A general method for synthesis of 2-heterocyclic *N*-metyliminodiacetic acid boronates

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Supporting Information

I. General methods

Materials. Commercial reagents were obtained from Sigma-Aldrich, Fisher Scientific, TCI America Frontier Scientific, Matrix Scientific, Combi-Blocks, Cambridge Isotopes Laboratories, Acros Organics, or Alfa Aesar and were used without further purification. Solvents were purified via passage through packed columns as described by Pangborn and coworkers[1] (THF, Et_2O, CH_3CN, CH_2Cl_2: dry neutral alumina; hexane, benzene, and toluene: dry neutral alumina and Q-5 reactant (copper(II) oxide on alumina); DMSO, DMF: activated molecular sieves). Water was deionized prior to use. *N*-methyliminodiacetic acid was prepared according to literature[2] or via the modified procedure described below and then subjected to additional drying using an Abderhalden pistol with toluene and phosphorous pentoxide. The following MIDA boronates are now commercially available from Sigma-Aldrich http://sigma-aldrich.com/mida: **1a** 719390, **1b** 723959, **1e** 723053.

General Experimental Procedures. Unless otherwise noted, all reactions were performed in flame-dried glassware under argon. Organic solutions were concentrated via rotary evaporation under reduced pressure with a bath temperature of 20-60 ºC. Reactions were monitored by analytical thin layer chromatography (TLC) performed using the indicated solvent on E. Merck silica gel 60 F254 plates (0.25mm). Compounds were visualized by exposure to a UV lamp (λ = 254 or 366 nm) and treatment with a solution of $KMnO_4$ followed by brief heating with a Varitemp heat gun. MIDA boronates are compatible with standard silica gel chromatography, including standard loading techniques. Column chromatography was performed using standard methods[3] or with a Teledyne-Isco CombiFlash R_f purification system. Both methods were performed using Merck silica gel grade 9385 60 Å (230-400 mesh). For loading, compounds were adsorbed onto non acid-washed Celite 545 (app.

[1] Pangborn, A. B.; Giardello, M. A; Grubbs, R. H.; Rosen, R. K.; Timmers, F.J. *Organometallics* **1996**, *15*, 1518-1520.
[2] Ballmer, S. G.; Gillis, E. P.; Burke, M. D. *Org. Syn.*, **2009**, *86*, 344-359.
[3] Still, W.C.; Kahn, M.; Mitra, A.; *J. Org. Chem.* **1978**, *43*, 2923-2925.

10 g/mmol crude product) *in vacuo* from an acetonitrile solution. Specifically, in each case the crude residue was dissolved/suspended in acetonitrile and to the mixture was added Celite. The mixture was concentrated *in vacuo* to afford a free flowing powder which was then loaded on top of a silica gel column. To ensure quantitative transfer, this procedure was repeated with a small amount of acetonitrile and Celite to transfer any remaining residue.

Structural analysis. ^{1}H-NMR spectra were recorded at 23 °C on a Varian Unity 500 MHz spectrometer or Varian Unity 400 MHz spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane and referenced to residual protium in the NMR solvent (CD_2HCN, δ = 1.93, center line). Alternatively, NMR-solvents designated as "w/ TMS" were referenced to tetramethylsilane (δ = 0.00 ppm) added as an internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet, m = multiplet, br = broad, app = apparent), coupling constant (*J*) in Hertz (Hz), and integration. ^{13}C NMR spectra were recorded at 23 °C on a Varian Unity 500 MHz spectrometer or a Varian Unity 400 MHz spectrometer. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane and referenced to carbon resonances in the NMR solvent (CD_3CN, δ = 1.30, center line, DMSO-d_6 δ = 39.5, center line) or to added tetramethylsilane (δ = 0.00). Carbons bearing boron substituents were not observed (quadrupolar relaxation). ^{11}B NMR were recorded using a Varian Unity Inova 400 instrument and referenced to an external standard of ($BF_3 \cdot Et_2O$). High resolution mass spectra (HRMS) were performed by Furong Sun and Dr. Steve Mullen at the University of Illinois School of Chemical Sciences Mass Spectrometry Laboratory. X-ray crystallographic analysis of **5** and **7** were carried out by Dr. Danielle Gray and Amy Fuller at the University of Illinois George L. Clark X-Ray facility.

II. Stability of 1a in hot DMSO

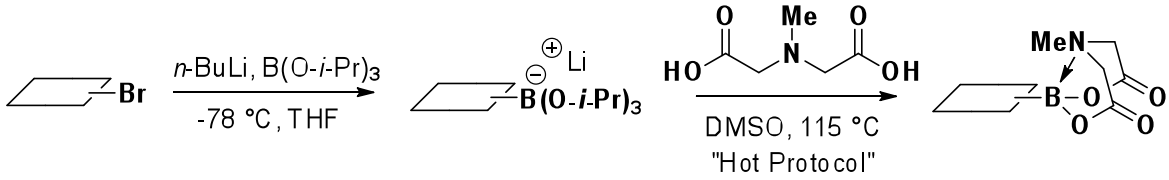
To a dry 7 mL vial equipped with a stir bar was added 2-pyridyl MIDA boronate (5 mg, 0.02 mmol), *p*-bromoanisole (3 μL, 0.02 mmol), and DMSO-d_6 (1 mL). The vial was sealed with a PTFE-lined cap and the mixture was heated to 130 °C with stirring for 1 h. ^{1}H-NMR spectra of the sample before and after heating were indistinguishable.

III. Yield of 1a as a function of internal reaction temperature (Fig. 2B)

To a 25 mL Schlenk flask equipped with a stir bar was added 2-bromopyridine (0.30 mL, 3.1 mmol), triisopropyl borate (0.70 mL, 3.0 mmol), and THF (6 mL). The resulting stirred solution was cooled to -78 °C. To the cooled solution was added dropwise over 5 min *n*-butyllithium (2.58 M in hexanes, 1.2 mL, 3.1 mmol). Following the addition, the reaction was stirred at -78 °C for 1 h, then warmed to 23 °C with stirring for 3 h. Separately, to a 3-neck 50 mL flask equipped with a 25 mL pressure equalizing addition funnel, a water-cooled short-path distillation apparatus, a thermometer, and a stir bar was added *N*-methyiminodiacetic acid (0.75 g, 5.1 mmol) and DMSO-d_6 (6 mL). The mixture was heated with stirring to the internal temperature as indicated (25 °C, 40 °C, 55 °C, 70 °C, 85 °C, 100 °C, 115 °C, or 130 °C). The borate mixture contained in the Schlenk flask was transferred to the addition funnel, washing with THF (6 mL). To the hot, stirred DMSO solution was added dropwise the borate solution at a rate necessary to maintain the internal temperature ± 5 °C from the indicated temperature (ca. 30 min.). Following the addition, the mixture was cooled to room temperature. Where necessary, residual THF was removed *in vacuo*. To the DMSO-d_6 solution was added 4-bromoanisole (0.190 mL, internal standard). The mixture was filtered through a short pad of Celite and the filtrate was then analyzed by ^{1}H-NMR to find the yield of **1a** as determined by reference to the internal standard.

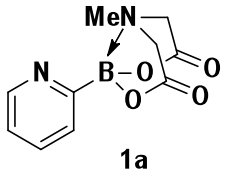
Specifically, the H_3C-N resonance of **1a** at 2.53 ppm was compared to the aromatic resonance of 4-bromoanisole at 6.88 ppm.

IV. Synthesis of MIDA boronates



General procedure for the synthesis of MIDA boronates. To a 50 mL Schlenk flask equipped with a stir bar was added halide (8.6 mmol), triisopropyl borate (2.4 mL, 10 mmol), and THF (17 mL). The resulting stirred solution was cooled to -78 °C. To the cooled solution was added dropwise *n*-butyllithium (2.5 M in hexanes, 8.5 mmol) (ca. 0.25 mL/min). Following the addition, the reaction was stirred at -78 °C for 1 h, then warmed to 23 °C with stirring for 3 h. Separately, to a 3-neck 100 mL flask equipped with a 50 mL pressure equalizing addition funnel, a water-cooled short-path distillation apparatus, a thermometer and a stir bar was added *N*-methyiminodiacetic acid (2.151 g, 14.62 mmol) and DMSO (17 mL). The mixture was heated with stirring to an internal temperature of 115 °C. The borate mixture contained in the Schlenk flask was transferred to the addition funnel, washing with THF (9 mL). To the hot, stirred DMSO solution was added dropwise the borate solution at a rate necessary to maintain the internal temperature at 110-120 °C (ca. 1 h). During the addition the THF was rapidly distilled (distillate temperature of app. 85 °C). Following the addition, the mixture was cooled to 50 °C and the DMSO was removed via distillation (250 mTorr at 50 °C). The resulting residue was cooled to 23 °C and then was adsorbed onto Celite from an acetonitrile suspension and placed under vacuum for 12 h to further remove residual DMSO. The Celite mixture was then subjected to column chromatography on SiO_2 to afford the purified product. Product mixtures containing undesired MIDA boronate byproducts could be recrystallized to afford the pure product as follows: The isolated product was dissolved in hot MeCN (app. 4 mL/mmol product), cooled to room temperature, and precipitated by the dropwise addition of CH_2Cl_2 (app. 16 mL/mmol) to the stirred solution, followed by dropwise addition of Et_2O (app. 50 mL/mmol).

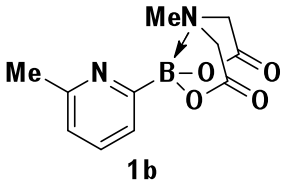
2-pyridyl MIDA boronate (1a). The general procedure was followed using 2-bromopyridine (0.860 mL, 8.82 mmol), triisopropyl borate (2.4 mL, 10 mmol), *n*-BuLi (4.15 mL, 2.29 M in hexanes), and *N*-methyliminodiacetic acid (2.463 g, 16.74 mmol). The product was purified via SiO_2 chromatography (Et_2O:MeCN 95:5 → 0:100) to afford **1a** as an off-white crystalline solid (1.212 g, 59%). Spectral characterization was consistent with literature data.[4]



1a

[4] Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961-6963.

MIDA boronate (1b). The general procedure was followed using 2-bromo-6-methylpyridine (0.98 mL, 8.6 mmol), triisopropyl borate (2.0 mL, 8.7 mmol), *n*-BuLi (3.75 mL, 2.29 M in hexanes), and *N*-methyliminodiacetic acid (2.311 g, 15.71 mmol). The product was purified by SiO_2 chromatography (EtOAc:MeCN 100:0 → 45:55) to afford **1b** as an off-white crystalline solid (1.243 g, 58%).



1b

TLC (MeCN)

R_f = 0.54, visualized by UV (λ = 254 nm) and $KMnO_4$ stain

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

δ 7.57 (app t, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 7.2, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 4.07 (d, *J* = 17 Hz, 2H), 4.00 (d, *J* = 17 Hz, 2H), 2.55 (s, 3H), 2.48 (s, 3H)

^{13}C-NMR (100 MHz, DMSO-d_6)

δ 169.3, 157.6, 135.0, 124.1, 122.5, 61.9, 46.8, 24.5

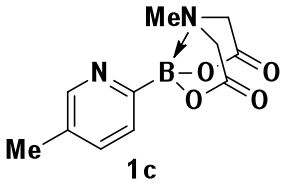
^{11}B-NMR (128 MHz, DMSO-d_6)

δ 9.6

HRMS (ES+)

Calculated for $C_{11}H_{14}O_4N_2B$ $(M+H)^+$:	249.1047
Found:	249.1051

MIDA boronate (1c). The general procedure was followed using 2-bromo-5-methylpyridine (1.489 g, 8.655 mmol), triisopropyl borate (2.4 mL, 10 mmol), *n*-BuLi (4.15 mL, 2.29 M in hexanes), and *N*-methyliminodiacetic acid (2.227 g, 15.14 mmol). The product was purified via SiO_2 chromatography (Et_2O:MeCN 95:5 → 0:100) to afford **1c** as an off-white crystalline solid (1.090 g, 51%).



1c

TLC (MeCN)

R_f = 0.43, visualized by UV (λ = 254 nm) and $KMnO_4$ stain

^{1}H-NMR (500 MHz, CD_3CN)

δ 8.53 (s, 1H), 7.51 (s, 2H), 4.07 (d, *J* = 17 Hz, 2H), 3.96 (d, *J* = 17 Hz, 2H), 2.53 (s, 3H), 2.31 (s,3H)

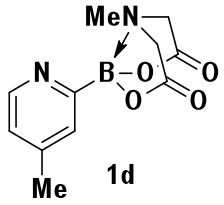
^{13}C-NMR (100 MHz, DMSO-d_6)
δ 169.3, 150.2, 135.1, 132.2, 126.6, 61.9, 46.8, 18.0

^{11}B-NMR (128 MHz, DMSO-d_6)
δ 9.6

HRMS (ES+)

Calculated for $C_{11}H_{14}O_4N_2B$ $(M+H)^+$:	249.1047
Found:	249.1039

MIDA boronate (1d). The general procedure was followed using 2-bromo-4-methylpyridine (0.960 mL, 8.62 mmol), triisopropyl borate (2.4 mL, 10 mmol), *n*-BuLi (4.15 mL, 2.29 M in hexanes), and *N*-methyliminodiacetic acid (2.264 g, 15.39 mmol). The product was purified by SiO_2 chromatography (Et_2O:MeCN 95:5 → 0:100) to afford **1d** as an off-white crystalline solid (897 mg, 42%).



1d

TLC (MeCN)
R_f = 0.29, visualized by UV (λ = 254 nm) and $KMnO_4$ stain

^{1}H-NMR (500 MHz, CD_3CN)
δ 8.51 (d, *J* = 5.0 Hz, 1H), 7.47 (s, 1H), 7.11 (d, *J* = 5.0 Hz, 1H), 4.08 (d, *J* = 17 Hz, 2H), 3.97 (d, *J* = 17 Hz, 2H), 2.54 (s, 3H), 2.33 (s,3H)

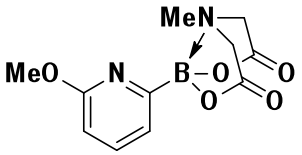
^{13}C-NMR (125 MHz, DMSO-d_6)
δ 169.3, 149.5, 145.2, 128.0, 123.9, 62.0, 46.8, 20.6

^{11}B-NMR (128 MHz, DMSO-d_6)
δ 9.8

HRMS (ES+)

Calculated for $C_{11}H_{14}O_4N_2B$ $(M+H)^+$:	249.1047
Found:	249.1052

MIDA boronate (1e). The general procedure was followed using 2-bromo-6-methoxypyridine (1.05 mL, 8.55 mmol), triisopropyl borate (2.0 mL, 8.7 mmol), *n*-BuLi (6.3 mL, 1.37 M in hexanes), and *N*-methyliminodiacetic acid (2.437 g, 16.56 mmol). The product was purified via SiO_2 chromatography (EtOAc:MeCN 100:0 → 60:40). The isolated product was dissolved in hot MeCN (20 mL), cooled to room temperature, and precipitated by the dropwise addition of Et_2O (200 mL) to the stirred solution. The crystals were collected to afford **1e** as an off-white crystalline solid (1.830 g, 81%).



1e

TLC (EtOAc)

R_f = 0.34, visualized by UV (λ = 254 nm) and $KMnO_4$ stain

^{1}H-NMR (500 MHz, CD_3CN)

δ 7.60 (dd, *J* = 7.5, 7 Hz, 1H), 7.22 (d, *J* = 7.0 Hz, 1H), 6.70 (d, *J* = 8 Hz, 1H), 4.09 (d, *J* = 17 Hz, 2H), 3.99 (d, *J* = 16.5 Hz, 2H), 3.83 (s, 3H), 2.60 (s, 3H)

^{13}C-NMR (100 MHz, DMSO-d_6)

δ 169.2, 163.1, 138.0, 120.4, 110.4, 61.8, 52.6, 46.5

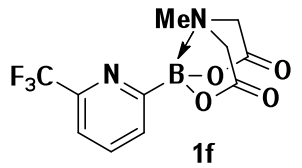
^{11}B-NMR (128 MHz, DMSO-d_6)

δ 9.3

HRMS (ES+)

Calculated for $C_{11}H_{14}O_5N_2B$ $(M+H)^+$:	265.0996
Found:	265.0989

MIDA boronate (1f). The general procedure was followed using 2-bromo-6-trifluoromethylpyridine (1.951g, 8.633 mmol), triisopropyl borate (2.4 mL, 10 mmol), *n*-BuLi (4.15 mL, 2.29 M in hexanes), and *N*-methyliminodiacetic acid (2.293 g, 15.58 mmol). The product was purified via SiO_2 chromatography (hexanes:EtOAc 100:0 → 0:100) to afford **1f** as a tan crystalline solid (2.328 g, 89%).



1f

TLC (EtOAc)

R_f = 0.57, visualized by UV (λ = 254 nm) and $KMnO_4$ stain

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

δ 7.95 (app t, *J* = 7.6 Hz, 1H), 7.88 (d, *J* = 7.2 Hz, 1H), 7.72 (dd, *J* = 7.6, 0.8 Hz, 1H), 4.13 (d, *J* = 17 Hz, 2H), 3.98 (d, *J* = 17 Hz, 2H), 2.57 (s, 3H)

^{13}C-NMR (125 MHz, DMSO-d_6)

δ 169.1, 146.7 (q, *J* = 33 Hz), 137.1, 130.4, 121.8 (q, *J* = 270 Hz), 120.0 (d, *J* = 2.8 Hz), 62.1, 47.1

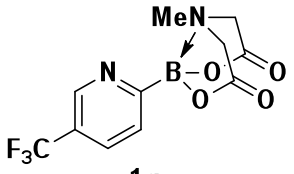
^{11}B-NMR (128 MHz, DMSO-d_6)

δ 9.5

HRMS (ES+)

Calculated for $C_{11}H_{11}O_4N_2BF_3$ $(M+H)^+$:	303.0764
Found:	303.0753

MIDA boronate (1g). The general procedure was followed using 2-bromo-5-trifluoromethylpyridine (1.936 g, 8.567 mmol), triisopropyl borate (2.0 mL, 8.7 mmol), *n*-BuLi (3.35 mL, 2.56 M in hexanes), and *N*-methyliminodiacetic acid (2.222 g, 15.10 mmol). The product was purified via SiO_2 chromatography (EtOAc:MeCN 100:0 → 90:10). The isolated product was dissolved in hot MeCN (8 mL), cooled to room temperature, and precipitated by the dropwise addition of Et_2O (80 mL) to the stirred solution. The crystals were collected to afford **1g** as an off-white crystalline solid (1.448 g, 56%).



1g

TLC (EtOAc)

R_f = 0.43, visualized by UV (λ = 254 nm) and $KMnO_4$ stain

^{1}H-NMR (500 MHz, CD_3CN)

δ 8.99 (s, 1H), 8.00 (dd, *J* = 8.0, 1.5Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 4.13 (d, *J* = 17 Hz, 2H), 4.00 (d, *J* = 17 Hz, 2H), 2.56 (s, 3H)

^{13}C-NMR (125 MHz, DMSO-d_6)

δ 169.2, 145.9, 132.1, 127.2, 124.3 (q, *J* = 32 Hz), 123.9 (q, *J* = 270 Hz), 62.1, 47.0

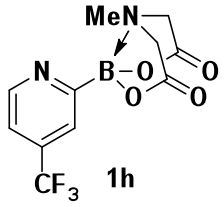
^{11}B-NMR (128 MHz, DMSO-d_6)

δ 8.3

HRMS (ES+)

Calculated for $C_{11}H_{11}O_4N_2BF_3$ $(M+H)^+$:	303.0764
Found:	303.0755

MIDA boronate (1h). The general procedure was followed using 2-bromo-4-trifluoromethylpyridine (1.05 mL, 8.49 mmol), triisopropyl borate (2.0 mL, 8.7 mmol), *n*-BuLi (6.3 mL, 1.37 M in hexanes), and *N*-methyliminodiacetic acid (2.418g, 16.43 mmol). [Note: The triisopropylborate mixture was transferred to the addition funnel using DMSO (43 mL) rather than THF.] The product was purified via SiO_2 chromatography (Et_2O:MeCN 95:5 → 75:25 → 50:50). The isolated product was dissolved in hot MeCN (5 mL), cooled to room temperature, and precipitated by the dropwise addition of Et_2O (50 mL) to the stirred solution. The precipitation procedure was repeated to afford **1h** as an off-white crystalline solid (1.350 g, 53%).



1h

TLC (EtOAc)

R_f = 0.17, visualized by UV (λ = 254 nm) and $KMnO_4$ stain

^{1}H-NMR (500 MHz, CD_3CN)

δ 8.92 (d, *J* = 5.0 Hz, 1H), 7.86 (s, 1H), 7.57 (d, *J* = 5.0 Hz, 1H), 4.13 (d, *J* = 17 Hz, 2H), 4.00 (d, *J* = 17 Hz, 2H), 2.56 (s, 3H)

^{13}C-NMR (125 MHz, DMSO-d_6)

δ 169.2, 151.2, 135.3 (q, *J* = 33 Hz), 123.3 (q, *J* = 270 Hz), 121.8, 118.5, 62.2, 47.1

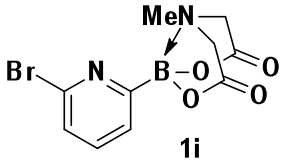
^{11}B-NMR (128 MHz, DMSO-d_6)

δ 9.5

HRMS (ES+)

Calculated for $C_{11}H_{11}O_4N_2BF_3$ $(M+H)^+$:	303.0764
Found:	303.0750

MIDA boronate (1i). The general procedure was followed using 2,6-dibromopyridine (2.036g, 8.594 mmol), triisopropyl borate (2.0 mL, 8.7 mmol), *n*-BuLi (3.4 mL, 2.54 M in hexanes), and *N*-methyliminodiacetic acid (2.2049 g, 14.99 mmol). The product was purified via SiO_2 chromatography (hexanes:EtOAc 25:75 → 0:100). The isolated product was dissolved in hot MeCN (3.5 mL), cooled to room temperature, and precipitated by the dropwise addition of CH_2Cl_2 (15 mL) to the stirred solution, followed by dropwise addition of Et_2O (40 mL). The crystals were collected to afford **1i** as a white crystalline solid (1.269 g, 47%).



1i

TLC (EtOAc)

R_f = 0.46, visualized by UV (λ = 254 nm) and $KMnO_4$ stain

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

δ 7.61 (m, 2H), 7.49 (m, 1H), 4.10 (d, *J* = 17 Hz, 2H), 3.96 (d, *J* = 17 Hz, 2H), 2.58 (s, 3H)

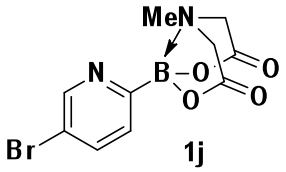
^{13}C-NMR (100 MHz, DMSO-d_6)

δ 169.1, 142.2, 138.5, 127.6, 126.9, 62.0, 47.2

^{11}B-NMR (128 MHz, DMSO-d_6)
δ 9.3

HRMS (ES+)
Calculated for $C_{10}H_{11}O_4N_2BBr$ $(M+H)^+$: 312.9995
Found: 312.9996

MIDA boronate (1j). The general procedure was followed using 2,5-dibromopyridine (2.042 g, 8.620 mmol), triisopropyl borate (2.0 mL, 8.7 mmol), *n*-BuLi (3.35 mL, 2.58 M in hexanes), and *N*-methyliminodiacetic acid (2.260 g, 15.36 mmol). The product was purified via SiO_2 chromatography (Et_2O:MeCN 95:5 → 50:50). The isolated product was dissolved in hot MeCN (3.5 mL), cooled to room temperature, and precipitated by the dropwise addition of CH_2Cl_2 (15 mL) to the stirred solution, followed by the dropwise addition of Et_2O (40 mL). The crystals were collected to afford **1j** as a white crystalline solid (1.856 g, 69%).



1j

TLC (EtOAc)
R_f = 0.24, visualized by UV (λ = 254 nm) and $KMnO_4$ stain

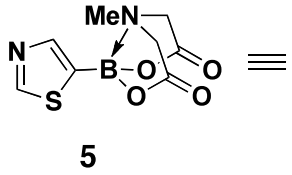
^{1}H-NMR (500 MHz, CD_3CN)
δ 8.42 (d, *J* = 1.5 Hz, 1H), 7.73 (dd, *J* = 8 Hz, 1.5 Hz, 1H), 7.54 (d, *J* = 8 Hz, 1H), 4.09 (d, *J* = 17 Hz, 2H), 3.96 (d, *J* = 17 Hz, 2H), 2.56 (s, 3H)

^{13}C-NMR (125 MHz, DMSO-d_6)
δ 169.1, 154.3, 143.8, 142.8, 127.4, 62.0, 47.8

^{11}B-NMR (128 MHz, DMSO-d_6)
δ 11.0

HRMS (ES+)
Calculated for $C_{10}H_{11}O_4N_2BBr$ $(M+H)^+$: 312.9995
Found: 312.9998

5-thiazolyl MIDA boronate (5). The general procedure was followed using 5-bromothiazole (0.270 mL, 3.02 mmol), triisopropyl borate (0.670 mL, 2.91 mmol), *n*-BuLi (1.2 mL, 2.58 M in hexanes), and *N*-methyliminodiacetic acid (775 mg, 5.27 mmol). The product was purified via SiO_2 chromatography (Et_2O:MecN 95:5 → 0:100). The isolated product was dissolved in hot MeCN (5 mL), cooled to room temperature, and precipitated by the dropwise addition of CH_2Cl_2 (20 mL) to the stirred solution, followed by dropwise addition of Et_2O (60 mL). The crystals were collected to afford **5** as a tan crystalline solid (213 mg, 30%).



5

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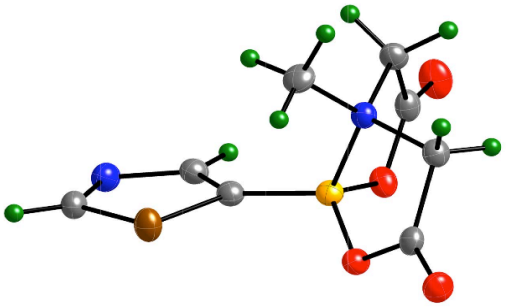


TLC (MeCN)

R_f = 0.67, visualized by UV (λ = 254 nm) and $KMnO_4$ stain

^{1}H-NMR (500 MHz, CD_3CN)

δ 9.03 (s, 1H), 7.98 (s, 1H), 4.10 (d, *J* = 18 Hz, 2H), 3.93 (d, *J* = 18 Hz, 2H), 2.63 (s, 3H)

^{13}C-NMR (125 MHz, CD_3CN)

δ 168.8, 158.1, 150.0, 62.6, 48.5

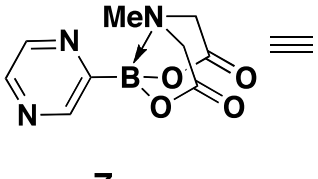
^{11}B-NMR (128 MHz, DMSO-d_6)

δ 10.7

HRMS (ES+)

Calculated for $C_8H_{10}O_4N_2BS$ $(M+H)^+$:	241.0454
Found:	241.0452

2-pyrazinyl MIDA boronate (7). The general procedure was followed using 2-bromopyrazine (0.275 mL, 2.96 mmol), triisopropyl borate (0.690 mL, 3.00 mmol), *n*-BuLi (1.2 mL, 2.54 M in hexanes), and *N*-methyliminodiacetic acid (774 mg, 5.26 mmol). The product was purified via SiO_2 chromatography (Et_2O:MeCN 95:5 → 0:100) to afford **7** as an orange crystalline solid (300 mg, 43%).



7

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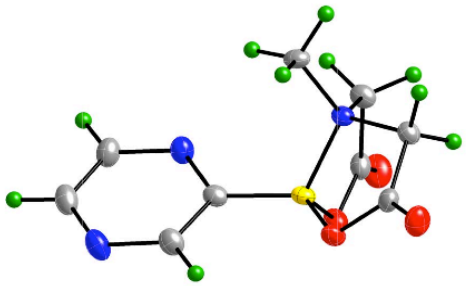


TLC (MeCN)

R_f = 0.56, visualized by UV (λ = 254 nm) and $KMnO_4$ stain

^{1}H-NMR (500 MHz, CD_3CN)

δ 8.77 (d, *J* = 1.5 Hz, 1H), 8.67 (dd, J = 2.0, 1.5 Hz, 1H), 8.53 (d, *J* = 2.5 Hz, 1H), 4.13 (d, *J* = 17 Hz, 2H), 3.98 (d, *J* = 17 Hz, 2H), 2.59 (s, 3H)

^{13}C-NMR (125 MHz, DMSO-d_6)
δ 169.1, 147.6, 145.4, 144.6, 62.0, 47.2

^{11}B-NMR (128 MHz, DMSO-d_6)
δ 9.6

HRMS (ES+)

Calculated for $C_9H_{11}O_4N_3B$ $(M+H)^+$:	236.0843
Found:	236.0840

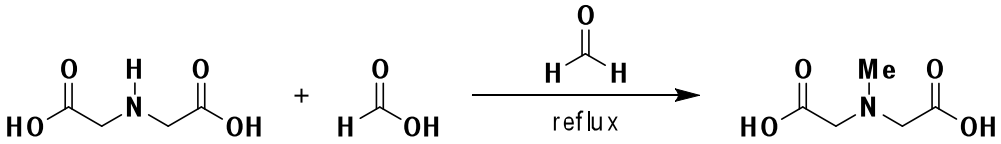
V. Scaled Synthesis of 2-pyridyl MIDA boronate

To a 3-neck 500 mL flask equipped with a stir bar, a gas adapter, and a 50 mL pressure-equalizing addition funnel was added 2-bromopyridine (9.5 mL, 97 mmol), triisopropyl borate (19.5 mL, 84.8 mmol), and THF (175 mL). The resulting stirred solution was cooled to -78 °C. To the solution was added dropwise *n*-BuLi (2.5 M in hexanes, 36 mL, 90 mmol) (ca. 0.56 mL/min). Following the addition the solution was stirred at -78 °C for 1 h, then warmed to 23 °C with stirring overnight. Separately, to a 3-neck 500 mL flask equipped with a 500 mL pressure-equalizing addition funnel, a water-cooled distillation apparatus, a thermometer and a stir bar was added *N*-methyiminodiacetic acid (25.4 g, 173 mmol) and DMSO (175 mL). The mixture was heated with stirring to an internal temperature of 115 °C. To the mixture was added hexanes (450 mL) to remove residual water via azeotropic distillation. The borate mixture contained in the Schlenk flask was transferred to the addition funnel, washing with THF (86 mL). To the hot, stirred DMSO solution was added dropwise the borate solution at a rate necessary to maintain the internal temperature at 110-130 °C (1 h). During the addition the THF was rapidly distilled (distillate temperature of app. 85 °C). The DMSO mixture was allowed to cool to 23 °C and then was filtered through Celite. The filtrate was treated with finely-ground K_3PO_4 (72.6 g, 342 mmol) with stirring for 30 min. The mixture was filtered through Celite washing with acetonitrile and the filtrate was concentrated *in vacuo* to afford a suspension of solids in DMSO that was further concentrated via distillation (bath temp = 60 °C, 0.25 Torr). The resulting residue, at 23 °C, was suspended in acetonitrile (50 mL) and to the stirred mixture was added dropwise CH_2Cl_2 (250 mL, ca. 2 h) followed by Et_2O (600 mL, ca. 6 h). The resulting solids were collected via filtration, washed with diethyl ether, and then the filter cake was extracted with acetonitrile (app. 250 mL). The resulting acetonitrile solution was treated with activated charcoal, filtered through Celite, and then concentrated *in vacuo* to afford **1a** as an off-white crystalline solid (11 g, 55%).

VI. Benchtop stability tests

The benchtop stability of MIDA boronates **1a-j**, **5**, and **7** stored as solids under air was determined according to the previously published procedure[4] with the following modifications: purity analysis was performed using DMSO-d_6 as the NMR solvent and 4-bromoanisole was utilized as the internal standard. Storage of 2-pyridyl MIDA boronate **1a** as a solid on the benchtop under air at 23 °C for 475 days resulted in no decomposition. Benchtop storage of **1b-1j**, **5**, **7** in the same manner for 14 days resulted in no decomposition.

VII. Synthesis of *N*-methyliminodiacetic acid (MIDA)



To a 3-neck 3 L round bottom flask equipped with a large stir bar was added iminodiacetic acid (500.0 g, 3.757 mol), water (420 mL) and formic acid (425 mL, 11.3 mol). The flask was fitted with a thermometer, a 500 mL pressure-equalizing addition funnel charged with formalin (425 mL, 5.67 mol), and a water-cooled Friedrichs condenser vented to ambient atmosphere. The mixture was heated to a gentle reflux. To the stirred mixture was added dropwise the formalin at a rate necessary to control the effervescence (ca. 30 mL/min.). Following the addition the mixture was maintained at reflux for an additional 2 h. The solution was cooled to room temperature and was then transferred, washing with water (100 mL), to a 20 L plastic bucket. Onto the aq. solution was layered acetone (10 L) such that the aq. phase remained undisturbed and the phases did not mix. The mixture was allowed to stand undisturbed in the sealed bucket for 3 days during which time the product crystallized as large colorless needle-like crystals. The crystals were collected via filtration, washed with acetone (2 x 500 mL), and residual solvent was removed *in vacuo* to afford N-methyliminodiacetic acid (480.5 g, 87%). Spectral characterization was consistent with the literature data.[2]