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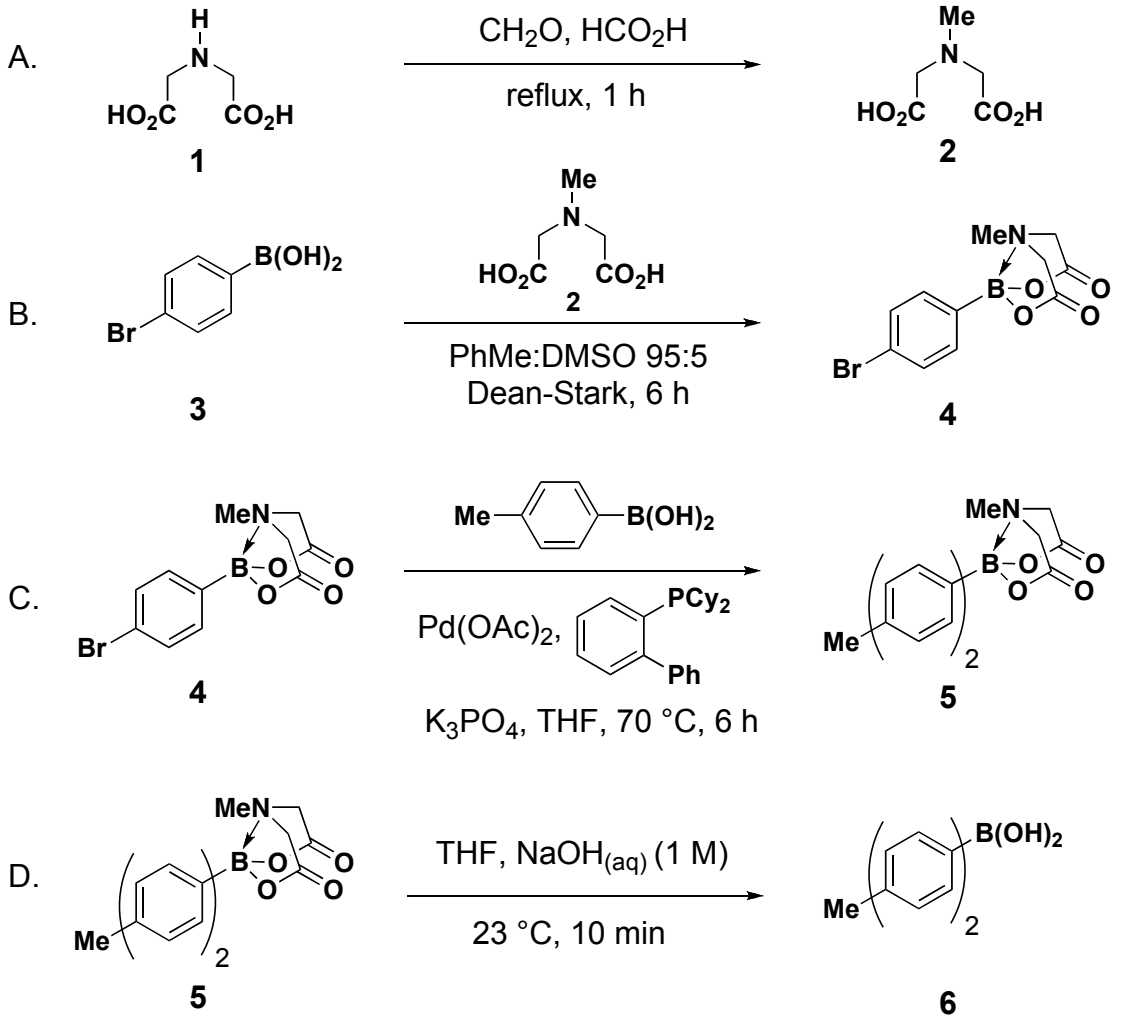
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.086.0344

B-PROTECTED HALOBORONIC ACIDS FOR ITERATIVE CROSS-COUPLING



Submitted by Steven G. Ballmer, Eric P. Gillis, and Martin D. Burke.[1]
Checked by Daniel Morton and Huw M. L. Davies.

1. Procedure

A. N-Methyliminodiacetic acid (MIDA, **2**) (Note 1). A 1000-mL, three-necked, round-bottomed flask equipped with a PTFE-coated magnetic stir bar is charged with iminodiacetic acid (**1**) (100.5 g, 755.2 mmol, 1 equiv) (Note 2) and formalin (84.5 mL, 92.1 g, 1.13 mol, 1.50 equiv) (Note 3) to give an off-white suspension. The flask is then fitted with a water-cooled Friedrichs condenser in the center neck, a 125-mL addition funnel (Note 4) containing formic acid (57.0 mL, 69.5 g, 1.51 mol, 2.00 equiv)

Org. Synth. **2009**, *86*, 344-359
Published on the Web 7/6/2009

(Note 5) in a side neck, and a thermometer in the other side neck. The stirred reaction mixture is brought to reflux (90 °C) using a heating mantle, and then maintained at reflux with stirring for 30 min. After 30 min the formic acid is added dropwise over 20 min (approx 3 mL/min) (Note 6). During this time, the reaction mixture becomes clear and yellow. The addition funnel stop-cock is then closed and the solution is allowed to reflux for one hour. At the end of one hour the heat source is removed and the solution is allowed to cool with stirring to 23 ºC over one hour. The Friedrichs condenser, addition funnel, and thermometer are then removed and the reaction mixture is poured into a 4000-mL Erlenmeyer flask equipped with a large PTFE-coated magnetic stir bar. Deionized water (2 x 25 mL) is used to quantitatively transfer the contents of the reaction mixture to the Erlenmeyer flask. To the stirred reaction mixture is then added absolute ethanol (750 mL) dropwise over one hour (approx 12.5 mL/min) (Note 7) leading to the precipitation of a colorless, crystalline powder. The precipitate is collected by vacuum filtration. The 4000-mL Erlenmeyer flask is then rinsed with absolute ethanol (4 x 200 mL), with each washing being poured over the collected precipitate. The precipitate is then washed with absolute ethanol (200 mL). The precipitate is allowed to air dry under vacuum suction for 10 min. The solid is then transferred to a tared 500-mL round-bottomed flask and residual solvent is removed under reduced pressure (23 ºC, 1 mmHg) for 12 h to give the title compound as a free-flowing, air-stable, white powder (98.30 g, 668.1 mmol, 88% yield) (Note 8).

B. 4-Bromophenylboronic MIDA ester (**4**). A 500-mL, single-necked, round-bottomed flask equipped with a PTFE-coated magnetic stir bar is charged with 4-bromophenylboronic acid (**3**) (24.99 g, 124.4 mmol, 1.0 equiv) (Note 9) and methyliminodiacetic acid (**2**) (18.31 g, 124.4 mmol, 1.0 equiv). To the flask is then added a freshly prepared 5% (v/v) solution of dimethyl sulfoxide in toluene (125 mL) (Note 10) to afford a white solid suspended in a clear, colorless solution. The flask is then fitted with a toluene-filled Dean-Stark trap topped with a water-cooled Friedrichs condenser (Note 11) and the stirred reaction mixture is brought to reflux using a heating mantle. The reaction mixture is allowed to reflux with stirring for 6 h, during which time the reaction remains heterogeneous, but darkens in color, giving a tan solid suspended in a clear, colorless solution. Approximately 2.1 mL of water was collected in the Dean-Stark trap. The heating mantle is removed, and the reaction is allowed to cool to 23 ºC with

stirring for one hour. The Dean-Stark trap and magnetic stir bar are removed (Note 12) and the reaction mixture is concentrated on a rotary evaporator (40 °C, 15 mmHg) (Note 13) to afford the crude product as a tan, chunky solid.

Acetone (15 mL) (Note 14) is then added and the flask is swirled vigorously to afford a white solid suspended in a clear tan solution. To this mixture is added diethyl ether (150 mL) (Note 15) in 25-mL portions. After the addition of each portion the flask is swirled gently causing the precipitation of additional white solid. The white solid is collected via vacuum filtration on a 150-mL medium-porosity glass frit. The collected product is then washed with diethyl ether (3 x 50 mL) and is allowed to dry for 5 min under vacuum suction (Note 16). The product is then transferred to a tared 250-mL round-bottomed flask and residual solvent is removed at reduced pressure (23 ºC, 1 mmHg) for 4 h to give 4-bromophenylboronic acid MIDA ester as a free-flowing, air-stable, white powder (36.30 g, 116.4 mmol, 94% yield) (Note 17).

C. 4-(p-Tolyl)-phenylboronic acid MIDA ester (**5**). An oven-dried, 500-mL Schlenk flask equipped with a magnetic stir bar is charged with palladium (II) acetate (361 mg, 1.61 mmol, 0.020 equiv) and (2-biphenyl)-dicyclohexylphosphine (1.160 g, 3.310 mmol, 0.041 equiv) (Note 18) and then quickly sealed with a rubber septum and placed under an inert atmosphere through five cycles of evacuation (1 mmHg) and purging with dry argon (Note 19). Tetrahydrofuran (400 mL) is then cannulated into the 500-mL Schlenk flask resulting in a clear, pale yellow-orange solution (Note 20). Under positive argon pressure the rubber septum is removed and replaced with an oven-dried water-cooled Graham condenser topped with an oven-dried hose barb adapter. Argon is allowed to flow through the system for 60 seconds at which point an argon inlet is attached to the hose barb and the Schlenk valve is closed. The reaction vessel is lowered into an oil bath preheated to 70 °C and the solution is allowed to reflux with stirring for 20 min, during which time the catalyst solution turns colorless. The heating bath is then removed and the catalyst solution is allowed to cool to 23 °C over 10 min. The Schlenk valve is reopened and under a positive argon pressure the Graham condenser is replaced with a rubber septum and the head space is purged for 60 sec through a 20G (1.5 inch) vent needle.

In parallel with the catalyst preparation, an oven-dried, 2000-mL, three-necked, round-bottomed flask equipped with a magnetic stir bar and fitted with an oven-dried water-cooled Graham condenser topped with a hose-barb

adapter in the center neck and a rubber septa on each side neck is charged with **4** (25.00 g, 80.15 mmol, 1 equiv), *p*-tolylboronic acid (16.39 g, 120.6 mmol, 1.50 equiv) (Note 21), and freshly-ground, anhydrous potassium phosphate (51.06 g, 240.5 mmol, 3.00 equiv) (Note 22). The reaction flask is then quickly placed under inert atmosphere (through the condenser top) through five cycles of evacuation (1 mmHg) and purging with dry argon. Tetrahydrofuran (400 mL) is then added into the 2000-mL flask through one of the side necks (Note 23) by syringe, resulting in a white suspension.

The catalyst solution is then cannulated into the 2000-mL reaction flask with stirring resulting in a yellow suspension. The reaction flask is lowered into an oil bath preheated to 70 °C and allowed to reflux with stirring for 6 h. The heat source is then removed and the reaction mixture is allowed to cool for 20 min with stirring. The Graham condenser and septa are removed from the flask necks and the reaction is quenched with 1000 mL saturated ammonium chloride (Note 24) giving a biphasic mixture comprised of a clear colorless bottom layer and a clear yellow top layer. This mixture is poured into a 4000-mL separatory funnel. The reaction mixture is quantitatively transferred to the separatory funnel with a freshly prepared THF:diethyl ether (1:1) solution (2 x 200-mL). The layers are separated, and the aqueous layer is extracted with THF:diethyl ether (1:1) solution (400 mL). The combined organic layers are washed with saturated aqueous sodium chloride (150 mL) (Note 25), dried over anhydrous $MgSO_4$, and filtered through Celite. The solvent is removed via rotary evaporation (40 °C, 20 mmHg). Residual solvent is removed at reduced pressure (23 °C, 1 mmHg) to afford the crude product as a yellow solid. Acetone (120 mL) is added to the crude product and the resulting mixture is swirled vigorously to give a yellow slurry. Diethyl ether (800 mL) is then added in 4 equal portions with swirling to give an off-white precipitate in a clear yellow solution. The precipitate is collected via vacuum filtration and allowed to air dry over vacuum for 5 minutes. The solid is transferred to a tared 100-mL round-bottomed flask and residual solvent is removed at reduced pressure (23 °C, 1 mmHg) to give the title compound as a free-flowing, air stable, off-white powder (19.86 g, 61.46 mmol, 77% yield).

To this solid is then added acetone (100 mL) and the thin slurry is heated with stirring at 60 °C until the volume is reduced to 60 mL. Diethyl ether (400 mL) is then added in 4 equal portions with swirling to give a white precipitate in a clear light yellow solution. The precipitate is collected via vacuum filtration and allowed to air dry over vacuum for 5 min. The solid is

then transferred to a tared 100-mL round-bottomed flask and residual solvent is removed under reduced pressure (23 °C, 1 mmHg) to give the title compound as a free-flowing, air stable, white powder (17.30 g, 53.53 mmol, 67% yield) (Note 26).

D. 4-(p-Tolyl)-phenylboronic acid (**6**). A 1000-mL, single-necked, round-bottomed flask equipped with a PTFE-coated magnetic stir bar is charged with **5** (10.11 g, 31.27 mmol, 1 equiv), tetrahydrofuran (220 mL), and an aqueous solution of 1 M sodium hydroxide (93.5 mL, 93.5 mmol, 2.99 equiv) to give a biphasic system consisting of a clear colorless bottom layer and a cloudy white top layer. The flask is covered with a polypropylene cap and the reaction is stirred vigorously at 23 ºC for 10 min to give a biphasic system consisting of a clear colorless bottom layer and a clear yellow top layer. A saturated aqueous solution of ammonium chloride (250 mL) is then added and the reaction is allowed to stir vigorously for five min. The resulting mixture is poured into a 1000-mL separatory funnel and the reaction vessel is rinsed with diethyl ether (4 x 50 mL), each washing being poured into the separatory funnel. The layers are separated and the aqueous layer is extracted with a freshly prepared tetrahydrofuran:diethyl ether (1:1) solution (400-mL). The combined organic layers are dried over anhydrous $MgSO_4$, filtered through Celite, and concentrated via rotary evaporation (40 °C, 20 mmHg). The residual solvent is removed via three azeotropic cycles with acetonitrile on a rotary evaporator (3 x 50 mL, 40 °C, 20 mmHg) and then at reduced pressure (23 °C, 1 mmHg) for 12 h to afford the title compound as a fine, off-white powder (6.24 g, 29.4 mmol, 94% yield) (Notes 27 and 28).

2. Notes

1. MIDA is a commercially available reagent. However, the synthesis described here is highly convenient and very inexpensive (estimated cost including all reagents and solvents is < 10 cents/gram of product).

2. Iminodiacetic acid (98%) was obtained from Alfa Aesar (Lot No. A13R006) and used as received.

3. Formalin (37 wt % formaldehyde) was obtained from Sigma-Aldrich (Lot No. 06010EH) and used as received.

4. Failure to condense the formaldehyde also results in significant formation of paraformaldehyde on the condenser and addition funnel.

Paraformaldehyde can be easily removed with an alcoholic sodium hydroxide solution. All ground glass joints were sealed with Apiezon H high temperature vacuum grease and secured with Keck clips.

5. Formic acid (98+%) was obtained from Acros (Lot No. A0254874) and used as received.

6. Addition of formic acid results in effervescence of CO_2, which can become vigorous if the addition is performed too quickly.

7. Ethyl alcohol (200 Proof, absolute, anhydrous, ACS/USP grade) was obtained by the submitters from Pharmco-Aaper, and by the checkers from Decon Labs, Inc., and used as received.

8. The physical and spectral data for **2** are as follows: mp 215–216 °C dec, uncorrected; ^{1}H NMR (400 MHz, D_2O) δ: 2.98 (s, 3 H), 3.96 (s, 4 H); ^{13}C NMR (100 MHz, 95:5 DMSO-d_6:D_2O w/ TMS) δ: 41.7, 56.7, 170.0; IR (thin film): 723, 886, 903, 958, 982, 1018, 1065, 1126, 1172, 1223, 1328, 1380, 1477, 1682, 2955, 2998 cm^{-1}; LRMS (ESI+) *m*/*z* (rel. intensity) 219.1 (24%), 148.1 (M^+, 100%), 102.1 (8%). HRMS (ESI+) for $C_5H_{10}NO_4$ [$M+H^+$] calcd 148.0604; Found: 148.0603 Anal. calcd. for $C_5H_9NO_4$: C, 40.82; H, 6.17; N, 9.52; found: C, 40.55; H, 6.13; N, 9.40.

9. 4-Bromophenylboronic acid (containing varying amounts of anhydride) was obtained from Aldrich (Lot No. 78396DJ) and used as received. To the best of the authors' knowledge, the amount of boroxine present in the starting boronic acid has no effect on the complexation reaction.

10. Toluene (certified ACS) was obtained from Fisher Scientific (Lot No. 072584) and used as received. Dimethyl sulfoxide (certified ACS) was obtained from Fisher Scientific (Lot No. 066635) and used as received.

11. All ground glass joints were sealed with Apiezon H high vacuum grease and secured with Keck clips. The arm of the Dean-Stark trap was wrapped in two layers of aluminum foil to facilitate refluxing.

12. The submitters removed the magnetic stir bar with forceps and rinsed with toluene in order to flush particulates back into the reaction flask, the checkers used a magnetic retriever and rinsed with toluene.

13. The reaction is concentrated to remove toluene. There is no need to remove the DMSO at this point.

14. Acetone (certified ACS) was obtained from Fisher Scientific and used as received.

15. Diethyl ether was obtained from a solvent delivery system, with solvent purified via passage through packed dry neutral alumina columns as described by Pangborn and coworkers.[0]

16. It should be noted that the tan filtrate may be concentrated and the tan solid purified via silica gel column chromatography to obtain a nearly quantitative yield of the title product.

17. In an experiment on 50% scale (12.5 g of 4-bromophenylboronic acid), the checkers obtained a yield of 83%. The physical and spectral data for **4** are as follows: mp 238–240 °C, uncorrected; ^{1}H NMR (400 MHz, CD_3CN) δ: 2.50 (s, 3 H), 3.89 (d, J = 16.0 Hz, 2 H), 4.07 (d, J = 16.0 Hz, 2 H), 7.41 (d, J = 8.0 Hz, 2 H), 7.55 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, CD_3CN) δ: 48.2, 62.5, 124.1, 131.6, 135.2, 169.2; ^{11}B NMR (100 MHz, CD_3CN) δ: 12.0; IR (thin film, acetone): 707, 812, 867, 995, 1037, 1187, 1216, 1237, 1294, 1339, 1459, 1584, 1745, 3012 cm^{-1}. LRMS (EI^{+}) *m*/*z* (rel. intensity) 314.0 (97%), 313.0 (20%), 312.0 ([M^{+}+H], 100%), 311.0 (23%), 283.0 (16%), 255.9 (16%). HRMS (EI+) for $C_{11}H_{12}BBrNO_4$ [M+H]$^{+}$ calcd: 312.0037, found: 312.0035; Anal. calcd. for $C_{11}H_{11}BBrNO_4$: C, 42.36; H, 3.55; N, 4.49; Found: C, 42.42; H, 3.61; N, 4.67.

18. Palladium (II) acetate (98%) was obtained from Sigma-Aldrich (Lot No. 09417MH) and used as received. (2-biphenyl)-dicyclohexylphosphine (97%) was obtained from Sigma-Aldrich (Lot No. 12209BH) and used as received. Both compounds were massed out at a bench-top balance open to air.

19. Although it is possible to perform this type of selective cross-coupling reaction without the use of a glovebox, it is very important that rigorous Schlenk techniques are utilized to exclude water. Failure to exclude water can result in hydrolysis of the MIDA boronate ester.

20. The submitters obtained tetrahydrofuran from a solvent delivery system, with solvent passage through packed dry neutral alumina columns as described by Pangborn and coworkers.[2] It was dispensed directly from the system into an oven-dried, 1000-mL single-necked, round-bottomed flask which was quickly sealed with a rubber septum. Immediately following, the head space of the flask was purged with dry argon for 60 sec. The checkers distilled tetrahydrofuran from sodium and benzophenone.

21. *p*-Tolylboronic acid was obtained from Oakwood Products, Inc. (Lot No. A30J) and used as received.

22. K_3PO_4 (anhydrous, 97%) was obtained from Alfa Aesar (Lot No. A23R022) and finely-ground just prior to use. It is very important that the

K_3PO_4 is finely ground and that it remains anhydrous throughout this process. This can be achieved using a glove box. Alternatively, a convenient way to achieve this without the use of a glove box is as follows: ~10% excess of the desired amount of K_3PO_4 is massed out on a benchtop balance and quickly poured into a hot mortar (removed from a 60 °C oven just prior to use) and finely ground quickly using a hot pestle (removed from a 60 °C oven just prior to use). The ground base is massed quickly on a benchtop balance and transferred to the reaction vessel. This was the method used by the checkers.

23. The submitters obtained tetrahydrofuran and diethyl ether from a solvent delivery system, with solvent purified via passage through packed dry neutral alumina columns as described by Pangborn and coworkers.[2] The checkers distilled the tetrahydrofuran from sodium and benzophenone.

24. Ammonium chloride (99.5% ACS reagent) was obtained from Sigma-Aldrich and added to deionized water until saturated.

25. Sodium chloride (ReagentPlus ≥ 99.5%) was obtained from Sigma-Aldrich and added to deionized water until saturated.

26. In an experiment on 50% scale (12.5 g of 4-bromophenylboronic acid MIDA **4**), the checkers obtained a yield of 70%. The physical and spectral data for **5** are as follows: mp 214–216 °C dec, uncorrected; ^{1}H NMR (400 MHz, CD_3CN) δ: 2.31 (s, 3 H), 2.54 (s, 3 H), 3.91 (d, J = 16.0, 2 H), 4.09 (d, J = 16.0 Hz, 2 H), 7.28 (d, J = 8.0 Hz, 2 H), 7.56 (d, J = 8.0 Hz, 4 H), 7.64 (dt, J = 8.0, 2.0 Hz, 2 H); ^{13}C NMR (100 MHz, CD_3CN) δ: 20.6, 48.0, 62.3, 126.6, 127.2, 130.0, 133.6, 137.9, 138.1, 142.0, 169.1; ^{11}B NMR (100 MHz, CD_3CN) δ: 12.4; IR (thin film): 800, 985, 1035, 1236, 1299, 1341, 1745, 3022 cm^{-1}; LRMS (EI$^+$) *m*/*z* (rel. intensity) 325.1 (18%), 324.1 (M+H, 100%), 323.1 (23%), 323.0 (15%); HRMS (EI+) for $C_{18}H_{19}BNO_4$ $[M+H]^+$ calcd: 324.1402, found: 324.1406; The submitters found: Anal. calcd. for $C_{18}H_{18}BNO_4$: C, 66.90; H, 5.61; N, 4.33; found: C, 66.72; H, 5.56; N, 4.47. An accurate microanalysis was not achieved by the checkers. The solid, free flowing product **5** was first dried under reduced pressure (23 °C, 1 mmHg), for a period of 5 h; found: C, 65.77; H, 5.56; N, 4.21. The solid was then re-precipitated from acetone and diethyl ether as described in the procedure and dried under reduced pressure (23 °C, 1 mmHg), for 24 h; found: C, 65.92; H, 5.70; N, 4.27. A sample that was precipitated twice and dried extensively under reduced pressure while being heated (35 °C, 1 mmHg), for 48 h, was further away than before; found: C, 63.90; H, 5.21; N, 4.23.

27. In an experiment on 50% scale (5.05 g of 4-(p-tolyl)-phenylboronic acid MIDA **5**), the checkers obtained a yield of 91%. The physical and spectral data for **6** are as follows: mp 136–138 °C dec, uncorrected; ^{1}H NMR (400 MHz, 95:5 DMSO-d_6:D_2O) δ: 2.29 (s, 3 H), 7.22 (d, J = 8.0 Hz, 2 H), 7.53 (d, J = 8.0 Hz, 2 H), 7.56 (d, J = 8.0 Hz, 2 H), 7.80 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, 95:5 DMSO-d_6:D_2O) δ: 20.9, 125.7, 126.8, 129.8, 135.0, 137.2, 137.4, 141.8; ^{11}B NMR (95:5 DMSO-d_6:D_2O w/ TMS) δ: 36.3; IR (thin film, acetone): 740, 806, 1003, 1093, 1154, 1339, 1530, 1607, 3331 cm^{-1}; LRMS (EI^{+}) *m*/*z* (rel. intensity) 212.1 (M+, 8%), 185.1 (16%), 170.1 (14%), 169.1 (M-BO_2, 100%); HRMS (EI+) for $C_{13}H_{13}BO_2$ [M^{+}] calcd: 212.1003, found: 212.1006. Due to the unpredictable composition of boronic acids and their corresponding boroxines, elemental analysis does not provide an accurate measure of purity. Based on the ^{1}H NMR the checkers afforded the title compound in 91–93% purity. Based on ^{1}H NMR, the submitters afforded the title compound in 82–87% purity (Note 28).

28. The ^{1}H NMR spectrum was obtained of a freshly prepared solution of product **6** in DMSO-d_6:D_2O 95:5 with tetramethylsilane (TMS) added as an internal reference. The following procedure was followed by the checkers to establish the purity of product **6**: The integration for the methyl resonance at 2.29 ppm was normalized to 3.00 and the two minor resonances at 2.30 and 2.25 ppm were integrated. The sum integration for the minor resonances was 0.21, which represented 7% of the total integration area in that region. Similarly, the aryl resonances at 7.80, 7.56, 7.53, and 7.22 ppm were integrated as were the eight minor resonances at 7.84, 7.74, 7.72, 7.65, 7.49, 7.41, 7.39, and 7.16 ppm. The sum integration for the minor resonances was 0.79, which represented 9% of the total integration area in that region. The combined calculations suggest the presence of 7–9% impurity (91–93% purity). The following procedure was followed by the submitters to establish the purity of product **6**: The integration for the methyl resonance at 2.35 ppm was normalized to 3.00 and the two minor resonances at 2.36 and 2.31 ppm were integrated. The sum integration for the minor resonances was 0.46, which represented 13% of the total integration area in that region. Similarly, the aryl resonances at 7.87, 7.62, 7.59, and 7.28 ppm were integrated as were the eight minor resonances at 7.91, 7.82, 7.77, 7.70, 7.55, 7.45, 7.34, and 7.23 ppm. The sum integration for the minor resonances was 1.90, which represented 18% of the total integration area in

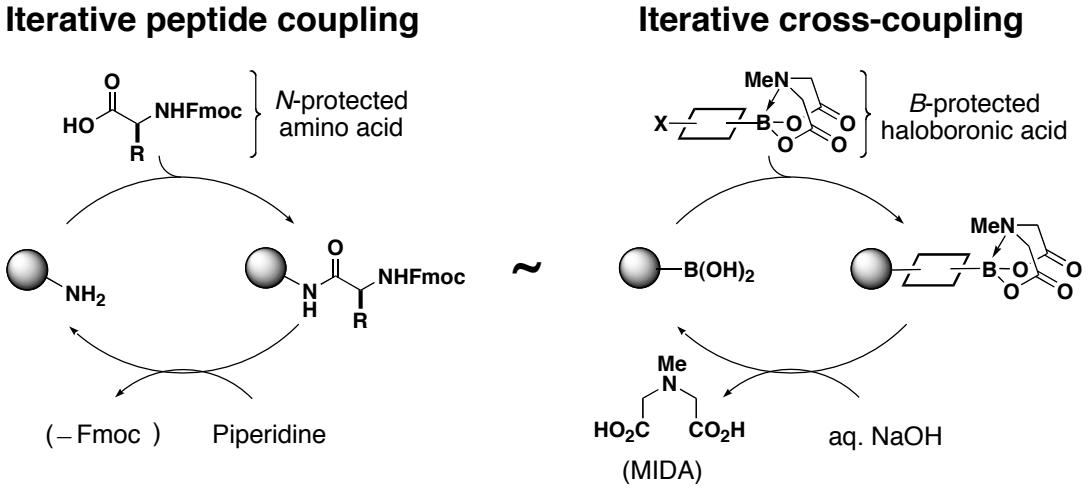
that region. The combined calculations suggest the presence of 13–18% impurity (82–87% purity).

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Figure 1. Analogous strategies for the synthesis of peptides and small molecules.

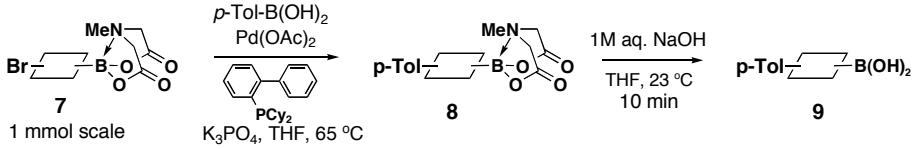


Inspired by the powerful simplicity of peptide coupling (Fig. 1, left), we recently reported an analogous strategy for the synthesis of small molecules involving the iterative cross-coupling (ICC) of B-protected "haloboronic acids" (Fig. 1, right).[3] In an ideal ICC pathway, only stereospecific cross-coupling reactions are utilized to assemble a collection of building blocks having all of the required functional groups preinstalled in the correct oxidation state and with the desired stereochemical relationships. This type of pathway is inherently modular and flexible, and thus highly amenable to analog and/or library synthesis. The approach is also well-suited for automation, a goal which is currently being pursued.

To avoid random oligomerization, this strategy necessitates methodology for reversibly attenuating the reactivity of one end of the bifunctional haloboronic acids, analogous to an Fmoc protective group routinely utilized to control the iterative coupling of amino acids. In this

vein, we discovered that the trivalent heteroatomic ligand MIDA can pyramidalize and thereby inhibit the reactivity of a boronic acid under anhydrous cross-coupling conditions.[3] This methodology enables the selective cross-coupling of B-protected haloboronic acids, and is general for aryl, heteroaryl, alkenyl, and alkyl derivatives (Table 1 and Fig. 2).[3] Critical

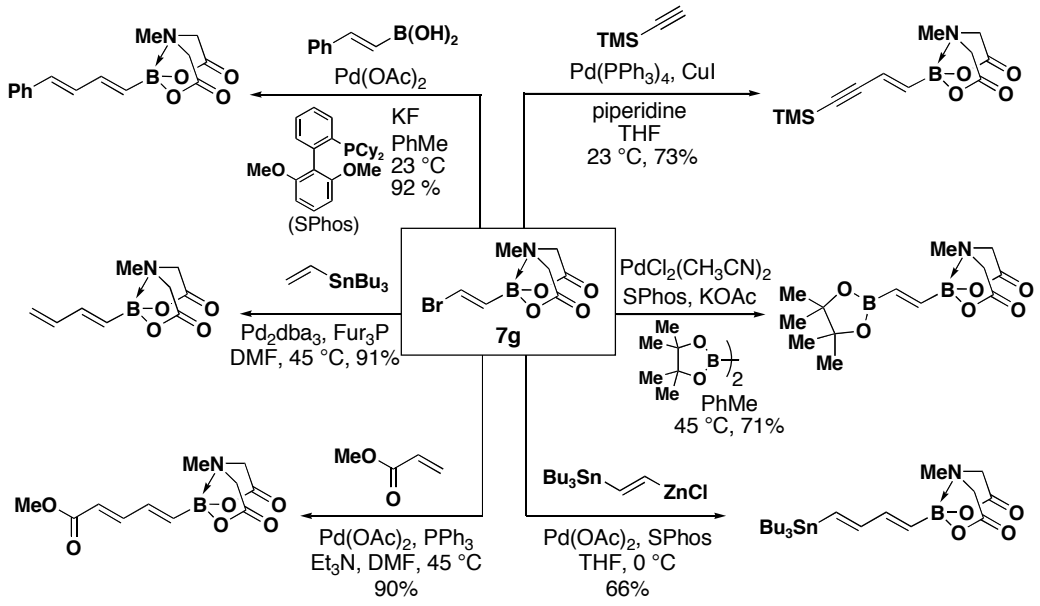
Table 1. Cross-coupling and Deprotection of B-Protected Haloboronic Acids



Entry	7	Protected product	% Yield	Deprotected product	% Yield
1	7a	8a (*para*)	87[a]	9a (*para*)	86
2	7b	8b (*meta*)	85	9b (*meta*)	92
3	7c	8c (*ortho*)	80	9c (*ortho*)	97[b]
4[c]	7d	8d	81	9d	88
5	7e	8e	82	9e	83
6	7f	(±) 8f	94	(±) 9f	91

[a] The same yield was observed whether this reaction was set up in the glovebox or in the air.
[b] *B*-Deprotection was achieved via treatment with saturated aq. $NaHCO_3$/MeOH, 23 °C, 6 h, (85%).
[c] 2-(Dicyclohexylphosphino)-2',4',6'-triisopropyl-1,1'-biphenyl was used as ligand.

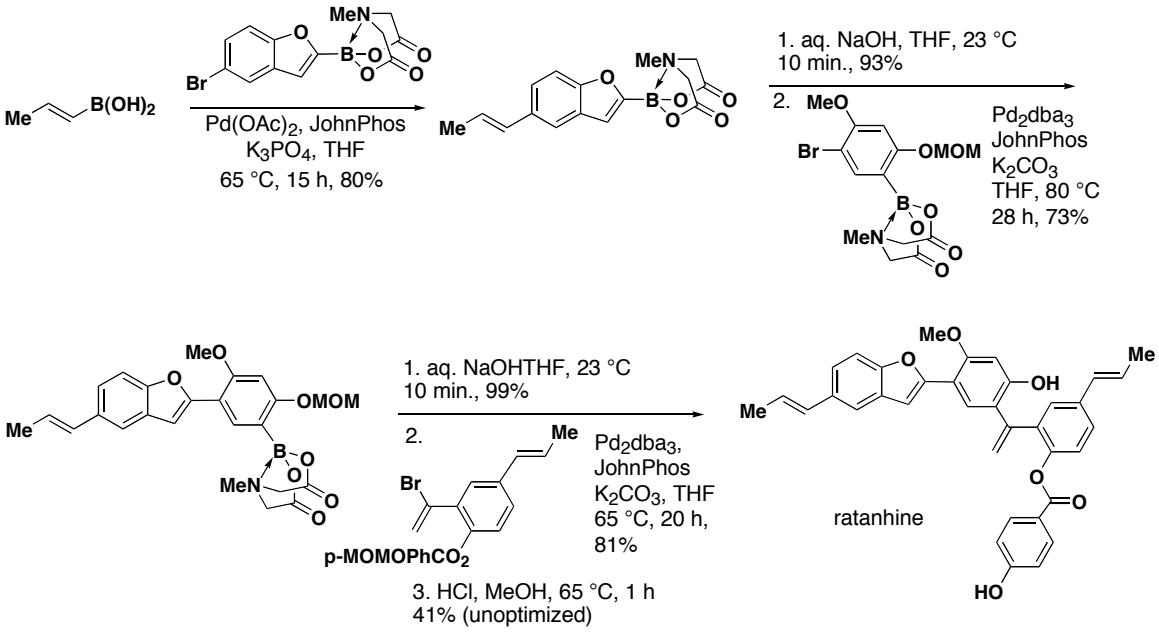
Figure 2. Diverse Uses of B-Protected Haloboronic Acids



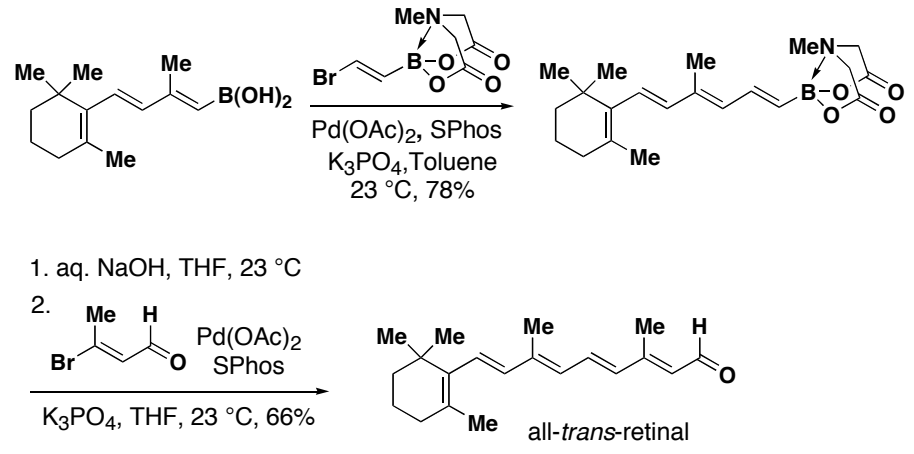
for applications in complex small molecule synthesis, this ligand can be removed under very mild aqueous basic conditions, including 1N aqueous NaOH or even saturated aqueous $NaHCO_3$ in methanol (Table 1).[3]

Our early studies have additionally demonstrated the feasibility of the ICC concept with the synthesis of a variety of small molecule natural products (for example, see Schemes 1 and 2).[3] We herein describe methods for translating some of this chemistry to the decagram scale.

Scheme 1



Scheme 2



Importantly, there are many features of this chemistry that make it very well-suited for execution on scale. First, MIDA is non-toxic, biodegradable,[4] and can be conveniently prepared in analytically pure form using the procedure described herein for very low cost (estimated cost including all solvents and reagents is < 10 cents/gram). In addition, the MIDA ligand is indefinitely stable on the benchtop under air. The low cost of this procedure is in large part because the key starting material, iminodiacetic acid, is a commodity chemical used in the preparation of herbicides (>60,000 metric tons of iminodiacetic acid is synthesized worldwide each year).[5] The only other reagents are formic acid and formaldehyde.

A previously reported synthesis of MIDA (**2**) proceeds in moderate yield from the reaction of methylamine and chloroacetic acid.[6] A more effective preparation utilizes formalin and formic acid to reductively methylate iminodiacetic acid in good yield (the Eschweiler-Clarke conditions).[7] The simple method described herein is an optimized version of this reaction, and is viewed by the submitters to be considerably more convenient and effective than syntheses reported previously.

The synthesis of MIDA boronates were first reported by Mancilla and coworkers.[8] We herein describe a simple and efficient procedure for preparing substantial quantities of B-protected haloboronic acids using a minimum volume of DMSO (employed to solubilize the MIDA ligand). Specifically, using a standard Dean-Stark apparatus, the complexation between *p*-bromophenylboronic acid and MIDA proceeds in excellent yield with purification via simple precipitation from acetone/Et_2O. Moreover, the selective Suzuki-Miyaura cross-coupling between *p*-tolylboronic acid and this B-protected haloboronic acid[3a] was achieved on the decagram scale without the use of a glove box. In order to avoid MIDA hydrolysis during the course of this reaction, it is critical to utilize rigorous Schlenk techniques and avoid the introduction of water. Freshly grinding anhydrous K_3PO_4 using a hot mortar and pestle (recently removed from a 60 °C oven) is a convenient way to maintain anhydrous conditions during the reaction setup. Alternatively, a glove box can be used. Finally, we demonstrate that the hydrolysis of the MIDA ligand can conveniently be performed on scale to yield the corresponding boronic acid.

In addition to the capacity for iterative cross-coupling, there are numerous enabling features that make MIDA boronates highly attractive intermediates for organic synthesis. In contrast to their boronic acid

counterparts, these compounds are invariably monomeric and highly crystalline free-flowing solids. They have also proven to be extremely stable to benchtop storage under air and universally compatible with silica gel chromatography.[3] As demonstrated herein, the synthesis, selective cross-coupling, and deprotection of MIDA boronates is also scalable. Moreover, we have recently discovered that the MIDA boronate functional group is stable to a wide range of common synthetic reagents, thereby enabling complex boronic acid building blocks to be reliably prepared from simple B-containing starting materials via multistep synthesis.[9] In addition, we have found that MIDA boronates can serve directly as cross-coupling partners under aqueous basic conditions via the in situ release of the corresponding boronic acids.[10] Collectively, these features suggest that MIDA boronates represent a superior platform for the preparation, purification, storage, and utilization of organoboranes in organic synthesis.

1. Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, IL 61801-3602, USA; E-mail: burke@scs.uiuc.edu; Sigma-Aldrich is gratefully acknowledged for generous gifts of 4-bromophenylboronic acid, (2-biphenyl)dicyclohexylphosphine, and palladium (II) acetate. We also thank the NSF (CAREER 0747778), Dreyfus Foundation, and the Arnold and Mabel Beckman Foundation for financial support. EPG is a Seemon H. Pines Graduate Fellow.

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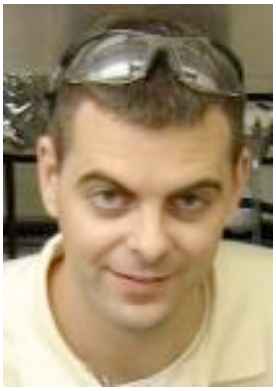
Appendix
Chemical Abstracts Nomenclature; (Registry Number)

N-Methyliminodiacetic acid;(4408-64-4)
Iminodiacetic acid; (142-73-4)
Formalin; (50-00-0)
Formic acid; (64-18-6)
4-Bromophenylboronic acid; (5467-74-3)
Palladium (II) acetate; (3375-31-3)
(2-Biphenyl)dicyclohexylphosphine; (247940-06-3)
p-Tolylboronic acid; (5720-05-8)



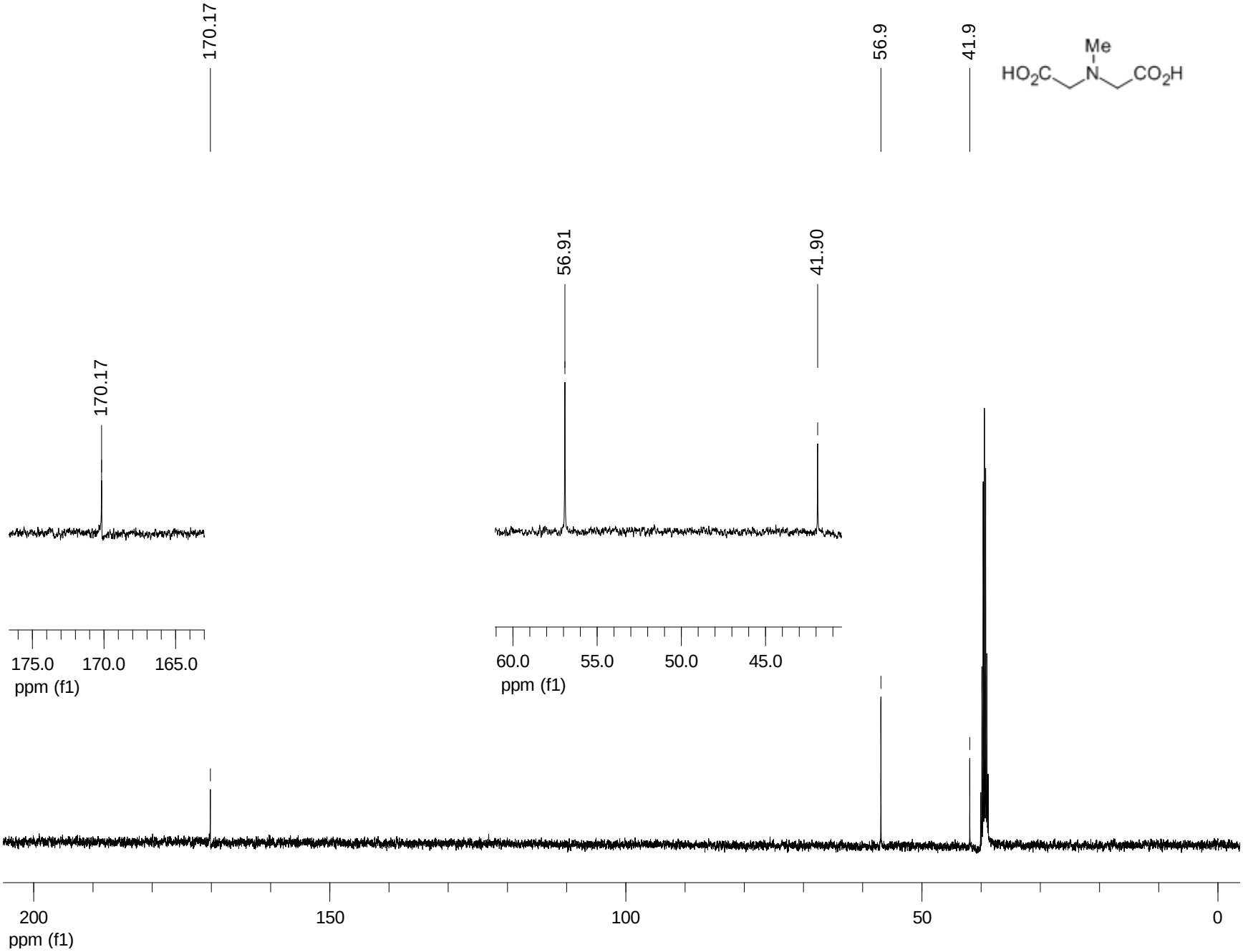
Marty Burke completed his undergraduate education at Johns Hopkins in 1998 and then moved to Harvard Medical School as a PhD/MD student in the Health Sciences and Technology program. He completed his thesis research under the direction of Prof. Stuart L. Schreiber and graduated from medical school in 2005. That same year, he began his independent career at the University of Illinois at Urbana-Champaign. His research program focuses on the synthesis and study of small molecules that perform protein-like functions. To enable these studies, Marty's group is developing a synthesis strategy, dubbed *iterative cross-coupling*, that aims to make the process of complex small molecule making as simple, efficient, and flexible as possible.

Steve Ballmer was born in Toledo, Ohio and attended Wright State University in Dayton, Ohio, where he majored in chemistry and received his bachelor's of science degree in 2007. There he performed undergraduate research under the supervision of Prof. Daniel M. Ketcha. He is currently pursuing a PhD under the supervision of Prof. Martin Burke.

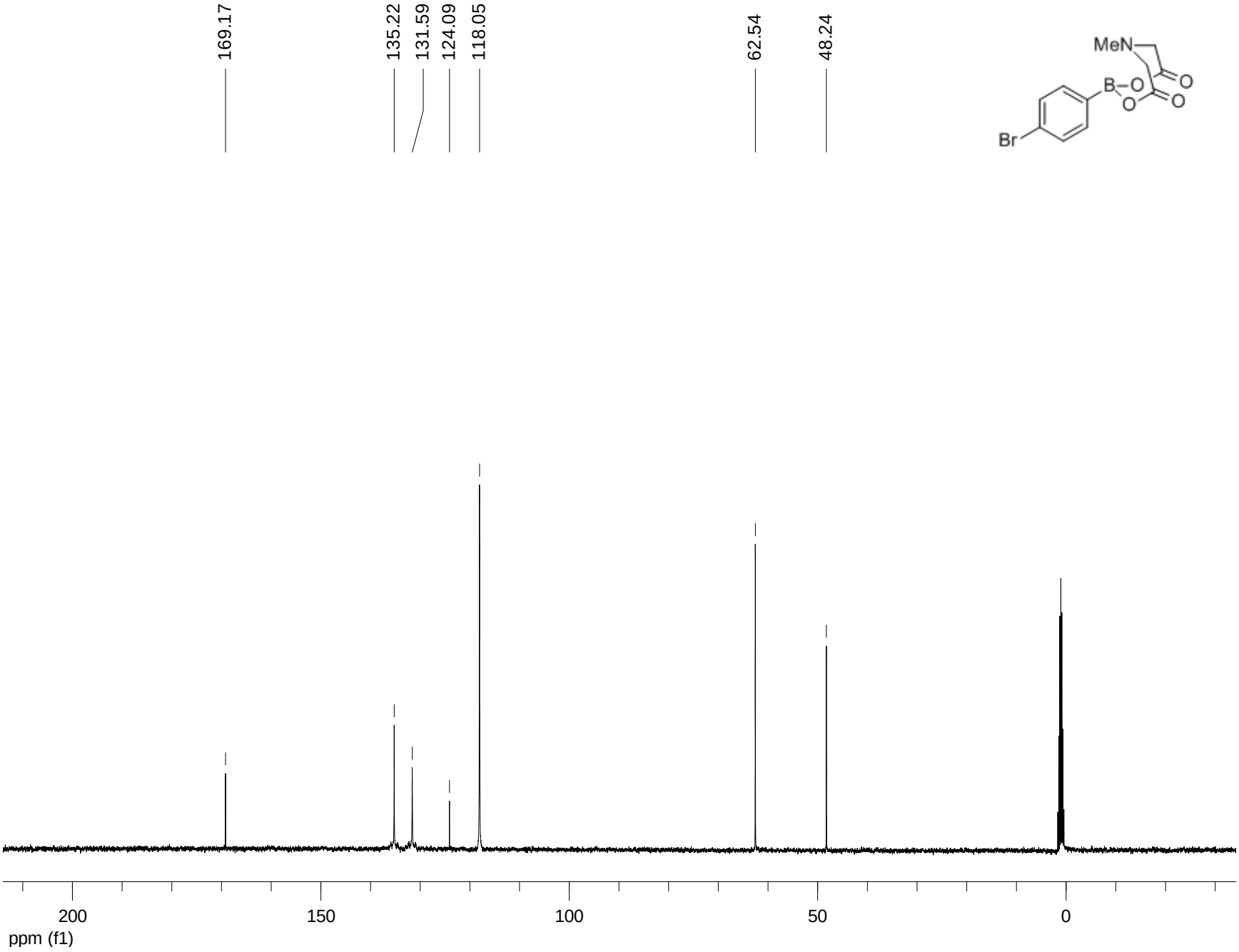
Eric Gillis grew up in Portland, ME and received his undergraduate education at Grinnell College in Grinnell, IA. While at Grinnell he worked with Professor T. Andrew Mobley on the synthesis and characterization of tungsten-tin complexes. In 2005 he began his doctoral studies under the direction of Martin Burke at the University of Illinois, Urbana-Champaign. His current research focuses on the development MIDA boronate esters as a platform to enable the simple, efficient, and flexible synthesis of small molecules.

Daniel Morton obtained his MChem from the University of East Anglia in 2001, where he remained for his PhD (supervised by Dr. Rob Stockman and Prof. Rob Field) which concerned the synthesis of chiral aziridines. In 2005, he joined the group of Prof. Adam Nelson at the University of Leeds, as a post-doctoral research associate, where he worked on the total synthesis of hemibrevetoxin B and the diversity-oriented synthesis of natural product-like molecules. In 2008 he moved to the group of Huw Davies, at Emory University, Atlanta, where he is currently exploring the use of C-H functionalization in the generation of molecular complexity.

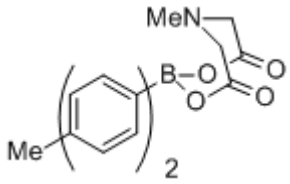
N-Methyliminodiacetic acid ***2***

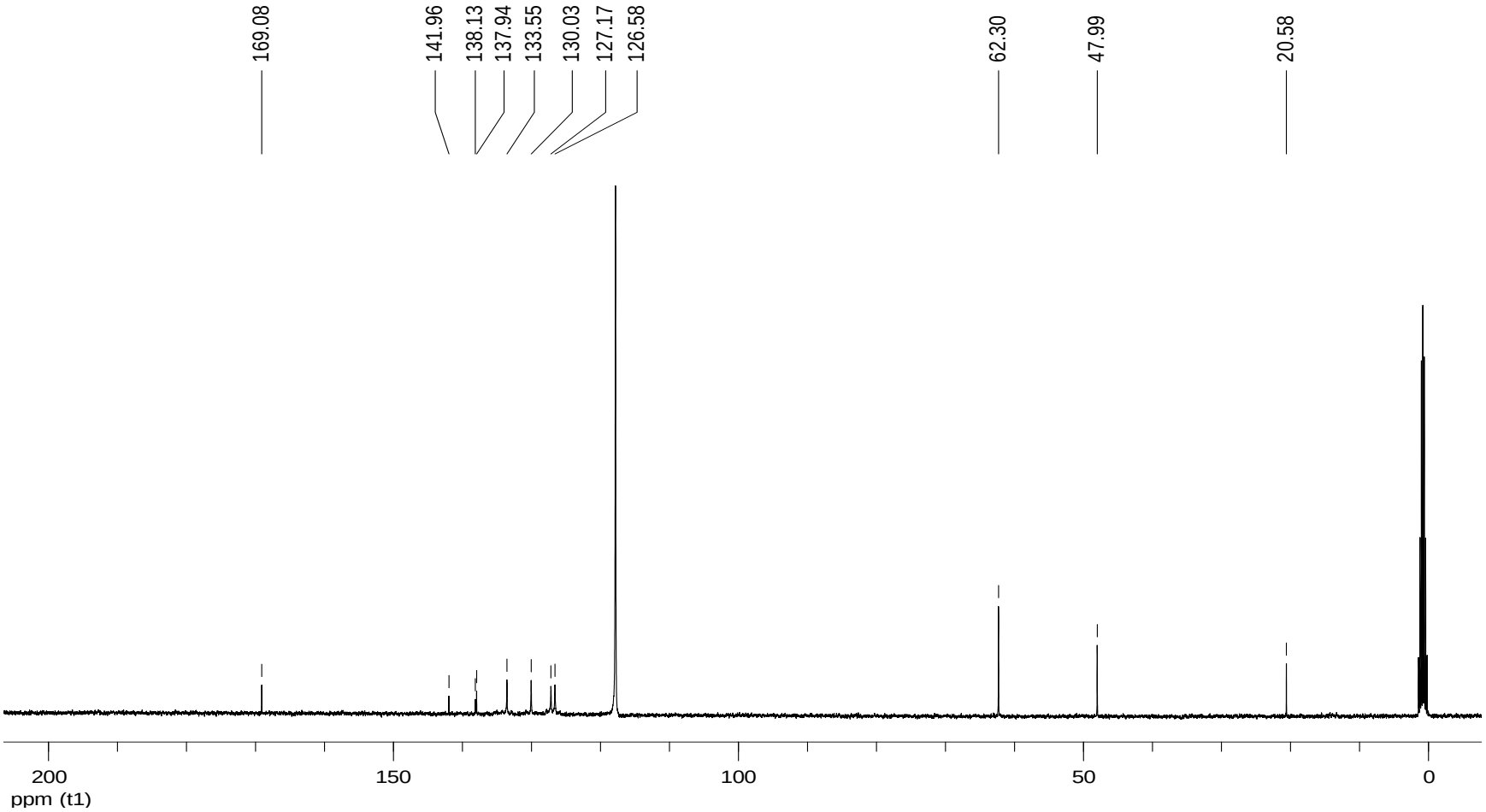


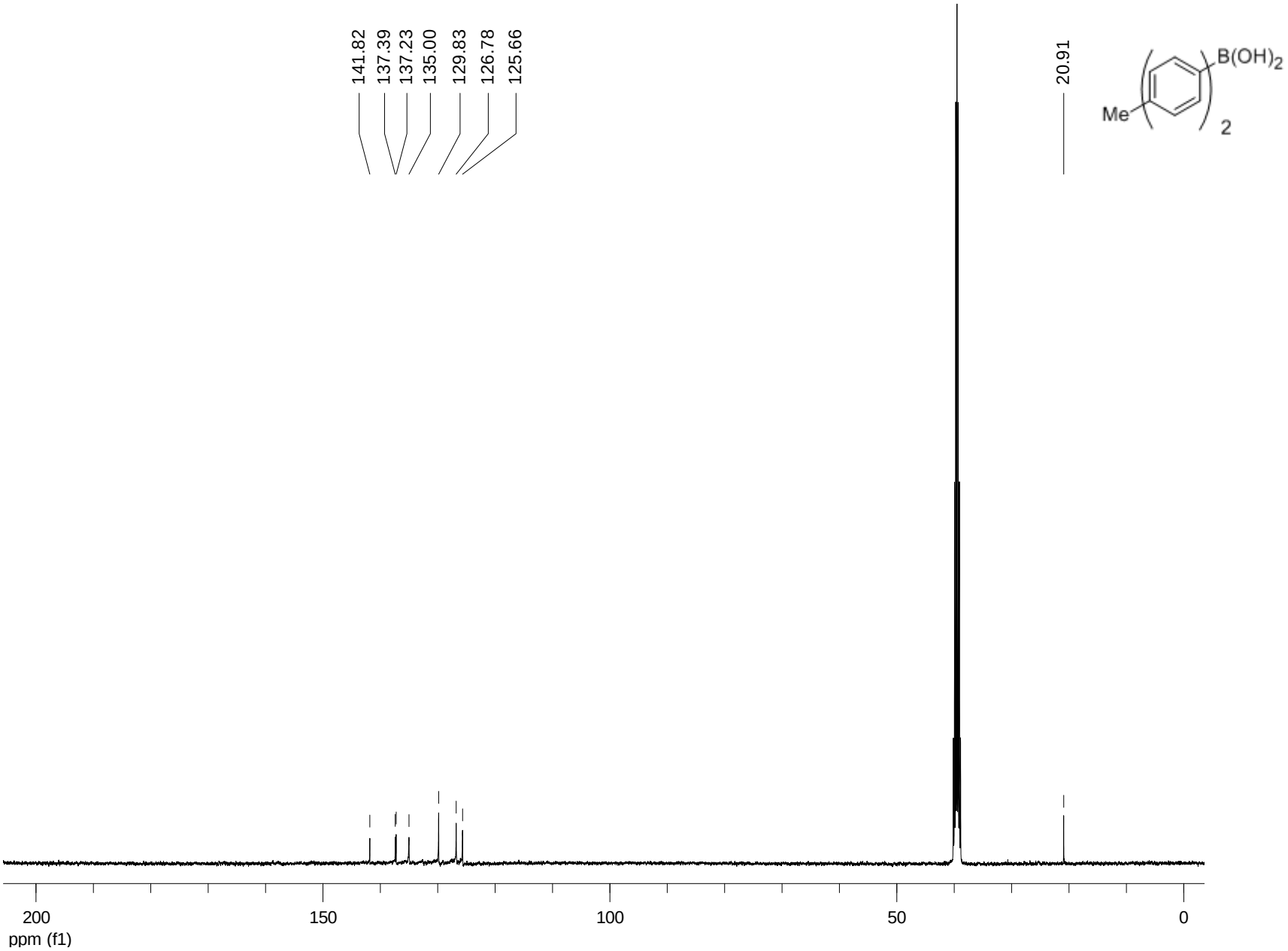
4-Bromophenylboronic MIDA Ester 4



4-(p-tolyl)-phenylboronic acid MIDA ester 5



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135.00
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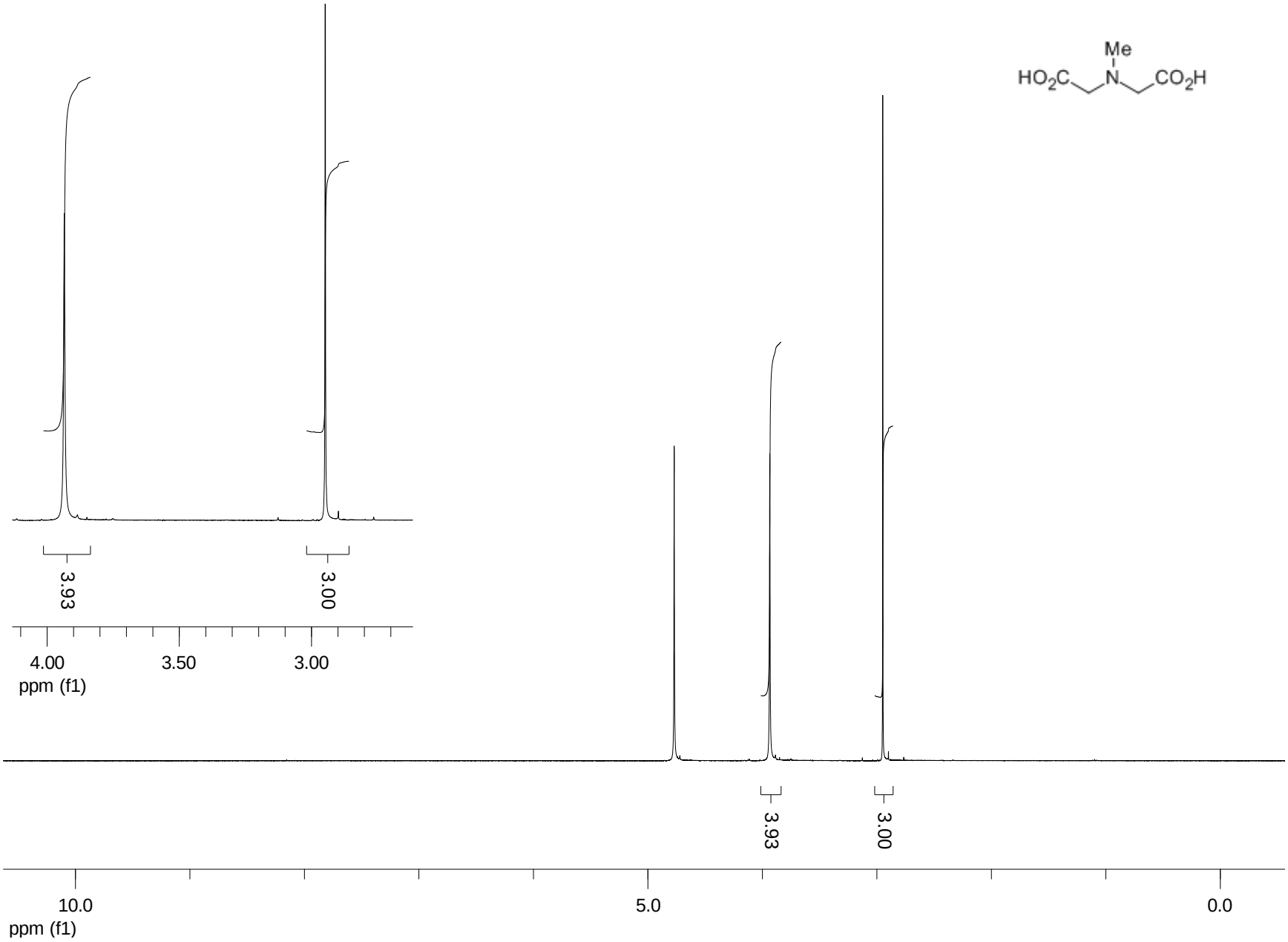
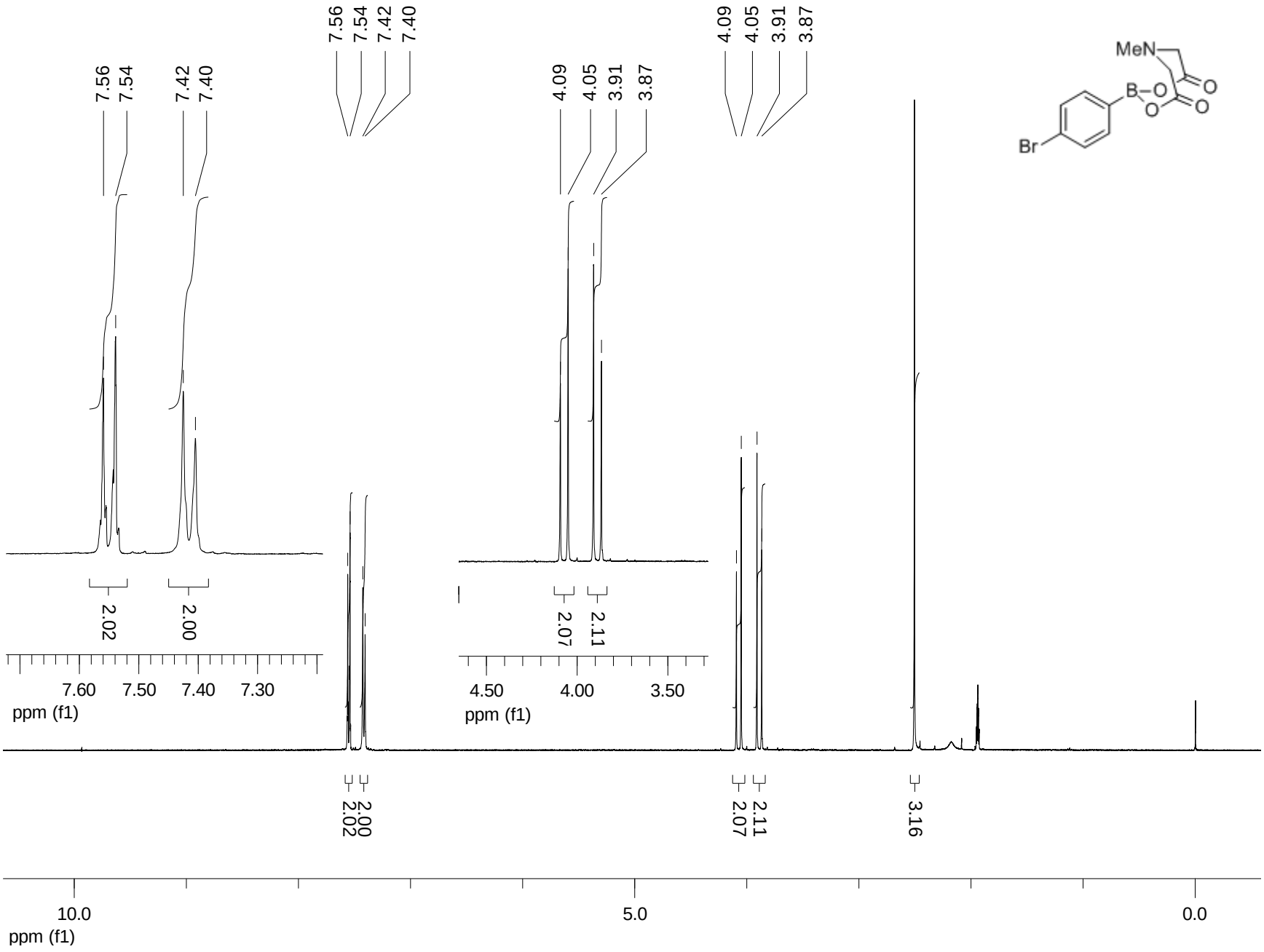
125.66
20.91
B(OH)2
Me
2
200
150
100
50
0
ppm (f1)

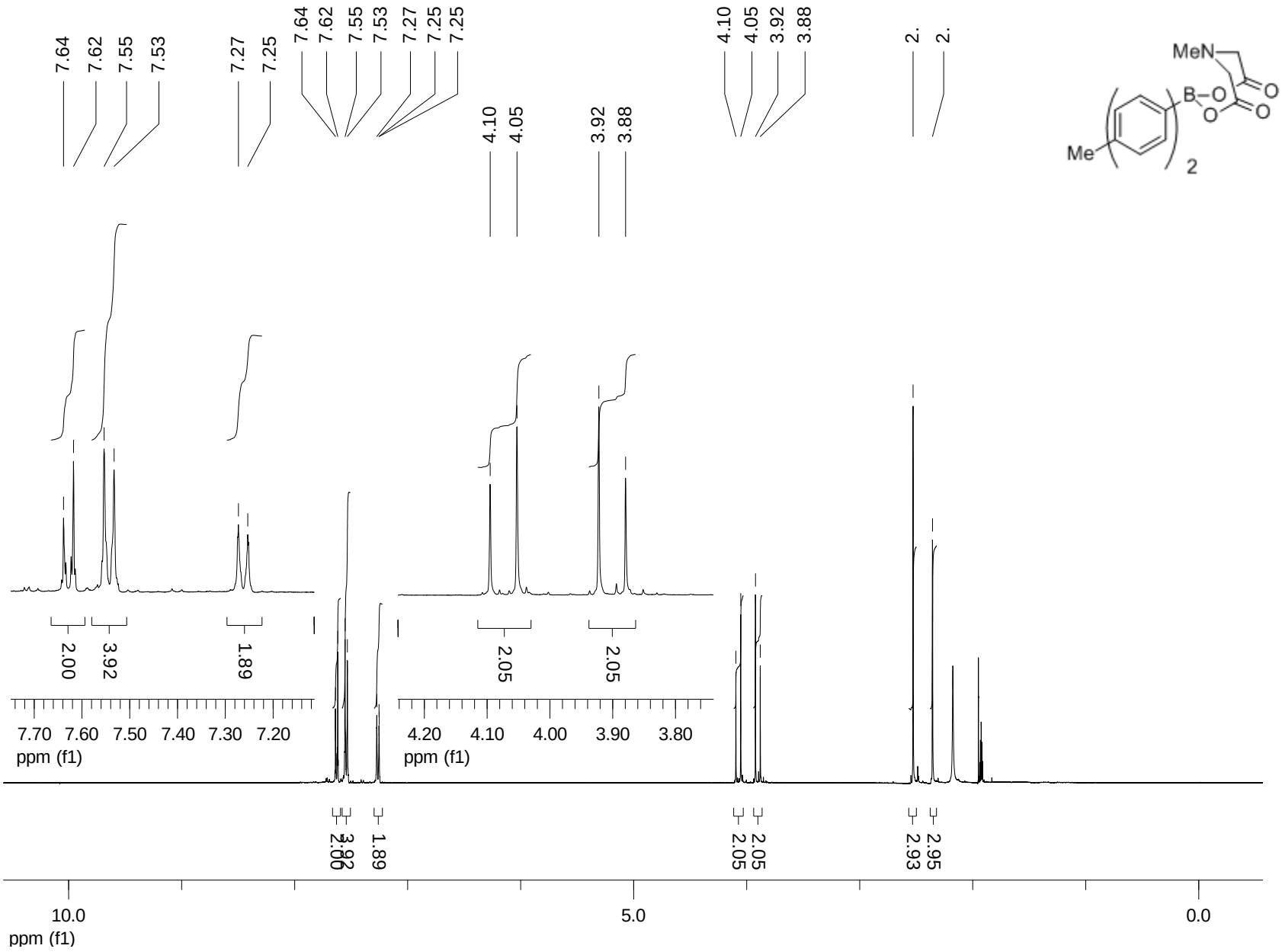
N-Methyliminodiacetic acid ***2***

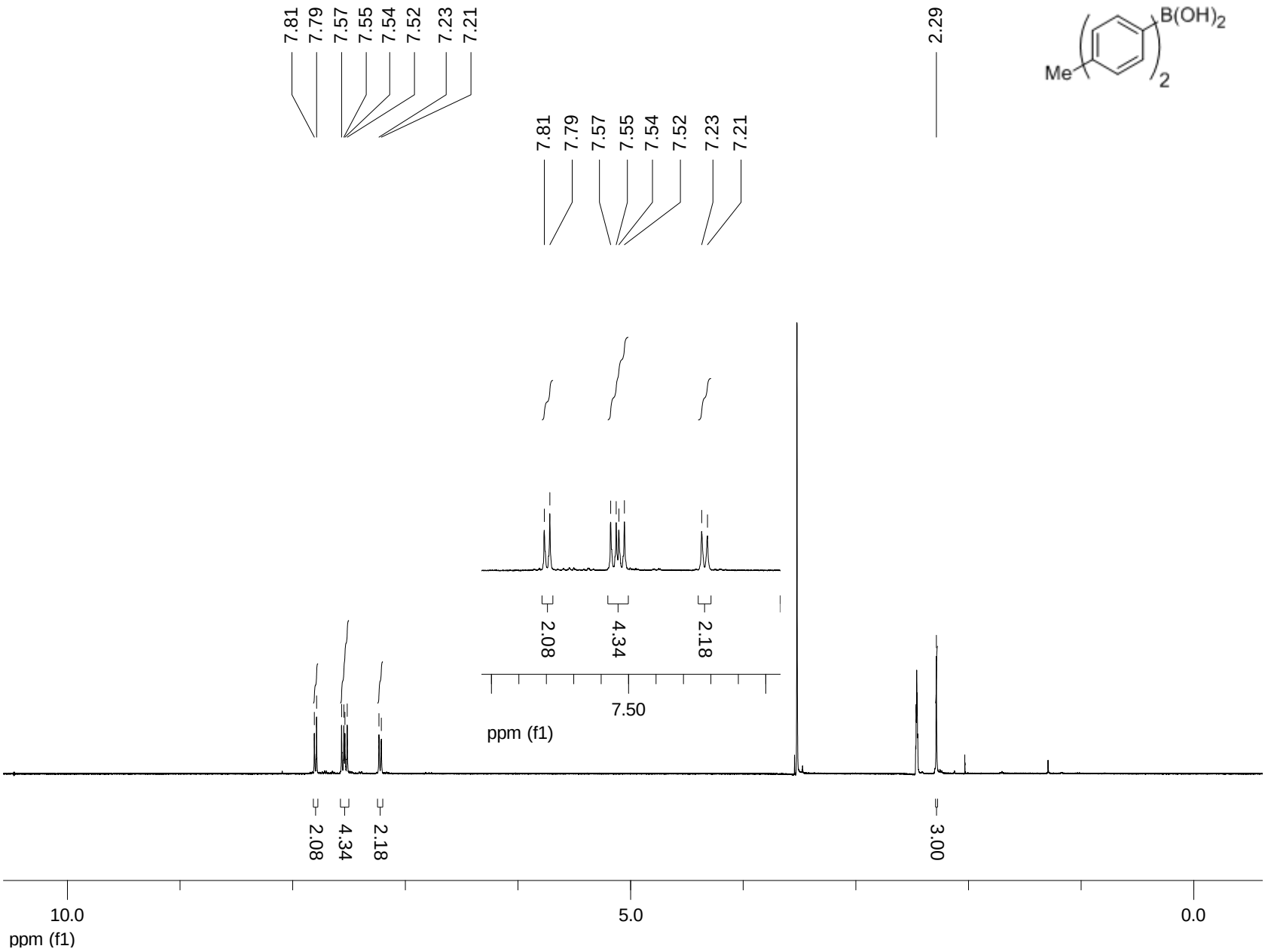


4-Bromophenylboronic MIDA Ester 4



4-(p-tolyl)-phenylboronic acid MIDA ester **5**

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7.21
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2.18
3.00
7.50
ppm (f1)
10.0
5.0
0.0
ppm (f1)