Supporting Information

Virtues of Volatility: A Facile Transesterification Approach to Boronic Acids

Stefan P. A. Hinkes and Christian D. P. Klein*
Institute of Pharmacy and Molecular Biotechnology (IPMB), Medicinal Chemistry, Heidelberg University, Im Neuenheimer Feld 364, 69120 Heidelberg.

Table of Contents

General Information ................................................................................................................................. 2
Part I: Synthesis of intermediates ............................................................................................................. 4
Part II: Monophasic transesterification .................................................................................................. 22
  General procedure A: Trifluoroacetic acid in methylene chloride .................................................... 22
  General procedure B: Aqueous hydrochloric acid ............................................................................. 28
  General procedure C: Aqueous sodium hydroxide ............................................................................ 33
  Transesterification of bis(pinacolato)diboron ................................................................................... 34
NMR spectra of intermediates .................................................................................................................. 35
NMR spectra of final compounds .......................................................................................................... 79
References .............................................................................................................................................. 130
General Information

Chemicals and reagents used for synthesis were purchased from Sigma Aldrich, TCI, Alfa Aesar or Carbolution and were used without further purification unless otherwise stated. Methylboronic acid was purchased from Carbolution at a cost of 117.50 € for 100 g quantities with an indicated purity of 98% and used without further purification.

Reactions were performed at ambient air and temperature with oven-dried glassware unless otherwise stated. Anhydrous solvents were usually purchased as such and stored under molecular sieves. Anhydrous THF was dried over sodium and freshly distilled before use.

Reported yields of final compounds are calculated based on the free acid form without consideration of anhydride formation. Therefore the actual yields are expected to be even higher, depending on the product’s tendency to form anhydrides, e.g. boroxines.

Flash column chromatography was done using a Biotage Isolera One system with silica gel (60 – 200 µm), deactivated with deionized water (SiO₂/H₂O 100:35, m/m) if indicated. Purifications were usually done by gradient elution using binary mixtures of cyclohexane and ethyl acetate and UV detection at 254 nm and 280 nm.

MS-ESI analysis was performed on a Bruker micrOTOF-Q II mass spectrometer. For high-resolution mass spectra, sodium formate was used as calibrating reagent.

NMR spectra were recorded on a 300 MHz Varian or a 500 MHz Varian instrument as indicated. Samples were dissolved in CDCl₃, acetone-d₆, DMSO-d₆, CD₃CN, CD₃OD, D₂O or mixtures thereof. To reverse anhydride formation that impedes NMR analysis of boronic acids, small amounts of D₂O were usually added to the samples. Chemical shifts are reported in ppm (relative to TMS) and were calibrated to the solvent residual peaks of the incompletely deuterated species as an internal standard. Solvent residual shifts were taken from the literature (CDCl₃: 7.26 ppm, 77.16 ppm; acetone-d₆: 2.05 ppm, 29.84 ppm; DMSO-d₆: 2.50 ppm, 39.50 ppm; CD₃OD: 3.31 ppm, 49.00 ppm; CD₃CN: 1.94 ppm, 1.32 ppm).¹ Coupling constants are given in Hz, multiplicity is reported as observed, with the following abbreviations used: s (singlet), d (doublet), t (triplet), q (quadruplet), qn (quintuplet), dd (doublet of doublet), ddd (doublet of doublet of doublet), dt (doublet of triplet), td (triplet of doublet), bs (broad singlet), m (multiplet). In ¹³C APT NMR spectra the carbon attached to boron was usually not observed due to the quadrupolar relaxation of ¹⁰B and ¹¹B nuclei. ¹¹B spectra were measured at 160 MHz
using BF₃·OEt₂ as an external standard. Due to broad background signals, ¹¹B spectra were processed with background subtraction, the unprocessed spectra are also provided.

NMR reaction controls for the optimization experiments were usually measured by diluting 10 µL of the crude reaction mixture with 500 µL of DMSO-d₆, mixed in the NMR tube. Conversion percentages were calculated using the integral ratio of pinacol signals of substrate and methylboronic acid pinacol ester and other significant signals (see Figure S-1).

Figure S-1: Example of proton NMR controls. (A) NMR of 3-aminophenylboronic acid pinacol ester, (B) NMR of 3-aminophenylboronic acid, (C) Extracts from NMR of crude reaction mixture using 10 equiv MeB(OH)₂ in 5% TMP/DMF (see manuscript, Table 1, entry 12) after 23 hours that resemble 57% conversion. All shown spectra were recorded at ambient temperature in DMSO-d₆.
Part I: Synthesis of intermediates

Synthesis of 3-aminophenylboronic acid pinanediol ester (1b)

To a solution of 3-aminophenylboronic acid (0.100 g, 0.730 mmol, 1.0 eq) in dry toluene (10 mL) was added (+)-pinanediol (0.131 g, 0.767 mmol, 1.05 eq) and anhydrous MgSO₄ (0.879 g, 7.30 mmol, 10.0 eq). After stirring at room temperature overnight, the reaction mixture was filtered, the filtrate was concentrated to dryness and the residue was purified by flash column chromatography using deactivated silica gel (SiO₂/H₂O 100:35, m/m) and cyclohexane/ethyl acetate mixtures to obtain the title compound (192.0 mg, 0.708 mmol, 97%) as a pale yellow solid.

¹H NMR (300 MHz, CDCl₃) δ 7.25 – 7.17 (m, 2H), 7.16 – 7.12 (m, 1H), 6.79 (ddd, J = 7.4, 2.5, 1.7 Hz, 1H), 4.44 (dd, J = 8.6, 1.7 Hz, 1H), 3.64 (bs, 2H), 2.48 – 2.35 (m, 1H), 2.28 – 2.17 (m, 1H), 2.14 (t, J = 5.5 Hz, 1H), 2.01 – 1.90 (m, 2H), 1.47 (s, 3H), 1.31 (s, 3H), 1.22 (d, J = 10.7 Hz, 1H), 0.89 (s, 3H) ppm.

¹³C NMR (75 MHz, CDCl₃) δ 145.9, 128.9, 125.2, 121.3, 118.1, 86.3, 78.3, 51.6, 39.7, 38.3, 35.7, 28.8, 27.3, 26.6, 24.2 ppm.

HRMS (ESI, m/z): Calcd for C₁₆H₂₃BNO₂ [M + H]⁺ 272.1819; found 272.1824.

Synthesis of pyrimidine-5-boronic acid pinacol ester (6a)

To solution of pyrimidine-5-boronic acid (0.113 g, 0.908 mmol, 1.0 eq) in dry toluene (10 mL) was added pinacol (0.113 g, 0.953 mmol, 1.05 eq) and anhydrous MgSO₄ (1.093 g, 9.08 mmol, 10.0 eq). After stirring at ambient temperature overnight, the reaction mixture was filtered, the filtrate was concentrated to dryness and the residue was purified by flash column chromatography using deactivated silica gel (SiO₂/H₂O 100:35, m/m) and cyclohexane/ethyl acetate mixtures to obtain the title compound (192.0 mg, 0.708 mmol, 97%) as a pale yellow solid.
acetate mixtures to obtain 174.5 mg (0.847 mmol, 93%) of the title compound as a pale yellow solid.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.27 (s, 1H), 9.01 (s, 2H), 1.36 (s, 12H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 162.7, 160.7, 84.9, 25.0 ppm.

HRMS (ESI, m/z): Calcd for C$_{10}$H$_{16}$BN$_2$O$_2$ [M + H]$^+$ 207.1301; found 207.1303.

**Synthesis of (R)-(1-amino-3-methylbutyl)boronic acid pinacol ester·HCl**

The synthesis was done using literature-known protocols with slight modifications.$^{2-4}$

Reagents and conditions: (a) (R)-tert-butanesulfinamide/PPTS/MgSO$_4$/CH$_2$Cl$_2$/rt; (b) B$_2$pin$_2$/PCy$_3$/HBF$_4$/CuSO$_4$/benzylamine/toluene/H$_2$O/rt; (c) HCl/MeOH/dioxane/rt.

**Synthesis of (R,E)-2-methyl-N-(3-methylbutylidene)propane-2-sulfinamide$^2$**

To a solution of (R)-tert-butanesulfinamide (1.00 g, 8.25 mmol, 1.0 eq) in dry methylene chloride (15 mL) were added pyridinium p-toluenesulfonate (PPTS, 0.104 g, 0.413 mmol, 0.05 eq), anhydrous MgSO$_4$ (4.97 g, 41.3 mmol, 5.0 eq) and 3-methylbutanal (1.07 g, 12.4 mmol, 1.5 eq). The reaction was stirred at room temperature overnight, filtered through a pad of celite and washed again with methylene chloride. After solvent evaporation the residue was purified by flash column chromatography to obtain the corresponding tert-butanesulfinyl aldimine (1.473 g, 7.78 mmol, 94%) as a colourless oil.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.06 (t, $J = 5.2$ Hz, 1H), 2.44 – 2.37 (m, 2H), 2.07 (m, 1H), 1.20 (s, 9H), 0.99 (d, $J = 6.7$ Hz, 6H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 169.6, 56.7, 45.1, 26.3, 22.8, 22.7, 22.5 ppm.
Synthesis of \((R)-1-(((R)\text{-}\text{tert-butylsulfinyl})\text{amino})\text{-}3\text{-methylbutyl})\text{boronic acid pinacol ester}^3

\[
\begin{align*}
\text{S} & \text{N} \\
\text{B} & \text{O} \\
\text{O} & \\
\text{H} & \\
\text{C} & \\
\end{align*}
\]

In a 10 mL round-bottom flask were added tricyclohexylphosphine tetrafluoroborate (PCy\textsubscript{3}·HBF\textsubscript{4}, 8.8 mg, 0.024 mmol, 1.2 mol-%), toluene (0.4 mL), a 30 mM aqueous solution of CuSO\textsubscript{4} (0.8 mL, 0.024 mmol, 1.2 mol-%) and benzylamine (10.9 µL, 0.100 mmol, 0.05 eq). After stirring vigorously for 10 minutes, toluene (3.6 mL), the corresponding tert-butanesulfinyl aldimine (378.6 mg, 2.00 mmol, 1.0 eq) and bis(pinacolato)diboron (B\textsubscript{2}pin\textsubscript{2}, 1.016 g, 4.00 mmol, 2.0 eq) were added to the catalyst mixture and stirred at room temperature overnight. After diluting with ethyl acetate, the precipitate was filtered through a short pad of deactivated silica gel (SiO\textsubscript{2}/H\textsubscript{2}O 100:35, m/m) and washed with ethyl acetate. The filtrate was concentrated \textit{in vacuo} and the residue was purified by flash column chromatography using deactivated silica gel (SiO\textsubscript{2}/H\textsubscript{2}O 100:35, m/m) and cyclohexane/ethyl acetate mixtures to obtain \((R)-1-N\text{-}\text{sulfinyl}-3\text{-methylbutane}-1\text{-boronic acid pinacol ester} (494.2 mg, 1.56 mmol, 78\%) as a colourless oil.

\(^1\text{H} \text{NMR} \ (300 \text{ MHz, CDCl}\textsubscript{3}) \ \delta \ 3.03 \ (t, J = 7.8 \text{ Hz, } 1\text{H}), \ 1.68 \ (m, 1\text{H}), \ 1.49 \ (m, 2\text{H}), \ 1.21 \ (s, 6\text{H}), \ 1.20 \ (s, 6\text{H}), \ 1.15 \ (s, 9\text{H}), \ 0.87 \ (d, J = 6.5 \text{ Hz, } 6\text{H}) \text{ ppm.}

\(^{13}\text{C} \text{NMR} \ (75 \text{ MHz, CDCl}\textsubscript{3}) \ \delta \ 84.0, \ 56.1, \ 42.6, \ 25.6, \ 25.0, \ 24.6, \ 22.8, \ 22.6 \text{ ppm.}

\text{HRMS (ESI, m/z): Calcd for C}_{11}\text{H}_{18}\text{BNO}_{3}\text{SNa} \ [M + Na]^{+} \ 212.1104; \text{ found } 212.1106.

Synthesis of \((R)-(1\text{-amino}-3\text{-methylbutyl})\text{boronic acid pinacol ester-HCl} \ (11\text{a})^4

\[
\begin{align*}
\text{ClH}_3\text{N} & \text{O} \\
\text{B} & \text{O} \\
\text{O} & \\
\text{H} & \\
\end{align*}
\]

SHRMS (ESI, m/z): Calcd for C\textsubscript{11}H\textsubscript{18}NOSNa [M + Na]\textsuperscript{+} 212.1104; found 212.1106.
In a 10 mL round-bottom flask the corresponding N-sulfinyl amide (363.4 mg, 1.15 mmol, 1.0 eq) was dissolved in 1,4-dioxane (5 mL). Afterwards methanol (0.47 mL, 11.5 mmol, 10.0 eq) was added, followed by the dropwise addition of a 4.0 M solution of HCl in 1,4-dioxane (288 µL, 1.15 mmol, 1.0 eq). The solution was stirred for 2 hours and concentrated to dryness. The crude residue was washed with ether and centrifuged. The white precipitate was washed again and collected to obtain the title compound (251.7 mg, 1.01 mmol, 88%) as a white solid.

\[ ^1H \text{NMR (300 MHz, CDCl}_3 \text{)} \delta 8.19 (s, 3H), 2.91 (m, 1H), 1.89 (m, 1H), 1.75 (m, 1H), 1.61 (m, 1H), 1.27 (s, 12H), 0.93 (d, } J = 6.5 \text{ Hz, 6H) ppm.} \]

\[ ^{13}C \text{NMR (75 MHz, CDCl}_3 \text{)} \delta 85.1, 38.6, 25.2, 25.1, 24.7, 22.6, 22.5 \text{ ppm.} \]


**Synthesis of (R)-(1-amino-3-methylbutyl)boronic acid pinanediol ester·HCl**

The synthesis was done using a protocol from the literature with slight modifications.\(^5\)

![Synthesis scheme](image)

Reagents and conditions: (a) (+)-pinanediol/THF/rt; (b) LDA/CH\(_2\)Cl\(_2\)/ZnCl\(_2\)/THF/hexanes/ether/−78°C to rt; (c) LHMDS/THF/−78°C to rt, then HCl/dioxane/ether/0°C to rt.

**Synthesis of iso-butylboronic acid pinanediol ester\(^5\)**

![Synthesis scheme](image)

To a solution of iso-butylboronic acid (0.513 g, 5.03 mmol, 1.0 eq) in anhydrous THF (10 mL) was added (+)-pinanediol (0.857 g, 5.03 mmol, 1.0 eq). The solution was stirred at room temperature overnight before the solvent was evaporated. The resulting residue was purified by flash column chromatography using silica gel and cyclohexane/ethyl acetate mixtures (detection at 214 nm) to obtain the title compound (1.051 g, 4.45 mmol, 89%) as a colourless liquid.
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.25 (dd, $J = 8.6$, 1.7 Hz, 1H), 2.40 – 2.28 (m, 1H), 2.27 – 2.15 (m, 1H), 2.05 (t, $J = 5.5$ Hz, 1H), 1.95 – 1.79 (m, 3H), 1.38 (s, 3H), 1.29 (s, 3H), 1.14 (d, $J = 10.8$ Hz, 1H), 0.94 (d, $J = 6.6$ Hz, 6H), 0.84 (s, 3H), 0.78 (d, $J = 7.1$ Hz, 2H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 85.4, 77.6, 51.4, 39.7, 38.3, 35.8, 28.9, 27.3, 26.7, 25.5, 25.4, 25.1, 24.2 ppm.

**Synthesis of (S)-(1-chloro-3-methylbutyl)boronic acid pinanediol ester**

Iso-butylboronic acid pinanediol ester (1.046 g, 4.43 mmol, 1.0 eq) was dissolved in anhydrous THF (15 mL) and dry methylene chloride (1.51 g, 17.7 mmol, 4.0 eq) under an argon atmosphere. The solution was cooled to $-78^{\circ}$C before a cold LDA solution (1.0 M in THF/hexanes, 5.32 mL, 5.32 mmol, 1.2 eq) was added dropwise within 20 minutes. The reaction was stirred for additional 30 minutes before a cold solution of ZnCl$_2$ (1.0 M in ether, 7.09 mL, 7.09 mmol, 1.6 eq) was added. The mixture was allowed to warm to room temperature overnight, concentrated and treated with saturated ammonium chloride solution (30 mL). After stirring for 10 minutes, the aqueous phase was extracted with hexanes (3×30 mL), the combined organic phases were washed with brine and dried over anhydrous MgSO$_4$. After solvent evaporation the title compound (1.228 g, 4.31 mmol, 97%) was obtained as a yellow oil with traces of unreacted starting material as described in the literature.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.40 – 4.33 (m, 1H), 3.53 (dd, $J = 9.9$, 6.0 Hz, 1H), 2.43 – 2.17 (m, 2H), 2.09 (t, $J = 5.4$ Hz, 1H), 1.94 – 1.74 (m, 4H), 1.68 – 1.57 (m, 1H), 1.42 (s, 3H), 1.30 (s, 3H), 1.19 (d, $J = 11.0$ Hz, 1H), 0.96 – 0.89 (m, 6H), 0.85 (s, 3H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 86.8, 78.6, 51.4, 42.9, 39.5, 38.4, 35.4, 28.6, 27.2, 26.5, 25.7, 24.1, 23.0, 21.4 ppm.
Synthesis of (R)-(1-amino-3-methylbutyl)boronic acid pinanediol ester·HCl\(^5\)

A solution of (S)-(1-chloro-3-methylbutyl)boronic acid pinanediol ester (1.219 g, 4.28 mmol, 1.0 eq) in anhydrous THF (12 mL) was cooled to −78°C before a cold solution of lithium bis(trimethylsilyl)amide (LHMDS, 1.0 M in THF, 4.71 mL, 4.71 mmol, 1.1 eq) was added over 30 minutes. The resulting solution was allowed to warm to room temperature overnight. Afterwards the mixture was concentrated, treated with hexanes (20 mL) and stirred for 1 hour. The resulting suspension was filtered through a pad of celite and washed multiple times with hexanes. The filtrate was concentrated to obtain 1.540 g of a yellow oil that was directly used in the next step without further purification.

The crude residue was dissolved in anhydrous 1,4-dioxane under an argon atmosphere. The solution was cooled to 0°C before a solution of hydrogen chloride (1.0 m in ether, 17.1 mL, 17.1 mmol, 4.0 eq) was added dropwise within 15 minutes. The resulting mixture was allowed to warm to room temperature and stirred for 4 hours before it was concentrated. The crude product was resuspended in hexanes (15 mL), stirred for another 30 minutes and dried in vacuo to obtain the title compound (1.222 g, 4.05 mmol, 95%) as a sticky brown solid that was directly used in the next step without further purification.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.28 (s, 3H), 4.36 (d, \(J = 8.6\) Hz, 1H), 2.95 (q, \(J = 6.5\) Hz, 1H), 2.35 – 2.15 (m, 2H), 2.03 (t, \(J = 5.0\) Hz, 1H), 1.96 – 1.73 (m, 4H), 1.68 – 1.56 (m, 1H), 1.40 (s, 3H), 1.26 (s, 3H), 1.16 (d, \(J = 11.3\) Hz, 1H), 0.93 (d, \(J = 6.4\) Hz, 6H), 0.80 (s, 3H) ppm.

\(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 87.5, 78.8, 51.2, 39.6, 38.7, 38.2, 35.2, 28.5, 27.1, 26.6, 25.0, 24.0, 22.7, 22.4 ppm.

HRMS (ESI, m/z): Calcd for C\(_{15}\)H\(_{29}\)BNO\(_2\) [M + H]\(^+\) 266.2289; found 266.2293.
Synthesis of diol protected bortezomib precursors

The synthesis of bortezomib precursors was done using literature-known protocols with slight modifications.\(^6,7\)

Reagents and conditions: (a) pyrazine-2-carboxylic acid/EDC·HCl/HOAt/NMM/THF/0°C to rt; (b) NaOH/H\(_2\)O/acetone/0°C; (c) \((R)-(1\text{-amino-3-methylbutyl})\text{boronic acid pinacol ester·HCl/HATU/DIPEA/CH}_2\text{Cl}_2/−10°C \text{ to } −5°C\); (d) \((R)-(1\text{-amino-3-methylbutyl})\text{boronic acid pinanediol ester·HCl/HATU/DIPEA/CH}_2\text{Cl}_2/−10°C \text{ to } −5°C\).

Synthesis of (pyrazine-2-carbonyl)-\(L\)-phenylalanine ethyl ester\(^6\)

Pyrazine-2-carboxylic acid (0.500 g, 4.03 mmol, 1.0 eq) was dissolved in 15 mL of anhydrous THF and stirred at 0°C. 1-Hydroxy-7-azabenzotriazole (HOAt, 0.658 g, 4.84 mmol, 1.2 eq) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl, 0.722 g, 4.03 mmol, 1.0 eq) were added. After stirring for 40 min, \(N\)-methylmorpholine (NMM, 0.99 mL, 8.87 mmol, 2.2 eq) and \(L\)-phenylalanine ethyl ester hydrochloride (H-Phe-OEt·HCl, 0.952 g, 4.03 mmol, 1.0 eq) were added. The resulting mixture was allowed to warm to room temperature and stirred for three additional hours. The suspension was filtered and the filtrate
was concentrated to dryness. The residue was dissolved in ethyl acetate (50 mL) and washed with 10% citric acid (3×10 mL), 5% NaHCO₃ (3×10 mL) and brine (1×10 mL). The organic phase was dried with anhydrous MgSO₄ and evaporated in vacuo to obtain the corresponding ethyl ester (0.779 g, 2.60 mmol, 65%) as a white solid.

¹H NMR (300 MHz, CDCl₃) δ 9.37 (d, J = 1.3 Hz, 1H), 8.74 (d, J = 2.4 Hz, 1H), 8.57 – 8.48 (m, 1H), 8.23 (d, J = 7.7 Hz, 1H), 7.34 – 7.19 (m, 3H), 7.17 (m, 2H), 5.05 (dt, J = 8.2, 6.1 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.33 – 3.15 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H) ppm.

¹³C NMR (75 MHz, CDCl₃) δ 171.2, 162.7, 147.6, 144.5, 144.2, 142.9, 135.9, 129.4, 128.7, 127.3, 61.8, 53.5, 38.4, 14.3 ppm.

HRMS (ESI, m/z): Calcd for C₁₆H₁₇N₃O₃Na [M + Na]⁺ 322.1162; found 322.1174.

**Synthesis of (pyrazine-2-carbonyl)-L-phenylalanine⁶**

![Pyrazine-2-carbonyl-L-phenylalanine](image)

The previously prepared ethyl ester (779 mg, 2.60 mmol, 1.0 eq) was dissolved in acetone (10 mL), cooled to 0°C and saponified with 2 N NaOHₐq (2 mL) for 2 hours at 0°C. After evaporation of acetone, the reaction system was carefully acidified with 2 N HCl to pH 2. The aqueous phase was extracted with ethyl acetate (3×5 mL), the combined organic phases were dried over anhydrous MgSO₄, solvent evaporation to dryness yielded the free carboxylic acid (704.4 mg, 2.60 mmol, 99%) as a pale yellow solid.

¹H NMR (300 MHz, acetone-d₆/CD₃OD 1:1) δ 9.16 (d, J = 1.1 Hz, 1H), 8.77 (d, J = 2.4 Hz, 1H), 8.66 – 8.52 (m, 2H), 7.26 – 7.08 (m, 5H), 4.98 – 4.85 (m, 1H), 3.39 – 3.14 (m, 2H) ppm. (COOH not observed)

¹³C NMR (75 MHz, acetone-d₆/CD₃OD 1:1) δ 173.2, 164.0, 148.7, 145.3, 144.6, 144.5, 137.9, 130.3, 129.3, 127.8, 54.5, 38.0 ppm.

HRMS (ESI, m/z): Calcd for C₁₄H₁₅N₃O₃ [M − H] − 270.0873; found 270.0903.
Synthesis of bortezomib pinacol ester (12a)\(^7\)

(Pyrazine-2-carbonyl)-L-phenylalanine (54.3 mg, 0.200 mmol, 1.0 eq), (R)-(1-amino-3-methylbutyl)boronic acid pinacol ester·HCl (50.0 mg, 0.200 mmol, 1.0 eq) and O-(7-azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorphosphate (HATU, 83.7 mg, 0.220 mmol, 1.1 eq) were suspended in dry methylene chloride (2 mL) and the mixture was cooled to \(-5^\circ\text{C}\). N,N-Diisopropylethylamine (DIPEA, 103 µL, 0.600 mmol, 3.0 eq) was added during 10 minutes to the stirred reaction mixture. The temperature was maintained at \(-10^\circ\text{C}\) to \(-5^\circ\text{C}\). After 3 hours, the solvent was removed \textit{in vacuo}, the residue was dissolved in ethyl acetate (10 mL), washed with water (8 mL), 3% aqueous K\(_2\)CO\(_3\) (3×10 mL), water (8 mL), 3% aqueous citric acid (3×10 mL), water (8 mL) and brine (8 mL). The organic phase was dried over anhydrous MgSO\(_4\), the solvent was evaporated to give a crude product that was further purified by flash column chromatography using deactivated silica gel and cyclohexane/ethyl acetate mixtures. The title compound (71.6 mg, 0.154 mmol, 77%) was obtained as colourless oil.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.30 (s, 1H), 8.71 (d, \(J = 2.3\) Hz, 1H), 8.50 (s, 1H), 8.36 (d, \(J = 8.0\) Hz, 1H), 7.32 – 7.14 (m, 5H), 6.26 (d, \(J = 3.7\) Hz, 1H), 4.84 (q, \(J = 7.2\) Hz, 1H), 3.17 (d, \(J = 7.0\) Hz, 2H), 3.03 (q, \(J = 7.3\) Hz, 1H), 1.49 – 1.30 (m, 3H), 1.23 (s, 12H), 0.80 (t, \(J = 6.4\) Hz, 6H) ppm.

\(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 171.0, 162.9, 147.5, 144.3, 144.1, 142.8, 136.5, 129.5, 128.7, 127.1, 83.3, 53.9, 39.7, 38.6, 25.5, 24.99, 24.96, 23.1, 22.1 ppm.

HRMS (ESI, m/z): Calcd for C\(_{25}\)H\(_{35}\)BN\(_4\)O\(_4\)Na [M + Na]\(^+\) 489.2648; found 489.2650.

Synthesis of bortezomib pinanediol ester (12b)\(^7\)
(Pyrazine-2-carbonyl)-L-phenylalanine (56.0 mg, 0.206 mmol, 1.0 eq), (R)-(1-amino-3-methylbutyl)boronic acid pinanediol ester·HCl (81.4 mg, 0.270 mmol, 1.3 eq) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorphosphate (HATU, 95.1 mg, 0.250 mmol, 1.2 eq) were suspended in dry methylene chloride (2 mL) and the mixture was cooled to –5°C. N,N-Diisopropylethylamine (DIPEA, 106 µL, 0.624 mmol, 3.0 eq) was added during 10 minutes to the stirred reaction mixture. The temperature was maintained at –10°C to –5°C. After 3 hours, the solvent was removed in vacuo, the residue was dissolved in ethyl acetate (10 mL), washed with water (8 mL), 3% aqueous K2CO3 (3×10 mL), water (8 mL), 3% aqueous citric acid (3×10 mL), water (8 mL) and brine (8 mL). The organic phase was dried over anhydrous MgSO4, the solvent was evaporated to give a crude product that was further purified by flash column chromatography using deactivated silica gel and cyclohexane/ethyl acetate mixtures. The title compound (77.1 mg, 0.149 mmol, 72%) was obtained as colourless oil.

1H NMR (300 MHz, CDCl3) δ 9.31 (s, 1H), 8.72 (s, 1H), 8.51 (s, 1H), 8.39 (d, J = 8.5 Hz, 1H), 7.35 – 7.11 (m, 5H), 6.13 (d, J = 4.9 Hz, 1H), 4.83 (q, J = 7.3 Hz, 1H), 4.34 – 4.20 (m, 1H), 3.28 – 3.05 (m, 3H), 2.40 – 2.23 (m, 1H), 2.23 – 2.07 (m, 1H), 2.07 – 1.94 (m, 1H), 1.93 – 1.74 (m, 2H), 1.43 – 1.20 (m, 10H), 0.86 – 0.76 (m, 9H) ppm.

13C NMR (75 MHz, CDCl3) δ 170.6, 162.8, 147.5, 144.3, 144.1, 142.8, 136.5, 129.5, 128.7, 127.0, 85.9, 77.9, 54.2, 51.5, 40.0, 39.6, 38.7, 38.2, 35.6, 28.6, 27.2, 26.4, 25.4, 24.1, 23.1, 22.1 ppm.

HRMS (ESI, m/z): Calcd for C29H39BN4O4Na [M + Na]+ 541.2962; found 541.2977.
Synthesis of diol protected ixazomib precursors

The preparation of ixazomib precursors was carried out analogously to those of bortezomib with some modifications as described below.6,7

Reagents and conditions: (a) 2,5-dichlorobenzoic acid/EDC·HCl/HOAt/NMM/THF/0°C to rt; (b) NaOH/H2O/acetone/0°C; (c) (R)-(1-amino-3-methylbutyl)boronic acid pinacol ester·HCl/HATU/DIPEA/CH2Cl2/−10°C to −5°C; (d) (R)-(1-amino-3-methylbutyl)boronic acid pinanediol ester·HCl/HATU/DIPEA/CH2Cl2/−10°C to −5°C.

Synthesis of (2,5-dichlorobenzoyl)glycine methyl ester6

2,5-Dichlorobenzoic acid (0.750 g, 3.93 mmol, 1.0 eq) was dissolved in 15 mL of anhydrous THF and stirred at 0°C. 1-Hydroxy-7-azabenzotriazole (HOAt, 0.641 g, 4.71 mmol, 1.2 eq) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl, 0.753 g, 3.93 mmol, 1.0 eq) were added. After stirring for 40 min, N-methylmorpholine (NMM, 0.97 mL, 8.64 mmol, 2.2 eq) and glycine methyl ester hydrochloride (H-Gly-OMe·HCl, 0.493 g, 3.93 mmol, 1.0 eq) were added. The resulting mixture was allowed to warm to room temperature and stirred for three additional hours. The suspension was filtered and the filtrate was concentrated to dryness. The residue was dissolved in 50 mL ethyl acetate and washed with 10% citric acid (3×10 mL), 5% NaHCO3 (3×10 mL) and brine (1×10 mL). The organic phase
was dried with anhydrous MgSO₄ and evaporated in vacuo to obtain the corresponding methyl ester (0.892 g, 3.40 mmol, 87%) as a white solid.

¹H NMR (300 MHz, CDCl₃) δ 7.72 (t, J = 1.5 Hz, 1H), 7.36 (m, 2H), 6.82 (s, 1H), 4.27 (d, J = 5.1 Hz, 2H), 3.82 (s, 3H) ppm.

HRMS (ESI, m/z): Calcd for C₁₀H₉Cl₂NO₃Na [M + Na]⁺ 283.9852; found 283.9879.

Synthesis of (2,5-dichlorobenzoyl)glycine⁶

The corresponding methyl ester (0.889 g, 3.39 mmol, 1.0 eq) was dissolved in acetone (10 mL), cooled to 0°C and saponified with 2 N NaOHaq (2 mL) for 2 hours at 0°C. After evaporation of acetone, the reaction system was carefully acidified with 2 N HCl to pH 2. The aqueous phase was extracted with ethyl acetate (3×5 mL), the combined organic phases were dried over anhydrous MgSO₄ and evaporation in vacuo yielded the free carboxylic acid (0.709 g, 2.86 mmol, 84%) as a white solid.

¹H NMR (300 MHz, DMSO-d₆) δ 12.68 (bs, 1H), 8.89 (t, J = 5.7 Hz, 1H), 7.57 – 7.52 (m, 2H), 7.47 (m, 1H), 3.92 (d, J = 5.9 Hz, 2H) ppm.

¹³C NMR (75 MHz, DMSO-d₆) δ 170.7, 165.2, 137.6, 131.6, 131.5, 130.8, 128.9, 128.7, 41.0 ppm.

HRMS (ESI, m/z): Calcd for C₉H₆Cl₂NO₃ [M − H] − 245.9719; found 245.9737.

Synthesis of ixazomib pinacol ester (13a)⁷

(2,5-Dichlorobenzoyl)glycine (54.3 mg, 0.200 mmol, 1.0 eq), (R)-(1-amino-3-methylbutyl)boronic acid pinacol ester·HCl (50.0 mg, 0.200 mmol, 1.0 eq) and O-(7-
azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate (HATU, 83.7 mg, 0.220 mmol, 1.1 eq) were suspended in dry methylene chloride (2 mL) and the mixture was cooled to –5°C. N,N-Diisopropylethylamine (DIPEA, 103 µL, 0.600 mmol, 3.0 eq) was added during 10 minutes to the stirred reaction mixture. The temperature was maintained at –10°C to –5°C. After 3 hours, the solvent was removed in vacuo, the residue was dissolved in ethyl acetate (10 mL), washed with water (8 mL), 3% aqueous K₂CO₃ (3×10 mL), water (8 mL), 3% aqueous citric acid (3×10 mL), water (8 mL) and brine (8 mL). The organic phase was dried over anhydrous MgSO₄, the solvent was evaporated to give a crude product that was further purified by flash column chromatography using deactivated silica gel and cyclohexane/ethyl acetate mixtures. The title compound (66.2 mg, 0.149 mmol, 75%) was obtained as colourless oil.

^1H NMR (300 MHz, acetone-d₆) δ 8.13 (t, J = 5.5 Hz, 1H), 7.92 (s, 1H), 7.60 (s, 1H), 7.50 (m, 2H), 4.16 (d, J = 5.8 Hz, 2H), 2.92 – 2.83 (m, 1H), 1.72 (m, 1H), 1.39 (m, 2H), 1.17 (s, 12H), 0.89 (m, 6H) ppm.

^13C NMR (75 MHz, acetone-d₆) δ 171.7, 166.3, 138.4, 133.2, 132.4, 131.8, 130.2, 130.1, 82.6, 42.0, 41.2, 26.1, 25.42, 25.37, 23.6, 22.4 ppm.


Synthesis of ixazomib pinanediol ester (13b)^7

(2,5-Dichlorobenzoyl)glycine (49.4 mg, 0.199 mmol, 1.0 eq), (R)-(1-amino-3-methylbutyl)boronic acid pinanediol ester-HCl (78.0 mg, 0.258 mmol, 1.3 eq) and O-(7-azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate (HATU, 90.5 mg, 0.238 mmol, 1.2 eq) were suspended in dry methylene chloride (2 mL) and the mixture was cooled to –5°C. N,N-Diisopropylethylamine (DIPEA, 102 µL, 0.596 mmol, 3.0 eq) was added during 10 minutes to the stirred reaction mixture. The temperature was maintained at –10°C to –5°C. After 3 hours, the solvent was removed in vacuo, the residue was dissolved in ethyl acetate (10 mL), washed with water (8 mL), 3% aqueous K₂CO₃ (3×10 mL), water (8 mL), 3% aqueous citric acid (3×10 mL), water (8 mL) and brine (8 mL). The organic phase was dried
over anhydrous MgSO₄, the solvent was evaporated to give a crude product that was further purified by flash column chromatography using deactivated silica gel and cyclohexane/ethyl acetate mixtures. The title compound (69.2 mg, 0.140 mmol, 70%) was obtained as colourless oil.

¹H NMR (300 MHz, CDCl₃) δ 7.59 – 7.49 (m, 2H), 7.32 (s, 2H), 6.80 (d, J = 4.3 Hz, 1H), 4.27 – 4.20 (m, 1H), 4.16 (d, J = 5.1 Hz, 2H), 3.33 – 3.10 (m, 1H), 2.35 – 2.21 (m, 1H), 2.20 – 2.05 (m, 1H), 2.01 – 1.90 (m, 1H), 1.90 – 1.82 (m, 1H), 1.82 – 1.71 (m, 1H), 1.69 – 1.56 (m, 1H), 1.52 – 1.37 (m, 2H), 1.35 (s, 3H), 1.25 (s, 3H), 1.18 (d, J = 10.7 Hz, 1H), 0.88 (d, J = 6.5 Hz, 6H), 0.81 (s, 3H) ppm.

¹³C NMR (75 MHz, CDCl₃) δ 169.3, 165.7, 135.9, 133.3, 131.5, 130.0, 129.3, 85.8, 77.8, 51.5, 42.9, 40.3, 39.7, 38.3, 35.7, 28.7, 27.2, 26.5, 25.6, 24.1, 23.2, 22.1 ppm.

HRMS (ESI, m/z): Calcd for C₂₄H₃₃BCl₂N₂O₄Na [M + Na]⁺ 517.1807; found 517.1822.

**Synthesis of N-Fmoc-(2-aminoethyl)boronic acid pinacol ester (14a)**

Reagents and conditions: (a) Fmoc-OSu/NaHCO₃/MeCN/H₂O/rt; (b) NHPI/DIC/DMAP/CH₂Cl₂/0°C to rt; (c) [B₂pin₂Me]Li/NiCl₂/4,4’-dimethoxy-2,2’-bipyridine/MgBr₂·OEt₂/THF/ether/0°C to rt.

**Synthesis of N-Fmoc-β-alanine**

In a 250 mL round-bottom flask, β-alanine (2.00 g, 22.5 mmol, 1.0 eq) was dissolved in acetonitrile and water, 40 mL each. To this solution were added sodium bicarbonate (5.66 g, 67.4 mmol, 3.0 eq) and Fmoc-N-hydroxysuccinimide ester (Fmoc-OSu, 8.34 g, 24.7 mmol, 1.1 eq). After stirring at room temperature overnight, the solution was acidified with to pH 1 with 1 N HCl, the aqueous phase was extracted with methylene chloride (3×50 mL), the combined organic phases were dried over anhydrous MgSO₄ and the solvent was removed in vacuo to obtain N-Fmoc-β-alanine (6.96 g, 22.4 mmol, 99%) as a white solid.

¹H NMR (300 MHz, DMSO-d₆): δ = 12.19 (bs, 1H), 7.89 (d, J = 7.6 Hz, 2H), 7.68 (d, J = 7.3 Hz, 2H), 7.41 (t, J = 7.4 Hz, 2H), 7.32 (m, 3H), 4.28 (d, J = 6.8 Hz, 2H), 4.24–4.16 (m, 1H), 3.19 (q, J = 6.6 Hz, 2H), 2.38 (t, J = 7.0 Hz, 2H) ppm.
$^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 172.7, 156.0, 143.9, 140.7, 127.6, 127.0, 125.1, 120.1, 65.3, 46.7, 36.5, 34.1 ppm.

HRMS (ESI, m/z): Calcd for C$_{18}$H$_{16}$NO$_4$ [M − H]$^-$ 310.1085; found 310.1079.

**Synthesis of N-Fmoc-$\beta$-alanine NHPI ester**

![Chemical Structure](attachment:image.png)

$N$-Fmoc-$\beta$-alanine (4.00 g, 12.8 mmol, 1.0 eq) was weighed into a 50 mL round-bottom flask, $N$-hydroxyphthalimide (NHPI, 2.10 g, 12.8 mmol, 1.0 eq) and 4-dimethylaminopyridine (DMAP, 0.157 g, 1.28 mmol, 0.1 eq) were added. After dissolving in dry methylene chloride (25 mL), the solution was cooled to 0°C. Afterwards, $N,N'$-diisopropylcarbodiimide (DIC, 2.21 mL, 14.1 mmol, 1.1 eq) was added dropwise, the reaction was stirred for 1 hour at 0°C and at room temperature overnight. The resulting precipitate was filtered off and washed with more methylene chloride. The filtrate was concentrated to dryness and purified by flash column chromatography using deactivated silica gel and a cyclohexane/ethyl acetate gradient to obtain the desired NPHI ester (5.04 g, 11.0 mmol, 86%) as a white solid.

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.97 – 7.88 (m, 2H), 7.87 – 7.79 (m, 2H), 7.76 (d, $J$ = 7.4 Hz, 2H), 7.62 (d, $J$ = 7.4 Hz, 2H), 7.39 (t, $J$ = 7.4 Hz, 2H), 7.31 (t, $J$ = 7.5 Hz, 2H), 5.52 (t, $J$ = 6.2 Hz, 1H), 4.40 (d, $J$ = 7.2 Hz, 2H), 4.25 (t, $J$ = 7.3 Hz, 1H), 3.66 (q, $J$ = 6.1 Hz, 2H), 2.93 (t, $J$ = 5.8 Hz, 2H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 168.6, 162.0, 156.4, 144.0, 141.4, 135.0, 128.9, 127.8, 127.2, 125.3, 124.2, 120.1, 67.1, 47.3, 36.8, 32.3 ppm.

HRMS (ESI, m/z): Calcd for C$_{26}$H$_{20}$N$_2$O$_6$Na [M + Na]$^+$ 479.1214; found 479.1192.

**Synthesis of N-Fmoc-(2-aminoethyl)boronic acid pinacol ester (14a)**

![Chemical Structure](attachment:image.png)

The compound was synthesized via decarboxylative borylation, adopting a recently published method.$^8$
A round-bottom flask was charged with N-Fmoc-β-alanine NHPI ester (1.31 g, 2.63 mmol, 1.0 eq) and MgBr$_2$·OEt$_2$ (1.018 g, 3.94 mmol, 1.5 eq). After evacuating and flushing the flask with nitrogen for three times, a suspension of NiCl$_2$·6 H$_2$O (62.5 mg, 0.263 mmol, 0.1 eq) and 4,4’-dimethoxy-2,2’-bypyridine (74.0 mg, 0.34 mmol, 0.13 eq) in THF (10.5 mL), prepared 24 hours prior to use, was added. The suspension was stirred for 10 minutes at room temperature and then cooled to 0°C. Afterwards a suspension of pre-complexed [B$_2$pin$_2$Me]Li (3.0 eq) in THF/ether, prepared one hour prior to use, was added in one portion. The resulting mixture was stirred for one hour at 0°C and for one additional hour at room temperature. For workup, the suspension was diluted with ether (50 mL), filtered through celite and silica gel, subsequently. After washing with additional ether (100 mL), the filtrate was concentrated in vacuo. The crude product was purified by flash column chromatography using deactivated silica gel (SiO$_2$/H$_2$O 100:35, m/m) to obtain the title compound as a colourless oil (349.5 mg, 0.89 mmol, 34%).

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.76 (d, $J$ = 7.4 Hz, 2H), 7.60 (d, $J$ = 7.3 Hz, 2H), 7.43 – 7.36 (m, 2H), 7.30 (td, $J$ = 7.4, 1.1 Hz, 2H), 5.09 – 5.01 (m, 1H), 4.37 (d, $J$ = 7.0 Hz, 2H), 4.23 (t, $J$ = 6.8 Hz, 1H), 3.34 (q, $J$ = 7.3 Hz, 2H), 1.26 (s, 12H), 1.07 (t, $J$ = 7.5 Hz, 2H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 156.3, 144.2, 141.4, 127.7, 127.1, 125.2, 120.0, 83.5, 66.6, 47.4, 37.0, 25.0 ppm.


Synthesis of N-Fmoc(4-aminobenzyl)boronic acid pinacol ester (15a)

Reagents and conditions: (a) Fmoc-OSu/NaHCO$_3$/MeCN/H$_2$O/rt; (b) NHPI/DIC/DMAP/CH$_2$Cl$_2$/0°C to rt; (c) [B$_2$pin$_2$Me]Li/NiCl$_2$/4,4’-dimethoxy-2,2’-bipyridine/MgBr$_2$·OEt$_2$/THF/ether/0°C to rt.
Synthesis of N-Fmoc-4-aminophenylacetic acid

4-Aminophenylacetic acid (1.50 g, 9.92 mmol, 1.0 eq) was dissolved in a water/acetonitrile mixture (1:1 v/v, 80 mL) and cooled to 0°C. Sodium bicarbonate (2.50 g, 29.8 mmol, 3.0 eq) and Fmoc-N-hydroxysuccinimide ester (Fmoc-OSu, 3.68 g, 10.9 mmol, 1.1 eq) were added subsequently. After one hour at 0°C the reaction was allowed to warm to room temperature and stirred overnight. The solution was acidified to pH 1 with 1 N HCl, the aqueous phase was extracted with methylene chloride (3×50 mL), the combined organic phases were dried over anhydrous MgSO₄ and the solvent was removed in vacuo to obtain N-Fmoc-4-aminophenylacetic acid (3.39 g, 9.08 mmol, 92%) as a white solid.

¹H NMR (300 MHz, DMSO-d₆) δ 12.24 (bs, 1H), 9.65 (s, 1H), 7.91 (d, J = 7.3 Hz, 2H), 7.75 (d, J = 7.4 Hz, 2H), 7.48 – 7.29 (m, 6H), 7.14 (d, J = 8.3 Hz, 2H), 4.47 (d, J = 6.9 Hz, 2H), 4.30 (t, J = 6.5 Hz, 1H), 3.48 (s, 2H) ppm.

¹³C NMR (75 MHz, DMSO-d₆) δ 172.8, 153.4, 143.8, 140.8, 137.5, 129.6, 129.0, 127.7, 127.1, 125.1, 120.2, 118.2, 65.5, 46.6, 40.0 (overlaps with solvent signal) ppm.

HRMS (ESI, m/z): Calcd for C₂₃H₁₈NO₄ [M – H]⁻ 372.1241; found 372.1220.

Synthesis of N-Fmoc-4-aminophenylacetic acid NHPI ester

N-Fmoc-4-aminophenylacetic acid (1.048 g, 2.81 mmol, 1.0 eq) was weighed into a 25 mL round-bottom flask, N-hydroxyphthalimide (NHPI, 0.458 g, 2.81 mmol, 1.0 eq) and 4-dimethylaminopyridine (DMAP, 0.034 g, 0.281 mmol, 0.1 eq) were added. After dissolving in dry methylene chloride (10 mL), the solution was cooled to 0°C. Afterwards, N,N'-diisopropylcarbodiimide (DIC, 0.483 mL, 3.09 mmol, 1.1 eq) was added dropwise, the reaction was stirred for 1 hour at 0°C and at room temperature overnight. The resulting precipitate was filtered off and washed with more methylene chloride. The filtrate was concentrated to dryness and purified by flash column chromatography using deactivated silica gel (SiO₂/H₂O 100:35, m/m) to obtain the desired NHPI ester (1.10 g, 2.12 mmol, 76%) as a pale yellow solid.
**Synthesis of N-Fmoc(4-aminobenzyl)boronic acid pinacol ester (15a)**

![Fmoc-N\(\text{H} \)\(\text{O} \) \(\text{B} \)\(\text{O} \) \(\text{O} \)](image)

The compound was synthesized via decarboxylative borylation, adopting a recently published method.\(^8\)

A round-bottom flask was charged with the corresponding NHPI ester (1.04 g, 2.00 mmol, 1.0 eq) and MgBr\(_2\)-OEt\(_2\) (0.775 g, 3.00 mmol, 1.5 eq). After evacuating and flushing the flask with nitrogen for three times, a suspension of NiCl\(_2\)-6 H\(_2\)O (47.5 mg, 0.200 mmol, 0.1 eq) and 4,4’-dimethoxy-2,2’-bipyridine (56.2 mg, 0.260 mmol, 0.13 eq) in THF (8.0 mL), prepared 24 hours prior to use, was added. The suspension was stirred for 10 minutes at room temperature and then cooled to 0°C. Afterwards a suspension of pre-complexed \([\text{B}_2\text{pin}_2\text{Me}]\text{Li}\) (3.0 eq) in THF/ether, prepared one hour prior to use, was added in one portion. The resulting mixture was stirred for one hour at 0°C and for one additional hour at room temperature. For workup, the suspension was diluted with ether (50 mL), filtered through celite and silica gel, subsequently. After washing with additional ether (100 mL), the filtrate was concentrated in vacuo. The crude product was purified by flash column chromatography using deactivated silica gel (SiO\(_2\)/H\(_2\)O 100:35, m/m) to obtain the title compound as a colourless oil (0.673 g, 1.48 mmol, 74%).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.78 \text{ (d, } J = 7.5 \text{ Hz, 2H)}\), 7.61 \(\text{ (d, } J = 7.3 \text{ Hz, 2H)}\), 7.41 \(\text{ (t, } J = 7.2 \text{ Hz, 2H)}\), 7.32 \(\text{ (td, } J = 7.4, 1.0 \text{ Hz, 2H)}\), 7.28 – 7.18 \(\text{ (m, 2H)}\), 7.12 \(\text{ (d, } J = 8.4 \text{ Hz, 2H)}\), 6.58 \(\text{ (s, 1H)}\), 4.52 \(\text{ (d, } J = 6.7 \text{ Hz, 2H)}\), 4.27 \(\text{ (t, } J = 6.7 \text{ Hz, 1H)}\), 2.25 \(\text{ (s, 2H)}\), 1.23 \(\text{ (s, 12H)}\) ppm.

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta 153.5, 143.6, 141.1, 134.8, 133.5, 129.2, 127.5, 126.9, 124.8, 119.8, 118.9, 83.2, 66.5, 46.9, 24.6 \text{ ppm.}\)

HRMS (ESI, m/z): Calcd for C\(_{28}\)H\(_{30}\)BNO\(_4\)Na [M + Na]\(^+\) 478.2165; found 478.2156.
Part II: Monophasic transesterification

General procedure A: Trifluoroacetic acid in methylene chloride

To a small round-bottom flask the corresponding pinacol ester or pinanediol ester (1.0 eq) and methylboronic acid (2 – 10 eq) were added and dissolved in a solution of trifluoroacetic acid (5% in methylene chloride, ~10 mL/mmol). The progress of the transesterification could be monitored by proton NMR of the crude mixture (see Figure S-1). After full conversion, all volatile compounds were evaporated at 40°C water bath temperature. To avoid mixed anhydride formation, the residue was redissolved in 0.1 N HCl (~10 mL/mmol), the mixture was evaporated and dried in vacuo to obtain the pure boronic acid.

Synthesis of 3-aminophenylboronic acid·HCl (1)

I: Deprotection of pinacol ester (1a)

The general procedure was followed with 3-aminophenylboronic acid pinacol ester (59.0 mg, 0.269 mmol, 1.0 eq) and methylboronic acid (48.3 mg, 0.807 mmol, 3.0 eq) to obtain 3-aminophenylboronic acid hydrochloride (45.5 mg, 0.263 mmol, 98%) as a pale yellow solid.

II: Deprotection of pinacol ester (1a, gram scale)

3-Aminophenylboronic acid pinacol ester (1.00 g, 4.56 mmol, 1.0 eq) and methylboronic acid (0.820 g, 13.7 mmol. 3.0 eq) were dissolved in methylene chloride (19 mL), trifluoroacetic acid (1 mL) was added. The reaction mixture was stirred at room temperature overnight, concentrated to dryness, redissolved in 0.1 N aqueous HCl (5 mL) and dried in vacuo to obtain the title compound (784.2 mg, 4.52 mmol, 99%) as a pale yellow solid.
**III: Deprotection of pinanediol ester (1b)**

The corresponding pinanediol ester (85.9 mg, 0.317 mmol, 1.0 eq) was dissolved in methylene chloride (1.9 mL), trifluoroacetic acid (100 µL) was added. After stirring at room temperature overnight, all volatiles were removed (40°C, ~ 10 mbar), the residue was redissolved in 0.1 N HCl\textsubscript{aq} and dried *in vacuo* until constant weight to obtain 3-aminophenylboronic acid hydrochloride (49.3 mg, 0.284 mmol, 94%) as a pale yellow solid.

$^1$H NMR (300 MHz, DMSO-\textit{d}$_6$/D\textsubscript{2}O 4:1) $\delta$ 7.76 (d, $J = 7.4$ Hz, 1H), 7.63 (s, 1H), 7.47 (t, $J = 7.6$ Hz, 1H), 7.35 (dd, $J = 7.8$, 2.3 Hz, 1H) ppm.

$^{13}$C NMR (75 MHz, DMSO-\textit{d}$_6$/D\textsubscript{2}O 4:1) $\delta$ 134.5, 131.5, 130.1, 128.6, 125.3 ppm.

$^{11}$B NMR (160 MHz, DMSO-\textit{d}$_6$/D\textsubscript{2}O 4:1) $\delta$ 28.8 ppm.

HRMS (ESI, m/z): Calcd for C$_6$H$_9$BNO$_2$ [M + H]$^+$ 138.0722; found 138.0722.

**Synthesis of phenylboronic acid (2)**

![phenylboronic acid](image)

The general procedure was followed with phenylboronic acid pinacol ester (51.6 mg, 0.253 mmol, 1.0 eq) and methylboronic acid (45.4 mg, 0.759 mmol, 3.0 eq) to obtain phenylboronic acid (30.0 mg, 0.246 mmol, 97%) as a white solid.

$^1$H NMR (300 MHz, DMSO-\textit{d}$_6$/D\textsubscript{2}O 4:1) $\delta$ 7.68 (dd, $J = 7.9$, 1.4 Hz, 2H), 7.43 – 7.35 (m, 1H), 7.31 (t, $J = 7.0$ Hz, 2H) ppm.

$^{13}$C NMR (75 MHz, DMSO-\textit{d}$_6$/D\textsubscript{2}O 4:1) $\delta$ 134.5, 131.5, 128.9 ppm.

$^{11}$B NMR (160 MHz, DMSO-\textit{d}$_6$/D\textsubscript{2}O 4:1) $\delta$ 29.3 ppm.

HRMS (ESI, m/z): Calcd for C$_6$H$_7$BO$_2$Na [M + Na]$^+$ 145.0432; found 145.0436.

**Synthesis of 2-hydroxyphenylboronic acid (3)**

![2-hydroxyphenylboronic acid](image)
The general procedure was followed with 2-hydroxyphenylboronic acid pinacol ester (86.3 mg, 0.392 mmol, 1.0 eq) and methylboronic acid (117.3 mg, 1.96 mmol, 5.0 eq) to obtain 2-hydroxyphenylboronic acid (50.3 mg, 0.365 mmol, 93%) as a white solid.

$^1$H NMR (500 MHz, acetone-$d_6$/D$_2$O 10:1) $\delta$ 7.70 (d, $J =$ 6.7 Hz, 1H), 7.25 (t, $J =$ 6.7 Hz, 1H), 6.85 – 6.73 (m, 2H) ppm.

$^{13}$C NMR (126 MHz, acetone-$d_6$/D$_2$O 10:1) $\delta$ 164.3, 136.5, 133.2, 119.9, 115.7 ppm.

$^{11}$B NMR (160 MHz, acetone-$d_6$/D$_2$O 10:1) $\delta$ 29.5 ppm.

HRMS (ESI, m/z): Calcd for C$_{18}$H$_{14}$B$_3$O$_6$ [Boroxine - H] $^-$ 359.1075; found 359.1111.

**Synthesis of 3-carboxyphenylboronic acid (4)**

![3-carboxyphenylboronic acid](https://via.placeholder.com/150)

The general procedure was followed with 3-carboxyphenylboronic acid pinacol ester (51.0 mg, 0.206 mmol, 1.0 eq) and methylboronic acid (37.0 mg, 0.618 mmol, 3.0 eq). Formation of a white precipitate was observed after 30 min, after 3 hours the resulting suspension was evaporated to dryness, redissolved in 0.1 N HCl and dried in vacuo to obtain 3-carboxyphenylboronic acid (34.1 mg, 0.205 mmol, 99%) as a white solid.

$^1$H NMR (300 MHz, DMSO-$d_6$/D$_2$O 4:1) $\delta$ 8.33 (t, $J =$ 1.5 Hz, 1H), 7.95 (dd, $J =$ 7.6, 1.6 Hz, 2H), 7.47 (t, $J =$ 7.6 Hz, 1H) ppm.

$^{13}$C NMR (75 MHz, DMSO-$d_6$/D$_2$O 4:1) $\delta$ 168.7, 139.3, 135.7, 131.9, 130.4, 128.8 ppm.

$^{11}$B NMR (160 MHz, DMSO-$d_6$/D$_2$O 4:1) $\delta$ 28.8 ppm.

HRMS (ESI, m/z): Calcd for C$_7$H$_6$BO$_4$ [M - H] $^-$ 165.0366; found 165.0362.

**Synthesis of 4-aminophenylboronic acid·HCl (5)**

![4-aminophenylboronic acid·HCl](https://via.placeholder.com/150)

The general procedure was followed with 4-aminophenylboronic acid pinacol ester (60.0 mg, 0.274 mmol, 1.0 eq) and methylboronic acid (82.0 mg, 1.37 mmol, 5.0 eq). Formation of a brown precipitate was observed after 30 min, after 3 hours the resulting suspension was
evaporated to dryness, redissolved in 0.1 N HCl and dried in vacuo to obtain 4-aminophenylboronic acid hydrochloride (43.9 mg, 0.253 mmol, 93%) as a pale brown solid.

$^1$H NMR (300 MHz, DMSO-$d_6$/D$_2$O 4:1) δ 7.84 – 7.74 (m, 2H), 7.24 – 7.18 (m, 2H) ppm.

$^{13}$C NMR (75 MHz, DMSO-$d_6$/D$_2$O 4:1) δ 136.4, 135.4, 121.9 ppm.

$^{11}$B NMR (160 MHz, DMSO-$d_6$/D$_2$O 4:1) δ 28.9 ppm.

HRMS (ESI, m/z): Calcd for C$_6$H$_9$BNO$_2$ [M + H]$^+$ 138.0722; found 138.0730.
Synthesis of pyrimidine-5-boronic acid·HCl (6)

The general procedure was followed with pyrimidine-5-boronic acid pinacol ester (70.1 mg, 0.340 mmol, 1.0 eq) and methylboronic acid (40.7 mg, 0.680 mmol, 2.0 eq) to obtain pyrimidine-5-boronic acid hydrochloride (50.7 mg, 0.316 mmol, 93%) as a white solid.

$^1$H NMR (300 MHz, DMSO-$d_6$/D$_2$O 4:1) $\delta$ 9.27 (s, 1H), 9.08 (s, 2H) ppm.

$^{13}$C NMR (75 MHz, DMSO-$d_6$/D$_2$O 4:1) $\delta$ 162.4, 157.4 ppm.

$^{11}$B NMR (160 MHz, DMSO-$d_6$/D$_2$O 4:1) $\delta$ 27.7 ppm.

HRMS (ESI, m/z): Calcd for C$_4$H$_6$BN$_2$O$_2$ [M + H]$^+$ 125.0518; found 125.0514.

Synthesis of piperidin-4-ylboronic acid·HCl (7)

The general procedure was followed with piperidine-4-boronic acid pinacol ester hydrochloride (48.2 mg, 0.195 mmol, 1.0 eq) and methylboronic acid (58.4 mg, 0.973 mmol, 5.0 eq). A white precipitate was observed after 10 minutes, the reaction was completed after 1 hour. After removal of all volatile compounds, piperidine-4-boronic acid hydrochloride (32.2 mg, 0.195 mmol, 99%) was obtained as a white solid.

$^1$H NMR (300 MHz, DMSO-$d_6$/D$_2$O 4:1) $\delta$ 3.13 (dt, $J = 12.6, 3.7$ Hz, 2H), 2.76 (td, $J = 12.2, 3.3$ Hz, 2H), 1.74 (dq, $J = 15.0, 3.5$ Hz, 2H), 1.50 (ddt, $J = 15.3, 11.8, 3.9$ Hz, 2H), 0.95 (tt, $J = 11.6, 3.5$ Hz, 1H) ppm.

$^{13}$C NMR (75 MHz, DMSO-$d_6$/D$_2$O 4:1) $\delta$ 45.0, 24.6 ppm.

$^{11}$B NMR (160 MHz, DMSO-$d_6$/D$_2$O 4:1) $\delta$ 31.7 ppm.

HRMS (ESI, m/z): Calcd for C$_5$H$_{13}$BNO$_2$ [M + H]$^+$ 130.1035; found 130.1043.
Synthesis of 3-bromopropylboronic acid (8)

\[
\text{Br} - \text{CH}_2\text{CH}_2\text{B} - \text{OH}
\]

The general procedure was followed with 3-bromopropylboronic acid pinacol ester (110.7 mg, 0.445 mmol, 1.0 eq) and methylboronic acid (53.2 mg, 0.889 mmol, 2.0 eq) to obtain 3-bromopropylboronic acid (56.7 mg, 0.340 mmol, 76%) as a white solid.

$^1$H NMR (300 MHz, DMSO-$d_6$/D$_2$O 4:1) $\delta$ 3.40 (t, $J = 6.4$ Hz, 2H), 1.84-1.72 (m, 2H), 0.69 (t, $J = 8.1$ Hz, 2H) ppm.

$^{13}$C NMR (75 MHz, DMSO-$d_6$/D$_2$O 4:1) $\delta$ 39.0 (overlapping with the solvent signal), 28.6 ppm.

$^{11}$B NMR (160 MHz, DMSO-$d_6$/D$_2$O 4:1) $\delta$ 32.2 ppm.

HRMS (ESI, m/z): Calcd for C$_3$H$_8$BBrO$_2$Na [M + Na]$^+$ 188.9693; found 188.9709.
**General procedure B: Aqueous hydrochloric acid**

For more sensitive substrates, alternative reagents were identified to replace trifluoroacetic acid.

![Chemical structure](image)

Into a small round-bottom flask, the corresponding pinacol ester or pinanediol ester (0.2 – 0.3 mmol, 1.0 eq) and methylboronic acid (5 – 10 eq) were added and dissolved in the appropriate solvent. The progress of the transesterification could be monitored by proton NMR of the crude mixture. Upon completion of the transesterification the reaction mixture was concentrated to dryness, redissolved in deionized water or acetone and dried *in vacuo* to obtain the pure boronic acid.

**Synthesis of thiophene-2-boronic acid (9)**

![Thiophene-2-boronic acid](image)

The synthesis was done using thiophene-2-boronic acid pinacol ester (87.5 mg, 0.416 mmol, 1.0 eq) and methylboronic acid (249.3 mg, 4.16 mmol, 10.0 eq) in acetone/0.2 N HCl (1:1, v/v) to obtain thiophene-2-boronic acid (51.1 mg, 0.399 mmol, 96%) as a white solid.

$^1$H NMR (300 MHz, acetone-$d_6$) δ 7.71 (d, $J = 3.4$ Hz, 1H), 7.68 (d, $J = 4.7$ Hz, 1H), 7.19 – 7.14 (m, 1H) ppm.

$^{13}$C NMR (75 MHz, acetone-$d_6$) δ 136.6, 132.2, 128.8 ppm.

$^{11}$B NMR (160 MHz, acetone-$d_6$) δ 27.4 ppm.

The spectroscopic data matches that reported in the literature.$^9,^{10}$
Synthesis of 1-phenylvinylboronic acid (10)

\[
\text{\begin{tikzpicture}
\node (a) at (0,0) {\text{\textbf{B}}};
\node (b) at (0.5,0.5) {\text{\textbf{OH}}};
\node (c) at (0.5,-0.5) {\text{\textbf{OH}}};
\end{tikzpicture}}
\]

The synthesis was done using 1-phenylvinylboronic acid pinacol ester (86.0 mg, 0.374 mmol, 1.0 eq) and methylboronic acid (111.9 mg, 1.869 mmol, 5.0 eq) in acetone/0.2 N HCl (1:1, v/v) to obtain 1-phenylvinylboronic acid (46.7 mg, 0.316 mmol, 84%) as a pale yellow solid, containing small amounts of impurities.

\(^1\text{H} \text{NMR} (300 \text{ MHz, acetone-}d_6/\text{D}_2\text{O 95:5}) \delta 7.42 - 7.35 (m, 2H), 7.27 (t, J = 7.3 \text{ Hz}, 2H), 7.19 (t, J = 7.2 \text{ Hz}, 1H), 5.96 - 5.79 (m, 2H) \text{ ppm}.

\(^{13}\text{C} \text{NMR} (75 \text{ MHz, acetone-}d_6/\text{D}_2\text{O 95:5}) \delta 143.8, 128.8, 128.1, 127.7, 127.3 \text{ ppm}.

\(^{11}\text{B} \text{NMR} (160 \text{ MHz, acetone-}d_6/\text{D}_2\text{O 95:5}) \delta 29.1 \text{ ppm}.

HRMS (ESI, m/z): Calcd for C_8H_9BO_2Na [M + Na]^+ 171.0589; found 171.0596.

Synthesis of \((R)-(1\text{-amino-3-methylbutyl})\text{boronic acid hydrochloride (11)}

\[
\text{\begin{tikzpicture}
\node (a) at (0,0) {\text{\textbf{Cl}}};
\node (b) at (0.5,0.5) {\text{\textbf{H}}};
\node (c) at (0.5,-0.5) {\text{\textbf{OH}}};
\end{tikzpicture}}
\]

The synthesis was done using \((R)-(1\text{-amino-3-methylbutyl})\text{boronic acid pinacol ester (51.1 mg, 0.205 mmol, 1.0 eq) and methylboronic acid (61.1 mg, 1.02 mmol, 5.0 eq) in acetone/0.2 N HCl (1:1, v/v) to obtain the title compound (34.3 mg, 0.205 mmol, 99%) as a white solid.}

\(^1\text{H} \text{NMR} (300 \text{ MHz, CD}_3\text{CN/}D_2\text{O 5:2}) \delta 2.76 (t, J = 7.3 \text{ Hz}, 1H), 1.72 - 1.58 (m, 1H), 1.57 - 1.44 (m, 2H), 0.88 (dd, J = 6.3, 4.4 Hz, 6H) \text{ ppm}.

\(^{13}\text{C} \text{NMR} (75 \text{ MHz, CD}_3\text{CN/}D_2\text{O 5:2}) \delta 39.1, 25.5, 23.0, 22.1 \text{ ppm}.

\(^{11}\text{B} \text{NMR} (160 \text{ MHz, CD}_3\text{CN/}D_2\text{O 5:2}) \delta 29.9 \text{ ppm}.

HRMS (ESI, m/z): Calcd for C_{8}\text{H}_{15}\text{BNO}_2 [M + H]^+ 132.1191; found 132.1192.
**Synthesis of bortezomib (12)**

![Chemical structure of bortezomib](image)

**Method A: Deprotection of bortezomib pinacol ester (12a)**

Bortezomib pinacol ester (71.6 mg, 0.154 mmol, 1.0 eq) and methylboronic acid (98.8 mg, 1.65 mmol, 10.0 eq) were dissolved in 1 mL of acetone and 1 mL of 0.2 N HCl. After stirring at room temperature overnight all volatiles were evaporated. The crude residue was redissolved in acetonitrile and deionized water and freeze-dried to obtain bortezomib (55.4 mg, 0.144 mmol, 94%) as a white powder.

**Method B: Deprotection of bortezomib pinanediol ester (12b)**

Bortezomib pinanediol ester (77.1 mg, 0.149 mmol, 1.0 eq) and methylboronic acid (89.2 mg, 1.49 mmol, 10.0 eq) were dissolved in 1 mL of acetone and 1 mL of 0.2 N HCl. After stirring at room temperature for 40 hours all volatiles were evaporated. The crude residue was redissolved in acetonitrile and deionized water and freeze-dried to obtain bortezomib (52.3 mg, 0.136 mmol, 92%) as a white powder.

$^1$H NMR (500 MHz, acetone-$d_6$/D$_2$O 10:1) δ 9.14 (s, 1H), 8.81 (s, 1H), 8.66 (s, 1H), 7.28 (d, $J = 7.5$ Hz, 2H), 7.20 (t, $J = 7.5$ Hz, 2H), 7.14 (t, $J = 7.2$ Hz, 1H), 4.92 – 4.87 (m, 1H), 3.27 (dd, $J = 13.8$, 5.7 Hz, 1H), 3.21 (dd, $J = 9.5$, 5.5 Hz, 1H), 3.15 (dd, $J = 13.8$, 8.0 Hz, 1H), 1.54 (tt, $J = 13.1$, 6.6 Hz, 1H), 1.46 (ddd, $J = 14.9$, 9.7, 5.4 Hz, 1H), 1.36 (ddd, $J = 13.9$, 8.4, 5.6 Hz, 1H), 0.81 (d, $J = 6.6$ Hz, 6H) ppm. (NH not observed)

$^{13}$C NMR (126 MHz, CD$_3$CN/D$_2$O 10:1) δ 172.3, 164.3, 148.8, 145.1, 144.6, 144.5, 137.8, 130.4, 129.5, 127.8, 54.9, 40.3, 38.6, 26.0, 23.6, 22.0 ppm.

$^{11}$B NMR (160 MHz, CD$_3$CN/D$_2$O 10:1) δ 29.3 ppm.

HRMS (ESI, m/z): Calcd for C$_{19}$H$_{24}$BN$_4$O$_3$ [M –H$_2$O + H]$^+$ 367.1936; found 367.1940.
Synthesis of ixazomib (13)

Method A: Deprotection of ixazomib pinacol ester (13a)

The synthesis was done using ixazomib pinacol ester (66.2 mg, 0.149 mmol, 1.0 eq) and methylboronic acid (89.2 mg, 1.49 mmol, 10.0 eq) and stirring at room temperature overnight. After stirring at room temperature overnight all volatiles were evaporated. The crude residue was redissolved in acetonitrile and deionized water and freeze-dried to obtain ixazomib (50.3 mg, 0.139 mmol, 93%) as a white powder.

Method B: Deprotection of ixazomib pinanediol ester (13b)

Ixazomib pinanediol ester (69.2 mg, 0.140 mmol, 1.0 eq) and methylboronic acid (83.6 mg, 1.40 mmol, 10.0 eq) were dissolved in 1 mL of acetone and 1 mL of 0.2 N HCl. After stirring at room temperature for 40 hours all volatiles were evaporated. The crude residue was redissolved in acetonitrile and deionized water and freeze-dried to obtain ixazomib (46.6 mg, 0.129 mmol, 92%) as a white powder.

$^1$H NMR (500 MHz, CD$_3$CN/D$_2$O 10:1) $\delta$ 7.57 – 7.52 (m, 1H), 7.45 (d, $J = 1.4$ Hz, 2H), 3.95 (s, 2H), 3.06 (dd, $J = 9.9$, 5.3 Hz, 1H), 1.65 – 1.55 (m, 1H), 1.49 – 1.41 (m, 1H), 1.37 – 1.29 (m, 1H), 0.88 (d, $J = 6.7$ Hz, 3H), 0.86 (d, $J = 6.6$ Hz, 3H) ppm. (NH not observed)

$^{13}$C NMR (126 MHz, CD$_3$CN/D$_2$O 10:1) $\delta$ 170.3, 167.4, 137.8, 133.5, 132.5, 132.2, 130.2, 130.0, 43.5, 40.4, 26.1, 23.6, 22.1 ppm.

$^{11}$B NMR (160 MHz, CD$_3$CN/D$_2$O 10:1) $\delta$ 29.5 ppm.

HRMS (ESI, m/z): Calcd for C$_{14}$H$_{19}$BCl$_2$N$_2$O$_4$Na [M + Na]$^+$ 383.0710; found 383.0702.

Synthesis of N-Fmoc-(2-aminoethyl)boronic acid (14)
The synthesis was done using N-Fmoc-(2-aminoethyl)boronic acid pinacol ester (51.7 mg, 0.131 mmol, 1.0 eq) and methylboronic acid (39.2 mg, 0.657 mmol, 5.0 eq) in acetone/0.2 N HCl (1:1, v/v) to obtain the title compound (36.6 mg, 0.118 mmol, 90%) as a white solid.

1H NMR (300 MHz, acetone-$d_6$/D$_2$O 10:1) δ 7.82 (d, $J = 7.5$ Hz, 2H), 7.67 (d, $J = 7.3$ Hz, 2H), 7.38 (t, $J = 7.3$ Hz, 2H), 7.30 (t, $J = 7.3$ Hz, 2H), 6.61 (s, 1H), 4.28 (d, $J = 6.7$ Hz, 2H), 4.23–4.14 (m, 1H), 3.25 (q, $J = 7.4$ Hz, 2H), 1.02 (t, $J = 7.8$ Hz, 2H) ppm.

13C NMR (75 MHz, acetone-$d_6$/D$_2$O 10:1) δ 157.6, 145.0, 141.9, 128.5, 127.9, 126.1, 120.7, 66.9, 47.9, 37.9 ppm.

11B NMR (160 MHz, acetone-$d_6$/D$_2$O 10:1) δ 32.1 ppm.

HRMS (ESI, m/z): Calcd for C$_{17}$H$_{18}$BNO$_4$Na [M + Na]$^+$ 334.1224; found 334.1222.

**Synthesis of N-Fmoc-(4-aminobenzyl)boronic acid (15)**

![Structure](attachment:image.png)

The synthesis was done using N-Fmoc(4-aminobenzyl)boronic acid pinacol ester (78.9 mg, 0.173 mmol, 1.0 eq) and methylboronic acid (103.6 mg, 1.73 mmol, 10.0 eq) in acetone/0.2 N HCl (1:1, v/v) to obtain the title compound (60.9 mg, 0.163 mmol, 94%) as a white solid.

1H NMR (500 MHz, CDCl$_3$/CD$_3$OD 10:1) δ 7.68 (d, $J = 7.2$ Hz, 2H), 7.55 (bs, 2H), 7.31 (t, $J = 7.0$ Hz, 2H), 7.25–7.10 (m, 4H, overlaps with solvent signal), 6.97 (d, $J = 7.2$ Hz, 2H), 4.42 (d, $J = 6.0$ Hz, 2H), 4.17 (t, $J = 5.9$ Hz, 1H), 2.16 (s, 2H) ppm (NH not observed).

13C NMR (126 MHz, CDCl$_3$/CD$_3$OD 10:1) δ 154.1, 143.8, 141.3, 134.9, 134.1, 129.4, 127.7, 127.1, 124.9, 119.9, 119.0, 66.5, 47.1 ppm.

11B NMR (160 MHz CDCl$_3$/CD$_3$OD 10:1) δ 31.2 ppm.

HRMS (ESI, m/z): Calcd for C$_{22}$H$_{20}$BNO$_4$Na [M + Na]$^+$ 396.1381; found 396.1383.
**General procedure C: Aqueous sodium hydroxide**

For acid-sensitive compounds the reaction was adapted to proceed under basic conditions.

![Reaction Scheme](attachment:image.png)

To a small round-bottom flask, the corresponding boronate ester (1.0 eq) and methylboronic acid (10.0 eq) were added and dissolved in 1 mL acetone. After addition of 0.1 N NaOH (1 mL) the resulting solution was stirred at room temperature overnight. The solution was carefully neutralized with 0.1 N HCl to pH ~ 7. The reaction mixture was concentrated to dryness, the crude residue was resuspended in acetone and filtered to remove NaCl. The filtrate was dried *in vacuo* to obtain the desired boronic acid.

**Synthesis of N-Boc-3-aminophenylboronic acid (16)**

![Amination Reaction](attachment:image.png)

The synthesis was done using N-Boc-3-aminoboronic acid pinacol ester (111.4 mg, 0.349 mmol, 1.0 eq) and methylboronic acid (208.9 mg, 3.49 mmol, 10.0 eq) to obtain the title compound (80.3 mg, 0.339 mmol, 97%) as a colourless oil.

\(^1\text{H NMR}\ (300 \text{ MHz, acetone-}d_6/\text{D}_2\text{O 95:5}) \ \delta 8.37 \ (s, 1\text{H}), 7.94 \ (s, 1\text{H}), 7.66 - 7.55 \ (m, 1\text{H}), 7.50 \ (d, J = 7.3 \text{ Hz}, 1\text{H}), 7.25 \ (t, J = 7.7 \text{ Hz}, 1\text{H}), 1.47 \ (s, 9\text{H}) \ \text{ppm.}

\(^{13}\text{C NMR}\ (75 \text{ MHz, acetone-}d_6/\text{D}_2\text{O 95:5}) \ \delta 153.9, 139.6, 129.0, 128.6, 124.9, 121.2, 79.8, 28.5 \ \text{ppm.}

\(^{11}\text{B NMR}\ (160 \text{ MHz acetone-}d_6/\text{D}_2\text{O 95:5}) \ \delta 29.5 \ \text{ppm.}

HRMS (ESI, m/z): Calcd for C\text{_{11}}H\text{_{16}}BNO\text{_{4}}Na [M + Na]^+ 260.1067; found 260.1081.
Transesterification of bis(pinacolato)diboron

According to general procedure A, bis(pinacolato)diboron ($\text{B}_2\text{pin}_2$, 72.1 mg, 0.284 mmol, 1.0 eq) and methylboronic acid (170.0 mg, 2.84 mmol, 10.0 eq) were dissolved in 1.9 mL methylene chloride, and trifluoroacetic acid (100 µL) was added. A white solid precipitated after 30 minutes. After stirring at room temperature overnight, all volatiles were evaporated, the crude residue was redissolved in 0.1 N HCl and dried in vacuo to give boric acid (28.7 mg, 0.464 mmol, 82%) as a white solid.

$^1$H NMR (300 MHz, DMSO-$d_6$/D$_2$O 4:1) $\delta$ 6.74 (s, 3H) ppm.

$^{13}$C NMR (75 MHz, DMSO-$d_6$/D$_2$O 4:1) no signals observed (spectra not shown).

$^{11}$B NMR (160 MHz, DMSO-$d_6$/D$_2$O 4:1) $\delta$ 20.2 ppm.

The spectroscopic data of the product is identical to that of commercially available authentic boric acid. The decomposition of tetrahydroxydiboron to boric acid has been previously reported.\textsuperscript{11}
NMR spectra of intermediates
$^1$H NMR (300 MHz, CDCl$_3$)
$^{13}$C APT NMR (75 MHz, CDCl$_3$)

1b
$^1$H NMR (300 MHz, CDCl$_3$)

6a
$^{13}$C APT NMR (75 MHz, CDCl$_3$)
$^{13}$C APT NMR (75 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)
$^{13}$C APT NMR (75 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

ClH$_3$N

11a
$^{13}$C APT NMR (75 MHz, CDCl$_3$)

![Chemical structure of 11a](image-url)
$^1$H NMR (300 MHz, CDCl$_3$)
$^{13}$C-APT NMR (75 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)
$^{13}$C-APT NMR (75 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)
$^{13}$C APT NMR (75 MHz, CDCl$_3$)
$^{1}$H NMR (300 MHz, CDCl$_3$)
$^{13}$C APT NMR (75 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, acetone-$d_6$/CD$_3$OD 1:1)
$^{13}$C APT NMR (75 MHz, acetone-$d_6$/CD$_3$OD 1:1)
^1H NMR (300 MHz, CDCl₃)

12a
$^{13}$C APT NMR (75 MHz, CDCl$_3$)

12a
$^1$H NMR (300 MHz, CDCl$_3$)

![NMR spectrum with chemical shifts and peaks labeled]

12b
$\text{${^{13}C}$ APT NMR (75 MHz, CDCl$_3$)}$

![Chemical structure image]

$12b$
$^1$H NMR (300 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, DMSO-$d_6$)
$^{13}$C NMR (75 MHz, DMSO-$d_6$)
$^1$H NMR (300 MHz, acetone-$d_6$)

13a
$^{13}$C APT NMR (75 MHz, acetone-$d_6$)
$^1$H NMR (300 MHz, CDCl$_3$)
$^{13}$C APT NMR (75 MHz, CDCl$_3$)

![Chemical Structure](image)

13b
$^1$H NMR (300 MHz, DMSO-$d_6$)
$^{13}\text{C APT NMR (75 MHz, DMSO-d}_6\text{)}$

![NMR Spectrum](image_url)
$^1$H NMR (300 MHz, CDCl$_3$)
$^{13}$C APT NMR (75 MHz, CDCl$_3$)

Fmoc

Chemical shift (ppm)
$^1$H NMR (300 MHz, CDCl$_3$)

14a
13C APT NMR (75 MHz, CDCl₃)

![Chemical structure of 14a](image)

Chemical shift (ppm):
- 156.3
- 144.2
- 141.4
- 127.7
- 127.1
- 125.2
- 120.0
- 83.5
- 77.2 (CDCl₃)
- 66.6
- 47.4
- 37.0
- 25.0
$^1$H NMR (300 MHz, DMSO-$d_6$)
$^{13}$C APT NMR (75 MHz, DMSO-$d_6$)
$^1$H NMR (300 MHz, CDCl$_3$)

\[
\text{Fmoc-}
\]

![Chemical shift diagram with peak assignments](image)
$^{13}$C APT NMR (75 MHz, CDCl$_3$)

Fmoc

Chemical shift (ppm)
$^1$H NMR (300 MHz, CDCl$_3$)

Fmoc

15a
$^{13}$C APT NMR (75 MHz, CDCl$_3$)

![Fmoc-structure](image)

15a
NMR spectra of final compounds
$^1$H NMR (300 MHz, DMSO-$d_6$/D$_2$O 4:1)
$^{13}$C APT NMR (75 MHz, DMSO-$d_6$/D$_2$O 4:1)

![Chemical structure](attachment:structure.png)

Chemical shift (ppm)
$^{11}$B NMR (160 MHz, DMSO-$d_6$/D$_2$O 4:1)
$^1$H NMR (300 MHz, DMSO-d$_6$/D$_2$O 4:1)
$^{13}$C APT NMR (75 MHz, DMSO-$d_6$/D$_2$O 4:1)
$^{11}$B NMR (160 MHz, DMSO-$d_6$/D$_2$O 4:1)
$^1$H NMR (300 MHz, acetone-$d_6$/D$_2$O 10:1)
$^{13}$C APT NMR (75 MHz, acetone-$d_6$/D$_2$O 10:1)
$^{11}$B NMR (160 MHz, acetone-$d_6$/D$_2$O 10:1)
$^1$H NMR (300 MHz, DMSO-$d_6$/D$_2$O 4:1)
$^{13}$C APT NMR (75 MHz, DMSO-$d_6$/D$_2$O 4:1)

![Chemical structure image]

Chemical shift (ppm)
$^1$B NMR (160 MHz, DMSO-$d_6$/D$_2$O 4:1)

![Chemical structure of compound 4](image)
\(^1\text{H NMR (300 MHz, DMSO-\textit{d}_6/D_2O 4:1)}\)
$^{13}$C APT NMR (75 MHz, DMSO-$d_6$/D$_2$O 4:1)
$^{11}$B NMR (160 MHz, DMSO-$d_6$/D$_2$O 4:1)
$^1$H NMR (300 MHz, DMSO-$d_6$/D$_2$O 4:1)
$^{13}$C APT NMR (75 MHz, DMSO-$d_6$/D$_2$O 4:1)
$^{11}$B NMR (160 MHz, DMSO-$d_6$/D$_2$O 4:1)
$^1$H NMR (300 MHz, DMSO-$d_6$/D$_2$O 4:1)
$^{13}$C APT NMR (75 MHz, DMSO-$d_6$/D$_2$O 4:1)
$^{11}$B NMR (160 MHz, DMSO-$d_6$/D$_2$O 4:1)
$^1$H NMR (300 MHz, DMSO-$d_6$/D$_2$O 4:1)

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

Chemical shift (ppm)
$^{13}$C NMR (75 MHz, CD$_3$CN/D$_2$O 10:1)
$^{11}$B NMR (160 MHz, DMSO-$d_6$/D$_2$O 4:1)

![Chemical structure and NMR spectrum of a compound with a bromine and boron atom connected by a chain with an OH group at the end.](image-url)
$^1$H NMR (300 MHz, acetone-$d_6$)
$^{13}$C APT NMR (75 MHz, acetone-$d_6$)
$^{11}B$ NMR (160 MHz, acetone-$d_6$)
$^1$H NMR (300 MHz, acetone-$d_6$/D$_2$O 95:5)
$^{13}$C NMR (75 MHz, acetone-$d_6$/D$_2$O 95:5)
$^{11}$B NMR (160 MHz, acetone-$d_6$/D$_2$O 95:5)
\(^{1}H\) NMR (300 MHz, CD\(_3\)CN/D\(_2\)O 5:2)
$^{13}$C APT NMR (75 MHz, CD$_3$CN/D$_2$O 5:2)

![Chemical structure diagram](image)

![NMR spectrum](image)
$^{11}$B NMR (160 MHz, CD$_3$CN/D$_2$O 5:2)

![NMR spectrum of compound 11](image)
$^1$H NMR (500 MHz, acetone-$d_6$/D$_2$O 10:1)
$^{13}$C APT NMR (126 MHz, CD$_3$CN/D$_2$O 10:1)

12

Chemical shift (ppm)
$^{11}$B NMR (160 MHz, CD$_3$CN/D$_2$O 10:1)

![Chemical structure](image)

**12**

- Chemical shift (ppm)
- 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90
$^1$H NMR (500 MHz, CD$_3$CN/D$_2$O 10:1)

![Chemical structure and NMR spectrum with peak assignments](image-url)
$^{13}$C NMR (126 MHz, CD$_3$CN/D$_2$O 10:1)

13

Chemical shift (ppm)

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
$^{11}$B NMR (160 MHz, CD$_3$CN/D$_2$O 10:1)

![Chemical structure image](image-url)

Chemical shift (ppm)
$^1$H NMR (300 MHz, acetone-$d_6$/D$_2$O 10:1)
$^{13}$C APT NMR (75 MHz, acetone-$d_6$/D$_2$O 10:1)
$^{11}$B NMR (160 MHz, acetone-$d_6$/D$_2$O 10:1)
$^1$H NMR (500 MHz, CDCl$_3$/CD$_3$OD 10:1)
$^{13}$C NMR (126 MHz, CDCl$_3$/CD$_3$OD 10:1)

Fmoc-$\text{NH}$-

15
$^{11}$B NMR (160 MHz, CDCl$_3$/CD$_3$OD 10:1)
$^1$H NMR (300 MHz, acetone-$d_6$/$D_2$O 95:5)

![Chemical Structure](image)

16
$^{13}$C NMR (75 MHz, acetone-$d_6$/D$_2$O 95:5)

![Carbon-13 NMR spectrum](image)
$^{11}$B NMR (160 MHz, acetone-$d_6$/D$_2$O 95:5)

![Chemical structure of compound 16](image)

[Chemical shift graph showing spectral data]
$^1$H NMR (300 MHz, DMSO-$d_6$/$^2$H$_2$O 4:1)
$^{11}$B NMR (160 MHz, DMSO-$d_6$/D$_2$O 4:1)
References