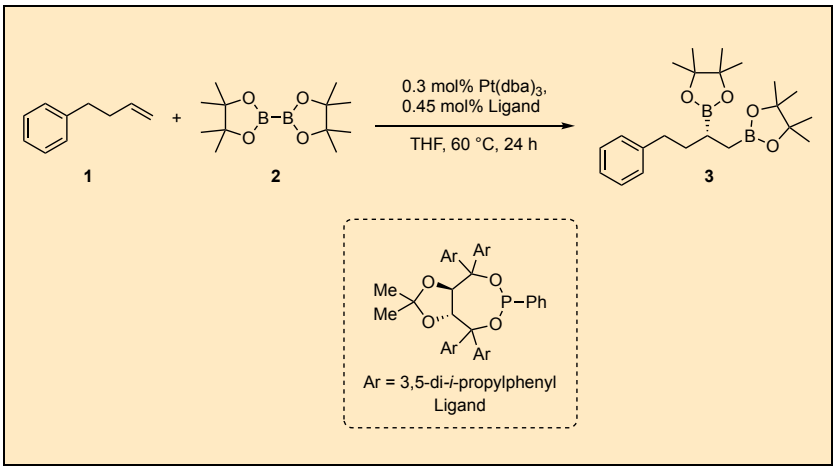
Organic Syntheses

Platinum-Catalyzed Enantioselective Diboration of Monosubstituted Alkenes

Chenpeng Gao, Paul S. Lee, and James P. Morken*[1]

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467, United States

Checked by Matthieu Maciejewski and Tehshik Yoon



Procedure (Note 1)

(R)-2,2′-(4-Phenylbutane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (**3**). An oven-dried 48 mL heavy-walled pressure vessel equipped with a Telfon-coated, football-shaped magnetic stir bar is charged with tris(dibenzylideneacetone)platinum(0) (26.9 mg, 0.03 mmol, 0.30 mol%) (Note 2), (R,R)-3,5-di-*iso*-propylphenyl-TADDOL-PPh (46.4 mg, 0.051 mmol, 0.51 mol%) (Note 3) and bis(pinacolato)diboron (2.67 g, 10.5 mmol, 1.05 equiv) (Note 4) in an atmosphere of air. The flask is sealed by a rubber septum, the septum wrapped with electrical tape, and a stainless-steel needle connected to a nitrogen/vacuum manifold affixed. The flask is then placed under vacuum (20 °C, manifold pressure is 0.1 mmHg) for 5 min, and then

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slowly backfilled with nitrogen. The vacuum–backfill process is repeated three times.

The flask is brought into a nitrogen glove box, and dry tetrahydrofuran (10 mL) (Note 5) is added to the flask. The flask is then sealed with a PTFE bushing screw cap, removed from the glove box, and placed in a preheated (80 °C) oil bath. The reaction mixture is allowed to stir (450 rpm) for 30 min (Figure 1) (Note 6).

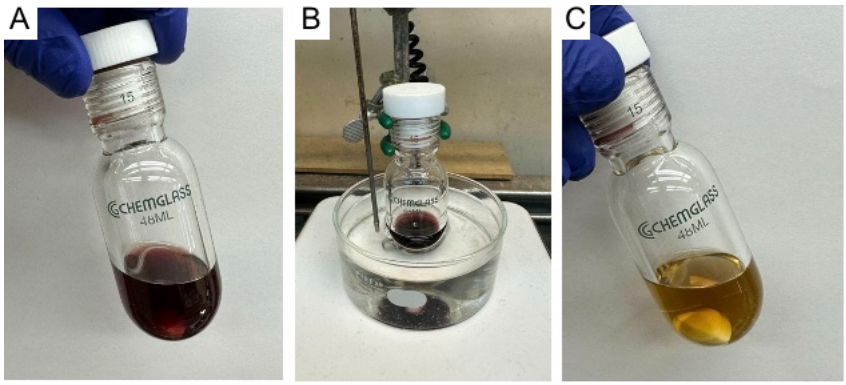


Figure 1. Color change of the reaction mixture during pre-complexation (A) The reaction mixture before heating at 80°C; (B) The heating apparatus; (C) The reaction mixture after heating at 80°C for 30 minutes (Photos provided by checkers)

After 30 min, the flask is removed from the oil bath, and allowed to cool to room temperature (20 °C). The flask is brought back into the glove box and 4-phenyl-1-butene (1.32 g, 1.50 mL, 10.0 mmol, 1.0 equiv) (Note 7) is added. The reaction flask is then removed from the glove box and placed in a preheated oil bath (60 °C) and stirred (450 rpm) for 24 h. After 24 h, the flask is removed from the oil bath and cooled to room temperature (20 °C). The solution is transferred to a 50 mL round-bottomed flask and the reaction flask is rinsed with diethyl ether (Note 8). The solution is concentrated by rotary evaporation under reduced pressure (35 °C, 30 mmHg) to afford a dark yellow oil.

For purification, a column (6.0 cm diameter) of silica gel (silica height of 15 cm) (Note 9) is prepared by presolvating with hexanes (300 mL) (Note 8). Once the eluent has eluted onto the column, sodium sulfate (Note 10) is added to protect the silica surface. Then the crude material is directly transferred onto the compacted column with a pipette. The flask containing

residual crude material is washed with additional hexanes (3 x 1.5 mL) (Note 8), and the washings are added to the column. The column is first eluted with hexanes (400 mL) and the eluent discarded. Then the column is eluted with hexanes/ethyl acetate (95/5, v/v) (2200 mL) (Note 8), and the first 150 mL eluent is discarded. The eluent is then collected in 15 x 250 mm test tubes. The product typically elutes in fractions 11 – 40 and is monitored by TLC (Note 11). The fractions are transferred to a 2 L round-bottomed flask, and the test tubes are subsequently rinsed with diethyl ether (3 x 5 mL) (Note 8) which is added to the combined fractions. The solvent is removed by rotary evaporation (35°C, 30 mmHg), after which diethyl ether (Note 8) is added and the solution is transferred to a 20-mL scintillation vial where it is concentrated in vacuo (35 °C, 30 mmHg). The yellow oil is kept under high vacuum (20 °C, 0.1 mmHg) overnight to afford 3.27 g (85%) of pure (R)-2,2'-(4-phenylbutane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (**3**) (Notes 12, 13, 14, and 15).

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out evaluating each chemical 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, Org. Synth. 2023, 100, 99–112 DOI: 10.15227/orgsyn.100.0099 102 D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-thelaboratory-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 this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with tris(dibenzylideneacetone)platinum(0), (R,R)-3,5-di-*iso*-propylphenyl-

TADDOLPPh, bis(pinacolato)diboron, 4-phenyl-1-butene, tetrahydrofuran, diethyl ether, hexanes, ethyl acetate, and 230-400 mesh silica gel. The temperature of the reaction exceeds the boiling point of tetrahydrofuran, and the reaction is performed in a closed system; therefore, use of a blast shield is recommended.

2. Tris(dibenzylideneacetone)platinum(0) was purchased from Strem Chemicals and used as received.
3. (R,R)-3,5-Di-*iso*-propylphenyl-TADDOLPPh was purchased from Ambeed, Inc. and used as received.
4. Bis(pinacolato)diboron was purchased from Oakwood Chemical and used as received.
5. Tetrahydrofuran (THF) was purified using the Pure Solv MD-4 solvent purification system from Innovative Technology, Inc.
6. The heating temperature exceeds the boiling point of tetrahydrofuran, and a blast shield is recommended.
7. 4-Phenyl-1-butene was purchased from Oakwood Chemical and used as received.
8. Hexanes, ethyl acetate and diethyl ether were purchased from Fisher Chemical and used as received.
9. Silica gel (230-400 mesh) was purchased from Silicycle as SiliaFlash® P60 and used as received.
10. Sodium sulfate (anhydrous) was purchased from Oakwood Chemical and used as received.
11. The column progress was monitored by TLC analysis, hexanes/ethyl acetate (9:1, v/v). R_f (product) = 0.5.

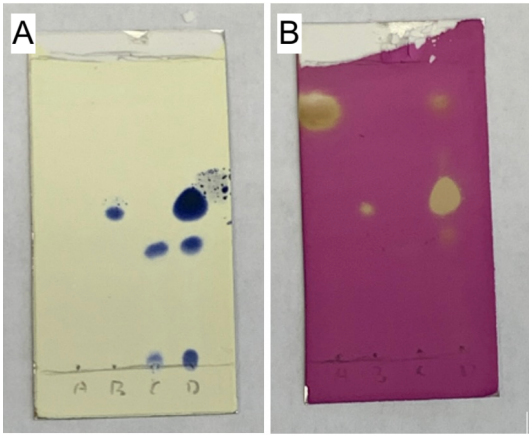


Figure 2. Thin-layer chromatography (TLC) analysis of the reaction mixture; (A) Visualized by ceric ammonium molybdate (CAM) stain; (B) Visualized by $KMnO_4$ stain; Left-to-right: Terminal alkene 1, pure product 3, B_2pin_2 2 and the reaction mixture (photos provided by authors)

12. Characterization data of product **3**. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.28 – 7.21 (m, 2H), 7.20 – 7.11 (m, 3H), 2.66 – 2.57 (m, 2H), 1.84 – 1.73 (m, 1H), 1.69 – 1.58 (m, 1H), 1.25 (s, 12H), 1.23 (s, 12H), 0.98 – 0.83 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 143.3, 128.4, 128.1, 125.4, 82.9, 35.9, 35.3, 24.9, 24.9, 24.8, 24.8. ^{11}B NMR (128 MHz, $CDCl_3$) δ: 34.3. IR (neat) ν_{max} 2977 (m), 1369 (s), 1311 (s), 1140 (s), 967 (w), 845 (w), 698 (w) cm^{-1}. HRMS (ESI) $[M + H]^+$ calcd for $C_{22}H_{37}B_2O_4$: 387.2872. Found: 387.2871. $[\alpha]_{20}^D$ –7.4 (c 1.0, $CHCl_3$). The product (**3**) is stable on the benchtop at room temperature under air atmosphere.
13. Product **3** was oxidized into the corresponding diol (Note 16) to determine the enantiomeric excess. Separation of the two enantiomers was accomplished using chiral HPLC (Waters Alliance), Daicel CHIRALCEL® columns, and Chromasolv®-grade solvents with isopropanol and hexanes as mobile phase. Chiral HPLC (OD-H, MPA: 10% IPA, MPB: 90% hexanes, 0.5 mL/min, 220 nm) retention times are 13.39 min (minor enantiomer) and 18.80 min (major enantiomer). The ee of the diol product was determined to be 94%.
14. A second reaction on half-scale performed by the checkers provided 1.51 g (78%) of the same product with 93% ee.

15. The purity of product **3** was determined by C/H elemental analysis. Anal. Calcd. For $C_{22}H_{36}B_2O_4$: C, 68.43; H, 9.40. Found: C, 68.52; H, 9.30.
16. A 20 mL scintillation vial equipped with a Telfon-coated, football-shaped magnetic stir bar is charged with product **3** (38.6 mg, 0.10 mmol, 1.0 equiv.) under an atmosphere of air. Tetrahydrofuran (1 mL) (Note 5) is added to the flask via a plastic syringe. The vial is then cooled to 0 °C in an ice-water bath. 3 M NaOH solution (0.8 mL, 2.4 mmol, 24 equiv) (Note 17) is added via a plastic syringe, followed by the dropwise addition over the course of 1 min of 30% H_2O_2 solution (0.4 mL) (Note 18). The reaction mixture is warmed to room temperature and stirred for 4 h. Upon completion, the reaction mixture is again cooled to 0 °C in an ice-water bath and quenched by addition of 1.0 mL of saturated sodium thiosulfate solution (Note 19). The reaction mixture is transferred to a 25 mL separatory funnel and extracted with diethyl ether (3 x 2 mL). The combined organic layers are dried over sodium sulfate and filtered through a silica plug with diethyl ether (10 mL). The solution is concentrated *in vacuo* under reduced pressure (35 °C, 30 mmHg) to afford a clear oil. The crude product is directly submitted for HPLC analysis without further purification.
17. Sodium hydroxide was purchased from Thermo Fisher Scientific Co.
18. Hydrogen peroxide solution was purchased from Thermo Fisher Scientific Co.
19. Sodium thiosulfate was purchased from Thermo Fisher Scientific Co.

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

Non-directed, catalytic enantioselective transformations of terminal alkenes are useful processes in synthetic chemistry; however, this class of reaction is largely underdeveloped. Enantioselective diboration followed by functionalization offers one strategy for converting terminal alkenes into an array of useful building blocks. While direct oxidation provides a useful route from terminal alkenes to chiral 1,2-diols (Figure 3), site-selective derivatization[2] enables transformations that, in many cases, retain a boronic ester that may engage in subsequent reactions.[3] Recent efforts in our laboratory have employed Pd-based site-selective catalytic cross-coupling of C(sp^2) electrophiles[4] and Cu-based catalytic coupling with allylic, propargylic, and alkynyl electrophiles as well as simple protonation.[5]

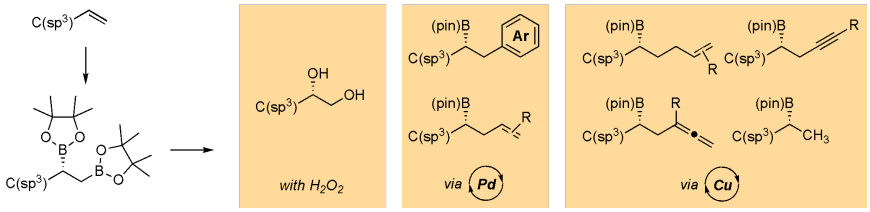
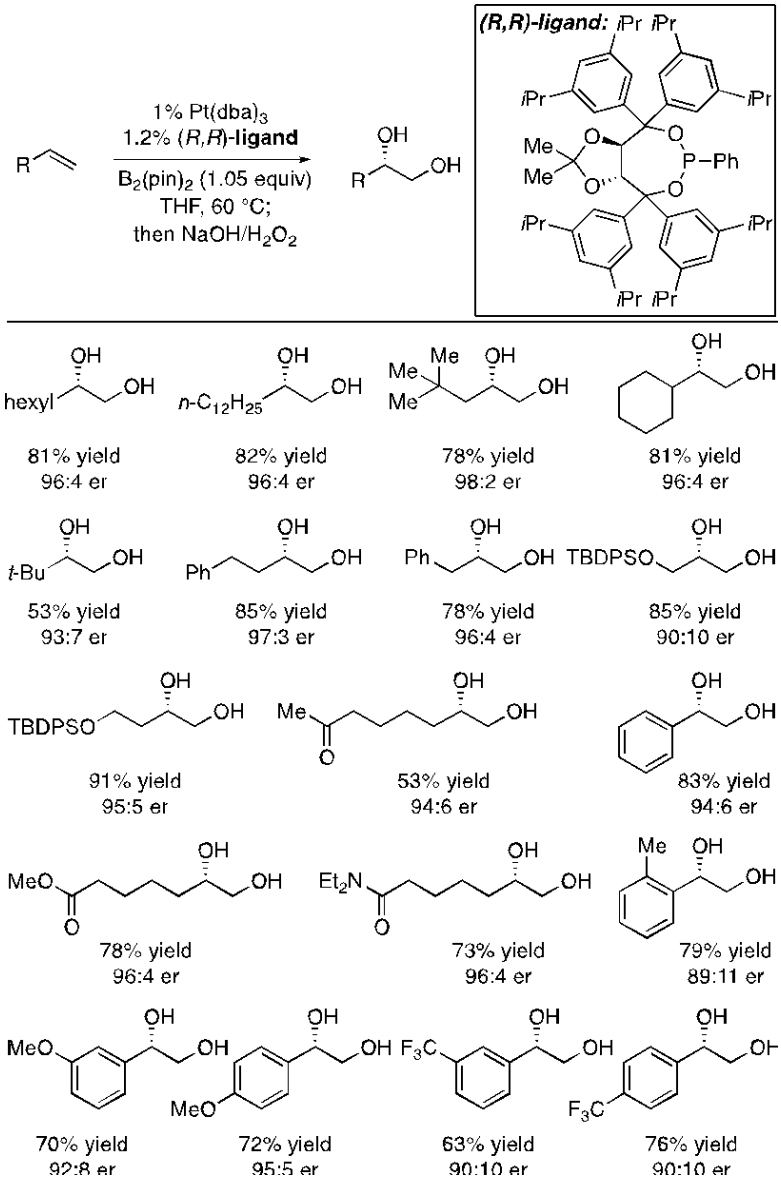


Figure 3. Transformations of vicinal bis(boronic esters) arising from alkene diboration

A number of catalytic processes have been advanced to effect the diboration of alkenes.[6] The diboration of terminal alkenes with platinum-based catalysts using bis(pinacolato)diboron was first reported by Miyaura in 1996.[7] An enantioselective Pt-catalyzed variant was reported in 2009[8] and further studied in 2013.[9] Using an air-stable platinum (0) source, a readily accessible TADDOL-derived phenyl phosphonite ligand, and bench-stable bis(pinacolato)diboron as boron source allows the reaction to proceed smoothly with low catalyst loading and functional group tolerance on a gram-scale. Results with several substrates that have been subjected to oxidative work-up[9] are presented in Table 1. The diboration process has also been employed in the synthesis of a number of natural products[10-19] and these examples give evidence of useful levels of functional group tolerance.

Table 1. Diboration/Oxidation of Terminal Alkenes



References

1. Department of Chemistry, Boston College, 2609 Beacon Street, Chestnut Hill MA, 02467 USA. JPM ORCID: 0000-0002-9123-9791, morken@bc.edu. Funding for NIGMS (R35-GM1217140) is gratefully acknowledged.
2. For the review on site-selective functionalization of vicinal boronates, see Viso, A.; Fernández de la Pradilla, R.; Tortosa, M. Site-Selective Functionalization of C(sp^3) Vicinal Boronic Esters. *ACS Catal.* **2022**, *12*, 10603–10620. doi: 10.1021/acscatal.2c02857
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Appendix
Chemical Abstracts Nomenclature (Registry Number)

Tris(dibenzylideneacetone)platinum(0); (11072-92-7)
(R,R)-3,5-di-*iso*-propylphenyl-TADDOLPPh; (1361146-90-8)
Bis(pinacolato)diboron; (73183-34-3)
4-phenyl-1-butene; (768-56-9)
Sodium hydroxide; (1310-73-2)
Hydrogen peroxide; (7722-84-1)
Sodium thiosulfate; (7772-98-7)

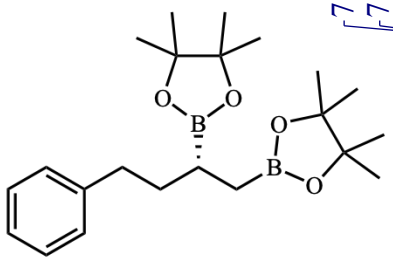
Chenpeng Gao was born in Shanghai, China. He received his B.S. in Chemistry from Boston College in 2019. He is continuing his graduate studies at Boston College under the supervision of Professor James Morken. His research focuses on the stereoselective synthesis of structural complex carbocycles through metal-catalyzed conjunctive cross-coupling reaction and electrophile-induced polyene cyclization reaction.

Paul Lee was born in Glasgow, Scotland, and grew up in Southern Spain. He received his B.S. in Chemistry from Furman University under the supervision of Professor Greg Springsteen in 2013. After seven years in the United States Air Force and 18 months at MilliporeSigma as an R&D Quality Control Scientist, he began studies at Boston College under the tutelage of Professor James Morken. His research focuses on the desymmetrisation of meso bis(boronic) esters to generate enantioenriched synthetic building blocks.

James P. Morken was born in Concord, California and obtained his B.S. in 1989 from UC Santa Barbara working with Prof. Bruce Rickborn. He obtained his Ph.D. from Boston College in 1995 with Prof. Amir Hoveyda and was an NSF Postdoctoral Fellow with Stuart Schreiber at Harvard University. In 1997, he became an Assistant Professor at the University of North Carolina at Chapel Hill. He was promoted to Associate Professor in 2002 and in 2006 joined the faculty of Boston College. In 2014, he was named the Louise and James Vanderslice and Family Chaired Professor of Chemistry at Boston College.

Matthieu Maciejewski was born in Paris, France and raised in Potomac, Maryland. He graduated from Haverford College in 2021 with a B.S. degree in chemistry and biochemistry concentration. He is currently pursuing a Ph.D. at the University of Wisconsin-Madison under the supervision of Tehshik P. Yoon.

1H NMR (500.02 MHz, CDCl3)



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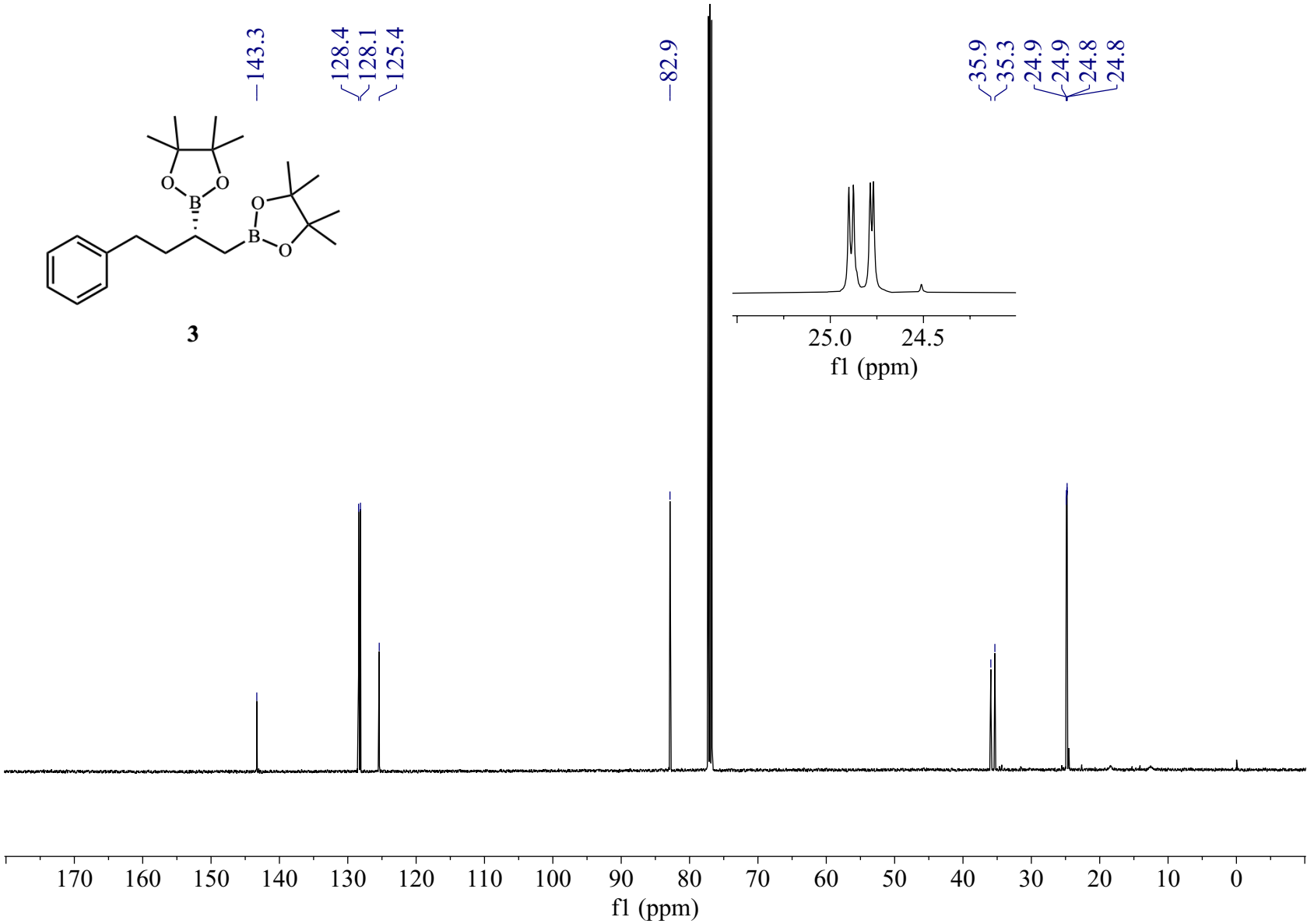
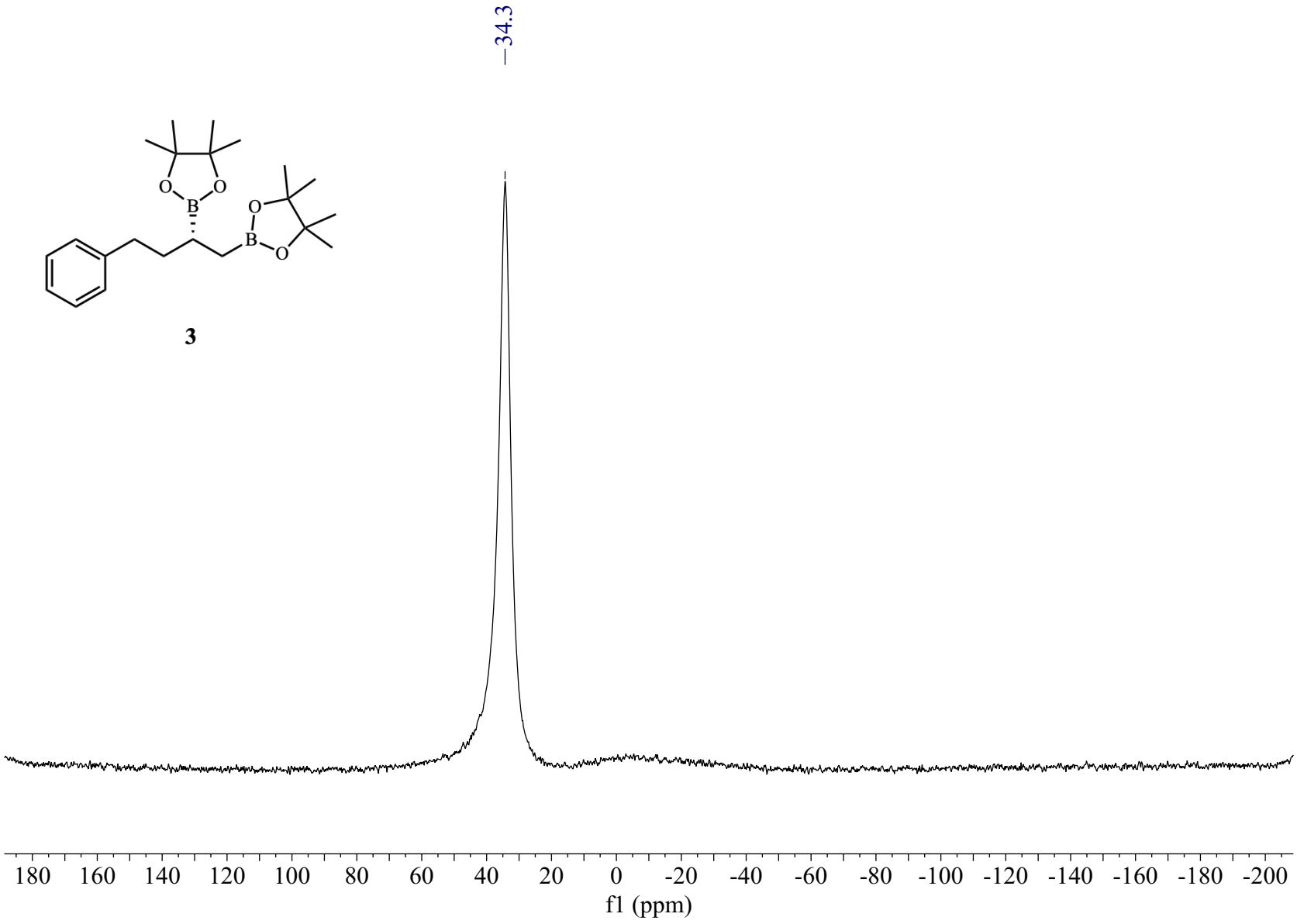
13C NMR (125.74 MHz, CDCl3)
Absolute Referencing used Me4Si CDCl3, ϕ = 1% and Ratio of 25.145020



11B NMR (128.39 MHz, CDCl3)
Absolute Referencing used BF3.Et2O CDCl3, ϕ = 15% and Ratio of 32.083974



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