  Gaussian 09:  AM64L-G09RevD.01 24-
Apr-2013
 =======================================
 =======================================
 ====
 #M062X/6-31G(d)
scf=(maxcycle=300,direct,tight) density=current
 SCRF=(PCM,SOLVENT=THF)
opt=(maxcycle=250,ts,calcfc,noeigentest,gdiis)
 iop(1/8=18) freq=noraman
 #N Geom=AllCheck Guess=TCheck
SCRF=Check Test GenChk RM062X/6-31G(d)
Freq
 ---------------------------------------------------------
 ---------------------
 Pointgroup= C1   Stoichiometry=
C11H14BFNNaO6   C1[X(C11H14BFNNaO6)]
#Atoms= 35
 Charge = 0     Multiplicity = 1
 ---------------------------------------------------------
 ---------------------
 SCF Energy= -1220.48215501     Predicted
Change= -8.027524D-10
 =======================================
 =======================================
 ====
 Optimization completed on the basis of negligible
forces.           {Found        2        times}
 Item      Max Val.    Criteria    Pass?      RMS Val.
Criteria    Pass?
 Force      0.00000 ||  0.00045    [ YES ]      0.00000
||  0.00030    [ YES ]
 Displ     0.00293 ||  0.00180    [ NO ]       0.00293 ||
0.00180    [ YES ]
 ---------------------------------------------------------
 ---------------------
     Atomic        Coordinates (Angstroms)
      Type      X          Y       Z
 ---------------------------------------------------------
 ---------------------
     N      -3.633190     -1.022567     -0.522453
     C      -4.618574     -1.969089     -1.029304
     C      -3.665789     -1.021333      0.946446
     C      -2.628871     -0.037825      1.503401
     O      -1.455499     -0.504244      1.618598
     O       0.795026      1.760408     -1.678394
     B       0.895134      0.610238     -0.948075
     C       2.306013      0.109994     -0.484863
     O      -0.120990     -0.405673     -1.012513
     C      -1.408843     -0.100836     -1.060008
     O      -1.821211      1.046314     -1.150326
     C      -2.312199     -1.319505     -1.046141
     C       3.464324      0.815638     -0.833524
     C       4.725127      0.392552     -0.421441
     C       4.809715     -0.753878      0.354000
     C       3.691298     -1.484915      0.728732
     C       2.443407     -1.042560      0.300871
     H      -4.646789     -1.923929     -2.121479
     H      -5.606558     -1.697600     -0.647702
     H      -4.405410     -3.008863     -0.724949
     H      -3.450629     -2.027976      1.345424
     H      -4.667437     -0.716567      1.258936
     H      -1.793722     -2.127460     -0.508529
     H      -2.409199     -1.628950     -2.094662
     H       3.377751      1.710606     -1.443911
     H       5.630167      0.927669     -0.687932
     H       3.811693     -2.374419      1.337873
     H       1.554661     -1.601634      0.583738
     O      -2.975317      1.143366      1.725891
     Na     -1.699863      2.603534      0.614580
     H      -0.129787      1.917947     -1.925928
     F       6.022157     -1.173326      0.758901
     H      -0.380908      0.582923      1.385878
     O       0.177448      1.332833      0.966721
     H       0.942593      1.482600      1.541461
 ---------------------------------------------------------
 ---------------------
 Statistical Thermodynamic Analysis
 Temperature= 298.150 Kelvin      Pressure=
1.00000 Atm
 =======================================
 =======================================
 ====
 SCF Energy=     -1220.48215501 Predicted
Change= -8.027524D-10
 Zero-point correction (ZPE)=        -1220.2209
0.26117
 Internal Energy (U)=               -1220.2014
0.28067
 Enthalpy (H)=                  -1220.2005   0.28162
 Gibbs Free Energy (G)=            -1220.2683
0.21376
```

```
---------------------------------------------------------
---------------------
 Frequencies --   -163.5426              -13.7997
36.0680
```

TS 9$_{OH}$

```
---------------------------------------------------------
 Using  Gaussian 09:  AM64L-G09RevD.01 24-
Apr-2013
======================================
 #M062X/6-31G(d)
scf=(maxcycle=300,direct,tight) density=current
 SCRF=(PCM,SOLVENT=THF)
opt=(maxcycle=250,ts,calcfc,noeigentest,gdiis)
 iop(1/8=18) freq=noraman
 #N Geom=AllCheck Guess=TCheck
SCRF=Check Test GenChk RM062X/6-31G(d)
Freq
---------------------------------------------------------
 Pointgroup= C1   Stoichiometry=
C11H13BFNNa2O6   C1[X(C11H13BFNNa2O6)]
#Atoms= 35
 Charge = 0          Multiplicity = 1
---------------------------------------------------------
 SCF Energy= -1382.20015120       Predicted
Change= -1.763390D-08
======================================
 Optimization completed.           {Found        1
times}
 Item      Max Val.    Criteria    Pass?      RMS Val.
Criteria    Pass?
 Force      0.00001 ||  0.00045    [ YES ]      0.00000
||  0.00030   [ YES ]
 Displ      0.00207 ||  0.00180   [ NO ]       0.00207 ||
0.00180   [ YES ]
---------------------------------------------------------
     Atomic              Coordinates (Angstroms)
      Type             X                Y           Z
---------------------------------------------------------
N       -1.994983      -1.910063      -0.298460
       C       -1.940224      -3.288994      -0.771663
       C       -3.336041      -1.351043      -0.513010
       C       -3.316451       0.177536      -0.362078
       O       -3.607019       0.668575       0.747966
       O       -0.392769       0.272389      -1.817657
       B        0.093262       0.182262      -0.571474
       C        1.606277      -0.168974      -0.339398
       O       -0.706602       0.389738       0.588137
       C       -1.137205      -0.449494       1.540650
       O       -1.147426      -0.115164       2.699500
       C       -1.581876      -1.830420       1.088679
       C        2.456183      -0.376431      -1.437169
       C        3.803423      -0.675536      -1.267732
       C        4.297895      -0.770199       0.026667
       C        3.500685      -0.578253       1.145181
       C        2.153799      -0.278588       0.948526
       H       -0.925887      -3.677885      -0.647420
       H       -2.192340      -3.315842      -1.834384
       H       -2.638335      -3.950389      -0.230456
       H       -4.064831      -1.784667       0.191863
       H       -3.636604      -1.594702      -1.534908
       H       -2.353820      -2.166147       1.800688
       H       -0.707696      -2.480545       1.228578
       H        2.045610      -0.302481      -2.440264
       H        4.469850      -0.841254      -2.107398
       H        3.933483      -0.670828       2.135429
       H        1.518342      -0.123000       1.818566
       O       -2.919698       0.849028      -1.367535
       Na      -1.984964       2.398341       0.129976
       H       -1.380931       0.409379      -1.796847
       O        0.049519       2.897034      -0.561720
       H        0.047142       2.624322      -1.489311
       Na       1.962860       2.847338       0.359395
       F        5.597877      -1.057747       0.200883
---------------------------------------------------------
 Statistical Thermodynamic Analysis
 Temperature= 298.150 Kelvin       Pressure=
1.00000 Atm
======================================
 SCF Energy=     -1382.20015120    Predicted
Change= -1.763390D-08
 Zero-point correction (ZPE)=                -1381.9511
             0.24903
 Internal Energy (U)=                        -1381.9285
             0.27164
 Enthalpy (H)=                               -1381.9275
             0.27259
 Gibbs Free Energy (G)=                      -1382.0038
             0.19626
---------------------------------------------------------
 Frequencies --    -48.6560              29.2721
39.7512
```

10

```
---------------------------------------------------------
---------------------
 Using  Gaussian 09:  AM64L-G09RevD.01 24-
Apr-2013
======================================
======================================
====
 #M062X/6-31G(d)
scf=(maxcycle=300,direct,tight) density=current
 SCRF=(PCM,SOLVENT=THF)
opt=(maxcycle=250) freq=noraman
 #N Geom=AllCheck Guess=TCheck
SCRF=Check GenChk RM062X/6-31G(d) Freq
---------------------------------------------------------
---------------------
 Pointgroup= C1   Stoichiometry=
C11H14BFNNaO6   C1[X(C11H14BFNNaO6)]
#Atoms= 35
 Charge = 0     Multiplicity = 1
---------------------------------------------------------
---------------------
 SCF Energy= -1220.49689491     Predicted
Change= -4.483678D-08
```

```
=====================================
=====================================
====
 Optimization completed.          {Found       2
times}
 Item      Max Val.    Criteria    Pass?      RMS Val.
Criteria    Pass?
 Force      0.00004 ||  0.00045    [ YES ]      0.00000
||  0.00030   [ YES ]
 Displ      0.00161 ||  0.00180   [ YES ]      0.00161 ||
0.00180   [ YES ]
-------------------------------------------------------
---------------------
     Atomic         Coordinates (Angstroms)
      Type      X          Y       Z
-------------------------------------------------------
---------------------
       N      -3.609756    -1.024941    -0.628883
       C      -4.580940    -1.946631    -1.207975
       C      -3.604290    -1.193248     0.829281
       C      -2.627591    -0.211058     1.449971
       O      -1.419434    -0.727160     1.584092
       O       0.787369     2.033848    -1.273346
       B       0.785981     0.885210    -0.414466
       C       2.253511     0.257870    -0.220660
       O      -0.148059    -0.225678    -0.926859
       C      -1.411070     0.028493    -1.078984
       O      -1.897836     1.161580    -1.097571
       C      -2.292408    -1.210272    -1.227158
       C       3.373009     0.769213    -0.885715
       C       4.648748     0.236318    -0.700758
       C       4.792552    -0.833817     0.167347
       C       3.716985    -1.384246     0.848230
       C       2.457037    -0.826256     0.645137
       H      -4.646216    -1.775709    -2.285374
       H      -5.564145    -1.758640    -0.768380
       H      -4.319643    -3.004536    -1.033364
       H      -3.318195    -2.216811     1.124051
       H      -4.607160    -0.975210     1.202974
       H      -1.749487    -2.078586    -0.823531
       H      -2.426799    -1.372159    -2.302702
       H       3.238763     1.605506    -1.566620
       H       5.520766     0.630886    -1.212365
       H       3.878986    -2.224362     1.515793
       H       1.604765    -1.252904     1.172249
       O      -2.905745     0.947314     1.712180
       Na     -1.603136     2.592547     0.664835
       H      -0.108582     2.159229    -1.616675
       F       6.020770    -1.359631     0.358171
       H      -0.729635     0.015438     1.583036
       O       0.179977     1.198462     0.962007
       H       0.889103     1.489914     1.552364
-------------------------------------------------------
---------------------
 Statistical Thermodynamic Analysis
 Temperature= 298.150 Kelvin       Pressure=
1.00000 Atm
=====================================
=====================================
====
```

```
 SCF Energy=     -1220.49689491 Predicted
Change= -4.483678D-08
 Zero-point correction (ZPE)=        -1220.2338
0.26306
 Internal Energy (U)=               -1220.2135
0.28339
 Enthalpy (H)=                     -1220.2125   0.28433
 Gibbs Free Energy (G)=            -1220.2828
0.21404
-------------------------------------------------------
---------------------
 Frequencies --    28.1408              37.6213
44.5463
```

10$_{OH}$

```
-------------------------------------------------------
Using  Gaussian 09:  AM64L-G09RevD.01 24-Apr-
2013
=====================================
 #M062X/6-31G(d)
scf=(maxcycle=300,direct,tight) density=current
 SCRF=(PCM,SOLVENT=THF)
opt=(maxcycle=250) freq=noraman
 #N Geom=AllCheck Guess=TCheck
SCRF=Check GenChk RM062X/6-31G(d) Freq
-------------------------------------------------------
 Pointgroup= C1   Stoichiometry=
C11H13BFNNa2O6   C1[X(C11H13BFNNa2O6)]
#Atoms= 35
 Charge = 0        Multiplicity = 1
-------------------------------------------------------
 SCF Energy= -1382.24928037       Predicted
Change= -1.075261D-08
=====================================
 Optimization completed.          {Found       1
times}
 Item      Max Val.    Criteria    Pass?      RMS Val.
Criteria    Pass?
 Force      0.00001 ||  0.00045   [ YES ]      0.00000
||  0.00030   [ YES ]
 Displ      0.00327 ||  0.00180   [ NO ]      0.00327 ||
0.00180   [ YES ]
-------------------------------------------------------
     Atomic            Coordinates (Angstroms)
      Type             X              Y            Z
-------------------------------------------------------
       N       2.603500     0.765599     1.377657
       C       3.668302     0.766669     2.370770
       C       2.180321    -0.604106     1.074721
       C       3.173098    -1.230549     0.090902
       O       4.017049    -2.048782     0.519004
       O      -1.601723     2.150211    -1.398122
       B      -1.350448     0.929884    -0.700089
       C      -2.708334     0.172969    -0.270650
       O      -0.577536     1.213353     0.656741
       C       0.576978     1.780423     0.577445
       O       1.018248     2.356827    -0.426814
       C       1.480334     1.601312     1.791626
       C      -2.699716    -0.914616     0.613704
```

```
C      -3.863329     -1.599972      0.960532
C      -5.060552     -1.176819      0.405040
C      -5.129581     -0.104628     -0.470187
C      -3.947229      0.558363     -0.796597
H       4.052269      1.782245      2.499812
H       4.481547      0.123542      2.023944
H       3.326521      0.389382      3.350540
H       1.196203     -0.579697      0.594546
H       2.108630     -1.220507      1.985388
H       0.910604      1.170520      2.630533
H       1.871073      2.578846      2.090034
H      -1.757916     -1.232326      1.060452
H      -3.858526     -2.440773      1.646721
H      -6.091544      0.194747     -0.874170
H      -3.983214      1.406967     -1.474765
O       3.102191     -0.851146     -1.122602
Na      4.957863     -2.160088     -1.553612
H      -0.750871      2.607589     -1.470437
O      -0.424334      0.041414     -1.456438
H      -0.583390     -0.879047     -1.209446
Na      1.687066      0.720364     -1.885260
F      -6.197862     -1.829160      0.730368
---------------------------------------------------------
Statistical Thermodynamic Analysis
 Temperature= 298.150 Kelvin       Pressure=
1.00000 Atm
=====================================
 SCF Energy=     -1382.24928037    Predicted
Change= -1.075261D-08
 Zero-point correction (ZPE)=              -1381.9980
          0.25127
 Internal Energy (U)=                      -1381.9753
          0.27395
 Enthalpy (H)=                             -1381.9743
          0.27490
 Gibbs Free Energy (G)=                    -1382.0526
          0.19665
---------------------------------------------------------
 Frequencies --      8.1681              34.1009
43.5398
```

TS-11

```
---------------------------------------------------------
---------------------
 Using  Gaussian 09:  AM64L-G09RevD.01 24-
Apr-2013
=====================================
=====================================
====
 #M062X/6-31G(d)
scf=(maxcycle=300,direct,tight) density=current
 SCRF=(PCM,SOLVENT=THF)
opt=(maxcycle=250,ts,calcfc,noeigentest,gdiis)
 iop(1/8=18) freq=noraman
 #N Geom=AllCheck Guess=TCheck
SCRF=Check Test GenChk RM062X/6-31G(d)
Freq
---------------------------------------------------------
---------------------
 Pointgroup= C1   Stoichiometry=
C11H14BFNNaO6   C1[X(C11H14BFNNaO6)]
#Atoms= 35
 Charge = 0     Multiplicity = 1
---------------------------------------------------------
---------------------
 SCF Energy= -1220.47272964     Predicted
Change= -1.934700D-09
=====================================
=====================================
====
 Optimization completed.          {Found       2
times}
 Item      Max Val.    Criteria    Pass?      RMS Val.
Criteria    Pass?
 Force      0.00001 ||  0.00045   [ YES ]      0.00000
||  0.00030   [ YES ]
 Displ      0.00068 ||  0.00180   [ YES ]      0.00068 ||
0.00180   [ YES ]
---------------------------------------------------------
---------------------
     Atomic        Coordinates (Angstroms)
      Type      X          Y       Z
---------------------------------------------------------
---------------------
      N      -3.877602     -0.916266     -0.467105
      C      -4.997323     -1.750978     -0.887506
      C      -3.900000     -0.805049      0.993164
      C      -2.797782      0.131623      1.439776
      O      -1.666180     -0.512230      1.686273
      O       0.763228      1.546217     -1.536464
      B       1.075671      0.948584     -0.349219
      C       2.502886      0.332207     -0.125625
      O      -0.304812     -0.867519     -0.843069
      C      -1.458355     -0.436191     -1.033153
      O      -1.763781      0.773702     -1.294998
      C      -2.613779     -1.452644     -0.970291
      C       3.483394      0.471256     -1.117435
      C       4.764287     -0.046621     -0.954544
      C       5.052328     -0.724895      0.220786
      C       4.114582     -0.902448      1.226963
      C       2.843978     -0.365933      1.040662
      H      -5.031883     -1.787563     -1.979224
      H      -5.933902     -1.316579     -0.526594
      H      -4.923966     -2.784092     -0.504455
      H      -3.762167     -1.783110      1.485733
      H      -4.859032     -0.378944      1.296352
      H      -2.272044     -2.329195     -0.396695
      H      -2.784407     -1.781654     -2.002037
      H       3.231974      0.997403     -2.033893
      H       5.532377      0.061460     -1.712706
      H       4.385314     -1.451449      2.122233
      H       2.100120     -0.518343      1.820262
      O      -2.909379      1.342924      1.502199
      Na     -1.586633      2.538208      0.080197
      H      -0.207821      1.413222     -1.678746
      F       6.286212     -1.232118      0.390112
      H      -0.908012      0.114532      1.594401
      O       0.286831      1.257125      0.806357
      H       0.862832      1.360298      1.578861
```

```
---------------------------------------------------------
---------------------
 Statistical Thermodynamic Analysis
 Temperature= 298.150 Kelvin       Pressure=
1.00000 Atm
=====================================
=====================================
====
 SCF Energy=     -1220.47272964 Predicted
Change= -1.934700D-09
 Zero-point correction (ZPE)=        -1220.2106
0.26210
 Internal Energy (U)=               -1220.1902
0.28243
 Enthalpy (H)=                  -1220.1893   0.28337
 Gibbs Free Energy (G)=           -1220.2603
0.21240
---------------------------------------------------------
---------------------
 Frequencies --   -133.9353              25.6992
32.8212
```

TS-11$_{OH}$

```
---------------------------------------------------------
 Using  Gaussian 09:  AM64L-G09RevD.01 24-
Apr-2013
=====================================
 #M062X/6-31G(d)
scf=(maxcycle=300,direct,tight) density=current
 SCRF=(PCM,SOLVENT=THF)
opt=(maxcycle=250,ts,calcfc,noeigentest)
 freq=noraman
 #N Geom=AllCheck Guess=TCheck
SCRF=Check GenChk RM062X/6-31G(d) Freq
---------------------------------------------------------
 Pointgroup= C1   Stoichiometry=
C11H13BFNNa2O6   C1[X(C11H13BFNNa2O6)]
#Atoms= 35
 Charge = 0         Multiplicity = 1
---------------------------------------------------------
SCF Energy= -1382.24460597        Predicted
Change= -1.030962D-08
=====================================
 Optimization completed.          {Found       2
times}
 Item      Max Val.    Criteria    Pass?      RMS Val.
Criteria    Pass?
 Force      0.00000 ||  0.00045    [ YES ]       0.00000
||  0.00030   [ YES ]
 Displ      0.00064 ||  0.00180    [ YES ]       0.00064 ||
0.00180   [ YES ]
---------------------------------------------------------
      Atomic               Coordinates (Angstroms)
       Type              X                Y            Z
---------------------------------------------------------
N       -0.821025      -1.821552       0.848002
      C        0.197731      -2.699284       1.387186
      C       -1.848012      -2.519669       0.084369
      C       -2.614998      -1.469254      -0.728292
      O       -3.674699      -1.008245      -0.230735
      O       -0.877968       1.387388      -1.969100
      B        0.054498       1.637153      -0.959190
      C        1.313239       0.700024      -0.739544
      O       -1.120087       1.126233       0.564555
      C       -0.728059       0.487036       1.617907
      O        0.106386       0.939777       2.417461
      C       -1.341586      -0.892560       1.848217
      C        2.519735       1.218315      -0.252716
      C        3.654714       0.424920      -0.094061
      C        3.568121      -0.911192      -0.448395
      C        2.402045      -1.471582      -0.948426
      C        1.279496      -0.659641      -1.084978
      H        0.993523      -2.096007       1.835888
      H        0.641100      -3.286884       0.577716
      H       -0.192081      -3.393816       2.153331
      H       -2.543487      -3.088358       0.725236
      H       -1.345353      -3.210144      -0.599446
      H       -2.428153      -0.808786       1.746714
      H       -1.107406      -1.225942       2.867209
      H        2.584439       2.275776      -0.005579
      H        4.591656       0.822472       0.281520
      H        2.389460      -2.522211      -1.220366
      H        0.353737      -1.098611      -1.449805
      O       -2.078972      -1.052661      -1.794872
      Na      -2.928919       1.051123      -0.886290
      H       -1.027841       0.425641      -2.094109
      O        0.267776       3.009622      -0.686131
      H       -0.419463       3.534140      -1.123086
      Na       0.171866       3.040933       1.588122
      F        4.657566      -1.692709      -0.312495
---------------------------------------------------------
Statistical Thermodynamic Analysis
 Temperature= 298.150 Kelvin       Pressure=
1.00000 Atm
=====================================
 SCF Energy=     -1382.24460597    Predicted
Change= -1.030962D-08
 Zero-point correction (ZPE)=                -1381.9931
              0.25144
 Internal Energy (U)=                         -1381.9714
              0.27317
 Enthalpy (H)=                               -1381.9704
              0.27412
 Gibbs Free Energy (G)=                      -1382.0433
              0.20130
---------------------------------------------------------
 Frequencies --   -210.2444              38.7881
45.1539
```

2+3

```
---------------------------------------------------------
 Using  Gaussian 09:  AM64L-G09RevD.01 24-
Apr-2013
=====================================
 #M062X/6-31G(d)
scf=(maxcycle=300,direct,tight) density=current
 SCRF=(PCM,SOLVENT=THF)
opt=(maxcycle=250) freq=noraman
```

```
 #N Geom=AllCheck Guess=TCheck
SCRF=Check GenChk RM062X/6-31G(d) Freq
-------------------------------------------------------
 Pointgroup= C1   Stoichiometry=
C11H13BFNNa2O6   C1[X(C11H13BFNNa2O6)]
#Atoms= 35
 Charge = 0          Multiplicity = 1
-------------------------------------------------------
 SCF Energy= -1382.27440700        Predicted
Change= -1.083996D-07
=======================================
 Optimization completed.           {Found        1
times}
 Item      Max Val.    Criteria    Pass?     RMS Val.
Criteria    Pass?
 Force      0.00004 ||  0.00045   [ YES ]       0.00000
||  0.00030   [ YES ]
 Displ      0.00390 ||  0.00180   [ NO ]       0.00390 ||
0.00180   [ YES ]
-------------------------------------------------------
      Atomic              Coordinates (Angstroms)
       Type              X                Y            Z
-------------------------------------------------------
       N       -4.176450      -0.256460      0.058205
       C       -5.611734      -0.502672      0.199659
       C       -3.482492      -0.545405      1.322176
       C       -1.983695      -0.839965      1.117859
       O       -1.716558      -1.816177      0.351816
       O        0.659900       0.716336     -0.705589
       B        1.382641      -0.428694     -0.451575
       C        2.940418      -0.259287     -0.276524
       C       -2.480182       1.413503     -0.659144
       O       -1.933836       2.399879     -0.126569
       C       -3.956712       1.138838     -0.337678
       C        3.731800      -1.343748      0.126840
       C        5.106052      -1.219666      0.307700
       C        5.686675       0.019229      0.078844
       C        4.950322       1.123654     -0.323165
       C        3.577722       0.969351     -0.498907
       H       -6.065817       0.125421      0.983411
       H       -5.780060      -1.552360      0.453488
       H       -6.112818      -0.287466     -0.748192
       H       -3.924862      -1.450686      1.750731
       H       -3.606542       0.276699      2.043569
       H       -4.544792       1.336744     -1.241482
       H       -4.286892       1.835103      0.448766
       H        3.254561      -2.303851      0.301942
       H        5.726889      -2.052718      0.619924
       H        5.452963       2.070173     -0.491351
       H        2.984939       1.822368     -0.818946
       O       -1.146496      -0.131370      1.711374
       Na      -0.192412       1.806162      1.158743
       H       -0.278593       0.581502     -1.016058
       Na      -2.786877      -1.494786     -1.582414
       O        0.853495      -1.670279     -0.325346
       H       -0.119498      -1.695127     -0.108616
       O       -1.916760       0.587798     -1.443129
       F        7.014184       0.155030      0.254135
-------------------------------------------------------
 Statistical Thermodynamic Analysis
 Temperature= 298.150 Kelvin       Pressure=
1.00000 Atm
=======================================
 SCF Energy=     -1382.27440700    Predicted
Change= -1.083996D-07
 Zero-point correction (ZPE)=              -1382.0226
              0.25178
 Internal Energy (U)=                      -1382.0002
              0.27412
 Enthalpy (H)=                             -1381.9993
              0.27506
 Gibbs Free Energy (G)=                    -1382.0755
              0.19884
-------------------------------------------------------
 Frequencies --     26.7532               28.4982
49.5303
```

4. Fast-Release Hydrolysis: Alternative Mechanism after First Hydroxide Attack

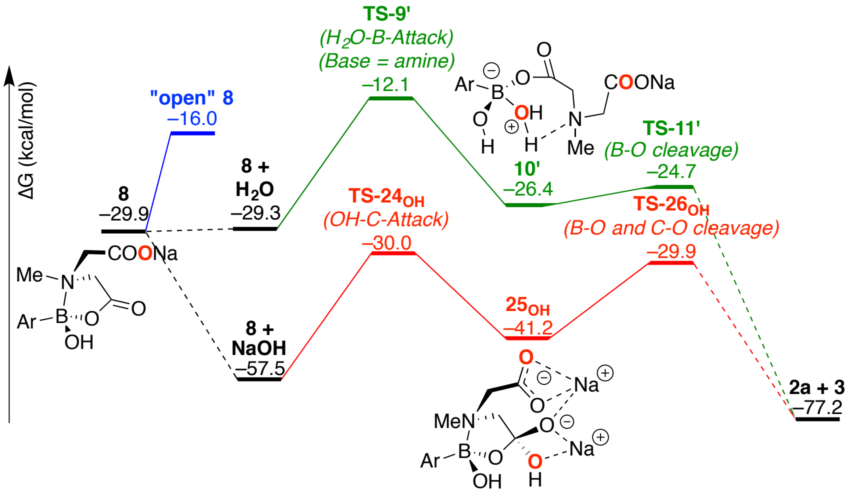


Figure 35. Alternate hydrolysis pathway after the first hydroxide attack.

MIDA amine-mediated water attack of 8 + H_2O: Water attack at the boron, mediated by the MIDA amine (**TS-9’**) forms the boron-hydrolyzed intermediate **10’**. B-O bond cleavage releases **2a** and **3**. The MIDA amine mediated second stage hydrolysis is disfavoured over the MIDA carboxylate-mediated process by 2.1 kcal/mol. However, this pathway results in single incorporation of ^{18}O into MIDA after hydrolysis, consistent with observations.

NaOH attack of 8 + NaOH: The second hydroxide attack at the bound MIDA ester carbonyl (**TS-24**) forms the ester-hydrolyzed intermediate **25**. Concurrent boronate and enolate tetrahedral collapse releases **2a** and **3**. The C-attack **TS-24** is disfavoured over the hydroxide Backside-S_N2-Attack **TS-9** by 2.2 kcal/mol. This pathway would also result in double incorporation of ^{18}O into MIDA after hydrolysis; an outcome inconsistent with observations.

B-N dissociation to “open” 8: The B-N bond in intermediate **8** is more labile than in MIDA **1a** (**$\Delta G_{\text{“open” – “closed” } \mathbf{8}}$** = 13.9 kcal/mol). Consequent attack at the boron with either hydroxide or water ultimately leads to **2a** and **3**.

Geometries, Energies, and Thermal Corrections

TS-9’

```
--------------------------------------------------------
---------------------
 Using  Gaussian 09:  AM64L-G09RevD.01 24-
Apr-2013
========================================
========================================
====
 #M062X/6-31G(d)
scf=(maxcycle=300,direct,tight) density=current
 SCRF=(PCM,SOLVENT=THF)
opt=(maxcycle=250,ts,calcfc,noeigentest,gdiis)
 iop(1/8=18) freq=noraman
 #N Geom=AllCheck Guess=TCheck
SCRF=Check Test GenChk RM062X/6-31G(d)
Freq
--------------------------------------------------------
---------------------
 Pointgroup= C1   Stoichiometry=
C11H14BFNNaO6   C1[X(C11H14BFNNaO6)]
#Atoms= 35
```

```
 Charge = 0     Multiplicity = 1
---------------------------------------------------------
---------------------
 SCF Energy= -1220.46771694     Predicted
Change= -1.523254D-08
=====================================
=====================================
====
 Optimization completed.           {Found       1
times}
 Item      Max Val.    Criteria    Pass?     RMS Val.
Criteria    Pass?
 Force      0.00002 ||  0.00045   [ YES ]      0.00000
||  0.00030   [ YES ]
 Displ      0.00228 ||  0.00180   [ NO ]       0.00228 ||
0.00180   [ YES ]
---------------------------------------------------------
---------------------
     Atomic        Coordinates (Angstroms)
      Type      X           Y       Z
---------------------------------------------------------
---------------------
      C       1.738721      1.130496      1.447199
      C       0.948922     -0.171430      1.486752
      B      -0.387565     -0.400653     -0.707525
      N       2.268659      1.563949      0.157956
      C      -1.901538     -0.244888     -0.371554
      C      -2.387515     -0.460082      0.924427
      C      -2.816342      0.105885     -1.374555
      C      -3.740559     -0.321994      1.222889
      H      -1.700580     -0.746023      1.717269
      C      -4.171473      0.250103     -1.102063
      H      -2.458160      0.268838     -2.387871
      C      -4.604416      0.034202      0.199175
      H      -4.131404     -0.483711      2.221585
      H      -4.889500      0.524444     -1.867360
      O       0.549257     -0.688118      0.309455
      O       0.716408     -0.728543      2.527021
      C       3.468423      0.823974     -0.264961
      C       3.162211     -0.665123     -0.434820
      O       0.065049     -0.536174     -1.974405
      O       3.326455     -1.395271      0.569728
      H       2.523144      1.034284      2.213221
      H       1.038359      1.898185      1.798372
      H       4.272867      0.942183      0.477351
      H       3.792429      1.242317     -1.220635
      C       2.595751      2.994054      0.231764
      H       2.972426      3.323938     -0.739108
      H       1.692145      3.562441      0.465712
      H       3.360309      3.200305      0.996302
      O      -0.137454      2.165979     -1.020062
      H      -0.321472      1.874728     -1.924910
      F      -5.912609      0.172567      0.474848
      H       0.787391      1.868559     -0.852020
      O       2.691287     -1.059420     -1.544753
      H       1.053120     -0.620206     -1.972844
      Na      1.803499     -2.846052     -0.317103
---------------------------------------------------------
---------------------
 Statistical Thermodynamic Analysis
 Temperature= 298.150 Kelvin       Pressure=
1.00000 Atm
=====================================
=====================================
====
 SCF Energy=     -1220.46771694 Predicted
Change= -1.523254D-08
 Zero-point correction (ZPE)=        -1220.2062
0.26146
 Internal Energy (U)=               -1220.1852
0.28250
 Enthalpy (H)=                    -1220.1842   0.28344
 Gibbs Free Energy (G)=           -1220.2568
0.21082
---------------------------------------------------------
---------------------
 Frequencies --    -39.8173              27.7342
39.4198
```

10’

```
---------------------------------------------------------
---------------------
 Using  Gaussian 09:  AM64L-G09RevD.01 24-
Apr-2013
=====================================
=====================================
====
 #M062X/6-31G(d)
scf=(maxcycle=300,direct,tight) density=current
 SCRF=(PCM,SOLVENT=THF)
opt=(maxcycle=250) freq=noraman
 #N Geom=AllCheck Guess=TCheck
SCRF=Check GenChk RM062X/6-31G(d) Freq
---------------------------------------------------------
---------------------
 Pointgroup= C1   Stoichiometry=
C11H14BFNNaO6   C1[X(C11H14BFNNaO6)]
#Atoms= 35
 Charge = 0     Multiplicity = 1
---------------------------------------------------------
---------------------
 SCF Energy= -1220.49489719     Predicted
Change= -3.125941D-07
=====================================
=====================================
====
 Optimization completed.           {Found       1
times}
 Item      Max Val.    Criteria    Pass?     RMS Val.
Criteria    Pass?
 Force      0.00009 ||  0.00045   [ YES ]      0.00001
||  0.00030   [ YES ]
 Displ      0.00482 ||  0.00180   [ NO ]       0.00482 ||
0.00180   [ YES ]
---------------------------------------------------------
---------------------
     Atomic        Coordinates (Angstroms)
      Type      X           Y       Z
```

```
---------------------------------------------------------
---------------------
      C      -1.605993    -1.812963     0.629067
      C      -0.959351    -0.633954     1.368155
      B       0.369739     0.316480    -0.730687
      N      -2.562062    -1.366711    -0.431866
      C       1.938727     0.120023    -0.415919
      C       2.429878    -1.116070     0.025902
      C       2.864926     1.158606    -0.568050
      C       3.776936    -1.319984     0.315964
      H       1.740978    -1.951565     0.141701
      C       4.220806     0.987993    -0.288178
      H       2.515826     2.124850    -0.923156
      C       4.648541    -0.253983     0.152208
      H       4.157828    -2.275906     0.660470
      H       4.942081     1.790060    -0.407326
      O      -0.393986     0.303980     0.653227
      O      -1.029373    -0.601170     2.579319
      C      -3.640957    -0.479119     0.112556
      C      -3.149794     0.984755     0.041889
      O       0.096957     1.625593    -1.285639
      O      -3.230644     1.675623     1.075527
      H      -2.158115    -2.414185     1.351867
      H      -0.839901    -2.410513     0.134067
      H      -3.874240    -0.792654     1.130578
      H      -4.520674    -0.594122    -0.523858
      C      -3.092115    -2.543897    -1.171229
      H      -3.731260    -2.186743    -1.978070
      H      -2.247303    -3.099862    -1.578755
      H      -3.664222    -3.167242    -0.482730
      O      -0.220879    -0.777876    -1.508189
      H       0.230821    -0.847150    -2.359595
      F       5.957452    -0.433959     0.427566
      H      -1.983899    -0.813649    -1.105317
      O      -2.660595     1.316137    -1.068125
      H      -0.805553     1.575046    -1.649685
      Na     -1.125015     2.551556     0.512279
---------------------------------------------------------
---------------------
 Statistical Thermodynamic Analysis
 Temperature= 298.150 Kelvin       Pressure=
1.00000 Atm
======================================
======================================
====
 SCF Energy=     -1220.49489719 Predicted
Change= -3.125941D-07
 Zero-point correction (ZPE)=         -1220.2300
0.26482
 Internal Energy (U)=              -1220.2093
0.28552
 Enthalpy (H)=                  -1220.2084   0.28647
 Gibbs Free Energy (G)=           -1220.2797
0.21513
---------------------------------------------------------
---------------------
 Frequencies --     32.9718              38.8499
48.5379
```

TS-11’

```
---------------------------------------------------------
---------------------
 Using  Gaussian 09:  AM64L-G09RevD.01 24-
Apr-2013
======================================
======================================
====
 #M062X/6-31G(d)
scf=(maxcycle=300,direct,tight) density=current
 SCRF=(PCM,SOLVENT=THF)
opt=(maxcycle=250,ts,calcfc,noeigentest,gdiis)
 iop(1/8=18) freq=noraman
 #N Geom=AllCheck Guess=TCheck
SCRF=Check Test GenChk RM062X/6-31G(d)
Freq
---------------------------------------------------------
---------------------
 Pointgroup= C1   Stoichiometry=
C11H14BFNNaO6   C1[X(C11H14BFNNaO6)]
#Atoms= 35
 Charge = 0     Multiplicity = 1
---------------------------------------------------------
---------------------
 SCF Energy= -1220.49212460     Predicted
Change= -3.874607D-10
======================================
======================================
====
 Optimization completed.          {Found       2
times}
 Item      Max Val.    Criteria    Pass?      RMS Val.
Criteria    Pass?
 Force      0.00000 ||  0.00045   [ YES ]      0.00000
||  0.00030   [ YES ]
 Displ      0.00038 ||  0.00180   [ YES ]      0.00038 ||
0.00180   [ YES ]
---------------------------------------------------------
---------------------
     Atomic        Coordinates (Angstroms)
      Type      X          Y      Z
---------------------------------------------------------
---------------------
      C      -1.792825    -2.072780     0.362466
      C      -0.703358    -1.307427     1.142849
      B       0.287649     0.481577    -0.871333
      N      -2.712467    -1.158231    -0.368392
      C       1.819308     0.221708    -0.548215
      C       2.319585    -1.061740    -0.286818
      C       2.727431     1.287659    -0.529821
      C       3.667156    -1.284556    -0.018309
      H       1.644288    -1.915789    -0.270109
      C       4.081940     1.095576    -0.264108
      H       2.365440     2.291768    -0.735470
      C       4.523853    -0.193616    -0.013514
      H       4.058728    -2.274597     0.189887
      H       4.790477     1.917165    -0.252280
      O      -0.544430    -0.072746     0.816701
      O      -0.087808    -1.941368     1.986859
```

```
      C      -3.402873     -0.179488      0.541600
      C      -2.993599      1.243184      0.105390
      O      -0.133008      1.813590     -0.845882
      O      -2.853687      2.093513      1.009503
      H      -2.380995     -2.689315      1.044819
      H      -1.315568     -2.723867     -0.375361
      H      -3.109028     -0.374316      1.571809
      H      -4.481996     -0.317484      0.443970
      C      -3.665050     -1.893154     -1.241801
      H      -4.248758     -1.153516     -1.789750
      H      -3.097802     -2.513654     -1.936142
      H      -4.312828     -2.513004     -0.620778
      O      -0.384037     -0.378497     -1.772143
      H       0.183135     -1.108415     -2.054406
      F       5.830494     -0.394858      0.243715
      H      -2.114889     -0.587109     -1.001105
      O      -2.808681      1.375755     -1.128020
      H      -1.060287      1.863434     -1.171966
      Na     -0.621959      2.099816      1.424037
-------------------------------------------------------
---------------------
 Statistical Thermodynamic Analysis
 Temperature= 298.150 Kelvin       Pressure=
1.00000 Atm
=====================================
=====================================
====
 SCF Energy=     -1220.49212460 Predicted
Change= -3.874607D-10
 Zero-point correction (ZPE)=        -1220.2278
0.26424
 Internal Energy (U)=               -1220.2076
0.28442
 Enthalpy (H)=                   -1220.2067   0.28537
 Gibbs Free Energy (G)=           -1220.2770
0.21506
-------------------------------------------------------
---------------------
 Frequencies --   -207.2653              28.4388
41.6082
```

TS-24$_{OH}$

```
-------------------------------------------------------
Using  Gaussian 09:  AM64L-G09RevD.01 24-Apr-
2013
=====================================
#M062X/6-31G(d) scf=(maxcycle=300,direct,tight)
density=current
 SCRF=(PCM,SOLVENT=THF)
opt=(maxcycle=250,ts,calcfc,noeigentest,gdiis)
 iop(1/8=18) freq=noraman
 #N Geom=AllCheck Guess=TCheck
SCRF=Check Test GenChk RM062X/6-31G(d)
Freq
-------------------------------------------------------
Pointgroup= C1   Stoichiometry=
C11H13BFNNa2O6   C1[X(C11H13BFNNa2O6)]
#Atoms= 35
 Charge = 0         Multiplicity = 1
-------------------------------------------------------
 SCF Energy= -1382.20301864       Predicted
Change= -3.903319D-08
=====================================
 Optimization completed.          {Found       2
times}
 Item      Max Val.    Criteria    Pass?     RMS Val.
Criteria    Pass?
 Force      0.00008 ||  0.00045   [ YES ]      0.00001
||  0.00030   [ YES ]
 Displ      0.00170 ||  0.00180   [ YES ]      0.00170 ||
0.00180   [ YES ]
-------------------------------------------------------
Atomic       Coordinates (Angstroms)
     Type             X              Y           Z
-------------------------------------------------------
N        -0.403250      -0.922877       1.066070
     C        0.599861      -1.234127       2.110360
     C       -1.421155      -2.024796       1.086366
     C       -2.666506      -1.686733       0.243584
     O       -3.629172      -1.155747       0.840110
     O        0.115110      -1.937783      -1.257600
     B        0.312893      -0.753112      -0.535329
     C        1.860940      -0.362385      -0.401001
     O       -0.576807       0.370877      -1.005500
     C       -1.361357       0.916522      -0.111327
     O       -2.444491       1.450008      -0.418240
     C       -1.035456       0.403602       1.290429
     C        2.837770      -1.322256      -0.697189
     C        4.199801      -1.049034      -0.583151
     C        4.579872       0.214766      -0.160452
     C        3.654377       1.200754       0.143233
     C        2.297825       0.903527       0.018203
     H        1.345054      -0.440716       2.144257
     H        1.091315      -2.174559       1.850431
     H        0.106350      -1.329066       3.081873
     H       -1.735447      -2.173105       2.122830
     H       -0.926328      -2.919721       0.706936
     H       -1.933783       0.321978       1.905835
     H       -0.307401       1.082534       1.730327
     H        2.519790      -2.305891      -1.032421
     H        4.959794      -1.788954      -0.812928
     H        4.001896       2.176678       0.467403
     H        1.559659       1.672278       0.253800
     O       -2.609873      -1.897781      -1.001722
     Na      -3.999045      -0.030203      -1.182293
     H       -0.847596      -2.062672      -1.395993
     Na      -2.197293       3.646062       0.099271
     O       -0.216979       2.835697       0.274663
     H        0.151962       2.862435      -0.621019
     F        5.894955       0.494314      -0.040216
-------------------------------------------------------
 Statistical Thermodynamic Analysis
 Temperature= 298.150 Kelvin       Pressure=
1.00000 Atm
=====================================
 SCF Energy=     -1382.20301864    Predicted
Change= -3.903319D-08
 Zero-point correction (ZPE)=              -1381.9511
            0.25184
```

```
 Internal Energy (U)=                    -1381.9300
          0.27300
 Enthalpy (H)=                          -1381.9290
          0.27394
 Gibbs Free Energy (G)=                 -1382.0003
          0.20263
-------------------------------------------------------
 Frequencies --   -227.9753             43.5680
44.8043
```

25$_{OH}$

```
-------------------------------------------------------
---------------------
 Using  Gaussian 09:  AM64L-G09RevD.01 24-
Apr-2013
=======================================
 #M062X/6-31G(d)
scf=(maxcycle=300,direct,tight) density=current
 SCRF=(PCM,SOLVENT=THF)
opt=(maxcycle=250) freq=noraman
 #N Geom=AllCheck Guess=TCheck
SCRF=Check GenChk RM062X/6-31G(d) Freq
-------------------------------------------------------
---------------------
 Pointgroup= C1   Stoichiometry=
C11H13BFNNa2O6   C1[X(C11H13BFNNa2O6)]
#Atoms= 35
 Charge = 0         Multiplicity = 1
-------------------------------------------------------
 SCF Energy= -1382.22522952       Predicted
Change= -4.238245D-08
=======================================
 Optimization completed.          {Found       1
times}
 Item     Max Val.   Criteria    Pass?     RMS Val.
Criteria    Pass?
 Force     0.00002 ||  0.00045   [ YES ]      0.00000
||  0.00030   [ YES ]
 Displ     0.00277 ||  0.00180   [ NO ]      0.00277 ||
0.00180   [ YES ]
-------------------------------------------------------
     Atomic               Coordinates (Angstroms)
      Type              X               Y            Z
-------------------------------------------------------
       N      -0.701066    -1.174395     1.023615
       C       0.159394    -1.820305     2.036260
       C      -1.802814    -2.143093     0.709685
       C      -2.872830    -1.555099    -0.235290
       O      -3.781585    -0.877909     0.287088
       O      -0.015725    -1.766582    -1.415110
       B       0.117757    -0.712929    -0.490498
       C       1.699159    -0.394952    -0.272044
       O      -0.709697     0.467895    -0.749179
       C      -1.134322     1.187287     0.398702
       O      -2.224893     1.890438     0.172451
       C      -1.238499     0.119610     1.537603
       C       2.627316    -1.377428     0.113528
       C       3.998065    -1.141240     0.148873
       C       4.462459     0.108489    -0.234986
       C       3.605778     1.104258    -0.667429
       C       2.235671     0.834540    -0.686052
       H       1.005513    -1.170216     2.261027
       H       0.525873    -2.769783     1.641556
       H      -0.415297    -2.009629     2.948648
       H      -2.283763    -2.419044     1.653491
       H      -1.334009    -3.017078     0.255934
       H      -2.284401     0.002453     1.822511
       H      -0.651669     0.425991     2.405912
       H       2.277904    -2.372150     0.375357
       H       4.705781    -1.905147     0.454175
       H       4.009031     2.057420    -0.993840
       H       1.561575     1.602054    -1.058033
       O      -2.721951    -1.740381    -1.478953
       Na     -3.026669     0.621196    -1.486648
       H      -0.964986    -1.864134    -1.647409
       O      -0.085299     2.136209     0.776407
       Na     -1.410983     3.923412     0.422131
       H       0.763830     1.672807     0.854327
       F       5.788268     0.350156    -0.201280
-------------------------------------------------------
 Statistical Thermodynamic Analysis
 Temperature= 298.150 Kelvin       Pressure=
1.00000 Atm
=======================================
SCF Energy=    -1382.22522952     Predicted
Change= -4.238245D-08
 Zero-point correction (ZPE)=            -1381.9700
          0.25515
 Internal Energy (U)=                    -1381.9496
          0.27554
 Enthalpy (H)=                          -1381.9487
          0.27649
 Gibbs Free Energy (G)=                 -1382.0182
          0.20702
-------------------------------------------------------
 Frequencies --     37.1186             47.9118
57.7289
```

TS-26$_{OH}$

```
-------------------------------------------------------
 Using  Gaussian 09:  AM64L-G09RevD.01 24-
Apr-2013
=======================================
 #M062X/6-31G(d)
scf=(maxcycle=300,direct,tight) density=current
 SCRF=(PCM,SOLVENT=THF)
opt=(maxcycle=250,ts,calcfc,noeigentest)
 freq=noraman
 #N Geom=AllCheck Guess=TCheck
SCRF=Check GenChk RM062X/6-31G(d) Freq
-------------------------------------------------------
Pointgroup= C1   Stoichiometry=
C11H13BFNNa2O6   C1[X(C11H13BFNNa2O6)]
#Atoms= 35
 Charge = 0         Multiplicity = 1
-------------------------------------------------------
 SCF Energy= -1382.20335026       Predicted
Change= -5.502870D-09
```

```
=====================================
 Optimization completed.          {Found       2
times}
 Item      Max Val.    Criteria    Pass?      RMS Val.
Criteria    Pass?
 Force      0.00002 ||  0.00045    [ YES ]       0.00000
||  0.00030    [ YES ]
 Displ      0.00068 ||  0.00180    [ YES ]       0.00068 ||
0.00180    [ YES ]
-----------------------------------------------------
Atomic        Coordinates (Angstroms)
      Type              X                 Y            Z
-----------------------------------------------------
N        -0.777098      -1.300120       1.001365
      C       0.181139     -2.073439      1.780939
      C      -1.802897     -2.200589      0.445450
      C      -2.903035     -1.442623     -0.321155
      O      -3.796105     -0.882286      0.359661
      O      -0.195387     -1.102883     -1.997350
      B       0.090565     -0.086167     -1.112769
      C       1.645200     -0.040715     -0.713195
      O      -0.816539      0.862409     -0.741882
      C      -1.147721      1.224841      1.123722
      O      -2.105733      2.015217      1.038108
      C      -1.328939     -0.175020      1.748268
      C       2.342883     -1.258586     -0.630309
      C       3.689816     -1.325743     -0.293373
      C       4.364938     -0.137985     -0.047247
      C       3.741359      1.094252     -0.134918
      C       2.385435      1.125176     -0.467873
      H       1.002146     -1.427311      2.106933
      H       0.604912     -2.862561      1.153264
      H      -0.276280     -2.543279      2.668066
      H      -2.288893     -2.777008      1.250313
      H      -1.295899     -2.891706     -0.233157
      H      -2.401429     -0.295000      1.908973
      H      -0.845382     -0.108279      2.730574
      H       1.803933     -2.176825     -0.845957
      H       4.222686     -2.268458     -0.223832
      H       4.310603      1.999400      0.048732
      H       1.911246      2.100491     -0.553362
      O      -2.817984     -1.355318     -1.580774
      Na     -3.125541      0.957341     -0.912266
      H      -1.174352     -1.227393     -2.028961
      O       0.070938      1.819224      1.397448
      Na     -0.704174      3.128360     -0.534213
      H       0.783252      1.169505      1.249721
      F       5.670509     -0.187880      0.276747
-----------------------------------------------------
 Statistical Thermodynamic Analysis
 Temperature= 298.150 Kelvin       Pressure=
1.00000 Atm
=====================================
 SCF Energy=     -1382.20335026    Predicted
Change= -5.502870D-09
 Zero-point correction (ZPE)=              -1381.9514
            0.25194
 Internal Energy (U)=                      -1381.9302
            0.27314
 Enthalpy (H)=                             -1381.9292
            0.27408
 Gibbs Free Energy (G)=                    -1382.0002
            0.20311
-----------------------------------------------------
 Frequencies --    -237.3512              42.7925
54.6157
```

“open” 8

```
-----------------------------------------------------------------------
-----

 Using  Gaussian 09:  AM64L-G09RevD.01 24-Apr-2013

============================================
================================

 #M062X/6-31G(d) scf=(maxcycle=300,direct,tight)
density=current

 SCRF=(PCM,SOLVENT=THF) opt=(maxcycle=250)
freq=noraman

 #N Geom=AllCheck Guess=TCheck SCRF=Check
GenChk RM062X/6-31G(d) Freq

-----------------------------------------------------------------------
-----

 Pointgroup= C1   Stoichiometry= C11H12BFNNaO5
C1[X(C11H12BFNNaO5)]  #Atoms= 32

 Charge = 0     Multiplicity = 1

-----------------------------------------------------------------------
-----

 SCF Energy= -1144.07301893     Predicted Change= -
4.207160D-08

============================================
================================

 Optimization completed.          {Found       2
times}

 Item     Max Val.    Criteria    Pass?    RMS Val.
Criteria    Pass?

 Force     0.00003 ||  0.00045   [ YES ]     0.00000 ||
0.00030   [ YES ]

 Displ     0.00169 ||  0.00180   [ YES ]     0.00169 ||
0.00180   [ YES ]

-----------------------------------------------------------------------
-----

     Atomic        Coordinates (Angstroms)
```

Type	X	Y	Z
N	3.489071	-1.277763	0.411434
C	4.233391	-2.485234	0.750918
C	3.855079	-0.830109	-0.937740
C	3.213856	0.532566	-1.221942
O	1.986748	0.529749	-1.530719
O	-0.804365	1.684291	1.443547
B	-1.047487	0.505567	0.825492
C	-2.479729	0.136817	0.348368
O	-0.035850	-0.446335	0.585852
C	1.268393	-0.251459	0.832822
O	1.709317	0.777222	1.313708
C	2.065352	-1.502611	0.539983
C	-3.553825	0.993878	0.630031
C	-4.847842	0.688597	0.225053
C	-5.053009	-0.493961	-0.471732
C	-4.022994	-1.373125	-0.774882
C	-2.737349	-1.047065	-0.357090
H	4.001255	-2.785335	1.776456
H	5.304275	-2.276471	0.687437
H	4.004949	-3.329223	0.076683
H	3.526910	-1.562303	-1.697630
H	4.942169	-0.733647	-0.977455
H	1.614168	-1.987368	-0.340616
H	1.880804	-2.162487	1.398126
H	-3.369995	1.913868	1.178018
H	-5.689514	1.338638	0.437092
H	-4.240044	-2.283562	-1.322555
H	-1.917361	-1.723048	-0.582518
O	3.906427	1.562742	-1.036465
Na	1.961067	2.582246	-0.468139
H	0.124989	1.729409	1.733605
F	-6.298505	-0.799753	-0.868305

Statistical Thermodynamic Analysis

Temperature= 298.150 Kelvin Pressure= 1.00000 Atm

===

SCF Energy= -1144.07301893 Predicted Change= -4.207160D-08

Zero-point correction (ZPE)= -1143.8366 0.23632

Internal Energy (U)= -1143.8173 0.25567

Enthalpy (H)= -1143.8163 0.25662

Gibbs Free Energy (G)= -1143.8865 0.18647

Frequencies -- 24.4516 36.8636 47.3497

5. NaOH Mediated Hydrolysis: S_N2-B-Attack-First Pathway

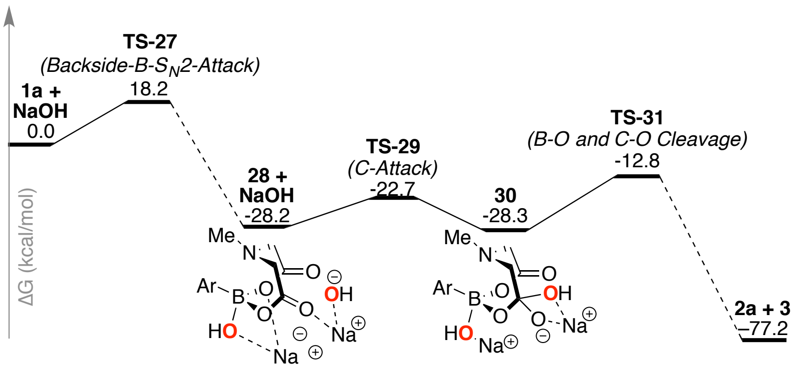


Figure 36. *B-attack-first pathway for the NaOH mediated hydrolysis of MIDA boronate **1a**.*

Geometries, Energies, and Thermal Corrections

TS-27

```
-------------------------------------------------------------
-----------------
 Using  Gaussian 09:  AM64L-G09RevD.01 24-Apr-
2013
=========================================
========================================
 #M062X/6-31G(d) scf=(maxcycle=300,direct,tight)
density=current
 SCRF=(PCM,SOLVENT=THF)
opt=(maxcycle=250,ts,calcfc,noeigentest,gdiis)
 iop(1/8=18) freq=noraman
 #N Geom=AllCheck Guess=TCheck SCRF=Check
Test GenChk RM062X/6-31G(d) Freq
-------------------------------------------------------------
-----------------
 Pointgroup= C1   Stoichiometry= C11H12BFNNaO5
C1[X(C11H12BFNNaO5)]  #Atoms= 32
 Charge = 0          Multiplicity = 1
-------------------------------------------------------------
-----------------
 SCF Energy= -1144.01906162        Predicted
Change= -9.992108D-09
=========================================
========================================
 Optimization completed.          {Found       2
times}
 Item      Max Val.    Criteria    Pass?      RMS Val.
Criteria    Pass?
 Force      0.00001 ||  0.00045   [ YES ]      0.00000 ||
0.00030   [ YES ]
```

```
 Displ      0.00098 ||  0.00180   [ YES ]      0.00098 ||
0.00180   [ YES ]
-------------------------------------------------------------
-----------------
    Atomic              Coordinates (Angstroms)
     Type              X              Y              Z
-------------------------------------------------------------
-----------------
      N          1.636791     -0.149394     -1.207398
      C          0.975803     -0.971179     -2.233135
      C          2.886828     -0.771550     -0.751023
      C          2.518275     -1.614060      0.464232
      O          3.186397     -2.527138      0.880778
      O          1.382445     -1.211637      1.013081
      B          0.740851     -0.026700      0.476443
      C         -0.779308     -0.109381      0.042644
      O          1.341919      1.284351      0.754750
      C          1.802003      2.017592     -0.248153
      O          2.179181      3.157480     -0.132967
      C          1.781586      1.257731     -1.569874
      C         -1.462813     -1.334274      0.055516
      C         -2.795617     -1.437185     -0.338511
      C         -3.450407     -0.289231     -0.762562
      C         -2.819573      0.945133     -0.801569
      C         -1.484187      1.020027     -0.399587
      H          0.004948     -0.535181     -2.472478
      H          0.818316     -1.976257     -1.832811
      H          1.593238     -1.030378     -3.135153
      H          3.599075     -0.004111     -0.430974
      H          3.361556     -1.382827     -1.522507
      H          2.676687      1.472715     -2.160139
      H          0.901924      1.573774     -2.139948
      H         -0.941314     -2.225711      0.395038
      H         -3.327620     -2.382892     -0.325496
```

```
 H      -3.367213      1.818399     -1.140794
 H      -0.996107      1.993186     -0.411488
 O      -0.127992      0.246514      2.651729
 H       0.435844      1.010606      2.828607
 Na     -2.182597      0.578467      2.420748
 F      -4.738190     -0.377055     -1.144149
----------------------------------------------------------
-----------------
 Statistical Thermodynamic Analysis
 Temperature= 298.150 Kelvin      Pressure= 1.00000
Atm
========================================
======================================
 SCF Energy=    -1144.01906162    Predicted
Change= -9.992108D-09
 Zero-point correction (ZPE)=            -1143.7849
0.23413
 Internal Energy (U)=                    -1143.7661
0.25291
 Enthalpy (H)=                           -1143.7652
0.25385
 Gibbs Free Energy (G)=                  -1143.8319
0.18709
----------------------------------------------------------
-----------------
 Frequencies --   -340.7085             50.6350
53.0778
```

28 + NaOH

```
----------------------------------------------------------
-----------------
 Using  Gaussian 09:  AM64L-G09RevD.01 24-Apr-
2013
========================================
======================================
 #M062X/6-31G(d) scf=(maxcycle=300,direct,tight)
density=current
 SCRF=(PCM,SOLVENT=THF) opt=(maxcycle=250)
freq=noraman
 #N Geom=AllCheck Guess=TCheck SCRF=Check
GenChk RM062X/6-31G(d) Freq
----------------------------------------------------------
-----------------
 Pointgroup= C1   Stoichiometry= C11H13BFNNa2O6
C1[X(C11H13BFNNa2O6)]  #Atoms= 35
 Charge = 0         Multiplicity = 1
----------------------------------------------------------
-----------------
 SCF Energy= -1382.19364753       Predicted
Change= -1.235537D-07
========================================
======================================
 Optimization completed.          {Found       1
times}
 Item      Max Val.    Criteria    Pass?      RMS Val.
Criteria    Pass?
 Force      0.00001 ||  0.00045   [ YES ]      0.00000 ||
0.00030   [ YES ]
 Displ     0.00309 ||  0.00180   [ NO ]      0.00309 ||
0.00180   [ YES ]
----------------------------------------------------------
-----------------
    Atomic              Coordinates (Angstroms)
    Type            X              Y           Z
----------------------------------------------------------
-----------------
    N       0.175784     -0.593741      1.611408
    C      -0.905114     -0.587158      2.569801
    C       1.308630      0.238037      1.937411
    C       1.218330      1.591796      1.264605
    O       1.652342      2.611661      1.764907
    O       0.705805      1.629007      0.040074
    B       0.148146      0.595737     -0.903047
    C      -1.392991      0.218780     -0.632213
    O       1.046747     -0.616178     -1.019145
    C       1.177308     -1.714302     -0.329261
    O       1.848662     -2.649802     -0.758805
    C       0.482398     -1.860090      1.019636
    C      -2.246958      1.097224      0.050542
    C      -3.592747      0.808320      0.262216
    C      -4.094698     -0.388552     -0.227860
    C      -3.301177     -1.288881     -0.918284
    C      -1.957275     -0.968158     -1.117596
    H      -1.792392     -1.045322      2.118638
    H      -1.159623      0.448273      2.819234
    H      -0.662626     -1.119070      3.505650
    H       2.253320     -0.176548      1.528627
    H       1.437537      0.395943      3.015903
    H       1.119518     -2.519048      1.632978
    H      -0.454840     -2.399380      0.829536
    H      -1.844114      2.027019      0.447395
    H      -4.250477      1.484599      0.799002
    H      -3.734008     -2.212111     -1.289643
    H      -1.335207     -1.674514     -1.666109
    O       0.330969      1.316241     -2.170566
    H      -0.215431      0.931318     -2.866086
    Na      1.305565      3.210091     -1.460914
    O       3.810657     -0.160957      0.214249
    Na      4.038157     -2.024296     -0.798648
    H       3.123638      0.207956     -0.360970
    F      -5.397018     -0.681915     -0.029254
----------------------------------------------------------
-----------------
 Statistical Thermodynamic Analysis
 Temperature= 298.150 Kelvin      Pressure= 1.00000
Atm
========================================
======================================
 SCF Energy=    -1382.19364753    Predicted
Change= -1.235537D-07
 Zero-point correction (ZPE)=            -1381.9445
0.24910
 Internal Energy (U)=                    -1381.9215
0.27207
 Enthalpy (H)=                           -1381.9206
0.27301
 Gibbs Free Energy (G)=                  -1381.9975
0.19606
```

```
---------------------------------------------------------------
-----------------
 Frequencies --     25.2546               35.7610
47.0861
```

TS-29

```
---------------------------------------------------------------
-----------------
 Using  Gaussian 09:  AM64L-G09RevD.01 24-Apr-
2013
=========================================
=====================================
 #M062X/6-31G(d) scf=(maxcycle=300,direct,tight)
density=current
 SCRF=(PCM,SOLVENT=THF)
opt=(maxcycle=250,ts,calcfc,noeigentest)
 freq=noraman
 #N Geom=AllCheck Guess=TCheck SCRF=Check
GenChk RM062X/6-31G(d) Freq
---------------------------------------------------------------
-----------------
 Pointgroup= C1   Stoichiometry= C11H13BFNNa2O6
C1[X(C11H13BFNNa2O6)]  #Atoms= 35
 Charge = 0          Multiplicity = 1
---------------------------------------------------------------
-----------------
 SCF Energy= -1382.18762251        Predicted
Change= -2.004827D-09
=========================================
=====================================
 Optimization completed.            {Found       2
times}
 Item      Max Val.    Criteria    Pass?      RMS Val.
Criteria    Pass?
 Force      0.00000 ||  0.00045    [ YES ]      0.00000 ||
0.00030   [ YES ]
 Displ     0.00089 ||  0.00180    [ YES ]      0.00089 ||
0.00180   [ YES ]
---------------------------------------------------------------
-----------------
     Atomic                Coordinates (Angstroms)
      Type              X                 Y            Z
---------------------------------------------------------------
-----------------
      N        0.192398     -0.924187      1.360300
      C       -0.916132     -1.517535      2.082450
      C        0.965974      0.018813      2.126319
      C        1.296236      1.307393      1.393900
      O        1.936487      2.185008      1.949434
      O        0.757777      1.550579      0.212093
      B        0.104522      0.750121     -0.890148
      C       -1.416411      0.303172     -0.586587
      O        0.963849     -0.352910     -1.378730
      C        1.526031     -1.366672     -0.744601
      O        2.209225     -2.176635     -1.399621
      C        0.939516     -1.868043      0.570925
      C       -2.245459      1.056087      0.257087
      C       -3.575206      0.712997      0.492041
      C       -4.087359     -0.407783     -0.144252
      C       -3.318191     -1.183537     -0.995420
      C       -1.988360     -0.814964     -1.206986
      H       -1.567705     -2.042399      1.375922
      H       -1.509757     -0.725552      2.548545
      H       -0.602250     -2.228814      2.866722
      H        1.920029     -0.385066      2.488057
      H        0.382704      0.327252      3.002352
      H        1.761998     -2.347568      1.127494
      H        0.246755     -2.664133      0.266605
      H       -1.833560      1.927541      0.764019
      H       -4.213707      1.293015      1.151102
      H       -3.759984     -2.052145     -1.473665
      H       -1.374343     -1.426881     -1.865448
      O        0.131847      1.783382     -1.953681
      H       -0.510848      1.570426     -2.640318
      Na       1.119955      3.478237     -0.873004
      O        3.066559     -0.220867      0.260892
      Na       4.238052     -1.828329     -0.573965
      H        3.037346      0.492854     -0.392602
      F       -5.377104     -0.750758      0.070463
---------------------------------------------------------------
-----------------
 Statistical Thermodynamic Analysis
 Temperature= 298.150 Kelvin       Pressure= 1.00000
Atm
=========================================
=====================================
 SCF Energy=     -1382.18762251    Predicted
Change= -2.004827D-09
 Zero-point correction (ZPE)=              -1381.9382
0.24932
 Internal Energy (U)=                      -1381.9164
0.27116
 Enthalpy (H)=                             -1381.9155
0.27211
 Gibbs Free Energy (G)=                    -1381.9887
0.19887
---------------------------------------------------------------
-----------------
 Frequencies --   -213.8591              38.2388
44.7383
```

30

```
---------------------------------------------------------------
-----------------
 Using  Gaussian 09:  AM64L-G09RevD.01 24-Apr-
2013
=========================================
=====================================
 #M062X/6-31G(d) scf=(maxcycle=300,direct,tight)
density=current
 SCRF=(PCM,SOLVENT=THF) opt=(maxcycle=250)
freq=noraman
 #N Geom=AllCheck Guess=TCheck SCRF=Check
GenChk RM062X/6-31G(d) Freq
---------------------------------------------------------------
-----------------
 Pointgroup= C1   Stoichiometry= C11H13BFNNa2O6
C1[X(C11H13BFNNa2O6)]  #Atoms= 35
```

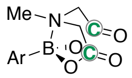
```
 Charge = 0         Multiplicity = 1
------------------------------------------------------------
-----------------
 SCF Energy= -1382.19802001       Predicted
Change= -7.603513D-08
=========================================
======================================
 Optimization completed.          {Found       1
times}
 Item      Max Val.    Criteria    Pass?      RMS Val.
Criteria    Pass?
 Force      0.00002 ||  0.00045   [ YES ]      0.00000 ||
0.00030   [ YES ]
 Displ      0.00309 ||  0.00180   [ NO ]       0.00309 ||
0.00180   [ YES ]
------------------------------------------------------------
-----------------
     Atomic              Coordinates (Angstroms)
      Type            X              Y           Z
------------------------------------------------------------
-----------------
      N       0.165767     -0.894833      1.379551
      C      -0.901303     -1.553405      2.102606
      C       0.915041      0.053120      2.156866
      C       1.251737      1.347827      1.429256
      O       1.941905      2.192598      1.980699
      O       0.723277      1.597330      0.252702
      B       0.112868      0.762825     -0.901756
      C      -1.406482      0.294143     -0.600432
      O       1.008405     -0.278652     -1.358630
      C       1.750060     -1.192753     -0.595554
      O       2.319823     -2.116314     -1.322834
      C       0.940598     -1.805725      0.566283
      C      -2.269146      1.026908      0.227282
      C      -3.590569      0.644533      0.450045
      C      -4.061115     -0.494665     -0.185656
      C      -3.258722     -1.251344     -1.023387
      C      -1.937750     -0.844226     -1.220591
      H      -1.548326     -2.074154      1.388303
      H      -1.512293     -0.806377      2.619004
      H      -0.542111     -2.287554      2.847085
      H       1.863605     -0.343276      2.551684
      H       0.316436      0.361477      3.022528
      H       1.645560     -2.407339      1.174866
      H       0.240464     -2.502068      0.092839
      H      -1.890276      1.912776      0.735645
      H      -4.254011      1.207702      1.099283
      H      -3.668719     -2.136190     -1.500583
      H      -1.290942     -1.438785     -1.862995
      O       0.100147      1.833060     -1.942630
      H      -0.668746      1.718712     -2.512652
      Na      1.007249      3.540514     -0.828124
      O       2.816004     -0.344640      0.091538
      Na      4.348848     -1.879130     -0.618856
      H       2.888043      0.431178     -0.486976
      F      -5.343449     -0.875017      0.017068
------------------------------------------------------------
-----------------
 Statistical Thermodynamic Analysis
 Temperature= 298.150 Kelvin      Pressure= 1.00000
Atm
=========================================
======================================
 SCF Energy=     -1382.19802001    Predicted
Change= -7.603513D-08
 Zero-point correction (ZPE)=               -1381.9469
0.25103
 Internal Energy (U)=                       -1381.9252
0.27276
 Enthalpy (H)=                              -1381.9243
0.27370
 Gibbs Free Energy (G)=                     -1381.9976
0.20037
------------------------------------------------------------
-----------------
 Frequencies --     31.8788              42.1727
56.4629
```

TS-31

```
------------------------------------------------------------
-----------------
 Using  Gaussian 09:  AM64L-G09RevD.01 24-Apr-
2013
=========================================
======================================
 #M062X/6-31G(d) scf=(maxcycle=300,direct,tight)
density=current
 SCRF=(PCM,SOLVENT=THF)
opt=(maxcycle=250,ts,calcfc,noeigentest,gdiis)
 iop(1/8=18) freq=noraman
 #N Geom=AllCheck Guess=TCheck SCRF=Check
Test GenChk RM062X/6-31G(d) Freq
------------------------------------------------------------
-----------------
 Pointgroup= C1   Stoichiometry= C11H13BFNNa2O6
C1[X(C11H13BFNNa2O6)]  #Atoms= 35
 Charge = 0         Multiplicity = 1
------------------------------------------------------------
-----------------
 SCF Energy= -1382.17033238       Predicted
Change= -1.586759D-09
=========================================
======================================
 Optimization completed on the basis of negligible
forces.           {Found        2        times}
 Item      Max Val.    Criteria    Pass?      RMS Val.
Criteria    Pass?
 Force      0.00000 ||  0.00045   [ YES ]      0.00000 ||
0.00030   [ YES ]
 Displ      0.00206 ||  0.00180   [ NO ]       0.00206 ||
0.00180   [ YES ]
------------------------------------------------------------
-----------------
     Atomic              Coordinates (Angstroms)
      Type            X              Y           Z
------------------------------------------------------------
-----------------
      N       0.784621     -1.733037     -0.386128
```

```
     C      -0.202323     -2.454281     -1.162371
     C       0.916202     -2.219867      0.970893
     C       0.513997     -1.182481      2.028534
     O       0.029315     -1.559797      3.087239
     O       0.803783      0.067053      1.771069
     B       0.392827      1.067711      0.412746
     C      -1.074432      0.524859     -0.061242
     O       1.428809      1.120097     -0.479211
     C       2.913249     -0.344065     -0.622256
     O       3.725166      0.120962     -1.431943
     C       2.000462     -1.467441     -1.110937
     C      -2.056863      0.019703      0.807371
     C      -3.322885     -0.379150      0.361319
     C      -3.608167     -0.264307     -0.987993
     C      -2.678654      0.227955     -1.894393
     C      -1.428984      0.615658     -1.417069
     H      -0.358539     -1.946178     -2.118400
     H      -1.158962     -2.446081     -0.628205
     H       0.078163     -3.504111     -1.365078
     H       1.955833     -2.508241      1.190605
     H       0.303250     -3.111864      1.135621
     H       2.663562     -2.357335     -1.161953
     H       1.737922     -1.204471     -2.137485
     H      -1.826810     -0.096868      1.866300
     H      -4.071365     -0.780603      1.037542
     H      -2.941973      0.290735     -2.945991
     H      -0.681791      0.979736     -2.118998
     O       0.144033      2.345367      1.142690
     H       1.005924      2.765194      1.265747
     Na     -1.959219      2.715372      1.503968
     O       3.226633     -0.297126      0.692365
     Na      2.885287      2.176030     -1.627942
     H       2.382201     -0.149446      1.189215
     F      -4.824684     -0.641681     -1.437204
---------------------------------------------------------------
-----------------
 Statistical Thermodynamic Analysis
 Temperature= 298.150 Kelvin       Pressure= 1.00000
Atm
=======================================
=====================================
 SCF Energy=     -1382.17033238    Predicted
Change= -1.586759D-09
 Zero-point correction (ZPE)=             -1381.9211
0.24915
 Internal Energy (U)=                     -1381.8991
0.27120
 Enthalpy (H)=                           -1381.8981
0.27215
 Gibbs Free Energy (G)=                  -1381.9730
0.19727
---------------------------------------------------------------
-----------------
 Frequencies --   -240.0036              21.2685
36.3338
```

6. NaOH Mediated Hydrolysis: Computed $^{12}C/^{13}C$ Kinetic Isotope Effects



● = **$^{12}C/^{13}C$ KIE**
comp. = 1.03
exp. = 1.049

Figure 37. *Computations predict a 12C/13C KIE of 1.03, consistent with experiments.*

We applied the Bigeleisen-Mayer approach (J. Bigeleisen, M. G. Mayer J. Chem. Phys. 1947, 15, 261–267) to obtain the kinetic isotope effect (KIE) data. All KIE computations were performed using M06-2X/6-31G*/PCM(THF) level of theory.

Parameters
Temperature: 21 °C (294.15 K)
Scaling factor: 1.0
Vibrational Frequencies:

C-Attack TS-5	C-Attack ^{13}C-TS-5	1 + NaOH	^{13}C-1+ NaOH
-236.2815	-233.4227	46.0313	46.0072
24.5821	24.5642	52.0689	51.9741
39.3362	39.3119	62.4743	62.3734
54.2161	54.2035	69.7919	69.6349
62.8129	62.6222	78.2478	78.1812
73.5524	73.412	110.6719	110.6397
136.9329	136.757	125.6703	125.5995
140.6368	140.4666	137.1435	136.7917
176.4308	176.369	164.275	164.1538
188.4414	188.2455	179.509	179.3528
204.4681	204.3826	192.3916	192.2027
244.8146	244.1167	220.3954	219.8707
266.1172	265.4988	250.1033	249.6569
284.9123	284.7578	292.6641	292.2001
290.191	289.8271	305.305	305.1986
317.7938	317.6983	339.8457	339.6324
341.245	341.0723	368.9496	368.9033
369.1036	368.6136	376.8069	376.3903
375.3622	374.878	389.9179	389.1296
378.2488	377.3336	393.8447	393.1543
407.6959	407.293	395.6159	395.4036

424.5171	424.4507	411.6268	411.4489
427.4239	427.1237	432.9892	432.5002
460.9661	460.8179	436.5717	436.5439
471.8892	468.9531	462.4012	459.4184
511.2214	508.854	477.4025	477.42
533.0565	530.8001	511.1893	507.4033
539.6172	536.8582	540.1182	535.3734
550.2227	542.9296	549.864	546.0218
563.4949	561.5727	578.5602	570.638
581.245	580.2145	580.0577	579.3421
602.2856	600.951	609.696	608.388
636.7121	633.922	635.2819	632.8203
646.3148	645.1884	644.9637	643.2617
652.0448	650.3465	656.2308	654.7284
723.3531	720.5702	724.9646	722.1919
745.3663	745.1401	746.8928	746.703
829.8438	829.6776	829.5501	829.4103
852.3675	852.3039	851.5897	851.5781
858.3078	858.2757	877.7556	877.6576
889.9998	888.9005	894.5628	893.908
915.59	912.755	924.729	922.0938
929.6899	927.8142	940.7957	938.8474
939.6656	937.2468	950.4336	947.365
979.7059	977.4521	992.2639	985.2711
981.5958	979.739	994.2243	993.9932
1006.2815	1005.9807	1020.2727	1014.4708
1018.5699	1013.4333	1037.8988	1037.0277
1031.1984	1029.6307	1059.1696	1057.5946
1045.3459	1044.3699	1075.7029	1075.4555
1063.4978	1062.8418	1078.4139	1077.5033
1099.8506	1099.2239	1095.8298	1094.8293

1124.3011	1123.4935	1127.1353	1126.821
1132.6447	1130.6297	1136.8209	1133.1293
1187.4202	1187.0309	1196.1071	1195.4666
1189.5865	1188.638	1199.5189	1198.8586
1244.3514	1243.4593	1245.0178	1244.0502
1263.8933	1261.8127	1273.2248	1272.6856
1290.9155	1266.475	1300.7049	1290.0966
1295.2524	1292.2837	1302.0524	1301.9788
1302.3635	1302.2049	1317.1688	1302.7972
1322.2899	1321.8566	1329.0395	1328.0743
1325.9706	1323.2393	1338.2574	1336.3468
1342.2058	1325.1824	1344.8774	1342.7824
1347.5513	1340.7355	1358.3414	1348.9751
1379.3756	1375.9926	1383.3957	1377.122
1392.367	1384.2679	1411.4529	1389.0623
1452.0354	1451.9495	1457.1392	1457.0301
1456.2369	1456.1701	1472.2249	1471.8247
1488.3837	1488.3154	1487.2686	1487.1544
1499.4678	1499.3603	1511.1149	1510.923
1512.0188	1511.9714	1525.195	1525.172
1553.0156	1553.0187	1560.2043	1560.1962
1576.6592	1576.6549	1579.0048	1579.003
1678.1582	1678.0428	1677.1611	1677.1291
1700.3404	1700.264	1700.7283	1700.7183
1766.9495	1721.2716	1840.2917	1792.779
1892.6306	1844.5136	1899.1675	1850.9884
3080.3635	3080.3519	3066.2654	3066.2758
3121.1828	3121.2282	3126.7448	3126.7332
3123.3885	3123.4252	3132.5223	3132.5088
3178.1304	3178.1161	3166.5267	3166.5213
3188.6223	3188.6133	3177.1021	3177.137

3191.6581	3191.6736	3194.6824	3194.7017
3203.9532	3203.9437	3208.8507	3208.8522
3210.0431	3210.083	3211.0493	3211.0594
3214.3625	3214.3911	3219.9826	3219.9827
3238.3163	3238.3352	3237.4369	3237.4301
3239.6934	3239.69	3249.4984	3249.4238
3833.2154	3833.2162	3809.9344	3809.8342

7. Computational exploration of the H_2O-mediated slow-release mechanism.

Several levels of theory have been used to study the slow-release reaction. For different experimental data, different concentrations and temperatures are relevant. The level of theory that provided best quantitative agreement between predicted and observed kinetic isotope effects was M06L/6-311+G** with solvation in both THF and water computed as a single point using the default PCM settings in Gaussian09 combined with the same level of theory (M06L/6-311+G**). This is the preferred level of theory, but has been reserved for calculations that probe quantitative aspects of the reaction. The computationally cheaper M06-2X/6-31+G* (incorporating solvation in THF using PCM) level was used to investigate the full reaction profile. A range of conformations have been considered in all relevant cases although in the later stages of the hydrolysis, after the initial ring opening and rate-limiting step, few conformations were considered. Unless otherwise stated, calculations were performed in Gaussian09.[7]

Throughout the text, the levels of theory are:

Level 1A – M06-2X/6-31+G* incorporating PCM solvation for THF in geometry optimization and in vibrational corrections. Thermodynamics for P = 1 atm and T = 298 K.

Level 1B – as 1A but thermodynamics are at P = 24.15 atm (1 M) and T = 294 K.

Level 2A - M06L/6-311+G** for geometry optimization and vibrational corrections. Solvation in THF is added as a single point. Solvation in water is included in parentheses. Thermodynamics for P = 1 atm and T = 298 K.

Level 2B – as 2A but thermodynamics are at P = 24.15 atm (1 M) and T = 294 K.

Level 2C – as 2A but thermodynamics are at P = 24.15 atm (1 M) and T = 294 K for all species except water which is at P = 217.35 (9 M) and T = 294K.

Level 3 – M06/6-311+G**//B3LYP/6-31+G** including solvation as a single point using PCM combined with B3LYP/6-31+G* with settings for THF (this single point is computed in Gaussian03).[8] This level of theory had been found previously to agree well with energies obtained using MP2.9[9]

A number of mechanistic possibilities were considered. The detailed studies of the mechanism that we consider to be in best agreement with experimental observation are presented first.

8. S$_N$2 attack at the "front" side of B (*syn* to N)

The presence of a boron and nitrogen kinetic isotope effects suggested the involvement of both in the key rate-limiting step. A simple possibility would be that as the B-N bond stretches, a water molecule could intrude into the bond; the oxygen lone pair of water would complement the Lewis acidic boron while the OH group would be able to form a hydrogen bond with the nascent amine. These interactions stabilize transition state **TS-12**, and hence it is significantly lower in energy than the ring-opened intermediate in the S$_N$1 mechanism, **32**, discussed below. Computations at most levels of theory suggest that this mechanism has the lowest barrier of the various mechanisms considered (Tables 20, 21 and 22). Hence the full reaction profile was explored, linking from reactants to products. The rate-limiting barrier involves **TS-12** and leads to the zwitterionic intermediate **13**.

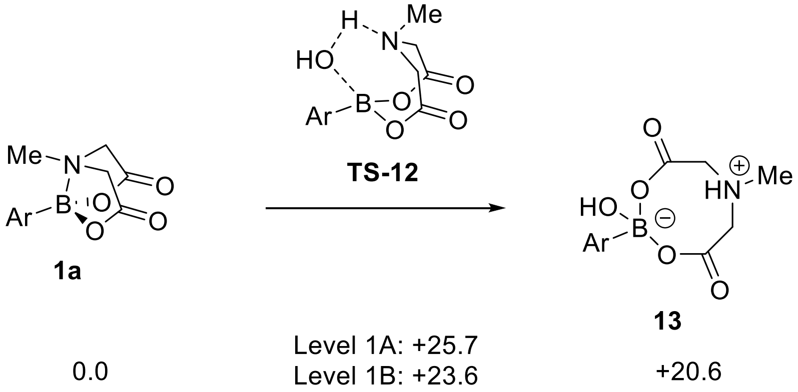


Figure 38. *The rate-limiting barrier, with free energies in kcal/mol relative to initial reactants computed at Level 1 (A and B).*

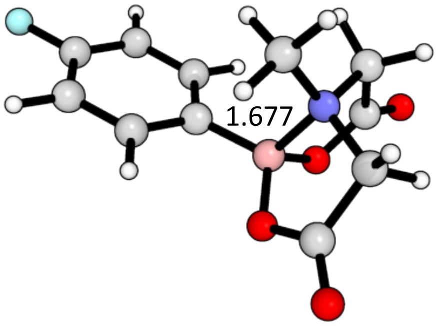


Figure 39*. The structure of* ***1a*** *optimized at Level 1. Distances are shown in Å.*

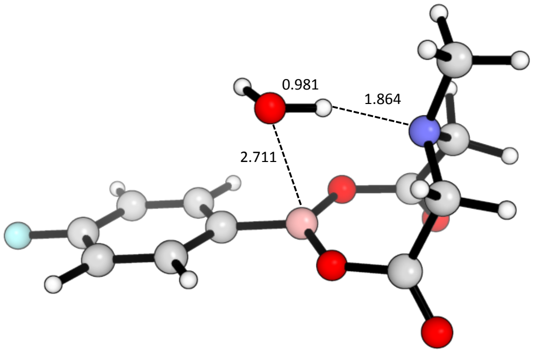


***Figure 40**.The structure of **TS-12** optimized at Level 1. Distances are shown in Å.*

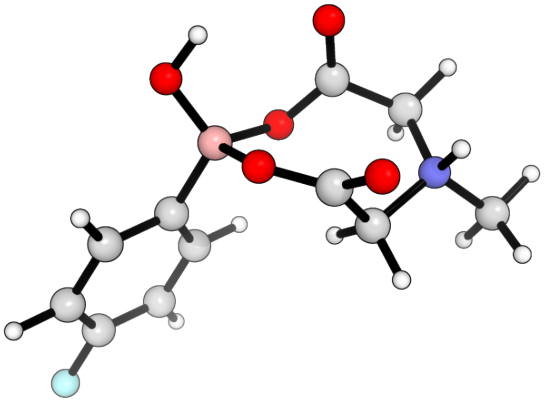


***Figure 41.** The structure of the lowest energy conformation of **13** optimized at Level 1.*

The zwitterion **13** can undergo cleavage of a B-OCO bond via **TS-14**; at 1 M concentration of reagents (Level 1B), the free energy of **TS-14** is significantly below **TS-12**. The protonated amine stabilizes the forming carboxylate in this bond breaking step. Subsequent to bond cleavage, proton transfer leaves the deprotonated amine able to reform the B-N bond in the lowest energy conformation of **15** The B-N bond in **15** is longer than in the reactant **1a** which suggests that any geometric strain in the bicyclic structure of **1a** is offset by the extra electron-withdrawing acyl group attached to the boron which makes that atom more Lewis-acidic. A second water molecules is then able to attack, via **TS-16** which leads to the water complex **TS-17**.

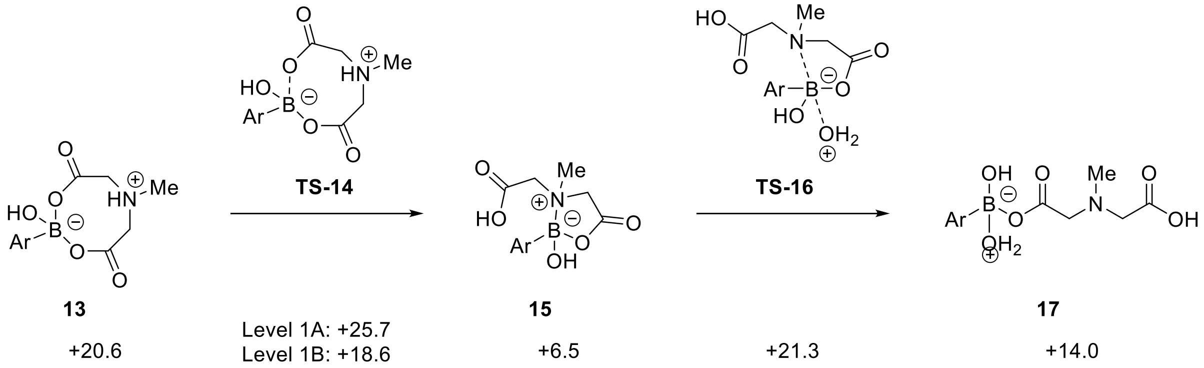


*Figure 42.*The steps linking the product of the first water addition (**13**) with the product of the second water addition (**17**). Free energies in kcal/mol relative to initial reactants computed at Level 1 are shown.

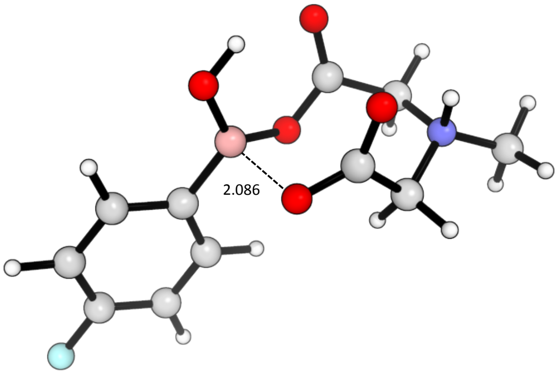


Figure 43. *The lowest energy conformation structure of **TS-14** optimized at Level 1. Distances are shown in Å.*

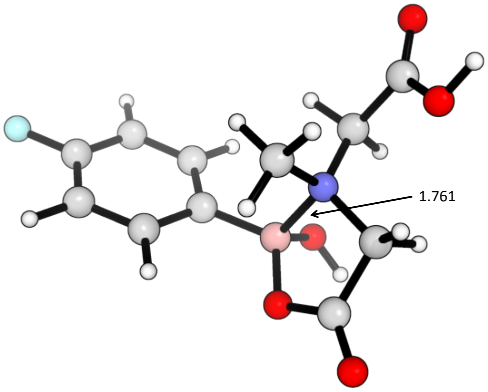


Figure 44. *The lowest energy conformation structure of **15** optimized at Level 1. Distances are shown in Å.*

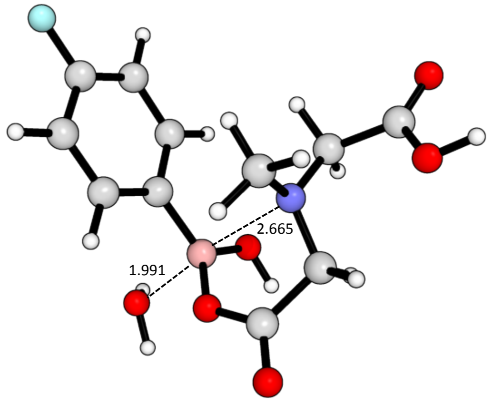


Figure 45. *The structure of* ***TS-16*** *optimized at Level 1. Distances are shown in Å.*

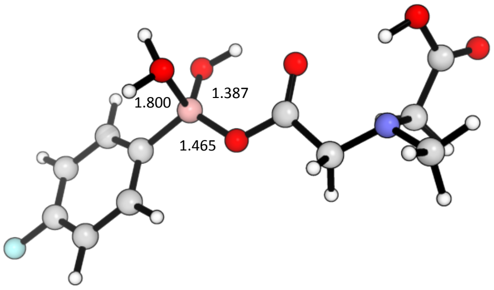


Figure 46. *The structure of* ***17*** *optimized at Level 1. Distances are shown in Å.*

The amine in **17** is then able to act as an intramolecular base in **TS-18** which yields the intermediate **19** which, like **13**, has a boron ate complex with a protonated amine poised to stabilize the carboxylate during B-O cleavage in transition state **TS-20**. It is unsurprising that the breaking B-O bond distance in **TS-20** is very similar to that in the equivalent transition state **TS-14** for cleavage of the B-O bond following the first water addition-proton transfer. Transition state **TS-20** leads to the boronic acid **2a** and the diacid **3** in zwitterionic form.

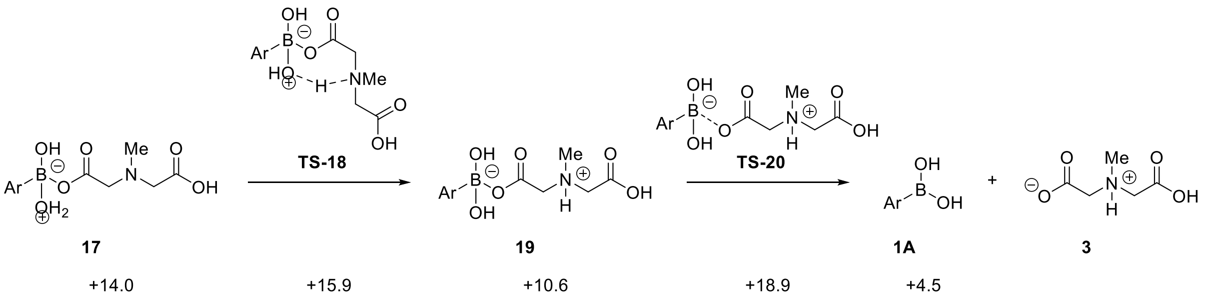


Figure 47. *The steps linking the product of the second water addition (***17***) with final hydrolysis products. Free energies in kcal/mol relative to initial reactants computed at Level 1A are shown.*

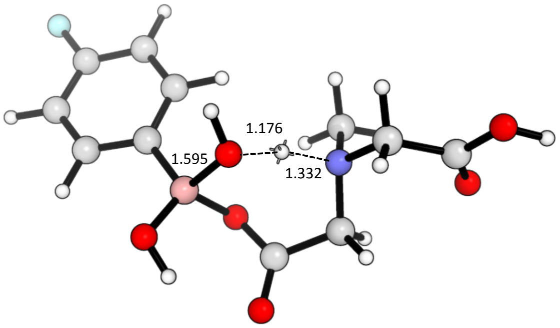


Figure 48.The structure of **TS-18** optimized at Level 1. Distances are shown in Å.

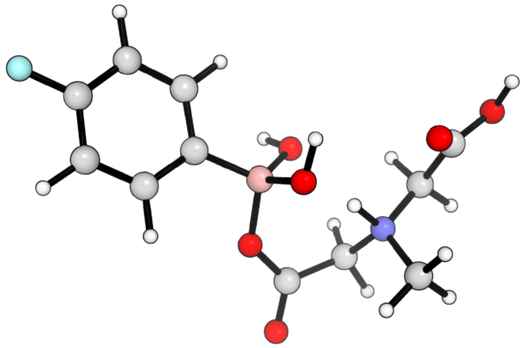


Figure 49*.The lowest energy conformation structure of* ***19*** *optimized at Level 1. Distances are shown in Å.*

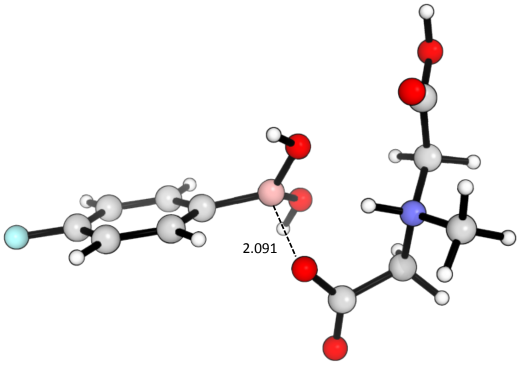


Figure 50. The structure of **TS-20** optimized at Level 1. Distances are shown in Å.

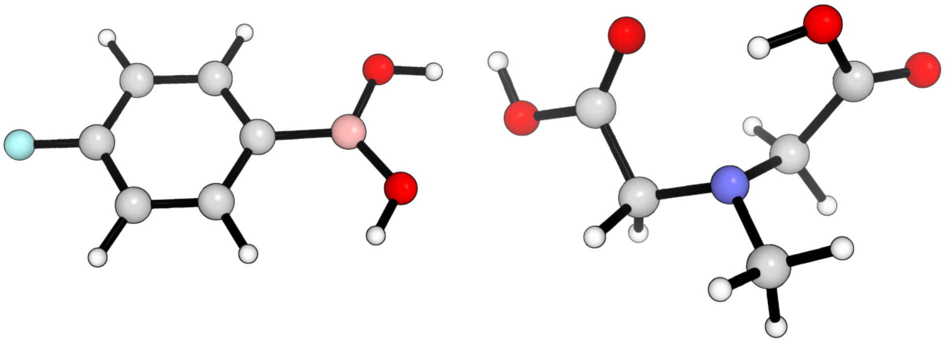


Figure 51*. The structure of the overall products of the reaction,* ***2a*** *and* ***3*** *optimized at Level 1.*

The later steps of this process (from **TS-17** onwards) are found to all involve structures that are rather lower in energy than the previous steps (but still high compared to reactants or products) and each individual step is low barrier suggesting that none of the intermediates would be predicted to be observed in appreciable quantities or to have particularly long lifetimes.

Having established a plausible mechanism, its ability to quantitatively rationalize the experimental observations was explored.

9. The order with respect to water

Modelling water remains one of the most challenging problems for computational chemistry, particularly for bulk water. The kinetics experiments were performed at a range of concentrations of water in THF in which the observed dependency can be rationalized as arising from the reaction of the MIDA with clusters of water. In calculations to study this, the sampling of cluster size, conformation and mechanistic alternatives is challenging and thus the calculations presented are not anticipated to have been exhaustive. The intention is to demonstrate that a single water molecules or clusters of two or three water molecules can all contribute to the observed reactivity. The enthalpic benefits of including an extra water molecule must offset the entropic costs.

The transition state for the reaction with a single water molecule, **TS-12** was optimized at several different levels of theory. Two levels of theory in particular are presented in Figure 52. Level 1 and Level 2 (geometries are the same for all variations of Levels 1 and 2). Two variations of reaction with water dimers were discovered, involving transition states **TS-25** and **TS-26**. These were also reoptimized at several levels of theory and again Levels 1 and 2 are summarized in Figure 53. Finally, some reactions with trimers of water were considered and again were investigated with several levels of theory. Only Levels 1 is shown in Figure 54 (Level 2 is excluded for reasons discussed below). The energy ordering of the different structures that incorporate dimers and trimers depends upon the level of theory.

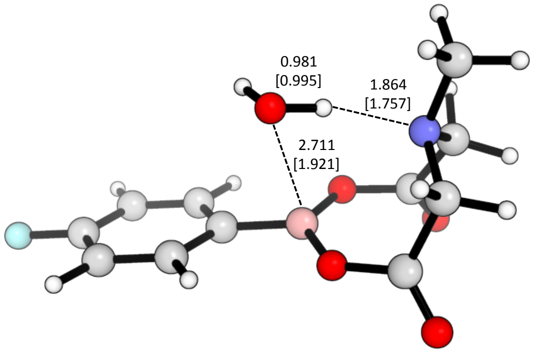


Figure 52. *Structures of transition states for the reaction of* ***1a*** *with a single water molecule. Distances are shown in Å for Level 1, with equivalent distances for Level 2 in brackets.*

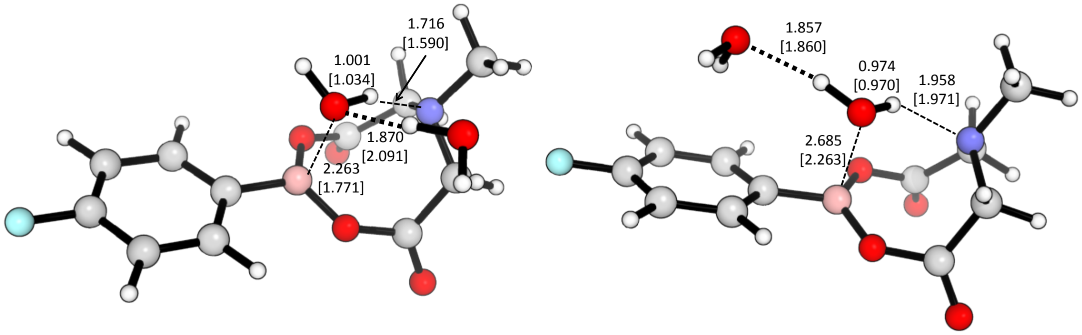


Figure 53. *Structures of transition states for the reaction of* ***1a*** *with water dimers. Distances are shown in Å for Level 1, with equivalent distances for Level 2 in brackets.*

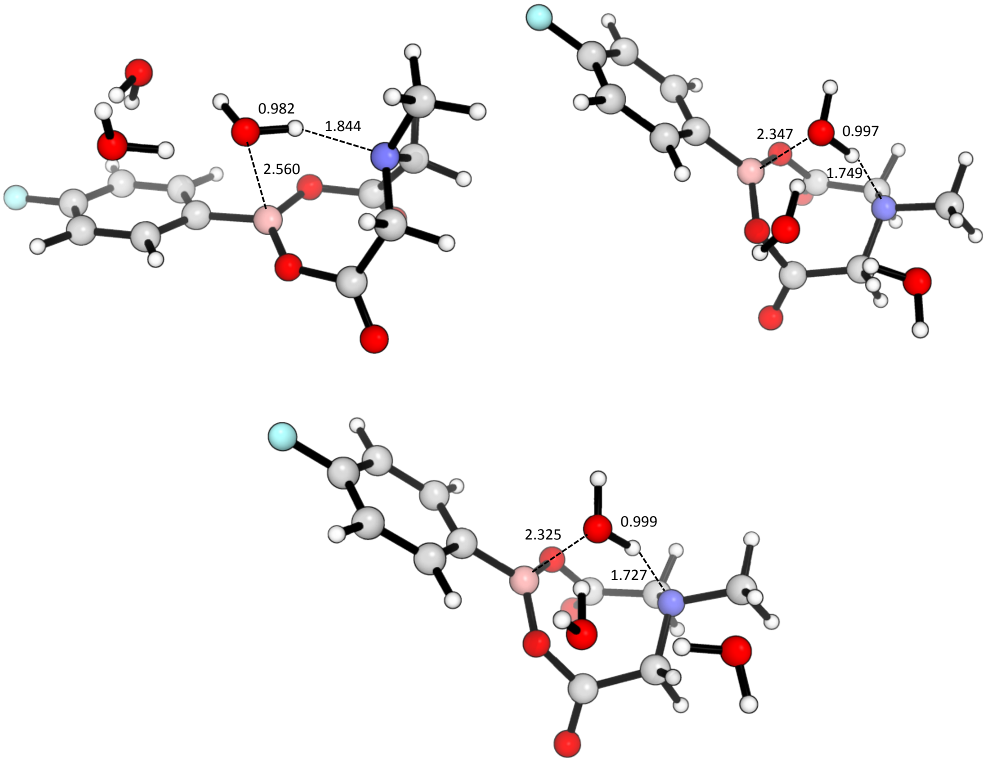


Figure 54. *Structures of transition states for the reaction of* ***1a*** *with water trimers. Distances are shown in Å for Level 1. The lowest energy structure is shown top left, the next lowest top right and the third lowest at the bottom.*

The relative energy of the transition states for reaction with dimers and trimers is summarized with the computed activation free energies computed at a range of levels of theory in Table 20. These calculations reveal that the lowest energy structure for the reaction with water dimers and trimers changes depending on the polarity of the solvent as does the energy difference between the reaction with different numbers of water molecules. When corrections to 1 M water for Level 1 (Level 1B) or 9 M water are included for Level 2 (Level 2C), the computed reaction barriers for all three water cluster types come close in energy.

These energies can be contrasted with the free energy changes computed for bringing together two or three water molecules, which are shown in Table 21. It may be more relevant to the experimental situation to consider the barriers for the reaction with water dimers or trimers themselves rather than the barriers computed assuming the water begins as a monomeric species. These free energy barriers are shown in Table 22. This reveals that in the circumstance where equal concentrations of monomeric, dimeric and trimeric water clusters are present, the free energy barrier for the reaction between those clusters and **1a** would be expected to be approximately the same. Presumably, larger clusters would also be able to participate in a similar fashion and the calculations are consistent with a non-integer order with respect to water in which reactivity would be intimately linked to the organization of the water molecules that is present in solution. The calculations also provide estimates of the entropy change for each step. When considered relative to monomeric, dimeric and trimeric water the corresponding values of $\Delta S^{\ddagger}$ are -26.3, -29.8 and -36.2 cal K^{-1} mol^{-1}. These are more negative than found experimentally but are consistent. By contrast for the dissociative mechanism via **23** discussed below, a value of +5.1 cal K^{-1} mol^{-1} is computed.

Level	**Lowest free energy barrier with 1 water molecule (kcal/mol)**	**Lowest free energy barrier with 2 water molecules (kcal/mol)**	**Lowest free energy barrier with 3 water molecules (kcal/mol)**
1A	25.7	27.1	27.9
1B	23.6	23.1	21.9
2A	29.0 (30.1)	32.1 (34.2)	37.1 (39.9)
2B	27.0 (28.1)	28.3 (30.2)	25.7 (27.6)
2C	25.7 (26.8)	25.7 (28.0)	27.3 (30.1)
3		32.7 (40.3)	37.0 (46.8)

Table 20. *Free energies of transition states for reaction with 1, 2 or 3 water molecules. These are relative to reactant **1a** and 1, 2 or 3 water molecules computed separately.*

Level	**Lowest free energy change between 2 isolated water molecules and a water dimer (kcal/mol)**	**Lowest free energy change between 3 isolated water molecules and a water trimer (kcal/mol)**
1A	+2.8	+2.5
2A	3.5 (3.9)	7.7 (9.0)
2B	1.6 (2.0)	3.8 (5.0)
2C	-1.0 (-0.6)	-0.1 (1.2)

Table 21. *Free energies of association of 2 or 3 water molecules forming dimers or trimers.*

Level	**Lowest free energy barrier with 1 water molecule (kcal/mol)**	**Lowest free energy barrier with a water dimer (kcal/mol)**	**Lowest free energy barrier with a water trimer (kcal/mol)**
1A	25.7	24.3	25.4
2A	29.0 (30.1)	28.6 (30.3)	29.4 (31.0)
2B	27.0 (28.1)	26.7 (28.2)	27.3 (28.9)

Table 22 *.Free energies of transition states for reaction with 1, 2 or 3 water molecules. These are relative to reactant **1a** and monomeric, dimeric and trimeric water.*

10. Kinetic isotope effects

Kinetic isotope effects are very sensitive to the geometry of the transition state. As can be seen in Figures 52, 53, 54, the bond making and breaking distances vary as the number of water molecules and the level of theory is changed. Thus, a range of levels of theory has been explored. Kinetic isotope effects have been computed by computing free energies of activation and then comparing them and assuming that $k_1/k_2 = e^{(\Delta G2-\Delta G1)/RT}$. Thermodynamic properties were computed at 294 K and 1 atm. The hydrogen isotope effects were computed for isotope exchange of the hydrogen that is being transferred to nitrogen (1) and for the other hydrogen in the same water molecule (2) separately and then for both being exchanged for deuterium. These were computed for the reaction with one, two and three water molecules. In reactions with dimers of water, the other water molecule was maintained as H_2O. Isotope effects for the reaction with a single water molecule are in Table 23 and for the reaction with two water molecules in Table 24.

Level	k_H/k_D(1)	k_H/k_D(2)	k_H/k_D(both)	$^{10/11}k_B$	$^{14/15}k_N$	$^{12/13}k_C$
1B	1.06	0.88	0.93	0.998	1.011	1.005
2B	1.03	0.92	0.88	1.023	1.011	1.005
M06/6-31+G*	0.92	0.91	0.84	1.018	1.011	1.004
M06L/6-31+G*	0.91	0.90	0.84	1.018	1.009	1.004
M062X/6-31+G*	0.94	0.89	0.84	1.018	1.009	0.995
BP86/6-31+G*	0.99	0.91	0.91	0.996	1.009	1.005
PBE0/6-31+G*	0.99	0.92	0.91	0.995	1.011	1.006

***Table 23**. Kinetic isotope effects computed for the mechanism with one water molecule.*

Level	k_H/k_D(1)	k_H/k_D(2)	k_H/k_D(both)	$^{10/11}k_B$	$^{14/15}k_N$	$^{12/13}k_C$
1B	0.98	0.94	0.93	1.017	1.013	1.005
2B	1.42	0.90	1.17	1.026	1.009	1.004
M06/6-31+G*	1.06	0.91	0.98	1.027	1.010	1.004
M06L/6-31+G*	1.11	0.90	1.02	1.028	1.009	1.004
M062X/6-31+G*	0.97	0.92	0.90	1.027	1.011	1.003
BP86/6-31+G*	1.09	0.95	1.05	1.014	1.006	1.005
PBE0/6-31+G*	1.07	0.95	1.03	1.019	1.009	1.006
BPW91/6-31+G*	1.07	0.94	1.02	1.015	1.006	1.005
BLYP/6-31+G*	1.21	0.91	1.12	1.020	1.005	1.004
B3LYP/6-31+G*	1.05	0.90	0.96	1.022	1.006	1.005

OLYP/6-31+G*	1.01	0.90	0.92	1.016	1.008	1.005
M06L/6-311++G**	1.27	0.90	1.17	1.027	1.010	1.005
B3LYP/6-311++G**	1.13	0.90	1.04	1.023	1.009	1.005
BLYP/6-311++G**	1.33	0.91	1.24	1.022	1.005	1.005
BP86/6-311++G**	1.17	0.95	1.13	1.017	1.008	1.005
M06/6-311++G**	1.13	0.91	1.05	1.028	1.009	1.004
OLYP/6-311++G**	1.07	0.92	0.99	1.018	1.006	1.005
M06L/ccpvdz	1.11	0.90	1.03	1.024	1.010	1.004

Table 24. Kinetic isotope effects computed for the mechanism with two water molecules.

The hydrogen isotope effects show that there is generally one KIE that is approximately 0.9 while the other is computed to range from 0.91 to 1.06 for the reaction with one water molecule and from 0.98 to 1.42 for the reaction with two water molecules. The reaction that is occurring is an addition of water to the boron atom in the cleaving B-N bond concerted with a proton transfer to nitrogen. The addition of water to the boron would be expected to show a secondary isotope effect and presumably the value of ~0.9 corresponds to the isotope effect for this process. The proton transfer would be expected to entail a primary isotope effect. Therefore, the net value of the KIE would be expected to depend upon the extent of B-O bond formation: a long B-O distance would suggest a transition state most like that for B-O addition while a short B-O distance would suggest a transition state more like that for proton transfer.

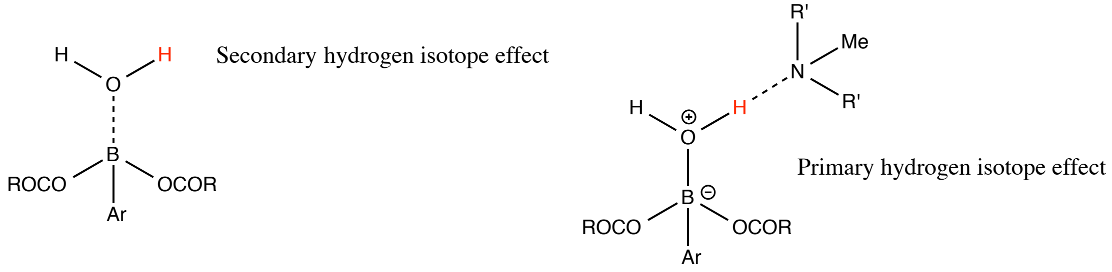


Figure 55. *The two processes contributing to the rate-limiting step and the KIEs expected for each.*

The boron isotope effect also depends upon the B-O distance in the transition state, as shown in Figure 56. The KIEs computed at the levels of theory shown in Tables 23 and 24 are plotted against the B-O distance in the optimized transition state geometry at that level. This reveals that the observed boron isotope effect of 1.032 is consistent with a B-O distance of approximately 1.70 Å. At this B-O distance the hydrogen isotope effect would be expected to be elevated with a contribution from the proton transfer part of the process. This is consistent with the observed value of 1.59.

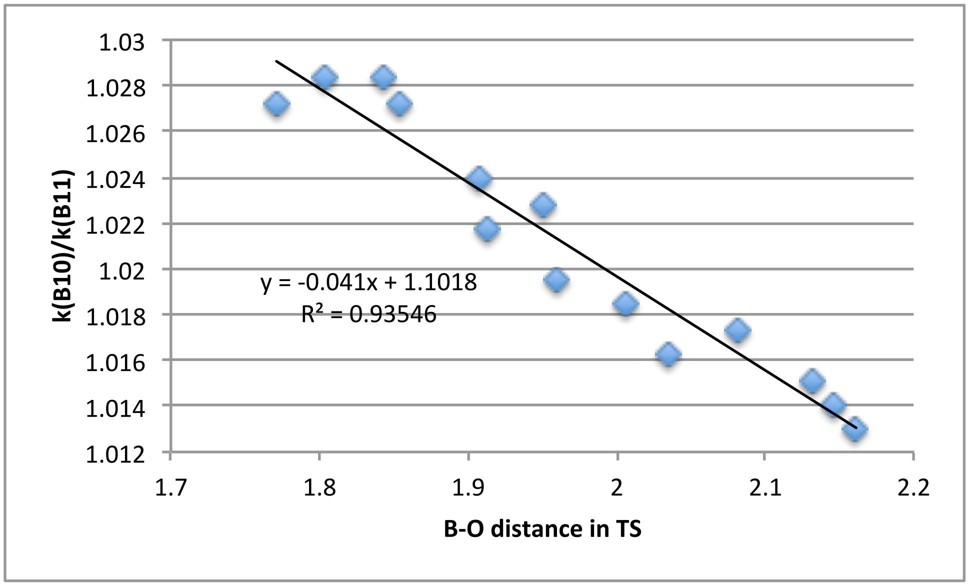
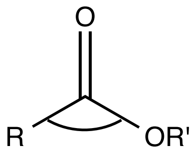


Figure 56. *The interdependence of the boron isotope effect ($^{10/11}k_B$) and the B-O distance in the transition state.*

Quantitative analysis of the isotope effects is complicated by the experimental and computational suggestion that the reaction proceeds with a variable number of water molecules involved. The equilibrium amount of water dimers, trimers etc would also depend upon the isotopic composition. A further complication is that the primary isotope effect would be increased by tunneling. No attempt to correct for this has been made but with these considerations in mind, the KIEs computed at level 2 B with two water molecules are considered to be in qualitative agreement and to provide a clear rationale for the observed values. Boron-oxygen bond formation is sufficiently advanced in the transition state for proton transfer to make a contribution and give an increased KIE for the hydrogen isotopes and to engage the nitrogen atom sufficiently to lead to a nitrogen isotope effect. The B-O engagement also leads to a significant boron isotope effect. The proton transfer is likely larger than that found in any of the computed transition states because none of them provide a nitrogen isotope effect as large as that observed (1.017). The computed carbon isotope effect is consistently about 1.005, which is larger than is observed experimentally. This isotope effect presumably arises because of the change in geometry around the carbonyl. As shown in Figure 55, the angle at the carbonyl is contracted in the MIDA reactant. This may be a result of the modelling employing gas phase or implicit solvation; interaction between real solvent molecules (THF or water) as weak Lewis bases with the Lewis acidic boron will presumably extend the B-N bond and reduce this effect. It may also be a factor in the nitrogen isotope effect.



Reactant: 110°
One water TS: 117°
Two water TS: 118°

Figure 57*. The C-C-O angle in structures of the reactant and transition states optimized at Level 1.*

11. Hammett relationship

The best agreement with the kinetic isotope effects was found for level 2B. This level was then applied to derive the effect of substituents on rates for the various mechanisms. The substituents studied computationally were H, *p*-Me, *p*-CF_3, and *m*-NO_2 alongside the originally studied p-F. For this set, the relative rates were computed assuming that $\log(k_{rel}) = \log(e^{-(Gact(X)-Gact(H))/RT})$. These are plotted against the sigma values in Figure 58. For the reaction with one water molecule, a ρ value of 0.4 was computed and for the reaction with two water molecules a value of 1.0 was found. The origin of the observed value of ρ can also be rationalized by considering the two contributing reactions illustrated in Figure 38. If B-O bond formation is significant in the transition state, then the boron atom will be more like that shown to the right for the proton transfer step and will bear a negative charge. This would explain why electron-withdrawing groups are better able to stabilize the transition state and hence promote a faster reaction.

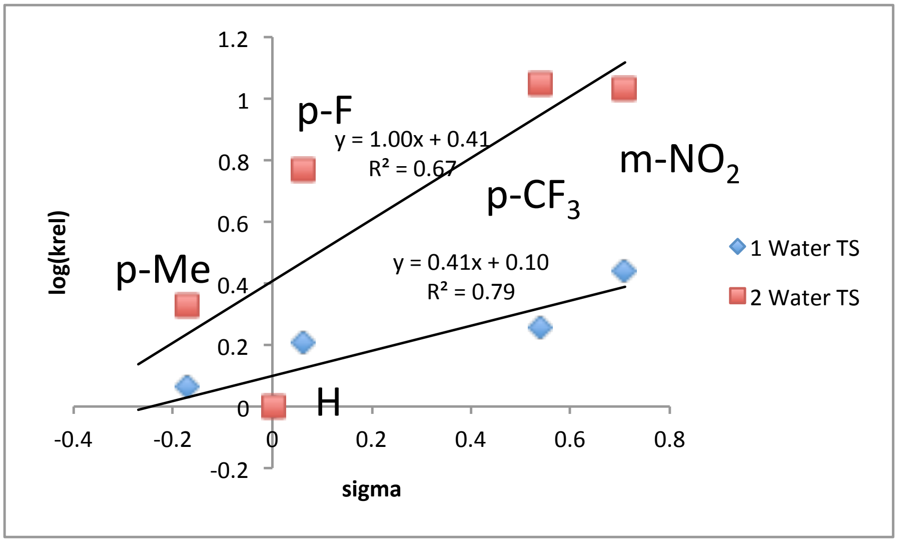


Figure 58*. Hammett plots of computed relative rate versus sigma values.*

When the calculations were extended to the reaction with three water molecules, the linear relationship broke down. Further investigation revealed that when there is an electron donating substituent at the para position, the trimer of water is large enough to reach over and form a polar interaction with the adjacent carbon atom (Figure 59); this is a consequence of gas phase or implicit calculation. In reality, the water molecules would interact with the surrounding solvent (the lone pairs of THF or of water).

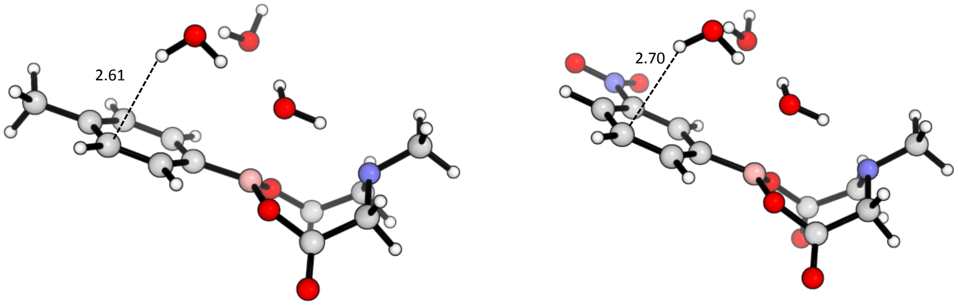
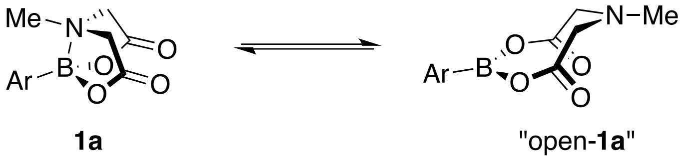


Figure 59.*The unrealistic interaction between one of the water molecules in a water trimer in the transition state for the reaction with p-Me substituted MIDA which is not observed in the m-NO_2 equivalent. The effect is revealed by the C_{ortho}-H distance (shown in Å).*

12. S_N1 via monocyclic intermediate

The ring-opened intermediate ("open-**1a**") was studied at Levels 1 and 2 which place it at 27-29 kcal/mol above the reactant. Experimentally, the barrier for the dissociative process is found to be >30 kcal/mol (see section IX above) which is consistent with the energies found for the intermediate and a small free energy barrier of 2-4 kcal/mol for reassociation of the B-N bond.



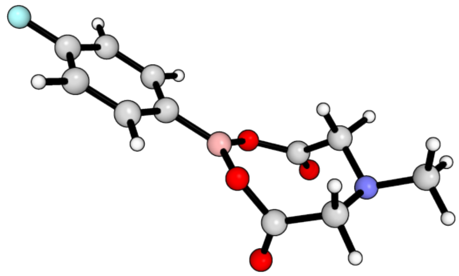


Figure 60. *The lowest energy conformation of "open-**1a**".*

Level	Lowest free energy of "open"-1a compared to 1a (kcal/mol)
1A	29.0
2A	26.9 (28.0)
2B	26.9 (28.0)
2C	26.9 (28.0)

***Table 25**. Free energies of open-chain S_N1 intermediate **1a** compared to "open-**1a**".*

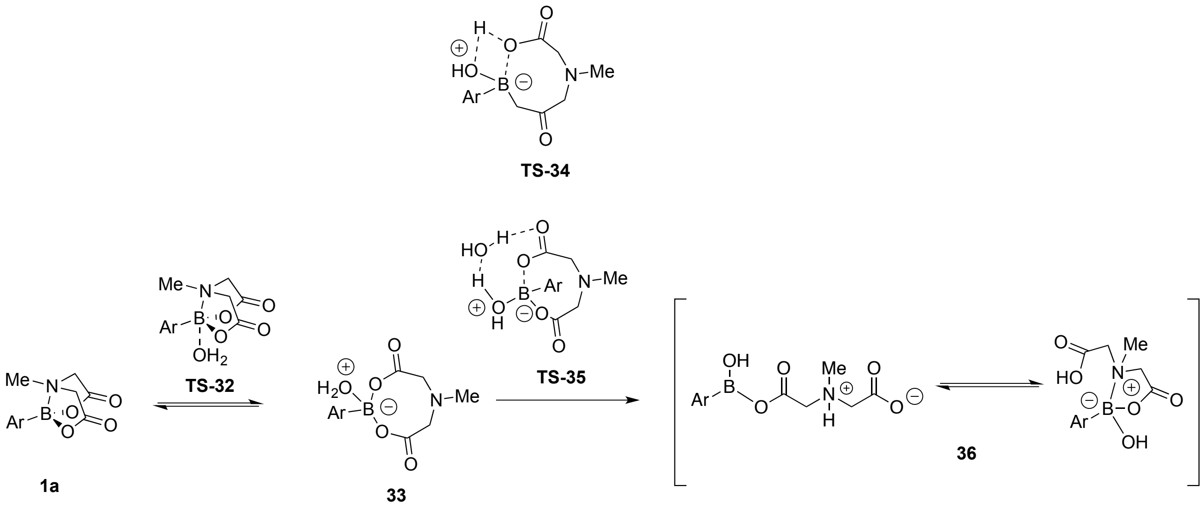
13. Backside-B-S_N2 Attack (*anti* to N)

The initial backside attack by a water molecule to cleave the B-N bond leads, via TS-**32**, to intermediate **33**. The geometry and energetics for this mechanism are affected by the level of theory employed. Level 1, which includes solvation in the geometry optimization, yields an intermediate, **33**, in which the nitrogen is held in proximity to the boron while Levels 2 and 3 require nitrogen inversion and hence the nitrogen is more remote. The energies computed for **33** suggest that it is at least 30 kcal/mol above reactants and hence the barrier to reach it must be at least this high. This would exclude this process from any significant contribution to the neutral hydrolysis reaction. The lower energy for **33** found by Level 1 is presumed to be an artifact of the continuum solvation model.

Two mechanisms were identified for the subsequent cleavage of the B-OCO bond in **33**, and both involve deprotonation of the B-bound water molecule. This process involves B-O_{water} bond forming and B-OCO bond breaking while the carboxylate acts as an intramolecular base. This is analogous to a mechanism proposed for the protodeboronation of boronic acids.[9]

The first involves the carboxylate deprotonating the water molecule as the B-OCO bond cleaves, with two types of transition structure identified for this: **TS-34** where one water molecule acts in a four-membered transition structure and **TS-35** where two water molecules act in an eight-membered transition structure. Both (**TS-34** and **TS-35**) are at high free energies (at least 36 kcal/mol above reactant). This process yields acyclic intermediate **36** but the lowest energy conformation of this structure involves reformation of a B-N bond. The hydrolysis of **36** is shared with the front side attack and is described above. The highest point along the whole "backside-B-SN2-attack" pathway (from **1a** and H_2O) is for the B-O cleavage step (converting **33** to **36**) with **TS-35** the lowest free energy transition state for this step. Most levels of theory suggest that the barrier for this process is significantly higher than the process passing through the "front side" transition state **TS-12** or through the open chain intermediate "open-**1a**". The kinetic isotope effects computed for reaction via **TS-35** at two levels of theory are shown in Table 26. These reveal that this process should be marked by a large primary isotope effect for the transferring hydrogen with an overall effect for exchanging H2O and D2O resulting in *k*H/*k*D ~3.8. This is inconsistent with the observed values. This, alongside the energetics (other than for

Level 1, which has artifacts from the continuum solvation model), suggests that this mechanism is not a dominant one.



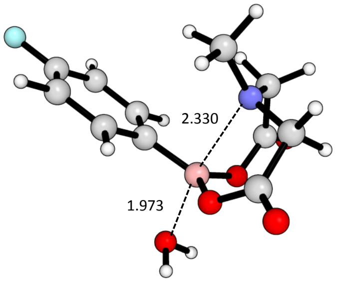


Figure 61. *The structure of **TS-32** optimized at Level 1.*

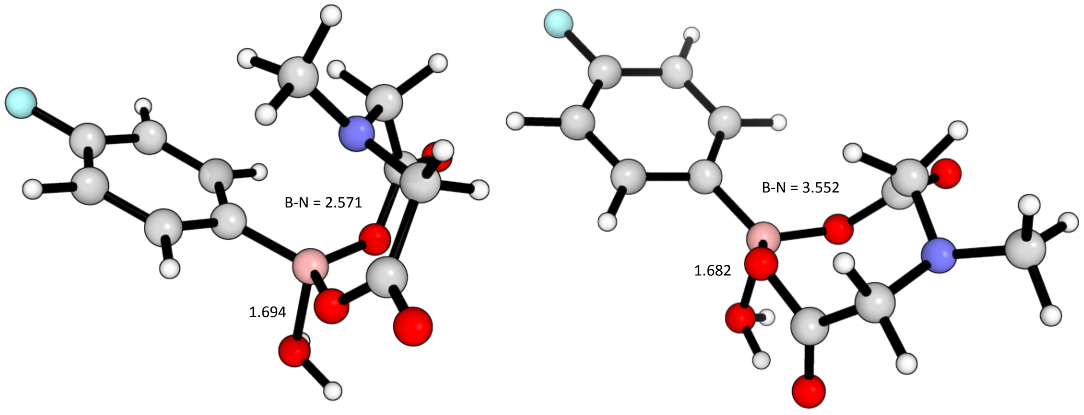


Figure 62. The lowest energy conformation of **33** optimized at Level 1 (left hand side) and at Level 2 (right hand side). Distances are given in Å.

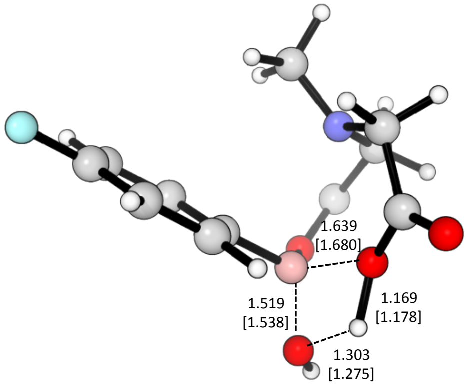


Figure 63. *The lowest energy conformation of* ***TS-34*** *optimized at Level 1. Distances are given in Å for Level 1 with equivalent distances for Level 2 in brackets.*

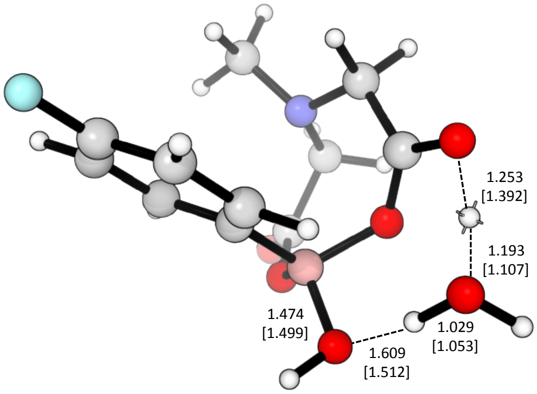


Figure 64. *The lowest energy conformation of* ***TS-35*** *optimized at Level 1. Distances are given in Å for Level 1 with equivalent distances for Level 2 in brackets.*

Level	**Lowest free energy conformation of TS-32 (kcal/mol)**	**Lowest free energy conformation of 33 (kcal/mol)**	**Lowest free energy conformation of TS-34 (kcal/mol)**	**Lowest free energy conformation of TS-35 (kcal/mol)**
1A	20.9	20.5	41.0	21.4
2A		32.8 (34.7)	47.6 (49.4)	36.7 (38.5)
3		30.5 (35.2)	46.3 (49.8)	36.3 (43.1)
B3LYP/6-31+G*(+PCM)		30.2 (34.8)	48.0 (51.6)	38.9 (45.8)

Table 25. *Free energies of transition states and minima for the "back side" reaction with 1 or 2 water molecules. These are relative to reactant* ***1a*** *and 1 or 2 water molecules computed separately.*

Level	k_H/k_D**(1)**	k_H/k_D**(2)**	k_H/k_D**(4 x D)**	$^{10/11}k_B$	$^{14/15}k_N$	$^{12/13}k_C$
1B	4.15, 1.10	0.90, 0.89	3.79	1.010	1.015	1.001
2B	3.19, 1.45	0.87, 0.92	3.82	1.011	1.010	1.001

Table 26*. Kinetic isotope effects computed for a process involving* ***TS-35*** *as rate-limiting transition state.*

The second possibility for hydrolysis via "backside-B-SN2-attack" involves the reversibly formed monocyclic intermediate **32** undergoing conformational changes until the nitrogen can act as a base to deprotonate the B-bound water. This would ultimately entail passing through transition state **TS-12** and would thus be kinetically indistinguishable from the "frontside-B-SN2-attack" process identified as the favourable pathway. However, the high energy of intermediate **33** (> 30 kcal/mol according to the majority of levels of theory employed) makes direct access to **TS-12** via front side attack by far the most likely pathway from reactants to products.

XIV - References

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