Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Switching Between Intermolecular and Intramolecular Reactions Using Flow Microreactors. Lithiation of 2-Bromo-2'-Silylbiphenyls

Aiichiro Nagaki, Songhee Kim, Nobuyuki Miuchi, Hiroki Yamashita, Katsuyuki Hirose, and Jun-ichi Yoshida

General

GC analysis was performed on a SHIMADZU GC-2014 gas chromatograph equipped with a flame ionization detector using a fused silica capillary column (column, CBPI; 0.25 mm x 25 m). ^{1}H and ^{13}C NMR spectra were recorded on Varian MERCURY plus-400 (^{1}H 400 MHz, ^{13}C 100 MHz) spectrometer with Me_4Si or $CHCl_3$ as a standard in $CDCl_3$ unless otherwise noted. EI mass spectra was recorded on JMS-SX102A spectrometer. Gel permeation chromatography was carried out with Japan Analytical Industry LC-9201 equipped with JAIGEL-1H and 2H using $CHCl_3$ as eluent.

THF and Et_2O were purchased from Kanto Chemical Co., Inc. as a dry solvent and used without further purification. Hexane was purchased from Wako, distilled before use, and stored over molecular sieves 4A. Methanol, *n*-BuLi, methyl trifluoromethanesulfonate, isopropoxy boronic acid pinacol ester, 2,2'-dibromobenzene, chlorotrimethylsilane, chlorodimethylphenylsilane, and chlorodiphenylmethylsilane were commercially available. Stainless steel (SUS304) T-shaped micromixer with inner diameter of 250 and 500 μm was manufactured by Sanko Seiki Co., Inc. Stainless steel (SUS316) microtube reactors with inner diameter of 1000 μm were purchased from GL Sciences and were cut into appropriate lengths (3.5, 12.5, 25, 50, 100, and 200 cm). The micromixers and the microtube reactors were connected with stainless steel fittings (GL Sciences, 1/16 OUW) to construct the integrated flow microreactor system in the laboratory. The flow microreactor system was dipped in a cooling bath to control the temperature. Solutions were continuously introduced to the flow microreactor system using syringe pumps, Harvard Model 11 Plus or Harvard PHD 2000, equipped with gastight syringes purchased from SGE. After a steady state was reached, the product solution was collected for 30 s. When the collection time was longer, the product solution can be obtained in a preparative scale.

Synthesis of 2-Bromo-2'-(trimethylsilyl)biphenyl

To a solution of 2,2'-dibromobiphenyl (21g (67 mmol)) in THF (300 mL) at -78 °C was added dropwise a 1.64 M solution of *n*-BuLi in hexane (47 mL (77 mmol)). The resulting solution was stirred for 15 min and chlorotrimethylsilane (11 g (101 mmol)) was added dropwise. The mixture was warmed to room temperature, saturated *aq*NH_4Cl was added, and the mixture was extracted with diethyl ether. The organic fractions were combined, washed (brine), dried (Na_2SO_4), concentrated under reduced pressure and the crude product was purified by using column chromatography (hexane) to give the pure product of 2-bromo-2'-(trimethylsilyl)biphenyl (69%). The spectral data were identical to those reported in the literature.[1]

Synthesis of 2-Bromo-2'-(dimethylphenylsilyl)biphenyl

To a solution of 2,2'-dibromobiphenyl (21g (67 mmol)) in THF (300 mL) at -78 °C was added dropwise a 1.64 M solution of *n*-BuLi in hexane (47 mL (77 mmol)). The resulting solution was stirred for 15 min and chlorodimethylphenylsilane (17 g (100 mmol)) was added dropwise. The mixture was warmed to room temperature, saturated *aq*NH_4Cl was added, and the mixture was extracted with diethyl ether. The organic fractions were combined, washed (brine), dried (Na_2SO_4), concentrated under reduced pressure and the crude product was purified by using column chromatography (hexane only) to give the pure product of 2-bromo-2'-(dimethylphenylsilyl)biphenyl (65%). The

spectral data were identical to those reported in the literature.[1]

Synthesis of 2-Bromo-2'-(diphenylmethylsilyl)biphenyl
To a solution of 2,2'-dibromobiphenyl (21g (67 mmol)) in THF (300 mL) at -78 °C was added dropwise a 1.64 M solution of *n*-BuLi in hexane (47 mL (77 mmol)). The resulting solution was stirred for 15 min and chlorodiphenylmethylsilane (20 g (86 mmol)) was added dropwise. The mixture was warmed to room temperature, saturated *aq*NH_4Cl was added, and the mixture was extracted with diethyl ether. The organic fractions were combined, washed (brine), dried (Na_2SO_4), concentrated under reduced pressure and the crude product was purified by using column chromatography (hexane only) to give the pure product of 2-bromo-2'-(diphenylmethylsilyl)biphenyl (39%).

2-Bromo-2'-(diphenylmethylsilyl)biphenyl: a white solid, GC ^tR 32.3 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.19 (s, 3H), 6.78 (dd, 1H, *J* = 1.6, 1.6 Hz), 6.96 (ddd, 1H, *J* = 7.6, 7.6, 1.2 Hz), 7.09 (ddd, 1H, *J* = 7.6, 7.6, 2.0 Hz), 7.21 (d, 1H, *J* = 8.0 Hz), 7.28-7.47 (m, 13H), 7.52 (dd, 1H, *J* = 1.2, 1.2 Hz) ppm ; ^{13}C NMR (100 MHz, $CDCl_3$) δ -3.5, 124.2, 126.4, 126.7, 127.7 (d, *J* = 2.0 Hz), 128.9 (d, *J* = 6.3 Hz), 129.0 (d, *J* = 3.6 Hz), 130.2, 131.6, 132.2, 134.6, 135.0, 135.2, 136.9, 137.3 (d, *J* = 4.3 Hz), 143.6, 148.2 ppm; HRMS (DART) m/z calcd for $C_{25}H_{20}Br_1Si_1(M^+-H)$: 427.0512, found: 427.0526.

The Br-Li Exchange Reaction of 2-Bromo-2'-(trimethylsilyl)biphenyl Followed by Reaction with Methanol in a macro batchreactor.

A solution of *n*-BuLi (0.44 M in *n*-hexane, 2.5 mL) was added dropwise to a solution of 2-bromo-2'-(trimethylsilyl)biphenyl (0.10 M in THF, 10 mL) in a 50 mL round bottom glass flask with magnetic stirring for 1.0 min under argon. The mixture was stirred for 7 min, and a solution of methanol (5.0 mL) was added. After being stirring for 7 min, the mixture was warmed to room temperature by removing the cooling bath, and then was poured into *sat. aq.* NH_4Cl. The reaction mixture was analyzed by GC. The results are summarized in Figure S-1.

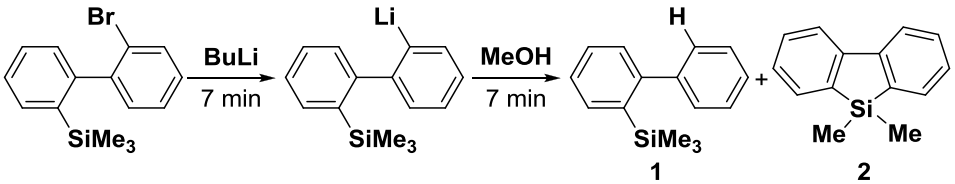
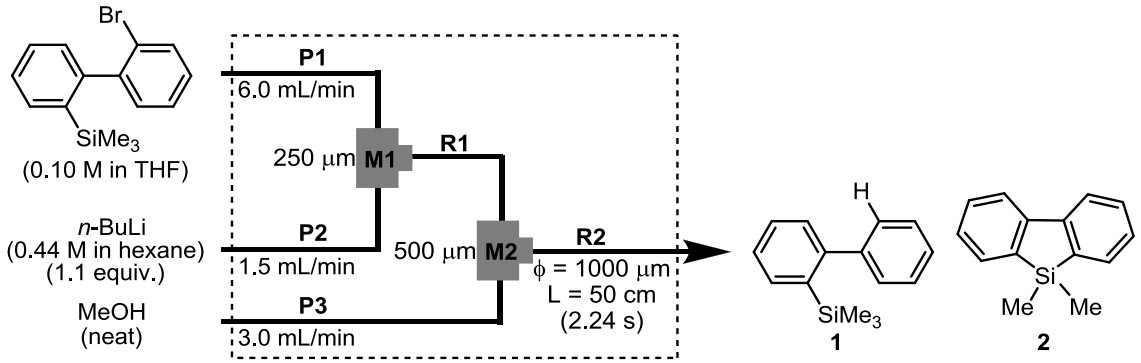


Figure S-1. Br-Li Exchange of 2-bromo-2'-(trimethylsilyl)biphenyl with *n*-BuLi followed by reaction with methanol in a macro batch reactor.

2-(Trimethylsilyl)biphenyl (1): The crude product at -78 °C was purified by flash chromatography (hexane only) to obtain 2-(trimethylsilyl)biphenyl. The analytical data were identical to those reported in the literature.[1]

9,9-Dimethyl-9-silafluorene (2): The crude product at 0 °C was purified by flash chromatography (hexane only) to obtain 2-(trimethylsilyl)biphenyl. The analytical data were identical to those reported in the literature.[1]

Typical Procedure for the Br-Li Exchange Reaction of 2-Bromo-2'-(trimethylsilyl)biphenyl Followed by Reaction with Methanol in Flow Microreactor Systems



A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2**), two microtube reactors (**R1** and **R2**) and three tube pre-cooling units (**P1** (ϕ = 1000 μm, length L = 100 cm), **P2** (ϕ = 1000 μm, L = 50 cm) and **P3** (ϕ = 1000 μm, L = 100 cm)) was used. A solution of 2-bromo-2'-(trimethylsilyl)biphenyl (0.10 M in THF) (flow rate: 6.0 mL min^{-1}) and a solution of *n*-BuLi (0.44 M in *n*-hexane) (flow rate: 1.5 mL min^{-1}) were introduced to **M1** (ϕ = 250 μm) by syringe pumps. The resulting solution was passed through **R1** and was mixed with a solution of methanol (flow rate: 3.0 mL min^{-1}) in **M2** (ϕ = 500 μm). The resulting solution was passed through **R2** (ϕ = 1000 μm, L = 50 cm). After a steady state was reached, the product solution was collected for 30 s and was quenched with saturated *aq*NH_4Cl. The reaction mixture was analyzed by GC. The results are summarized in Table S-1.

Table S-1. The Br-Li exchange reaction of 2-bromo-2'-(trimethylsilyl)biphenyl followed by reaction with methanol in the flow microreactor systems

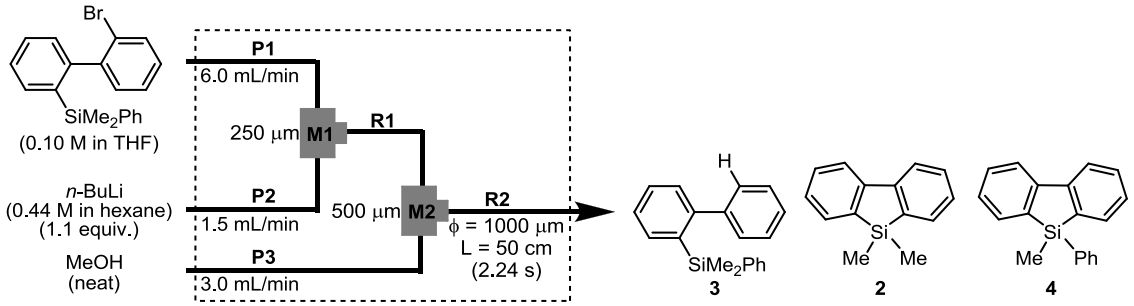
inner diameter of **R1** (μm)	length of **R1** (cm)	residence time (s)	temperature (^oC)	conv. (%)	yield of **1** (%)	yield of **2** (%)
1000	3.5	0.220	20	98	2	93
1000	12.5	0.785		97	1	94
1000	25	1.57		100	1	93
1000	50	3.14		100	1	95
1000	100	6.28		100	1	95
1000	200	12.6		100	1	95
1000	3.5	0.220	0	98	23	74
1000	12.5	0.785		100	1	96
1000	25	1.57		100	1	95
1000	50	3.14		100	1	95
1000	100	6.28		100	1	94
1000	200	12.6		100	2	97
1000	3.5	0.220	-20	95	87	8
1000	12.5	0.785		100	73	26

1000	25	1.57		100	53	46
1000	50	3.14		100	36	61
1000	100	6.28		100	5	91
1000	200	12.6		100	3	96
1000	3.5	0.220	-40	91	89	2
1000	12.5	0.785		99	96	3
1000	25	1.57		100	96	4
1000	50	3.14		100	95	5
1000	100	6.28		100	92	8
1000	200	12.6		100	85	14
1000	3.5	0.220	-60	73	72	1
1000	12.5	0.785		97	96	1
1000	25	1.57		99	98	1
1000	50	3.14		100	98	2
1000	100	6.28		98	97	1
1000	200	12.6		100	98	2
1000	3.5	0.220	-78	22	21	1
1000	12.5	0.785		43	42	1
1000	25	1.57		72	71	1
1000	50	3.14		89	88	1
1000	100	6.28		95	94	1
1000	200	12.6		99	98	1

The reaction with methyl trifluoromethanesulfonate was carried out under the following conditions (temperature: -40 ^{o}C, **R1**: ϕ = 1000 μm, *L* = 12.5 cm (0.79 s)) to obtain 2-methyl-2'-(trimethylsilyl)biphenyl in 94% yield (determined by GC). After extraction, the crude product was purified by using column chromatography (hexane). The spectral data were identical to those reported in the literature.[2]

The reaction with isopropyl pinacol borate was carried out under the following conditions (temperature: -40 ^{o}C, **R1**: ϕ = 1000 μm, *L* = 12.5 cm (0.79 s)) to obtain 4,4,5,5-tetramethyl-2-[2'-(trimethylsilyl)[1,1'-biphenyl]-2-yl]-1,3,2-dioxaborolane in 81% yield (determined by GC). After extraction, the crude product was purified by using column chromatography (Hexane : AcOEt = 20 : 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.06 (s, 9H), 1.05 (d, 12H, *J* = 12.4 Hz), 7.09-7.11 (m, 1H), 7.20-7.41 (m, 5H), 7.52-7.54 (m, 1H), 7.70 (dd, 1H, *J* = 7.2, 1.6 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.4, 24.4, 24.6, 83.2, 125.7, 126.3, 127.3, 129.1, 129.7, 129.8, 133.6, 133.7, 138.2, 149.6, 149.8 ppm; HRMS (ESI) m/z calcd for $C_{21}H_{29}B_1O_2Si_1Na$ ($[M+Na]^+$): 375.1922, found: 375.1923.

Typical Procedure for the Br-Li Exchange Reaction of 2-Bromo-2'-(dimethylphenylsilyl)biphenyl Followed by Reaction with Methanol in Flow Microreactor Systems



A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2**), two microtube reactors (**R1** and **R2**) and three tube pre-cooling units (**P1** (ϕ = 1000 μm, length L = 100 cm), **P2** (ϕ = 1000 μm, L = 50 cm) and **P3** (ϕ = 1000 μm, L = 100 cm)) was used. A solution of 2-bromo-2'-(dimethylphenylsilyl)biphenyl (0.10 M in THF) (flow rate: 6.0 mL min^{-1}) and a solution of *n*-BuLi (0.44 M in *n*-hexane) (flow rate: 1.5 mL min^{-1}) were introduced to **M1** (ϕ = 250 μm) by syringe pumps. The resulting solution was passed through **R1** and was mixed with a solution of methanol (flow rate: 3.0 mL min^{-1}) in **M2** (ϕ = 500 μm). The resulting solution was passed through **R2** (ϕ = 1000 μm, L = 50 cm). After a steady state was reached, the product solution was collected for 30 s and was quenched with saturated *aq*NH_4Cl. The reaction mixture was analyzed by GC. The results are summarized in Table S-2.

Table S-2. The Br-Li exchange reaction of 2-bromo-2'-(dimethylphenylsilyl)biphenyl followed by reaction with methanol in flow microreactor systems

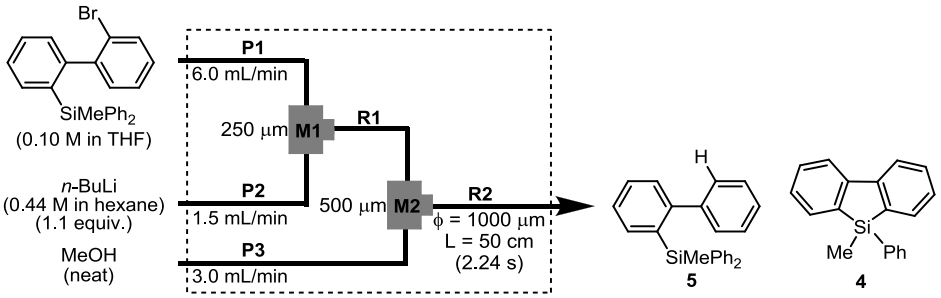
inner diameter of **R1** (μm)	length of **R1** (cm)	residence time (s)	temperature (^oC)	conv. (%)	yield of **3** (%)	yield of **2** (%)	yield of **4** (%)
1000	3.5	0.220	20	98	1	84	13
1000	12.5	0.785		100	1	84	10
1000	25	1.57		100	1	85	9
1000	50	3.14		100	2	84	6
1000	100	6.28		100	2	87	5
1000	200	12.6		100	1	92	5
1000	3.5	0.220	0	100	2	86	9
1000	12.5	0.785		100	1	87	9
1000	25	1.57		99	1	86	8
1000	50	3.14		100	2	86	7
1000	100	6.28		100	2	87	5
1000	200	12.6		100	1	92	5
1000	3.5	0.220	-20	99	71	26	2
1000	12.5	0.785		100	31	65	4
1000	25	1.57		100	9	83	5
1000	50	3.14		100	2	90	5
1000	100	6.28		100	2	90	4
1000	200	12.6		100	2	93	4

1000	3.5	0.220	-40	97	94	3	0
1000	12.5	0.785		100	93	7	0
1000	25	1.57		100	90	10	0
1000	50	3.14		100	83	16	1
1000	100	6.28		100	69	30	1
1000	200	12.6		100	48	51	1
1000	3.5	0.220	-60	81	79	2	0
1000	12.5	0.785		96	94	2	0
1000	25	1.57		99	97	2	0
1000	50	3.14		100	97	3	0
1000	100	6.28		100	96	4	0
1000	200	12.6		99	95	4	0
1000	3.5	0.220	-78	2	2	0	0
1000	12.5	0.785		35	35	0	0
1000	25	1.57		63	63	0	0
1000	50	3.14		85	85	0	0
1000	100	6.28		92	91	1	0
1000	200	12.6		97	95	2	0

2-(Dimethylphenylsilyl)biphenyl (3): The crude product was purified by flash chromatography (hexane) to obtain 2-(dimethylphenylsilyl)biphenyl. The analytical data were identical to those reported in the literature.[3]

9-Methyl-9-phenyl-9-silafluorene (4): The crude product was purified by using flash chromatography (hexane) to obtain 9-methyl-9-phenyl-9-silafluorene. The spectral data were identical to those reported in the literature.[1]

Typical Procedure for the Br-Li Exchange Reaction of 2-Bromo-2'-(methyldiphenylsilyl)biphenyl Followed by Reaction with Methanol in Flow Microreactor Systems



A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2**), two microtube reactors (**R1** and **R2**) and three tube pre-cooling units (**P1** (ϕ = 1000 μm, length L = 100 cm), **P2** (ϕ = 1000 μm, L = 50 cm) and **P3** (ϕ = 1000 μm, L = 100 cm)) was used. A solution of 2-bromo-2'-(methyldiphenylsilyl)biphenyl (0.10 M in THF) (flow rate: 6.0 mL min^{-1}) and a solution of *n*-BuLi (0.44 M in *n*-hexane) (flow rate: 1.5 mL min^{-1}) were introduced to **M1** (ϕ = 250 μm) by syringe pumps. The resulting

solution was passed through **R1** and was mixed with a solution of methanol (flow rate: 3.0 mL min^{-1}) in **M2** (ϕ = 500 μm). The resulting solution was passed through **R2** (ϕ = 1000 μm, L = 50 cm). After a steady state was reached, the product solution was collected for 30 s and was quenched with saturated *aq*NH_4Cl. The reaction mixture was analyzed by GC. The results are summarized in Table S-3.

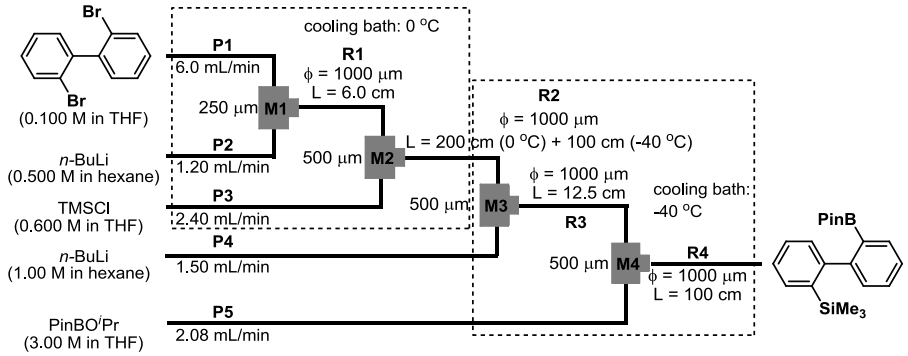
Table S-3. The Br-Li exchange reaction of 2-bromo-2'-(methyldiphenylsilyl)biphenyl followed by reaction with methanol in flow microreactor systems

inner diameter of **R1** (μm)	length of **R1** (cm)	residence time (s)	temperature (^oC)	conv. (%)	yield of **5** (%)	yield of **4** (%)
1000	3.5	0.220	20	100	17	83
1000	12.5	0.785		99	3	96
1000	25	1.57		100	2	90
1000	50	3.14		99	3	96
1000	100	6.28		100	2	90
1000	200	12.6		100	2	87
1000	3.5	0.220	0	100	85	15
1000	12.5	0.785		99	62	37
1000	25	1.57		100	34	63
1000	50	3.14		99	18	81
1000	100	6.28		100	6	88
1000	200	12.6		100	4	87
1000	3.5	0.220	-20	100	98	2
1000	12.5	0.785		100	98	2
1000	25	1.57		99	95	4
1000	50	3.14		100	94	6
1000	100	6.28		100	91	9
1000	200	12.6		100	85	15
1000	3.5	0.220	-40	97	96	1
1000	12.5	0.785		100	100	0
1000	25	1.57		100	100	0
1000	50	3.14		100	99	1
1000	100	6.28		100	100	0
1000	200	12.6		100	99	1
1000	3.5	0.220	-60	57	57	0
1000	12.5	0.785		74	74	0
1000	25	1.57		90	90	0
1000	50	3.14		97	97	0
1000	100	6.28		98	98	0
1000	200	12.6		100	100	0
1000	3.5	0.220	-78	9	9	0
1000	12.5	0.785		14	14	0

1000	25	1.57	38	38	0
1000	50	3.14	70	70	0
1000	100	6.28	84	84	0
1000	200	12.6	97	97	0

2-(Diphenylmethylsilyl)biphenyl (5): The crude product was purified by flash chromatography (hexane only) to obtain 2-(diphenylmethylsilyl)biphenyl. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 3H), 7.04-7.07 (m, 2H), 7.13-7.18 (m, 2H), 7.22-7.47 (m, 15H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ -3.4, 126.1, 127.0, 127.6, 127.7, 129.0, 129.2, 129.4, 129.8, 134.6, 135.1, 137.6, 137.8, 143.8, 150.0 ppm; HRMS (DART) m/z calcd for $C_{25}H_{21}Si_1$ (M^+-H) : 349.1407, found: 349.1413.

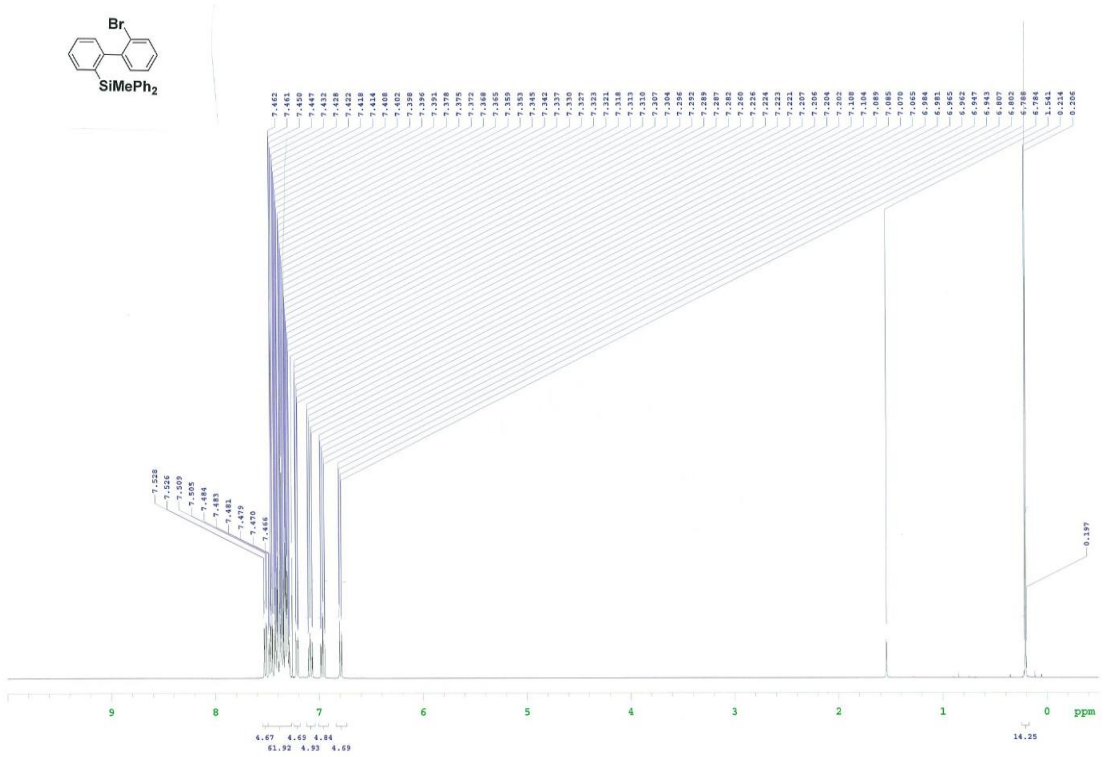
An integrated flow microreactor system for two sets of Br-Li exchange reaction starting from 2,2'-dibromobiphenyl



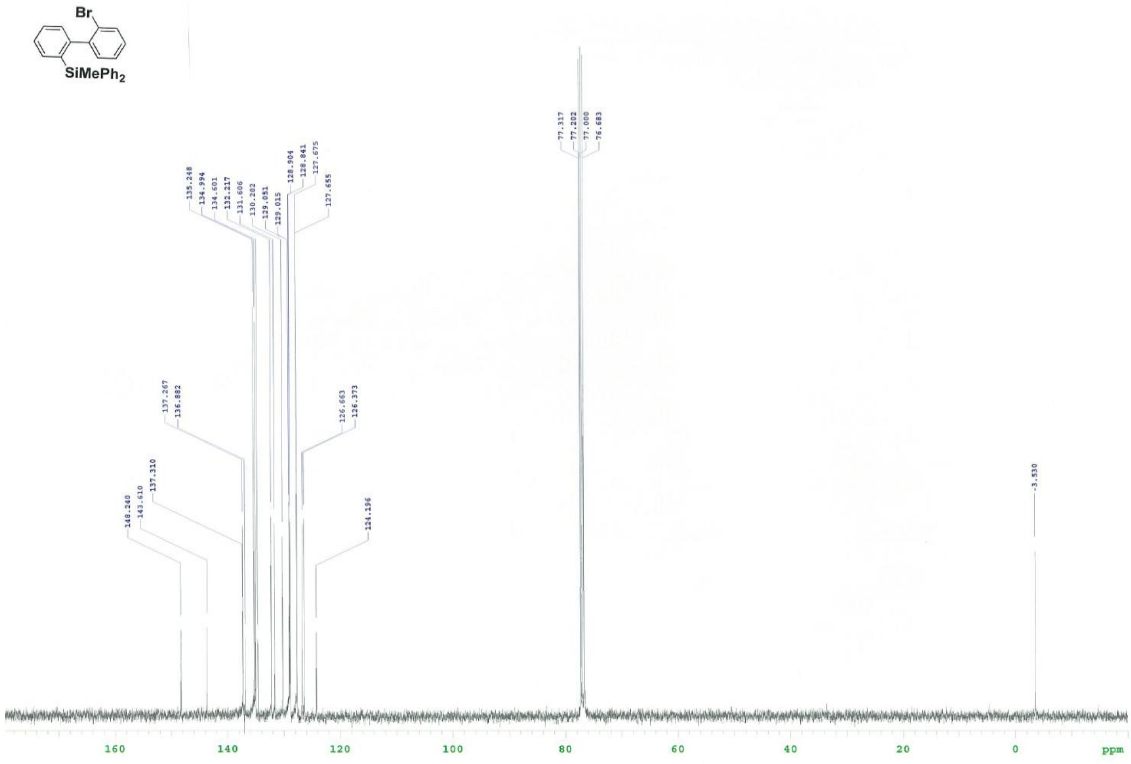
An integrated flow microreactor system consisting of four T-shaped micromixers (**M1**, **M2**, **M3,** and **M4**), four microtube reactors (**R1**, **R2**, **R3,** and **R4**) and five pre-cooling units (**P1**, **P2**, **P3**, **P4,** and **P5** (inner diameter ϕ = 1000 μm, length L = 100 cm)) was used. A solution of 2,2'-dibromobiphenyl (0.100 M in THF) (flow rate: 6.00 mL min^{-1}) and a solution of *n*-BuLi (0.500 M in *n*-hexane) (flow rate: 1.20 mL min^{-1}) were introduced to **M1** (ϕ = 250 μm) by syringe pumps. The resulting solution was passed through **R1** (ϕ = 1000 μm, L = 6.0 cm (0.39 s)) and was mixed with a solution of TMSCl (0.600 M in THF) (flow rate: 2.40 mL min^{-1}) in **M2** (ϕ = 500 μm). The resulting solution was passed through **R2** (ϕ = 1000 μm, L = 300 cm (200 cm (0 °C) + 100 cm (-40 °C) (15 s)) and was mixed with a solution of *n*-BuLi (1.00 M in *n*-hexane) (flow rate: 1.50 mL min^{-1}) in **M3** (ϕ = 500 μm). The resulting solution was passed through **R3** (ϕ = 1000 μm, *L* = 12.5 cm (0.53 s)) and was mixed with a solution of isopropyl pinacol borate (3.00 M) (flow rate: 2.08 mL min^{-1}) in **M4** (ϕ = 500 μm). The resulting solution was passed through **R4** (ϕ = 1000 μm, L = 100 cm (3.6 s)). After a steady state was reached, the product solution was collected for 30 s and was quenched with saturated *aq*NH_4Cl. The reaction mixture was analyzed by GC, which indicated the formation of 4,4,5,5-tetramethyl-2-[2'-(trimethylsilyl)[1,1'-biphenyl]-2-yl]-1,3,2 -dioxaborolane in 71% yield. After purification with column chromatography (Hexane : AcOEt = 20 : 1), the spectral data of the desired product were identical.

References

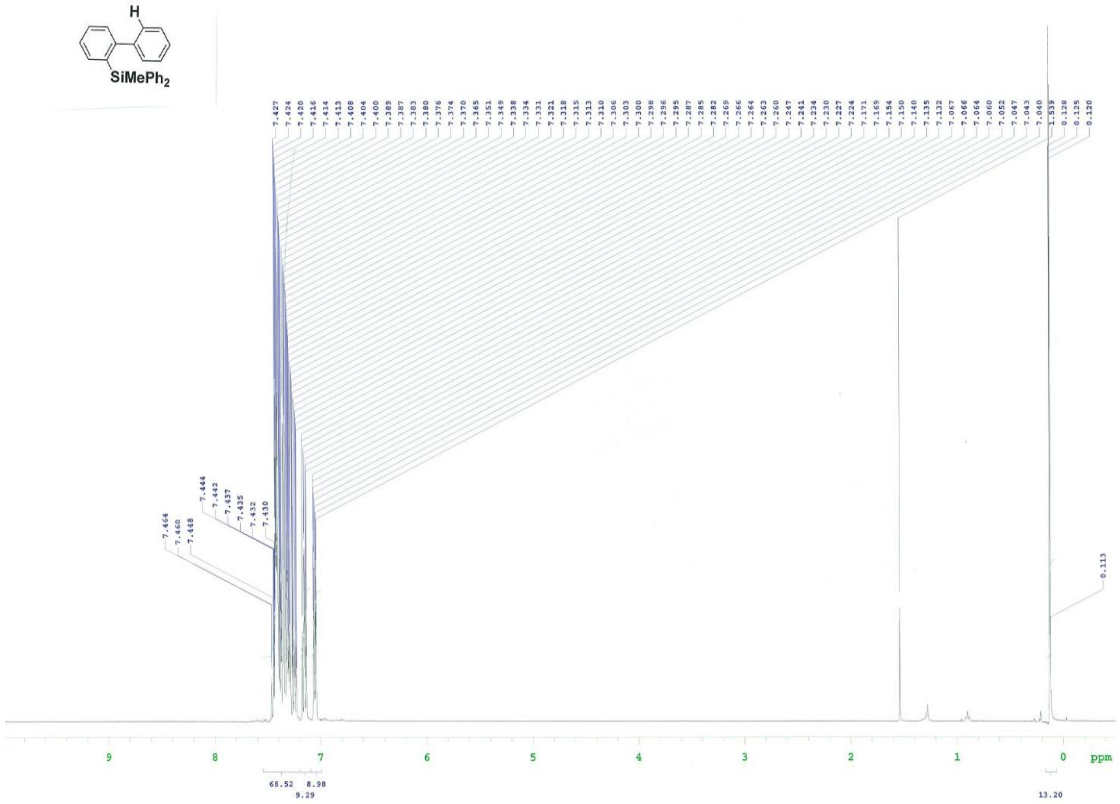
1) Liang, Y.; Zhang, S.; Xi, Z. *J. Am. Chem. Soc.* **2011**, 133 (24), 9204.
2) Nagaki, A.; Takabayashi, N.; Tomida, Y.; Yoshida, J. *Beilstein J. Org. Chem.* **2009**, *5*, 16.
3) Matsuda, T.; Kirikae, H. *Organometallics*, **2011**, 30 (15), 3923.



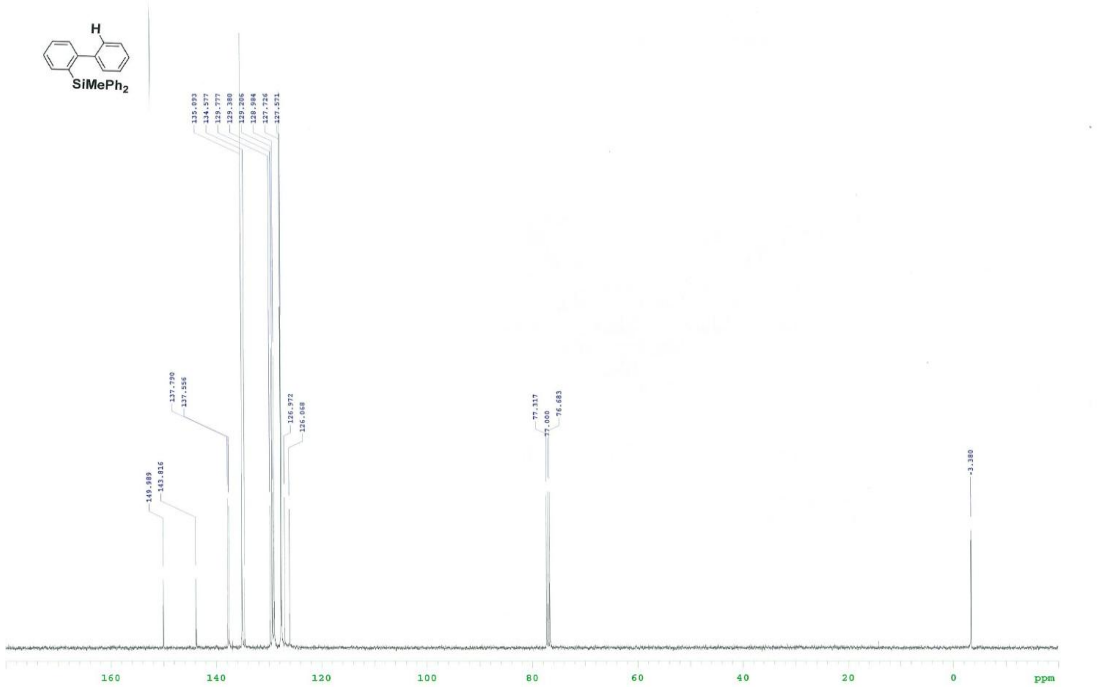
^{1}H NMR spectrum of 2-bromo-2'-(diphenylmethylsilyl)biphenyl



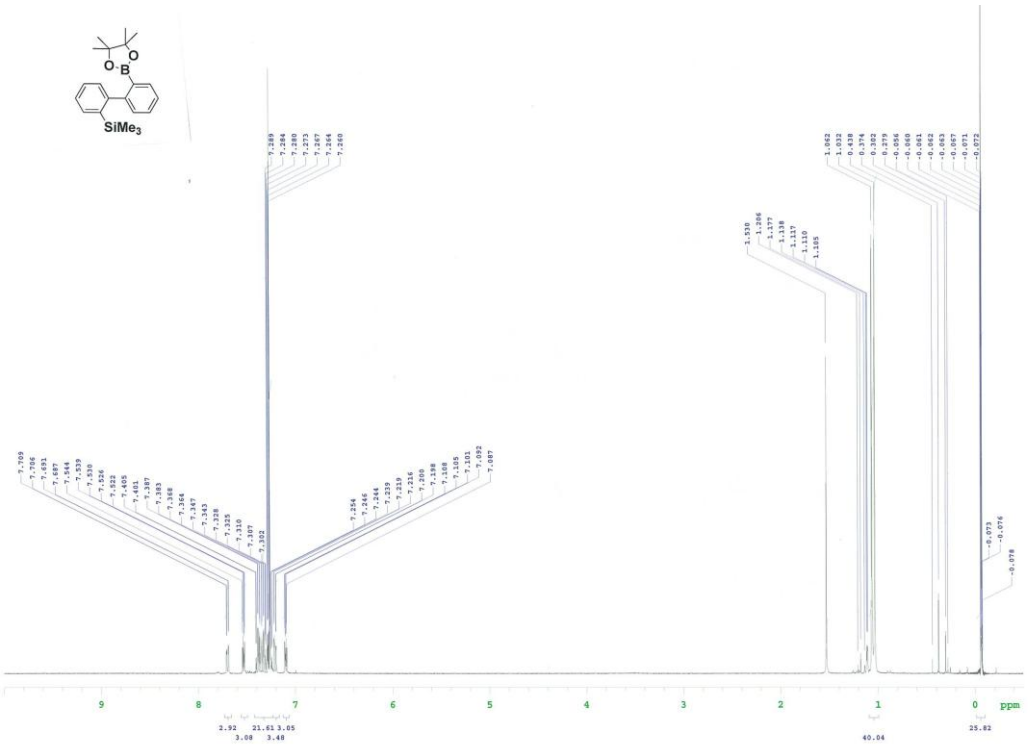
^{13}C NMR spectrum of 2-bromo-2'-(diphenylmethylsilyl)biphenyl



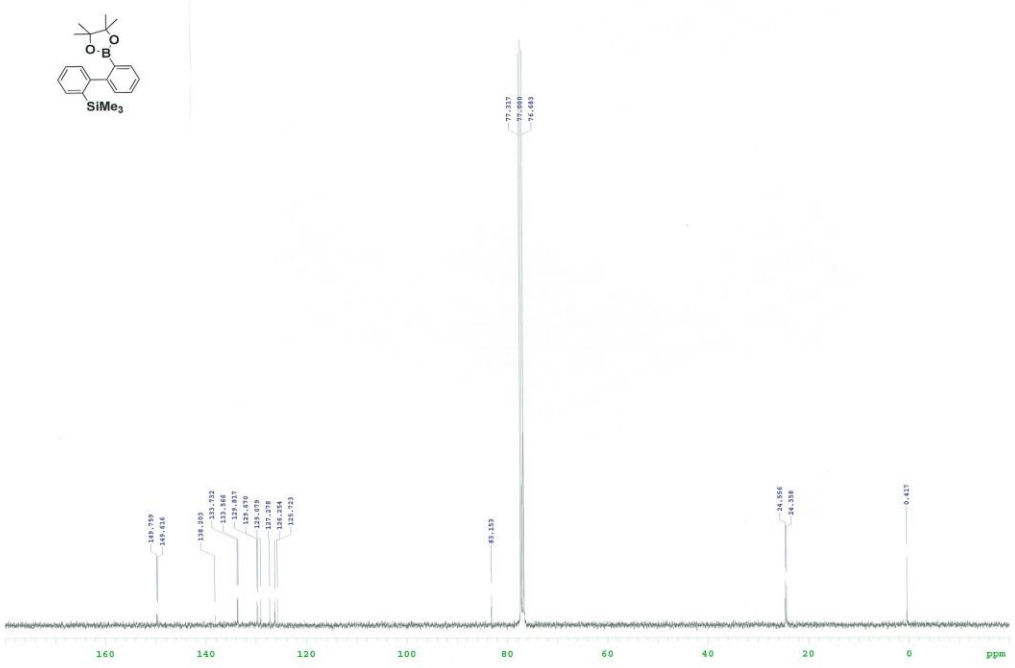
^{1}H NMR spectrum of 2-(Diphenylmethylsilyl)biphenyl (5)



^{13}C NMR spectrum of 2-(Diphenylmethylsilyl)biphenyl (5)



^{1}H NMR spectrum of
4,4,5,5-tetramethyl-2-[2'-(trimethylsilyl)[1,1'-biphenyl]-2-yl]-1,3,2-dioxaborolane



^{13}C NMR spectrum of
4,4,5,5-tetramethyl-2-[2'-(trimethylsilyl)[1,1'-biphenyl]-2-yl]-1,3,2-dioxaborolane