Supplementary Material (ESI) for Organic and Biomolecular Chemistry

Generation and Reaction of Cyano-Substituted Aryllithium Compounds Using Microreactors

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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). ¹H and ¹³C NMR spectra were recorded on Varian MERCURY plus-400 (¹H 400 MHz, ¹³C 100 MHz) spectrometer with Me₄Si or CDCl₃ as a standard in CDCl₃ unless otherwise noted. EI mass spectra were recorded on JMS-SX102A spectrometer. Gel permeation chromatography (GPC) was carried out on Japan Analytical Industry LC-908. THF was 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. *o*-Bromobenzonitrile (**1a**), *m*-bromobenzonitrile (**1b**), *p*bromobenzonitrile (**1c**), *n*-BuLi, methanol, chlorotrimethylsilane, chlorotributylstannane, iodomethane, benzaldehyde, *n*-heptanal, benzophenone, acetyl chloride, dimethyl sulfate, HMPA were commercially available and used without further purification. Stainless steel (SUS304) T-shaped micromixers having inner diameter of 250 µm or 500 µm were manufactured by Sanko Seiki Co., Inc. Stainless steel (SUS316) microtube reactors having inner diameter of 250, 500 and 1000 µm were purchased from GL Sciences, 1/16 OUW). The microflow system was dipped in a cooling bath to control the temperature. Solutions were introduced to a microflow system using syringe pumps, Harvard Model 11, equipped with gastight syringes purchased from SGE.

Typical Procedure for the Br-Li Exchange Reaction of Bromobenzonitriles Followed by Reaction with Methanol in a Macrobatch System



A solution of *n*-BuLi (0.42 M, 0.75 mL) in hexane was added dropwise to a solution of bromobenzonitriles (0.10M, 3.0 mL) in THF in a 10 mL round bottom glass flask at regular pace with magnetic stirring for 1.0 min at T $^{\circ}$ C. The mixture was stirred for 10 min, and a solution of methanol (0.60 M, 1.5 mL) in THF was added. After stirring for 10 min, a cooling bath was removed. The mixture was analyzed by GC (Table S-1).

Table S-1. The Br-Li exchange	reaction o	of bromo	benzonitriles	followed	by	reaction	with
methanol in a macrobatch system					•		

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bromobenzonitrile	$T(^{\circ}C)$	conv. (%)	yield (%)
0-	-78	97	86
<i>m</i> -		90	68
р-		90	61
0-	0	100	3
<i>m</i> -		99	8
р-		94	6

Typical Procedure for the Br-Li Exchange Reaction of Bromobenzonitriles Followed by Reaction with Methanol in Microflow Systems



A microflow system consisting of two T-shaped micromixers (**M1** and **M2**), two microtube reactors (**R1** and **R2**) and three tube pre-cooling units (**P1** (inner diameter $\phi = 1000 \mu$ m, length L = 100 cm), **P2** ($\phi = 1000 \mu$ m, L = 50 cm) and **P3** ($\phi = 1000 \mu$ m, L = 100 cm)) was used. A solution of bromobenzonitrile (0.10 M) in THF (flow rate: 6.0 mL min⁻¹) and a solution of *n*-BuLi (0.42 M) in hexane (flow rate: 1.5 mL min⁻¹) were introduced to **M1** ($\phi = 250 \mu$ m) by syringe pumps. The resulting solution was passed through **R1** and was mixed with a solution of methanol (0.60 M) in THF (flow rate: 3.0 mL min⁻¹) in **M2** ($\phi = 500 \mu$ m). The resulting solution was collected for 30 s while being quenched with H₂O. The reaction mixture was analyzed by GC. The results are summarized in Table S-2, S-3, and S-4.

Table S-2. The Br-Li exchange reaction of *o*-bromobenzonitrile followed by reaction with methanol in microflow systems

inner diameter	length	residence time	temperature	conv.	yield
of R1 (µm)	of R1 (cm)	(s)	$(^{\circ}C)$	(%)	(%)
250	3.5	0.014	20	100	90
500	3.5	0.055		100	82
1000	3.5	0.22		100	83
1000	6	0.38		100	82
1000	12.5	0.76		100	80
1000	100	6.3		100	71
250	3.5	0.014	0	100	91
500	3.5	0.055		100	87
1000	3.5	0.22		100	86
1000	6	0.38		100	87
1000	12.5	0.76		100	87
1000	100	6.3		100	83
250	3.5	0.014	-28	100	89
500	3.5	0.055		100	88
1000	3.5	0.22		100	85
1000	6	0.38		100	84
1000	12.5	0.76		100	86
1000	100	6.3		100	84
250	3.5	0.014	-48	26	25
500	3.5	0.055		74	72
1000	3.5	0.22		94	93
1000	6	0.38		100	86
1000	12.5	0.76		100	92
1000	100	6.3		100	85
250	3.5	0.014	-58	13	13
500	3.5	0.055		43	40
1000	3.5	0.22		60	56
1000	6	0.38		100	89
1000	12.5	0.76		100	87
1000	100	6.3		100	87
250	3.5	0.014	-78	6	6
500	3.5	0.055		12	12
1000	3.5	0.22		49	40
1000	6	0.38		56	48
1000	12.5	0.76		74	62
1000	100	6.3		100	81

Table S-3. The Br-Li exchange reaction of *m*-bromobenzonitrile followed by reaction with methanol in microflow systems

inner diameter	length	residence time	temperature	conv.	yield
of R1 (µm)	of R1 (cm)	(S)	(°C)	(%)	(%)
250	3.5	0.014	20	100	80
500	3.5	0.055		100	75
1000	3.5	0.22		100	76
1000	6	0.38		100	74
1000	12.5	0.76		100	73
1000	100	6.3		100	44
250	3.5	0.014	0	100	80

500	3.5	0.055		100	80
1000	3.5	0.22		100	83
1000	6	0.38		100	84
1000	12.5	0.76		100	83
1000	100	6.3		100	52
250	3.5	0.014	-28	100	83
500	3.5	0.055		100	85
1000	3.5	0.22		100	84
1000	6	0.38		100	85
1000	12.5	0.76		100	83
1000	100	6.3		100	81
250	3.5	0.014	-48	47	28
500	3.5	0.055		93	73
1000	3.5	0.22		100	80
1000	6	0.38		100	82
1000	12.5	0.76		100	82
1000	100	6.3		100	83
250	3.5	0.014	-58	17	8
500	3.5	0.055		67	41
1000	3.5	0.22		98	82
1000	6	0.38		100	84
1000	12.5	0.76		100	86
1000	100	6.3		100	88
250	3.5	0.014	-78	7	3
500	3.5	0.055		26	19
1000	3.5	0.22		44	36
1000	6	0.38		51	42
1000	12.5	0.76		76	67
1000	100	6.3		100	84

Table S-4. The Br-Li exchange reaction of *p*-bromobenzonitrile followed by reaction with methanol in microflow systems

inner diameter	length	residence time	temperature	conv.	yield
of R1 (µm)	of R1 (cm)	(s)	$(^{\circ}C)$	(%)	(%)
250	3.5	0.014	20	100	82
500	3.5	0.055		100	78
1000	3.5	0.22		100	78
1000	6	0.38		100	72
1000	12.5	0.76		100	77
1000	100	6.3		100	41
250	3.5	0.014	0	100	88
500	3.5	0.055		100	82
1000	3.5	0.22		100	85
1000	6	0.38		100	82
1000	12.5	0.76		100	84
1000	100	6.3		100	48
250	3.5	0.014	-28	100	87
500	3.5	0.055		100	89
1000	3.5	0.22		100	87
1000	6	0.38		100	88
1000	12.5	0.76		100	88
1000	100	6.3		100	85
250	3.5	0.014	-48	50	33
500	3.5	0.055		84	63
1000	3.5	0.22		100	85
1000	6	0.38		100	86
1000	12.5	0.76		100	89
1000	100	6.3		100	86
250	3.5	0.014	-58	34	17
500	3.5	0.055		54	37
1000	3.5	0.22		68	51
1000	6	0.38		95	79
1000	12.5	0.76		100	87

1000	100	6.3		100	91
250	3.5	0.014	-78	7	2
500	3.5	0.055		38	27
1000	3.5	0.22		45	30
1000	6	0.38		50	41
1000	12.5	0.76		73	61
1000	100	6.3		100	92

Typical Procedure for	the Br-Li Exchange	Reaction of	Bromobenzonitriles	Followed by
Reaction with Electro	philes in Microflow Sy	ystems		·



A microflow system consisting of two T-shaped micromixers (**M1** and **M2**), two microtube reactors (**R1** and **R2**) and three tube pre-cooling units (**P1** (inner diameter $\phi = 1000$ µm, length L = 100 cm), **P2** ($\phi = 1000$ µm, L = 50 cm) and **P3** ($\phi = 1000$ µm, L = 100 cm)) was used. A solution of bromobenzonitriles (0.10 M) in THF (flow rate: 6.0 mL min⁻¹) and a solution of *n*-BuLi (0.42 M) in hexane (flow rate: 1.5 mL min⁻¹) were introduced to **M1** ($\phi = 250$ µm). The resulting solution was passed through **R1** ($\phi = 250$ µm, L = 3.5 cm) and was mixed with a solution of electrophile (0.60 M) in THF (flow rate: 3.0 mL min⁻¹) in **M2** ($\phi = 500$ µm). The resulting solution was passed through **R2** ($\phi = 1000$ µm, L = 50 cm). After a steady state was reached, the product solution was collected for 30 s while being quenched with H₂O (or 1 M HCl aqueous solution when carbonyl compound was used as an electrophile). The reaction mixture was analyzed by GC. The reactions of *o*bromobenzonitrile (**1a**) were carried out at 20 °C. The reactions of *m*-bromobenzonitrile (**1b**) and *p*-bromobenzonitrile (**1c**) were carried out at 0 °C.

2-Trimethylsilylbenzonitrile: The product was obtained in 90% yield (GC ${}^{t}R$ 15.8 min) when *o*-bromobenzonitrile and chlorotrimethylsilane were used for the reaction. The spectral data were identical to those reported in the literature.¹

2-Tributylstannylbenzonitrile: The product was obtained in 85% yield (GC ^{*t*}R 26.7 min) when *o*-bromobenzonitrile and chlorotributylstannane were used for the reaction. The spectral data were identical to those reported in the literature.²

2-Methylbenzonitrile: The product was obtained in 93% yield (GC ${}^{t}R$ 11.8 min) when *o*-bromobenzonitrile and methyl iodide were used for the reaction. The spectral data were identical to those of commercially available compound.

3-Phenylphthalide: The product was obtained in 98% yield (GC ${}^{t}R$ 24.2 min) when *o*-bromobenzonitrile and benzaldehyde were used for the reaction. The spectral data were identical to those reported in the literature.³

3-Hexylphthalide: The product was obtained when *o*-bromobenzonitrile and *n*-heptanal were used for the reaction. After extraction, the crude product was purified by silica gel chromatography (hexane/AcOEt=5/1) to afford 52.9 mg of 3-hexylphthalide (81% yield). The spectral data were identical to those reported in the literature.³

3,3-Diphenyl-1(3*H***)-isobenzofuranone:** The product was obtained when *o*-bromobenzonitrile and benzophenone were used for the reaction. After extraction, the crude product was purified by silica gel chromatography (hexane/AcOEt=3/1) to afford 81.3 mg of 3,3diphenyl-1(3*H*)-isobenzofuranone (94% yield). The spectral data were identical to those reported in the literature.⁴

3-Trimethylsilylbenzonitrile: The product was obtained in 96% yield (GC ${}^{t}R$ 16.3 min)

when *m*-bromobenzonitrile and chlorotrimethylsilane were used for the reaction. After extraction, the crude product was purified by silica gel chromatography (hexane/AcOEt=50/1): ¹H NMR (400 MHz, CDCl₃) δ 0.28 (s, 9H), 7.41-7.46 (m, 1H), 7.59-7.64 (m, 1H), 7.69-7.74 (m, 1H), 7.75-7.79 ppm (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ –1.8, 111.7, 118.8, 128.0, 131.8, 136.5, 137.1, 142.1 ppm; HRMS (EI) *m/z* calcd for C₁₀H₁₃NSi: 175.0817, found: 175.0817.

3-Tributylstannylbenzonitrile: The product was obtained in 95% yield (GC ^{*t*}R 27.8 min) when *m*-bromobenzonitrile and chlorotributylstannane were used for the reaction. After extraction, the crude product was purified by silica gel chromatography (hexane/AcOEt=20/1): ¹H NMR (400 MHz, CDCl₃) δ 0.88 (t, *J* = 7.4 Hz, 9H), 0.98-1.18 (m, 6H), 1.32 (sext, *J* = 7.3 Hz, 6H), 1.40-1.62 (m, 6H), 7.34-7.42 (m, 1H), 7.53-7.78 ppm (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 9.5, 13.4, 27.1, 28.8, 112.0, 119.1, 127.9, 131.2, 139.4, 140.3, 143.9 ppm; HRMS (EI) *m/z* calcd for C₁₉H₃₁NSn: 393.1478, found: 393.1479.

3-Methylbenzonitrile: The product was obtained in 81% yield (GC ${}^{t}R$ 12.2 min) when *m*-bromobenzonitrile and methyl iodide were used for the reaction. The spectral data were identical to those of commercially available compound.

3-(Hydroxyphenylmethyl)-benzonitrile: The product was obtained in 81% yield (GC ${}^{t}R$ 24.6 min) when *m*-bromobenzonitrile and benzaldehyde were used for the reaction. The spectral data were identical to those reported in the literature.⁵

4-Trimethylsilylbenzonitrile: The product was obtained in 85% yield (GC ${}^{t}R$ 16.4 min) when *p*-bromobenzonitrile and chlorotrimethylsilane were used for the reaction. The spectral data were identical to those reported in the literature.⁶

4-TributyIstannylbenzonitrile: The product was obtained in 93% yield (GC ${}^{t}R$ 28.3 min) when *p*-bromobenzonitrile and chlorotributyIstannane were used for the reaction. The spectral data were identical to those reported in the literature.⁷

4-Methylbenzonitrile: The product was obtained in 90% yield (GC ${}^{t}R$ 12.5 min) when *p*-bromobenzonitrile and methyl iodide were used for the reaction. The spectral data were identical to those of commercially available compound.

4-(Hydroxyphenylmethyl)-benzonitrile: The product was obtained in 93% yield (GC ${}^{t}R$ 24.7 min) when *p*-bromobenzonitrile and benzaldehyde were used for the reaction. The spectral data were identical to those reported in the literature.⁸

Reaction of *o***-Lithiobenzonitrile with Carbonyl Compounds Followed by Sequential Reaction with Electrophiles**



A microflow system consisting of three T-shaped micromixers (**M1**, **M2**, and **M3**), three microtube reactors (**R1**, **R2**, and **R3**) and four tube pre-cooling units (**P1**, **P3**, (inner diameter $\phi = 1000 \,\mu\text{m}$, length L = 100 cm), **P2**, **P4** ($\phi = 1000 \,\mu\text{m}$, L = 50 cm)) was used. A solution of *o*-bromobenzonitrile (0.10 M) in THF (flow rate: 6.0 mL min⁻¹) and a solution of *n*-BuLi (0.42 M) in hexane (flow rate: 1.5 mL min⁻¹) were introduced to **M1** ($\phi = 250 \,\mu\text{m}$). The resulting solution was passed through **R1** ($\phi = 250 \,\mu\text{m}$, L = 3.5 cm) and was mixed with a solution of carbonyl compound (0.22 M) in THF (flow rate: 3.0 mL min⁻¹) in **M2** ($\phi = 500 \,\mu\text{m}$). The resulting solution was passed through **R2** ($\phi = 1000 \,\mu\text{m}$, L = 50 cm) and was mixed with a solution of electrophile (0.90 M) in THF (flow rate: 2.0 mL min⁻¹) in **M3** ($\phi =$

500 μ m). The resulting solution was passed through **R3**. After a steady state was reached, the product solution was collected for 30's while being quenched with H₂O. The microtube reactor **R3** ($\phi = 1000 \ \mu m$, L = 50 cm) was used for the reaction with acetyl

chloride or methyl chlorocarbonate as an electrophile. For the reaction with dimethyl sulfate (with 3 eq of HMPA), longer microtube reactor **R3** ($\phi = 1000 \ \mu m$, L = 2560 cm (50 cm at 0 °C, 10 cm at ambient temperature, and 2500 cm at 50 °C)) was used in order to complete the reaction.

(2-Cyanophenyl)(phenyl)methyl acetate: After extraction, the crude product was purified by silica gel chromatography (hexane/AcOEt=5/1) to afford 62.6 mg of 2-cyanophenyl)(phenyl)methyl acetate (83% yield): ¹H NMR (400 MHz, CDCl₃) δ 3.19 (s, 3H), 7.10 (s, 1H), 7.29-7.43 (m, 6H), 7.55-7.68 ppm (m, 3H); ¹³C NMR (100MHz, CDCl₃) δ 20.9, 74.8, 111.2, 117.2, 127.1, 127.2, 128.2, 128.5, 128.7, 133.0, 133.3, 138.1, 143.8, 169.5 ppm; HRMS (EI) *m/z* calcd for C₁₆H₁₃NO₂: 251.0946, found: 251.0945.

2-(Methoxy(phenyl)methyl)benzonitrile: After extraction, the crude product was purified by silica gel chromatography (hexane/AcOEt=10/1) to afford 62.7 mg of 2-(methoxy(phenyl)methyl)benzonitrile (93% yield): ¹H NMR (400 MHz, CDCl₃) δ 3.43 (s, 3H), 5.64 (s, 1H), 7.26-7.39 (m 4H), 7.42-7.46 (m, 2H), 7.55-7.65 ppm (m, 3H); ¹³C NMR (100MHz, CDCl₃) δ 57.3, 82.6, 111.3, 117.7, 126.9, 127.0, 127.9, 128.1, 128.6, 132.8, 133.1, 120.8, 1460 promy HDMS (FD) w/c prefer bed for C H. NO: 2020 0007 form th 2222 1002 139.8, 146.0 ppm; HRMS (EI) m/z calcd for $C_{15}H_{13}NO$: 223.0997, found: 223.1002.

1-(2-Cyanophenyl)heptyl ethyl carbonate: After extraction, the crude product was purified by silica gel chromatography (hexane/AcOEt=5/1) to afford 62.1 mg of 1-(2-cyanophenyl)heptyl ethyl carbonate (75% yield): ¹H NMR (400 MHz, CDCl₃) δ 0.87 (t, J = 6.8 Hz, 3H), 1.20-1.38 (m, 7H), 1.38-1.50 (m, 1H), 1.79-1.90 (m, 1H), 1.93-2.05 (m 1H), 3.76 (s, 3H), 5.84-5.90 (m, 1H), 7.40 (td, J = 7.8, 1.2 Hz, 1H), 7.50-7.55 (m, 1H), 7.57-7.63 (m, 1H), 7.63-7.67 ppm (m, 1H); ¹³C NMR (100MHz, CDCl₃) δ 13.9, 22.4, 25.1, 28.7, 31.5, 36.1, 54.9, 77.6, 110.9, 117.0, 126.3, 128.3, 132.8, 133.1, 144.3, 154.9 ppm; HRMS (EI) m/z calcd for C₁₆H₂₁NO₃: 275.1521, found: 275.1524.

2-(1-Methoxyheptyl)benzonitrile: After extraction, the crude product was purified by silica gel chromatography (hexane/AcOEt=10/1) to afford 35.4 mg of 2-(1-methoxyheptyl)benzonitrile (51% yield): ¹H NMR (400 MHz, CDCl₃) δ 0.86 (t, *J* = 6.8 Hz, 3H), 1.20-1.38 (m, 7H), 1.38-1.50 (m, 1H), 1.62-1.73 (m, 1H), 1.73-1.85 (m, 1H), 4.52-4.58 (m, 1H), 7.37 (td, *J* = 7.5, 1.6 Hz, 1H), 7.52-7.58 (m 1H), 7.58-7.68 ppm (m, 2H); ¹³C NMR (100MHz, CDCl₃) δ 14.0, 22.5, 25.5, 29.0, 31.7, 37.8, 57.1, 81.4, 111.4, 117.4, 126.6, 127.8, 132.7, 133.1, 146.9 ppm; HRMS (FAB) *m/z* calcd for C₁₅H₂₂NO: 232.1701, found: 232.1697.

2-(Methoxydiphenylmethyl)benzonitrile: After extraction, the crude product was purified by silica gel chromatography (hexane/AcOEt=10/1) to afford 59.6 mg of 2-(methoxydiphenylmethyl)benzonitrile (66% yield): ¹H NMR (400 MHz, CDCl₃) δ 3.10 (s, 3H), 7.28-7.39 (m 7H), 7.45-7.51 (m, 5H), 7.63-7.67 ppm (m, 2H); ¹³C NMR (100MHz, CDCl₃) δ 52.2, 87.0, 111.7, 118.8, 127.2, 127.7, 128.0, 129.1, 129.3, 131.8, 135.5, 141.1, 148.9 ppm; HRMS (ÉI) m/z calcd for C₂₁H₁₇NO: 299.1310, found: 299.1313.

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¹H NMR spectrum of 3-trimethylsilylbenzonitrile



¹³C NMR spectrum of 3-trimethylsilylbenzonitrile



¹H NMR spectrum of 3-tributylstannylbenzonitrile



¹³C NMR spectrum of 3-tributylstannylbenzonitrile



¹H NMR spectrum of (2-cyanophenyl)(phenyl)methyl acetate



¹³C NMR spectrum of (2-cyanophenyl)(phenyl)methyl acetate



¹H NMR spectrum of 2-(methoxy(phenyl)methyl)benzonitrile



¹³C NMR spectrum of 2-(methoxy(phenyl)methyl)benzonitrile



¹H NMR spectrum of 1-(2-cyanophenyl)heptyl ethyl carbonate



¹³C NMR spectrum of 1-(2-cyanophenyl)heptyl ethyl carbonate



¹H NMR spectrum of 2-(1-methoxyheptyl)benzonitrile



¹³C NMR spectrum of 2-(1-methoxyheptyl)benzonitrile



¹H NMR spectrum of 2-(methoxydiphenylmethyl)benzonitrile



¹³C NMR spectrum of 2-(methoxydiphenylmethyl)benzonitrile