Synthesis C.-H. Tien et al. Special Topic

Synthesis of Borylated Hydrazino Acid Derivatives

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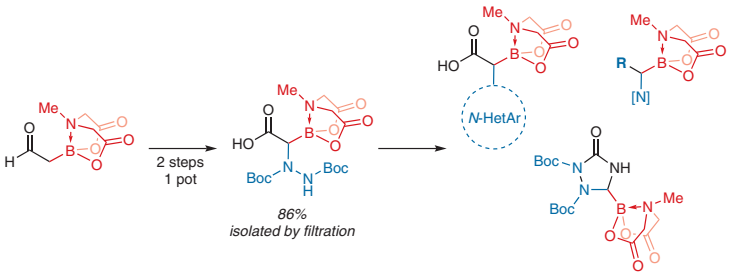

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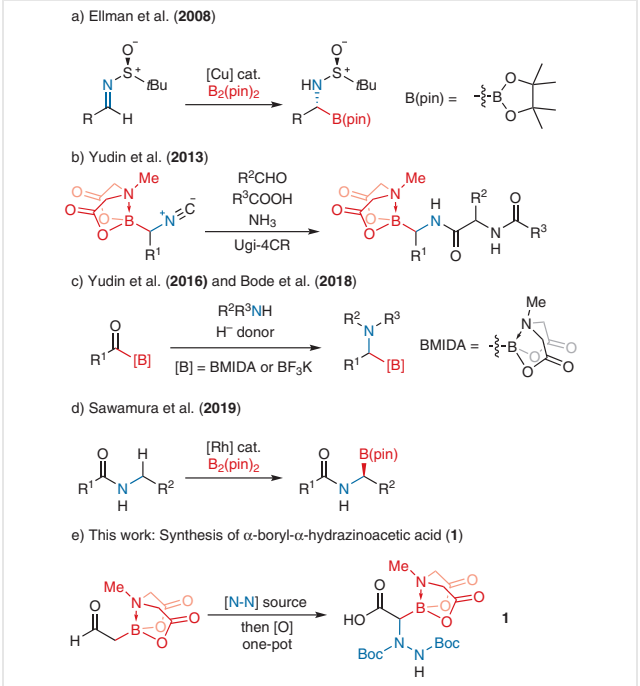
Abstract α-Boryl-α-hydrazinoacetic acid is a highly functionalized boron-containing building block that can be easily accessed from readily available α-borylacetaldehyde. The hydrazine motif can be converted into a variety of α-borylated azoles and diazines in a straightforward protocol. Furthermore, the carboxy group can be derivatized to afford novel organoboron compounds that should find applications in various cross-coupling transformations.

Key words hydrazinoboronates, aminoboronic acids, organoboron, borylated heterocycles, BMIDA

Organoboron compounds have found widespread applications in various fields of inquiry.[1] The ability of boron to reversibly bind to heteroatom nucleophiles, combined with boric acid's low toxicity (main metabolite of organoboron compounds; LD_{50} comparable to table salt) have allowed the identification of numerous boron-containing molecules as promising candidates in drug discovery.[1d,2] Among the many boron-containing scaffolds, borylated peptidomimetics derived from α-aminoboronic acids often display potent antitumor properties.[3] As such, the synthesis of α-aminoboronic acids has been a subject of ongoing interest (Scheme 1).[4]

Compared to α-aminoboronic acids, α-hydrazinoboronic acids have received no attention despite the prevalence of hydrazine building blocks in organic chemistry.[5] The hydrazine motif is frequently employed in the synthesis of heterocyclic scaffolds with biomedical applications.[6] In addition to being versatile synthetic handles, incorporation of the hydrazine functional group in peptidic scaffolds results in aza-β-peptides, which can display new secondary structures when compared to the parental forms.[7] As part of our ongoing efforts in the pursuit of unique boron-containing building blocks,[8] we report the synthesis and utility of α-boryl-α-hydrazinoacetic acid **1**.

Treatment of readily available α-borylacetaldehyde **2**[8a] with DBAD (di-*tert*-butyl azodicarboxylate) in the presence of catalytic amount of proline yielded α-boryl-α-hydrazinoacetaldehyde **3** with complete consumption of **2** (Scheme 2).[9] No side products were generated based on ^{1}H NMR



Scheme 1 Synthesis of α-aminoboronates: (a) Cu-catalyzed borylation of enantiopure sulfinyl imines. (b) Ugi 4C reaction using α-boryl isocyanides with aldehydes, carboxylic acids, and ammonia. (c) Reductive amination of MIDA acyl boronates and potassium acyltrifluoroborates. (d) Rh-catalyzed amine-directed C(sp^3)–H borylation. (e) Synthesis of α-boryl-α-hydrazinoacetic acid **1**.

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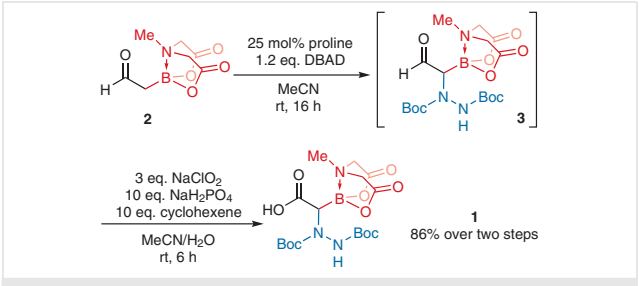
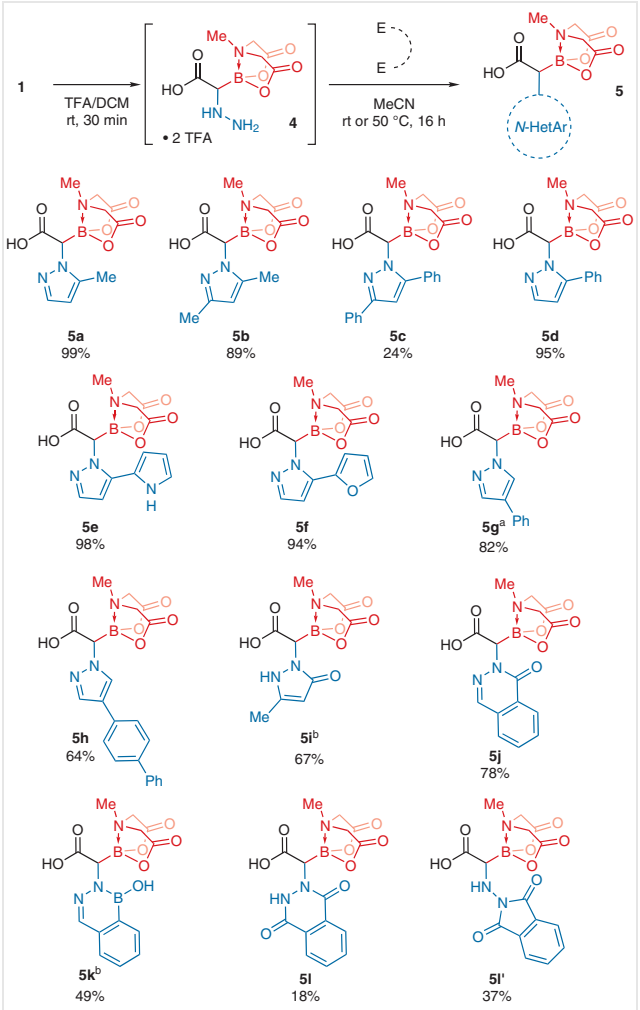
spectroscopy of the crude reaction mixture. Accordingly, we moved forward with the reaction by carrying out a Pinnick oxidation.[8a] To our delight, highly functionalized MIDA boronate **1** was isolated by filtration in 86% yield over two steps in a one-pot fashion.



Scheme 2 Synthesis of MIDA boronate **1** via a proline-catalyzed α-amination of α-borylacetaldehyde **2** then subsequent Pinnick oxidation in one pot

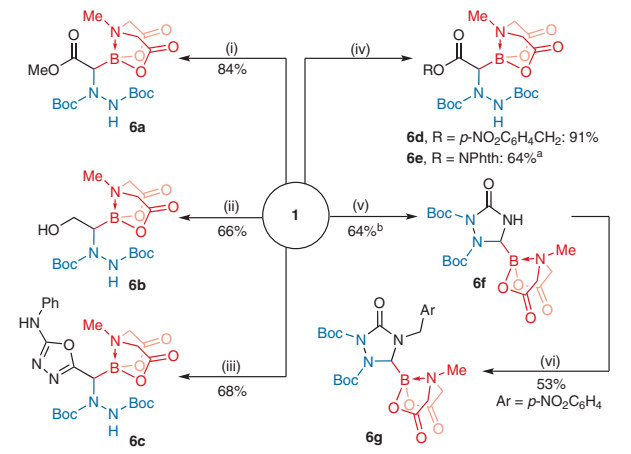
With **1** in hand, we set out to explore the utility of the hydrazine moiety. Deprotection of the Boc (*tert*-butoxycarbonyl) group in a DCM/TFA mixture provided the free hydrazine salt **4** in quantitative yield after 30 minutes without any signs of MIDA deprotection or protodeboronation. Upon evaporation of the solvent, reaction with 1,3- or 1,4-electrophiles in MeCN yielded a series of *N*-heterocycle-substituted α-carboxy MIDA boronates **5** (Scheme 3). Reaction with acetylacetaldehyde dimethyl acetal produced a 4:1 mixture of 1,5- and 1,3-substituted pyrazole **5a** in quantitative yield. Condensation with acetylacetone and dibenzoylmethane gave **5b** and **5c**, respectively. However, the reaction to give **5c** did not go to completion after 20 h, presumably due to reduced reactivity of dibenzoylmethane. Aryl keto-enamines reacted efficiently with **4** to form the corresponding 5-arylpyrazoles in high yields (**5d–5f**). Cyclization with arylated malondialdehydes successfully gave the corresponding 4-arylpyrazoles (**5g** and **5h**). Pyrazolone **5i** was generated when ethyl acetoacetate was used as the bis-electrophile. Similarly, methyl 2-formylbenzoate and 2-formylphenylboronic acid were suitable 1,4-electrophiles under these conditions and the reactions provided phthalazinone **5j** and 1,2,3-diazaborinine **5k**, respectively. Lastly, condensation with phthalic anhydride afforded a mixture of phthalazinedione **5l** and *N*-aminophthalimide **5l′** which are separable by column chromatography.

We next turned our attention towards the derivatization of the carboxy functional group (Scheme 4). Methylation of the carboxylic acid with $TMSCHN_2$ gave the methyl ester in good yield (**6a**). Activation of the acid with HATU and subsequent reduction of the activated ester with $NaBH_4$ gave β-hydrazino alcohol **6b**. Similarly, borylated oxadiazole **6c** could be synthesized using a one-pot HATU-mediated coupling protocol adapted from our previous report.[8e] Activation of the carboxylic acid with DIC in the presence of 4-nitrobenzyl alcohol provided the corresponding 4-nitrobenzyl ester **6d** in excellent yield.[10] Additionally, redox-active ester **6e** could be synthesized on a 1-g scale in good yield using *N*-hydroxyphthalimide as the nucleophile. Reaction with DPPA (diphenylphosphoryl azide) under mild heat provided triazolidinone **6f** via the Curtius rearrangement. This represents one of the few examples of a boronate that is attached to a carbon atom with the oxidation state of an aldehyde.[11] Subsequent *N*-alkylation of **6f** with 4-nitrobenzyl bromide gave **6g**, the structure of which was confirmed by single crystal X-ray diffraction (Figure 1).



Scheme 3 Scope of *N*-heterocycle substituted α-carboxy MIDA boronates from the condensation of **4** with a variety of electrophilic acceptors. [a] Reaction was performed on a 1.05 mmol scale. [b] The product was isolated as a TFA salt.

In conclusion, we have developed a straightforward synthesis of α-carboxy-α-hydrazino MIDA boronate **1** using a column-free protocol from readily available aldehyde **2**. The highly functionalized building block was used to access a variety of boro-methylated heterocycles and carboxy derivatives. The resulting borylated compounds **5** and **6** have



Scheme 4 Functionalization of the carboxy moiety of **1**. *Reagents and conditions*: (i) $TMSCHN_2$ (2 equiv), THF/MeOH then AcOH, 84%; (ii) HATU (1.2 equiv), DIPEA (3 equiv), MeCN then $NaBH_4$ (3 equiv), 66%; (iii) HATU (1.1 equiv), DIPEA (3 equiv), $PhNHC(S)NHNH_2$ (1.1 equiv), MeCN then TsCl (3.2 equiv) and DIPEA (3 equiv), 68%; (iv) DIC (1.1–1.2 equiv), DMAP (10 mol%), ROH (1.1–1.2 equiv), DCM/MeCN, 91% and 64%; (v) DPPA (1.1 equiv), DIPEA (2.2 equiv), MeCN, 64%; (vi) 4-nitrobenzyl bromide (1.2 equiv), K_2CO_3 (2 equiv), TBAB (10 mol%), DMF, 53%. [a] Reaction was performed on a 2.7 mmol scale. [b] Reaction was performed on a 5.4 mmol scale.

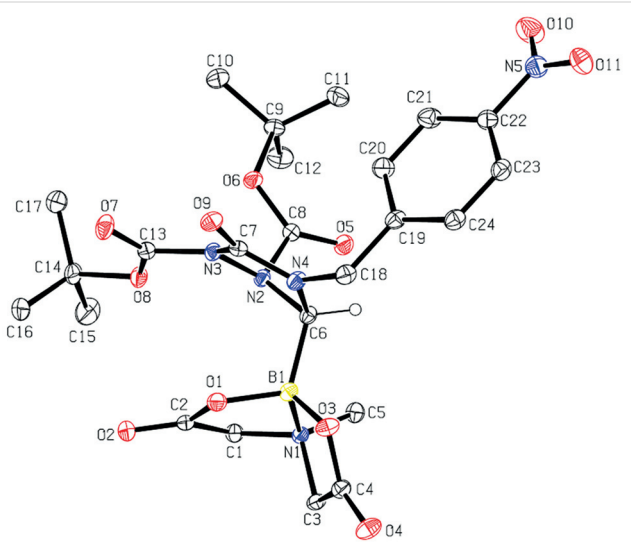


Figure 1 X-ray crystal structure of **6g**. Thermal ellipsoid probabilities set at 50%. Hydrogen atoms are omitted for clarity.

considerable potential in transition-metal-catalyzed Suzuki–Miyaura cross-coupling and decarboxylative cross-coupling to access value-added products.

All solvents and reagents were purchased from commercial sources and used as received unless otherwise stated. HPLC grade MeCN, hexane, and *i*-PrOH were purchased from MilliporeSigma and used as received. THF was distilled from Na benzophenone ketyl prior to use. Aryl keto-enamine,[12] malondialdehydes,[13] and **2**[8c] were synthesized according to literature procedures. 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 F^{254} and visualized using a UV lamp (254 nm) and curcumin stain. Reverse-phase chromatography was carried out using Biotage SNAP ultra C18 on a Teledyne-Isco Combiflash system. ^1H, ^{11}B, ^{13}C, and ^{19}F NMR spectra were recorded on Bruker 400 MHz and 500 MHz spectrometers at 23 °C unless otherwise stated. ^1H NMR chemical shifts are referenced to residual protonated solvent peak (MeCN-d_3: δ = 1.94; DMSO-d_6: δ = 2.50). ^{11}B NMR chemical shifts are referenced to an external standard of $BF_3{\cdot}OEt_2$ (δ = 0.0). ^{13}C NMR chemical shifts are referenced to the corresponding solvent peaks (MeCN-d_3: δ = 118.2; DMSO-d_6: δ = 39.5). Carbon atoms exhibiting significant line broadening brought about by boron substituents were not reported due to quadrupolar relaxation. ^{19}F NMR chemical shifts are referenced to an external standard of $CFCl_3$ (δ = 0.0). HRMS 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 sources, MS/MS and accurate mass capabilities. Low-resolution mass spectra (ESI) were collected on an Agilent Technologies 1200 series HPLC paired to a 6130 Mass Spectrometer. FTIR analysis was carried out on a Bruker Alpha Platinum ATP spectrometer and peaks below 1500 cm^{-1} are not reported. Melting points were measured uncorrected utilizing a Mel-Temp capillary melting point apparatus.

α-Boryl-α-hydrazinoacetic Acid 1

To a stirred suspension of **2** (1.00 g, 5.03 mmol, 1 equiv) in MeCN (50 mL) were added di-*tert*-butyl azodicarboxylate (1.39 g, 6.03 mmol, 1.2 equiv) and L-proline (145 mg, 1.26 mmol, 25 mol%). The mixture was stirred at rt for 16 h. Cyclohexene (5.1 mL, 50.3 mmol, 10 equiv), $NaH_2PO_4{\cdot}H_2O$ (6.94 g, 50.3 mmol, 10 equiv), $NaClO_2$ (1.36 g, 15.1 mmol, 3 equiv), and water (30 mL) were subsequently added. The mixture was stirred at rt for 6 h. Upon completion of reaction as indicated by ^1H NMR spectroscopy, the organic layer was removed from the biphasic mixture in vacuo. MeCN (10 mL) was added, then the mixture was cooled for 1 h in a 4 °C fridge. The mixture was filtered, then the filter cake was washed with water (20 mL) and Et_2O (50 mL) to afford **1** (1.93 g, 4.33 mmol, 86%) as a colorless solid; mp 207–210 °C.

IR (neat): 3173, 2979, 1799, 1773, 1726, 1714, 1662, 1524 cm^{-1}.

^1H NMR (500 MHz, 333 K, DMSO-d_6): δ = 8.12 (br s, 1 H), 4.37 (s, 1 H), 4.27 (d, *J* = 17.5 Hz, 1 H), 4.21 (d, *J* = 17.0 Hz, 1 H), 4.00 (d, *J* = 17.5 Hz, 1 H), 3.95 (d, *J* = 17.0 Hz, 1 H), 3.16 (s, 3 H), 1.43 (s, 9 H), 1.40 (s, 9 H).

^{13}C NMR (126 MHz, 333 K, DMSO-d_6): δ = 173.6, 168.0, 167.7, 80.7, 80.2, 62.7, 46.3, 27.7, 27.5.

^{11}B NMR (160 MHz, 333 K, DMSO-d_6): δ = 9.8.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{28}BN_3NaO_{10}$: 467.1796; found: 467.1795.

α-Boryl-α-hydrazinoacetaldehyde 3

To a stirred suspension of **2** (0.400 g, 2.01 mmol, 1 equiv) in MeCN (10 mL) were added di-*tert*-butyl azodicarboxylate (0.555 g, 2.41 mmol, 1.2 equiv) and L-proline (58 mg, 0.50 mmol, 25 mol%). The mixture was stirred at rt for 16 h. The mixture was diluted with MeCN (100 mL) and loaded onto Celite. The volatiles were removed in vacuo, then

the residue was purified by normal-phase column chromatography (mixture hexanes/acetone) to afford **3** (0.656 g, 1.53 mmol, 76%) as a colorless solid; mp 120–122 °C.

IR (neat): 3274, 2932, 2861, 1772, 1717, 1685, 1500 cm^{-1}.

^1H NMR (500 MHz, MeCN-d_3): δ = 9.73 (s, 1 H), 6.95–7.10 (br, 1 H), 4.63–4.78 (br, 1 H), 3.96–4.09 (m, 4 H), 3.22 (s, 3 H), 1.41 (s, 18 H).

^{13}C NMR (126 MHz, MeCN-d_3): δ = 203.1, 167.7, 156.2, 156.1, 81.4, 80.7, 63.4, 63.0, 47.0, 27.5, 27.3.

^{11}B NMR (160 MHz, MeCN-d_3): δ = 10.2.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{17}H_{28}BN_3NaO_9$: 451.1847; found: 451.1851.

Hydrazine Condensation; General Procedure

To a 1-dram vial containing **1** (44.5 mg, 0.1 mmol, 1 equiv) was added DCM (0.5 mL) and TFA (0.5 mL). The mixture was stirred for 30 min at rt. The volatiles were removed in vacuo, then MeCN (1 mL) was added. To the stirring solution was added the appropriate electrophile (1–1.1 equiv), then the mixture was stirred at rt or 50 °C for 16 h. The mixture was loaded onto Celite, then the volatiles were removed in vacuo. The residue was subjected to reversed-phase column chromatography (gradient of water/MeCN 95:5 to 0:100) to afford the corresponding products upon removal of solvents. Alternatively, if the product precipitated from the mixture, then the mixture was filtered, and the filter cake was washed with MeCN (1 mL) to afford the corresponding products.

2-(5-Methyl-1*H*-pyrazol-1-yl)-2-(MIDA-boryl)acetic Acid (5a)

The reaction was carried out according to the general procedure using acetylacetaldehyde dimethyl acetal (14.6 mL, 0.11 mmol, 1.1 equiv) at rt and purified by reversed-phase column chromatography to afford **5a** (29.2 mg, 0.099 mmol, 99%) as a colorless solid; mp 176–180 °C (decomp.).

IR (neat): 2982, 1771, 1746, 1717, 1527 cm^{-1}.

^1H NMR (500 MHz, MeCN-d_3): δ = 7.44 (d, J = 2.5 Hz, 1 H), 7.35* (d, J = 1.5 Hz), 6.10 (d, J = 2.0 Hz, 1 H), 6.09* (d, J = 1.0 Hz), 4.98 (s, 1 H), 4.89* (s), 4.30* (d, J = 16.5 Hz), 4.20 (d, J = 16.0 Hz, 1 H), 4.1–4.02 (overlapped, 2 H), 4.08–4.02* (overlapped), 3.12 (s, 3 H), 3.07* (s), 2.23* (s), 2.22 (s, 3 H); * minor 1,3-regioisomer.

^{13}C NMR (126 MHz, MeCN-d_3): δ = 173.2, 172.8*, 169.0*, 168.9*, 168.8, 168.6, 148.7, 141.5*, 138.6*, 133.6, 106.1 (major and minor), 65.1*, 65.0*, 64.8, 64.5, 47.9*, 47.9, 13.3, 11.1*; * minor regioisomer.

^{11}B NMR (128 MHz, MeCN-d_3): δ = 10.4.

HRMS (ESI): m/z $[M - H]^-$ calcd for $C_{11}H_{13}BN_3O_6$: 293.0939; found: 293.0944.

2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-2-(MIDA-boryl)acetic Acid (5b)

The reaction was carried out according to the general procedure using acetylacetone (11.2 µL, 0.11 mmol, 1.1 equiv) at rt and purified by reversed-phase column chromatography to afford **5b** (27.4 mg, 0.089 mmol, 89%) as a colorless solid ; mp 110–115 °C (decomp.).

IR (neat): 2968, 2551, 1768, 1669, 1586, 1520 cm^{-1}.

^1H NMR (500 MHz, MeCN-d_3): δ = 5.85 (s, 1 H),4.76 (s, 1 H), 4.27 (d, J = 16.5 Hz, 2 H), 4.08–3.99 (m, 3 H), 3.07 (s, 3 H), 2.14 (s, 3 H), 2.12 (s, 3 H).

^{13}C NMR (126 MHz, MeCN-d_3): δ = 173.4, 169.1, 168.9, 147.7, 142.3, 105.8, 65.1, 65.0, 48.0, 13.4, 11.1.

^{11}B NMR (128 MHz, MeCN-d_3): δ = 10.6.

HRMS (ESI): m/z $[M - H]^-$ calcd for $C_{12}H_{15}BN_3O_6$: 307.1096; found: 307.1097.

2-(3,5-Diphenyl-1*H*-pyrazol-1-yl)-2-(MIDA-boryl)acetic Acid (5c)

The reaction was carried out according to the general procedure using 1,3-diphenylpropane-1,3-dione (14.6 µL, 0.11 mmol, 1.1 equiv) at 50 °C and purified by reversed-phase column chromatography to afford **5c** (10.2 mg, 0.024 mmol, 24%) as a colorless solid; mp 208–213 °C.

IR (neat): 2968, 1772, 1766, 1607, 1557 cm^{-1}.

^1H NMR (500 MHz, MeCN-d_3): δ = 7.80–7.78 (m, 2 H), 7.51–7.49 (m, 3 H), 7.44–7.42 (m, 4 H), 7.38–7.36 (m, 1 H), 6.77 (s, 1 H), 4.86 (s, 1 H), 4.21 (d, J = 17.0 Hz, 1 H), 4.09–3.99 (m, 3 H), 3.04 (s, 3 H).

^{13}C NMR (126 MHz, MeCN-d_3): δ = 173.0, 169.0, 168.8, 146.1, 139.4, 131.3, 129.8, 129.8, 129.8, 107.1, 65.1, 64.9, 47.9.

^{11}B NMR (128 MHz, MeCN-d_3): δ = 10.6.

HRMS (ESI): m/z $[M - H]^-$ calcd for $C_{22}H_{19}BN_3O_6$: 431.1409; found: 431.1413.

2-(MIDA-Boryl)-2-(5-phenyl-1*H*-pyrazol-1-yl)acetic Acid (5d)

The reaction was carried out according to the general procedure using (*E*)-3-(dimethylamino)-1-phenylprop-2-en-1-one (18.4, 0.105 mmol, 1.05 equiv) at rt and purified by reversed-phase column chromatography to afford **5d** (33.9 mg, 0.095 mmol, 95%) as a colorless solid; mp 165–168 °C.

IR (neat): 3029, 2799, 2475, 1769, 1670, 1553 cm^{-1}.

^1H NMR (500 MHz, MeCN-d_3): δ = 7.52 (d, J = 2.0 Hz, 1 H), 7.49–7.46 (m, 3 H), 7.38–7.36 (m, 2 H), 6.36 (d, J = 1.5 Hz, 1 H), 4.86 (s, 1 H), 4.28 (d, J = 17.0 Hz, 1 H), 4.09–3.99 (m, 3 H), 3.04 (s, 3 H).

^{13}C NMR (126 MHz, MeCN-d_3): δ = 173.0, 169.0, 168.7, 148.1, 139.4, 131.3, 129.8, 129.8, 129.8, 107.1, 65.1, 64.9, 47.9.

^{11}B NMR (128 MHz, MeCN-d_3): δ = 10.6.

HRMS (ESI): m/z $[M - H]^-$ calcd for $C_{16}H_{15}BN_3O_6$: 355.1096; found: 355.1099.

2-[5-(1*H*-Pyrrol-2-yl)-1*H*-pyrazol-1-yl]-2-(MIDA-boryl)acetic Acid (5e)

The reaction was carried out according to the general procedure using (*E*)-3-(dimethylamino)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one (18.1 mg, 0.11 mmol, 1.1 equiv) at rt and purified by reversed-phase column chromatography to afford **5e** (33.9 mg, 0.098 mmol, 98%) as a brown solid; mp 170–175 °C (decomp.).

IR (neat): 3374, 3146, 2982, 2262, 1748, 1607, 1511 cm^{-1}.

^1H NMR (500 MHz, MeCN-d_3): δ = 9.51 (br s), 7.47 (d, J = 2.0 Hz, 1 H), 6.90–6.89 (m, 1 H), 6.38 (d, J = 2.0 Hz, 1 H), 6.27–6.25 (m, 1 H), 6.24–6.23 (m, 1 H), 5.06 (s, 1 H), 4.29 (d, J = 16.5 Hz, 1 H), 4.10–4.01 (m, 3 H), 3.02 (s, 3 H).

^{13}C NMR (126 MHz, MeCN-d_3): δ = 173.0, 169.1, 168.9, 139.3, 138.8, 121.3, 120.7, 110.2, 109.1, 105.1, 65.1, 65.0, 47.9.

^{11}B NMR (128 MHz, MeCN-d_3): δ = 10.6.

HRMS (ESI): m/z $[M - H]^-$ calcd for $C_{14}H_{14}BN_4O_6$: 344.1048; found: 344.1052.

2-[5-(Furan-2-yl)-1*H*-pyrazol-1-yl]-2-(MIDA-boryl)acetic Acid (5f)

The reaction was carried out according to the general procedure using (*E*)-3-(dimethylamino)-1-(furan-2-yl)prop-2-en-1-one (18.2 mg, 0.11 mmol, 1.1 equiv) at rt and purified by reversed-phase column chromatography to afford **5f** (32.6 mg, 0.094 mmol, 94%) as a brown solid; mp 140–142 °C (decomp.).

IR (neat): 2982, 2886, 1746, 1527 cm^{-1}.

^1H NMR (500 MHz, MeCN-d_3): δ = 7.60 (dd, *J* = 1.9, 1.0 Hz, 1 H), 7.49 (d, *J* = 2.0 Hz, 1 H), 6.67 (dd, *J* = 3.5, 1.0 Hz, 1 H), 6.56 (dd, *J* = 3.5, 2.0 Hz, 1 H), 6.55 (d, *J* = 2.0 Hz, 1 H), 5.26 (s, 1 H), 4.31 (d, *J* = 16.5 Hz, 1 H), 4.11–4.02 (m, 3 H), 3.05 (s, 3 H).

^{13}C NMR (126 MHz, MeCN-d_3): δ = 172.9, 169.0, 168.9, 145.2, 144.3, 139.5, 136.3, 112.5, 110.1, 106.0, 65.2, 65.1, 48.0.

^{11}B NMR (128 MHz, MeCN-d_3): δ = 10.7.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{14}H_{13}BN_3O_7$: 345.0888; found: 345.0894.

2-(MIDA-Boryl)-2-(4-phenyl-1*H*-pyrazol-1-yl)acetic Acid (5g)

The reaction was carried out on a 1-mmol scale according to the general procedure using 2-phenylmalonaldehyde (156 mg, 1.05 mmol, 1.05 equiv) at rt and purified by reversed-phase column chromatography to afford **5g** (294 mg, 0.82 mmol, 82%) as a colorless solid; mp 150–152 °C (decomp.).

IR (neat): 3000, 2981, 1757, 1729, 1608, 1570 cm^{-1}.

^1H NMR (500 MHz, MeCN-d_3): δ = 7.88 (s, 1 H), 7.80 (s, 1 H), 7.55–7.54 (m, 2 H), 7.38–7.35 (m, 2 H), 7.24–7.22 (m, 1 H), 5.04 (s, 1 H), 4.21 (d, *J* = 17.0 Hz, 1 H), 4.08 (d, *J* = 17.0 Hz, 1 H), 4.04 (d, *J* = 17.0 Hz, 1 H), 3.95 (d, *J* = 17.0 Hz, 1 H), 3.11 (s, 3 H).

^{13}C NMR (126 MHz, MeCN-d_3): δ = 172.8, 168.8, 168.6, 137.0, 133.4, 129.8, 129.8, 127.3, 126.2, 123.8, 64.8, 64.5, 47.9.

^{11}B NMR (128 MHz, MeCN-d_3): δ = 10.5.

HRMS (ESI): *m*/*z* [M-H]$^-$ calcd for $C_{16}H_{15}BN_3O_6$: 355.1096; found: 355.1100.

2-[4-(Biphenyl-4-yl)-1*H*-pyrazol-1-yl]-2-(MIDA-boryl)acetic Acid (5h)

The reaction was carried out according to the general procedure using 2-(biphenyl-4-yl)malonaldehyde (24.7 mg, 0.11 mmol, 1.1 equiv) at rt and purified by reversed-phase column chromatography to afford **5h** (27.7 mg, 0.064 mmol, 64%) as a colorless solid; mp 213–215 °C (decomp.).

IR (neat): 3034, 2964, 1769, 1716, 1615, 1575 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.07 (s, 1 H), 7.91 (s, 1 H), 7.70–7.64 (m, 6 H), 7.46 (t, *J* = 7.5 Hz, 2 H), 7.35 (t, *J* = 7.5 Hz, 1 H), 5.09 (s, 1 H), 4.45 (d, *J* = 17.0 Hz, 1 H), 4.32 (d, *J* = 17.0 Hz, 1 H), 4.18 (d, *J* = 17.0 Hz, 1 H), 4.05 (d, *J* = 17.0 Hz, 1 H), 3.08 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 172.6, 168.8, 168.3, 139.8, 137.5, 135.8, 131.7, 128.8, 127.2, 127.1, 126.3, 125.4, 121.2, 63.5, 63.2, 46.9.

^{11}B NMR (128 MHz, DMSO-d_6): δ = 11.2.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{22}H_{19}BN_3O_6$: 431.1409; found: 431.1399.

2-(MIDA-Boryl)-2-(3-methyl-5-oxo-2,5-dihydro-1*H*-pyrazol-1-yl)acetic Acid·Trifluoroacetic Acid (5i)

The reaction was carried out according to the general procedure using ethyl acetoacetate (10.8 μL, 0.1 mmol, 1 equiv) at rt and purified by filtration to afford **5i** (28.4 mg, 0.067 mmol, 67%) as a colorless solid; mp 158–161 °C.

IR (neat): 3217, 2969, 2541, 1909, 1770. 1736, 1639, 1575 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 5.36 (br s, 1 H), 4.66 (br s, 1 H), 4.44 (d, *J* = 17.0 Hz, 1 H), 4.27 (d, *J* = 16.5 Hz, 1 H), 4.16–4.11 (m, 2 H), 3.06 (s, 3 H), 2.10 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 172.8, 172.0, 168.8, 168.4, 158.3 (q, *J* = 36.6 Hz), 145.7, 115.5 (q, *J* = 292.8 Hz), 87.1, 63.7, 63.4, 47.1, 13.2.

^{11}B NMR (128 MHz, DMSO-d_6): δ = 10.9.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –74.7.

HRMS (ESI): *m*/*z* [M – $CF_3CO_2H_2$]$^-$ calcd for $C_{11}H_{13}BN_3O_7$: 309.0888; found: 309.0891.

2-(MIDA-Boryl)-2-(1-oxophthalazin-2(1*H*)-yl)acetic Acid (5j)

The reaction was carried out according to the general procedure using methyl 2-formylbenzoate (18.1 mg, 0.11 mmol, 1.1 equiv) at rt and purified by filtration to afford **5j** (28.1 mg, 0.078 mmol, 78%) as a colorless solid; mp 235–236 °C (decomp.).

IR (neat): 3072, 3013, 2970, 2908, 1753, 1726, 1624, 1574 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 12.9 (s, 1 H), 8.45 (s, 1 H), 8.26 (dd, *J* = 7.8 Hz, 1 H), 7.97–7.96 (m, 2 H), 7.91–7.87 (m, 1 H), 5.39 (s, 1 H), 4.50 (d, *J* = 17.2 Hz, 1 H), 4.28 (d, *J* = 16.8 Hz, 1 H), 4.20–4.14 (m, 2 H), 3.13 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 172.7, 169.0, 168.6, 158.8, 137.2, 133.7, 132.1, 129.2, 126.8, 126.8, 125.9, 63.8, 63.5, 47.7.

^{11}B NMR (128 MHz, DMSO-d_6): δ = 11.3.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{15}H_{13}BN_3O_7$: 357.0888; found: 357.0891.

2-(1-Hydroxybenzo[*d*][1,2,3]diazaborinin-2(1*H*)-yl)-2-(MIDA-boryl)acetic Acid·Trifluoroacetic Acid (5k)

The reaction was carried out according to the general procedure using 2-formylphenylboronic acid (15.0 mg, 0.1 mmol, 1 equiv) at rt and purified by filtration to afford **5k** (23.2 mg, 0.049 mmol, 49%) as a colorless solid; mp >250 °C.

IR (neat): 3312, 2982, 1780, 1754. 1722, 1674, 1524 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.26 (d, *J* = 7.5 Hz, 1 H), 7.99 (s, 3 H), 7.72–7.71 (m, 2 H), 7.61–7.58 (m, 1 H), 4.84 (s, 1 H), 4.46 (d, *J* = 17.5 Hz, 1 H), 4.20–4.11 (m, 3 H), 3.12 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 175.2, 169.2, 168.6, 158.3 (q, *J* = 38.1 Hz), 136.8, 135.2, 131.2, 130.9, 128.4, 126.6, 115.1 (q, *J* = 289.9 Hz), 63.7, 63.6, 47.3.

^{11}B NMR (128 MHz, DMSO-d_6): δ = 29.0, 10.3.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –74.8.

HRMS (ESI): *m*/*z* [M – $CF_3CO_2H_2$]$^-$ calcd for $C_{14}H_{14}B_2N_3O_7$: 356.1096; found: 356.1102.

2-[1,4-Dioxo-3,4-dihydrophthalazin-2(1*H*)-yl]-2-(MIDA-boryl)acetic Acid (5l)

The reaction was carried out according to the general procedure using phthalic anhydride (16.3 mg, 0.11 mmol, 1.1 equiv) at 50 °C and purified by reversed-phase column chromatography to afford **5l** (6.6 mg, 0.018 mmol, 18%) as a colorless solid; mp 185–190 °C.

IR (neat): 2983, 1751, 1645, 1571, 1500 cm^{-1}.

^{1}H NMR (500 MHz, MeCN-d_3): δ = 8.31–8.29 (m, 1 H), 7.96–7.95 (m, 1 H), 7.88–7.85 (m, 2 H), 5.57 (s, 1 H), 4.26 (d, *J* = 17.0 Hz, 1 H), 4.12 (d, *J* = 17.5 Hz, 1 H), 4.06 (d, *J* = 17.0 Hz, 1 H), 4.02 (d, *J* = 17.5 Hz, 1 H), 3.23 (s, 3 H).

^{13}C NMR (126 MHz, MeCN-d_3): δ = 173.5, 169.1, 169.0, 159.6, 150.4, 134.2, 133.5, 129.7, 127.8, 125.2, 125.1, 65.1, 64.5, 48.6.

^{11}B NMR (128 MHz, MeCN-d_3): δ = 10.9.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{15}H_{13}BN_3O_8$: 373.0838; found: 373.0837.

2-[(1,3-Dioxoisoindolin-2-yl)amino]-2-(MIDA-boryl)acetic Acid (5l′)

The reaction was carried out according to the general procedure using phthalic anhydride (16.3 mg, 0.11 mmol, 1.1 equiv) at 50 °C and purified by reversed-phase column chromatography to afford **5l′** (13.7 mg, 0.037 mmol, 37%) as a colorless solid; mp >250 °C.

IR (neat): 2972, 1746, 1639, 1544, 1500 cm^{-1}.

^{1}H NMR (500 MHz, MeCN-d_3): δ = 7.84–7.79 (m, 4 H), 5.21 (br s, 1 H), 4.23 (d, *J* = 17.0 Hz, 1 H), 4.10 (d, *J* = 17.0 Hz, 1 H), 4.05 (d, *J* = 17.5 Hz, 1 H), 3.94 (d, *J* = 17.0 Hz, 1 H), 3.69 (br s, 1 H), 3.17 (s, 3 H).

^{13}C NMR (126 MHz, MeCN-d_3): δ = 175.2, 168.6, 168.4, 167.8, 135.5, 131.2, 124.1, 63.8, 63.5, 47.6.

^{11}B NMR (128 MHz, MeCN-d_3): δ = 9.8.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{15}H_{13}BN_3O_8$: 373.0838; found: 373.0831.

2-[1,2-Bis(*tert*-butoxycarbonyl)hydrazinyl]-2-(MIDA-boryl)acetic Acid (6a)

To a stirred suspension of **1** (44.5 mg, 0.1 mmol, 1 equiv) in THF (0.35 mL) and MeOH (0.15 mL) at 0 °C was added $TMSCHN_2$ (2 M in hexane, 0.1 mL, 0.2 mmol, 2 equiv). The mixture was stirred for 30 min at 0 °C. After addition of AcOH (0.1 mL), the mixture was loaded onto Celite, then the volatiles were removed in vacuo. The residue was subjected to normal-phase column chromatography to afford **6a** (38.5 mg, 0.084 mmol, 84%) as a colorless solid; mp 115–117 °C.

IR (neat): 2983, 1760, 1713 cm^{-1}.

^{1}H NMR (500 MHz, MeCN-d_3): δ = 6.97 (br s, 1 H), 4.58 (br s, 1 H), 4.02–3.92 (m, 4 H), 3.68 (s, 3 H), 3.19 (s, 3 H), 1.43–1.41 (overlapped, 18 H).

^{13}C NMR (126 MHz, MeCN-d_3): δ = 174.1, 168.8, 82.7, 81.4, 64.5, 63.9, 52.7, 47.6, 28.4, 28.2.

^{11}B NMR (128 MHz, MeCN-d_3): δ = 10.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{30}BN_3NaO_{10}$: 481.1953; found: 481.1952.

Di-*tert*-butyl 1-[2-Hydroxy-1-(MIDA-boryl)ethyl]hydrazine-1,2-dicarboxylate (6b)

To a stirred suspension of **1** (44.5 mg, 0.1 mmol, 1 equiv) and HATU (45.6 mg, 0.12 mmol, 1.2 equiv) in MeCN (1 mL) was added DIPEA (34.8 μL, 0.2 mmol, 2 equiv). The mixture was stirred at rt for 15 min. $NaBH_4$ (11.3 mg, 0.3 mmol, 3 equiv) was added to the solution, then the mixture was stirred at rt for 3 h. After addition of MeOH (0.5 mL), the mixture was loaded onto Celite, then the volatiles were removed in vacuo. The residue was subjected to reversed-phase column chromatography to afford **6b** (28.3 mg, 0.066 mmol, 66%) as a colorless solid; mp 148–150 °C.

IR (neat): 3411, 2981, 2962, 2906, 1768, 1705 cm^{-1}.

^{1}H NMR (500 MHz, MeCN-d_3): δ = 7.04–6.82 (br, 1 H), 4.12–3.85 (m, 5 H), 3.65–3.53 (br, 2 H), 3.24–2.99 (br, 3 H), 1.43–1.40 (overlapped, 18 H).

^{13}C NMR (126 MHz, MeCN-d_3): δ = 169.0, 168.7, 82.1, 81.4, 63.9, 63.0, 60.2, 47.9, 46.8, 28.4, 28.4.

^{11}B NMR (128 MHz, MeCN-d_3): δ = 10.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{30}BN_3NaO_9$: 453.2004; found: 453.1994.

Di-*tert*-butyl {(MIDA-boryl)[5-(phenylamino)-1,3,4-oxadiazol-2-yl]methyl}hydrazine-1,2-dicarboxylate (6c)

To a stirred suspension of **1** (44.5 mg, 0.1 mmol, 1 equiv) and HATU (41.8 mg, 0.11 mmol, 1.1 equiv) in MeCN (1 mL) was added DIPEA (52.3 μL, 0.3 mmol, 3 equiv). The mixture was stirred at rt for 15 min. *N*-Phenylhydrazinecarbothioamide (18.4 mg, 0.11 mmol, 1.1 equiv) was added to the solution, then the mixture was stirred at rt for 30 min. TsCl (41.9 mg, 0.22 mmol, 2.2 equiv) was added, then the mixture was stirred at rt for 4 h. After 4 h, another aliquot of TsCl (19.1 mg, 0.1 mmol, 1 equiv) and DIPEA (52.3 μL, 0.3 mmol, 3 equiv) were added, then the mixture was stirred at rt for 20 h. The mixture was loaded onto Celite, then the volatiles were removed in vacuo. The residue was subjected to reversed-phase column chromatography to afford **6c** (38.2 mg, 0.068 mmol, 68%) as a colorless solid; mp 157–160 °C.

IR (neat): 3328, 2982, 2936, 1778, 1740, 1700, 1515 cm^{-1}.

^{1}H NMR (500 MHz, MeCN-d_3): δ = 7.92–7.88 (m, 4 H), 7.17–7.02 (br, 1 H), 5.10 (br s, 1 H), 4.14–3.99 (m, 4 H), 3.28 (s, 3 H), 1.44 (overlapped, 18 H).

^{13}C NMR (126 MHz, MeCN-d_3): δ = 168.5, 168.4, 163.1, 136.3, 129.6, 124.9, 82.1, 65.0, 64.3, 47.9, 28.4, 28.1.

^{11}B NMR (128 MHz, MeCN-d_3): δ = 10.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{31}BN_4NaO_{12}$: 612.1960; found: 612.1959.

Di-*tert*-butyl 1-[1-(MIDA-boryl)-2-(4-nitrobenzyloxy)-2-oxoethyl]hydrazine-1,2-dicarboxylate (6d)

To a stirred suspension of **1** (44.5 mg, 0.1 mmol, 1 equiv), 4-nitrobenzyl alcohol (18 mg, 0.12 mmol, 1.2 equiv), and DMAP (1.2 mg, 0.01 mmol, 10 mol%) in DCM (0.66 mL) and MeCN (0.33 mL) was added DIC (18.7 μL, 0.12 mmol, 1.2 equiv). The mixture was stirred at rt for 20 h. The mixture was filtered then loaded onto Celite, then the volatiles were removed in vacuo. The residue was subjected to normal-phase column chromatography to afford **6d** (52.7 mg, 0.091 mmol, 91%) as a colorless solid; mp 155–158 °C.

IR (neat): 3314, 2982, 2942, 1779, 1757, 1724, 1675, 1605, 1514 cm^{-1}.

^{1}H NMR (500 MHz, MeCN-d_3): δ = 8.21–8.19 (m, 2 H), 7.63 (d, *J* = 8.5 Hz, 2 H), 7.03 (br s, 1 H), 5.33 (second order, 1 H), 5.25 (second order, 1 H), 4.71 (br, 1 H), 4.05–3.93 (m, 4 H), 3.21 (s, 3 H), 1.42 (s, 9 H), 1.39 (s, 9 H).

^{13}C NMR (126 MHz, MeCN-d_3): δ = 173.5, 168.7, 168.7, 148.6, 144.7, 129.3, 124.5, 81.6, 66.2, 64.6, 63.9, 47.6, 28.4, 28.2.

^{11}B NMR (128 MHz, MeCN-d_3): δ = 10.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{33}BN_4NaO_{12}$: 602.2117; found: 602.2115.

Di-*tert*-butyl 1-{2-[(1,3-Dioxoisoindolin-2-yl)oxy]-1-(MIDA-boryl)-2-oxoethyl}hydrazine-1,2-dicarboxylate (6e)

To a stirred suspension of **1** (1.2 g, 2.70 mmol, 1 equiv), *N*-hydroxyphthalimide (484 mg, 2.97 mmol, 1.1 equiv), and DMAP (33 mg, 0.27 mmol, 10 mol%) in DCM (20 mL) and MeCN (7 mL) was added DIC (0.464 mL, 2.97 mmol, 1.1 equiv). The mixture was stirred at rt for 14 h. The mixture was filtered then loaded onto Celite, then the volatiles were removed in vacuo. The residue was subjected to normal-phase column chromatography to afford **6e** (1.02 g, 1.73 mmol, 64%) as a colorless solid; mp 155–158 °C.

IR (neat): 3328, 2982, 2936, 1778, 1740, 1700, 1515 cm^{-1}.

^1H NMR (500 MHz, MeCN-d_3): δ = 7.92–7.88 (m, 4 H), 7.17–7.02 (br, 1 H), 5.10 (br s, 1 H), 4.14–3.99 (m, 4 H), 3.28 (s, 3 H), 1.44 (overlapped, 18 H).

^{13}C NMR (126 MHz, MeCN-d_3): δ = 168.5, 168.4, 163.1, 136.3, 129.6, 124.9, 82.1, 65.0, 64.3, 47.9, 28.4, 28.1.

^{11}B NMR (128 MHz, MeCN-d_3): δ = 10.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{31}BN_4NaO_{12}$: 612.1960; found: 612.1959.

Di-*tert*-butyl 3-(MIDA-boryl)-5-oxo-1,2,4-triazolidine-1,2-dicarboxylate (6f)

To a stirred suspension of **1** (2.4 g, 5.39 mmol, 1 equiv) in MeCN (36 mL) at rt was added DIPEA (2.07 mL, 11.86 mmol, 2.2 equiv) and DPPA (1.28 mL, 5.93 mmol, 1.1 equiv). The mixture was stirred at 50 °C for 1.5 h. The mixture was cooled and loaded onto Celite, then the volatiles were removed in vacuo. The residue was subjected to normal-phase column chromatography to afford **6f** (1.53 g, 3.46 mmol, 64%) as a colorless solid; mp 172–177 °C (decomp.).

IR (neat): 3328, 2982, 2936, 1778, 1740, 1700, 1515 cm^{-1}.

^1H NMR (500 MHz, MeCN-d_3): δ = 6.16 (br s, 1 H), 5.05 (s, 1 H), 4.07–4.03 (m, 2 H), 3.94–3.88 (m, 2 H), 3.07 (s, 3 H), 1.47 (s, 9 H), 1.45 (s, 9 H).

^{13}C NMR (126 MHz, MeCN-d_3): δ = 168.7, 167.9, 158.8, 153.9, 84.6, 83.7, 63.7, 63.4, 47.1, 28.2, 28.1.

^{11}B NMR (128 MHz, MeCN-d_3): δ = 8.9.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{17}H_{26}BN_4O_9$: 440.1835; found: 440.1838.

Di-*tert*-butyl 3-(MIDA-boryl)-4-(4-nitrobenzyl)-5-oxo-1,2,4-triazolidine-1,2-dicarboxylate (6g)

To a stirred suspension of **6f** (100 mg, 0.23 mmol, 1 equiv), K_2CO_3 (63.6 mg, 46 mmol, 2 equiv), and TBAB (7.3 mg, 0.023 mmol, 10 mol%) in DMF (2 mL) at rt was added 4-nitrobenzyl bromide (57.8 mg, 0.27 mmol, 1.2 equiv). The mixture was stirred at 60 °C for 20 h. The mixture was cooled and loaded onto Celite, then the volatiles were removed in vacuo. The residue was subjected to normal-phase column chromatography. Upon removal of volatiles and trituration with Et_2O, **6g** (70.2 mg, 0.12 mmol, 53%) was afforded as a colorless solid. Crystals suitable for X-ray diffraction were grown in MeCN/Et_2O using the vapor diffusion method; mp 195–200 °C (decomp.).

IR (neat): 3312, 2982, 1780, 1754, 1722, 1674, 1524 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ =8.21 (d, *J* = 9.0 Hz, 2 H), 7.44 (d, *J* = 8.5 Hz, 2 H), 5.07 (s, 1 H), 4.84 (d, *J* = 17.0 Hz, 1 H), 4.40 (d, *J* = 17.5 Hz, 1 H), 4.34 (d, *J* = 17.0 Hz, 1 H), 4.26 (d, *J* = 17.0 Hz, 1 H), 4.08 (d, *J* = 17.0 Hz, 1 H), 3.92 (d, *J* = 17.0 Hz, 1 H), 3.03 (s, 3 H), 1.42 (s, 9 H), 1.40 (s, 9 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 168.4, 167.6, 157.4, 150.9, 146.9, 144.8, 128.0, 123.7, 83.5, 82.3, 62.5, 62.4, 46.3, 44.3, 27.6, 27.4.

^{11}B NMR (128 MHz, DMSO-d_6): δ = 9.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{32}BN_5NaO_{11}$: 599.2120; found: 599.2109.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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