# Intramolecular Coupling for General Synthesis of Backbone Substituted Bicyclo[1.1.1]pentyl Boronates

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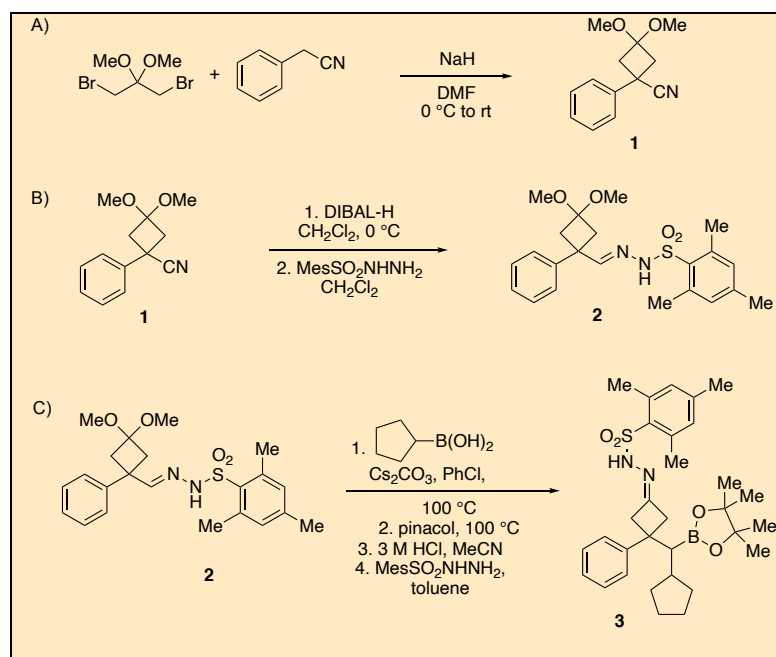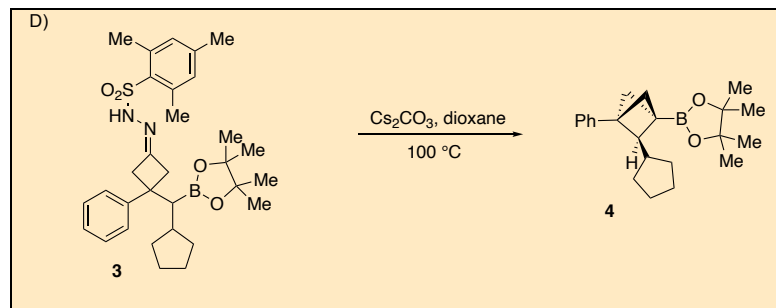
Procedure (Note 1)

A. *3,3-Dimethoxy-1-phenylcyclobutane-1-carbonitrile (1)*. A 1000-mL single-necked round-bottomed flask is equipped with a 6.4 cm Teflon-coated magnetic stir bar. The apparatus is flame-dried under vacuum, cooled to 25 °C and refilled with argon three times (Figure 1A). The flask is charged with sodium hydride (60%, 500 mmol, 20.0 g, 2.5 equiv) (Note 2). Then *N,N*-dimethylformamide (470 mL) (Note 3) is added into the flask, and the mixture is cooled to 0 °C in an ice-water bath and stirred for 15 min at 280 rpm (Figure 1B). Then an *N,N*-dimethylformamide (30 mL) solution of benzyl cyanide (200 mmol, 23.4 g, 23.1 mL, 1.0 equiv) (Note 4) is added dropwise into the flask through a dropping funnel at 0 °C over a period of 40 min (Note 5) (Figure 1C). After benzyl cyanide is added, the reaction system is allowed to warm up to room temperature (22–26 °C) and stirred at 280 rpm until the hydrogen release stops (typically 0.5 h) (Figure 1D). Then 1,3-dibromo-2,2-dimethoxy-propane (240 mmol, 62.8 g, 1.2 equiv) (Note 6) is added through a feeding funnel into the flask at room temperature (22–26 °C), and the mixture turns into a dark green suspension (Figure 1E). The reaction is allowed to stir at the ambient temperature at 280 rpm for another 16 h (Note 7). Reaction progress is monitored by TLC analysis (Note 8) (Figure 1F).

After benzyl cyanide is totally consumed as determined by TLC analysis, the reaction is cooled to 0 °C in an ice-water bath. Excess sodium hydride is quenched by dropwise addition of water (50 mL x 2) (Note 9) through a 60 mL syringe over 30 min (Figure 1G). The stir bar is removed, and the reaction mixture is concentrated to remove DMF solvent by rotary evaporation (30 °C, 45 mmHg to 50 °C, 15 mmHg) (Figure 1H). Next, the remaining reaction mixture (about ~150 mL) is diluted with water (400 mL)

and diethyl ether (250 mL) (Note 10), and the solution is transferred to a 1000-mL separatory funnel (Figure 1I). The aqueous phase is separated (Note 11) and extracted with diethyl ether (3 x 150 mL) . The combined organic layers are washed with water (100 mL) and saturated NaCl solution (100 mL) and then dried over 60 g of anhydrous Na_2SO_4. The solution is filtered through Celite (60 g, prewet with 100 mL diethyl ether) (Note 12) in a 350-mL large porosity sintered glass funnel into a 1000 mL round-bottomed flask using diethyl ether as eluent (300 mL) (Figure 1J). To the reaction mixture is added 178 g silica gel (Note 13) and concentrated by rotary evaporation (30°C, 375 mmHg to 30 °C, 15 mmHg) to afford a homogeneous yellow solid (Figure 1K), which is loaded onto a chromatography column (7.0-cm width and 50-cm height), prepared from 430 g silica gel (Note 14) and with 500 mL of hexanes (Note 15) (Figure 1L). At this point, fraction collection (250-mL fractions) begins, and elution is continued with 500 mL hexanes, 500 mL of 10% EtOAc-hexane (9: 1 hexanes:EtOAc) (Note 16) and then 3.5 L of 20% EtOAc-hexane (4: 1 hexanes:EtOAc). The desired product is obtained in fractions 12-16 (Figure 1M) (Note 17), which are concentrated by rotary evaporation (30 °C, 175 mmHg to 30 °C, 15 mmHg) to afford a yellow solid as the crude product (Figure 1N).

The yellow solid is redissolved in hot EtOAc (7.0 mL) (Figure 1O) and then allowed to cool to room temperature (23–26 °C) until the solids precipitate. Additional hexanes (40.0 mL) are added dropwise at the rate of 40 mL/h. This solution is cooled at 0 °C in an ice-water bath and stirred for 1 h, and the resulting solids (Figure 1P) are collected by suction filtration on a Büchner funnel. The residual solid is further washed with 14% EtOAc-hexane (40 mL) (6:1 hexanes:EtOAc), and then transferred to a 100-mL round-bottomed flask and dried at 1 mmHg for 2 h to provide white solid as the product (19.1 g, 44%) (Notes 18, 19, and 20) (Figure 1Q).
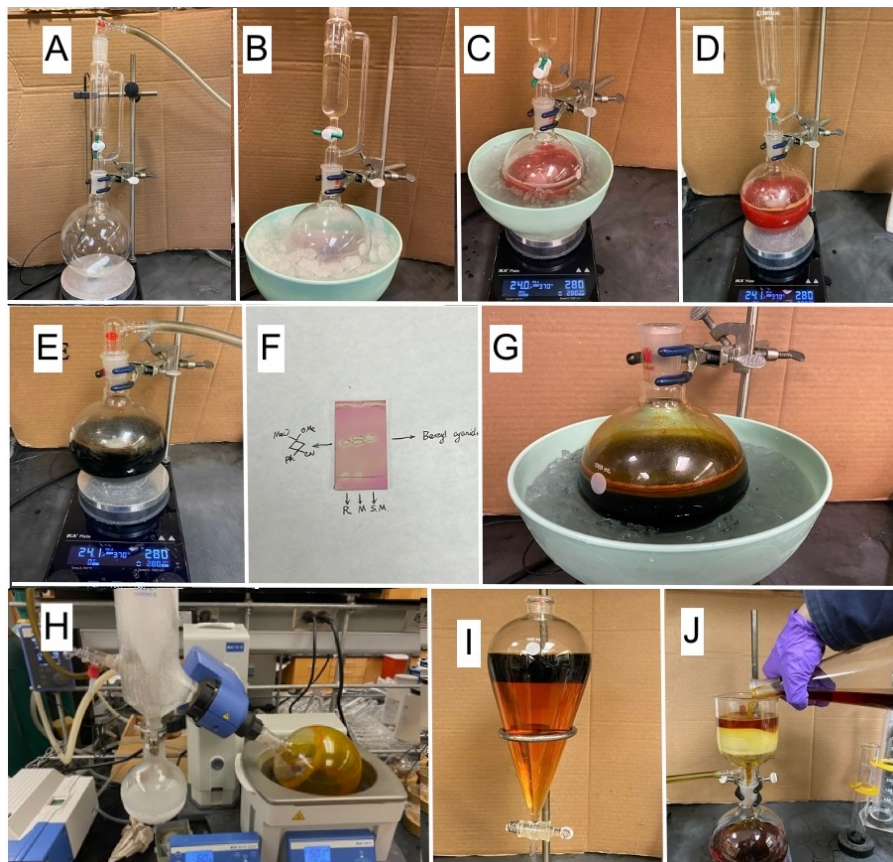
Figure 1. Synthesis of Compound 1: (A) Reaction equipment setup; (B) Reaction set-up containing NaH solution in DMF; (C) Benzyl cyanide is added; (D) The reaction is warmed up to room temperature; (E) 1,3-dibromo-2,2-dimethoxypropane is added; (F) TLC plate of the reaction mixture; (G) Reaction mixture is quenched; (H) Reaction mixture is concentrated; (I) Aqueous and organic layers; (J) Dried organic layers are filtered; (photos provided by authors)
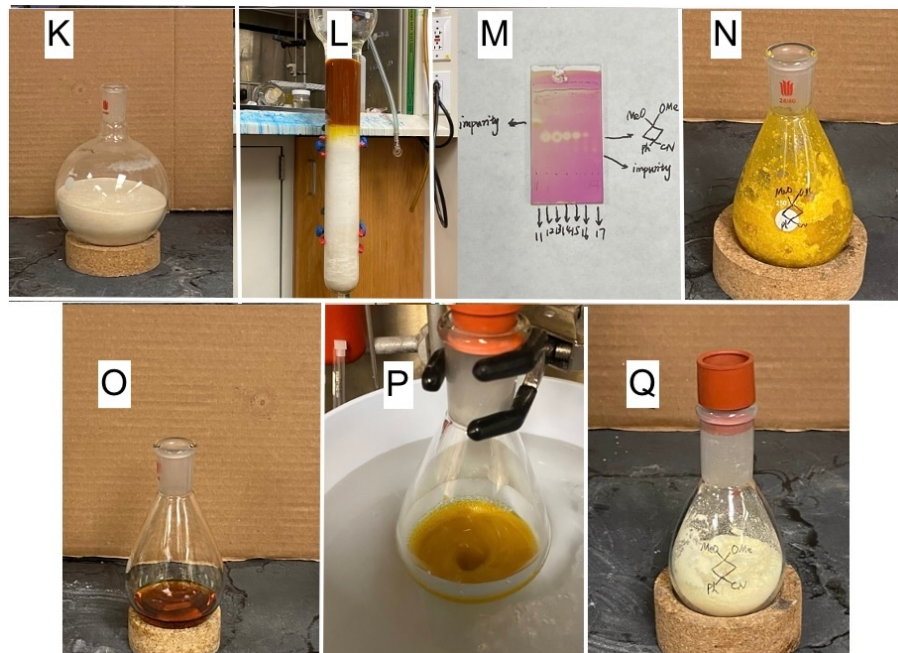
Figure 1 (continued). K) Reaction crude with silica gel for chromatographic purification; (L) Column chromatography with reaction crude; (M) TLC of fractions; (N) Concentrated crude oil after chromatography purification; (O) Oil is dissolved in hot EtOAc-hexane solvent. (P) Solids in the reaction crude after being cooled; (Q) Pure product 1. (photos provided by authors)

B. *N'-((3,3-Dimethoxy-1-phenylcyclobutyl)methylene)-2,4,6-trimethylbenzene-sulfonohydrazide (2)*. A flame-dried 1000-mL single-necked round-bottomed flask is equipped with a 5 cm Teflon-coated football-shape magnetic stir bar. The apparatus is flame-dried under vacuum, then cooled to 25 °C and refilled with argon three times. The flask is charged with **1** (16.3 g, 75.0 mmol, 1.0 equiv) under an atmosphere of argon (Figure 2A) and methylene chloride (300 mL) (Note 21) is then added into the flask. After the reaction mixture is cooled at 0 °C in an ice-water bath and stirred for 15 min at 310 rpm (Figure 2B), a solution of DIBAL-H (98 mL, 1.0 M, 98 mmol, 1.3 equiv) (Note 22) in hexanes is added dropwise into the flask twice through a 60-mL syringe pushed by a syringe pump at 0 °C at the speed of 30 mL/h (Note 23). (Figure 2C). After the addition of DIBAL-H is completed, the reaction mixture is allowed to stir at 0 °C for 1 h and reaction progress is monitored by TLC analysis (Figure 2D) (Note 24).

The excess DIBAL-H is quenched by dropwise addition of methanol (10 mL) at 0 °C over the course of 20 min. When bubbling ceases, a saturated aqueous solution of potassium sodium tartrate (100 mL) (Note 25) is added to the reaction mixture and the solution vigorously stirred at 310 rpm for 2.5 h to form a two-phase solution, which appears when stirring is stopped (Figure 2E). The mixture is transferred into a 1000-mL separatory funnel. The aqueous layer is separated and further extracted with methylene chloride (3 x 100 mL). The combined organic layers are dried over anhydrous Na_2SO_4 (60 g) and filtered through Celite (60 g, prewet with 100 mL diethyl ether) that is placed in a 350-mL large porosity sintered glass funnel into a 1000 mL round-bottomed flask using methylene chloride as eluent (200 mL) (Figure 2F). The filtered solution is concentrated to around 100 mL using a rotary evaporator (30 °C, 225 mmHg to 45 mmHg).

The concentrated reaction mixture is transferred into another 250-mL round-bottomed flask, and methylene chloride (20 mL) is used to rinse the original 1000-mL flask. Then 2-mesitylenesulfonyl hydrazide (16.1 g, 75.0 mmol, 1.0 equiv) is added in one portion (Note 26), and the reaction mixture is stirred at room temperature (22–26 °C) for 1.0 h (Figure 2G). After the aldehyde is confirmed to be completely consumed through TLC analysis (Note 27) (Figure 2H), silica gel (105 g) is added to the reaction mixture, which is concentrated by rotary evaporation (30 °C, 375 mmHg to 30 °C, 15 mmHg) to afford a homogeneous white solid (Figure 2I). This solid is loaded onto a chromatography column (6.0 x 32 cm), which consists of 168.4 g silica gel that had been wet-packed with 500 mL hexanes and eluted with 250 mL hexanes (Figure 2J). At that point, elution continues sequentially with 2.0 L of hexanes:EtOAc (4:1) and 1.5 L of hexanes: EtOAc (3:1). The eluate is collected (50 mL fractions) to provide the pure product in fractions 34–-52 and the product containing impurities in fractions 28–34 and 53–68. (Note 28) (Figure 2K). Fractions 33–54 are combined in a 1000-mL collection flask and concentrated by rotary evaporation under reduced pressure (30 °C, 45 mmHg). Then the concentrated product is then transferred to a 100-mL flask and dried under vacuum for 1 h (1 mmHg) to afford *N'*-((3,3-dimethoxy-1-phenylcyclobutyl)methylene)-2,4,6-trimethylbenzene-sulfonohydrazide (**2**) as a white powder (15.0 g, 48%) (Figure 2L) (Notes 29, 30, and 31).
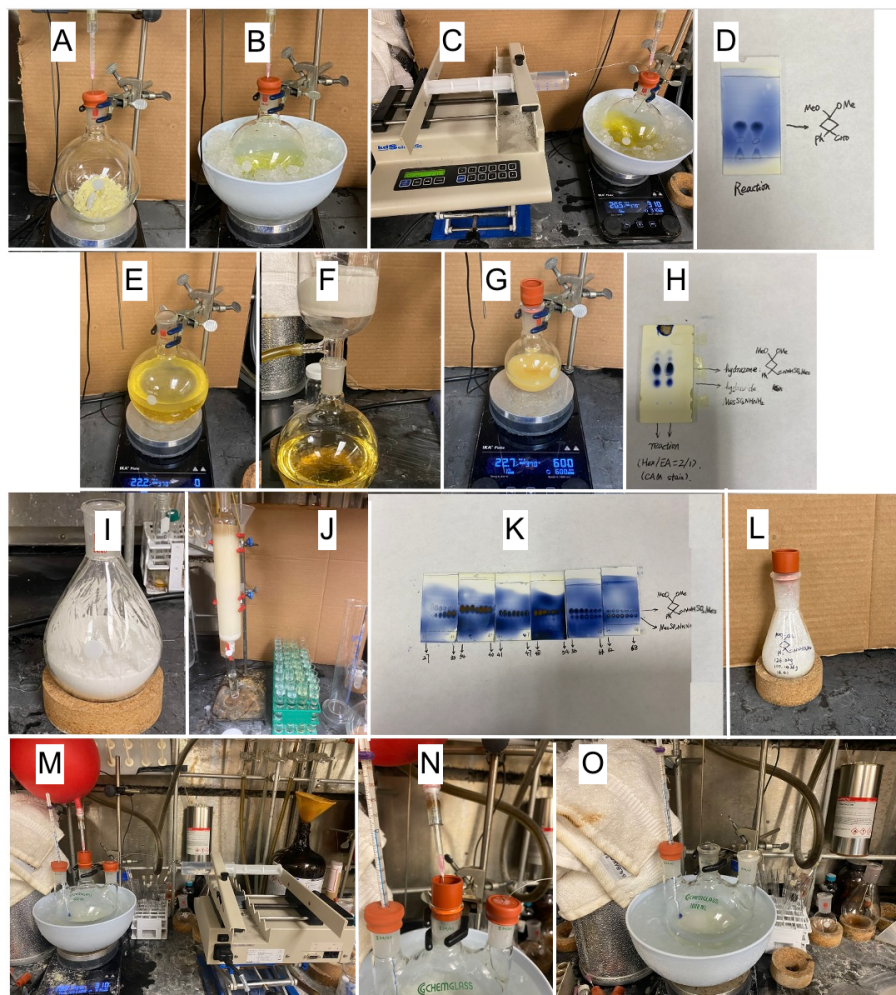
Figure 2. Synthesis of Compound 2: **(A)** Reaction equipment with compound 1; **(B)** CH₂Cl₂ solution of 1 in a cooled bath; **(C)** Addition of DIBAL-H; **(D)** TLC plate of the crude reaction mixture; **(E)** Two-phase layers after addition of Rochelle salt solution; **(F)** Dried organic layers are filtered; **(G)** 2-Mesitylenesulfonyl hydrazide is added; **(H)** TLC plate of the crude condensation; **(I)** Reaction crude with silica gel for chromatographic purification; **(J)** Column chromatography with reaction crude; **(K)** TLC of fractions; **(L)** Pure product 2. **(M)** Addition of DIBAL-H with internal temperature control; **(N)** Internal temperature measurement; **(O)** Quench the reaction with Rochelle salt solution. (photos provided by authors)

C. *N'-(3-(Cyclopentyl(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)-3-phenylcyclobutylidene)-2,4,6-trimethylbenzenesulfonohydrazide* (**3**). An oven-dried 250-mL single-necked (24/40 joint) round-bottomed flask is equipped with a 3 cm Teflon-coated football-shape magnetic stir bar. The apparatus is charged with **2** (12 mmol, 5.0 g, 1.0 equiv), cyclopentyl boronic acid (4.1 g, 36 mmol, 3.0 equiv) (Note 32), and cesium carbonate (11.7 g, 36 mmol, 3.0 equiv) (Note 33) under an atmosphere of argon (Figure 3A). Chlorobenzene (60 mL) (Note 34) is added to the reaction, and the flask is heated in a 100 °C oil-bath and stirred at 650 rpm (Figure 3B). After heating for 2 h, the nitrogen is totally released (Note 35), and it is confirmed by TLC analysis that hydrazone is totally consumed (Figure 3C) (Note 36). The reaction mixture is cooled to room temperature (22–26 °C) and pinacol (7.1 g, 60 mmol, 5.0 equiv) is added to the mixture under the argon atmosphere (Note 37). Then the reaction mixture is reheated in a 100 °C oil-bath and stirred at 650 rpm for another 30 min (Figure 3D). The boronic ester formation process is monitored by TLC analysis (Figure 3E) (Note 38). After the flask is re-cooled to room temperature (22–26 °C), the reaction mixture is filtered through Celite (30 g, prewet with 50 mL diethyl ether), placed in a 150-mL large porosity sintered glass funnel, into a 500 mL round-bottomed flask using diethyl ether as eluent (200 mL) (Figure 3F). The filtered solution is concentrated by rotary evaporation (30 °C, 225 mmHg to 35 °C, 7.5 mmHg) to remove excess diethyl ether and chlorobenzene (Figure 3G).

The concentrated crude reaction is dissolved in 50 mL of acetonitrile (Note 39), to which is added HCl solution (48 mmol, 3 M, 16 mL, 4.0 equiv) (Note 40). The solution is stirred at 400 rpm for 60 min (Figure 3H). The hydrolysis is monitored by TLC analysis (Note 41) (Figure 3I). After the acetal is totally consumed, as determined by TLC analysis, the crude reaction is concentrated by rotary evaporation (30 °C, 225 mmHg to 32 °C, 7.5 mmHg) to remove excess acetonitrile (Figure 3J). Diethyl ether (100 mL) and saturated brine (50 mL) are added to the reaction mixture, and this solution is transferred to a 500-mL separatory funnel (Figure 3K). The aqueous layer is separated and further extracted with diethyl ether (3 x 50 mL). The combined organic layers are dried over anhydrous Na_2SO_4 (50 g), filtered through Celite (20 g, prewet with 50 mL diethyl ether) that is placed a 150-mL large porosity sintered glass funnel into a 500 mL round-bottomed flask. Diethyl ether (50 mL) is used to wash the Celite, and the resulting solution is concentrated by rotary evaporation (30 °C, 225 mmHg to 32 °C, 7.5 mmHg) to remove excess solvent.

After solvent removal, a 3 cm Teflon-coated football-shape magnetic stir bar, 2-mesitylenesulfonyl hydrazide (18 mmol, 3.9 g, 1.5 equiv) and toluene (50 mL) (Note 42) are added into the flask, and the reaction mixture is stirred at room temperature (23–26 °C) at 500 rpm for 12 h (Figure 3L). The hydrazone formation process is monitored by TLC analysis (Note 43) (Figure 3M). After the ketone is confirmed to be totally consumed, the reaction crude is concentrated by rotary evaporation (30 °C, 225 mmHg to 35 °C, 7.5 mmHg) to remove excess toluene.

The crude product is dissolved in methylene chloride (100 mL) and then silica gel (23.7 g) is added. The mixture is concentrated in vacuo to afford a homogeneous yellow solid. The solid is loaded onto a chromatography column (4.6 x 45.7 cm) that contains 104.5 g silica gel, which had been wet-packed with 500 mL hexanes (Figure 3O).   The column is eluted within 30 min (Note 44) with 550 mL of hexanes: ethyl acetate: methylene chloride (20:1:1). At that point, elution is continued sequentially with 525 mL of hexanes: ethyl acetate: methylene chloride (18:2:1), and then 550 mL of hexanes: ethyl acetate: methylene chloride (18:3:1). The desired product is obtained in fractions 41–76 (Note 45) (Figure 3P), which are concentrated by rotary evaporation (30 °C, 275 mmHg to 30 °C, 15 mmHg) to afford a yellow solid collected in a 100-mL single-necked flask. Hexanes (40 mL) are added into the flask, and the mixture is stirred at room temperature (23–26 °C) for 0.5 h (Figure 3Q). The resulting solids (Figure 3R) are collected by suction filtration on a Büchner funnel. The residual solid is further washed with hexanes (50 mL) , and then transferred to a 20 mL vial and dried at 1 mmHg for 2 h to provide the white solid as the product (2.62 g, 40%) (Notes 46, 47, and 48) (Figure 3S).
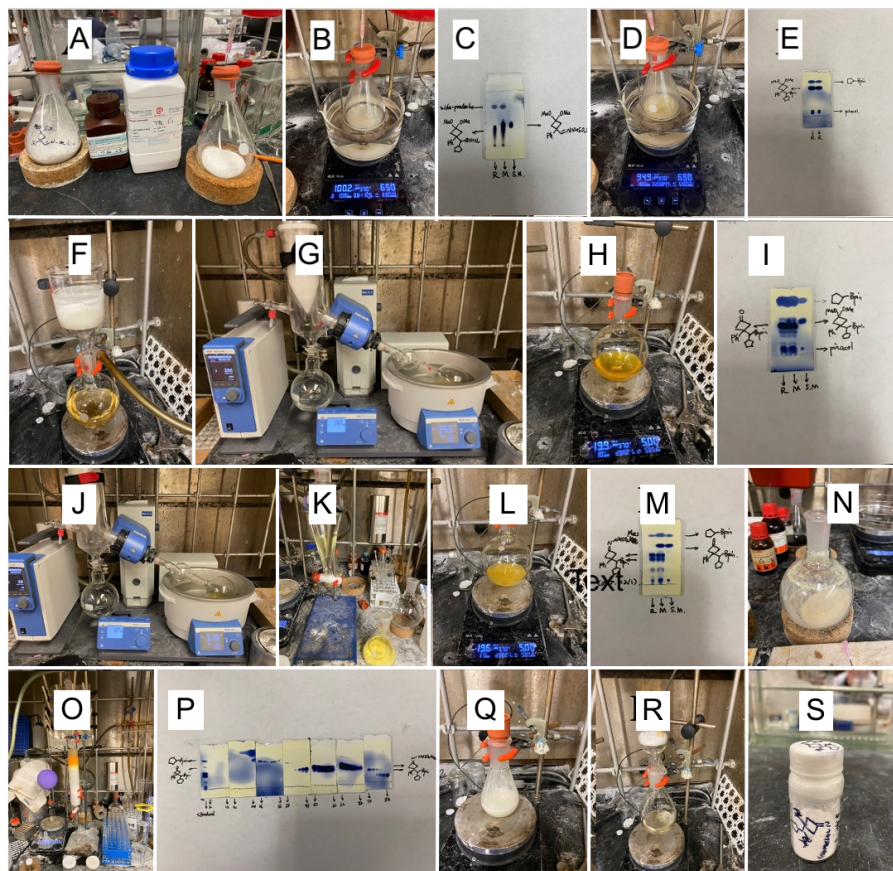
Figure 3. Synthesis of Compound 3: (A) Reaction setup with solid reagents; **(B)** Reaction mixture being heated with nitrogen released; **(C)** TLC plate of the boronic acid; **(D)** Reaction mixture forming boronic pinacol ester; **(E)** TLC plate of the boronic pinacol ester; **(F)** Filtered reaction crude; **(G)** Excess solvent is removed; **(H)** Hydrolysis reaction; **(I)** TLC plate of the crude hydrolysis; **(J)** Excess acetonitrile is removed; **(K)** Aqueous and organic layers; **(L)** Reaction mixture forming sulfonyl hydrazone; **(M)** TLC plate of sulfonyl hydrazone formation; **(N)** Crude reaction product on silica gel; **(O)** Column chromatography with reaction crude; **(P)** TLC plates of fractions; **(Q)** purified product washed with hexanes; **(R)** Filtration of washed products; **(S)** Pure product 3. (photos provided by authors)

D.   *2-(2-Cyclopentyl-3-phenylbicyclo[1.1.1]pentan-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4).* An oven-dried 250-mL single-necked round-bottomed flask is equipped with a 3-cm Teflon-coated football-shape magnetic stir bar. The apparatus is charged with compound **3** (4.95 g, 9.0 mmol, 1.0 equiv) and cesium carbonate (8.8 g, 27 mmol, 3.0 equiv) under argon atmosphere (Figure 4A). Then dioxane (90 mL) (Note 49) is added into the flask and the reaction mixture is heated in a 100 °C oil-bath and stirred at 600 rpm for 2 h (Figure 4B). The cyclization process is also monitored by TLC analysis (Note 50) (Figure 4C). After the flask is cooled to room temperature (22–26 °C), diethyl ether (100 mL) is added into the reaction mixture and the reaction mixture is filtered through Celite (30 g, prewet with 50 mL diethyl ether), which is placed in a 150-mL large porosity sintered glass funnel, into a 500 mL round-bottomed flask using diethyl ether as eluent (200 mL) (Figure 4D). The filtered solution is concentrated to remove diethyl ether and dioxane by rotary evaporation (30 °C, 225 mmHg to 35 °C, 7.5 mmHg) (Figure 4E).

After concentration, the crude product is dissolved in methylene chloride (30 mL) and then 9.8 g silica gel is added. The mixture is concentrated in vacuo to afford a homogeneous white solid. The solid is loaded onto a 4.6 x 45.7 cm chromatography column of 118.0 g silica gel, which had been wet-packed with 500 mL hexanes (500 mL). The column is eluted with 300 mL of hexanes: CH_2Cl_2 (11: 1) (Figure 4F), followed sequentially by 400 mL of hexanes: CH_2Cl_2 (7: 1), 300 mL of hexanes: CH_2Cl_2 (5: 1), 1000 mL of hexanes: CH_2Cl_2 (3: 1), and finally 400 mL of CH_2Cl_2: EtOAc (100 : 1). The pure desired product is obtained in fractions 96–126 (Note 51) (Figure 4G), which are concentrated by rotary evaporation (30 °C, 275 mmHg to 30 °C, 15 mmHg) to afford a colorless oil. This oil is placed in a –20 °C freezer, and a white solid forms (Figure 4H), which is the pure product (2.09 g, 69%) (Notes 52, 53, 54, and 55).
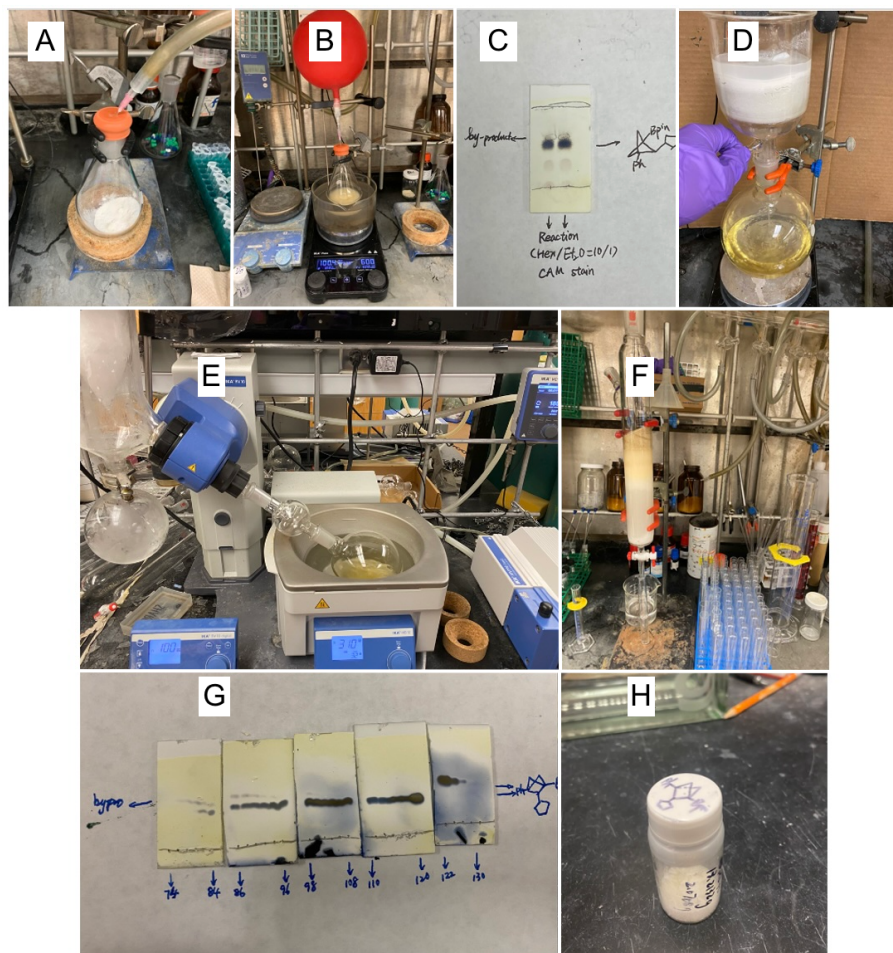
Figure 4. Synthesis of Compound 4: (A) Reaction setup with solid reagents; (B) Reaction mixture being heated at 100 °C; (C) TLC plate of the cyclization; (D) Filtered crude reaction mixture; (E) Excess solvent is removed; (F) Column chromatography with reaction crude; (G) TLC plate of fractions; (H) Pure product 4. (photos provided by authors)

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance

and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical. See also "Identifying and Evaluating Hazards in Research Laboratories" (American Chemical Society, 2015) which is available via the associated website "Hazard Assessment in Research Laboratories" at https://www.acs.org/content/acs/en/about/governance/committees /chemicalsafety/hazard-assessment.html. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with sodium hydride, benzyl cyanide, 1,3-dibromo-2,2-dimethoxy-propane, N,N-dimethylformamide, diethyl ether, NaCl, Na_2SO_4, silica gel, Rochelle salt, hexanes, ethyl acetate, methylene chloride, DIBAL-H, Celite, 2-mesitylenesulfonyl hydrazide, cyclopentyl boronic acid, cesium carbonate, chlorobenzene, pinacol, acetonitrile, HCl solution, brine, toluene, dioxane, and 1,3,5- trimethoxybenzene.

2. Sodium hydride (60%, dispersion in Paraffin Liquid) was purchased from TCI and used as received immediately upon receipt.

3. N, N-Dimethylformamide (99.8%, Super Dry, with molecular sieves) was purchased from Acros Organics and used as received. The checkers observed that the use of fresh and dry DMF was important for the success of the reaction.

4. Benzyl cyanide (98%) was purchased from Sigma-Aldrich and used as received.

5. Hydrogen was released during the addition of benzyl cyanide. Therefore, the speed of addition of benzyl cyanide should be slow. With benzyl cyanide added, the color of reaction mixture turned from grey to red suspension through pale yellow for a short time (Figure 1C).

6. 1,3-Dibromo-2,2-dimethoxypropane (98%) was purchased from BLD Pharmatech Co. and used as received.

7. Hydrogen gas evolved as the reaction warmed to room temperature (22–26 °C) and continued with slight exotherms (Figure 1D).

8. An aliquot (0.1 mL) was removed and mixed with sat. NH_4Cl (1 mL) and diethyl ether (1 mL), and the contents were thoroughly mixed. The

organic layer was used for TLC monitoring, and reaction progress was determined by TLC analysis on silica gel using 1:4 EtOAc: hexanes as eluent and visualization with KMnO$_4$ (R_f = 0.55). The reaction was determined to be completed when benzyl cyanide was totally consumed (Figure 1F).

9. Additional hydrogen bubbles were also released during quenching the reaction with water. Thus, the speed of adding water to quench reaction should be controlled.

10. Diethyl ether (99.0%) was purchased from Fisher and used as received.

11. The interface between the dark aqueous and the organic phase can be difficult to discern.

12. Celite (545 Filter Aid, not acid-washed) was purchased from Fisher and used as received.

13. SiliaFlash P60 (particle size 0.040–0.063 mm) was purchased from SiliCycle and used as received.

14. The column is wet-packed using 430 g of silica and 1.0 L of hexanes.

15. Hexanes (98.5%) was purchased from Fisher and used as received.

16. Ethyl acetate (99.5%) was purchased from Fisher and used as received.

17. Fractions (250 mL) containing the product were identified by TLC analysis (4:1 hexanes: EtOAc as eluent, R_f = 0.55). Fractions 12-14 contained only the desired product while fractions 15-16 contained the desired product and two impurities that can be visualized by UV irradiation and by KMnO$_4$ stain as two spots (Figure 1M). This impurity does not impact the trituration of the desired product **1,** so these fractions were also collected. Test tubes containing the desired product were each rinsed with EtOAc (2 x 2 mL), and the rinses were transferred into the collection flask.

18. 3,3-Dimethoxy-1-phenylcyclobutane-1-carbonitrile (**1**): mp 53–55 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ: 7.51 – 7.45 (m, 2H), 7.43 – 7.37 (m, 2H), 7.35 – 7.29 (m, 1H), 3.28 (s, 3H), 3.18 (s, 3H), 3.13 – 3.07 (m, 2H), 2.76 – 2.70 (m, 2H) ppm; ^{13}C NMR (151 MHz, CDCl$_3$) δ: 139.5, 129.1, 128.1, 125.9, 123.7, 98.1, 49.0, 48.7, 45.8, 31.2 ppm; HRMS (ESI+) calc. for C$_{13}$H$_{16}$NO$_2$ [M+H]$^+$ 218.1176, found 218.1177.

19. The purity of **1** was determined to be 97.9 wt% by qNMR using 1,3,5-trimethoxybenzene (Sigma-Aldrich, 99%) as the external standard.

20. A second run performed at full scale provided 20.9 g (48%) of **1** at 98.8 % purity.

21. Methylene chloride (>99.9%, Optima™ for HPLC and GC) was purchased from Fisher and dried through passing an activated alumina column.

22. DIBAL-H (1.0 M in hexanes) was purchased from Sigma-Aldrich and used as received without further titration.

23. Control of the addition rate of DIBAL-H is critical to the yield of compound **2**. The yields are decreased when DIBAL-H solution is added too quickly because of difficulties in controlling the reaction temperature. During the DIBAL addition, the internal temperature did not exceed 5 °C (Figures 2M and 2N).

24. An aliquot (0.1 mL) used for TLC monitoring was removed and diluted with 0.9 mL methylene chloride, and reaction progress was determined by TLC analysis on silica gel using 1:4 EtOAc: hexanes as eluent and visualization with CAM stain (Figure 2D, R_f = 0.36).

25. Rochelle salt (potassium sodium tartrate tetrahydrate) was purchased from BLD Pharmatech Co. The use of 1 mL of the saturated solution per 1.0 mmol of DIBAL-H was found to be optimal. During the quench process, the internal temperature did not exceed 10 °C (Figure 2O)

26. 2-Mesitylsulfonyl hydrazide (98%) was purchased from Combi-Blocks and used as received.

27. An aliquot (0.1 mL) used for TLC monitoring was removed and diluted with 0.9 mL methylene chloride, and reaction progress was determined by TLC analysis on silica gel with 1:4 EtOAc: hexanes as eluent and visualization with CAM stain (Figure 2H, R_f = 0.43).

28. Fractions (50 mL) containing the product were identified by TLC analysis (4:1 hexanes: EtOAc as eluent). Fractions 34–52 contained only the desired product, while fractions 28–33 contained the desired product and one impurity that can be visualized by UV irradiation and by CAM stain as two spots (Figure 2K). Fractions 53-68 contained the desired product and excess 2-mesitylene hydrazide. For fraction 33, 53, and 54, impurities do not impact the purity of the desired compound as judged by qNMR so these fractions were also collected. Test tubes containing the desired product were each rinsed with EtOAc (2 x 3 mL), and the rinses were transferred into the collection flask.

29. *N′*-((3,3-Dimethoxy-1-phenylcyclobutyl)methylene)-2,4,6-trimethylben-zenesulfonohydrazide (**2**): mp 104–106 °C; ^{1}H NMR (600 MHz, Acetone-d[6]) δ: 9.71 (s, 1H), 7.38 (s, 1H), 7.28 – 7.22 (m, 2H), 7.18 (ddt, *J* = 8.1, 6.7, 1.3 Hz, 1H), 7.07 – 7.02 (m, 4H), 3.02 (s, 3H), 2.90 (s, 3H), 2.82 – 2.76 (m, 2H), 2.62 (s, 6H), 2.46 – 2.40 (m, 2H), 2.31 (s, 3H); ^{13}C NMR (151 MHz,

Acetone-d$_6$) δ: 153.8, 145.4, 143.3, 140.7, 134.4, 132.5, 129.2, 127.2, 127.1, 99.3, 48.3, 48.2, 41.9, 41.03, 23.4, 20.9; HRMS (ESI+) calc. for C$_{22}$H$_{28}$N$_2$O$_4$S [M+Na]$^+$ 439.1662, found 439.1666.

30. The purity of **2** was determined to be 99.0 wt% by qNMR using 1,3,5-trimethoxybenzene (Sigma-Aldrich, 99%) as the external standard.

31. A second run performed at full scale provided 16.1 g (50%) of **2** at 98.6% purity.

32. Cyclopentyl boronic acid (97%) was purchased from Combi-Blocks and used as received.

33. Cesium carbonate was purchased from BLD Pharmatech Co. and used as received.

34. Chlorobenzene (99.9%) was purchased from Sigma-Aldrich and used as received.

35. As the reaction continues, nitrogen was released from the diazo intermediate. White solid, which could not dissolve in chlorobenzene, was also observed in the reaction mixture (Figure 3B).

36. An aliquot (0.1 mL) used for TLC monitoring was removed and diluted with 0.9 mL diethyl ether, and reaction progress was determined by TLC analysis on silica gel with 1:3 EtOAc: hexanes as eluent and visualization with CAM stain (Figure 3C, R_f = 0.31). The side product, which was strongly visualized by UV light, was (3,3-dimethoxycyclopent-1-en-1-yl)benzene (**5**) (Figure 5), which was formed owing to self-rearrangement of diazo intermediate.

37. Pinacol was purchased from TCI and used as received. The boronic acid formed in the first coupling step is sensitive to air at 100 °C, thus operations before forming the boronic ester should be performed under argon atmosphere.

38. An aliquot (0.1 mL) used for TLC monitoring was removed and diluted with 0.9 mL diethyl ether, and reaction progress was determined by TLC analysis on silica gel with 1:4 EtOAc: hexanes as eluent and visualization with CAM stain (Figure 3E, R_f = 0.75).

39. Acetonitrile (HPLC grade, 99.9%) was purchased from Fisher and used as received.

40. 3 M HCl solution was prepared by slowly adding HCl (36.5%–38% w.t., 125 mL) to 375 mL water. Be careful with the exotherms owing to HCl dissolution. HCl (36.5%–38% w.t.) was purchased from Fisher and used as received.

41. An aliquot (0.1 mL) used for TLC monitoring was removed and diluted with 0.9 mL diethyl ether, and reaction progress was determined by

TLC analysis on silica gel with 1:8 acetone: hexanes as eluent and visualization with CAM stain (Figure 3I, $R_f = 0.44$). Cerium ammonium molybdate stain (CAM stain) was prepared by dissolving 12.5 g ammonium molybdate tetrahydrate and 5 g cerium ammonium sulfate dihydrate in 500 mL 10% H_2SO_4. The authors report that the spot which appears above the desired product is the impurity **5,** and the spot which appears below the desired product is the hydrolyzed impurity **6**, 3-phenylcyclopent-2-en-1-one (Figure 5).
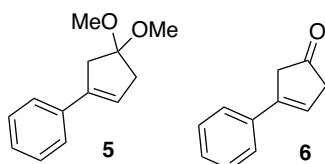
Figure 5. Impurities 5 & 6 observed during the synthesis of 3

42. Toluene (>99.8%) was purchased from Fisher and dried through passing an activated alumina column.
43. An aliquot (0.1 mL) used for TLC monitoring was removed and diluted with 0.9 mL methylene chloride, and reaction progress was determined by TLC analysis on silica gel with 1:3 EtOAc: hexanes as eluent and visualization with CAM stain (Figure 3M, $R_f = 0.41$).
44. The column was eluted with the solvents described in the procedure immediately after loading the sample on the column. The chromatographic separation took around 30 minutes. Eluting the column for longer time would result in a lower yield owing to sulfonyl hydrazone product crashing out and decomposition.
45. Fractions (25 mL) containing the product were identified by TLC analysis (4:1 hexane: ethyl acetate as eluent, $R_f = 0.41$) (Figure 3P). Fractions 41-74 containing the pure desired product were collected while fractions 76-80 contained products with other impurities. Test tubes containing the pure desired product were each rinsed with EtOAc (2 x 3 mL), and the rinses were transferred into the collection flask.
46. N'-(3-(Cyclopentyl(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)-3-phenylcyclobutylidene)-2,4,6-trimethylbenzenesulfonohydrazide (**3**): *Note: The Z/E mixture (ratio: 2/1) was observed via ¹H NMR and NMR characterization for the mixture was given.* mp >200 °C ¹H NMR (500 MHz, acetone-d₆) δ: 9.22 – 8.94 (m, 1H), 7.57 – 7.23 (m, 4H), 7.18 (ddt, $J = 7.5, 5.2, 1.5$ Hz, 1H), 6.98 (s, 2H), 3.50 – 3.35 (m, 1H), 3.33 – 3.03 (m, 3H), 2.62 (s,

3H), 2.61 (s, 3H), 2.26 (d, *J* = 1.9 Hz, 3H), 1.61 – 1.43 (m, 6H), 1.37 – 1.23 (m, 2H), 1.19 – 1.16 (m, 13H), 1.12 – 1.04 (m, 1H). ^{13}C NMR (151 MHz, acetone-d$_6$) δ: 155.7, 155.6, 148.9, 148.9, 143.1, 143.1, 140.8, 140.8, 134.8, 134.8, 132.5, 128.7, 128.7, 127.9, 127.9, 126.7, 84.0, 84.0, 48.4, 47.1, 44.8, 43.6, 43.4, 43.4, 40.4, 40.3, 34.7, 34.6, 31.6, 31.5, l25.9, 25.9, 25.5, 25.4, 25.4, 25.4, 25.2, 23.4, 23.4, 20.9; ^{11}B NMR (128 MHz, CDCl$_3$) δ: 34.83; HRMS (ESI+) calc. for C$_{31}$H$_{43}$BN$_2$O$_4$S [M+H]$^+$ 551.3109, found 551.3101.

47. The purity of **3** was determined to be 97.9 wt% by qNMR using 1,3,5-trimethoxybenzene (Sigma-Aldrich, >99%) as the external standard.

48. A second run performed at full scale provided 2.76 g (42%) of **3** at 97.7% purity.

49. Dioxane (99.5%, extra dry with molecular sieves, stabilized) was purchased from Acros Organics and used after it was received.

50. An aliquot (0.1 mL) used for TLC monitoring was removed and diluted with 0.9 mL diethyl ether, and reaction progress was determined by TLC analysis on silica gel with 1:3 EtOAc: hexanes as eluent and visualization with CAM stain (Figure 4C, R_f = 0.57).

51. Fractions (25 mL) containing the product were identified by TLC analysis (10:1 hexane:diethyl ether as eluent, R_f = 0.57). Fractions 82-126 mainly contained the desired product. For fraction 96-126, pure products are contained. Fractions 82-94 contained the product with the side-pro which could be purified via another column chromatography. Test tubes containing the desired product were each rinsed with Et$_2$O (2 x 3 mL), and the rinses were transferred into the collection flask.

52. 2-(2-Cyclopentyl-3-phenylbicyclo[1.1.1]pentan-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**4**): mp 41–43 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ: 7.30 – 7.23 (m, 2H), 7.22 – 7.13 (m, 3H), 2.75 (dd, *J* = 9.8, 2.8 Hz, 1H), 2.38 – 2.25 (m, 2H), 2.08 – 2.01 (m, 2H), 1.98 (d, *J* = 1.6 Hz, 1H), 1.82 (ddt, *J* = 11.6, 7.2, 3.9 Hz, 1H), 1.65 – 1.37 (m, 5H), 1.279 (s, 6H), 1.276 (s, 6H), 1.25 – 1.13 (m, 1H), 0.96 – 0.86 (m, 1H) ppm; ^{13}C NMR (151 MHz, CDCl$_3$) δ: 141.7, 128.0, 126.2 (2C), 83.4, 73.4, 52.8, 50.1, 45.5, 37.1, 32.7, 32.2, 25.8, 25.2, 25.0, 24.9 ppm; ^{11}B NMR (128 MHz, CDCl$_3$) δ: 31.74 ppm; HRMS (ESI+) calc. for C$_{22}$H$_{31}$NO$_2$ [M+H]$^+$ 339.2490, found 339.2492.

53. The purity of **4** was determined to be 97.7 wt% by qNMR using 1,3,5-trimethoxybenzene (Sigma-Aldrich, >99%) as the external standard.

54. The compound **4** could be converted into colorless crystal from its saturated solution in CH$_2$Cl$_2$. The X-ray crystallographic coordinates for compounds **4** have been deposited at the Cambridge Crystallographic Data Center (CCDC) with accession code 2062924.

55. A second run performed at full scale provided 2.31 g (76%) of **4** at 97.2% purity.

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

Discussion

Saturated three-dimensional high-strained bicyclic scaffolds play an important role in modern pharmaceutical chemistry. Among these motifs, bicyclo[1.1.1]pentane (BCP) is a high-value bioisostere for 1,4-disubstituted

phenyl rings[2], generally offering high water solubility, improved metabolic stability, and high passive permeability. At present, synthesis of disubstituted BCPs are mainly focused on transformations of strained [1.1.1]propellane[3] through either single- or two-electron transfer pathways.[4] However, functionalization of the backbone (C2) of BCPs is less reported[5]. Analogously, scaffolds containing C2-substituted BCPs are regarded as ideal bioisosteres of ortho- or meta- substituted benzenes[6] with the potential to provide greater opportunities for optimizing drug candidates and to expand the available chemical space of drugs. In this context, based on our previous research,[7] we developed a synthesis of multi-substituted BCPs including C2-substitution via a novel and practical intramolecular cyclization of cyclobutane-tethered sulfonyl hydrazones that were synthesized from commercially available reagents (Scheme 1).[8]
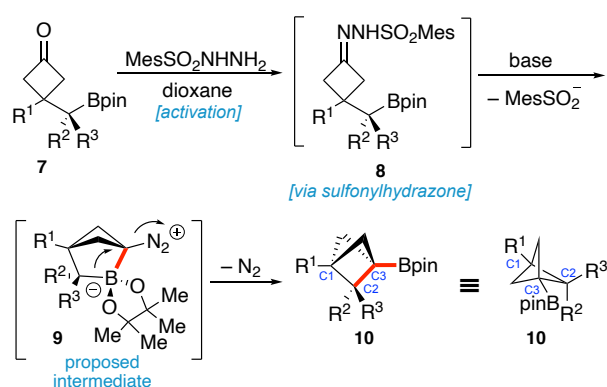
Scheme 1: Intramolecular coupling to access substituted BCPs

The advantage of this methodology was demonstrated in the synthesis of di-, tri-, and tetra-substituted BCPs. Cyclization of cyclobutanone derivatives bearing primary and secondary Bpin side chains afforded di-substituted (C1 and C3), tri-substituted (C1, C2, and C3) and tetra-substituted (C1, C2, C2 and C3) BCPs (**11, 12** and **13**) in good yields. Further functional group tolerance of the reaction was investigated. Substrates bearing pyridine, esters, amide, and terminal alkyne underwent the cyclization smoothly (**14, 15, 16** and **17**). Furthermore, cyclization of gem-diborylated precursors afforded di-Bpin substituted BCP (**18**), which was further applied into sequential functionalization to prepare tri-substituted BCP library. [9]
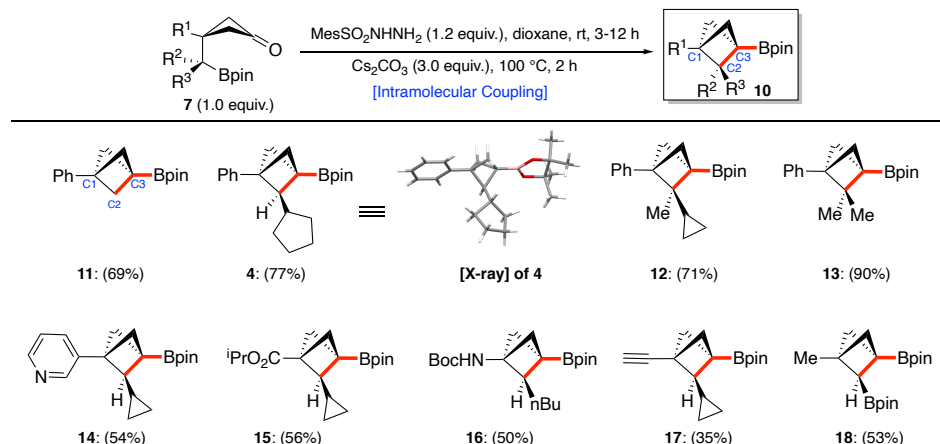
Scheme 2: Substrate scope of intramolecular coupling

References

1. Financial support for this work was provided by Welch Foundation (I-2155-20230405), National Institutes of Health (R01GM141088), and American Chemistry Society Petroleum Research Fund (62223-DNI1). We thank Feng Lin (UTSW) for assistance with NMR spectroscopy; Hamid Baniasadi (UTSW) for HRMS; Vincent Lynch (UT-Austin) for X-ray crystallographic analysis. We are grateful to Jennifer V. Obligacion, Matthew Winston, Artis Klapars, David Thaisrivongs, James McCabe Dunn and LC Campeau (Merck & Co., Inc., Kenilworth, NJ, USA) for feedback on this manuscript.

2. (a) Talele, T. T. Opportunities for Tapping into Three-Dimensional Chemical Space through a Quaternary Carbon. *J. Med. Chem.* **2020**, 63, 13291–13315; doi.org/10.1021/acs.jmedchem.0c00829. (b) Bauer, M. R.; Di Fruscia, P.; Lucas, S. C. C.; Michaelides, I. N.; Nelson, J. E.; Storer, R. I.; Whitehurst, B. C. Put a ring on it: application of small aliphatic rings in medicinal chemistry. *RSC Med. Chem.* **2021**, 12, 448–471; doi.org/10.1039/D0MD00370K.

3. Wiberg, K. B.; Walker, F. H. [1.1.1]Propellane. *J. Am. Chem. Soc.* **1982**, *104*, 5239–5240; doi.org/10.1021/ja00383a046.

4. (a) Ma, X.; Nhat Pham, L. Selective topics in the syntheses of bicyclo[1.1.1]- pentane (BCP) analogues. *Asian J. Org. Chem.* **2020**, *9*, 8–22;

https://doi.org/10.1002/ajoc.201900589. (b) Kanazawa, J.; Uchiyama, M. Recent Advances in the Synthetic Chemistry of Bicyclo[1.1.1]pentane. *Synlett* **2019**, *30*, 1–11; doi/org/10.1055/s-0037-1610314. (c) Shire, B. R.; Anderson, E. A. Conquering the synthesis and functionalization of bicyclo[1.1.1]pentanes. *JACS Au* **2023**, *3*, 1539–1553; doi.org/10.1021/jacsau.3c00014.

5. (a) Ma, X.; Han, Y.; Bennett, D. J. Selective Synthesis of 1-Dialkylamino-2-alkylbicyclo-[1.1.1]pentanes. *Org. Lett.* **2020**, *22*, 9133–9138; doi.org/10.1021/acs.orglett.0c03612. (b) Zhao, J.-X.; Chang, Y.; Elleraas, J.; Montgomery, T. P.; Spangler, J. E.; Nair, S. K.; Bel, M. D.; Gallego, G. M.; Mousseau, J. J.; Perry, M. A.; Collins, M. R.; Vantourout, J. C. V.; Baran, P. S. 1,2-Difunctionalized bicyclo[1.1.1]pentanes: long-sought-after mimetics for ortho/meta-substituted arenes. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2108881118.; doi.org/10.1073/pnas.21088811. (c) Wright, B. A.; Matviitsuk, A.; Black, M. J.; arcia-Reynaga, P.; Hanna, L. E.;Herrmann, A. T.; Ameriks, M. K.; Sarpong, R.; Lebold, T. P. Skeletal editing approach to bridge-functionalized bicyclo[1.1.1] pentanes from azabicyclo[2.1.1] hexanes. *J. Am. Chem. Soc.* **2023**, *145*, 10960–10966; doi.org/10.1021/jacs.3c02616. (d) Garry, O. L.; Heilmann, M.; Chen, J.; Liang, Y.; Zhang, X.; Ma, X.; Yeung, C. S.; Bennett, J. D.; MacMillan, D. W. C. Rapid access to 2-substituted bicyclo[1.1.1]pentanes. *J. Am. Chem. Soc.* **2023**, *145*, 3092–3100; doi.org/10.1021/jacs.2c12163.

6. (a) Mykhailiuk, P. K. Saturated bioisoteres of benzene: where to go next? *Org. Biomol. Chem.* **2019**, *17*, 2839–2849; DOI: 10.1039/C8OB02812E. (b) Denisenko, A.; Garbuz, P.; Shishkina, S. V.; Voloshchuk, N. M.; Mykhailiuk, P. K. Saturated Bioisosteres of *ortho*-Substituted Benzenes. *Angew. Chem. Int. Ed.* **2020**, *59*, 20515–20521; doi.org/10.1002/anie.202004183.

7. Yang, Y.; Tsien, J.; Ben David, A.; Hughes, J. M. E.; Merchant, R. R.; Qin, T. Practical and Modular Construction of C(sp^3)–Rich Alkyl Boron Compounds. *J. Am. Soc. Chem.* **2021**, *143*, 471–480; doi.org/10.1021/jacs.0c11964.

8. Yang, Y.; Tsien, J.; Hughes, J. M. E.; Peters, B. K.; Merchant, R. R.; Qin, T. An Intramolecular Coupling Approach to Alkyl Bioisosteres for the Synthesis of Multi-Substituted Bicycloalkyl Boronates. *Nat. Chem.* **2021**, *13*, 950–955; doi.org/10.1038/s41557-021-00786-z.;

9. Yang, Y.; Tsien, J.; Dykstra, R.; Chen, S-J.; Wang, J. B.; Merchant, R. R.; Hughes, J. M. E.; Peters, B. K.; Gutierrez, O.; Qin, T. Programmable late-stage functionalization of bridge-substituted bicyclo[1.1.1]pentane bis-

boronates. *Nat. Chem.* **2024**, *16*, 285–293; doi.org/10.1038/s41557-023-01342-7.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

Sodium hydride; (7646-69-7)
Benzyl cyanide; (140-29-4)
1,3-Dibromo-2,2-dimethoxy-propane; (22094-18-4)
DIBAL-H: (Diisobutylaluminum hydride solution); (1191-15-7)
Potassium sodium tartrate; (6381-59-5)
2-Mesitylenesulfonyl hydrazide; (16182-15-3)
Cyclopentyl boronic acid; (63076-51-7)
Cesium carbonate; (534-17-8)
Pinacol;(76-09-5)
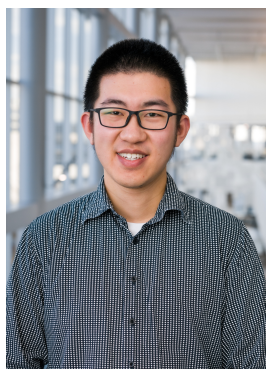
Jet Tsien was born in Anhui, China, in 1997. He received his B.S. in Chemistry from University of Science and Technology of China in 2018. Now he is continuing his graduate studies at UT Southwestern Medical Center under the supervision of Professor Tian Qin. His research focused on sulfur- and boron- mediated hindered cross-coupling reactions.

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Yangyang Yang obtained his B.A. in Chemistry from Qingdao University of Science and Technology in 2011, received his M.Sc. (2014) in Shanghai Institute of Organic Chemistry under the supervision of professor Yikang Wu, and completed his Ph.D. (2019) under the supervision of Professor A. Stephen K. Hashmi at Heidelberg University. In 2020 he joined the Tian Qin group as a postdoctoral fellow, where he studied the use of boronate compounds in transition metal free cross-coupling reactions.

René García-Del Valle was born in San Lorenzo, Puerto Rico, in 1999. He earned his B.S. in Chemistry from the University of Puerto Rico: Río Piedras Campus in 2022. Now he is starting his graduate studies at the UT Southwestern Medical Center.

Jonathan Hughes was born in Regina, Saskatchewan, Canada and graduated with his BSc in Chemistry from the University of Regina (2012). He then completed his PhD studies at McGill University (2018), working with Professor James L. Gleason. He is now employed as an Associate Principal Scientist in the Process Research & Development department at Merck & Co., Inc. in Rahway, NJ, USA.

Byron K. Peters completed his graduate studies in asymmetric catalysis and synthesis at the universities of Uppsala and Stockholm (Sweden, 2011-2015) under the supervision of Prof. Pher Andersson. Thereafter, he began research on beta-lactam antibiotics as a postdoc at the university of KwaZulu Natal (South Africa, 2015-2017) as a postdoctoral researcher with Prof. Tricia Naicker. He then joined Prof. Phil Baran's team at Scripps Research (La Jolla, California, USA, 2018-2020) as a postdoc to develop electrochemical methods for the synthetic chemist. Currently, he is at Merck & Co. in Rahway (New Jersey, USA, 2020-) as a member of the process chemistry team.

Rohan Merchant received his B.Sc. in Chemistry from University College London (2013) and M.Phil under the supervision of Prof. Steven V. Ley at University of Cambridge (2014). After completing his Ph.D. studies in the group of Prof. Phil S. Baran at the Scripps Research Institute (2018), he has since been in the Discovery Chemistry department at Merck Research Laboratories (South San Francisco).
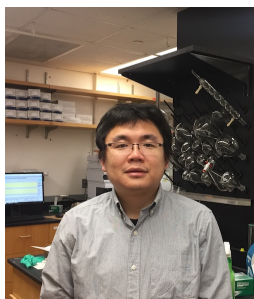
Tian Qin received his B.Sc. from University of Science and Technology of China. He then completed his Ph.D. at Boston University in 2015 with Prof. John A. Porco, Jr. After he completed his postdoctoral research with Prof. Phil S. Baran at the Scripps Research Institute, he started his independent group at UT Southwestern Medical Center since 2018.

Sota Akiyama was born in Chiba, Japan in 1994. He received his Ph.D. from Hokkaido University, Japan in 2021 under the supervision of Professor Hajime Ito. In 2021, he joined the Richmond Sarpong group as a postdoctoral fellow, where he studied the total synthesis of morphinans derivatives.

Paul Sinclair completed his B.S. in Chemistry at the University of Rochester, studying cationic cascade reactions under Prof. Alison Frontier. In 2020, he joined the lab of Prof. Richmond Sarpong where he is currently a graduate student investigating natural product synthesis using oxidative ring contractions.

MeO OMe

CN

1

(^{1}H NMR)

MeO   OMe

CN

1

(^{13}C NMR)

139.53
129.10
128.09
125.89
123.70
98.10
77.16 CDCl3
49.03
48.71
45.81
31.16
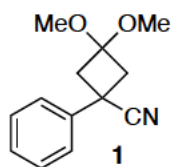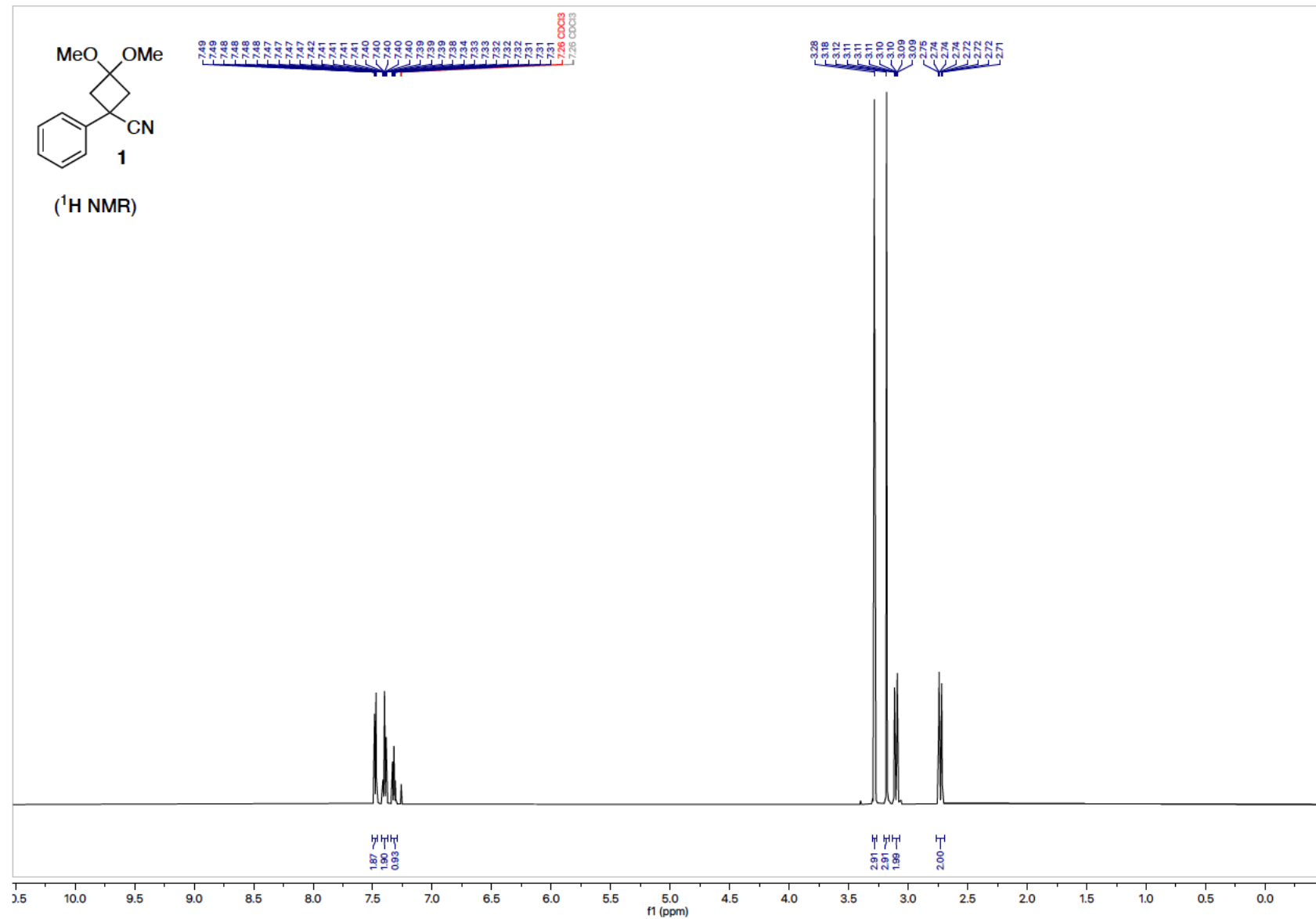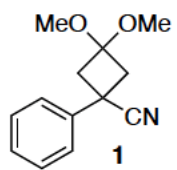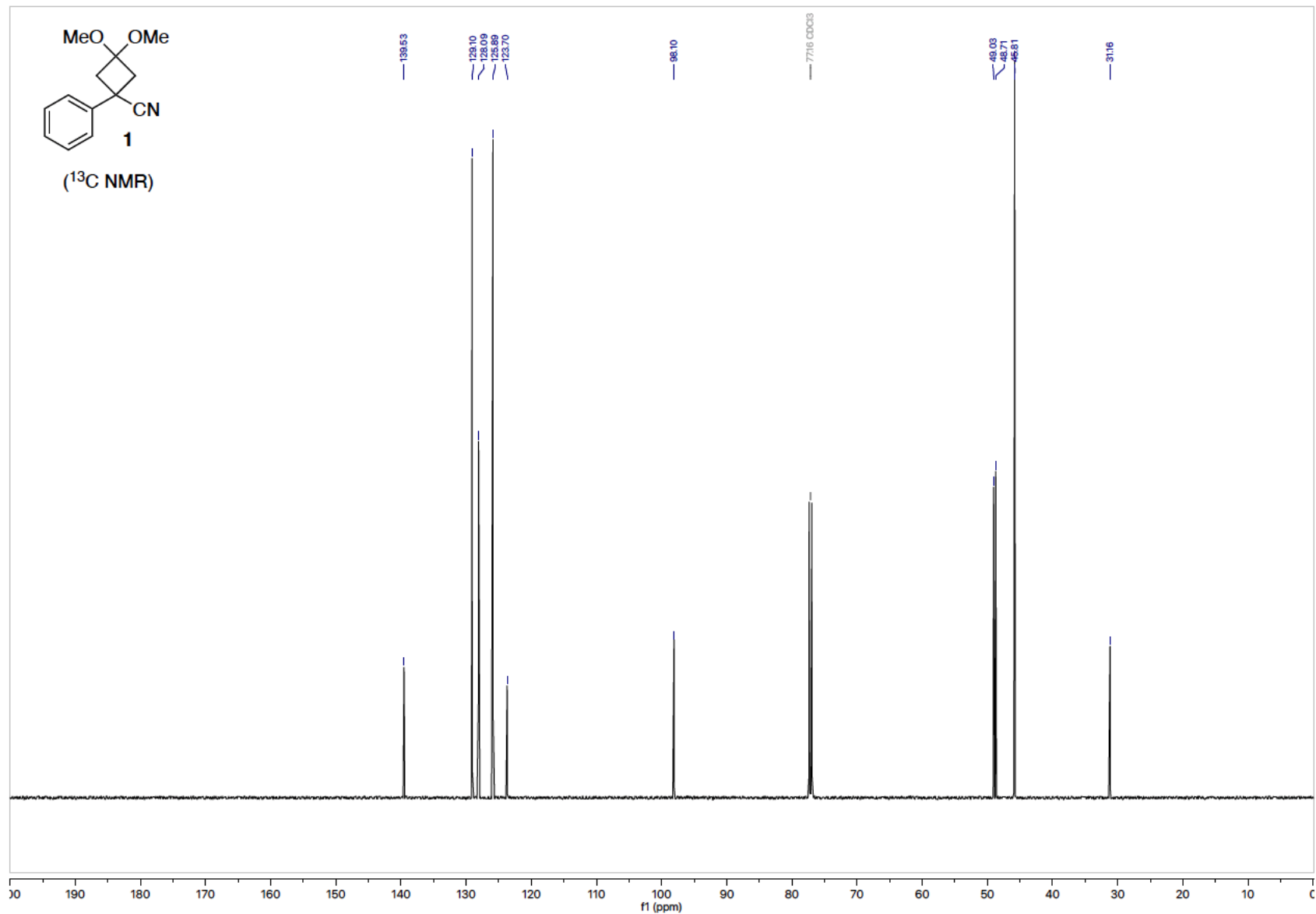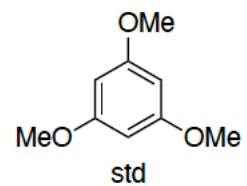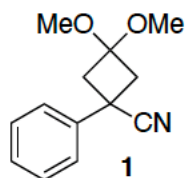
qNMR

mg$_{std}$ = 18.5 mg;
MW$_{std}$ = 168.19 g/mol
mg$_1$ = 29.2 mg;
MW$_1$ = 217.27 g/mol
molar ratio = 1.21;
P$_{std}$ = 99%

Thus: wt$_1$% = (18.5*217.27*1.21*0.99)/(29.2*168.19)*100
              = 98.0 %

2

(¹H NMR)

MeO OMe

Me

O₂
S

N
N
H

2

Me   Me

(¹³C NMR)

153.80
145.44
143.25
140.73
134.41
132.49
129.24
127.19
127.11
99.33
48.29
48.18
41.92
41.03
30.22 Acetone
30.10 Acetone
29.97 Acetone
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29.71 Acetone
29.58 Acetone
29.45 Acetone
23.39
20.90

f1 (ppm)
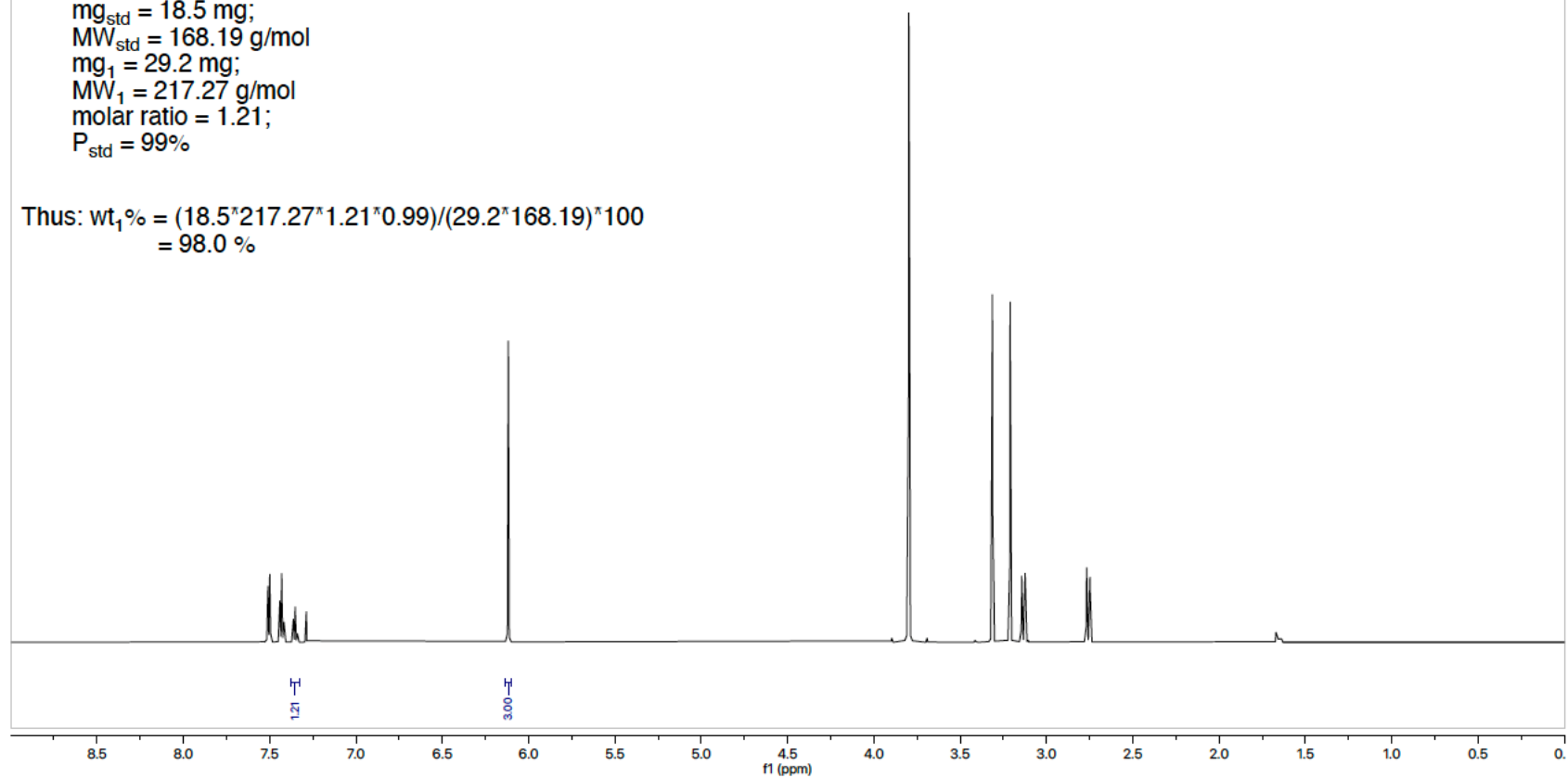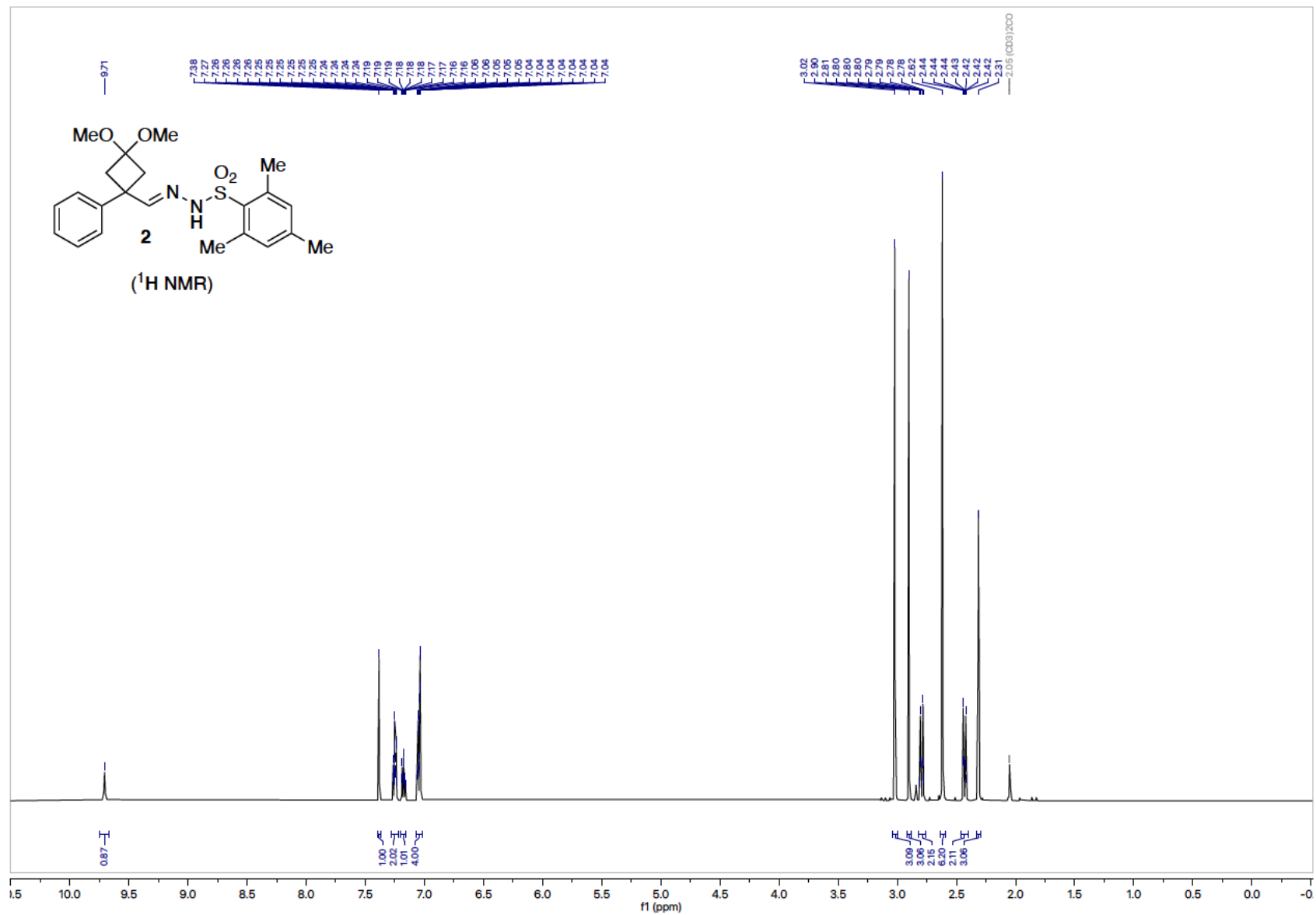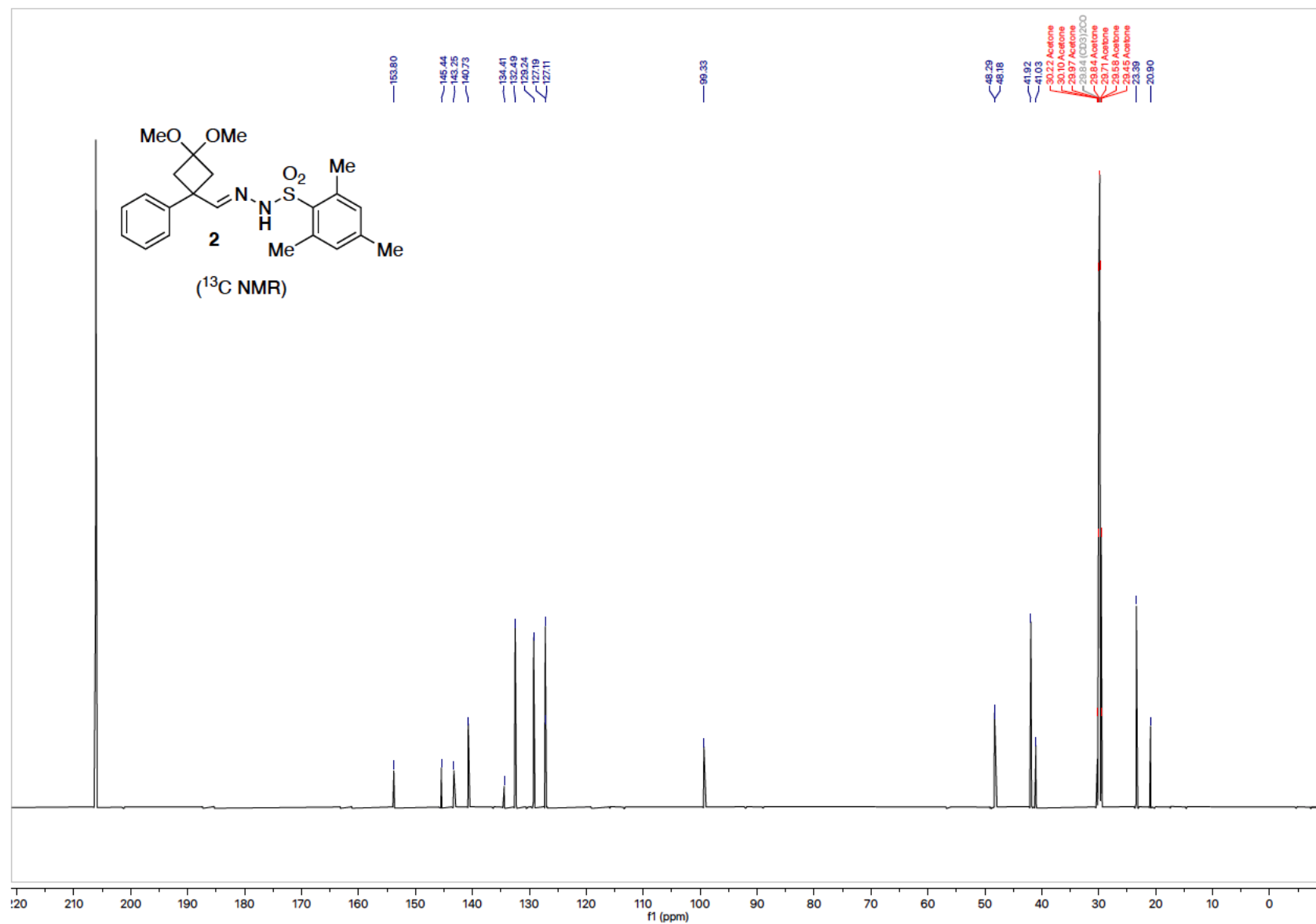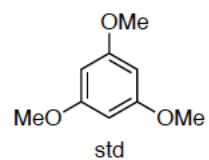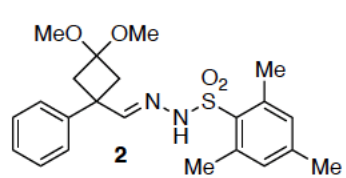
qNMR

mg_{std} = 19.6 mg;
MW_{std} = 168.19 g/mol
mg_2 = 49.5 mg;
MW_2 = 416.54 g/mol
molar ratio = 6.10/6 = 1.02;
P_{std} = 99%

Thus: wt_2% = (19.6*416.54*1.02*0.99)/(49.5*168.19)*100
= 99.0 %

(¹H NMR)

3

Me   Me

O₂S

HN   N   Me

Me

Me   Me

B

Me

O

O

Me

3

(¹¹B NMR)

34.83

f1 (ppm)

$(^{13}C$ NMR)

3
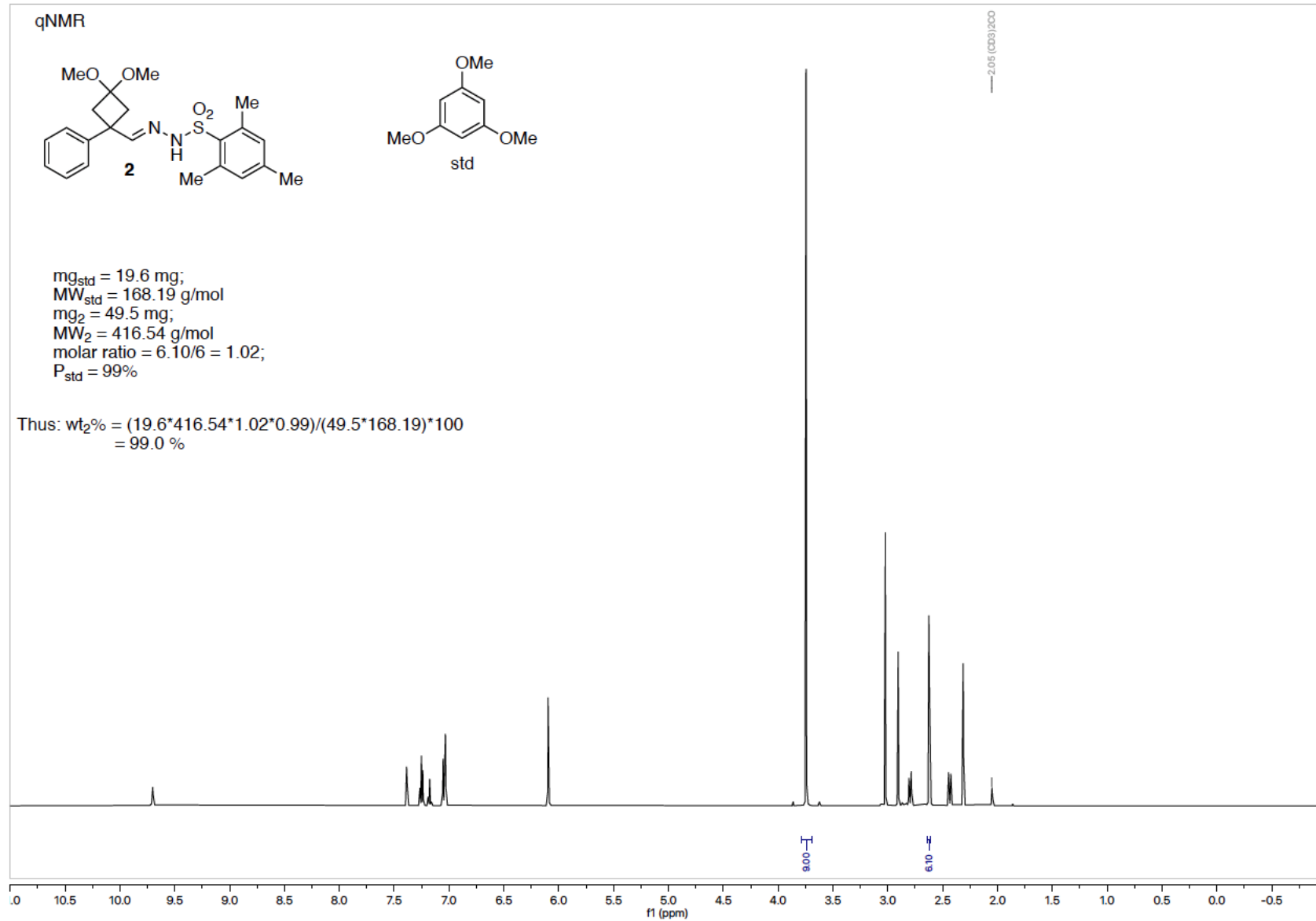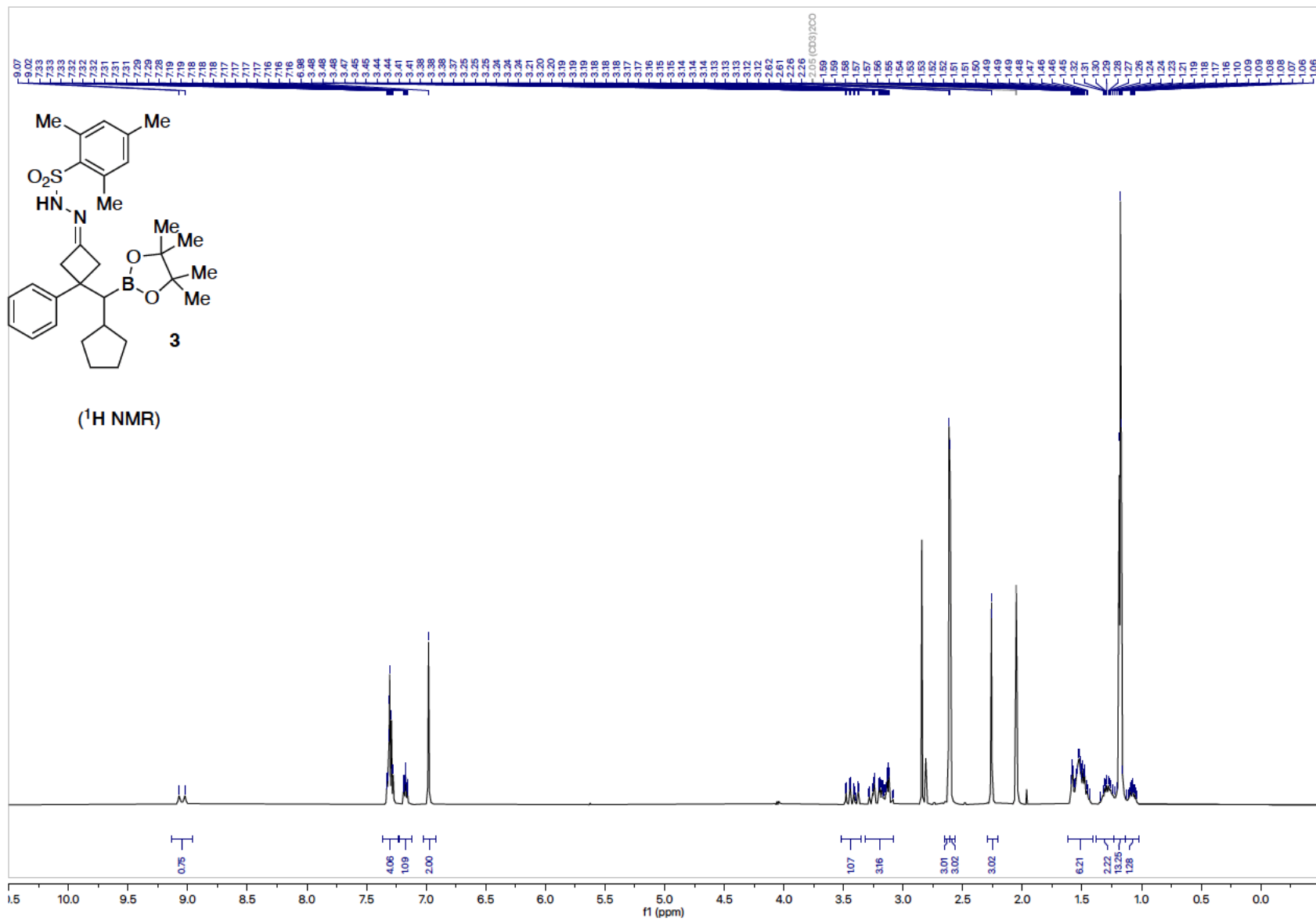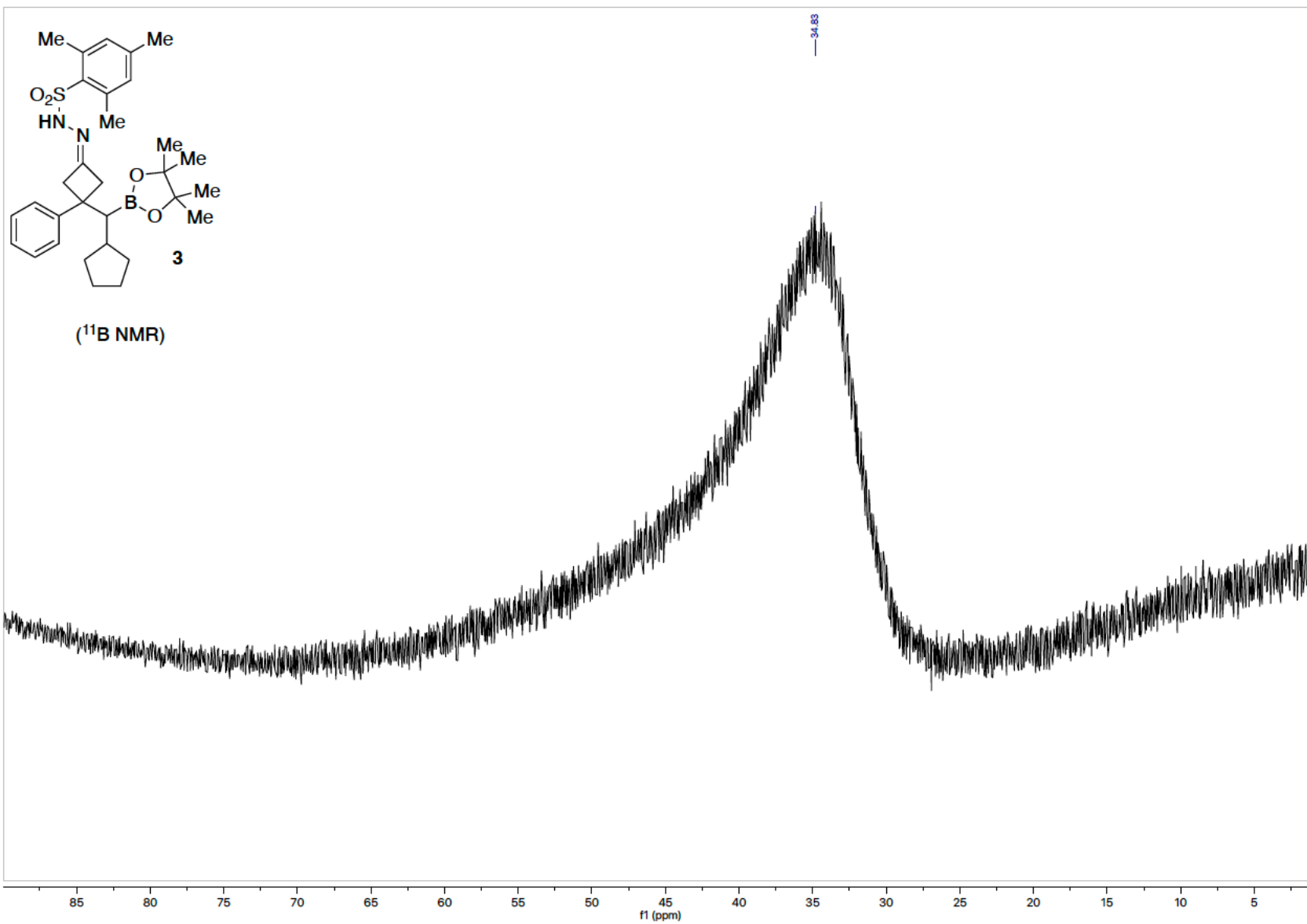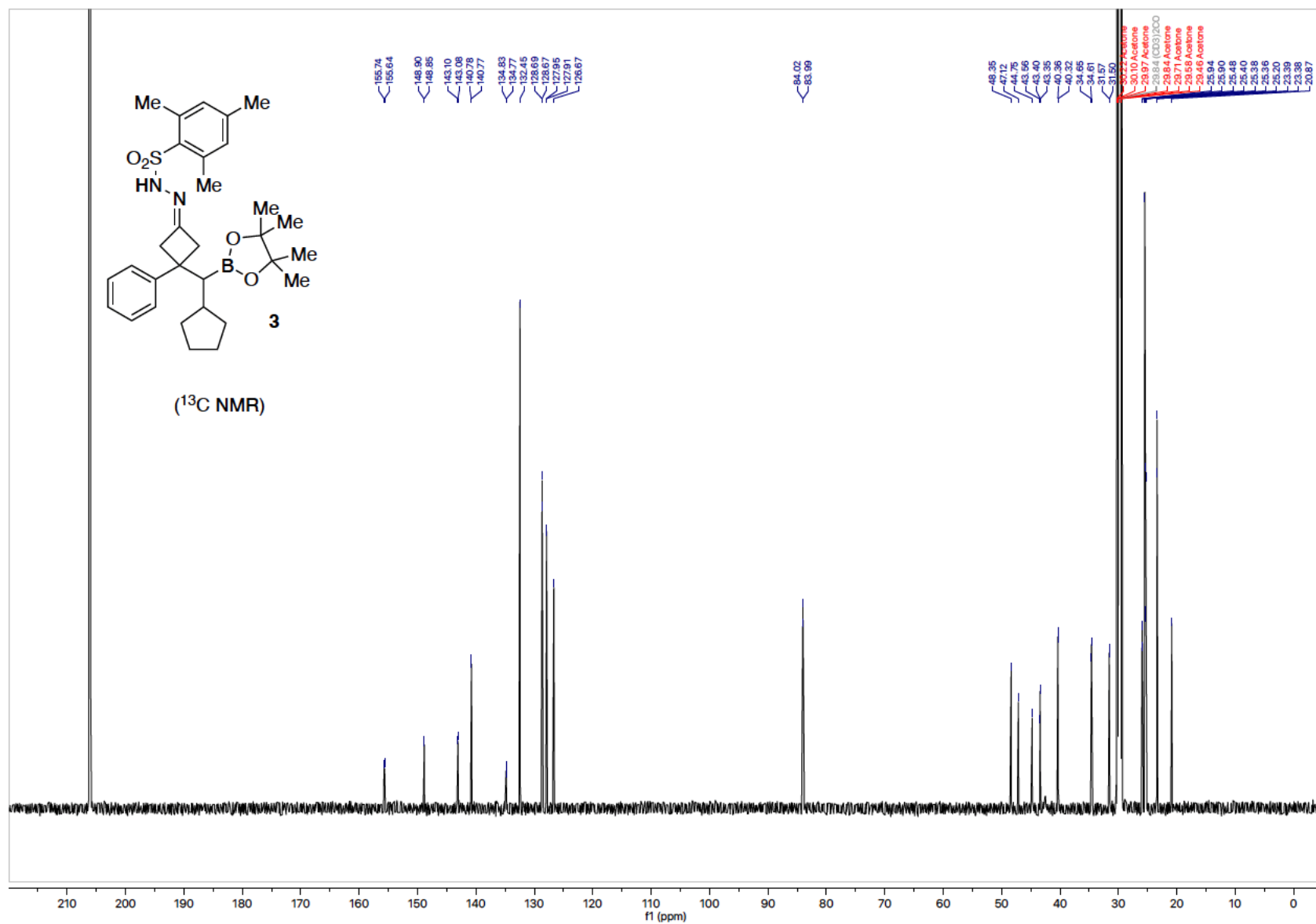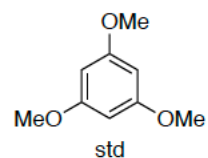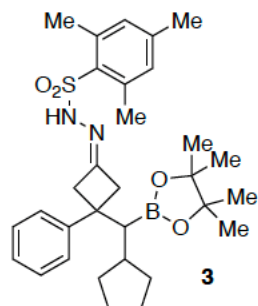
qNMR

mg$_{std}$ = 30.4 mg;
MW$_{std}$ = 168.19 g/mol
mg$_3$ = 37.3 mg;
MW$_3$ = 550.57 g/mol
molar ratio = 2.24/6 = 0.37;
P$_{std}$ = 99%

Thus: wt$_3$% = (30.4*550.57*0.37*0.99)/(37.3*168.19)*100
          = 97.7 %

(^{1}H NMR)

Ph

H

Me
Me
Me
Me
B
O
O

4

(^{11}B NMR)

(^{13}C NMR)

4

qNMR

4

std
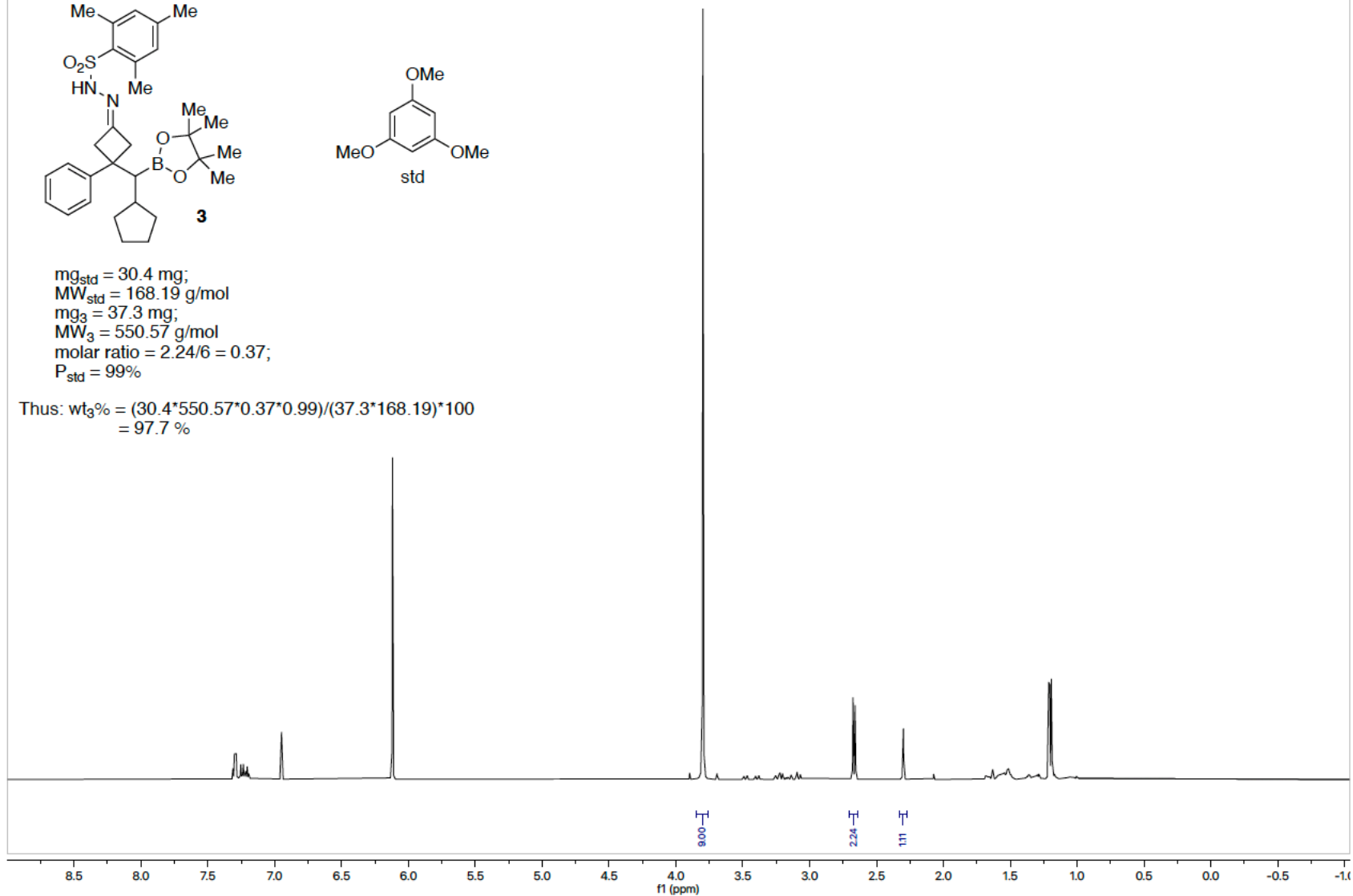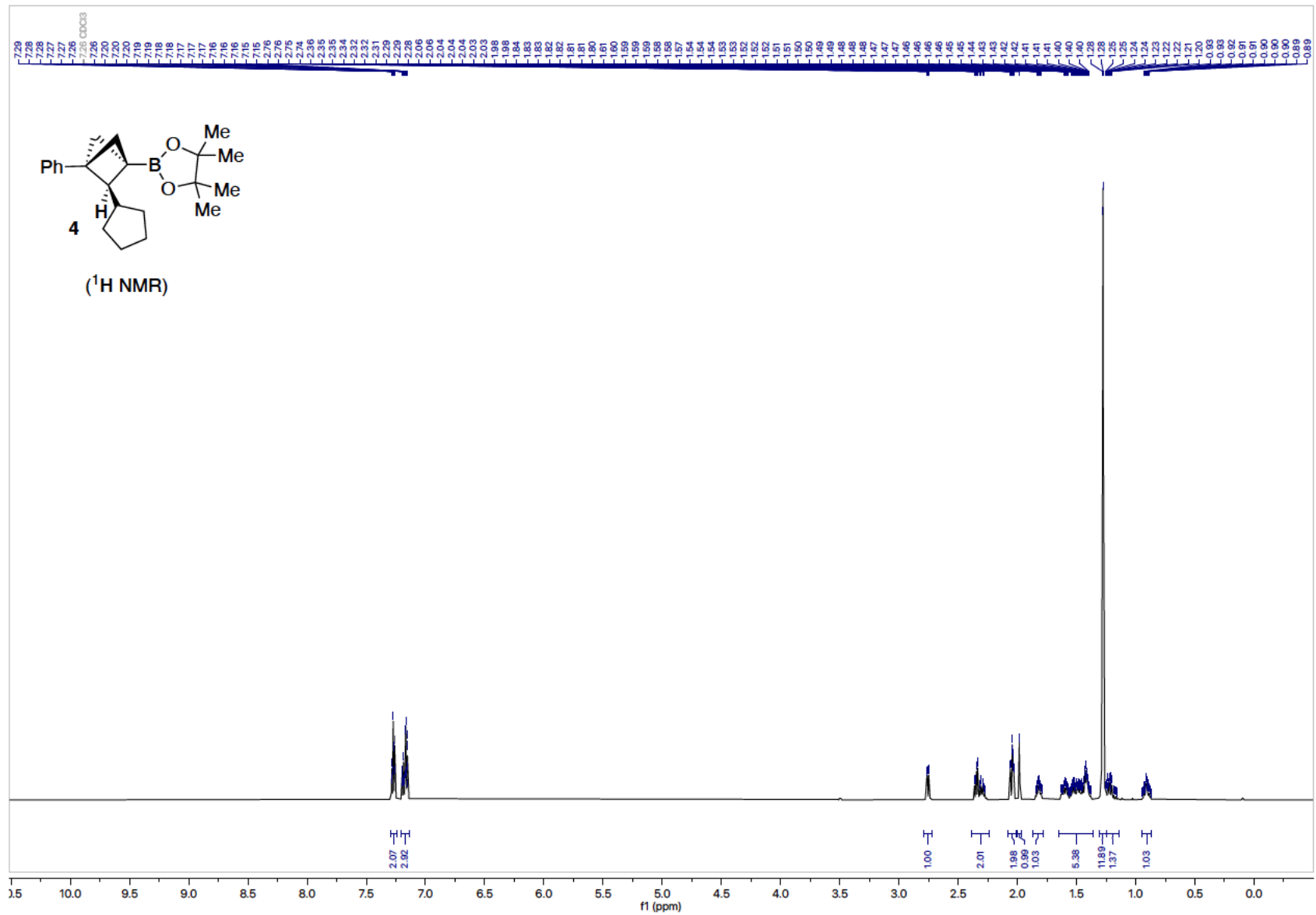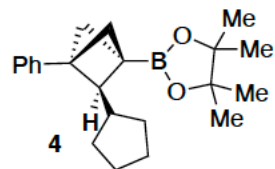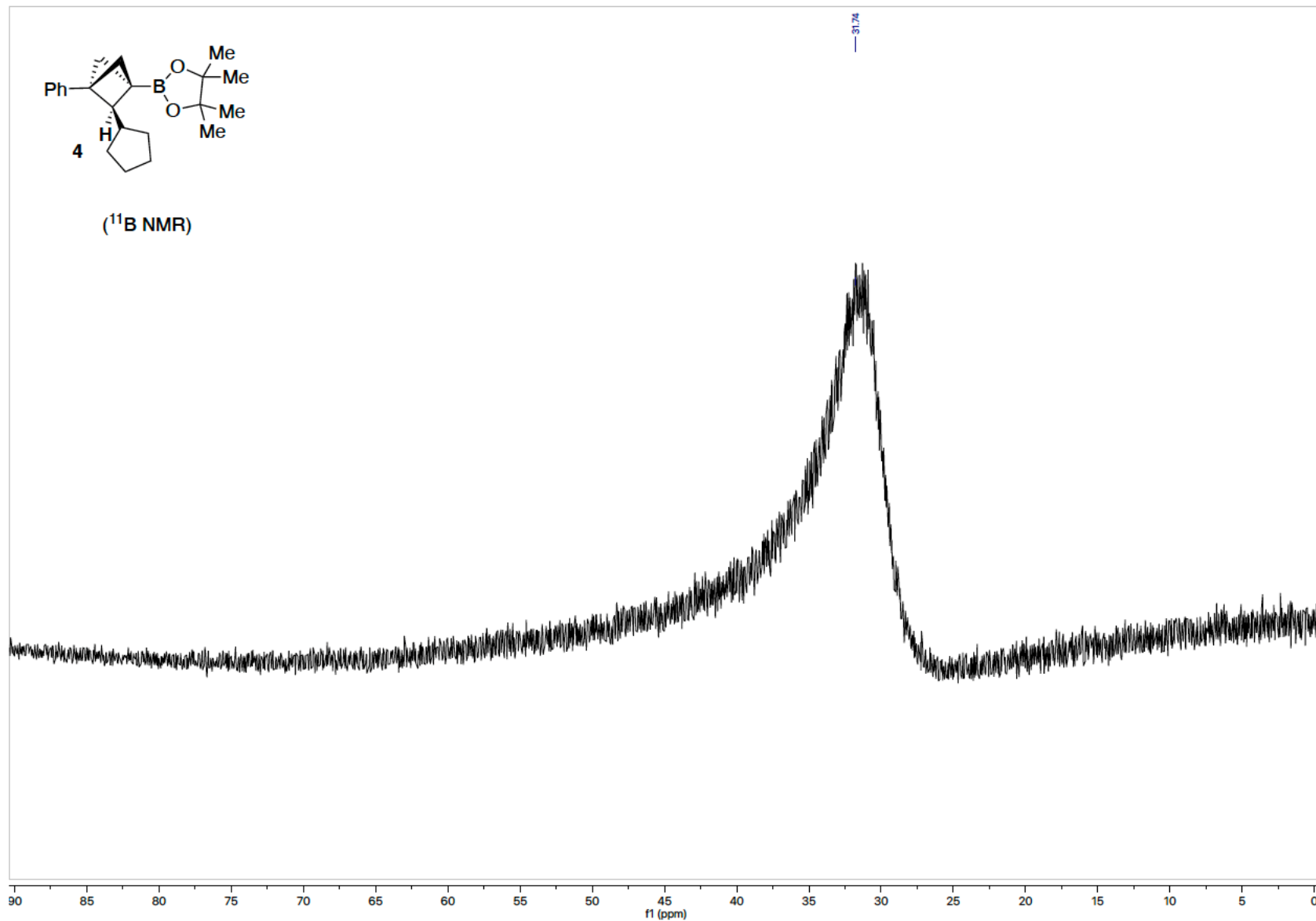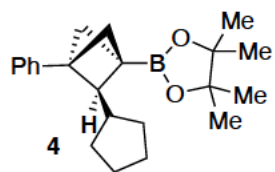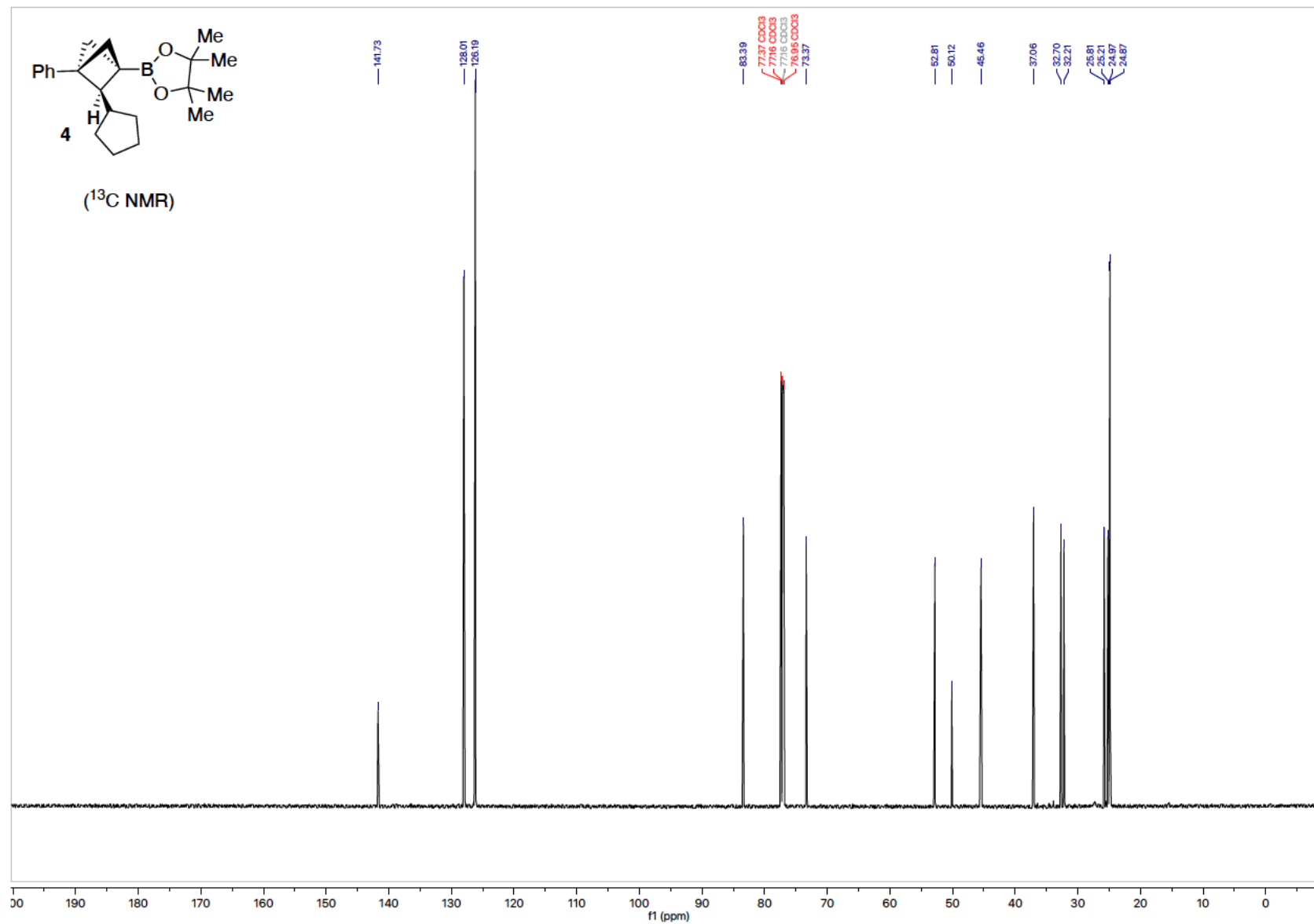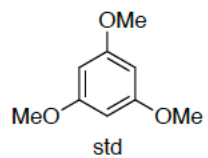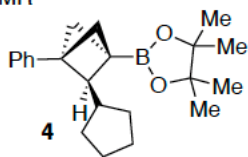
$mg_{std} = 30.6$ mg;
$MW_{std} = 168.19$ g/mol
$mg_4 = 54.9$ mg;
$MW_4 = 338.30$ g/mol
molar ratio = 0.88
$P_{std} = 99\%$

Thus: $wt_4\% = (30.6*338.30*0.88*0.99)/(54.9*168.19)*100$
$= 97.7\ \%$

Ph

Me
Me
Me
Me

B

O
O

H

OMe
MeO
OMe

6.00

0.88

f1 (ppm)

8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5