Organic Syntheses

Preparation of Alkyl Boronic Esters Using Radical-Polar Crossover Reactions of Vinylboron Ate Complexes

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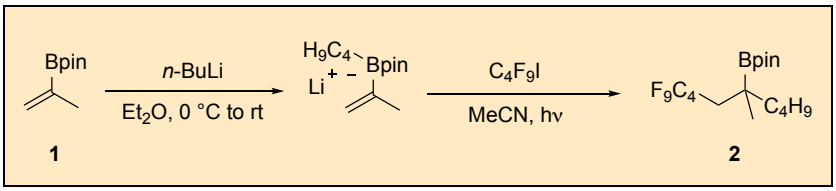
Checked by Helene Wolleb and Erick M. Carreira



Procedure (Note 1)

*4,4,5,5-Tetramethyl-2-(7,7,8,8,9,9,10,10,10-nonafluoro-5-methyldecan-5-yl)-1,3,2-dioxaborolane (***2***).* An oven-dried 400 mL Schlenk tube equipped with a 3 cm Teflon-coated magnetic stir bar and a glass stopper is evacuated and backfilled with argon three times (Note 2). The glass stopper is substituted by a rubber septum and the tube is charged with diethyl ether (65 mL) (Note 3) and isopropenyl boronic acid pinacol ester (95%, 3.76 mL, 20.0 mmol, 1.00 equiv) (Note 4) (Figure 1). The vigorously stirred mixture is cooled to 0 °C by a water/ice bath and *n*-butyllithium (1.6 M in hexanes, 13.8 mL, 22.0 mmol, 1.10 equiv) (Note 5) is added dropwise over 10 min using a syringe pump (Note 6) (Figure 2).

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Figure 1. Reaction set-up

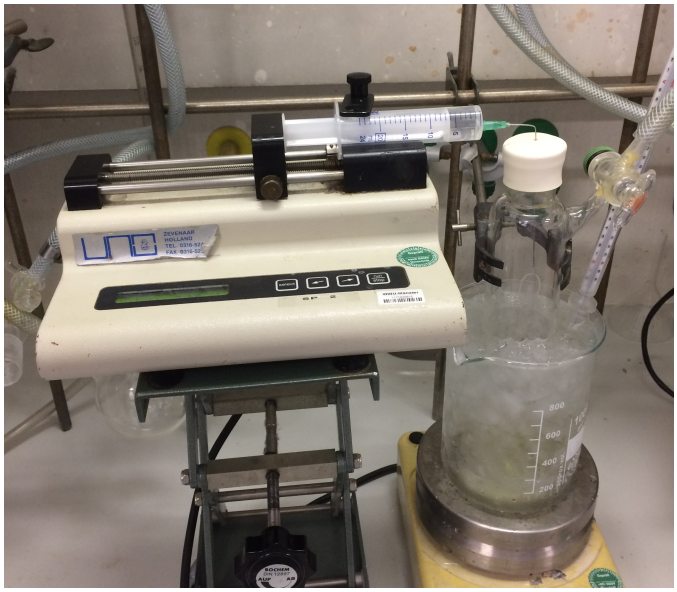


Figure 2. Reaction setup for addition of *n*-butyllithium (formation of boron ate complex)

After the addition is completed the pale yellow mixture is stirred for 5 min at 0 °C, the cooling bath is removed and stirring is continued at room temperature for 30 min (Note 7) (Figure 3). The septum of the flask is switched to a vacuum connection with a separate evacuated cooling trap in liquid nitrogen (Note 8) (Figure 4).

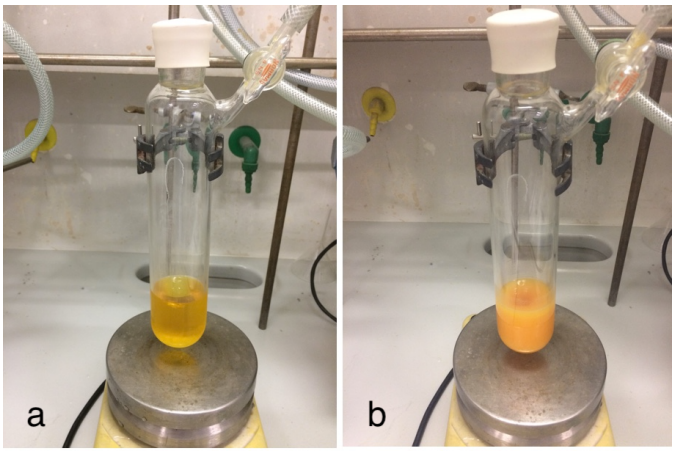


Figure 3. (a) Pale yellow solution after completed addition of *n*-butyllithium and removal of the cooling bath (b) Yellow suspension after stirring at room temperature for 30 min

Figure 4. Setup for solvent removal under reduced pressure using a separate cooling trap

The solvents are carefully removed under reduced pressure (0.4 mmHg, 23 °C) and the resulting boron ate complex is further dried for 30 min (0.06 mmHg, 23 °C) and appears as a yellow solid (Figure 5).

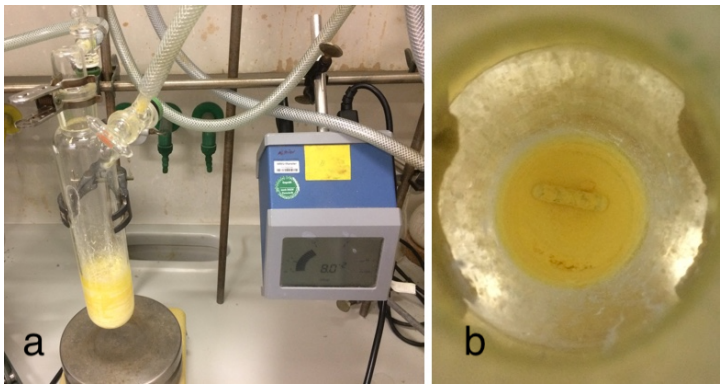


Figure 5. (a) Yellow solid after solvent removal (b) Dried boron ate complex after 30 min

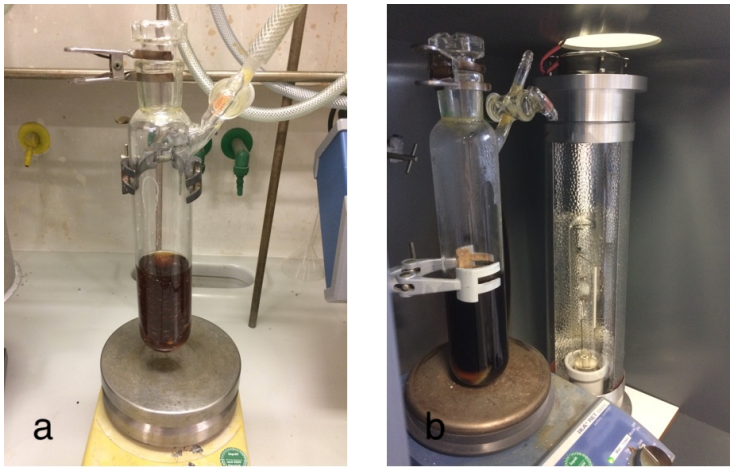


Figure 6. (a) Reaction mixture after addition of nonafluoro-1-iodobutane (b) Reaction mixture in light chamber after 18 h

The vacuum connection is closed, the Schlenk tube is backfilled with argon, the vacuum connection is substituted by a rubber septum and the residue is dissolved with the addition of acetonitrile (130 mL) (Note 9). To the resulting flaky suspension, nonafluoro-1-iodobutane (5.2 mL, 30 mmol,

1.5 equiv) (Note 10) is added under stirring in one portion and the mixture turns brown. The Schlenk tube is sealed with a glass stopper, which is fixed with a metal clamp. The reaction is transferred to a light chamber and stirred for 18 h under irradiation with visible light (Note 11) (Figure 6).

The resulting dark brown solution is transferred to a 500 mL round-bottomed flask [The Schlenk tube is rinsed with diethyl ether (3 x 15 mL)] and then concentrated under reduced pressure by rotary evaporation (7.5 mmHg, 40 °C) (Note 12). The concentrated mixture is transferred with diethyl ether (3 x 60 mL) to a 500 mL separatory funnel and washed with saturated aqueous solution of sodium thiosulfate (90 mL) (Note 13). The separated organic phase is washed with demineralized water (90 mL) and dried over sodium sulfate (30 g). The drying agent is removed by a glass sinter (porosity 4) and flushed with diethyl ether (3 x 25 mL). The filtrate is concentrated under reduced pressure by rotary evaporation (7.5 mmHg, 40 °C).

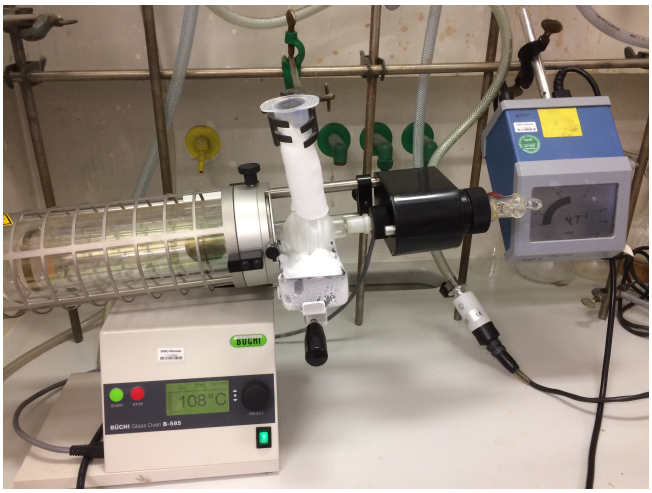


Figure 7. Kugelrohr distillation with dry ice cooling and manometer

The brown oily residue is purified by Kugelrohr distillation (Figure 7) (Note 14). The air bath temperature is slowly increased from room temperature at a pressure of 0.35 mmHg. Pure product is collected (air bath temperature 110 – 115 °C, 0.35 mmHg) as the first fraction in a bulb that is continuously cooled with dry ice over a period of approximately 2 h. The desired 4,4,5,5-tetramethyl-2-(7,7,8,8,9,9,10,10,10-nonafluoro-5-methyldecan-

5-yl)-1,3,2-dioxaborolane (**2**) is obtained as a pale yellow oil (7.76 g, 87%) (Notes 15, 16 and 17) (Figure 8).

Figure 8. Pure product after Kugelrohr distillation

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 isopropenyl boronic acid pinacol ester, diethyl ether, *n*-butyllithium, acetonitrile, nonafluoro-1-iodobutane, sodium thiosulfate and sodium sulfate.

2. All glassware was oven-dried, quickly assembled, and evacuated under vacuum (0.075 mmHg) before backfilling with argon. All reaction steps are performed under a partial positive argon atmosphere using an argon gas line connected to an external paraffin oil bubbler.
3. Diethyl ether (99%) was purchased from Acros Organics, refluxed over K and was freshly distilled from K-Na-alloy before use. The checkers used diethyl ether from a LC Technology Solutions SP-1 solvent purification system.
4. Isopropenyl boronic acid pinacol ester (95%, contains phenothiazine as stabilizer) was purchased from Sigma Aldrich and used as received.
5. *n*-Butyllithium (1.6 M solution in hexanes, AcroSeal) was purchased from Acros Organics and used as received.
6. A syringe pump from UNO B.V. was used with the following settings: diameter: 20 mm; flow rate: 89 mL/h; total time: 10 min.
7. After addition of *n*-butyllithium the mixture turns yellow (sometimes dark yellow to orange). After completed addition, the cooling bath was removed and stirring was continued at room temperature for 30 min while the mixture becomes cloudy.
8. The boron ate complex is sensitive to water and oxygen. The switch from the septum to the evacuated cooling trap was performed under positive argon atmosphere of the Schlenk tube. The side arm of the Schlenk tube was closed, the vacuum connection was carefully opened and the solvents were condensed in a separate cooling trap (250 mL Schlenk round-bottomed flask in a liquid nitrogen filled dewar).
9. Acetonitrile (99.9%), Extra Dry over Molecular Sieve, AcroSeal was purchased from Acros Organics and used as received.
10. Nonafluoro-1-iodobutane (98%) was purchased from Sigma Aldrich and used as received.
11. The light chamber is equipped with a Philips Master HPI-T Plus (400W) light source. The distance between bulb and the reaction tube is approximately 20 cm. Although the light chamber is equipped with a ventilator a temperature of approximately 40 °C is reached in the chamber due the heat of the bulb. The checkers used a fume hood shielded with aluminum foil as a substitute for the light chamber.
12. First diethyl ether was removed (600 mmHg, 40 °C) before the pressure was gradually reduced (7.5 mmHg, 40 °C) and held for approximately 30 min. Due to the volatility of the fluorinated product the pressure should not be further decreased.

13. The saturated aqueous solution of sodium thiosulfate (90 mL) was also used to transfer the Et_2O insoluble residue from the 500 mL flask to the 500 mL separatory funnel. As a precaution the first 10 mL of this solution were added dropwise over 5 min at room temperature to the separatory funnel. As a precaution the first 10 mL of this solution were added dropwise over 5 min at room temperature to the separatory funnel and the remaining solution can then be added in one portion.
14. A Kugelrohr Distillation Apparatus Büchi Glass Oven B-585 from Büchi Labortechnik GmbH was used with the following settings: temperature: 110 °C (±5 °C); rotation: 15 rpm; pressure: 0.35 mmHg.
15. If the distilled product shows turbidity after distillation, it can be passed through a disposable syringe filter (PTFE membrane, pore size 0.2 μm).
16. 4,4,5,5-Tetramethyl-2-(7,7,8,8,9,9,10,10,10-nonafluoro-5-methyldecan-5-yl)-1,3,2-dioxaborolane (**2**) has the following spectroscopic properties: FTIR (neat): ν (cm^{-1}) 2980, 2963, 2934, 2876, 1472, 1380, 1374, 1324, 1233, 1216, 1133, 1020, 878, 849, 738, 729. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.89 (t, J = 7.2 Hz, 3H), 1.08 (d, J = 2.1 Hz, 3H), 1.15 – 1.24 (m, 13H), 1.25 – 1.36 (m, 4H), 1.42 – 1.51 (m, 1H), 1.88 (dddt, J = 32.3, 14.9, 10.0, 2.2 Hz, 1H), 2.27–2.42 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 14.0 (s, 1C), 20.8 (s, 1C), 23.4 (s, 1C), 24.6 (s, 2C), 24.7 (s, 2C), 27.1 (s, 1C), 38.4 (t, J = 20.7 Hz, 1C), 39.3 (s, 1C), 83.5 (s, 2C), 104.9 –122.9 (m, 4C). The signal of the α-B-carbon was not observed. ^{19}F NMR (470 MHz, $CDCl_3$) δ: –81.1 (tt, J = 9.7, 3.4 Hz, 3F), –106.9 – –107.8 (m, 1F), –110.8 – –111.7 (m, 1F), –124.9 – –125.1 (m, 2F), –125.7 – –125.9 (m, 2F). ^{11}B NMR (160 MHz, $CDCl_3$) δ (ppm) 34.1. HRMS (EI) m/z = 443.17984 calcd. for $C_{17}H_{25}BF_9O_2$ $[M–H]^+$; found: 443.17982. CHN Anal. calcd for $C_{17}H_{26}BF_9O_2$: C, 45.97; H, 5.90; found: C, 46.03; H, 6.03.
17. A second reaction on equivalent scale provided 7.58 g (85%). When using 5.0 equiv of nonafluoro-1-iodobutane on the same scale the yield can be improved to 94%.

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

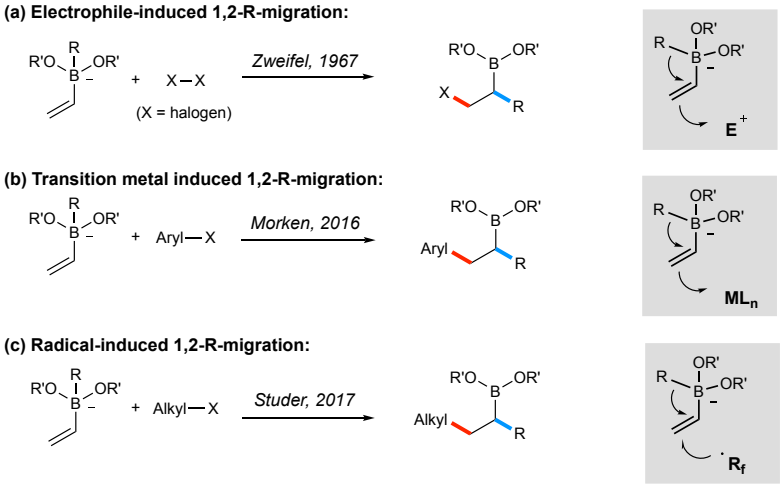
Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, 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.

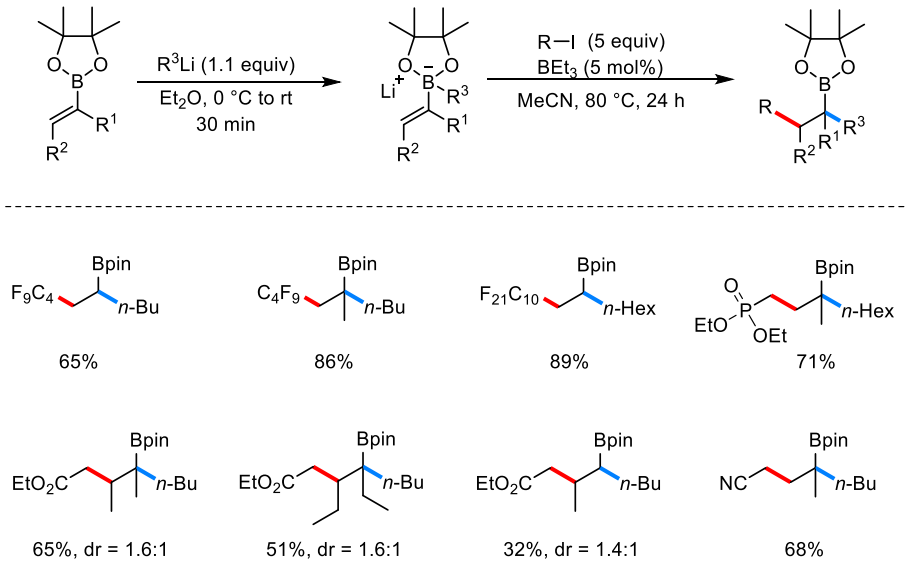
Discussion

Vinyl boronic esters are highly important building blocks for C–C bond formations in the *Suzuki-Miyaura* coupling.[2] Furthermore, vinyl boronic esters can be used in three component coupling reactions, in which two new bonds are formed and the valuable boronic ester moiety remains in the product. The strategy is based on the ability of vinyl boronic esters to form boron ate complexes with carbon nucleophiles. A subsequent 1,2-metalate rearrangement can be triggered by different mechanisms (Scheme 1).



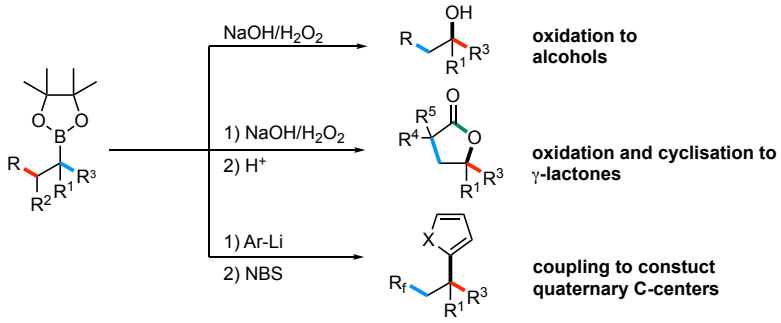
Scheme 1. Reactivity of vinyl boron ate complexes in three component couplings

In the *Zweifel* reaction the 1,2-R-shift is induced by initial electrophilic halogenation of the vinyl group.[3] In 2016 *Morken et al*. utilized *in situ* generated vinyl boron ate complexes in transition metal-catalyzed enantioselective conjunctive cross-couplings with aryl iodides.[4] Along these lines, we recently demonstrated that *in situ* generated vinyl boron ate complexes react efficiently with electrophilic alkyl radicals, generated from alkyl iodides. The resulting radical anions undergo a radical-polar crossover reaction and a 1,2-alkyl/aryl shift from boron to the α-carbon sp^2 center eventually provides valuable secondary and tertiary alkyl boronic esters.[5] Notably, the cascade proceeds without the help of any transition metal and uses commercial starting materials, allowing a rapid construction of molecular complexity. The reaction sequence tolerates α- and β-substituted vinyl boronic esters and the scope of the radical precursor includes perfluoralkyl iodides, α-iodo esters, iodoacetonitrile and α-iodo phosphonates. Initiation of the chain reaction can be achieved either by addition of catalytic amounts of BEt_3 (Scheme 2),[5] by photo-[6] or photoredox initiation.[7]



Scheme 2. Selected examples for radical-polar cross over reactions towards secondary and tertiary alkyl boronic esters[4]

To demonstrate the potential of the boronic ester moiety in versatile follow-up chemistry, we used the boron intermediate for the synthesis of alcohols and valuable γ -lactones. Furthermore, the alkyl boronic ester could be used for the construction of quaternary C-centers.[5]



Scheme 3. Various transformations of alkyl boronic esters[5]

References

1. Organisch-Chemisches Institut, Westfälische Wilhelms-Universität, Corrensstraße 40, 48149, Münster (Germany). E-mail: studer@uni-muenster.de. We thank the European Research Council ERC (Advanced Grant agreement No. 692640) for supporting this work.
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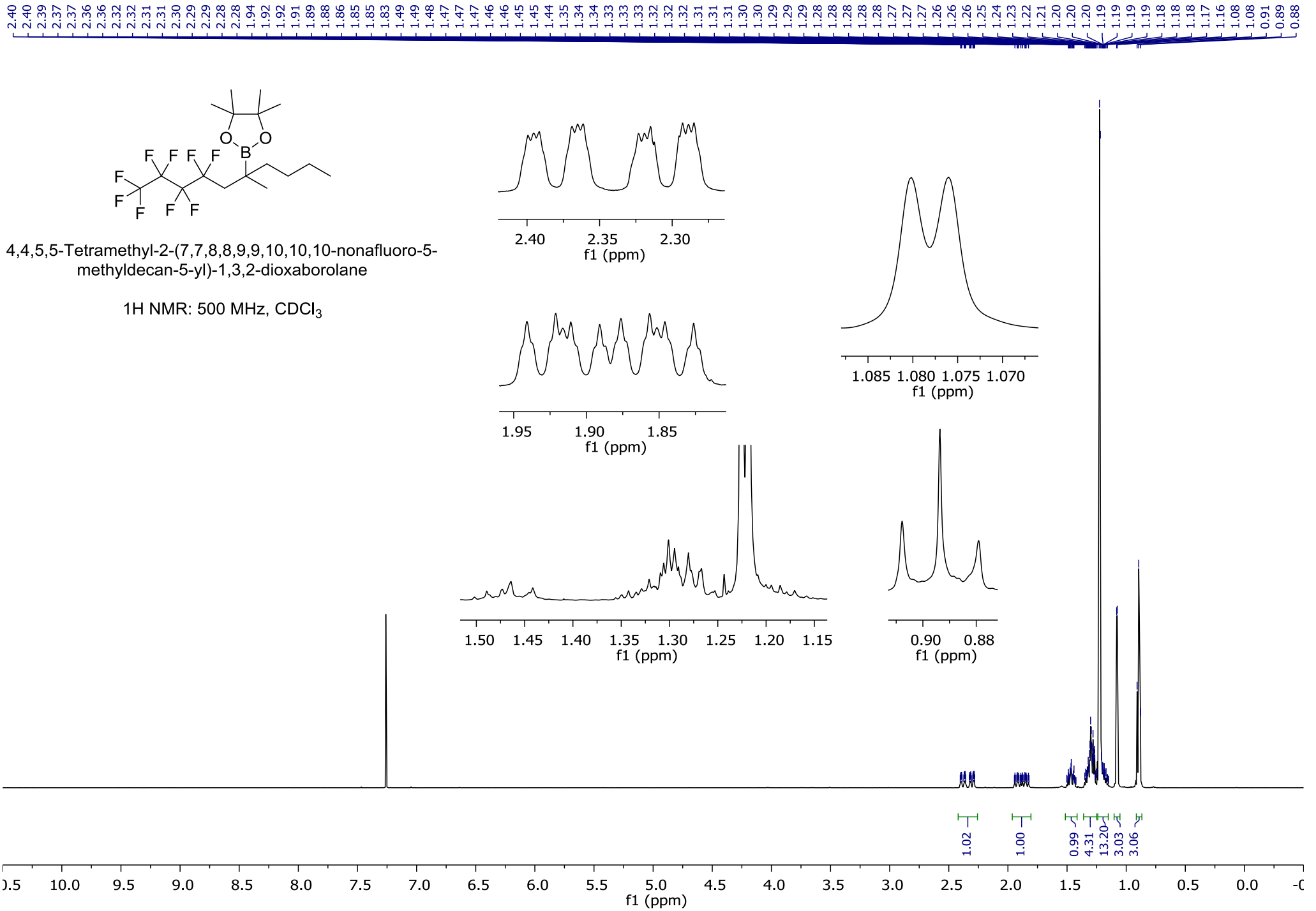
Appendix
Chemical Abstracts Nomenclature (Registry Number)

Isopropenyl boronic acid pinacol ester; (126726-62-3)
n-Butyllithium; (109-72-8)
Nonafluoro-1-iodobutane; (423-39-2)
Sodium thiosulfate; (7772-98-7)
Sodium sulfate; (7757-82-6)

Marvin Kischkewitz obtained his B.Sc. degree in chemistry in 2013 from the Westfälische Wilhelms-University of Münster. During his following master studies in Münster, he did a research stay in the laboratory of Prof. Mark Lautens at the University of Toronto. In 2015 he completed his master thesis in the group of Prof. Armido Studer, where he is currently pursuing his doctoral studies in the field of organic chemistry. His research focuses on radical reactions and electron catalysis.

Armido Studer received his Diploma in 1991 and his Ph.D. in 1995 from ETH Zürich with Prof. Dieter Seebach. He then did postdoctoral studies at the University of Pittsburgh with Prof. Dennis P. Curran. In 1996 he started his independent career at the ETH Zürich. In 2000 he was appointed Associate Professor of Organic Chemistry at the Philipps-University in Marburg, and in 2004 Professor of Organic Chemistry at the Westfälische Wilhelms-University in Münster.

Helene Wolleb obtained her B.Sc. and M.Sc. degree in chemistry from ETH Zürich, conducting research with Prof. Erick M. Carreira and Prof. Antonio Togni at the same institution, and with Prof. Steven V. Ley at the University of Cambridge. After an internship at Bayer HealthCare AG in Wuppertal, she joined the group of Prof. Erick M. Carreira for her doctoral studies in 2015 to work on the synthesis of complex natural products.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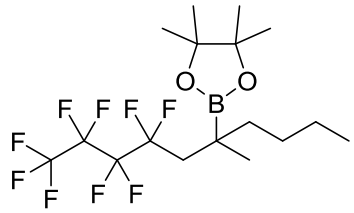
4,4,5,5-Tetramethyl-2-(7,7,8,8,9,9,10,10,10-nonafluoro-5-methyldecan-5-yl)-1,3,2-dioxaborolane
1H NMR: 500 MHz, CDCl3
2.40
2.35
2.30
f1 (ppm)
1.95
1.90
1.85
f1 (ppm)
1.50 1.45 1.40 1.35 1.30 1.25 1.20 1.15
f1 (ppm)
1.085 1.080 1.075 1.070
f1 (ppm)
0.90 0.88
f1 (ppm)
1.02
1.00
0.99
4.31
13.20
3.03
3.06
10.0 9.5 9.0 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
f1 (ppm)

4,4,5,5-Tetramethyl-2-(7,7,8,8,9,9,10,10,10-nonafluoro-5-methyldecan-5-yl)-1,3,2-dioxaborolane

13C NMR: 126 MHz, $CDCl_3$



4,4,5,5-Tetramethyl-2-(7,7,8,8,9,9,10,10,10-nonafluoro-5-methyldecan-5-yl)-1,3,2-dioxaborolane

19F NMR: 470 MHz, $CDCl_3$