SUPPORTING INFORMATION

Solid Phase Synthesis of C-Terminal Boronic Acid Peptides

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Experimental section

General
Chemicals used for synthesis were obtained from Sigma-Aldrich (Germany) and were of analytical grade. All solvents were used as obtained from the commercial sources. The protected amino acids were purchased from Orpegen (Germany) and Carbolution Chemicals (Germany). HATU was purchased from Carbolution Chemicals (Germany). The 1-glycerol resin was purchased from Iris Biotech (Germany) and was of a loading capacity of 0.6 mmol/g.

$^1$H NMR spectra were recorded on Varian NMR instruments at 300 or 500 MHz in acetone-$d_6$, methanol-$d_6$ or D$_2$O. $^{13}$C NMR spectra were recorded on Varian NMR instruments at 75 or 126 MHz in acetone-$d_6$, methanol-$d_6$ or D$_2$O. $^{11}$B NMR spectra were recorded on Varian NMR instruments at 160 MHz in acetone-$d_6$, methanol-$d_6$ or D$_2$O in a Wilmad® quartz NMR tube. Chemical shifts (δ) are given in parts per million (ppm) in reference to residuals of nondeuterated solvents as internal standard. ($^1$H NMR: acetone-$d_6$ δ = 2.05 ppm, methanol-$d_4$ δ = 3.31 ppm, D$_2$O δ = 4.79 ppm; $^{13}$C NMR (APT): acetone-$d_6$ δ = 29.84 ppm, methanol-$d_4$ δ = 49.00 ppm). Coupling constants (J) are given in hertz (Hz). Multiplicity is reported as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), dt (doublet of triplet), td (triplet of doublet), and m (multiplet). The $^{11}$B NMR spectra were processed with background subtraction. In the $^{13}$C NMR spectra, the carbon attached to boron was in some cases not observed due to quadrupole broadening caused by $^{11}$B nucleus.

HR-ESI mass spectra were measured on Bruker microTOF-Q II instrument. Purity analysis was carried out using 50 μM samples in water/acetonitrile (1:1) and was determined by HPLC on a Jasco HPLC system with a UV-detector on an RP-18 column (ReproSil-Pur-ODS-3, Dr. Maisch GmbH, Germany, 5 μm, 50 mm × 2 mm).
The conditions for the method used were: eluent A: water (0.1% TFA), eluent B: acetonitrile (0.1% TFA), linear gradient: 1% B (0.2 min), 100% B (3.5 min), 100% B (4.5 min), 1% B (4.6 min), 1% B (5 min). UV-detection was performed at 214 nm and 254 nm.

**Synthesis of N α-Fmoc–(3-amino)-phenylboronic acid (1)**

As described before, a solution of 3-aminophenylboronic acid monohydrate (465 mg, 3 mmol) and DIPEA (1.05 ml, 6 mmol) in 20 ml acetonitrile/water (1:1) is stirred at room temperature for 20 min, then and Fmoc-MOSu (911 mg, 2.7 mmol) is added. After 30 min, most of the solids have dissolved. The reaction progress was monitored for the disappearance of Fmoc-OSu by TLC (solvent system: ethylacetate). When the reaction was completed (1.5-2 h), the solution was acidified to pH 2 using 1M aqueous HCl, 10 ml water was added and mixture was allowed to stir for an additional hour. Finally, the resulting precipitate was collected by filtration, washed with water, dried under reduced pressure and used as crude product without further purification for solid phase peptide synthesis. The final product was obtained as white solid (682 mg, 70% yield). $^1$H NMR (300 MHz, acetone-$d_6$) $\delta$ 8.80 (s, 1H), 7.96 (s, 1H), 7.88 (d, $J = 7.4$ Hz, 2H), 7.76 (d, $J = 7.6$ Hz, 2H), 7.67 (d, $J = 7.7$ Hz, 1H), 7.54 (d, $J = 7.3$ Hz, 1H), 7.43 (t, $J = 7.2$ Hz, 2H), 7.34 (td, $J = 7.5$, 1.3 Hz, 2H), 7.27 (d, $J = 7.7$ Hz, 1H), 7.16 (s, 1H), 4.47 (d, $J = 7.0$ Hz, 2H), 4.31 (t, $J = 7.0$ Hz, 1H), 3.76 (s, 1H); $^{13}$C NMR (APT, 75 MHz, acetone-$d_6$) $\delta$ 154.44, 145.05, 142.15, 129.46, 128.76, 128.58, 127.97, 126.09, 120.85, 67.05, 47.99; $^{11}$B NMR (160 MHz, acetone-$d_6$) $\delta$ 28.73; HRMS (ESI): $m/z$ [M + Na]$^+$ calcd for C$_{21}$H$_{18}$BNO$_4$Na: 382.1225, found: 382.1401.
For the one-pot synthesis, the resin (100 mg, 0.06 mmol) was placed in a syringe equipped with a frit and swollen in DCM for 30 min. DCM was removed and a solution of 3-aminophenylboronic acid monohydrate (11.2 mg, 0.072 mmol) and Fmoc-Cl (56 mg, 0.216 mmol) in 1 ml dry THF is added. In case the aminoboronic acid was not soluble in THF, the solid compound and Fmoc-Cl were mixed with the preswollen resin and 1 ml dry THF was subsequently added. After shaking at room temperature for 20 min, most of the solids have dissolved and DIPEA (38 µl, 0.216 mmol) in 0.5 ml dry THF is added. Shaking was continued for another 2 h. After that, the resin is washed 3x with THF and 3x with DCM and dried under vacuum. To the dry resin was added the cleavage solution (THF:TFA:H₂O, 70:20:10, 1 ml per 50 mg resin). The cleavage was carried out under shaking at room temperature for 3 h. The solution with the cleaved product was collected, THF was removed by evaporation and the remaining aqueous solution was lyophilized to yield the product 1 as a white solid (21.4 mg, 99% yield). ¹H NMR (500 MHz, acetone-d₆) δ 8.80 (s, 1H), 7.97 (s, 1H), 7.88 (d, J = 7.6 Hz, 2H), 7.75 (d, J = 7.5 Hz, 2H), 7.67 (s, 1H), 7.55 (d, J = 7.3 Hz, 1H), 7.42 (t, J = 7.5 Hz, 2H), 7.31 (td, J = 7.5, 1.3 Hz, 2H), 7.17 (s, 1H), 4.47 (d, J = 7.0 Hz, 2H), 4.31 (t, J = 7.0 Hz, 1H); HRMS (ESI): m/z [M + Na]⁺ calcd for C₂₁H₁₈BNO₄Na: 382.1225, found: 382.1403.

**Synthesis of piperidin-4-ylboronic acid hydrochloride**

Piperidin-4-boronic acid pinacol ester hydrochloride (0.200 g, 0.81 mmol) and phenylboronic acid (0.094 g, 0.769 mmol) were added to a two-phase system of 0.1M HCl/acetonitrile (9:1) (12 ml) and hexane (12 ml). After the mixture was stirred for 24 h and the hexane was exchanged several times the aqueous layer was concentrated
in vacuo. The clean product was obtained as a pale yellow solid (0.119 g, 89%).\(^1\)H NMR (300 MHz, D\(_2\)O) \(\delta\) 3.39 (dt, \(J = 12.6, 3.4\) Hz, 2H), 2.98 (td, \(J = 12.4, 2.1\) Hz, 2H), 1.95 (dd, \(J = 15.1, 3.2\) Hz, 2H), 1.80 – 1.55 (m, 2H), 1.32 – 1.12 (m, 1H); \(^{13}\)C NMR (75 MHz, D\(_2\)O) \(\delta\) 44.68, 23.61; \(^{11}\)B NMR (160 MHz, D\(_2\)O) \(\delta\) 31.35; HRMS (ESI): m/z [M+H]\(^+\) calcd for C\(_{5}\)H\(_{13}\)BNO\(_{2}\): 130.1035, found: 130.1038.

**Synthesis of \(N_\alpha\)-Fmoc–piperidin-4-ylboronic acid (2)**

\[
\begin{align*}
&\text{OH} \\
\text{Fmoc} &\quad \text{B} \\
&\quad \text{OH}
\end{align*}
\]

The one-pot synthesis was carried out as described for derivative 1, using the resin (100 mg, 0.06 mmol), piperidine-4ylboronic acid hydrochloride (9.3 mg, 0.072 mmol), Fmoc-Cl (56 mg, 0.216 mmol) and DIPEA (38 \(\mu\)l, 0.216 mmol). After lyophilization, the product 2 was obtained as a white solid (17.7 mg, 84% yield).\(^1\)H NMR (500 MHz, acetone-\(d_6\)) \(\delta\) 7.87 (d, \(J = 7.2\) Hz, 2H), 7.67 (dd, \(J = 7.6, 0.8\) Hz, 2H), 7.42 (td, \(J = 7.5, 0.8\) Hz, 2H), 7.34 (td, \(J = 7.4, 1.3\) Hz, 2H), 4.36 (d, \(J = 5.7\) Hz, 2H), 4.29 (d, \(J = 6.6\) Hz, 1H), 3.95 (d, \(J = 12.7\) Hz, 2H), 2.26 (dt, \(J = 4.4, 2.2\) Hz, 1H), 1.84 (dt, \(J = 4.4, 2.2\) Hz, 1H), 1.68 (dd, \(J = 13.2, 3.5\) Hz, 2H), 1.47 – 1.39 (m, 3H), 1.29 (s, 1H), 1.08 – 1.02 (m, 1H), 0.91 – 0.83 (m, 2H); \(^{13}\)C NMR (75 MHz, acetone-\(d_6\)) \(\delta\) 145.29, 142.17, 128.49, 127.94, 125.96, 120.82, 67.54, 48.21; \(^{11}\)B NMR (160 MHz, acetone-\(d_6\)) \(\delta\) 31.66, 20.16; HRMS (ESI): m/z [M + H]\(^+\) calcd for C\(_{20}\)H\(_{23}\)BNO\(_{4}\): 352.1718, found: 352.1708.
**General procedures for the synthesis of peptide-boronic acids**

All peptide-boronic acid sequences were assembled by stepwise solid-phase synthesis on 1-glycerol resin using standard Fmoc-strategy. Solid phase synthesis was done manually in syringes equipped with a frit; all steps were performed at room temperature under continuous shaking. The 1-glycerol resin (loading capacity 0.6 mmol/g) was preswollen in DCM for 30 min.

For the one-pot synthesis, all reagents were added to the resin as described for compound 1. After shaking for 2 h the resin was washed 3x with THF, 3x with DCM and 3x with DMF. For Fmoc-group deprotection, a piperidine solution (10% in DMF) was added 2x for 10 min and 5 min, respectively. Following each deprotection or coupling step, the resin was washed 3x with DMF, again 3x with DCM. HATU/DIPEA were used for coupling steps. In detail, the coupling solution contained the Nα-Fmoc-protected amino acid or N-terminal carboxylic acid capping group (3 equiv), HATU (3 equiv) and DIPEA (4 equiv) in DCM/DMF (1:1, ~1.0 ml per 100 mg resin). The solution was added to the resin and the reaction was performed for 1 h. In case of Fmoc-arginine(Pbf)-OH, the coupling procedure was performed twice. Afterwards the resin was washed as described before. Fmoc-deprotection and coupling steps were iteratively repeated until the desired sequence was obtained. The benzene sulfonyl chloride was coupled (4 equiv) with NMM (6 equiv) in DCM for 3 h. For the synthesis of peptide hybrids sharing identical amino acid sequence but differing for the N-terminal cap, the Fmoc-protected peptide sequence was synthesized on a large scale, split and stored at 4 °C until use.

The resin loaded with the finished peptide was washed 3x with DCM and 3x with diethyl ether and dried under reduced pressure. Cleavage was performed with the cocktail described in Table 1, which is discussed in the paper. The cleavage solution was lyophilized (after removal of THF, in case it was used). Sufficiently polar
Compounds, such as 7 and 9, are collected by precipitation in ether. In detail, the cleavage solution was dispensed into cold diethyl ether (20 ml per 100 mg resin) and the resulting precipitate was centrifuged (4000 g, 10 min), washed with diethyl ether and dried under reduced pressure. Purity was assessed for crude peptides. Compound 9 in the first attempt of cleavage needed purification by preparative HPLC, after optimization the crude product was pure and this was not necessary. This was done using ÄKTA Purifier, GE Healthcare (Germany), with an RP-18 pre and main column (Rephospher, Dr. Maisch GmbH, Germany, C18-DE, 5 µm, 30 mm × 16 mm and 120 mm × 16 mm). The following conditions were used: eluent A: water (0.1% TFA), eluent B: methanol (0.1 % TFA), flow rate: 8 ml/min, gradient: 10% B (2.5 min), 100% B (23.5 min), 100% B (26 min) 10% B (26.1 min), 10% B (30 min). Detection was performed at 214 nm, 254 nm and 280 nm. After purification, methanol was evaporated and the peptide was freeze-dried in water and stored at –20 °C.

**Data for the peptide-boronic acids compounds**

3 was obtained according to the general procedure as a white solid. Yields for the different conditions using 50 mg resin: conditions B or C, 90%, 8.4 mg; conditions D, E, G, or I, 98%, 9.1 mg; conditions A or H, 96%, 9.1 mg; conditions F or K, 95%, 8.9 mg; condition J, 62%, 5.8 mg. $^1$H NMR (500 MHz, acetone- $d_6$) δ 7.98 – 7.96 (m, 2H), 7.95 (d, $J = 1.5$ Hz, 1H), 7.83 (ddd, $J = 8.1$, 2.3, 1.1 Hz, 1H), 7.57 (d, $J = 7.3$ Hz, 1H), 7.54 (dt, $J = 2.7$, 1.8 Hz, 1H), 7.49 – 7.45 (m, 2H), 7.29 (t, $J = 7.7$ Hz, 1H), 4.79 (q, $J = 7.1$ Hz, 1H), 1.53 (d, $J = 7.1$ Hz, 3H); $^{13}$C NMR (75 MHz, acetone- $d_6$) δ 171.59, 139.21, 135.25, 132.25, 130.21, 129.18, 128.67, 128.24, 126.07, 122.37, 50.94,
18.12, 17.33; $^{11}$B NMR (160 MHz, acetone-$d_6$) δ 28.57; HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{16}$H$_{18}$BN$_2$O$_4$: 313.1357, found: 313.1350. (NMR spectra are shown for the one-pot synthesis followed by cleavage using condition A)

![Chemical Structure](image)

4 was obtained according to the general procedure as a white solid. Yields for the different conditions using 50 mg resin: condition A, 96 %, 9.7 mg; condition J, 59 %, 6.0 mg. $^1$H NMR (500 MHz, acetone-$d_6$) δ 8.02 (s, 1H), 7.96 (d, J = 7.2 Hz, 2H), 7.85 (ddd, J = 7.0, 2.7, 1.5 Hz, 1H), 7.58 (dt, J = 7.4, 1.1 Hz, 1H), 7.56 – 7.52 (m, 1H), 7.50 – 7.45 (m, 2H), 7.30 (t, J = 7.7 Hz, 1H), 7.23 (s, 1H), 4.63 – 4.58 (m, 1H), 3.75 (s, 1H), 2.17 (dt, J = 4.4, 2.2 Hz, 2H), 1.92 (dt, J = 4.4, 2.2 Hz, 1H), 1.41 (s, 1H), 1.07 (dd, J = 6.8, 3.3 Hz, 6H); $^{13}$C NMR (75 MHz, acetone-$d_6$) δ 170.76, 167.66, 138.99, 135.48, 132.19, 130.35, 129.19, 128.67, 128.23, 126.20, 122.45, 60.74, 60.66, 47.05, 31.85, 19.92, 18.92, 8.98. $^{11}$B NMR (160 MHz, acetone-$d_6$) δ 28.78, 20.25; HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{18}$H$_{22}$BN$_2$O$_4$: 341.1670, found: 341.1657.

![Chemical Structure](image)

5 was obtained according to the general procedure as a white solid using condition A (yield 76 %, 6.6 mg for 50 mg resin). $^1$H NMR (500 MHz, acetone-$d_6$) δ 7.92 – 7.88 (m, 2H), 7.56 – 7.52 (m, 1H), 7.51 – 7.46 (m, 2H), 4.31 (dt, J = 8.2, 2.4 Hz, 1H), 4.19 (d, J = 2.6 Hz, 2H), 3.82 (dt, J = 6.0, 4.5 Hz, 1H), 3.18 – 3.09 (m, 1H), 2.80 (dd, J = 17.4, 7.3 Hz, 2H), 1.77 (ddd, J = 36.6, 12.9, 2.5 Hz, 2H), 1.62 – 1.42 (m, 2H), 1.21 – 1.10 (m, 1H), 0.94 – 0.82 (m, 1H); $^{13}$C NMR (75 MHz, acetone-$d_6$) δ 167.04, 135.56,
132.10, 129.28, 127.90, 46.68, 44.16, 41.89, 28.82, 28.16; $^{11}$B NMR (160 MHz, acetone-$d_6$) δ 31.80, 20.23; HRMS (ESI): $m/z$ [M + H]$^+$ calcd for C$_{14}$H$_{20}$BN$_2$O$_4$: 291.1513, found: 291.1509.

6 was obtained according to the general procedure as a white solid. Yields for the different conditions using 50 mg resin: condition B, 60 %, 15.8 mg; condition K, 65 %, 17.1 mg. $^1$H NMR (300 MHz, acetone-$d_6$) δ 9.18 (s, 1H), 8.75 (dd, $J = 4.4$, 1.3 Hz, 1H), 8.43 (dd, $J = 8.4$, 1.4 Hz, 1H), 8.09 (s, 1H), 8.02 – 7.92 (m, 2H), 7.87 (dd, $J = 8.5$, 1.6 Hz, 1H), 7.77 (dd, $J = 10.9$, 4.9 Hz, 1H), 7.60 – 7.45 (m, 3H), 7.29 (t, $J = 7.7$ Hz, 1H), 4.21 (dd, $J = 5.7$, 2.6 Hz, 1H), 3.92 (dd, $J = 8.0$, 5.3 Hz, 3H), 3.43 – 3.37 (m, 3H), 2.96 (d, $J = 12.3$ Hz, 2H), 2.78 (s, 1H), 2.74 (s, 1H), 2.58 (s, 2H), 2.50 (s, 2H), 1.49 – 1.44 (m, 24H), 1.41 (s, 2H), 1.38 (s, 4H), 0.97 – 0.87 (m, 3H); $^{13}$C NMR (126 MHz, acetone-$d_6$) δ 171.10, 151.86, 139.10, 136.85, 134.92, 132.40, 132.02, 131.47, 130.50, 130.32, 129.63, 129.46, 129.21, 128.62, 128.50, 128.45, 126.29, 126.05, 122.48, 121.31, 68.33, 55.35, 43.60, 43.39, 39.68, 24.52, 19.49, 18.67, 17.35, 14.32, 12.84, 12.53, 11.32; $^{11}$B NMR (160 MHz, acetone-$d_6$) δ 20.22; HRMS (ESI): $m/z$ [M + H]$^+$ calcd for C$_{43}$H$_{61}$BN$_7$O$_{10}$S: 878.4296, found: 878.4278.
was obtained according to the general procedure as a white solid using condition L (yield 94 %, 14.8 mg for 50 mg resin). $^1$H NMR (500 MHz, D$_2$O) δ 7.80 (dd, $J = 8.3$, 1.2 Hz, 2H), 7.66 (t, $J = 7.5$ Hz, 1H), 7.56 (t, $J = 7.7$ Hz, 2H), 7.31 (t, $J = 8.1$ Hz, 1H), 7.04 (t, $J = 2.2$ Hz, 1H), 6.98 (dd, $J = 8.2$, 1.8 Hz, 1H), 6.78 (dd, $J = 8.2$, 2.6 Hz, 1H), 4.55 (t, $J = 7.1$ Hz, 2H), 4.49 (dd, $J = 8.9$, 5.9 Hz, 2H), 3.75 – 3.66 (m, 1H), 3.23 (t, $J = 7.1$ Hz, 2H), 3.00 (t, $J = 7.6$ Hz, 2H), 2.08 – 1.82 (m, 5H), 1.82 – 1.64 (m, 5H), 1.63 – 1.41 (m, 2H), 1.39 – 1.21 (m, 1H); $^{13}$C NMR (75 MHz, methanol-d$_4$) δ 174.62, 172.56, 170.64, 158.14, 134.94, 133.03, 130.68, 129.60, 129.14, 128.64, 55.47, 55.35, 49.00, 42.01, 40.46, 32.35, 29.84, 27.99, 26.42, 23.83; $^{11}$B NMR (160 MHz, methanol-d$_4$) δ 28.49; HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{25}$H$_{37}$BN$_7$O$_5$: 526.2948, found: 526.2943.

8 was obtained according to the general procedure as a white solid. Yields for the different conditions using 50 mg resin: condition B, 49 %, 12.7 mg; condition K, 50 %,
13.0 mg. $^1$H NMR (300 MHz, acetone-$d_6$) δ 8.54 (s, 1H), 8.25 (d, $J = 8.6$ Hz, 1H), 7.92 (d, $J = 7.4$ Hz, 2H), 7.78 (d, $J = 6.6$ Hz, 1H), 7.53 (dd, $J = 11.4$, 4.5 Hz, 1H), 7.50 – 7.43 (m, 2H), 7.30 (dd, $J = 7.3$, 4.3 Hz, 1H), 6.51 (s, 1H), 4.87 (p, $J = 4.1$ Hz, 1H), 4.77 – 4.62 (m, 1H), 3.95 – 3.84 (m, 1H), 3.75 (s, 1H), 3.59 (s, 2H), 3.28 – 3.20 (m, 2H), 2.99 (s, 2H), 2.57 (s, 2H), 2.50 (s, 2H), 2.26 (dt, $J = 4.4$, 2.2 Hz, 2H), 1.84 (dt, $J = 4.4$, 2.2 Hz, 3H), 1.44 (s, 6H), 1.41 (s, 1H), 1.38 (s, 8H), 1.29 (s, 2H), 1.22 (d, $J = 5.8$ Hz, 16H), 1.07 – 0.94 (m, 2H), 0.87 (dd, $J = 7.0$, 4.7 Hz, 2H); $^{13}$C NMR (75 MHz, acetone-$d_6$) δ 158.90, 138.74, 132.86, 132.20, 130.39, 129.25, 129.18, 129.11, 128.33, 128.27, 125.28, 119.94, 117.46, 86.93, 67.59, 54.70, 43.63, 42.96, 38.73, 36.16, 28.75, 28.70, 19.50, 18.26, 13.15, 12.55. $^{11}$B NMR (160 MHz, acetone-$d_6$) δ 20.25; HRMS (ESI): $m/z$ [M + H]$^+$ calcd for C$_{42}$H$_{65}$BN$_7$O$_{10}$S: 870.4608, found: 870.4588.

9 was obtained according to the general procedure as a white solid. Yields for the different conditions using 50 mg resin: condition L, 62 %, 9.6 mg; condition B then L, 49 %, 7.6 mg. $^1$H NMR (500 MHz, D$_2$O) δ 7.80 (dt, $J = 8.5$, 1.2 Hz, 2H), 7.69 – 7.64 (m, 1H), 7.56 (dt, $J = 6.7$, 1.0 Hz, 2H), 4.57 – 4.51 (m, 1H), 4.31 (dd, $J = 24.4$, 13.6 Hz, 1H), 4.08 – 3.95 (m, 1H), 3.32 – 3.17 (m, 3H), 2.97 (td, $J = 7.4$, 3.3 Hz, 2H), 2.86 – 2.74 (m, 1H), 2.00 – 1.87 (m, 3H), 1.87 – 1.62 (m, 10H), 1.61 – 1.32 (m, 5H), 1.30 – 1.18 (m, 1H); $^{13}$C NMR (75 MHz, methanol-$d_4$) δ 173.95, 158.61, 135.04, 133.01,
$^{11}$B NMR (160 MHz, methanol-$d_4$) $\delta$ 30.75, 18.50; HRMS (ESI): $m/z$ [M + H]$^+$ calcd for C$_{14}$H$_4$BN$_7$O$_5$: 518.3261, found: 518.3248.

10 was obtained according to the general procedure as white solid. Yields for the different conditions using 50 mg resin: condition A, 96 %, 6.9 mg; condition H, 95 %, 6.8 mg; condition J, 69 %, 5.0 mg. $^1$H NMR (500 MHz, acetone-$d_6$) $\delta$ 8.87 (s, 1H), 7.80 – 7.79 (m, 1H), 7.78 (t, $J = 1.3$ Hz, 1H), 7.68 (dd, $J = 1.2$, 0.5 Hz, 1H), 7.60 – 7.56 (m, 2H), 7.53 – 7.48 (m, 2H), 7.27 (ddd, $J = 8.0$, 2.3, 1.3 Hz, 1H), 7.25 – 7.21 (m, 1H); $^{13}$C NMR (75 MHz, acetone-$d_6$) $\delta$ 133.51, 131.29, 129.80, 129.05, 127.92, 123.92; $^{11}$B NMR (160 MHz, acetone-$d_6$) $\delta$ 28.31; HRMS (ESI): $m/z$ [M + H]$^+$ calcd for C$_{12}$H$_{13}$BNO$_4$: 278.0655, found: 278.0655.

11 was obtained according to the general procedure as a white solid using condition C (yield 81 %, 8.4 mg for 50 mg resin). $^1$H NMR (300 MHz, acetone-$d_6$) $\delta$ 8.60 (dd, $J = 3.4$, 1.5 Hz, 1H), 7.98 (dd, $J = 8.3$, 1.4 Hz, 2H), 7.61 – 7.45 (m, 4H), 7.40 (d, $J = 8.0$ Hz, 1H), 4.88 (q, $J = 7.2$ Hz, 1H), 1.57 (d, $J = 7.1$ Hz, 3H); $^{13}$C NMR (75 MHz, acetone-$d_6$) $\delta$ 176.24, 169.68, 132.42, 131.87, 129.75, 129.24, 129.17, 128.31, 50.70, 17.26; $^{11}$B NMR (160 MHz, acetone-$d_6$) $\delta$ 28.63; HRMS (ESI): $m/z$ [M + Na]$^+$ calcd for C$_{16}$H$_{16}$BCIN$_2$O$_4$Na: 369.0787, found: 369.0784.
12 was obtained according to the general procedure as a white solid using condition C (yield 87 %, 8.5 mg for 50 mg resin). $^1$H NMR (300 MHz, acetone-$d_6$) $\delta$ 8.08 (d, $J$ = 4.8 Hz, 1H), 7.97 (dd, $J$ = 8.3, 1.3 Hz, 2H), 7.60 – 7.52 (m, 2H), 7.50 – 7.47 (m, 1H), 7.18 (t, $J$ = 3.7 Hz, 2H), 4.83 (q, $J$ = 7.1 Hz, 1H), 2.27 (s, 3H), 1.56 (d, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (126 MHz, acetone-$d_6$) $\delta$ 171.49, 167.77, 135.23, 132.31, 131.94, 130.88, 130.43, 129.21, 128.27, 50.85, 18.25, 17.91. $^{11}$B NMR (160 MHz, acetone-$d_6$) $\delta$ 28.63, 20.21; HRMS (ESI): m/z [M + Na]$^+$ calcd for C$_{17}$H$_{19}$BN$_2$O$_4$Na: 349.1333, found: 349.1360.

13 was obtained according to the general procedure as a white solid using condition C (yield 77 %, 40.0 mg for 200 mg resin). $^1$H NMR (300 MHz, acetone-$d_6$) $\delta$ 7.97 – 7.93 (m, 2H), 7.82 (ddd, $J$ = 8.1, 2.3, 1.1 Hz, 1H), 7.68 (d, $J$ = 7.9 Hz, 1H), 7.64 – 7.44 (m, 4H), 7.38 (dd, $J$ = 7.9, 1.7 Hz, 2H), 7.35 – 7.19 (m, 4H), 4.92 (dd, $J$ = 8.1, 3.6 Hz, 1H), 4.74 (d, $J$ = 11.9 Hz, 1H), 4.65 (d, $J$ = 11.9 Hz, 1H), 4.31 (q, $J$ = 6.3 Hz, 1H), 1.32 (d, $J$ = 6.3 Hz, 3H); $^{13}$C NMR (126 MHz, acetone-$d_6$) $\delta$ 169.20, 167.70, 139.60, 138.91, 135.31, 132.38, 130.46, 129.30, 129.20, 129.14, 129.11, 128.72, 128.52, 128.42, 128.29, 128.23, 128.21, 126.47, 122.76, 75.79, 71.78, 67.61, 59.17, 16.74; $^{11}$B NMR (160 MHz, acetone-$d_6$) $\delta$ 28.60, 20.22; HRMS (ESI): m/z [M + Na]$^+$ calcd for C$_{24}$H$_{25}$BN$_2$O$_5$Na: 455.1753, found: 455.1770.
A solution of 13 (30 mg, 0.069 mmol) in dry methanol (5 ml) was treated with palladium (10%) on charcoal (0.010 g) and stirred under a balloon filled with H₂ overnight. The mixture was filtered through Celite® and the filtrate was evaporated to dryness to yield 14 as a white powder (22 mg, 93% yield) (observed lower purity maybe due to boronic ester formation with methanol). ¹H NMR (300 MHz, methanol-d₄) δ 7.93 (dt, J = 7.0, 1.4 Hz, 2H), 7.78 (s, 1H), 7.71 – 7.62 (m, 1H), 7.62 – 7.45 (m, 4H), 7.40 – 7.26 (m, 2H), 4.70 (d, J = 4.3 Hz, 1H), 4.33 (p, J = 6.0, 5.6 Hz, 1H), 1.31 (d, J = 6.4 Hz, 3H); ¹³C NMR (126 MHz, methanol-d₄) δ 171.03, 170.32, 135.20, 133.02, 129.82, 129.66, 129.05, 128.50, 121.50, 68.92, 61.30, 20.51; ¹¹B NMR (160 MHz, methanol-d₄) δ 27.13; HRMS (ESI): m/z [M + Na]⁺ calcd for C₁₇H₁₉BN₂O₅Na: 365.1282, found: 365.1301.

15 was obtained according to the general procedure as a white solid using condition B followed by L (yield 46 %, 9.0 mg for 50 mg resin). ¹H NMR (300 MHz, methanol-d₄) δ 7.90 (d, J = 6.8 Hz, 2H), 7.57 (t, J = 7.2 Hz, 1H), 7.48 (t, J = 7.5 Hz, 2H), 4.82 – 4.67 (m, 1H), 4.48 – 4.24 (m, 2H), 4.21 – 3.96 (m, 2H), 3.88 (s, 1H), 3.24 – 3.03 (m, 3H), 2.89 (t, 2H), 2.79 – 2.60 (m, 1H), 2.02 – 1.78 (m, 3H), 1.78 – 1.51 (m, 8H), 1.51 – 1.23 (m, 7H); ¹³C NMR (75 MHz, methanol-d₄) δ 175.39, 173.39, 172.18, 171.21,
170.56, 158.60, 134.81, 133.08, 129.65, 128.55, 54.18, 51.02, 44.30, 41.93, 40.53, 28.00, 26.22, 23.41, 17.50; $^{11}$B NMR (160 MHz, methanol-$d_4$) δ 18.55; HRMS (ESI): $m/z \ [M + Na]^+ \text{ calcld for } \text{C}_{29}\text{H}_{48}\text{BN}_9\text{O}_7\text{Na}: 646.3848, \text{ found: } 646.3851.$
$^1$H, $^{13}$C and $^{11}$B NMR spectra

Compound 1, (using in-solution Fmoc-protection) $^1$H NMR (300 MHz, acetone-$d_6$)
Compound 1 (using one-pot method), \(^1\)H NMR (500 MHz, acetone-\(d_6\))
Compound 1, $^{13}$C NMR (APT, 75 MHz, acetone-$d_6$)
Compound 1, $^{11}$B NMR (160 MHz, acetone-$d_6$)

[Chemical structure image]

background

unprocessed spectrum

processed spectrum

f1 (ppm)
Piperidin-4-ylboronic acid hydrochloride, $^1$H NMR (300 MHz, D$_2$O)
Piperedin-4-ylboronic acid hydrochloride, $^{13}$C NMR (75 MHz, $\text{D}_2\text{O}$)
Piperidin-4-ylboronic acid hydrochloride, $^{11}\text{B}$ NMR (160 MHz, D$_2$O)

background

unprocessed spectrum

processed spectrum
Compound 2, $^1$H NMR (500 MHz, acetone-$d_6$)
Compound 2, $^{13}$C NMR (75 MHz, acetone-$d_6$)
Compound 2, $^{11}$B NMR (160 MHz, acetone-$d_6$)
Compound 3, $^1$H NMR (500 MHz, acetone-$d_6$)
Compound 3, $^{13}$C NMR (75 MHz, acetone-$d_6$)
Compound 3, $^{11}$B NMR (160 MHz, acetone-$d_6$)
Compound 4, $^1$H NMR (500 MHz, acetone-$d_6$)
Compound 4, $^{13}$C NMR (75 MHz, acetone-$d_6$)
Compound 4, **$^{11}$B NMR (160 MHz, acetone-$d_6$)**
Compound 5, $^1$H NMR (500 MHz, acetone-$d_6$)
Compound 5, $^{13}$C NMR (75 MHz, acetone-$d_6$)
Compound 5, $^{11}$B NMR (160 MHz, acetone-$d_6$)
Compound 6, $^1$H NMR (300 MHz, acetone-$d_6$)
Compound 6, $^{13}$C NMR (126 MHz, acetone-$d_6$)
Compound 6, $^{11}$B NMR (160 MHz, acetone-$d_6$)
Compound 7, $^1$H NMR (500 MHz, D$_2$O)
Compound 7, $^{13}$C NMR (75 MHz, methanol-$d_4$)
Compound 7, $^{11}$B NMR (160 MHz, methanol-$d_4$)
Compound 8, $^1$H NMR (500 MHz, acetone-$d_6$)
Compound 8, $^{13}$C NMR (75 MHz, acetone-$d_6$)
Compound 8, $^{11}$B NMR (160 MHz, acetone-$d_6$)
Compound 9, $^1$H NMR (500 MHz, D$_2$O)
Compound 9, $^{13}$C NMR (75 MHz, methanol-$d_4$)
Compound 9, $^{11}$B NMR (160 MHz, methanol-$d_4$)
Compound 10, $^1$H NMR (500 MHz, acetone-$d_6$)
Compound 10, $^{13}$C NMR (75 MHz, acetone-$d_6$)
Compound 10, $^{11}$B NMR (160 MHz, acetone-$d_6$)
Compound 11, $^1$H NMR (300 MHz, acetone-$d_6$)
Compound 11, $^{13}$C NMR (75 MHz, acetone-$d_6$)
Compound 11, $^{11}$B NMR (160 MHz, acetone-$d_6$)
Compound 12, $^1$H NMR (300 MHz, acetone-$d_6$)
Compound 12, $^{13}$C NMR (126 MHz, acetone-$d_6$)
Compound 12, $^{11}$B NMR (160 MHz, acetone-$d_6$)
Compound 13, $^1$H NMR (300 MHz, acetone-$d_6$)
Compound 13, $^{13}$C NMR (75 MHz, acetone-$d_6$)
Compound 13, $^{11}$B NMR (160 MHz, acetone-$d_6$)
Compound 14, $^1$H NMR (300 MHz, methanol-$d_4$)
Compound 14, $^{13}$C NMR (126 MHz, methanol-$d_4$)
Compound 14, $^{11}$B NMR (160 MHz, methanol-$d_4$)
Compound 15, $^1$H NMR (300 MHz, methanol-$d_4$)
Compound 15, $^{13}$C NMR (75 MHz, methanol-$d_4$)
Compound 15, $^{11}$B NMR (160 MHz, methanol-$d_4$)

![Diagram of Compound 15]
HPLC Chromatograms
Chromatograms for compounds 1-15 following SPPBS synthesis using the developed one-pot method are listed below. For compounds with different listed cleavage conditions in Table 1, only one representative chromatogram was shown: compound 3, condition A; compound 4, condition A, compound 6, condition B; compound 8, condition C; compound 9, condition B followed by L; compound 10, condition A.
Mass analysis for compounds 7 and 9 using high-resolution ESI

- **Compound 7**
  - Found mass

- **Calculated mass**
  - \([M+H]^+\)

- **Calculated mass**
  - \([M-H_2O+H]^+\)
References
