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# An Exploration of Regioselectivity During Formation of Aminoboronates from Epoxides

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# General Information

## Solvents

All solvents and reagents were purchased from commercial sources and dried over 4Å MS prior to use unless otherwise stated. Dichloromethane (DCM) was distilled from sodium benzophenone ketyl prior to use. Acetonitrile (MeCN) was distilled from calcium hydride prior to use. Dimethyl sulfoxide (DMSO) was purchased from MilliporeSigma and dried over 4Å MS prior to use. Boron trifluoride diethyl etherate, azidotrimethylsilane, manganese(II) chloride, sodium azide, triphenylphosphine were purchased from MilliporeSigma and used as received.

## Chromatography

Flash column chromatography was carried out using Silicycle 230-400 mesh silica gel. Thin-layer chromatography was performed on Merck Aluminum-backed TLC Silica gel 60 F254 and visualized using a UV lamp (254 nm) and curcumin stain.

## Nuclear Magnetic Resonance Spectroscopy

$^{1}H$, $^{11}B$, and $^{13}C$ NMR and 2D NMR experiments were performed on Varian Mercury 300 MHz, 400 MHz, 500 MHz, 600 MHz or Bruker 400 MHz spectrometers. $^{11}B$ NMR chemical shifts(δ) are reported in parts per million (ppm) referenced to an external standard of $BF_3 \cdot Et_2O$ (δ = 0 ppm). $^{1}H$ NMR chemical shifts (δ) are reported in parts per million (ppm) referenced to residual protonated solvent peak ($CD_3CN$ δ = 1.94 ppm, $CDCl_3$ δ = 7.26 ppm, DMSO δ = 2.50). Spectral data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, ddt = doublet of doublet of triplets, dtd = doublet of triplet of doublets, m = multiplet, br = broad), coupling constant (*J*) in Hertz (Hz), and integration. $^{13}C$ NMR spectra chemical shifts (δ) are reported in parts per million (ppm) and were referenced to carbon resonances in the corresponding NMR solvent ($CD_3CN$ δ = 118.2, 1.3 (center line), $CDCl_3$ δ = 77.1 (center line), DMSO δ = 39.5 (center line)). Carbon atoms exhibiting significant line broadening brought about by boron substituents were not reported due to quadrupolar relaxation.

## Mass Spectroscopy

High-resolution mass spectra were obtained on a VG 70-250S (double focusing) mass spectrometer at 70 eV or on an ABI/Sciex Qstar mass spectrometer with ESI or DART source, MS/MS and accurate mass capabilities.

## RP-HPLC/MS

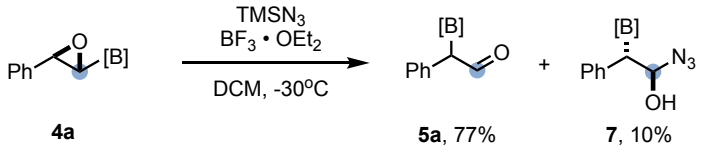
Low-resolution mass spectra (ESI) were collected on an Agilent Technologies 1200 series HPLC paired to a 6130 Mass Spectrometer. Compounds were resolved on Phenomenex's Kinetex 2.6u C18 50x4.6mm column at room temperature with a flow of 1 mL/min. The gradient consisted of eluents A (0.1% formic acid in double distilled water) and B (0.1% formic acid in HPLC-grade acetonitrile).

# Experimental Procedures and Characterization

MIDA (*trans*-3-phenyloxiran-2-yl)boronate (**4a**),[1] MIDA (2-oxo-1-phenylethyl)boronate (**5a**),[1] MIDA (2-phenyloxiran-2-yl)boronate (**8a**),[1] vinyl MIDA boronate (**9a**),[2] $\alpha$-bromoacetyl MIDA boronate (**3b**)[3] were synthesized according to literature procedures.

## Preparation and Characterization of Compounds

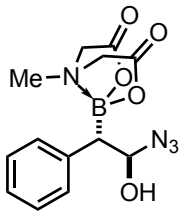
**Synthesis of Boryl 1,1-Azidoalcohol (7) From 4a**




**4a** **5a**, 77% **7**, 10%

To a flame-dried flask equipped with a magnetic stirring bar and a rubber septum was added oxiranyl MIDA boronate **4a** (0.3 mmol, 1.0 equiv., 83 mg) in 3 mL anhydrous DCM. The solution was cooled to –30°C. $TMSN_3$ (0.6 mmol, 2.0 equiv., 0.079 mL) was added dropwise with stirring. After that, $BF_3 \cdot Et_2O$ (0.3 mmol, 1.0 equiv., 0.037 mL) was added dropwise with stirring at –30°C. The mixture was then stirred at –30°C to 0°C over 30 min. The reaction was quenched by saturated aqueous $NaHCO_3$. The organic layer was then separated using DCM for washing the flask; the aqueous layer was extracted with EtOAc (5 mL × 2). The combined organic layer was dried over

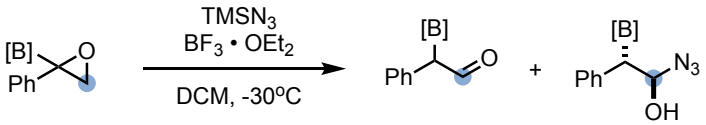
anhydrous $Na_2SO_4$ and concentrated to dryness. The crude residue was purified using flash column chromatography on silica gel (Hexanes/EtOAc 1:1 → EtOAc → EtOAc/MeCN 9:1) to afford pure products **5a** (77% isolated yield, 63 mg) and **7** (10% isolated yield, 9 mg). The NMR spectra matched the reported spectra of **5a**.



**7**

White solid; 10% isolated yield, 9 mg. $^1$H NMR (600 MHz, $CD_3CN$) δ 7.35 – 7.29 (m, 4H), 7.28 – 7.23 (m, 1H), 5.40 (d, $J$ = 8.7 Hz, 1H), 4.13 – 3.87 (m, 3H), 3.49 (d, $J$ = 17.2 Hz, 1H), 2.94 (s, 3H), 2.64 (d, $J$ = 8.7 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CD_3CN$) δ 168.8, 168.7, 140.2, 130.8, 129.4, 127.5, 81.4, 64.3, 63.8, 47.7 ppm; $^{11}$B NMR (128 MHz, $CD_3CN$) δ 11.5 ppm. As the carbon directly attached to the boron atom exhibited significant line broadening due to quadrupolar relaxation, its chemical shift was deduced from HMBC spectra and was 42.1 ppm.

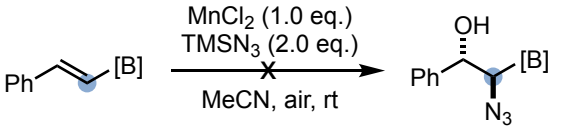
**Synthesis of Boryl 1,1-Azidoalcohol (7) From 8a**



**8a** **5a**, 80% **7**, 8%

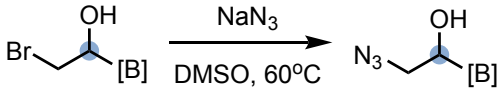
To a flame-dried flask equipped with a magnetic stirring bar and a rubber septum was added MIDA (2-phenyloxiran-2-yl)boronate **8a** (0.3 mmol, 1.0 equiv., 83 mg) in 3 mL anhydrous DCM. The solution was cooled to –30°C. $TMSN_3$ (0.6 mmol, 2.0 equiv., 0.079 mL) was added dropwise with stirring. After that, $BF_3{\cdot}Et_2O$ (0.3 mmol, 1.0 equiv., 0.037 mL) was added dropwise with stirring at –30°C. The mixture was then stirred at –30°C to 0°C over 30 min. The reaction was quenched by saturated aqueous $NaHCO_3$. The organic layer was then separated using DCM for washing the flask; the aqueous layer was extracted with EtOAc (5 mL × 2). The combined organic layer was dried over anhydrous $Na_2SO_4$ and concentrated to dryness. The crude residue was purified using flash column chromatography on silica gel (Hexanes/EtOAc 1:1 → EtOAc → EtOAc/MeCN 9:1) to afford pure products **5a** (80% isolated yield, 65 mg) and **7** (8% isolated yield, 7 mg). The NMR spectra matched the reported spectra of **5a**.

**Attempted Synthesis of Boryl 1,2-Azidoalcohol (6a) From 9a**

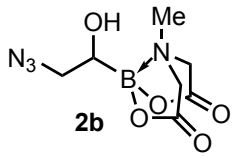



To a flask equipped with a magnetic stirring bar and a rubber septum was added vinyl MIDA boronate **9a** (0.3 mmol, 1.0 equiv., 78 mg), $TMSN_3$ (0.6 mmol, 2.0 equiv., 79 μL), $MnCl_2$ (0.3 mmol, 1.0 equiv., 38 mg) and $H_2O$ (54 μL, 3 mmol) in 2 mL MeCN at room temperature under ambient air. The reaction was monitored by TLC and $^1H$ and $^{11}B$ NMR. The formation of 1,2-azidoalcohol **6a** was not observed.

**Synthesis of Boryl 1,2-Azidoalcohol (2b)**

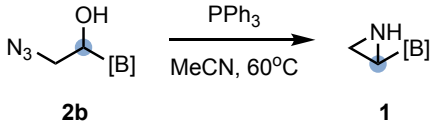



To a flask equipped with a magnetic stirring bar and a rubber septum was added *α*-bromoacetyl MIDA boronate **3b** (2.82 mmol, 1.0 equiv., 790 mg) in 5.6 mL DMSO (0.5 M) at room temperature under air. To a solution was added sodium azide (8.47 mmol, 3.0 equiv., 550 mg). The mixture was then heated to 60°C and the reaction was stirred at 60°C for 18 hours or as indicated by TLC. Upon completion, the reaction mixture was diluted with water and EtOAc and transferred to a separatory funnel. The organic layer was then separated. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous $Na_2SO_4$ and concentrated to dryness. The crude residue was purified using flash column chromatography on silica gel (EtOAc → EtOAc/MeCN 9:1) to afford pure product **2b** (42% isolated yield, 287 mg).



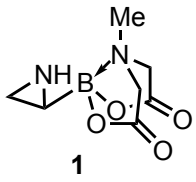

White solid; 42% isolated yield, 287 mg. $^1H$ NMR (400 MHz, $CD_3CN$) δ 3.96 (dd, *J* = 16.8, 2.0 Hz, 2H), 3.83 (dd, *J* = 16.8, 2.8 Hz, 2H), 3.53 – 3.42 (m, 2H), 3.33 (dd, *J* = 12.9, 10.0 Hz, 1H), 3.04 (s, 3H) ppm; $^{13}C$ NMR (126 MHz, $CD_3CN$) δ 169.5, 168.8, 63.1, 62.9, 56.2, 46.4 ppm; $^{11}B$ NMR (128 MHz, $CD_3CN$) δ 10.3 ppm. HRMS (DART-AccuTOF 4G) [$M+NH_4^+$] *m/z* calculated for $C_7H_{15}BN_5O_5$ = 260.1161; *m/z* found = 260.1164.

**Synthesis of Boryl Aziridine (1)**




**2b** **1**

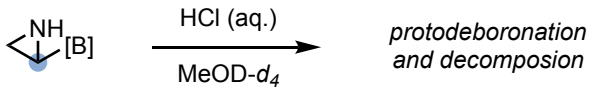
To a flame-dried flask equipped with a magnetic stirring bar and a rubber septum was added 1,2-azidoalcohol **2b** (0.48 mmol, 1.0 equiv., 116 mg) in 5 mL anhydrous MeCN at room temperature. Triphenylphosphine (0.96 mmol, 2.0 equiv., 251 mg) was then added to the solution. The mixture was allowed to stir at room temperature for 1 hour. The mixture was then heated to 60°C and the reaction was stirred at 60°C for 2 hours or as indicated by TLC. Upon completion, the reaction mixture was concentrated in vacuo to dryness. $Et_2O$ was added to a crude reaction and sonicated under air. $Et_2O$ was decanted and the washing was repeated 2 times. The white solid was then dried in vacuo to afford pure product **1** (88% isolated yield, 83 mg).




**1**

White solid; 88% isolated yield, 83 mg. $^1$H NMR (400 MHz, $CD_3CN$) δ 3.97 – 3.77 (m, 4H), 3.03 (s, 3H), 1.72 (d, *J* = 6.9 Hz, 1H), 1.36 (d, *J* = 4.2 Hz, 1H), 0.99 (dd, *J* = 6.9, 4.4 Hz, 1H) ppm; $^{13}$C NMR (126 MHz, $CD_3CN$) δ 168.9, 63.1, 62.7, 46.8, 22.5 ppm; $^{11}$B NMR (128 MHz, $CD_3CN$) δ 11.3 ppm. HRMS (ESI-MS) [M+H$^+$] *m/z* calculated for $C_7H_{12}BN_2O_4$ = 198.0921; *m/z* found = 198.0921.

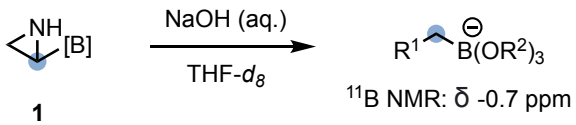
**Deprotection of 1 Under Acidic Conditions**




**1**

**1** (10 mg, 0.05 mmol, 1.0 equiv.) was transferred to a 5 mm NMR tube in 250 µL of MeOD-*d*$_4$. An aqueous solution of 2 M HCl (250 µL, 0.5 mmol, 10 equiv.) was added to the tube at room temperature. The reaction was monitored by $^1$H and $^{11}$B NMR. Decomposition of **1** was observed after 20 minutes.

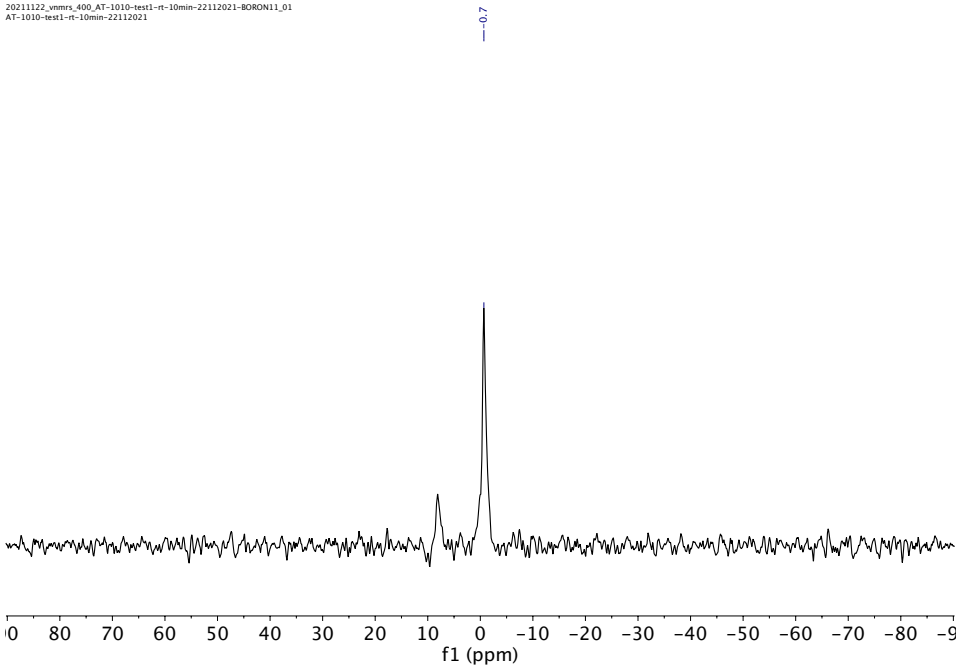
**Deprotection of 1 Under Basic Conditions**



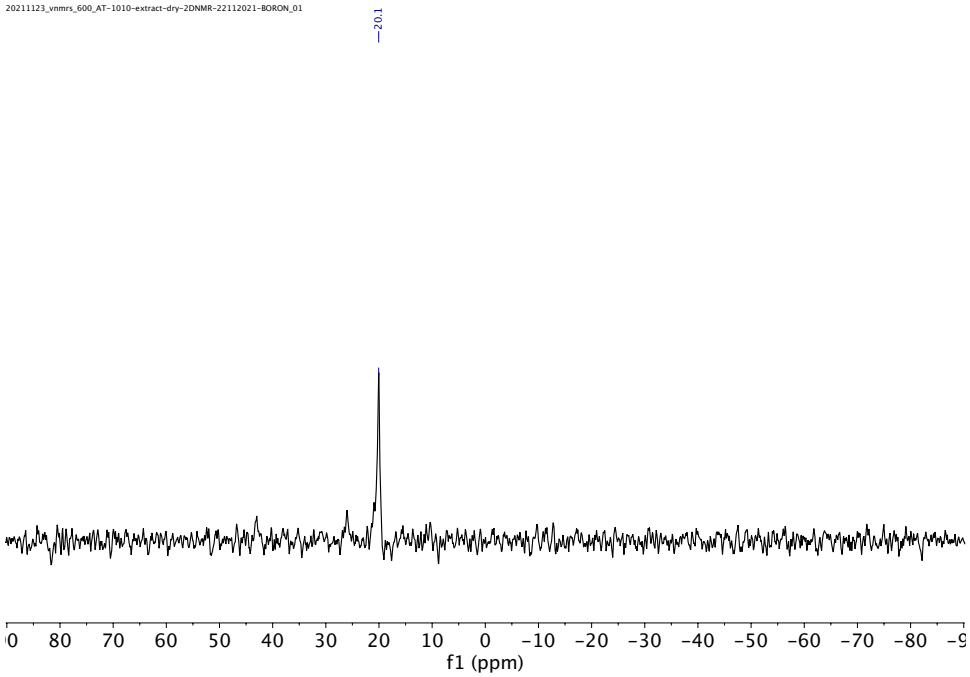

**1**

**1** (10 mg, 0.05 mmol, 1.0 equiv.) was transferred to a 5 mm NMR tube in 250 µL of THF-$d_8$. An aqueous solution of 1 M NaOH (150 µL, 0.150 mmol, 3.0 equiv.) was added to the tube at room temperature. The reaction was monitored by $^{1}$H and $^{11}$B NMR. The boron-containing species with a chemical shift of -0.7 ppm was observed by $^{11}$B NMR after 10 minutes. Decomposition to boric acid was observed after aqueous work-up.

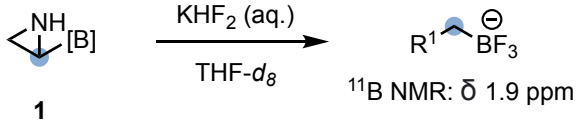
$^{11}$B NMR (128 MHz, THF-$d_8$) of the crude reaction after 10 minutes at room temperature:




$^{11}$B NMR (192 MHz, $CD_3CN$-$d_3$) of the crude reaction after aqueous work-up:



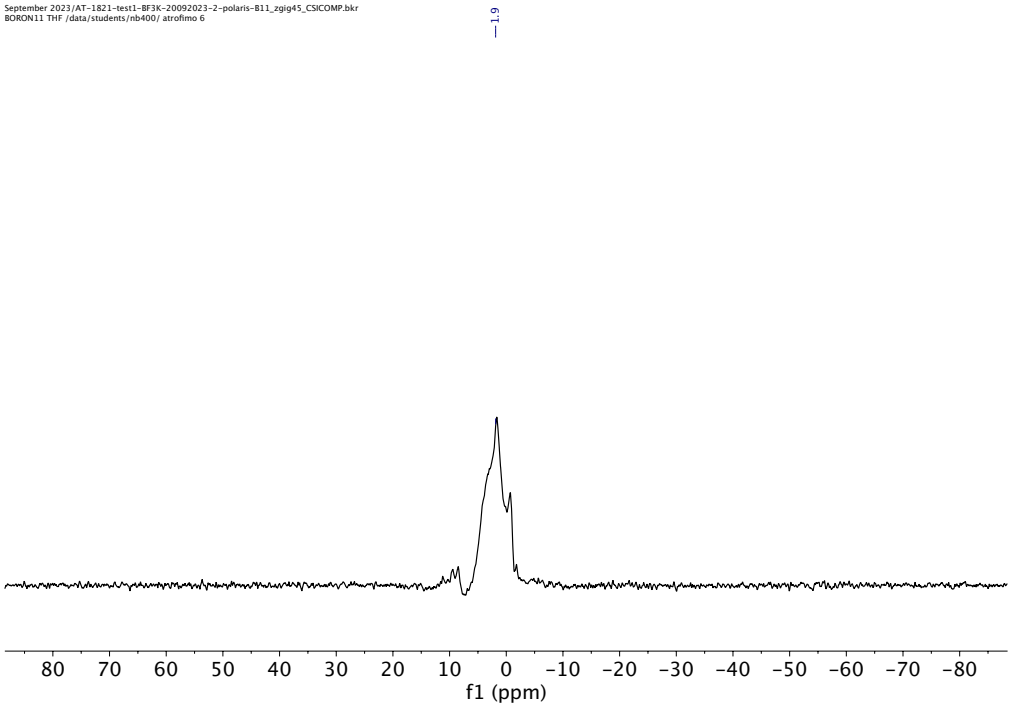
**Preparation of Potassium Trifluroboronate Salt from 1**



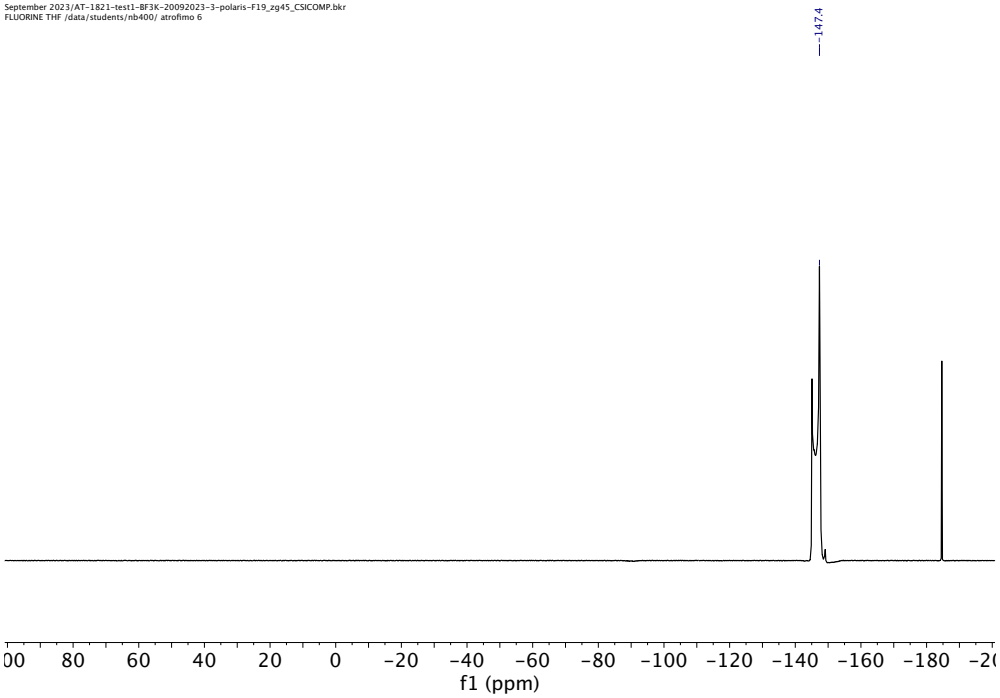

**1**

**1** (10 mg, 0.05 mmol, 1.0 equiv.) was transferred to a 5 mm NMR tube in 330 µL of THF-$d_8$. A $KHF_2$ saturated aqueous solution (165 µL) was added to the tube at room temperature. The reaction was monitored by $^{1}H$,$^{11}B$, and $^{19}F$ NMR. The boron-containing species with the chemical shift of 1.9 ppm was observed by $^{11}B$ NMR after 10 minutes.

$^{11}B$ NMR (128 MHz, THF-$d_8$) of the crude reaction after 10 minutes at room temperature:



$^{19}$F NMR (377 MHz, THF-$d_8$) of the crude reaction after 10 minutes at room temperature:




# References:


1. He, Z.; Yudin, A.K. *J. Am. Chem. Soc*. **2011**, *133*, 13770.

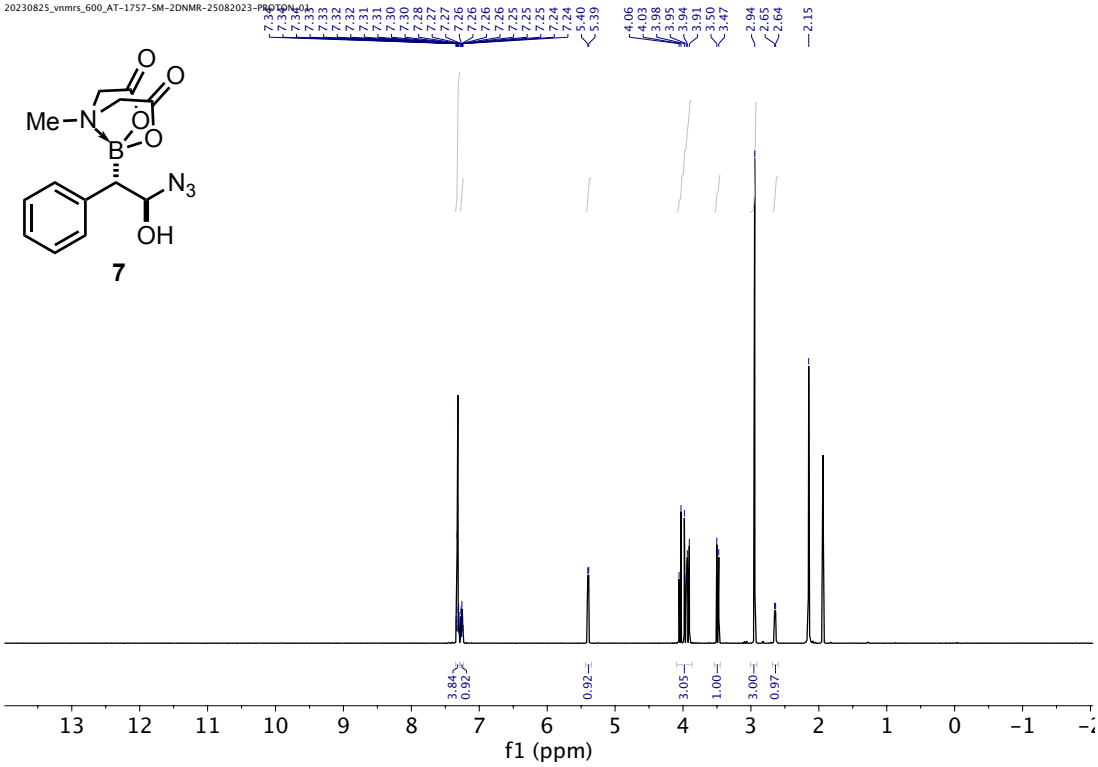
2. Uno, B. E.; Gillis, E. P.; Burke, M. D. *Tetrahedron* **2009**, *65*, 3130.

3. a) Lee, C. F.; Tien, C.-H.; Adachi, S.; Yudin, A. K. *Org. Synth.* **2020**, *97*, 157; b) Adachi, S.; Liew, S. K.; Lee, C. F.; Lough, A.; He, Z.; Denis, J. D. S.; Poda, G.; Yudin, A. K. *Org. Lett.* **2015**, *17*, 5594.

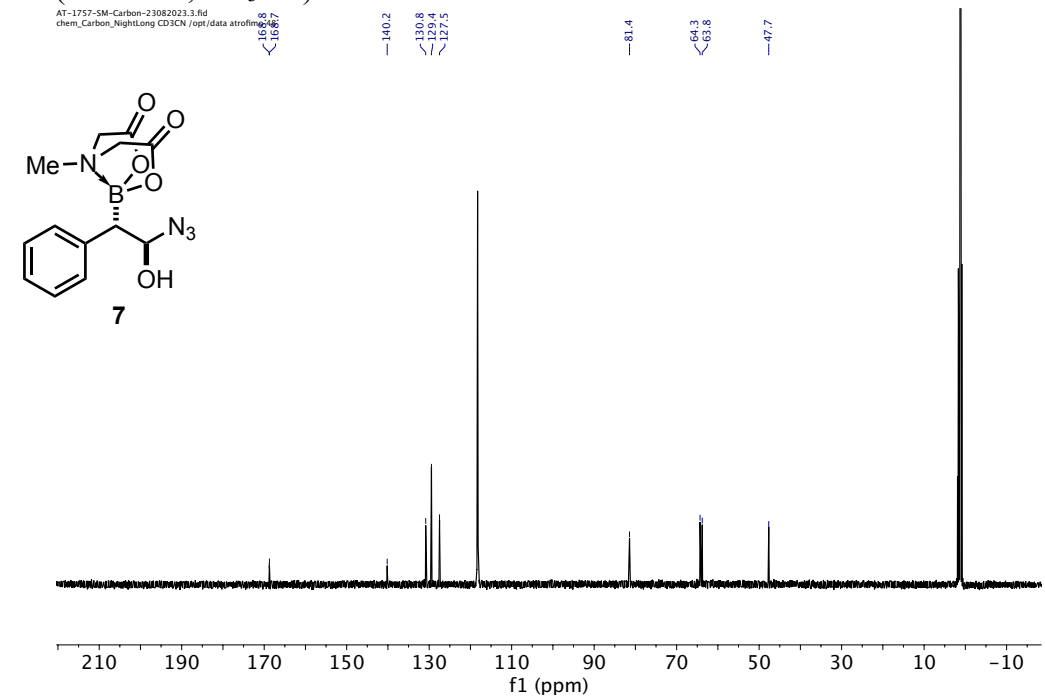
# NMR Spectra

## Boryl 1,1-azidoalcohol (7)

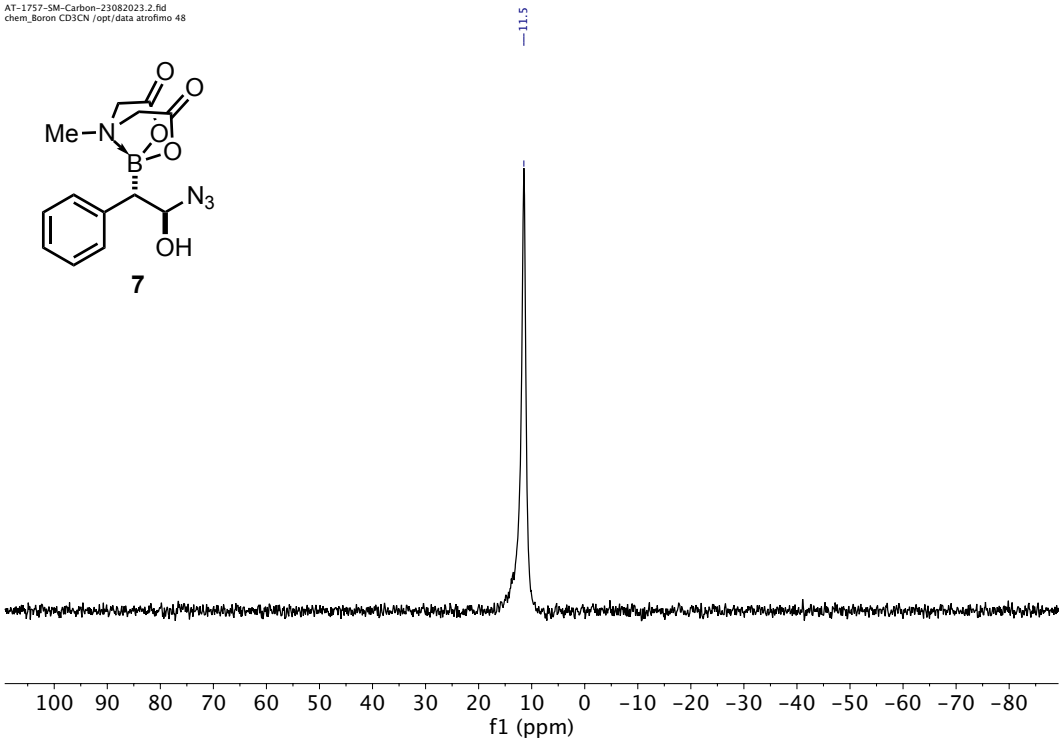
$^{1}$H NMR (600 MHz, $CD_3CN$)



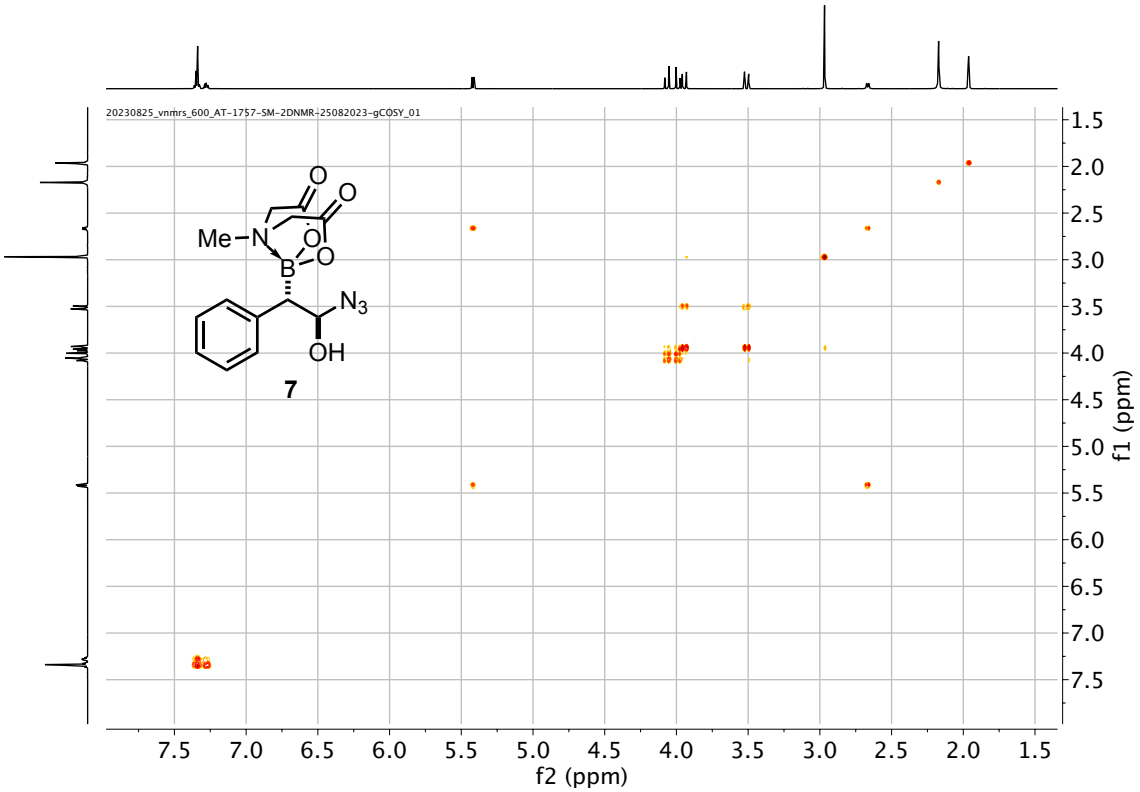

$^{13}$C NMR (101 MHz, $CD_3CN$)



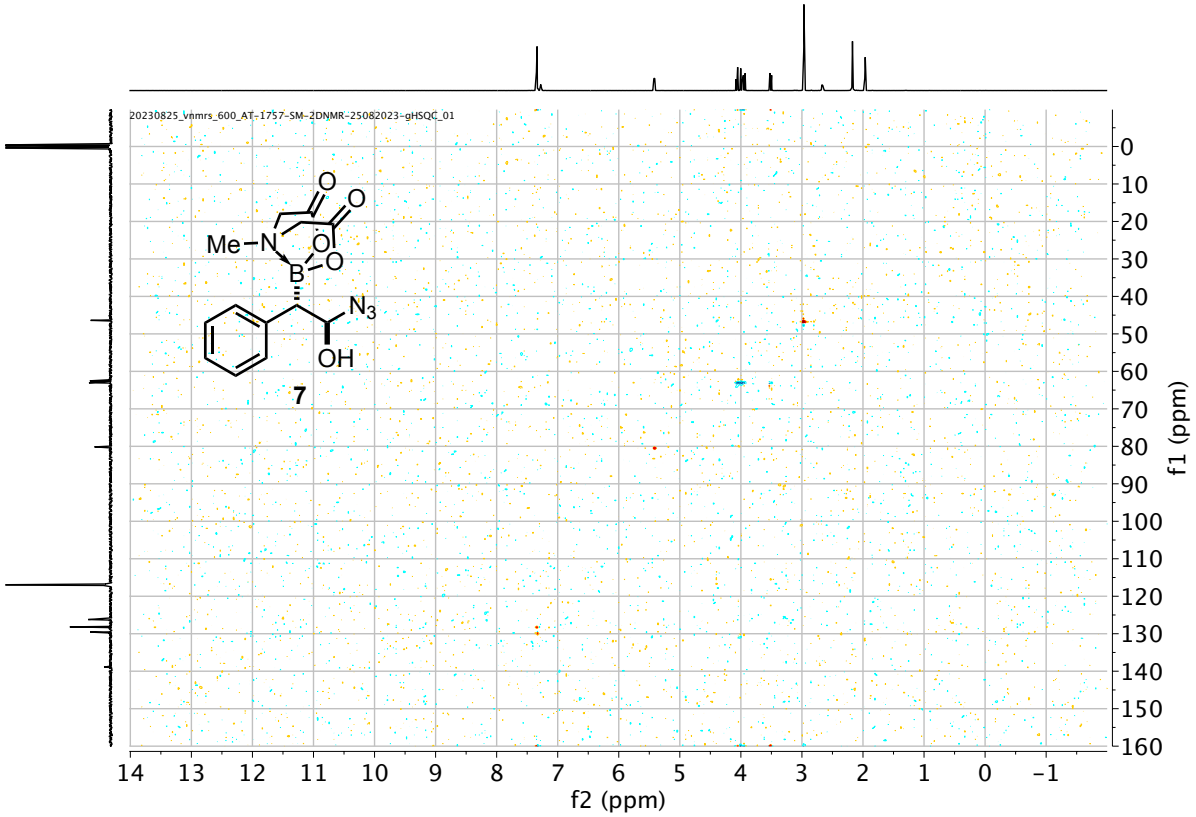
$^{11}$B NMR (128 MHz, $CD_3CN$)



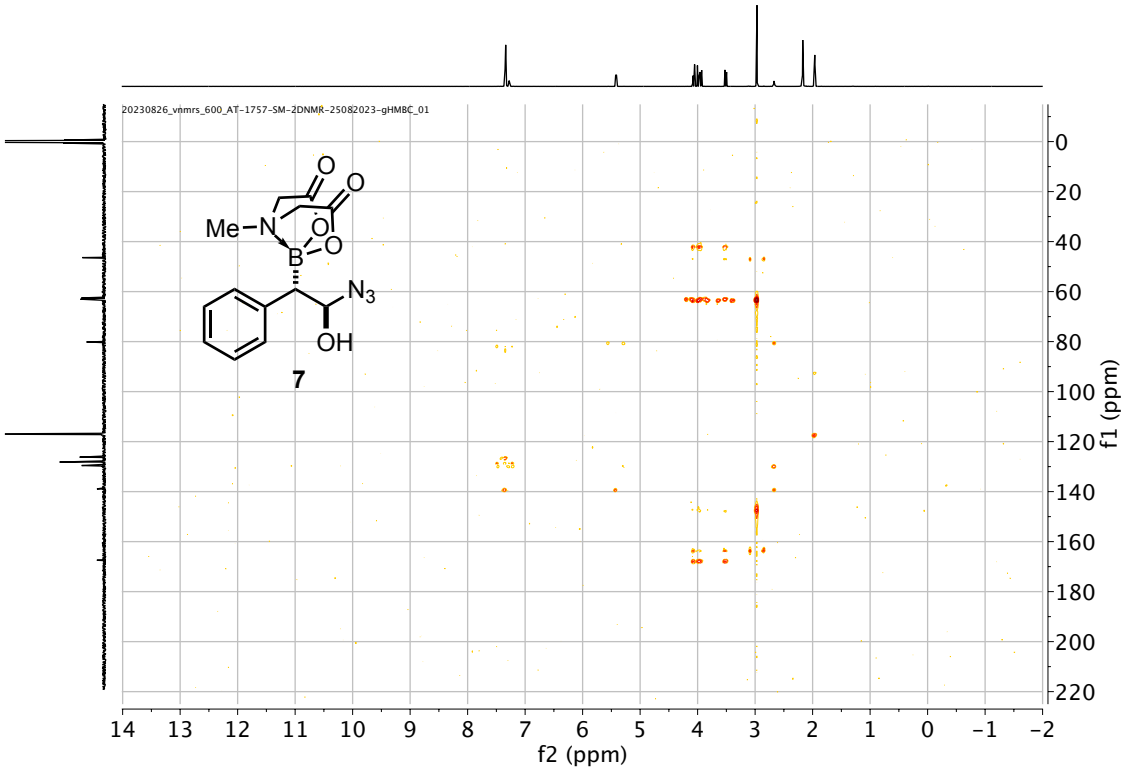

gCOSY NMR (600 MHz, $CD_3CN$)



gHSQC NMR (600 MHz, $CD_3CN$)

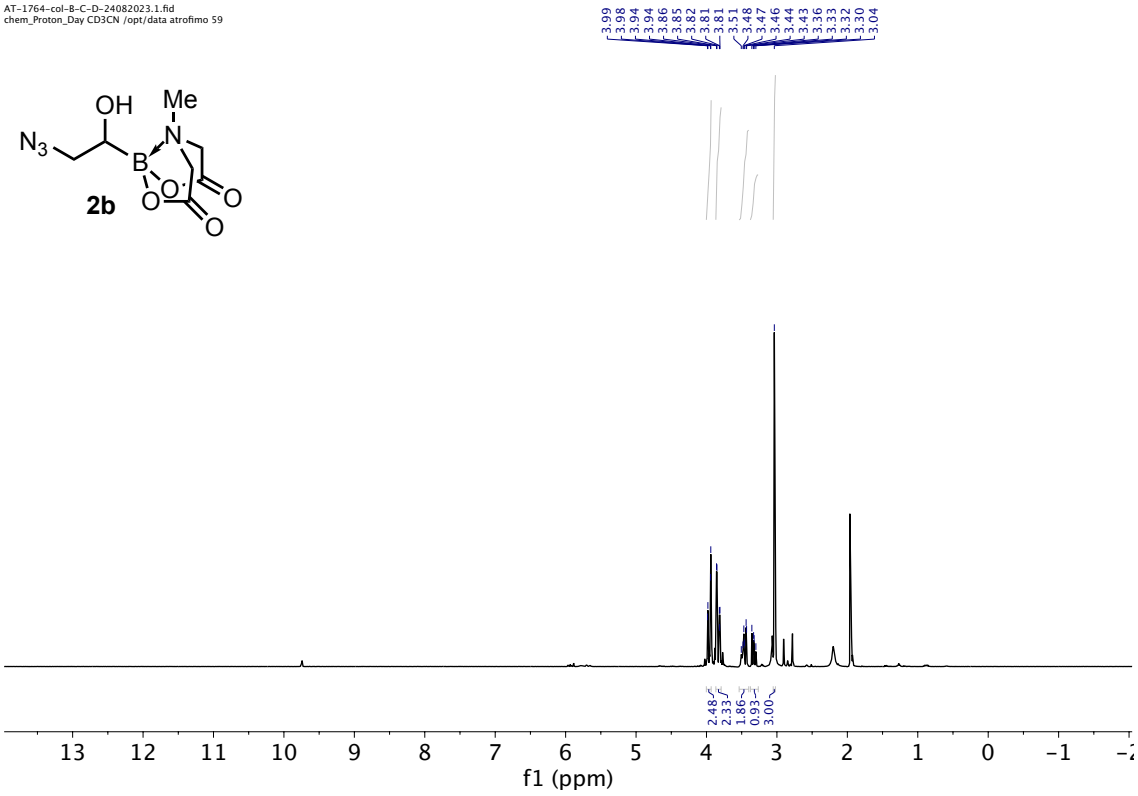



gHMBC NMR (600 MHz, $CD_3CN$)

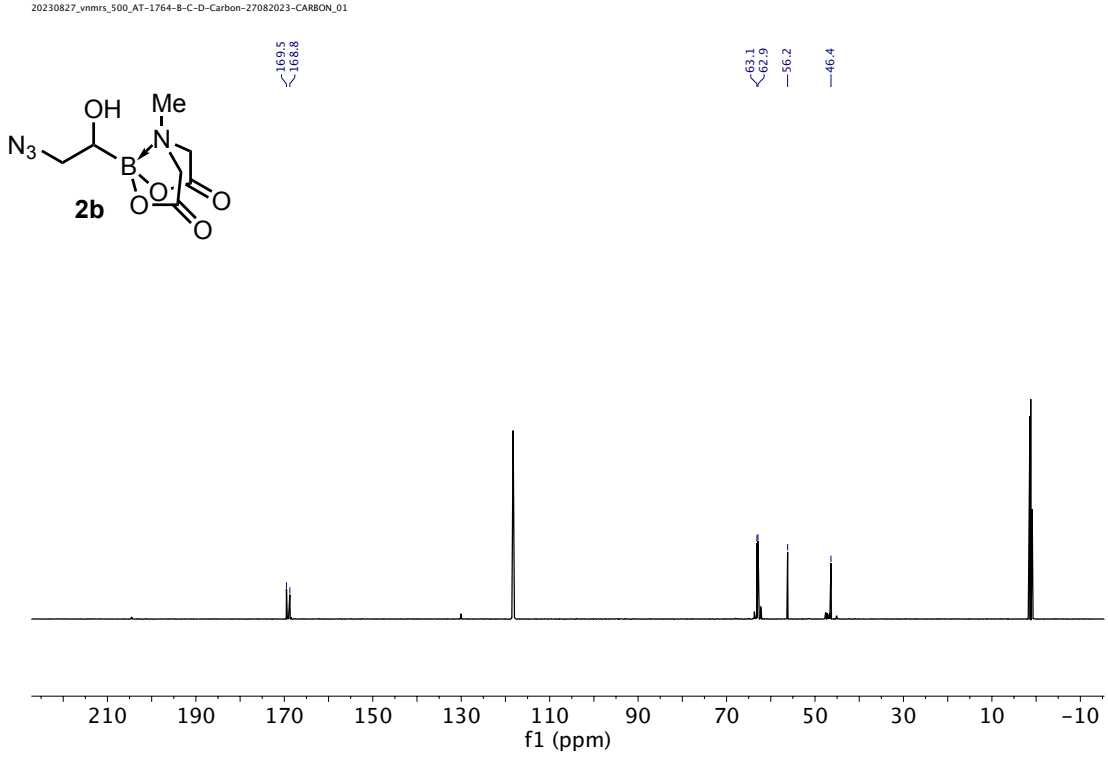


## Boryl 1,2-azidoalcohol (2b)

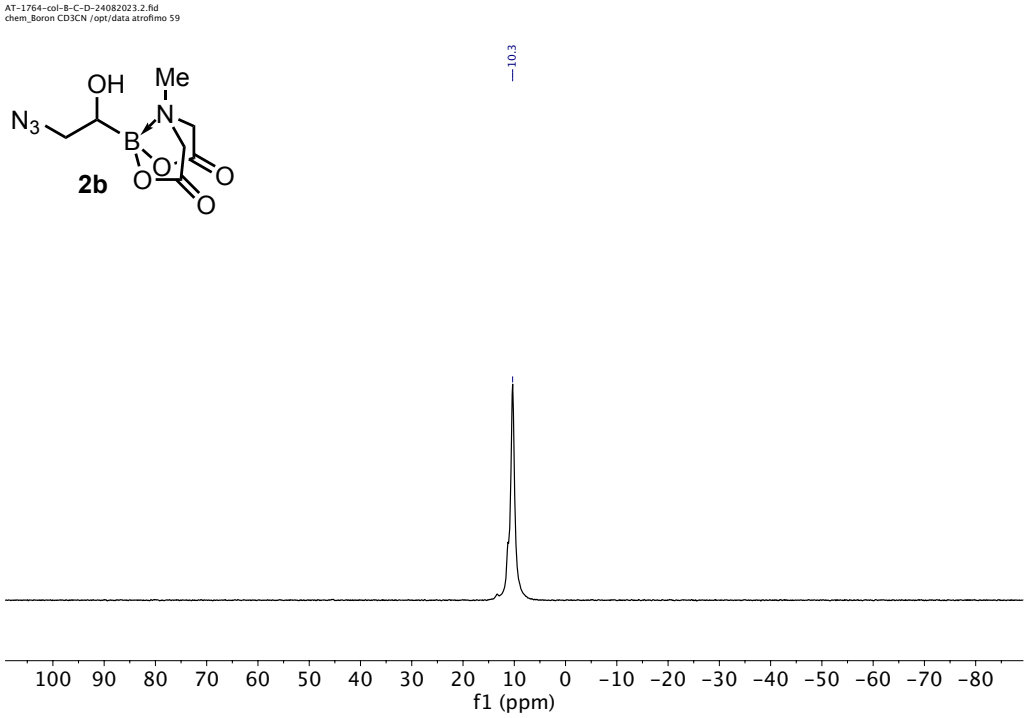
$^{1}$H NMR (400 MHz, $CD_3CN$)




$^{13}$C NMR (101 MHz, $CD_3CN$)

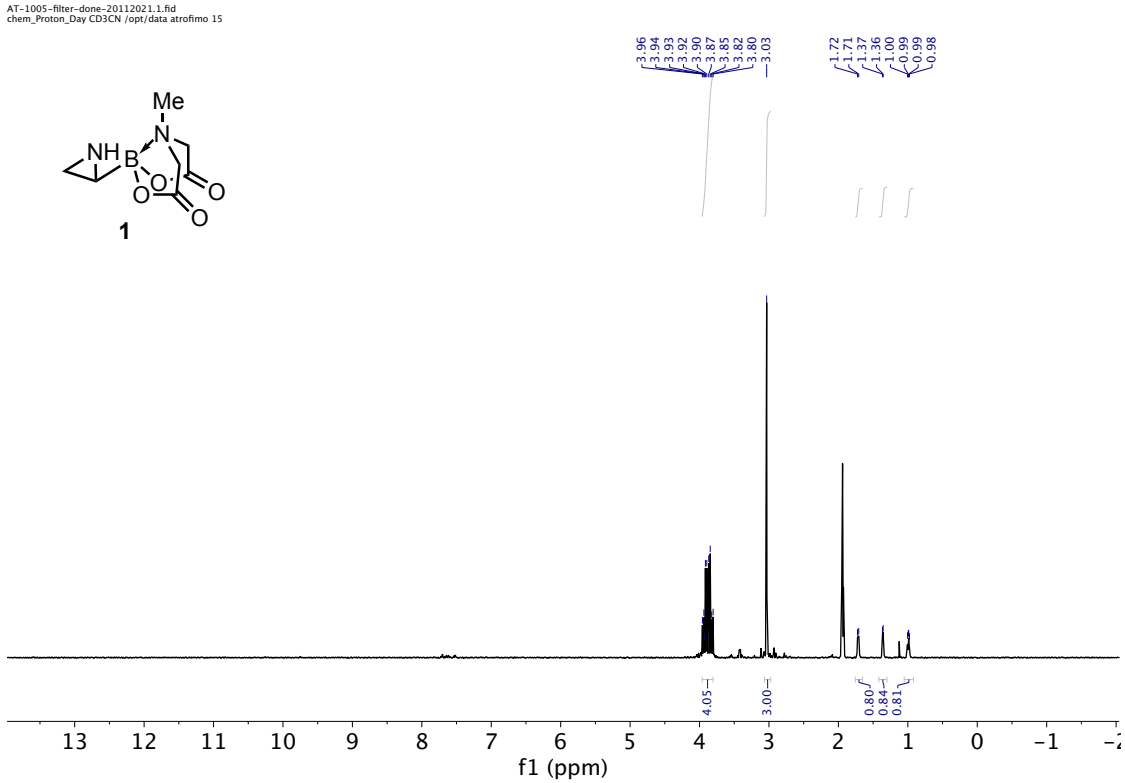


$^{11}$B NMR (128 MHz, $CD_3CN$)

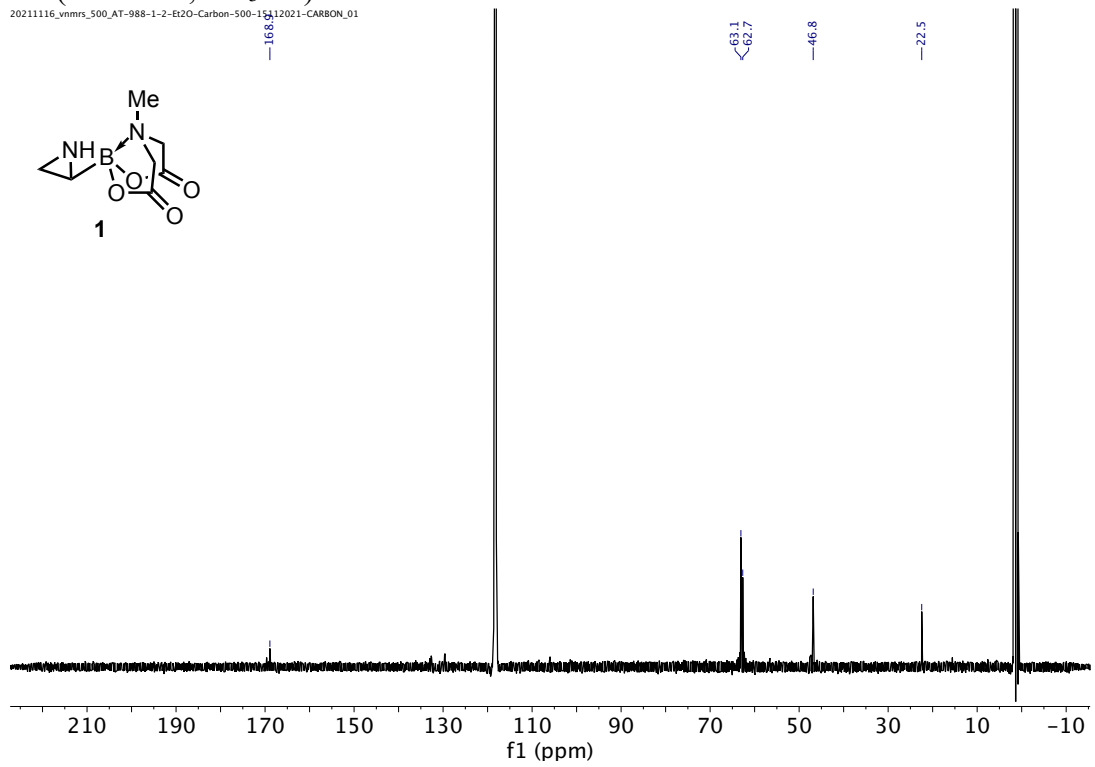



## Boryl aziridine (1)

$^{1}$H NMR (400 MHz, $CD_3CN$)



$^{13}$C NMR (101 MHz, $CD_3CN$)




$^{11}$B NMR (128 MHz, $CD_3CN$)