Generation and reaction of cyano-substituted aryllithium compounds using microreactors†‡

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We developed a microflow method for the generation and reactions of aryllithiums bearing a cyano group, including *o*-lithiobenzonitrile, *m*-lithiobenzonitrile and *p*-lithiobenzonitrile. The method was effective at much higher temperatures than are required for conventional macrobatch reactions, by virtue of rapid mixing, short residence time, and efficient temperature control. In addition, reactions of *o*-lithiobenzonitrile with carbonyl compounds followed by trapping of the resulting lithium alkoxides with electrophiles were achieved in an integrated microflow system.

Introduction

Chemical conversions involving functionalized organometallic compounds such as organolithium, organomagnesium, organozinc and organocopper compounds are important procedures in organic synthesis.[1] These types of transformations are among the most straightforward methods for the synthesis of complicated organic molecules.[2] Especially, organometallic compounds bearing a cyano group are very important because of the activating effect of the cyano group such as the *ortho*-directing effect and its transformation into various other functional groups are advantageous from a synthetic point of view.[3] To generate functionalized organometallic compounds such as arylmetallics, halogen–metal exchange reactions involving halogen–Mg,[4] halogen–Cu[5] and halogen–Zn[6] have been extensively investigated, as they allow conventional access to functionalized organometallics; such reactions are often essential in the use of aryl iodides. Because of the high reactivity of halogen–Li exchange reactions, their application in the generation of functionalized aryllithiums enables the use of aryl bromide. However, the carbon attached to the Li center behaves as a nucleophile that reacts strongly with cyano, nitro, alkoxycarbonyl and other electrophilic functional groups.[7–9] To overcome this problem the reactions are often conducted at very low temperatures, but even under these conditions it is difficult to prepare organolithium compounds having highly reactive functional groups.

We recently demonstrated that microflow systems[10,11] are effective in controlling extremely rapid reactions involving highly unstable intermediates,[12] such as organolithium compounds,[13] and report here that features of these systems are highly applicable to the generation and reaction of unstable aryllithium compounds bearing a cyano group.

Results and discussion

The study focused on Br–Li exchange reactions of bromobenzonitriles.[14] Lithiation of bromobenzonitriles followed by reaction with electrophiles in a conventional macrobatch reactor requires very low temperatures, in the range −78 to −100 °C, to avoid unwanted reactions at the cyano group. To confirm this we used a conventional macrobatch reactor to investigate Br–Li exchange reactions of bromobenzonitriles such as *o*-bromobenzonitrile (**1a**), *m*-bromobenzonitrile (**1b**) and *p*-bromobenzonitrile (**1c**) (Table 1). A solution of *n*-BuLi in hexane was added dropwise (1 min) to tetrahydrofuran solutions of the bromobenzonitriles (**1**) in 10 mL round-bottom flasks at −78 °C or 0 °C; this generated lithiobenzonitriles (**2**). The solution was stirred for 10 min at the same temperature, methanol was added, and the solution was stirred for a further 10 min, at which point the yield of benzonitrile (**3**) was determined. The Br–Li exchange reaction with **1a** followed by protonation at −78 °C achieved a high yield. The reaction at 0 °C afforded **3** but in only 3% yield. The reactions of *m*- and *p*-bromobenzonitirile (**1b** and **1c**) were not as effective as with *o*-bromobenzonitrile (**1a**) affording 61% and 68% of desired product, respectively; and at 0 °C, as in the case of **1a**, **1b** and **1c** also afforded very poor yields of **3** (Table 1).

The Br–Li exchange reactions with *o*-bromobenzonitrile (**1a**), *m*-bromobenzonitrile (**1b**) and *p*-bromobenzonitrile (**1c**), and subsequent reactions with methanol, were then investigated using a microflow system consisting of two T-shaped micromixers (**M1** and **M2**) and two microtube reactors (**R1** and **R2**), as shown in Fig. 1. The reactions were carried out with varying residence times

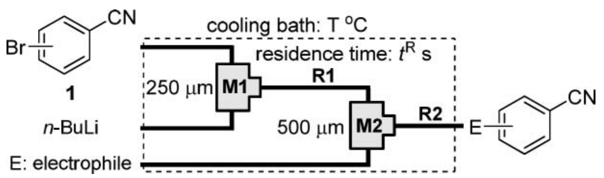

Fig. 1 A microflow system for Br–Li exchange reactions with bromobenzonitriles (**1**) followed by reaction with electrophiles§.

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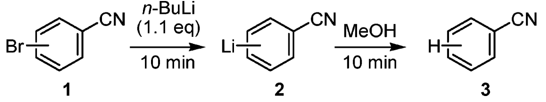
‡ Electronic supplementary information (ESI) available: Further experimental details and ^1H and ^{13}C NMR spectra. See DOI: 10.1039/b919325c

§ Flow rate of a solution of **1** (0.10 M in THF): 6.00 mL min^{-1}, flow rate of *n*-BuLi (0.42 M in hexane): 1.50 mL min^{-1}, flow rate of a solution of an electrophile (0.60 M in THF): 3.00 mL min^{-1}.

Table 1 Br–Li exchange reaction of bromobenzonitriles (**1**) followed by reaction with methanol in a conventional macrobatch system[a]



bromobenzonitrile	*T*/°C	conv. (%) **1**	yield (%) **3**
o-bromobenzonitrile (**1a**)	−78	97	86
	0	100	3
m-bromobenzonitrile (**1b**)	−78	90	61
	0	94	6
p-bromobenzonitrile (**1c**)	−78	90	68
	0	99	8

[a] A solution of *n*-BuLi in hexane was added dropwise to a solution of bromobenzonitriles (**1**) in THF at −78 °C or 0 °C. After stirring for 10 min at the same temperature, methanol was added. After stirring for 10 min, the yield of benzonitrile (**3**) was determined by GC.

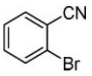
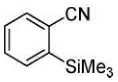
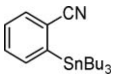
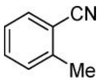
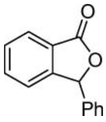
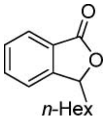
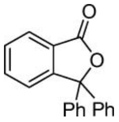
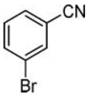
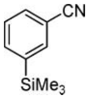
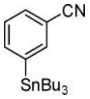
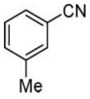
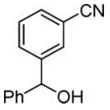
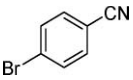
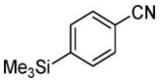
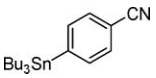
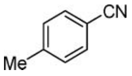
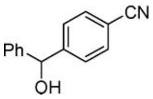
(t^R s) in **R1**, and varying reaction temperature (*T* °C) in the microflow system.

As shown in Fig. 2, the yield depended on both temperature and residence time. We found that the reaction of **1a**, **1b** and **1c** was achieved in high yields at 20 °C (**1a**: 90%, **1b**: 82%, **1c**: 82%) and 0 °C (**1a**: 90%, **1b**: 80%, **1c**: 88%). With increased residence time the lower yield was probably because of side reactions of the cyano group with lithiobenzonitriles. Fig. 2 also shows that the stabilities of *m*-lithiobenzonitrile (**2b**) and *p*-lithiobenzonitrile (**2c**) were similar. In contrast, the stability of *o*-lithiobenzonitrile (**2a**) was higher than that of **2b** and **2c** because of the *ortho*-directing effect of the cyano group for the Li center of **2a**. These results demonstrate that the microflow system is a more efficient method for the generation and reactions of lithiobenzonitriles under mild conditions than the conventional macrobatch system.[15]

The reactions of various electrophiles with **2a**, **2b** and **2c** were investigated in the microflow system under optimized conditions. As shown in Table 2, the reactions with chlorotrimethylsilane, chlorotributylstannane, methyl iodide and carbonyl compounds were effective in providing good yields of the corresponding products.

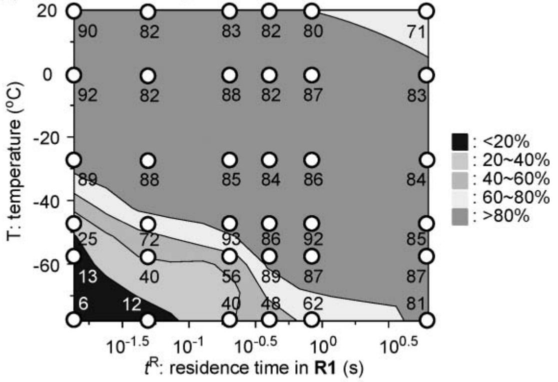
The integration of chemical reactions is of significant research interest because combining reactions avoids the need for isolation of intermediate products. The easy modulation of microflow systems aids the integration of chemical reactions. To demonstrate the utility of the present microflow method, sequential reactions were investigated using an integrated microflow system. As shown in Table 2, the reaction of carbonyl compounds with **2a** gave lactone derivatives (cyclization products) after cyclization of the nitrile group with alkoxylithium followed by hydrolysis. We hypothesized that sequential trapping reactions for alkoxylithium compounds generated by reaction of carbonyl compounds with **2a** could be achieved by the addition of an electrophile. The integrated microflow system consisted of three T-shaped micromixers (**M1**, **M2** and **M3**) and three microtube reactors (**R1**, **R2** and **R3**), as shown in Fig. 3. The sequential transformations were effective in providing good yields of the corresponding products (Table 3).

Table 2 Reaction of lithiobenzonitriles (**2**) with electrophiles[a]

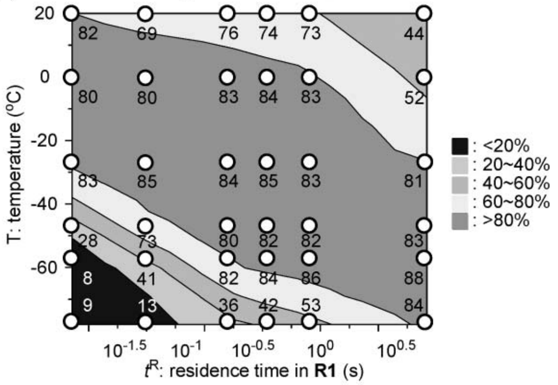
bromobenzonitrile	electrophile	product	yield (%)
	Me_3SiCl		90
1a	Bu_3SnCl		85
	MeI		93
	PhCHO		92
	n-HexCHO		81[b]
	Ph_2CO		94[b]
	Me_3SiCl		96
1b	Bu_3SnCl		95
	MeI		81
	PhCHO		81
	Me_3SiCl		85
1c	Bu_3SnCl		93
	MeI		90
	PhCHO		87

[a] Bromobenzonitriles (**1a–1c**) in THF (0.10 M), *n*-BuLi in hexane (0.42 M), and an electrophile in THF (0.60 M) were reacted in the microflow system under the following optimized conditions: **1a**: 20 °C (residence time: 0.01 s), **1b**: 0 °C (residence time: 0.01 s), **1c**: 0 °C (residence time: 0.01 s). The yield was determined by GC. [b] Isolated yield.

(a) *o*-lithiobenzonitrile generated from **1a**



(b) *m*-lithiobenzonitrile generated from **1b**



(c) *p*-lithiobenzonitrile generated from **1c**

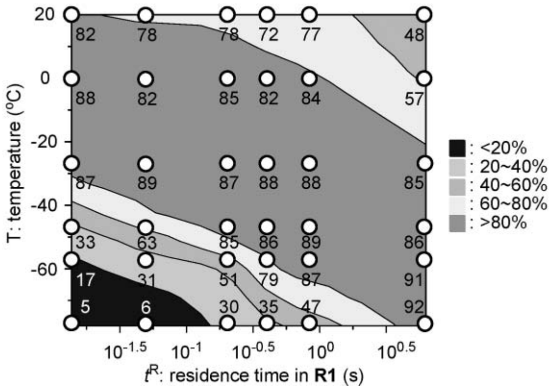
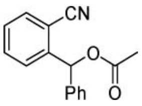
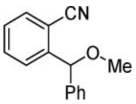
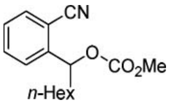
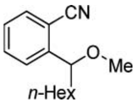
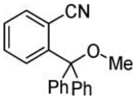


Fig. 2 Effects of reaction temperature and residence time in **R1** on the yield of benzonitrile in Br–Li exchange reactions involving *o*-bromobenzonitrile (**1a**), *m*-bromobenzonitrile (**1b**), and *p*-bromobenzonitrile (**1c**) with *n*-BuLi in a microflow system.

Conclusions

In conclusion, we have developed an effective method for the generation and reactions of cyano-substituted aryllithium through use of a microflow system involving a short residence time in combination with rapid mixing and efficient temperature control. In addition, sequential transformations were achieved in an integrated microflow system through generation and reactions of *o*-lithiobenzonitrile followed by trapping reactions with electrophiles. The method provides a new dimension in functionalized organolithium chemistry, and its application to the synthesis of various aromatic compounds is in progress.

Table 3 Reaction of *o*-lithiobenzonitrile (**2a**) with carbonyl compounds followed by reaction with electrophiles[a]

carbonyl compound	electrophile	product	yield (%)
PhCHO	AcCl		97
	Me_2SO_4[b]		83
n-HexCHO	MeO_2CCl		75
	Me_2SO_4[b]		51
Ph_2CO	Me_2SO_4[b]		66

[a] The reaction was conducted under the following optimized conditions: temperature: 20 °C, residence time of **R1**: 0.01 s, residence time of **R2**: 2.3 s (See the supporting information for details). [b] 3 eq of HMPA was added to a solution of Me_2SO_4.

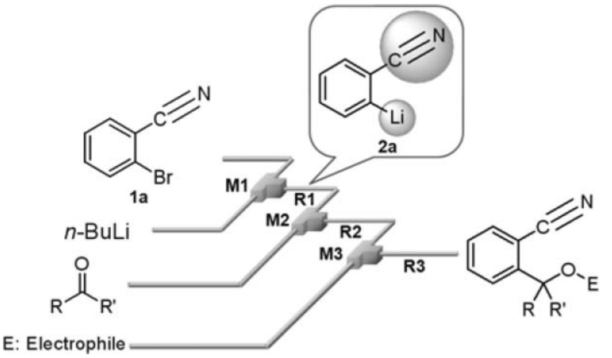


Fig. 3 An integrated microflow system for reaction of *o*-lithiobenzonitrile with carbonyl compounds followed by reaction with electrophiles¶.

Experimental

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 × 25 m). ^1H and ^{13}C NMR spectra were recorded on Varian MERCURY plus-400 (^1H 400 MHz, ^{13}C 100 MHz) spectrometer with Me_4Si or $CDCl_3$ as a standard in $CDCl_3$ unless otherwise noted. EI

¶ Flow rate of a solution of **1a** (0.10 M in THF): 6.00 mL min^{-1}, flow rate of *n*-BuLi (0.42 M in hexane): 1.20 mL min^{-1}, flow rate of a solution of carbonyl compound (0.22 M in hexane): 3.00 mL min^{-1}, flow rate of a solution of an electrophile (0.90 M in THF): 2.00 mL min^{-1}.

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. Micromixers and microtube reactors were connected with stainless steel fittings (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 (0.10 M, 3.0 mL) in THF in a 20 mL round bottom glass flask at regular pace with magnetic stirring for 1.0 min at T °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.

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 $\phi = 1000$ 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 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** ($\phi = 250$ µm) 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** ($\phi = 500$ 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 H_2O. The reaction mixture was analyzed by GC.

Typical procedure for the Br–Li exchange reaction of bromobenzonitriles followed by reaction with electrophiles 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 $\phi = 1000$ 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** 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 H_2O (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.[16]

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.[17]

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.[18]

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.[18]

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.[19]

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): ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.8, 111.7, 118.8, 128.0, 131.8, 136.5, 137.1, 142.1 ppm; HRMS (EI) m/z calcd for $C_{10}H_{13}NSi$: 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): ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C 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 $C_{19}H_{31}NSn$: 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.[20]

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.[21]

4-Tributylstannylbenzonitrile. The product was obtained in 93% yield (GC ^{t}R 28.3 min) when *p*-bromobenzonitrile and chlorotributylstannane were used for the reaction. The spectral data were identical to those reported in the literature.[22]

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.[23]

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 ϕ = 1000 µm, length L = 100 cm), **P2**, **P4** (ϕ = 1000 µm, 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** (ϕ = 250 µm). The resulting solution was passed through **R1** and was mixed with a solution of carbonyl compound (0.22 M) in THF (flow rate: 3.0 mL min^{-1}) in **M2** (ϕ = 500 µm). The resulting solution was passed through **R2** and was mixed with a solution of electrophile (0.90 M) in THF (flow rate: 2.0 mL min^{-1}) in **M3** (ϕ = 500 µm). 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 H_2O. The microtube reactor **R3** (ϕ = 1000 µm, L = 50 cm) was used for the reaction with acetyl chloride or methyl chlorocarbonate as an electrophile. For the reaction with dimethyl sulfate, a longer microtube reactor **R3** (ϕ = 1000 µm, 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): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.19 (s, 3H), 7.10 (s, 1H), 7.29–7.43 (m, 6H), 7.55–7.68 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{16}H_{13}NO_2$: 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): ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 57.3, 82.6, 111.3, 117.7, 126.9, 127.0, 127.9, 128.1, 128.6, 132.8, 133.1, 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): ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{16}H_{21}NO_3$: 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): ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{15}H_{22}NO$: 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): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.10 (s, 3H), 7.28–7.39 (m, 7H), 7.45–7.51 (m, 5H), 7.63–7.67 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 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 (EI) m/z calcd for $C_{21}H_{17}NO$: 299.1310, found: 299.1313.

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