

A Synthetic Approach to Dimetallated Arenes Using Flow Microreactors and the Switchable Application to Chemoselective Cross-Coupling Reactions

Yosuke Ashikari, Tomoko Kawaguchi, Kyoko Mandai, Yoko Aizawa, and Aiichiro Nagaki*

index

1. General Remarks
2. Halogen–Lithium Exchange Reaction of 4-Bromophenylboronic Acid Pinacol Ester Followed by Reaction of Tri-*n*-Butylthiin Chloride in a Flow Microreactor (Negative Control)
3. Generation of Lithium Arylboron-ate Complex 4 in a Flow Microreactor
4. Reactions of Lithium Arylboron-ate Complexes in a Flow Microreactor
5. Cross Coupling Reactions of Bimetallic Arenes
6. Synthetic Utility of Stannyli Biphenyl 11 and Boryl Biphenyl 12.
7. References
8. ^1H and ^{13}C NMR Spectra

1. General Remarks.

Abbreviations. atmospheric pressure chemical ionization (APCI), approximately (approx.), aqueous (aq.), aryl (Ar), boron trifluoride ethyl diether complex ($\text{BF}_3\cdot\text{OEt}_2$), broad (br), butyl (Bu), degrees Celsius ($^{\circ}\text{C}$), calculated (calcd), deuterated chloroform (CDCl_3), centimeter(s) (cm), doublet (d), dimethyl sulfoxide (DMSO), deuterated dimethyl sulfoxide ($\text{DMSO}-d_6$), 1,1'-bis(diphenylphosphino)ferrocene (dppf), electron ionization (EI), equivalent (equiv or eq), electrospray ionization (ESI), ethyl acetate (EtOAc), gram(s) (g), gas chromatography (GC), hour(s) (h), high resolution mass-spectrometry (HRMS), hertz (Hz), isopropyl (*i*Pr), coupling constant (*J*), length of tubes (L), liter(s) (L), mol L^{-1} of molar concentration (M), multiplet (m), methyl (Me), metallic atom (Met), deuterated methanol (methanol-*d*₄), milligram(s) (mg), megahertz (MHz), minute(s) (min), milliliter(s) (mL), millimole(s) (mmol), mole(s) (mol), *normal* (n), mol L^{-1} of equivalent concentration (N), nuclear magnetic resonance (NMR), *para* (p), dichloro-[1,3-bis(diisopropylpenyl)-2-imidazolidinyliden]-[3-Chloropyridyl]palladium (II) (PEPPSI-SIPr), pinacol boranyl group (pinB), tetramethylethylenedioxy group (pin), parts per million (ppm), polytetrafluoro-ethylene or Teflon (PTFE), quartet (q), retention factor for TLC (*R*_f), room temperature (25 ± 3 $^{\circ}\text{C}$, rt), *secondary* (s or sec), second(s) (s), singlet (s), saturated (sat.), septet (sept), triplet (t), *tertiary* (t or tert), tri-*n*-butylammonium fluoride (TBAF), 1,1,2,2-tetrachloroethane (TCE), tetrahydrofuran (THF), thin layer chromatography (TLC), tetramethylsilane (TMS), residence time of microtube reactor R_n (*t*^{R_n}), volume ratio of two solvents (v/v), chemical shift in ppm downfield from TMS (δ), inner diameter of tubes and mixers (ϕ), microliter(s) (μL), micrometer(s) (μm).

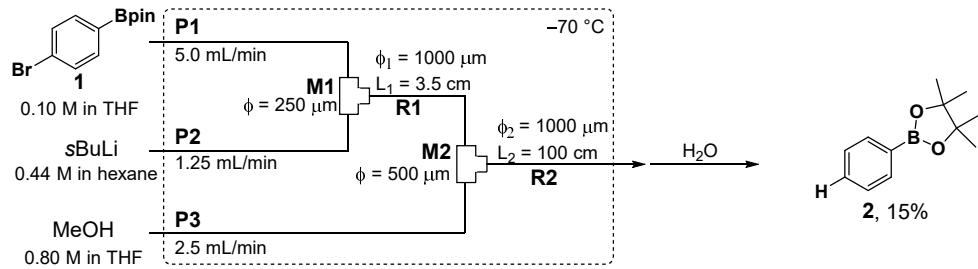
General. ^1H and ^{13}C NMR spectra were recorded in on Varian MERCURY plus-400 (^1H 400 MHz, ^{13}C 100 MHz), or on JEOL ECA-600P spectrometer (^1H 600 MHz, ^{13}C 150 MHz). Chemical shifts are recorded using TMS (0.0 ppm) or solvent (DMSO: 2.50 ppm) signals as an internal standard for ^1H NMR, and methin signal of CHCl_3 for ^{13}C NMR (77.0 ppm) unless otherwise noted. Because of a quadrupolar moment of naturally-occurring boron isotopes (^{10}B and ^{11}B), a ^{13}C NMR signal of a carbon directly attached to a boron atom becomes significantly broad, and often becomes invisible in the chart.^[1] ^{11}B NMR spectra were recorded on JEOL ECA-500P spectrometer (160 MHz) using $\text{BF}_3\cdot\text{OEt}_2$ in CDCl_3 as an external standard (0.0 ppm). For ^{11}B NMR analyses,

a quartz NMR tube was used. NMR yields were calculated by ^1H NMR analyses using TCE as an internal standard. GC analysis was performed on a SHIMADZU GC-2014 gas chromatograph equipped with a flame ionization detector using a fused silica capillary column (column, CBP1; 0.22 mm x 25 m). GC yields were calculated by GC analyses with *n*-tetradecane as an internal standard using calibration lines derived from commercial or isolated compounds with the internal standards. Mass spectra were obtained on Thermo Fisher Scientific EXACTIVE plus (ESI and APCI) and JEOL JMS-700 (EI). Merck pre-coated silica gel F₂₅₄ plates (thickness 0.25 mm) were used for TLC analyses. Flash chromatography was carried out on a silica gel (Kanto Chem. Co., Silica Gel N, spherical, neutral, 40–100 μm). All batch reactions were carried out in a flame-dried glassware under argon atmosphere unless otherwise noted.

Flow Synthesis. Stainless steel (SUS304) T-shaped micromixers with inner diameter of 500 μm and 250 μm were manufactured by Sanko Seiki Co., Inc. Stainless steel (SUS316) microtube reactors with 1000 μm inner diameter were purchased from GL Sciences. PTFE tube with inner diameter of 1000 μm was purchased from ISIS Co, Ltd. The syringe pumps (Harvard Model PHD 2000 or PHD ULTRA) equipped with gastight syringes (purchased from SGE) were used for introduction of the solutions into the micromixer systems *via* stainless steel fittings (GL Sciences, 1/16 OUW). Flow microreactor system is composed with stainless steel pre-cooling units (**P1**, **P2**, etc.), stainless steel microtube reactors (**R1**, **R2**, etc.), T-shaped micromixers (**M1**, **M2**, etc.), and, if necessary, PTFE tube with inner diameter of 1000 μm . The solution of *n*-butyllithium and *sec*-butyllithium was prepared by dilution of those commercial solution with dehydrated *n*-hexane.

Materials. Dehydrated THF and *n*-hexane were purchased from FUJIFILM Wako Pure Chemical Corporation, and were used without further purification. A solution of *sec*-butyllithium (in cyclohexane and *n*-hexane, 1.03 M) was purchased from Kanto Chemical Co., Inc. and stored at $-20\text{ }^\circ\text{C}$. A solution of zinc chloride (in THF, 1.0 M) was purchased from FUJIFILM Wako, and was diluted with dry THF. 2-(4-Bromophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1**), 1,4-dibromobenzene (**3a**), 1,3-dibromobenzene (**3b**), 1,3,5-tribromobenzene (**3c**), 2,5-dibromothiophene (**3e**), 2,3-dibromopyridine (**3f**), 2,5-dibromopyridine (**3g**), 2,2'-dibromobiphenyl (**3h**), B(O*i*Pr)₃, B(O*i*Pr)₃, B(OMe)₃, Bu₃SnCl, 1,4-benzenediboronic acid bis(pinacol) ester (**9a-B**), 1,3-benzenediboronic acid bis(pinacol) ester (**9b-B**), biphenyl (**15**), 4-cyanobiphenyl (**17**), and aryl iodides were purchased from commercial suppliers. *tert*-butyl 3,5-dibromobenzoate (**3d**) was synthesized according to the reported procedure.^[2]

2. Halogen–Lithium Exchange Reaction of 4-Bromophenylboronic Acid Pinacol Ester Followed by Reaction of Tri-*n*-Butyltin Chloride in a Flow Microreactor (Negative Control).

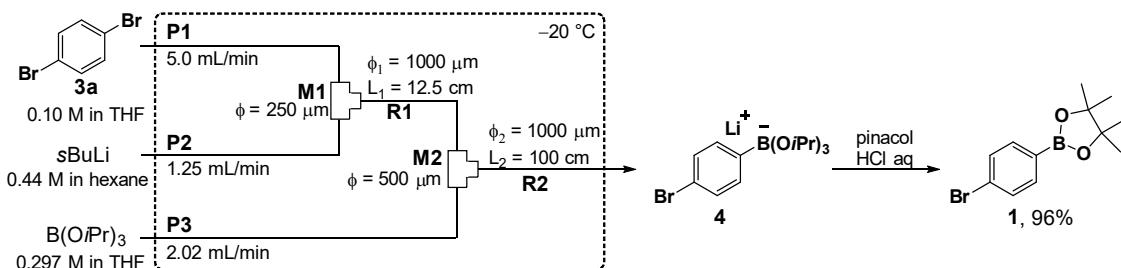


A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2**), two microtube reactors (**R1** and **R2**), and three pre-cooling units (**P1** ($L = 100\text{ cm}$), **P2** (50 cm) and **P3** (50 cm)) was used in a cooling bath at $-70\text{ }^\circ\text{C}$. A solution of 4-bromophenylboronic acid pinacol ester (**1**, 0.10 M in THF, flow rate: 5.0 mL/min) and a solution of *s*BuLi (0.44 M in hexane, flow rate: 1.25 mL/min) were introduced to **M1** ($\phi = 250\text{ }\mu\text{m}$) using syringe pumps, and the mixture was passed through **R1** (3.5 cm, residence time $t^{\text{R1}} = 0.26\text{ s}$). The resulting solution was introduced to **M2** ($\phi = 500\text{ }\mu\text{m}$), where a solution of methanol (0.80 M in THF) was also introduced (flow rate: 2.50 mL/min). The resulting solution was passed through **R2** ($\phi = 1000\text{ }\mu\text{m}$, $L = 100\text{ cm}$,

residence time = 5.4 s). After a steady state was reached, the product solution was collected for 30 seconds. To the aliquot, sat. NH₄Cl aq., EtOAc, and *n*-tetradecane were added, and then the organic phase was analyzed by GC, which indicated the yield of phenylboronic acid pinacol ester (**1**) was 15% and conversion of **1** was 83%.

3. Generation of Lithium Arylboron-ate Complex **4** in a Flow Microreactor.

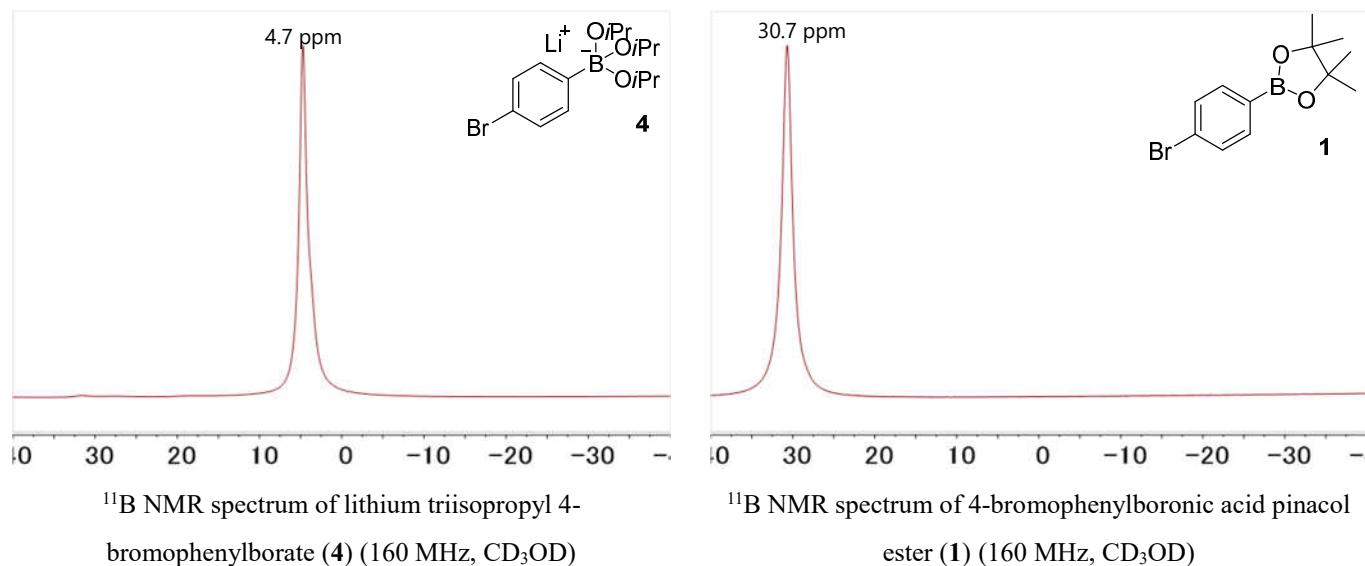
3-1. Halogen–Lithium Exchange Reaction of 1,4-Dibromobenzene (**3a**) Followed by the Reaction with triisopropyl borate in the Flow Microreactor System



A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2**), two microtube reactors (**R1** and **R2**), and three pre-cooling units (**P1** (100 cm), **P2** (50 cm) and **P3** (50 cm)) was used in a cooling bath at $-20\text{ }^{\circ}\text{C}$. A solution of 1,4-dibromobenzene (**3a**, 0.10 M in THF, flow rate: 5.0 mL/min) and a solution of *s*BuLi (0.44 M in hexane, flow rate: 1.25 mL/min) were introduced to **M1** ($\phi = 250\text{ }\mu\text{m}$) using syringe pumps, and the mixture was passed through **R1** (12.5 cm, residence time $t^{\text{R1}} = 0.90\text{ s}$). The resulting solution was introduced to **M2** ($\phi = 500\text{ }\mu\text{m}$), where a solution of triisopropyl borate (0.297 M in THF) was also introduced (flow rate: 2.02 mL/min). The resulting solution was passed through **R2** ($\phi = 1000\text{ }\mu\text{m}$, $L = 100\text{ cm}$, $t^{\text{R2}} = 5.7\text{ s}$). After a steady state was reached, the product solution (lithium triisopropyl 4-bromophenylborate, **4**) was taken into a 100 mL round-bottomed flask. An aliquot (3.0 mL) of the solution was treated with 1 mL of pinacol solution (0.75 M in Et₂O) and 1 mL of HCl aq. (1 N) in a 20 mL round-bottomed flask. The reaction mixture was stirred at r.t. for 30 min. The GC analysis indicated 4-bromophenylboronic acid pinacol ester (**1**) was obtained in 96% yield (*n*-tetradecane was used as an internal standard).

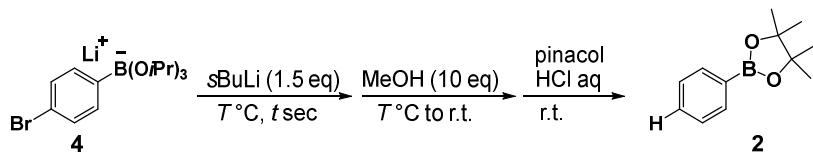
3-2. ¹¹B NMR analyses of Arylboron-ate Complex **4**.

The aliquot of the solution of **4** (3.5 mL, 0.2 mmol) was concentrated under reduced pressure. Thus-obtained white solid was dissolved in 0.7 mL of methanol-*d*₄, and the solution was analyzed by ¹¹B NMR, which showed a singlet peak on 4.7 ppm.



4. Reactions of Lithium Arylboron-ate Complexes in a Flow Microreactor.

4-1. Halogen–Lithium Exchange Reaction of Lithium Arylboron-ate Complex 4 Followed by the Reaction with Methanol in a Batch Reactor.

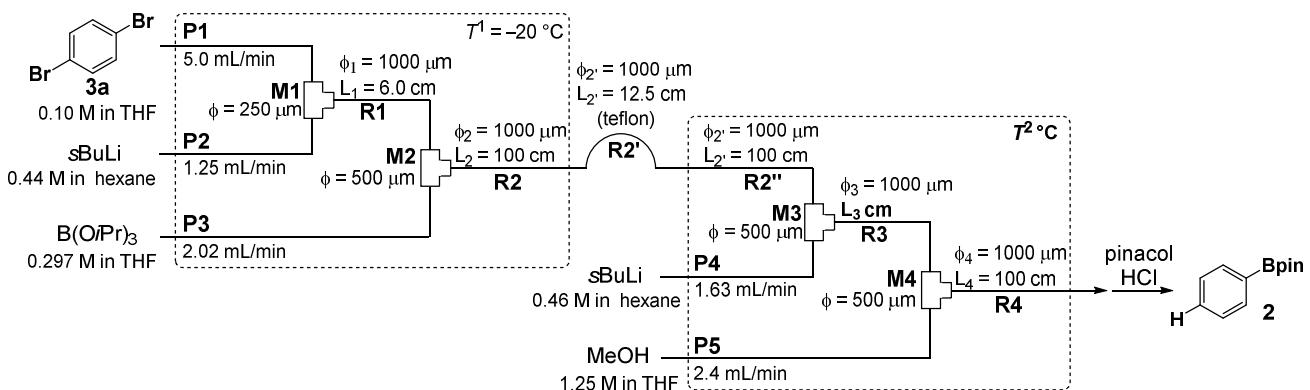


The solution of **4** was collected in a flame dried 20 mL round-bottomed-flask for 30 seconds (approx. 4.1 mL, 0.25 mmol. See section 3 of SI), and was stirred at T °C (0, -50, or -70 °C). To the solution, 0.85 mL of *sec*-BuLi (0.44 M in hexane and cyclohexane, 1.5 eq) was added rapidly. After t seconds (10 or 60 sec), 100 μ L of methanol (10 eq) was added at same temperature, and then the mixture was allowed to be warmed to room temperature. After stirring at room temperature for 30 minutes, and the reaction mixture was then treated with 1 mL of 1 N HCl and 1 mL of pinacol solution (0.8 M in Et₂O). After addition of EtOAc (2 mL), brine (2 mL), *n*-tetradecane (internal standard), the organic phase was analyzed by GC to determine the yields of **2**. The result is summarized in Table S-1.

Table S-1. Synthesis of phenylboronic acid pinacol ester (**5**) from 1,4-dibromobenzene (**3a**) using a batch system

T °C	$t = 10$ (sec)	$t = 60$ sec
0	16	20
-50	23	29
-70	33	30

4-2. Halogen–Lithium Exchange Reaction of Lithium Arylboron-ate Complex 4 Followed by the Reaction with Methanol in the Flow Microreactor System



An integrated flow microreactor system consisting of four T-shaped micromixers (**M1**, **M2**, **M3** and **M4**), microtube reactors (**R1**, **R2**, **R2''**, **R3**, and **R4**), and five pre-cooling units (**P1** (100 cm), **P2** (50 cm), **P3** (50 cm), **P4** (50 cm), and **P5** (100 cm)) was used. The part of the flow microreactor system composed with **P1**, **P2**, **P3**, **M1**, **M2**, **R1**, and **R2** was cooled at -20 °C and the part composed with **P4**, **P5**, **M3**, **M4**, **R2''**, **R3**, and **R4** was cooled at T^2 °C. The reactors in different cooling baths were connected by a PTFE tube **R2'** (12.5 cm). A solution of 1,4-dibromobenzene (**3a**, 0.10 M in THF, flow rate: 5.0 mL/ min) and a solution of *sec*-BuLi (0.44 M in hexane, flow rate: 1.25 mL/min) were introduced into **M1** ($\phi = 250$ μ m) by syringe pumps, and the mixture was passed through **R1** (6 cm, $t^{R1} = 0.45$ s). The solution of monolithiated arenes (flow rate: 6.25 mL/min) and a solution of B(O*i*Pr)₃ (0.297 M in THF, flow rate: 2.02 mL/min) were introduced to **M2** ($\phi = 500$ μ m), and the mixture was passed through **R2** (100 cm, $t^{R2} = 5.7$ s). The solution of boron-ate complex (flow rate: 8.27 mL/min) was passed through **R2'** (12.5 cm, $t^{R2'} = 0.71$ s) and **R2''** (100 cm, $t^{R2''} = 5.7$ s). Then, the solution of boron-ate complex and a solution of *sec*-BuLi (0.46 M in hexane, flow rate: 1.63

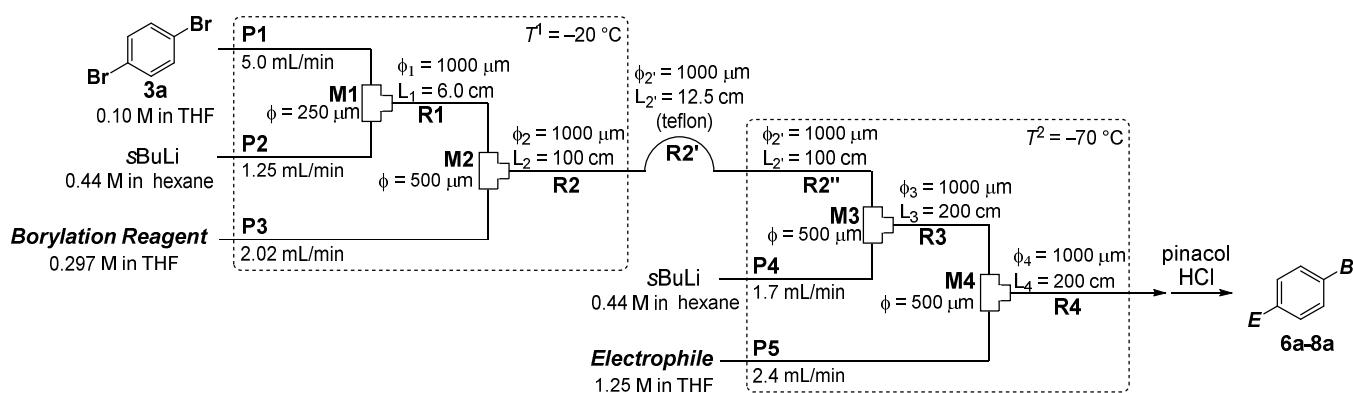
mL/min) were mixed in **M3** ($\phi = 500 \mu\text{m}$), and the mixture was passed through **R3** ($L_3 = 3 \text{ cm}$). The resulting solution was introduced to **M4** ($\phi = 500 \mu\text{m}$) where a solution of MeOH (1.25 M in THF, flow rate: 2.4 mL/min) was introduced, and the mixture was passed through **R4** (100 cm, $t^{R4} = 3.8 \text{ s}$). After a steady state was reached, an aliquot of the product solution was collected for 30 seconds. The aliquot was treated with 1 ml of 1 N HCl aq. and 0.8 ml of pinacol solution (0.3 M in Et₂O), and the mixture was stirred at r.t. for 30 min to be converted to phenylboronic acid pinacol ester (**2**). After addition of EtOAc (2 mL), brine (2 mL), and *n*-tetradecane, the organic phase was analyzed by GC to determine the yields of **5**. The result is summarized in Table S-2.

Table S-2. Synthesis of phenylboronic acid pinacol ester (**5**) from 1,4-dibromobenzene (**3a**) using the integrated flow microreactor system

T^2 (°C)	L_3 (cm)	t^{R3} (s)	Yield of 5 (%)	T^2 (°C)	L_3 (cm)	t^{R3} (s)	Yield of 5 (%)
0	3	0.14	24	-50	3	0.14	27
	6	0.29	42		6	0.29	44
	25	1.19	23		25	1.19	67
	50	2.38	16		50	2.38	66
	100	4.76	6		100	4.76	64
	200	9.52	2		200	9.52	60
-20	3	0.14	37	-70	3	0.14	24
	6	0.29	49		6	0.29	40
	25	1.19	59		25	1.19	71
	50	2.38	57		50	2.38	70
	100	4.76	15		100	4.76	71
	200	9.52	6		200	9.52	72

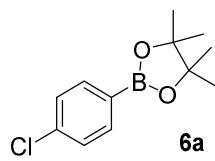
4-3. Halogen–Lithium Exchange Reaction of Lithium Arylboron-ate Complex **4** Followed by the Reaction with Electrophiles in the Flow Microreactor System

Typical Procedure for the Reaction of Borylated Aryllithiums with Electrophiles.

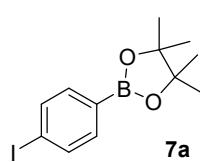


An integrated flow microreactor system consisting of four T-shaped micromixers (**M1**, **M2**, **M3** and **M4**), microtube reactors (**R1**, **R2**, **R2''**, **R3**, and **R4**), and five pre-cooling units (**P1** (100 cm), **P2** (50 cm), **P3** (50 cm), **P4** (50 cm), and **P5** (100 cm)) was used. The part of the flow microreactor system composed with **P1**, **P2**, **P3**, **M1**, **M2**, **R1**, and **R2** was cooled at -20 °C and the part composed with **P4**, **P5**, **M3**, **M4**, **R2''**, **R3**, and **R4** was cooled at -70 °C. A solution of dibromoarene **3** (0.10 M in THF, flow rate: 5.0 mL/min) and a solution of *sec*-BuLi (0.44 M in hexane, flow rate: 1.25 mL/min) were introduced into **M1** ($\phi = 250 \mu\text{m}$) by syringe pumps, and the mixture was passed through **R1** (6 cm, -20 °C, $t^{R1} = 0.45 \text{ s}$). The solution of monolithiated aryls (flow rate: 6.25 mL/min) and a solution of borylation reagent ($\text{B}(\text{O}i\text{Pr})_3$ or $\text{B}(\text{O}i\text{Pr})\text{pin}$, 0.297 M in THF, flow rate: 2.02 mL/min) were

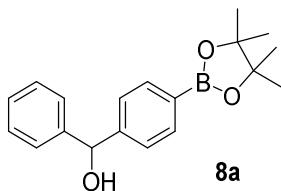
introduced to **M2** ($\phi = 500 \mu\text{m}$), and the mixture was passed through **R2** (100 cm, -20°C , $t^{\text{R}2} = 5.7$ s). The solution of boron-ate complex (flow rate: 8.27 mL/min) was passed through **R2'** (12.5 cm, $t^{\text{R}2'} = 0.71$ s) and **R2''** (100 cm, $t^{\text{R}2''} = 5.7$ s), and was cooled to -70°C . Then, the solution of boron-ate complex and a solution of *sec*-BuLi (0.44 M in hexane, flow rate: 1.7 mL/min) were mixed in **M3** ($\phi = 500 \mu\text{m}$), and the mixture was passed through **R3** (200 cm). The resulting solution was introduced to **M4** ($\phi = 500 \mu\text{m}$) where a solution of electrophile (0.675 M in THF, flow rate: 2.4 mL/min) was added, and the mixture was passed through **R4** (200 cm). After a steady state was reached (typically 90 seconds), an aliquot of the product solution was collected for 30 seconds, or the solution was collected in a flame-dried round-bottomed-flask. The aliquot derived from $\text{B}(\text{O}i\text{Pr})_3$ was treated with 1 ml of 1 N HCl aq. and 1 ml of pinacol solution (0.3 M in Et_2O), and the mixture was stirred at r.t. for 30 min to converted a triisopropoxy borate moiety to a pinacolboranyl group, whereas the aliquot derived from 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ($\text{B}(\text{O}i\text{Pr})\text{pin}$) was treated with NH_4Cl aq. After addition of EtOAc (2 mL) and brine (2 mL), *n*-tetradecane was added, and the organic phase was analyzed by GC to determine the yields of products, and was purified by flash chromatography.



4-Chlorophenylboronic acid pinacol ester (6a). The reaction solution derived from 1,4-dibromobenzene (**3a**), triisopropyl borate, and hexachloroethane was collected for 30 seconds. The aliquot was analyzed by GC after working-up, and the yield was indicated as 78%. The GC peak was identical with that of the commercial one.

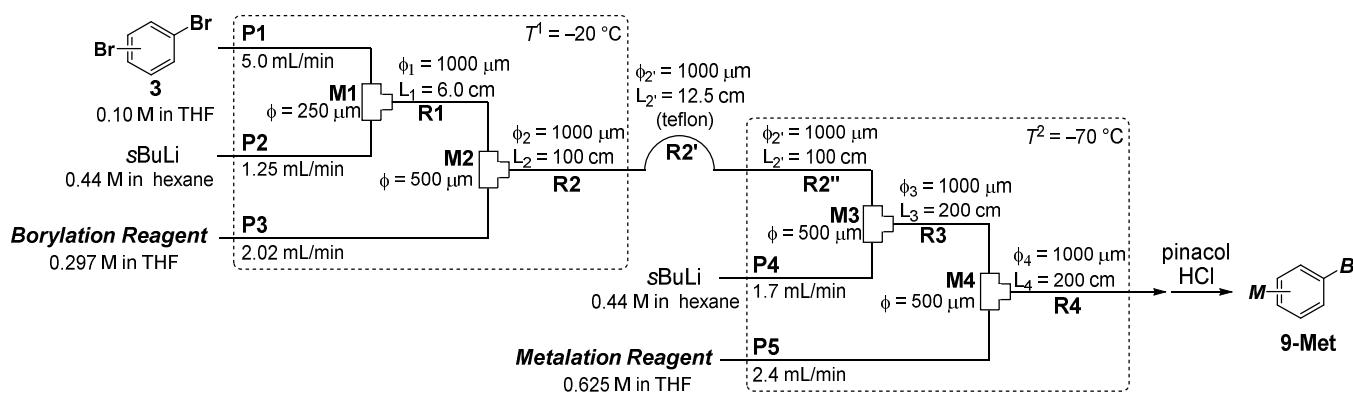


4-Iodophenylboronic acid pinacol ester (7a). The reaction solution derived from 1,4-dibromobenzene (**3a**), triisopropyl borate, and iodine was collected for 30 seconds. The aliquot was analyzed by GC after working-up, and the yield was indicated as 93%. The GC peak was identical with that of the commercial one.

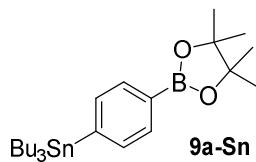


4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzhydrol (8a). The reaction solution derived from 1,4-dibromobenzene (**3a**), 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, and benzaldehyde was collected for 30 seconds. The aliquot was analyzed by GC after working-up, and the yield was indicated as 80%; ^1H NMR (400 MHz, CDCl_3) δ 1.32 (s, 12 H), 5.82 (s, 1 H), 7.22–7.26 (m, 1 H), 7.29–7.39 (m, 6 H), 7.78 (d, $J = 8.4$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 24.8, 76.1, 83.7, 125.7, 126.5, 127.5, 128.4, 134.9, 143.6, 146.8 (one carbon attached to B atom is not visible); HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{23}\text{BO}_3\text{Na} [\text{M}+\text{Na}^+]$: 333.1632, found 333.1635.

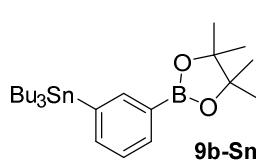
4-4. Halogen–Lithium Exchange Reaction of Lithium Arylboron-ate Complex 4 Followed by the Reaction with Metalation Reagents in the Flow Microreactor System. Typical Procedure for Synthesizing Bi-Metallic Arenes.



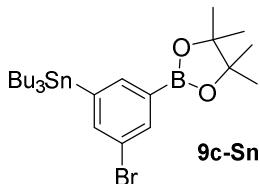
An integrated flow microreactor system consisting of four T-shaped micromixers (**M1**, **M2**, **M3** and **M4**), microtube reactors (**R1**, **R2**, **R2**”, **R3**, and **R4**), and five pre-cooling units (**P1** (100 cm), **P2** (50 cm), **P3** (50 cm), **P4** (50 cm), and **P5** (100 cm)) was used. The part of the flow microreactor system composed with **P1**, **P2**, **P3**, **M1**, **M2**, **R1**, and **R2** was cooled at -20 °C and the part composed with **P4**, **P5**, **M3**, **M4**, **R2**”, **R3**, and **R4** was cooled at -70 °C. A solution of dibromoarenes **3** (0.10 M in THF, flow rate: 5.0 mL/ min) and a solution of *sec*-BuLi (0.44 M in hexane, flow rate: 1.25 mL/min) were introduced into **M1** (ϕ = 250 μ m) by syringe pumps, and the mixture was passed through **R1** (6 cm, -20 °C, t^{R1} = 0.45 s). The solution of monolithiated arenes (flow rate: 6.25 mL/min) and a solution of borylation reagent (B(O*i*Pr)₃ or B(O*i*Pr)pin, 0.297 M in THF, flow rate: 2.02 mL/min) were introduced to **M2** (ϕ = 500 μ m), and the mixture was passed through **R2** (100 cm, -20 °C, t^{R2} = 5.7 s). The solution of boron-ate complex (flow rate: 8.27 mL/min) was passed through **R2**” (12.5 cm, $t^{R2''}$ = 0.71 s) and **R2**” (100 cm, $t^{R2''}$ = 5.7 s), and was cooled to -70 °C. Then, the solution of boron-ate complex and a solution of *sec*-BuLi (0.46 M in hexane, flow rate: 1.63 mL/min) were mixed in **M3** (ϕ = 500 μ m), and the mixture was passed through **R3** (200 cm). The resulting solution of **5a-Li** was introduced to **M4** (ϕ = 500 μ m) where a solution of metalation reagent (0.625 M in THF, flow rate: 2.4 mL/min) was added, and the mixture was passed through **R4** (200 cm). After a steady state was reached (typically 90 seconds), an aliquot of the product solution was collected for 30 seconds, or the solution was collected in a flame-dried round-bottomed-flask. The aliquot derived from B(O*i*Pr)₃ was treated with 1 ml of 1 N HCl aq. and 1 ml of pinacol solution (0.3 M in Et₂O), and the mixture was stirred at r.t. for 30 min to converted triisopropoxy borate moiety to pinacolboranyl group, whereas the aliquot derived from B(O*i*Pr)pin was treated with NH₄Cl aq. After addition of EtOAc (2 mL) and brine (2 mL), *n*-tetradecane was added, and the organic phase was analyzed by GC to determine the yields of product **9-Met**, and was purified by flash chromatography.



4-Tri-n-butylstannylphenylboronic acid pinacol ester (9a-Sn, Table 1, entry 1–3). For entry 1, L₁ = 12.5 cm, t^{R1} = 0.93 s). The reaction solution was obtained from the reaction of 1,4-dibromobenzene (**3a**), triisopropyl borate, and tri-*n*-butylstannyl chloride, and collected in a 100 mL round-bottomed flask. The aliquot (3 mL) was analyzed by GC after working-up, and the yield was indicated as 77%, or the aliquot (6 mL) was purified by flash chromatography using 1–3% EtOAc/hexane as an eluent to obtain the title compound in 75% yield (89.8 mg, 0.182 mmol); Colorless oil. TLC R_f 0.18 (hexane/EtOAc 50:1): ¹H NMR (400 MHz, CDCl₃) δ 0.87 (t, *J* = 7.2 Hz, 9 H), 1.05 (dd, *J* = 8.0, 8.0 Hz, 6 H), 1.27–1.36 (m, 6 H), 1.34 (s, 12 H), 1.49–1.57 (m, 6 H), 7.48 (d, *J* = 6.8 Hz, 2 H), 7.74 (d, *J* = 6.8 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 9.5, 13.7, 24.8, 27.4, 29.1, 83.7, 133.8, 135.9, 146.5 (one carbon attached to B atom is not visible); HRMS (ESI) calcd for C₂₄H₄₃BO₂SnNa [M+Na⁺]: 517.2270, found 517.2276.

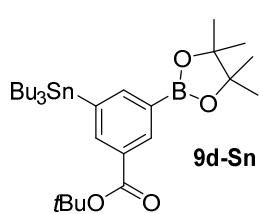


3-Tri-n-butylstannylphenylboronic acid pinacol ester (9b-Sn, Table 1, entry 4 and 5). The reaction solution derived from 1,3-dibromobenzene (**3b**), triisopropyl borate, and tri-*n*-butylstannyl chloride was collected for 30 seconds. The aliquot was analyzed by GC after working-up, and the yield was indicated as 69%; Colorless oil. TLC R_f 0.19 (hexane/EtOAc 50:1): ¹H NMR (400 MHz, CDCl₃) δ 0.88 (t, *J* = 7.2 Hz, 9 H), 1.06 (dd, *J* = 8.0, 8.0 Hz, 6 H), 1.34 (s, 12 H), 1.28–1.37 (m, 6 H), 1.49–1.59 (m, 6 H), 7.32 (dt, *J* = 0.8, 7.6 Hz, 1 H), 7.55 (dt, *J* = 1.2, 7.2 Hz, 1 H), 7.74 (dt, *J* = 1.2, 7.2 Hz, 1 H), 7.88 (s, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 9.5, 13.7, 24.9, 27.4, 29.1, 83.6, 127.2, 134.4, 139.4, 141.1, 142.8 (one carbon attached to B atom is not visible); HRMS (ESI) calcd for C₂₄H₄₃BO₂SnNa [M+Na⁺]: 517.2270, found 517.2271.

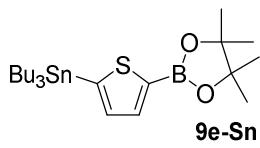


3-Bromo-5-tri-n-butylstannylphenylboronic acid pinacol ester (9c-Sn, Table 1, entry 6).

The reaction solution derived from 1,3,5-tribromobenzene (**3c**), triisopropyl borate, and tri-*n*-butylstannyl chloride was collected for 30 seconds. The aliquot was analyzed by GC after working-up, and the yield was indicated as 92%; TLC R_f 0.59 (hexane/EtOAc 50:1): ^1H NMR (400 MHz, CDCl_3) δ 0.89 (t, J = 7.6 Hz, 9 H), 1.07 (dd, J = 8.0, 8.0 Hz, 6 H), 1.28–1.37 (m, 6 H), 1.34 (s, 12 H), 1.43–1.61 (m, 6 H), 7.63 (d, J = 0.8, 2.0 Hz, 1 H), 7.76 (dd, J = 0.8, 0.8 Hz, 1 H), 7.85 (dd, J = 0.8, 2.0 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 9.7, 13.7, 24.8, 27.3, 29.0, 84.0, 123.2, 136.9, 140.8, 141.3, 144.5 (one carbon attached to B atom is not visible); HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{42}\text{BBrO}_2\text{SnNa} [\text{M}+\text{Na}^+]$: 595.1375, found 595.1370.



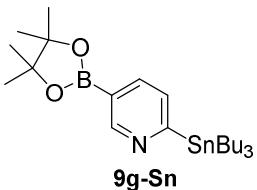
3-tert-Butoxycarbonyl-5-tri-n-butylstannylphenylboronic acid pinacol ester (9d-Sn, Table 1, entry 7). The reaction solution derived from *tert*-butyl 3,5-dibromobenzoate (**3d**), triisopropyl borate, and tri-*n*-butylstannyl chloride was collected for 30 seconds. The aliquot was analyzed by GC after working-up, and the yield was indicated as 80%; Colorless oil. TLC R_f 0.47 (hexane/EtOAc 10:1): ^1H NMR (400 MHz, CDCl_3) δ 0.90 (t, J = 7.6 Hz, 9 H), 1.11 (dd, J = 8.0, 8.0 Hz, 6 H), 1.34–1.39 (m, 18 H), 1.52–1.60 (m, 6 H), 1.61 (s, 9 H), 8.04 (dd, J = 1.2, 2.0 Hz, 1 H), 8.20–8.21 (m, 1 H), 8.32–8.34 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 9.8, 13.9, 25.1, 27.6, 28.4, 29.3, 80.9, 84.1, 130.7, 135.5, 140.2, 141.5, 147.0, 166.6 (one carbon attached to B atom is not visible); HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{51}\text{BO}_4\text{SnNa} [\text{M}+\text{Na}^+]$: 617.2795, found 617.2783.



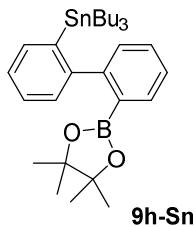
5-Tri-n-butylstannyl-2-thiopheneboronic acid pinacol ester (9e-Sn, Table 1, entry 8). The reaction solution derived from 2,5-dibromothiophene (**3e**), triisopropyl borate, and tri-*n*-butylstannyl chloride was collected for 30 seconds. The aliquot was analyzed by GC after working-up, and the yield was indicated as 58%; Colorless oil. TLC R_f 0.20 (hexane/EtOAc 10:1): ^1H NMR (400 MHz, CDCl_3) δ 0.89 (t, J = 7.2 Hz, 9 H), 1.09–1.13 (m, 6 H), 1.28–1.37 (m, 6 H), 1.35 (s, 12 H), 1.46–1.68 (m, 6 H), 7.28 (d, J = 3.2 Hz, 1 H), 7.78 (d, J = 3.2 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 10.8, 13.6, 24.7, 27.2, 28.9, 83.9, 136.3, 137.6, 145.5 (one carbon attached to B atom is not visible); HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{41}\text{BO}_2\text{SSnNa} [\text{M}+\text{Na}^+]$: 523.1834, found 523.1822.



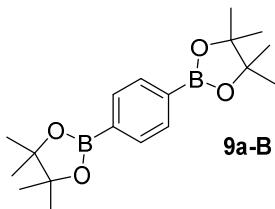
2-Tri-n-butylstannylpyridin-3-boronic acid pinacol ester (9f-Sn, Table 1, entry 9). The reaction (L_2 = 200 cm, 3.0 eq. of second *s*BuLi) was performed with 2,3-dibromopyridine (**3f**), 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, and tri-*n*-butylstannyl chloride (5.0 eq). The aliquot collected in 30 seconds was analyzed by GC after working-up, and the yield was indicated as 51%; Pale yellow oil. TLC R_f 0.85 ($\text{CHCl}_3/\text{MeOH}$ 10:1): ^1H NMR (400 MHz, CDCl_3) δ 0.86 (t, J = 7.6 Hz, 9 H), 1.13 (dd, J = 8.0, 8.0 Hz, 6 H), 1.31 (sextet, J = 7.6 Hz, 6 H), 1.35 (s, 12 H), 1.49–1.59 (m, 6 H), 7.10 (dd, J = 5.2, 7.6 Hz, 1 H), 7.99 (dd, J = 2.0, 7.6 Hz, 1 H), 8.75 (dd, J = 2.0, 5.2 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 11.5, 13.8, 24.8, 27.5, 29.2, 84.1, 120.9, 140.9, 151.4, 182.1 (one carbon attached to B atom is not visible); HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{42}\text{BNO}_2\text{SnNa} [\text{M}+\text{Na}^+]$: 518.2223, found 518.2221.



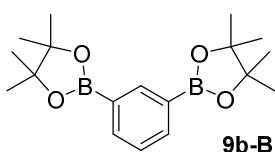
2-Tri-n-butylstannylypyridin-5-boronic acid pinacol ester (9g-Sn, Table 1, entry 10). The reaction ($L_2 = 200$ cm, 3.0 eq. of second *s*BuLi) was performed with 2,5-dibromopyridine (**3g**), 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, and tri-*n*-butylstannyl chloride (5.0 eq). The aliquot collected in 30 seconds was analyzed by GC after working-up, and the yield was indicated as 48%; Colorless oil. TLC R_f 0.42 (CHCl₃/MeOH 10:1): ¹H NMR (400 MHz, CDCl₃) δ 0.87 (t, *J* = 7.6 Hz, 9 H), 1.12 (m, 6 H), 1.27–1.36 (m, 6 H), 1.34 (s, 12 H), 1.51–1.59 (m, 6 H), 7.41 (dd, *J* = 0.8, 7.2 Hz, 1 H), 7.84 (dd, *J* = 1.6, 7.6 Hz, 1 H), 9.03 (dd, *J* = 0.8, 1.6 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 9.8, 13.7, 24.8, 27.3, 29.0, 84.0, 131.8, 139.0, 155.5, 177.7 (one carbon attached to B atom is not visible); HRMS (ESI) calcd for C₂₃H₄₃BNO₂SnNa [M+H⁺]: 496.2403, found 496.2411.



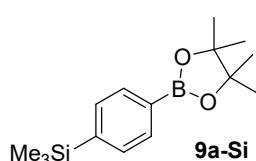
2'-Tri-n-butylstannylbiphenyl-2-boronic acid pinacol ester (9h-Sn, Table 1, entry 11). The reaction solution derived from 2,2'-dibromobiphenyl (**3h**), 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, and tri-*n*-butylstannyl chloride was collected for 30 seconds. The aliquot was analyzed by GC after working-up, and the yield was indicated as 73%; Colorless oil. TLC R_f 0.52 (hexane/EtOAc 10:1): ¹H NMR (400 MHz, CDCl₃) δ 0.67 (dd, *J* = 8.0, 8.0 Hz, 6 H), 0.82 (t, *J* = 7.2 Hz, 9 H), 1.08 (br, d, *J* = 8.0 Hz, 12 H), 1.21 (tq, *J* = 7.2, 7.2 Hz, 6 H), 1.27–1.36 (m, 6 H), 7.15–7.26 (m, 4 H), 7.31 (ddd, *J* = 1.2, 7.2, 7.2 Hz, 1 H), 7.39 (ddd, *J* = 1.6, 7.2, 7.2 Hz, 1 H), 7.46 (dd, *J* = 1.6, 6.8 Hz, 1 H), 7.71 (dd, *J* = 1.6, 7.2 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 10.2, 13.6, 24.3 and 24.7 (rotameric), 27.4, 28.9, 83.2, 125.7, 126.2, 12.6, 129.2, 129.5, 129.6, 134.2, 135.8, 141.7, 150.9, 151.3 (one carbon attached to B atom is not visible); HRMS (ESI) calcd for C₃₀H₄₇BO₂SnNa [M+Na⁺]: 593.2583, found 593.2573.



1,4-Benzenediboronic acid bis(pinacol) ester (9a-B, Table 1, entry 12). The reaction solution derived from 1,4-dibromobenzene (**3a**) and isopropoxyboronic acid pinacol ester (as both borylation and metalation reagent) was collected for 30 seconds. The aliquot was analyzed by GC after working-up, and the yield was indicated as 68%. The GC peak was identical with that of the commercial one.

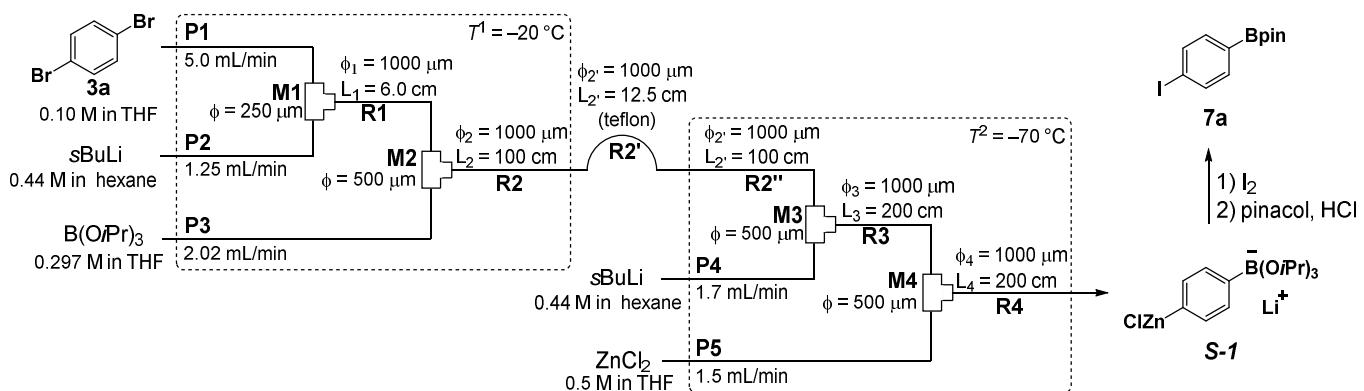


1,3-Benzenediboronic Acid Bis(pinacol) Ester (9b-B, Table 1, entry 13). The reaction solution derived from 1,3-dibromobenzene (**3b**) and isopropoxyboronic acid pinacol ester (as both borylation and metalation reagent) was collected for 30 seconds. The aliquot was analyzed by GC after working-up, and the yield was indicated as 66%. The GC peak was identical with that of the commercial one.

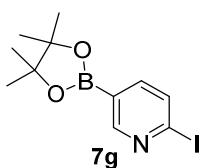


4-Trimethylphenylboronic acid pinacol ester (9a-Si, Table 1, entry 14). The reaction solution derived from 1,4-dibromobenzene (**3a**), triisopropyl borate, and trimethylsilyl chloride was collected for 30 seconds. The aliquot was analyzed by GC after working-up, and the yield was indicated as 78%; White solid. TLC R_f 0.22 (hexane/EtOAc 10:1): ¹H NMR (400 MHz, CDCl₃) δ 0.27 (s, 9 H), 1.34 (s, 12 H), 7.53 (d, *J* = 8.0 Hz, 2 H), 7.79 (d, *J* = 8.0 Hz, 2 H). The NMR spectrum was in a good agreement with the reported one.^[3]

4-5. Flow Synthesis for Zn-B Bimetallic Arenes and their Transformation.



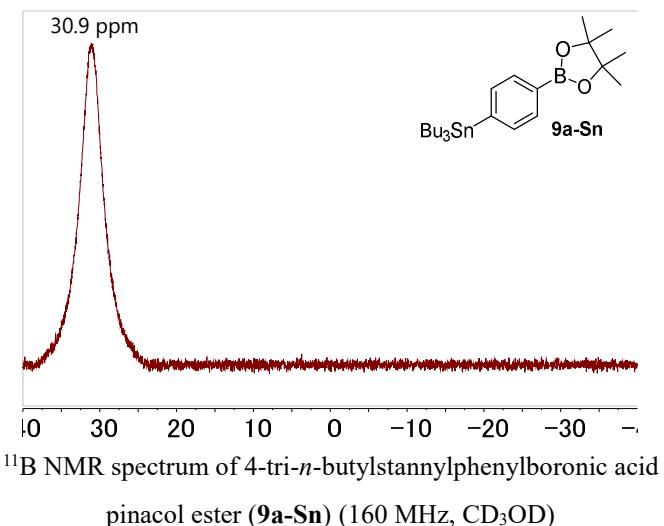
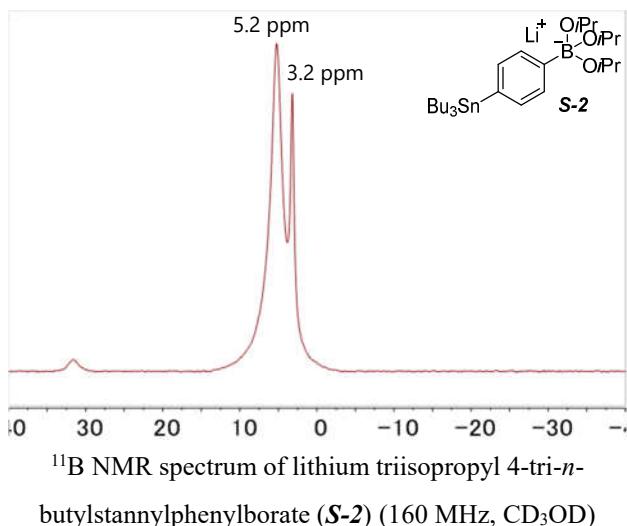
An integrated flow microreactor system consisting of four T-shaped micromixers (**M1**, **M2**, **M3** and **M4**), microtube reactors (**R1**, **R2**, **R2''**, **R3**, and **R4**), and five pre-cooling units (**P1** (100 cm), **P2** (50 cm), **P3** (50 cm), **P4** (50 cm), and **P5** (100 cm)) was used. The part of the flow microreactor system composed with **P1**, **P2**, **P3**, **M1**, **M2**, **R1**, and **R2** was cooled at $-20\text{ }^{\circ}\text{C}$ and the part composed with **P4**, **P5**, **M3**, **M4**, **R2''**, **R3**, and **R4** was cooled at $-70\text{ }^{\circ}\text{C}$. Those two parts were connected by PTFE tube **R2'** (12.5 cm). A solution of dibromoarenes **3a** (0.10 M in THF, flow rate: 5.0 mL/ min) and a solution of *sec*-BuLi (0.44 M in hexane, flow rate: 1.25 mL/min) were introduced into **M1** ($\phi = 250\text{ }\mu\text{m}$) by syringe pumps, and the mixture was passed through **R1** (6 cm, $-20\text{ }^{\circ}\text{C}$, $t^{R1} = 0.45\text{ s}$). The solution of monolithiated aryls (flow rate: 6.25 mL/min) and a solution of $\text{B}(\text{O}i\text{Pr})_3$ (0.297 M in THF, flow rate: 2.02 mL/min) were introduced to **M2** ($\phi = 500\text{ }\mu\text{m}$), and the mixture was passed through **R2** (100 cm, $-20\text{ }^{\circ}\text{C}$, $t^{R2} = 5.7\text{ s}$). The solution of boron-ate complex (flow rate: 8.27 mL/min) was passed through **R2'** (12.5 cm, $t^{R2'} = 0.71\text{ s}$) and **R2''** (100 cm, $t^{R2''} = 5.7\text{ s}$), and was cooled to $-70\text{ }^{\circ}\text{C}$. Then, the solution of boron-ate complex and a solution of *sec*-BuLi (0.44 M in hexane, flow rate: 1.7 mL/min) were mixed in **M3** ($\phi = 500\text{ }\mu\text{m}$), and the mixture was passed through **R3** (200 cm). The resulting solution was introduced to **M4** ($\phi = 500\text{ }\mu\text{m}$) where a solution of electrophile (0.5 M in THF, flow rate: 1.5 mL/min) was added, and the mixture was passed through **R4** (200 cm). After a steady state was reached (90 seconds), the solution was collected in a flame-dried round-bottomed-flask as the solution of **Zn-B** bimetallic arenes. To the aliquot (3.0 mL, 0.131 mmol) of the solution, was added iodine (230 mg, 0.91 mmol). The mixture was stirred at room temperature for 2 hours, and then was treated with pinacol and HCl. The yield of **7a** was determined by GC analysis (68%).



2-Iodopyridyl-5-boronic acid pinacol ester (7g). The reaction was performed with **R2** (200 cm) and isopropoxyboronic acid pinacol ester (1.2 eq), followed by the reaction with iodine (300 mg). The mixture was washed with $\text{Na}_2\text{S}_2\text{O}_3\text{aq}$ and the solution was analyzed by GC to determine the yield (56%); White solid: ^1H NMR (400 MHz, CDCl_3) δ 1.34 (s, 12 H), 7.65 (dd, $J = 2.0, 8.0\text{ Hz}$, 1 H), 7.74 (dd, $J = 0.8, 8.0\text{ Hz}$, 2 H), 8.65 (dd, $J = 0.8, 2.0\text{ Hz}$, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 24.8, 84.5, 122.0, 134.4, 143.3, 156.2 (one carbon attached to B atom is not visible); HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{16}\text{BINO}_2$ [$\text{M}+\text{H}^+$]: 332.0313, found 332.0318.

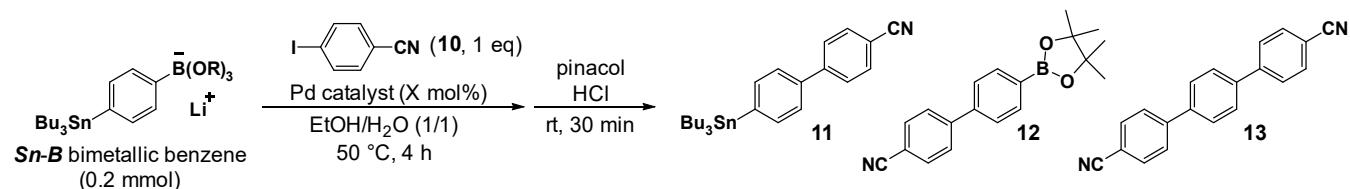
4-6. ^{11}B NMR analyses of Sn-B Bimetallic Benzene **S-2**.

Before working-up, the aliquot (6.9 mL) of the reaction solution of **9a-Sn** (e.g. 0.029 M) was concentrated under reduced pressure. Thus-obtained white solid (lithium triisopropyl 4-tri-*n*-butylstannylphenylborate, **S-2**, approx. 0.2 mmol) was dissolved in 0.7 mL of methanol-*d*₄, and the solution was analyzed by ^{11}B NMR, which showed two singlet peaks on 5.2 and 3.2 ppm.

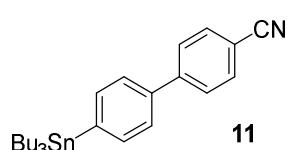


5. Cross Coupling Reactions of Bimetallic Arenes.

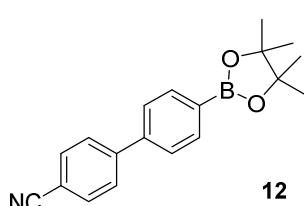
5-1. Optimization of Cross Coupling Reactions of *Sn-B* Bimetallic Benzene **5a-Sn**.



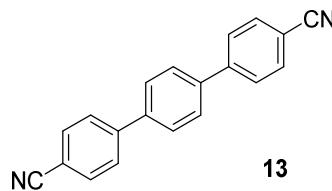
The aliquot (6.9 mL) of the reaction solution of **Sn-B** bimetallic benzene (e.g. 0.029 M, same procedure for 4-4 before working-up of HCl with pinacol) was concentrated under reduced pressure. The resulting solid (approx. 0.2 mmol) was dissolved in 1 mL of EtOH/H₂O (50/50 v/v, degassed by argon), and was added 4-iodobenzonitrile (**10**, 0.20 mmol) and Pd catalysts (0.01 or 0.02 mmol). The mixture was stirred at 50 °C under argon atmosphere for 4 hours, then was allowed to be cooled to room temperature. The solutions were treated with 1 mL of 1 N HCl aq. with 1 mL of pinacol solution (0.75 M in Et₂O), and were stirred for 30 minutes at room temperature. After addition of EtOAc (2 mL), brine (2 mL), and *n*-tetradecane as an internal standard, the organic phase was analyzed by GC to determine the product yields. In Table 2, entry 6, the product (**11**) was isolated by flash chromatography. The results are summarized in Table S-3.



4-Tri-n-butylstannyl-4'-cyanobiphenyl (11). Colorless oil. TLC R_f 0.76 (hexane/EtOAc 10:1); ¹H NMR (400 MHz, CDCl₃) δ 0.90 (t, J = 7.2 Hz, 9 H), 1.09 (dd, J = 8.0, 8.0 Hz, 6 H), 1.35 (tq, J = 7.2, 7.2 Hz, 6 H), 1.53–1.60 (m, 6 H), 7.53–7.59 (m, 4 H), 7.68–7.73 (m, 4 H); ¹³C NMR (100 MHz, CDCl₃) δ 9.7, 13.7, 27.4, 29.1, 110.7, 119.0, 126.5, 127.6, 132.6, 137.2, 138.6, 143.2, 145.8; HRMS (ESI) calcd for C₂₅H₃₅NSnNa [M+Na⁺]: 492.1684, found 492.1684.



4'-Cyano-4-biphenylboronic acid pinacol ester (12). TLC R_f 0.43 (hexane/EtOAc 5:1); ¹H NMR (400 MHz, CDCl₃) δ 1.37 (s, 12 H), 7.59 (d, J = 8.0 Hz, 2 H), 7.67–7.73 (m, 4 H), 7.92 (d, J = 8.0 Hz, 2 H). The spectrum was in a good agreement with that of the previous report.^[4]



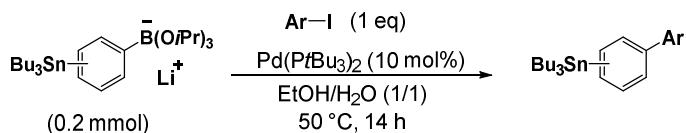
4,4''-Dicyano-p-terphenyl (13). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.92 (s, 4 H), 7.95–7.97 (m, 8 H). The NMR spectrum was in a good agreement with the reported one.^[5]

Table S-3. Cross-Coupling Reactions of Stannyli Aryl Borate with 4-Iodobenzonitrile (**10**).

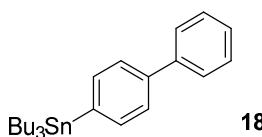
Stannyli Aryl Borate	Pd catalyst	X (mol%)	Yield of 11 (%)	Yield of 12 (%)	Yield of 13 (%)
 5a-Sn	Pd(PPh_3) ₄	5	5	5	n.d.
	Pd(OAc) ₂	5	5	43	<1
	PdCl ₂ (PPh_3) ₂	5	17	5	3
	PdCl ₂ (dppf)· CH_2Cl_2	5	42	10	5
	Pd($\text{P}t\text{Bu}_3$) ₂	5	64	2	1
	Pd($\text{P}t\text{Bu}_3$) ₂	10	86	1	1
 S-3	Pd($\text{P}t\text{Bu}_3$) ₂	10	74	1	1
 S-4	Pd($\text{P}t\text{Bu}_3$) ₂	10	49	4	1
 9a-Sn	Pd($\text{P}t\text{Bu}_3$) ₂	10	5	25	2

5-2. Cross Coupling Reactions of Stannyli Arylboron-ate Complexes with Aryl Iodides.

Typical Procedure for Cross Coupling Reactions of Stannyli Arylboron-ate Complexes with Aryl Iodides.

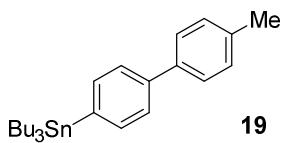


The concentration of stannyli arylboron-ate complexes synthesized by the procedure described in section 4-3 was calculated by a sampling of the solution with was reacted with pinacol to be converted to the corresponding pinacol esters. After concentration under a reduced pressure, the stannyli arylboron-ate complexes (approx. 0.2 mmol) was dissolved in 1 mL of EtOH/H₂O (50/50 v/v, degassed by argon), and were added aryl iodide (0.20 mmol) and Pd($\text{P}t\text{Bu}_3$)₂ (0.02 mmol). The mixture was stirred at 50 °C under argon atmosphere for 14 hours, then was allowed to be cooled to room temperature. The solutions were treated with NH₄Cl (1 mL). After addition of EtOAc (2 mL), brine (2 mL), and *n*-tetradecane as an internal standard, the organic phase was analyzed by GC to determine the product yields.

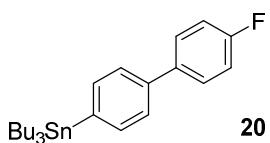


4-Tri-*n*-butylstannylbiphenyl (18). The reaction of **S-2** (0.199 mmol) with phenyl iodide (40.5 mg, 0.199 mmol) provided the title compound in 67% yield determined by GC; Colorless oil. TLC R_f 0.68 (hexane/EtOAc 10:1): ^1H NMR (400 MHz, CDCl_3) δ 0.90 (t, J = 7.2 Hz, 9 H),

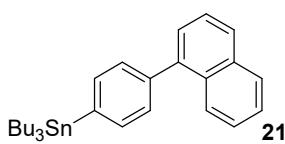
1.08 (dd, $J = 8.0, 8.0$ Hz, 6 H), 1.35 (tq, $J = 7.2, 7.2$ Hz, 6 H), 1.47–1.66 (m, 6 H), 7.34 (tt, $J = 2.0, 7.2$ Hz, 1 H), 7.44 (t, $J = 7.6$ Hz, 2 H), 7.53–7.58 (m, 4 H), 7.60 (d, $J = 7.2$ Hz, 2 H). The NMR spectrum was in a good agreement with the reported one.^[6]



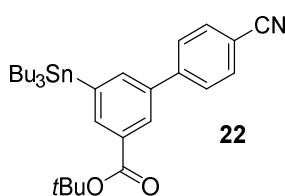
4-Tri-n-butylstannyl-4'-methylbiphenyl (19). The reaction of **S-2** (0.199 mmol) with 4-iodotoluene (42.6 mg, 0.195 mmol) provided the title compound in 66% yield determined by GC; Colorless oil. TLC R_f 0.68 (hexane/EtOAc 10:1): ^1H NMR (400 MHz, CDCl_3) δ 0.90 (t, $J = 7.2$ Hz, 9 H), 1.07 (dd, $J = 8.0, 8.0$ Hz, 6 H), 1.35 (tq, $J = 7.2, 7.2$ Hz, 6 H), 1.53–1.60 (m, 6 H), 2.39 (s, 3 H), 7.24 (d, $J = 8.0$ Hz, 2 H), 7.47–7.56 (m, 6 H); ^{13}C NMR (100 MHz, CDCl_3) δ 9.6, 13.7, 21.1, 27.4, 29.1, 126.4, 126.9, 129.4, 136.8, 136.9, 138.4, 140.4, 140.6; HRMS (APCI) calcd for $\text{C}_{21}\text{H}_{29}\text{Sn}$ $[(\text{M}-\text{Bu})^+]$: 401.1286, found 401.1287.



4-Tri-n-butylstannyl-4'-fluorobiphenyl (20). The reaction of **S-2** (0.199 mmol) with 4-fluoroiodobenzene (44.1 mg, 0.199 mmol) provided the title compound in 56% yield determined by GC; Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 0.90 (t, $J = 7.2$ Hz, 9 H), 1.08 (dd, $J = 8.0, 8.0$ Hz, 6 H), 1.35 (tq, $J = 7.2, 7.2$ Hz, 6 H), 1.52–1.60 (m, 6 H), 7.12 (dd, $J = 8.8, 8.8$ Hz, 1 H), 7.49–7.57 (m, 6 H). The NMR spectrum was in a good agreement with the reported one.^[7]

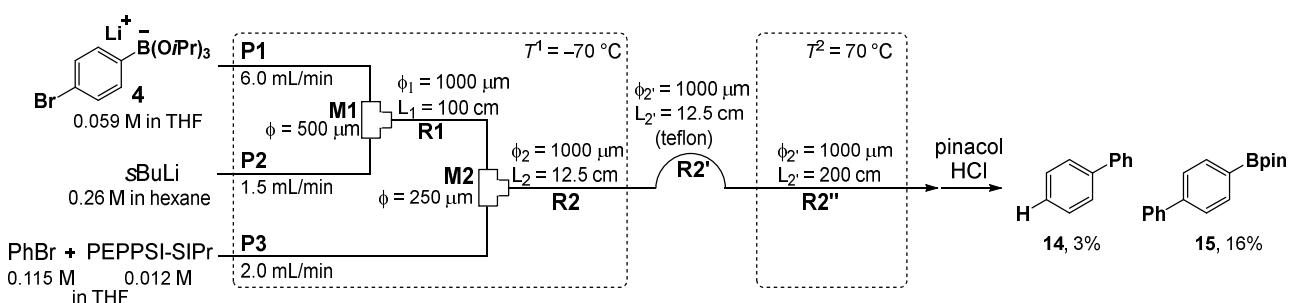


Tri-n-butyl-4-(1-naphthyl)phenylstannane (21). The reaction of **S-2** (0.199 mmol) with 1-iodonaphthalene (50.3 mg, 0.198 mmol) provided the title compound in 58% yield determined by GC; Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 0.92 (t, $J = 7.2$ Hz, 9 H), 1.18 (dd, $J = 8.0, 8.0$ Hz, 6 H), 1.37 (tq, $J = 7.6, 7.6$ Hz, 6 H), 1.51–1.70 (m, 6 H), 7.34–7.51 (m, 6 H), 7.58 (d, $J = 8.0$ Hz, 2 H), 7.82 (d, $J = 8.0$ Hz, 1 H), 7.87 (d, $J = 8.0$ Hz, 1 H), 7.95 (d, $J = 8.0$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 9.6, 13.7, 27.4, 29.1, 125.4, 125.7, 125.9, 126.1, 126.9, 127.5, 128.2, 129.5, 131.6, 133.8, 136.3, 140.2, 140.3, 140.8; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{29}\text{Sn}$ $[(\text{M}-\text{Bu})^+]$: 437.1286, found 437.1282.



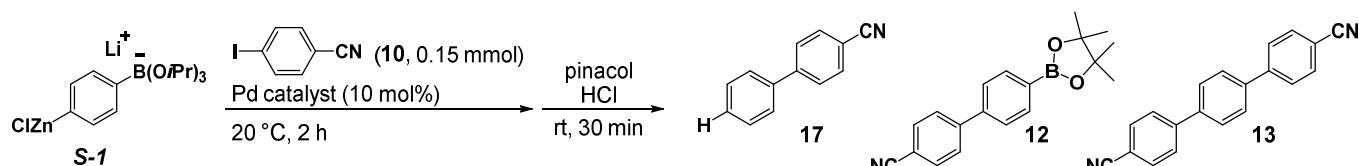
3-tert-Butoxycarbonyl-5-tri-n-butylstannyl-4'-cyanobiphenyl (22). The reaction of lithium 3-tert-butoxycarbonyl-5-tri-n-butylstannylphenyl-triisopropylborate (**S-5**, 0.199 mmol) with 4-iodobenzonitrile (**10**, 44.2 mg, 0.193 mmol) provided the title compound in 76% yield determined by ^1H NMR; Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 0.90 (t, $J = 7.2$ Hz, 9 H), 1.13 (dd, $J = 8.0, 8.0$ Hz, 6 H), 1.35 (tq, $J = 7.2, 7.2$ Hz, 6 H), 1.41–1.62 (m, 6 H), 1.63 (s, 9 H), 7.70 (d, $J = 8.4$ Hz, 2 H), 7.76 (d, $J = 8.4$ Hz, 2 H), 7.78 (dt, $J = 0.4, 1.6$ Hz, 1 H), 8.10 (d, $J = 2.0$ Hz, 1 H), .15 (dd, $J = 0.8, 1.6$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 9.7, 13.7, 27.3, 28.2, 29.0, 81.3, 111.0, 118.9, 127.9 (two carbons are overlapping), 131.8, 132.6, 137.2, 138.5, 138.8, 143.7, 145.4, 165.8; HRMS (ESI) calcd for $\text{C}_{30}\text{H}_{43}\text{NO}_2\text{SnNa}$ $[(\text{M}+\text{Na})^+]$: 592.2208, found 592.2211.

5-3. Trial for Cross Coupling Reaction of Lithium Arylboron-Ate Complex 11a-Li.



An integrated flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2**), microtube reactors (**R1**, **R2**, and **R2''**), and three pre-cooling units (**P1** (100 cm), **P2** (50 cm), and **P3** (50 cm)) was used. The part of the flow microreactor system composed with **P1**, **P2**, **P3**, **M1**, **M2**, **R1**, and **R2** was cooled at $-70\text{ }^{\circ}\text{C}$ and the tube reactor **R2''** was heated at $70\text{ }^{\circ}\text{C}$. Those two parts were connected by PTFE tube **R2'** (12.5 cm). Lithium triisopropyl 4-bromophenylborate (**4**) was synthesized according to the procedure described in section 3 as a 0.059 M solution. The solution of **4** (flow rate: 6.0 mL/min) and a solution of *sec*-BuLi (0.26 M in hexane, flow rate: 1.5 mL/min) were introduced into **M1** ($\phi = 500\text{ }\mu\text{m}$) by syringe pumps, and the mixture was passed through **R1** (100 cm, $-70\text{ }^{\circ}\text{C}$, $t^{R1} = 7.2\text{ s}$). Thus-generated solution (flow rate: 6.5 mL/min) was introduced into **M2** ($\phi = 250\text{ }\mu\text{m}$) where a THF solution of bromobenzene (0.115 M) with PEPPSI-SIPr (0.012 M) was introduced (flow rate: 2.0 mL/min). The mixture was passed through **R2** (12.5 cm, $-70\text{ }^{\circ}\text{C}$, $t^{R2} = 0.69\text{ s}$) and **R2'** (12.5 cm, $t^{R2'} = 0.69\text{ s}$), and was introduced to **R2''** (200 cm, $t^{R2''} = 11\text{ s}$) which was heated at $70\text{ }^{\circ}\text{C}$. After a steady state was reached (30 seconds), an aliquot of the product solution was collected for 30 seconds. The aliquot was treated with 1 ml of 1 N HCl aq. and 1 ml of pinacol solution (0.3 M in Et_2O), and the mixture was stirred at r.t. for 30 min to converted a triisopropoxy borate moiety to a pinacolboranyl group. After addition of EtOAc (2 mL) and brine (2 mL), *n*-tetradecane was added, and the organic phase was analyzed by GC to determine the yields of product **14** (3%) and **15** (16%). No multi-adduct was observed.

5-4. Optimization of Cross Coupling Reactions of Zn-B Bimetallic Benzene **S-1**.



To a flame-dried schlenk tube, were added the aliquot (6 mL) of the B-Zn bimetallic benzene **S-1** (generated by the procedure described in section 5-4), 4-iodobenzonitrile (**10**, 0.15 mmol), and Pd catalysts (0.015 mmol). The mixture was stirred at $20\text{ }^{\circ}\text{C}$ under argon atmosphere for 2 hours. Then the solutions were treated with 1 mL of 1N HCl aq. and 1 mL of pinacol solution (0.75 M in Et_2O), and were stirred for 30 minutes at room temperature. After addition of EtOAc (2 mL), brine (2 mL), and *n*-tetradecane as an internal standard, the organic phase was analyzed by GC to determine the product yields. The result is summarized in Table S-4.

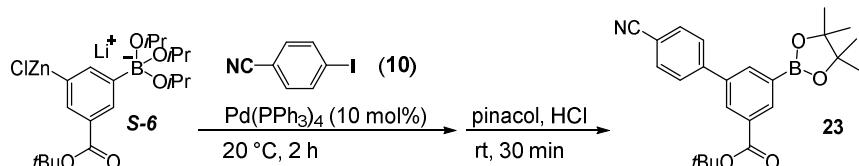
Table S-4. Optimization of Cross-Coupling Reaction of Zn-B Bimetallic Benzene **S-1** with 4-Iodobenzonitrile (**10**).

Pd catalyst	Yield of 17 (%)	Yield of 12 (%)	Yield of 13 (%)
Pd(<i>PtBu</i> ₃) ₂	1	37	n.d.
PEPPSI-SIPr	1	23	n.d.
PdCl ₂ (dppf)·CH ₂ Cl ₂	1	26	n.d.
Pd(OAc) ₂	2	34	n.d.

PdCl ₂ (PPh ₃) ₂	1	19	n.d.
Pd(PPh ₃) ₄	3	73	n.d.

5-5. Cross Coupling Reactions of **Zn-B** Bimetallic Arenes with Aryl Iodides.

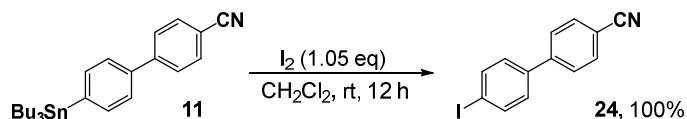
Cross Coupling of **S-6** with **10**: Typical Procedure for Cross Coupling Reactions of Zincyl Arylboron-ate Complex with Aryl Iodides.



The solution of **Zn-B** bimetallic arenes (8 mL) was transferred to a flame-dried schlenk tube. Then, 4-iodobenzonitrile (**10**, 35.5 mg, 0.155 mmol) and Pd(PPh₃)₄ (17 mg, 0.015 mmol) were added. The mixture was stirred at 20 °C under argon atmosphere for 2 hours, then was reacted with pinacol and 1 N HCl at room temperature for 30 minutes. After addition of EtOAc (2 mL), brine (2 mL), the NMR analysis indicated **3-tert-butoxycarbonyl-5-(4-cyanophenyl)phenylboronic acid pinacol ester (23)** was obtained in 66% yield; white solid; ¹H NMR (400 MHz, CDCl₃) δ 1.38 (s, 12 H), 1.63 (s, 9 H), 7.73–7.78 (m, 4 H), 8.18 (dd, *J* = 0.8, 2.0 Hz, 1 H), 8.30 (d, *J* = 1.6 Hz, 2 H), 8.44 (dd, *J* = 1.2, 1.2 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 24.8, 28.2, 81.5, 84.3, 111.2, 118.8, 127.8, 130.7, 132.3, 132.6, 135.6, 137.2, 138.6, 144.7, 165.4 (one carbon attached to B atom is not visible); HRMS (ESI) calcd for C₂₄H₂₈BNO₄Na [(M+Na)⁺]: 428.2004, found 428.2002.

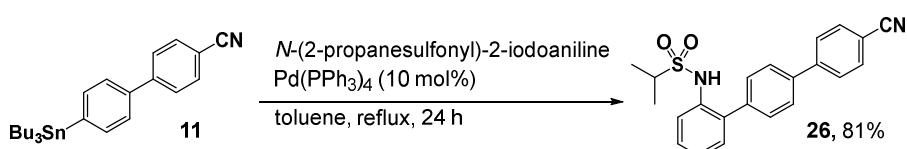
6. Synthetic Utility of Stannyli Biphenyl **11** and Boryl Biphenyl **12**.

6-1. Iodination of **11**.



To a 50 mL round-bottom flask were added 4-tri-*n*-butylstannyl-4'-cyanobiphenyl (**11**, 92.5 mg, 0.197 mmol), iodine (51.9 mg, 0.204 mmol), and dichloromethane (2 mL). The mixture was stirred at room temperature for 12 hours, and then concentrated under reduced pressure. Dichloromethane (20 mL) and Na₂S₂O₃aq (20 mL) was added, and the mixture was extracted by dichloromethane (15 mL × 3). The combined organic phase was washed by brine (10 mL × 3), and was dried over Na₂SO₄. After removal of the solvent under reduced pressure, the desired product, **4-cyano-4'-iodobiphenyl (24)** was obtained in quantitative yield (59.9 mg, 0.196 mmol): ¹H NMR (400 MHz, CDCl₃) δ 7.32 (d, *J* = 8.4 Hz, 2 H), 7.64 (d, *J* = 8.4 Hz, 2 H), 7.73 (d, *J* = 8.4 Hz, 2 H), 7.81 (d, *J* = 8.4 Hz, 2 H). The NMR analysis was in a good agreement with the reported one.^[8]

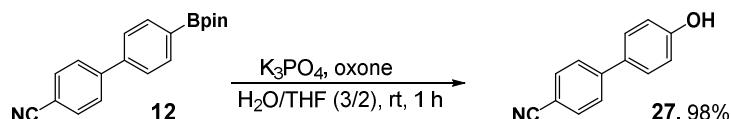
6-2. Stille Coupling Reaction of **11**.



To a 10 mL schlenk tube, were added 4-tri-*n*-butylstannyl-4'-cyanobiphenyl (**11**, 94.4 mg, 0.202 mmol), *N*-(2-propanesulfonyl)-2-iodoaniline (**25**, 74.5 mg, 0.229 mmol), and dry toluene (1 mL). After degasification of the mixture by argon gas,

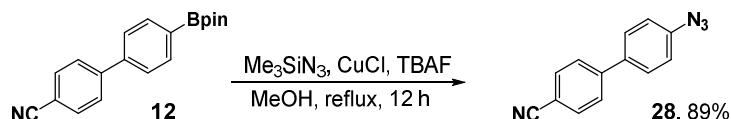
tetrakis(triphenylphosphine) palladium (0) (23.8 mg, 0.021 mmol) was added, and the mixture was stirred at 110 °C for 24 hours under argon atmosphere. Then the reaction mixture was allowed to be cooled at room temperature, and was passed through a silica plug using 2% MeOH/CH₂Cl₂ as an eluent. After purification by flash chromatography (0 to 1% MeOH/CH₂Cl₂), **N**-Isopropyl-(4"-cyano-[1,1';4',1'']terphenyl-2-yl)sulfonamide (**26**) was obtained in 81% yield as a white solid (61.7 mg, 0.164 mmol); TLC *R*_f 0.77 (CH₂Cl₂/MeOH 50:1); ¹H NMR (400 MHz, CDCl₃) δ 1.27 (d, *J* = 7.2 Hz, 6 H), 3.28 (sept, *J* = 6.8 Hz, 1 H), 6.37 (br, s, 1 H), 7.20 (dt, *J* = 1.2, 7.6 Hz, 1 H), 7.28 (dd, *J* = 1.2, 7.6 Hz, 1 H), 7.39 (dt, *J* = 2.0, 8.0 Hz, 1 H), 7.49 (d, *J* = 7.6 Hz, 2 H), 7.68–7.79 (m, 7 H); ¹³C NMR (100 MHz, CDCl₃) δ 16.3, 52.8, 111.3, 118.8, 119.1, 124.3, 127.7, 128.2, 129.1, 129.8, 130.6, 131.4, 132.7, 134.4, 137.8, 139.1, 144.6; HRMS (ESI) calcd for C₂₂H₂₀N₂SO₂Na [M+Na⁺]: 399.1138, found 399.1141.

6-3. Hydroxylation of 12.



To a vial, were added 4'-cyano-4-biphenylboronic acid pinacol ester (**12**, 48.8 mg, 0.160 mmol), oxone (246 mg, 0.4 mmol), K₃PO₄ (102 mg, 0.48 mmol), THF (0.8 mL), and water (1.2 mL). The mixture was stirred at room temperature for 1 hour under air vigorously, and then the reaction was quenched by the addition of Na₂S₂O₅. The organic layer was extracted with EtOAc, was dried over MgSO₄, and was concentrated in vacuo. The crude solid was washed with hexane twice, and then dissolved in chloroform. The solution was filtered by a celite plug, and was concentrated in vacuo to afford **4-hydroxy-4'-cyanobiphenyl** (**27**, 30.7 mg, 0.157 mmol) in 98% yield as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 5.08 (br, 1 H), 6.94 (d, *J* = 8.4 Hz, 2 H), 7.50 (d, *J* = 8.8 Hz, 2 H), 7.63 (d, *J* = 8.4 Hz, 2 H), 7.70 (d, *J* = 8.8 Hz, 2 H). The NMR spectrum was in a good agreement with the reported one.^[9]

6-4. Azidation of 12.



To a 50 mL round-bottomed flask, were added 4'-cyano-4-biphenylboronic acid pinacol ester (**12**, 46.0 mg, 0.151 mmol), trimethylsilyl azide (27 μ L, 0.205 mmol), CuCl (2 mg, 0.02 mmol), TBAF (1 M in THF, 0.2 mL, 0.2 mmol), and methanol (1 mL). The mixture was stirred at 80 °C for 12 hours. The reaction mixture was concentrated, and was passed through a silica plug with 10% EtOAc/hexane as an eluent. After removal of the solvent under reduced pressure, the desired product **4-azido-4'-cyanobiphenyl** (**28**) was obtained in 89% yield (29.5 mg, 0.134 mmol) as a yellowish solid; ¹H NMR (400 MHz, CDCl₃) δ 7.14 (d, *J* = 8.8 Hz, 2 H), 7.59 (d, *J* = 8.8 Hz, 2 H), 7.66 (d, *J* = 8.8 Hz, 2 H), 7.72 (d, *J* = 8.8 Hz, 2 H). The NMR spectrum was in a good agreement with the reported one.^[10]

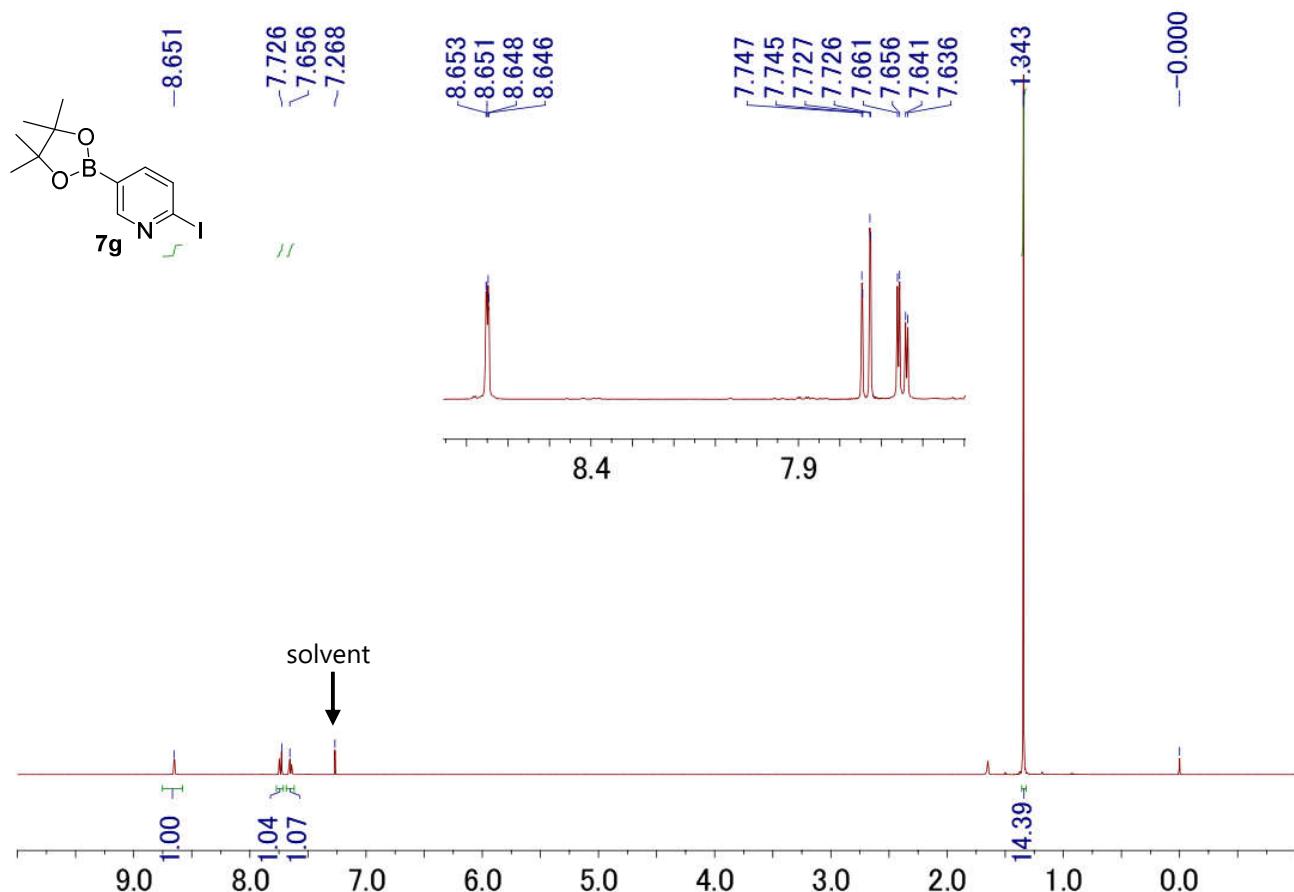
7. References.

- [1] Wrackmeyer, B. *Prog. Nucl. Magn. Reson. Spectrosc.* **1979**, *12*, 227.
- [2] Yamazaki, Y.; Ajioka, N.; Yokoyama, A.; Yokozawa, T. *Macromolecules* **2009**, *42*, 606.
- [3] Tsoi, Y.-T.; Zhou, Z.; Yu, W.-Y. *Org. Lett.* **2011**, *13*, 5370.
- [4] Lindner, M.; Valášek, M.; Mayor, M.; Frauhammer, T.; Wulfhekel, W.; Gerhard, L. *Angew. Chem. Int. Ed.* **2017**, *56*, 8290.
- [5] Ismail, M. A.; Arafa, R. K.; Brun, R.; Wenzler, T.; Miao, Y.; Wilson, W. D.; Generaux, C.; Bridges, A.; Hall, J. E.; Boykin, D.

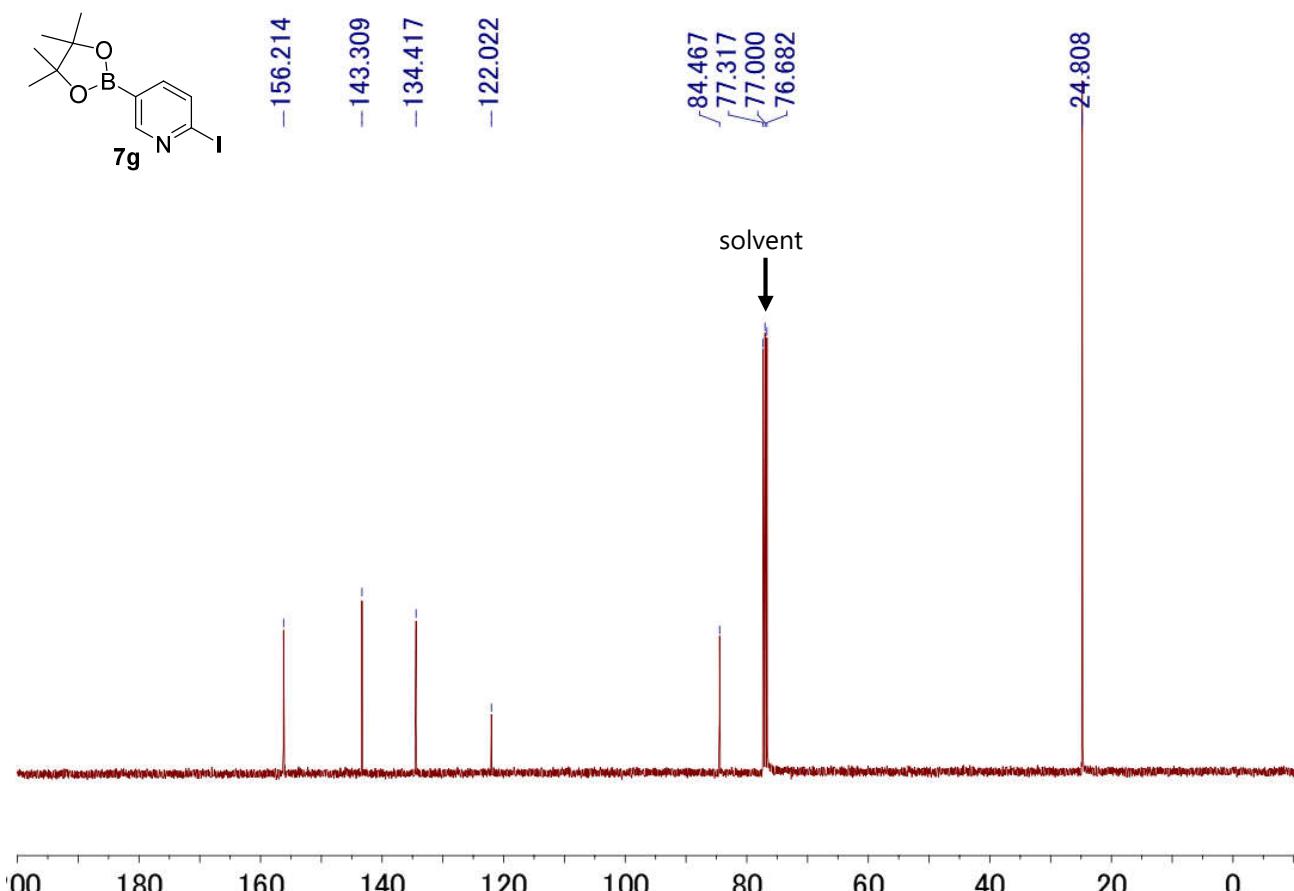
W. J. Med. Chem. **2006**, *49*, 5324.

- [6] Furuya, T.; Strom, A. E.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 1662.
- [7] Yue, H.; Zhu, C.; Rueping, M. *Org. Lett.* **2018**, *20*, 385.
- [8] Schiek, M.; Al-Shamery, K.; Lützen, A. *Synthesis* **2007**, 613.
- [9] Dutronc, T.; Terazzi, E.; Guénée, L.; Buchwalder, K.-L.; Spoerri, A.; Emery, D.; Mareda, J.; Floquet, S.; Piguet, C. *Chem. Eur. J.* **2013**, *19*, 8447.
- [10] Hommersom, C. A.; Matt, B.; van der Ham, A.; Cornelissen, J. J. L. M.; Katsonis, N. *Org. Biomol. Chem.* **2014**, *12*, 4065.

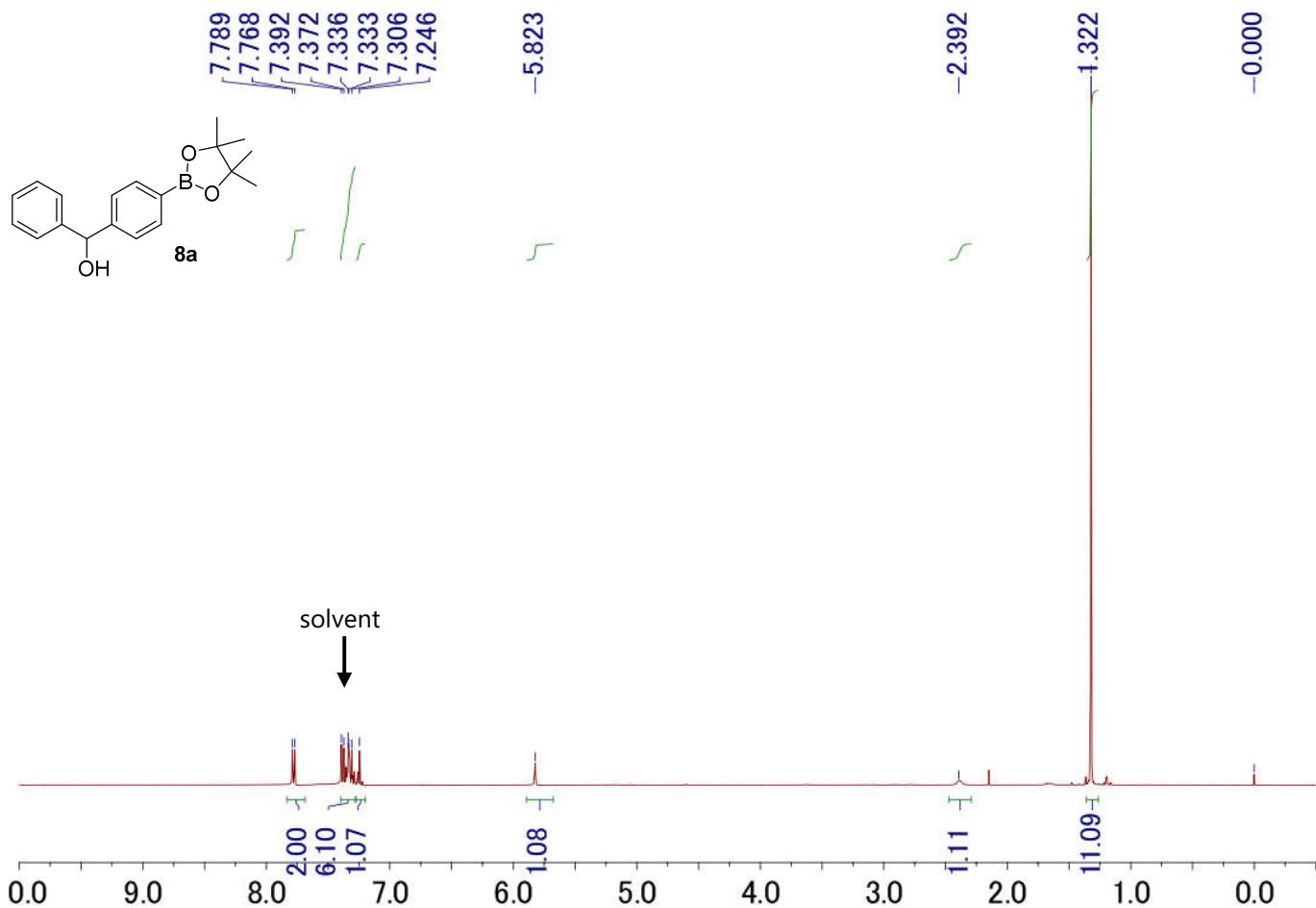
8. ^1H and ^{13}C NMR Spectra



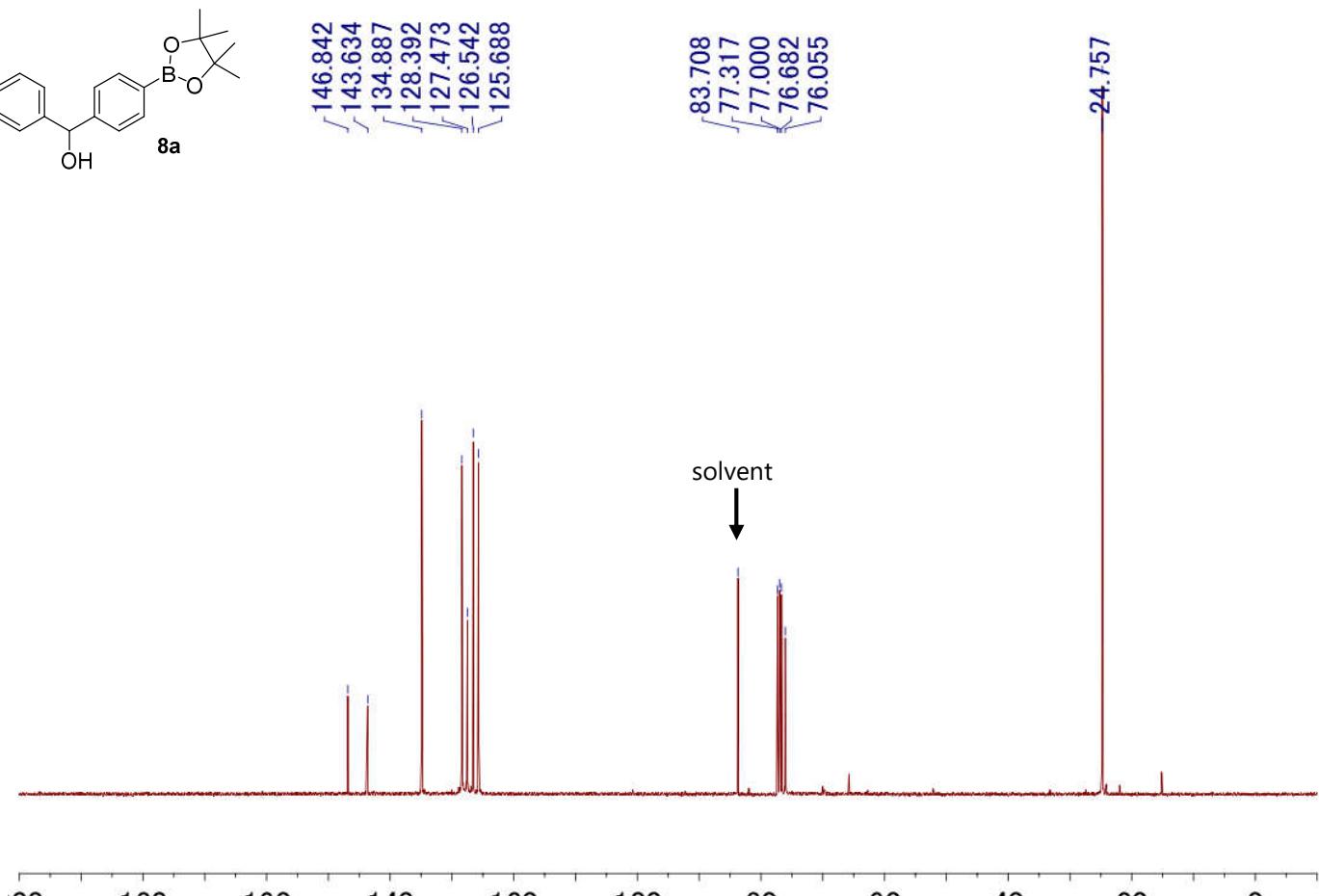
^1H NMR spectrum of 2-iodopyridyl-5-boronic acid pinacol ester (7g) (400 MHz, CDCl_3).



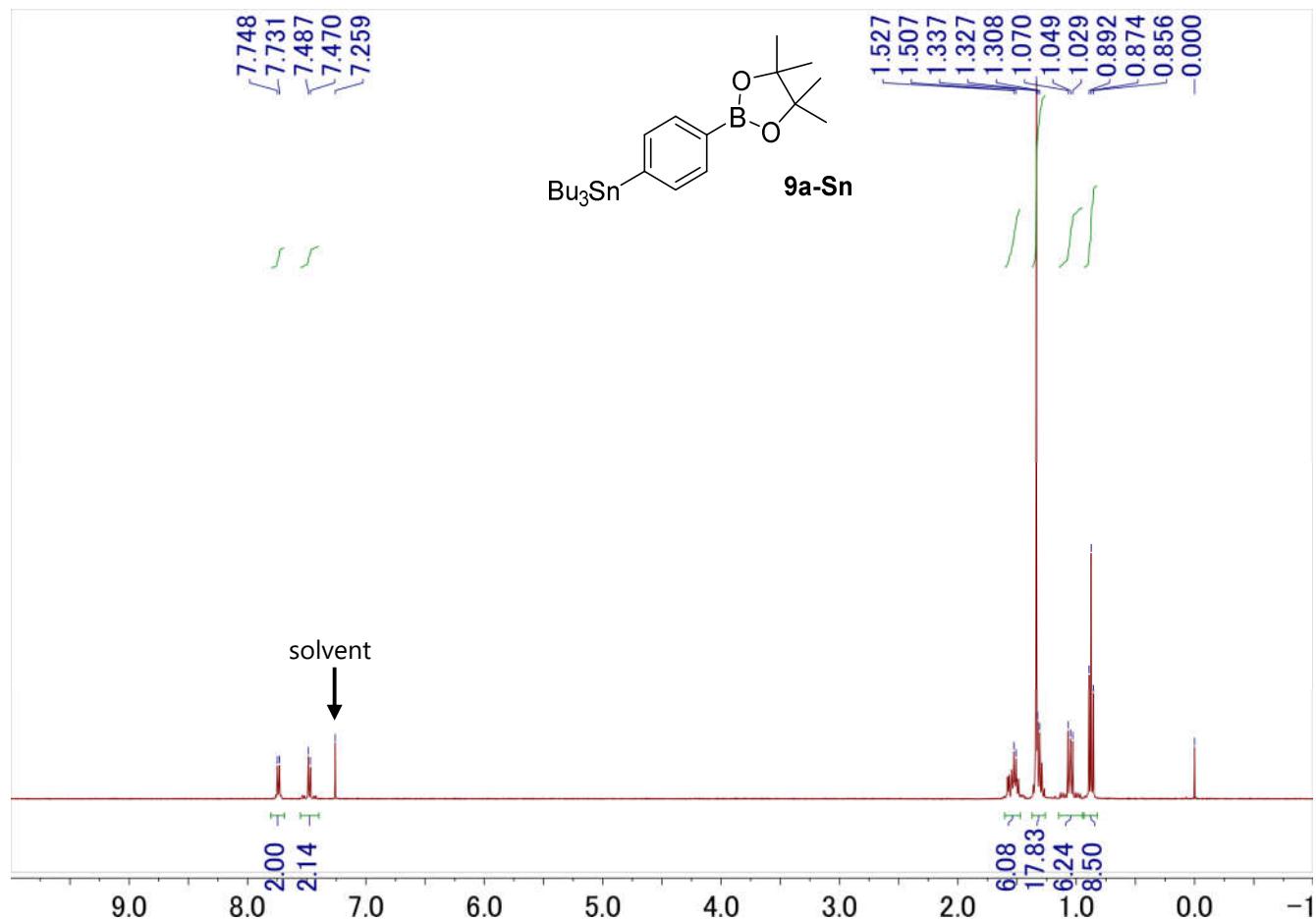
^{13}C NMR spectrum of 2-iodopyridyl-5-boronic acid pinacol ester (7g) (100 MHz, CDCl_3).



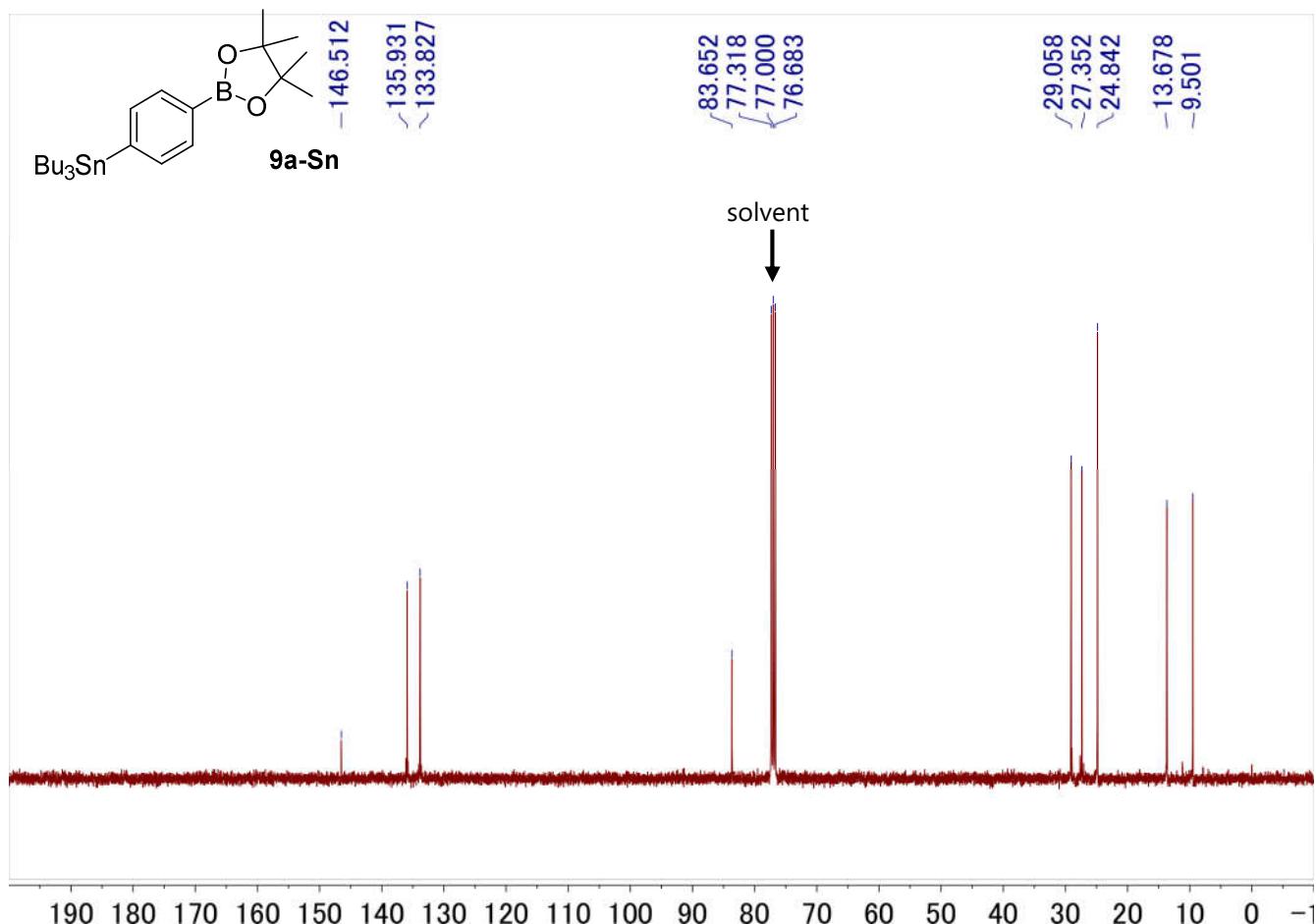
¹H NMR spectrum of 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzhydrol (8a) (400 MHz, CDCl₃).



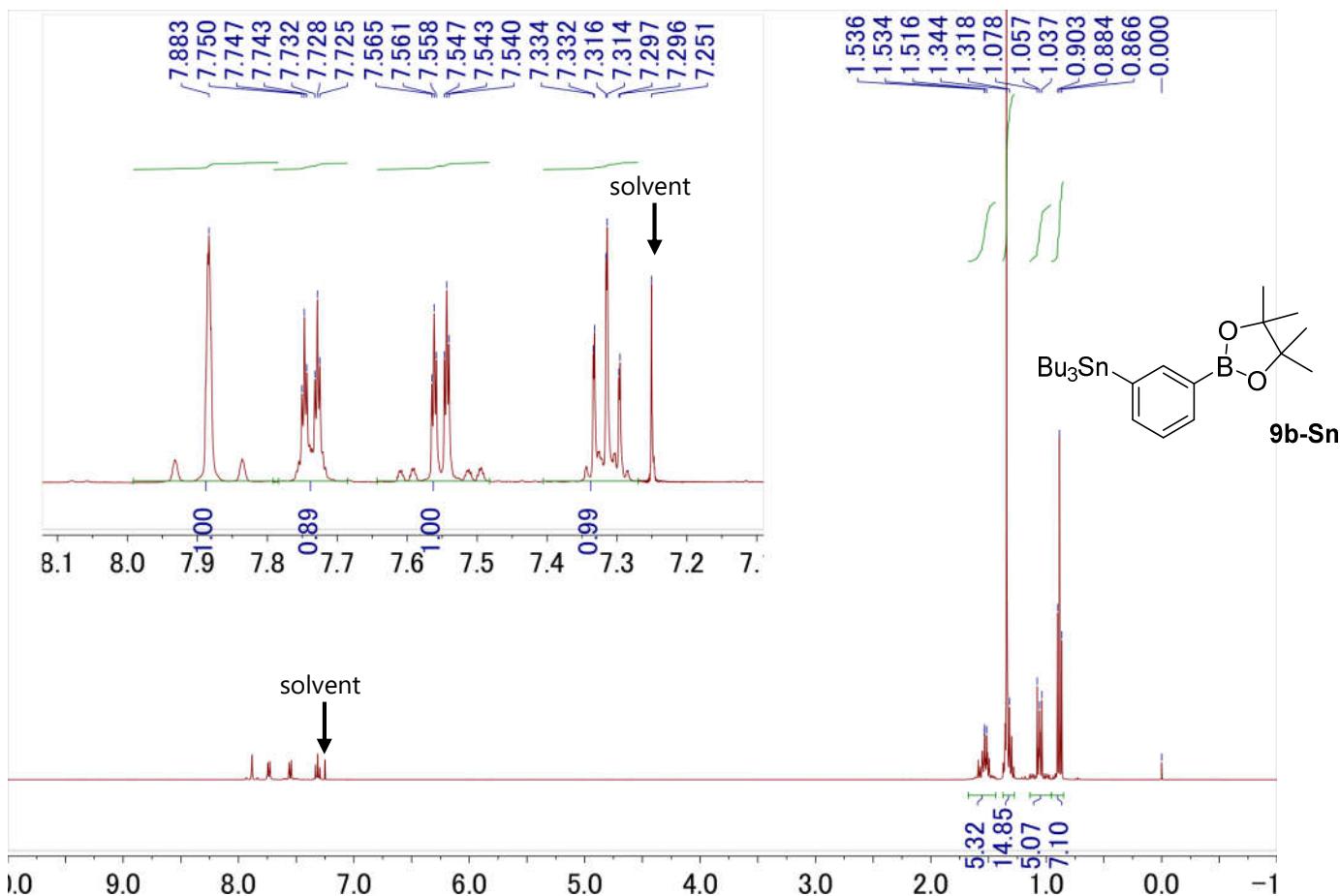
¹³C NMR spectrum of 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzhydrol (8a) (100 MHz, CDCl₃).



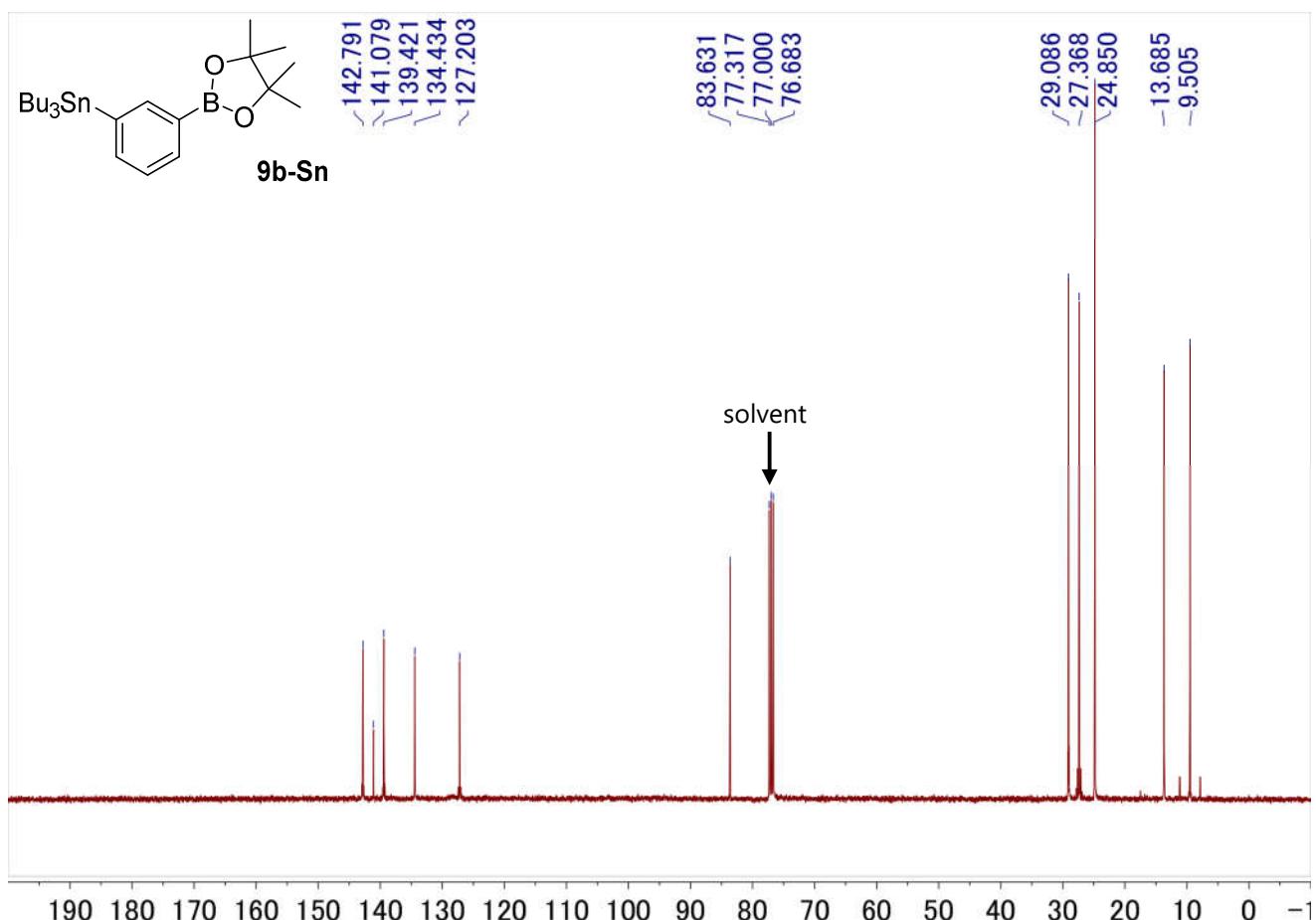
¹H NMR spectrum of 4-tri-*n*-butylstannylphenylboronic acid pinacol ester (9a-Sn) (400 MHz, CDCl₃).

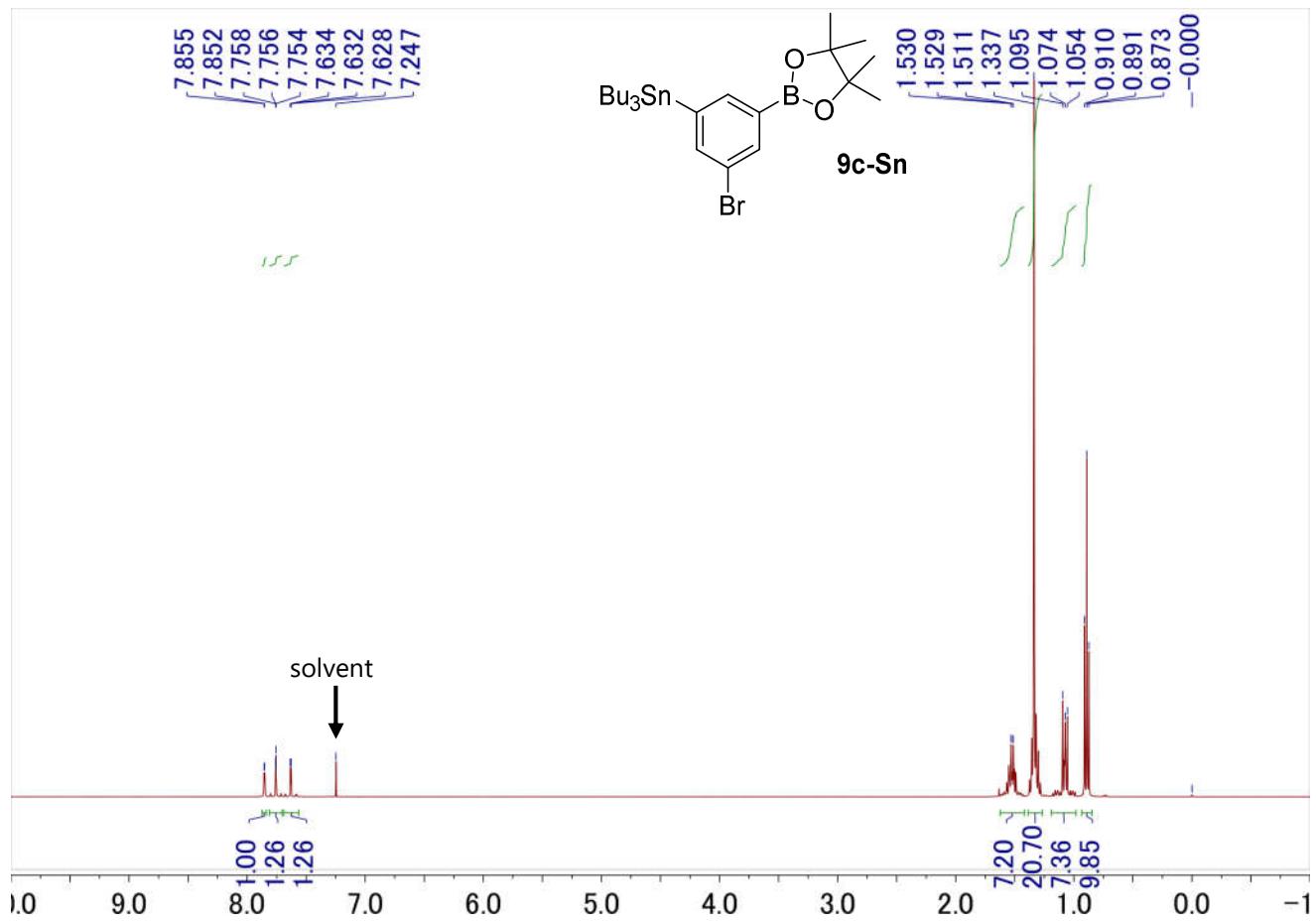


¹³C NMR spectrum of 4-tri-*n*-butylstannylphenylboronic acid pinacol ester (9a-Sn) (100 MHz, CDCl₃).

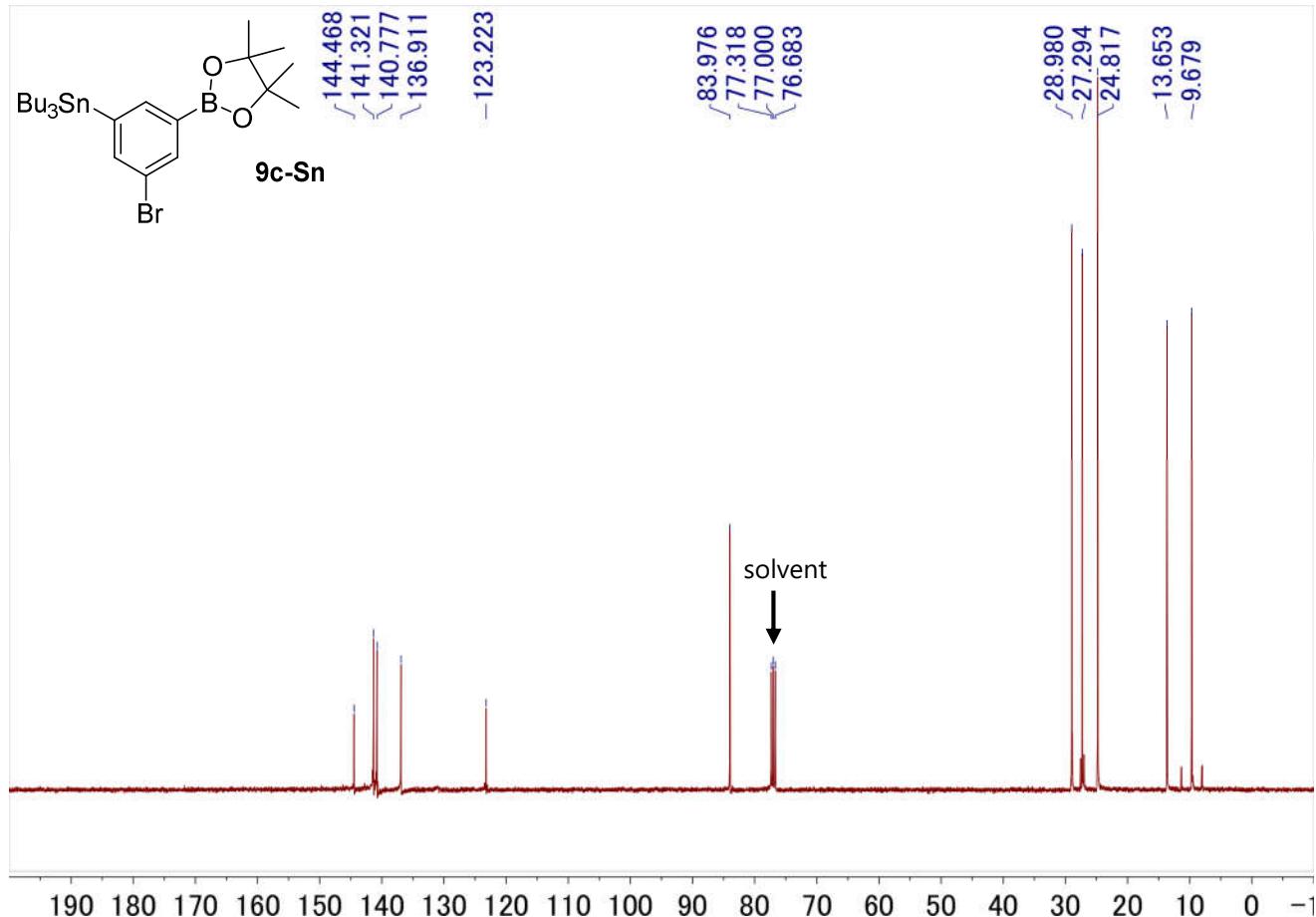


¹H NMR spectrum of 3-tri-*n*-butylstannylphenylboronic acid pinacol ester (9b-Sn) (400 MHz, CDCl₃).

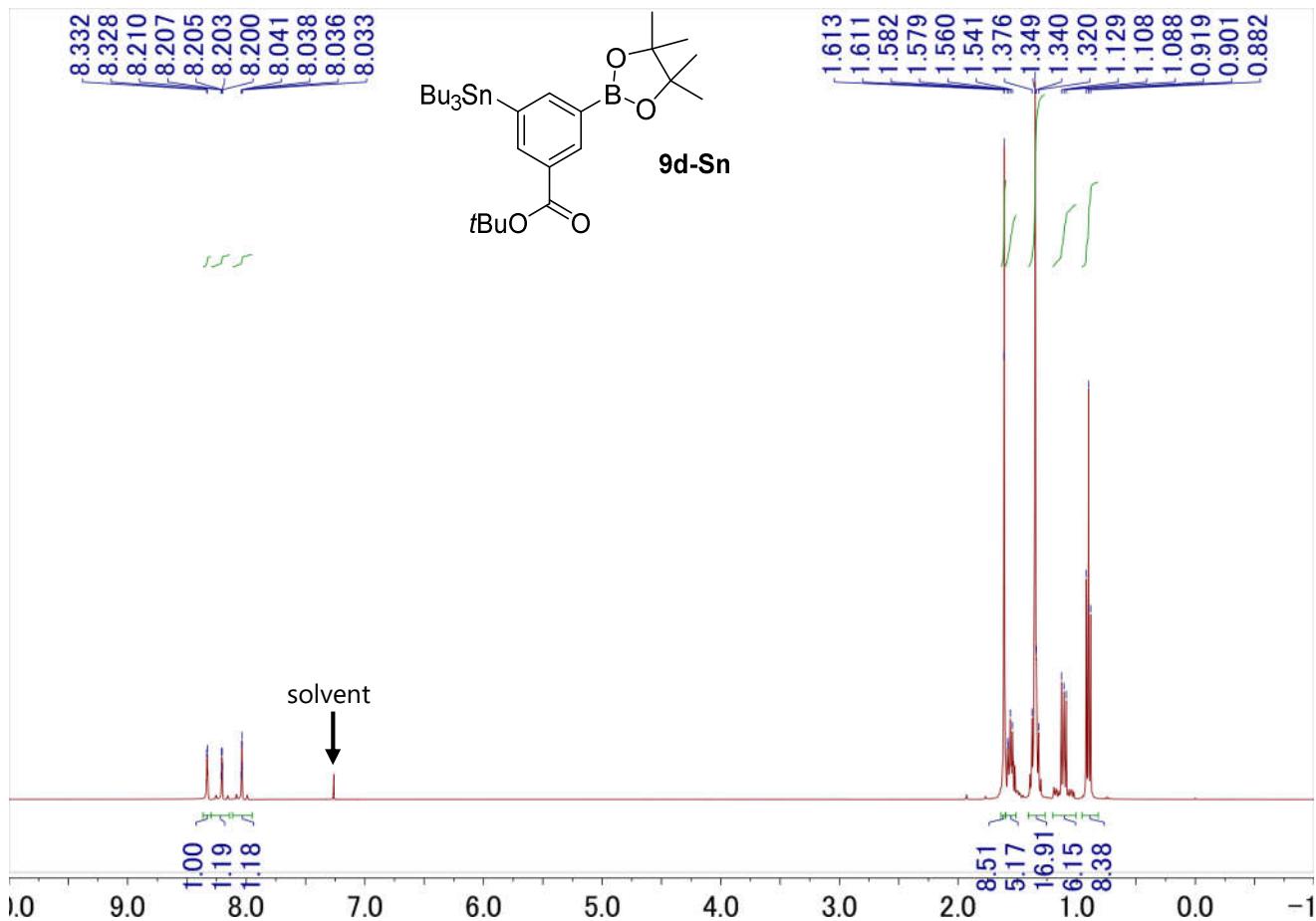




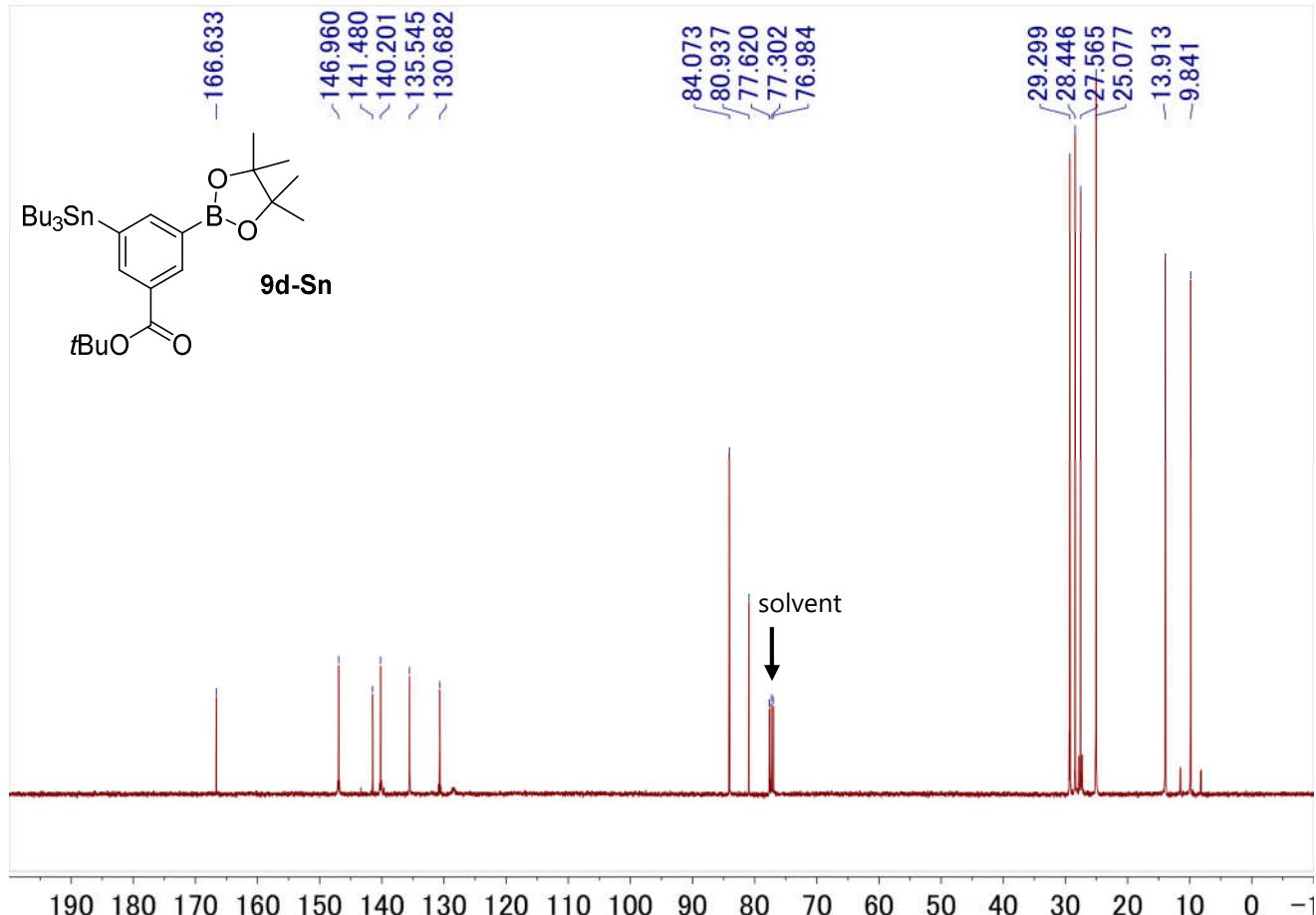
¹H NMR spectrum of 3-bromo-5-tri-*n*-butylstannylphenylboronic acid pinacol ester (9c-Sn) (400 MHz, CDCl₃).



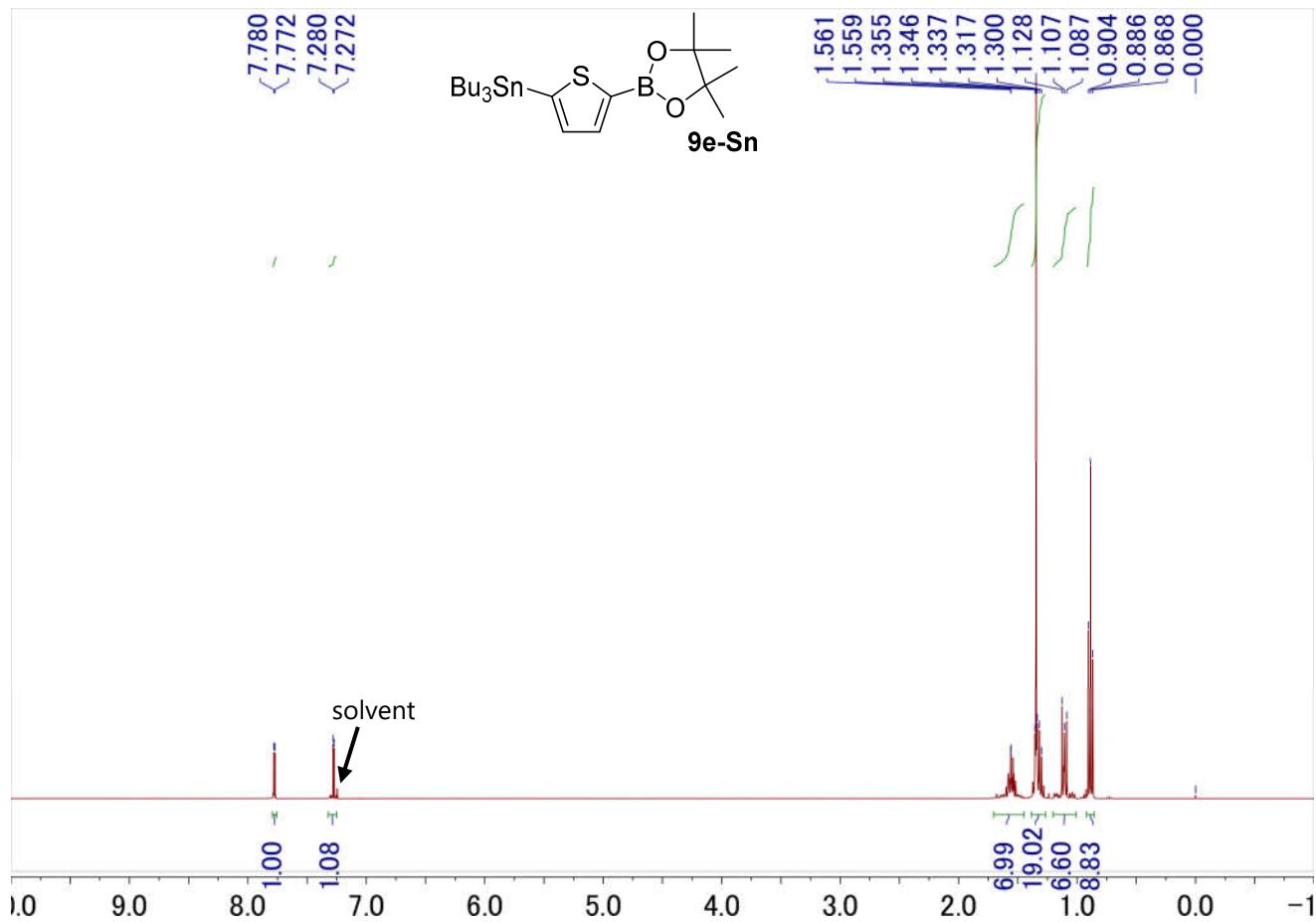
¹³C NMR spectrum of 3-bromo-5-tri-*n*-butylstannylphenylboronic acid pinacol ester (9c-Sn) (100 MHz, CDCl₃).



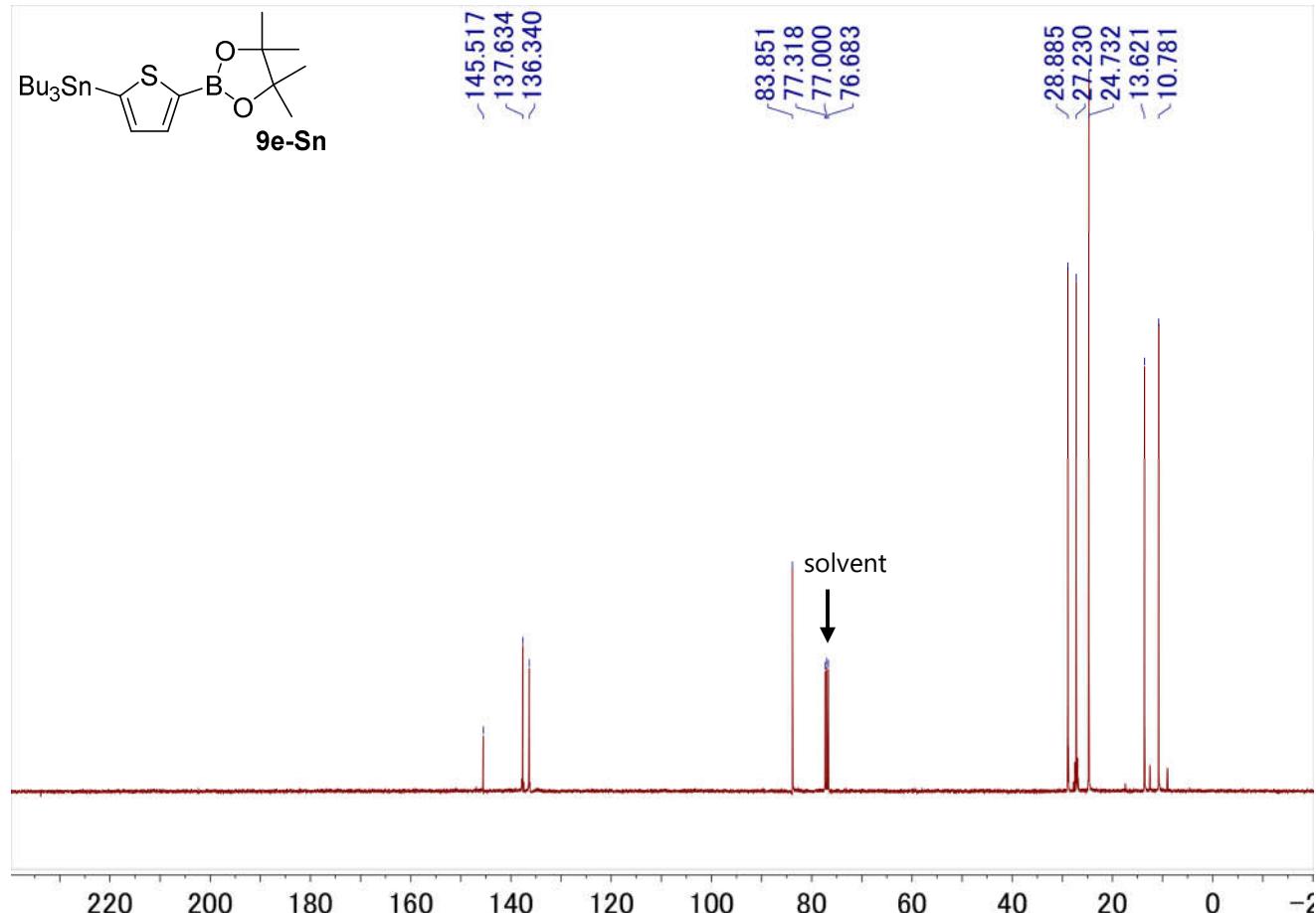
¹H NMR spectrum of 3-tert-butyl-5-tri-n-butylstannylphenylboronic acid pinacol ester (9d-Sn) (400 MHz, CDCl₃).



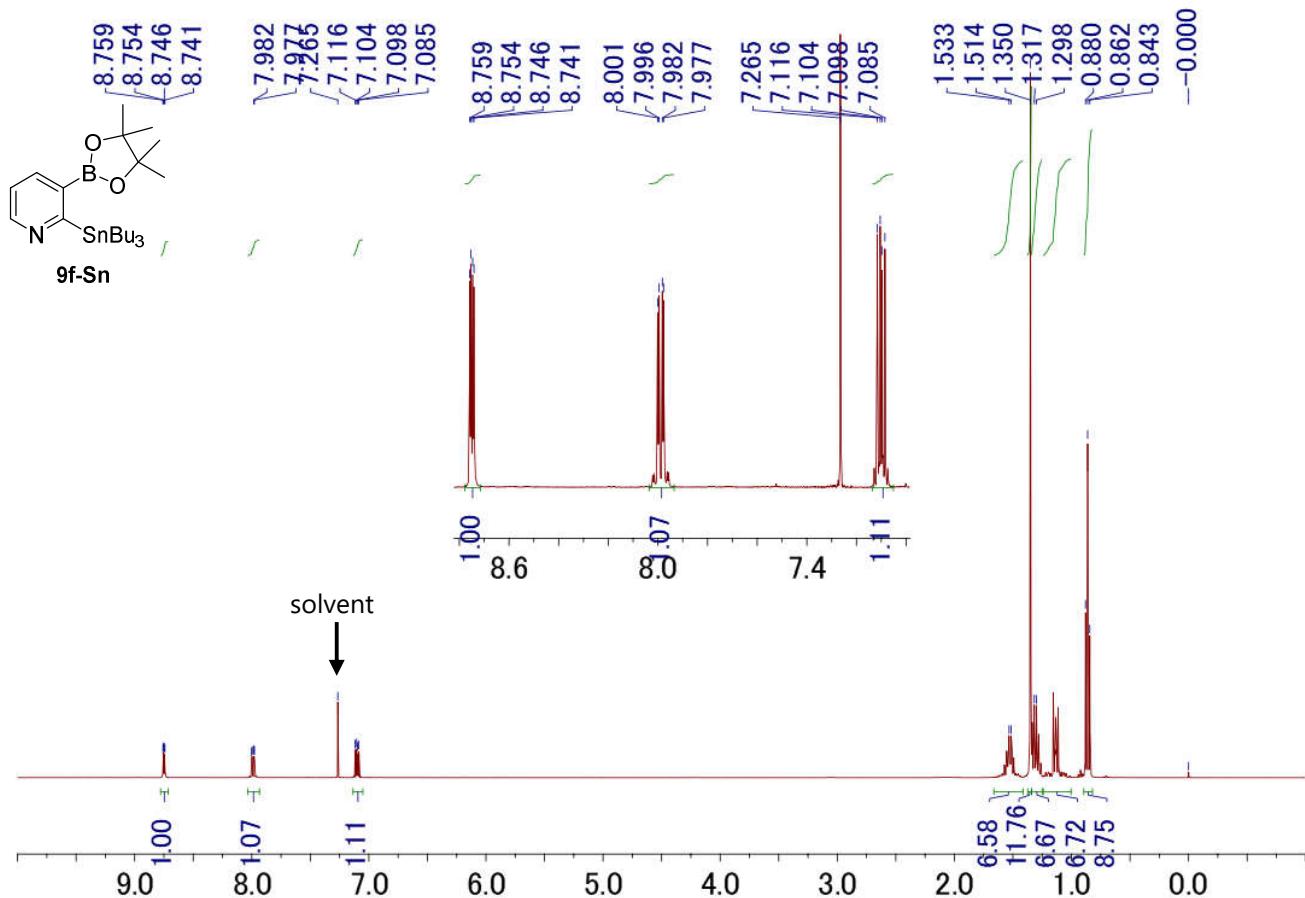
¹³C NMR spectrum of 3-tert-butyl-5-tri-n-butylstannylphenylboronic acid pinacol ester (9d-Sn) (100 MHz, CDCl₃).



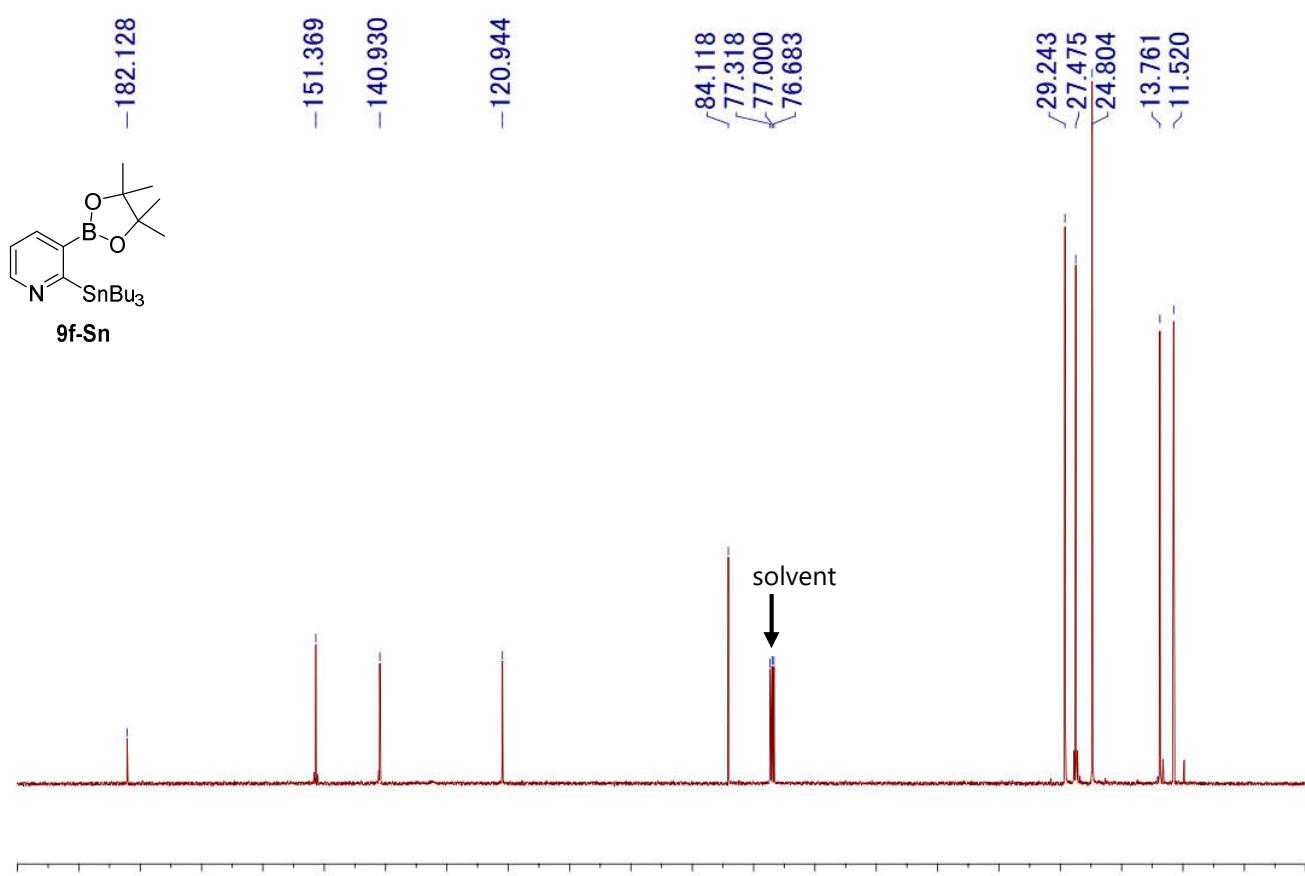
¹H NMR spectrum of 5-tri-*n*-butylstannyl-2-thiopheneboronic acid pinacol ester (9e-Sn) (400 MHz, CDCl₃).



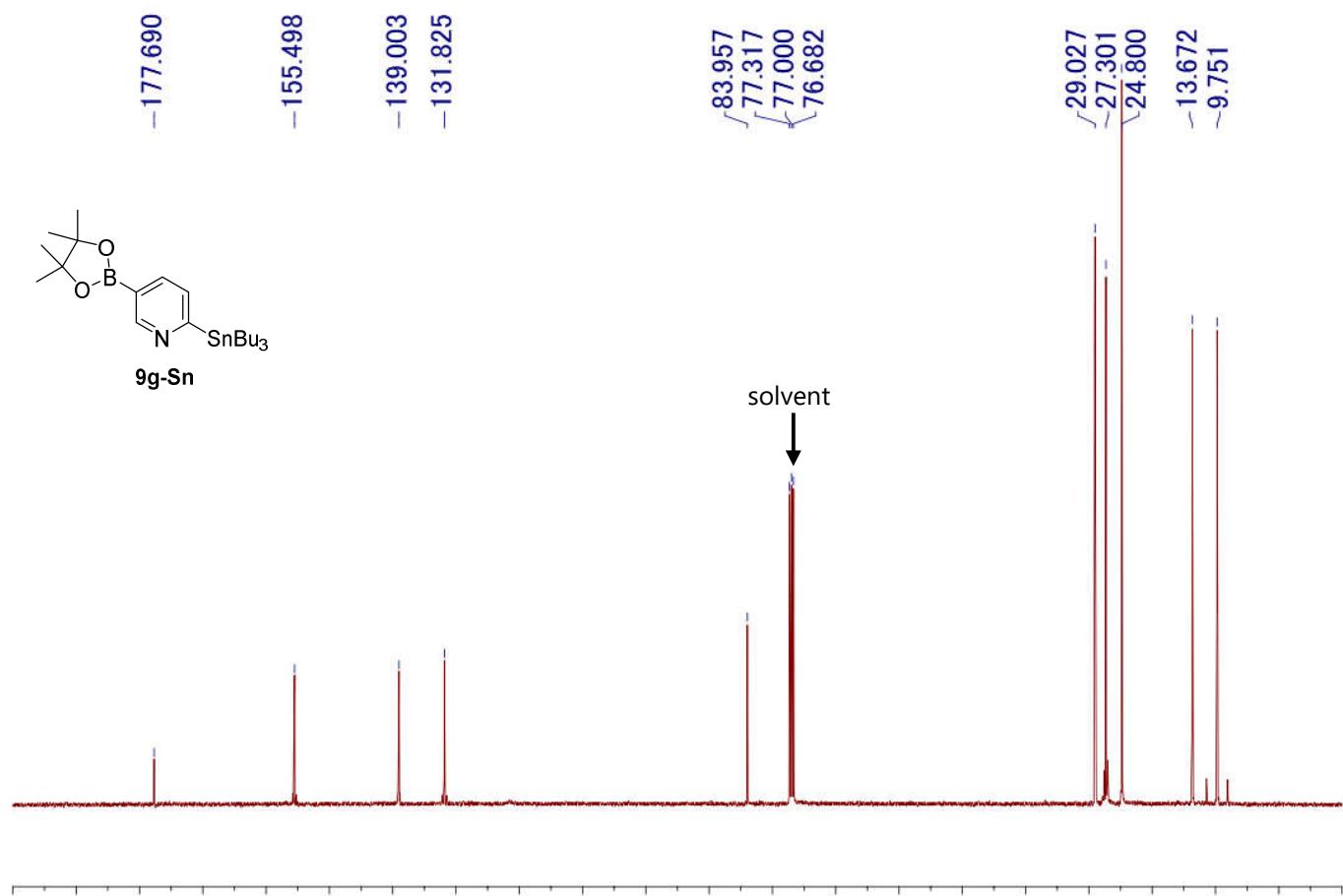
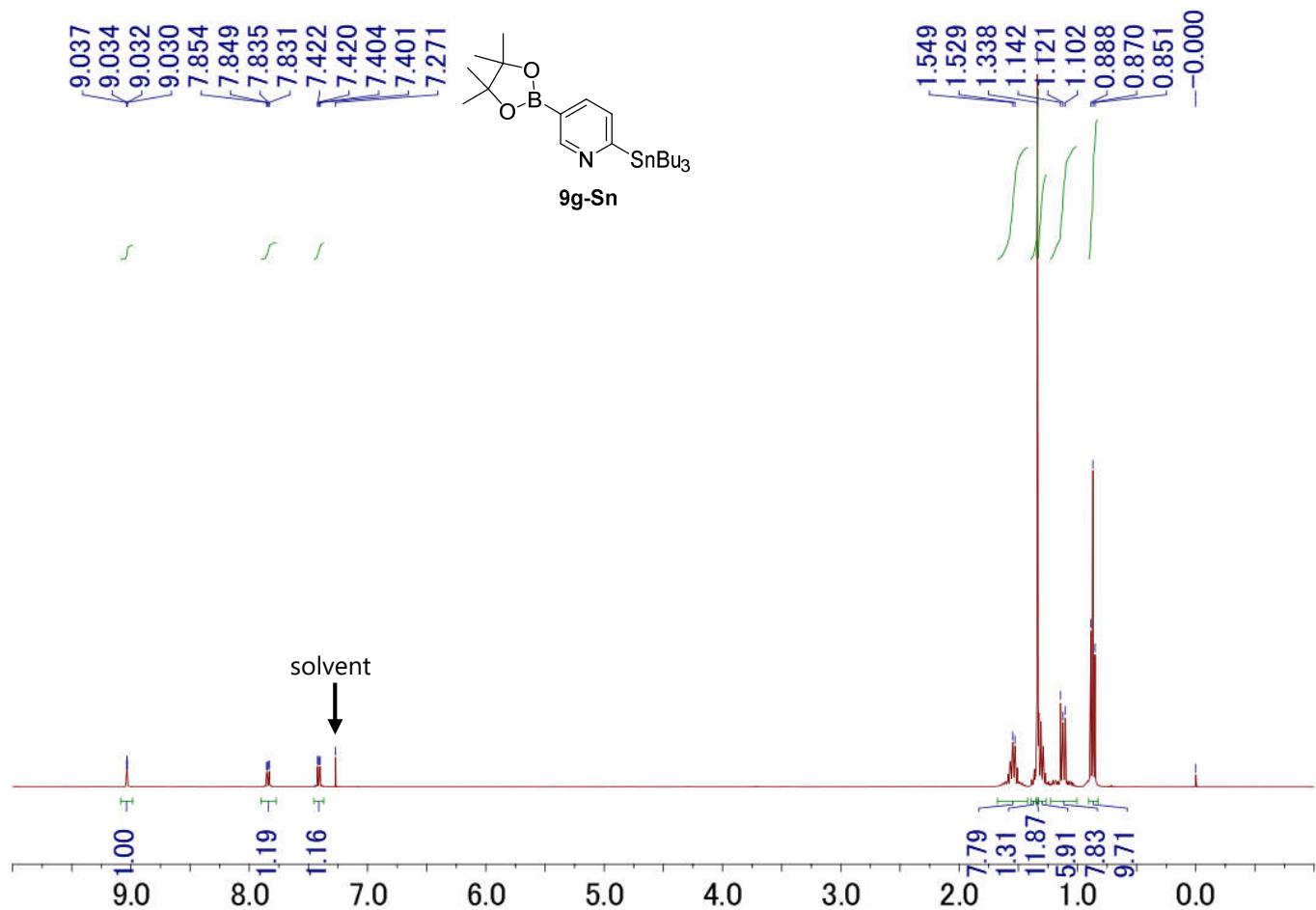
¹³C NMR spectrum of 5-tri-*n*-butylstannyl-2-thiopheneboronic acid pinacol ester (9e-Sn) (100 MHz, CDCl₃).



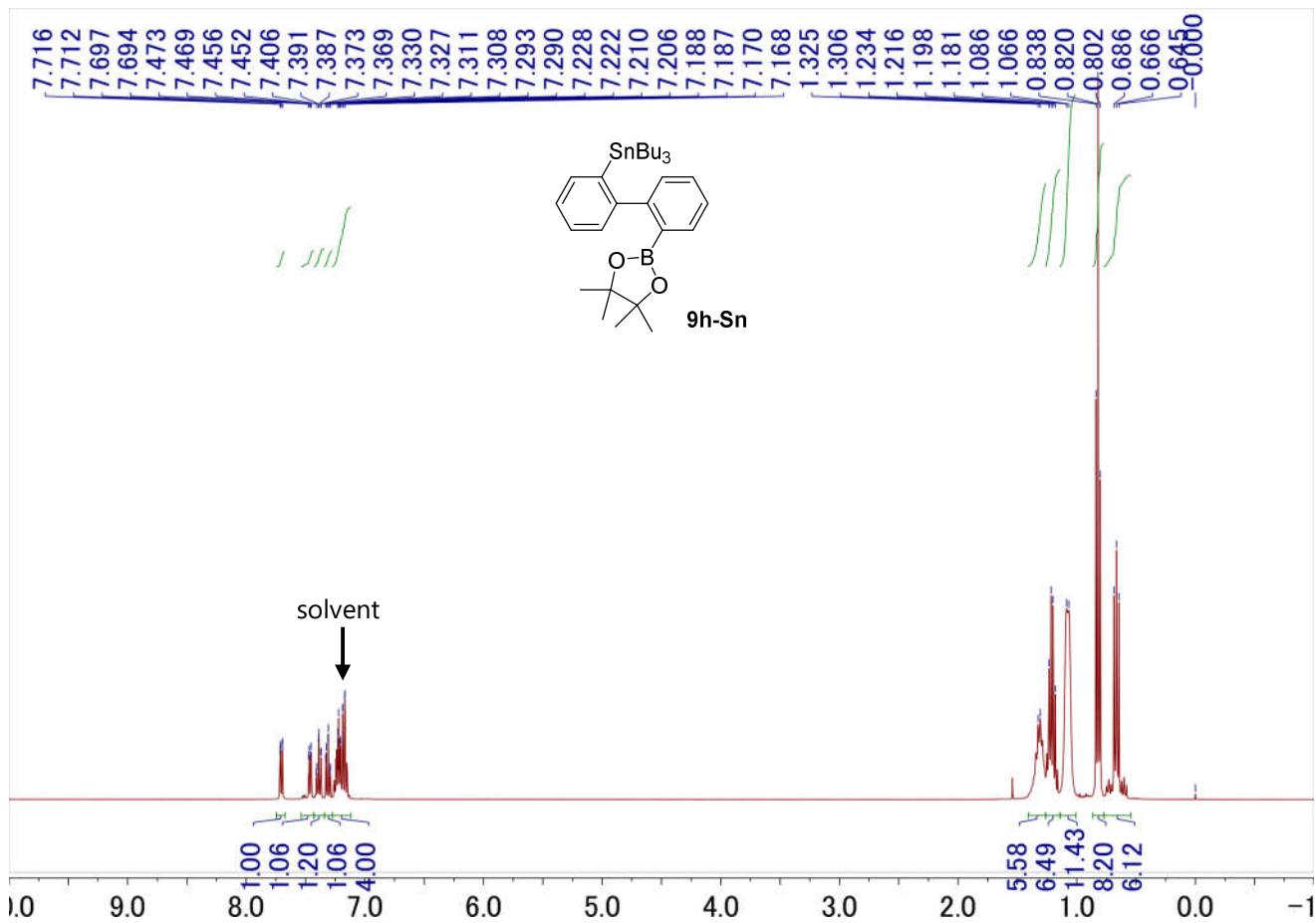
¹H NMR spectrum of 2-tri-*n*-butylstannylpyridin-3-boronic acid pinacol ester (9f-Sn) (400 MHz, CDCl₃).



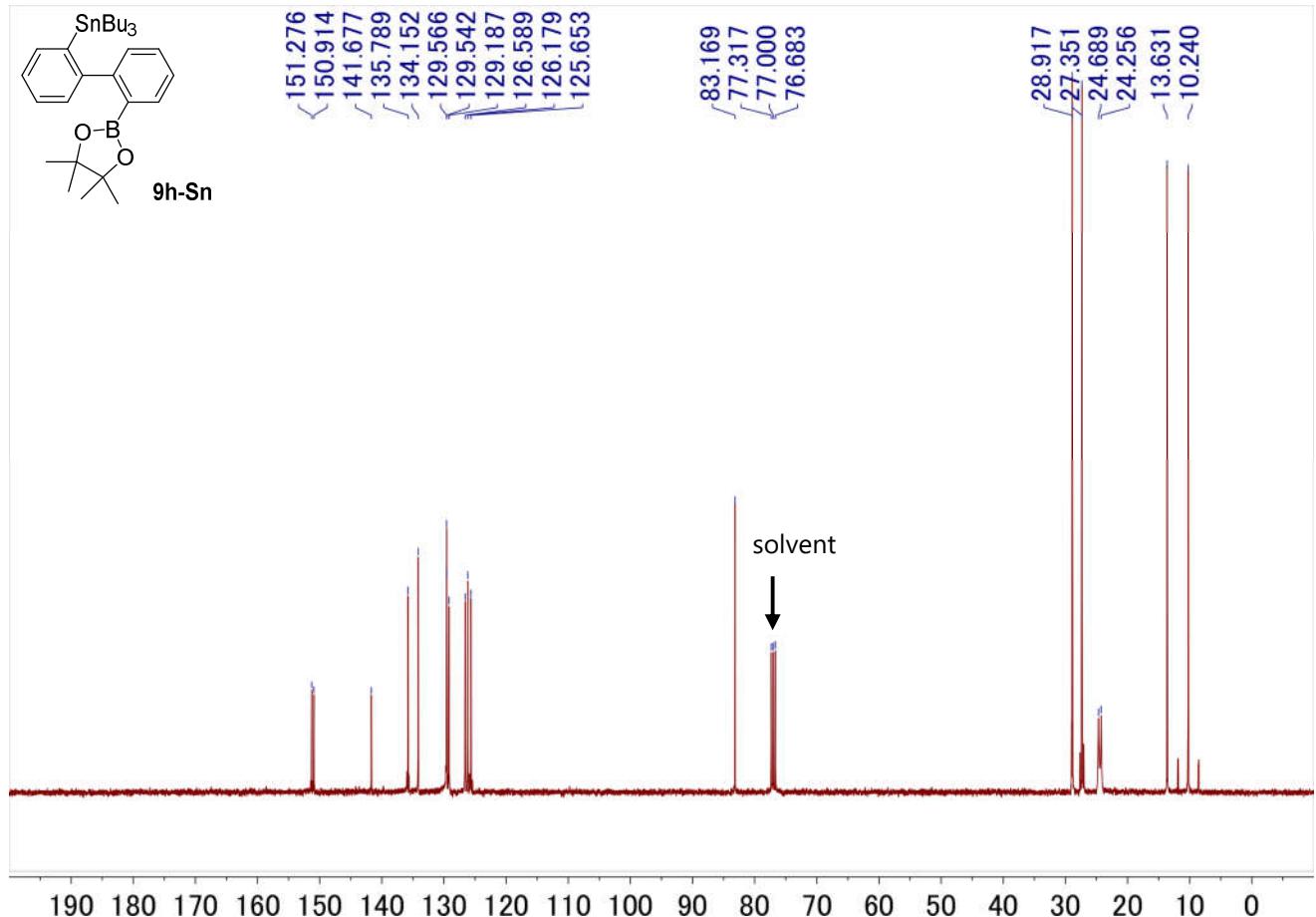
¹³C NMR spectrum of 2-tri-*n*-butylstannylpyridin-3-boronic acid pinacol ester (9f-Sn) (100 MHz, CDCl₃)



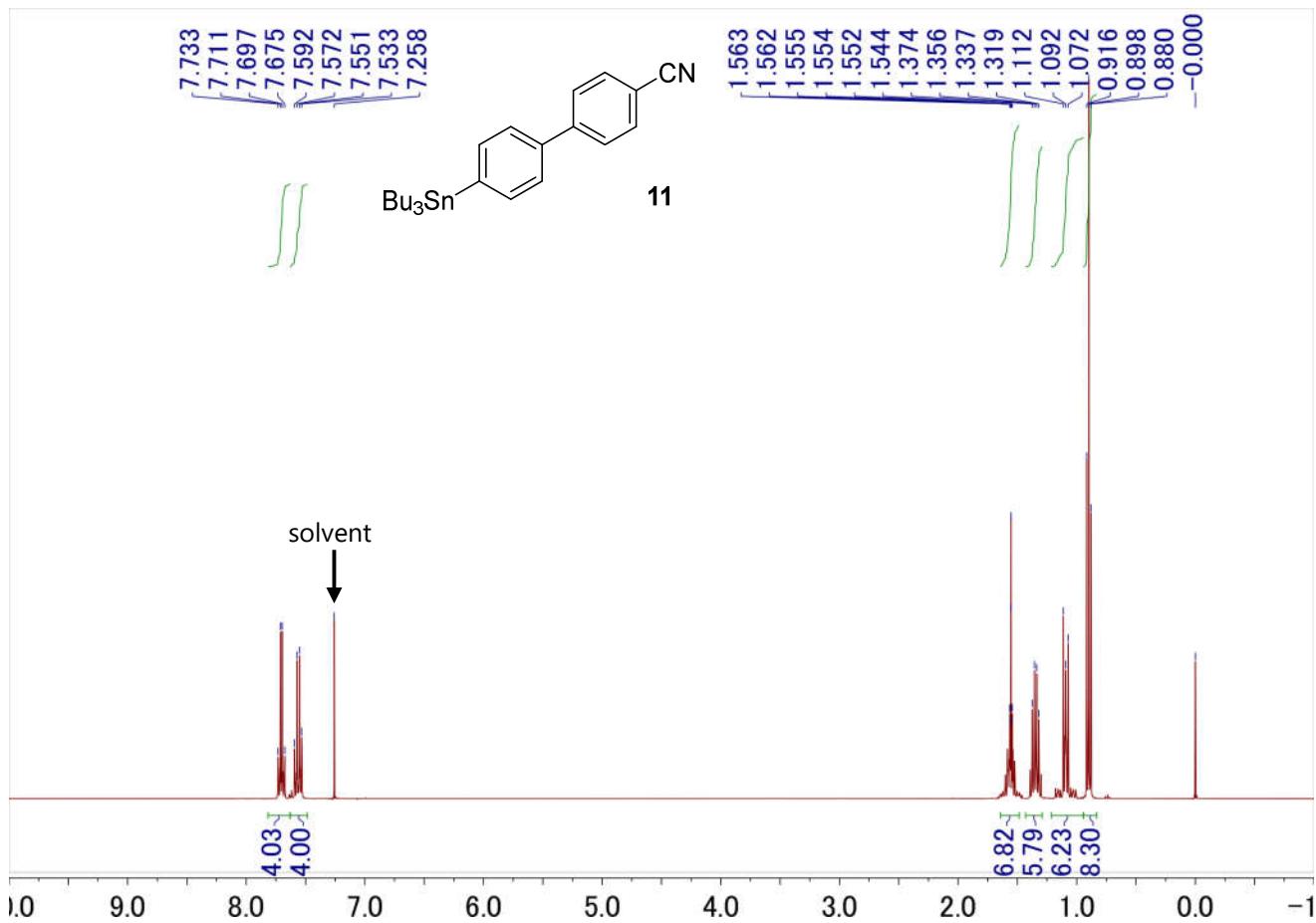
¹³C NMR spectrum of 2-tri-*n*-butylstannylpyridin-5-boronic acid pinacol ester (9g-Sn) (100 MHz, CDCl₃).



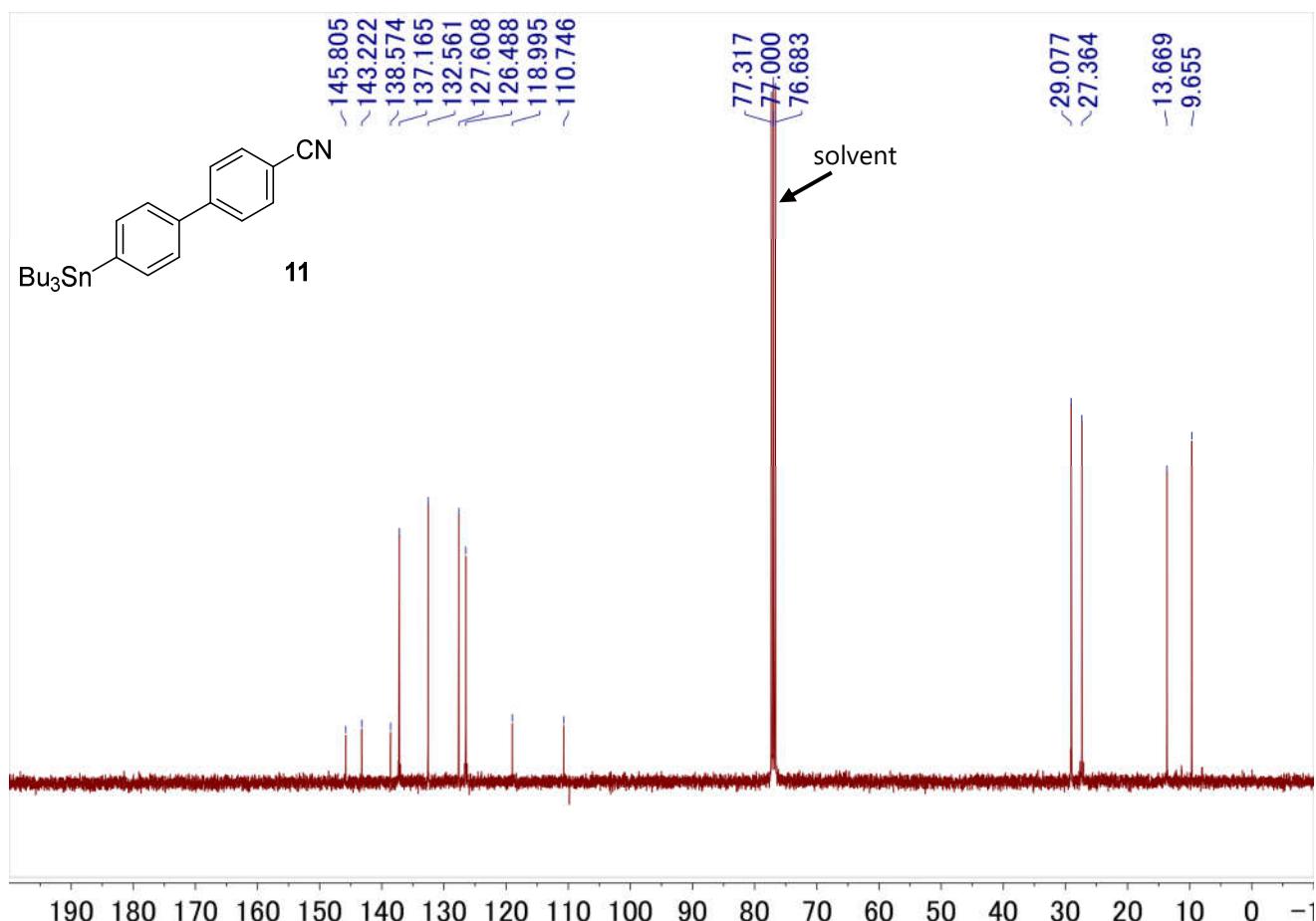
¹H NMR spectrum of 2'-tri-n-butylstannylbiphenyl-2-boronic acid pinacol ester (9h-Sn) (400 MHz, CDCl_3).



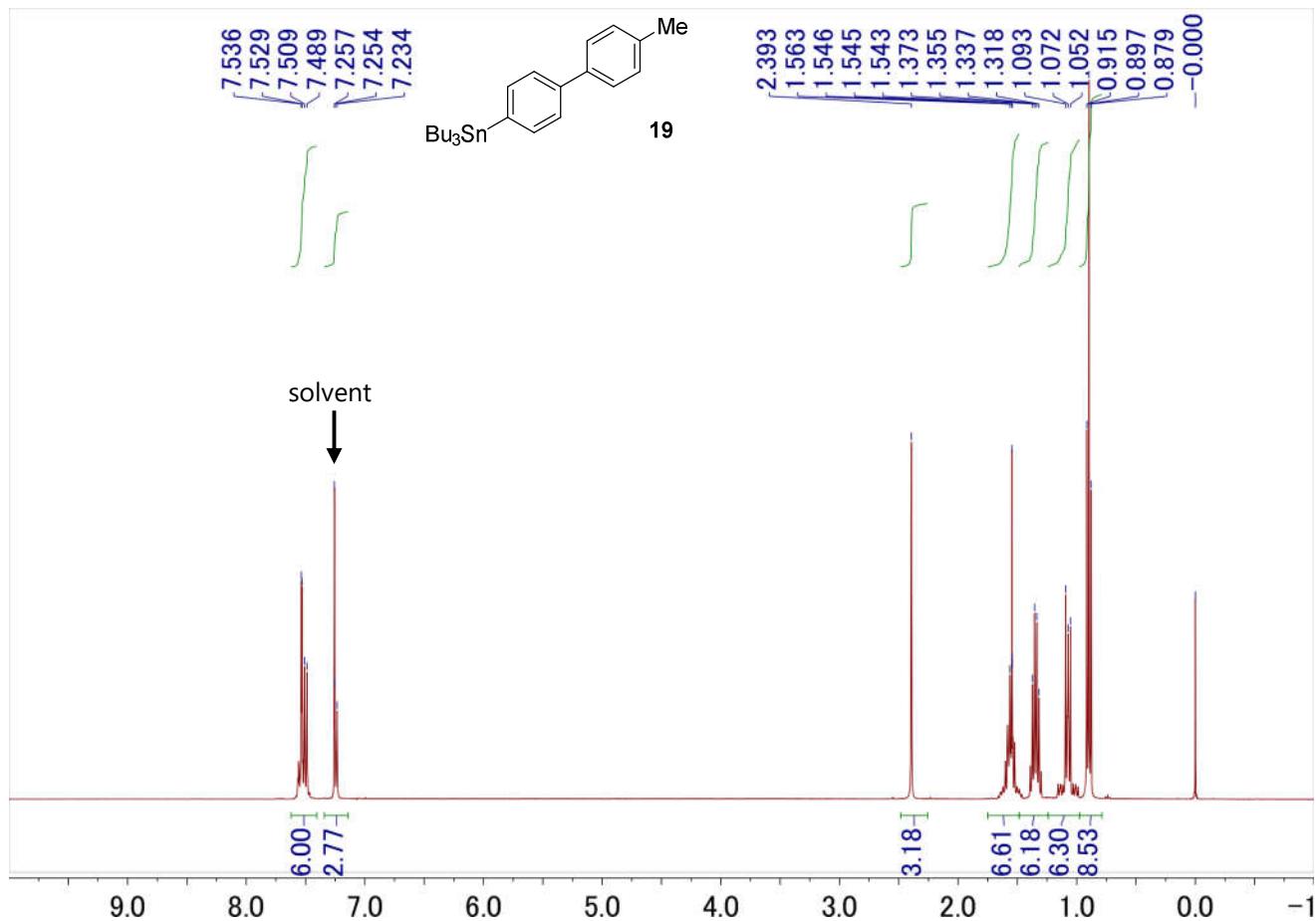
¹³C NMR spectrum of 2'-tri-n-butylstannylbiphenyl-2-boronic acid pinacol ester (9h-Sn) (100 MHz, CDCl_3).



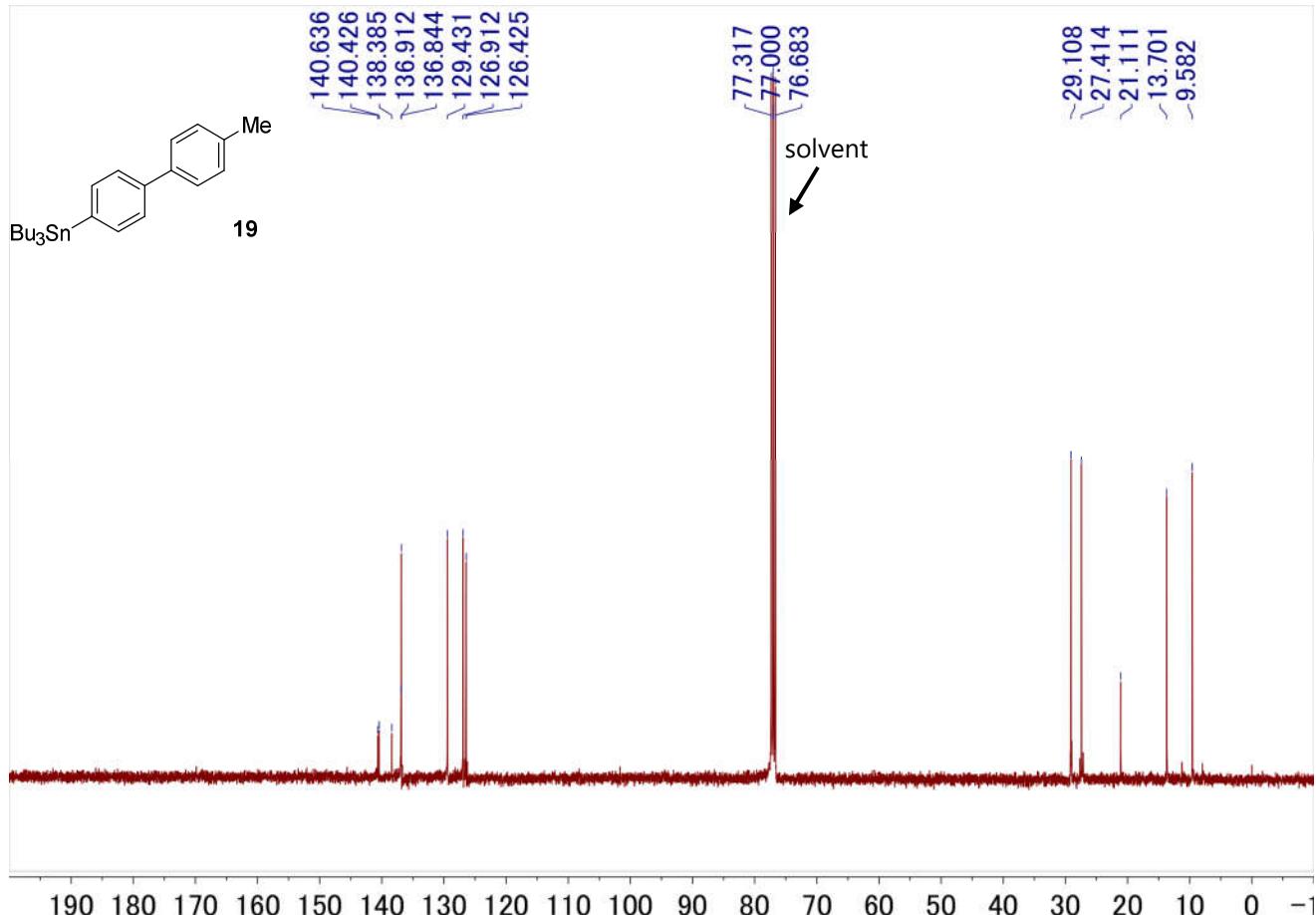
¹H NMR spectrum of 4-tri-*n*-butylstannyl-4'-cyanobiphenyl (**11**) (400 MHz, CDCl₃).



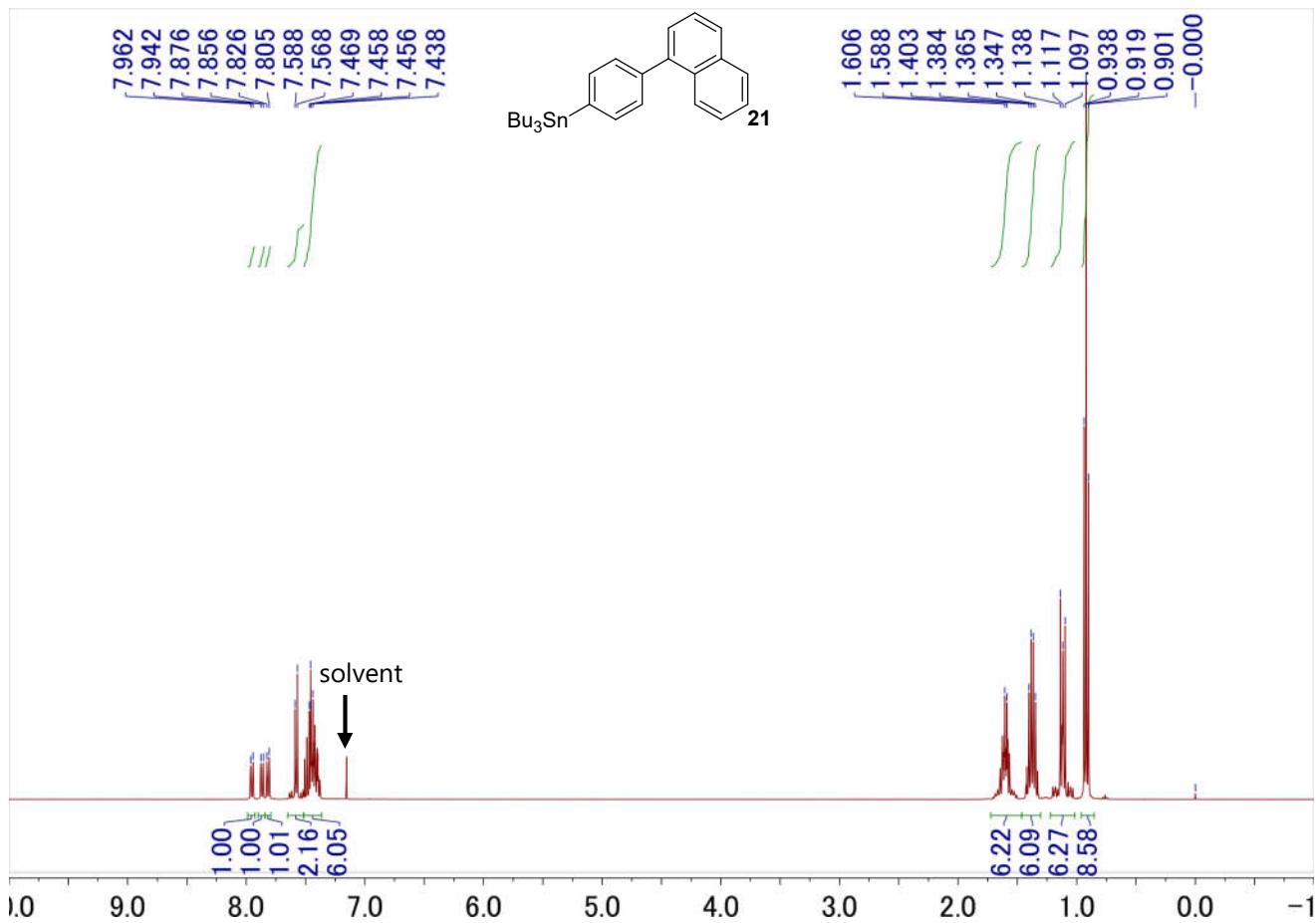
¹³C NMR spectrum of 4-tri-*n*-butylstannyl-4'-cyanobiphenyl (**11**) (100 MHz, CDCl₃).



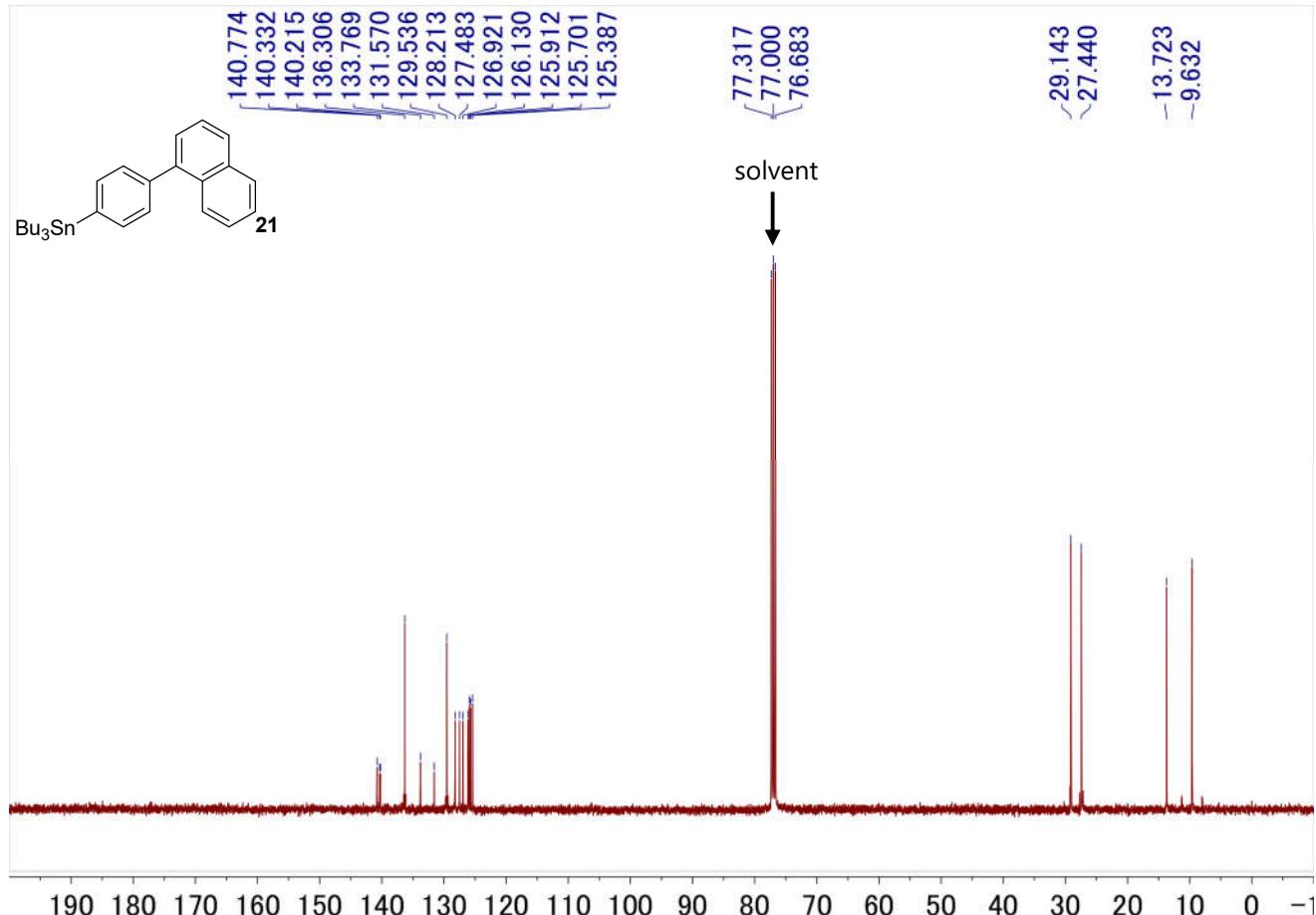
¹H NMR spectrum of 4-tri-*n*-butylstannyl-4'-methylbiphenyl (**19**) (400 MHz, CDCl₃).



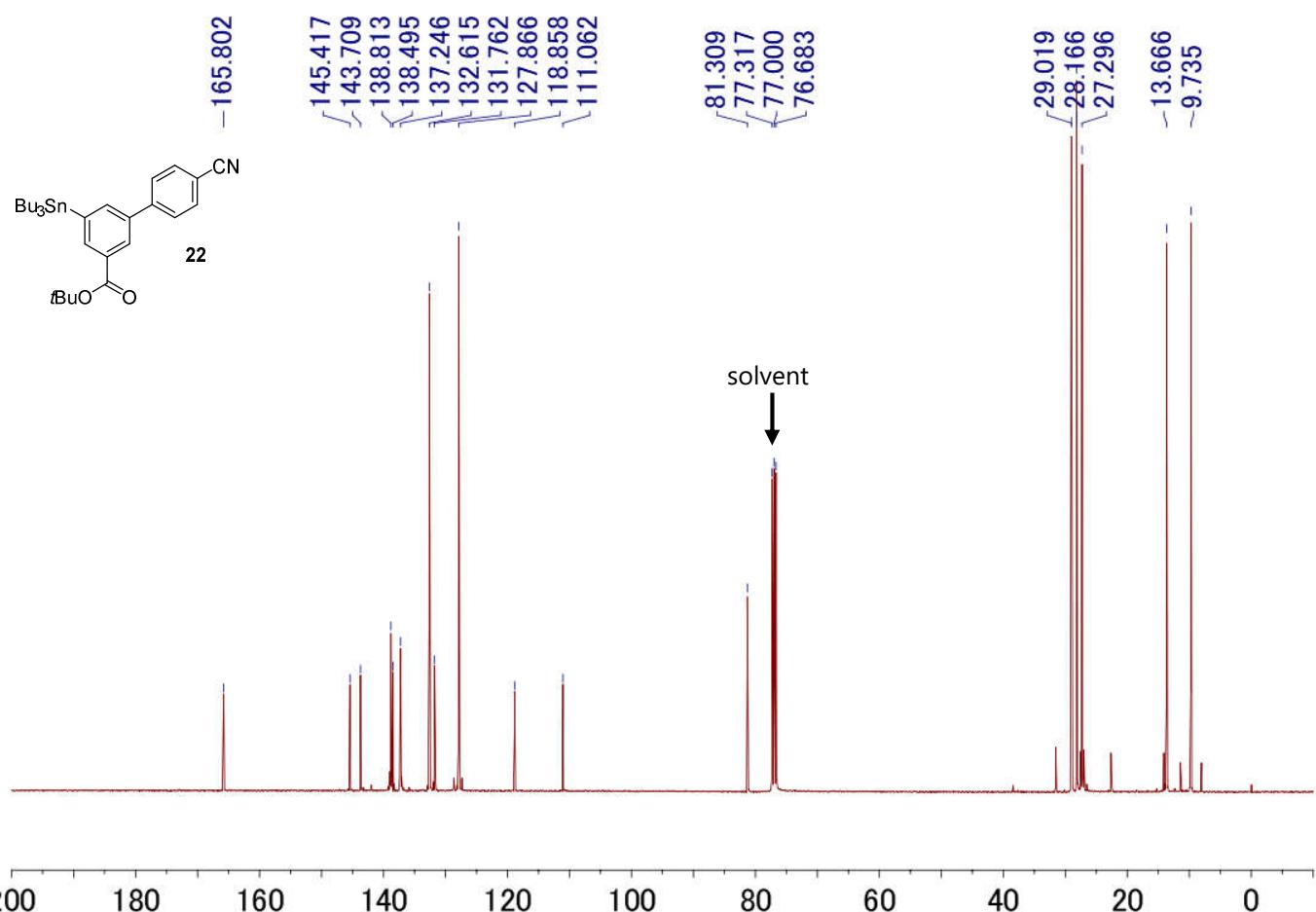
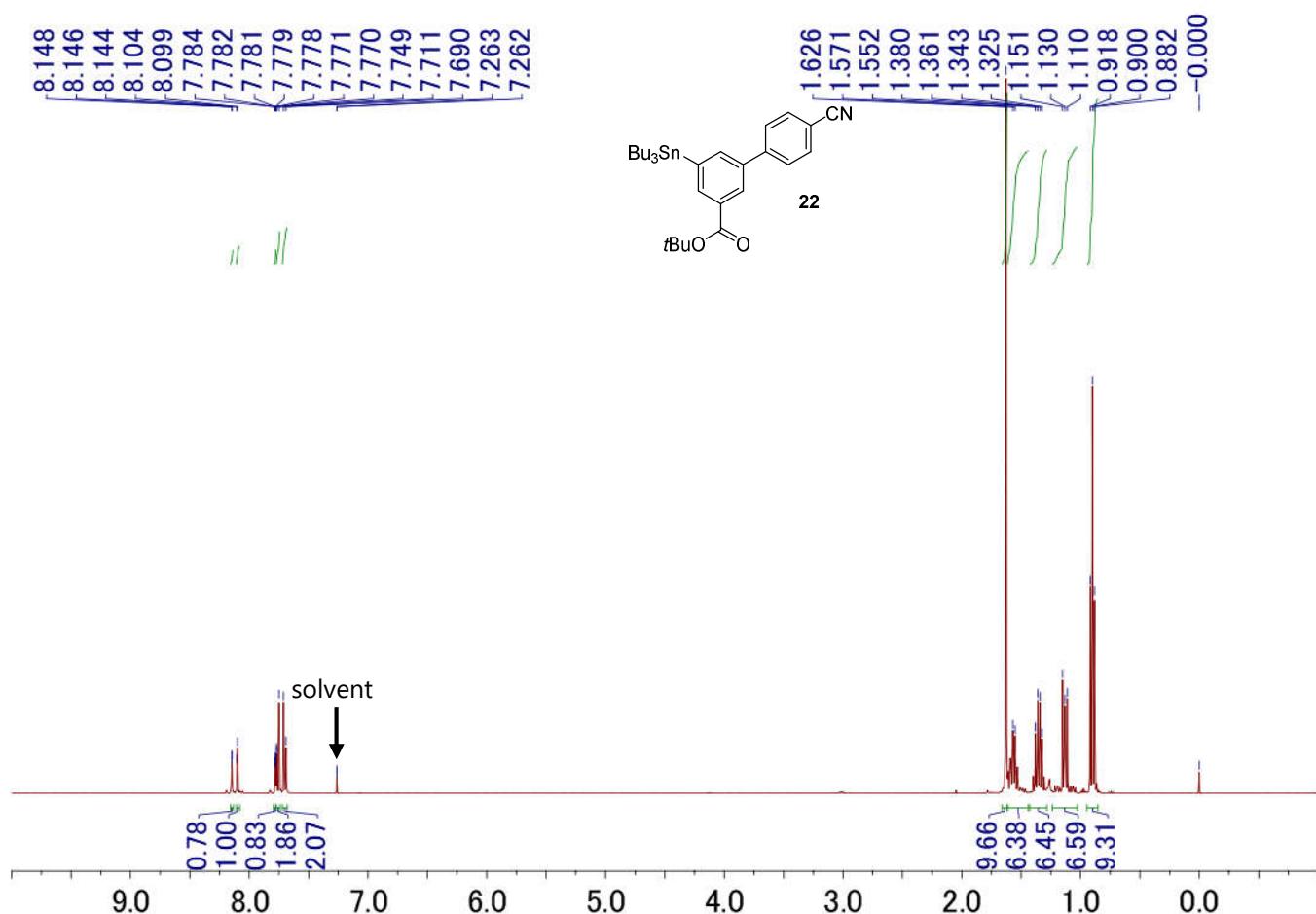
¹³C NMR spectrum of 4-tri-*n*-butylstannyl-4'-methylbiphenyl (**19**) (100 MHz, CDCl₃).

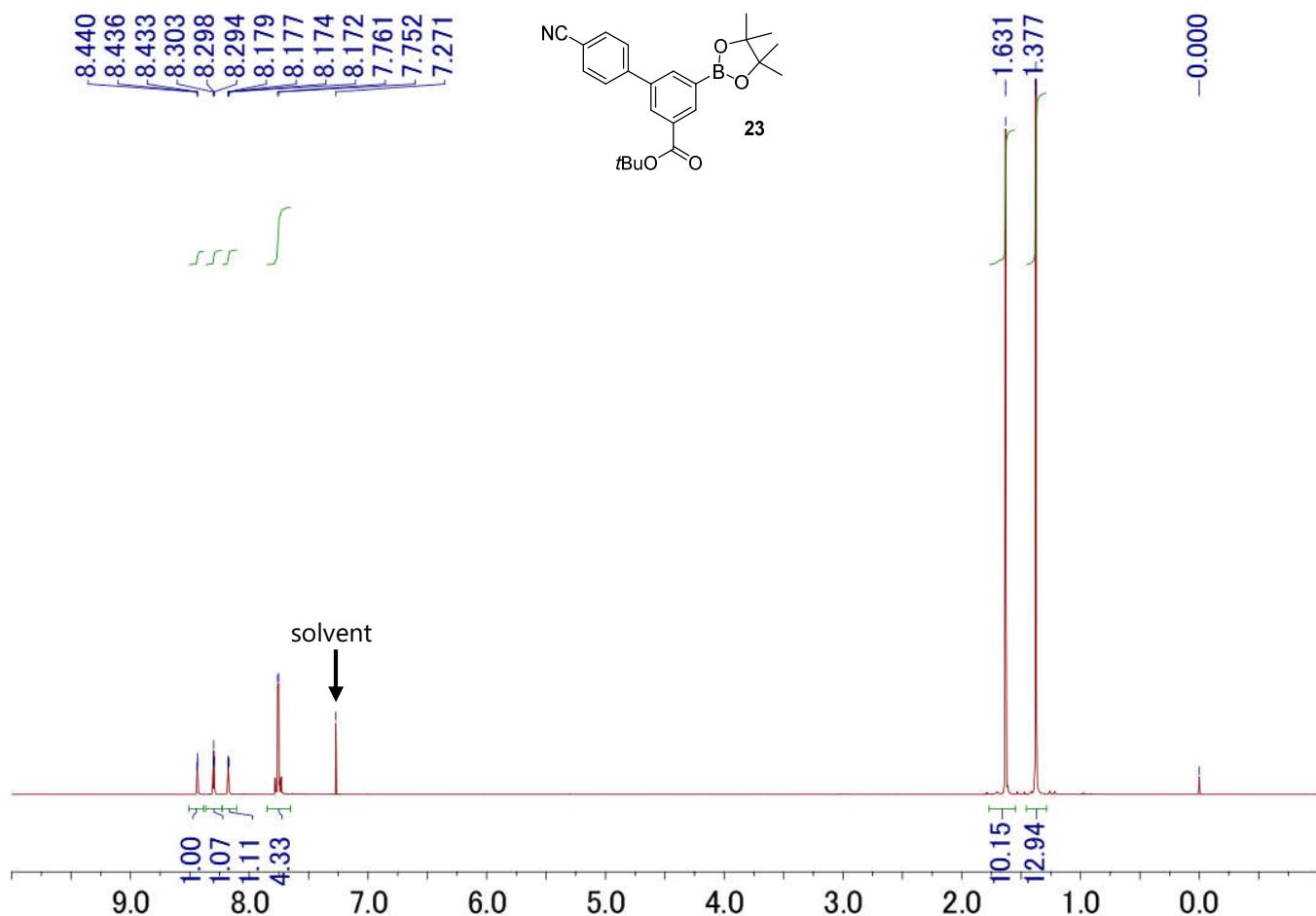


¹H NMR spectrum of tri-*n*-butyl-4-(1-naphthyl)phenylstannane (**21**) (400 MHz, CDCl_3).

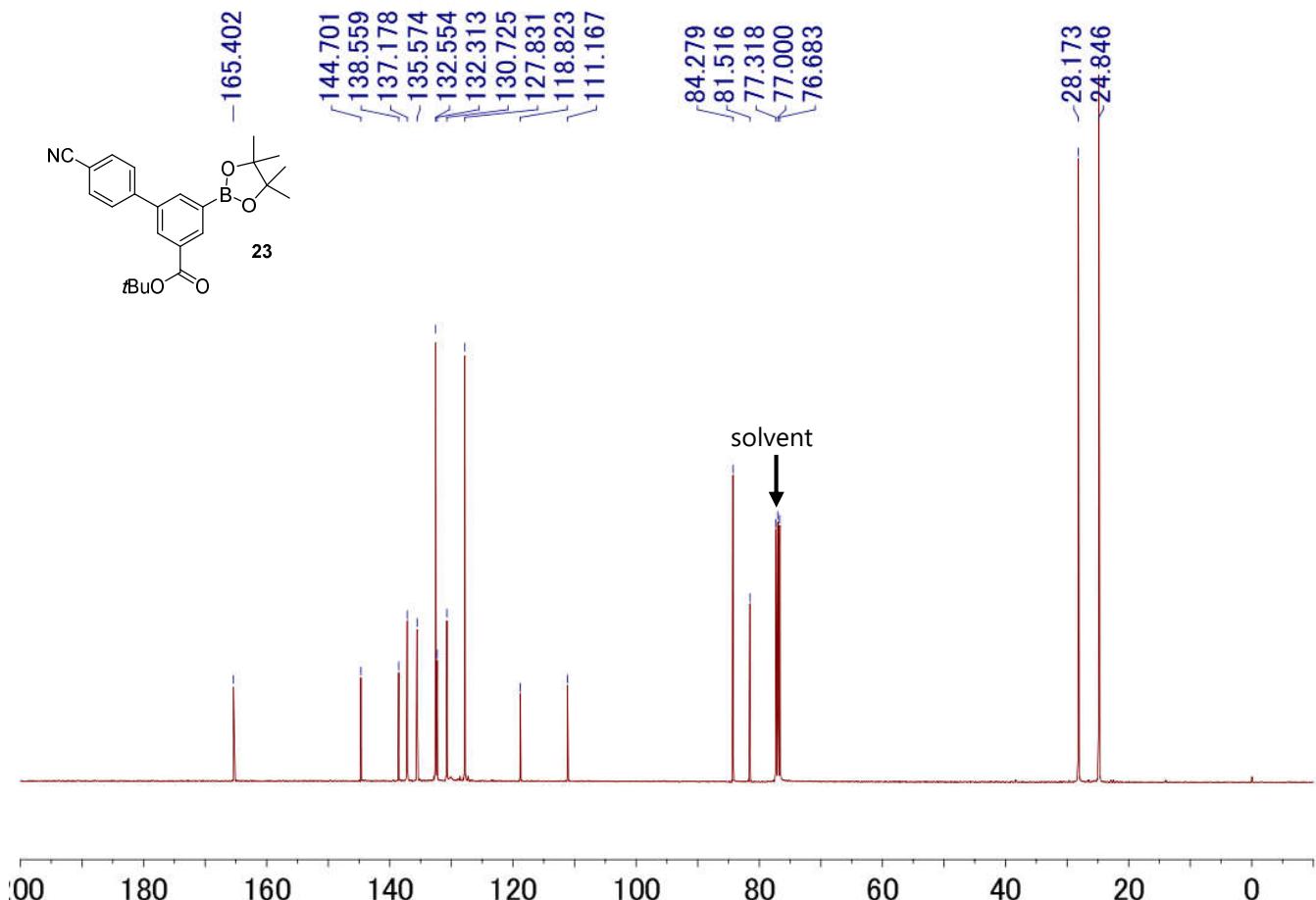


¹³C NMR spectrum of tri-*n*-butyl-4-(1-naphthyl)phenylstannane (**21**) (100 MHz, CDCl_3).

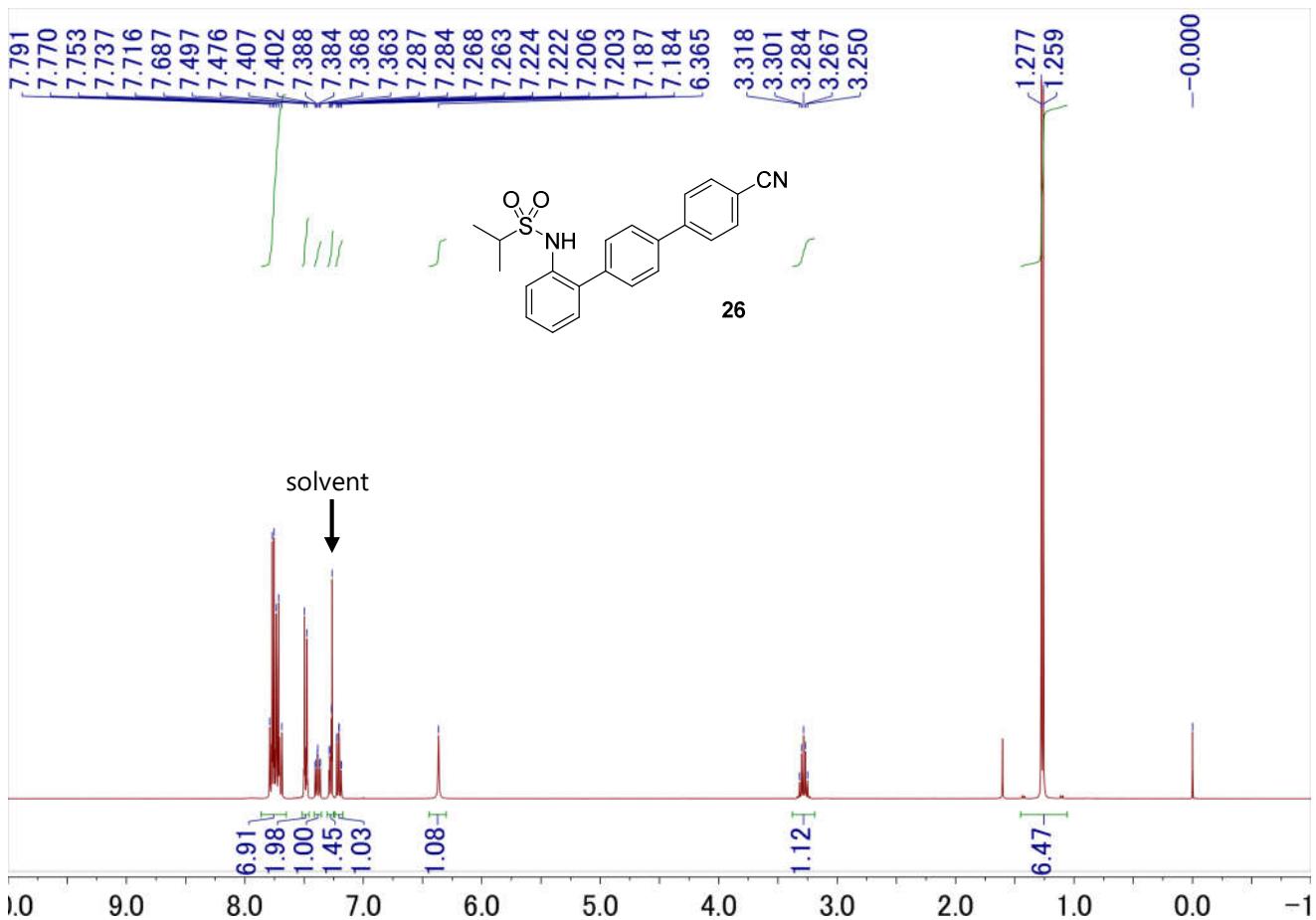




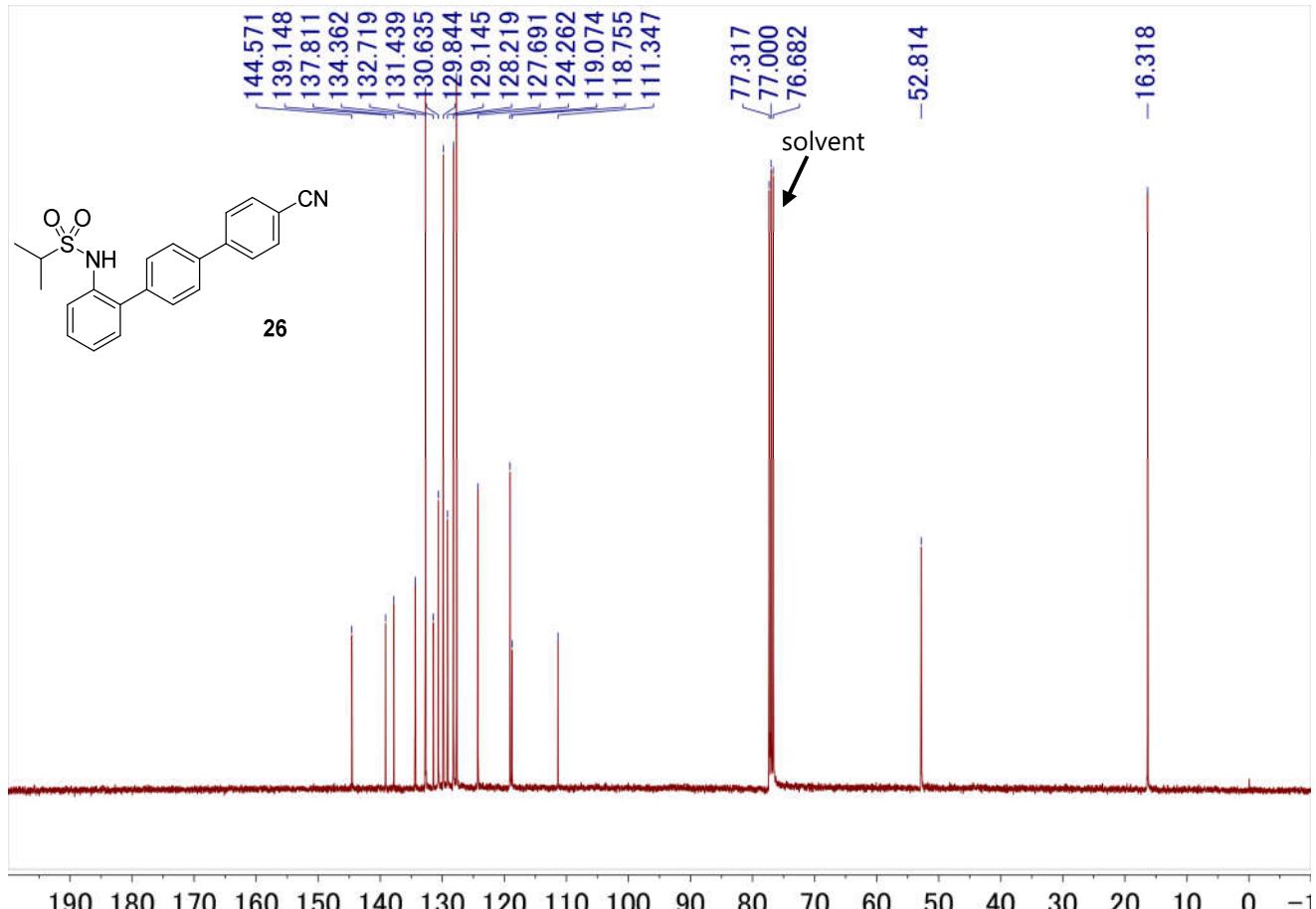
¹H NMR spectrum of 3-tert-butoxycarbonyl-5-(4-cyanophenyl)phenylboronic acid pinacol ester (23) (400 MHz, CDCl₃).



¹³C NMR spectrum of 3-tert-butoxycarbonyl-5-(4-cyanophenyl)phenylboronic acid pinacol ester (23) (100 MHz, CDCl₃).



¹H NMR spectrum of *N*-isopropyl(4"-cyano-[1',1";4',1"]terphenyl-2-yl)sulfonamide (26) (400 MHz, CDCl₃).



¹³C NMR spectrum of *N*-isopropyl(4"-cyano-[1,1';4',1'']terphenyl-2-yl)sulfonamide (26) (100 MHz, CDCl₃).