Flow Microreactor Synthesis Using Short-Lived Organolithium Intermediates

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2016

Preface

The studies presented in this thesis have been carried out under the direction of Professor Jun-ichi Yoshida at the Department of Synthetic Chemistry and Biological Chemistry of Kyoto University during 2011-2016. The studies are concerned with flow microreactor synthesis using short-lived organolithium intermediates.

The author would like to express his sincerest gratitude to Professor Jun-ichi Yoshida for his kind guidance and valuable discussions throughout this work. The author appreciates the circumstance to investigate in the field of the chemistry. The author is greatly indebted to Dr. Aiichiro Nagaki for his constant advice and valuable discussions during the course of this work. The author deeply appreciates to Dr. Akihiro Shimizu and Dr. Heejin Kim for his kind guidance and encouragement. The author is also thankful to Associate Professor Toshiki Nokami of Tottori University and Dr. Keisuke Asano for their helpful advice.

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Contents

General Introduction

Various methods have been developed to synthesize structurally-complex functional materials and biologically active compounds in fast, atom and step-economical, and environmentally-friendly ways. In particular, fast synthesis is advantageous for time-efficient synthesis number of compounds to discover lead compounds as well as industrial production of commercial products. To achieve fast synthesis, one of the most straightforward strategies is to use highly-reactive intermediates. Organolithiums are one of the most reactive carbanion equivalents which can be used for constructing carbon-carbon frameworks. For example, organolithium species react with carbon electrophiles such as carbonyl compounds very quickly to give the corresponding carbon-carbon bond formation products. However, organolithiums suffer from several problems inherent in their high reactivity, such as incompatibility with various functional groups. For example, generation and reactions of aryllithiums bearing electrophilic functional groups such as carbonyl groups are very difficult or practically impossible using conventional batch reactors even at low temperatures such as -78 ºC.[1] This disadvantage significantly diminishes the usefulness of organolithiums in organic synthesis.

Flow microreactor systems[2,3] serve as powerful tools for fast chemical synthesis because of the following reasons. a) Fast mixing: short diffusion path in a flow microreactor results in extremely high speed mixing. b) Precise temperature control: heat transfer occurs rapidly because of high surface-to-volume ratio of microspace. c) Precise residence time control: short residence time can be achieved by virtue of small structure and flow nature of the system. These features allow advanced control, compared with conventional batch reactors, of fast chemical reactions involving highly-reactive short-lived intermediates, which can be transferred to another location to be used in the next reaction before they decompose. Extremely fast synthesis by taking advantage of characteristic feastures of flow microreactors is called flash chemistry.[4] For example, short-lived aryllithiums bearing electrophilic functional groups such as cyano-[5], nitro-[6], alcoxycarbonyl-[7], and acyl[8] groups can be generated by halogen/lithium exchange and reacted with electrophiles before they decompose using a flow microreactor system (Figure 1).

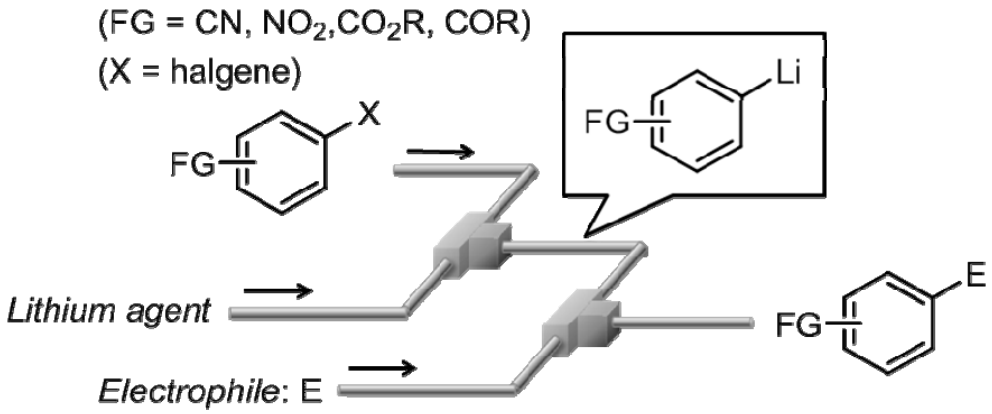

Figure 1. Generation of aryllithiums bearing electrophilic functional groups and their reactions with electrophiles using a flow microreactor system

Reaction integration which combines multiple reactions in a single operation in one pot or in a flow system without isolating intermediates enhances the power and speed of organic synthesis. Recently, our group proposed to classify reaction integration into three types (Figure 2)[9]. a) Time and space integration: All reaction components are mixed at once to perform a sequence of reactions. b) Time integration: A sequence of reactions is conducted in one-pot by adding components at intervals. c) Space integration: A sequence of reactions is conducted in one-flow by adding components at different places. Space integration using flow microreactor systems enables multi-step synthesis via short-lived intermediates such as organolithiums bearing electrophilic functional groups by virtue of short residence times.

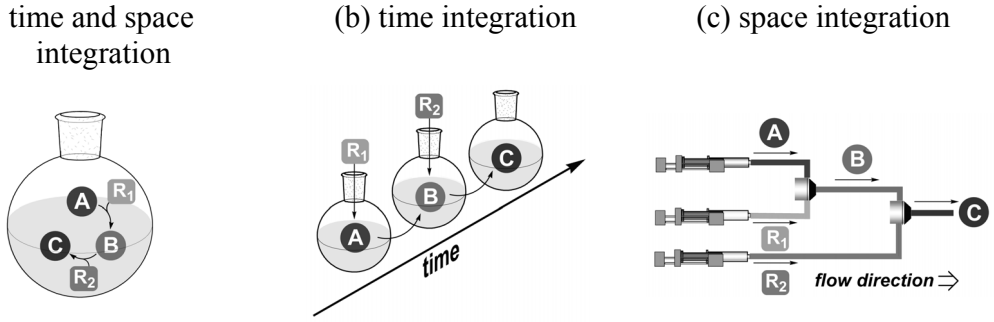

Figure 2. Classification of integrated synthesis. A: Starting material, B: intermediate, C: product, R_1 and R_2: reagents.

This thesis focuses on generation and reactions of short-lived organolithiums in a highly controlled manner and space integration of reactions using such unstable intermediates by virtue of the characteristic features of flow microreactor systems.

In chapter 1, the synthesis of α-ketoamides using carbamoyllithiums generated by reductive lithiation of carbamoyl chloride is described. α-Ketoamide structures serve as key motifs of various natural products and drug candidates. The generation of carbamoyllithiums by virtue of fast mixing followed by reactions with electrophiles such as acid chloride was successfully conducted using a flow microreactor system. This method enables the synthesis of various amides including α-ketoamides. Space integration enables three-component synthesis of functional α-ketoamides using a carbamoyllithium, methyl chloroformate, and a functional organolithium. (Figure 3).

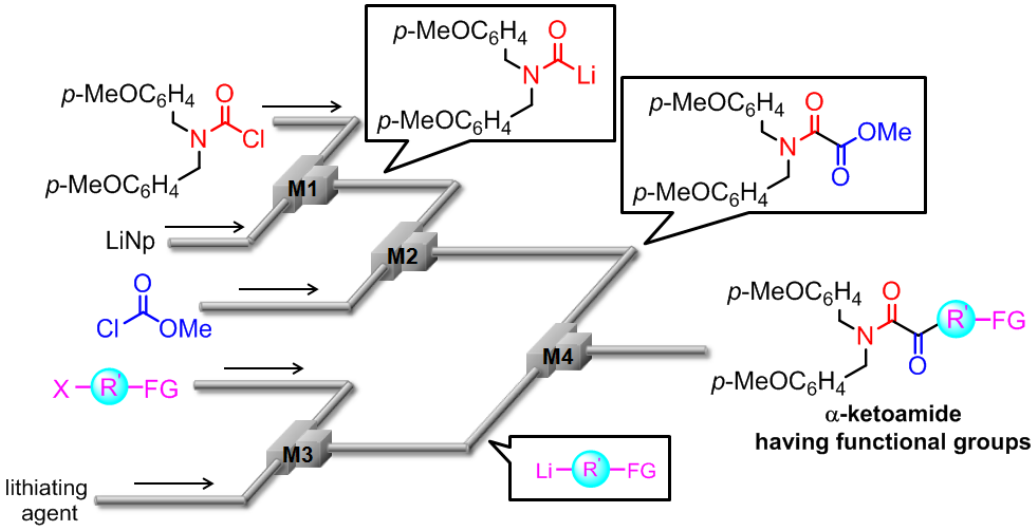

Figure 3. Three-component synthesis using carbamoyllithium, methyl chloroformate and unstable organolithiums.

Chapter 2 describes the selective synthesis of substituted alkenes and alkynes via trichlorovinyllithium generated by the H/Li exchange of trichloroethene in a flow microreactor system. The precise residence time and temperature control using a flow microreactor make it possible to suppress the β-elimination of LiCl and synthesis of 1,1,2-trichloroalkenes after the reaction with electrophiles. On the other hand, prolonged residence times lead to complete elimination of LiCl to give 1,2-dichloroethyne. The Cl/Li exchange followed by the reaction with electrophiles enables the synthesis of substituted ethynes (Figure 4).

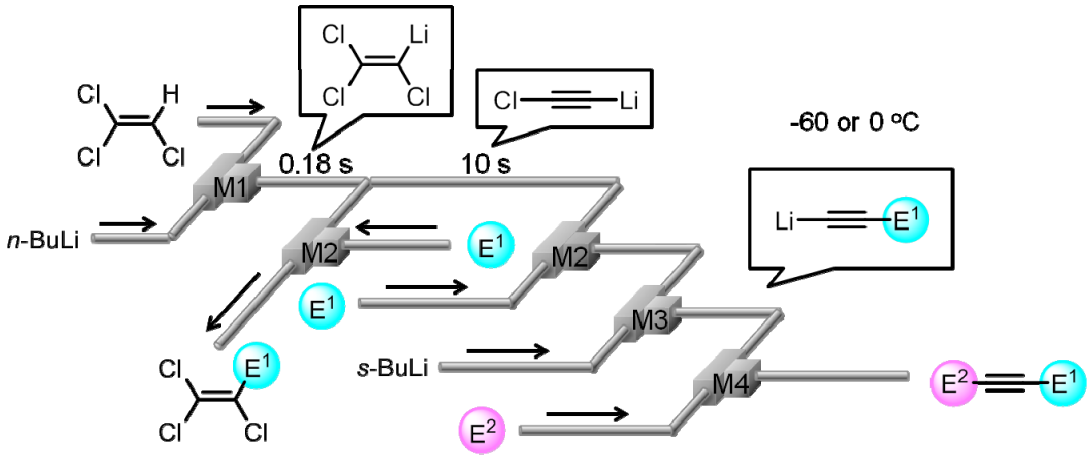

Figure 4. Selective synthesis of alkenes and alkynes by switching of the reaction-pathways of trichlorovinyllithium based on the residence time control.

Chapter 3 describes the synthesis of carboxylic acids and active esters by carboxylation of unstable organolithiums bearing electrophilic functional groups using a flow microreactor. Carboxylation reactions of cyano-, nitro-, ethoxycarbonylphenyllithiums with gaseous CO_2 were successfully accomplished to obtain the corresponding carboxylic acid in reasonable yields, indicating that gas/liquid mass transfer and reaction of organolithiums with CO_2 are extremely fast so that electrophilic functional groups survived. Furthermore, lithium carboxylates could be directly used for synthesis of active esters without adding a base (Figure 5).

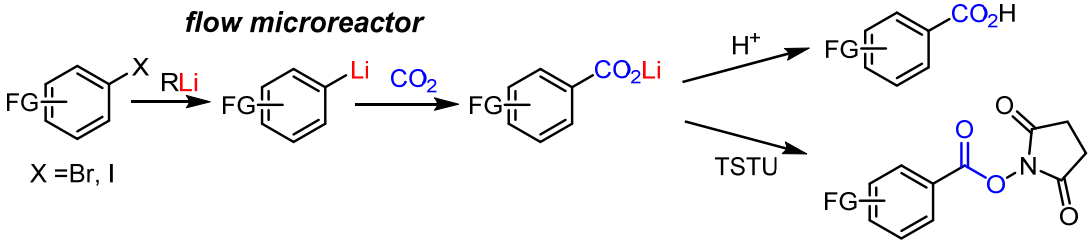

Figure 5. Synthesis of carboxylic acids and active esters by carboxylation of functional aryllithiums using CO_2 gas.

In chapter 4, the synthesis of poly(*tert*-butyl acrylate) by living anionic polymerization using a flow microreactor system is described. The anionic polymerization of *tert*-butyl acrylate in a conventional batch reactor requires low temperatures such as -78 °C and significant amount of lithium salts for control of the molecular weight distribution. However, the use of the flow microreactor system enables anionic polymerization of *tert*-butyl acrylate at -20 °C and reduction of amount of lithium chloride. Block copolymerization of *tert*-butyl acrylate/alkyl methacrulates could be achieved (Figure 6).

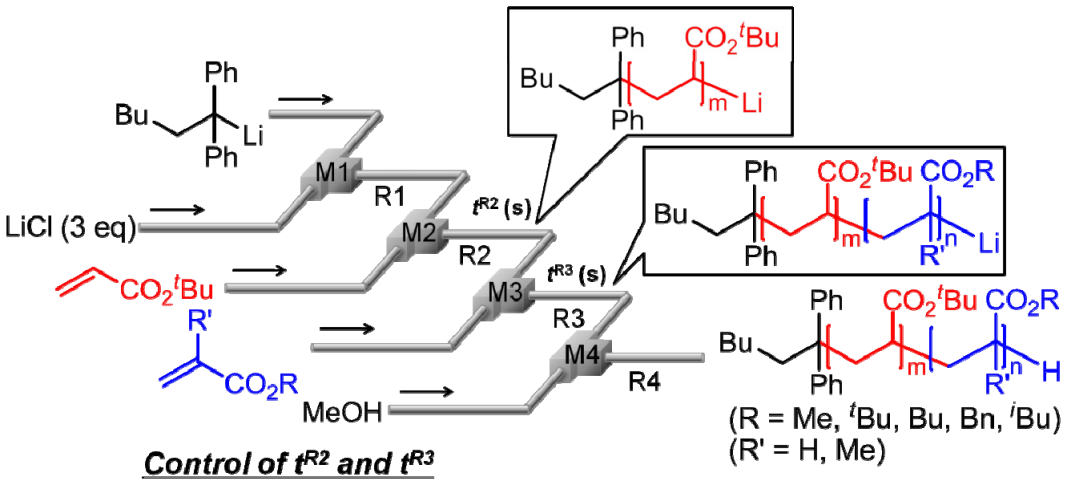

Figure 6. Controlled anionic polymerization of *tert*-butyl acrylate to obtain block copolymers.

In chapter 5, the synthesis of poly(perfluoroalkyl methacrylates) initiated by 1,1-diphenylhexyllithium using a flow microreactor system is described. Fluorine-containing polymers have attracted a great deal of attention because of their unique characteristics such as thermal stability. Living anionic polymerization of perfluoroalkyl methacrylates was achieved at higher temperatures than those required for polymerization in a conventional batch reactor. Block copolymerization of perfluoroalkyl methacrylates/alkyl methacrylates was also achieved (Figure 7).

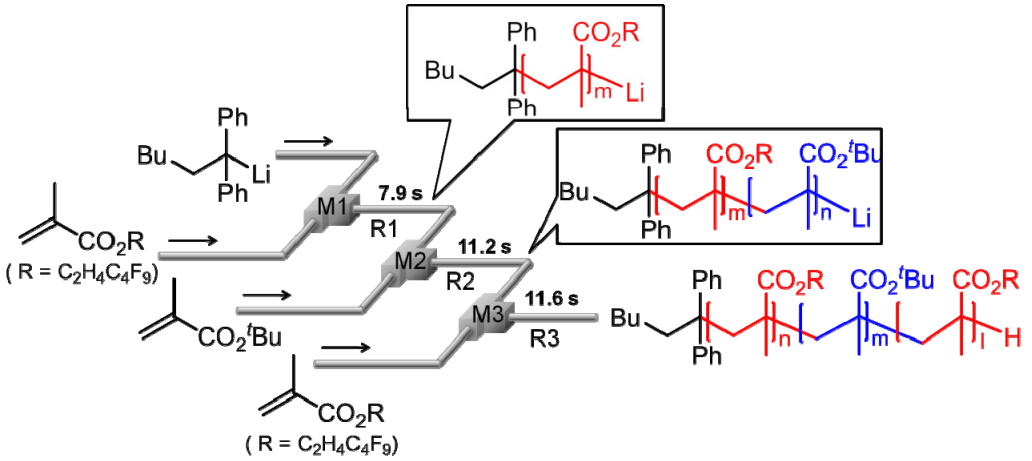

Figure 7. Controlled anionic polymerization of perfluoroalkyl methacrylates to obtain block copolymers.

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Chapter 1

Generation and Reactions of Carbamoyllithiums

Abstract

1,2-Dicarbonyl derivatives involving α-ketoamides synthesis via carbamoyllithiums generated by reductive lithiation of carbamoyl chloride was achieved using a flow microreactor system. The method was successfully applied to continuous three-component synthesis of 1,2-dicarbonyl derivatives bearing various functionalities.

Introduction

Carbonyl groups are central functionalities in organic chemistry, and the use of carbonyl anions, in principle, can serve as one of the most straightforward methods for constructing carbonyl compounds.[1] However, carbonyl anions are too unstable to be used in organic synthesis, and therefore carbanions with masked or protected carbonyl groups are often used as carbonyl anion equivalents in organic synthesis. However, such an approach suffers from problems of atom-economy[2] and step-economy[3] because of the need of deprotection steps. To avoid such problems the direct use of carbonyl anions is highly desirable in organic synthesis. We envisaged that flow microreactors enable the use of carbanyl anions.

We focused on carbamoyl anions as carbonyl anions, because they are useful for making amide structures which often occur in naturally occuring and/or biologically active compounds. A carbamoyl anion or a carbamoyllithium was first generated from bis(diethylcarbamoyl)mercury by Schöllkopf and Gerhart in 1967.[4] Lithium-tellurium exchange,[5] lithium-hydrogen exchange or deprotonation of formamides with lithium diisopropylamide (LDA),[6] and reductive lithiation[7] can also be used for generating carbamoyllithium. Although carbamoyllithiums are among the most stable of the carbonyllithiums, even those bearing bulky isopropyl groups on nitrogen should be quickly

generated and used for the reactions with electrophiles at very low temperatures. Moreover, in most cases carbamoyllithiums should be generated in the presence of electrophiles because of their instability. Such requirements, however, limit the scope of electrophiles and therefore significantly reduce the usefulness of carbamoyllithium. In this chapter, we show that the flash chemistry[8] using flow microreactors solves the problem.

Results and Discussions

First, we chose to study reductive lithiation of *N*,*N*-bis(*p*-methoxybenzyl)carbamoyl chloride with lithium naphthalenide (LiNp) to generate the carbamoyllithium followed by trapping with methyl chloroformate. The conventional batch method suffers from low yields of desired product **1** as shown in Table 1. Wurtz-type coupling gave **2** and the consecutive reaction of **1** with the carbamoyllithium gave 1,2,3-tricarbonyl compound **3**. Release of carbon monoxide from the carbamoyllithium gave methyl carbamate **4**. The reverse addition improved the yield of **1**, but the yield was still unsatisfactory.

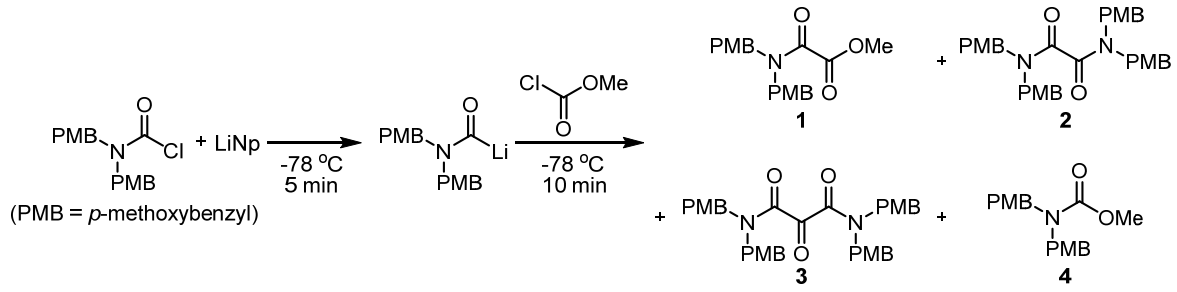


Table 1. Generation of carbamoyllithiums followed by reaction with methyl chloroformate in batch

way of addition	conv. (%)[a]	yield (%)			
		1[b]	**2**[a]	**3**[a]	**4**[b]
addition of LiNp to bis(*p*-methoxybenzyl)carbamoyl chloride	100	9	44	n.d.	9
addition of bis(*p*-methoxybenzyl)carbamoyl chloride to LiNp	100	44	2	18	14

a) Determined by HPLC analysis with *p*-diisopropyl benzene as internal standard.

b) Determined by GC analysis with $C_{15}H_{32}$ as internal standard.

Thus, a flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2**) and two microtube reactors (**R1** (ϕ = 1000 μm, length = 100 cm) and **R2** (ϕ = 1000 μm, length = 100 cm)) was used for generation and trapping of the carbamoyllithium (Figure 1).

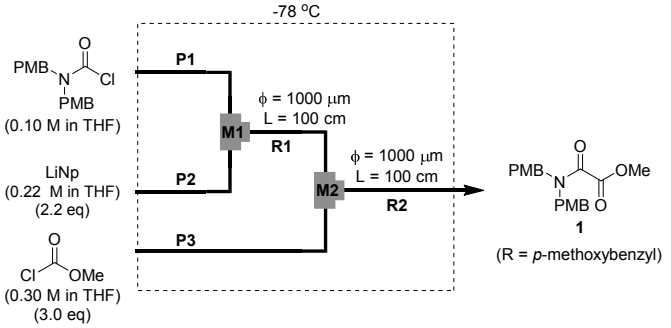


Figure 1. A flow microreactor system for generation of the carbamoyllithium followed by the reaction with methyl chloroformate

As shown in Table 2, the product selectivity strongly depends on the total flow rate. The yield of **1** was low at a low flow rate (run 1), but at high flow rates, satisfactory yields were obtained (runs 2 – 5). Because the mixing speed generally depends on the flow rate, the results indicate that good selectivity observed at high flow rates is ascribed to high mixing speeds. The mixing speed also depends on the inner diameter of micromixers. The increase in the inner diameter of micromixer **M1** causes a decrease in the yield of **1** (runs 2, 6, and 7). The increase in the inner diameter of **M2** also caused a decrease in the yield of **1** (runs 2, 8, and 9). Therefore, it is reasonable to conclude that extremely fast micromixing is responsible for selective formation of **1**.

Table 2. Generation of carbamoyllithium followed by reaction with methyl chloroformate using flow microreactors

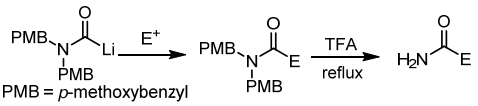
run	inner diameter (μm)		total flow rate (mL/min)		Conv.	yield (%)			
	M1	**M2**	**M1**	**M2**	(%)[a]	**1**[b]	**2**[a]	**3**[a]	**4**[b]
1	250	250	6	9	73	24	18	4	9
2	250	250	12	18	100	72	2	14	3
3	250	250	15	22.5	100	76	1	14	4
4	250	250	18	27	100	83	1	13	2
5	250	250	21	31.5	100	81	1	14	2
6	500	250	12	18	94	58	4	9	7
7	1000	250	12	18	94	57	5	8	7
8	250	500	12	18	100	62	1	23	5
9	250	1000	12	18	100	64	1	24	6
10	1000	1000	12	18	98	48	3	18	10

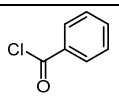
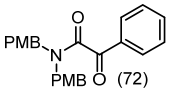
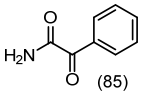
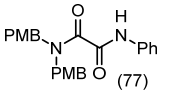
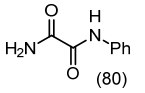
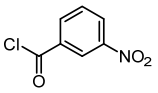
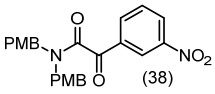
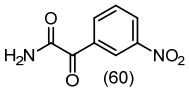
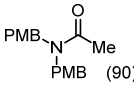
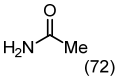
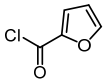
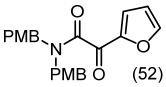
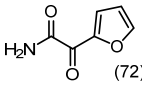
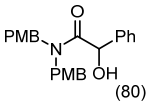
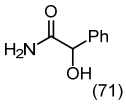
a) Determined by HPLC analysis with *p*-diisopropyl benzene as internal standard.

b) Determined by GC analysis with $C_{15}H_{32}$ as internal standard.

Under the optimized conditions (inner diameter of **M1** = 250 μm, inner diameter of **M2** = 250 μm, total flow rate at **M1** = 18.0 mL/min, total flow rate at **M2** = 27.0 mL/min), we next examined reactions with various electrophiles. The reaction with benzoyl chloride was successfully carried out to obtain the corresponding α-ketoamides in good yields (Table 3). The use of benzoyl chloride having a nitro group gave rise to very low yields of the desired product, presumably because of the reaction of the carbamoyllithium with the nitro group. The reactions with other electrophiles such as 2-furoyl chloride, phenylisocyanate, methyl trifluoromethanesulfonate, and benzaldehyde also took place to give the corresponding products in good yields. Notably, the *p*-methoyxbenzyl protecting groups could be successfully removed by the treatment with trifluoroacetic acid to obtain the products having two hydrogens on the nitrogen in good yields.[5]

Table 3. Generation of *N*,*N*-bis(*p*-methoxybenzyl)carbamoyllithium followed by reactions with electrophiles and the subsequent deprotection with trifluoroacetic acid in a flow microreactor system



electrophile	product (% yield)[a]	deprotected product (% yield)[a]	electrophile	product (% yield)[a]	deprotected product (% yield)[a]
	 (72)	 (85)	PhNCO	 (77)	 (80)
	 (38)	 (60)	MeOTf	 (90)	 (72)
	 (52)	 (72)	PhCHO	 (80)	 (71)

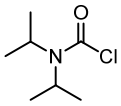
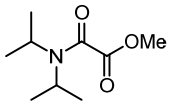
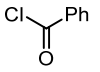
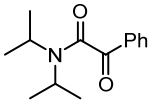
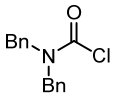
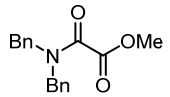
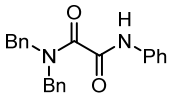
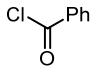
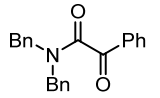
a) Isolated yield

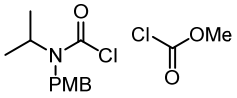
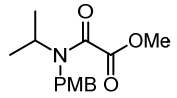
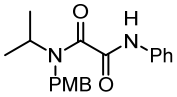
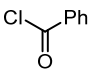
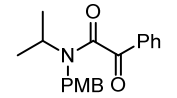
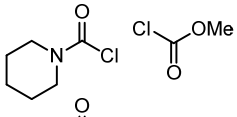
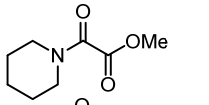
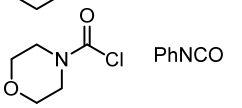
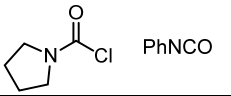
Next, generations and reactions of various carbamoyllithiums were examined, and the corresponding products were obtained in good yields as shown in Table 4.

α-Ketoamides occur in various natural products as well as drug candidates.[9] They are also very useful precursors for various fuctional group transformations.[10] Consequently, a number of methods for synthesis of α-ketoamides have been developed so far: the amidation of α-ketoacids and α-keto acyl halides,[11] the oxidation of α-hydroxyamides and α-aminoamides,[12] transition-metal-catalyzed double carbonylative amination of aryl halides,[13] and others.[14] However, the reaction of carbamoyllithiums with acid halides serves

as one of the most straightforward and useful methods for synthesizing α-ketoamides. However, the method suffers from the problem of the compatibility of functional groups in acid halides.

Table 4. Generation of various carbamoyllithiums followed by reaction with electrophiles using flow microreactors

electrophile	product	yield [%][a]
		78
		74
 Bn = benzyl		66
PhNCO		71
		54

electrophile	product	yield [%][a]
 PMB = *p*-methoxybenzyl		72
PhNCO		85
		73
		65
PhNCO		47
PhNCO		54

a) Isolated yield

For example, the reaction with *m*-nitrobenzoyl chloride gave the desired product only in a low yield as shown in Table 3, presumably because of nucleophilic attack on the nitro group. Thus, we envisioned that three-component synthesis involving the reaction of carbamoyllithiums with methyl chloroformate followed by the reaction with functional organolithiums would solve the problem (Figure 2).

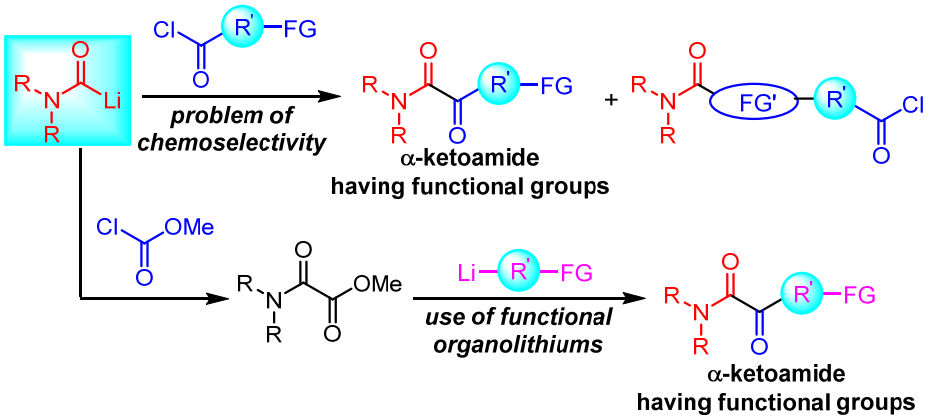


Figure 2. Synthesis of α-ketoamides having functional groups via carbamoyllithiums

An integrated flow microreactor system shown in Figure 3 was used. A carbamoyllithium was generated by reductive lithiation in **M1**/**R1**. Trapping of the carbamoyllithium with methyl chloroformate in **M2**/**R2** gave the corresponding α-amide ester. A functional organolithium was generated in **M3**/**R3** and was allowed to react with the α-amide ester in **M4**/**R4**. We have already reported that functional organolithiums can be generated and used by virtue of short residence times in flow microreactors.[15]As shown in Table 5, the reactions were successfully achieved to obtain the corresponding three-component coupling products, α-ketoamides in good yields. It should be noted that the batch method cannot be applied to this transformation because functional organolithiums decompose very quickly. Extremely short residence times and effective heat transfer are responsible for the success of synthesis of functional α-ketoamides.

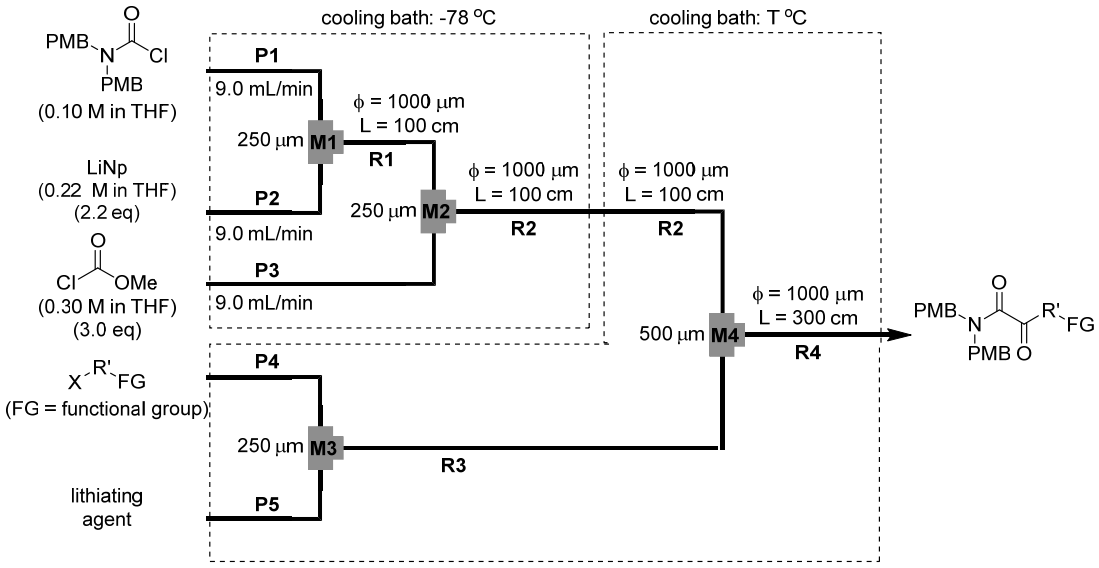
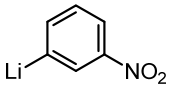
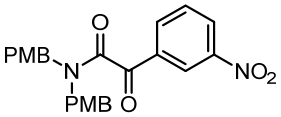
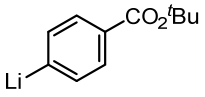
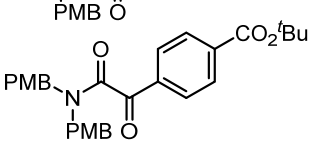
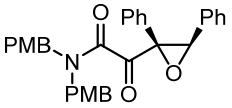
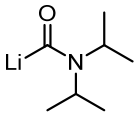
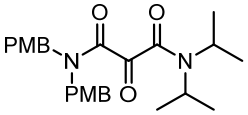


Figure 3. An integrated flow microreactor system for the three-component coupling of carbamoyllithiums, methyl chloroformate, and functional organolithiums. T-shaped micromixers: **M1**, **M2**, **M3**, and **M4**, microtube reactors: **R1**, **R2**, **R3**, and **R4.**

Table 5. Three-component coupling using functional organolithiums

functional organolithium	lithiating agent	residence time in **R3** [s]	product	yield [%][a)]
	PhLi	6.4		63
	*s*-BuLi	5.4		70
	*s*-BuLi	5.4		61
	LiNp	2.7		51

a) Isolated yield

The following formal total synthesis of a 5-amino-1,2,4-triazine derivative, GW356194, a potential sodium channel blocker for the treatment of disorders of the central nervous system, demonstrates the power and usefulness of the present method. Generation of *N*,*N*-bis(*p*-methoxybenzyl)carbamoyllithium followed by the reaction with methyl chloroformate and the subsequent reaction with (2,3,5-trichlorophenyl)lithium afforded **5** in 55% yield (Figure 4). Deprotection with trifluoroacetic acid gave **6** in 62% yield, which can be converted to 5-amino-1,2,4-triazine, GW356194 according to the literature procedure.[16]

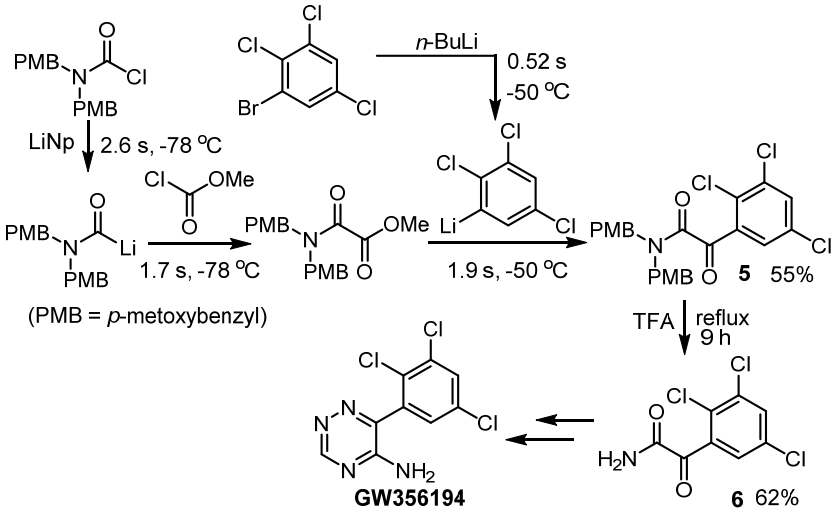


Figure 4. Formal synthesis of GW356194.

Conclusion

We have developed a flash method for harnessing unstable carbamoyl anions, *i.e.* carbamoyllithiums using a flow microreactor system by virtue of extremely fast mixing. The method can be applicable to synthesis of various amides including α-ketoamides. Functional α-ketoamides can be efficiently synthesized by the three-component of a carbamoyllithium, methyl chloroformation, and a functional organolithium. Such transformations are practically impossible by the conventional batch method. The power of the method was demonstrated by the straightforward short-step synthesis of GW356194, a potential sodium channel blocker.

Experimental Section

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, CBP1; 0.22 mm x 25 m). HPLC analysis was performed on a HITACHI D-2000 ELITE with a diode array detector using YMC-Triart C18 (250 x 4.6 mmI.D.). ^{1}H and ^{13}C NMR spectra were recorded on Varian MERCURYplus-400 (^{1}H 400 MHz and ^{13}C 100 MHz) spectrometer with Me_4Si as a standard in $CDCl_3$ unless otherwise noted. ESI mass spectra were recorded on a JEOL JMS-T100CS spectrometer. FT-IR spectra were recorded on SHIMADZU IRAffinity-1 spectrometer. Gel permeation chromatography (GPC) was carried out on Japan Analytical Industry LC-908 and LC-9201. Diethyl ether and tetrahydrofuran were purchased from Sigma-Aldrich Co. as a dry solvent and used without further purification. Hexane was purchased from Wako, distilled before use, and stored over molecular sieves 4A. (*p*-Methoxyphenyl)methanamine, *p*-methoxybenzaldehyde, sodium triacetoxyborohydride, triphosgene, lithium, naphthalene, methyl chloroformate, benzoyl chloride, 3-nitrobenzoyl chloride, furan-2-carbonyl chloride, phenyl isocyanate, methyl trifluoromethanesulfonate, benzaldehyde, diisopropylcarbamic chloride, dibenzylamine, acetone, piperidinecarbonyl chloride, morpholinecarbonyl chloride, pyrrolidinecarbonyl chloride, 1-iodo-3-nitrobenzene, *tert*-butyl 4-bromobenzoate, (2S*,3R*)-2,3-diphenyloxirane, 1-bromo-2,3,5-trichlorobenzene, trifluoroacetic acid (TFA) and lithium reagents were commercially available.

Stainless steel (SUS304) T-shaped micromixers with inner diameter of 250, 500 and 1000 μm were 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 (25, 100, 150, 200 and 300 cm). The micromixers and microtube reactors were connected with stainless steel fittings (GL Sciences, 1/16 OUW) to construct the flow microreactor in the laboratory. Flow microreactor systems were dipped in the bath to control the temperature. Solutions of the reaction components, except that of lithium naphthalenide were introduced to the flow microreactor system using SHIMAZU LC-6AD plunger pumps. A solution of lithium naphthalenide was introduced to the flow microreactor system using Hurue Science *JP-H* micro feeder pumps equipped with stainless steel syringes.

Synthesis of *N*,*N*-bis(*p*-methoxybenzyl)carbamoyl chloride

p-Methoxybenzaldehyde (53.1 g, 390 mmol), (*p*-methoxyphenyl)methanamine (53.2 g, 388 mmol) and toluene (700 mL) were combined in a 1000 mL flask equipped with a condenser and Dean-Stark trap. The reaction mixture was heated to reflux at 130 ^{o}C for 3 h and was cooled and evaporated under reduced pressure. The resulting yellow oil was dissolved into MeOH (500 mL), and to the mixture was added $NaBH_4$ (19.2 g, 508 mmol) slowly at 0 ^{o}C. The mixture was slowly warmed up to room temperature and was refluxed at 90 ^{o}C for 3 h. The resulting mixture was evaporated under reduced pressure. The residue was dissolved into EtOAc and washed with *aq* NaOH and brine, then dried over Na_2SO_4 and evaporated under reduced pressure. The residue was added to a solution of triphosgene (0.18 M solution in anhydrous CH_2Cl_2, 600 ml, 109 mmol) and triethylamine (47.8 g, 472 mmol) at -78 ^{o}C, and the mixture was stirred at 20 ^{o}C for 12 h. The reaction mixture was poured into water and was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The silica gel column chromatography (hexane : EtOAc = 95 : 5) afforded *N*,*N*-bis(*p*-methoxybenzyl)carbamoyl chloride (91.9 g, 92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (d, *J* = 2.2 Hz, 6H), 4.43 (s, 2H), 4.55 (s, 2H), 6.87-6.92 (m, 4H), 7.17-7.20 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.6 and 52.3, 55.4, 114.3 and 114.4, 127.2 and 127.5, 128.9 and 130.0, 150.2, 159.6 ppm; HRMS (ESI) *m/z* calcd for $(M+H)^+$ $C_{14}H_{19}O$: 320.1053, found: 320.1037; IR (neat) 1736 cm^{-1}.

Synthesis of isopropyl(*p* -methoxybenzyl)carbamoyl chloride

To a 200 mL flask, were added 1,2-dichloroethane (90 mL), (*p*-methoxyphenyl)methanamine (11.6 g, 84.8 mmol), anhydrous acetone (5.96 g, 103 mmol), sodium triacetoxyborohydride (21.6 g, 102 mmol), and acetic acid (9 ml), and the mixture was stirred at 25 ^{o}C for 19 h. The reaction mixture was filtrated with celite, and the filtrate was evaporated under reduced pressure. To the residue was added 1.0 M HCl-Et_2O, and the mixture was filtered. The precipitate was dissolved into *aq* NaOH and extracted

with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was added to a solution of triphosgene (0.17 M solution in anhydrous CH_2Cl_2, 100 ml, 17.4 mmol) and triethylamine (7.29 g, 72.0 mmol) at -78 °C, and the mixture was stirred at 20 °C for 1.5 h. The reaction mixture was partitioned between CH_2Cl_2 and water. The organic layer was separted and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The silica gel column chromatography (hexane : EtOAc = 95 : 5) followed by distillation (121 – 123 °C/ 3.7 mmHg) afforded isopropyl(*p*-methoxybenzyl)carbamoyl chloride (4.81 g, 20%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, *J* = 3.4 Hz, 6H), 3.80-3.81 (m, 3H), 4.15-4.22 (m, 1H), 4.49 (s) and 4.61 (s) (2H), 6.84-6.90 (m, 2H), 7.20-7.23 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1 and 21.2, 47.5, 51.4 and 52.7, 55.4, 114.1 and 114.2, 128.1 and 128.7, 128.9 and 129.6, 149.0, 159.2 ppm; HRMS (ESI) *m/z* calcd for $(M+Na)^+$ $C_{12}H_{16}ClNNaO_2$: 264.0767, found: 264.0757; IR (neat) 1725 cm^{-1}.

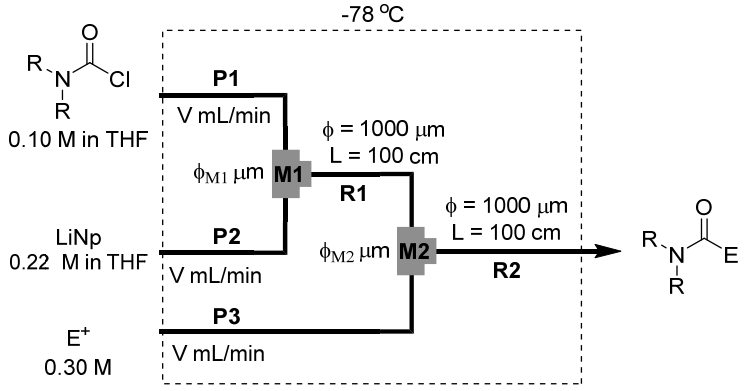
Preparation of lithium naphthalenide (LiNp)

Lithium naphthalenide was prepared in a glovebox. To a 200 mL flask, were added naphthalene (5.67 g, 44.2 mmol, 0.22 M), lithium (386 mg, 55.6 mmol), anhydrous THF (200 ml). The resulting mixture was stirred for 3 h at room temperature until the solution became dark green.

Generation of carbamoyllithiums followed by reaction with methyl chloroformate using a macro batchreactor.

A solution of a LiNp (0.22 M in THF, 4.5 mL) was added dropwise to a solution of *N*,*N*-bis(*p*-methoxybenzyl)carbamoyl chloride (0.100 M in THF, 4.5 mL) in a 50 mL round bottom glass flask with magnetic stirring for 1.0 min at -78 °C under argon. The mixture was stirred for 5 min, and a solution of methyl chloroformate (0.300 M in THF, 4.5 mL) was added. After being stirring for 10 min, the mixture was warmed to room temperature by removing the cooling bath, and then was poured into *sat. aq.* NH_4Cl. After extraction with Et_2O, the organic layer was analyzed by GC and HPLC. (Table 1)

General procedure for generation of carbamoyllithiums followed by reaction with electrophiles using a flow microreactor system.



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, P2** and **P3** (inner diameter ϕ = 1000 μm, length L = 300 cm)) was used. A solution of carbamoyl chloride (0.10 M in THF) (flow rate: V mL/min) and a solution of lithium naphthalenide (0.22 M in THF) (flow rate: V mL/min) were introduced to **M1** by a plunger pump and a micro feeder pump, respectively, and the mixture was passed through **R1** (ϕ = 1000 μm, L = 100 cm). The resulting solution was mixed with electrophile (0.30 M) (flow rate: V mL/min) in **M2**. The mixture was passed through **R2** (ϕ = 1000 μm, L = 100 cm). After a steady state was reached, the product solution was collected for 30 s while being quenched with *sat. aq.* NH_4Cl and was analyzed by GC and HPLC. The results obtained by changing the flow rate and the inner diameter of micromixers are summarized in Table 2. The product was isolated by silica gel column chromatography followed by preparative HPLC. The results are summarized in Table 3 and 4.

Methyl 2-(bis(*p*-methoxybenzyl)amino)-2-oxoacetate: Lithiation of *N*,*N*-bis(*p*-methoxybenzyl)carbamoyl chloride followed by the reaction with methyl chloroformate (0.30 M in THF) was carried out to obtain the title compound. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 3 : 1) followed by preparative HPLC. (GC yield, 83%, isolated yield, 77%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (d, *J* = 2.2 Hz, 6H), 3.88 (s, 3H), 4.23 (s, 2H), 4.41 (s, 2H), 6.85-6.92 (m, 4H), 7.13-7.20 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.3, 49.7 and 52.8, 55.4 and 55.4, 114.3 and 114.4, 126.8 and 127.6, 129.5 and 130.1, 159.4 and 159.7, 162.0, 163.7 ppm; HRMS (ESI) *m/z* calcd for $(M+H)^+$ $C_{19}H_{22}NO_5$: 344.1498, found: 344.1483; IR (neat) 1740, 1651 cm^{-1}.

***N*^{1},*N*^{1},*N*^{2},*N*^{2}-Tetrakis(*p*-methoxybenzyl)oxalamide:** Lithiation of *N*,*N*-bis(*p*-methoxybenzyl)carbamoyl chloride followed by the reaction with methyl chloroformate (0.30 M in THF) was carried out to obtain the title compound. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 2 : 1) followed by preparative HPLC. (HPLC yield: 1%): ^{1}H NMR (400 MHz, CD_2Cl_2) δ 3.76 (s, 6H), 3.80 (s, 6H), 4.24 (s, 4H), 4.41 (s, 4H), 6.78-6.82 (m, 4H), 6.85-6.89 (m, 4H), 7.08-7.12 (m, 4H), 7.20-7.24 (m, 4H), ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.0 and 49.5, 55.4 and 55.5, 114.2 and 114.3, 127.2 and 128.2, 129.8 and 130.1, 159.2 and 159.6, 165.1 ppm; HRMS (ESI) *m/z* calcd for $(M+H)^+$ $C_{34}H_{37}N_2O_6$: 569.2652, found: 569.2640; IR (neat) 1636 cm^{-1}.

***N*^{1},*N*^{1},*N*^{3},*N*^{3}-Tetrakis(*p*-methoxybenzyl)-2-oxomalonamide:** Lithiation of *N*,*N*-bis(*p*-methoxybenzyl)carbamoyl chloride followed by reaction with methyl chloroformate (0.30 M in THF) was carried out to obtain the title compound. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 2 : 1) followed by preparative HPLC. (HPLC yield: 13%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (d, *J* = 2.2 Hz, 12H), 4.48 (s, 8H), 6.87-6.94 (m, 8H), 7.15-7.18 (m, 4H), 7.31-7.35 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.6 and 49.5, 55.4 and 55.4, 114.3 and 114.3, 127.0 and 127.4, 129.8 and 130.0, 159.3 and 159.6, 166.2, 182.4 ppm; HRMS (ESI) *m/z* calcd for $(M+H)^+$ $C_{35}H_{37}N_2O_7$: 597.2601, found: 597.2581; IR (neat) 1720, 1636 cm^{-1}.

Methyl bis(*p*-methoxybenzyl)carbamate: Lithiation of *N*,*N*-bis(*p*-methoxybenzyl)carbamoyl chloride followed by reaction with methyl chloroformate (0.30 M in THF) was carried out to obtain the title compound. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 2 : 1) followed by preparative HPLC. (HPLC yield: 2%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79-3.81 (m, 9H), 4.32 (brd, *J* = 10.6 Hz, 4H), 6.86 (d, *J* = 4.2 Hz, 4H), 7.14 (brd, *J* = 9.2 Hz, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 48.1 and 48.6, 53.0, 55.4, 114.0, 129.0, 129.5 and 129.7, 157.4, 159.0 ppm; HRMS (ESI) *m/z* calcd for $(M+H)^+$ $C_{18}H_{22}NO_4$: 316.1549, found: 316.1537; IR (neat) 1693 cm^{-1}.

***N*,*N*-Bis(*p*-methoxybenzyl)-2-oxo-2-phenylacetamide:** Lithiation of *N*,*N*-bis(*p*-methoxybenzyl)carbamoyl chloride followed by reaction with benzoyl chloride (0.30 M in THF) was carried out to obtain the title compound. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 3 : 1) followed by preparative HPLC. (72%): ^{1}H NMR (400 MHz, CD_2Cl_2) δ 3.78 (s, 3H), 3.82 (s, 3H), 4.19

(s, 2H), 4.52 (s, 2H), 6.83-6.86 (m, 2H), 6.90-6.94 (m, 2H), 7.13-7.16 (m, 2H), 7.23-7.27 (m, 2H), 7.51-7.55 (m, 2H), 7.64-7.69 (m, 1H), 7.94-7.96 (m, 2H) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2) δ 45.7 and 49.8, 55.6 and 55.6, 114.4 and 114.5, 127.3, 128.6, 129.4 and 129.9, 130.0 and 130.3, 133.7, 135.1, 159.7 and 159.9, 167.6, 192.0 ppm; HRMS (ESI) *m/z* calcd for $(M+H)^+$ $C_{24}H_{24}NO_4$: 390.1705, found: 390.1687; IR (neat) 1678, 1647 cm^{-1}.

***N*,*N*-Bis(*p*-methoxybenzyl)-2-(3-nitrophenyl)-2-oxoacetamide:** Lithiation of *N*,*N*-bis(*p*-methoxybenzyl)carbamoyl chloride followed by reaction with 3-nitrobenzoyl chloride (0.30 M in THF) was carried out to obtain the title compound. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 3 : 1) followed by preparative HPLC. (38%): ^{1}H NMR (400 MHz, CD_2Cl_2) δ 3.73 (s, 3H), 3.83 (s, 3H), 4.25 (s, 2H), 4.60 (s, 2H), 6.76-6.80 (m, 2H), 6.93-6.96 (m, 2H), 7.07-7.11 (m, 2H), 7.28-7.31 (m, 2H), 7.68-7.72 (m, 1H), 8.22-8.25 (m, 1H), 8.42-8.45 (m, 1H), 8.65-8.66 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.5 and 49.6, 55.4 and 55.5, 114.3 and 114.5, 124.8, 126.7, 127.9, 128.6, 129.7, 130.2 and 130.2, 134.8 and 134.9, 148.5, 159.6 and 159.6, 166.3, 188.6 ppm; HRMS (ESI) *m/z* calcd for $(M+Na)^+$ $C_{24}H_{22}N_2NaO_6$: 457.1376, found: 457.1365; IR (neat) 1686, 1620 cm^{-1}.

2-(Furan-2-yl)-*N*,*N*-bis(*p*-methoxybenzyl)-2-oxoacetamide: Lithiation of *N*,*N*-bis(*p*-methoxybenzyl)carbamoyl chloride followed by reaction with furan-2-carbonyl chloride (0.30 M in THF) was carried out to obtain the title compound. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 3 : 1) followed by preparative HPLC. (52%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 3.83 (s, 3H), 4.27 (s, 2H), 4.51 (s, 2H), 6.61-6.62 (m, 1H), 6.84-6.87 (m, 2H), 6.89-6.92 (m, 2H), 7.14-7.17 (m, 2H), 7.21-7.24 (m, 2H), 7.35-7.36 (m, 1H), 7.71-7.72 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.5 and 49.4, 55.4, 113.1, 114.2 and 114.3, 122.2, 127.0 and 128.0, 129.6 and 130.0, 148.8, 150.4, 159.3 and 159.5, 166.0, 178.6 ppm; HRMS (ESI) *m/z* calcd for $(M+Na)^+$ $C_{22}H_{21}NNaO_5$: 402.1317, found: 402.1311; IR (neat) 1663, 1639 cm^{-1}.

***N*^{1},*N*^{1}-Bis(*p*-methoxybenzyl)-*N*^{2}-phenyloxalamide:** Lithiation of *N*,*N*-bis(*p*-methoxybenzyl)carbamoyl chloride followed by reaction with phenyl isocyanate (0.30 M in THF) was carried out to obtain the title compound. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 3 : 1) followed by preparative HPLC. (77%): ^{1}H NMR (400 MHz, CD_2Cl_2) δ 3.80 (d, J = 0.8 Hz, 6H), 4.48 (s, 2H), 4.96 (s, 2H), 6.86-6.92 (m, 4H), 7.15-7.21 (m, 3H), 7.25-7.29 (m, 2H), 7.34-7.39 (m, 2H), 7.63-7.65 (m, 2H), 9.37 (br, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 48.3 and 50.1, 55.4, 114.2 and 114.2, 120.0, 125.1, 128.1 and 128.3, 129.1, 129.5 and 129.9, 137.0, 158.9,

159.3 and 159.3, 162.4 ppm; HRMS (ESI) *m/z* calcd for $(M+H)^+$ $C_{24}H_{25}N_2O_4$: 405.1814, found: 405.1798; IR (neat) 1693, 1636 cm^{-1}.

***N*,*N*-Bis(*p*-methoxybenzyl)acetamide:** Lithiation of *N*,*N*-bis(*p*-methoxybenzyl)carbamoyl chloride followed by reaction with methyl trifluoromethanesulfonate (0.30 M in Et_2O) was carried out to obtain the title compound. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 1 : 1) followed by preparative HPLC. (90%): ^1H NMR (400 MHz, $CDCl_3$) δ 2.21 (s, 3H), 3.81 (d, *J* = 3.8 Hz, 6H), 4.35 (s, 2H), 4.50 (s, 2H), 6.83-6.86 (m, 2H), 6.88-6.92 (m, 2H), 7.06-7.09 (m, 2H), 7.14-7.18 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 47.1 and 50.0, 55.3 and 55.4, 114.0 and 114.4, 127.8 and 128.3, 129.5 and 129.8, 159.0and 159.2, 171.0 ppm; HRMS (ESI) *m/z* calcd for $(M+H)^+$ $C_{18}H_{22}NO_3$: 300.1600, found: 300.1588; IR (neat) 1636 cm^{-1}.

2-Hydroxy-*N*,*N*-bis(*p*-methoxybenzyl)-2-phenylacetamide: Lithiation of *N*,*N*-bis(*p*-methoxybenzyl)carbamoyl chloride followed by reaction with benzaldehyde (0.30 M in THF) was carried out to obtain the title compound. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 3 : 1) followed by preparative HPLC. (80%): ^1H NMR (400 MHz, $CDCl_3$) δ 3.79 (d, *J* = 1.0 Hz, 6H), 4.02 (d, *J* = 8.0 Hz, 1H), 4.18-4.27 (m, 2H), 4.77-4.87 (m, 2H), 5.29 (d, *J* = 3.4 Hz, 1H), 6.76-6.82 (m, 6H), 7.03-7.05 (m, 2H), 7.33-7.36 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.7 and 48.2, 55.4 and 55.4, 71.9, 114.1 and 114.4, 127.0, 127.6, 128.3, 128.4 and 128.8, 129.3 and 129.8, 139.5, 159.2 and 159.4, 173.0 ppm; HRMS (ESI) *m/z* calcd for $(M+H)^+$ $C_{24}H_{26}NO_4$: 392.1862, found: 392.1852; IR (neat) 1639 cm^{-1}.

Methyl 2-(diisopropylamino)-2-oxoacetate: Lithiation of diisopropylcarbamoyl chloride followed by reaction with methyl chloroformate (0.30 M in THF) was carried out to obtain the title compound. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 2 : 1) followed by preparative HPLC. (78%): ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, *J* = 3.4 Hz, 6H), 1.45 (d, *J* = 3.4 Hz, 6H), 3.48-3.55 (m, 1H), 3.64-3.85 (m, 1H), 3.85 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1 and 20.8, 46.1, 50.8 and 52.4, 161.5, 164.0 ppm; HRMS (ESI) *m/z* calcd for $(M+H)^+$ $C_9H_{18}NO_3$: 188.1287, found: 188.1279; IR (neat) 1736, 1651 cm^{-1}.

***N*,*N*-Diisopropyl-2-oxo-2-phenylacetamide:** Lithiation of diisopropylcarbamoyl chloride followed by reaction with benzoyl chloride (0.30 M in THF) was carried out to obtain the title compound. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 3 : 1) followed by preparative HPLC. (74%): The spectral data were

identical to those reported in the literature.[17]

Methyl 2-(dibenzylamino)-2-oxoacetate: Lithiation of dibenzylcarbamoyl chloride followed by reaction with methyl chloroformate (0.30 M in THF) was carried out to obtain the title compound. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 5 : 1) followed by preparative HPLC. (66%): ^{1}H NMR (400 MHz, CD_2Cl_2) δ 3.86 (s, 3H), 4.33 (s, 2H), 4.46 (s, 2H), 7.20-7.41 (m, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.3, 50.5 and 52.9, 128.0 and 128.1, 128.4 and 128.7, 128.9 and 129.0, 134.9 and 135.5, 162.2, 163.5 ppm; HRMS (ESI) *m/z* calcd for $(M+H)^+$ $C_{17}H_{18}NO_3$: 284.1287, found: 284.1276; IR (neat) 1740, 1655 cm^{-1}.

***N*^{1},*N*^{1}-Dibenzyl-*N*^{2}-phenyloxalamide:** Lithiation of dibenzylcarbamoyl chloride followed by reaction with phenyl isocyanate (0.30 M in THF) was carried out to obtain the title compound. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 10 : 1) followed by preparative HPLC. (71%): ^{1}H NMR (400 MHz, CD_2Cl_2) δ 4.58 (s, 2H), 5.09 (s, 2H), 7.15-7.19 (m, 1H), 7.26-7.38 (m, 12H), 7.62-7.65 (m, 2H), 9.36 (br, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.5 and 51.1, 120.0, 125.2, 127.9 and 128.0, 128.5, 128.9, 129.2, 136.0 and 136.4, 136.9, 158.5, 162.3 ppm; HRMS (ESI) *m/z* calcd for $(M+H)^+$ $C_{22}H_{21}N_2O_2$: 345.1603, found: 345.1592; IR (neat) 1694, 1628 cm^{-1}.

***N*,*N*-Dibenzyl-2-oxo-2-phenylacetamide:** Lithiation of dibenzylcarbamoyl chloride followed by reaction with benzoyl chloride (0.30 M in THF) was carried out to obtain the title compound. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 10 : 1) followed by preparative HPLC. (54%): The spectral data were identical to those reported in the literature.[18]

Methyl 2-(isopropyl(*p*-methoxybenzyl)amino)-2-oxoacetate: Lithiation of isopropyl(*p*-methoxybenzyl)carbamic chloride followed by reaction with methyl chloroformate (0.30 M in THF) was carried out to obtain the title compound. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 3 : 1) followed by preparative HPLC. (72%): The ^{1}H NMR analysis indicates the presence of two rotamers (1 : 1.2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15-1.18 (m, 6H), 3.73 (s) and 3.79 (s) (total 3H), 3.80 (s) and 3.90 (s) (total 3H), 3.85-3.91 (m) and 4.39-4.46 (m) (total 1H), 4.37 (s) and 4.52 (s) (total 2H), 6.82-6.89 (m, 2H), 7.20-7.24 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 21.6, 42.7, 47.3, 48.1, 50.7, 52.5, 52.6, 55.3, 55.4, 114.0, 114.1, 128.7, 128.8, 128.9, 130.1, 158.8, 159.3, 162.2, 162.6, 163.8, 164.1 ppm; HRMS (ESI) *m/z* calcd for $(M+H)^+$ $C_{14}H_{20}NO_4$: 266.1392, found: 266.1382; IR (neat) 1740, 1647 cm^{-1}.

***N*^{1}-Isopropyl-*N*^{1}-(*p*-methoxybenzyl)-*N*^{2}-phenyloxalamide:** Lithiation of isopropyl(*p*-methoxybenzyl)carbamic chloride followed by reaction with phenyl isocyanate (0.30 M in THF) was carried out to obtain the title compound. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 5 : 1) followed by preparative HPLC. (85%): The ^{1}H NMR analysis indicates the presence of two rotamers (1 : 1.3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, *J* = 3.4 Hz, 3H), 1.26 (d, *J* = 3.4 Hz, 3H), 3.78 (d, *J* = 2.6 Hz, 3H), 4.34-4.41 (m) and 5.35-5.42 (m) (total 1H), 4.57 (s, 1H), 4.99 (s, 1H), 6.83-6.87 (m, 2H), 7.11-7.18 (m, 1H), 7.20-7.25 (m, 2H), 7.30-7.38 (m, 2H), 7.54-7.61 (m, 2H), 9.16 (d, *J* = 12.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 22.0, 29.8, 45.0, 48.7, 49.9, 50.1, 55.4, 114.0, 114.0, 120.0, 125.0, 125.1, 128.4, 128.6, 129.1, 129.2, 130.1, 130.3, 137.0, 137.1, 158.7, 158.9, 159.3, 159.3, 162.3, 163.0 ppm; HRMS (ESI) *m/z* calcd for $(M+Na)^+$ $C_{19}H_{22}N_2NaO_3$: 349.1528, found: 349.1516; IR (neat) 1682, 1616 cm^{-1}.

***N*-Isopropyl-*N*-(*p*-methoxybenzyl)-2-oxo-2-phenylacetamide:** Lithiation of isopropyl(*p*-methoxybenzyl)carbamic chloride followed by reaction with benzoyl chloride (0.30 M in THF) was carried out to obtain the title compound. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 3 : 1) followed by preparative HPLC. (73%): The ^{1}H NMR analysis indicates the presence of two rotamers (1 : 1.4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, *J* = 3.2 Hz) and 1.27 (d, *J* = 3.4 Hz) (total 6H), 3.73 (s) and 3.82 (s) (total 3H), 3.83-3.90 (m) and 4.53-4.60 (m) (total 1H), 4.32 (s) and 4.66 (s) (total 2H), 6.74-6.78 (m) and 6.87-6.91 (m) and 7.18-7.22 (m) and 7.34-7.37 (m) and 7.43-7.47 (m) and 7.50-7.54 (m) and 7.56-7.60 (m) and 7.63-7.67 (m) and 7.85-7.88 (m) and 7.96-7.99 (m) (total 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 21.6, 42.9, 47.3, 48.1, 50.5, 55.3, 55.4, 114.0, 114.1, 128.7, 128.8, 129.1, 129.2, 129.4, 129.7, 129.8, 130.8, 133.3, 133.4, 134.4, 134.8, 158.9, 159.3, 167.7, 167.9, 191.2, 191.9 ppm; HRMS (ESI) *m/z* calcd for $(M+H)^+$ $C_{19}H_{22}NO_3$: 312.1600, found: 312.1586; IR (neat) 1678, 1632 cm^{-1}.

Methyl 2-oxo-2-(piperidin-1-yl)acetate: Lithiation of piperidinecarbonyl chloride followed by reaction with methyl chloroformate (0.30 M in THF) was carried out to obtain the title compound. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 3 : 1) followed by preparative HPLC. (65%). The spectral data were identical to those reported in the literature.[19]

2-Morpholino-2-oxo-*N*-phenylacetamide: Lithiation of morpholinecarbonyl chloride followed by reaction with phenyl isocyanate (0.30 M in THF) was carried out to obtain the title compound. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 3 : 1) followed by preparative HPLC. (47%). The spectral data were identical to those reported in the literature.[20]

2-Oxo-*N*-phenyl-2-(pyrrolidin-1-yl)acetamide: Lithiation of pyrrolidinecarbonyl chloride followed by reaction with phenyl isocyanate (0.30 M in THF) was carried out to obtain the title compound. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 3 : 1) followed by preparative HPLC. (54%): The spectral data were identical to those reported in the literature.[20]

2-Oxo-2-phenylacetamide: A solution of a *N*,*N*-bis(*p*-methoxybenzyl)-2-oxo-2-phenylacetamide (0.05 M in TFA, 5.0 mL) was heated to reflux for 17 h at 85 ºC. The product solution was concentrated under reduced pressure. After the addition of EtOAc (10 mL), the organic layer was washed with *sat. aq.* $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 2 : 1) followed by preparative HPLC. (85%). The spectral data were identical to those reported in the literature.[21]

2-(3-Nitrophenyl)-2-oxoacetamide: A solution of a *N*,*N*-bis(*p*-methoxybenzyl)-2-(3-nitrophenyl)-2-oxoacetamide (0.05 M in TFA, 5.0 mL) was heated to reflux for 21.5 h at 90 ºC. The product solution was concentrated under reduced pressure. After the addition of EtOAc (10 mL), the organic layer was washed with *sat. aq.* $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 2 : 1) followed by preparative HPLC. (60%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (br, 1H), 7.03 (br, 1H), 7.70-7.74 (m, 1H), 8.48-8.51 (m, 1H), 8.71-8.74 (m, 1H), 9.18-9.19 (m, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d6) δ 124.3, 128.5, 130.8, 134.1, 135.8, 147.9, 165.4, 188.0 ppm; HRMS (ESI) *m/z* calcd for $(M-H)^+$ $C_8H_5N_2O_4$: 193.0249, found: 193.0249; IR (neat) 1667, 1612 cm^{-1}.

2-(Furan-2-yl)-2-oxoacetamide: A solution of a 2-(furan-2-yl)-*N*,*N*-bis(*p*-methoxybenzyl)-2-oxoacetamide (0.05 M in TFA, 5.0 mL) was

heated to reflux for 17 h at 90 °C. The product solution was concentrated under reduced pressure. After the addition of EtOAc (10 mL), the organic layer was washed with *sat. aq.* $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 2 : 1) and preparative HPLC. (72%): ^{1}H NMR (400 MHz, DMSO-d6) δ 6.78-6.79 (m, 1H), 7.79-7.80 (m, 1H), 7.94 (br, 1H), 8.16-8.16 (m, 1H), 8.26 (br, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d6) δ 113.2, 124.9, 149.2, 150.1, 164.0, 175.9 ppm; HRMS (ESI) *m/z* calcd for $(M+Na)^+$ $C_6H_5NNaO_3$: 162.0167, found: 162.0157; IR (neat) 1655, 1632 cm^{-1}.

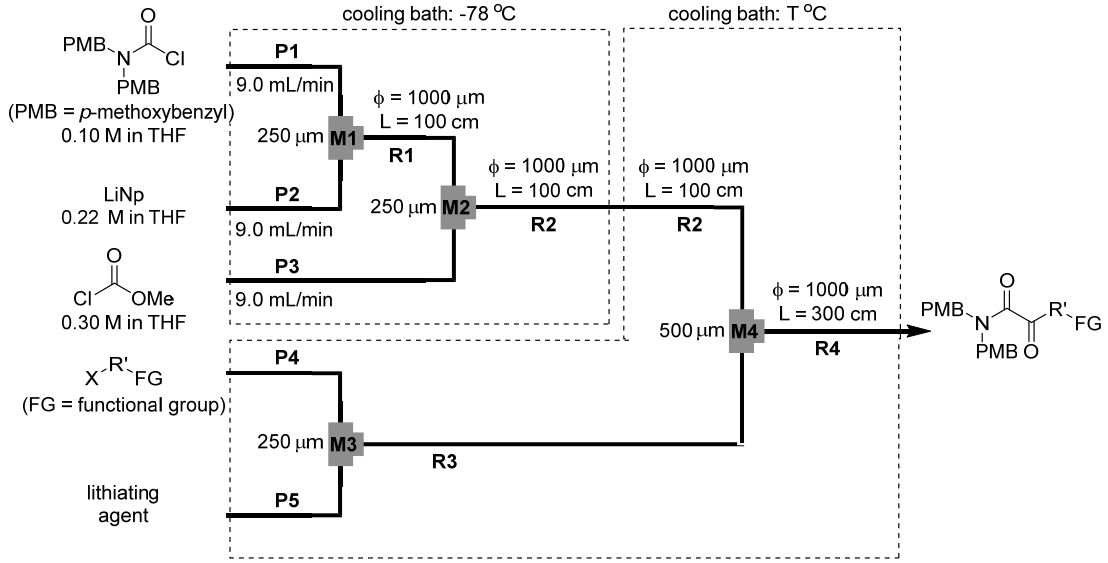
Phenyloxalamide: A solution of a N^1,N^1-bis(*p*-methoxybenzyl)-N^2-phenyloxalamide (0.05 M in TFA, 5.0 mL) was heated to reflux for 38 h at 90 °C. The product solution was concentrated under reduced pressure. After the addition of EtOAc (10 mL), the organic layer was washed with *sat. aq.* $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 2 : 1) followed by preparative HPLC. (80%): ^{1}H NMR (400 MHz, DMSO-d6) δ 7.10-7.14 (m, 1H), 7.32-7.36 (m, 2H), 7.80-7.83 (m, 2H), 8.00 (br, 1H), 8.33 (br, 1H), 10.6 (br, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d6) δ 120.2, 124.4, 128.7, 137.8, 158.9, 162.2 ppm; HRMS (EI) *m/z* calcd for $C_8H_8N_2O_2$: 164.0586, found: 164.0583; IR (neat) 1666, 1597 cm^{-1}.

Acetamide: A solution of a *N*,*N*-bis(*p*-methoxybenzyl)acetamide (0.05 M in TFA, 5.0 mL) was heated to reflux for 17 h at 90 °C. The product solution was concentrated under reduced pressure. After the addition of EtOAc (10 mL), the organic layer was washed with *sat. aq*. $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography ($ChCl_3$: CH_3OH = 9 : 1) followed by preparative HPLC. (72%): The analytical data were identical to those reported in the literature.[22]

2-Hydroxy-2-phenylacetamide: A solution of a 2-hydroxy-*N*,*N*-bis(*p*-methoxybenzyl)-2-phenylacetamide (0.05 M in TFA, 5.0 mL) was heated to reflux for 15 h at 85 °C. The product solution was concentrated under reduced pressure. After the addition of EtOAc (10 mL), the organic layer was washed with *sat. aq.* $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) and the

combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was washed with $CHCl_3$ and then with CH_3OH, was dried in vacuo to obtain the title compound (71%). The analytical data were identical to those reported in the literature.[23]

Typical procedure for three-component coupling using a flow microreactor system.



A flow microreactor system consisting of four T-shaped micromixers (**M1**, **M2**, **M3** and **M4**), four microtube reactors (**R1**, **R2**, **R3** and **R4**), and five tube pre-cooling units (**P1**, **P2**, **P3**, **P4** and **P5** (inner diameter ϕ = 1000 μm, length L = 300 cm)) was used. A solution of *N*,*N*-bis(*p*-methoxybenzyl)carbamoyl chloride (0.10 M in THF) (flow rate: 9.0 mL/min) and a solution of lithium naphthalenide (0.22 M in THF) (flow rate: 9.0 mL/min) were introduced to **M1** (ϕ = 250 μm) by a plunger pump and a micro feeder pump, respectively. The mixture was passed through **R1** (ϕ = 1000 μm, L = 100 cm). The resulting solution was mixed with methyl chloroformate (0.30 M in THF) (flow rate: 9.0 mL/min) in **M2** (ϕ = 250 μm). The mixture was passed through **R2** (ϕ = 1000 μm, L = 100 cm) and was introduced to **M4** (ϕ = 500 μm). A solution of functionalized organic compounds and a solution of lithiating agents were introduced to **M3** (ϕ = 250 μm) by plunger pumps, and the mixture was passed through **R3**. The resulting solution was introduced to **M4**. After a steady state was reached, the product solution was collected for 1 min while being quenched with *sat. aq*. NH_4Cl. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure.

***N*,*N*-Bis(*p*-methoxybenzyl)-2-(3-nitrophenyl)-2-oxoacetamide:** Reaction conditions: 1-iodo-3-nitrobenzene (0.45 M in THF, flow rate: 16.96 mL/min), PhLi (1.20 M in Et_2O, flow rate: 5.30 mL/min), **R2** (ϕ = 1000 μm, L = 300 cm), T = -78 °C. Purified by silica gel chromatography (hexane/ethyl acetate 3/1) followed by preparative HPLC. 63% isolated yield: The analytical data were same as above.

***tert*-Butyl 4-(2-(bis(*p*-methoxybenzyl)amino)-2-oxoacetyl)benzoate:** Reaction conditions: *tert*-butyl 4-bromobenzoate (0.40 M in THF, flow rate: 16.19 mL/min), *s*-BuLi (0.54 M in hexane, flow rate: 10.0 mL/min), **R2** (ϕ = 1000 μm, L = 300 cm), T = -78 °C. Purified by silica gel chromatography (hexane/ethyl acetate 5/1) followed by preparative HPLC. 70% Isolated yield: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 1.60 (s, 9H), 3.76 (s, 3H), 3.82 (s, 3H), 4.19 (s, 2H), 4.53 (s, 2H), 6.81-6.84 (m, 2H), 6.91-6.95 (m, 2H), 7.10-7.13 (m, 2H), 7.24-7.27 (m, 2H), 7.95-7.98 (m, 2H), 8.07-8.10 (m, 2H) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2) δ 28.2, 46.0 and 49.8, 55.6 and 55.7, 82.3, 114.5 and 114.5, 127.1, 128.4, 129.8 and 129.9, 130.1 and 130.3, 136.3, 137.6, 159.7 and 159.9, 164.8, 167.2, 191.3 ppm; HRMS (ESI) *m/z* calcd for $(M+H)^+$ $C_{29}H_{32}NO_6$: 490.2230, found: 490.2211; IR (neat) 1713, 1682, 1640 cm^{-1}.

2-((2S*,3R*)-2,3-Diphenyloxiran-2-yl)-*N*,*N*-bis(*p*-methoxybenzyl)-2-oxoacetamide: Reaction conditions: (2S*,3R*)-2,3-diphenyloxirane (0.40 M in THF, flow rate: 16.19 mL/min), *s*-BuLi (0.54 M in hexane, flow rate: 10.0 mL/min), **R2** (ϕ = 1000 μm, L = 300 cm), T = -78 °C. Purified by silica gel chromatography (hexane/ethyl acetate 4/1) followed by preparative HPLC. 61% isolated yield: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 3.78 (d, *J* = 0.6 Hz, 6H), 4.05-4.18 (m, 2H), 4.20-4.48 (m, 2H), 4.99 (s, 1H), 6.81-6.88 (m, 4H), 6.99-7.03 (m, 2H), 7.08-7.26 (m, 12H) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2) δ 45.3 and 49.4, 55.6 and 55.7, 65.5, 69.6, 114.4 and 114.5, 126.8, 127.3, 127.8, 128.3 and 128.4, 128.8, 129.0, 129.5, 129.9 and 129.9, 130.0, 133.2, 159.6 and 160.1, 166.7, 197.8 ppm; HRMS (ESI) *m/z* calcd for $(M+H)^+$ $C_{32}H_{30}NO_5$: 508.2124, found: 508.2115; IR (neat) 1713, 1640 cm^{-1}.

***N*^{1},*N*^{1}-Diisopropyl-*N*^{3},*N*^{3}-bis(*p*-methoxybenzyl)-2-oxomalonamide:** Reaction conditions: diisopropylcarbamic chloride (0.50 M in THF, flow rate: 13.0 mL/min), LiNp (0.50 M in THF, flow rate: 13.0 mL/min), **R2** (ϕ = 1000 μm, L = 150 cm), T = -78 °C. Purified by silica gel chromatography (hexane/ethyl acetate 5/1) followed by preparative HPLC. 51% isolated yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, *J* = 3.4 Hz, 6H), 1.50 (d, *J* = 3.4 Hz, 6H), 3.56-3.63 (m, 1H), 3.81 (d, *J* = 2.6 Hz, 6H), 4.13-4.20 (m, 1H), 4.42 (d, *J* = 2.6 Hz, 4H), 6.85-6.92 (m, 4H), 7.10-7.13 (m, 2H), 7.28-7.30 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2 and 20.8, 45.4 and 46.4, 49.5 and 50.7, 55.4, 114.2 and 114.3, 127.1 and

127.5, 129.7 and 130.0, 159.2 and 159.5, 166.1, 166.5, 182.0 ppm; HRMS (ESI) *m/z* calcd for $(M+H)^+$ $C_{25}H_{33}N_2O_5$: 441.2389, found: 441.2371; IR (neat) 1713, 1636 cm^{-1}.

***N*,*N*-Bis(*p*-methoxybenzyl)-2-oxo-2-(2,3,5-trichlorophenyl)acetamide:** Reaction conditions: 1-bromo-2,3,5-trichlorobenzene (0.30 M in THF, flow rate: 18.0 mL/min), *n*-BuLi (1.26 M in hexane, flow rate: 4.50 mL/min), **R2** (ϕ = 1000 μm, L = 25 cm), T = -50 °C. Purified by silica gel chromatography (hexane/ethyl acetate 91/9) followed by preparative HPLC. 55% isolated yield: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 3.81-3.81 (m, 6H), 4.31 (s, 2H), 4.46 (s, 2H), 6.87-6.93 (m, 4H), 7.20-7.31 (m, 4H), 7.70-7.73 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.0 and 49.4, 55.4 and 55.5, 114.2 and 114.4, 126.6, 127.3, 129.9, 130.1 and 130.4, 130.9, 133.9 and 134.2, 135.1, 137.0, 159.5 and 159.7, 166.0, 188.2 ppm; HRMS (ESI) *m/z* calcd for $(M+Na)^+$ $C_{24}H_{20}Cl_3NNaO_4$: 514.0356, found: 514.0348; IR (neat) 1686, 1643 cm^{-1}.

2-Oxo-2-(2,3,5-trichlorophenyl)acetamide: A solution of a *N*,*N*-bis(*p*-methoxybenzyl)-2-oxo-2-(2,3,5-trichlorophenyl)acetamide (0.05 M in TFA, 5.0 mL) was heated to reflux for 9 h (bath temperature 75 °C). The product solution was concentrated under reduced pressure. After the addition of EtOAc (10 mL), the organic layer was separated and washed with *sat. aq.* $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 5 : 1) followed by preparative HPLC. (62%): ^{1}H NMR (400 MHz, DMSO-d6) δ 7.76 (d, *J* = 1.4 Hz, 1H), 8.09 (d, *J* = 1.4 Hz, 1H), 8.13 (br, 1H), 8.47 (br, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d6) δ 127.8, 128.7, 132.5, 132.6, 133.4, 138.6, 162.6, 188.9 ppm; HRMS (EI) *m/z* calcd for $C_8H_4Cl_3NO_2$: 250.9308, found: 250.9302; IR (neat) 1698, 1555 cm^{-1}.

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Chapter 2

Generation and Reactions of Trichlorovinyllithium

Abstract

High-resolution reaction time control in flow microreactors enables the reaction-pathway switching of trichlorovinyllithium generated by the H/Li exchange of trichloroethene. The method was successfully applied to the synthesis of 1,1,2-trichloroalkenes, 1-chloroalkynes, and unsymmetrically disubstituted ethynes.

Introduction

The development of reactions in which one set of starting materials results in selective formation of different compounds at will has attracted significant interest in the recent organic chemistry.[1] If one set of starting materials gives more than one compound by simply changing the reaction conditions, the method provides a powerful tool in organic synthesis.

Carbon-carbon triple and double bonds frequently occur in a variety of organic molecules and the development of new versatile methods for synthesis of alkenes and alkynes has still received significant research interest. Reactions of 2-halovinylmetals serve as powerful methods for this purpose.[2,3] Especially, 2-halovinyllithiums are attractive intermediates because of their high reactivity compared to other 2-halovinylmetals.[4] Direct reactions with electrophiles give alkenes and the elimination of lithium halides gives alkynes, but control of β-elimination is often problematic. We have recently, however, found that the elimination of LiCl from *trans*-1,2-dichlorovinyllithium, which is generated by H/Li exchange of *trans*-1,2-dichloroethene was successfully controlled by adjusting the residence time in flow microreactors.[5] Either the direct reaction with an electrophile to give

substituted 1,2-dichloroethenes or the β-elimination followed by the reaction with an electrophile to give substituted ethynes was performed selectively at will. We envisaged that the use of trichlorovinyllithium should also be a useful for similar transformation.[6] Notably, the starting material, trichloroethene is much cheaper than *trans*-1,2-dichloroethene. However, to the best of our knowledge, such studies have not been reported so far presumably because of the difficulty in the control of β-elimination of LiCl from trichlorovinyllithium. In this chapter, we show that the reaction pathways of trichlorovinyllithium generated by the H/Li exchange of trichloroethene can be switched at will based on high-resolution reaction time control in flow microreactors to obtain 1,1,2-trichloroalkenes and 1-chloroalkynes after the reaction with electrophiles (Figure 1). Chlorine functionality in the products can be used for further transformation. For example, Cl/Li exchange of 1-chloroalkynes followed by the reaction with electrophiles enables the synthesis of unsymmetrically disubstituted ethynes (Figure 1).

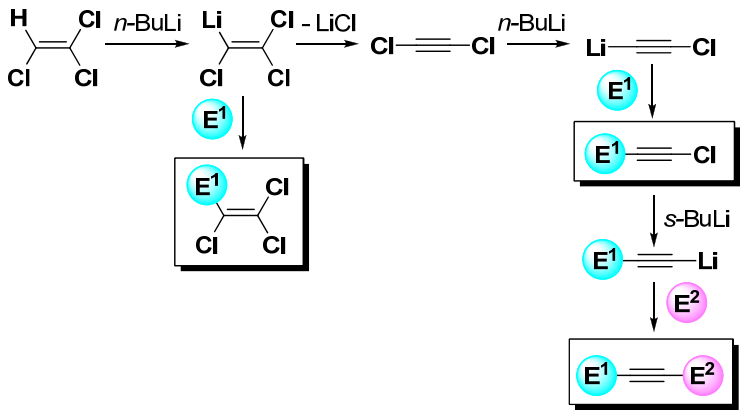
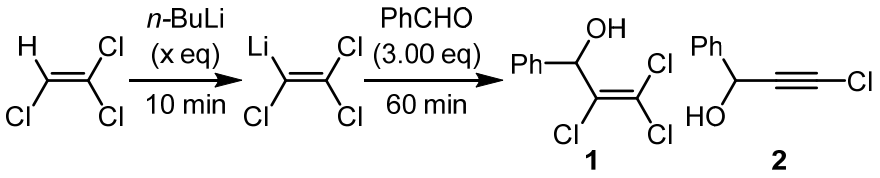


Figure 1. Synthesis of chloroalkenes and alkynes from trichloroethene.

Results and Discussions

We examined the H/Li exchange of trichloroethene with *n*-BuLi (1.05 or 2.00 eq) followed by the reaction with benzaldehyde in a conventional batch macro reactor. As shown in Table 1, 2,3,3-trichloro-1-phenylprop-2-en-1-ol (**1**) was not obtained at all. A significant amount of 3-chloro-1- phenyl-prop-2-yn-1-ol (**2**) was produced in all cases, presumably because of the extremely fast elimination of LiCl from trichlorovinyllithium under the conditions.

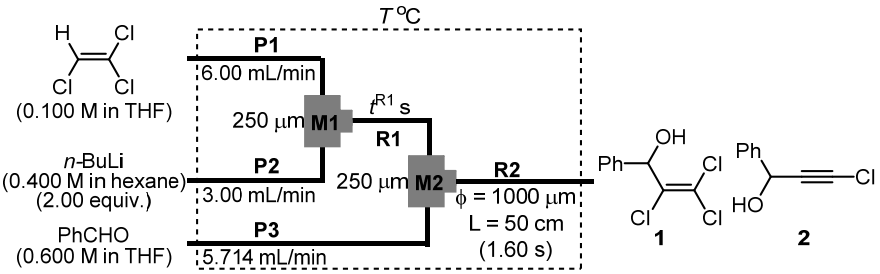
Table 1. H/Li exchange of trichloroethene with *n*-BuLi followed by reaction with benzaldehyde in a batch macro reactor.



T (°C)	x (eq)	yield (%) [a]	
		1	**2**
-78	1.05	0	44
	2.00	0	89
0	1.05	0	48
	2.00	0	75

a) Determined by GC analysis with an internal standard

Next, the reaction was examined using a flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2**) and two microtube reactors (**R1** and **R2**) shown in Scheme 1 with varying the residence time (t^{R1}) in **R1**, and temperature (T).



Scheme 1. A flow microreactor system for the H/Li exchange of trichloroethene with *n*-BuLi (2.00 eq) and the subsequent reaction with electrophiles. T-shaped micromixers: **M1** and **M2**, microtube reactors: **R1** and **R2**.

The results are summarized in Figure 2, in which the yields of **1** and **2** are plotted against T and t^{R1} as a contour map with scattered overlay. As shown in Figure 2a, high yields of **1** (> 80%) were obtained with short t^{R1} such as 0.18 s at −60 °C. The increase in t^{R1} and T caused a decrease in the yield of **1** because of the elimination of LiCl from trichlorovinyllithium. In fact, trichlorovinyllithium undergoes the β-elimination in the high temperature − long residence time region to give **2**. Presumably, the initially formed dichloroethyne undergoes Cl/Li exchange and the subsequent reaction with benzaldehyde gives **2** (Figure 2b). These results demonstrate that the high-resolution residence time

control enables the control of β-elimination and that the present method is effective for the selective synthesis of either alkene **1** or alkyne **2** at will.

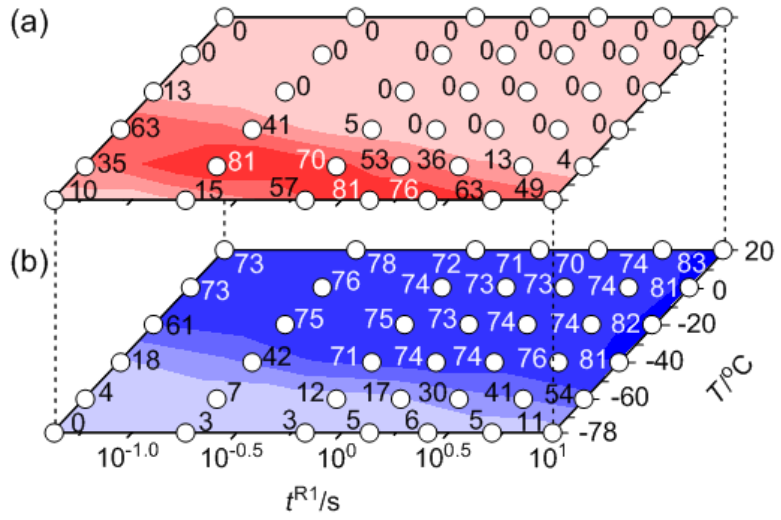
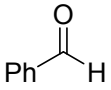
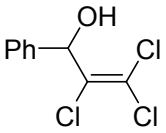
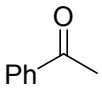
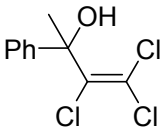
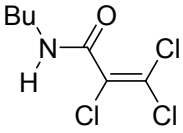


Figure 2. Effects of temperature (T) and residence time (t^{R1}) for H/Li exchange of trichloroethene with *n*-BuLi (2.00 eq) followed by the reaction with benzaldehyde using the flow microreactor system. (a) Contour map with scattered overlay of the yield of 2,3,3-trichloro-1-phenylprop-2-en-1-ol (**1**), and (b) contour map with scattered overlay of the yield of 3-chloro-1-phenyl-prop-2-yn-1-ol (**2**).

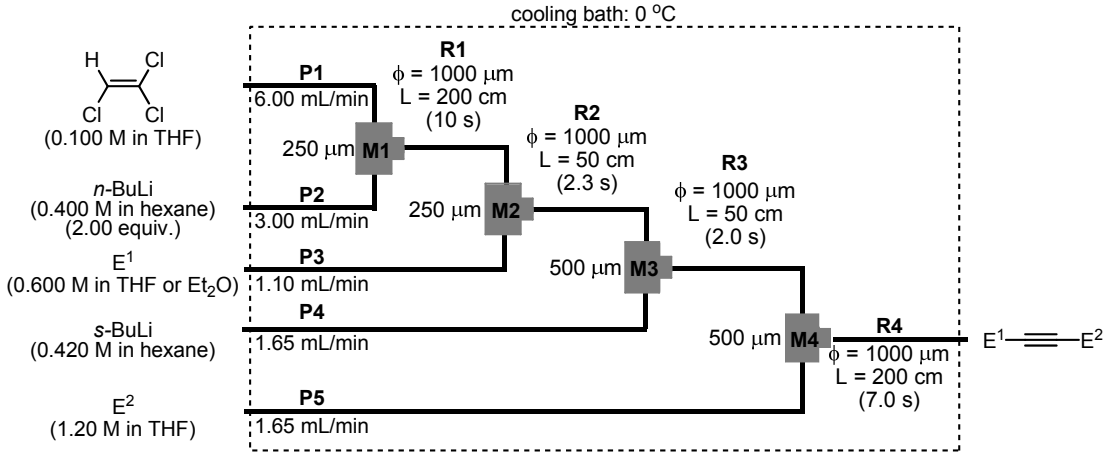
Under the optimized conditions (T = −60 °C, t^{R1} = 0.18 s) for the synthesis of **1**, the reactions with various electrophiles such as benzaldehyde, acetophenone, and butyl isocyanate were successfully carried out to obtain the corresponding 1,1,2-trichloroalkenes in good yields (Table 2). The three chlorine atoms could be used for further transformations to give a variety of substituted alkenes.[7]

Table 2. Reactions of trichlorovinyllithium with various electrophiles.

Electrophile	Product	Yield/%[a)]
		81[a)](64)[b)]
		46[b)]
Bu−N=C=O		57[b)]

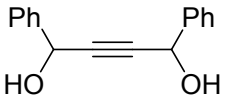
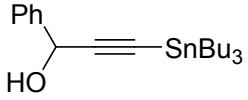
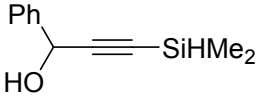
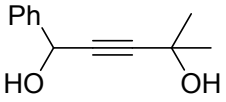
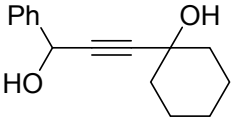
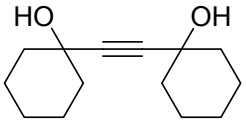
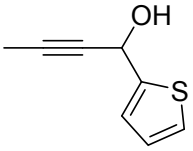
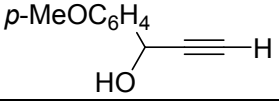
a) GC yield. b) Yield of isolated product.

Next, we focused on the synthesis of unsymmetrically disubstituted ethynes via β-elimination using an integrated flow microreactor system consisting of four micromixers (**M1**, **M2**, **M3**, and **M4**) and four microtube reactors (**R1**, **R2**, **R3**, and **R4**) shown in Scheme 2. The use of two equivalents of *n*-BuLi led to Cl/Li exchange of the initially formed dichloroethyne. The resulting chloroethynyllithium was reacted with electrophile E^1 in **M2** and **R2**. The second Cl/Li exchange with *s*-BuLi in **M3** and **R3** followed by reactions with electrophile E^2 in **M4** and **R4** gave unsymmetrically disubstituted ethynes as shown in Table 3. It is important to note that the whole transformation can be performed at 0 °C.



Scheme 2. An integrated flow microreactor system for the synthesis of unsymmetrically disubstituted ethynes by sequential introduction of two electrophiles. T-shaped micromixers: **M1**, **M2**, **M3**, and **M4**, microtube reactors: **R1**, **R2**, **R3**, and **R4**.

Table 3. Synthesis of unsymmetrically disubstituted ethynes from trichloroethene via sequential lithiations followed by reactions with various electrophiles.

Electrophile	Product	Yield/%[a)]
E^1: PhCHO E^2: PhCHO		88
E^1: PhCHO E^2: Bu_3SnCl		79
E^1: PhCHO E^2: Me_2SiHCl		74
E^1: PhCHO E^2: $(CH_3)_2CO$		56
E^1: PhCHO E^2: $(CH_2)_5CO$		67
E^1: $(CH_2)_5CO$ E^2: $(CH_2)_5CO$		56
E^1: MeOTf E^2: 2-thiophenaldehyde		48
E^1: *p*-$MeOC_6H_4CHO$ E^2: H_2O		52

a) Yield of isolated product.

Conclusion

We demonstrated that flash chemistry using flow microreactor systems enables switching of the reaction pathways of trichlorovinyllithium and that a variety of 1,1,2-trichloroalkenes, 1-chloroalkynes, and unsymmetrically disubstituted ethynes can be selectively synthesized from a single starting material, trichloroethene at will by changing the residence time and the temperature.

Experimental Section

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. ESI mass spectra were recorded on EXACTIVE 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. Trichloroethene, benzaldehyde, acetophenone, butyl isocyanate, chlorotributylstannane, chlorodimethylsilane, acetone, cyclohexanone, methyl trifluoromethanesulfonate, 2-thiophenaldehyde, *p*-methoxybenzaldehyde and lithium reagents 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 500 and 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 or 2 min. When the collection time was longer, the product solution can be obtained in a preparative scale.

H/Li exchange of trichloroethene with *n*-BuLi (1.05 or 2.00 eq) followed by reaction with benzaldehyde in a macro batch System

A solution of *n*-BuLi (0.21 M or 0.40 M in hexane, 6.0 mL) was added dropwise to a solution of trichloroethene (0.10 M in THF, 12.0 mL) in a 50 mL round bottom glass flask at regular pace with magnetic stirring for 5.0 min at T ^{o}C under argon. The mixture was stirred for 10 min, and a solution of benzaldehyde (0.60 M in THF, 6.0 mL) was added. After stirring for 60 min, a cooling bath was removed and quenched with sat. aq. NH_4Cl. The reaction mixture was analyzed by GC (Table 1).

3-Chloro-1-phenylprop-2-yn-1-ol (2): The crude product was purified by flash chromatography (hexane : AcOEt = 20 : 1) and GPC. The analytical data were identical to those reported in the literature.[8]

H/Li exchange of trichloroethene with *n*-BuLi followed by the reaction with benzaldehyde 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**, **P2** and **P3** (inner diameter ϕ = 1000 μm, length L = 100 cm)) was used. The whole flow microreactor system was dipped in a cooling bath (*T* °C).

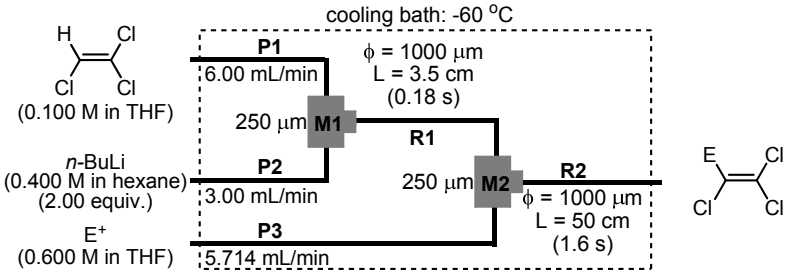
A solution of trichloroethene (0.100 M in THF) (flow rate: 6.00 mL min^{-1}) and a solution of *n*-BuLi (0.400 M in *n*-hexane) (flow rate: 3.00 mL min^{-1}) were introduced to **M1** (ϕ = 250 μm) by syringe pumps. The resulting solution was passed through **R1** and was mixed with a solution of benzaldehyde (0.600 M in THF) (flow rate: 5.714 mL min^{-1}) in **M2** (ϕ = 250 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 while being quenched with sat. aq. NH_4Cl and was analyzed by GC. The results are summarized in Table 4.

Table 4. H/Li exchange of trichloroethene with *n*-BuLi followed by reaction with benzaldehyde in flow microreactor systems

T (°C)	inner diameter of **R1** (μm)	length of **R1** (cm)	residence time in **R1** t^{R1} (s)	yield (%) **1**	yield (%) **2**
20	500	3.5	0.046	0	73
20	1000	3.5	0.18	0	78
20	1000	12.5	0.65	0	72
20	1000	25	1.3	0	71
20	1000	50	2.6	0	70
20	1000	100	5.2	0	74
20	1000	200	11	0	83
0	500	3.5	0.046	0	73
0	1000	3.5	0.18	0	76
0	1000	12.5	0.65	0	74
0	1000	25	1.3	0	73
0	1000	50	2.6	0	73
0	1000	100	5.2	0	74
0	1000	200	11	0	81
-20	500	3.5	0.046	13	61
-20	1000	3.5	0.18	0	75
-20	1000	12.5	0.65	0	75
-20	1000	25	1.3	0	73
-20	1000	50	2.6	0	74
-20	1000	100	5.2	0	74
-20	1000	200	11	0	82
-40	500	3.5	0.046	63	18
-40	1000	3.5	0.18	41	42
-40	1000	12.5	0.65	5	71
-40	1000	25	1.3	0	74

-40	1000	50	2.6	0	74
-40	1000	100	5.2	0	76
-40	1000	200	11	0	81
-60	500	3.5	0.046	35	4
-60	1000	3.5	0.18	81	7
-60	1000	12.5	0.65	70	12
-60	1000	25	1.3	53	17
-60	1000	50	2.6	36	30
-60	1000	100	5.2	13	41
-60	1000	200	11	4	54
-78	500	3.5	0.046	10	0
-78	1000	3.5	0.18	15	3
-78	1000	12.5	0.65	57	3
-78	1000	25	1.3	81	5
-78	1000	50	2.6	76	6
-78	1000	100	5.2	63	5
-78	1000	200	11	49	11

H/Li exchange of trichloroethene with *n*-BuLi followed by the reaction with electrophiles in the flow microreactor system



Scheme 3. A flow microreactor system for the H/Li exchange of trichloroethene with *n*-BuLi (2.00 eq) and the subsequent reaction with electrophiles. T-shaped micromixers: **M1** and **M2**, microtube reactors: **R1** and **R2**.

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**, **P2,** and **P3** (inner diameter ϕ = 1000 μm, length L = 100 cm)) was used. The whole flow microreactor system was dipped in a cooling bath (-60 °C).

A solution of trichloroethene (0.100 M in THF) (flow rate: 6.00 mL min^{-1}) and a solution of *n*-BuLi (0.400 M in *n*-hexane) (flow rate: 3.00 mL min^{-1}) were introduced to **M1** (ϕ = 250 μm) by syringe pumps. The resulting solution was passed through **R1** (ϕ = 1000 μm, L = 3.5 cm) and was mixed with a solution of electrophile (0.600 M in THF) (flow rate: 5.714 mL min^{-1}) in **M2** (ϕ = 250 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 2 min while being quenched with sat. aq. NH_4Cl. The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic layers were washed with brine, dried over with Na_2SO_4 and concentrated under reduced pressure.

2,3,3-Trichloro-1-phenylprop-2-en-1-ol (1): The crude product was purified by flash chromatography (hexane : AcOEt = 20 : 1) to obtain 2,3,3-trichloro-1-phenylprop-2-en-1-ol (**1**) in 64% yield.: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48-2.51 (m, 1H), 6.11-6.13 (m, 1H), 7.33-7.44 (m, 5H) ppm; ^{13}C NMR (100 MHz, CDCl3) δ 71.9, 119.8, 125.6, 128.4, 128.6, 134.3, 138.7 ppm; HRMS (ESI) *m/z* calcd for $C_9H_8Cl_2O$ $[M+Cl]^-$: 270.9251, found: 270.9261.

3,4,4-Trichloro-2-phenylbut-3-en-2-ol: The crude product was purified by flash chromatography (hexane : AcOEt = 20 : 1) to obtain 3,4,4-trichloro-2-phenylbut-3-en-2-ol in 46% yield.: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84-1.85 (m, 3H), 3.04-3.05 (m, 1H), 7.30-7.43 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.4, 78.4, 120.6, 124.5, 127.7, 128.5, 138.2, 145.2 ppm; HRMS (ESI) *m/z* calcd for $C_9H_8Cl_2O$ $[M+Cl]^-$: 284.9408, found: 284.9417.

***N*-Butyl-2,3,3-trichloroacrylamide:** The crude product was purified by flash chromatography (hexane : AcOEt = 20 : 1) to obtain *N*-butyl-2,3,3-trichloroacrylamide in 57% yield.: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93-0.97 (m, 3H), 1.34-1.43 (m, 2H), 1.53-1.60 (m, 2H), 3.33-3.38 (m, 2H), 6.10 (br, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 19.9, 31.0, 39.9, 124.1, 124.9, 160.6 ppm; HRMS (ESI) *m/z* calcd for $C_9H_8Cl_2O$ $[M+H]^-$: 229.9906, found: 229.9894.

Alkynes synthesis from trichloroethene by sequential introduction of two electrophiles using the integrated flow microreactor system

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. The whole flow microreactor system was dipped in a cooling bath. A solution of trichloroethene (0.100 M in THF) (flow rate: 6.00 mL min^{-1}) and a solution of *n*-BuLi (0.400 M in *n*-hexane) (flow rate: 3.00 mL min^{-1}) were introduced to **M1** (ϕ = 250 μm) by syringe pumps. The resulting solution was passed through **R1** (ϕ = 1000 μm, L = 200 cm) and was mixed with a solution of electrophile-1 (E^1) (0.600 M in THF or Et_2O) (flow rate: 1.10 mL min^{-1}) in **M2** (ϕ = 250 μm). The resulting solution was passed through **R2** (ϕ = 1000 μm, L = 50 cm) and was mixed with a solution of *s*-BuLi (0.420 M in *n*-hexane/cyclohexane) (flow rate: 1.65 mL min^{-1}) in **M3** (ϕ = 500 μm). The resulting solution was passed through **R3** and was mixed with a solution of electrophile-2 (E^2) (1.20 M in THF) (flow rate: 1.65 mL min^{-1}) in **M4** (ϕ = 500 μm). The resulting solution was passed through **R4** (ϕ = 1000 μm, L = 200 cm). After a steady state was reached, the product solution was collected for 2 min while being quenched with sat. aq. NH_4Cl. The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic layers were washed with brine, dried over with Na_2SO_4 and concentrated under reduced pressure.

1,4-Diphenylbut-2-yne-1,4-diol: When the reaction with benzaldehyde (E^1) and benzaldehyde (E^2) was carried out, the crude product was purified by flash chromatography (hexane : AcOEt = 2:1) to obtain 1,4-diphenylbut-2-yne-1,4-diol in 88% yield. The analytical data were identical to those reported in the literature.[8]

1-Phenyl-3-(tributylstannyl)prop-2-yn-1-ol: When the reactions with benzaldehyde (E^1) and chlorotributylstannane (E^2) were carried out, the crude product was purified by flash chromatography (hexane : AcOEt = 10 : 1) to obtain 1-phenyl-3-(tributylstannyl)prop-2-yn-1-ol in 79% yield. The analytical data were identical to those reported in the literature.[8]

3-Dimethylsilyl-1-phenylprop-2-yn-1-ol: When the reactions with benzaldehyde (E^1) and dimethylchlorosilane (E^2) were carried out, the crude product was purified by flash chromatography (hexane : AcOEt = 10 : 1) and GPC to obtain 3-dimethylsilyl-1-phenylprop-2-yn-1-ol in 74% yield. The analytical data were identical to those reported in the literature.[8]

4-Methyl-1-phenylpent-2-yne-1,4-diol: When the reaction with benzaldehyde (E^1) and acetone (E^2) was carried out, the crude product was purified by flash chromatography (hexane : AcOEt = 4:1) and GPC to obtain 4-methyl-1-phenylpent-2-yne-1,4-diol in 56% yield. The analytical data were identical to those reported in the literature.[9]

1-(3-Hydroxy-3-phenylprop-1-yn-1-yl)cyclohexan-1-ol: When the reaction with benzaldehyde (E^1) and cyclohexanone (E^2) was carried out, the crude product was purified by flash chromatography (hexane : AcOEt = 2:1) and GPC to obtain 1-(3-Hydroxy-3-phenylprop-1-yn-1-yl)cyclohexan-1-ol in 67% yield. The analytical data were identical to those reported in the literature.[9]

1,1'-(Ethyne-1,2-diyl)bis(cyclohexan-1-ol): When the reaction with cyclohexanone (E^1) and cyclohexanone (E^2) was carried out, the crude product was purified by flash chromatography (hexane : AcOEt = 2:1) to obtain 1,1'-(ethyne-1,2-diyl) bis(cyclohexan-1-ol) in 56% yield. The analytical data were identical to those reported in the literature.[9]

1-(Thiophen-2-yl)but-2-yn-1-ol: When the reaction with methyl trifluoromethanesulfonate (E^1) and 2-thiophenaldehyde (E^2) was carried out, the crude product was purified by flash chromatography (hexane : AcOEt = 5 : 1) and GPC to obtain 1-(thiophen-2-yl)but-2-yn-1-ol in 48% yield. Et_2O instead of THF was used as a solvent of the solution of methyl trifluoromethanesulfonate (E^1). The analytical data were identical to those reported in the literature.[10]

1-(4-Methoxyphenyl)prop-2-yn-1-ol: The reaction with *p*-methoxybenzaldehyde (E^1) and H_2O (E^2) was carried out, the crude product was purified by flash chromatography (hexane : AcOEt = 5 : 1) to obtain 1-(4-methoxyphenyl)prop-2-yn-1-ol in 52% yield. The analytical data were identical to those reported in the literature.[11]

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Chapter 3

Reactions of Short-Lived Aryllithiums with CO_2

Abstract

Carboxylation of short-lived aryllithiums bearing electrophilic functional groups such as nitro, cyano, and alkoxycarbonyl groups with CO_2 to give carboxylic acids and active esters was accomplished in a flow microreactor system. The successful reactions indicate that gas/liquid mass transfer and the subsequent chemical reaction with CO_2 are extremely fast.

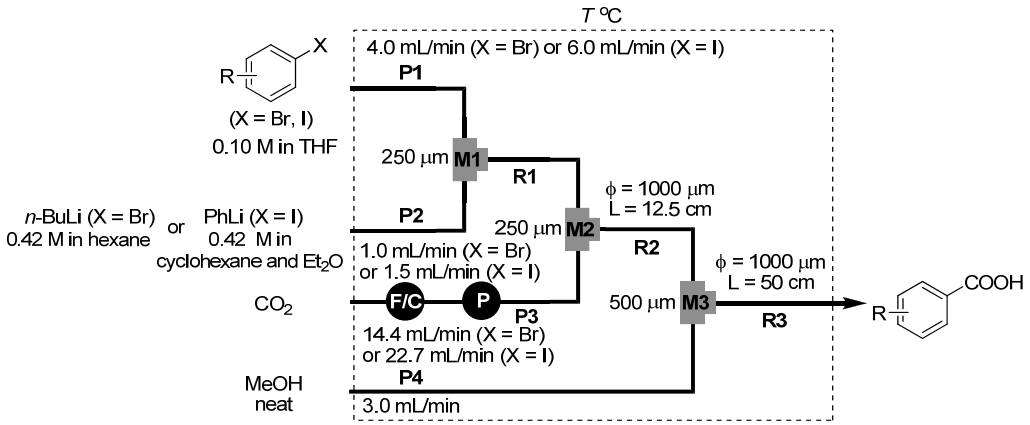
Introduction

Carboxylic acids and their derivatives are important classes of compounds in organic chemistry. Although various methods for synthesis of carboxylic acids have been used so far, carboxylation using CO_2 gas as a carbon feedstock[1] is useful and attractive from an environmental point of view.[2] Despite recent remarkable advances in this field,[3] classical carboxylation of organometallics with CO_2 still serves as a powerful method because of efficiency and convenience.[4] However, the method suffers from the problem of incompatibility of electrophilic functional groups such as nitro, cyano, and carbonyl groups, which causes severe limitations in the synthesis of carboxylic acids and their derivatives having a variety of functions and biological activities. Recently, we have reported that various short-lived highly unstable organolithiums such as aryllithiums bearing electrophilic functional groups could be generated and used for reactions with subsequently added electrophiles before they decompose[5] by taking advantages extremely short residence times, which is one of the characteristic features of flow microreactors.[6,7,8] There are two hurdles that we expected in the implementation of CO_2 as an electrophile in the reactions of short-lived aryllithium species; the mass transfer between the CO_2 gas phase and the solution phase and the rate of the chemical reaction of aryllithium species with dissolved

CO_2. The first one seems to be mainly the issue of fluidics although the mass transfer rate also depends on the nature of the gas and that of the solution. It is well known that the use of flow microreactors enables fast mass transfer in gas–liquid biphasic reactions.[9,10] The second one is the issue of chemistry. The reaction with CO_2 should be faster than that with an electrophilic functional group in the aryllithium species, although the rate depends on the concentration of CO_2 in the solution. The question is what kind of electrophilic functional groups are compatible with the carboxylation. In this chapter we show that these hurdles were overcome using the flow microreactor system and that aromatic carboxylic acids bearing electrophilic functional groups were synthesized from the corresponding aromatic halides.

Results and Discussions

The reactions were carried out using a flow microreactor system composed of three T-shaped micromixers (**M1**, **M2**, and **M3**) and three microtube reactors (**R1**, **R2**, and **R3**) as shown in Scheme 1. An aryl halide and *n*BuLi or PhLi were mixed in **M1** and the halogen/lithium exchange was carried out in **R1** to generate the corresponding aryllithium. In the next step, CO_2 gas (1.5 equiv) that was pressurized to 3.0 bar with a gas pressure regulator valve was introduced at **M2** using a flow controller, and the carboxylation was carried out in **R2**. In the last step the reaction was quenched by MeOH at **M3** and **R3**.

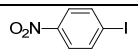
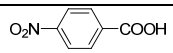
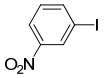
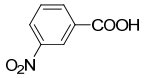
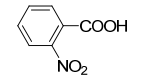
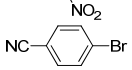
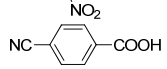
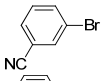
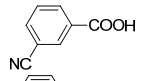
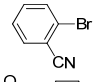
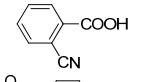
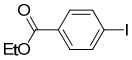
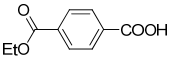
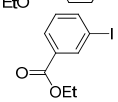
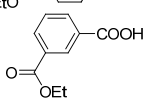
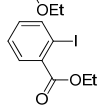
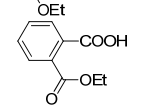
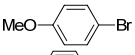
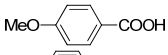
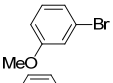
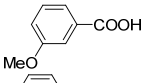
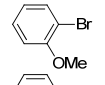
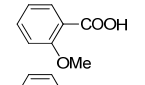
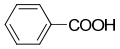


Scheme 1. A flow microreactor system for the reactions of aryllithiums with CO_2 gas. T-shaped micromixers: **M1**, **M2**, **M3**; microtube reactors: **R1**, **R2**, **R3**; flow controller: FC; pressure gage: P.

The carboxylation of *p*-nitrophenyllithium[11] was first examined. The iodine/lithium exchange reaction was carried out with the residence time of 0.014 s at -20 °C. In the previous work,[11] we have already revealed that *p*-nitrophenyllithium can be effectively generated under these conditions. We have also revealed that *p*-nitrophenyllithium decomposes with the residence time longer than ca. 0.4 s at -20 °C. As shown in Table 1,

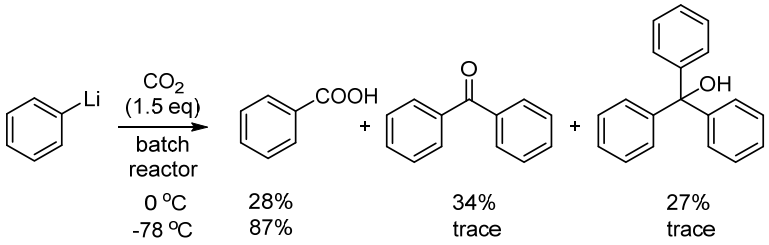
the corresponding carboxylic acid was obtained in 78% yield. This means gas/liquid mass transfer and the chemical reaction of *p*-nitrophenyllithium with CO_2 are much faster than its decomposition. Under similar conditions m- and *o*-nitrophenyllithiums were carboxylated effectively. The carboxylation reactions of *p*-, *m*-, and *o*-cyanophenyllithiums[12] were also successfully accomplished using the flow microreactor system. The carboxylation of alkoxycarbonylphenyllithiums[13] was more challenging, because esters react with organolithiums very quickly. We have already revealed that *p*-ethoxycarbonylphenyllithium decomposes with the residence time longer than ca. 0.4 s at -60 °C.[13] However, the carboxylation of *p*-ethoxycarbonylphenyllithium could be accomplished to obtain the corresponding carboxylic acid in a reasonable yield. Therefore, the gas/liquid mass transfer and the carboxylation reactions are unexpectedly fast, and are much faster than the decomposition even at low temperatures such as -60 °C. Thus, carboxylation of aryllithiums bearing electrophilic functional groups, which is very difficult or impossible by conventional batch reactions, was achieved by using flow microreactors.

Table 1. Carboxylation of aryllithiums with CO_2 gas using a flow microreactor system.[a)]

Halobenzene	RLi	*T* (°C)	t^{R1} (s)	product	yield (%)
	PhLi	-20	0.014		78
	PhLi	-20	0.014		85
	PhLi	-20	0.014		59
	BuLi	-20	0.33		75
	BuLi	-20	0.33		88
	BuLi	-20	0.33		87
	PhLi	-60	0.055		87
	PhLi	-60	0.014		77
	PhLi	-60	0.014		89
	BuLi	-20	2.4		86
	BuLi	-20	2.4		88
	BuLi	-20	2.4		87
	BuLi	-20	4.7		85
		0	4.7		87

a) The reactions were carried out using 1.05 equiv of a lithiating agent and 1.50 equiv of CO_2.

The carboxylation of phenyllithiums bearing electron-donating substituents such methoxy group and unsubstituted phenyllithium are easier as shown in Table 1. Notably, the carboxylation of phenyllithium using CO_2 (1.5 equiv)[14] could be carried out at 0 °C. It is known that at such temperatures the carboxylation of aryllithiums using CO_2 often leads to the formation of significant amounts of byproducts. For example, the carboxylation of phenyllithium at 0 °C in a batch macro reactor gave a mixture of benzoic acid, benzophenone, and triphenylmethanol, although the reaction at -78 °C gave benzoic acid in good selectivity (87% yield; Scheme 2). In contrast, the reaction in the flow microreactor system gave benzoic acid in 87% yield even at 0 °C. This feature of flow microreactor systems, presumably because of fast heat transfer, is especially important from a view point of industrial production.



Scheme 2. Reaction of phenyllithium with carbon dioxide using a conventional macro batch reactor.

The initial products before quenching with methanol in the present reaction are lithium salts of carboxylic acids, which are highly reactive toward activating agents such as TSTU (*O*-(*N*-succinimidyl)-1,1,3,3-tetramethyl uronium tetrafluoroborate) or PyBop (1H-benzotriazole-1-yloxytris(pyrrolidine-1-yl)phosphonium hexafluorophosphate). Therefore, active esters (esters with a good leaving group), which are commonly used for making peptides from carboxylic acids can be directly synthesized. Thus, the product solutions were treated with the activating agents without methanol quenching. No intentionally added base was required. The corresponding active esters were obtained in good yields as shown in Figure 1.

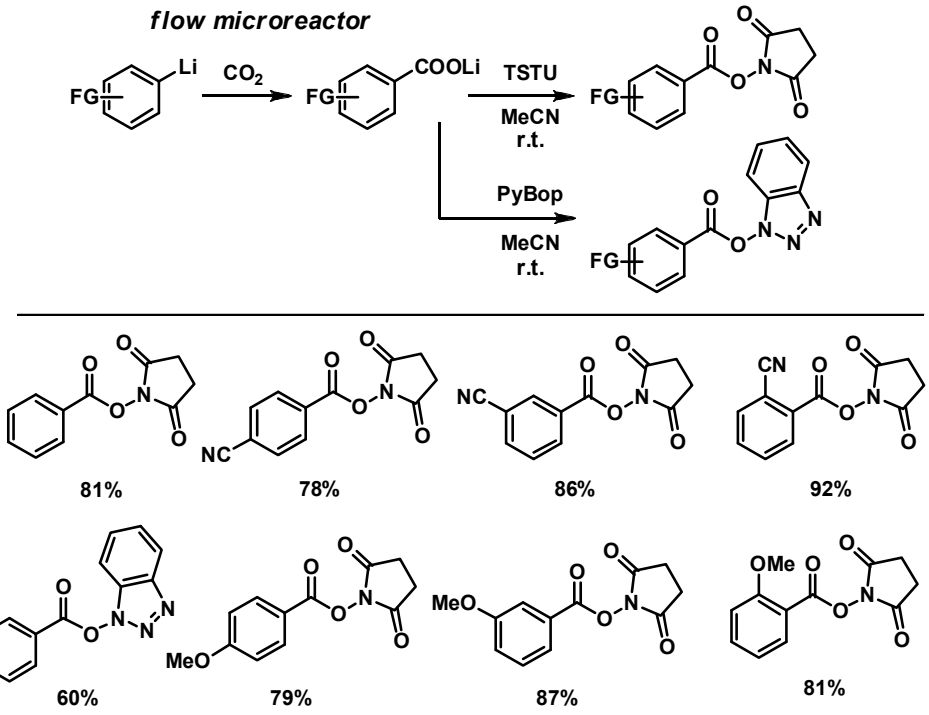


Figure 1. Flow microreactor synthesis of activative esters.

N-Succinimidyl-4-[^{18}F]fluorobenzoate ([^{18}F]SFB) is most commonly used to acylate lysine residues and *N*-terminal amine groups of peptides for positron emission tomography (PET).[15] The following application to this protocol demonstrates the power of the present method, although cold ^{19}F was used instead of hot ^{18}F. The carboxylation of *p*-fluorophenyllithium generated from 1-bromo-4-fluorobenzene with CO_2 followed by the reaction with TSTU was completed within 1 min to give the *N*-succinimidyl-4-fluorobenzoate (SFB) in 55% yield. Then, a solution of SFB and triethylamine in CH_3CN was added to a solution of *cyclo*(Arg-Gly-Asp-d-Phe-Lys) (c(RGDfK)) in H_2O and CH_3CN. The mixture was incubated at 37 °C for 10 min and was purified by preparative HPLC to give the desired coupling product in 91% (Figure 2). The present fast synthesis also demonstrates the possibility of synthesizing compounds containing short-lived positron emitting radionuclide ^{11}C ($t_{1/2}$=20.4 min) using $^{11}CO_2$ [16].

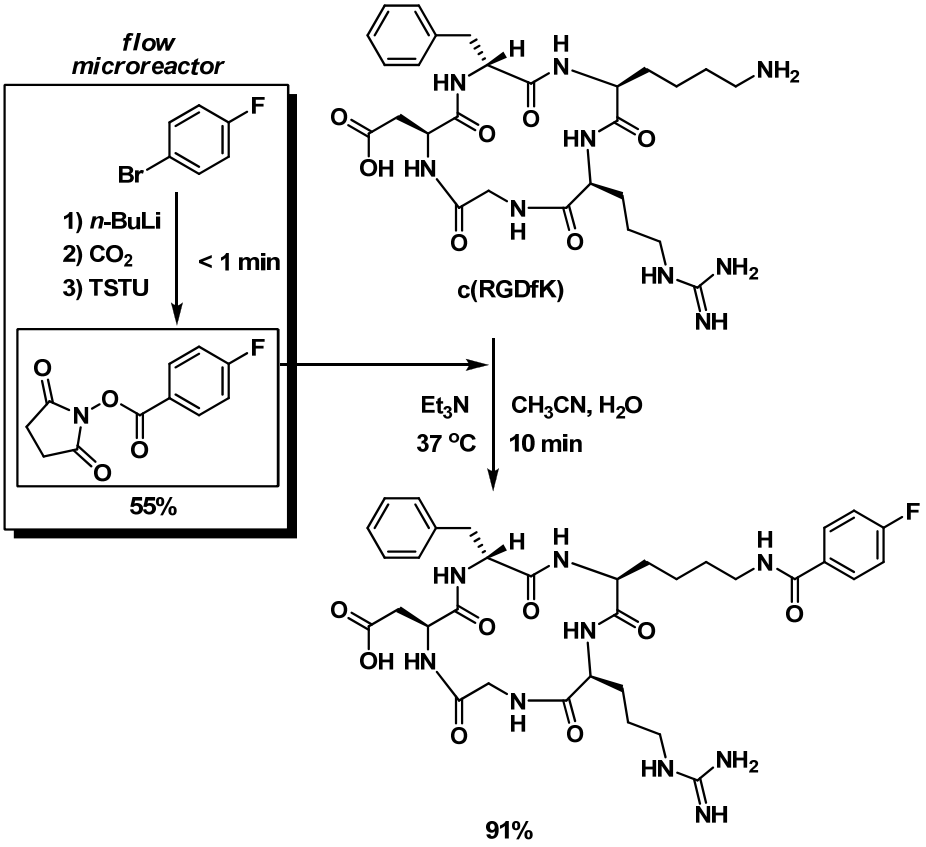


Figure 2. Coupling reaction of *cyclo*(Arg-Gly-Asp-D-Phe-Lys) (c(RGDfK)) with *N*-succinimidyl-4-fluorobenzoate (SFB).

Conclusion

We have developed an extremely fast and efficient method for carboxylation of shortlived Aryllithiums with CO_2 gas by virtue of fast gas/liquid mass transfer and short and precise residence time control in flow microreactors. We anticipate that this new tactic will provide an access to a wide range of carboxylic acids and their derivatives bearing electrophilic functional groups.

Experimental Section

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, CBP1; 0.22

mm x 25 m). ^{1}H and ^{13}C NMR spectra were recorded on Varian MERCURYplus-400 (^{1}H 400 MHz and ^{13}C 100 MHz) spectrometer with Me_4Si or $CDCl_3$ as a standard in $CDCl_3$ unless otherwise noted. ESI mass spectra were recorded on a JEOL JMS-T100CS spectrometer. Gel permeation chromatography (GPC) was carried out on Japan Analytical Industry LC-908 and LC-9201. Diethyl ether and tetrahydrofuran 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. 4-Iodonitrobenzene, 3-iodonitrobenzene, 2-iodonitrobenzene, 4-bromobenzonitrile, 3-bromobenzonitrile, 2-bromobenzonitrile, ethyl 4-iodobenzoate, ethyl 3-iodobenzoate, ethyl 2-iodobenzoate, 4-bromoanisole, 3-bromoanisole, 2-bromoanisole, bromobenzene, methanol and lithium reagents were commercially available. A *cyclo*(Arg-Gly-Asp-D-Phe-Lys) was purchased from peptides international inc as a TFA salt.

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 250, 500 and 1000 μm were purchased from GL Sciences and were cut into appropriate lengths (3.5, 12.5, 25, 50, 100 and 400 cm). The micromixer and microtube reactors were connected with stainless steel fittings (GL Sciences, 1/16 OUW) to construct the flow microreactor in the laboratory. The flow microreactor was dipped in the bath to control the temperature. Solutions were continuously introduced to the flow microreactor using syringe pumps, Harvard PHD2000. After a steady state was reached, the product solution was collected for 2.0 min. When the collection time was longer, the product solution can be obtained in a preparative scale. Carbon dioxide was delivered to the micromixer at a constant rate through a gas pressure regulator valve (3.0 bar), a mass flow controller (Fujikin Inc., FCST1005ZFC-4F2-F100-N2-R2) and a pressure gage (KEYENCE, AP-V80) from a CO_2 gas cylinder.

Typical procedure for synthesis of carboxylic acids.

A flow microreactor 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** (inner diameter ϕ = 1000 μm, length L = 100 cm), **P2** (ϕ = 1000 μm, L = 50 cm), **P3** (ϕ = 1000 μm, L = 400 cm) and **P4** (ϕ = 1000 μm, L = 100 cm)) was used. A solution of halobenzene (0.10 M in THF) (flow rate: 4.0 mL/min (X = Br) or 6.0 mL/min (X = I)) and a solution of lithiating reagent (*n*-BuLi (X = Br) (0.42 M in hexane) (flow rate: 1.0 mL/min) or PhLi (X = I) (0.42 M in cyclohexane and Et_2O) (flow rate: 1.5 mL/min)) were introduced to **M1** (ϕ = 250 μm) by S2 syringe pumps, and the solution was passed through **R1**. The resulting solution was mixed with carbon dioxide (flow rate: 14.4 mL/min (X = Br) or 22.7 mL/min (X = I) (1.50 eq)) in **M2** (ϕ = 250 μm) by a mass flow controller, and was passed through

R2 (ϕ = 1000 μm, L = 12.5 cm). The reaction mixture was quenched with methanol (neat) (flow rate: 3.0 mL/min) in **M3** (ϕ = 500 μm), and the resulting solution was passed through **R3** (ϕ = 1000 μm, L = 50 cm). After a steady state was reached, an aliquot of the product solution was collected for 120 s. The collected solution was treated with sat. aqueous $NaHCO_3$ solution and washed with Et_2O. The aqueous solution was acidified with HCl until pH = 2. Then, the resulting carboxylic acid was extracted several times with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The purity of the carboxylic acids was verified by ^1H NMR.

4-Nitrobenzoic Acid: Obtained in 78% yield (T = -20 °C, t^{R1} = 0.014 s (ϕ = 250 μm, L = 3.5 cm), X = I). The spectral data were identical to those reported in the literature.[17]

3-Nitrobenzoic Acid: Obtained in 85% yield (T = -20 °C, t^{R1} = 0.014 s (ϕ = 250 μm, L = 3.5 cm), X = I). The spectral data were identical to those reported in the literature. [17]

2-Nitrobenzoic Acid: Obtained in 59% yield (T = -20 °C, t^{R1} = 0.014 s (ϕ = 250 μm, L = 3.5 cm), X = I). The spectral data were identical to those reported in the literature. [17]

4-Cyanobenzoic Acid: Obtained in 75% yield (T = -20 °C, t^{R1} = 0.33 s (ϕ = 1000 μm, L = 3.5 cm), X = Br). The spectral data were identical to those reported in the literature.[18]

3-Cyanobenzoic Acid: Obtained in 88% yield (T = -20 °C, t^{R1} = 0.33 s (ϕ = 1000 μm, L = 3.5 cm), X = Br). The spectral data were identical to those reported in the literature.[19]

2-Cyanobenzoic Acid: Obtained in 87% yield (T = -20 °C, t^{R1} = 0.33 s (ϕ = 1000 μm, L = 3.5 cm), X = Br). The spectral data were identical to those reported in the literature.[20]

4-(Ethoxycarbonyl)benzoic Acid: Obtained in 87% yield (T = -60 °C, t^{R1} = 0.055 s (ϕ = 500 μm, L = 3.5 cm), X = I). The spectral data were identical to those reported in the literature.[21]

3-(Ethoxycarbonyl)benzoic Acid: Obtained in 77% yield (T = -60 °C, t^{R1} = 0.014 s (ϕ = 250 μm, L = 3.5 cm), X = I). The spectral data were identical to those commercially available 3-(ethoxycarbonyl)benzoic acid.

2-(Ethoxycarbonyl)benzoic Acid: Obtained in 89% yield (T = -60 °C, t^{R1} = 0.014 s (ϕ = 250 μm, L = 3.5 cm), X = I). The spectral data were identical to those commercially available 2-(ethoxycarbonyl)benzoic acid.

4-Methoxybenzoic Acid: Obtained in 86% yield (T = -20 °C, t^{R1} = 2.4 s (ϕ = 1000 μm, L = 25 cm), X = Br). The spectral data were identical to those reported in the literature.[22]

3-Methoxybenzoic Acid: Obtained in 88% yield (T = -20 °C, t^{R1} = 2.4 s (ϕ = 1000 μm, L = 25 cm), X = Br). The spectral data were identical to those reported in the literature. [22]

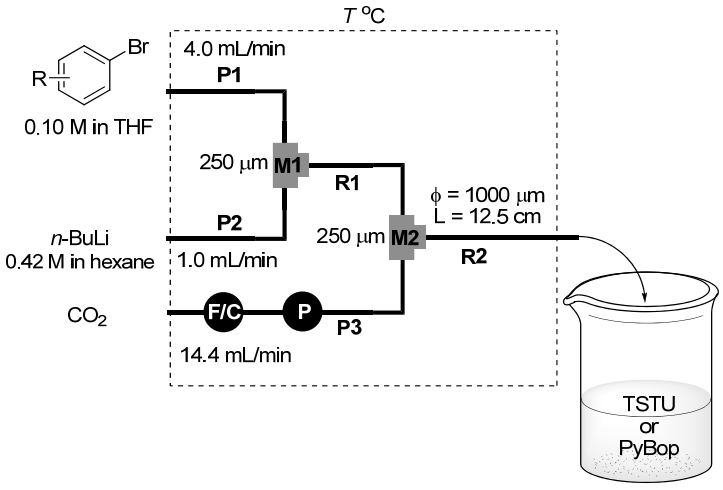
2-Methoxybenzoic Acid: Obtained in 87% yield (T = -20 °C, t^{R1} = 2.4 s (ϕ = 1000 μm, L = 25 cm), X = Br). The spectral data were identical to those reported in the literature. [22]

Benzoic Acid: Obtained in 85% yield (T = -20 °C, t_{R1} = 4.7 s (ϕ = 1000 μm, L = 50 cm), X = Br) or 87% yield (T = 0 °C, t^{R1} = 4.7 s (ϕ = 1000 μm, L = 50 cm), X = Br)). Obtained in 70% yield (T = -20 °C, t^{R1} = 4.7 s (ϕ = 1000 μm, L = 50 cm), X = Br, CO_2 (1.00 eq)). The spectral data were identical to those reported in the literature.[22]

Carboxylation of phenyllithium with CO_2 in a macro batch reactor.

To a solution of phenyllithium (1.08 M in THF, 20 mL, 2.16 mmol) in a 50 mL flask at 0 or -78 °C was added a carbon dioxide (30 mL/min, 2.5 min). After 1 min, the reaction mixture was quenched by sat. aqueous $NaHCO_3$ (20 mL) at 0 °C and washed with Et_2O. The resulting solution was acidified with HCl until pH = 2. Then, the resulting carboxylic acid was extracted several times with ethyl acetate. Yield of benzoic acid was determined by isolation. Yields of benzophenone, and triphenylmethanol were determined by GC analysis using an internal standard. The spectral data were identical to those commercially available benzophenone and triphenylmethanol.

Typical procedure for synthesis of active esters.



Scheme 3. A flow microreactor system for the synthesis of active esters with CO_2 gas. T-shaped micromixers: **M1**, **M2**; microtube reactors: **R1**, **R2**; flow controller: FC; pressure gage: P.

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** (inner diameter ϕ = 1000 μm, length L = 100 cm), **P2** (ϕ = 1000 μm, L = 50 cm) and **P3** (ϕ = 1000 μm, L = 400 cm)) was used. A solution of bromobenzene (0.10 M in THF) (flow rate: 4.0 mL/min) and a solution of BuLi (0.42 M in hexane) (flow rate: 1.0 mL/min)) were introduced to **M1** (ϕ = 250 μm) by syringe pumps, and the solution was passed through **R1**. The resulting solution was mixed with carbon dioxide (flow rate: 14.4 mL/min) in **M2** (ϕ = 250 μm) by a mass flow controller and was passed through **R2** (ϕ = 1000 μm, L = 12.5 cm). After a steady state was reached, the product solution was introduced (120 s) to a solution of TSTU (*O*-(*N*-succinimidyl)-1,1,3,3-tetramethyl uronium tetrafluoroborate) or PyBop (1H-benzotriazole-1-yloxytris(pyrrolidine-1-yl)phosphonium hexafluorophosphate) (0.086 M in CH_3CN/H_2O (6:1), 14 mL (1.50 eq)). After stirring at the same temperature for 1 min, MeOH was added. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. A yield of desired product was determined by isolation by column chromatography or crystallization.

2,5-Dioxopyrrolidin-1-yl Benzoate: Obtained in 81% yield (T = -20 °C, t^{R1} = 4.7 s (ϕ = 1000 μm, L = 50 cm)). After extraction with ethyl acetate, the crude product was purified by column chromatography (hexane/toluene/ethyl acetate = 2/2/1). The spectral data were identical to those reported in the literature.[23]

1H-Benzo[d][1,2,3]triazol-1-yl Benzoate: Obtained in 60% yield (T = -20 °C, t^{R1} = 4.7 s (ϕ = 1000 μm, L = 50 cm)). After extraction with ethyl acetate, the crude product was purified by crystallization with ethyl acetate. The spectral data were identical to those reported in the literature.[24]

2,5-Dioxopyrrolidin-1-yl 4-cyanobenzoate: Obtained in 78% yield (T = -20 °C, t^{R1} = 0.33 s (ϕ = 1000 μm, L = 3.5 cm)). After extraction with ethyl acetate, the crude product was purified by crystallization with ethyl acetate. The spectral data were identical to those reported in the literature. [23]

2,5-Dioxopyrrolidin-1-yl 3-cyanobenzoate: Obtained in 86% yield (T = -20 °C, t^{R1} = 0.33 s (ϕ = 1000 μm, L = 3.5 cm)). After extraction with ethyl acetate, the crude product was purified by crystallization with ethyl acetate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.94 (s, 4H), 7.69 (t, J = 8.0 Hz, 1H), 7.97 (m, 1H) , 8.36 (m, 2H), 8.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 113.7, 117.2, 126.6, 130.0, 134.0, 134.4, 137.8, 160.2, 168.8; HRMS (ESI) *m/z* calcd for $C_{12}H_8N_2O_4$ ($[M+NH_4]^+$): 262.0822, found: 262.0820.

2,5-Dioxopyrrolidin-1-yl 2-cyanobenzoate: Obtained in 92% yield (T = -20 °C, t^{R1} = 0.33 s (ϕ = 1000 μm, L = 3.5 cm)). After extraction with ethyl acetate, the crude product was

purified by crystallization with ethyl acetate. ^{1}H NMR (400 MHz, CDCl3) δ 2.94 (s, 4H), 7.81 (m, 2H), 7.93 (m, 1H) , 8.34 (m, 1H); ^{13}C NMR (100 MHz, Acetone-d6) δ 25.8, 113.7, 116.3, 127.2, 131.8, 133.7, 135.5, 136.0, 160.1, 169.7; HRMS (ESI) *m/z* calcd for $C_{12}H_8N_2O_4$ ($[M+H]^+$): 245.0557, found: 245.0553.

2,5-Dioxopyrrolidin-1-yl 4-methoxybenzoate: Obtained in 79% yield (T = -20 °C, t^{R1} = 2.4 s (ϕ = 1000 μm, L = 25 cm)). After extraction with ethyl acetate, the crude product was purified by crystallization with ethyl acetate. The spectral data were identical to those reported in the literature. [23]

2,5-Dioxopyrrolidin-1-yl 3-methoxybenzoate: Obtained in 87% yield (T = -20 °C, t^{R1} = 2.4 s (ϕ = 1000 μm, L = 25 cm)). After extraction with ethyl acetate, the crude product was purified by crystallization with ethyl acetate. ^{1}H NMR (400 MHz, CDCl3) δ 2.92 (s, 4H), 3.87 (s, 3H), 7.22 (m, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.62 (m, 1H), 7.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.7, 55.5, 114.6, 121.7, 123.0, 126.2, 129.9, 159.7, 161.8, 169.2; HRMS (ESI) *m/z* calcd for $C_{12}H_{11}NO_5$ ($[M+H]^+$): 250.0710, found: 250.0711.

2,5-Dioxopyrrolidin-1-yl 2-methoxybenzoate: Obtained in 81% yield (T = -20 °C, t^{R1} = 2.4 s (ϕ = 1000 μm, L = 25 cm)). After extraction with ethyl acetate, the crude product was purified by crystallization with ethyl acetate. ^{1}H NMR (400 MHz, CDCl3) δ 2.90 (s, 4H), 3.93 (s, 3H), 7.04 (t, J = 8.0 Hz, 2H) , 7.60 (m, 1H), 8.06 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.7, 56.1, 112.2, 113.9, 120.3, 132.7, 136.0, 160.3, 160.6, 169.5; HRMS (ESI) *m/z* calcd for $C_{12}H_{11}NO_5$ ($[M+H]^+$): 250.0710, found: 250.0711.

2,5-Dioxopyrrolidin-1-yl 4-fluorobenzoate: Obtained in 55% yield (T = 0 °C, t^{R1} = 0.22 s (ϕ = 1000 μm, L = 3.5 cm)). After extraction with ethyl acetate, the crude product was purified by column chromatography (hexane/ethyl acetate = 4/1). The spectral data were identical to those reported in the literature.[25]

Coupling reaction of *cyclo*(Arg-Gly-Asp-D-Phe-Lys) and *N*-succinimidyl-4-fluorobenzoate (SFB).

A *cyclo*(Arg-Gly-Asp-D-Phe-Lys) was purchased from Peptides International Inc as a TFA salt. A Shimadzu Prominence HPLC system (System Controller CBM-20A, Solvent Delivery Units LC-20AT, On-line Degassing Unit DGU-20A3, UV-VIS detector SPD-20A and Column Oven CTO-20AC) was used for analytical and preparative HPLC. A YMC-Triart C18/S-5 μm/12 nm 100 x 4.6 mmI.D. column was used for analytical HPLC analysis. A YMC-Triart C18/S-5 μm/12 nm 150 x 10 mm I.D. column with a YMC-Guardpack Triart C18/S-5 μm/12 nm 30 x 10 mmI.D. column were used for preparative HPLC purification. Analytical HPLC used the following mobile phases: 0.1% (v/v) TAF in water (A), 0.1% (v/v) TFA in acetonitrile (B). Program: linear gradient from

5.0% (B) to 95% (B) in 10 min with total flow rate of the solvents 1.0 ml/min. The temperature of the column was 40 °C.Preparative HPLC used the same mobile phases as analytical HPLC. Program: linear gradient from 5.0% (B) to 80% (B) in 20 min with total flow rate of the solvents 5.0 ml/min. The temperature of the column was 40 °C.

To a solution of *cyclo*(Arg-Gly-Asp-D-Phe-Lys) (TFA salt, 0.50 mg, 0.70 nmol) in 100 μL of water and 70 μL of acetonitrile were added a solution of *N*-succinimidyl-4-fluorobenzoate (1.65 mg in 100 μL of acetonitrile, 15 μL, 1.0 nmol) and a solution of triethylamine (14 mg in 1.0 mL of acetonitrile, 15 μL, 2.1 nmol). The mixture was incubated at 37 °C for 10 min. For HPLC analysis, 2.5 μL of the mixture was separated and diluted with 5 μL of 5%(v/v) acetic acid in water and used. 20 μL of 5% (v/v) acetic acid in water was added to the reaction mixture and the mixture was purified by preparative HPLC. The fraction containing the desired product was collected and dried over under reduced pressure to give 0.46 mg (6.3 nmol, 91%) of white solid. MS (ESI, m/z): 726.40 $(M+H)^+$, 724.25 $(M-H)^-$. Purity > 99% (HPLC, UV 220 nm).

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Chapter 4

Anionic Polymerization of *tert*-Butyl Acrylate

Abstract

Living anionic polymerization of *tert*-butyl acrylate initiated by 1,1-diphenylhexyllithium is conducted in a flow microreactor system in the presence of lithium chloride. A high degree of control of the molecular weight distribution is achieved under easily accessible conditions, for example at -20 °C. The subsequent reaction of a reactive polymer chain end with an alkyl methacrylate using an integrated flow micoreactor system leads to the formation of a block copolymer with a narrow molecular weight distribution.

Introduction

Anionic polymerization serves as an excellent method for the synthesis of polymers of well-defined end structures, because the anionic reactive polymer ends are living even in the absence of a capping agent.[1] However, in a conventional macrobatch reactor, living anionic polymerizations in a polar solvent should be carried out at low temperatures such as -78 °C to obtain polymers of narrow molecular weight distribution. The requirement of such low temperatures causes severe limitations in the use of this highly useful polymerization technology in industry. In contrast, such a drawback can be overcome using flow microreactor[2,3,4] systems. Recently, it has been reported that flow microreactors are effective for controlled anionic polymerization[5] of styrenes or alkyl methacrylates and that a high level of control of the molecular weight distribution can be achieved under easily accessible temperatures such as 24 to -28 °C by virtue of the characteristic features of flow microreactors[6,7,8] including fast mixing, fast heat transfer, and precise residence time control.[9,10,11,12,13,14]

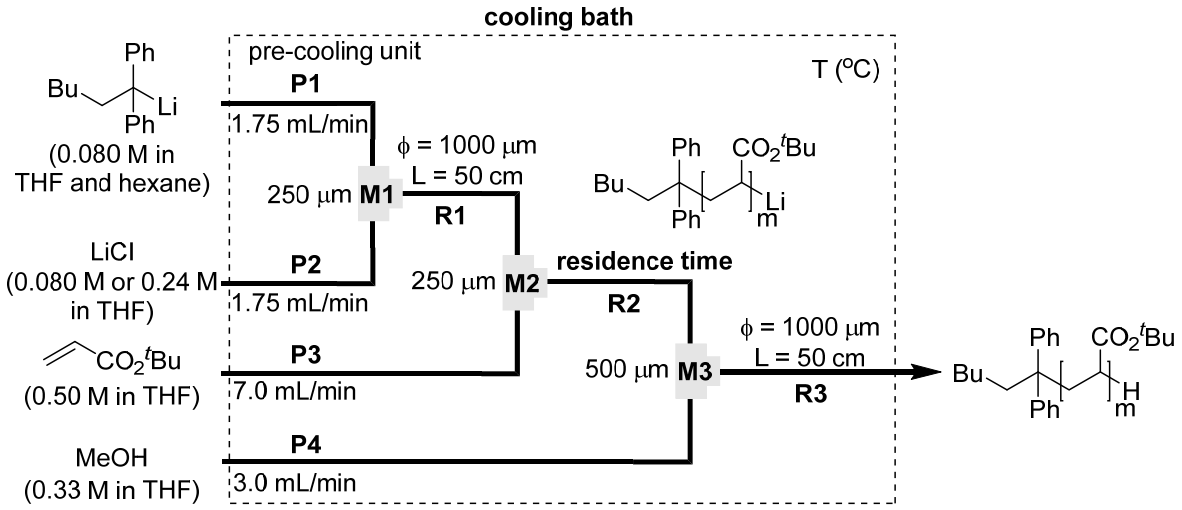
It is well known that anionic polymerization of acrylates[15,16] is more problematic than

that of styrenes or alkyl methacrylates in terms of polymer yield, molecular weight, and its molecular weight distribution because of inherent side reactions such as the nucleophilic attack of the initiator and/or the propagating enolate anion on the ester carbonyl group and the abstraction of an acidic hydrogen on the carbon α to the ester carbonyl group.[17] Therefore, the polymerization should be carried out not only at low temperatures such as -78 °C but also under the addition of significant amount of inorganic lithium salts or lithium alkoxides to prevent such side reactions.[18] However, such requirements cause severe limitations in industry. Moreover, studies on the synthesis of block polymers involving poly(alkyl acrylate) units have been keen.[19]

In this chapter we show that the anionic polymerization of *tert*-butyl acrylate could be more effectively accomplished in a flow microreactor system than in conventional batch macro reactors. The polymers were obtained with a narrow molecular weight distribution under easily accessible conditions such as -20 °C. Moreover, the amount of LiCl as an additive could be significantly reduced in flow microreactors compared with batch macroreactors. Furthermore, structurally well-defined poly(*tert*-butyl acrylate)-block-poly(alkyl methacrylates) copolymers could also synthesized based on livingness of the polymer chain end by virtue of high-resolution reaction time control in an integrated-flow microreactor.

Results and Discussions

The anionic polymerization of *tert*-butyl acrylate in flow microreactors was carried out in the presence of lithium chloride (LiCl). A flow microreactor system composed of three T-shaped micromixers (**M1**, **M2**, and **M3**) and three microtube reactors (**R1**, **R2**, and **R3**) was used (Scheme 1). To suppress the pressure increase in the system micromixer **M3** with an inside diameter of 500 instead of 250 μm was used, although the mixing speed decreases with an increase in the inner diameter.[5b,d] A solution of 1,1-diphenylhexyllithium in tetrahydrofuran (THF)/hexane (97/3 v/v, 0.080 M) and a solution of LiCl in THF were mixed at **M1**, and through **R1** the resulting solution was introduced to **M2**, where a solution of *tert*-butyl acrylate in THF (0.50 M) were mixed. The solution was passed through **R2**, where the polymerization took place. The polymerization was quenched by adding a solution of methanol in THF using **M3** and **R3**. The polymerization was carried out with varying the temperature (T: 20, 0, -20, and -40 °C), the residence time in **R2** (t^{R2}), and the amount of LiCl.



Scheme 1. A flow microreactor system for anionic polymerization of *tert*-butyl acrylate initiated by 1,1-diphenylhexyllithium. T-shaped micromixer: **M1**, **M2** and **M3**. Microtube reactor: **R1**, **R2** and **R3**.

As shown in Table 1, the polymerization could be carried out at 20 °C (entries 1–16), although the reaction in a macro batch reactor should be performed at -78 °C. It is also noteworthy that the polymer was obtained with good molecular-weight distribution control even in the presence of one equivalent of LiCl although itwasreported that use of 10 equivalents of LiCl is needed to get good controllability in batch macroreactors.[19c] Extremely fast heat transfer of the flow microreactor system seems to be responsible for preventing decomposition of the reactive carbanionic polymer chain end. The use of three equivalents of LiCl gave rise to significant improvement of the molecularweight distribution (entries 17–32). The decomposition of the active polymer ends seemed to be greatly suppressed by the presence of an excess amount of LiCl. As shown in Figure 1, polymerization with a residence time (t^{R2}) above ca 0.5 s gave quantitative conversions. Therefore, hereafter the residence time was varied in such region ($t^{R2} > 0.5$ s), where the monomer was consumed completely.

Table 1. Anionic polymerization of *tert*-butyl acrylate in the presence of LiCl initiated by 1,1-diphenylhexyllithium using a flow microreactor system.

entry	[LiCl]/ [initiator]	T (°C)	t^{R2} (s)	conversion (%)	Mn	Mw/Mn
1	1	20	0.16	100	5700	1.24
2			0.56	100	4700	1.24
3			1.12	100	5100	1.26
4			2.24	100	4600	1.24

5		0	0.16	99.3	4600	1.20
6			0.56	100	4700	1.22
7			1.12	100	4900	1.24
8			2.24	100	4400	1.22
9		-20	0.16	96.0	4500	1.19
10			0.56	100	4500	1.20
11			1.12	100	4500	1.22
12			2.24	100	4300	1.20
13		-40	0.16	79.4	3900	1.26
14			0.56	100	4500	1.22
15			1.12	100	4700	1.21
16			2.24	100	4400	1.21
17	3	20	0.16	97.9	5300	1.15
18			0.56	100	5900	1.17
19			1.12	100	5300	1.16
20			2.24	100	5400	1.16
21		0	0.16	93.7	4900	1.14
22			0.56	100	4900	1.13
23			1.12	100	5000	1.14
24			2.24	100	5200	1.14
25		-20	0.16	79.2	4200	1.15
26			0.56	100	4800	1.12
27			1.12	100	4800	1.12
28			2.24	100	5100	1.12
29		-40	0.16	56.7	3200	1.19
30			0.56	98.0	4600	1.13
31			1.12	100	5200	1.12
32			2.24	100	4900	1.12

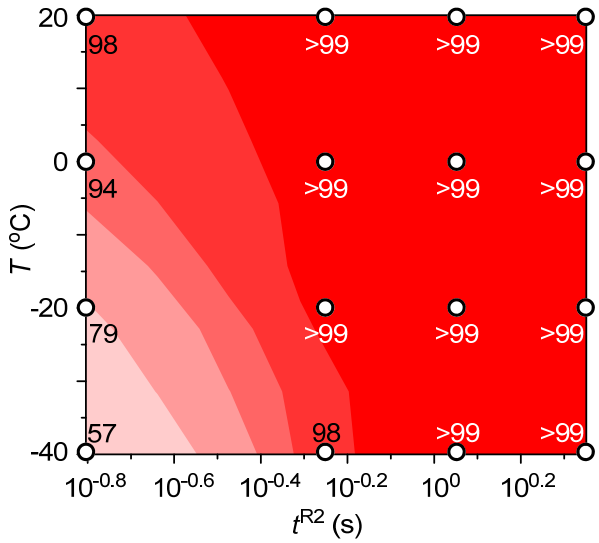
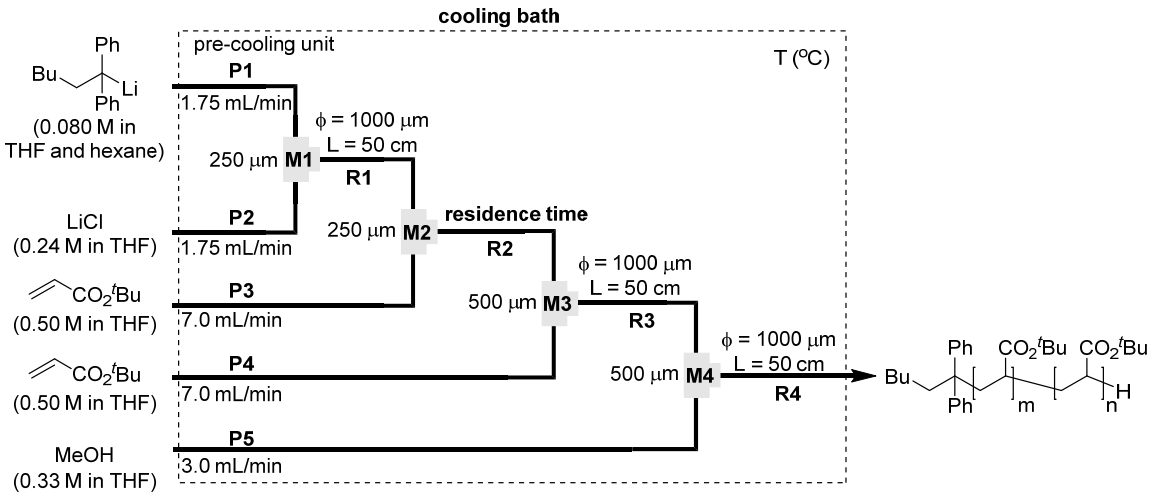


Figure 1. Temperature/residence time map. Contour plots with scatter overlay of the conversion of *tert*-butyl acrylate, which are indicated by numbered circles.

Livingness of the reactive carbanionic polymer chain end is important for synthesis of end functionalized polymers and block copolymers. Thus, the following experiments were carried out to verify the living nature of the polymer chain end using a flow microreactor system consisting of four micromixers (**M1**,**M2**,**M3**, and **M4**) and four microtube reactors (**R1**, **R2**, **R3**, and **R4**) as shown in Scheme 2. A solution of 1,1-diphenylhexyllithium in THF/hexane (97/3 v/v) and a solution of LiCl in THF were mixed using **M1**, and the resulting solution was introduced through **R1** to **M2**, where a solution of *tert*-butyl acrylate in THF was added. The polymerization was carried out in **R2**. Then, a solution of the same monomer in THF was introduced to **M3**, which was connected to **R3** where the second polymerization took place. The polymerization was quenched by adding a solution of methanol using **M4** and **R4**.



Scheme 2. A flow microreactor system for the Sequential anionic polymerization of *tert*-butyl acrylate initiated by 1,1-diphenylhexyllithium. T-shaped micromixer: **M1**, **M2**, **M3** and **M4**. Microtube reactor: **R1**, **R2**, **R3** and **R4**.

First, we examined the effect of reaction temperature (T). The residence time in **R2** (t^{R2}) was fixed to 2.24 s. As shown in Figure 2 the polymer of higher molecular weight was obtained with narrow molecular weight distribution (Mw/Mn = 1.13) at -20 and -40 °C. The increase in the reaction temperature resulted in an increase in theMw/Mn presumably because of decomposition of the reactive polymer chain end. In fact, the bimodal GPC traces indicated that the polymer obtained in **R2** remained unchanged in some extent. Next, the sequential polymerizations were carried out with varying both the temperature (T) and the residence time in **R2** ($t^{R2} > 0.5$ s), and Mw/Mn is plotted against T and t^{R2} (Figure 3). At low temperatures ($T < 0$ °C) the polymer of the narrow molecular-weight distribution (Mw/Mn < 1.15) was obtained, indicating that the sequential polymerization reactions took place without significant decomposition of the living polymer end.

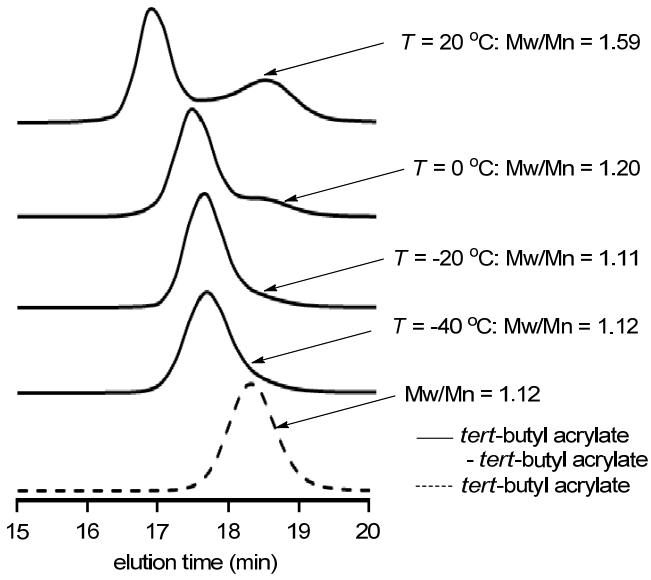


Figure 2. Size exclusion chromatography traces of sequential anionic polymerization of *tert*-butyl acrylate in the integrated flow microreactor system. Effect of reaction temperature (T) in t^{R2}=2.24 s.

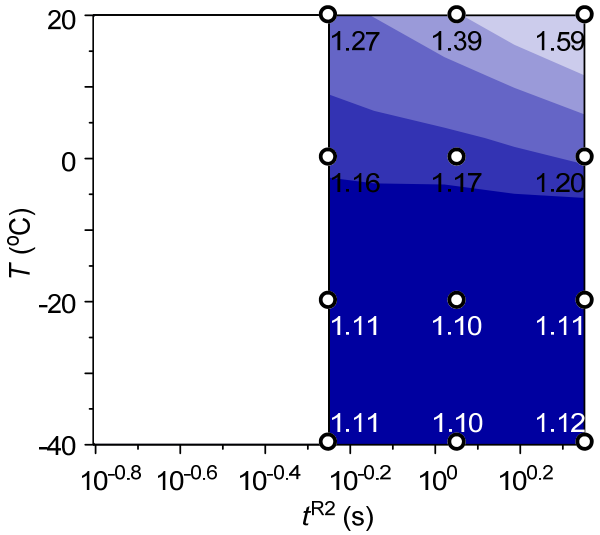


Figure 3. Temperature-residence time map for the sequential anionic polymerization reactions of *tert*-butyl acrylate initiated by 1,1-diphenylhexyllithium in an flow microreactor system. Contour plots with scatter overlay of the molecular-weight distribution, which are indicated by numbered circles.

Based on the livingness of the polymer chain end, we synthesized structurally defined block copolymers of *tert*-butyl acrylateandother alkyl methacrylates such as methyl methacrylate, *tert*-butyl methacrylate, butyl methacrylate and benzyl methacrylate using the

flow microreactor system (T = -20 °C, t^{R2} = 0.56 s). After the polymerization of a *tert*-butyl acrylate in **R2** was complete, a solution of an alkyl methacrylate was introduced to **M3** (See the Supporting Information for details). A polymer of higher Mn was obtained with narrow molecular-weight distribution (Figure 4), indicating that the present method serves as an effective method for the synthesis of block copolymer of *tert*-butyl acrylate and alkyl methacrylates.

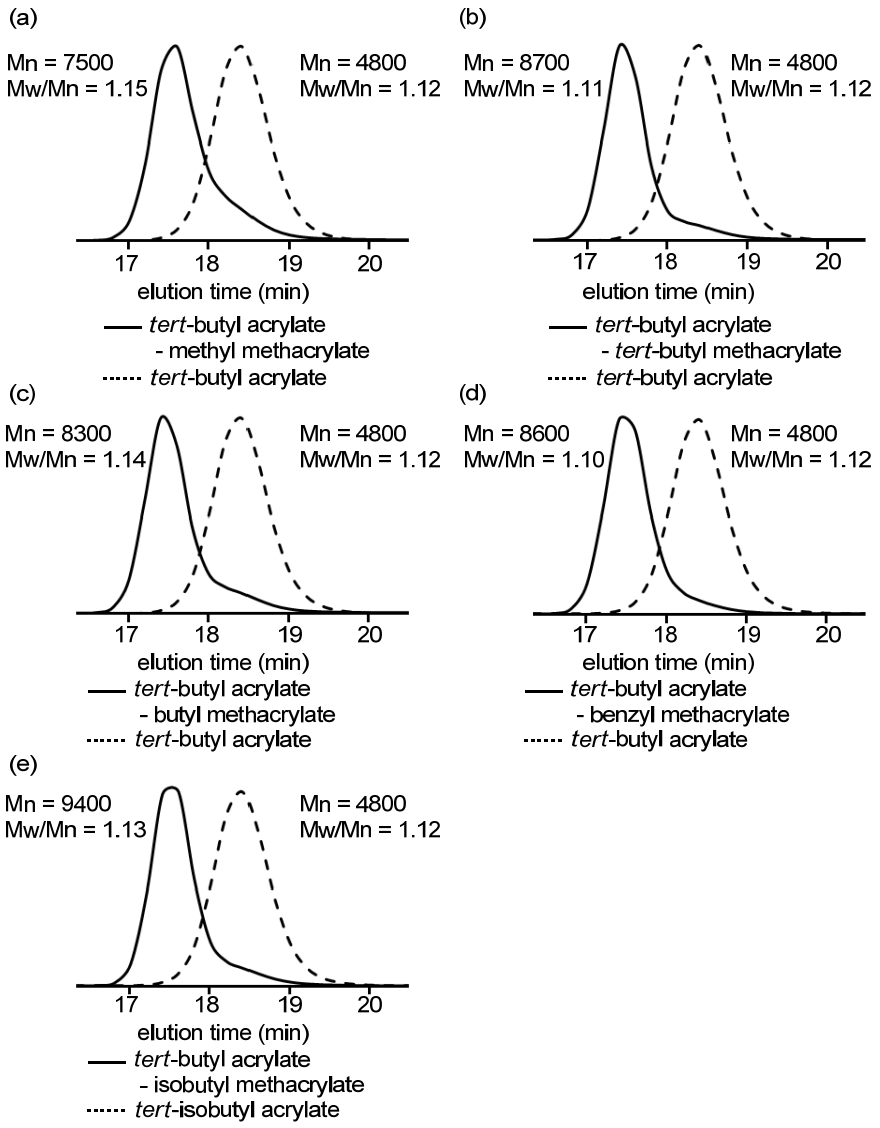


Figure 4. Size exclusion chromatography traces of block copolymers obtained in the integrated flow microreactor system. (a) *tert*-butyl acrylate (-20 °C)/methyl methacrylate (-20 °C), (b) *tert*-butyl acrylate (-20 °C)/*tert*-butyl methacrylate (20 °C), (c) *tert*-butyl acrylate (-20 °C)/butyl methacrylate (-20 °C), (d) *tert*-butyl acrylate (-20 °C)/benzyl methacrylate (-20 °C), (e) *tert*-butyl acrylate (-20 °C)/isobutyl methacrylate (-20 °C).

Conclusion

The use of flow microreactors enables the anionic polymerization of *tert*-butyl acrylate at easily accessible temperatures -20 °C and the amount of LiCl can be significantly reduced while keeping a narrow molecularweight distribution. Block copolymerization reactions of *tert*-butyl acrylate/alkyl methacrylates could be achieved by virtue of the livingness of the polymer chain end. The observations illustrated here open a new possibility for the synthesis of structurally well-defined polymers using flow-microreactor-system controlled anionic polymerization.

Experimental Section

General.

GC analysis was performed on a SHIMADZU GC-2014 gas chromatograph equipped with a flame ionization detector using a fused silica capillary columm. Tetrahydrofuran (THF) was purchased from Kanto as a dry solvent and used as obtained. Lithium chloride (LiCl) was purchased from Sigma Aldrich as a THF solution. All monomer was distilled twice over CaH_2 before use. Stainless steel (SUS304) T-shaped micromixers having inner diameter of 250 and 500 μm were manufactured by Sanko Seiki Co., Inc. Stainless steel (SUS316) microtube reactors having inner diameter of 1000 μm were purchased from GL Sciences. Micromixers and microtube reactors were connected with stainless type fittings (GL Sciences, 1/16 OUW). The flow microreactor system was dipped in a cooling bath to control the temperature. Solutions were introduced to a flow microreactor system using syringe pumps, Harvard Model 11, equipped with gastight syringes purchased from SGE.

Molecular weight and molecular weight distribution.

The molecular weight (Mn) and molecular weight distribution (Mw/Mn) were determined in THF at 40 °C with a Shodex GPC-101 equipped with two LF-804L columns (Shodex) and an RI detector using a polystyrene (polySt) standard sample for calibration.

Preparation of a solution of 1,1-diphenylhexyllithium (DPHLi).

To a solution of a little excess amount of 1,1-diphenylethylene in THF (1.1 eq) was added a solution of *n*-BuLi in hexane at 0 °C, and the solution was warmed to room temperature.

Typical procedure for anionic polymerization of *tert*-butyl acrylate (^{t}BuA) using a flow microreactor system

A flow microreactor system composed of three T-shaped micromixers (**M1**, **M2**, **M3**) and three microtube reactors (**R1**, **R2**, **R3**) was used. Microtube pre-cooling units (**P1**, **P2**: ϕ = 1000 μm, length = 50 cm, **P3**, **P4**: ϕ = 1000 μm, length = 100 cm) were connected to each inlet of **M1**, **M2**, **M3**. The whole flow microreactor system was dipped in a cooling bath of 20 ºC, 0 ºC, -20 ºC or -40 ºC. A solution of 1,1-diphenylhexyllithium in THF/hexane (97/3 v/v) (0.080 M) (flow rate: 1.75 mL min^{-1}) and a solution of lithium chloride in THF (0.08 M or 0.24 M) (flow rate: 1.75 mL min^{-1}) were introduced to **M1** (ϕ = 250 μm) by syringe pumps. The resulting solution was passed through **R1** (ϕ = 1000 μm, length = 50 cm) and was mixed with *tert*-butyl acrylate in THF (0.50 M) (flow rate: 7.0 mL min^{-1}) in **M2** (ϕ = 250 μm). The resulting solution was passed through **R2** (ϕ = 1000 μm, length = 3.5, 12.5, 25 or 50 cm) and was quenched with a solution of methanol in THF (0.33M) (flow rate: 3.0 mL min^{-1}) in **M3** (ϕ = 500 μm). The resulting solution was passed through **R3** (ϕ = 1000 μm, length = 50 cm). After a steady state was reached, the product solution was taken (30 s). The conversion of *tert*-butyl acrylate was determined by GC. The solvent was removed under reduced pressure to obtain the polymer product and the polymer sample was analyzed with size exclusion chromatography with the calibration using standard polystyrene samples.

Flow microreactor system for the sequential anionic polymerization of *tert*-butyl acrylate.

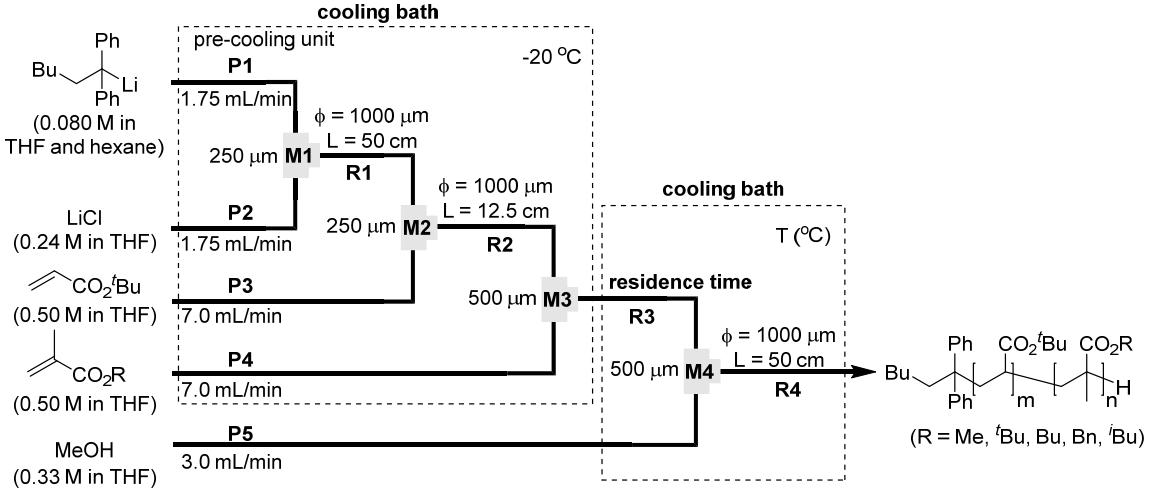
A flow microreactor system composed of four T-shaped micromixers (**M1**, **M2**, **M3**, **M4**) and four microtube reactors (**R1**, **R2**, **R3**, **R4**) was used. Microtube pre-cooling units (**P1**, **P2**: ϕ = 1000 μm, length = 50 cm, **P3**, **P4**, **P5**: ϕ = 1000 μm, length = 100 cm) were connected to each inlet of the micromixers **M1**, **M2**, **M3**, **M4**. The whole flow microreactor system was dipped in a cooling bath of 20 ºC, 0 ºC, -20 ºC or -40 ºC. A solution of 1,1-diphenylhexyllithium in THF/hexane (97/3 v/v) (0.080 M) (flow rate: 1.75 mL min^{-1}) and a solution of lithium chloride in THF (0.24 M) (flow rate: 1.75 mL min^{-1}) were introduced to **M1**(ϕ = 250 μm) by syringe pumps. The resulting solution was passed through **R1** (ϕ = 1000 μm, length = 50 cm) and was mixed with *tert*-butyl acrylate in THF (0.50 M) (flow rate: 7.0 mL min^{-1}) in **M2** (ϕ = 250 μm). The resulting solution was passed through **R2** (ϕ = 1000 μm, length = 3.5, 12.5, 25 or 50 cm) and was mixed with *tert*-butyl acrylate in THF (0.50 M) (flow rate: 7.0 mL min^{-1}) in **M3** (ϕ = 500 μm). The resulting solution was passed through **R3** (ϕ = 1000 μm, length = 50 cm) and was quenched with a solution of methanol in THF (0.33M) (flow rate: 3.0 mL min^{-1}) in **M4** (ϕ = 500 μm). The resulting solution was passed through **R4** (ϕ = 1000 μm, length = 50 cm). After a steady

state was reached, the product solution was taken (30 s). The conversions of the *tert*-butyl acrylate was determined by GC. The solvent was removed under reduced pressure to obtain the polymer product and the polymer sample was analyzed with size exclusion chromatography with the calibration using standard polystyrene samples and the results are summarized in Table 2.

Table 2. Sequential anionic polymerization of *tert*-butyl acrylate in a flow microreactor system.

bath temperature (°C)	residence time in **R2** (s)	conv. (%)	Mn	Mw/Mn
20	0.16	100	9000	1.21
	0.56	100	9100	1.27
	1.12	100	8300	1.39
	2.24	100	8600	1.59
0	0.16	100	8700	1.11
	0.56	100	9400	1.16
	1.12	100	9000	1.17
	2.24	100	9000	1.20
-20	0.16	100	8500	1.11
	0.56	100	9200	1.11
	1.12	100	8500	1.10
	2.24	100	8900	1.11
-40	0.16	100	8600	1.11
	0.56	99.6	9000	1.11
	1.12	100	8600	1.10
	2.24	100	8800	1.12

Flow microreactor system for the block copolymerization of *tert*-butyl acrylate and alkyl methacrylates.



A flow microreactor system composed of four T-shaped micromixers (**M1**, **M2**, **M3**, **M4**) and four microtube reactors (**R1**, **R2**, **R3**, **R4**) was used. Microtube pre-cooling units (**P1**, **P2**: ϕ = 1000 μm, length = 50 cm, **P3**, **P4**, **P5**: ϕ = 1000 μm, length = 100 cm) were connected to each inlet of the micromixers **M1**, **M2**, **M3** and **M4**. **M1**, **R1**, **M2**, **R2** and **M3** were dipped in a cooling bath of -20 °C. **R3**, **M4** and **R4** were dipped in a cooling bath of different temperature (T °C). A solution of 1,1-diphenylhexyllithium in THF/hexane (97/3 v/v) (0.080 M) and a solution of lithium chloride in THF (0.24 M) were introduced to **M1**(ϕ = 250 μm) by syringe pumps. The resulting solution was passed through **R1** (ϕ = 1000 μm, length = 50 cm) and was mixed with *tert*-butyl acrylate in THF (0.50 M) (flow rate: 7.0 mL min^{-1}) in **M2** (ϕ = 250 μm). The resulting solution was passed through **R2** (ϕ = 1000 μm, length = 12.5 cm) and was mixed with alkyl methacrylates in THF (0.50 M) (flow rate: 7.0 mL min^{-1}) in **M3** (ϕ = 500 μm). The resulting solution was passed through **R3** (ϕ = 1000 μm, length = 800 (methyl methacrylate) or ϕ = 1000 μm, length = 50 cm + 1200 cm (*tert*-butyl methacrylate, butyl methacrylate, benzyl methacrylate, isobutyl methacrylate)) and was quenched with a solution of methanol in THF (0.33M) (flow rate: 3.0 mL min^{-1}) in **M4** (ϕ = 500 μm). The resulting solution was passed through **R4** (ϕ = 1000 μm, length = 50 cm). After a steady state was reached, the product solution was taken (30 s). Cooling bath was controlled at the appropriate temperature (MMA, BuMA, BnMA, ^{i}BuMA: T = -20 °C, ^{t}BuMA: T = 20 °C (**R3** (50 cm) was carried out at -20 °C)). The conversions of the *tert*-butyl acrylate and alkyl methacrylates were determined by GC. The solvent was removed under reduced pressure to obtain the polymer product and the polymer sample was analyzed with size exclusion chromatography with the calibration using standard polystyrene samples and the results are summarized in Table 3. The crude product was purified by gel permeation chromatography ($CHCl_3$).

Table 3. Controlled block copolymerization of *tert*-butyl acrylate and alkyl methacrylates in a flow microreactor system.

tert-butyl acrylate (**m1**)	alkyl methacrylates (**m2**)	Bath temperature (°C)	residence time in **R3** (s)	conv. (%)		Mn	Mw/Mn
				m1	**m2**		
^{t}BuA	MMA	-20	21.54	100	98.1	7500	1.15
	^{t}BuMA	20	33.66	100	98.9	8700	1.11
	BuMA	-20	33.66	100	100	8300	1.14
	BnMA	-20	33.66	100	100	8600	1.10
	^{i}BuMA	-20	33.66	100	100	9400	1.13

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Chapter 5

Anionic Polymerization of Fluorine-Containing Methacrylates

Abstract

Living anionic polymerization of perfluoroalkyl methacrylates initiated by 1,1-diphenylhexyllithium was conducted without adding lithium chloride in an integrated flow microreactor system. The high degree of molecular weight distribution (Mw/Mn) control was achieved at 0 °C (2-(nonafluorobutyl)ethyl and 2-(tridecafluorohexyl)ethyl methacrylates) or −40 °C (2,2,2-trifluoroethyl methacrylate). The subsequent reaction of a reactive polymer chain end with alkyl methacrylates or *tert*-butyl acrylate led to the formation of fluorine-containing block copolymers with narrow Mw/Mn.

Introduction

Fluorine-containing polymers have attracted a great deal of attention because of their unique characteristics, namely, low surface energy, oil and water repellence, low refractive index, and high chemical and thermal stability.[1] Such polymers can be utilized for various applications such as electronics, biomaterials, optical devices, and coatings.[2] Although radical polymerization of fluorine-containing vinyl monomers has been studied mainly,[3] the anionic polymerization should be one of the key technologies to obtain the fluorine-containing polymers because fluorine and perfluoroalkyl substituents reduce the electron density of the carbon–carbon double bond of vinyl monomers.

Perfluoroalkyl methacrylates seem to be suitable monomers for anionic polymerization because of large electron-withdrawing inductive effect of perfluoroalkoxycarbonyl groups.[4] In fact, the *e*-values of perfluoroalkyl methacrylates are larger than alkyl methacrylates, although perfluoroalkyl substituents are linked at the position remote from the vinyl group. For example, the *e*-value of 2,2,2-trifluoroethyl methacrylate ($e = 0.98$) is much larger than that of ethyl methacrylate ($e = 0.44$).[5] However, it is well known that anionic

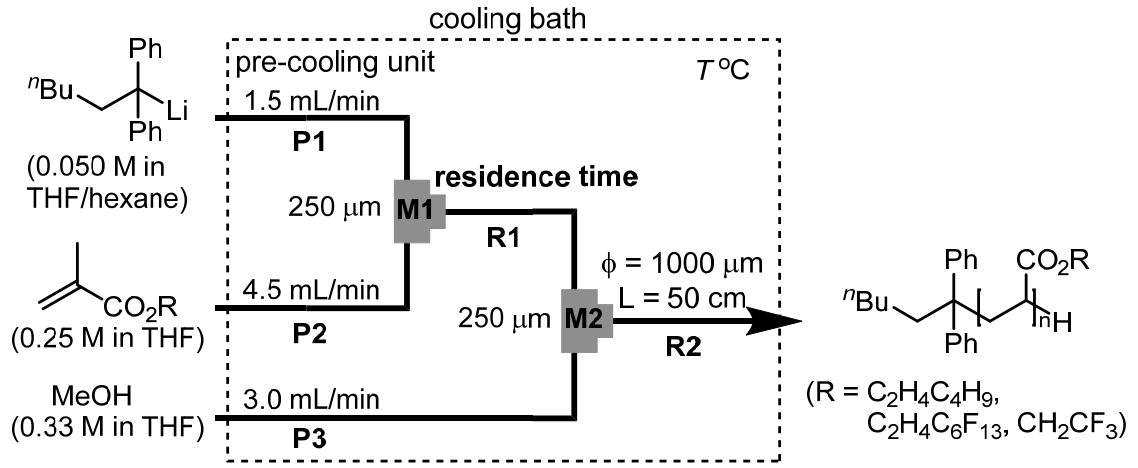
polymerization of perfluoroalkyl methacrylates is more problematic compared with that of alkyl methacrylates in terms of the polymer yield, molecular weight, and Mw/Mn because of inherent side reactions such as the nucleophilic attack of the initiator and/or the propagating enolate anion on the ester carbonyl group.[4] Narita et al. reported anionic polymerization of perfluoroalkyl methacrylates using various initiators, namely, zincate complexes, Grignard reagents, and organolithiums, but the yields of the polymers were far from quantitative and the livingness of the polymerization was ambiguous.[6] Recently, Nakahama and Hirao reported that anionic polymerization of perfluoroalkyl methacrylates initiated by 1,1-diphenyl-3-methylpentyllithium was successfully carried out to obtain the polymers in quantitative yields, but very low temperatures such as −78 °C and the use of four equivalents of lithium chloride to prevent side reactions were required.[7]

In this chapter, we show that flow microreactors can serve as effective tools for the anionic polymerization of perfluoroalkyl methacrylates. The polymers were obtained with narrow Mw/Mn under easily accessible temperatures without using lithium chloride which might cause polymer product contamination. Furthermore, structurally well-defined block copolymers containing poly(perfluoroalkyl methacrylate) segment were synthesized because of the livingness of the polymer chain end by virtue of high-resolution reaction time control[8] in an integrated flow microreactor.

Results and Discussions

We first examined the anionic polymerization of 2-(nonafluorobutyl) ethyl methacrylate in the absence of lithium chloride (LiCl) using a flow microreactor system composed of two T-shaped micromixers (**M1** and **M2**) and two microtube reactors (**R1** and **R2**) (Scheme 1). The inner diameter of **M1** and **M2** was 250 μm.

A solution of 1,1-diphenylhexyllithium in tetrahydrofuran (THF)–hexane (98:2 v/v, 0.050 M) and a solution of 2-(nonafluorobutyl) ethyl methacrylate in THF (0.25 M) were mixed at **M1**, and the resulting solution was introduced to **R1**, where the polymerization took place. The solution was passed through **M2** and **R2**, where the polymerization was quenched by adding a solution of alcohol in THF. The polymerization was carried out with varying the temperature (T: 20, 0, −20, −30, and −40 °C), and the residence time in **R1** (t^{R1}).



Scheme 1. A flow microreactor system for anionic polymerization of perfluoroalkyl methacrylates initiated by 1,1-diphenylhexyllithium. T-shaped micromixer: **M1**, and **M2**. Microtube reactor: **R1**, and **R2**.

As shown in Table 1, the polymerization of 2-(nonafluorobutyl)ethyl methacrylate could be carried out at 20 °C (entries 1–7), although the reaction in a macro batch reactor should be performed at −78 °C. It is also noteworthy that the polymer was obtained with good Mw/Mn control even in the absence of LiCl (entries 1–35). Higher temperatures led to the formation of the polymers of higher Mn presumably because of side reactions such as the attack of organolithium intermediates on the carbonyl groups. Extremely fast heat transfer of the flow microreactor system seems to be responsible for preventing decomposition of the reactive carbanionic polymer chain end. The Mn is plotted against the conversion in Figure 1a, and the obtained lines for different temperatures are almost the same with the theoretically expected line. Plots of $\ln(M/M_0)$ against residence time in **R1** display a nice correlation with the temperature (Figure 1b). Therefore, the reactive carbanionic polymer chain end is really living during the polymerization. Polymerization reactions of other perfluoroalkyl methacrylates were also examined using the flow microreactor system. Thus, 2-(tridecafluorohexyl)ethyl methacrylate and 2,2,2-trifluoroethyl methacrylate underwent the polymerization in a highly controlled manner to give the polymers of narrow Mw/Mn at 20 or −40 °C (entries 36–50). These results indicate that the use of flow microreactor systems opens a new possibility of living anionic polymerization of perfluoroalkyl methacrylates.

Table 1. Anionic polymerization of perfluoroalkyl methacrylates initiated by 1,1-diphenylhexyllithium using flow microreactors

entry	R	T (°C)	t^{R1} (s)	conv. (%)	Mn	Mw/Mn
1	$C_2H_4C_4F_9$	20	0.27	80	4800	1.14
2			0.47	87	5200	1.13
3			0.98	96	5600	1.13
4			2.0	97	5800	1.14
5			3.9	100	6200	1.14
6			7.9	100	6100	1.14
7			16	100	6300	1.15
8		0	0.27	70	4200	1.13
9			0.47	84	4800	1.11
10			0.98	94	5300	1.10
11			2.0	100	5300	1.10
12			3.9	100	6000	1.11
13			7.9	100	5900	1.11
14			16	100	6000	1.12
15		-20	0.27	47	3000	1.23
16			0.47	56	3500	1.12
17			0.98	81	4500	1.09
18			2.0	95	4900	1.07
19			3.9	100	5700	1.08
20			7.9	100	5600	1.08
21			16	100	5700	1.08
22		-30	0.27	44	2800	-
23			0.47	47	2800	-
24			0.98	71	3600	1.17
25			2.0	86	4500	1.08
26			3.9	100	5000	1.07
27			7.9	100	5600	1.07
28			16	100	5600	1.08
29		-40	0.27	34	2000	-
30			0.47	32	2400	-
31			0.98	49	2900	-
32			2.0	78	3900	1.11
33			3.9	89	4600	1.08

34			7.9	95	5500	1.08
35			16	100	5500	1.06
36	$C_2H_4C_6F_{13}$	20	16	98	5400	1.11
37			31	97	5400	1.10
38			63	97	5200	1.14
39		0	16	100	5600	1.08
40			31	100	5300	1.11
41			63	100	5500	1.08
42		-15	16	100	5700	1.07
43			31	100	5700	1.07
44			63	100	5700	1.07
45	CH_2CF_3	-20	63	89	2400	1.37
46			94	88	2300	1.34
47		-40	63	100	3000	1.21
48			94	100	2900	1.22
49		-60	63	100	3300	1.21
50			94	100	3300	1.20

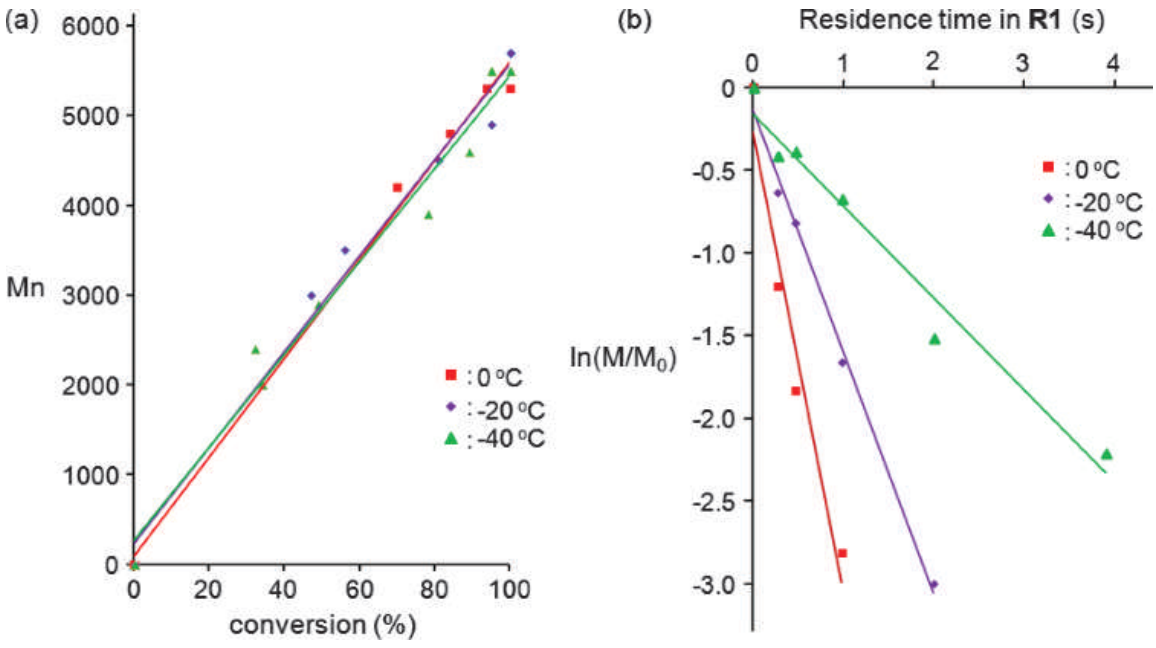
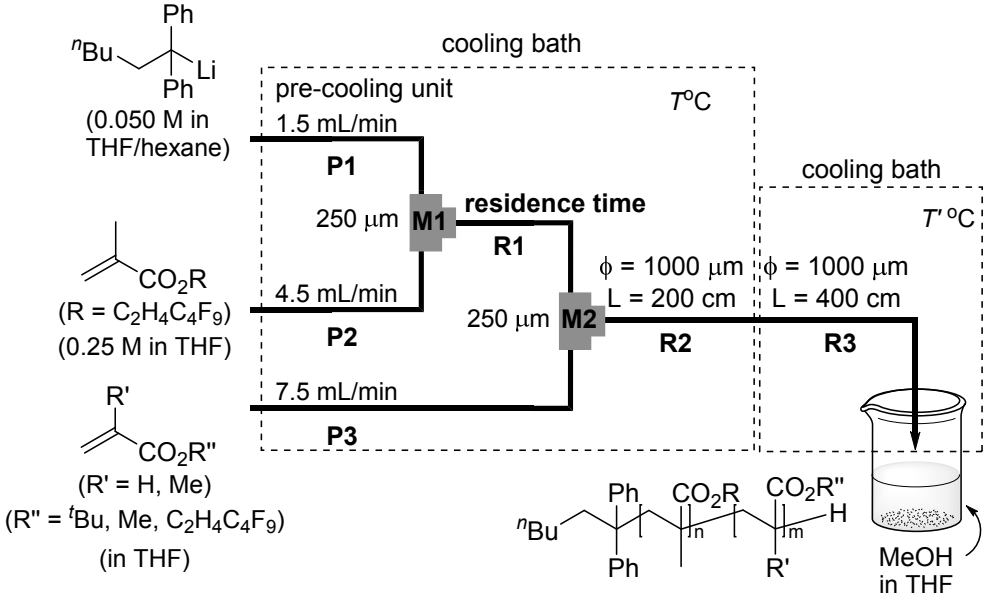


Figure 1. Anionic polymerization of 2-(nonafluorobutyl)ethyl methacrylate initiated by 1,1-diphenylhexyllithium. (a) Plots of *M*n against the conversion and (b) plots of ln(M/M_0) against the residence time in **R1**

Livingness of the reactive carbanionic polymer chain end is important for synthesis of end functionalized polymers and block copolymers. Thus, the following experiments were carried out to verify the living nature of the polymer chain end using flow microreactor systems consisting of two micromixers (**M1** and **M2**) and three microtube reactors (**R1**, **R2**, and **R3**) as shown in Scheme 2. A solution of 1,1-diphenylhexyllithium in THF–hexane (98:2 v/v) and a solution of 2-(nonafluorobutyl)ethyl methacrylate in THF were mixed using **M1**, and the resulting solution was introduced through **R1**, where the polymerization was carried out. Then, a solution of the same or another monomer in THF was introduced to **M2**, which was connected to **R2** and **R3** where the second polymerization took place. The results obtained with varying the temperature (T: 0, −20, −30, and −40 °C) and the residence time in **R1** (t^{R1}: 0.27, 0.47, 0.98, 2.0, 3.9, 7.9 and 16 s) are profiled in Figure 2.



Scheme 2. Flow microreactor system for anionic polymerization of perfluoroalkyl methacrylates initiated by 1,1-diphenylhexyllithium. T-shaped micromixer: **M1** and **M2**; Microtube reactor: **R1**, **R2** and **R3**.

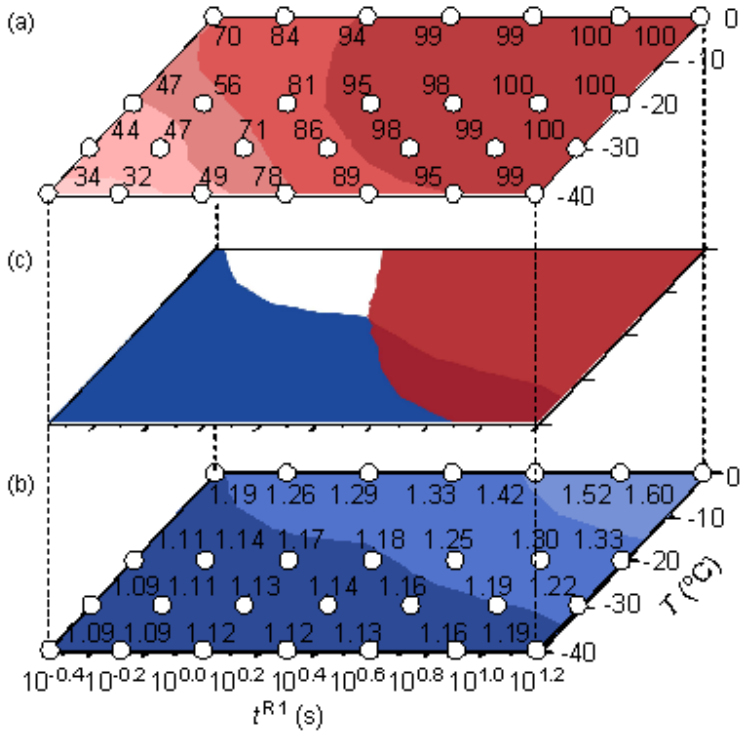


Figure 2. Temperature–residence time (in **R1**) map for the sequential anionic polymerization of 2-(nonafluorobutyl)ethyl methacrylate initiated by 1,1-diphenylhexyllithium in flow microreactors. (a) Contour map with scatter overlay of the conversion of 2-(nonafluorobutyl)ethylmethacrylate in the first polymerization of 2-(nonafluorobutyl)ethylmethacrylate,which is indicated by numbered circles; (b) contour map with scatter overlay of the Mw/Mn in the sequential polymerization of 2-(nonafluorobutyl)ethyl methacrylate, which is indicated by numbered circles; and (c) the domain that gave high conversion (>95 %) and narrow Mw/Mn (Mw/Mn<1.2)

In Figure 2a, the conversion for the first polymerization of 2-(nonafluorobutyl)ethyl methacrylate is plotted against the temperature (T) and the residence time in **R1** (t^{R1}). In the low temperature (T)–short residence time (t^{R1}) region, 2-(nonafluorobutyl) ethyl methacrylate remained unchanged to some extent because polymerization is rather slow at low temperatures. In Figure 2b, the Mw/Mn of polymer thus obtained by sequential anionic polymerization of 2-(nonafluorobutyl)ethyl methacrylate is plotted against T and t^{R1}. The increase in T and t^{R1} resulted in an increase in the Mw/Mn (Figure 2b) presumably because of decomposition of the reactive polymer chain end. However, narrow Mw/Mn (Mw/Mn<1.2) with quantitative conversion in the first polymerization of 2-(nonafluorobutyl)ethyl methacrylate (>95 %) was obtained with the appropriate residence time and temperature shown in Figure 2c. It is important to note that the sequential polymerization can be successfully carried out without significant decomposition of the

living polymer end even in the absence of LiCl.

Based on the livingness of the polymer chain end, we synthesized structurally defined block copolymers of 2-(nonafluorobutyl) ethyl methacrylate (NFBEMA) and other alkyl (meth) acrylates such as *tert*-butyl methacrylate (^{t}BuMA), methyl methacrylate (MMA) and *tert*-butyl acrylate (^{t}BuA) using the flow microreactor. Based on the temperature residence time map shown in Figure 2c, we carried out the first polymerization of 2-(nonafluorobutyl)ethyl methacrylate in **R1** with the residence time of 7.9 s at −40 °C. Then, a solution of a second monomer was introduced to **M2** (Scheme 2). A polymer of higher Mn was obtained with narrow Mw/Mn (Figure 3), indicating that the present method serves as an effective method for the synthesis of block copolymer involving poly(2-(nonafluorobutyl) ethyl methacrylate).

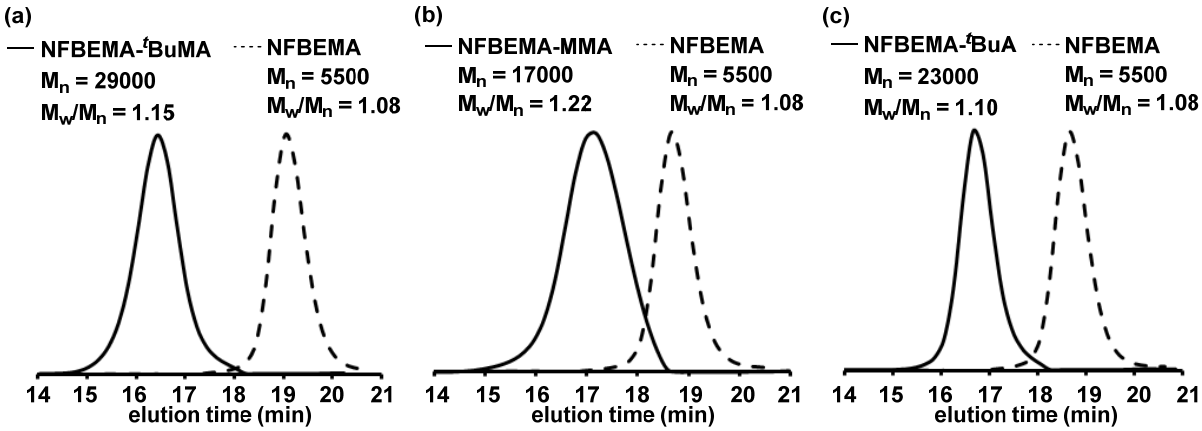
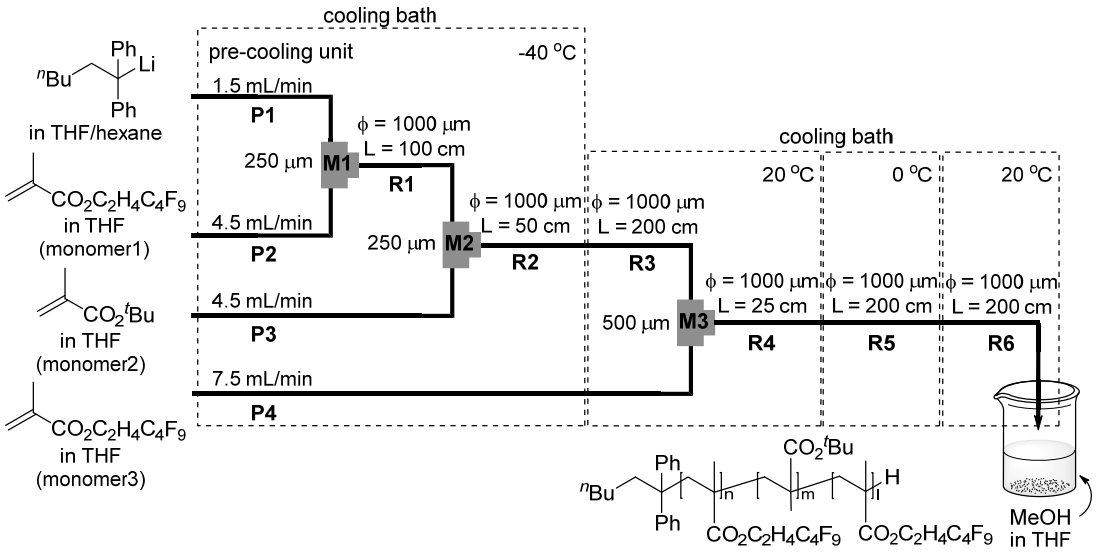


Figure 3. Size exclusion chromatography traces of block copolymers obtained in the integrated flow microreactor system. (a) 2-(Nonafluorobutyl) ethyl methacrylate (NFBEMA) (−40 °C)–*tert*-butyl methacrylate (tBuMA) (20 °C), (b) 2-(nonafluorobutyl)ethyl methacrylate (NFBEMA) (−40 °C) – methyl methacrylate (MMA) (−30 °C), and (c) 2-(nonafluorobutyl)ethyl methacrylate (NFBEMA) (−40 °C) – *tert*-butyl acrylate (tBuA) (−20 °C)

Next, we examined the sequential polymerization of 2-(nonafluorobutyl) ethyl methacrylate, *tert*-butyl methacrylate, and 2- (nonafluorobutyl)ethyl methacrylate to make the corresponding ABA type block copolymer using an integrated flow microreactor composed of three T-shaped micromixers (**M1**, **M2**, and **M3**) and three microtube reactors (**R1**, **R2**, and **R3**) shown in Scheme 3. Solutions of 2-(nonafluorobutyl)ethyl methacrylate (0.25 M in hexane, 4.5 mL min^{-1}, 15 equiv. based on 1,1-diphenylhexyllithium) and 1,1-diphenylhexyllithium (0.050 M in THF–hexane (98:2 v/v), 1.5 mL min^{-1}) were introduced to micromixer **M1** using syringe pumps, and the mixture was introduced into microtube reactor **R1**, in which the first polymerization took place. In the next stage, a solution of *tert*-butyl methacrylate (0.50 M in THF, 4.5 mL min^{-1}, 30 equiv. based on

1,1-diphenylhexyllithium) was passed through micromixer **M2** and microtube reactor **R2** where the second polymerization took place. In the third stage, a solution of 2-(nonafluorobutyl)ethyl methacrylate (0.25 M in THF, 7.5 mL min^{-1}, 25 equiv. based on 1,1- diphenylhexyllithium) was introduced to micromixer **M3**. The reaction mixture was introduced to microtube reactor **R3**, where the third polymerization took place. After the resulting solution was introduced to a solution of methanol in THF (0.33 M) to quench the polymerization, the polymer was analyzed by gel permeation chromatography (GPC). For nuclear magnetic resonance (NMR) analysis, the polymer was further purified by preparative GPC. The copolymerization took place with good control of the Mw/Mn (Mw/Mn=1.10) (Figure 4). The molecular weight of the triblock copolymer (Mn=16,000) was higher than that of the polymer obtainedwithout adding the thirdmonomer (Mn=13,000) and the polymer obtained without adding the second and third monomers (Mn=5500). Poly(2-(nonafluorobutyl)ethyl methacrylate) – poly(*tert*-butyl methacrylate)–poly(2-(nonafluorobutyl) ethyl methacrylate) triblock copolymer could be synthesized with good control of the Mw/Mn.



Scheme 3. Integrated flow microreactor system Triblock anionic polymerization of 2-(nonafluorobutyl)ethyl methacrylate (NFBEMA), *tert*-butyl methacrylate (tBuMA), and 2-(nonafluorobutyl) ethyl methacrylate (NFBEMA) initiated by 1,1-diphenylhexyllithium. T-shaped micromixer: **M1**, **M2** and **M3**; Microtube reactor: **R1**, **R2**, **R3**, **R4**, **R5** and **R6**.

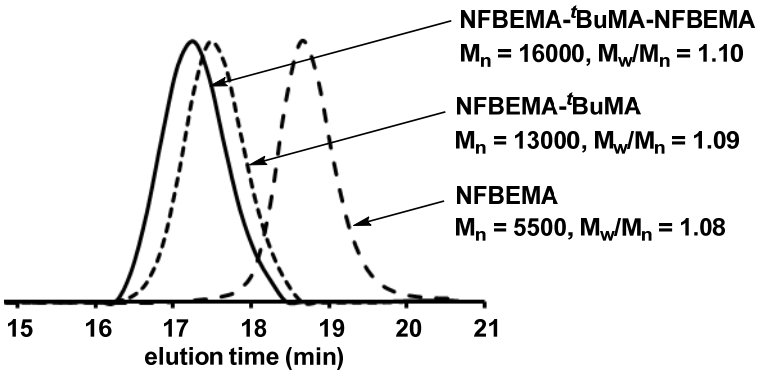


Figure 4. Size exclusion chromatography traces of block copolymers obtained in the integrated flow microreactor system.

Conclusion

In conclusion, we have developed an efficient method for anionic block copolymerization of perfluoroalkyl methacrylate and alkyl (meth)acrylates based on the concept of flash chemistry using integrated flow microreactor systems. The present method opens possibilities of making various fluorine-containing block copolymers.

Experimental Section

General.

GC analysis was performed on a SHIMADZU GC-2014 gas chromatograph equipped with a flame ionization detector using a fused silica capillary columm. Tetrahydrofuran (THF) was purchased from Kanto as a dry solvent and used as obtained. Lithium chloride (LiCl) was purchased from Sigma Aldrich as a THF solution. All monomer was distilled twice over CaH_2 before use. Stainless steel (SUS304) T-shaped micromixers having inner diameter of 250 and 500 μm were manufactured by Sanko Seiki Co., Inc. Stainless steel (SUS316) microtube reactors having inner diameter of 1000 μm were purchased from GL Sciences. Micromixers and microtube reactors were connected with stainless type fittings (GL Sciences, 1/16 OUW). The flow microreactor system was dipped in a cooling bath to control the temperature. Solutions were introduced to a flow microreactor system using syringe pumps, Harvard Model 11, equipped with gastight syringes purchased from SGE.

Molecular weight and molecular weight distribution.

The molecular weight (Mn) and molecular weight distribution (Mw/Mn) were determined in THF at 40 °C with a Shodex GPC-101 equipped with two LF-804L columns (Shodex) and an RI detector using a polystyrene (polySt) standard sample for calibration.

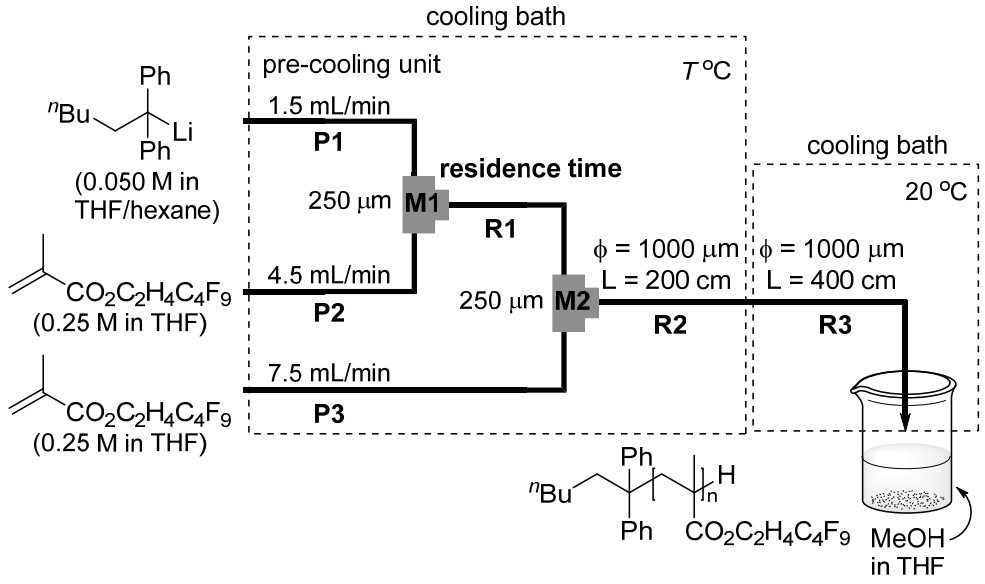
Preparation of a solution of 1,1-diphenylhexyllithium (DPHLi).

To a solution of a little excess amount of 1,1-diphenylethylene in THF (1.0 eq) was added a solution of *n*-BuLi in hexane at 0 °C, and the solution was warmed to room temperature.

Typical procedure for anionic polymerization of perfluoroalkyl methacrylates using a flow microreactor system

A flow microreactor composed of two T-shaped micromixers (**M1** and **M2**) and two microtube reactors (**R1** and **R2**) was used. Three pre-cooling units (**P1**: ϕ = 1000 μm, length = 50 cm, **P2**, **P3**: ϕ = 1000 μm, length = 100 cm) were connected to each inlet of the micromixers **M1** and **M2**. The whole flow microreactor system was dipped in a cooling bath of 20 °C, 0 °C, -15 °C, -20 °C, -30 °C, -40 °C or -60 °C. A solution of 1,1-diphenylhexyllithium in THF/*n*-hexane (98/2 v/v) (0.050 M) (flow rate: 1.5 mL min^{-1}) and a solution of perfluoroalkyl methacrylates in THF (0.25 M) (flow rate: 4.5 mL min^{-1}) were introduced to **M1** (ϕ = 250 μm) by syringe pumps. The resulting solution was passed through **R1** (ϕ = 1000 μm, length = 3.5, 6.0, 12.5, 25, 50, 100, 200, 400, 800 or 1200 cm) and was quenched with a solution of methanol in THF (0.33 M) (flow rate: 3.0 mL min^{-1}) in **M2** (ϕ = 250 μm). The resulting solution was passed through **R2** (ϕ = 1000 μm, length = 50 cm). After a steady state was reached, the product solution was taken (30 s). In the case of 2,2,2-trifluoroethyl methacrylate, 2,2,2-Trifluoroethanol was used as a quenching agent. The conversion of perfluoroalkyl methacrylates was determined by GC. The solvent was removed under reduced pressure to obtain the polymer product and the polymer sample was analyzed with size exclusion chromatography with the calibration using standard polystyrene samples and the results are summarized in Table 1.

Flow microreactor system for the sequential anionic polymerization of 2-(nonafluorobutyl)ethyl methacrylate (NFBEMA).

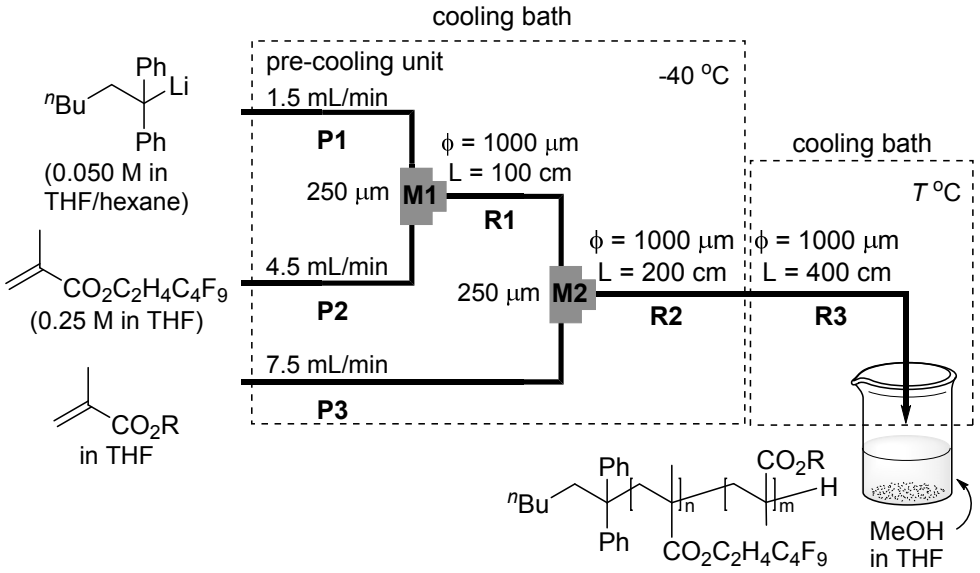


A flow microreactor composed of two T-shaped micromixers (**M1** and **M2**) and three microtube reactors (**R1**, **R2** and **R3**) was used. Three pre-cooling units (**P1**: ϕ = 1000 μm, length = 50 cm, **P2**, **P3**: ϕ = 1000 μm, length = 100 cm) were connected to each inlet of the micromixers **M1** and **M2**. **M1**, **R1**, **M2** and **R2** were dipped in a cooling bath of 0 °C, -20 °C, -30 °C or -40 °C. **R3** were dipped in a cooling bath of different temperature (20 °C). A solution of 1,1-diphenylhexyllithium in THF/*n*-hexane (98/2 v/v) (0.050 M) (flow rate: 1.5 mL min^{-1}) and a solution of 2-(nonafluorobutyl)ethyl methacrylate in THF (0.25 M) (flow rate: 4.5 mL min^{-1}) were introduced to **M1** (ϕ = 250 μm) by syringe pumping. The resulting solution was passed through **R1** (ϕ = 1000 μm, length = 3.5, 6.0, 12.5, 25, 50, 100 or 200 cm) and reacted with a solution of 2-(nonafluorobutyl)ethyl methacrylate in THF (0.25 M) (flow rate: 7.5 mL min^{-1}) in **M2** (ϕ = 250 μm). The resulting solution was passed through **R2** (ϕ = 1000 μm, length = 200 cm) and **R3** (ϕ = 1000 μm, length = 400 cm). After a steady state was reached, the product solution was introduced (30 s) to a solution of methanol in THF (0.33 M) to quench the polymerization. The conversion of 2-(nonafluorobutyl)ethyl methacrylate was determined by GC. The solvent was removed under reduced pressure to obtain the polymer product and the polymer sample was analyzed with size exclusion chromatography with the calibration using standard polystyrene samples and the results are summarized in Table 2.

Table 2. Sequential anionic polymerization of 2-(nonafluorobutyl)ethyl methacrylate (NFBEMA) in a flow microreactor system.

T (°C)	Residence time in **R1** (s)	Conv. (%) (total)	Mn	Mw/Mn
0	0.27	97	11000	1.19
	0.47	96	11000	1.26
	0.98	94	12000	1.29
	2.0	92	12000	1.33
	3.9	90	11000	1.42
	7.9	84	10000	1.52
	16	76	8600	1.60
-20	0.27	99	11000	1.11
	0.47	98	11000	1.14
	0.98	98	11000	1.17
	2.0	97	11000	1.18
	3.9	97	11000	1.25
	7.9	96	11000	1.30
	16	96	11000	1.33
-30	0.27	99	11000	1.09
	0.47	99	11000	1.11
	0.98	98	11000	1.13
	2.0	98	11000	1.14
	3.9	98	11000	1.16
	7.9	98	11000	1.19
	16	97	11000	1.22
-40	0.27	99	11000	1.09
	0.47	99	11000	1.09
	0.98	98	11000	1.12
	2.0	98	11000	1.12
	3.9	99	11000	1.13
	7.9	98	11000	1.16
	16	98	11000	1.19

Flow microreactor system for the block copolymerization of 2-(nonafluorobutyl)-ethyl methacrylate and alkyl (meth)acrylates.



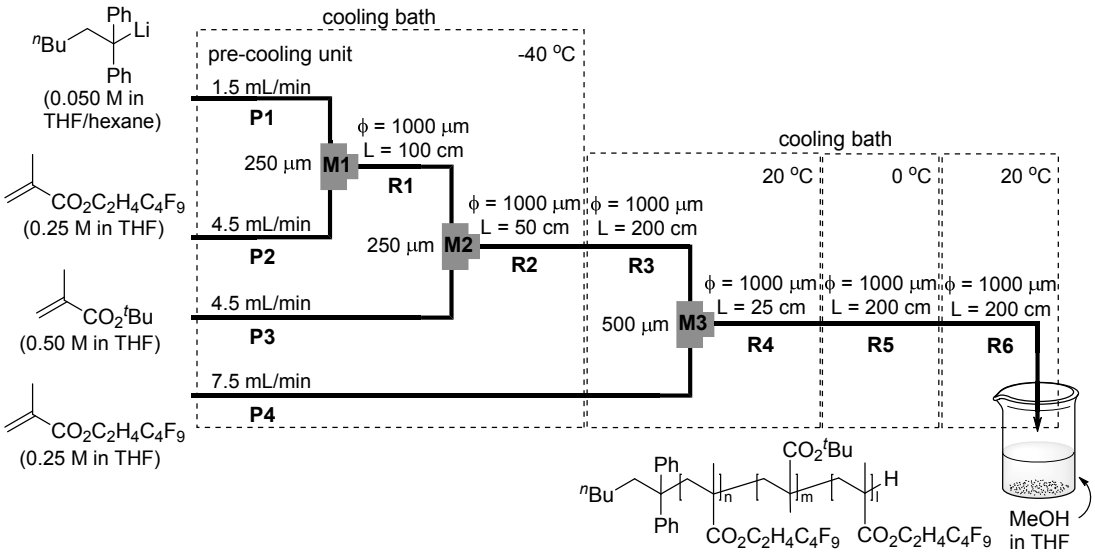
A flow microreactor composed of two T-shaped micromixers (**M1** and **M2**) and three microtube reactors (**R1**, **R2** and **R3**) was used. Three pre-cooling units (**P1**: ϕ = 1000 μm, length = 50 cm, **P2**, **P3**: ϕ = 1000 μm, length = 100 cm) were connected to each inlet of the micromixers **M1** and **M2**. **M1**, **R1**, **M2** and **R2** were dipped in a cooling bath of -40 °C. **R3** were dipped in a cooling bath of different temperature (*T* °C). A solution of 1,1-diphenylhexyllithium in THF/*n*-hexane (98/2 v/v) (0.050 M) (flow rate: 1.5 mL min^{-1}) and a solution of 2-(nonafluorobutyl)ethyl methacrylate (NFBEMA) in THF (0.25 M) (flow rate: 4.5 mL min^{-1}) were introduced to **M1** (ϕ = 250 μm) by syringe pumping. The resulting solution was passed through **R1** (ϕ = 1000 μm, length = 100 cm) and reacted with a solution of alkyl (meth)acrylates in THF (*tert*-butyl methacrylate, methyl methacrylate: 0.50 M) (*tert*-butyl acrylate: 0.50 M ^{t}BuA + 0.030 M LiCl) (flow rate: 7.5 mL min^{-1}) in **M2** (ϕ = 250 μm). The resulting solution was passed through **R2** (ϕ = 1000 μm, length = 200 cm) and **R3** (ϕ = 1000 μm, length = 400 cm). After a steady state was reached, the product solution was introduced (30 s) to a solution of methanol in THF (0.33 M) to quench the polymerization. Cooling bath was controlled at the appropriate temperature (^{t}BuMA: T = 20 °C, MMA: T = -30 °C, ^{t}BuA: T = -20 °C). The conversion of 2-(nonafluorobutyl)ethyl methacrylate and alkyl (meth)acrylates was determined by GC. The solvent was removed under reduced pressure to obtain the polymer product and the polymer sample was analyzed with size exclusion chromatography with the calibration using standard polystyrene samples and the results are summarized in Table 3.

Table 3. Controlled block copolymerization of 2-(nonafluorobutyl)ethyl methacrylate and alkyl (meth)acrylates in a flow microreactor system.

monomer1	monomer2	*T* (°C)	Conv. (%) of monomer1	Conv. (%) of monomer2	Mn	Mw/Mn
NFBEMA	-	-	95[a]	-	5500	1.08
NFBEMA	^{t}BuMA	20	100[b]	99[b]	29000	1.15
NFBEMA	MMA	-30	100[c]	98[c]	17000	1.22
NFBEMA	^{t}BuA +LiCl (3 eq)	-20	100[d]	100[d]	23000	1.10

[a] Polymer obtained in 98% after GPC purification, [b] Polymer obtained in 89% after GPC purification, [c] Polymer obtained in 88% after GPC purification, [d] Polymer obtained in 85% after GPC purification

Triblock copolymerization of 2-(nonafluorobutyl)ethyl methacrylate, *tert*-butyl methacrylate and 2-(nonafluorobutyl)ethyl methacrylate using a flow microreactor system.



A flow microreactor composed of three T-shaped micromixers (**M1**, **M2** and **M3**) and six microtube reactors (**R1**, **R2**, **R3**, **R4**, **R5** and **R6**) was used. Four pre-cooling units (**P1**: ϕ = 1000 μm, length = 50 cm, **P2**, **P3**, **P4**: ϕ = 1000 μm, length = 100 cm) were connected to each inlet of the micromixers **M1**, **M2** and **M3**. **M1**, **R1**, **M2** and **R2** were dipped in a cooling bath of -40 °C. **R3**, **M3**, **R4** were dipped in a cooling bath of different temperature (20 °C). **R5** were dipped in a cooling bath of 0 °C and **R6** were dipped in a cooling bath of 20 °C. A solution of 1,1-diphenylhexyllithium in THF/*n*-hexane (98/2 v/v) (0.050 M) (flow rate: 1.5 mL min^{-1}) and a solution of 2-(nonafluorobutyl)ethyl methacrylate (NFBEMA) in THF (0.25 M) (flow rate: 4.5 mL min^{-1}) were introduced to **M1** (ϕ = 250 μm) by syringe

pumping. The resulting solution was passed through **R1** (ϕ = 1000 μm, length = 100 cm) and reacted with a solution of *tert*-butyl methacrylate in THF (0.50 M) (flow rate: 4.5 mL min^{-1}) in **M2** (ϕ = 250 μm). The resulting solution was passed through **R2** (ϕ = 1000 μm, length = 50 cm) and **R3** (ϕ = 1000 μm, length = 200 cm) and reacted with a solution of 2-(nonafluorobutyl)ethyl methacrylate in THF (0.25 M) (flow rate: 7.5 mL min^{-1}) in **M3** (ϕ = 500 μm). The resulting solution was passed through **R4** (ϕ = 1000 mm, length = 25 cm), **R5** (ϕ = 1000 μm, length = 200 cm) and **R6** (ϕ = 1000 μm, length = 200 cm). After a steady state was reached, the product solution was introduced (30 s) to a solution of methanol in THF (0.33 M) to quench the polymerization. The conversion of 2-(nonafluorobutyl)ethyl methacrylate and *tert*-butyl methacrylate was determined by GC. The solvent was removed under reduced pressure to obtain the polymer product and the polymer sample was analyzed with size exclusion chromatography with the calibration using standard polystyrene samples and the results are summarized in Table 4.

Table 4. Controlled triblock copolymerization of 2-(nonafluorobutyl)ethyl methacrylate, *tert*-butyl methacrylate and 2-(nonafluorobutyl)ethyl methacrylate in a flow microreactor system.

monomer1	monomer2	monomer3	Conv. (%) of NFBEMA	Conv. (%) of ^{t}BuMA	Mn	Mw/Mn
NFBEMA	-	-	95	-	5500	1.08
NFBEMA	^{t}BuMA	-	100	99	13000	1.09
NFBEMA	^{t}BuMA	NFBEMA	95	100	16000	1.10

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List of Publications

1. A Flow Microreactor Approach to α-Ketoamides Synthesis Based on Generation of Carbamoyllithiums
   Nagaki, A.; Takahashi, Y.; Yoshida, J. to be submitted.
   (Chapter 1)

2. Flash Chemistry Using Trichlorovinyllithium: Switching the Reaction Pathways by High-resolution Reaction Time Control
   Nagaki, A.; Takahashi, Y.; Henseler, A.; Matsuo, C.; Yoshida, J. *Chem. Lett.* **2015**, *44,* 214-216.
   (Chapter 2)

3. Extremely Fast Gas/Liquid Reactions in Flow Microreactors: Carboxylation of Short-Lived Organolithiums
   Nagaki, A.; Takahashi, Y.; Yoshida, J. *Chem. Eur. J.* **2014**, *20*, 7931-7934.
   (Chapter 3)

4. Living Anionic Polymerization of tert-Butyl Acrylate in a Flow Microreactor System and Its Applications to the Synthesis of Block Copolymers
   Nagaki, A.; Takahashi, Y.; Akahori, K.; Yoshida, J. *Macromol. React. Eng.* **2012**, *6*, 467–472.
   (Chapter 4)

5. Flow Microreactor Synthesis of Fluorine-Containing Block Copolymers
   Nagaki, A.; Akahori, K.; Takahashi, Y.; Yoshida, J. *J. Flow Chem.* **2014**, *4, 168-172.*
   (Chapter 5)

Other Publications

1. Generation and Reactions of Vinyllithiums Using Flow Microreactor Systems
   Nagaki, A.; Takahashi, Y.; Yamada, S.; Matsuo, C.; Haraki, S.; Moriwaki, Y.; Kim, S.; Yoshida, J. *J. Flow Chem.* **2012**, *2, 70-72.*

2. Flash Chemistry: Flow Chemistry That Cannot Be Done in Batch
   Yoshida, J.; Takahashi, Y.; Nagaki, A. *Chem. Commun.* **2013**, *49*, 9896-9904.

3. Flash Chemistry: New Synthetic Chemistry Using Flow Microreactors
   Yoshida, J.; Takahashi, Y.; Nagaki, A. *Kagaku Kogaku*, **2013**, *77*, 785-787.