Facile amidinations of 2-aminophenylboronic acid promoted by boronate ester formation

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General Experimental Methods:

Acetonitrile was distilled prior to use. All chemicals were purchased as reagent grade and used without further purification with the exception that 2-amino phenylboronic acid **1** (Alfa Aesar) was recrystallised from MeOH/H_2O before use. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker spectrometer (400 MHz). Signals are reported in terms of their chemical shift (δ in ppm) relative to DMSO (^{1}H, 2.50 and ^{13}C, 39.5) and *J* coupling constants are in hertz (Hz). For ^{1}H spectra, multiplicity, integration, intensity, coupling constants and assignment values are reported. Multiplicities are indicated using standard notation; singlet (s), doublet (d), doublet of doublets (dd), triplet (t) and multiplet (m). Mass spectral analysis (MS) was performed using a Bruker Esquire 3000 electrospray ionisation mass spectrometer. IUPAC names are derived from structures where B-N interactions are treated as dative bonds (non-covalent) for all compounds.

General Method A for amidination of 2-aminophenylboronic acid (**1**):

To a neat solution of nitrile (2 mL), salicylic acid (10 mg, 0.072 mmol) and **1** as free base (9.9 mg, 0.072 mmol) were added and stirred at 343 K for 2 hours under argon, monitoring via TLC (DCM:MeOH, 10:1, R_f 0.28 for **5**). The reaction mixture was then allowed to crystallise out of solution to give the desired amidine product as crystalline solid in most cases. The yields listed for compounds **5**-**7** below are isolated yields using this method.

General Method B for amidination of 2-aminophenylboronic acid (**1**):

2-aminophenylboronic acid **1** (9.9 mg, 0.072 mmol) was dissolved in dry $CHCl_3$ (4 ml) in a glass round bottom by stirring under argon. Salicylic acid (10 mg, 0.072 mmol) was added and left to stir for 1 hour during which time a white precipitate formed. The sample was filtered to collect 17.5 mg a white solid. ESMS +ve ion mode (MeOH): *m/z* observed 261.6, calculated [M+Na^+] 262.06, Boron Isotopes: ^{10}B 22% and ^{11}B 78%.

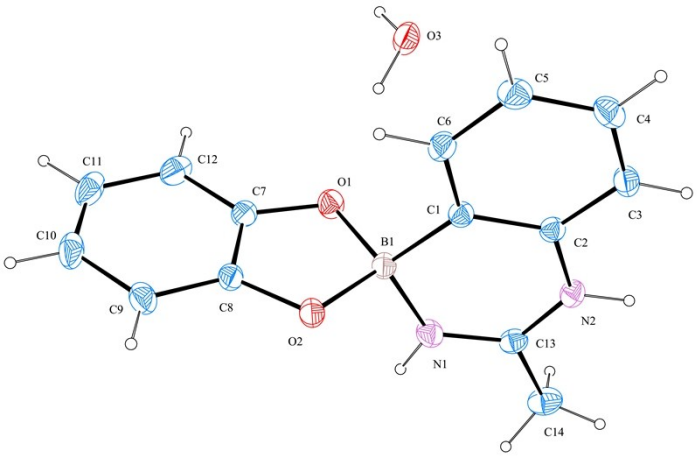
This sample was left under high vacuum for 24 hours before it was dissolved in nitrile under argon and heated at 303 K for 4 hours. Percent conversion was estimated by NMR integration of the amidine NH proton peaks relative to the total aromatic proton peaks (including both **1** and product) in DMSO-d_6 solvent.

Catechol and salicylate esters of (2-acetimidamidophenyl)boronic acid:

Yield 33% and 68% (respectively). Clear crystalline solids.

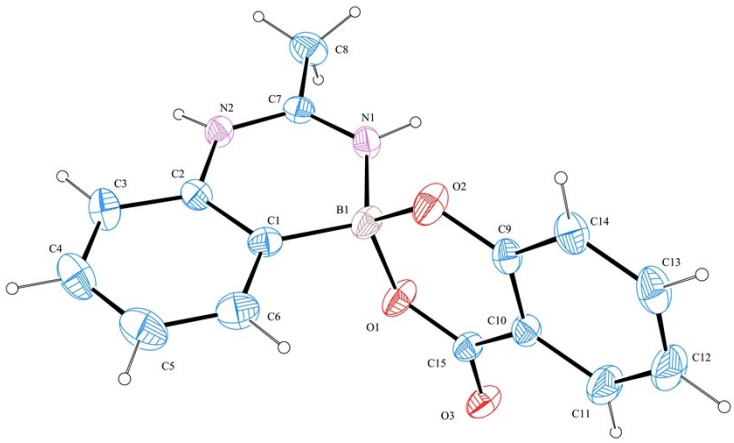
Catechol ester: ^{1}H NMR (400 MHz, DMSO): δ 2.30 (s, 3H, CH_3), 6.50 (m, 4H, ArH), 6.99 (m, 2H, ArH), 7.30 (m, 2H, ArH), 9.19 (s, 1H, NH), 11.04 (s, 1H, C=NH) ppm. ESMS (*m/z*) [M-H^+] observed 250.5, calculated [$C_{14}H_{12}BN_2O_2^-$] 251.07. Boron isotopes: ^{10}B 23.6% and ^{11}B 76.4%.

Crystal data for $C_{14}H_{13}BN_2O_2$-H_2O (1118th21): M = 270.1, monoclinic, space group $P2_1/c$, a =7.0763(5), b = 9.3343(7), c = 20.5929(14) Å, β = 92.821(7)°, U = 1358.6(2) Å^0, Z = 4, D_c = 1.32 g cm^{-3}, μ = 0.092 mm^{-1}, Crystal size: 0.47 x 0.37 x 0.34 mm. $T_{min/max}$ = 0.97, 1.00. 8052 reflections collected, 3760 unique (R_{int} = 0.025), R = 0.054 [2877 reflections with I > 2s(I)], wRF_2 = 0.185 (all data). CCDC#1848684. IUPAC name: *N*-(2-(benzo[d][1,3,2]dioxaborol-2-yl)phenyl)acetimidamide.

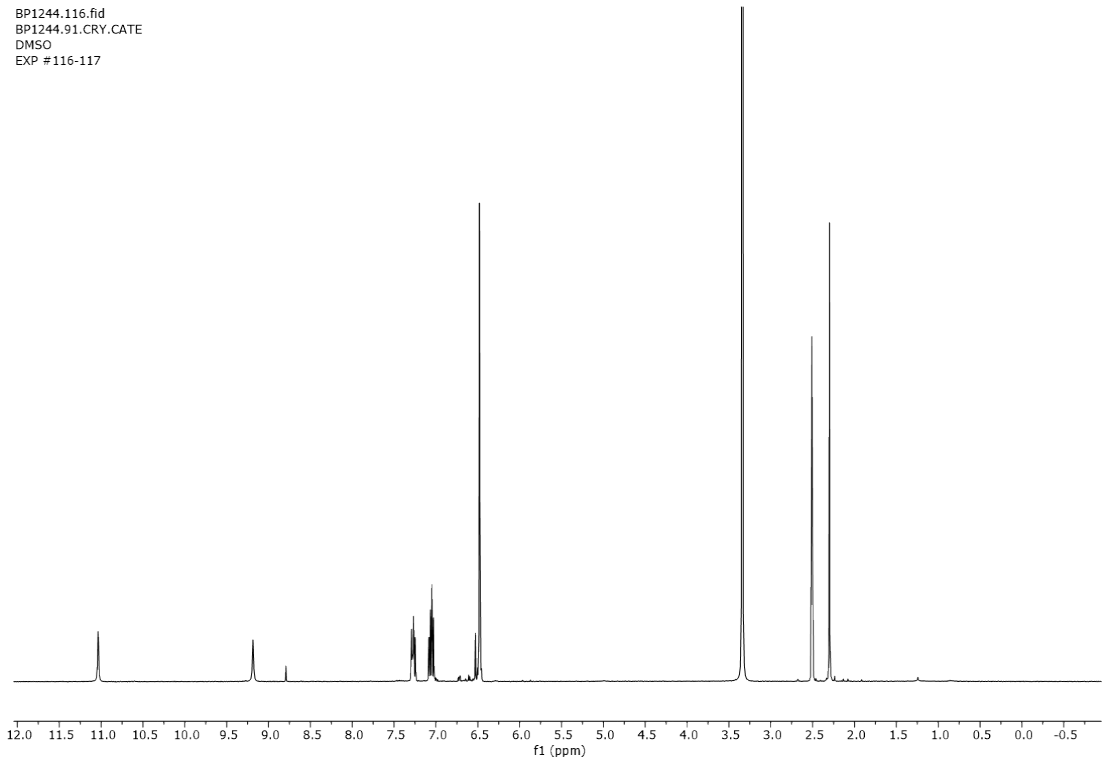


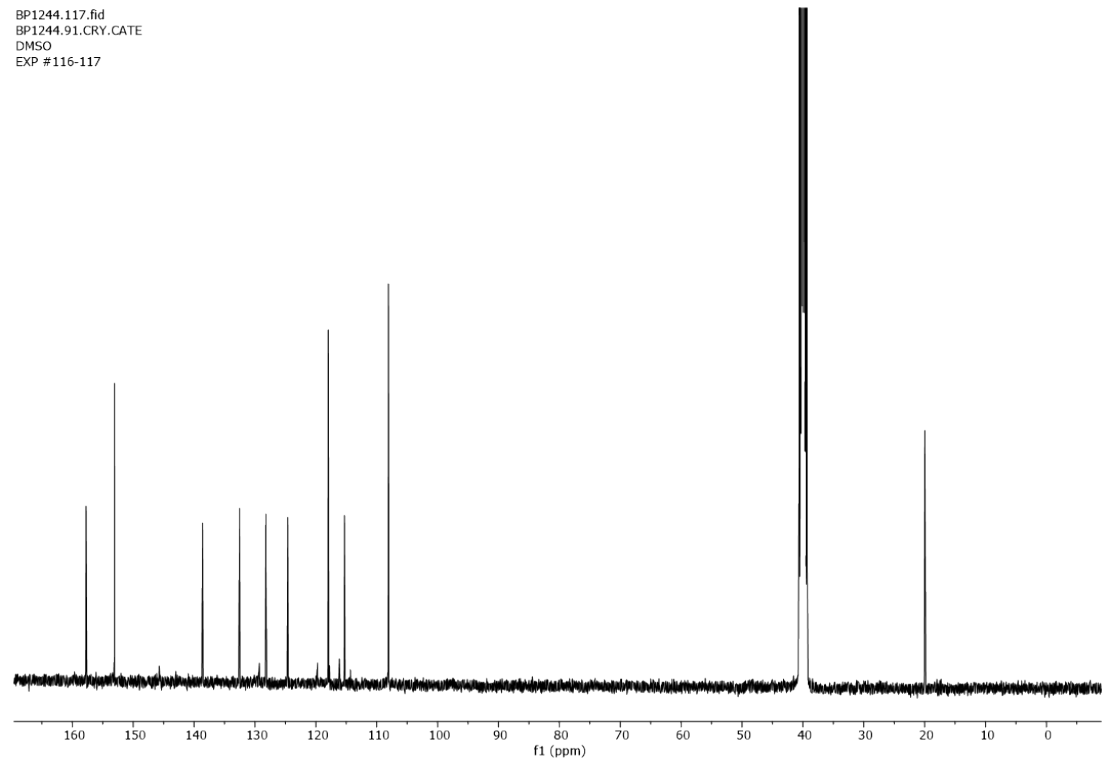
Salicylate ester (**5**): ^{1}H NMR (400 MHz, DMSO): δ: 2.33 (s, 3H, CH_3), 6.76 (dd, J = 8.2, 1.0 Hz, 1H, ArH), 6.86 (td, J = 7.5, 1.1 Hz, 1H, ArH), 7.08 (m, 2H, ArH), 7.29 (t, J = 7.4 Hz, 2H), 7.40 (ddd, J = 8.3, 7.2, 1.8 Hz, 1H), 7.78 (dd, J = 7.7, 1.8 Hz, 1H), 9.38 (s, 1H, NH), 11.16 (s, 1H, C=NH) ppm.

Crystal data for $C_{15}H_{13}BN_2O_3$ (1110th19): M = 280.1, monoclinic, space group $P2_1/c$, a = 11.2723(8), b = 11.6971(6), c = 10.6896(6) Å, β = 101.099(6)^0, U = 1383.1(2) Å^3, Z = 4, D_c = 1.34 g cm^{-3}, μ = 0.094 mm^{-1}, Crystal size: 0.35 x 0.25 x 0.15 mm. $T_{min/max}$ = 0.99, 1.00. 6482 reflections collected, 3718 unique (R_{int} = 0.027), R = 0.058 [2422 reflections with I > 2s(I)], wRF^2 = 0.174 (all data). CCDC#1848682. IUPAC name: *N*-(2-(4-oxo-4H-benzo[d][1,3,2]dioxaborinin-2-yl)phenyl)acetimidamide.

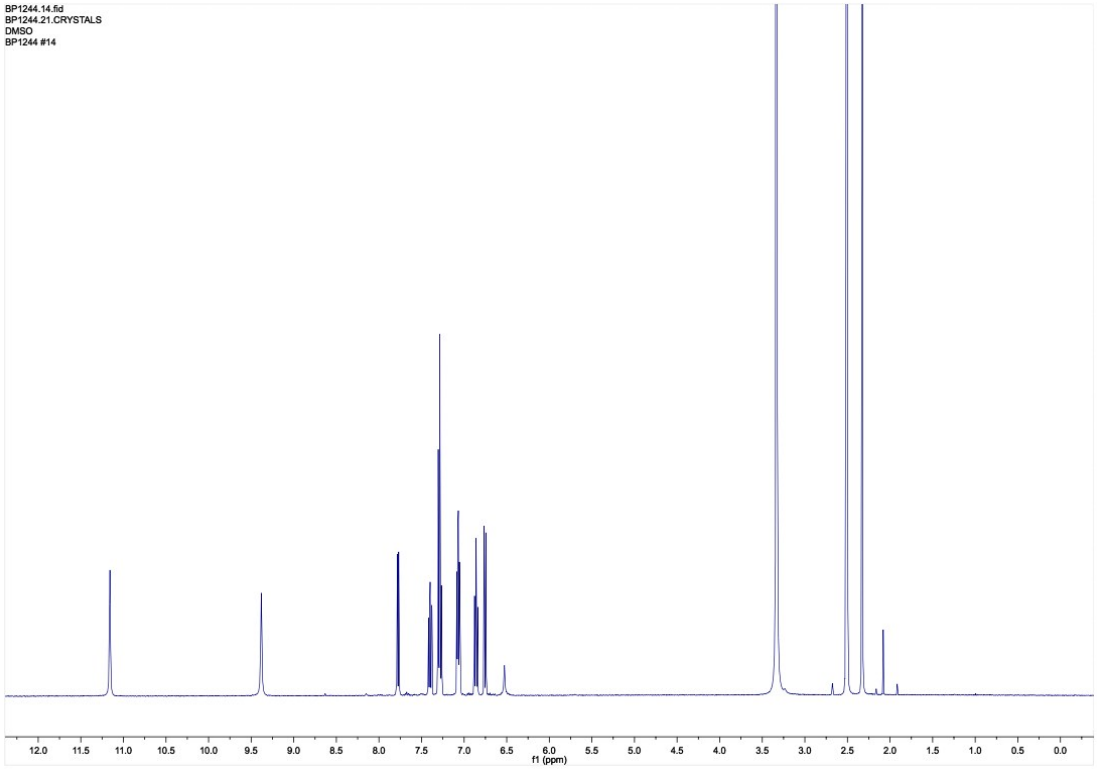


Proton- and C13-NMR of catechol ester of (2-acetimidamidophenyl)boronic acid:





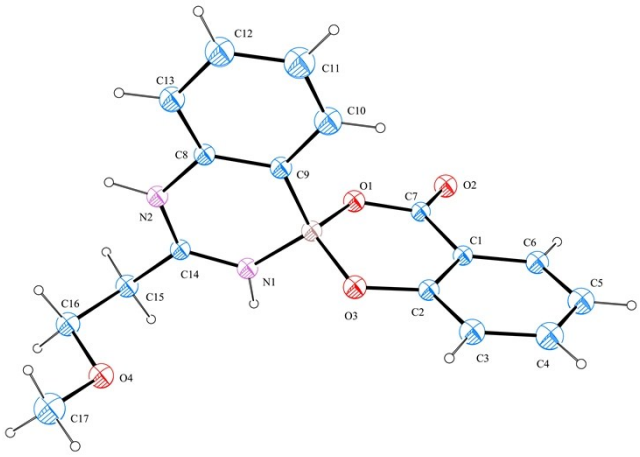
Proton NMR of salicylate ester of (2-acetimidamidophenyl)boronic acid (**5**):



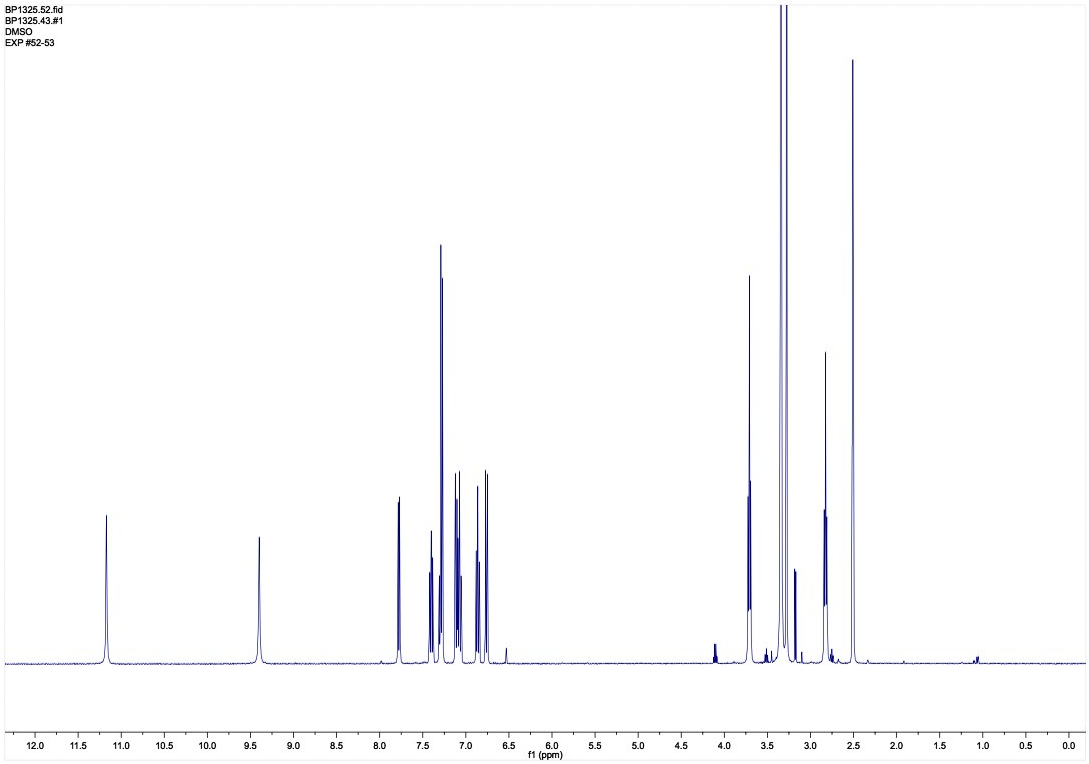
Salicylate ester of (2-(2-methoxyacetimidamido)phenyl)boronic acid (**6**):

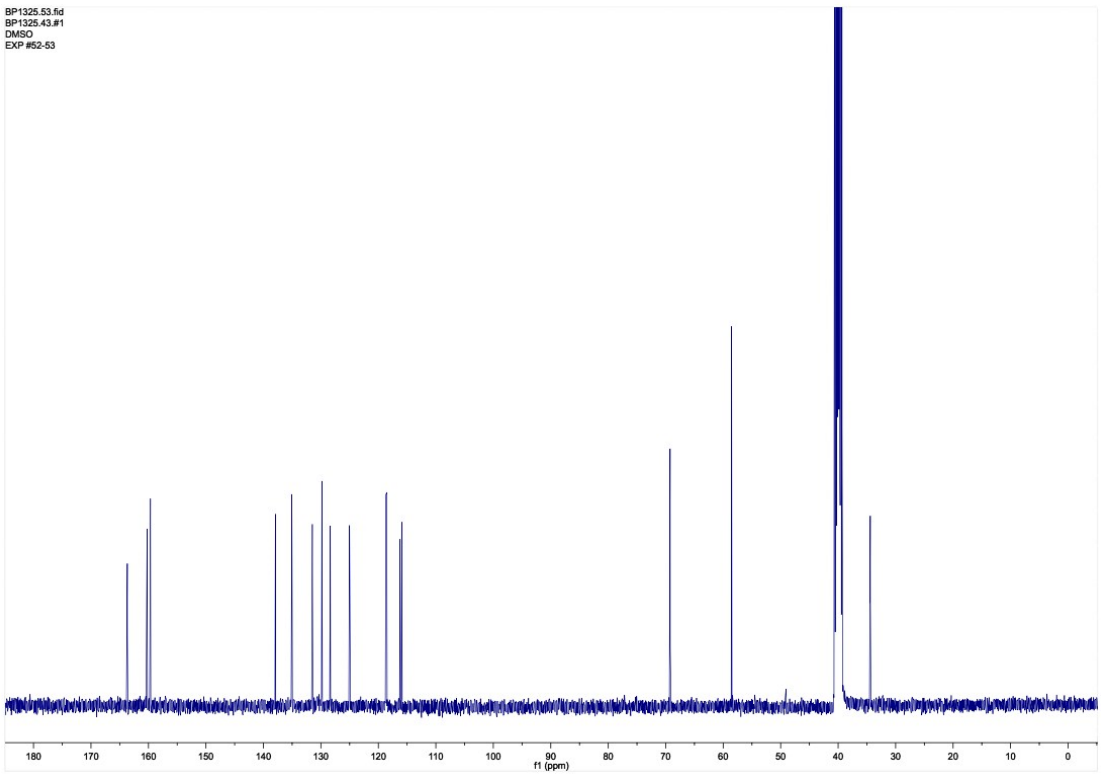
Yield 60%. Clear crystalline solid; ^{1}H NMR (400 MHZ, DMSO): δ 2.51 (s, 3H, CH_3) 2.83 (t, *J* = 6.2 Hz, 2H, CH_2), 3.71 (t, *J* = 6.2 Hz, 2H, CH_2), 6.76 (dd, *J* = 8.2, 1.0 Hz, 1H, ArH), 6.86 (td, *J* = 7.5, 1.1 Hz, 1H, ArH), 7.10 (m, 2H, ArH), 7.28 (dd, *J* = 7.5, 1.4 Hz, 2H, ArH), 7.40 (ddd, *J* = 8.3, 7.2, 1.9 Hz, 1H, ArH), 7.78 (dd, *J* = 7.8, 1.8 Hz, 1H, ArH), 9.40 (s, 1H, NH), 11.17 (s, 1H, C=NH) ppm. ^{13}C NMR (100 MHz, DMSO solution): δ 34.0, 58.4, 69.5, 115.3, 116.4, 118.7, 118.9, 125.1, 128.3, 129.8, 131.8, 135.0, 137.8, 159.8, 160.2, 163.6 ppm. ESMS (*m/z*) [M+Na^+] observed 346.5, calculated [$C_{17}H_{17}BN_2NaO_4^+$] 347.1. Boron isotopes ^{10}B 20.7% and ^{11}B 79.3%.

Crystal data for $C_{17}H_{17}BN_2O_4$ (1122th23): M = 324.13 monoclinic, space group $P2_1/c$, a = 14.4042(11), b = 9.165(5), c = 13.2350(9) Å, β = 113.504(8)°, U = 1602.2(2) Å^3, Z = 4, D_c = 1.34 g cm^{-3}, μ = 0.095 mm^{-1}, Crystal size: 0.52 x 0.27 x 0.22 mm. $T_{min/max}$ = 0.98, 1.00. 10442 reflections collected, 4470 unique (R_{int} = 0.029) R = 0.049 [3341 reflections with I > 2s(I)], wRF^2 = 0.152 (all data). CCDC#1848685. IUPAC name: 2-methoxy-*N*-(2-(4-oxo-4H-benzo[d][1,3,2]dioxaborinin-2-yl)phenyl)acetimidamide.



Proton- and C13-NMR of **6**:

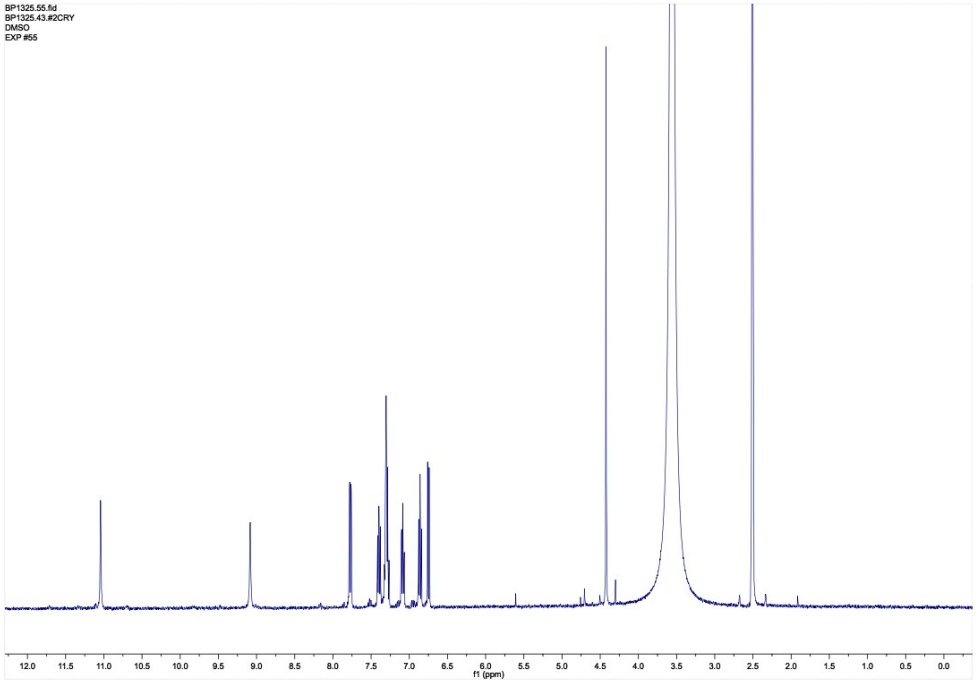


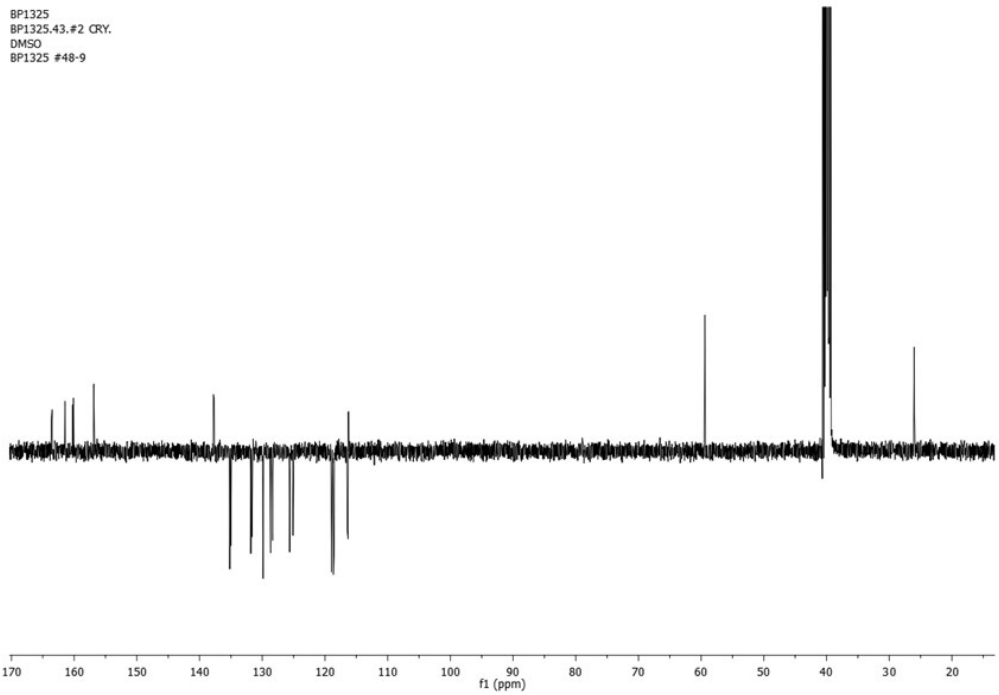


Salicylate ester of (2-(2-bromoacetimidamido)phenyl)boronic acid (**7**):

Yield 95%. Clear crystalline solid; ^{1}H NMR (400 MHZ, DMSO solution): δ 4.42 (s, 2H, CH_2), 6.75 (d, *J* = 8.2 Hz, 1H, CH), 6.86 (t, *J* = 7.4 Hz, 1H. ArH), 7.08 (td, *J* = 7.0, 1.6 Hz, 1H, ArH), 7.30 (m, 3H, ArH), 7.39 (m, 2H, ArH), 7.77 (dd, *J* = 7.7, 1.9 Hz, 1H, ArH), 9.08 (s, 1H, NH), 11.04 (s, 1H, C=NH) ppm. ^{13}C NMR (100 MHZ, DMSO solution): δ: 59.8, 116.2, 117.7, 118.9, 125.6, 128.3, 129.9, 131.8, 135.2, 137.8, 156.8, 160.2, 161.4, 163.6 ppm. HRMS (*m/z*) [$M+H^+$] observed 359.0198/361.0178, calculated [$C_{15}H_{13}BBrN_2O_3^+$] 359.0203/361.0182. IUPAC name: 2-bromo-*N*-(2-(4-oxo-4H-benzo[d][1,3,2]dioxaborinin-2-yl)phenyl) acetimidamide.

Proton- and DEPT C13-NMR of **7**:

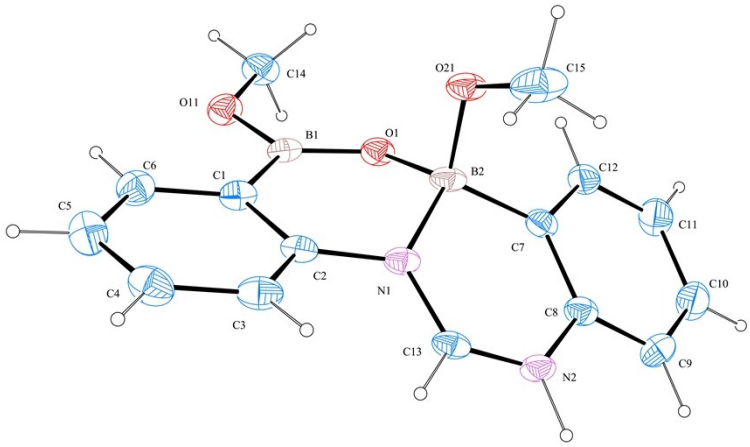




(*E*)-5H-dibenzo[c,h][1,5,7,2,10]oxadiazadiborecine-5,7(12H)-diol (**10**):
A solution of **1** (117.7 mg, 0.8 mmol), catechol (85.9 mg, 0.8 mmol) and 3-phenyl-2-propynenitrile (100.0 mg, 0.8 mmol) in DMF (4 mL) was heated at 338 K for 5 hours. At this time no product had been produced via TLC (DCM:MeOH, 10:1) so the reaction mixture was increased to 383 K for 2 hours and monitored via TLC (DCM:MeOH, 10:1, R_f = 0.08) indicating the formation of a single product. The reaction mixture was concentrated *in vacuo* to yield **10** as a white solid.
^{1}H NMR (400 MHz, DMSO solution): δ 2.57 (s, 1H, CH), 7.05 (m, 1H, ArH), 7.11 (td, *J* = 7.2, 1.2 Hz, 1H, ArH), 7.20 (dtd, *J* = 11.4, 7.4, 1.3 Hz, 2H, ArH), 7.47 (td, *J* = 7.6, 1.6 Hz, 1H, ArH), 7.56 (m, 1H, ArH), 7.60 (d, *J* = 8.7 Hz, 1H, ArH), 7.70 (dd, *J* = 7.3, 1.6 Hz, 1H, ArH), 8.42 (s, 1H, NH) ppm. ^{13}C NMR (100 MHz, DMSO solution): δ 115.6, 118.2, 124.7, 125.1, 126.8, 131.4, 132.8, 134.0, 137.2, 145.9, 147.8 ppm.

This material was dissolved in MeOH and cooled to produce flat disk-like crystals of **15** (~20 mg, 9%) that were suitable for analysis by X-ray crystallographic techniques.
ESMS (m/z) [M-H$^+$] observed 292.4, calculated [$C_{15}H_{15}B_2N_2O_3^-$] 292.92.

Crystal data for $C_{15}H_{16}B_2N_2O_3$ (1113th20): M = 293.9, monoclinic, space group $P2_1/c$, a = 11.3834(13), b = 10.8026(9), c = 12.7677(10) Å, β = 103.589(10)°, U = 1526.1(3) Å^3, Z = 4, D_c = 1.33 g cm^{-3}, μ = 0.087 mm^{-1}, Crystal size: 0.24 x 0.19 x 0.10 mm. $T_{min/max}$= 0.11, 1.00. 6288 reflections collected, 4066 unique (R_{int} = 0.064), R = 0.081 [2170 reflections with I > 2s(I)], wRF^2 = 0.217 (all data). CCDC#1848683. IUPAC name: (*E*)-5,7-dimethoxy-7,12-dihydro-5H-dibenzo[c,h][1,5,7,2,10]oxadiazadiborecine.



Proton- and C13-NMR spectra of **10**: