

A Divalent Protecting Group for Benzoxaboroles

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Materials

Silica gel (40 μm) was from SiliCycle. All reagent-grade materials were from Sigma–Aldrich (St. Louis, MO) and were used without further purification, except for 2-hydroxymethylphenylboronic acid and 5-amino-2-hydroxymethylphenylboronic acid, which were from Combi-Blocks (San Diego, CA).

General Experimental

Solvent removal. The phrase “concentrated under reduced pressure” refers to the removal of solvents and other volatile materials using a rotary evaporator at water aspirator pressure (<20 torr) while maintaining the water-bath temperature below 40 °C. Residual solvent was removed from samples at high vacuum (<0.1 torr). The term “high vacuum” refers to vacuum achieved by mechanical belt-drive oil pump.

NMR spectroscopy. ^1H , ^{13}C , and ^{11}B NMR spectra for all compounds were acquired on Bruker Spectrometers in the NMRFAM at the University of Wisconsin–Madison operating at 500 and 125 MHz. The chemical shift data are reported in units of δ (ppm) relative to residual solvent and to 20% v/v BF_3 -etherate in CDCl_3 as an external standard for ^{11}B NMR spectroscopy.

Absorption and emission spectroscopy. Fluorescence spectra were measured with a Photon Technology International 810 fluorometer using right-angle detection. Ultraviolet–visible absorption spectra were measured with a Varian Cary 300 Bio diode array spectrophotometer and corrected for background signal with a solvent-filled cuvette. Fluorescence quantum yields in CHCl_3 were determined relative to quinine sulfate in 1 N H_2SO_4 , and were corrected for solvent refractive index and absorption differences at the excitation wavelength.

Analyses of deprotection. Deprotection reactions were run with 4-bromo-2,6-dimethylaniline as an internal standard. Samples were taken from the deprotection reaction mixtures at known times and diluted with methanol, and the extent of cleavage was analyzed with an LCMS-2020 single quadrupole liquid chromatograph mass spectrometer from Shimadzu (Kyoto, Japan) using an $\text{H}_2\text{O}/\text{MeCN}$ (0.1% v/v formic acid) gradient suitable for baseline separation of starting material and the internal standard.

Evaluation of Other Protecting Groups

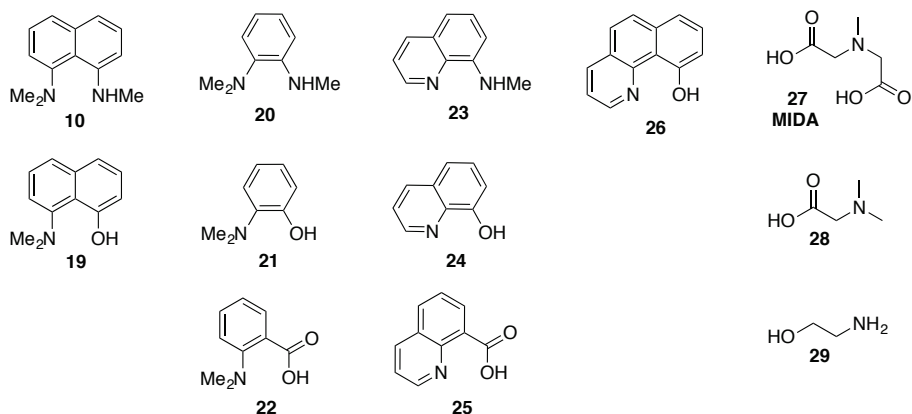


Fig. S1 Other potential protecting groups evaluated experimentally.

The above compounds were tested for complexation of **1a** by refluxing in ethanol or toluene. (Dean–Stark conditions applied in the case of toluene.) The potential protecting groups were selected because they possess a donor nitrogen ligand that would lead to a charge neutral complex (*i.e.*, a tertiary or pyridine nitrogen).

Discussion. Except for **10**, all of the protecting groups above did not form complexes with **1a** that were stable to chromatographic and/or extractive purification. Notably, **19**, **26** and **28** formed complexes that were stable enough for characterization (see table of contents), but were too fragile for further manipulation. Compounds **28** and **29** have been described to form complexes with borinic acids, but were not effective for benzoxaborole.¹ Of particular note is the failure of **20**—a 5-membered variant of **10**—as a protecting group. Potential protecting groups with oxygen ligands (-OH, -CO₂H) would often form protected products that were distinguishable by TLC, but would decompose during subsequent extractive or chromatographic purification. Finally, protecting groups that were able to form 6-membered ring complexes with **1a** were formed more readily.

Deprotection Analyses

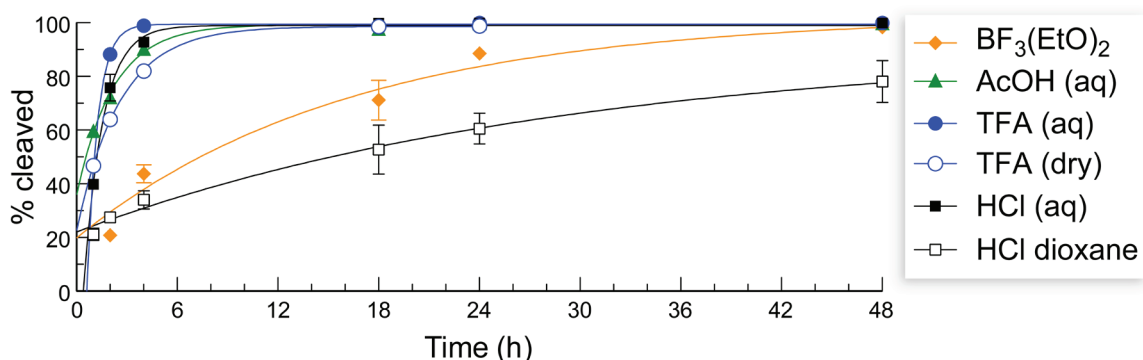
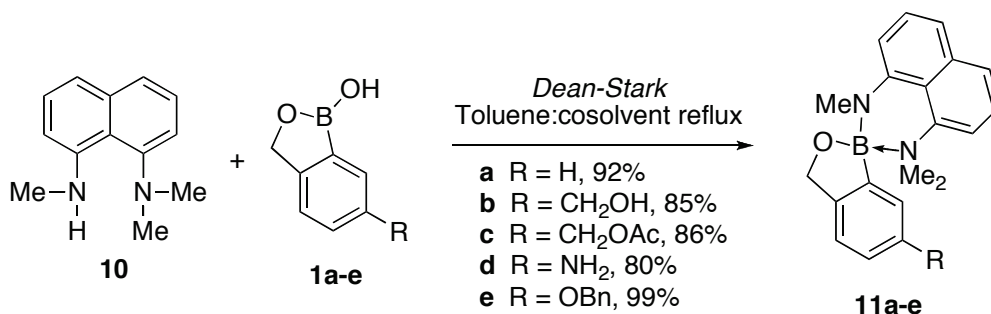


Fig. S2. Kinetic traces for the deprotection of compound **11a**. Percent cleavage was determined through comparison of integrations against the internal standard from the LCMS trace and averaged from replicates. Data were fitted to an exponential decay curve with the program Prism 5.0 from GraphPad Software (La Jolla, CA).

Discussion. The complex shows modest kinetic stability in the presence of certain anhydrous acids such as $\text{BF}_3(\text{EtO})_2$ and 4 M HCl in dioxane. The initial cleavage rates for these two acids began at 20% due to contaminating water. The synthesis of **17** and **18** confirms the complexes kinetic stability to anhydrous acid and susceptibility to aqueous acid (see Scheme 3 in the main text). Finally, extent of cleavage was made based on disappearance of **11a** because boronic acids have poor detection thresholds under LCMS. The cleaved product was confirmed to be the expected benzoxaborole as shown in Fig. S32.

Synthetic Procedures



Synthesis of 1c. 2,5-Bis(hydroxymethyl)phenylboronic acid (0.41 g, 2.5 mmol) was dissolved in DCM (25 mL). Triethylamine (0.35 mL, 2.5 mmol), dimethylaminopyridine (0.015 g, 0.125 mmol), and acetic anhydride (0.473 mL, 5 mmol) were added, and the resulting mixture was stirred for 12 h. The reaction mixture was concentrated under reduced pressure, dissolved in EtOAc (15 mL), and washed with 1 M sodium citrate (3×10 mL), dried over $\text{Na}_2\text{SO}_4(\text{s})$, and concentrated under reduced pressure to yield **1c** (80%). ^1H NMR (400 MHz, CDCl_3) δ 7.63 (s, 1H), 7.47 (d, $J=7.8$ Hz, 1H), 7.37 (d, $J=7.8$ Hz, 1H), 5.13 (s, 2H), 5.06 (s, 2H), 2.07 (s, 3H). ^{13}C NMR (125 MHz, MeOD) δ 172.37, 136.30, 132.00, 130.99, 129.22, 122.27, 67.14, 66.76, 20.85. ^{11}B NMR (CDCl_3 , 96 MHz) δ 33.20. HRMS (ESI) calcd. for $\text{C}_{11}\text{H}_{13}\text{BO}_4$ $[\text{M}+\text{NH}_4]^+$ 237.1282, found 237.1288.

Synthesis of 1e: 6-Benzyloxy-1,3-dihydro-1-hydroxy-2,1-benzoxaborole was prepared following the reported method of Qiao and coworkers,³ with the following changes. 5-(Benzyloxy)-2-formylphenylboronic acid (0.5 g, 1.95 mmol) was dissolved in THF (15 mL), and the resulting solution was cooled to 0 °C. To this solution under stirring, NaBH₄ (0.094 g, 2.5 mmol) was added. After stirring for 2 h, 1 M HCl (6 mL) was added, and the resulting mixture was concentrated under reduced pressure, extracted with EtOAc (3 × 10 mL), and dried over Na₂SO₄(s). The resulting white solid was recrystallized from water to give **1e** (6-benzyloxy-1,3-dihydro-1-hydroxy-2,1-benzoxaborole) (94%).

Synthesis of 11a. 1-Dimethylamino-8-methylaminonaphthalene (**10**)² (0.540 g, 2.7 mmol), and (2-hydroxymethyl)phenylboronic acid (0.120 g, 0.9 mmol) were dissolved in 20 mL of dry toluene. The reaction mixture was fitted with a Dean–Stark trap (filled with 5 mL of dry toluene) and condenser, then heated at 125 °C for 24 h. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, dissolved in DCM (5 mL), washed with 2.5 M NaOH (3 × 10 mL), dried over Na₂SO₄(s), and concentrated under reduced pressure to a brown oil. The residue was purified by silica gel chromatography (1% MeOH in DCM) to provide **11a** (92%) and quantitative re-isolation of **10**. ¹H NMR (500 MHz, CDCl₃) δ 7.76 (d, *J*=8.3 Hz, 1H), 7.45 (t, *J*=7.9 Hz, 1H), 7.35 (t, *J*=7.9 Hz, 1H), 7.18 (d, *J*=8.3 Hz, 1H), 7.11 (m, 2H), 6.77 (m, 1H), 6.59 (d, *J*=7.8 Hz, 1H), 6.14 (bs, 1H), 5.22 (d, *J*=13.9 Hz, 2H), 5.13 (d, *J*=13.9 Hz, 2H), 2.88 (s, 3H), 2.86 (s, 3H), 2.71 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 149.17, 146.75, 143.66, 135.87, 129.00, 128.87, 128.58, 127.20, 126.13, 124.79, 120.14, 117.49, 113.32, 112.61, 105.43, 72.80, 46.29, 32.17. ¹¹B NMR (CDCl₃, 96 MHz) δ 9.25. HRMS (ESI) calcd. for C₂₀H₂₁BN₂O [M⁺] 316.1857, found 316.1841.

Synthesis of 11b from 1b. 2,5-Bis(hydroxymethyl)phenylboronic acid (0.164 g, 1 mmol) was dissolved in 1 mL of dry DMSO. To this solution was added compound **10** (1-dimethylamino-8-methylaminonaphthalene) (0.6 g, 3 mmol), and 20 mL of dry toluene. The reaction mixture was fitted with a Dean–Stark trap (filled with 5 mL of dry toluene) and condenser, then heated at 130 °C for 24 h. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, dissolved in chloroform (5 mL), washed with 2.5 M NaOH (3 × 10 mL), dried over Na₂SO₄(s), and concentrated under reduced pressure to a brown oil. The residue was purified by silica gel chromatography (2.5% v/v MeOH in DCM) to provide **11b** (85%) and quantitative re-isolation of **10**. ¹H-NMR (500 MHz, CDCl₃): δ 7.78 (d 1H), 7.45 (t 1H), 7.37 (t 1H), 7.22 (d 1H), 7.17 (bd 1H), 7.13 (d 2H), 6.09 (d 1H), 5.21 (d 1H), 5.13 (d 1H), 4.29 (s 2H), 2.91 (bs 3H), 2.87 (s 3H), 2.75 (s 3H). ¹³C NMR (125 MHz, CDCl₃): δ 149.00, 146.55, 143.50, 138.57, 135.87, 128.99, 128.67, 127.72, 126.82, 124.81, 120.40, 117.33, 113.43, 112.62, 105.37, 72.55, 65.78, 50.11, 44.60, 32.18. ¹¹B NMR (DMSO-*d*₆, 96 MHz): δ 8.53. HRMS (ESI) calcd. for C₂₁H₂₄BN₂O₂ [M⁺] 346.1962, found 346.1972.

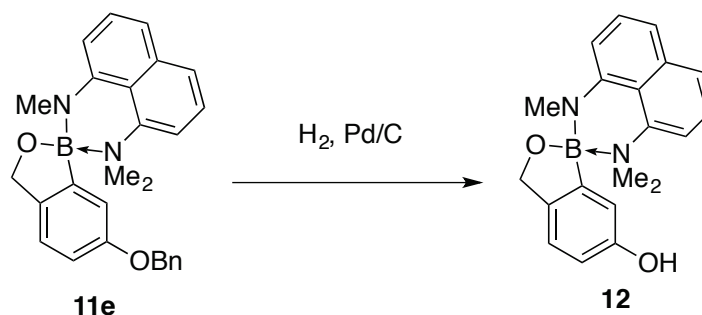
Synthesis of 11c. Compound **1c** (0.368 g, 1.91 mmol) and **10** (1-dimethylamino-8-methylaminonaphthalene) (0.6 g, 3 mmol), were dissolved in 35 mL of dry toluene. The reaction mixture was fitted with a Dean–Stark trap (filled with 5 mL of dry toluene), and condenser, then heated at 125 °C for 15 h. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, dissolved in chloroform (5 mL), washed with 2.5 M NaOH (3 × 10 mL), dried over Na₂SO₄(s), and concentrated under reduced pressure to a brown oil. The residue was

purified by silica gel chromatography (97.5:2.5 DCM:MeOH) to provide **11c** (86%) and quantitative re-isolation of **10**. $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ 7.78 (d 1H), 7.46 (t 1H), 7.38 (t 1H), 7.22 (d 1H), 7.12 (m 3H), 6.61 (d 1H), 6.04 (bs 1H), 5.20 (d 1H), 5.13 (d 1H), 4.73 (m 2H), 2.90 (s 3H), 2.87 (s 3H), 2.74 (s 3H), 1.93 (s 3H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ 170.98, 149.44, 146.56, 143.48, 135.86, 133.42, 128.98, 128.65, 128.48, 127.25, 124.74, 120.31, 117.37, 113.46, 112.60, 105.43, 72.59, 66.73, 32.13, 21.08. $^{11}\text{B NMR}$ (CDCl_3 , 96 MHz) δ 9.13. HRMS (ESI) calcd. for $\text{C}_{23}\text{H}_{25}\text{BN}_2\text{O}_3$ $[\text{M}]^+$ 388.2067, found 388.2080.

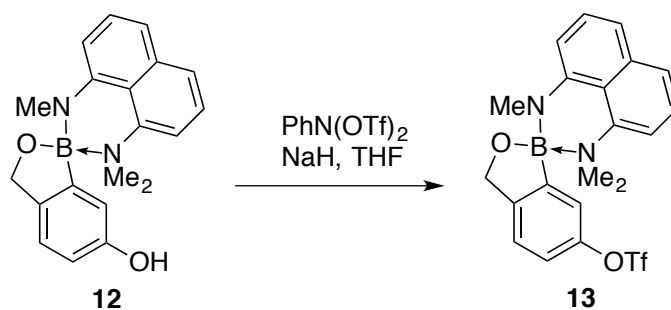
Synthesis of 11d. 5-Amino-2-hydroxymethylphenylboronic acid (0.4 g, 2.7 mmol) was dissolved in 3 mL of MeOH and added to **10**² (0.8 g, 4 mmol) in 3 mL of toluene. The mixture was then evaporated to dryness to give an oil. The residue was dissolved in 20 mL of toluene and heated to reflux under Dean–Stark conditions for 12 h under $\text{N}_2(\text{g})$. The solution was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (95:5, DCM:MeOH) to give **11d** (88%) and quantitative re-isolation of **10**. $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 7.76 (d, $J=8.5$ Hz, 1H), 7.46 (dd, app t, $J=8$, 8 Hz, 1H), 7.37 (dd, app t, $J=8$, 8 Hz, 1H), 7.22 (d, $J=7.5$ Hz, 1H), 7.11 (d, $J=8$ Hz, 1H), 6.91 (d, $J=8$ Hz, 1H), 6.60 (d, $J=8$ Hz, 1H), 6.49 (dd, $J=8$, 2 Hz, 1H), 5.49 (br s, 1H, **H'**), 5.14 (d, $J=13$ Hz, 1H), 5.06 (d, $J=13$ Hz, 1H), 2.89 (s, 3H), 2.87 (s, 3H), 2.76 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz) δ 146.6, 144.2, 143.6, 139.7, 135.8, 128.9, 128.4, 124.8, 120.6, 117.3, 115.3, 115.1, 113.1, 112.6, 105.2, 72.4, 50.1, 44.3, 32.1. $^{11}\text{B NMR}$ (CDCl_3 , 96 MHz) δ 9.01. HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{22}\text{BN}_3\text{O}$ $[\text{M}+\text{H}]^+$ 331.1966, found 331.1967.

Assignment of **H'** based on 2D NMR data (Fig. S11 and S12), which showed that, despite its upfield position and broad appearance, **H'** was attached to an aromatic carbon and coupled to the aromatic protons on the ring and the benzylic methylene protons. Further, **H'** was not exchangeable with D_2O .

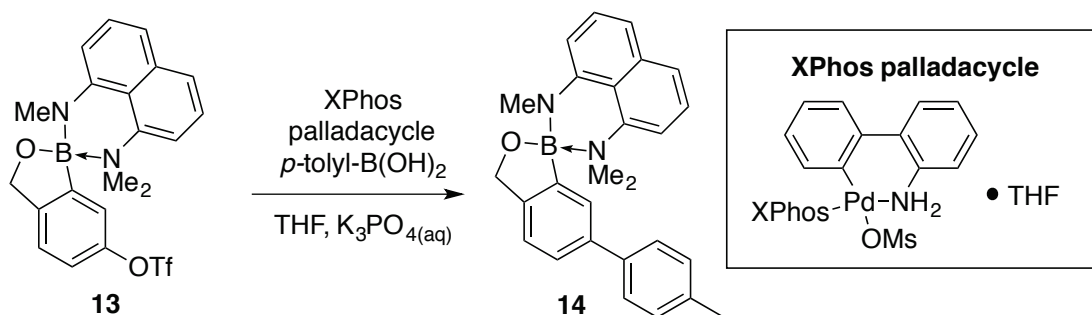
Synthesis of 11e from 1e. Compound **1e** (6-Benzyloxy-1,3-dihydro-1-hydroxy-2,1-benzoxaborole) (0.4 g, 1.61 mmol) and 1-dimethylamino-8-methylaminonaphthalene (0.96 g 4.8 mmol) was dissolved in DMSO (5 mL), to which was added toluene (20 mL). The reaction mixture was heated at reflux under Dean–Stark conditions for 12 h under $\text{N}_2(\text{g})$. The solution was concentration under reduced pressure, and the residue was purified by silica gel chromatography (98:1:1, DCM:MeOH:TEA) to give **11e** (99.5%) and quantitative re-isolation of **10**. $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 7.74 (d, $J=8$ Hz, 1H), 7.43 (t, $J=7$ Hz, 1H), 7.34 (t, $J=7$ Hz, 1H), 7.22 (m, 3H), 7.18 (d, $J=8$ Hz, 1H), 7.11 (m, 3H), 7.01 (d, $J=8$ Hz, 1H), 6.72 (dd, $J=8$, 2.5 Hz, 1H), 6.57 (d, $J=8$ Hz, 1H), 5.75 (bs, 1H), 5.15 (d, $J=13$ Hz, 1H), 5.06 (d, $J=13$ Hz, 1H), 4.59 (s, 2H), 2.85 (s, 3H), 2.84 (s 3H), 2.70 (s 3H). $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz) δ 157.04, 146.31, 143.25, 141.35, 136.95, 135.53, 128.68, 128.27, 128.21, 127.53, 127.51, 124.60, 120.63, 117.04, 114.09, 113.17, 112.46, 105.07, 72.03, 69.42, 49.68, 44.27, 31.92. $^{11}\text{B NMR}$ (CDCl_3 , 96 MHz) δ 8.83. HRMS (ESI) calcd. for $\text{C}_{27}\text{H}_{27}\text{BN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 422.2275, found 422.2261.



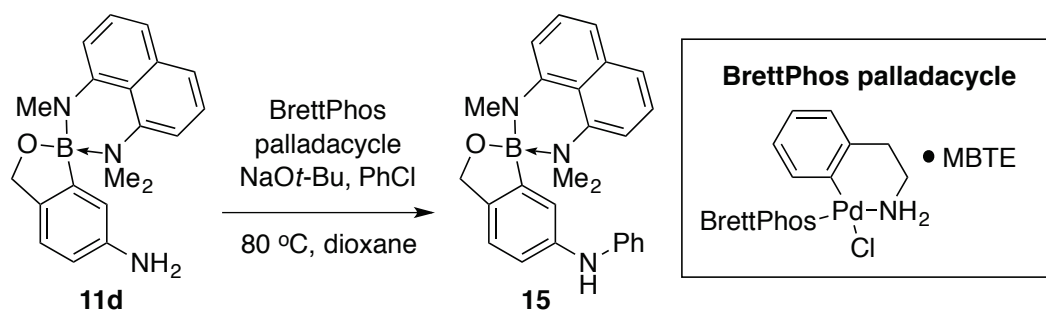
Synthesis of 12 from 11e. Compound **11e** (0.21 g, 0.5 mmol) was dissolved in 10 mL of 6:4 MeOH/EtOAc. To this solution under N₂(g) was added 10% Pd/C (0.1 g, 0.1 mmol Pd). The reaction mixture was purged with H₂(g) via a balloon, and the resulting slurry was stirred for 1 h. The reaction mixture was filtered through a sintered glass funnel, and concentrated under reduced pressure. The residue was then purified by silica gel chromatography (98:1:1 DCM:MeOH:TEA) to give **12** (86% based on re-isolated starting material). ¹H NMR (600 MHz, Methylene Chloride-d₂) δ 7.77 (d, *J*=8.2 Hz, 1H), 7.46–7.39 (m, 2H), 7.27 (d, *J*=7.6 Hz, 1H), 7.11 (d, *J*=7.9 Hz, 1H), 6.97 (d, *J*=8.1 Hz, 1H), 6.58 (t, *J*=7.7 Hz, 2H), 5.53–5.44 (bs, 1H), 5.08 (d, *J*=13.3 Hz, 1H), 5.01 (d, *J*=13.3 Hz, 1H), 2.86 (s, 3H), 2.82 (s, 3H), 2.73 (s, 3H). ¹³C NMR (126 MHz, CD₂Cl₂) δ 153.75, 146.23, 143.21, 140.97, 135.37, 128.38, 127.88, 124.41, 120.55, 116.92, 113.98, 112.70, 112.42, 104.61, 71.66, 49.48, 43.77, 31.29. ¹¹B NMR (CDCl₃, 96 MHz) δ 8.76. HRMS (ESI) calcd. for C₂₀H₂₁BN₂O₂ [M+H]⁺ 332.1806, found 332.1818.



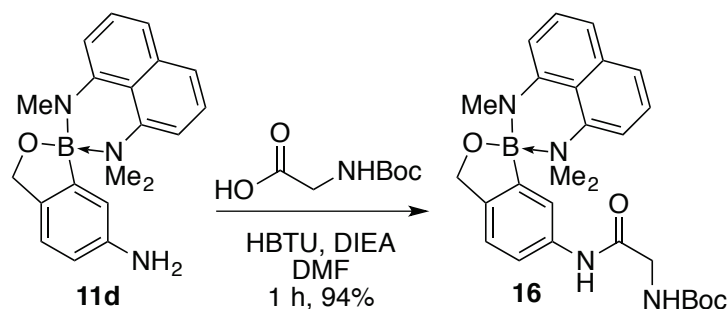
Synthesis of 13. To a solution of **12** (0.1 g, 0.3 mmol) and PhN(OTf)₂ (0.22 g, 0.6 mmol) in 10 mL of THF was added NaH as a 60% dispersion in mineral oil (0.120 g, 3.0 mmol). The reaction mixture was stirred for 1 h, diluted with DCM, and washed with sat. NaHCO₃(aq). The organic layer was dried over MgSO₄(s), concentrated under reduced pressure, and purified by silica gel chromatography (6:4 hexanes/EtOAc) to give **13** (77%) that was deemed of sufficient purity for the subsequent step. ¹H NMR (CDCl₃, 500 MHz) δ 7.80 (d, *J*=8.5 Hz, 1H), 7.47 (m, 1H), 7.39 (m, 1H), 7.21 (d, *J*=7.5 Hz, 1H), 7.16 (d, *J*=8 Hz, 1H), 7.14 (d, *J*=8 Hz, 1H), 6.97 (dd, *J*=8.5, 2 Hz, 1H), 6.62 (d, *J*=7.5 Hz, 1H), 5.80 (br s, 1H), 5.21 (d, *J*=14.5 Hz, 1H), 5.12 (d, *J*=14.5 Hz, 1H), 2.90 (s, 3H), 2.86 (s, 3H), 2.71 (s, 3H). ¹³C NMR (CDCl₃, 125 MHz) δ 163.6, 149.9, 148.9, 148.8, 146.2, 142.9, 138.4, 137.4, 135.9, 129.1, 128.9, 128.7, 128.5, 127.9, 127.8, 126.5, 125.5, 124.8, 124.6, 123.9, 123.0, 121.8, 121.3, 119.9, 117.4, 117.2, 116.7, 114.1, 112.9, 105.8, 72.3, 50.1, 45.6, 44.3, 34.6, 31.9. ¹¹B NMR (CDCl₃, 96 MHz) δ 8.63. HRMS (ESI) calcd. for C₂₁H₂₀BF₃N₂O₄S [M+H]⁺ 464.1284, found 464.1299.



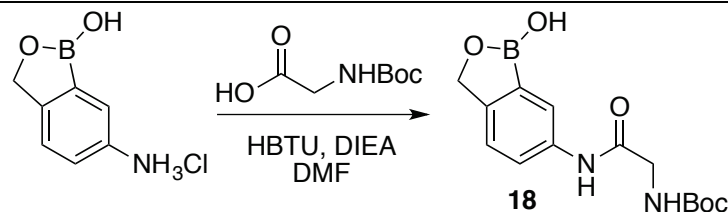
Synthesis of 14. To a solution of **13** (60 mg, 0.13 mmol), XPhos palladacycle (2.35 mg, 0.013 mmol), and *p*-tolylboronic acid (70 mg, 0.52 mmol) in 1 mL of degassed THF under N₂(g) was added 2 mL of degassed 0.5 M K₃PO₄. The reaction mixture was stirred overnight, and then partitioned between DCM and water. The organic layer was dried over MgSO₄(s), concentrated under reduced pressure, and purified by silica gel chromatography (7:3 hexanes/EtOAc) to give **14** (83%). ¹H NMR (CDCl₃, 500 MHz) δ 7.77 (d, *J*=8.5 Hz, 1H), 7.45 (m, 1H), 7.36 (m, 2H), 7.24 (m, 2H), 7.18 (d, *J*=8 Hz, 1H), 7.11 (d, *J*=8 Hz, 1H), 7.06 (br s, 3H), 6.61 (d, *J*=8 Hz, 1H), 6.39 (br s, 1H), 5.25 (d, *J*=14 Hz, 1H), 5.17 (d, *J*=14 Hz, 1H), 2.92 (s, 3H), 2.90 (s, 3H), 2.79 (s, 3H), 2.29 (s, 3H). ¹³C NMR (CDCl₃, 125 MHz) δ 148.3, 146.5, 143.5, 139.0, 138.7, 136.2, 135.8, 129.2, 128.9, 128.5, 128.4, 127.7, 127.2, 126.8, 126.8, 126.3, 124.6, 120.3, 117.3, 113.4, 112.5, 105.4, 72.5, 49.7, 44.7, 32.2, 14.2. ¹¹B NMR (CDCl₃, 96 MHz) δ 8.72. HRMS (ESI) calcd. for C₂₇H₂₇BN₂O [M+H] 406.2336, found 406.2326.



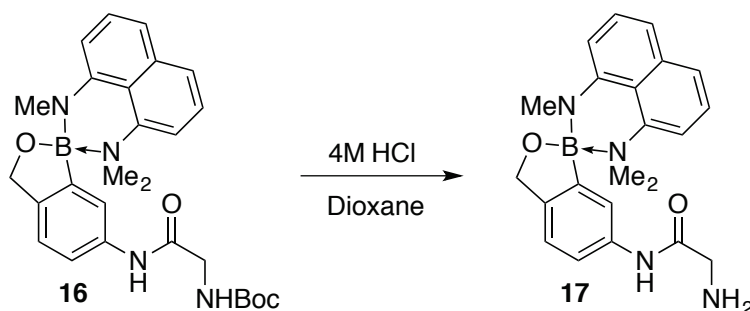
Synthesis of 15. Compound **11d** (0.1 g, 0.3 mmol), BrettPhos Palladacycle (2.4 mg, 3 μmol), and NaOt-Bu (58 mg, 0.6 mmol) were dissolved in 2 mL of dry, degassed dioxane under N₂(g). Chlorobenzene (35 mg, 0.31 mmol) was added, and the reaction mixture was sealed and heated at 80 °C for 3 h. The solution was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (60:39:1 hexanes/EtOAc/NEt₃) to give **15** (89%). ¹H NMR (CDCl₃, 750 MHz) δ 7.78 (d, *J*=8 Hz, 1H), 7.48 (dd, app t, *J*=8, 8 Hz, 1H), 7.41 (dd, app t, *J*=8, 8 Hz, 1H), 7.28 (dd, *J*=7.5 Hz, 1H), 7.13 (d, *J*=7.5 Hz, 1H), 7.10 (dd, app t, *J*=7.5, 7.5 Hz, 2H), 7.05 (d, *J*=8 Hz, 1H), 6.95 (d, *J*=7.5 Hz, 1H), 6.78 (dd, app t, *J*=7.5 Hz, 1H), 6.72 (d, *J*=8 Hz, 2H), 6.64 (d, *J*=8 Hz, 1H), 5.84 (br s, 1H), 5.33 (br s, 1H), 5.23 (d, *J*=13 Hz, 1H), 5.14 (d, *J*=13 Hz, 1H), 2.95 (s, 3H), 2.92 (s, 3H), 2.82 (s, 3H). ¹³C NMR (CDCl₃, 125 MHz) δ 146.7, 143.9, 143.6, 142.3, 140.5, 135.8, 129.1, 129.0, 128.6, 124.8, 120.6, 119.5, 118.9, 118.1, 115.9, 113.4, 112.6, 105.4, 72.5, 50.1, 44.3, 32.2. ¹¹B NMR (CDCl₃, 96 MHz) δ 9.07. HRMS (ESI) calcd. for C₂₆H₂₆BN₃O [M+H]⁺ 407.2279, found 407.2264.



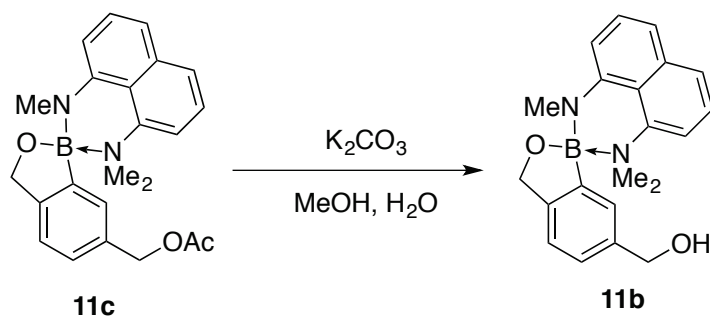
Synthesis of 16. Compound **11d** (0.1 g, 0.3 mmol), Boc-glycine (0.069 g, 0.39 mmol), and HBTU (0.15 g, 0.39 mmol) were dissolved in 4 mL of DMF. DIEA (0.16 g, 1.2 mmol) was added, and the reaction mixture was stirred for 1 h. The solution was concentrated under reduced pressure, and the residue was dissolved in DCM and extracted with sat. NaHCO₃(aq) (2×) and water (2×). The organic layer was dried over Na₂SO₄(s) and concentrated under reduced pressure. The residue was purified by silica gel chromatography (96:4, DCM:MeOH) to give **16** (94%). ¹H NMR (CDCl₃, 500 MHz) δ 7.77 (d, *J*=8 Hz, 1H), 7.66 (dd, *J*=8, 1 Hz, 1H), 7.47 (dd, app t, *J*=8, 8 Hz, 1H), 7.39 (dd, app t, *J*=8, 8 Hz, 1H), 7.23 (d, *J*=7.5 Hz, 1H), 7.11 (dd, *J*=11.5, 8 Hz, 2H), 6.60 (d, *J*=7.5 Hz, 1H), 5.81 (br s, 1H), 5.18 (d, *J*=14 Hz, 1H), 5.10 (d, *J*=14 Hz, 1H), 3.72 (m, 2H), 2.89-2.75 (isomeric Me, 9H), 1.40 (br s, 9H). ¹³C NMR (CDCl₃, 125 MHz) δ 167.2, 155.4, 146.5, 145.7, 143.4, 135.9, 135.1, 129.1, 128.7, 125.0, 120.8, 120.2, 119.9, 117.3, 113.5, 112.8, 105.4, 80.5, 72.5, 50.2, 45.1, 44.5, 38.8, 32.2, 28.4. ¹¹B NMR (CDCl₃, 96 MHz) δ 8.95. HRMS (ESI) calcd. for C₂₇H₃₃BN₄O₄ [M+H] 488.2704, found 488.2721.



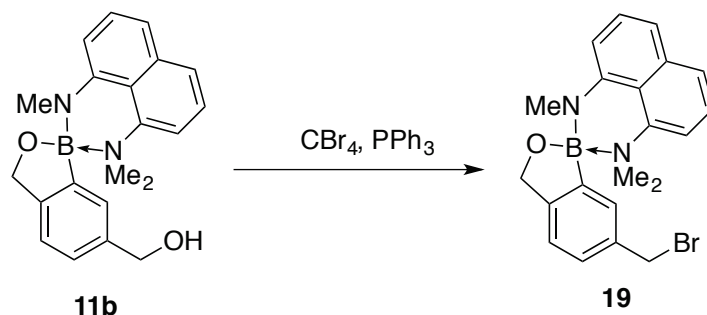
Synthesis of 18. 5-Amino-2-hydroxymethylphenylboronic acid HCl salt (0.056 g, 0.3 mmol), Boc-glycine (0.069 g, 0.39 mmol), and HBTU (0.15 g, 0.39 mmol) were dissolved in 4 mL of DMF. DIEA (0.16 g, 1.2 mmol) was added, and the reaction mixture was stirred for 1 h. The solution was concentrated under reduced pressure, and the residue was dissolved in DCM and extracted with 0.05 M HCl (2×). The organic layer was dried over Na₂SO₄(s) and concentrated under reduced pressure. The residue was purified by silica gel chromatography (93:6:1, DCM:MeOH:HCO₂H) to give **16-unprotected** (23%). ¹H NMR (CD₃OD, 500 MHz) δ 7.80 (d, *J*=1.5 Hz, 1H), 7.67 (dd, *J*=8.5, 2 Hz, 1H), 7.34 (d, *J*=8 Hz, 1H), 5.04 (s, 2H), 3.86 (s, 2H), 1.47 (s, 9H). ¹³C NMR (CD₃OD, 125 MHz) δ 170.7, 158.8, 151.1, 138.8, 124.7, 122.8, 122.7, 80.9, 72.3, 45.1, 28.9. ¹¹B NMR (MeOD-*d*₄, 96 MHz) δ 31.13. HRMS (ESI) calcd. for C₉H₉BN₄O₃ [M-H] 304.1350, found 304.1363.



Synthesis of 17. Compound **16** (0.120 g, 0.25 mmol) was dissolved in 3 mL of 4 M HCl in anhydrous dioxane, and the reaction mixture was stirred for 30 min. The solution was concentrated under reduced pressure, and the residue was suspended in 30 mL of DCM, washed with 10% NaOH (2×), dried over Na₂SO₄(s), and evaporated to dryness. The residue was purified by silica gel chromatography (85:14:1, DCM:MeOH:NEt₃) to give **17** (78%). ¹H NMR (CDCl₃, 500 MHz) δ 8.77 (br s, 1H), 7.78 (d, *J*=8.5 Hz, 1H), 7.72 (dd, *J*=8.5, 2 Hz, 1H), 7.47 (dd, app t, *J*=8, 8 Hz, 1H), 7.39 (dd, app t, *J*=8, 8 Hz, 1H), 7.24 (d, *J*=7.5 Hz, 1H), 7.13 (dd, *J*=7.5, 2.5 Hz, 2H), 6.62 (d, *J*=8 Hz, 1H), 6.04 (br s, 1H), 5.20 (d, *J*=13.5 Hz, 1H), 5.11 (d, *J*=13.5 Hz, 1H), 3.26 (s, 2H), 2.90 (s, 3H), 2.88 (s, 3H), 2.78 (s, 2H), 1.65 (br s, 2H). ¹³C NMR (CDCl₃, 125 MHz) δ 170.5, 146.4, 145.3, 143.4, 135.8, 135.6, 128.9, 128.5, 124.8, 120.6, 119.8, 119.6, 117.1, 113.3, 112.7, 105.2, 72.4, 49.8, 45.8, 45.1, 44.8, 32.3. ¹¹B NMR (CDCl₃, 96 MHz) δ 9.13. HRMS (ESI) calcd. for C₂₂H₂₅BN₄O₂ [M+H] 388.2180, found 388.2198.



Synthesis of 11b from 11c. Compound **11c** (0.730 g, 1.88 mmol) was dissolved in 18 mL of MeOH, and 18 mL of sat. K₂CO₃(aq) was added. The resulting slurry was stirred overnight. The solution was concentrated under reduced pressure, and the residue was extracted with DCM (3×), dried over Na₂SO₄(s), and concentrated under reduced pressure. The residue was purified by silica gel chromatography (95:5 DCM/MeOH) to give **11b** (80%).



Synthesis of 19. Compound **11b** (0.02 mg, 0.058 mmol) was dissolved in DCM (0.6 mL), and the resulting solution was cooled to 0 °C. Triphenylphosphine (0.023 mg, 0.088 mmol) and CBr_4 (0.029 mg, 0.088 mmol) were added, and the reaction mixture was allowed to warm to room temperature and stirred for 12 h. The solution was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (96.5:2.5:1 DCM/MeOH/ NEt_3) to give **18** (91%). $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.78 (d 1H), 7.47 (t 1H), 7.39 (t 1H), 7.22 (d 1H), 7.17 (bd 1H), 7.14 (d 2H), 7.10 (d 2H), 6.60 (d 2H), 6.11 (d 1H), 5.19 (d 1H), 5.10 (d 1H), 4.16 (s 2H), 2.89 (bs 3H), 2.86 (s 3H), 2.73 (s 3H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ 146.46, 143.39, 135.87, 135.52, 129.31, 129.02, 128.73, 128.58, 127.48, 124.89, 120.66, 119.37, 117.28, 113.53, 112.70, 105.44, 72.57, 50.11, 44.60, 35.01. $^{11}\text{B NMR}$ (CDCl_3 , 96 MHz) δ 8.91. HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{22}\text{BBrN}_2\text{O}$ $[\text{M}+\text{H}]^+$ 408.1118, found 408.1126.

NMR SPECTRA

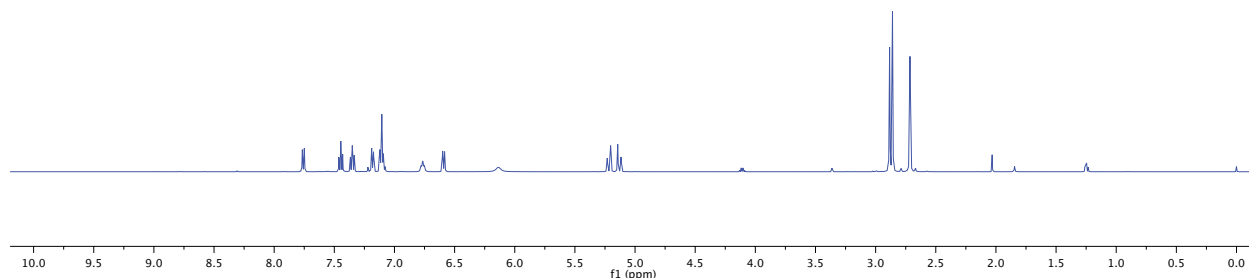


Fig. S3 ^1H NMR spectrum of **11a** in CDCl_3 (500 MHz)

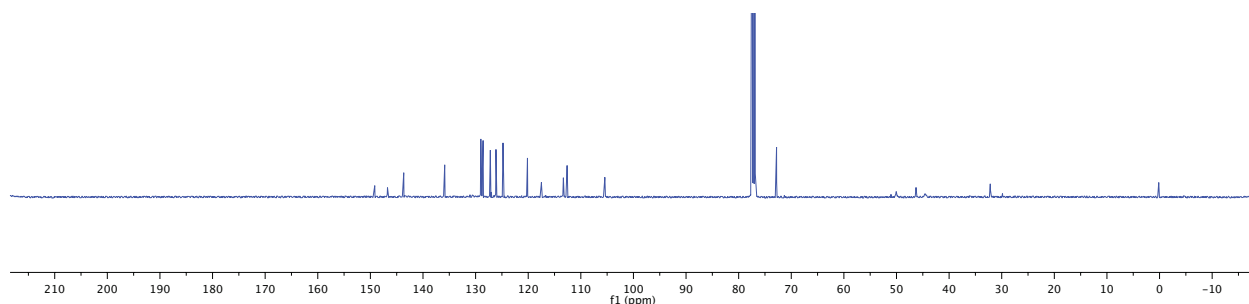


Fig. S4 ^{13}C NMR spectrum of **11a** in CDCl_3 (125 MHz)

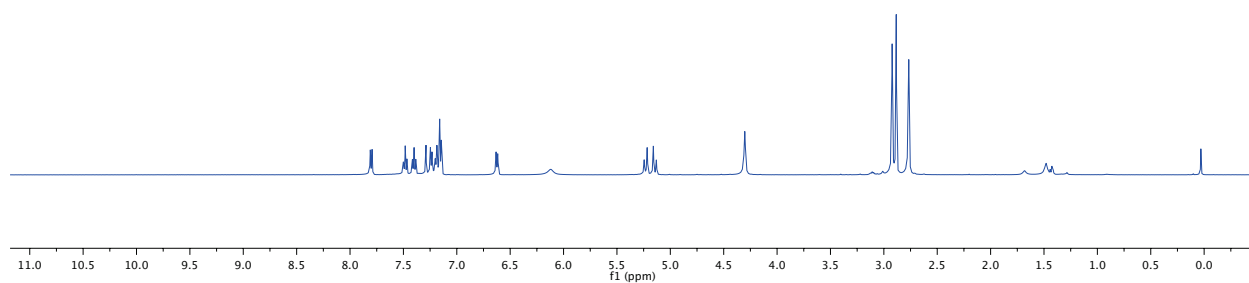


Fig. S5 ^1H NMR spectrum of **11b** in CDCl_3 (500 MHz).

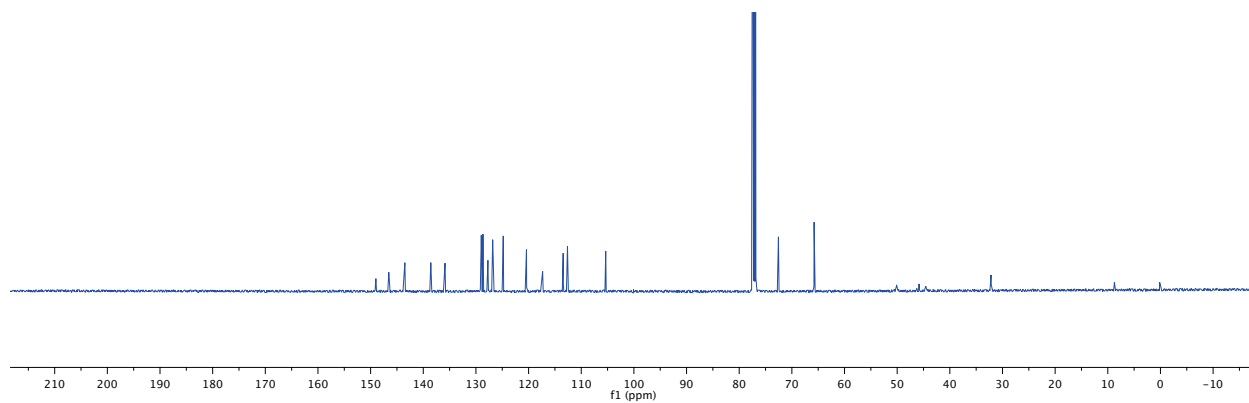


Fig. S6 ^{13}C NMR spectrum of **11b** in CDCl_3 (125 MHz).

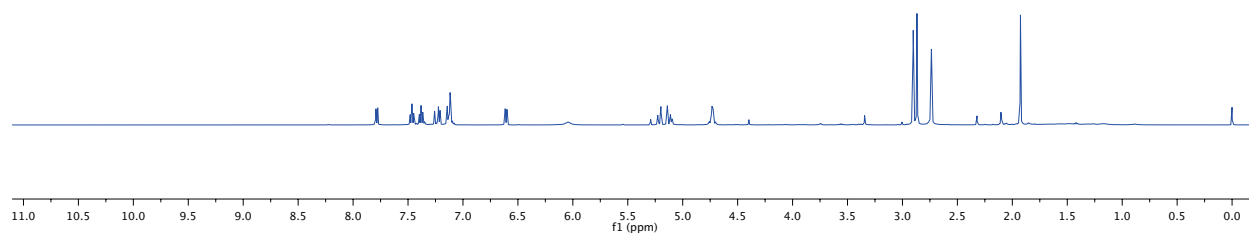


Fig. S7 ^1H NMR spectrum of **11c** in CDCl_3 (500 MHz).

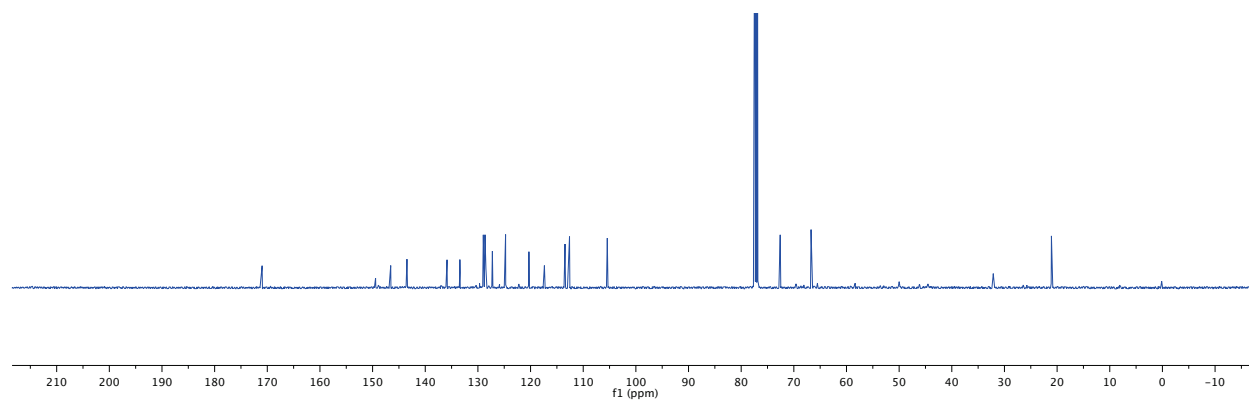


Fig. S8 ^{13}C NMR spectrum of **11c** in CDCl_3 (125 MHz).

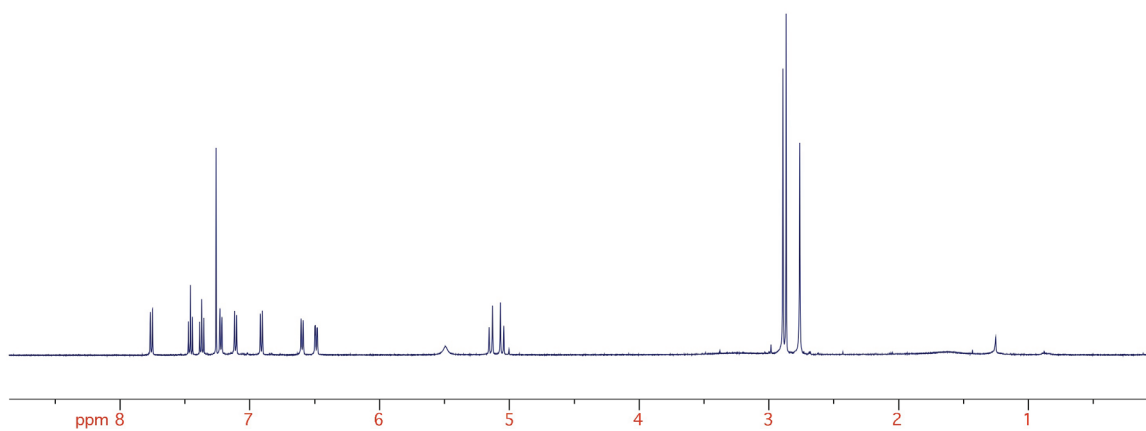


Fig. S9 ^1H NMR spectrum of **11d** in CDCl_3 (500 MHz).

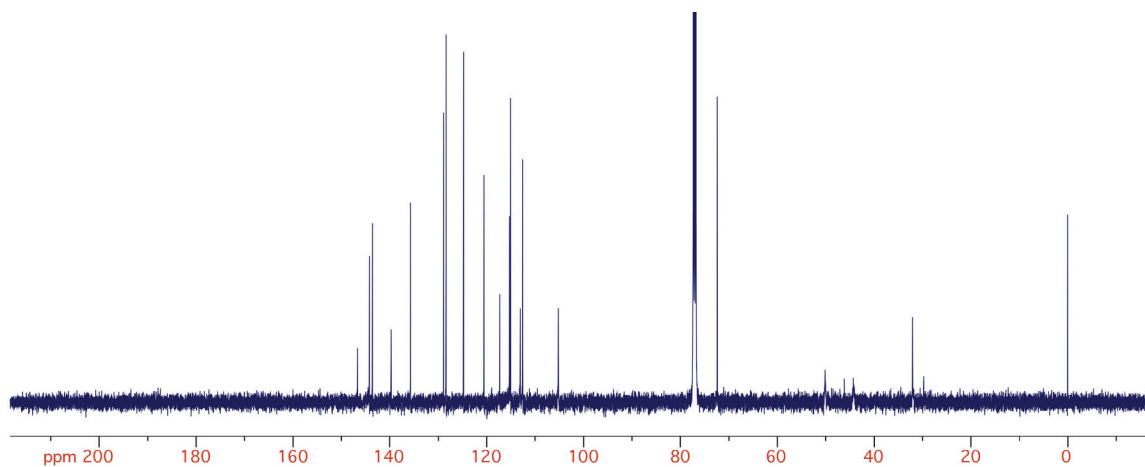


Fig. S10 ^{13}C NMR spectrum of **11d** in CDCl_3 (125 MHz).

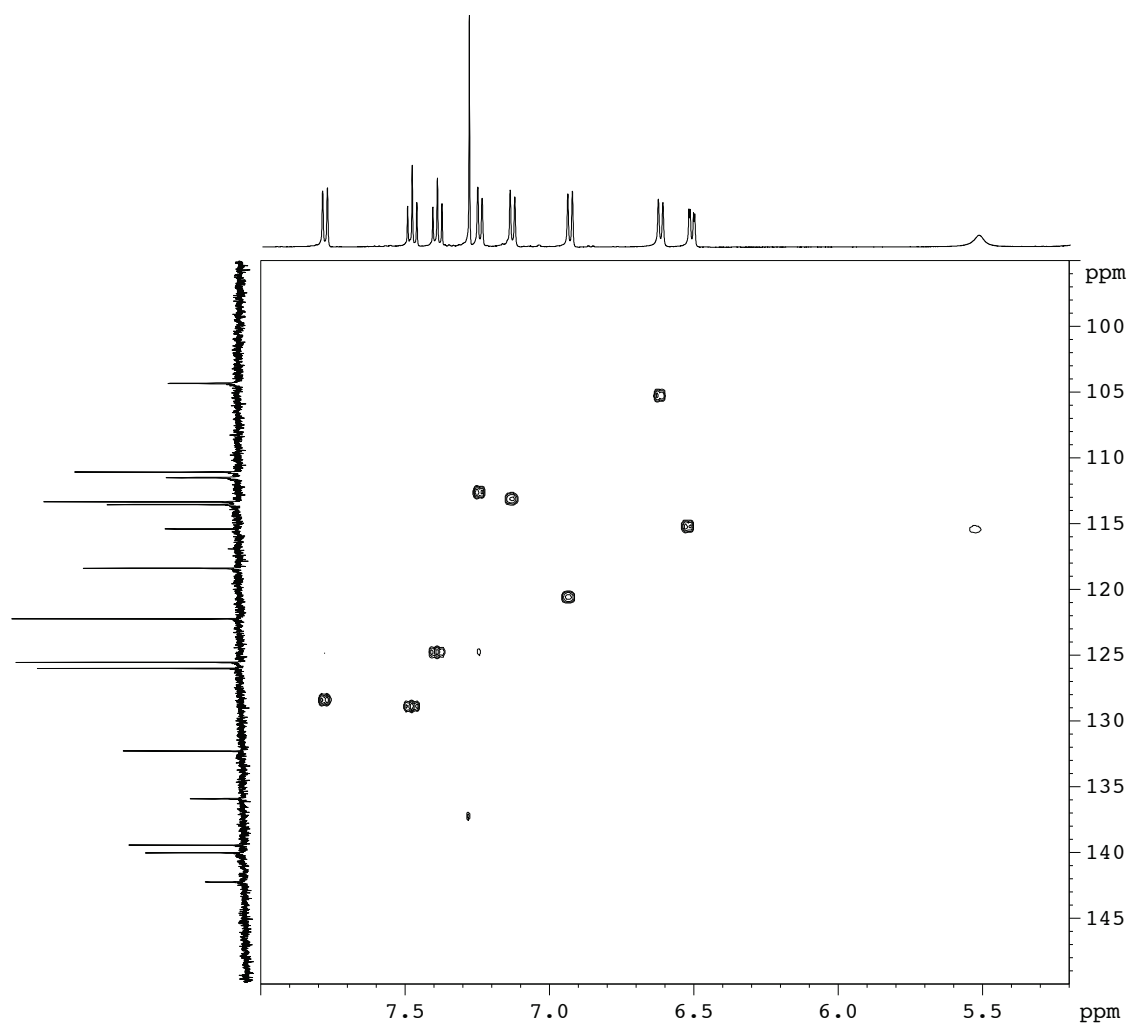


Fig. S11 ^1H - ^{13}C HSQC 2D NMR spectrum of **11d** in CDCl_3 (500 MHz).

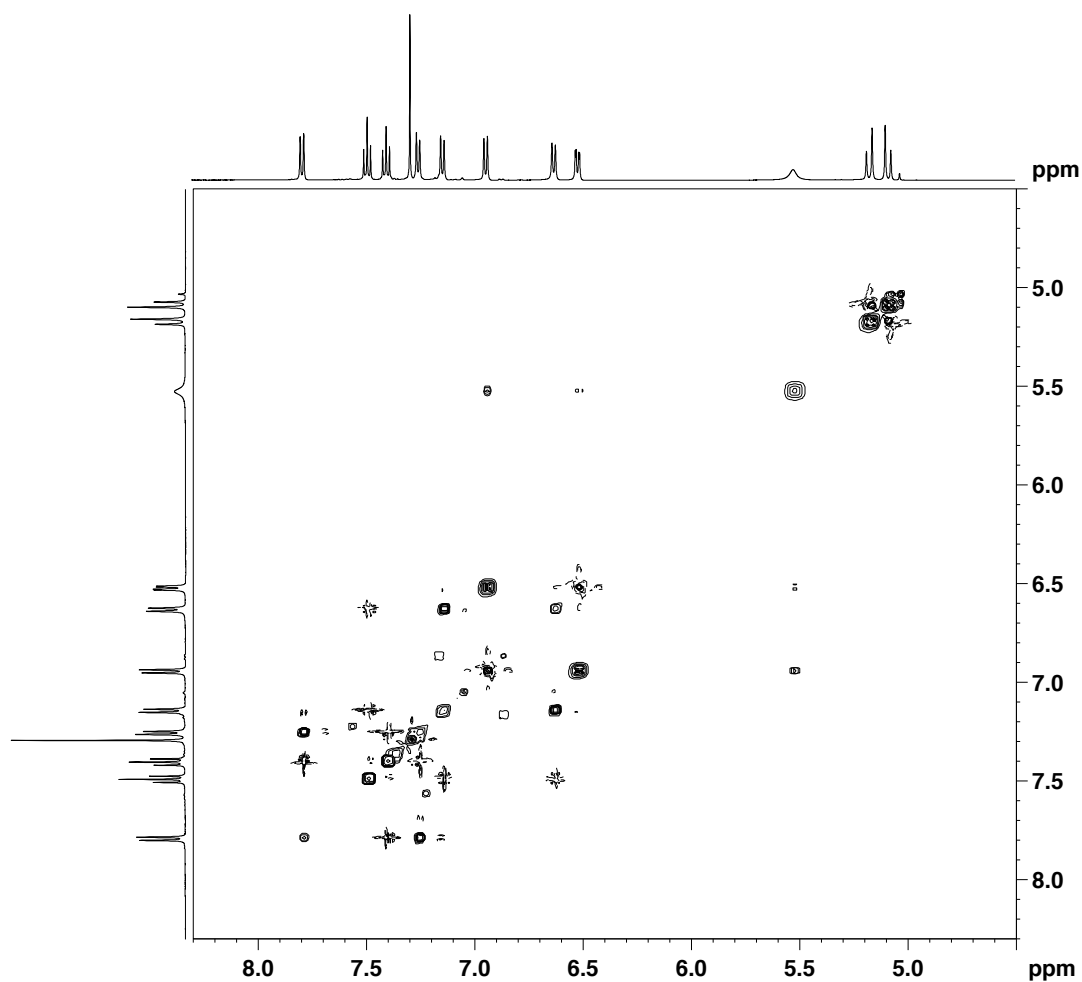


Fig. S12 ¹H-¹H TOCSY 2D NMR spectrum of **11d** in CDCl₃ (500 MHz)

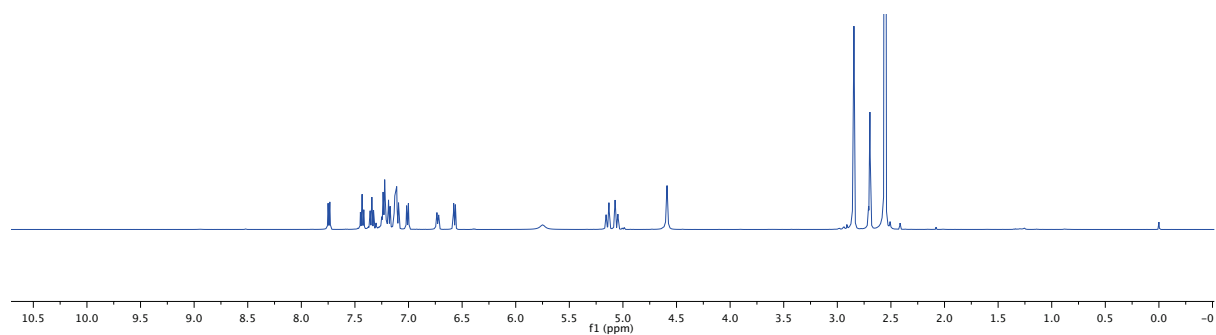


Fig. S13 ¹H NMR spectrum of **11e** in CDCl₃ (500 MHz).

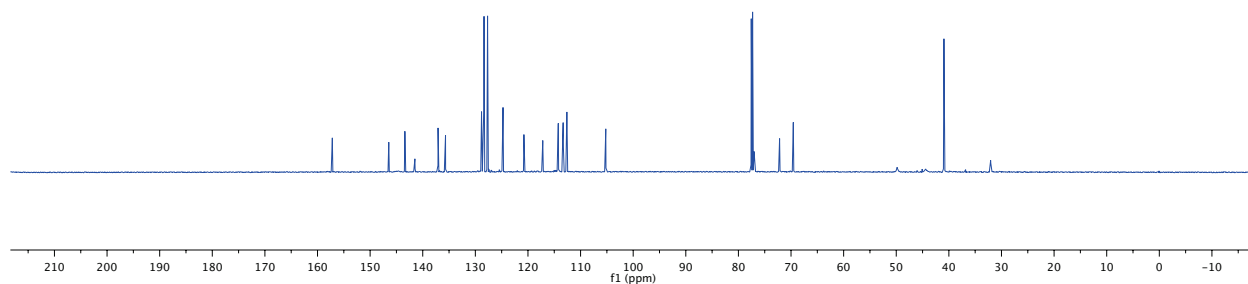


Fig. S14 ^{13}C NMR spectrum of **11e** in CDCl_3 (125 MHz).

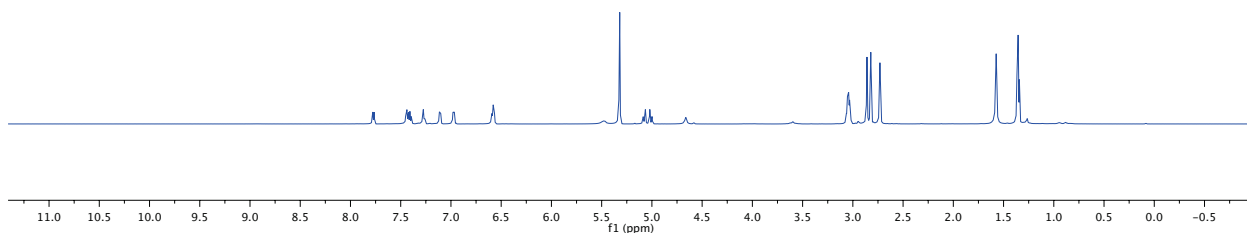


Fig. S15 ^1H NMR spectrum of **12** in CD_2Cl_2 (600 MHz).

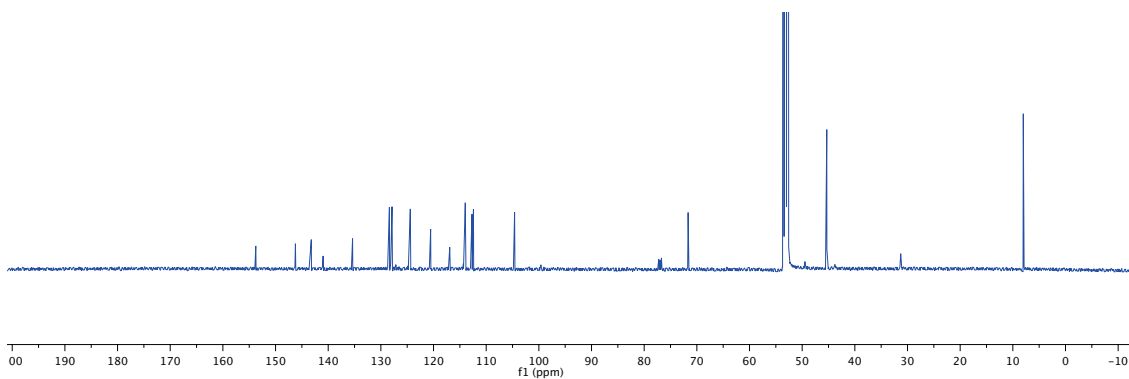


Fig. S16 ^{13}C NMR spectrum of **12** in CD_2Cl_2 (125 MHz).

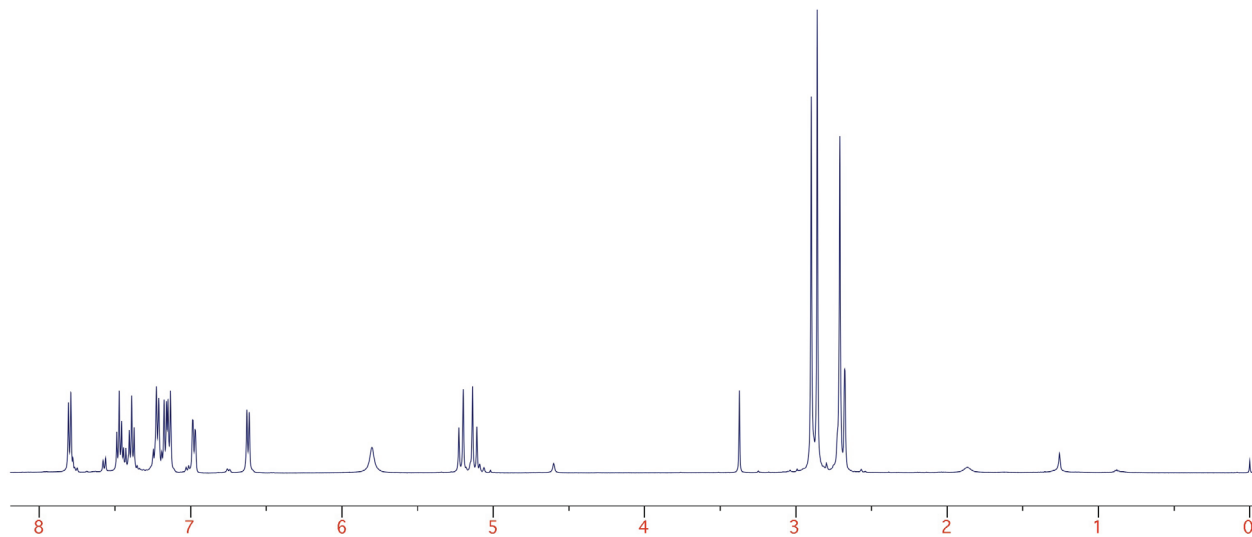


Fig. S17 ^1H NMR spectrum of **13** in CDCl_3 (750 MHz).

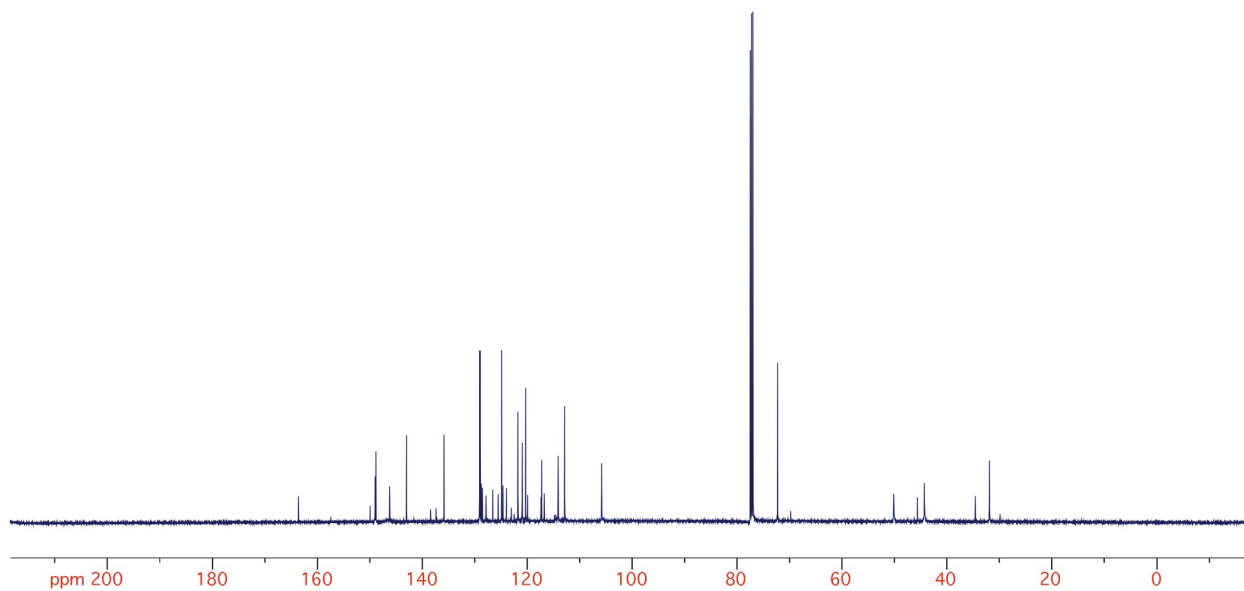


Fig. S18 ^{13}C NMR spectrum of **13** in CDCl_3 (125 MHz).

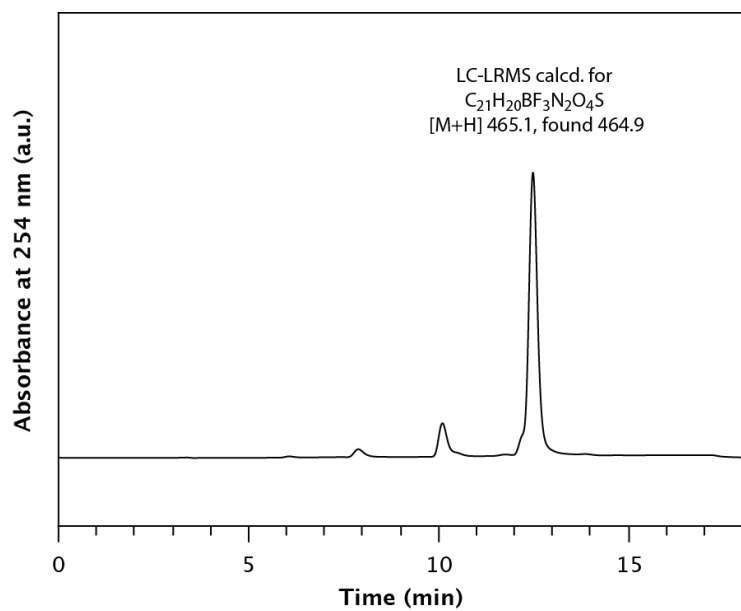


Fig. S19 LC-LRMS trace of **13**.

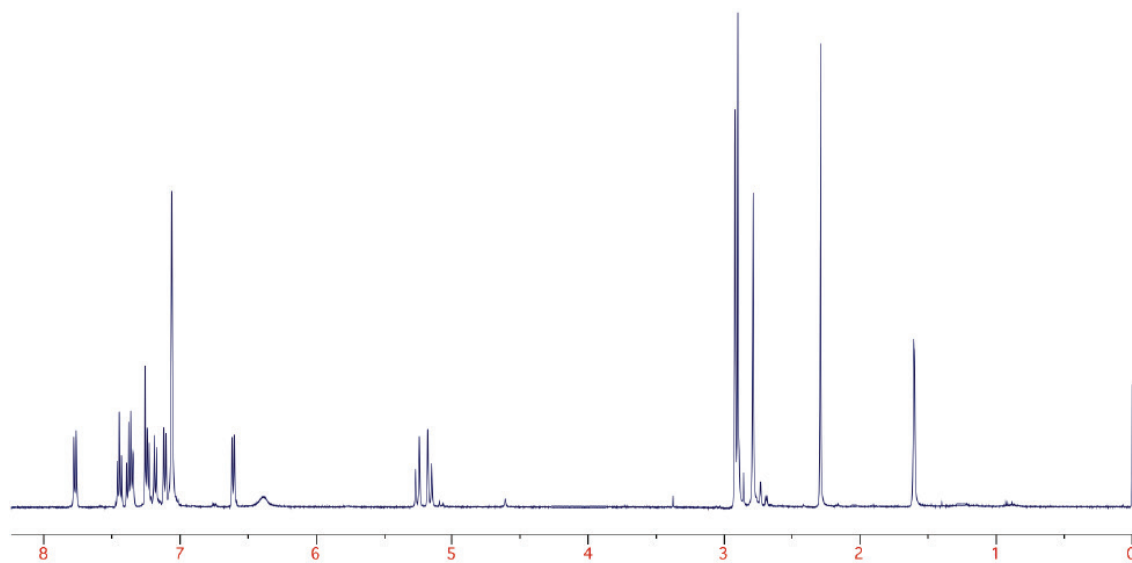


Fig. S20 1H NMR spectrum of **14** in $CDCl_3$ (750 MHz).

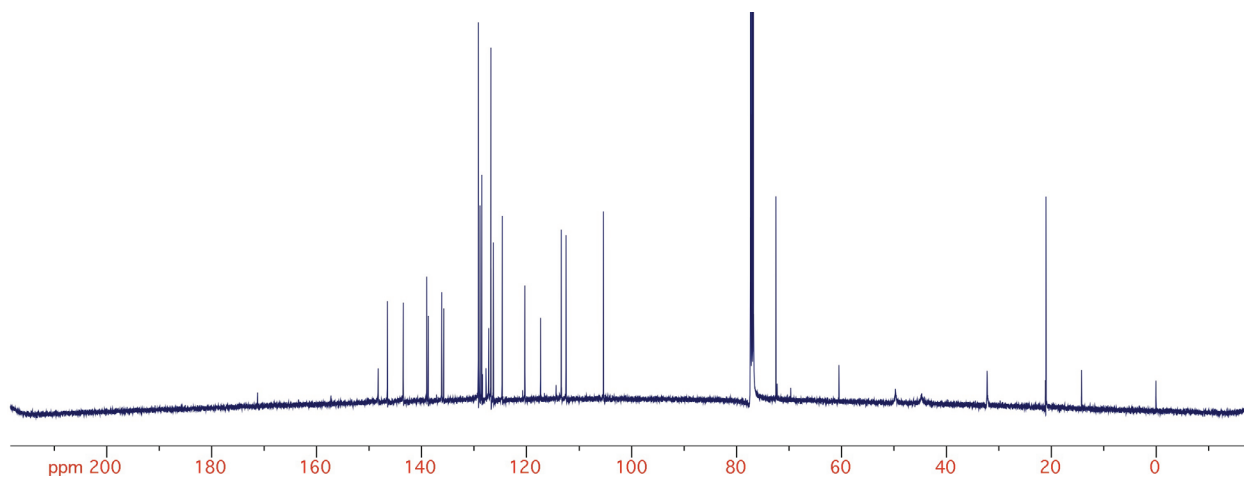


Fig. S21 ^{13}C NMR spectrum of **14** in CDCl_3 (125 MHz).

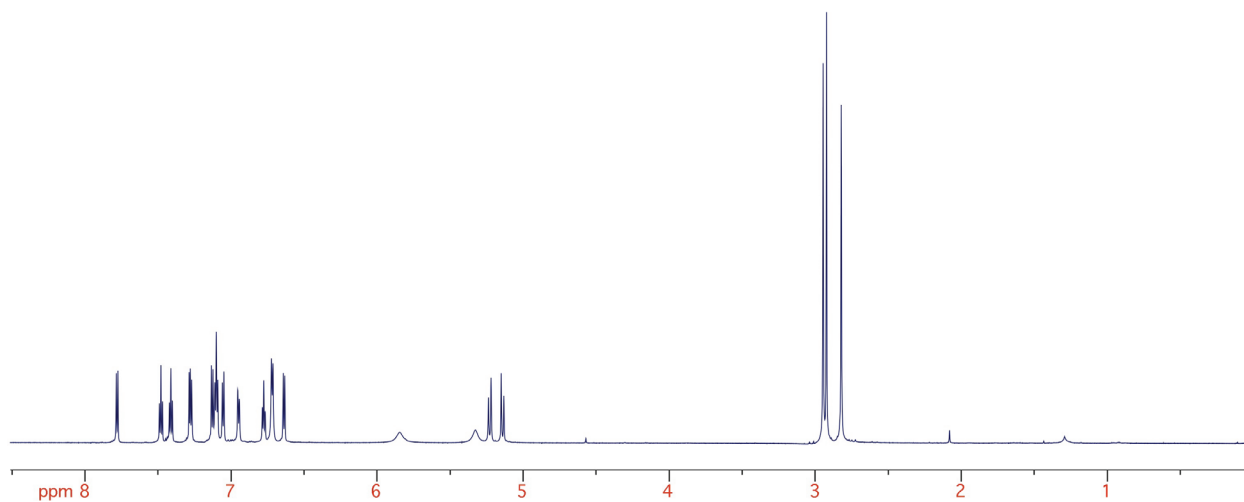


Fig. S22 ^1H NMR spectrum of **15** in CDCl_3 (750 MHz).

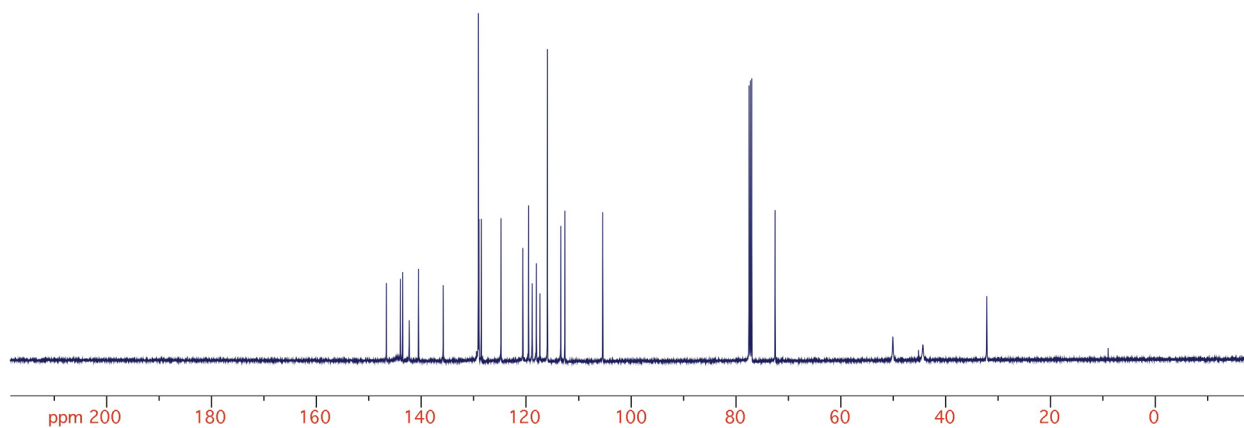


Fig. S23 ^{13}C NMR spectrum of **15** in CDCl_3 (125 MHz).

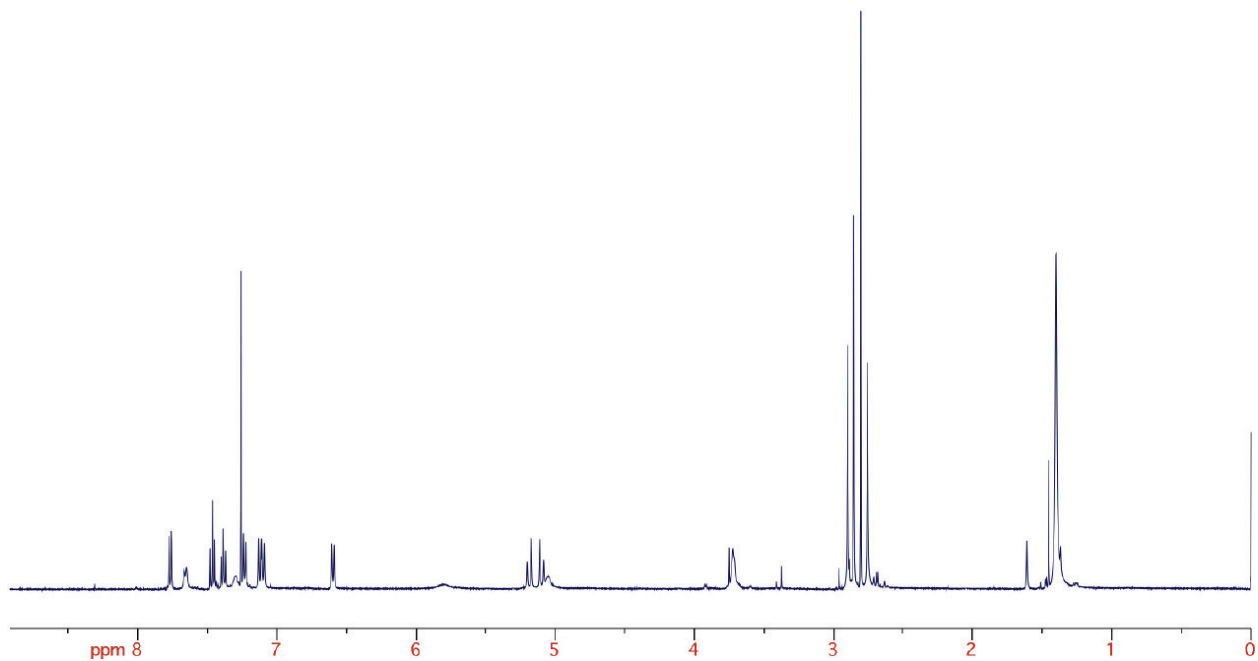


Fig. S24 ^1H NMR spectrum of **16** in CDCl_3 (500 MHz).

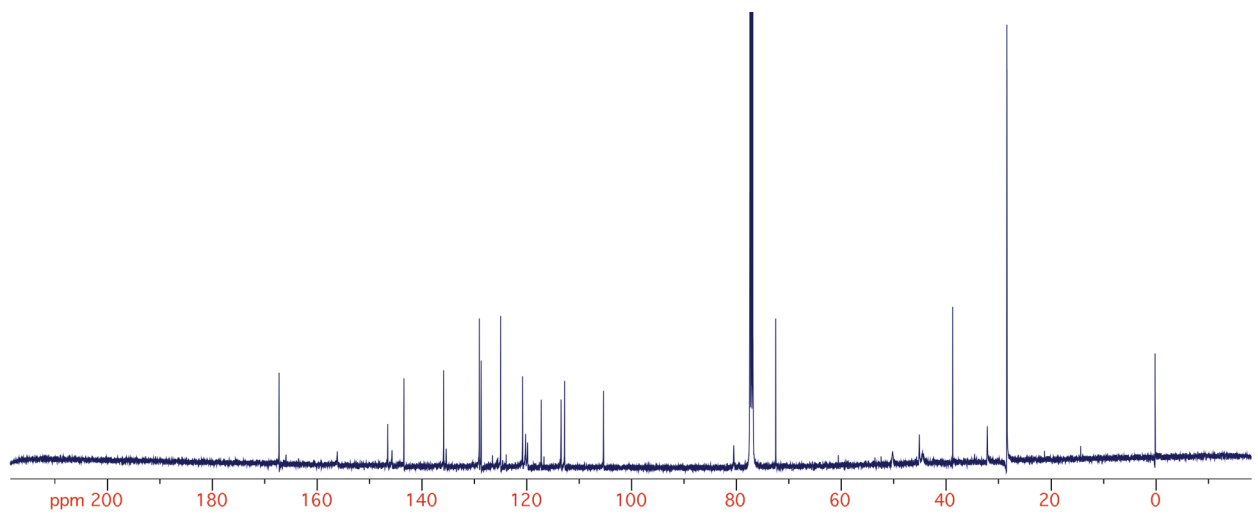


Fig. S25 ^{13}C NMR spectrum of **16** in CDCl_3 (125 MHz).

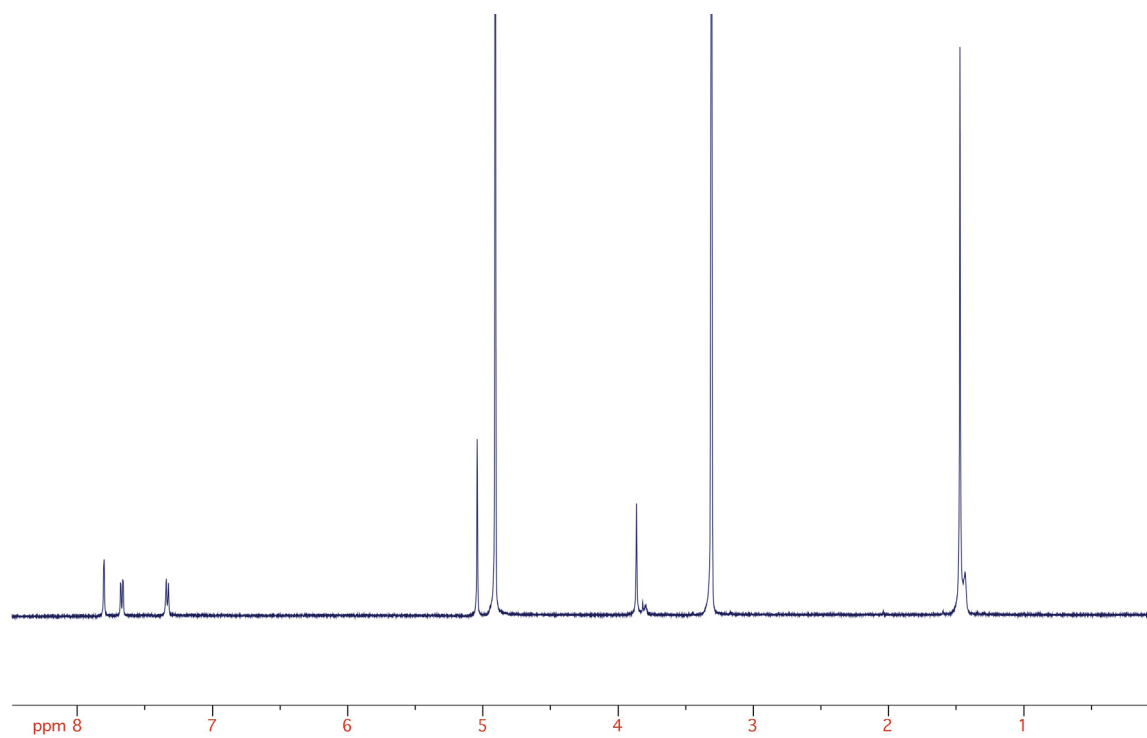


Fig. S26 ^1H NMR spectrum of **18** in CDCl_3 (500 MHz).

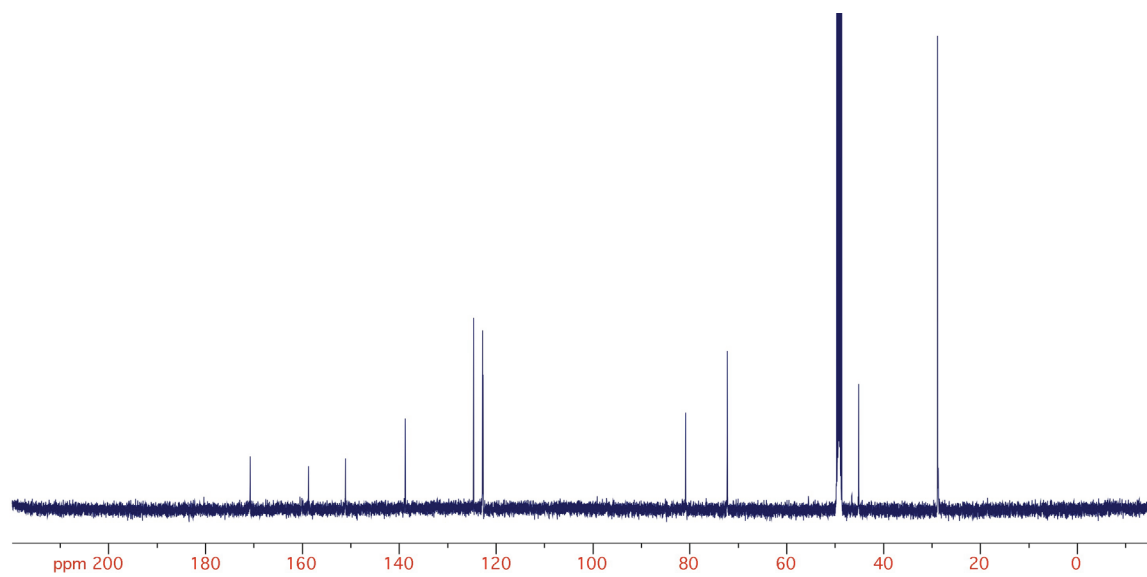


Fig. S27 ^{13}C NMR spectrum of **18** in CDCl_3 (125 MHz).

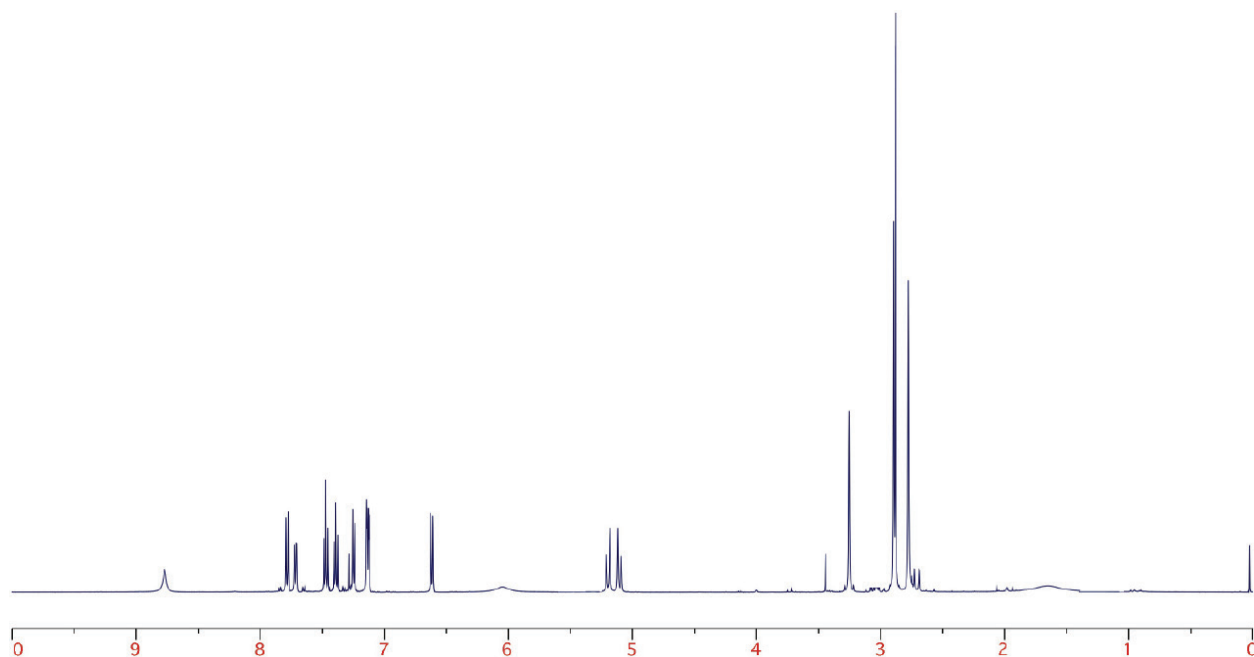


Fig. S28 ^1H NMR spectrum of **17** in CDCl_3 (500 MHz).

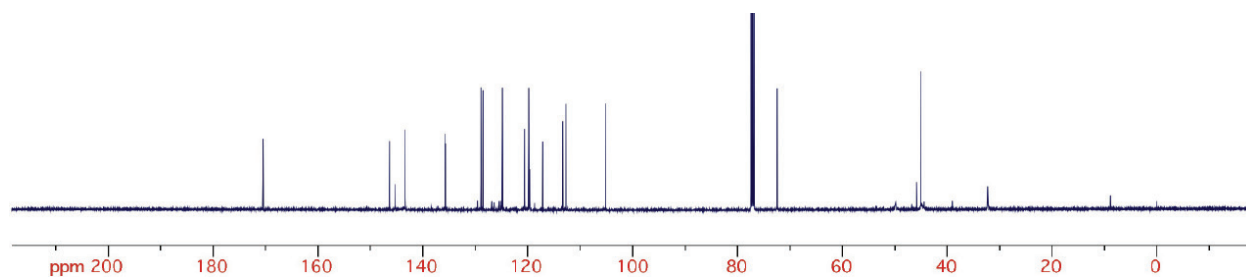


Fig. S29 ^{13}C NMR spectrum of **17** in CDCl_3 (125 MHz).

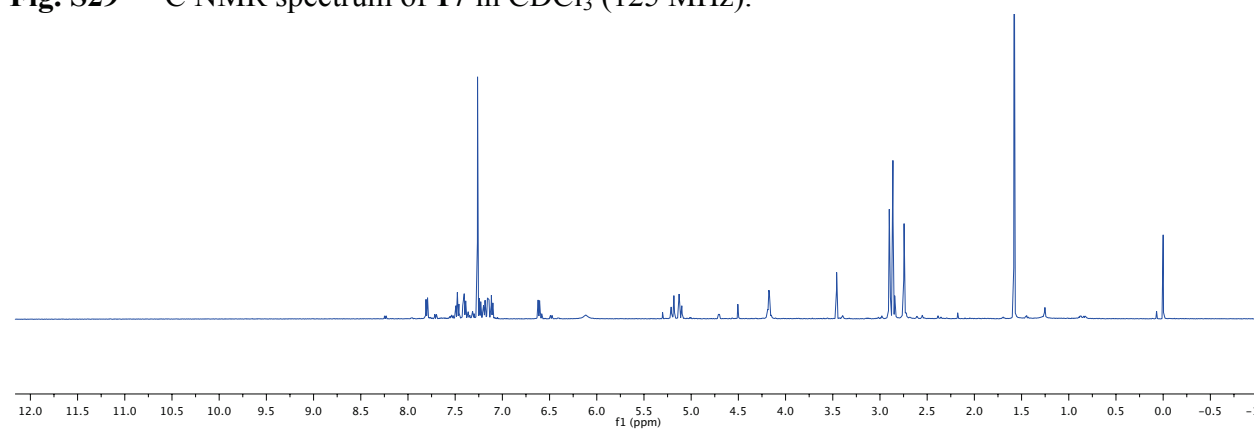


Fig. S30 ^1H NMR spectrum of **19** in CDCl_3 (500 MHz).

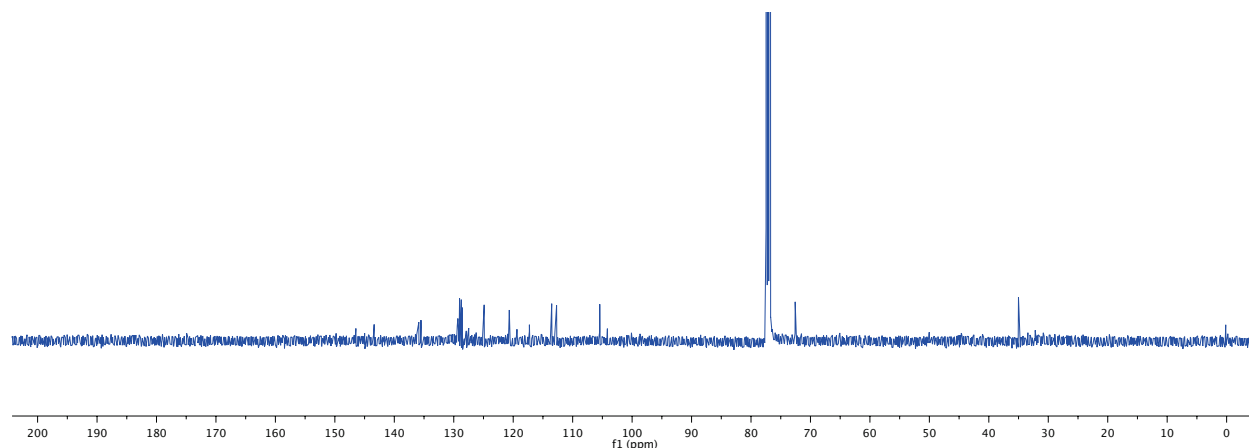
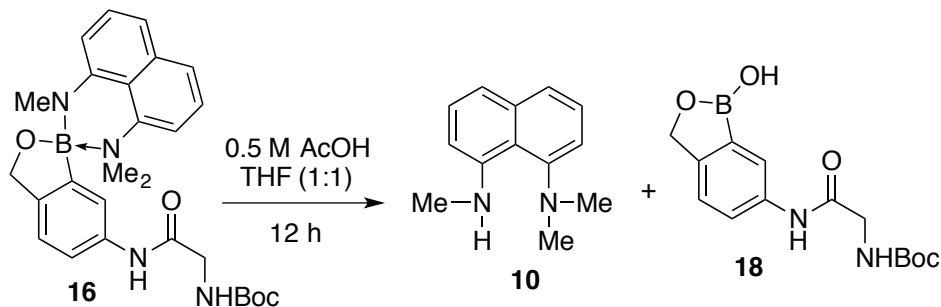


Fig. S31 ^{13}C NMR spectrum of **19** in CDCl_3 (125 MHz).



Synthesis of 18 from 16. Compound **16** (10 mg, 20 μmol) was dissolved in 2 mL of 0.5 1:1 AcOH/THF, and the resulting solution was stirred for 12 h. The solution was concentrated under reduced pressure, and the residue was dissolved in methanol- d_4 for analysis by ^1H NMR spectroscopy (see: Fig. S32). Compounds **10** and **18** were subjected to the same conditions as was compound **16**, for comparison.

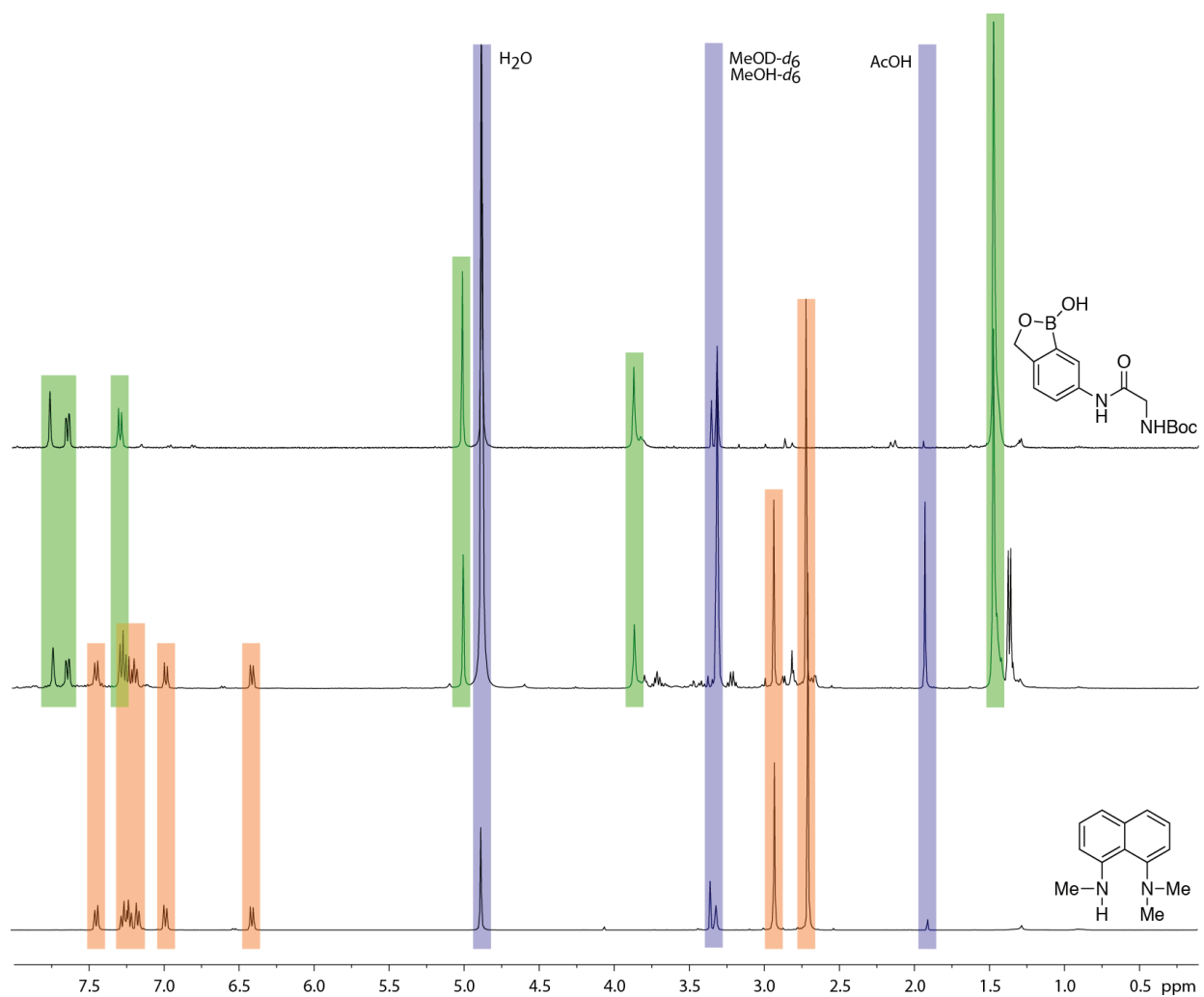
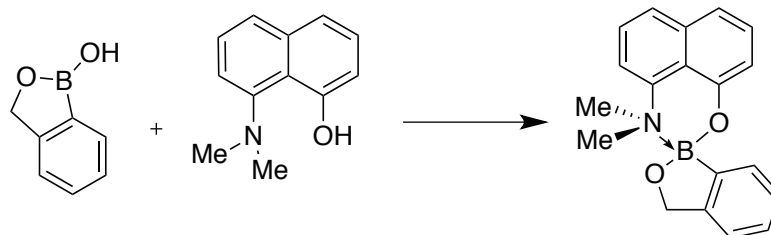


Fig. S32 ¹H NMR spectra (MeOD-*d*₆, 400 MHz) comparing compound **18** (top), compound **10** (bottom), and the reaction products from compound **16** (middle; for experimental details, see: page S24). Colored bars (**18**, green; **10**, orange; solvent, blue) are used to indicate that the expected products are indeed present.

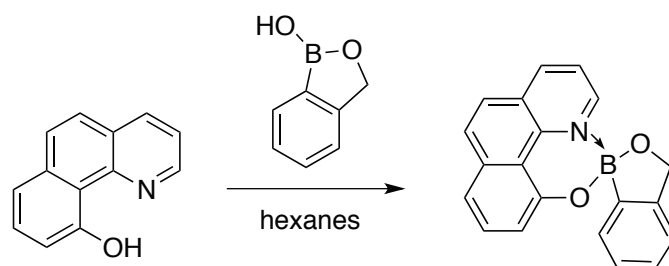
Table S1 Photophysical Data for Compound **11a**

abs λ_{\max} (nm) ^a	em λ_{\max} (nm) ^a	log ϵ	Φ_F
366	424	3.24	0.45

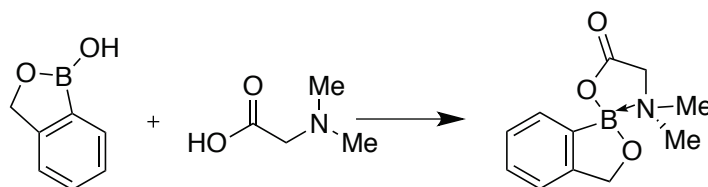
^a In CHCl₃.



Protection of 1a with 19: 8-(dimethylamino)naphthalen-1-ol (0.427 mmol, 80 mg) and benzoxaborole (0.5127 mmol, 69 mg) were dissolved in toluene (20 mL) and heated at reflux with azeotropic removal of water overnight. The reaction mixture was then concentrated *in vacuo*, and the solid was dissolved in chloroform and washed with aqueous base (10% NaOH) to yield MRA 086 as a white precipitate (72%). ^1H NMR (500 MHz, CDCl_3) δ 7.90–7.85 (m, 1H), 7.53–7.44 (m, 2H), 7.36–7.32 (m, 2H), 7.10 (dd, $J = 7.5, 1.2$ Hz, 1H), 6.85 (dd, $J = 7.6, 1.2$ Hz, 1H), 6.12 (bs, 1H), 5.28 (d, $J = 14.0$ Hz, 1H), 5.11 (d, $J = 14.1$ Hz, 1H), 3.03 (s, 3H), 2.84 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 156.87, 150.04, 143.06, 135.42, 129.00, 127.84, 126.79, 126.26, 125.69, 125.20, 120.67, 118.64, 116.90, 113.97, 110.02, 72.55, 49.35, 46.47. HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{18}\text{BNO}_2$ $[\text{M}+\text{Na}]^+$ 325.1360, found 325.1367.



Protection of 1a with 26: Following a previous literature procedure,⁴ benzoxaborole (1 mmol, 134 mg) and 10-hydroxybenzo[h]quinoline (1 mmol, 195 mg) were stirred in dry hexanes for 2 h. The resulting precipitate was filtered, and rinsed with hexanes. ^1H NMR (500 MHz, CDCl_3) δ 8.49–8.42 (m, 2H), 7.99 (d, $J = 8.9$ Hz, 1H), 7.78 (t, $J = 7.9$ Hz, 1H), 7.74 (d, $J = 9.0$ Hz, 1H), 7.64 (dd, $J = 7.9, 5.6$ Hz, 1H), 7.52–7.48 (m, 1H), 7.38 (dd, $J = 8.0, 0.9$ Hz, 1H), 7.31–7.28 (m, 2H), 7.19 (d, $J = 7.2$ Hz, 1H), 7.13–7.09 (m, 1H), 5.35 (d, $J = 14.0$ Hz, 1H), 5.18 (d, $J = 13.9$ Hz, 1H). ^{13}C NMR (125 MHz, CDCl_3): δ 159, 155.9, 148.8, 142.3, 139.6, 134.5, 132.8, 130.6, 128.4, 127.8, 126.5, 123.4, 121.5, 120.8, 117.9, 116.9, 72.3. HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{14}\text{BNO}_2$ $[\text{M}+\text{Na}]^+$ 333.1047, found 333.1031.



Protection of 1a with 28: Benzoxaborole (1.25 mmole, 167 mg) and N,N-dimethylglycine (1.25 mmole, 129 mg) were dissolved in methanol (5 mL) in a sealed vial, heated at reflux for 1.5 h, and then concentrated. The viscous solid was then dissolved in THF (5 mL), heated at reflux for 1 h, and concentrated under reduce pressure to a white solid (quant.). ^1H NMR (500

MHz, CDCl₃) δ 7.48 (d, $J = 7.2$ Hz, 1H), 7.37–7.32 (t, $J = 7.2$, 1H), 7.29–7.22 (m, 2H), 5.07 (d, $J = 14.0$ Hz, 1H), 5.01 (d, $J = 14.0$ Hz, 1H), 3.83 (d, $J = 15.2$ Hz, 1H), 3.50 (d, $J = 15.1$ Hz, 1H), 2.74 (s, 3H), 2.63 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 169.54, 150.52, 130.03, 128.55, 126.45, 120.88, 71.74, 60.95, 47.57, 44.82.

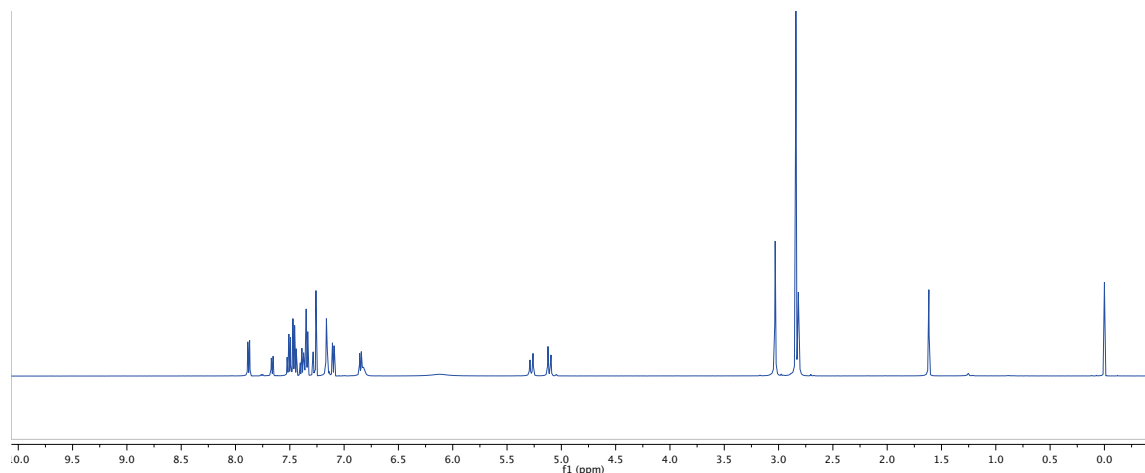


Fig. S32: ¹H NMR spectrum of the complex of **1a** and **19** in CDCl₃ (500 MHz).

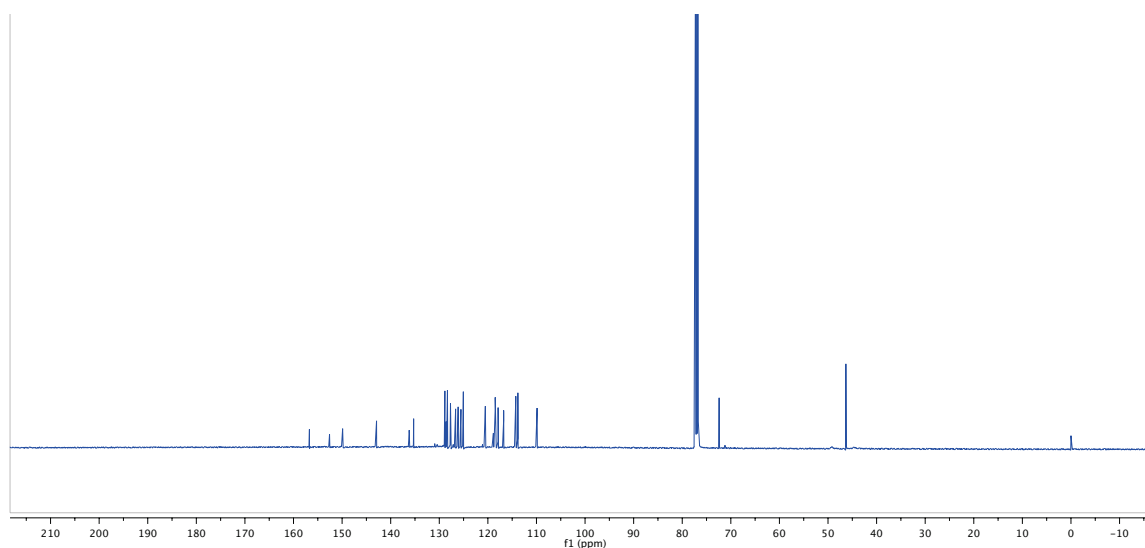


Fig. S33: ¹³C NMR spectrum of the complex of **1a** and **26** in CDCl₃ (125 MHz).

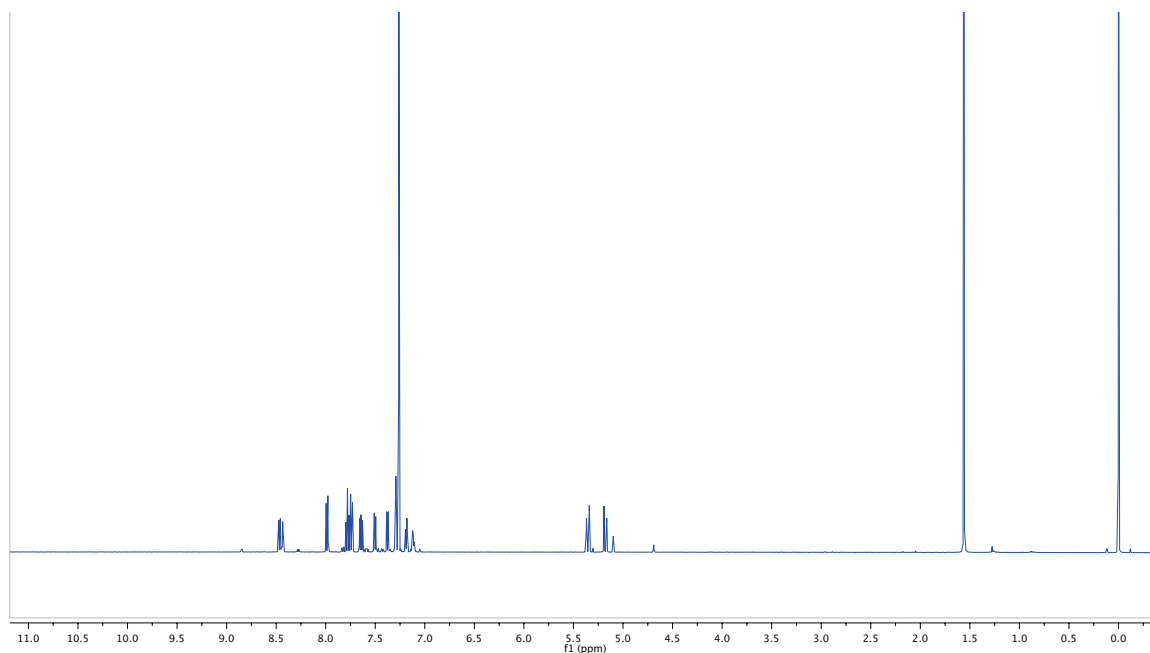


Fig. S34: ^1H NMR spectrum of the complex of **1a** and **26** in CDCl_3 (500 MHz).

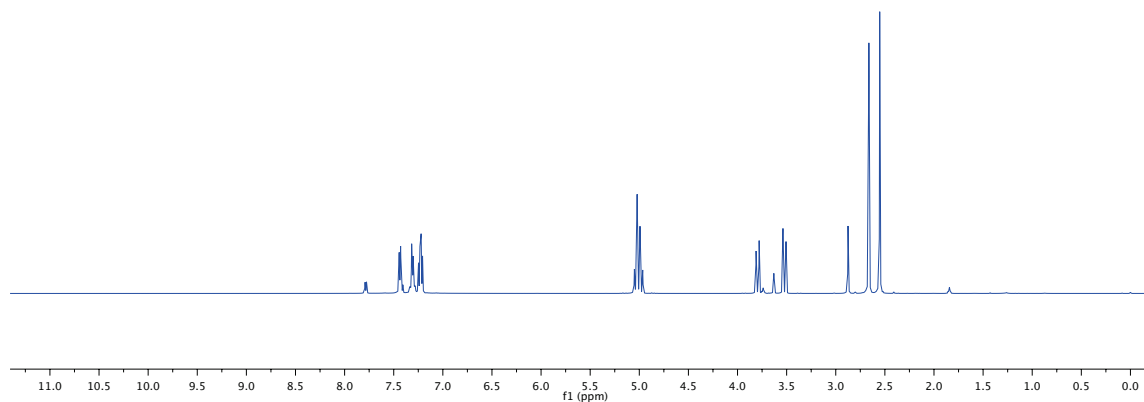


Fig. S35: ^1H NMR spectrum of the complex of **1a** and **28** in CDCl_3 (500 MHz).

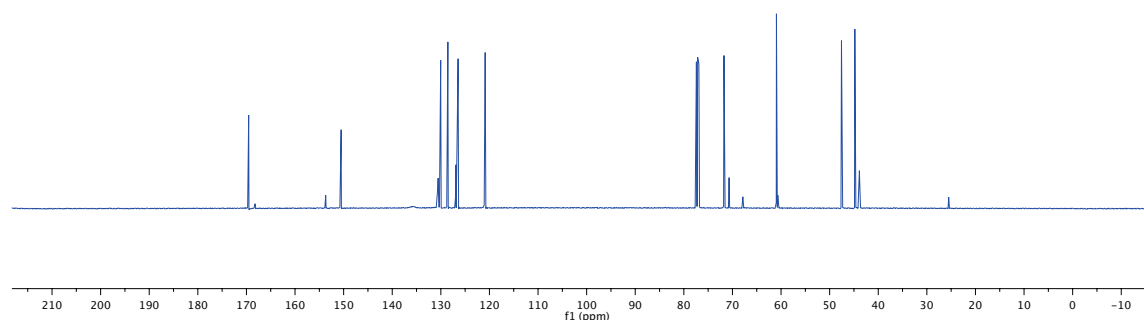


Fig. S36: ^{13}C NMR spectrum of the complex of **1a** and **28** in CDCl_3 (125 MHz).

Notes and references

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