

Flow Microreactor Synthesis
via Unstable Organolithium Intermediates Bearing
Electrophilic Functional Groups

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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 April 2007 – November 2011. The studies are concerned with a flow microreactor synthesis via unstable organolithium intermediates bearing electrophilic functional groups.

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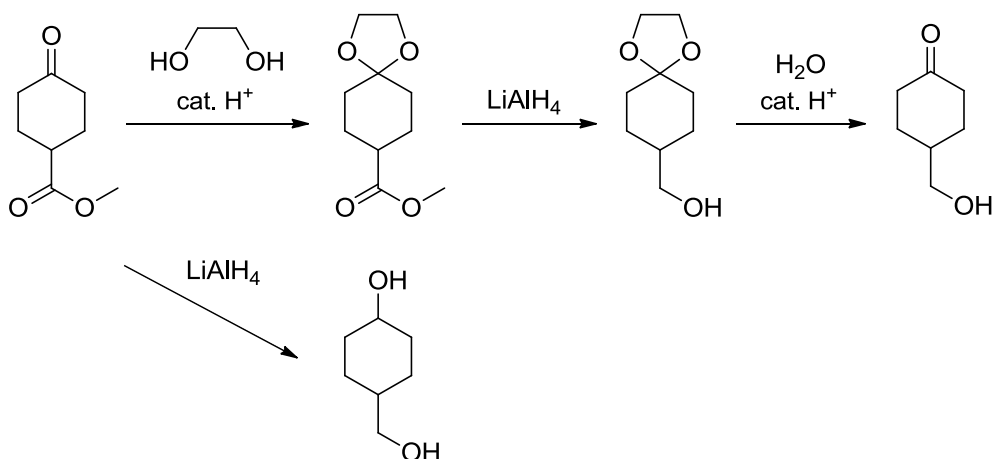
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General Introduction

I. Protecting-Group-Free Synthesis

Organic chemists have relied upon protecting groups for chemoselective synthesis. In syntheses of complicated organic molecules, some functional groups in a molecule often cannot survive a particular transformation. Therefore, the introduction and removal of protecting group is regarded as an indispensable process in the organic synthesis.¹ For example, lithium aluminium hydride (LiAlH_4) is reactive to both an ester and a ketone. In order to conduct a selective reduction of an ester, a ketone should be converted to a protected form, *i.e.* an acetal in advance of the reduction as shown in Scheme 1.

Scheme 1. The protection of a ketone for a selective reduction of an ester



However, it is certain that the introduction and removal of protecting groups increase the total steps of the synthesis and bring a loss of materials. Recently, the construction of complicated molecules without using protecting group² has attracted a great deal of attention from the viewpoints of atom economy³, step economy⁴ and redox economy.⁵ A lot of protecting-group-free synthesis has been developed in an endeavor to the ideal synthesis⁶ and green sustainable chemistry⁷ in recent years. Generally, a skeleton-building reaction is one of the most difficult steps with respect to avoiding usage of protecting groups because such reaction often uses strongly nucleophilic reagents. Among such reagents, organolithium reagents are the most reactive, although its high reactivity makes them very useful in organic synthesis.

II. Functionalized Organolithium Intermediates

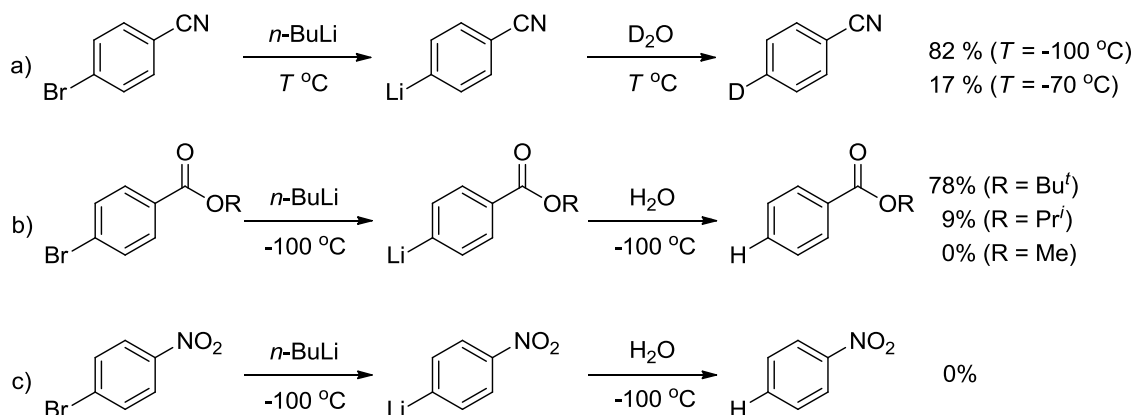
Functionalized organometallic compounds provide a straightforward and powerful access to complicated molecules, since the protection of functional group is not necessary, as well as functional groups can be used directly in a subsequent reaction.⁸ There are two difficulties associated with generating functionalized organometallic compounds: 1) preventing the reaction of the nucleophilic organometallic part with the functional group; 2) having an enough reactivity for reactions with various electrophiles, otherwise generated organometallic compounds would be not useful. For this type of transformations, functionalized organomagnesium⁹ and organozinc¹⁰ compounds are often used, because they can tolerate many functional groups. However, there are some limitations on availability of substrates and electrophiles. Functionalized organomagnesium and organozinc intermediates sometimes could not prepared from relatively less reactive precursors and hardly react with some electrophiles, because of their low reactivity.¹¹

On the other hand, organolithium compounds are the most reactive among main group organometallic compounds. They have been widely used and played a major role in synthetic organic chemistry. However, its high reactivity inevitably makes them suffer from incompatibility of electrophilic functional groups.¹² For example, the generation and reactions of aryllithium species bearing electrophilic functional groups such as cyano, alkoxycarbonyl and nitro groups are generally very difficult or impossible even at low temperatures because of their instability. In some cases, such reaction can be partially achieved at extremely low temperatures such as -100 °C (Scheme 2).

Moreover, ketones react with organolithiums very rapidly, and therefore the organic textbooks say that ketone carbonyl groups should be protected before an organolithium reaction if it is not involved in the desired transformation.

Owing to this critical drawback of organolithiums, transformations via functionalized organolithium compounds could not be used for the synthesis of complicated molecules. As an alternative method, functional group should be protected prior to organolithium reaction,¹³ or another synthetic route has to be concerned.¹⁴

Scheme 2. Generation and reactions of aryllithium compounds bearing an electrophilic functional group using conventional batch reactor



III. Continuous-Flow Microreactor

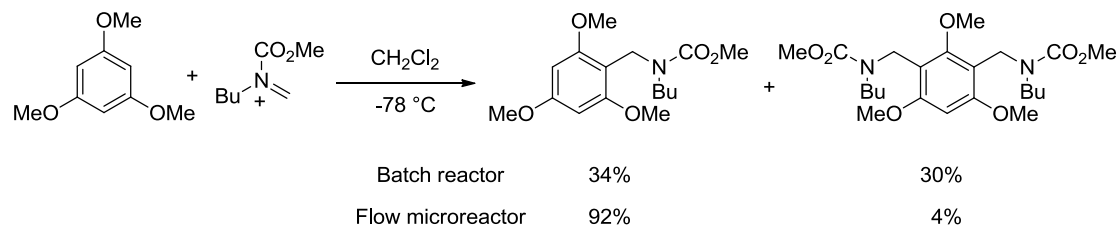
Continuous-flow microreactors¹⁵ have emerged as innovative and powerful tools for chemical syntheses in recent years. Although tools for chemical reactions had rarely changed for a long time, now a day, chemists have focus on the development of the flow microreactors for laboratory synthesis and applications to industrial scale production.¹⁶ Flow microreactors have following characteristic features derived from their small size and flow nature.

1) Fast micromixing

Many chemical reactions are initiated by mixing two substances, and for this reason mixing to achieve a good level of homogeneity in solution is important, especially for fast reactions. Time needed for mixing is proportional to the square of the length of the diffusion path, since mixing occurs by molecular diffusion. Therefore, the marked shortening of the diffusion path in a flow microreactor results in very fast mixing which is unobtainable in batch macro reactors.

For example, the product selectivity of Friedel-Crafts alkylation can be greatly improved by fast micromixing (Scheme 3).¹⁷ The reaction of the *N*-acyliminium ion pool with 1,3,5-trimethoxybenzene in a batch reactor results in the formation of a 1:1 mixture of the monoalkylation product and the dialkylation product. However, the use of a flow microreactor (IMM single mixer, lamination width: 25 μm) leads to an excellent selectivity of the monoalkylation product, and the amount of the dialkylation product was very small. Therefore, the product selectivity strongly depends on the manner of mixing.

Scheme 3. Effect of the manner of mixing on the product selectivity of Friedel-Crafts monoalkylation with an *N*-acylliminium ion



2) Effective temperature control

Heat is transferred between the interior and exterior of a reactor via the reactor surface. Therefore, surface area per unit volume of the reactor is a crucial factor for heat transfer. Because the downsizing of reactor results in a high surface-to-volume ratio as shown in Figure 1, a flow microreactor system has superior ability on the temperature control than conventional batch reactors.¹⁸

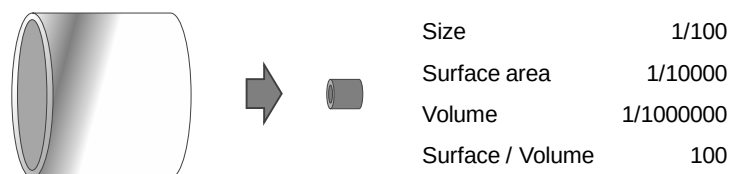


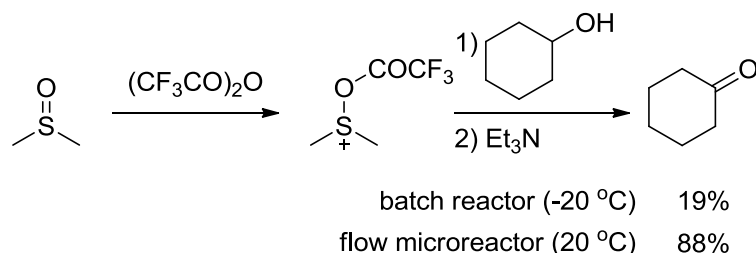
Figure 1. Numerical aspects of downsizing

3) Precise residence time control

Residence time is defined as the length of time that the solution remains in the reactor. In the flow reactors, the residence time increases with the length of the channel and decreases with the flow rate. In flow microreactors, the residence time can be precisely controlled, also greatly reduced by reducing the length of the microchannels and increasing flow speed. This feature of flow microreactor is extremely useful in controlling chemical reactions involving short-lived reactive species, because the reactive species can be moved to another location to be used in the next reaction before they decompose. By taking the advantage of short residence time in flow microreactor systems, Swern-Moffatt oxidation can be carried out at room temperature as shown in Scheme 4.¹⁹ In the first step, DMSO reacts with trifluoroacetic anhydride to form cationic reactive species which is known to be unstable above -30 °C. Actually, the batch reaction at -20 °C leads to the formation of significant amount of byproducts derived from the decomposition of reactive species. In a flow microreactor system,

however, the reaction time can be greatly shortened by reducing the residence time to avoid undesired decomposition. The reaction in flow microreactor gives rise to the formation of the desired product in high yields even at room temperature by virtue of short residence time.

Scheme 4. Swern-Moffatt oxidation using flow microreactor system

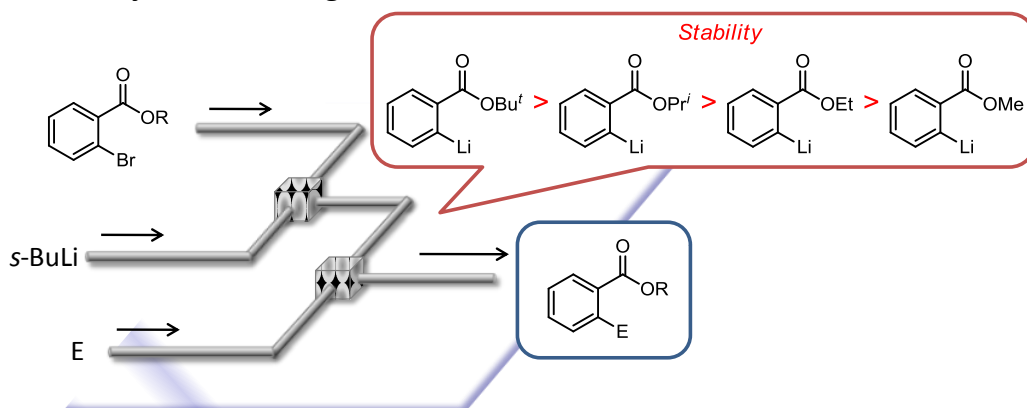


IV. Flow Microreactor Synthesis via Organolithiums Bearing Electrophilic Functional Groups

The examples shown in the previous section imply that features of the flow microreactor system is quite effective for extremely fast reactions via unstable intermediates, such as functionalized organolithium compounds. We envisioned that fast mixing could be effective to increase the selectivity of the halogen-lithium exchange reactions of functionalized aryl halide, and that the resulting aryllithium compounds bearing functional group can react with an electrophile before they decompose by virtue of precise residence time control in the flow microreactor system. Moreover, it is expected that effective temperature control of the flow microreactor system can minimize the undesired side reactions caused by the local deviation of the temperature.

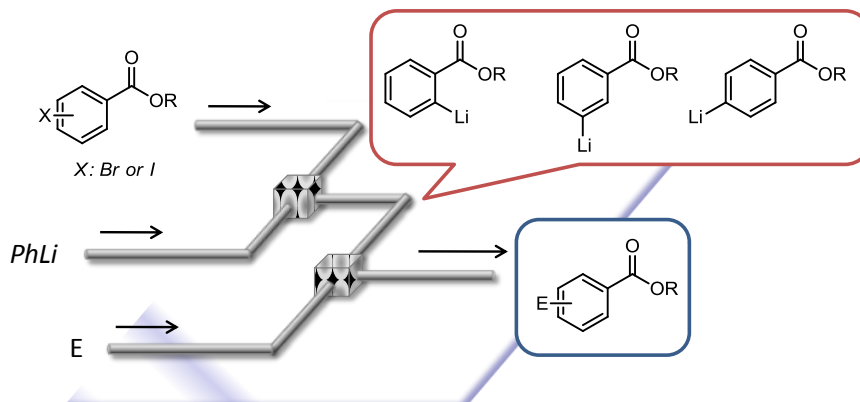
In chapter 1, the generation and reactions of *o*-alkoxycarbonyl-substituted aryllithium intermediates by Br-Li exchange reaction using flow microreactor is described. The Br-Li exchange reaction of alkyl *o*-bromobenzoates, followed by the reaction with electrophiles can be conducted using flow microreactor system. Although the methyl or ethyl ester could not tolerate in organolithium reactions in conventional batch reactor, the desired products could be obtained in satisfactory yields by using a flow microreactor (Scheme 5).

Scheme 5. Generation and reactions of *ortho*-alkoxycarbonyl-substituted aryllithium intermediates by Br-Li exchange



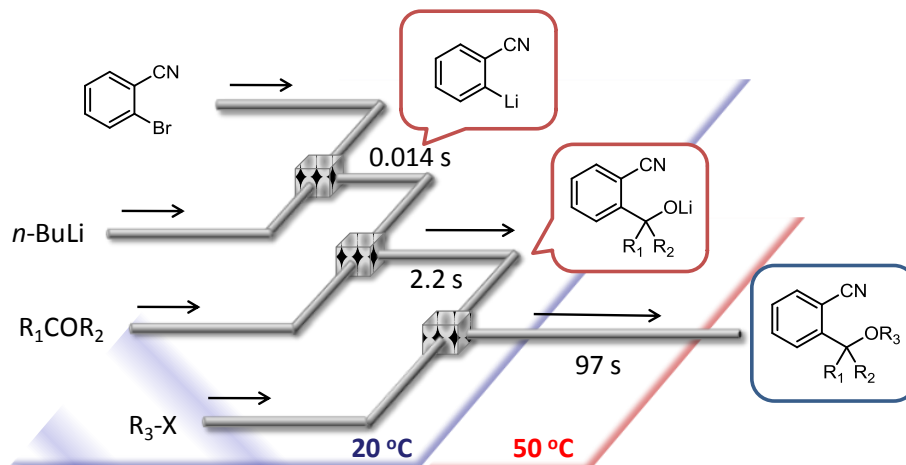
Chapter 2 describes the generation and reactions of *m*- and *p*-alkoxycarbonyl-substituted aryllithiums by I-Li exchange reaction using flow microreactor. The *m*- and *p*-alkoxycarbonyl-substituted aryllithiums is known to be less stable than *o*-substituted ones, because of absence of *ortho*-chelation. By optimizing reaction conditions such as the reaction temperature and the residence time, the flow microreactor synthesis via *m*- and *p*-alkoxycarbonyl-substituted aryllithiums was achieved (Scheme 6).

Scheme 6. Generation and reactions of *meta*- and *para*-alkoxycarbonyl-substituted aryllithium intermediates by I-Li exchange



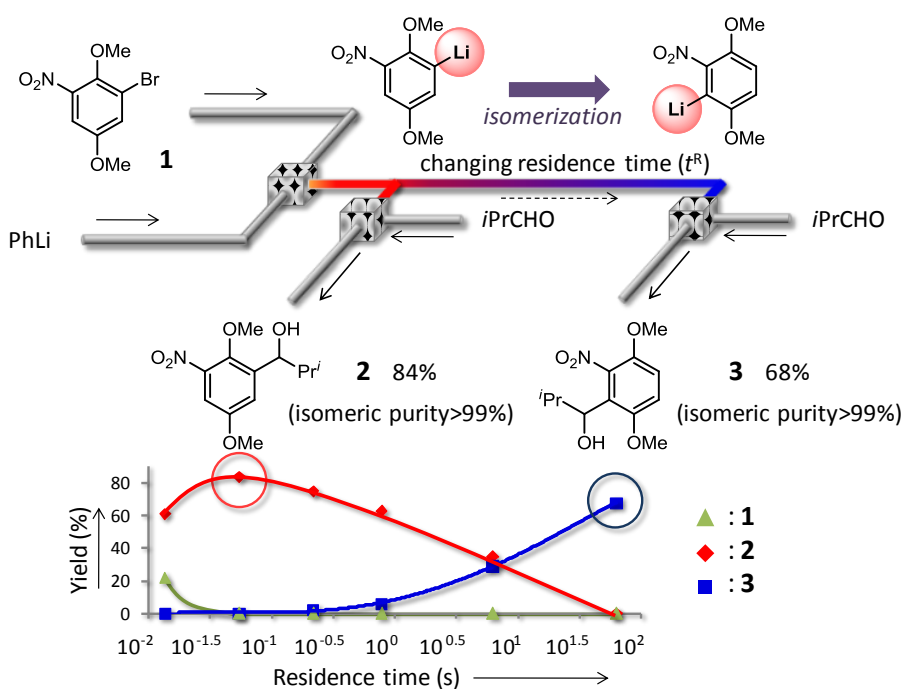
In chapter 3, a flow microreactor synthesis via cyano-substituted aryllithium intermediates is described. The Br-Li exchange reaction of bromobenzonitriles can be conducted at 0 or 20 °C using flow microreactor. In addition, reactions of *o*-lithiobenzonitriles with carbonyl compounds followed by alkylation of the resulting lithium alkoxides were achieved in an integrated flow microreactor system (Scheme 7).

Scheme 7. Multistep transformations via cyano-substituted aryllithiums



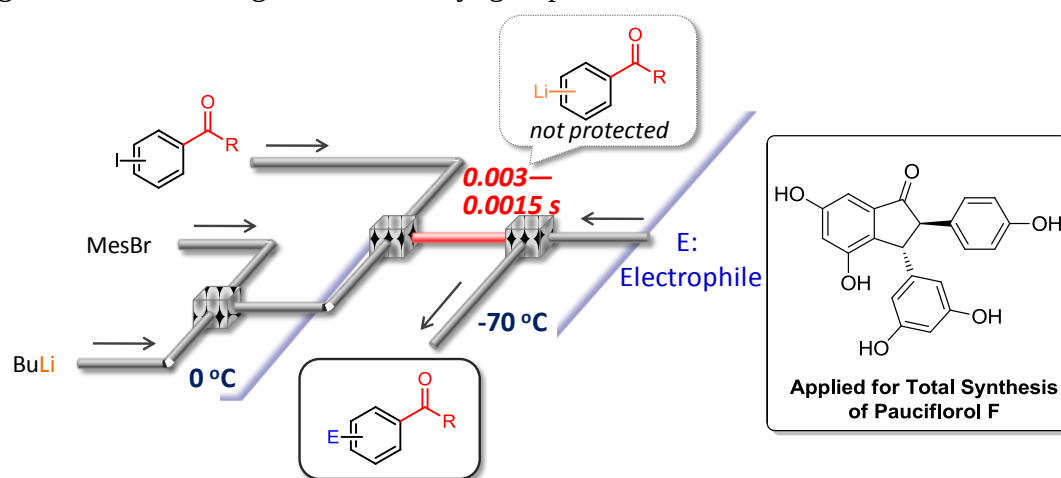
Chapter 4 describes that the flow microreactor synthesis via nitro-substituted aryllithiums and its applications. We have developed an effective flow microreactor system for generation and transformations of *o*-, *m*- and *p*-nitro-substituted aryllithium intermediates. Furthermore, the selective use of either kinetically formed or thermodynamically preferred organolithiums bearing a nitro group could be achieved by changing the residence time as shown in Scheme 8.

Scheme 8. Switch between kinetic and thermodynamic control by changing the residence time



In chapter 5, a flow microreactor synthesis via organolithium intermediates bearing ketone carbonyl groups is described. Generally, organolithium species react with ketones very rapidly, and therefore ketone carbonyl groups should be protected before an organolithium reaction, if they are not involved in the desired transformation. We show that a flow microreactor enables protecting-group-free organolithium reactions by greatly reducing the residence time. The present method has been successfully applied to the formal total synthesis of Pauciflorol F (Scheme 9).

Scheme 9. A flow microreactor approach to protecting-group-free synthesis using organolithiums bearing ketone carbonyl groups



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Chapter 1

Generation and Reactions of *o*-Alkoxy carbonyl-Substituted Aryllithiums Based on Br-Li Exchange Using Flow Microreactor System

Abstract

A flow microreactor system consisting of micromixers and microtube reactors provides very effective method for the generation of *o*-alkoxycarbonyl-substituted aryllithium intermediates followed by reactions with electrophiles, which is very difficult to achieve using conventional batch reactors even at very low temperature. The key features of the method include an extremely short residence time, fast mixing, and effective temperature control.

Introduction

Control of reactive intermediates¹ to selectively obtain desired products is a central issue in organic synthesis. In batch macro reactors, operation time for generation of a reactive intermediate usually takes minutes or hours, because usually a reagent should be added slowly to avoid undesirable temperature increase. If the lifetime of the intermediate is shorter than such a time range, it is difficult to obtain a solution of the intermediate because of its decomposition during the accumulation. In such a case, the intermediate cannot be used for the subsequent reaction. To avoid the decomposition of the reactive intermediate, the generation is usually carried out at very low temperatures in batch macro reactors. In flash chemistry^{2,3} using a flow microreactor system, however, a reactive intermediate can be rapidly generated and transferred for use in a subsequent reaction before decomposition, because the residence time can be greatly reduced.⁴ Therefore, chemical conversions that are impossible in conventional batch macro reactors can become possible using flow microreactors. In this chapter, we report that aryllithium compounds having a highly reactive alkoxycarbonyl group, such as ethoxycarbonyl and methoxycarbonyl, can be easily generated and used for reactions with electrophiles by exploiting the features of flow microreactor systems.⁵

Organolithium compounds, such as aryllithiums, have been widely used in organic synthesis because of their high reactivity.^{6,7} However, aryllithium compounds suffer from the problem of functional group compatibility.⁸ In fact, it is difficult to prepare organolithium compounds bearing electrophilic functional groups such as alkoxycarbonyl groups, because they react with aryllithium species. To overcome this problem, generation reactions, such as Br-Li exchange reactions of organic bromides, are often conducted at very low temperatures. It is, however, still difficult to prepare aryllithium compounds having highly reactive functional groups, such as methoxycarbonyl and ethoxycarbonyl groups.⁹ The second approach is the use of less-reactive, hence more-stable, arylmetallic compounds,¹⁰ such as arylmagnesium¹¹ and arylzinc compounds.¹² However, preparation of such organometallic compounds by a metal-metal exchange reaction of aryllithium compounds suffers from the problem of undesirable reaction of aryllithium species bearing such functional groups. Such arylmetallic compounds can also be prepared directly without using aryllithium reagents. However, direct preparation requires the use of highly reactive precursors such as aryl iodides, which are usually more difficult to prepare.¹³ We envisaged that the concept of flash chemistry using a flow microreactor system would solve the problem.

Results and Discussion

We focused on the Br-Li exchange reaction of alkyl *o*-bromobenzoates.⁵ The Br-Li exchange reaction of alkyl bromobenzoates, followed by the reaction with an electrophile, can be performed in a conventional batch macro reactor only in the case of *tert*-butyl bromobenzoates at very low temperatures (*e.g.* -100 °C). The use of esters of secondary and primary alcohols dramatically decreases the yields. To confirm this, we reexamined the Br-Li exchange reactions of *tert*-butyl *o*-bromobenzoate (**1a**), isopropyl *o*-bromobenzoate (**1b**), ethyl *o*-bromobenzoate (**1c**), and methyl *o*-bromobenzoate (**1d**) in a conventional batch macro reactor (Table 1).

Table 1. The Br-Li exchange reaction of alkyl *o*-bromobenzoates **1** followed by reaction with ROH in a conventional batch macro reactor.

<i>o</i> -Bromobenzoates 1	Conversion of 1 (%)	Yield of 3 (%) ^a
R = <i>tert</i> -butyl: 1a	100	61
R = isopropyl: 1b	100	12
R = ethyl: 1c	100	0
R = methyl: 1d	100	0

^a Determined by GC.

The exchange reaction of **1a** at -78 °C, followed by quenching with an alcohol, gave *tert*-butyl benzoate (**3a**) in 61% yield. The moderate yield seems to be attributed to partial decomposition of **2a** at this temperature. According to the literature, the reaction at lower temperatures (-100 °C) gives **3a** in higher yields.⁹ The use of **1b** led to lower yield of **3b**. Moreover, in reactions of **1c** and **1d**, the desired products were not obtained at all.

We examined the reactions using a flow microreactor system consisting of two T-shaped micromixers (M1 and M2; inner diameter: 250 μm) and two microtube reactors (R1 and R2; Figure 1). The reactions were carried with varying temperatures (*T*) and residence times (*t*^R) in R1. The results are summarized in Figure 2, in which the yield of **3** is plotted against *T* and *t*^R in R1 as a contour map with a scattered overlay.

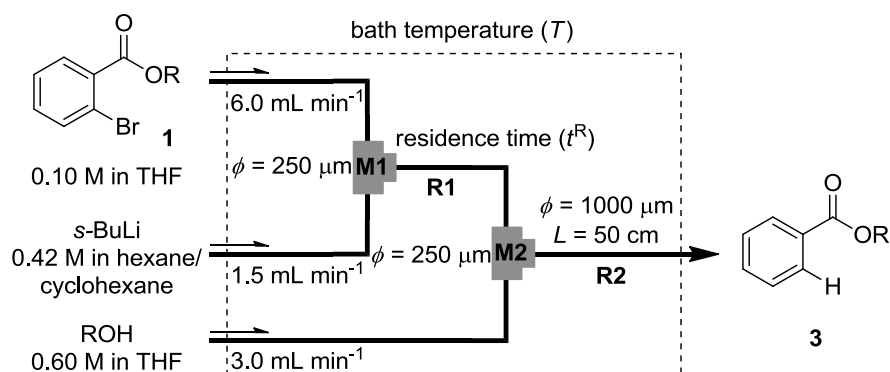


Figure 1. A microreactor system for the Br-Li exchange reaction of alkyl *o*-bromobenzoates **1** followed by reaction with alcohols.

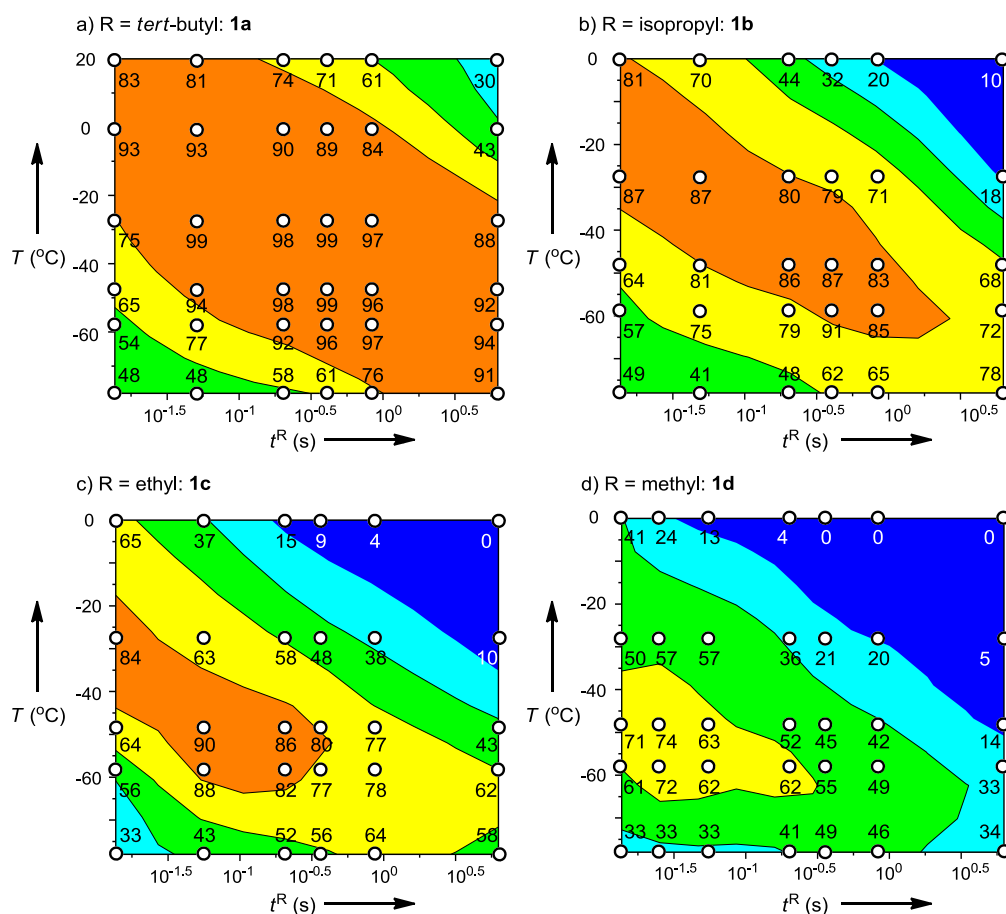


Figure 2. Effect of the temperature and the residence time on the yield in the Br-Li exchange reaction of a) *tert*-butyl *o*-bromobenzene (**1a**), b) isopropyl *o*-bromobenzene (**1b**), c) ethyl *o*-bromobenzene (**1c**), d) methyl *o*-bromobenzene (**1d**), followed by reaction with ROH in the flow microreactor system.

In reactions of *tert*-butyl *o*-bromobenzoate (**1a**), the desired product **3a** was obtained in high yields (> 80%, brown region) for a wide range of temperatures and residence times. At low temperatures and short residence times, the yield was low because of an incomplete Br-Li exchange reaction. Low yield was also observed in the high-temperature/long- residence-time region, probably because of decomposition of **2a**.

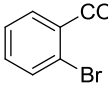
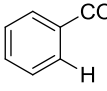
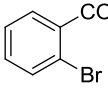
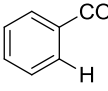
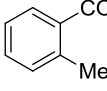
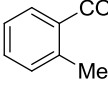
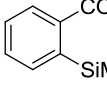
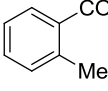
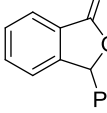
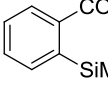
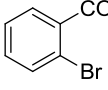
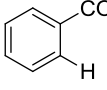
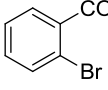
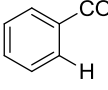
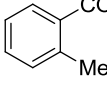
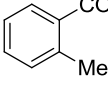
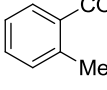
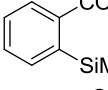
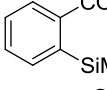
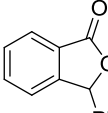
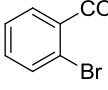
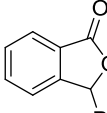
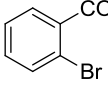
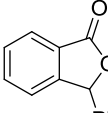
In the case of isopropyl *o*-bromobenzoate (**1b**), a similar reaction profile was observed, although the high-yield region became smaller. The reaction of ethyl *o*-bromobenzoate (**1c**) also exhibited a similar profile. The high-yield region shifted to a lower temperature and shorter residence-time region, probably because of faster decomposition of organolithium compound **2c**. However, it is noteworthy that the reaction can be effectively performed to give **3c** in 90% yield by choosing an appropriate temperature (-48 °C) and residence time (0.06 s).

Of even greater significance is the fact that **3d** can be obtained in relatively good yields (> 70%) from methyl *o*-bromobenzoate (**1d**), although the high-yield region (> 80%) disappeared, presumably because of the small steric demand of the methoxycarbonyl group for the reaction with organolithium species, leading to the nucleophilic attack on the carbonyl group in some extent.

These results clearly show that the stability of the aryllithium compounds decreases in the order **2a** > **2b** > **2c** > **2d**. However, it is important to note that the Br-Li exchange reaction followed by reaction with an electrophile can be successfully carried out without significant decomposition of the aryllithium intermediate **2** by optimizing temperature and residence time, even in the case of methyl ester.

Under the optimized conditions obtained for the Br-Li exchange reaction followed by reaction with an alcohol, the reactions of **2a-2d** with other electrophiles, such as methyl iodide, methyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, and benzaldehyde were examined. The reactions were successful and the corresponding products were obtained in good yields (Table 2). Interestingly, methyl iodide can be used as an electrophile for the reactions of **1a** and **1b** whereas, for the reactions of **1c** and **1d**, methyl triflate should be used. The reaction of the aryllithium with methyl iodide is relatively slow, and therefore only the more sterically demanding *tert*-butoxycarbonyl and isopropoxycarbonyl groups can survive until the reaction is complete. However, the reaction of the aryllithium with methyl triflate is much faster. Therefore, the reaction can be conducted at much lower temperatures with shorter residence times. Consequently, even the less sterically demanding ethoxycarbonyl and methoxycarbonyl groups can survive until the reaction is complete.

Table 2. The Br-Li exchange reaction of alkyl *o*-bromobenzoates **1** followed by reaction with an electrophile under optimized conditions.^a

Ester	Electrophile	Product	Yield (%) ^b	Ester	Electrophile	Product	Yield (%) ^b
 1a	<i>t</i> BuOH		93	 1c	EtOH		90
	MeI		88		MeI		12
	Me ₃ SiCl		96		MeOTf		62
	PhCHO		82		Me ₃ SiCl		61
 1b	<i>i</i> PrOH		87	 1d	MeOH		74
	MeI		62		MeOTf		65
	MeOTf		82		Me ₃ SiOTf		82
	Me ₃ SiCl		93		PhCHO		85
 1b	PhCHO		66	 1d	PhCHO		85

^a For **1a**, *T* = 0 °C (*t*^R = 0.01 s); **1b**, *T* = -28 °C (*t*^R = 0.01 s); **1c**, *T* = -48 °C (*t*^R = 0.06 s); **1d**, *T* = -48 °C (*t*^R = 0.02 s).^b Determined by GC.

Conclusion

We have developed an effective method for the generation and reactions of aryllithium compounds having an alkoxycarbonyl group. The key features of the method are a very short residence time, together with fast mixing¹⁴ and efficient temperature control in flow microreactor systems. A wide range of alkoxycarbonyl groups including ethoxycarbonyl and methoxycarbonyl groups can tolerate the microflow conditions. These results bode well for the utility of flash chemistry, and the method adds a new dimension in the chemistry of functionalized aryllithium compounds and their applications in organic synthesis.

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; initial oven temperature, 50 °C; rate of temperature increase, 10 °C min⁻¹). ¹H and ¹³C NMR spectra were recorded on Varian MERCURY plus-400 (¹H 400 MHz, ¹³C 100 MHz) spectrometer with Me₄Si or CDCl₃ as a standard in CDCl₃ unless otherwise noted. EI mass spectra were recorded on JMS-SX102A spectrometer. THF and Et₂O 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. All materials were obtained from commercial supplier and used without purification unless otherwise noted. *tert*-Butyl *o*-bromobenzoate, and isopropyl *o*-bromobenzoate were prepared according to the literature.¹⁵

Stainless steel (SUS304) T-shaped micromixers with inner diameter of 250 μm were manufactured by Sanko Seiki Co., Inc (Figure 3).

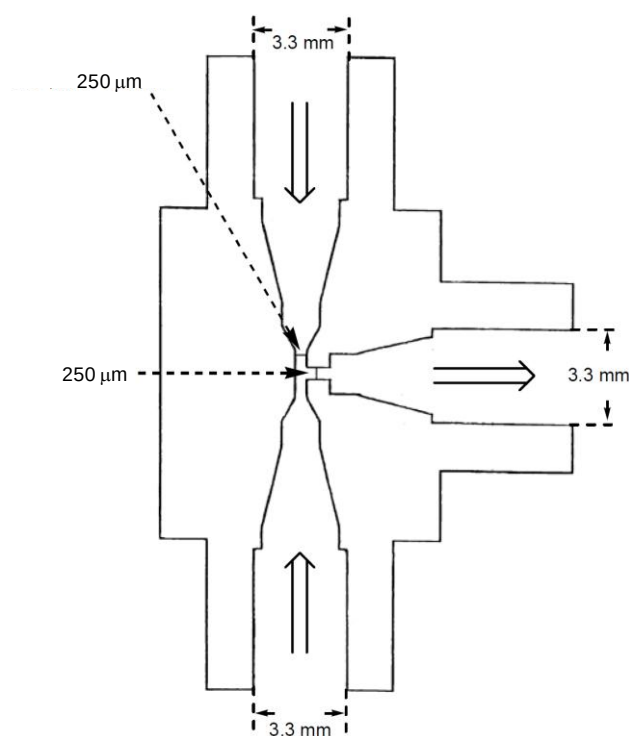


Figure 3. Stainless steel (SUS304) T-shaped micromixers.

Stainless steel (SUS316) microtube reactors with inner diameter of 250, 500 and 1000 μm were purchased from GL Sciences. The micromixers and the microtube reactors were connected with stainless steel fittings (GL Sciences, 1/16 OUN). The flow microreactor system was dipped in a cooling bath to control the temperature (T). Solutions prepared under Ar atmosphere were taken by gastight syringes purchased from SGE, and introduced to a flow microreactor system using syringe pumps, Harvard Model 11.

The Br-Li Exchange Reaction of Alkyl *o*-Bromobenzoates Followed by Reaction with Alcohols Using a Batch Reactor. A solution of *s*-BuLi (0.42 M, 0.75 mL) in hexane/cyclohexane (19/31 v/v) was added dropwise to a solution of an alkyl *o*-bromobenzoate (0.10 M, 3.0 mL) in THF in a 20 mL round bottom glass flask for 1 min at $-78\text{ }^{\circ}\text{C}$. The mixture was stirred for 10 min, and a solution of the corresponding alcohol (0.60 M, 1.5 mL) in THF was added. After stirring for 10 min, a cooling bath was removed. The mixture was analyzed by GC.

The Br-Li Exchange Reaction of Alkyl *o*-Bromobenzoates Followed by Reaction with Alcohols Using Flow Microreactor Systems. A flow microreactor system consisting of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2) was used. A solution of an alkyl *o*-bromobenzoate (0.10 M) in THF (flow rate: 6.0 mL min^{-1}) and a solution of *s*-BuLi (0.42 M) in hexane/cyclohexane (19/31 v/v) (flow rate: 1.5 mL min^{-1}) were introduced to M1 (inner diameter $\phi = 250\text{ }\mu\text{m}$) by syringe pumps. The resulting solution was passed through R1 and was mixed with a solution of alcohol (0.60 M) in THF (flow rate: 3.0 mL min^{-1}) in M2 ($\phi = 250\text{ }\mu\text{m}$). The resulting solution was passed through R2 ($\phi = 1000\text{ }\mu\text{m}$, tube length $L = 50\text{ cm}$). After a steady state was reached, the product solution was collected for 30 s while being quenched with 1 M HCl aqueous solution. The reaction mixture was analyzed by GC. The results are summarized in Table 3 and 4.

Table 3. The Br-Li exchange reaction of *tert*-butyl *o*-bromobenzoate (**1a**) and isopropyl *o*-bromobenzoate (**1b**) followed by reaction with alcohol in flow microreactor systems

ϕ in R1 (μm)	L in R1 (cm)	t^{R} (s)	T ($^{\circ}\text{C}$)	Conv. ^a (%)	Yield ^a (%)	Conv. ^b (%)	Yield ^b (%)
250	3.5	0.014	0	97	93	100	81
500	3.5	0.055		100	93	100	70
1000	3.5	0.22		100	90	100	44
1000	6.0	0.38		97	89	100	32
1000	12.5	0.79		97	84	100	20
1000	100	6.3		100	43	100	10
250	3.5	0.014	-28	96	75	97	87
500	3.5	0.055		100	99	100	87
1000	3.5	0.22		100	98	100	80
1000	6.0	0.38		100	99	100	79
1000	12.5	0.79		100	97	100	71
1000	100	6.3		100	88	100	18
250	3.5	0.014	-48	73	65	73	64
500	3.5	0.055		94	94	93	81
1000	3.5	0.22		100	98	100	86
1000	6.0	0.38		100	99	100	87
1000	12.5	0.79		100	96	100	83
1000	100	6.3		100	92	100	68
250	3.5	0.014	-58	69	54	67	57
500	3.5	0.055		80	77	91	75
1000	3.5	0.22		94	92	96	78
1000	6.0	0.38		98	96	100	91
1000	12.5	0.79		100	97	100	85
1000	100	6.3		100	94	100	72
250	3.5	0.014	-78	59	48	57	49
500	3.5	0.055		65	48	48	41
1000	3.5	0.22		67	58	62	48
1000	6.0	0.38		70	61	75	62
1000	12.5	0.79		87	76	76	65
1000	100	6.3		100	91	95	78

^a *tert*-Butyl *o*-bromobenzoate (**1a**) was used as a substrate. ^b isopropyl *o*-bromo-benzoate (**1b**) was used as a substrate

Table 4. The Br-Li exchange reaction of ethyl *o*-bromobenzoate (**1c**) and methyl *o*-bromobenzoate (**1d**) followed by reaction with alcohol in flow microreactor systems

ϕ in R1 (μm)	L in R1 (cm)	t^R (s)	T ($^{\circ}\text{C}$)	Conv. ^a (%)	Yield ^a (%)	Conv. ^b (%)	Yield ^b (%)
250	3.5	0.014	0	100	65	90	41
250	6.0	0.028		- ^c	- ^c	86	24
500	3.5	0.055		100	37	88	13
1000	3.5	0.22		100	15	91	4
1000	6.0	0.38		100	9	92	0
1000	12.5	0.79		100	4	88	0
1000	100	6.3		100	0	88	0
250	3.5	0.014	-28	100	84	85	50
250	6.0	0.028		- ^c	- ^c	91	57
500	3.5	0.055		100	63	95	57
1000	3.5	0.22		100	58	96	36
1000	6.0	0.38		100	48	95	21
1000	12.5	0.79		100	38	100	20
1000	100	6.3		100	10	100	5
250	3.5	0.014	-48	80	64	89	71
250	6.0	0.028		- ^c	- ^c	95	74
500	3.5	0.055		100	90	89	63
1000	3.5	0.22		100	86	89	52
1000	6.0	0.38		100	80	89	45
1000	12.5	0.79		100	77	94	42
1000	100	6.3		100	43	100	14
250	3.5	0.014	-58	64	56	86	61
250	6.0	0.028		- ^c	- ^c	89	72
500	3.5	0.055		100	88	87	62
1000	3.5	0.22		100	82	90	62
1000	6.0	0.38		100	77	90	55
1000	12.5	0.79		100	78	92	49
1000	100	6.3		100	62	100	33
250	3.5	0.014	-78	51	33	52	33
250	6.0	0.028		- ^c	- ^c	51	33
500	3.5	0.055		60	43	58	33
1000	3.5	0.22		67	52	66	41
1000	6.0	0.38		85	56	76	49
1000	12.5	0.79		89	64	85	46
1000	100	6.3		96	58	81	34

^a Ethyl *o*-bromobenzoate (**1c**) was used as a substrate. ^b Methyl *o*-bromobenzoate (**1d**) was used as a substrate. ^c The reaction was not conducted.

The Br-Li Exchange Reaction of *o*-Bromobenzoates Followed by Reaction with Electrophiles Using Microflow Systems. A flow microreactor system consisting of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2) was used. A solution of an alkyl *o*-bromobenzoate (0.10 M) in THF (flow rate: 6.0 mL min⁻¹) and a solution of *s*-BuLi (0.42 M) in hexane/cyclohexane (19/31 v/v) (flow rate: 1.5 mL min⁻¹) were introduced to M1 (ϕ = 250 μ m) by syringe pumps. The resulting solution was passed through R1 and was mixed with a solution of electrophile (0.60 M) in THF (Et₂O in case of methyl triflate and trimethylsilyl triflate; flow rate: 3.0 mL min⁻¹) in M2 (ϕ = 250 μ m). The resulting solution was passed through R2 (ϕ = 1000 μ m, L = 50 cm). After a steady state was reached, the product solution was collected for 30 s while being quenched with H₂O (1 M HCl aqueous solution when benzaldehyde was used as an electrophile). The reaction mixture was analyzed by GC.

The reactions were carried out under the following conditions: for **1a**, T = 0 °C and t^R = 0.01 s; **1b**, T = -28 °C and t^R = 0.01 s; **1c**, T = -48 °C and t^R = 0.06 s; **1d**, T = -48 °C and t^R = 0.02 s.

***tert*-Butyl *o*-methylbenzoate.** 88% yield (GC t^R 16.1 min) from **1a** and iodomethane. The spectral data were identical to those reported in the literature.¹⁶

***tert*-Butyl *o*-trimethylsilylbenzoate.** 96% yield (GC t^R 18.6 min) from **1a** and chlorotrimethylsilane. After extraction, the crude product was purified by flash chromatography (hexane/ethyl acetate = 100 : 1): ¹H NMR (400 MHz, CDCl₃) δ 0.33 (s, 9H), 1.60 (s, 9H), 7.38 (ddd, J = 7.2, 7.2, 1.6 Hz, 1H), 7.46 (ddd, J = 7.2, 7.2, 1.6 Hz, 1H), 7.66 (dd, J = 7.2, 1.6 Hz, 1H), 7.88-7.92 ppm (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 0.55, 28.3, 80.8, 128.4, 129.4, 130.6, 135.1, 137.7, 142.0, 167.3 ppm; HRMS (EI) m/z calcd for C₁₄H₂₁O₂Si (M⁺-H): 249.1311, found: 249.1299.

3-Phenylphthalide. 82% yield (GC t^R 23.7 min) from **1a** and benzaldehyde. The spectral data were identical to those reported in the literature.¹⁷

Isopropyl *o*-methylbenzoate. 62% yield (GC t^R 16.0 min) from **1b** and iodomethane. 82% yield from **1b** and methyl triflate. The spectral data were identical to those reported in the literature.¹⁸

Isopropyl *o*-trimethylsilylbenzoate. 93% yield (GC t_R 18.2 min) from **1b** and chlorotrimethylsilane. After extraction, the crude product was purified by flash chromatography (hexane/ethyl acetate = 20 : 1): ^1H NMR (400 MHz, CDCl_3) δ 0.33 (s, 9H), 1.38 (d, J = 6.4 Hz, 6H), 5.22 (hept, J = 6.2 Hz, 1H), 7.40 (ddd, J = 7.4, 7.4, 1.6 Hz, 1H), 7.47 (ddd, J = 7.6, 7.2, 1.2 Hz, 1H), 7.67 (dd, J = 6.8, 1.2 Hz, 1H), 7.95-7.99 ppm (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 0.48, 22.1, 68.4, 128.5, 129.5, 131.0, 135.2, 136.2, 142.3, 167.5 ppm; HRMS (EI) m/z calcd for $\text{C}_{13}\text{H}_{21}\text{O}_2\text{Si}$ (MH^+): 237.1311, found: 237.1299.

3-Phenylphthalide. 77% yield from **1b** and benzaldehyde.

Ethyl *o*-methylbenzoate. 12% yield (GC t_R 15.5 min) from **1c** and iodomethane. 61% yield from **1c** and methyl triflate. The spectral data were identical to those reported in the literature.¹⁸

Ethyl *o*-trimethylsilylbenzoate. 61% yield (GC t_R 17.8 min) from **1c** and chlorotrimethylsilane. 79% yield from **1c** and trimethylsilyl triflate. After extraction, the crude product was purified by flash chromatography (hexane/ethyl acetate = 20 : 1): ^1H NMR (400 MHz, CDCl_3) δ 0.36 (s, 9H), 1.42 (t, J = 7.0 Hz, 3H), 4.39 (q, J = 7.1 Hz, 2H), 7.42 (m, 1H), 7.50 (m, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.99-8.02 ppm (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 0.45, 14.5, 61.0, 128.6, 129.7, 131.1, 135.2, 135.8, 142.2, 168.0 ppm; HRMS (EI) m/z calcd for $\text{C}_{12}\text{H}_{17}\text{O}_2\text{Si}$ ($\text{M}^+ - \text{H}$): 221.0998, found: 221.0997.

3-Phenylphthalide. 70% yield from **1c** and benzaldehyde.

Methyl *o*-methylbenzoate. 65% yield (GC t_R 14.1 min) from **1d** and methyl triflate. The spectral data were identical to those reported in the literature.¹⁹

Methyl *o*-trimethylsilylbenzoate. 82% yield (GC t_R 17.4 min) from **1d** and trimethylsilyl triflate. The spectral data were identical to those reported in the literature.²⁰

3-Phenylphthalide. 85% yield from **1d** and benzaldehyde.

References

- (1) For example, Moss, R. A.; Platz, M. S.; Jones Jr, M. *Reactive Intermediate Chemistry*, Wiley, Hoboken, **2004**.
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Chapter 2

Generation and Reactions of *m*- and *p*- Alkoxy carbonyl-Substituted Aryllithiums Based on I-Li Exchange Using Flow Microreactor System

Abstract

A flow microreactor system consisting of micromixers and microtube reactors provides an effective tool for the generation and reactions of aryllithiums bearing an alkoxy carbonyl group at *para*- and *meta*-positions. Alkyl *p*- and *m*-lithiobenzoates were generated by the I-Li exchange reaction with PhLi, because the Br-Li exchange reaction were unsuccessful. Subsequent reactions of the resulting aryllithiums with electrophiles gave the desired products in good yields.

Introduction

In general, it is well known that the generation of aryllithium compounds bearing an electrophilic functional group at the *para*- and *meta*-position is more difficult than those at the *ortho*-position. It has been reported that *ortho*-, *meta*-, and *para-tert*-butoxycarbonyl-substituted aryllithiums could be generated by halogen-lithium exchange reactions in conventional batch macro reactors only at -100 °C in spite of the presence of a highly sterically demanding *tert*-butyl group.¹ Generation and reactions of aryllithium compounds bearing an isopropoxycarbonyl group at the *ortho*-position could also be achieved though the yield was moderate. Presumably, the carbonyl group facilitates the halogen-lithium exchange reaction as a directing group. However, a similar transformation of aryllithiums bearing an isopropoxycarbonyl group at the *meta*- and *para*-position has been known to be impossible because of the lack of the directing effect.¹

In the *ortho* case, the coordination of the carbonyl oxygen atom in a neighboring position to lithium seems to accelerate the rate of the halogen-lithium exchange reaction, which may be much faster than the nucleophilic attack on the carbonyl group. In the *meta* and *para* cases, however, such coordination is impossible, and therefore the rate of halogen-lithium exchange and that of the nucleophilic attack seem to be closer, giving rise to lower selectivity. Furthermore, generation and reactions of aryllithium compounds bearing less sterically demanding alkoxycarbonyl groups, such as ethoxycarbonyl and methoxycarbonyl, have also been known to be impossible.

Results and Discussions

Generation and reactions of alkyl *p*-lithiobenzoates by Br-Li exchange

First, we examined Br-Li exchange reactions of alkyl *p*-bromobenzoates **1** to generate the corresponding alkyl *p*-lithiobenzoates **2**. It is well known that the Br-Li exchange reaction of alkyl bromobenzoates followed by a reaction with an electrophile, can be performed in a conventional batch macro reactor only when *tert*-butyl bromobenzoates are used at very low temperatures, such as -100 °C.¹ The use of esters bearing less sterically demanding alkoxycarbonyl groups, such as isopropoxycarbonyl, ethoxycarbonyl, and methoxycarbonyl groups, is known to be unsuccessful as mentioned above. To confirm this, we reexamined the Br-Li exchange reactions of alkyl

p-bromobenzoates **1** using a conventional batch macro reactor (Table 1).

Table 1. The Br-Li exchange reaction of alkyl *p*-bromobenzoates **1** followed by reaction with alcohols in a conventional batch reactor.

<i>p</i> -Bromobenzoates 1	Conversion of 1 (%)	Yield of 3 (%) ^a
R = <i>tert</i> -butyl: 1a	98	35 (49) ^b
R = isopropyl: 1b	74	trace (7) ^b
R = ethyl: 1c	82	0
R = methyl: 1d	42	0

^a Determined by GC. ^b The reaction time for Br-Li exchange reaction was 1 min.

The reaction of **1a** (R = *t*-Bu) at -78 °C gave the desired product **3a** in 35% yield (Table 1). A low yield of **3a** seems to be attributed to partial decomposition of **2a** at this temperature. According to the literature,¹ the reaction should be carried out at -100 °C, because significant amounts of byproducts were produced when the reaction was conducted at -78 °C. In the case of **1b** (R = *i*-Pr), only a trace amount of **3b** was obtained. Although the reaction time for the Br-Li exchange reaction was reduced to 1 min to prevent the decomposition of generated aryllithium compounds bearing alkoxy carbonyl group, significant increase of yields was not observed. Moreover, in the cases of **1c** (R = Et) and **1d** (R = Me), the desired products were not obtained at all. In case of **1d**, the conversion was quite low (42%) though the 1.1 equiv. of *s*-BuLi was used, presumably because the organolithium reagent was partially consumed for the nucleophilic attack to the sterically small methoxycarbonyl group.

Next, the reaction was conducted in a flow microreactor system consisting of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2) as shown in Figure 1. The reaction temperature was controlled by adjusting the temperature of a cooling bath (*T*). The residence time in R1 (*t*^R) was adjusted by changing the length and diameter of R1 with a fixed flow rate. The results are summarized in Figure 2 in which the yield of **3** is plotted against the *T* and *t*^R as a contour map with a scattered overlay.

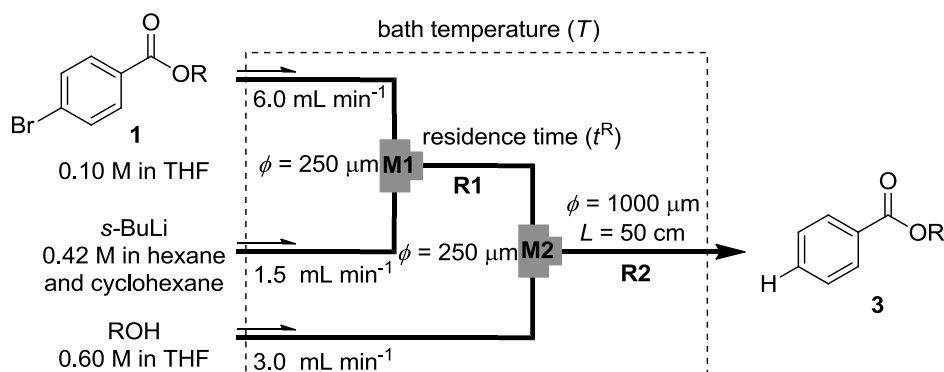


Figure 1. A microreactor system for the Br-Li exchange reaction of alkyl *p*-bromobenzoates **1** followed by reaction with alcohols.

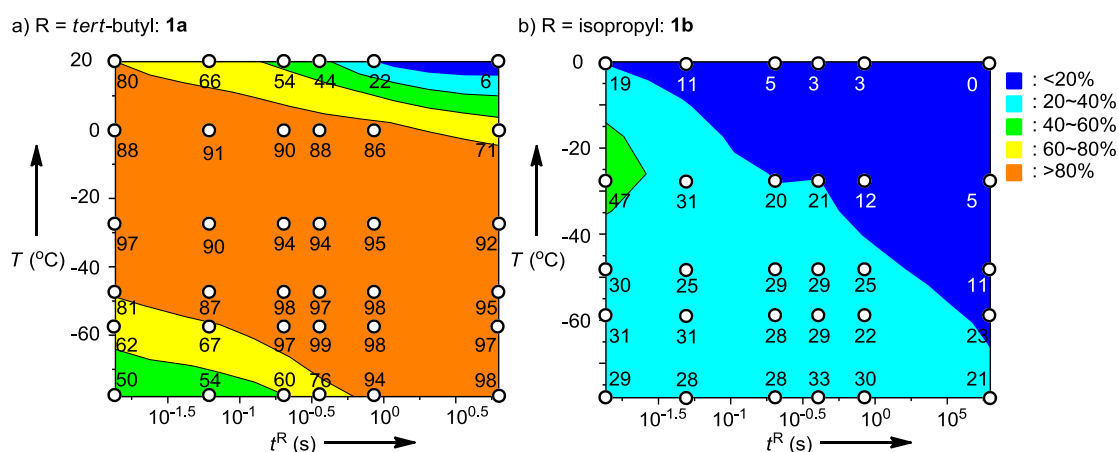


Figure 2. Effects of temperature and residence time on the yield in the Br-Li exchange reaction of a) *tert*-butyl *p*-bromobenzoates (**1a**) and b) isopropyl *p*-bromobenzoates (**1b**) with *s*-BuLi in the flow microreactor system.

In the case of **1a** ($R = t\text{-Bu}$), the desired product **3a** was obtained in high yields (> 80%) over a wide range of temperatures and residence times, which demonstrated that the flow microreactor system is more efficient for the generation and reactions of *tert*-butyl *p*-lithiobenzoate under milder conditions than conventional batch macro reactors. At low temperatures and short residence times the yields were low, presumably because of incomplete Br-Li exchange reactions. Low yields were also observed in the high-temperature long-residence-time region, probably because of the decomposition of aryllithium intermediates **2a**. In the case of **1b** ($R = i\text{-Pr}$), the yields were much lower throughout all regions (> 47%), though it was better than results using batch reactor. This is presumably because the isopropyl group is less sterically demanding than the *tert*-butyl group. Therefore, it was difficult to generate aryllithium compounds bearing

an isopropoxycarbonyl group without decomposition even in a flow microreactor system. This means that it must be also difficult to generate less hindered alkoxy carbonyl-substituted aryllithium compounds in a similar manner.

Generation and reactions of alkyl *p*-lithiobenzoates by I-Li exchange

We decided to conduct the I-Li exchange reaction of alkyl *p*-iodobenzoates **4** because I-Li exchange reactions are generally much faster than the corresponding Br-Li exchange reactions.² Before using a flow microreactor system, the reaction in a conventional batch reactor was examined. It is noteworthy that PhLi, which is less nucleophilic than *s*-BuLi, could be used for I-Li exchange reactions.

Table 2. The I-Li exchange reaction of alkyl *p*-iodobenzoates **1** followed by reaction with alcohols in a conventional batch macro reactor.

<i>p</i> -Iodobenzoates 4	Conversion of 4 (%)	Yield of 3 (%) ^a
R= <i>tert</i> -butyl: 4a	100	81 (99) ^b
R=isopropyl: 4b	100	7 (24) ^b
R=ethyl: 4c	100	trace
R=methyl: 4d	67	trace

^a Determined by GC. ^b The reaction time for I-Li exchange reaction was 1 min.

The reactions of *tert*-butyl *p*-iodobenzoate (**4a**) proceeded at -78 °C to give **3** (81%), after treatment with *tert*-butyl alcohol (Table 2). These results indicate that iodobenzoates are more effective than bromobenzoates as precursors of aryllithium compounds. In the case of isopropyl *p*-iodobenzoate (**4b**), the yield of the desired product was very low. When the reaction time for the I-Li exchange reaction was reduced to 1 min, yield was slightly increased, because the decomposition was partially prevented. However, in the case of ethyl and methyl *p*-iodobenzoates (**4c** and **4d**), the desired products were obtained in trace amounts.

Next, we examined the reactions in a flow microreactor system consisting of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2) as shown in Figure 3.

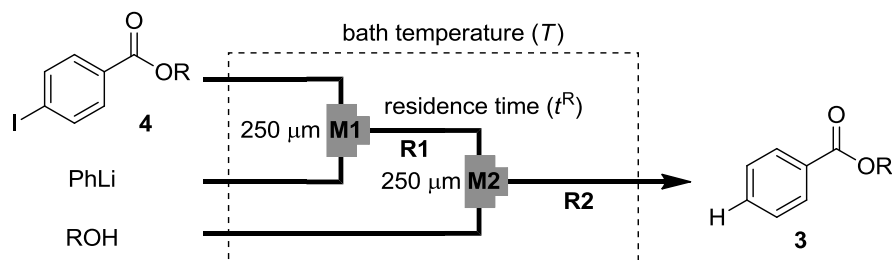


Figure 3. A microreactor system for the I-Li exchange reaction of alkyl *p*-iodobenzoates **4** followed by reaction with alcohols.

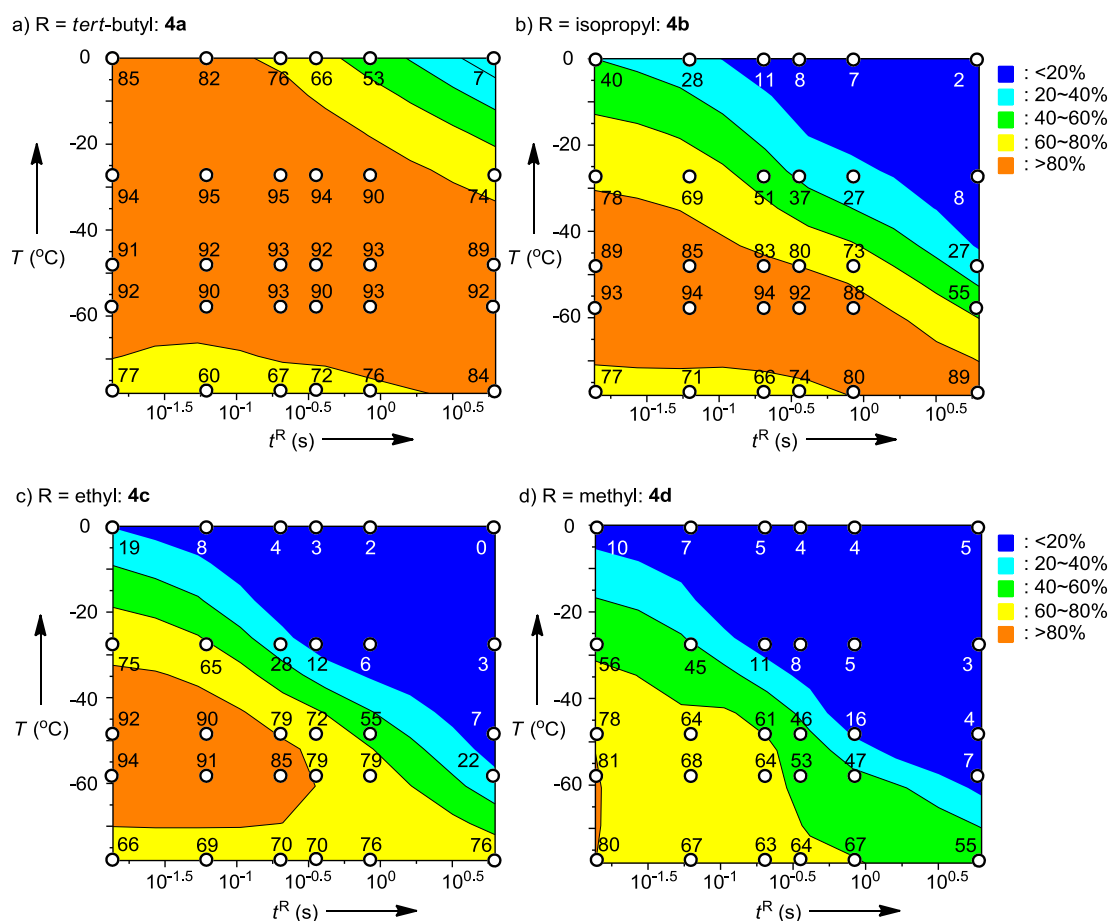


Figure 4. Effects of temperature and residence time on the yield in the Br-Li exchange reaction of a) *tert*-butyl *p*-iodobenzoates (**4a**), b) isopropyl *p*-iodobenzoates (**4b**), c) ethyl *p*-iodobenzoates (**4c**) and d) methyl *p*-iodobenzoates (**4d**) with PhLi in the flow microreactor system.

The residence time in R1 was adjusted by changing the length and diameter of R1 with a fixed flow rate. The results obtained with varying T ($-78 \sim 0$ °C) and t^R (0.01 ~ 6.3 s) are shown in Figure 4.

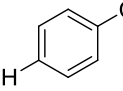
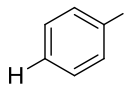
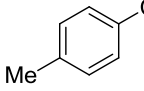
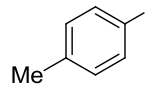
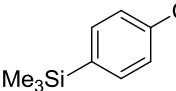
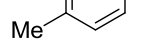
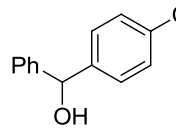
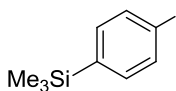
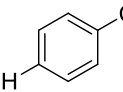
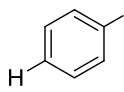
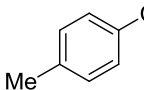
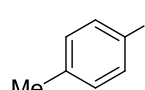
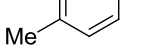
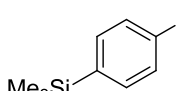
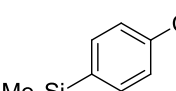
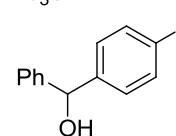
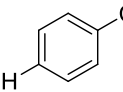
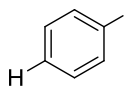
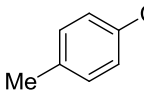
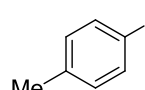
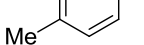
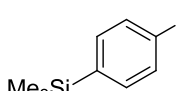
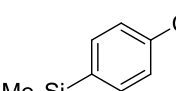
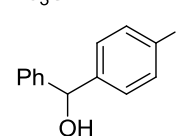
In the case of **4a** ($R = t\text{-Bu}$), the corresponding product **3a** was obtained in high yields ($> 80\%$) for a wide range of temperatures and residence times. The reaction can be conducted even at 0 °C, which demonstrates a significant advantage of flow microreactor systems. This means that the present reaction can be inherently conducted at 0 °C, although the reaction in conventional batch macro reactors requires over-cooling because of insufficient heat removal. The yields were low at low temperatures and short residence times, because of incomplete I-Li exchange reaction. Low yields were also observed in the high-temperature/long-residence-time region, probably because of the decomposition of aryllithium intermediates **2a**. In the case of **4b** ($R = i\text{-Pr}$), a similar reaction profile was observed, although the high-yield region became smaller. The reaction of **4c** also exhibited a similar profile. The ridge shifted to a lower temperature and shorter residence time region, because of faster decomposition of organolithium compounds **2c**. More astounding is the observation that methyl benzoates (**3d**) can be obtained in good yields ($> 80\%$) from **4d**, although the high-yield region was very small presumably because steric hindrance of the methoxycarbonyl group is small.

These results clearly show that the stability of the aryllithium compounds decreases in the order of **2a** > **2b** > **2c** > **2d**. The present temperature-residence time profile is quite effective at unveiling the features of the I-Li exchange reaction and stability of the resulting aryllithium intermediate. In addition, it is important to note that the I-Li exchange reaction followed by reaction with an electrophile can be successfully carried out without significant decomposition of the aryllithium intermediate **2** by optimizing temperature and residence time even in case of methyl ester.

Under the optimized conditions, the reactions of **2a-d** with other electrophiles, such as iodomethane, methyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, and benzaldehyde, were examined. As shown in Table 3, the reactions took place successfully and the corresponding products were obtained in good yields. For the generation of *p*-*tert*-butoxycarbonyl-substituted aryllithium compound, arylbromide **1a** can be used as a precursor and desired product was also obtained in good yields. It is interesting that iodomethane can be used as an electrophile for the reactions of **4a**, whereas methyl triflate should be used for the reactions of **4b-d**. The reaction of the aryllithium with iodomethane is slow, and therefore only the more sterically demanding *tert*-butoxycarbonyl groups can survive until the reaction is complete. However, methyl

triflate is more reactive, and therefore can trap less stable aryllithium compounds before they decompose.

Table 3. The optimized I-Li exchange reaction of alkyl *p*-iodobenzoates **4** followed by reaction with electrophiles.^a

Ester	Electrophile	Product	Yield (%) ^b	Ester	Electrophile	Product	Yield (%) ^b
R= <i>t</i> -Bu : 4a	<i>t</i> -BuOH		85 (88) ^c	R=Et : 4c	EtOH		84
	MeI		74 (81) ^c		MeI		25
	Me ₃ SiCl		87 (87) ^c		MeOTf		77
	PhCHO		67 ^d		MeI		67
R= <i>i</i> -Pr : 4b	<i>i</i> -PrOH		89	R=Me : 4d	MeOH		80
	MeI		38		MeOTf		81
	MeOTf		82		Me ₃ SiCl		81
	Me ₃ SiCl		74		PhCHO		80
R= <i>i</i> -Pr : 4b	<i>i</i> -PrOH		89	R=Me : 4d	MeOH		80
	MeI		38		MeOTf		81
	MeOTf		82		Me ₃ SiCl		81
	Me ₃ SiCl		74		PhCHO		80

^a For **4a**, *T* = 0 °C; **4b**, *T* = -48 °C; **4c**, *T* = -58 °C; **4d**, *T* = -78 °C; *t*^R was 0.01 s in all cases.

^b Determined by GC. ^c *tert*-butyl *p*-bromobenzene (**1a**) and *s*-BuLi were used. ^d Isolated yield.

Generation and reactions of alkyl *m*-lithiobenzoates by Br-Li exchange

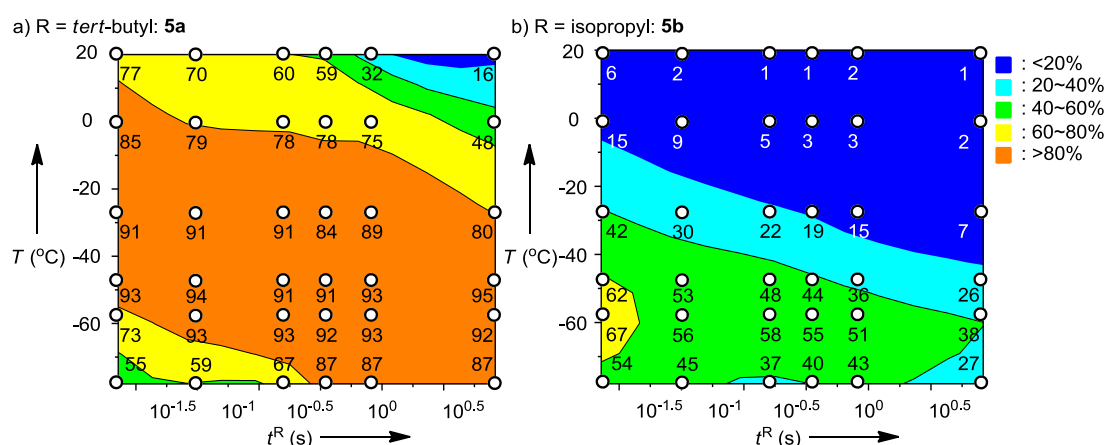
Next, we examined the Br-Li exchange reactions of alkyl *m*-bromobenzoates **5**. Reactions in a conventional batch macro reactor were carried out and the results are summarized in Table 4. Reactions of **5a** (R = *t*-Bu) at -78 °C gave the desired product in 40% yield, presumably because of partial decomposition of **6a**. The use of **5b** (R = *i*-Pr) caused a significant decrease in the yield of the product (**3b**). Moreover, in the case of **5c** (R = Et) and **5d** (R = Me), the yields of the desired products were negligibly low.

Table 4. The Br-Li exchange reaction of alkyl *m*-bromobenzoates **5** followed by the reaction with alcohols in a batch reactor

$ \begin{array}{ccccc} \text{C}_6\text{H}_4(\text{Br})\text{C}(=\text{O})\text{OR} & \xrightarrow[\text{-78 } ^\circ\text{C, 10 min}]{\text{s-BuLi (1.1 equiv)}} & \text{C}_6\text{H}_4(\text{Li})\text{C}(=\text{O})\text{OR} & \xrightarrow[\text{-78 } ^\circ\text{C, 10 min}]{\text{ROH (3.0 equiv)}} & \text{C}_6\text{H}_4(\text{H})\text{C}(=\text{O})\text{OR} \\ \text{5} & & \text{6} & & \text{3} \end{array} $		
<i>m</i> -Bromobenzoates 5	Conversion of 5 (%)	Yield of 3 (%) ^a
R = <i>tert</i> -butyl: 5a	96	40
R = isopropyl: 5b	80	5
R = ethyl: 5c	73	trace
R = methyl: 5d	56	0

^a Determined by GC

Next, the reactions were conducted in the flow microreactor. The results are summarized in Figure 5, in which the yield of **3** is plotted against the temperature and t^R as a contour map with scattered overlay. In the case of **5a** (R = *t*-Bu), the desired product was obtained in high yields over a wide range of residence times and temperatures. In the case of **5b** (R = *i*-Pr), the yields were much lower. This is presumably because the isopropyl group is less sterically demanding than the *tert*-butyl group. Therefore, it was difficult to generate *m*-isopropoxycarbonyl-substituted aryllithium compounds by Br-Li exchange reaction without decomposition even in a flow microreactor system as the case of *para*-substituted one.

**Figure 5.** Effects of temperature and residence time on the yield in the Br-Li exchange reaction of a) *tert*-butyl *m*-bromobenzoates (**5a**) and b) isopropyl *m*-bromobenzoates (**5b**) with *s*-BuLi in the flow microreactor system.

Generation and reactions of alkyl *m*-lithiobenzoates by I-Li exchange

Next, we examined the I-Li exchange reaction of alkyl *m*-iodobenzoates **7** to generate the corresponding *m*-alkoxycarbonyl-substituted aryllithiums **6**. Before using a flow microreactor system, the reaction in a batch macro reactor was examined and the results are summarized in Table 5.

The reaction of **7a** proceeded at -78 °C to give **3a** in 78% yield. These results indicate that iodobenzoates are more effective than bromobenzoates as precursors of aryllithium compounds. However, in the case of **7b**, the yield of the desired product was very low. In case of ethyl or methyl iodobenzoates (**7c** and **7d**), the desired products were obtained only in trace amounts.

Table 5. The I-Li exchange reaction of alkyl *m*-iodobenzoates **7** followed by the reaction with alcohols in a batch macro reactor

<i>m</i> -Iodobenzoates 7	Conversion of 7 (%)	Yield of 3 (%) ^a
R = <i>tert</i> -butyl: 7a	100	78
R = isopropyl: 7b	100	12
R = ethyl: 7c	98	trace
R = methyl: 7d	54	trace

^a Determined by GC

Next, we examined the reactions in a flow microreactor system. As shown in Figure 6, in the case of **7a** (R = *t*-Bu), the corresponding product **3a** was obtained in high yields (>80%) for a wide range of temperatures and residence times. In the case of **7b** (R = *i*-Pr), a similar reaction profile was observed, although the high-yield region became smaller. The reaction of **7c** also exhibited a similar profile, though the ridge shifted to a lower temperature and shorter residence time region because of faster decomposition of organolithium compounds **6c**. Methyl benzoates (**3d**) can be obtained in good yields (> 80%) from **7d**, although the high-yield region was very small.

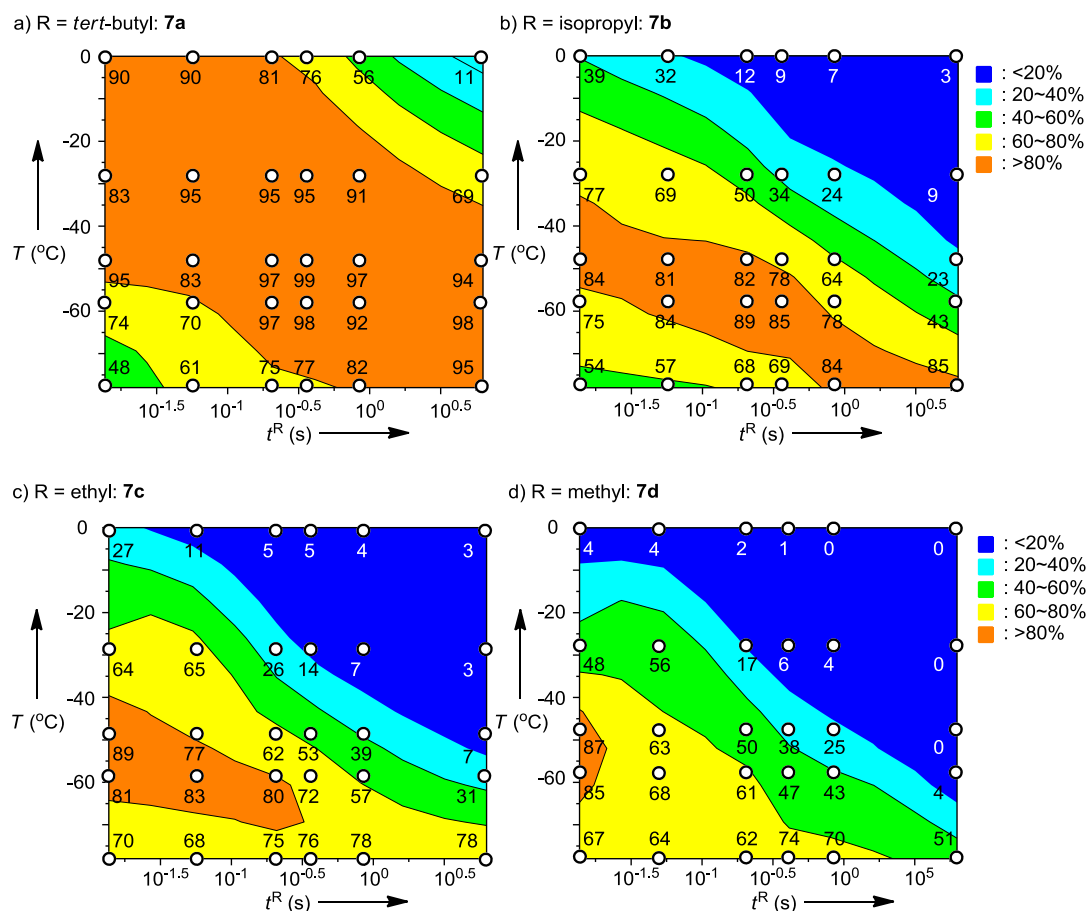


Figure 6. Effects of temperature and residence time on the yield in the Br-Li exchange reaction of a) *tert*-butyl *m*-iodobenzoates (**7a**), b) isopropyl *m*-iodobenzoates (**7b**), c) ethyl *m*-iodobenzoates (**7c**) and d) methyl *m*-iodobenzoates (**7d**) with PhLi in the flow microreactor system.

These results clearly show that the stability of the aryllithium compounds decreases in the order of **6a** ($R = t\text{-Bu}$) > **6b** ($R = i\text{-Pr}$) > **6c** ($R = \text{Et}$) > **6d** ($R = \text{Me}$). It is also noteworthy that the comparison between Figures 4 and 2 revealed that *m*-lithiobenzoates and *p*-lithiobenzoates have similar stability.

Under the optimized conditions, the reactions of **6a-d** with other electrophiles were examined. As shown in Table 6, the reactions took place successfully and the corresponding products were obtained in good yields.

Table 6. The optimized I-Li exchange reaction of alkyl *m*-iodobenzoates **7** followed by reaction with electrophiles.^a

Ester	Electrophile	Product	Yield (%) ^b	Ester	Electrophile	Product	Yield (%) ^b
R= <i>t</i> -Bu : 7a	<i>t</i> -BuOH		90	R=Et : 7c	EtOH		81
	MeI		78		MeI		21
	Me ₃ SiCl		94		MeOTf		78
	PhCHO		90		Me ₃ SiOTf		74
R= <i>i</i> -Pr : 7b	<i>i</i> -PrOH		84	R=Me : 7d	PhCHO		72 ^c
	MeI		34		MeOH		85
	MeOTf		75		MeOTf		79
	Me ₃ SiCl		78		Me ₃ SiOTf		87
	PhCHO		67		PhCHO		81 ^c

^a For **7a**, *T* = 0 °C; **7b**, *T* = -48 °C; **7c**, *T* = -58 °C; **7d**, *T* = -78 °C; *t*^R was 0.01 s in all cases.^b Determined by GC. ^c Isolated yield.

Conclusion

Generation of *m*- and *p*-alkoxycarbonyl-substituted aryllithium compounds followed by reaction with electrophiles has been accomplished by using a flow microreactor system consisting of micromixers and microtube reactors by virtue of precise residence time control and temperature control. Sterically less-demanding ethoxycarbonyl and methoxycarbonyl groups can survive by choosing appropriate conditions. The present method enables not only the generation of a variety of *tert*-butoxycarbonyl-substituted aryllithiums at much higher temperatures than those required for conventional macrobatch reactors but also the generation of less stable isopropoxycarbonyl-, ethoxycarbonyl-, and methoxycarbonyl-substituted aryllithiums, which are practically impossible to achieve by using conventional batch macro reactors. Therefore, the present method serves as a straightforward and powerful method for introducing substituents into the benzene ring of alkyl benzoates without protecting the alkoxycarbonyl group. The observations illustrated here open a new possibility of organic synthesis via unstable functionalized organolithiums.

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; initial oven temperature, 50 °C; rate of temperature increase, 10 °C min⁻¹). ¹H and ¹³C NMR spectra were recorded on Varian MERCURY plus-400 (¹H 400 MHz, ¹³C 100 MHz) spectrometer with Me₄Si or CDCl₃ as a standard in CDCl₃ unless otherwise noted. EI mass spectra were recorded on JMS-SX102A spectrometer. THF and Et₂O 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. All materials were obtained from commercial supplier and used without purification unless otherwise noted. *tert*-Butyl *p*-bromobenzoate (**1a**), isopropyl *p*-bromobenzoate (**1b**), *tert*-butyl *m*-bromobenzoate (**5a**), isopropyl *m*-bromobenzoate (**5b**) were prepared according to the literature.³ *tert*-Butyl *p*-iodobenzoate (**4a**), isopropyl *p*-iodobenzoate (**4b**), *tert*-butyl *m*-iodobenzoate (**7a**), isopropyl *m*-iodobenzoate (**7b**) were prepared according to the literature.⁴ The flow microreactor system was identical with that which was used in chapter 1.

The Br-Li Exchange Reaction of Alkyl Bromobenzoates Followed by Reaction with Alcohols Using a Batch Reactor. A solution of *s*-BuLi (0.42 M, 0.75 mL) in hexane/cyclohexane (19/31 v/v) was added dropwise to a solution of an alkyl bromobenzoate (0.10 M, 3.0 mL) in THF in a 20 mL round bottom glass flask for 1 min at -78 °C. The mixture was stirred for 10 min, and a solution of the corresponding alcohol (0.60 M, 1.5 mL) in THF was added. After stirring for 10 min, a cooling bath was removed. The mixture was analyzed by GC.

The Br-Li Exchange Reaction of Alkyl Bromobenzoates Followed by Reaction with Alcohols Using Flow Microreactor Systems. A flow microreactor system consisting of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2) was used. A solution of an alkyl *p*- or *m*-bromobenzoate (0.10 M) in THF (flow rate: 6.0 mL min⁻¹) and a solution of *s*-BuLi (0.42 M) in hexane/cyclohexane (19/31 v/v; flow rate: 1.5 mL min⁻¹) were introduced to M1 ($\phi = 250\ \mu\text{m}$) by syringe pumps. The resulting solution was passed through R1 and was mixed with a solution of alcohol (0.60 M) in THF (flow rate: 3.0 mL min⁻¹) in M2 ($\phi = 250\ \mu\text{m}$). The resulting solution was passed through R2 ($\phi = 1000\ \mu\text{m}$, $L = 50\ \text{cm}$). After a steady state was reached, the product solution was collected for 30 s while being quenched with sat. NH₄Cl aq. solution. The reaction mixture was analyzed by GC. The results are summarized in Table 7 and 8.

Table 7. The Br-Li exchange reaction of *tert*-butyl *p*-bromobenzoate (**1a**) and isopropyl *p*-bromobenzoate (**1b**) followed by reaction with alcohols in flow microreactor systems

ϕ in R1 (μm)	L in R1 (cm)	t^{R} (s)	T ($^{\circ}\text{C}$)	Conv. ^a (%)	Yield ^a (%)	Conv. ^b (%)	Yield ^b (%)
250	3.5	0.014	0	100	88	82	19
500	3.5	0.055		100	91	87	11
1000	3.5	0.22		100	90	88	5
1000	6.0	0.38		100	88	88	3
1000	12.5	0.79		100	86	93	3
1000	100	6.3		100	71	97	0
250	3.5	0.014	-28	100	97	78	47
500	3.5	0.055		100	90	84	31
1000	3.5	0.22		100	94	89	20
1000	6.0	0.38		100	94	94	21
1000	12.5	0.79		100	95	92	12
1000	100	6.3		100	92	95	5
250	3.5	0.014	-48	92	81	57	30
500	3.5	0.055		96	87	59	25
1000	3.5	0.22		100	98	62	29
1000	6.0	0.38		100	97	87	29
1000	12.5	0.79		100	98	84	25
1000	100	6.3		100	95	93	11
250	3.5	0.014	-58	69	62	51	31
500	3.5	0.055		76	67	73	31
1000	3.5	0.22		100	97	81	28
1000	6.0	0.38		100	99	88	29
1000	12.5	0.79		100	98	94	22
1000	100	6.3		100	97	91	23
250	3.5	0.014	-78	59	50	45	29
500	3.5	0.055		65	54	54	28
1000	3.5	0.22		67	60	59	28
1000	6.0	0.38		81	76	56	33
1000	12.5	0.79		100	94	64	30
1000	100	6.3		100	98	94	21

^a *tert*-Butyl *p*-bromobenzoate (**1a**) was used as a substrate. ^b Isopropyl *p*-bromobenzoate (**1b**) was used as a substrate.

Table 8. The Br-Li exchange reaction of *tert*-butyl *m*-bromobenzoate (**5a**) and isopropyl *m*-bromobenzoate (**5b**) followed by reaction with alcohols in flow microreactor systems

ϕ in R1 (μm)	L in R1 (cm)	t^{R} (s)	T ($^{\circ}\text{C}$)	Conv. ^a (%)	Yield ^a (%)	Conv. ^b (%)	Yield ^b (%)
250	3.5	0.014	0	97	85	84	15
500	3.5	0.055		98	79	97	9
1000	3.5	0.22		99	78	90	5
1000	6.0	0.38		99	78	90	3
1000	12.5	0.79		99	75	92	3
1000	100	6.3		99	48	91	2
250	3.5	0.014	-28	99	91	91	42
500	3.5	0.055		99	91	93	30
1000	3.5	0.22		99	91	95	22
1000	6.0	0.38		98	84	97	19
1000	12.5	0.79		99	89	98	15
1000	100	6.3		99	80	99	7
250	3.5	0.014	-48	97	93	93	62
500	3.5	0.055		99	94	94	53
1000	3.5	0.22		99	91	98	48
1000	6.0	0.38		99	91	99	44
1000	12.5	0.79		99	93	99	36
1000	100	6.3		99	95	99	26
250	3.5	0.014	-58	83	73	91	67
500	3.5	0.055		85	93	85	56
1000	3.5	0.22		98	93	97	58
1000	6.0	0.38		98	92	98	55
1000	12.5	0.79		99	93	99	51
1000	100	6.3		99	92	99	38
250	3.5	0.014	-78	61	55	65	54
500	3.5	0.055		69	59	63	45
1000	3.5	0.22		77	67	65	37
1000	6.0	0.38		98	87	70	40
1000	12.5	0.79		98	87	78	43
1000	100	6.3		95	87	85	27

^a *tert*-Butyl *m*-bromobenzoate (**5a**) was used as a substrate. ^b Isopropyl *m*-bromobenzoate (**5b**) was used as a substrate.

The I-Li Exchange Reaction of Alkyl Iodobenzoates Followed by Reaction with Alcohols Using a Batch Reactor. A solution of PhLi (0.42 M, 0.75 mL) in Et₂O/cyclohexane (72/28 v/v) was added dropwise to a solution of an alkyl iodobenzoate (0.10 M, 3.0 mL) in THF in a 20 mL round bottom glass flask for 1 min at -78 °C. The mixture was stirred for 10 min, and a solution of the corresponding alcohol (0.60 M, 1.5 mL) in THF was added. After stirring for 10 min, a cooling bath was removed. The mixture was analyzed by GC.

The I-Li Exchange Reaction of Alkyl Iodobenzoates Followed by Reaction with Alcohols Using Flow Microreactor Systems. A flow microreactor system consisting of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2) was used. A solution of an alkyl *p*- or *m*-iodobenzoate (0.10 M) in THF (flow rate: 6.0 mL min⁻¹) and a solution of PhLi (0.42 M) in Et₂O/cyclohexane (28/72 v/v; flow rate: 1.5 mL min⁻¹) were introduced to M1 (ϕ = 250 μ m) by syringe pumps. The resulting solution was passed through R1 and was mixed with a solution of alcohol (0.60 M) in THF (flow rate: 3.0 mL min⁻¹) in M2 (ϕ = 250 μ m). The resulting solution was passed through R2 (ϕ = 1000 μ m, L = 50 cm). After a steady state was reached, the product solution was collected for 30 s while being quenched with sat. NH₄Cl aqueous solution. The reaction mixture was analyzed by GC. The results are summarized in Table 9, 10, 11 and 12.

Table 9. The I-Li exchange reaction of *tert*-butyl *p*-iodobenzoate (**4a**) and isopropyl *p*-iodobenzoate (**4b**) followed by reaction with alcohols in flow microreactor systems

ϕ in R1 (μm)	L in R1 (cm)	t^{R} (s)	T ($^{\circ}\text{C}$)	Conv. ^a (%)	Yield ^a (%)	Conv. ^b (%)	Yield ^b (%)
250	3.5	0.014	0	96	85	95	40
500	3.5	0.055		93	82	93	28
1000	3.5	0.22		97	76	97	11
1000	6.0	0.38		97	66	97	8
1000	12.5	0.79		97	53	89	7
1000	100	6.3		98	7	100	2
250	3.5	0.014	-28	96	94	92	78
500	3.5	0.055		97	95	94	69
1000	3.5	0.22		97	95	96	51
1000	6.0	0.38		97	94	97	37
1000	12.5	0.79		97	90	100	27
1000	100	6.3		98	74	100	8
250	3.5	0.014	-48	93	91	92	89
500	3.5	0.055		94	92	90	85
1000	3.5	0.22		94	93	91	83
1000	6.0	0.38		95	92	93	80
1000	12.5	0.79		94	93	96	73
1000	100	6.3		96	89	100	27
250	3.5	0.014	-58	93	92	93	93
500	3.5	0.055		91	90	96	94
1000	3.5	0.22		94	93	97	94
1000	6.0	0.38		92	90	97	92
1000	12.5	0.79		95	93	97	88
1000	100	6.3		95	92	98	55
250	3.5	0.014	-78	81	77	79	77
500	3.5	0.055		84	60	73	71
1000	3.5	0.22		69	67	69	66
1000	6.0	0.38		65	72	77	74
1000	12.5	0.79		86	76	84	80
1000	100	6.3		84	84	95	89

^a *tert*-Butyl *p*-iodobenzoate (**4a**) was used as a substrate. ^b Isopropyl *p*-iodobenzoate (**4b**) was used as a substrate.

Table 10. The I-Li exchange reaction of ethyl *p*-iodobenzoate (**4c**) and methyl *p*-iodobenzoate (**4d**) followed by reaction with alcohols in flow microreactor systems

ϕ in R1 (μm)	L in R1 (cm)	t^{R} (s)	T ($^{\circ}\text{C}$)	Conv. ^a (%)	Yield ^a (%)	Conv. ^b (%)	Yield ^b (%)
250	3.5	0.014	0	98	19	89	10
500	3.5	0.055		100	8	93	7
1000	3.5	0.22		97	4	100	5
1000	6.0	0.38		100	3	95	4
1000	12.5	0.79		100	2	100	4
1000	100	6.3		100	0	88	5
250	3.5	0.014	-28	98	75	97	56
500	3.5	0.055		100	65	100	45
1000	3.5	0.22		100	28	100	11
1000	6.0	0.38		100	12	100	8
1000	12.5	0.79		100	6	100	5
1000	100	6.3		100	3	100	3
250	3.5	0.014	-48	98	92	95	78
500	3.5	0.055		98	90	94	64
1000	3.5	0.22		100	79	100	61
1000	6.0	0.38		100	72	100	46
1000	12.5	0.79		100	55	100	16
1000	100	6.3		100	7	100	4
250	3.5	0.014	-58	97	94	91	81
500	3.5	0.055		97	91	79	68
1000	3.5	0.22		96	85	92	64
1000	6.0	0.38		96	79	90	53
1000	12.5	0.79		100	79	100	47
1000	100	6.3		100	22	100	7
250	3.5	0.014	-78	69	66	84	80
500	3.5	0.055		71	69	72	67
1000	3.5	0.22		74	70	70	63
1000	6.0	0.38		73	70	71	64
1000	12.5	0.79		82	76	87	67
1000	100	6.3		96	76	93	55

^a Ethyl *p*-iodobenzoate (**4c**) was used as a substrate. ^b Methyl *p*-iodobenzoate (**4d**) was used as a substrate.

Table 11. The I-Li exchange reaction of *tert*-butyl *m*-iodobenzoate (**7a**) and isopropyl *m*-iodobenzoate (**7b**) followed by reaction with alcohols in flow microreactor systems

ϕ in R1 (μm)	L in R1 (cm)	t^{R} (s)	T ($^{\circ}\text{C}$)	Conv. ^a (%)	Yield ^a (%)	Conv. ^b (%)	Yield ^b (%)
250	3.5	0.014	0	95	90	95	39
500	3.5	0.055		96	90	97	22
1000	3.5	0.22		100	81	100	12
1000	6.0	0.38		100	76	100	9
1000	12.5	0.79		100	56	100	7
1000	100	6.3		100	11	100	3
250	3.5	0.014	-28	85	83	93	77
500	3.5	0.055		97	95	97	69
1000	3.5	0.22		100	95	100	50
1000	6.0	0.38		100	95	100	34
1000	12.5	0.79		100	91	100	24
1000	100	6.3		100	69	100	9
250	3.5	0.014	-48	95	95	87	84
500	3.5	0.055		84	83	90	81
1000	3.5	0.22		100	97	98	82
1000	6.0	0.38		100	99	98	78
1000	12.5	0.79		100	97	100	64
1000	100	6.3		100	94	100	23
250	3.5	0.014	-58	76	74	79	75
500	3.5	0.055		71	70	87	84
1000	3.5	0.22		100	97	95	89
1000	6.0	0.38		100	98	95	85
1000	12.5	0.79		100	92	96	78
1000	100	6.3		100	98	100	43
250	3.5	0.014	-78	65	63	55	54
500	3.5	0.055		64	61	58	57
1000	3.5	0.22		76	75	69	68
1000	6.0	0.38		80	77	71	69
1000	12.5	0.79		84	82	84	84
1000	100	6.3		95	95	94	85

^a *tert*-Butyl *m*-iodobenzoate (**7a**) was used as a substrate. ^b Isopropyl *m*-iodobenzoate (**7a**) was used as a substrate.

Table 12. The I-Li exchange reaction of ethyl *m*-iodobenzoate (**7c**) and methyl *m*-iodobenzoate (**7d**) followed by reaction with alcohols in flow microreactor systems

ϕ in R1 (μm)	L in R1 (cm)	t^{R} (s)	T ($^{\circ}\text{C}$)	Conv. ^a (%)	Yield ^a (%)	Conv. ^b (%)	Yield ^b (%)
250	3.5	0.014	0	97	27	99	5
500	3.5	0.055		98	11	97	4
1000	3.5	0.22		95	5	100	2
1000	6.0	0.38		97	5	100	1
1000	12.5	0.79		97	4	80	0
1000	100	6.3		97	3	100	0
250	3.5	0.014	-28	96	64	100	48
500	3.5	0.055		99	65	99	53
1000	3.5	0.22		99	26	100	17
1000	6.0	0.38		98	14	100	6
1000	12.5	0.79		98	7	100	4
1000	100	6.3		97	3	100	0
250	3.5	0.014	-48	94	89	97	87
500	3.5	0.055		96	77	97	63
1000	3.5	0.22		94	62	99	50
1000	6.0	0.38		97	53	99	38
1000	12.5	0.79		99	39	99	25
1000	100	6.3		99	7	100	5
250	3.5	0.014	-58	86	81	93	85
500	3.5	0.055		90	81	100	68
1000	3.5	0.22		96	80	96	61
1000	6.0	0.38		97	72	99	47
1000	12.5	0.79		99	57	99	43
1000	100	6.3		99	31	100	13
250	3.5	0.014	-78	72	70	83	67
500	3.5	0.055		69	68	81	64
1000	3.5	0.22		72	75	79	62
1000	6.0	0.38		81	76	88	74
1000	12.5	0.79		84	78	84	70
1000	100	6.3		99	78	100	51

^a Ethyl *m*-iodobenzoate (**7c**) was used as a substrate. ^b Methyl *m*-iodobenzoate (**7d**) was used as a substrate.

The Br-Li Exchange Reaction of Iodobenzoates Followed by Reaction with Electrophiles Using Microflow Systems. A flow microreactor system consisting of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2) was used. A solution of an alkyl *p*- or *m*-iodobenzoate (0.10 M) in THF (flow rate: 6.0 mL min⁻¹) and a solution of PhLi (0.42 M) in Et₂O/cyclohexane (28/72 v/v; flow rate: 1.5 mL min⁻¹) were introduced to M1 (ϕ = 250 μ m) by syringe pumps. The resulting solution was passed through R1 (ϕ = 250 μ m, L = 3.5 cm, t^R = 0.014 s) and was mixed with a solution of electrophile (0.60 M) in THF (Et₂O in case of methyl triflate and trimethylsilyl triflate; flow rate: 3.0 mL min⁻¹) in M2 (ϕ = 250 μ m). The resulting solution was passed through R2 (ϕ = 1000 μ m, L = 50 cm). After a steady state was reached, the product solution was collected for 30 s while being quenched with sat. NH₄Cl aqueous solution. The reaction mixture was analyzed by GC.

The reactions were carried out at 0 °C for **4a** and **7a**; -48 °C for **4b** and **7b**; -58 °C for **4c**, **7c** and **7d**.; -78 °C for **4d**.

***tert*-Butyl *p*-methylbenzoate.** 74% yield (GC ^tR 17.2 min) from **4a** and iodomethane. The spectral data were identical to those reported in the literature.⁵

***tert*-Butyl *p*-trimethylsilylbenzoate.** 87% yield (GC ^tR 20.4 min) from **4a** and chlorotrimethylsilane. The spectral data were identical to those reported in the literature.⁶

***tert*-Butyl *p*-(hydroxy(phenyl)methyl)benzoate.** 67% isolated yield from **4a** and benzaldehyde. After extraction, the crude product was purified by chromatography (hexane/ethyl acetate=3/1): The spectral data were identical to those reported in the literature.⁷

Isopropyl *p*-methylbenzoate. 38% yield (GC ^tR 16.7 min) from **4b** and iodomethane. 82% yield from **4b** and methyl triflate. The spectral data were identical to those reported in the literature.⁸

Isopropyl *p*-trimethylsilylbenzoate. 74% yield (GC ^tR 19.9 min) from **4b** and chlorotrimethylsilane. After extraction, the crude product was purified by chromatography (hexane/ethyl acetate=30/1): ¹H NMR (400 MHz, CDCl₃) δ 0.27 (s, 9H), 1.37 (d, J = 6.4 Hz, 6H), 5.25 (sept, J = 6.4 Hz, 1H), 7.58 (d, J = 7.6 Hz, 2H), 7.99 ppm (d, J = 7.2 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ -1.38, 21.9, 68.1, 128.4, 131.0,

133.1, 146.4, 166.2 ppm; HRMS (EI) m/z calcd for $C_{13}H_{20}O_2Si$ (M^+): 236.1233, found: 236.1236.

Isopropyl *p*-(hydroxy(phenyl)methyl)benzoate. 79% yield (GC t_R 27.6 min) from **4b** and benzaldehyde. After extraction, the crude product was purified by chromatography (hexane/ethyl acetate = 3:1): 1H NMR (400 MHz, $CDCl_3$) δ 1.35 (d, J = 6.4 Hz, 6H), 2.25 (d, J = 3.6 Hz, 1H), 5.24 (sept, J = 6.2 Hz, 1H), 5.89 (d, J = 3.6 Hz, 1H), 7.28-7.38 (m, 5H), 7.47 (d, J = 8.0 Hz, 2H), 8.01 ppm (d, J = 8.8 Hz 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 68.2, 75.2, 126.0, 126.3, 127.3, 128.2, 129.2, 129.3, 143.2, 148.8, 165.9 ppm; HRMS (EI) m/z calcd for $C_{17}H_{18}O_3$ (M^+): 270.1256, found: 270.1253.

Ethyl *p*-methylbenzoate. 25% yield (GC t_R 16.2 min) from **4c** and iodomethane. 77% from **4c** and methyl triflate.

Ethyl *p*-trimethylsilylbenzoate. 67% yield (GC t_R 19.6 min) from **4c** and chlorotrimethylsilane. 88% yield from **4c** and trimethylsilyl triflate. The spectral data were identical to those reported in the literature.⁹

Ethyl *p*-(hydroxy(phenyl)methyl)benzoate. 81% yield (GC t_R 27.4 min) from **4c** and benzaldehyde. The spectral data were identical to those reported in the literature.¹⁰

Methyl *p*-methylbenzoate. 81% yield (GC t_R 14.8 min) from **4d** and methyl triflate.

Methyl *p*-trimethylsilylbenzoate. 81% yield (GC t_R 18.4 min) from **4d** and trimethylsilyl triflate. The spectral data were identical to those reported in the literature.⁶

Methyl *p*-(hydroxy(phenyl)methyl)benzoate. 80% yield (GC t_R 26.2 min) from **4d** and benzaldehyde. The spectral data were identical to those reported in the literature.¹¹

***tert*-Butyl *m*-methylbenzoate.** 78% yield (GC t_R 17.1 min) from **7a** and iodomethane. After extraction, the crude product was purified by chromatography (hexane/ethyl acetate = 20:1): 1H NMR (400 MHz, $CDCl_3$) δ 1.59 (s, 9H), 2.39 (s, 3H), 7.26-7.38 (m, 2H), 7.77-7.83 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 28.2, 80.8, 126.5, 128.0, 129.9, 131.9, 133.1, 137.9, 165.9 ppm; HRMS (EI) m/z calcd for $C_{12}H_{16}O_2$ (M^+): 192.1150, found: 192.1149.

***tert*-Butyl *m*-trimethylsilylbenzoate.** 94% yield (GC t_R 19.7 min) from **7a** and chlorotrimethylsilane. After extraction, the crude product was purified by chromatography (hexane/ethyl acetate = 50:1): ^1H NMR (400 MHz, CDCl_3) δ 0.28 (s, 9H), 1.59 (s, 9H), 7.39 (td, $J = 7.6, 0.5$ Hz, 1H), 7.66 (dt, $J = 7.2, 1.3$ Hz, 1H), 7.92-7.97 (m, 1H), 8.13-8.16 ppm (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ -1.25, 28.2, 80.8, 127.5, 129.7, 131.1, 134.2, 137.3, 140.7, 166.1 ppm; HRMS (EI) m/z calcd for $\text{C}_{14}\text{H}_{22}\text{O}_2\text{Si}$ (M^+): 250.1389, found: 250.1394.

***tert*-Butyl *m*-(hydroxy(phenyl)methyl)benzoate.** 90% yield (GC t_R 26.9 min) from **7a** and benzaldehyde. After extraction, the crude product was purified by chromatography (hexane/ethyl acetate = 3:1): ^1H NMR (400 MHz, CDCl_3) δ 1.58 (s, 9H), 2.31 (s, 1H), 5.89 (s, 1H), 7.24-7.42 (m, 6H), 7.51-7.58 (m, 1H), 7.89 (d, $J = 7.6$ Hz, 1H), 8.00-8.04 ppm (m, 1H); ^{13}C NMR (100 MHz, CDCl_3 , Some of the ^{13}C NMR signals were the same places.) δ 28.1, 75.9, 81.1, 126.5, 127.4, 127.7, 128.3, 128.6, 130.5, 132.1, 143.4, 144.0, 165.6 ppm; HRMS (EI) m/z calcd for $\text{C}_{18}\text{H}_{20}\text{O}_3$ (M^+): 284.1412, found: 284.1412.

Isopropyl *m*-methylbenzoate. 34% yield (GC t_R 16.5 min) from **7b** and iodomethane. 75% yield from **7b** and methyl triflate. After extraction, the crude product was purified by chromatography (hexane/ethyl acetate = 20:1): ^1H NMR (400 MHz, CDCl_3) δ 1.37 (d, $J = 6.4$ Hz, 6H), 2.40 (s, 3H), 5.25 (sept, $J = 6.2$ Hz, 1H), 7.27-7.39 (m, 2H), 7.80-7.87 ppm (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.4, 22.1, 68.2, 126.5, 128.0, 129.8, 130.6, 133.3, 137.8, 166.0 ppm; HRMS (EI) m/z calcd for $\text{C}_{11}\text{H}_{14}\text{O}_2$ (M^+): 178.0994, found: 178.0996.

Isopropyl *m*-trimethylsilylbenzoate. 78% yield (GC t_R 19.3 min) from **7b** and chlorotrimethylsilane. After extraction, the crude product was purified by chromatography (hexane/ethyl acetate = 50:1): ^1H NMR (400 MHz, CDCl_3) δ 0.29 (s, 9H), 1.37 (d, $J = 6.8$ Hz, 6H), 5.26 (sept, $J = 6.2$ Hz, 1H), 7.41 (t, $J = 7.6$ Hz, 1H), 7.68-7.72 (m, 1H), 7.98-8.04 (m, 1H), 8.16-8.20 ppm (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ -1.25, 21.9, 68.2, 127.6, 129.8, 130.1, 134.2, 137.6, 140.8, 166.4 ppm; HRMS (EI) m/z calcd for $\text{C}_{13}\text{H}_{20}\text{O}_2\text{Si}$ (M^+): 236.1233, found: 236.1237.

Isopropyl *m*-(hydroxy(phenyl)methyl)benzoate. 67% yield (GC t_R 26.6 min) from **7b** and benzaldehyde. After extraction, the crude product was purified by chromatography (hexane/ethyl acetate = 3:1): ^1H NMR (400 MHz, CDCl_3) δ 1.36 (d, $J = 6.0$ Hz, 6H),

2.26 (d, $J = 3.6$ Hz, 1H), 5.24 (sept, $J = 6.3$ Hz, 1H), 5.91 (d, $J = 3.2$ Hz, 1H), 7.24-7.46 (m, 6H), 7.54-7.58 (m, 1H), 7.84 (dt, $J = 8.0, 1.6$ Hz, 1H), 8.07-8.13 ppm (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.7, 68.4, 75.4, 126.4, 127.4, 127.4, 128.2, 128.3, 128.3, 130.6, 130.7, 143.4, 144.2, 166.0 ppm; HRMS (EI) m/z calcd for $\text{C}_{17}\text{H}_{18}\text{O}_3$ (M^+): 270.1256, found: 270.1260.

Ethyl *m*-methylbenzoate. 21% yield (GC t_R 16.0 min) from **7c** and iodomethane. 78% yield from **7c** and methyl triflate.

Ethyl *m*-trimethylsilylbenzoate. 74% yield (GC t_R 19.1 min) from **7c** and trimethylsilyl triflate. The spectral data were identical to those reported in the literature.⁹

Ethyl *m*-(hydroxy(phenyl)methyl)benzoate. 72% isolated yield from **7b** and benzaldehyde. After extraction, the crude product was purified by chromatography (hexane/ethyl acetate = 3:1): ^1H NMR (400 MHz, CDCl_3) δ 1.37 (t, $J = 7.0$ Hz, 3H), 2.63 (s, 1H), 4.34 (q, $J = 7.2$ Hz, 2H), 5.85 (s, 1H), 7.23-7.29 (m, 1H), 7.29-7.41 (m, 5H), 7.55 (d, $J = 7.6$ Hz, 1H), 7.92 (dt, $J = 7.6, 1.2$ Hz, 1H), 8.07 ppm (t, $J = 1.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.3, 61.0, 75.8, 126.5, 127.5, 127.8, 128.5, 128.6, 128.6, 130.6, 130.8, 143.4, 144.1, 166.5 ppm; HRMS (EI) m/z calcd for $\text{C}_{16}\text{H}_{16}\text{O}_3$ (M^+): 256.1099, found: 256.1100.

Methyl *m*-methylbenzoate. 79% yield (GC t_R 14.8 min) from **7d** and methyl trifluoromethanesulfonate.

Methyl *m*-trimethylsilylbenzoate: 87% yield (GC t_R 18.1 min) from **7d** and trimethylsilyl triflate. The spectral data were identical to those reported in the literature.¹²

Methyl *m*-(hydroxy(phenyl)methyl)benzoate: 81% isolated yield from **7d** and benzaldehyde. After extraction, the crude product was purified by chromatography (hexane/ethyl acetate = 3:1): ^1H NMR (400 MHz, CDCl_3) δ 2.42 (d, $J = 3.2$ Hz, 1H), 3.89 (s, 3H), 5.88 (d, $J = 3.2$ Hz, 1H), 7.24-7.43 (m, 6H), 7.55-7.61 (m, 1H), 7.93 (dt, $J = 7.6, 1.4$ Hz, 1H), 8.07-8.11 ppm (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 52.1, 75.9, 126.5, 127.5, 127.8, 128.6, 128.6, 128.7, 130.3, 130.9, 143.4, 144.2, 167.0 ppm; HRMS (EI) m/z calcd for $\text{C}_{15}\text{H}_{14}\text{O}_3$ (M^+): 242.0943, found: 242.0941.

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Chapter 3

Flow Microreactor Synthesis via Cyano-Substituted Aryllithiums: Multistep Transformations

Abstract

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

Introduction

Organometallic compounds bearing a cyano group is very important because the activating effect of the cyano group such as the *ortho*-directing effect and its transformation into various other functional groups are advantageous from a synthetic point of view.¹ To generate the cyano-substituted organometallic compounds such as arylmetallics, halogen–metal exchange reactions involving halogen–Mg,² halogen–Cu³ and halogen–Zn⁴ have been extensively investigated, as they allow conventional access to functionalized arylmetallics; such reactions are often essential in the use of aryl iodides. Because of the high reactivity of halogen–Li exchange reactions, their application in the generation of functionalized aryllithiums enables the use of aryl bromide.

The remarkable pioneer work of Parham et al. has shown that various aryl- or heteroaryllithium compounds bearing a cyano group can be prepared by a Br–Li exchange reaction.⁵ However, it has been reported that the Br–Li exchange reaction of bromobenzonitrile and *n*-BuLi requires extremely low temperature such as -100 °C to obtain satisfactory yields. The work of Zajak *et al.*⁶ has shown that two major pathways could occur at the initial stage of the Br–Li exchange reaction of bromobenzonitriles at relatively high temperatures. One is the nucleophilic addition of generated lithiobenzonitrile to a cyano group of substrate (bromobenzonitrile), and the other is deprotonation of substrate with lithiobenzonitrile. It is revealed that the reaction could be conducted at a little bit higher temperatures (*c.a.* -70 °C) if the reverse addition (addition of bromobenzonitrile to *n*-BuLi) was employed.

Results and Discussions

This study focused on Br–Li exchange reactions of bromobenzonitriles. Lithiation of bromobenzonitriles followed by reaction with electrophiles in a conventional batch macro reactor requires very low temperatures, in the range of -70 to -100 °C, to avoid unwanted reactions at the cyano group as mentioned above.⁵ To confirm this we examined the Br–Li exchange reactions of the bromobenzonitriles such as *o*-bromobenzonitrile (**1a**), *m*-bromobenzonitrile (**1b**) and *p*-bromobenzonitrile (**1c**) using a conventional batch macro reactor and the results are shown in Table 1. The Br–Li exchange reaction with **1a** followed by protonation at -78 °C gave benzonitrile (**3**) in high yield. The reactions of *m*- and *p*-bromobenzonitrile (**1b** and **1c**) were not as

effective as that of **1a** (61% and 68%, respectively). At 0 °C, however, the reactions of **1** afforded **3** in very poor yields (Table 1). These results are in agreement with the results reported in the literature.

Table 1. Br-Li exchange reaction of bromobenzonitrile **1** in conventional batch reactor.

$ \begin{array}{ccccc} \text{Br}-\text{C}_6\text{H}_4-\text{CN} & \xrightarrow[\text{T } ^\circ\text{C, 10 min}]{n\text{-BuLi (1.1 equiv)}} & \text{Li}-\text{C}_6\text{H}_4-\text{CN} & \xrightarrow[\text{-78 } ^\circ\text{C, 10 min}]{\text{MeOH (3.0 equiv)}} & \text{H}-\text{C}_6\text{H}_4-\text{CN} \\ \mathbf{1} & & \mathbf{2} & & \mathbf{3} \end{array} $			
Bromobenzonitrile 1	<i>T</i> (°C)	Conversion of 1 (%)	Yield of 3 (%) ^a
<i>ortho</i> :-: 1a	-78	97	86
	0	100	3
<i>meta</i> :-: 1b	-78	90	61
	0	94	6
<i>para</i> :-: 1c	-78	90	68
	0	99	8

^a Determined by GC.

We then examined the Br-Li exchange reaction of *o*-, *m*- and *p*-bromobenzonitriles and sequential reactions with methanol using flow microreactor consisting of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2) as shown in Figure 1. The reactions were carried out with varying residence times (t^R) in R1, and varying reaction temperature (*T*) in the flow microreactor system.

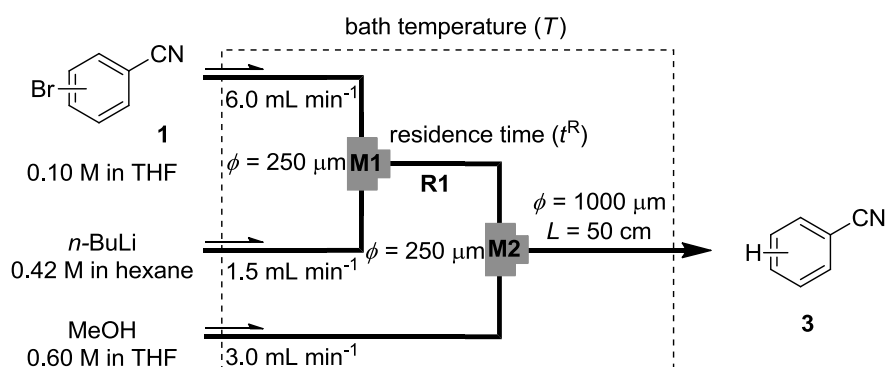


Figure 1. A microreactor system for the Br-Li exchange reaction of benzonitriles **1** followed by reaction with MeOH.

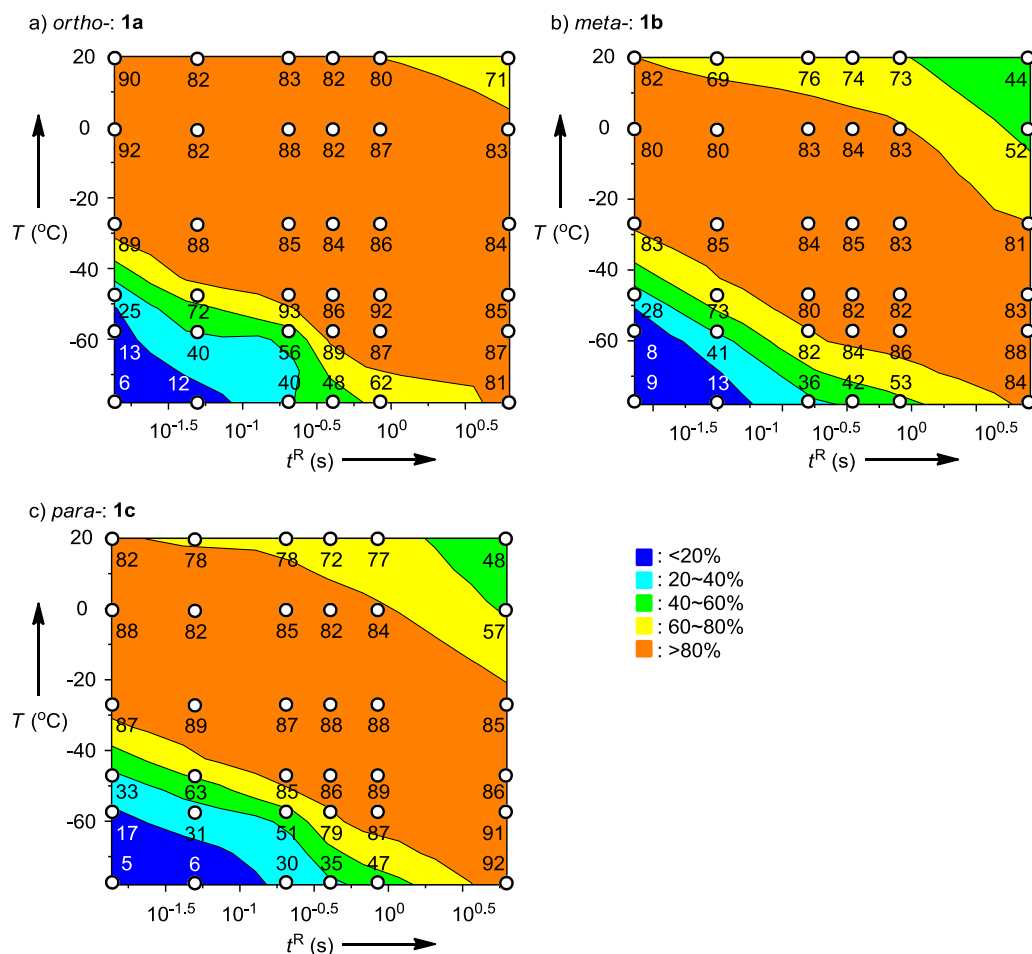
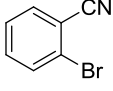
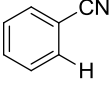
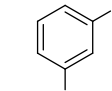
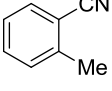
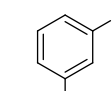
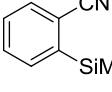
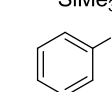
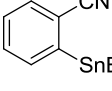
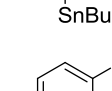
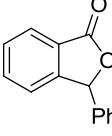
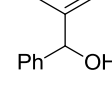
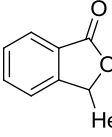
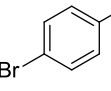
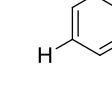
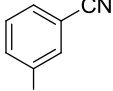
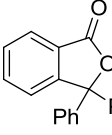
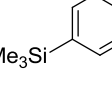
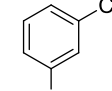
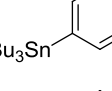
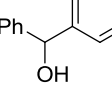


Figure 2. Effect of the temperature and the residence time on the yield of **3** in the Br-Li exchange reaction of a) *o*-bromobenzonitrile (**1a**), b) *m*-bromobenzonitrile (**1b**), c) *p*-bromobenzonitrile (**1c**) in flow microreactor systems.

As shown in Figure 2, the yield depended on both the temperature and the residence time. With a short residence time the reaction of **1a**, **1b** and **1c** gave **3** in high yields even at 20 °C (**1a**: 90%, **1b**: 82%, **1c**: 82%). An increase in the residence time caused a decrease in the yield probably because the nucleophilic attack on the cyano group. Figure 2 also shows that the stabilities of *m*-lithiobenzonitrile (**2b**) and *p*-lithiobenzonitrile (**2c**) are similar. In contrast, the stability of *o*-lithiobenzonitrile (**2a**) is higher than that of **2b** and **2c** because of the *ortho*-directing effect of the cyano group.

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

Table 2. The Br-Li exchange reaction of bromobenzonitrile **1** followed by reaction with an electrophile under the optimized conditions.^a

Nitrile	Electrophile	Product	Yield (%) ^b	Nitrile	Electrophile	Product	Yield (%) ^b
 1a	MeOH		90	 1b	MeI		81
	MeI		93		Me ₃ SiCl		96
	Me ₃ SiCl		90		Bu ₃ SnCl		95
	Bu ₃ SnCl		85		PhCHO		81
	PhCHO		92		MeOH		88
	<i>n</i> -HexCHO		81 ^c	 1c	MeI		90
 1b	PhCHO		94 ^c		Me ₃ SiCl		85
	MeOH		80		Bu ₃ SnCl		93
					PhCHO		87

^a For **1a**, T = 20 °C; for **1b** and **1c**, T = 0 °C; in all case t^R = 0.01 s.^b Determined by GC. ^c Isolated yield.

The integration of chemical reactions is of significant research interest because combining reactions avoids the isolation of intermediate products. The easy modulation of flow microreactor systems is advantageous for the integration of chemical reactions. To demonstrate the utility of the present flow microreactor method, sequential reactions were conducted using an integrated flow microreactor system. As shown in Table 2, the reaction of carbonyl compounds with **2a** gave lactone derivatives (cyclization products) after cyclization of the nitrile group with alkoxyolithium followed by hydrolysis. We

hypothesized that sequential protecting reactions of alkoxy lithium compounds generated by reaction of carbonyl compounds with **2a** could be achieved by the addition of an electrophile. The integrated flow microreactor system consisted of three T-shaped micromixers (M1, M2 and M3) and three microtube reactors (R1, R2 and R3) shown in Figure 3 was used.

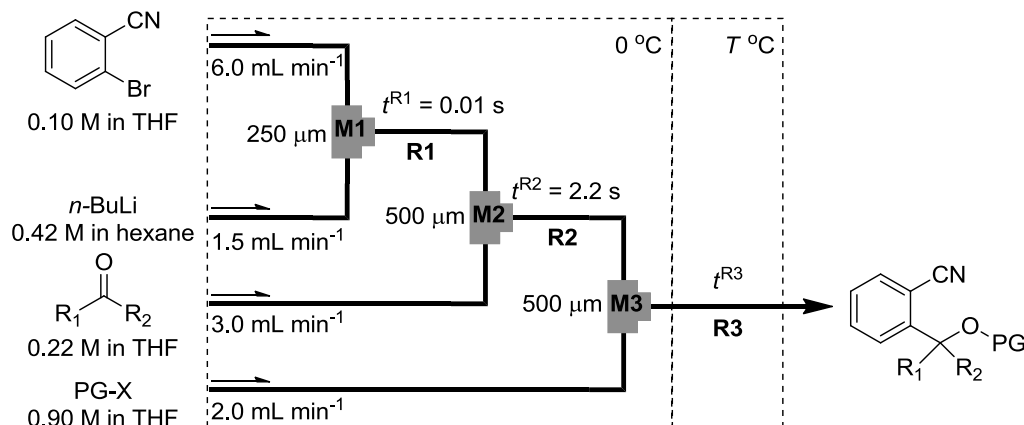
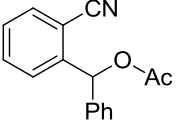
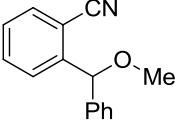
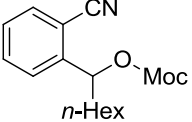
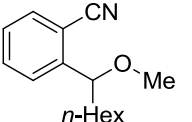
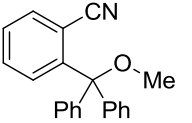


Figure 3. A flow microreactor system for the generation of *o*-lithiobenzonitriles and reaction with carbonyl compounds followed by the protection.

Table 3. Generation of *o*-lithiobenzonitriles and reaction with carbonyl compounds followed by the protection.

RCOR'	PG-X	<i>T</i> (°C)	<i>t</i> ^{R3} (s)	Product	Yield (%) ^a
PhCHO	AcCl	0	1.9		97
	Me ₂ SO ₄ ^b	50	97		83
<i>n</i> -HexCHO	MeO ₂ CCl	0	1.9		75
	Me ₂ SO ₄ ^b	50	97		51
Ph ₂ CO	Me ₂ SO ₄ ^b	50	97		66

^a Isolated yield. ^b 3 eq of HMPA was added to a solution of Me₂SO₄ as an additive.

The sequential transformations were successfully achieved to give the corresponding products in good yields as shown in Table 3. In case of the reactions with acetyl chloride and methyl chlorocarbonate, the reactions were fast even at 0 °C and the desired products were obtained in high yields within 2 s of residence time in R3. In case of methylation using dimethyl sulfate, the reaction was relatively slow. Although higher temperature (50 °C), longer residence time (97 s) and an additive (HMPA) were necessary for the full conversion, the desired compounds were also obtained in good yields.

Conclusions

We have developed an effective method for the generation and reactions of cyano-substituted aryllithium using a flow microreactor system based on a short residence time, fast mixing, and efficient temperature control. In addition, sequential transformations were achieved using an integrated flow microreactor system; the generation and reactions of *o*-lithiobenzonitrile followed by trapping reactions with electrophiles. The method provides a new dimension in functionalized organolithium chemistry.

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; initial oven temperature, 50 °C; rate of temperature increase, 10 °C min⁻¹). ¹H and ¹³C NMR spectra were recorded on Varian MERCURY plus-400 (¹H 400 MHz, ¹³C 100 MHz) spectrometer with Me₄Si or CDCl₃ as a standard in CDCl₃ unless otherwise noted. EI mass spectra were recorded on JMS-SX102A spectrometer. THF and Et₂O 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. All materials were obtained from commercial supplier and used without purification unless otherwise noted. The flow microreactor system was identical with that which was used in chapter 1.

The Br-Li Exchange Reaction of Bromobenzonitriles Followed by Reaction with MeOH Using a Batch Reactor. A solution of *n*-BuLi (0.42 M, 0.75 mL) in hexane was added dropwise to a solution of a bromobenzonitrile (0.10 M, 3.0 mL) in THF in a 20 mL round bottom glass flask for 1 min at -78 °C. The mixture was stirred for 10 min, and a solution of the MeOH (0.60 M, 1.5 mL) in THF was added. After stirring for 10 min, a cooling bath was removed. The mixture was analyzed by GC.

The Br-Li Exchange Reaction of Bromobenzonitriles Followed by Reaction with MeOH Using Flow Microreactor Systems. A flow microreactor system consisting of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2) was used. A solution of a bromobenzonitrile (0.10 M) in THF (flow rate: 6.0 mL min⁻¹) and a solution of *n*-BuLi (0.42 M) in hexane (flow rate: 1.5 mL min⁻¹) were introduced to M1 ($\phi = 250\ \mu\text{m}$) by syringe pumps. The resulting solution was passed through R1 and was mixed with a solution of MeOH (0.60 M) in THF (flow rate: 3.0 mL min⁻¹) in M2 ($\phi = 500\ \mu\text{m}$). The resulting solution was passed through R2 ($\phi = 1000\ \mu\text{m}$, $L = 50\ \text{cm}$). After a steady state was reached, the product solution was collected for 30 s while being quenched with H₂O. The reaction mixture was analyzed by GC. The results are summarized in Table 4.

Table 4. The Br-Li exchange reaction of bromobenzonitrile **1** followed by reaction with MeOH in flow microreactor systems.

ϕ of R1 (μm)	L of R1 (cm)	t^{R} (s)	T ($^{\circ}\text{C}$)	Conv. ^a (%)	Yield ^a (%)	Conv. ^b (%)	Yield ^b (%)	Conv. ^c (%)	Yield ^c (%)
250	3.5	0.014	20	100	90	100	80	100	82
500	3.5	0.055		100	82	100	75	100	78
1000	3.5	0.22		100	83	100	76	100	78
1000	6.0	0.38		100	82	100	74	100	72
1000	12.5	0.79		100	80	100	73	100	77
1000	100	6.3		100	71	100	44	100	41
250	3.5	0.014	0	100	91	100	80	100	88
500	3.5	0.055		100	87	100	80	100	82
1000	3.5	0.22		100	86	100	83	100	85
1000	6.0	0.38		100	87	100	84	100	82
1000	12.5	0.79		100	87	100	83	100	84
1000	100	6.3		100	83	100	52	100	48
250	3.5	0.014	-28	100	89	100	83	100	87
500	3.5	0.055		100	88	100	85	100	89
1000	3.5	0.22		100	85	100	84	100	87
1000	6.0	0.38		100	84	100	85	100	88
1000	12.5	0.79		100	86	100	83	100	88
1000	100	6.3		100	84	100	81	100	85
250	3.5	0.014	-48	26	25	47	28	50	33
500	3.5	0.055		74	72	93	73	84	63
1000	3.5	0.22		94	93	100	80	100	85
1000	6.0	0.38		100	86	100	82	100	86
1000	12.5	0.79		100	92	100	82	100	89
1000	100	6.3		100	85	100	83	100	86
250	3.5	0.014	-58	13	13	17	8	34	17
500	3.5	0.055		43	40	67	41	54	37
1000	3.5	0.22		60	56	98	82	68	51
1000	6.0	0.38		100	89	100	84	95	79
1000	12.5	0.79		100	87	100	86	100	87
1000	100	6.3		100	87	100	88	100	91
250	3.5	0.014	-78	6	6	7	3	7	2
500	3.5	0.055		12	12	26	19	38	27
1000	3.5	0.22		49	40	44	36	45	30
1000	6.0	0.38		56	48	51	42	50	41
1000	12.5	0.79		74	62	76	67	73	61
1000	100	6.3		100	81	100	84	100	92

^a *o*-Bromobenzonitrile (**1a**) was used as a substrate. ^b *m*-Bromobenzonitrile (**1b**) was used as a substrate. ^c *p*-Bromobenzonitrile (**1c**) was used as a substrate.

The Br-Li Exchange Reaction of Bromobenzonitriles Followed by Reaction with Electrophiles Using Microflow Systems. A flow microreactor system consisting of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2) was used. A solution of a bromobenzonitrile (0.10 M) in THF (flow rate: 6.0 mL min⁻¹) and a solution of *n*-BuLi (0.42 M) in hexane (flow rate: 1.5 mL min⁻¹) were introduced to M1 (ϕ = 250 μ m) by syringe pumps. The resulting solution was passed through R1 (ϕ = 250 μ m, L = 3.5 cm, t^R = 0.014 s) and was mixed with a solution of electrophile (0.60 M) in THF (flow rate: 3.0 mL min⁻¹) in M2 (ϕ = 500 μ m). The resulting solution was passed through R2 (ϕ = 1000 μ m, L = 50 cm). After a steady state was reached, the product solution was collected for 30 s while being quenched with H₂O (or 1 M HCl aqueous solution when carbonyl compound was used as an electrophile). The reaction mixture was analyzed by GC. The reactions were carried out at 20 °C when **1a** was used as a substrate, or 0 °C for **1b** and **1c**.

2-Trimethylsilylbenzonitrile. 90% yield (GC t^R 15.8 min) from **1a** and chlorotrimethylsilane. The spectral data were identical to those reported in the literature.⁶

2-Tributylstannylbenzonitrile. 85% yield (GC t^R 26.7 min) from **1a** and chlorotributylstannane. The spectral data were identical to those reported in the literature.⁷

2-Methylbenzonitrile. 93% yield (GC t^R 11.8 min) from **1a** and methyl iodide.

3-Phenylphthalide. 98% yield (GC t^R 24.2 min) from **1a** and benzaldehyde. The spectral data were identical to those reported in the literature.⁸

3-Hexylphthalide. 81% isolated yield from **1a** and *n*-heptanal. After extraction, the crude product was purified by silica gel chromatography (hexane/ethyl acetate = 5:1) to afford 52.9 mg of product. The spectral data were identical to those reported in the literature.⁸

3,3-Diphenyl-1(3*H*)-isobenzofuranone. 94% isolated yield from **1a** and benzophenone. After extraction, the crude product was purified by silica gel chromatography (hexane/ethyl acetate = 3:1) to afford 81.3 mg of the product. The spectral data were identical to those reported in the literature.⁹

3-Trimethylsilylbenzonitrile. 96% yield (GC t_R 16.3 min) from **1b** and chlorotrimethylsilane. After extraction, the crude product was purified by silica gel chromatography (hexane/ethyl acetate = 50:1): 1H NMR (400 MHz, $CDCl_3$) δ 0.28 (s, 9H), 7.41-7.46 (m, 1H), 7.59-7.64 (m, 1H), 7.69-7.74 (m, 1H), 7.75-7.79 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -1.8, 111.7, 118.8, 128.0, 131.8, 136.5, 137.1, 142.1 ppm; HRMS (EI) m/z calcd for $C_{10}H_{13}NSi$: 175.0817, found: 175.0817.

3-Tributylstannylbenzonitrile. 95% yield (GC t_R 27.8 min) from **1b** and chlorotributylstannane. After extraction, the crude product was purified by silica gel chromatography (hexane/ethyl acetate = 20:1): 1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 7.4 Hz, 9H), 0.98-1.18 (m, 6H), 1.32 (sext, J = 7.3 Hz, 6H), 1.40-1.62 (m, 6H), 7.34-7.42 (m, 1H), 7.53-7.78 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.5, 13.4, 27.1, 28.8, 112.0, 119.1, 127.9, 131.2, 139.4, 140.3, 143.9 ppm; HRMS (EI) m/z calcd for $C_{19}H_{31}NSn$: 393.1478, found: 393.1479.

3-Methylbenzonitrile. 81% yield (GC t_R 12.2 min) from **1b** and methyl iodide.

3-(Hydroxyphenylmethyl)-benzonitrile. 81% yield (GC t_R 24.6 min) from **1b** and benzaldehyde. The spectral data were identical to those reported in the literature.¹⁰

4-Trimethylsilylbenzonitrile. 85% yield (GC t_R 16.4 min) from **1c** and chlorotrimethylsilane. The spectral data were identical to those reported in the literature.¹¹

4-Tributylstannylbenzonitrile. 93% yield (GC t_R 28.3 min) from **1c** and chlorotributylstannane. The spectral data were identical to those reported in the literature.¹²

4-Methylbenzonitrile. 90% yield (GC t_R 12.5 min) from **1c** and methyl iodide.

4-(Hydroxyphenylmethyl)-benzonitrile. 93% yield (GC t_R 24.7 min) from **1c** and benzaldehyde. The spectral data were identical to those reported in the literature.¹³

The Br-Li Exchange Reaction of *o*-Bromobenzonitrile and Reactions with Carbonyl Compounds Followed by Protection. A flow microreactor system consisting of three T-shaped micromixers (M1, M2 and M3) and three microtube reactors (R1, R2 and R3) was used. A solution of *o*-bromobenzonitrile (0.10 M) in THF (flow rate: 6.0 mL min⁻¹) and a solution of *n*-BuLi (0.42 M) in hexane (flow rate: 1.5 mL min⁻¹) were introduced to M1 (ϕ = 250 μ m) by syringe pumps. The resulting solution was passed through R1 (ϕ = 250 μ m, L = 3.5 cm, t^R = 0.014 s) and was mixed with a solution of carbonyl compound (0.22 M) in THF (flow rate: 3.0 mL min⁻¹) in M2 (ϕ = 500 μ m). The resulting solution was passed through R2 (ϕ = 1000 μ m, L = 50 cm) and was mixed a solution of electrophile (0.90 M) in THF (flow rate: 2.0 mL min⁻¹) in M3 (ϕ = 500 μ m). The resulting solution was passed through R3. After a steady state was reached, the product solution was collected for 30 s while being quenched with H₂O. The microtube reactor R3 (ϕ = 1000 μ m, L = 50 cm) was used for the reaction with acetyl chloride or methyl chlorocarbonate as an electrophile. For the reaction with dimethyl sulfate (with 3 eq of HMPA), longer microtube reactor R3 (ϕ = 1000 μ m, L = 2560 cm (50 cm at 0 °C, 10 cm at ambient temperature, and 2500 cm at 50 °C)) was used for the full conversion.

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

2-(Methoxy(phenyl)methyl)benzonitrile. 93% isolated yield from benzaldehyde and dimethyl sulfate. After extraction, the crude product was purified by silica gel chromatography (hexane/ethyl acetate = 10:1) to afford 62.7 mg of the product: ¹H NMR (400 MHz, CDCl₃) δ 3.43 (s, 3H), 5.64 (s, 1H), 7.26-7.39 (m 4H), 7.42-7.46 (m, 2H), 7.55-7.65 ppm (m, 3H); ¹³C NMR (100MHz, CDCl₃) δ 57.3, 82.6, 111.3, 117.7, 126.9, 127.0, 127.9, 128.1, 128.6, 132.8, 133.1, 139.8, 146.0 ppm; HRMS (EI) m/z calcd for C₁₅H₁₃NO: 223.0997, found: 223.1002.

1-(2-Cyanophenyl)heptyl ethyl carbonate. 75% isolated yield from *n*-heptanal and methyl chlorocarbonate. After extraction, the crude product was purified by silica gel

chromatography (hexane/ethyl acetate = 5:1) to afford 62.1 mg of the product: ^1H NMR (400 MHz, CDCl_3) δ 0.87 (t, J = 6.8 Hz, 3H), 1.20-1.38 (m, 7H), 1.38-1.50 (m, 1H), 1.79-1.90 (m, 1H), 1.93-2.05 (m, 1H), 3.76 (s, 3H), 5.84-5.90 (m, 1H), 7.40 (td, J = 7.8, 1.2 Hz, 1H), 7.50-7.55 (m, 1H), 7.57-7.63 (m, 1H), 7.63-7.67 ppm (m, 1H); ^{13}C NMR (100MHz, CDCl_3) δ 13.9, 22.4, 25.1, 28.7, 31.5, 36.1, 54.9, 77.6, 110.9, 117.0, 126.3, 128.3, 132.8, 133.1, 144.3, 154.9 ppm; HRMS (EI) m/z calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_3$: 275.1521, found: 275.1524.

2-(1-Methoxyheptyl)benzonitrile. 51% isolated yield from *n*-heptanal and dimethyl sulfate. After extraction, the crude product was purified by silica gel chromatography (hexane/ethyl acetate = 10:1) to afford 35.4 mg of the product: ^1H NMR (400 MHz, CDCl_3) δ 0.86 (t, J = 6.8 Hz, 3H), 1.20-1.38 (m, 7H), 1.38-1.50 (m, 1H), 1.62-1.73 (m, 1H), 1.73-1.85 (m, 1H), 4.52-4.58 (m, 1H), 7.37 (td, J = 7.5, 1.6 Hz, 1H), 7.52-7.58 (m, 1H), 7.58-7.68 ppm (m, 2H); ^{13}C NMR (100MHz, CDCl_3) δ 14.0, 22.5, 25.5, 29.0, 31.7, 37.8, 57.1, 81.4, 111.4, 117.4, 126.6, 127.8, 132.7, 133.1, 146.9 ppm; HRMS (FAB) m/z calcd for $\text{C}_{15}\text{H}_{22}\text{NO}$: 232.1701, found: 232.1697.

2-(Methoxydiphenylmethyl)benzonitrile: 66% isolated yield from benzophenone and dimethyl sulfate. After extraction, the crude product was purified by silica gel chromatography (hexane/ethyl acetate = 10:1) to afford 59.6 mg of the product: ^1H NMR (400 MHz, CDCl_3) δ 3.10 (s, 3H), 7.28-7.39 (m, 7H), 7.45-7.51 (m, 5H), 7.63-7.67 ppm (m, 2H); ^{13}C NMR (100MHz, CDCl_3) δ 52.2, 87.0, 111.7, 118.8, 127.2, 127.7, 128.0, 129.1, 129.3, 131.8, 135.5, 141.1, 148.9 ppm; HRMS (EI) m/z calcd for $\text{C}_{21}\text{H}_{17}\text{NO}$: 299.1310, found: 299.1313.

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Chapter 4

Flow Microreactor Synthesis via Nitro-Substituted

Aryllithiums:

Switch between Kinetic and Thermodynamic Control

Abstract

We developed a flow microreactor method for the generation and reactions of aryllithiums bearing a nitro group. The flow microreactor method enabled the selective use of either the kinetically or the thermodynamically preferred intermediate. This transformation via a nitro-substituted aryllithium reagent would serve as an alternative straightforward route for the synthesis of Macbecin I.

Introduction

The synthetic importance of nitro compounds has ensured longstanding studies of their utilization in organic synthesis.¹ The activating effect of the nitro group is exploited in carrying out many organic reactions and its facile transformation into various functional groups has broadened the utility of nitro compounds in the synthesis of complex molecules.² Such advantages can boost the usefulness of organometallic compounds bearing a nitro group.³

However, use of nitro compounds in organic synthesis has been very limited, presumably because of their incompatibility with various nucleophilic and electrophilic reagents.⁴ In fact, a nitro group reacts with organometallic compounds such as organolithium reagents and Grignard reagents very quickly.⁵ For example, in case of Bartoli's indole synthesis, the nitro group reacts with vinylmagnesium bromide at -40 °C even in the presence of bromine atom.^{5a} Moreover, the reaction of arylmagnesium compounds and the nitroarenes serves as an effective route for the preparative synthesis of diarylamines.⁶

For these reasons, only scarce examples of the transformation via nitro-substituted arylmagnesium and aryllithium compounds have been reported. The generation of aryllithium and arylmagnesium compounds bearing a nitro group at the *ortho*-position can be conducted at low temperatures (generally -100 °C for Li and -40 °C for Mg).⁷ For these type of transformations, the *ortho* relationship between the carbon-metal bond and the nitro group is known to be essential for a selective halogen-metal exchange reaction.⁸ Actually, all attempts for the generation of *m*- or *p*-nitro substituted aryllithium and arylmagnesium compounds and their reactions with electrophiles failed. For example, the addition of PhMgCl to *m*- or *p*-iodonitrobenzene did not lead to any exchange product, but instead led only to reduction of the nitro group.⁸ Therefore, there is no general method to prepare all three isomers (*ortho*, *meta* and *para*) of lithiated or magnesiated nitroarenes.

Results and Discussions

At first, we examined the halogen-lithium exchange reactions of *p*-nitro-substituted halobenzenes with various commercial available organolithiums such as *s*-BuLi, *n*-BuLi, MeLi and PhLi using a conventional batch macro reactor.

Table 1. The I-Li exchange reaction of *p*-halonitrobenzenes **1** followed by reaction with MeOH in a conventional batch macro reactor.

X	RLi	Conversion of 1 (%)	Yield of 3 (%) ^a	
Br	<i>s</i> -BuLi	51	0	
	<i>n</i> -BuLi	63	0	
	MeLi	47	0	
	PhLi	44	0	
I	<i>s</i> -BuLi	36	11	
	<i>n</i> -BuLi	55	22	
	MeLi	77	23	
	PhLi	83	39	

^a Determined by GC.

The exchange reaction of *p*-bromonitrobenzene at -78 °C, followed by quenching with an alcohol, did not give the desired product **3** at all. This result can be attributed to the selective nucleophilic attack to the nitro group (reduction) by an added organolithium reagent as reported in the literature. When PhLi was used for this reaction, large amount of phenol (> 50%) was detected as a by-product. The use of *p*-iodonitrobenzene as the starting material, however, resulted in a formation of desired product though the yield was very low. In addition, we found that PhLi is quite effective for selective halogen-lithium exchange of halonitrobenzenes, presumably because of the low nucleophilicity of PhLi to the nitro group, whereas the use of *s*-BuLi, *n*-BuLi and MeLi gave rise to lower conversions of the starting material and lower yields of the product.

Next, the reaction was conducted in a flow microreactor system consisting of T-shaped micromixers (M1 and M2) and microtube reactors (R1 and R2) as shown in Figure 1. *o*-Iodonitrobenzene (**1a**), *m*-iodonitrobenzene (**1b**) and *p*-iodonitrobenzene (**1c**) were used and the reactions were conducted with varying temperatures (*T*) and the residence time (*t*^R) in R1.

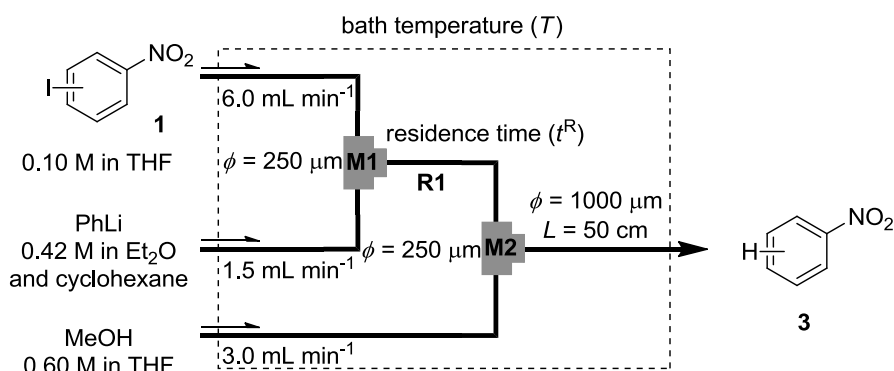


Figure 1. A microreactor system for the I-Li exchange reaction of iodonitrobenzenes **1** followed by reaction with MeOH.

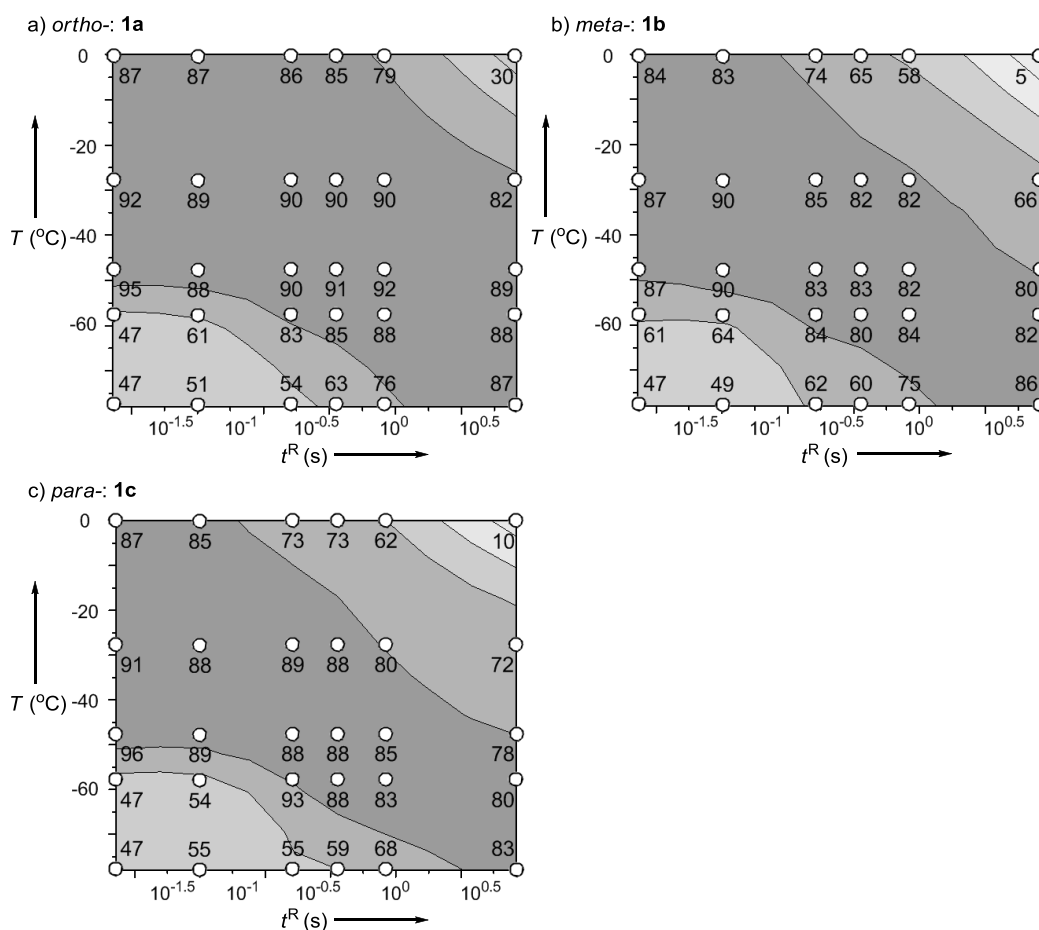


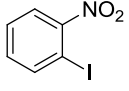
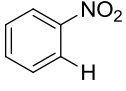
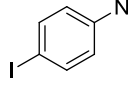
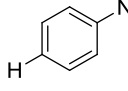
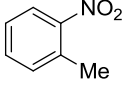
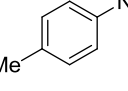
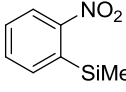
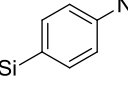
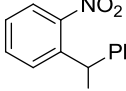
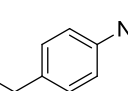
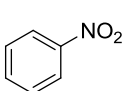
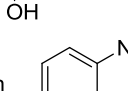
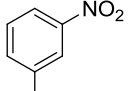
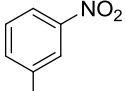
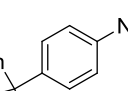
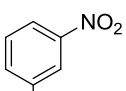
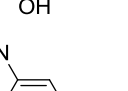
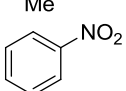
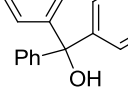
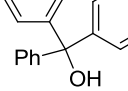
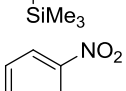
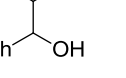
Figure 2. Effects of the reaction temperature and residence time on the yield of nitrobenzene (**3**) in the I-Li exchange reaction of a) *o*-iodonitrobenzene (**1a**), b) *m*-iodonitrobenzene (**1b**), and c) *p*-iodonitrobenzene (**1c**) with PhLi in the flow microreactor system.

Figure 2 summarizes the results obtained with varying the temperature and residence time. Irrespective of the substitution pattern, the products were obtained in high yields even at 0 °C by choosing an appropriate residence time. This result demonstrates a significant advantage of a flow microreactor system over a conventional batch macro system, which requires much lower temperatures (yield of **3**: 70% from **1a**, 43% from **1b**, 39% from **1c** at -78 °C). The yield obtained with the flow microreactor system decreased with an increase in t^R , presumably because of decomposition of the nitrophenyllithiums. These results show that shorter residence time is required at higher temperatures to get the products in good yields. The higher stability of *o*-nitrophenyllithium (**2a**) than those of *m*- and *p*-nitrophenyllithiums (**2b** and **2c**), respectively is also noteworthy. This is presumably because of the chelation effect. Slightly better yields were observed when the reactions were conducted at -28 °C.

Under the optimized conditions, reactions with various electrophiles were conducted using flow microreactor systems (Table 2). In case of the reactions with iodomethane, the longer reaction time was necessary for the full conversion. For example, if the residence time in R2 was relatively short (2.2 s) in the reaction of *p*-nitro-substituted aryllithium (**2c**) and iodomethane at -28 °C, the desired product was obtained in lower yield (31%) and a large amount of nitrobenzene (31%) derived from unreacted nitro-substituted aryllithium was detected (Table 4 of Experimental Section). It seems that strong electron-withdrawing ability of nitro group makes the reactivity of aryllithiums low. When the residence time in R2 was increased to 4.5 s, the generated aryllithium compounds seem to be almost consumed (2% of nitrobenzene was detected) and the yield of the desired product was enhanced, however, it is still low (45%), presumably because of a partial decomposition of generated aryllithium species. Moreover, in case of *o*-nitro-substituted aryllithium (**2a**), the reaction with iodomethane was slower than **2c**, (6% of desired product and 72% of nitrobenzene at the same condition; $T = -28$ °C, $t^R = 4.5$ s), because of *o*-chelation effect as well as electron-withdrawing ability of nitro group. This problem can be solved by using more reactive electrophiles.

The reactions with methyl triflate, trimethylsilyl triflate, benzaldehyde and benzophenone were successfully achieved and the products were obtained in high yields. Moreover, functionalized ketones such as 4-nitrobenzophenone and 4-(dimethylamino)-benzophenone could be used in this reaction, and desired carbinol compounds were successfully obtained in high yields.

Table 2. The I-Li exchange reaction of iodonitrobenzenes **1** followed by reaction with electrophiles.^a

Nitro	Electrophile	Product	Yield (%) ^b	Nitro	Electrophile	Product	Yield (%) ^b
 1a	MeOH		87	 1c	MeOH		91
	MeI		36		MeI		46 (31) ^c
	MeOTf		82		MeOTf		82
	Me ₃ SiCl		62		Me ₃ SiCl		70
	Me ₃ SiOTf		88		Me ₃ SiOTf		80
 1b	PhCHO		93	PhCHO		86	
	MeOH		87	Ph ₂ CO		95 ^{c,d}	
	MeI		44			86 ^{c,d}	
	MeOTf		86				
	Me ₃ SiCl		85				
	PhCHO		93			88 ^{c,d}	

^a t^R in R1 = 0.01 s, t^R in R2 = 9.0 s, $T = 0\text{ }^\circ\text{C}$ for **1a**; $T = -28\text{ }^\circ\text{C}$ for **1b** and **1c**.^b Determined by GC. ^c t^R in R2 = 2.2 s. ^d Isolated yield.

This type of reaction via nitro-substituted aryllithium species using flow microreactor system could be applied to the target-oriented synthesis. In the synthesis of Macbecin I, Micalizio *et. al* used compound **4**, which was converted to compound **7** in 5 steps including protection/deprotection process.⁹ In their synthesis, compound **4** was reduced to the amine which was protected as diallylamine (Figure 3). Then, the aryllithium bearing a protected amino group was generated by Br-Li exchange and was reacted with an aldehyde. The resulting alcohol was methylated, and the deprotection of the amino group gave compound **7**.

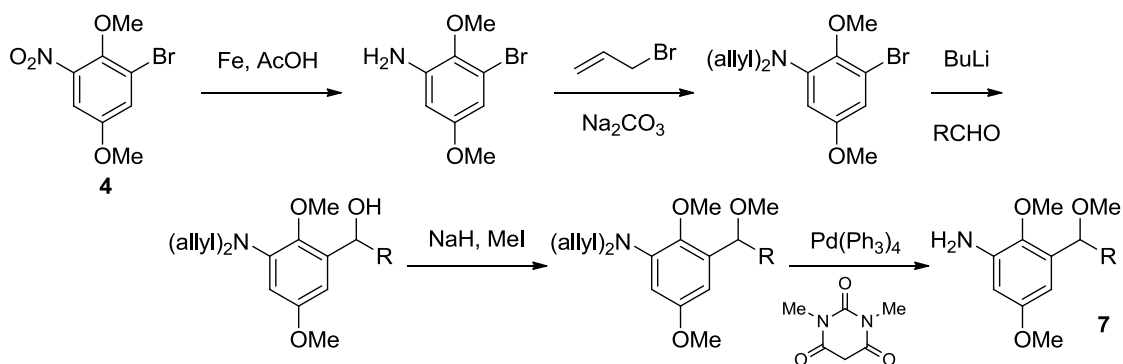


Figure 3. Synthesis of compound **7** as an intermediate for Macbecin I.^{9,10}

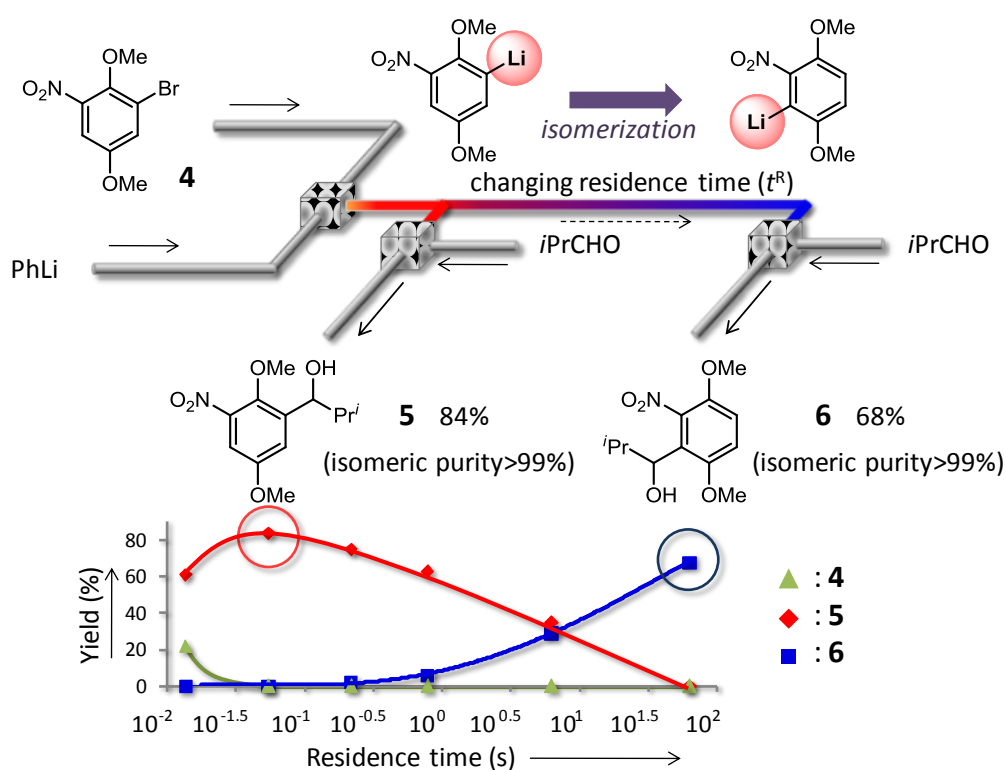


Figure 4. Switch between kinetic and thermodynamic control by changing the residence time.

As shown in Figure 4, the organolithium reaction of unprotected **4** demonstrates the potential of the flow microreactor method. The treatment with PhLi ($t^R = 0.06$ s at -48 °C) followed by the reaction with an aldehyde gave product **5** in 82% yield. It is also noteworthy that an increase in t^R resulted in the formation of a significant amount of isomeric product **6**, which was derived from isomerization of the aryllithium.¹¹ With t^R equal to 63 s, product **6** was obtained exclusively, indicating that the isomerization was complete in this period. The present result demonstrates that the flow microreactor

method is quite effective for the selective use of either the kinetically preferred organolithiums or the thermodynamically preferred organolithiums by controlling the residence time.

Next, we conducted the sequential methylation of generated lithium alkoxide in one flow. By simple optimizing the reaction conditions including flow rate, temperature and equivalence of reagents, the desired product was obtained in 73% yield as shown in Figure 5.

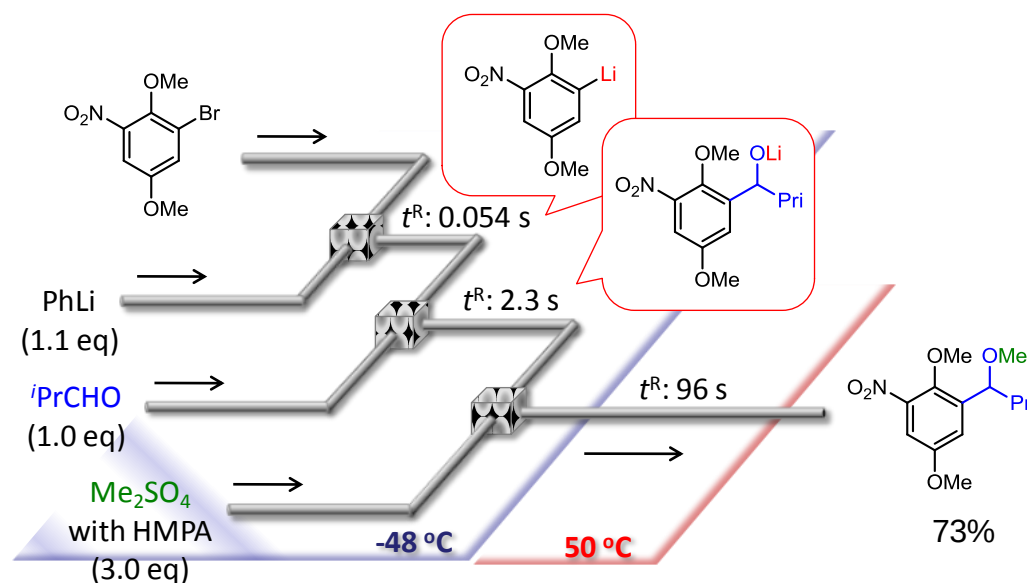


Figure 5. One-flow synthesis involving Br-Li exchange, reaction with an aldehyde and subsequent O-methylation.

The present transformation using a nitro-substituted aryllithium would serve as an alternative straightforward route for the synthesis of Macbecn I. After the flow reaction, simple reduction of the nitro group should give the desired compound **7** avoiding the protection–deprotection processes.¹²

Conclusion

We have developed the flow microreactor method for the generation and reaction of *o*-, *m*- and *p*-nitrophenyllithiums, which are known to be very difficult or impossible to generate and use in a conventional macrobatch method. Furthermore, the selective use of either kinetically preferred organolithiums or thermodynamically preferred organolithiums by changing the residence time demonstrates the power of the flow microreactor method in organic synthesis.

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. ^1H and ^{13}C NMR spectra were recorded on Varian MERCURYplus-400 (^1H 400 MHz, ^{13}C 100 MHz) spectrometer with CDCl_3 . EI and CI mass spectra were recorded on JMS-SX102A spectrometer. Gel permeation chromatography (GPC) was carried out on Japan Analytical Industry LC-9201. Unless otherwise noted, all materials were obtained from commercial supplier and used without further purification. 1-Bromo-2,5-dimethoxy-3-nitrobenzene (**4**) was prepared according to the literature.¹³ The flow microreactor system was identical with that which was used in chapter 1.

The Halogen-Lithium Exchange Reaction of Halonitrobenzenes Followed by Reaction with Methanol in a Batch Reactor. A solution of organolithium reagent (0.42 M, 0.75 mL) was added dropwise to a solution of halonitrobenzene (0.10 M in THF, 3.0 mL) for 1.0 min at $-78\text{ }^\circ\text{C}$. The mixture was stirred for 10 min, and a solution of methanol (0.60 M in THF, 1.5 mL) was added. After stirring for 10 min, a cooling bath was removed. The reaction mixture was analyzed by GC.

The I-Li Exchange Reaction of Iodonitrobenzenes Followed by Reaction with Methanol. A Flow microreactor system consisting of two T-shaped micromixers (M1 and M2), two microtube reactors (R1 and R2) was used. A solution of iodonitrobenzene (0.10 M in THF, flow rate: 6.0 mL min^{-1}) and a solution of PhLi (0.42 M in Et_2O and cyclohexane (72/28 v/v), flow rate: 1.5 mL min^{-1}) were introduced to M1 ($\phi = 250\text{ }\mu\text{m}$) by syringe pumps. The resulting solution was passed through R1 and was mixed with a solution of methanol (0.60 M in THF, flow rate: 3.0 mL min^{-1}) in M2 ($\phi = 250\text{ }\mu\text{m}$). The resulting solution was passed through R2 ($\phi = 1000\text{ }\mu\text{m}$, $L = 50\text{ cm}$). After a steady state was reached, the product solution was collected for 30 s while being quenched with H_2O . The reaction mixture was analyzed by GC. The results are summarized in Table 3.

Table 3. The I-Li exchange reaction of iodonitrobenzene **1** followed by reaction with methanol in flow microreactor systems.

ϕ in R1 (μm)	L in R1 (cm)	t^{R} (s)	T ($^{\circ}\text{C}$)	Conv. ^a (%)	Yield ^a (%)	Conv. ^b (%)	Yield ^b (%)	Conv. ^c (%)	Yield ^c (%)
250	3.5	0.014	0	97	87	100	84	97	87
500	3.5	0.055		99	87	100	83	100	85
1000	3.5	0.22		98	86	100	74	100	73
1000	6.0	0.38		98	85	100	75	100	73
1000	12.5	0.79		98	79	100	58	100	62
1000	100	6.3		100	30	96	5	96	10
250	3.5	0.014	-28	100	92	100	87	100	91
500	3.5	0.055		100	89	100	90	100	88
1000	3.5	0.22		100	90	100	85	100	89
1000	6.0	0.38		100	90	100	82	100	88
1000	12.5	0.79		100	92	100	82	100	80
1000	100	6.3		100	89	100	66	100	72
250	3.5	0.014	-48	100	95	97	87	100	96
500	3.5	0.055		100	88	100	90	100	89
1000	3.5	0.22		100	90	100	83	100	88
1000	6.0	0.38		100	91	100	83	100	88
1000	12.5	0.79		100	92	100	82	100	85
1000	100	6.3		100	89	100	80	97	78
250	3.5	0.014	-58	65	47	61	61	62	51
500	3.5	0.055		68	61	64	64	69	54
1000	3.5	0.22		97	83	100	84	100	93
1000	6.0	0.38		100	85	100	80	100	88
1000	12.5	0.79		100	88	100	84	100	83
1000	100	6.3		100	88	100	82	100	80
250	3.5	0.014	-78	68	47	52	47	65	47
500	3.5	0.055		72	51	59	49	68	55
1000	3.5	0.22		76	54	79	62	77	55
1000	6.0	0.38		82	63	79	60	74	59
1000	12.5	0.79		85	76	90	75	80	68
1000	100	6.3		96	87	100	86	100	83

^a *o*-Iodonitrobenzene (**1a**) was used as a substrate. ^b *m*-Iodonitrobenzene (**1b**) was used as a substrate. ^c *p*-Iodonitrobenzene (**1c**) was used as a substrate.

The I-Li Exchange Reaction of Iodonitrobenzenes Followed by Reaction with Electrophiles. A Flow microreactor system consisting of two T-shaped micromixers (M1 and M2), two microtube reactors (R1 and R2) was used. A solution of iodonitrobenzene (0.10 M in THF, flow rate: 6.0 mL min⁻¹) and a solution of PhLi (0.42 M in Et₂O and cyclohexane (72/28 v/v), flow rate: 1.5 mL min⁻¹) were introduced to M1 (ϕ = 250 μ m) by syringe pumps. The resulting solution was passed through R1 and was mixed with a solution of electrophile (0.60 M in THF or Et₂O for methyl triflate and trimethylsilyl triflate, flow rate: 3.0 mL min⁻¹) in M2 (ϕ = 250 μ m). The resulting solution was passed through R2 (ϕ = 1000 μ m, L = 400 cm). After a steady state was reached, the product solution was collected for 30 s while being quenched with H₂O. The reaction mixture was analyzed by GC. The organic phase was separated and the aqueous phase was extracted with ethyl acetate. After the combined organic phase was dried over Na₂SO₄, and solvent was removed, the reaction mixture was analyzed by ¹H and ¹³C NMR.

2-Methyl-1-nitrobenzene. 36% yield from **1a** and iodomethane. 82% yield from **1a** and methyl triflate.

2-Trimethylsilyl-1-nitrobenzene. 62% yield from **1a** and chlorotrimethylsilane. 88% yield from **1a** and trimethylsilyl triflate. The spectral data were identical to those reported in the literature.¹⁴

(2-Nitrophenyl)(phenyl)methanol. 93% yield from **1a** and benzaldehyde. The spectral data were identical to those reported in the literature.¹⁵

3-Methyl-1-nitrobenzene. 44% yield from **1b** and iodomethane. 86% yield from **1b** and methyl triflate.

3-Trimethylsilyl-1-nitrobenzene. 85% yield from **1b** and chlorotrimethylsilane. The spectral data were identical to those reported in the literature.¹⁴

(3-Nitrophenyl)(phenyl)methanol. 93% yield from **1b** and benzaldehyde. The spectral data were identical to those reported in the literature.¹⁵

4-Methyl-1-nitrobenzene. 46% yield from **1c** and iodomethane. 82% yield from **1c** and methyl trifluoromethanesulfonate.

4-Trimethylsilyl-1-nitrobenzene. 70% yield from **1c** and chlorotrimethylsilane. 80% yield from **1c** and trimethylsilyl triflate. The spectral data were identical to those reported in the literature.¹⁶

(4-Nitrophenyl)(phenyl)methanol. 86% yield from **1c** and benzaldehyde. The spectral data were identical to those reported in the literature.¹⁴

(4-Nitrophenyl)diphenylmethanol. 95% isolated yield from **1c** and benzophenone. After extraction, the crude product was purified by chromatography (hexane/ethyl acetate = 5:1). The spectral data were identical to those reported in the literature.¹⁷

Bis(4-nitrophenyl)(phenyl)methanol. 86% isolated yield from **1c** and 4-nitrobenzophenone. After extraction, the crude product was purified by chromatography (hexane/ethyl acetate = 5:1): ¹H NMR (400 MHz, CDCl₃) δ 2.93 (s, 1H), 7.16-7.22 (m, 2H), 7.36-7.42 (m, 3H), 7.54 (dt, *J* = 9.2, 2.4 Hz, 4H), 8.21 ppm (dt, *J* = 9.2, 2.4 Hz, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 81.4, 123.4, 127.6, 128.6, 128.6, 128.8, 144.5, 147.2, 152.3 ppm; HRMS (APCI) calcd. for C₁₉H₁₄ClN₂O₅⁻ [M+Cl]⁻: 385.0587; found: 385.0586.

(4-(Dimethylamino)phenyl)(4-nitrophenyl)(phenyl)methanol. 88% isolated yield from **1c** and 4-(dimethylamino)benzophenone. After extraction, the crude product was purified by chromatography (hexane/ethyl acetate = 5:1): ¹H NMR (400 MHz, CDCl₃) δ 2.74 (s, 1H), 2.96 (s, 1H), 6.66 (dt, *J* = 9.2, 2.4 Hz, 2H), 7.04 (dt, *J* = 8.8, 2.4 Hz, 2H), 7.25-7.37 (m, 5H), 7.56 (dt, *J* = 9.2, 2.4 Hz, 2H), 8.15 ppm (dt, *J* = 8.8, 2.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 40.6, 81.8, 112.0, 123.2, 127.8, 128.0, 128.4, 128.9, 129.1, 133.6, 146.4, 147.0, 150.2, 154.8 ppm; HRMS (APCI) calcd. for C₂₁H₂₀ClN₂O₃⁻ [M+Cl]⁻: 383.1162; found: 383.1157.

Table 4. The I-Li exchange reaction of iodonitrobenzene **1** followed by reaction with iodomethane in flow microreactor systems.^a

substrate	<i>T</i> (°C)	ϕ in R2 (μm)	<i>L</i> in R2 (cm)	<i>t</i> ^R in R2 (s)	GC Yield	
					MePhNO ₂ (%)	PhNO ₂ (%)
1a	0	1000	200	4.5	29	30
	0	1000	400	9.0	36	25
	-28	1000	200	4.5	6	72
	-48	1000	200	4.5	2	86
1b	-28	1000	50	2.2	28	34
	-28	1000	200	4.5	42	4
	-28	1000	400	9.0	44	3
1c	-28	1000	50	2.2	31	31
	-28	1000	200	4.5	45	2
	-28	1000	400	9.0	46	1

^a *t*^R in R1 = 0.01 s

The I-Li Exchange Reaction of 1-Bromo-2,5-dimethoxy-3-nitrobenzene (4) Followed by Reaction with Isobutyraldehyde in Flow Microreactor Systems. A flow microreactor system consisting of two T-shaped micromixers (M1 and M2), two microtube reactors (R1 and R2) was used. A solution of 1-bromo-2,5-dimethoxy-3-nitrobenzene (**3**, 0.10 M in THF, flow rate: 6.0 mL min⁻¹) and a solution of PhLi (0.42 M in Et₂O and cyclohexane (72/28 v/v), flow rate: 1.5 mL min⁻¹) were introduced to M1 (ϕ = 250 μm) by syringe pumps. The resulting solution was passed through R1 and was mixed with a solution of isobutyraldehyde (0.22 M in THF, flow rate: 3.0 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. NH₄Cl aqueous solution. The reaction mixture was analyzed by GC. The results are summarized in Table 5.

1-(2,5-Dimethoxy-3-nitrophenyl)-2-methylpropan-1-ol (5). 84% yield (residence time in R1: 0.06 s). After extraction, the crude product was purified by flash chromatography (hexane/ethyl acetate = 3:1). Then, **4** was isolated with GPC: ¹H NMR (400 MHz, CDCl₃) δ 0.87 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.4 Hz, 3H), 1.91-2.04 (m, 2H), 3.85 (d, *J* = 2.4 Hz, 6H), 4.74 (d, *J* = 6.8 Hz, 1H), 7.23 (d, *J* = 3.2 Hz, 1H), 7.26 ppm (d, *J* = 3.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 17.4, 19.3, 34.5, 55.9, 62.8, 73.3, 108.5, 118.8, 141.0, 143.4, 144.5, 155.1 ppm; HRMS (EI) *m/z* calcd for C₁₂H₁₇NO₅ (M⁺): 255.1107, found: 255.1111.

1-(3,6-Dimethoxy-2-nitrophenyl)-2-methylpropan-1-ol (6). 68% yield (residence time in R1: 63 s). After extraction, the crude product was purified by chromatography (hexane/ethyl acetate = 3:1): ^1H NMR (400 MHz, CDCl_3) δ 0.72 (d, J = 6.8 Hz, 3H), 1.06 (d, J = 6.4 Hz, 3H), 2.17-2.31 (m, 1H), 3.15 (d, J = 10.0 Hz, 1H), 3.81 (s, 3H), 3.85 (s, 1H), 4.14 (t, 1H), 6.90 (d, J = 8.8 Hz, 1H), 6.96 ppm (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 19.2, 19.3, 33.6, 56.0, 56.6, 75.7, 111.5, 112.6, 124.2, 141.3, 144.2, 150.7 ppm; HRMS (EI) m/z calcd for $\text{C}_{12}\text{H}_{17}\text{NO}_5$ (M^+): 255.1107, found: 255.1111.

Table 5. The I-Li exchange reaction of 1-bromo-2,5-dimethoxy-3-nitrobenzene (**4**) followed by reaction with isobutyraldehyde in flow microreactor systems.

ϕ in R1 (μm)	L in R1 (cm)	t^{R} (s)	Conv. (%)	GC yield (%)	
				5	6
250	3.5	0.014	78	61	0
500	3.5	0.055	100	84	0
1000	3.5	0.22	100	75	2
1000	12.5	0.76	100	63	6
1000	100	6.3	100	35	29
1000	1000	63	100	0	68

The I-Li Exchange Reaction of 1-Bromo-2,5-dimethoxy-3-nitrobenzene (4) and Reaction with Isobutyraldehyde Followed by Methylation in a Flow Microreactor System. A flow microreactor system consisting of three T-shaped micromixers (M1, M2 and M3), three microtube reactors (R1, R2 and R3) was used. A solution of 1-bromo-2,5-dimethoxy-3-nitrobenzene (**3**, 0.10 M in THF, flow rate: 6.0 mL min^{-1}) and a solution of PhLi (0.42 M in Et_2O and cyclohexane (72/28 v/v; flow rate: 1.6 mL min^{-1}) were introduced to M1 ($\phi = 250 \mu\text{m}$) by syringe pumps. The resulting solution was passed through R1 and was mixed with a solution of isobutyraldehyde (0.22 M in THF, flow rate: 2.8 mL min^{-1}) in M2 ($\phi = 250 \mu\text{m}$). The resulting solution was passed through R2 ($\phi = 1000 \mu\text{m}$, $L = 50 \text{ cm}$) and was mixed a solution of dimethyl sulfate (0.90 M) containing HMPA (0.90 M) in THF (flow rate: 2.0 mL min^{-1}) in M3 ($\phi = 500 \mu\text{m}$). The resulting solution was passed through R3 ($\phi = 1000 \mu\text{m}$, $L = 2560 \text{ cm}$ (50 cm at 0°C , 10 cm at ambient temperature, and 2500 cm at 50°C)). After a steady state was reached, the product solution was collected for 30 s while being quenched with sat. NH_4Cl aq. solution. The reaction mixture was analyzed by GC.

2,5-Dimethoxy-1-(1-methoxy-2-methylpropyl)-3-nitrobenzene. 73% GC yield: ^1H NMR (400 MHz, CDCl_3) δ 0.83 (d, $J = 6.8$ Hz, 3H), 0.98 (d, $J = 6.4$ Hz, 3H), 1.89 (sext, $J = 6.8$ Hz, 1H), 3.24 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 4.25 (d, $J = 6.4$ Hz, 1H), 7.16 (d, $J = 2.8$ Hz, 1H), 7.29 ppm ($J = 3.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 18.0 and 19.0, 34.5, 55.9, 57.3, 62.7, 82.3, 108.9, 118.4, 139.2, 143.6, 145.6, 155.2 ppm; HRMS (APCI) calcd. for $\text{C}_{13}\text{H}_{20}\text{NO}_5^+ [\text{M}+\text{H}]^+$: 270.1328; found: 270.1336.

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Chapter 5

A Flow Microreactor Synthesis via Organolithium

Intermediates Bearing Ketone Carbonyl Groups:

A New Approach to Protecting-Group-Free Synthesis

Abstract

Protecting-group-free synthesis has received significant recent research interest in the context of ideal synthesis and green sustainable chemistry. In general, organolithium species react with ketones very rapidly, and therefore ketone carbonyl groups should be protected before an organolithium reaction, if they are not involved in the desired transformation. If organolithium chemistry could be free from such a limitation, its power would be greatly enhanced. Here we show that a flow microreactor enables such protecting-group-free organolithium reactions by greatly reducing the residence time (0.003 s or less). Aryllithium species bearing ketone carbonyl groups are generated by iodine-lithium exchange reactions of the corresponding aryl iodides with mesityllithium and are reacted with various electrophiles using a flow microreactor system. The present method has been successfully applied to the formal synthesis of Pauciflorol F.

Introduction

Although organolithium species serve as powerful reagents in organic synthesis, they are not compatible with electrophilic functional groups such as ketone carbonyl groups. In fact, organolithium species react with ketones very rapidly. In some cases, organolithium species can be generated in the presence of ketones and quenched *in situ* by the ketone carbonyl group.¹ However, if a ketone carbonyl group is not involved in the desired transformation, it should be protected before an organolithium reaction, although ketone carbonyl groups survive in reactions of some less reactive organometallics.² Therefore, if organolithium reactions can be conducted without protecting the ketone carbonyl groups, the power of organolithium chemistry will be greatly enhanced.

Results and Discussions

We began our investigation by conducting the I–Li exchange reaction of *o*- and *p*-acyliodobenzenes followed by trapping with methanol using the flow microreactor system, as shown in Figure 1.

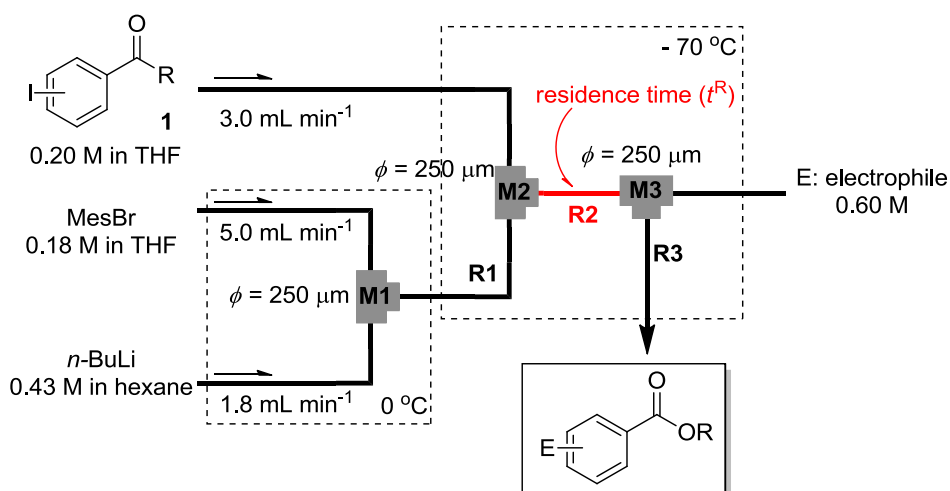


Figure 1. A microreactor system for the I–Li exchange reaction of iodoarenes bearing ketone carbonyl group followed by reaction with alcohols.

Mesityllithium was first generated by a Br-Li exchange reaction of 2-bromo-1,3,5-trimethylbenzene (mesityl bromide) and *n*-BuLi at 0 °C, because preliminary studies showed that mesityllithium was the most effective compound for this purpose. The I-Li exchange reaction of an acyliodobenzene using the resulting mesityllithium was conducted at -70 °C. The short-lived acylphenyllithium species thus produced was trapped with methanol as an electrophile at -70 °C (Figure 1a).

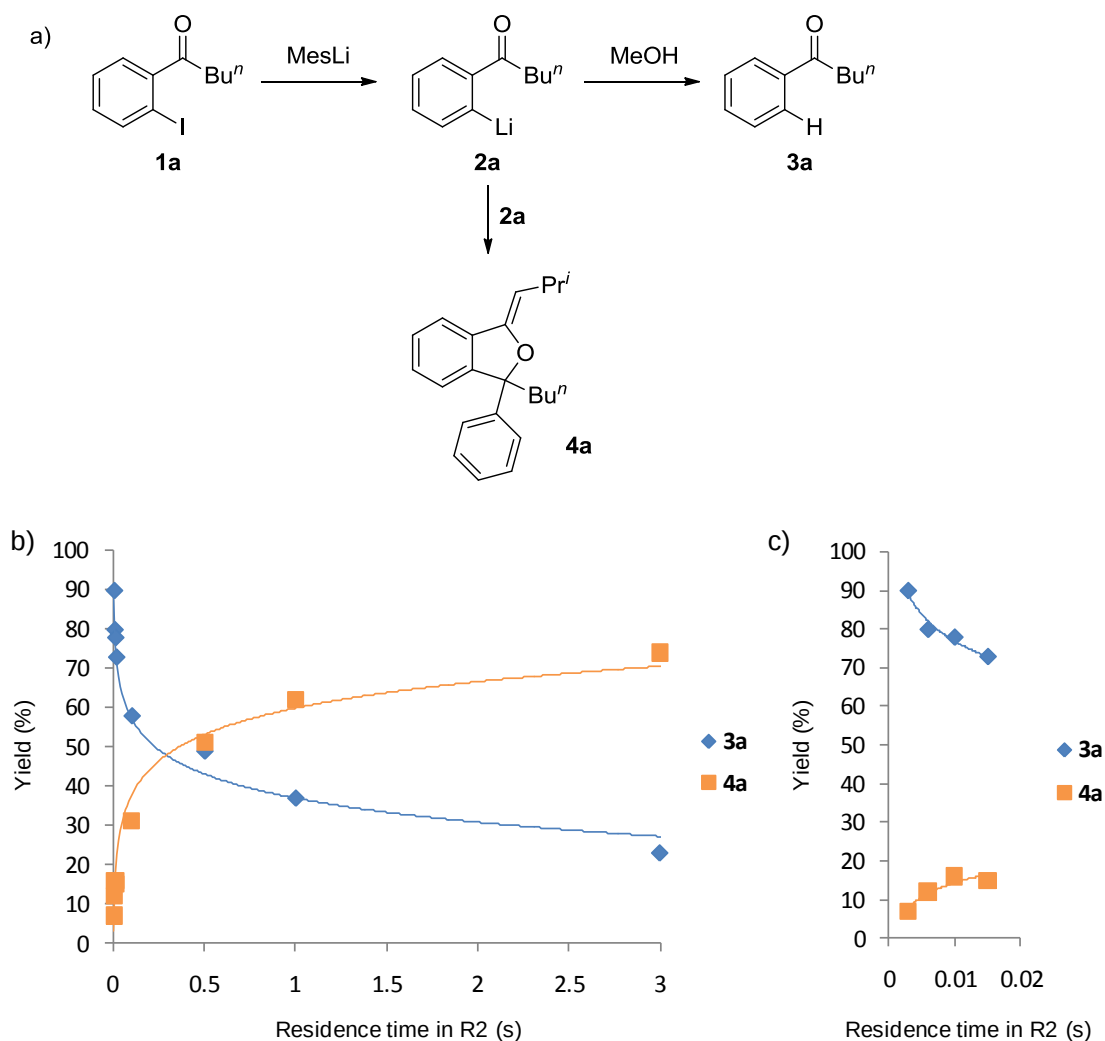


Figure 2. Effect of residence time on the yield in the I-Li exchange reaction of *o*-pentanoyliodobenzene (**1a**) followed by reaction with MeOH in the flow microreactor systems.

We focused on the generation of *o*-pentanoyl-substituted phenyllithium (**2a**) generated from *o*-pentanoyliodobenzene (**1a**). Methanol was used as a quenching electrophile (Fig. 2a). The reactions were carried out with variation in the residence

time in R2, and the yield of the protonated product **3a** was determined by gas chromatography (GC). The yield of **3a** increased with a decrease in the residence time (Figure 2b). However, acceptable yields were not obtained even at the minimum limit of the residence time of our current system (0.01 s), although this residence time was successful for the generation of alkoxycarbonyl-³, nitro-⁴ and cyano-substituted⁵ aryllithiums. Aryllithium **2a** bearing a ketone carbonyl group decomposed very rapidly, the major by-product being dimeric compound **4**.

To avoid the decomposition of **2a**, we developed a new integrated device in which two T-shaped micromixers and one microreactor are combined (Figure 3). Although the Reynolds number is $\sim 10^2$, extremely fast mixing takes place at the T-shaped mixers, presumably because of engulfment flow.⁸ Using this device, the residence time could be reduced to 0.003 s, giving rise to a dramatic increase in the yield of product **3a** (Figure 2c). The result clearly indicates that a ketone carbonyl group could survive a residence time of a few milliseconds.

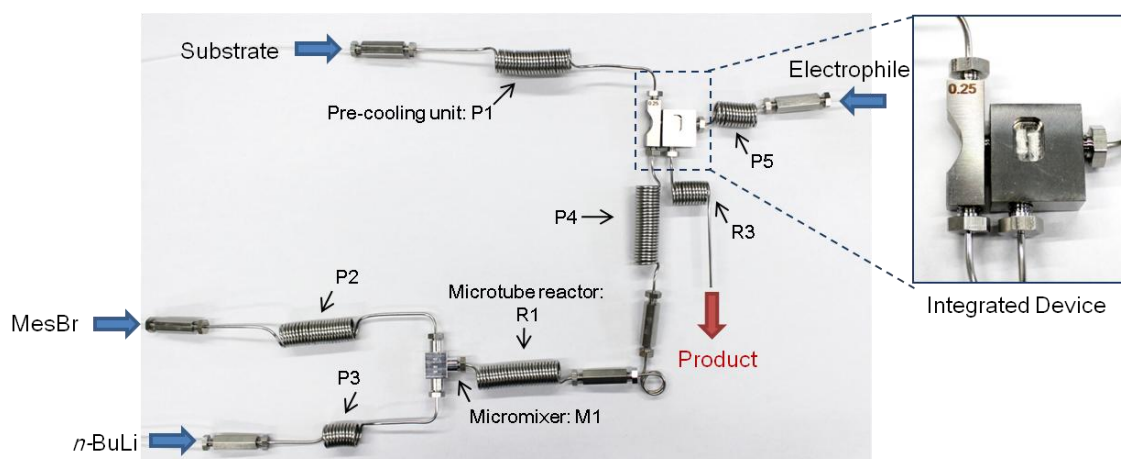


Figure 3. A picture of the system including the integrated device in which R2, M2 and M3 are combined.

Next, we conducted the I-Li exchange reaction of four iodoarenes bearing different ketone carbonyl groups (Figure 4). Aryllithium intermediates were generated from *o*-propanoyliodobenzene (**1b**), *o*-acetyliodobenzene (**1c**), *p*-pentanoyliodobenzene (**1d**) and *p*-acetyliodobenzene (**1e**). As shown in Figure 3, an increase in the residence time led to the decrease in the yield of the desired protonated product (**3**). In general, *o*-substituent gave the better result than *p*-substituent, presumably because of the coordination of the ketone carbonyl group to lithium. By reducing the residence time to 3 ms using an integrated device, the protonated products were obtained in good yields.

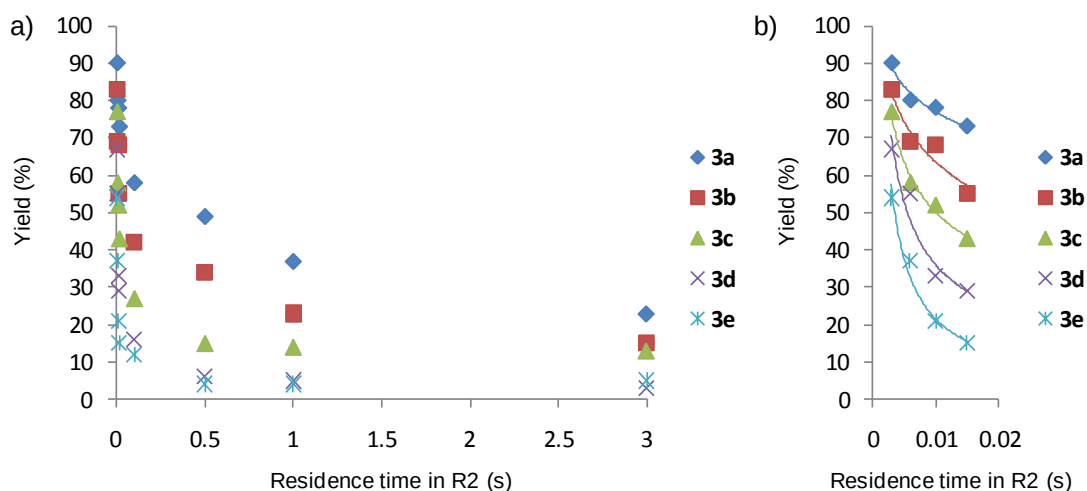
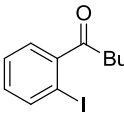
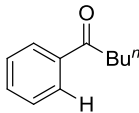
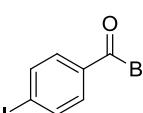
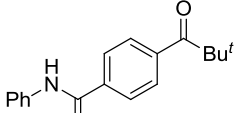
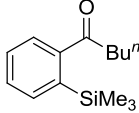
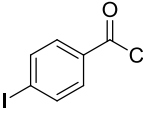
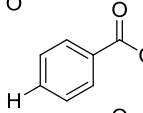
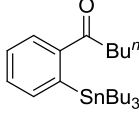
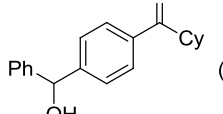
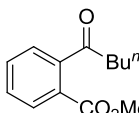
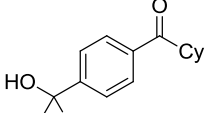
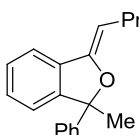
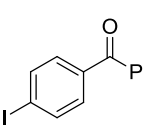
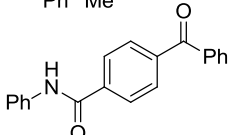
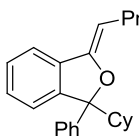
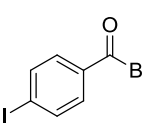
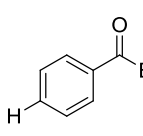
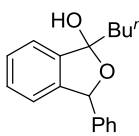
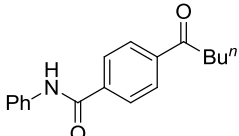
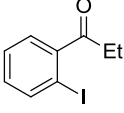
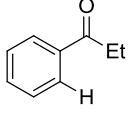
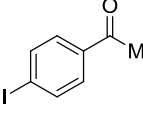
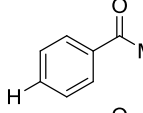
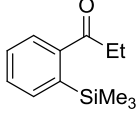
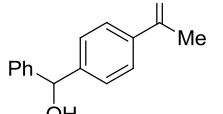
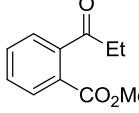
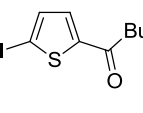
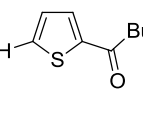
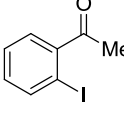
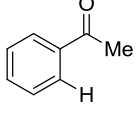
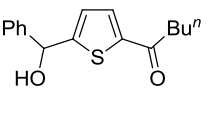
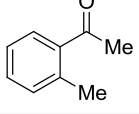
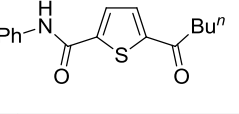


Figure 4. Effect of residence time on the yield in the I-Li exchange reaction of **1** followed by reaction with MeOH in the flow microreactor systems.

At a residence time of 0.003 s, generation of various *o*-acyl-substituted aryllithium species followed by reactions with various electrophiles including Me₃SiOTf, Bu₃SnCl and ClCO₂Me were successfully conducted, and the corresponding products bearing unchanged ketone carbonyl groups were obtained in good yields and in good productivity (0.25-0.54 mmol/min; Table 1). It is interesting that some ketones could be used as electrophiles, although they should be more reactive than the carbonyl group of the acylphenyllithium species.

The generation and reaction of *p*-acyl-substituted phenyllithiums led to slightly lower yields of the products compared with the corresponding *o*-acyl-substituted phenyllithiums, presumably because of the lack of coordination of the carbonyl group to lithium. In particular, in the case of *p*-acetylphenyllithium (**2e**) generated from *p*-acetyliodobenzene (**1e**), the protonated product **3e** was obtained only in moderate yield (54%). This problem could be solved by further reducing the residence time in R2, which was achieved by increasing the flow rate using high-pressure syringe pumps. As shown in Figure 5, the yield of **3e** increased with a decrease in the residence time, and an acceptable yield (76%) was obtained at a residence time of 0.0015 s. This residence time also allowed efficient reaction with PhCHO to produce the corresponding product in 78% yield. Heteroaromatic iodides such as 1-(5-iodothiophen-2-yl)pentan-1-one could also be lithiated and the resulting organolithium compounds were effectively trapped with electrophiles without affecting the ketone carbonyl group.

Table 1. The optimized I-Li exchange reaction of acyl-substituted iodobenzenes **1** followed by reaction with an electrophile.^a

Substrate	Electrophile	Product	Yield (%) ^a	Substrate	Electrophile	Product	Yield (%) ^a
	MeOH		90 (91) ^b		PhNCO		87
	Me ₃ SiOTf		86 (91) ^b		MeOH		78 ^b
	Bu ₃ SnCl		86		PhCHO		73 (75) ^b
	MeO ₂ CCl		68 (70) ^b		PhCOMe		76
	PhCOMe		81		PhNCO		71
	PhCOCy		81		MeOH		67 ^b
	PhCHO		60		PhNCO		51
	MeOH		83		MeOH		54 (76) ^c
	Me ₃ SiOTf		81 (84) ^b		PhCHO		78 ^c
	MeO ₂ CCl		65 (69) ^b		MeOH		74
	MeOH		77 ^b		PhCHO		77
	MeOTf		42 ^b		PhNCO		59

^a Isolated yield. ^b Determined by GC. ^c Residence time=0.00015 s

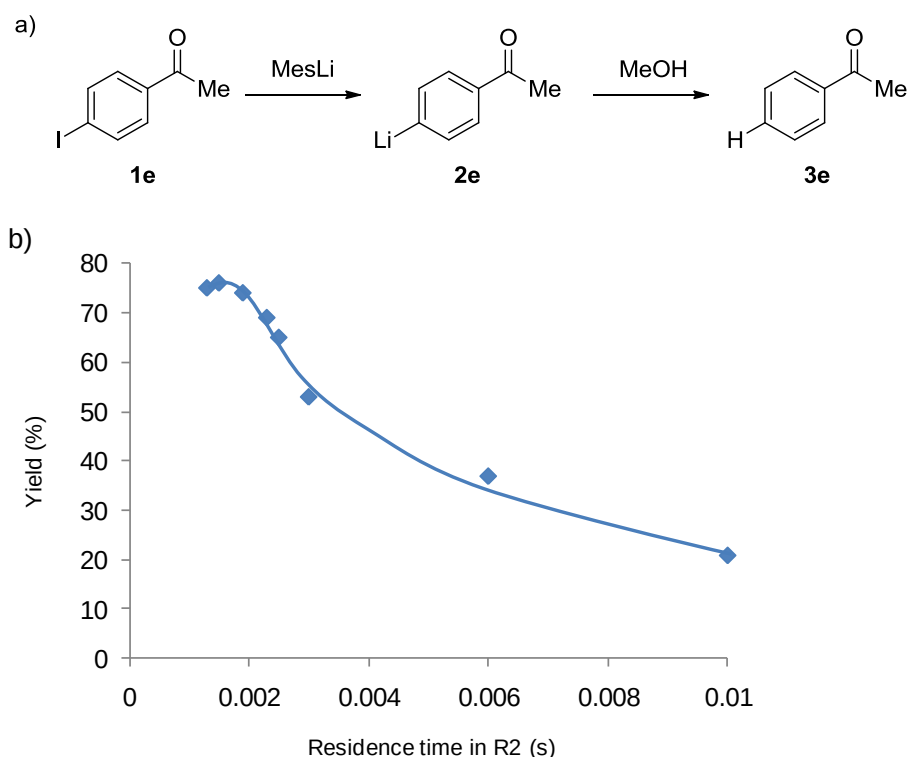


Figure 5. The effect of residence time in R2 for the reaction of *p*-acyliodobenzene **1e**.

a) Reaction of **1e** with MesLi followed by reaction with MeOH. b) Dependence of the yield **3e** on the residence time in R2 (< 0.01 s).

Using the present method, Pauciflorol F⁶, a natural product isolated from stem bark, which has recently been synthesized by Snyder's group⁷ and Sarpong's group⁸, was synthesized. The starting material **5** was prepared from commercially available 3,5-dimethoxyphenylmagnesium chloride in two steps (67% yield; Figure 6). The iodine-lithium exchange reaction of **5** followed by reaction with 3,5-dimethoxybenzaldehyde was conducted using a flow microreactor system consisting of the integrated device (residence time in R2: 0.003 s) to produce **6** (ref. 49) in 81% isolated yield. Presumably, dehydration took place upon acidic work-up. Treatment of **6** with HCl/*i*-PrOH in the presence of O₂ in a batch macro reactor gave **7** in 75% yield, which can be converted to Pauciflorol F by one-pot hydrogenation and epimerization (87%)⁸ followed by deprotection (86%).⁷

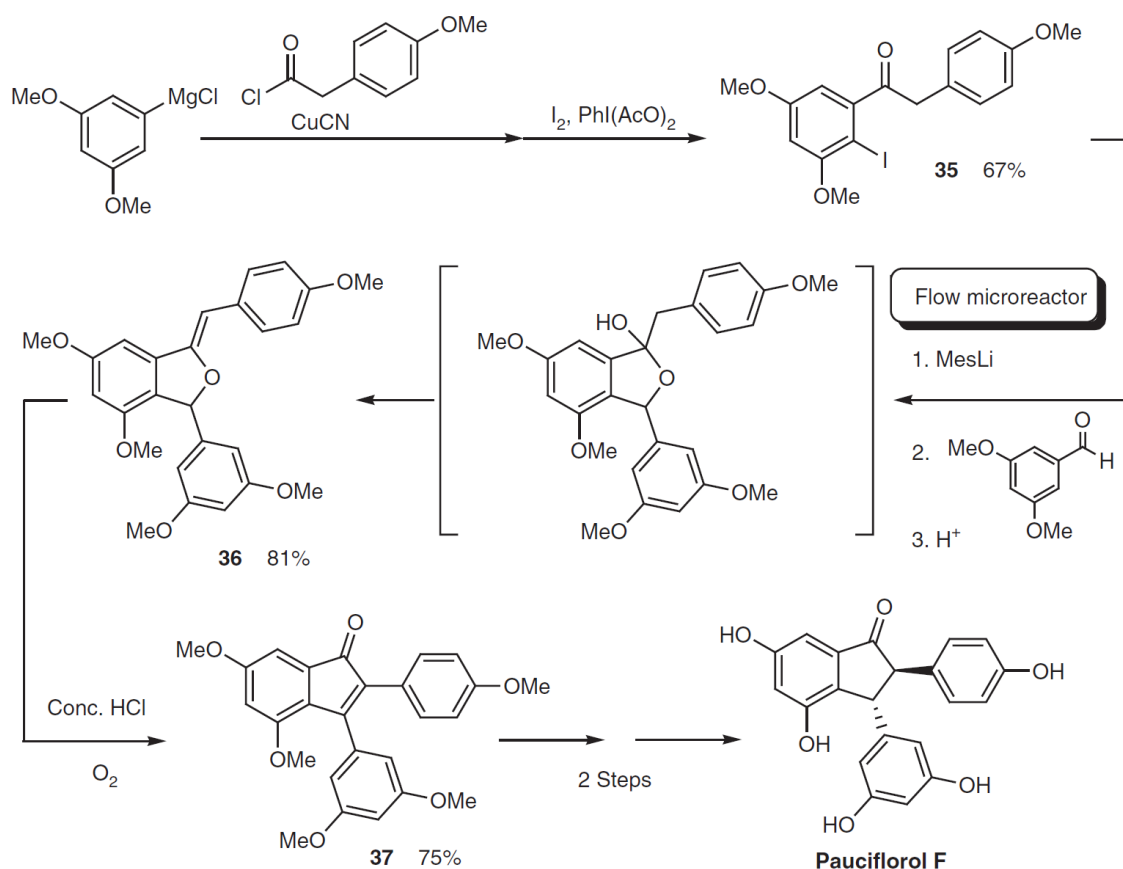


Figure 6. Formal total synthesis of Pauciflorol F.

The formal synthesis of Pauciflorol F achieved in this study (Figure 6) demonstrates the potential of the present flow microreactor approach. Although the synthesis by Snyder's group based on a biomimetic strategy and the synthesis by Sarpong's group based on a Larock annulations strategy are elegant and concise, our synthesis is comparable from the viewpoints of atom economy and step economy. Because the productivity of the present method is relatively high (1.06 g for 5 min operation), it is hoped that the flow microreactor method will provide a green and sustainable way of producing useful compounds such as Pauciflorol F in the pharmaceutical and fine chemicals industries in the future.

Conclusion

The present approach based on control of the residence time in a flow microreactor serves as a powerful method for protecting-group-free synthesis using organolithium reagents, which is complementary to other approaches using less reactive and more chemoselective reagents. Although the flow microreactor approach is still in its infancy, it is clearly capable, powerful and useful from both scientific and practical viewpoints.

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). ^1H and ^{13}C NMR spectra were recorded on Varian MERCURYplus-400 (^1H 400 MHz, ^{13}C 100 MHz) spectrometer with Me_4Si or CDCl_3 as a standard in CDCl_3 unless otherwise noted. EI and CI mass spectra were recorded on a JEOL JMS-SX102A spectrometer. ESI mass spectra were recorded on a JEOL JMS-T100CS spectrometer. THF and Et_2O were purchased from Kanto Chemical Co., Inc. as a dry solvent and used without further purification. Hexane was purchased from Wako, distilled before use, and stored over molecular sieves 4A. $n\text{-BuLi}$ was purchased from Kanto Chemical Co., Inc.. Commercial available starting materials were purchased from commercial sources and used without further purification.

Stainless steel (SUS304) T-shaped micromixer with inner diameter of 250 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 (Figure 7a). The micromixer and microtube reactors were connected with stainless steel fittings (GL Sciences, 1/16 OUW). Stainless steel (SUS316) integrated device (inner diameter of M2, M3 and R2: 250 μm , length of R2: 10 mm) was manufactured by YMC Co., Ltd. (Figure 7b and 7c). The flow microreactor system was dipped in a cooling bath to control the temperature. Solutions were introduced to the flow microreactor system using syringe pumps, Harvard Apparatus PHD 2200, equipped with gastight syringes purchased from SGE, (basically) or using syringe pumps, Harvard Apparatus PHD 4400 equipped with stainless steel syringes (#70-2255) purchased from Harvard Apparatus PHD for control the residence time to less of 3 ms.

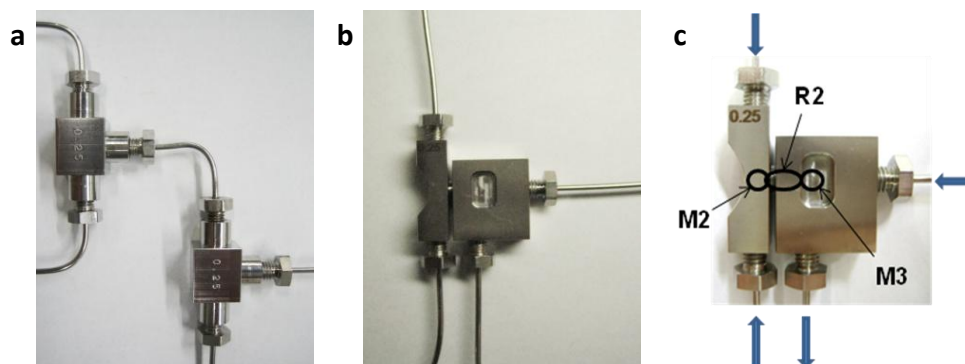


Figure 7. a) Conventional flow microreactor system, b) and c) Integrated device

1. Synthesis of Acyl-Substituted Iodobenzenes

1-(2-iodophenyl)-1-pentanone (1a).⁹ *n*-Butyllithium (2.64 M in THF, 69 mL, 182.2 mmol) was added dropwise to a solution of 2-aminobenzonitrile (10.452 g, 88.5 mmol) in THF (80 mL) at 0 °C for 23 min (3 mL min⁻¹). After stirred for 1 h at this temperature, the reaction was quenched by slow addition of 1 M HCl solution (300 mL). The organic layer was separated and the remaining aqueous layer was extracted with ethyl acetate (300 mL × 3). The combined organic layers were dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography (hexane/ethyl acetate = 20:1) to give 1-(2-aminophenyl)-1-pentanone (8.752 g, 56%) as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 7.75 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.25 (td, *J* = 7.6, 1.2 Hz, 1H), 6.70–6.58 (m, 2H), 6.26 (br s, 2H), 2.93 (t, *J* = 7.6 Hz, 2H), 1.70 (quint, *J* = 7.5 Hz, 2H), 1.41 (sext, *J* = 7.5 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). *p*-TsOH·H₂O (11.990 g, 63.0 mmol) was added to a solution of 1-(2-aminophenyl)-1-pentanone (3.480 g, 19.6 mmol) in CH₃CN (80 mL). The resulting suspension of amine salt was cooled to 0 °C and a solution of NaNO₂ (2.713 g, 39.3 mmol) and KI (8.190 g, 49.3 mmol) in H₂O (12 mL) was added very slowly (0.1 mL/min to 0.5 mL/min) for 80 min, causing a vigorous emission of nitrogen. Then, the cooling bath was removed and allowed to stir for 1 h (30 min at ambient temperature and 30 min at 40 °C). The reaction was quenched by addition of H₂O (100 mL), sat. NaHCO₃ solution (25 mL) and sat. Na₂S₂O₃ solution (25 mL). The organic layer was separated and the remaining aqueous layer was extracted with Et₂O (100 mL × 3). The combined organic layers were dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography (hexane/ethyl acetate = 20:1) to give the title product (5.055 g, 89%) as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 7.76 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.42–7.32 (m, 2H), 7.11 (td, *J* = 7.5, 1.8 Hz, 1H), 2.89 (t, *J* = 7.4 Hz, 2H), 1.71 (quint, *J* = 7.6 Hz, 2H), 1.41 (sext, *J* = 7.4 Hz,

2H), 0.94 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (400 MHz, CDCl_3): δ 204.8, 144.6, 140.2, 131.2, 127.8, 127.4, 90.7, 41.6, 25.9, 22.1, 13.7; HRMS (APCI) calcd. for $\text{C}_{11}\text{H}_{14}\text{IO}^+$ $[\text{M}+\text{H}]^+$: 289.0084; found: 289.0089.

1-(2-Iodophenyl)-1-propanone (1b). Ethylmagnesium chloride (2.0 M in THF, 159 mL, 318.0 mmol) was added dropwise to a solution of 2-aminobenzonitrile (12.530 g, 106.1 mmol) in THF (40 mL) at 0 °C for 30 min. After stirred for 30 min at this temperature, the cooling bath was removed and allowed to stir at ambient temperature for 11.5 h. The reaction was quenched at 0 °C by slow addition of 1 M HCl solution. Then, a solution was made basic (pH 8) by the addition of sat. NaHCO_3 solution. The organic layer was separated and the remaining aqueous layer was extracted with Et_2O (300 mL $\times$ 3). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (hexane/ethyl acetate = 10:1) to give 1-(2-aminophenyl)-1-propanone (9.481 g, 60%) as a yellow solid: ^1H NMR (400 MHz, CDCl_3) δ 7.75 (dd, $J = 8.2, 1.4$ Hz, 1H), 7.29–7.22 (m, 1H), 6.68–6.61 (m, 2H), 6.26 (br s, 1H), 2.98 (q, $J = 7.2$ Hz, 2H), 1.21 (t, $J = 7.2$ Hz, 3H). The transformation from 1-(2-aminophenyl)-1-propanone to title product was carried out as described above. The crude product was purified by column chromatography (hexane/ethyl acetate = 15:1) to give the title product (20 mmol scale, 77%) as a yellow oil: ^1H NMR (400 MHz, CDCl_3) δ 7.91 (d, $J = 8.0$ Hz, 1H), 7.44–7.32 (m, 2H), 7.12 (td, $J = 7.6, 1.6$ Hz, 1H), 2.91 (q, $J = 7.3$ Hz, 2H), 1.23 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (400 MHz, CDCl_3): δ 205.2, 144.6, 140.1, 131.2, 127.8, 127.3, 90.6, 35.1, 7.9; HRMS (APCI) calcd. for $\text{C}_9\text{H}_{10}\text{IO}^+$ $[\text{M}+\text{H}]^+$: 260.9771; found: 260.9776.

1-(4-Iodophenyl)-2,2-dimethyl-1-propanone. *n*-Butyllithium (1.57 M in THF, 48 mL, 75.4 mmol) was added dropwise to a solution of *p*-diiodobenzene (25.074 g, 76.0 mmol) in THF (250 mL) at -78 °C for 16 min (3 mL min^{-1}). After stirred for 10 min at this temperature, trimethylacetaldehyde (6.822 g, 79.2 mmol) was added dropwise for 2 min. After stirred for 20 min, MeOH (6 mL) was added. Then, the cooling bath was removed and allowed to ambient temperature. The solution was quenched by addition of sat. NH_4Cl solution (100 mL). The organic layer was separated and the remaining aqueous layer was extracted with ethyl acetate (150 mL $\times$ 3). The combined organic layers were dried over Na_2SO_4 and concentrated to afford 1-(4-iodophenyl)-2,2-dimethylpropan-1-ol (22.017 g, quant) as a yellow solid which was carried forward without additional purification: ^1H NMR (400 MHz, CDCl_3) δ 7.64 (dd, $J = 6.8, 2.0$ Hz, 2H), 7.06 (dd, $J = 6.6, 1.4$ Hz, 2H), 4.34 (d, $J = 2.8$ Hz, 1H), 1.83 (d, $J = 2.8$ Hz, 1H),

0.90 (s, 9H). A solution of DMSO (14.2 mL, 200 mmol) in CH_2Cl_2 was added to a solution of oxalyl chloride in CH_2Cl_2 (0.67 M, 150 mL, 100 mmol) at $-55\text{ }^\circ\text{C}$ for 10 min. After stirred for 5 min, a solution of 4-iodophenyl-*t*-butylmethanol (22.017 g) in CH_2Cl_2 (30 mL) was added dropwise for 10 min. After stirred 20 min at this temperature, the mixture was quenched by triethylamine (40 mL). Then, the cooling bath was removed and allowed to ambient temperature. After addition of H_2O (200 mL), the organic layer was separated and the remaining aqueous layer was extracted with ethyl acetate (200 mL $\times$ 3). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by distillation and flash column chromatography (hexane/ethyl acetate = 50:1) to give the title product (15.80 g, 72% in two steps) as a white solid: ^1H NMR (400 MHz, CDCl_3) δ 7.76 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 1.33 (s, 9H); ^{13}C NMR (400 MHz, CDCl_3) δ 208.1, 137.6, 137.2, 129.5, 97.9, 44.1, 27.9; HRMS (EI) m/z calcd. for $\text{C}_{11}\text{H}_{13}\text{IO}$: 288.0011; found: 288.0007.

Cyclohexyl(4-iodophenyl)methanone. *n*-Butyllithium (1.57 M in THF, 20 mL, 31.4 mmol) was added dropwise to a solution of *p*-diiodobenzene (9.901 g, 30.0 mmol) in THF (100 mL) at $-78\text{ }^\circ\text{C}$ for 10 min (2 mL/min). After stirred for 10 min at this temperature, a solution of CuCN (2.970 g, 33.2 mmol) and LiCl (2.801 g, 66.1 mmol) in THF (35 mL) was added dropwise for 10 min. After stirred for 10 min, cyclohexanecarbonyl chloride (5.823 g, 39.7 mmol) was added. The reaction mixture was slowly warmed to reach ambient temperature, and then was quenched by sat. NH_4Cl solution (50 mL). The organic layer was separated and the remaining aqueous layer was extracted with Et_2O (200 mL $\times$ 3). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (hexane/ethyl acetate = 20:1) to give the title product (6.581 g, 70%) as a white solid: ^1H NMR (400 MHz, CDCl_3) δ 7.82 (dt, J = 8.6 Hz, 2.0 Hz, 2H), 7.65 (dt, J = 8.4 Hz, 2.0 Hz, 2H), 3.18 (tt, J = 11.2, 3.0 Hz, 1H), 1.92–1.80 (m, 4H), 1.78–1.69 (m, 1H), 1.55–1.18 (m, 5H); ^{13}C NMR (400 MHz, CDCl_3) δ 203.1, 137.9, 135.5, 129.7, 100.5, 45.5, 29.3, 25.9, 25.8; HRMS (EI) m/z calcd. for $\text{C}_{13}\text{H}_{15}\text{IO}$: 314.0168; found: 314.0169.

4-Iodobenzophenone. The synthesis from commercially available 4-aminobenzophenone was carried out as described above. The crude product was purified by column chromatography (hexane/ethyl acetate = 30:1) to give the title product (127 mmol scale) as a white solid: ^1H NMR (400 MHz, CDCl_3) δ 7.85 (dt, J = 8.4 Hz, 2.0 Hz, 2H), 7.79–7.75 (m, 2H), 7.60 (tt, J = 7.4, 2.9 Hz, 1H), 7.55–7.46 (m,

4H); ^{13}C NMR (400 MHz, CDCl_3) δ 195.8, 137.5, 137.0, 136.8, 132.6, 131.4, 129.9, 128.4, 100.1; HRMS (EI) m/z calcd. for $\text{C}_{13}\text{H}_9\text{IO}$: 307.9698; found: 307.9697.

1-(4-Iodophenyl)-1-pentanone (1d). The synthesis from *p*-diiodobenzene and pentanoyl chloride was carried out as described above. The crude product was purified by column chromatography (hexane/ethyl acetate = 20:1) to give the title product (76 mmol scale, 77%) as a white solid: ^1H NMR (400 MHz, CDCl_3) δ 7.82 (dt, J = 8.8 Hz, 2.0 Hz, 2H), 7.67 (dt, J = 8.4 Hz, 2.2 Hz, 2H), 2.92 (t, J = 7.4 Hz, 2H), 1.71 (quint, J = 7.6 Hz, 2H), 1.40 (sext, J = 7.4 Hz, 2H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, CDCl_3) δ 199.7, 137.8, 136.3, 129.5, 100.7, 38.2, 26.3, 22.4, 13.9; HRMS (EI) m/z calcd. for $\text{C}_{11}\text{H}_{13}\text{IO}$: 288.0011; found: 288.0016.

1-(4-Iodophenyl)-1-propanone. The synthesis *p*-diiodobenzene and propanoyl chloride was carried out as described above. The crude product was purified by column chromatography (hexane/ethyl acetate = 20:1) to give the title product (76 mmol scale, 56%) as a white solid: ^1H NMR (400 MHz, CDCl_3) δ 7.81 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 2.96 (q, J = 7.3 Hz, 2H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, CDCl_3): δ 200.0, 137.8, 136.1, 129.4, 100.7, 31.7, 8.1; HRMS (EI) m/z calcd. for $\text{C}_9\text{H}_9\text{IO}$: 259.9698; found: 259.9698.

1-(5-Iodothiophen-2-yl)pentan-1-one. The synthesis from 2,5-diiodothiophene and pentanoyl chloride was carried out as described above. The crude product was purified by column chromatography (hexane/ethyl acetate = 20:1) to give the title product (30 mmol scale, 53%) as a slightly yellow solid: ^1H NMR (400 MHz, CDCl_3) δ 7.32 (d, J = 4.0 Hz, 1H), 7.29 (d, J = 4.0 Hz, 1H), 2.82 (t, J = 7.6 Hz, 2H), 1.71 (quint, J = 7.5 Hz, 2H), 1.39 (sext, J = 7.4 Hz, 2H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR (400 MHz, CDCl_3): δ 192.0, 150.2, 138.0, 132.4, 84.8, 38.7, 26.7, 22.4, 13.8; HRMS (APCI) calcd. for $\text{C}_9\text{H}_{12}\text{IOS}^+ [\text{M}+\text{H}]^+$: 294.9648; found: 294.9640.

2. Generation and Reactions of Acyl-Substituted Aryllithium Species with MeOH (General Procedure). A flow microreactor system consisting of three T-shaped micromixers (M1, M2 and M3), three microtube reactors (R1, R2 and R3) was used. A solution of 2-bromomesitylene (0.18 M in THF, 5.0 mL min⁻¹) and a solution of *n*-BuLi (0.43 M in hexane, 1.8 mL min⁻¹) were introduced to M2 ($\phi = 250\ \mu\text{m}$) by syringe pumps. The resulting solution was passed through R1 ($\phi = 1000\ \mu\text{m}$, $L = 210\ \text{cm}$ (100 cm at 0 °C, 10 cm at ambient temperature and 100 cm at -70 °C)) and was mixed with a solution of acyliodobenzene (0.20 M in THF, 3 mL min⁻¹) in M2 ($\phi = 250\ \mu\text{m}$). The resulting solution was passed through R2 (various size) and was mixed with a solution of MeOH (0.60 M in THF, 2.0 mL min⁻¹) in M3 ($\phi = 250\ \mu\text{m}$). The resulting solution was passed through R3 ($\phi = 1000\ \mu\text{m}$, $L = 50\ \text{cm}$). After a steady state was reached, the product solution was collected for 30 s while being quenched with sat. NH₄Cl solution. The reaction mixture was analyzed by GC. The results are summarized in Table 2 and Table 3.

Table 2. The I-Li exchange reaction of acyliodobenzene **1** and reaction with MeOH.^a

Substrate	ϕ of R2 (μm)	L of R2 (μm)	t^{R} in R2 (s)	GC yield of 3 (%)
<i>o</i> -COBu 1a	250	1.0 ^b	0.003	90
	250	2.0 ^b	0.006	80
	250	3.3	0.010	78
	250	5.0	0.015	73
	500	8.3	0.100	58
	1000	10.4	0.500	49
	1000	20.8	1.000	37
	1000	62.4	3.000	23
<i>o</i> -COEt 1b	250	1.0 ^b	0.003	83
	250	2.0 ^b	0.006	69
	250	3.3	0.010	68
	250	5.0	0.015	55
	500	8.3	0.100	42
	1000	10.4	0.500	34
	1000	20.8	1.000	23
	1000	62.4	3.000	15
<i>o</i> -COMe 1c	250	1.0 ^b	0.003	77
	250	2.0 ^b	0.006	58
	250	3.3	0.010	52
	250	5.0	0.015	43
	500	8.3	0.100	27
	1000	10.4	0.500	15
	1000	20.8	1.000	14
	1000	62.4	3.000	13
<i>p</i> -COBu 1d	250	1.0 ^b	0.003	67
	250	2.0 ^b	0.006	55
	250	3.3	0.010	33
	250	5.0	0.015	29
	500	8.3	0.100	16
	1000	10.4	0.500	6
	1000	20.8	1.000	5
	1000	62.4	3.000	3
<i>p</i> -COMe 1e	250	1.0 ^b	0.003	54
	250	2.0 ^b	0.006	37
	250	3.3	0.010	21
	250	5.0	0.015	15
	500	8.3	0.100	12
	1000	10.4	0.500	4
	1000	20.8	1.000	4
	1000	62.4	3.000	5

^a In all cases, conversion > 90%. ^b The integrated microreactor was used to control residence time very shortly.

Table 3. The I-Li exchange reaction of **1a** and reaction with MeOH.^a

ϕ of R2 (μm)	L of R2 (μm)	t^R in R2 (s)	GC yield of product 3a (%)	GC yield of byproduct 4 (%)
250	1.0 ^a	0.003	90	7
250	2.0 ^a	0.006	80	12
250	3.3	0.010	78	16
250	5.0	0.015	73	15
500	8.3	0.100	58	31
1000	10.4	0.500	49	51
1000	20.8	1.000	37	62
1000	62.4	3.000	23	74

^a The integrated microreactor was used to control residence time very shortly.

Valerophenone (3a). Colorless oil; 90% yield; the spectral data were identical to those of commercially available compound.

1-Butyl-3-butyldiene-1-phenyl-1,3-dihydroisobenzofuran (4). To characterize byproduct **4** the reaction was carried out using longer **R2** (ϕ = 1000 μm , L = 62.4 cm), which led to the formation of **4** as a major product. The product solution was collected for 180 s while being quenched with 1 M HCl solution (50 mL). The organic layer was separated and the remaining aqueous layer was extracted with Et₂O (50 mL $\times$ 3). The combined organic layers were dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography (hexane) to give the title product (98.2 mg, 71%) as a colorless oil; Slightly unstable in air; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.57–7.50 (m, 2H), 7.50–7.45 (m, 2H), 7.36–7.18 (m, 5H), 5.06 (t, J = 7.4 Hz, 1H), 2.37–2.13 (m, 4H), 1.49 (sext, J = 7.0 Hz, 2H), 1.30–0.99 (m, 4H), 0.96 (t, J = 7.2 Hz, 3H), 0.76 (t, J = 7.0 Hz, 3H); ¹³C NMR (400 MHz, DMSO-*d*₆): δ 153.5, 145.2, 144.4, 132.6, 128.3, 128.2, 127.9, 126.9, 124.3, 121.8, 119.4, 94.8, 91.2, 39.8, 26.8, 25.5, 22.6, 22.1, 13.7, 13.7; HRMS (ESI) calcd. for C₂₂H₂₇O⁺ [M+H]⁺: 307.2056; found: 307.2057.

3. Reactions with various electrophiles. A flow microreactor system consisting of three T-shaped micromixers (M1, M2 and M3), three microtube reactors (R1, R2 and R3) was used. A solution of 2-bromomesitylene (0.18 M in THF, 5.0 mL min⁻¹) and a solution of *n*-BuLi (0.43 M in hexane, 1.8 mL min⁻¹) were introduced to M2 (ϕ = 250 μm) by syringe pumps. The resulting solution was passed through R1 (ϕ = 1000 μm ,

$L = 210$ cm (100 cm at 0 °C, 10 cm at ambient temperature and 100 cm at -70 °C)) and was mixed with a solution of acyliodobenzene (0.20 M in THF, 3.0 mL min⁻¹) in M2 ($\phi = 250$ μ m). The resulting solution was passed through R2 (various size) and was mixed with a solution of electrophile (0.60 M in THF or Et₂O for methyl triflate or trimethylsilyl triflate, 2 mL min⁻¹) in M3 ($\phi = 250$ μ m). The resulting solution was passed through R3 ($\phi = 1000$ μ m, $L = 50$ cm). After a steady state was reached, the product solution was collected for 30 s while being quenched with 15 mL of sat. NH₄Cl solution (or 1 M HCl solution to form dehydrated compound). After Et₂O (20 mL) was added, the organic layer was separated and the remaining aqueous layer was extracted with Et₂O (25 mL $\times 3$). The combined organic layers were dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography. *Only in case of 1-butyl-3-phenyl-1,3-dihydroisobenzofuran-1-ol, the crude product was purified by recrystallization, because the compound was seemed to be unstable in acidic condition.*

Methyl 2-pentanoylbenzoate. Colorless oil; 68% yield; ¹H NMR (400 MHz, CDCl₃) δ 7.89 (ddd, $J = 7.6, 1.4, 0.4$ Hz, 1H), 7.56 (td, $J = 7.5, 1.3$ Hz, 1H), 7.49 (td, $J = 7.7, 1.5$ Hz, 1H), 7.35 (ddd, $J = 7.7, 1.3, 0.7$ Hz, 1H), 3.89 (s, 3H), 2.80 (t, $J = 7.6$ Hz, 2H), 1.71 (quint, 7.5 Hz, 2H), 1.40 (sext, $J = 7.4$ Hz, 2H), 0.94 (t, $J = 7.2$ Hz, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 205.5, 167.0, 143.0, 131.9, 129.6, 129.4, 128.3, 126.1, 52.2, 42.2, 25.9, 22.0, 13.7; HRMS (EI) m/z calcd. for C₁₃H₁₆O₃: 220.1099; found: 220.1133.

1-(2-(Trimethylsilyl)phenyl)pentan-1-one. White solid; 86% yield; ¹H NMR (400 MHz, CDCl₃) δ 7.87 (d, $J = 7.6$ Hz, 1H), 7.74 (d, $J = 7.6$ Hz, 1H), 7.54–7.41 (m, 2H), 2.97 (t, $J = 7.4$ Hz, 2H), 1.72 (quint, 7.6 Hz, 2H), 1.42 (sext, $J = 7.5$ Hz, 2H), 0.96 (t, $J = 7.4$ Hz, 3H), 0.29 (s, 1H); ¹³C NMR (400 MHz, CDCl₃) δ 203.1, 142.9, 141.9, 136.0, 131.2, 128.7, 128.7, 39.1, 26.7, 22.5, 13.9, 0.38; HRMS (ESI) calcd. for C₁₄H₂₂OSiNa⁺ [M+Na]⁺: 257.1332; found: 257.1332.

1-(2-(Tributylstannyl)phenyl)pentan-1-one. Colorless oil; 86% yield; ¹H NMR (400 MHz, CDCl₃) δ 7.99 (d, $J = 6.8$ Hz, 1H), 7.77–7.63 (m, 1H), 7.54–7.46 (m, 1H), 7.44–7.37 (m, 1H), 3.00 (t, $J = 7.4$ Hz, 2H), 1.71 (quint, 7.5 Hz, 2H), 1.54–1.34 (m, 8H), 1.29 (sext, $J = 7.3$ Hz, 6H), 1.11–0.89 (m, 9H), 0.85 (t, $J = 7.4$ Hz, 9H); ¹³C NMR (400 MHz, CDCl₃) δ 202.1, 146.0, 141.6, 137.5, 131.8, 129.4, 127.9, 38.1, 29.3, 27.5, 27.1, 22.5, 13.9, 13.7, 11.0; HRMS (APCI) calcd. for C₂₃H₃₉OSn⁻ [M-H]⁻: 451.2028; found: 451.2009.

3-Butylidene-1-methyl-1-phenyl-1,3-dihydroisobenzofuran. Colorless oil; Slightly unstable in air; 81% yield; ^1H NMR (400 MHz, DMSO-d_6) δ 7.57–7.40 (m, 4H), 7.37–7.22 (m, 5H), 5.09 (t, $J = 7.4$ Hz, 1H), 2.34–2.17 (m, 2H), 1.48 (sext, $J = 7.4$ Hz, 2H), 0.96 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 153.0, 146.4, 144.8, 132.1, 128.4, 128.3, 128.0, 127.2, 124.3, 121.7, 119.5, 95.1, 88.8, 27.5, 26.8, 22.6, 13.7; HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{21}\text{O}^+$ $[\text{M}+\text{H}]^+$: 265.1587; found: 265.1588.

3-Butylidene-1-cyclohexyl-1-phenyl-1,3-dihydroisobenzofuran. Colorless oil; Slightly unstable in air; 81% yield; ^1H NMR (400 MHz, DMSO-d_6) δ 7.61–7.53 (m, 3H), 7.49–7.43 (m, 1H), 7.37–7.17 (m, 5H), 5.03 (t, $J = 7.6$ Hz, 1H), 2.44–2.26 (m, 3H), 1.69–1.45 (m, 5H), 1.43–1.31 (m, 1H), 1.22–0.90 (m, 5H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 153.8, 144.5, 143.8, 132.8, 128.3, 128.2, 127.8, 126.7, 124.3, 121.9, 119.3, 94.4, 93.5, 45.7, 26.8 and 26.8, 26.1, 25.8 and 26.8, 25.5, 22.6, 13.8; HRMS (APCI) calcd. for $\text{C}_{24}\text{H}_{29}\text{O}^+$ $[\text{M}+\text{H}]^+$: 333.2213; found: 333.2216.

1-Butyl-3-phenyl-1,3-dihydroisobenzofuran-1-ol. White solid; 60% yield; ^1H NMR (400 MHz, DMSO-d_6) δ 7.51 (d, $J = 7.2$ Hz, 2H), 7.38–7.24 (m, 6H), 6.98 (d, $J = 7.2$ Hz, 1H), 6.63 (s, 1H), 5.99 (s, 1H), 2.05–1.89 (m, 2H), 1.42–1.18 (m, 3H), 1.12–0.95 (m, 1H), 0.82 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 142.7, 142.6, 141.2, 128.5, 128.0, 127.6, 127.4, 126.8, 122.2, 121.7, 109.0, 83.1, 40.5, 25.8, 22.2, 13.9; HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{19}\text{O}_2^-$ $[\text{M}-\text{H}]^-$: 267.1391; found: 267.1382.

Propiophenone. 83% GC yield (GC t_R 13.9 min).

1-(2-(Trimethylsilyl)phenyl)propa-1-one. Colorless oil; 81% yield; ^1H NMR (400 MHz, CDCl_3) δ 7.85 (dd, $J = 7.6, 0.8$ Hz, 1H), 7.73 (ddd, $J = 7.2, 1.4, 0.5$ Hz, 1H), 7.50 (td, $J = 7.3, 1.5$ Hz, 1H), 7.44 (td, $J = 7.6, 1.6$ Hz, 1H), 3.00 (q, $J = 7.3$ Hz, 2H), 1.23 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (400 MHz, CDCl_3) δ 203.6, 142.9, 141.7, 135.9, 131.2, 128.7, 128.5, 32.6, 8.5, 0.32; HRMS (APCI) calcd. for $\text{C}_{12}\text{H}_{17}\text{OSi}^-$ $[\text{M}-\text{H}]^-$: 205.1054; found: 205.1043.

Methyl 2-propionylbenzoate. Colorless oil; 65% yield; ^1H NMR (400 MHz, CDCl_3) δ 7.90 (dd, $J = 8.2, 1.4$ Hz, 1H), 7.57 (td, $J = 7.5, 1.3$ Hz, 1H), 7.49 (td, $J = 7.6, 1.2$ Hz, 1H), 7.34 (dd, $J = 7.4, 1.4$ Hz, 1H), 3.89 (s, 3H), 2.81 (q, $J = 7.2$ Hz, 2H), 1.23 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (400 MHz, CDCl_3) δ 206.5, 167.1, 143.4, 122.2, 129.9, 129.6, 128.2, 126.1, 52.5, 36.1, 8.1; HRMS (ESI) calcd. for $\text{C}_{11}\text{H}_{12}\text{O}_3\text{Na}^+$ $[\text{M}+\text{Na}]^+$: 215.0679;

found: 215.0679.

Acetophenone. 77% GC yield (GC t_R 11.9 min).

2'-Methylacetophenone. 42% GC yield (GC t_R 13.4 min).

N-Phenyl-4-pivaloylbenzamide. White solid; 84% yield; ^1H NMR (400 MHz, CDCl_3) δ 7.90 (dt, J = 8.8, 2.0 Hz, 2H), 7.83 (br s, 1H), 7.74 (dt, J = 8.8, 2.0 Hz, 2H), 7.65 (d, J = 7.6 Hz, 2H), 7.39 (tt, J = 8.0, 2.0 Hz, 2H), 7.18 (tt, J = 7.4, 1.2 Hz, 1H), 1.36 (s, 9H); ^{13}C NMR (400 MHz, CDCl_3) δ 209.4, 165.2, 141.5, 137.8, 136.6, 129.0, 127.7, 126.9, 124.7, 120.4, 44.3, 27.7; HRMS (APCI) calcd for $\text{C}_{18}\text{H}_{20}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$: 282.1489; found: 282.1492.

Cyclohexyl phenyl ketone. 78% GC yield (GC t_R 20.6 min).

Cyclohexyl(4-(hydroxy(phenyl)methyl)phenyl)methanone. White solid; 73% yield; ^1H NMR (400 MHz, CDCl_3) δ 7.91 (dt, J = 8.4, 2.0 Hz, 2H), 7.51–7.46 (m, 2H), 7.39–7.25 (m, 5H), 5.88 (s, 1H), 3.23 (tt, J = 11.2, 3.2 Hz, 1H), 1.93–1.78 (m, 4H), 1.78–1.19 (m, 7H); ^{13}C NMR (400 MHz, CDCl_3) δ 203.7, 148.7, 143.3, 135.1, 128.5, 128.4, 127.7, 126.5, 126.4, 75.6, 45.5, 29.3, 25.8, 25.7; HRMS (APCI) calcd. for $\text{C}_{20}\text{H}_{23}\text{O}_2^+$ $[\text{M}+\text{H}]^+$: 295.1693 found: 295.1693.

Cyclohexyl(4-(1-hydroxy-1-phenylethyl)phenyl)methanone. White solid; 76% yield; ^1H NMR (400 MHz, CDCl_3) δ 7.87 (dt, J = 8.8, 2.0 Hz, 2H), 7.50 (dt, J = 8.8, 2.0 Hz, 2H), 7.44–7.38 (m, 2H), 7.35–7.28 (m, 2H), 7.25 (tt, J = 7.2, 1.7 Hz, 1H), 3.22 (tt, J = 11.2, 3.2 Hz, 1H), 2.51 (br s, 1H), 1.96 (s, 3H), 1.91–1.77 (m, 4H), 1.77–1.65 (m, 1H), 1.53–1.19 (m, 5H); ^{13}C NMR (400 MHz, CDCl_3) δ 203.6, 152.8, 147.2, 134.7, 128.3, 128.2, 127.2, 125.9, 125.8, 76.0, 45.6, 30.5, 29.3, 25.9, 25.8; HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{24}\text{O}_2\text{Na}^+$ $[\text{M}+\text{Na}]^+$: 331.1669; found: 331.1670.

4-Benzoyl-N-phenylbenzamide. White solid; 70% yield; ^1H NMR (400 MHz, CDCl_3) δ 7.98 (d, J = 8.0 Hz, 2H), 7.93 (br s, 1H), 7.89 (d, J = 8.0 Hz, 2H), 7.84–7.79 (m, 2H), 7.67 (d, J = 7.6 Hz, 2H), 7.62 (dt, J = 7.2, 1.6 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.40 (t, J = 7.8 Hz), 7.19 (tt, J = 7.4, 1.6 Hz, 1H); ^{13}C NMR (400 MHz, CDCl_3) δ 196.1, 165.1, 140.1, 138.2, 137.7, 136.8, 133.0, 130.1, 130.0, 129.0, 128.4, 127.1, 124.8, 120.4; HRMS (APCI) calcd. for $\text{C}_{20}\text{H}_{16}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$: 302.1176; found: 302.1172.

Valerophenone. 67% GC yield (GC t_R 17.1 min); the spectral data were identical to those of commercially available compound.

4-Pentanoyl-*N*-phenylbenzamide. White solid; 51% yield; ^1H NMR (400 MHz, CDCl_3) δ 8.07 (dt, $J = 8.4, 1.6$ Hz, 2H), 7.96 (dt, $J = 8.4, 1.6$ Hz, 2H), 7.81 (br s, 1H), 7.65 (d, $J = 8.0$ Hz, 2H), 7.40 (t, $J = 7.8$ Hz, 2H), 7.19 (tt, $J = 7.4, 1.2$ Hz, 1H), 3.01 (t, $J = 7.4$ Hz, 2H), 1.75 (quint, $J = 7.5$ Hz, 2H), 1.43 (sext, $J = 7.4$ Hz, 2H), 0.97 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (400 MHz, CDCl_3) δ 199.9, 164.8, 139.5, 138.6, 137.6, 129.2, 128.5, 127.3, 124.9, 120.3, 38.7, 26.3, 22.4, 13.9; HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{20}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$: 282.1489; found: 282.1490.

Acetophenone. 54% GC yield (GC t_R 11.9 min); the spectral data were identical to those of commercially available compound.

1-(Thiophen-2-yl)pentan-1-one. Slightly yellow oil; 74% yield; ^1H NMR (400 MHz, CDCl_3) δ 7.71 (dd, $J = 3.8, 1.4$ Hz, 1H), 7.62 (dd, $J = 4.8, 1.2$ Hz, 1H), 7.13 (dd, $J = 5.2, 3.6$ Hz, 1H), 2.90 (t, $J = 7.4$ Hz, 2H), 1.74 (quint, $J = 7.5$ Hz, 2H), 1.41 (sext, $J = 7.5$ Hz, 2H), 0.95 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (400 MHz, CDCl_3) δ 193.5, 144.5, 133.3, 131.6, 128.0, 39.1, 26.9, 22.4, 13.9; HRMS (ESI) calcd. for $\text{C}_9\text{H}_{13}\text{OS}^+$ $[\text{M}+\text{H}]^+$: 169.0682; found: 169.0674.

1-(5-(Hydroxy(phenyl)methyl)thiophen-2-yl)pentan-1-one. Colorless oil; 77% yield; ^1H NMR (400 MHz, CDCl_3) δ 7.55 (d, $J = 4.0$ Hz, 1H), 7.46–7.30 (m, 5H), 6.91 (dd, $J = 3.8, 0.5$ Hz, 1H), 6.03 (d, $J = 4.0$ Hz, 1H), 2.83 (t, $J = 7.4$ Hz, 2H), 2.47 (d, $J = 4.0$ Hz, 1H), 1.70 (quint, $J = 7.5$ Hz, 2H), 1.39 (sext, $J = 7.4$ Hz, 2H), 0.93 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (400 MHz, CDCl_3) δ 193.8, 156.9, 143.2, 142.4, 131.7, 128.7, 128.3, 126.3, 125.2, 72.6, 38.8, 26.9, 22.4, 13.8; HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{18}\text{O}_2\text{SNa}^+$ $[\text{M}+\text{Na}]^+$: 297.0920; found: 297.0921.

5-Pentanoyl-*N*-phenylthiophene-2-carboxamide. White solid; 59% yield (purified by recrystallization from $\text{MeOH}/\text{CH}_2\text{Cl}_2$ mixture); ^1H NMR (400 MHz, CDCl_3) δ 7.71–7.57 (m, 4H), 7.66 (br s, 1H), 7.42–7.34 (m, 2H), 7.22–7.15 (m, 1H), 2.93 (t, $J = 7.6$ Hz, 2H), 1.75 (quint, $J = 7.6$ Hz, 2H), 1.42 (sext, $J = 7.4$ Hz, 2H), 0.96 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (400 MHz, $\text{DMSO}-d_6$) δ 193.7, 159.1, 146.7, 146.1, 138.2, 132.9, 129.6, 128.7, 124.1, 120.4, 37.9, 26.0, 21.7, 13.7; HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{17}\text{NO}_2\text{SNa}^+$ $[\text{M}+\text{Na}]^+$: 310.0872; found: 310.0875.

4. The Reactions Using High-Pressure Syringe Pumps. Solutions were introduced to the flow microreactor system using syringe pumps, Harvard Apparatus PHD 4400, equipped with stainless steel syringes purchased from Harvard Apparatus (#70-2255). A flow microreactor system consisting of T-shaped micromixer (M), integrated micro device (I), two microtube reactors (R1 and R2) was used. A solution of mesitylbromide (0.18 M in THF, 5X mL min⁻¹) and a solution of *n*-BuLi (0.43 M in hexane, 1.8X mL min⁻¹) were introduced to M (ϕ = 250 μ m) by syringe pumps. The resulting solution was passed through R1 (ϕ = 1000 μ m, L = 210 cm (100 cm at 0 °C, 10 cm at ambient temperature and 100 cm at -70 °C)) and was subsequently mixed with a solution of *p*-iodoacetophenone **1e** (0.18 M in THF, 5X mL min⁻¹) and a solution of MeOH (0.6 M in THF, 2X mL min⁻¹) in I (ϕ = 250 μ m, L = 10 cm). The resulting solution was passed through R3 (ϕ = 1000 μ m, L = 50 cm). After a steady state was reached, the product solution was collected for 30 s while being quenched with sat. NH₄Cl solution. The reaction mixture was analyzed by GC. The results are summarized in Table4.

Table 4. The I-Li exchange reaction of *p*-iodoacetophenone (**1e**) using high-pressure syringe pumps.

X	Total flow rate (mL min ⁻¹)	Residence time (s)	Yield (%)
1.0	11.8	3.0	53
1.2	14.2	2.5	65
1.3	15.3	2.3	69
1.6	18.9	1.9	74
2.0	23.6	1.5	76
2.3	27.1	1.3	75

When benzaldehyde was used as electrophile instead of MeOH, desired product was formed in 78% isolated yield.

1-(4-(Hydroxy(phenyl)methyl)phenyl)ethanone. Colorless oil; 78% isolated yield; the spectral data were identical to those of reported in the literature.¹⁰

5. Formal Total Synthesis of Pauciflorol F

1-(3,5-Dimethoxyphenyl)-2-(4-methoxyphenyl)ethanone. 1 M CuCN·2LiCl THF solution (44 mL, 44.0 mmol) was added dropwise to a solution of 3,5-dimethoxyphenylmagnesium chloride (0.5 M in THF, 80 mL, 40.0 mmol) at -25 °C for 10 min. After stirred for 40 min at -20 °C, 4-methoxyphenylacetyl chloride (9.793 g, 53.0 mmol) was added dropwise for 5 min. After a solution was slowly warmed to -10 °C during 1 h, the reaction was quenched by slow addition of sat. NH₄Cl solution (120 mL). The organic layer was separated and the remaining aqueous layer was extracted with Et₂O (150 mL × 3). The combined organic layers were dried over Na₂SO₄ and concentrated. The crude product was purified by flash column chromatography (CHCl₃) and washed with cold hexane to obtain the title compound: slight red solid; 91% (10.390 g); ¹H NMR (400 MHz, CDCl₃) δ 7.18 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 2.0 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.63 (t, *J* = 2.2 Hz, 1H), 4.18 (s, 2H), 3.82 (s, 6H), 3.79 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 197.4, 160.7, 158.4, 138.4, 130.3, 126.4, 114.0, 106.3, 105.1, 55.4, 55.0, 44.6; HRMS (APCI) calcd. for C₁₇H₁₉O₄⁺ [M+H]⁺: 287.1278; found: 287.1280.

1-(2-Iodo-3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)ethanone (5). Iodobenzene diacetate (242.0 mg, 0.75 mmol) was added to a solution of 1-(3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)ethanone (146.8 mg, 0.51 mmol) and iodine (70.9 mg, 0.28 mmol) in CH₂Cl₂ (4 mL) at 0 °C. After stirred for 0 °C for 10 h, a solution was slowly warmed to ambient temperature. After stirred for 14 h, the reaction was quenched by addition of half-saturated Na₂S₂O₃ solution (10 mL). The organic layer was separated and the remaining aqueous layer was extracted with CH₂Cl₂ (25 mL × 3). The combined organic layers were dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography (hexane/ethyl acetate = 4:1) to obtain the title compound: white solid; 74% (156.2 mg); ¹H NMR (400 MHz, CDCl₃) δ 7.19 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.43 (d, *J* = 2.8 Hz, 1H), 6.28 (d, *J* = 2.8 Hz, 1H), 4.13 (s, 2H), 3.89 (s, 3H), 3.80 (s, 3H), 3.75 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 203.7, 161.1, 158.8, 158.6, 147.9, 130.8, 125.2, 113.9, 104.1, 99.5, 71.8, 56.5, 55.6, 55.2, 48.4; HRMS (APCI) calcd. for C₁₇H₁₈IO₄⁺ [M+H]⁺: 413.0244; found: 413.0238.

3-(3,5-Dimethoxyphenyl)-4,6-dimethoxy-1-(4-methoxybenzylidene)-1,3-dihydroisobenzofuran (6). A flow microreactor system consisting of T-shaped micromixer (M), integrated micro device (I), two microtube reactors (R1 and R2) was used. A solution of

mesitylbromide (0.18 M in THF, 5.0 mL min⁻¹) and a solution of *n*-BuLi (0.43 M in hexane, 1.8 mL min⁻¹) were introduced to M (ϕ = 250 μ m) by syringe pumps. The resulting solution was passed through R1 (ϕ = 1000 μ m, *L* = 210 cm (100 cm at 0 °C, 10 cm at ambient temperature and 100 cm at -70 °C)) and was subsequently mixed with a solution of acyliodobenzene **5** (0.18 M in THF, 5.0 mL min⁻¹) and a solution of 3,5-dimethoxybenzaldehyde (0.60 M in THF, 2.0 mL min⁻¹) in I (ϕ = 250 μ m, *L* = 10 cm). The resulting solution was passed through R2 (ϕ = 1000 μ m, *L* = 50 cm). After a steady state was reached, the product solution was collected for 5 min while being quenched with H₂O (20 mL). After 1M HCl solution (80 mL) was added, the organic layer was separated and the remaining aqueous layer was extracted with Et₂O (100 mL $\times$ 3). The combined organic layers were dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography (hexane/ethyl acetate = 2:1) to obtain the title compound: white solid; Slightly unstable in air; 81% yield (1.058 g); ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.59 (dt, *J* = 9.2, 2.4 Hz, 2H), 6.93 (d, *J* = 1.6 Hz, 1H), 6.89 (dt, *J* = 9.2, 2.4 Hz, 2H), 6.53 (s, 1H), 6.52 (d, *J* = 2.0 Hz, 1H), 6.45 (t, *J* = 2.4 Hz, 1H), 6.41 (d, *J* = 2.4 Hz, 2H), 6.12 (s, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 3.69 (s, 3H), 3.69 (s, 6H); ¹³C NMR (400 MHz, DMSO-*d*₆) δ 162.0, 160.3, 157.1, 154.8, 153.5, 142.1, 136.8, 128.8, 128.6, 121.6, 113.8, 104.9, 99.7, 99.4, 95.9, 95.1, 85.3, 55.6, 55.5, 55.0, 54.9; HRMS (APCI) calcd. for C₂₆H₂₇O₆⁺ [M+H]⁺: 435.1802; found: 435.1795.

3-(3,4-Dimethoxyphenyl)-4,6-dimethoxy-2-(4-methoxyphenyl)-1H-inden-1-one (**7**).

The conc. HCl aqueous solution (4 mL) was added dropwise for 30 min to a solution of **6** (44.0 mg, 0.101 mmol) in *i*-PrOH (20 mL) at 25 °C. After stirred for 12 h, the reaction was quenched by slow addition of sat. NaHCO₃ aqueous solution (60 mL) and water (40 mL) at 0 °C. The organic layers were extracted with ethyl acetate (40 mL $\times$ 3) and washed with brine (40 mL). The combined organic layers were dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography (hexane/ethyl acetate = 3:1) to obtain the title compound: red solid; 75% (32.7 mg); ¹H NMR (400 MHz, CDCl₃) δ 7.12 (dt, *J* = 9.2, 2.6 Hz, 2H), 6.86 (d, *J* = 2.0 Hz, 1H), 6.75 (dt, *J* = 8.8, 2.6 Hz, 2H), 6.49 (d, *J* = 2.4 Hz, 2H), 6.43 (t, *J* = 2.2 Hz, 2H), 3.86 (s, 3H), 3.76 (s, 3H), 3.70 (s, 6H), 3.61 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 196.6, 162.5, 160.2, 158.7, 156.6, 154.7, 137.0, 134.1, 131.0, 130.6, 123.6, 122.7, 113.4, 106.5, 104.1, 102.7, 101.0, 55.9, 55.7, 55.3, 55.1; HRMS (ESI) calcd. for C₂₆H₂₄NaO₆⁺ [M+Na]⁺: 455.1465; found: 455.1451.

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1. Aryllithium Compounds Bearing Alkoxy carbonyl Groups: Generation and Reactions Using a Microflow System
Nagaki, A.; Kim, H.; Yoshida, J.
Angew. Chem. Int. Ed. **2008**, *47*, 7833-7836.
(Chapter 1)
2. Nitro-Substituted Aryl Lithium Compounds in Microreactor Synthesis: Switch between Kinetic and Thermodynamic Control
Nagaki, A.; Kim, H.; Yoshida, J.
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3. Generation and Reaction of Cyano-Substituted Aryllithium Compounds Using Microreactors
Nagaki, A.; Kim, H.; Usutani, H.; Matsuo, C.; Yoshida, J.
Org. Biomol. Chem. **2010**, *8*, 1212-1217.
(Chapter 3)
4. A Flow Microreactor System Enables Organolithium Reactions without Protecting Alkoxy carbonyl Groups
Nagaki, A.; Kim, H.; Moriwaki, Y.; Matsuo, C.; Yoshida, J.
Chem. Eur. J. **2010**, *16*, 11167-11177.
(Chapter 1 and 2)
5. A Flow-Microreactor Approach to Protecting-Group-Free Synthesis Using Organolithium Compounds
Kim, H.; Nagaki, A.; Yoshida, J.
Nature Commun. **2011**, *2*, 264.
(Chapter 5)

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1. Integrated Micro Flow Synthesis Based on Sequential Br-Li Exchange Reactions of *p*-, *m*- and *o*-Dibromobenzenes
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RSC Adv. in press.

**Flow Microreactor Synthesis
via Unstable Organolithium Intermediates Bearing
Electrophilic Functional Groups**

Heejin Kim

2011

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 April 2007 – November 2011. The studies are concerned with a flow microreactor synthesis via unstable organolithium intermediates bearing electrophilic functional groups.

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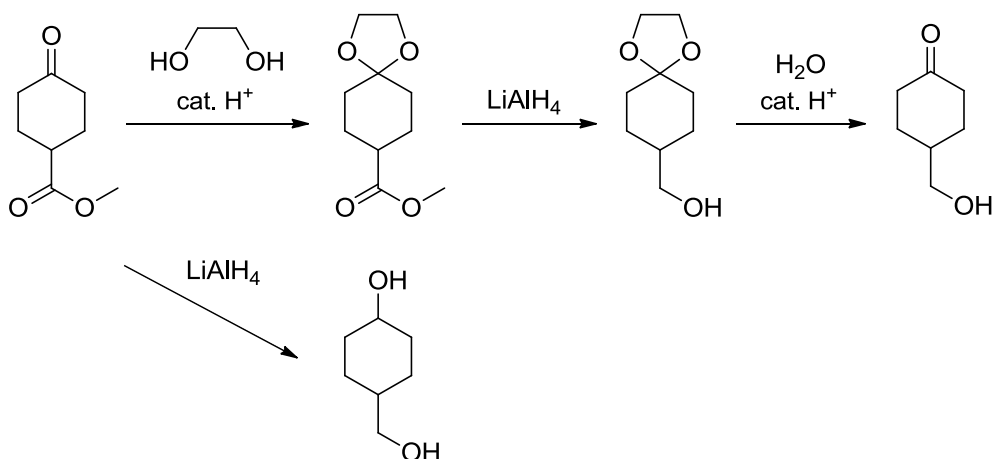
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General Introduction

I. Protecting-Group-Free Synthesis

Organic chemists have relied upon protecting groups for chemoselective synthesis. In syntheses of complicated organic molecules, some functional groups in a molecule often cannot survive a particular transformation. Therefore, the introduction and removal of protecting group is regarded as an indispensable process in the organic synthesis.¹ For example, lithium aluminium hydride (LiAlH_4) is reactive to both an ester and a ketone. In order to conduct a selective reduction of an ester, a ketone should be converted to a protected form, *i.e.* an acetal in advance of the reduction as shown in Scheme 1.

Scheme 1. The protection of a ketone for a selective reduction of an ester



However, it is certain that the introduction and removal of protecting groups increase the total steps of the synthesis and bring a loss of materials. Recently, the construction of complicated molecules without using protecting group² has attracted a great deal of attention from the viewpoints of atom economy³, step economy⁴ and redox economy.⁵ A lot of protecting-group-free synthesis has been developed in an endeavor to the ideal synthesis⁶ and green sustainable chemistry⁷ in recent years. Generally, a skeleton-building reaction is one of the most difficult steps with respect to avoiding usage of protecting groups because such reaction often uses strongly nucleophilic reagents. Among such reagents, organolithium reagents are the most reactive, although its high reactivity makes them very useful in organic synthesis.

II. Functionalized Organolithium Intermediates

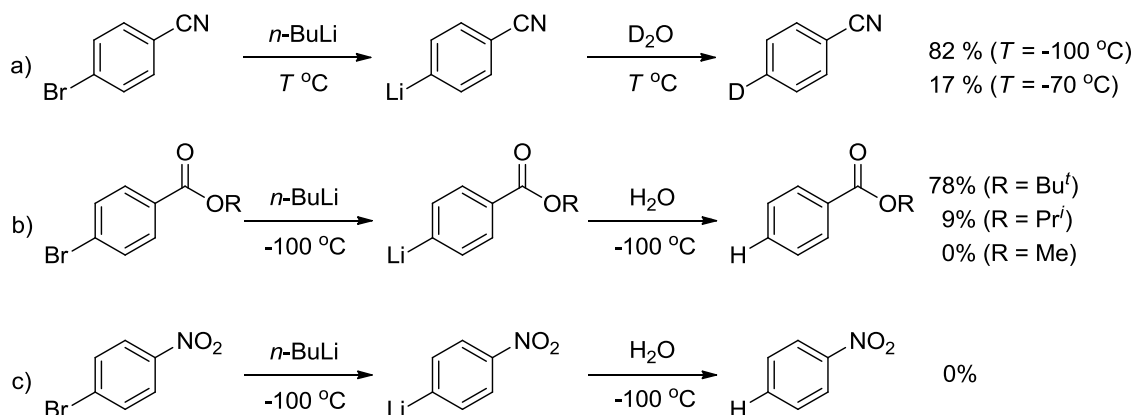
Functionalized organometallic compounds provide a straightforward and powerful access to complicated molecules, since the protection of functional group is not necessary, as well as functional groups can be used directly in a subsequent reaction.⁸ There are two difficulties associated with generating functionalized organometallic compounds: 1) preventing the reaction of the nucleophilic organometallic part with the functional group; 2) having an enough reactivity for reactions with various electrophiles, otherwise generated organometallic compounds would be not useful. For this type of transformations, functionalized organomagnesium⁹ and organozinc¹⁰ compounds are often used, because they can tolerate many functional groups. However, there are some limitations on availability of substrates and electrophiles. Functionalized organomagnesium and organozinc intermediates sometimes could not prepared from relatively less reactive precursors and hardly react with some electrophiles, because of their low reactivity.¹¹

On the other hand, organolithium compounds are the most reactive among main group organometallic compounds. They have been widely used and played a major role in synthetic organic chemistry. However, its high reactivity inevitably makes them suffer from incompatibility of electrophilic functional groups.¹² For example, the generation and reactions of aryllithium species bearing electrophilic functional groups such as cyano, alkoxycarbonyl and nitro groups are generally very difficult or impossible even at low temperatures because of their instability. In some cases, such reaction can be partially achieved at extremely low temperatures such as -100 °C (Scheme 2).

Moreover, ketones react with organolithiums very rapidly, and therefore the organic textbooks say that ketone carbonyl groups should be protected before an organolithium reaction if it is not involved in the desired transformation.

Owing to this critical drawback of organolithiums, transformations via functionalized organolithium compounds could not be used for the synthesis of complicated molecules. As an alternative method, functional group should be protected prior to organolithium reaction,¹³ or another synthetic route has to be concerned.¹⁴

Scheme 2. Generation and reactions of aryllithium compounds bearing an electrophilic functional group using conventional batch reactor



III. Continuous-Flow Microreactor

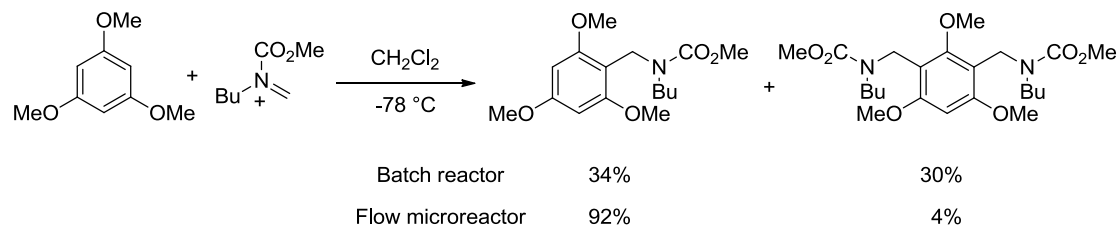
Continuous-flow microreactors¹⁵ have emerged as innovative and powerful tools for chemical syntheses in recent years. Although tools for chemical reactions had rarely changed for a long time, now a day, chemists have focus on the development of the flow microreactors for laboratory synthesis and applications to industrial scale production.¹⁶ Flow microreactors have following characteristic features derived from their small size and flow nature.

1) Fast micromixing

Many chemical reactions are initiated by mixing two substances, and for this reason mixing to achieve a good level of homogeneity in solution is important, especially for fast reactions. Time needed for mixing is proportional to the square of the length of the diffusion path, since mixing occurs by molecular diffusion. Therefore, the marked shortening of the diffusion path in a flow microreactor results in very fast mixing which is unobtainable in batch macro reactors.

For example, the product selectivity of Friedel-Crafts alkylation can be greatly improved by fast micromixing (Scheme 3).¹⁷ The reaction of the *N*-acyliminium ion pool with 1,3,5-trimethoxybenzene in a batch reactor results in the formation of a 1:1 mixture of the monoalkylation product and the dialkylation product. However, the use of a flow microreactor (IMM single mixer, lamination width: 25 μm) leads to an excellent selectivity of the monoalkylation product, and the amount of the dialkylation product was very small. Therefore, the product selectivity strongly depends on the manner of mixing.

Scheme 3. Effect of the manner of mixing on the product selectivity of Friedel-Crafts monoalkylation with an *N*-acylliminium ion



2) Effective temperature control

Heat is transferred between the interior and exterior of a reactor via the reactor surface. Therefore, surface area per unit volume of the reactor is a crucial factor for heat transfer. Because the downsizing of reactor results in a high surface-to-volume ratio as shown in Figure 1, a flow microreactor system has superior ability on the temperature control than conventional batch reactors.¹⁸

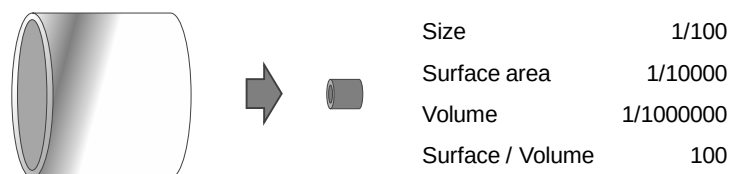


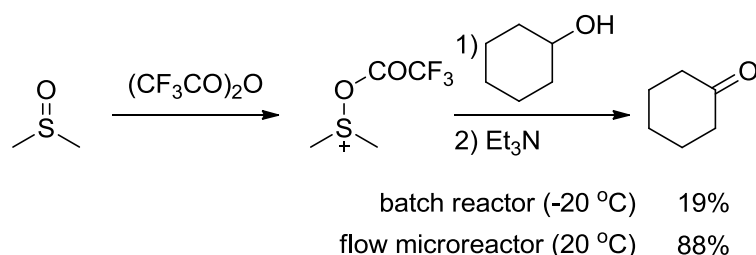
Figure 1. Numerical aspects of downsizing

3) Precise residence time control

Residence time is defined as the length of time that the solution remains in the reactor. In the flow reactors, the residence time increases with the length of the channel and decreases with the flow rate. In flow microreactors, the residence time can be precisely controlled, also greatly reduced by reducing the length of the microchannels and increasing flow speed. This feature of flow microreactor is extremely useful in controlling chemical reactions involving short-lived reactive species, because the reactive species can be moved to another location to be used in the next reaction before they decompose. By taking the advantage of short residence time in flow microreactor systems, Swern-Moffatt oxidation can be carried out at room temperature as shown in Scheme 4.¹⁹ In the first step, DMSO reacts with trifluoroacetic anhydride to form cationic reactive species which is known to be unstable above -30 °C. Actually, the batch reaction at -20 °C leads to the formation of significant amount of byproducts derived from the decomposition of reactive species. In a flow microreactor system,

however, the reaction time can be greatly shortened by reducing the residence time to avoid undesired decomposition. The reaction in flow microreactor gives rise to the formation of the desired product in high yields even at room temperature by virtue of short residence time.

Scheme 4. Swern-Moffatt oxidation using flow microreactor system

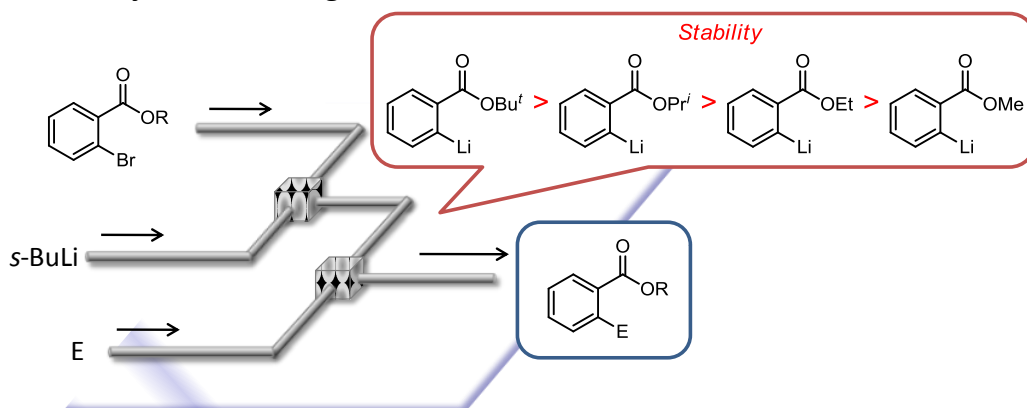


IV. Flow Microreactor Synthesis via Organolithiums Bearing Electrophilic Functional Groups

The examples shown in the previous section imply that features of the flow microreactor system is quite effective for extremely fast reactions via unstable intermediates, such as functionalized organolithium compounds. We envisioned that fast mixing could be effective to increase the selectivity of the halogen-lithium exchange reactions of functionalized aryl halide, and that the resulting aryllithium compounds bearing functional group can react with an electrophile before they decompose by virtue of precise residence time control in the flow microreactor system. Moreover, it is expected that effective temperature control of the flow microreactor system can minimize the undesired side reactions caused by the local deviation of the temperature.

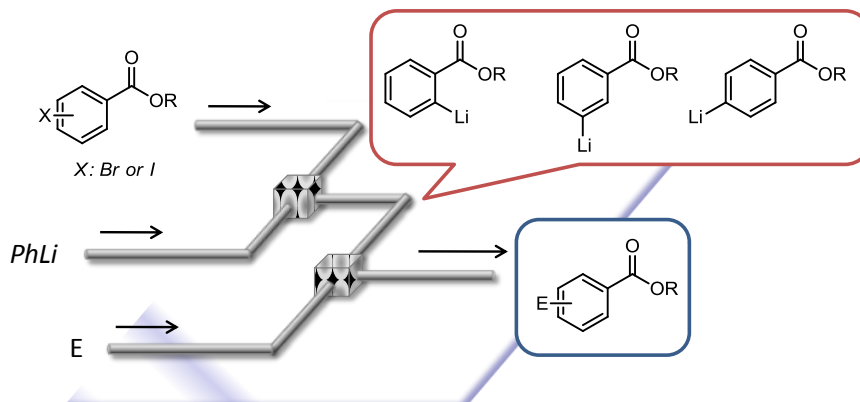
In chapter 1, the generation and reactions of *o*-alkoxycarbonyl-substituted aryllithium intermediates by Br-Li exchange reaction using flow microreactor is described. The Br-Li exchange reaction of alkyl *o*-bromobenzoates, followed by the reaction with electrophiles can be conducted using flow microreactor system. Although the methyl or ethyl ester could not tolerate in organolithium reactions in conventional batch reactor, the desired products could be obtained in satisfactory yields by using a flow microreactor (Scheme 5).

Scheme 5. Generation and reactions of *ortho*-alkoxycarbonyl-substituted aryllithium intermediates by Br-Li exchange



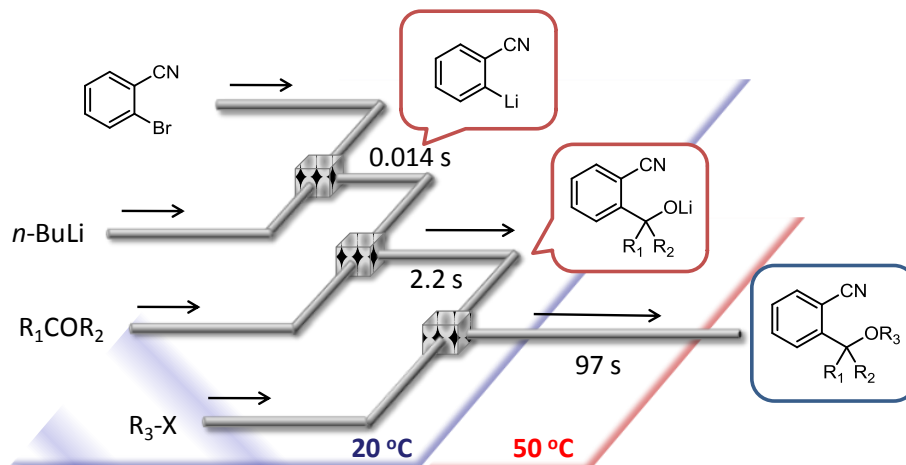
Chapter 2 describes the generation and reactions of *m*- and *p*-alkoxycarbonyl-substituted aryllithiums by I-Li exchange reaction using flow microreactor. The *m*- and *p*-alkoxycarbonyl-substituted aryllithiums is known to be less stable than *o*-substituted ones, because of absence of *ortho*-chelation. By optimizing reaction conditions such as the reaction temperature and the residence time, the flow microreactor synthesis via *m*- and *p*-alkoxycarbonyl-substituted aryllithiums was achieved (Scheme 6).

Scheme 6. Generation and reactions of *meta*- and *para*-alkoxycarbonyl-substituted aryllithium intermediates by I-Li exchange



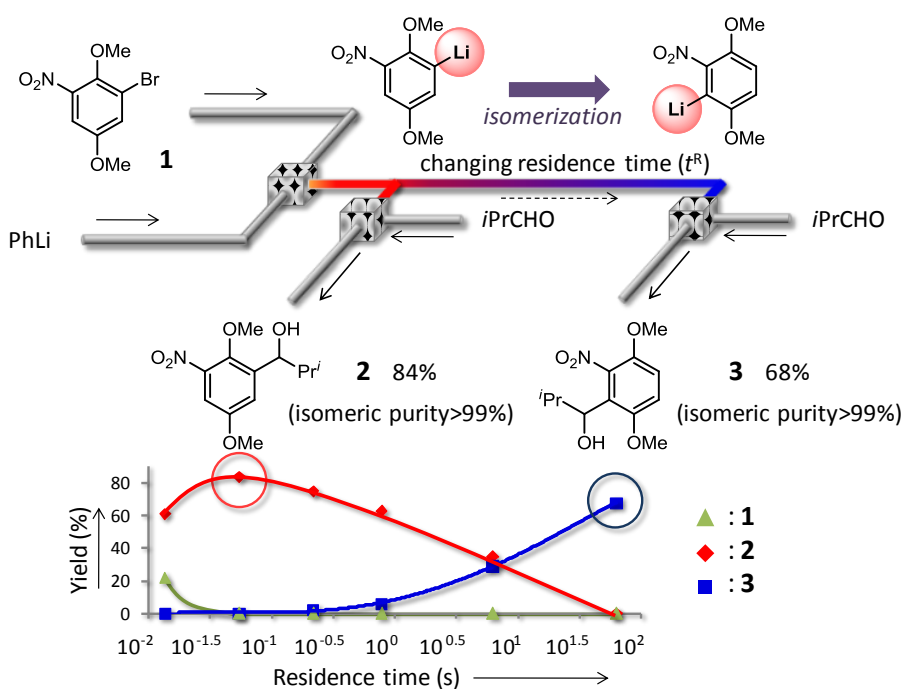
In chapter 3, a flow microreactor synthesis via cyano-substituted aryllithium intermediates is described. The Br-Li exchange reaction of bromobenzonitriles can be conducted at 0 or 20 °C using flow microreactor. In addition, reactions of *o*-lithiobenzonitriles with carbonyl compounds followed by alkylation of the resulting lithium alkoxides were achieved in an integrated flow microreactor system (Scheme 7).

Scheme 7. Multistep transformations via cyano-substituted aryllithiums



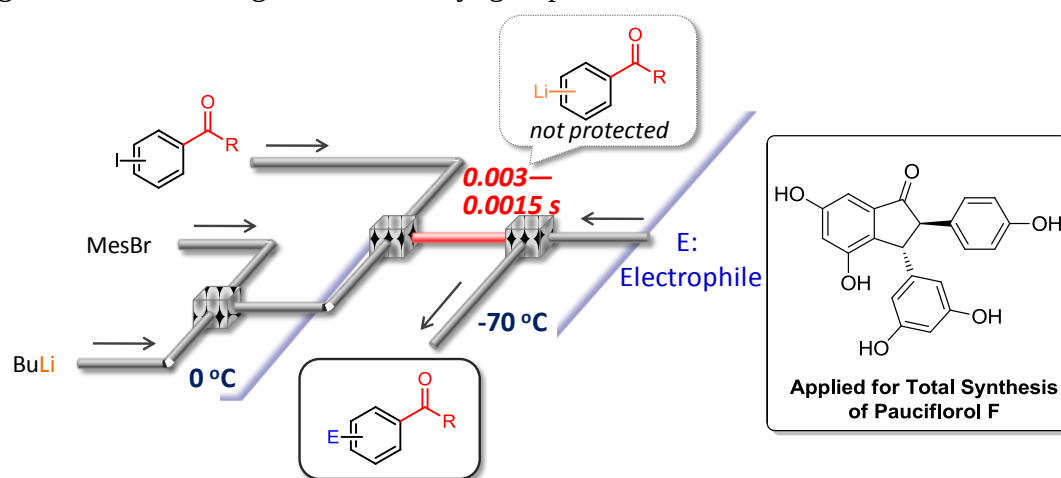
Chapter 4 describes that the flow microreactor synthesis via nitro-substituted aryllithiums and its applications. We have developed an effective flow microreactor system for generation and transformations of *o*-, *m*- and *p*-nitro-substituted aryllithium intermediates. Furthermore, the selective use of either kinetically formed or thermodynamically preferred organolithiums bearing a nitro group could be achieved by changing the residence time as shown in Scheme 8.

Scheme 8. Switch between kinetic and thermodynamic control by changing the residence time



In chapter 5, a flow microreactor synthesis via organolithium intermediates bearing ketone carbonyl groups is described. Generally, organolithium species react with ketones very rapidly, and therefore ketone carbonyl groups should be protected before an organolithium reaction, if they are not involved in the desired transformation. We show that a flow microreactor enables protecting-group-free organolithium reactions by greatly reducing the residence time. The present method has been successfully applied to the formal total synthesis of Pauciflorol F (Scheme 9).

Scheme 9. A flow microreactor approach to protecting-group-free synthesis using organolithiums bearing ketone carbonyl groups



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Chapter 1

Generation and Reactions of *o*-Alkoxy carbonyl-Substituted Aryllithiums Based on Br-Li Exchange Using Flow Microreactor System

Abstract

A flow microreactor system consisting of micromixers and microtube reactors provides very effective method for the generation of *o*-alkoxycarbonyl-substituted aryllithium intermediates followed by reactions with electrophiles, which is very difficult to achieve using conventional batch reactors even at very low temperature. The key features of the method include an extremely short residence time, fast mixing, and effective temperature control.

Introduction

Control of reactive intermediates¹ to selectively obtain desired products is a central issue in organic synthesis. In batch macro reactors, operation time for generation of a reactive intermediate usually takes minutes or hours, because usually a reagent should be added slowly to avoid undesirable temperature increase. If the lifetime of the intermediate is shorter than such a time range, it is difficult to obtain a solution of the intermediate because of its decomposition during the accumulation. In such a case, the intermediate cannot be used for the subsequent reaction. To avoid the decomposition of the reactive intermediate, the generation is usually carried out at very low temperatures in batch macro reactors. In flash chemistry^{2,3} using a flow microreactor system, however, a reactive intermediate can be rapidly generated and transferred for use in a subsequent reaction before decomposition, because the residence time can be greatly reduced.⁴ Therefore, chemical conversions that are impossible in conventional batch macro reactors can become possible using flow microreactors. In this chapter, we report that aryllithium compounds having a highly reactive alkoxycarbonyl group, such as ethoxycarbonyl and methoxycarbonyl, can be easily generated and used for reactions with electrophiles by exploiting the features of flow microreactor systems.⁵

Organolithium compounds, such as aryllithiums, have been widely used in organic synthesis because of their high reactivity.^{6,7} However, aryllithium compounds suffer from the problem of functional group compatibility.⁸ In fact, it is difficult to prepare organolithium compounds bearing electrophilic functional groups such as alkoxycarbonyl groups, because they react with aryllithium species. To overcome this problem, generation reactions, such as Br-Li exchange reactions of organic bromides, are often conducted at very low temperatures. It is, however, still difficult to prepare aryllithium compounds having highly reactive functional groups, such as methoxycarbonyl and ethoxycarbonyl groups.⁹ The second approach is the use of less-reactive, hence more-stable, arylmetallic compounds,¹⁰ such as arylmagnesium¹¹ and arylzinc compounds.¹² However, preparation of such organometallic compounds by a metal-metal exchange reaction of aryllithium compounds suffers from the problem of undesirable reaction of aryllithium species bearing such functional groups. Such arylmetallic compounds can also be prepared directly without using aryllithium reagents. However, direct preparation requires the use of highly reactive precursors such as aryl iodides, which are usually more difficult to prepare.¹³ We envisaged that the concept of flash chemistry using a flow microreactor system would solve the problem.

Results and Discussion

We focused on the Br-Li exchange reaction of alkyl *o*-bromobenzoates.⁵ The Br-Li exchange reaction of alkyl bromobenzoates, followed by the reaction with an electrophile, can be performed in a conventional batch macro reactor only in the case of *tert*-butyl bromobenzoates at very low temperatures (*e.g.* -100 °C). The use of esters of secondary and primary alcohols dramatically decreases the yields. To confirm this, we reexamined the Br-Li exchange reactions of *tert*-butyl *o*-bromobenzoate (**1a**), isopropyl *o*-bromobenzoate (**1b**), ethyl *o*-bromobenzoate (**1c**), and methyl *o*-bromobenzoate (**1d**) in a conventional batch macro reactor (Table 1).

Table 1. The Br-Li exchange reaction of alkyl *o*-bromobenzoates **1** followed by reaction with ROH in a conventional batch macro reactor.

<i>o</i> -Bromobenzoates 1	Conversion of 1 (%)	Yield of 3 (%) ^a
R = <i>tert</i> -butyl: 1a	100	61
R = isopropyl: 1b	100	12
R = ethyl: 1c	100	0
R = methyl: 1d	100	0

^a Determined by GC.

The exchange reaction of **1a** at -78 °C, followed by quenching with an alcohol, gave *tert*-butyl benzoate (**3a**) in 61% yield. The moderate yield seems to be attributed to partial decomposition of **2a** at this temperature. According to the literature, the reaction at lower temperatures (-100 °C) gives **3a** in higher yields.⁹ The use of **1b** led to lower yield of **3b**. Moreover, in reactions of **1c** and **1d**, the desired products were not obtained at all.

We examined the reactions using a flow microreactor system consisting of two T-shaped micromixers (M1 and M2; inner diameter: 250 μm) and two microtube reactors (R1 and R2; Figure 1). The reactions were carried with varying temperatures (*T*) and residence times (*t*^R) in R1. The results are summarized in Figure 2, in which the yield of **3** is plotted against *T* and *t*^R in R1 as a contour map with a scattered overlay.

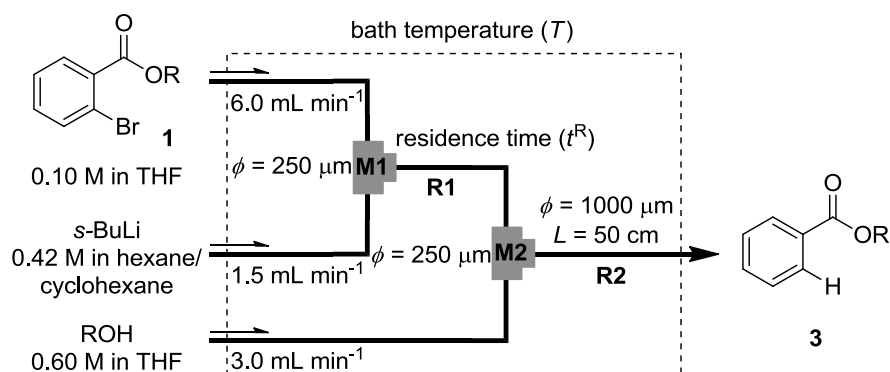


Figure 1. A microreactor system for the Br-Li exchange reaction of alkyl *o*-bromobenzoates **1** followed by reaction with alcohols.

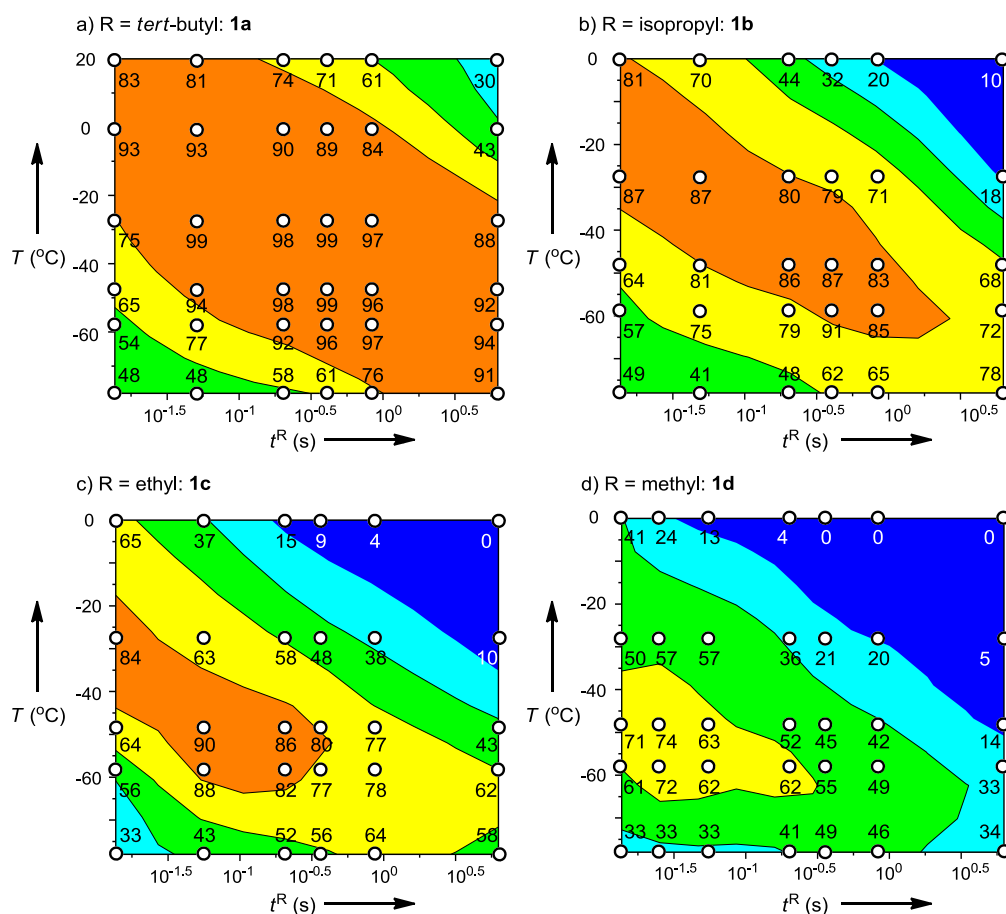


Figure 2. Effect of the temperature and the residence time on the yield in the Br-Li exchange reaction of a) *tert*-butyl *o*-bromobenzene (**1a**), b) isopropyl *o*-bromobenzene (**1b**), c) ethyl *o*-bromobenzene (**1c**), d) methyl *o*-bromobenzene (**1d**), followed by reaction with ROH in the flow microreactor system.

In reactions of *tert*-butyl *o*-bromobenzoate (**1a**), the desired product **3a** was obtained in high yields (> 80%, brown region) for a wide range of temperatures and residence times. At low temperatures and short residence times, the yield was low because of an incomplete Br-Li exchange reaction. Low yield was also observed in the high-temperature/long- residence-time region, probably because of decomposition of **2a**.

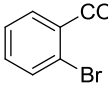
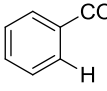
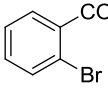
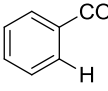
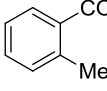
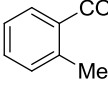
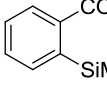
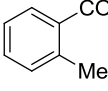
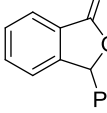
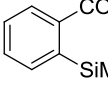
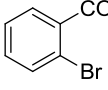
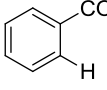
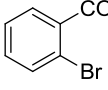
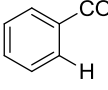
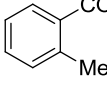
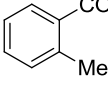
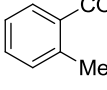
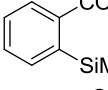
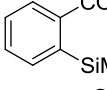
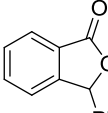
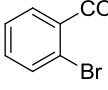
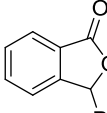
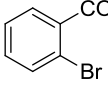
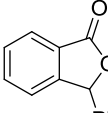
In the case of isopropyl *o*-bromobenzoate (**1b**), a similar reaction profile was observed, although the high-yield region became smaller. The reaction of ethyl *o*-bromobenzoate (**1c**) also exhibited a similar profile. The high-yield region shifted to a lower temperature and shorter residence-time region, probably because of faster decomposition of organolithium compound **2c**. However, it is noteworthy that the reaction can be effectively performed to give **3c** in 90% yield by choosing an appropriate temperature (-48 °C) and residence time (0.06 s).

Of even greater significance is the fact that **3d** can be obtained in relatively good yields (> 70%) from methyl *o*-bromobenzoate (**1d**), although the high-yield region (> 80%) disappeared, presumably because of the small steric demand of the methoxycarbonyl group for the reaction with organolithium species, leading to the nucleophilic attack on the carbonyl group in some extent.

These results clearly show that the stability of the aryllithium compounds decreases in the order **2a** > **2b** > **2c** > **2d**. However, it is important to note that the Br-Li exchange reaction followed by reaction with an electrophile can be successfully carried out without significant decomposition of the aryllithium intermediate **2** by optimizing temperature and residence time, even in the case of methyl ester.

Under the optimized conditions obtained for the Br-Li exchange reaction followed by reaction with an alcohol, the reactions of **2a-2d** with other electrophiles, such as methyl iodide, methyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, and benzaldehyde were examined. The reactions were successful and the corresponding products were obtained in good yields (Table 2). Interestingly, methyl iodide can be used as an electrophile for the reactions of **1a** and **1b** whereas, for the reactions of **1c** and **1d**, methyl triflate should be used. The reaction of the aryllithium with methyl iodide is relatively slow, and therefore only the more sterically demanding *tert*-butoxycarbonyl and isopropoxycarbonyl groups can survive until the reaction is complete. However, the reaction of the aryllithium with methyl triflate is much faster. Therefore, the reaction can be conducted at much lower temperatures with shorter residence times. Consequently, even the less sterically demanding ethoxycarbonyl and methoxycarbonyl groups can survive until the reaction is complete.

Table 2. The Br-Li exchange reaction of alkyl *o*-bromobenzoates **1** followed by reaction with an electrophile under optimized conditions.^a

Ester	Electrophile	Product	Yield (%) ^b	Ester	Electrophile	Product	Yield (%) ^b
 1a	<i>t</i> BuOH		93	 1c	EtOH		90
	MeI		88		MeI		12
	Me ₃ SiCl		96		MeOTf		62
	PhCHO		82		Me ₃ SiCl		61
 1b	<i>i</i> PrOH		87	 1d	MeOH		74
	MeI		62		MeOTf		65
	MeOTf		82		Me ₃ SiOTf		82
	Me ₃ SiCl		93		PhCHO		85
 1b	PhCHO		66	 1d	PhCHO		85

^a For **1a**, *T* = 0 °C (*t*^R = 0.01 s); **1b**, *T* = -28 °C (*t*^R = 0.01 s); **1c**, *T* = -48 °C (*t*^R = 0.06 s); **1d**, *T* = -48 °C (*t*^R = 0.02 s).^b Determined by GC.

Conclusion

We have developed an effective method for the generation and reactions of aryllithium compounds having an alkoxycarbonyl group. The key features of the method are a very short residence time, together with fast mixing¹⁴ and efficient temperature control in flow microreactor systems. A wide range of alkoxycarbonyl groups including ethoxycarbonyl and methoxycarbonyl groups can tolerate the microflow conditions. These results bode well for the utility of flash chemistry, and the method adds a new dimension in the chemistry of functionalized aryllithium compounds and their applications in organic synthesis.

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; initial oven temperature, 50 °C; rate of temperature increase, 10 °C min⁻¹). ¹H and ¹³C NMR spectra were recorded on Varian MERCURY plus-400 (¹H 400 MHz, ¹³C 100 MHz) spectrometer with Me₄Si or CDCl₃ as a standard in CDCl₃ unless otherwise noted. EI mass spectra were recorded on JMS-SX102A spectrometer. THF and Et₂O 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. All materials were obtained from commercial supplier and used without purification unless otherwise noted. *tert*-Butyl *o*-bromobenzoate, and isopropyl *o*-bromobenzoate were prepared according to the literature.¹⁵

Stainless steel (SUS304) T-shaped micromixers with inner diameter of 250 μm were manufactured by Sanko Seiki Co., Inc (Figure 3).

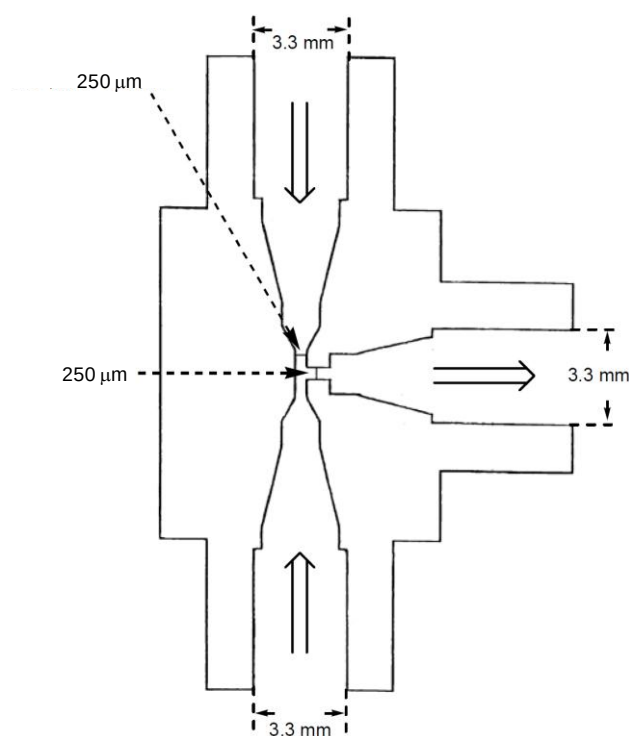


Figure 3. Stainless steel (SUS304) T-shaped micromixers.

Stainless steel (SUS316) microtube reactors with inner diameter of 250, 500 and 1000 μm were purchased from GL Sciences. The micromixers and the microtube reactors were connected with stainless steel fittings (GL Sciences, 1/16 OUN). The flow microreactor system was dipped in a cooling bath to control the temperature (T). Solutions prepared under Ar atmosphere were taken by gastight syringes purchased from SGE, and introduced to a flow microreactor system using syringe pumps, Harvard Model 11.

The Br-Li Exchange Reaction of Alkyl *o*-Bromobenzoates Followed by Reaction with Alcohols Using a Batch Reactor. A solution of *s*-BuLi (0.42 M, 0.75 mL) in hexane/cyclohexane (19/31 v/v) was added dropwise to a solution of an alkyl *o*-bromobenzoate (0.10 M, 3.0 mL) in THF in a 20 mL round bottom glass flask for 1 min at $-78\text{ }^{\circ}\text{C}$. The mixture was stirred for 10 min, and a solution of the corresponding alcohol (0.60 M, 1.5 mL) in THF was added. After stirring for 10 min, a cooling bath was removed. The mixture was analyzed by GC.

The Br-Li Exchange Reaction of Alkyl *o*-Bromobenzoates Followed by Reaction with Alcohols Using Flow Microreactor Systems. A flow microreactor system consisting of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2) was used. A solution of an alkyl *o*-bromobenzoate (0.10 M) in THF (flow rate: 6.0 mL min^{-1}) and a solution of *s*-BuLi (0.42 M) in hexane/cyclohexane (19/31 v/v) (flow rate: 1.5 mL min^{-1}) were introduced to M1 (inner diameter $\phi = 250\text{ }\mu\text{m}$) by syringe pumps. The resulting solution was passed through R1 and was mixed with a solution of alcohol (0.60 M) in THF (flow rate: 3.0 mL min^{-1}) in M2 ($\phi = 250\text{ }\mu\text{m}$). The resulting solution was passed through R2 ($\phi = 1000\text{ }\mu\text{m}$, tube length $L = 50\text{ cm}$). After a steady state was reached, the product solution was collected for 30 s while being quenched with 1 M HCl aqueous solution. The reaction mixture was analyzed by GC. The results are summarized in Table 3 and 4.

Table 3. The Br-Li exchange reaction of *tert*-butyl *o*-bromobenzoate (**1a**) and isopropyl *o*-bromobenzoate (**1b**) followed by reaction with alcohol in flow microreactor systems

ϕ in R1 (μm)	L in R1 (cm)	t^{R} (s)	T ($^{\circ}\text{C}$)	Conv. ^a (%)	Yield ^a (%)	Conv. ^b (%)	Yield ^b (%)
250	3.5	0.014	0	97	93	100	81
500	3.5	0.055		100	93	100	70
1000	3.5	0.22		100	90	100	44
1000	6.0	0.38		97	89	100	32
1000	12.5	0.79		97	84	100	20
1000	100	6.3		100	43	100	10
250	3.5	0.014	-28	96	75	97	87
500	3.5	0.055		100	99	100	87
1000	3.5	0.22		100	98	100	80
1000	6.0	0.38		100	99	100	79
1000	12.5	0.79		100	97	100	71
1000	100	6.3		100	88	100	18
250	3.5	0.014	-48	73	65	73	64
500	3.5	0.055		94	94	93	81
1000	3.5	0.22		100	98	100	86
1000	6.0	0.38		100	99	100	87
1000	12.5	0.79		100	96	100	83
1000	100	6.3		100	92	100	68
250	3.5	0.014	-58	69	54	67	57
500	3.5	0.055		80	77	91	75
1000	3.5	0.22		94	92	96	78
1000	6.0	0.38		98	96	100	91
1000	12.5	0.79		100	97	100	85
1000	100	6.3		100	94	100	72
250	3.5	0.014	-78	59	48	57	49
500	3.5	0.055		65	48	48	41
1000	3.5	0.22		67	58	62	48
1000	6.0	0.38		70	61	75	62
1000	12.5	0.79		87	76	76	65
1000	100	6.3		100	91	95	78

^a *tert*-Butyl *o*-bromobenzoate (**1a**) was used as a substrate. ^b isopropyl *o*-bromo-benzoate (**1b**) was used as a substrate

Table 4. The Br-Li exchange reaction of ethyl *o*-bromobenzoate (**1c**) and methyl *o*-bromobenzoate (**1d**) followed by reaction with alcohol in flow microreactor systems

ϕ in R1 (μm)	L in R1 (cm)	t^{R} (s)	T ($^{\circ}\text{C}$)	Conv. ^a (%)	Yield ^a (%)	Conv. ^b (%)	Yield ^b (%)
250	3.5	0.014	0	100	65	90	41
250	6.0	0.028		- ^c	- ^c	86	24
500	3.5	0.055		100	37	88	13
1000	3.5	0.22		100	15	91	4
1000	6.0	0.38		100	9	92	0
1000	12.5	0.79		100	4	88	0
1000	100	6.3		100	0	88	0
250	3.5	0.014	-28	100	84	85	50
250	6.0	0.028		- ^c	- ^c	91	57
500	3.5	0.055		100	63	95	57
1000	3.5	0.22		100	58	96	36
1000	6.0	0.38		100	48	95	21
1000	12.5	0.79		100	38	100	20
1000	100	6.3		100	10	100	5
250	3.5	0.014	-48	80	64	89	71
250	6.0	0.028		- ^c	- ^c	95	74
500	3.5	0.055		100	90	89	63
1000	3.5	0.22		100	86	89	52
1000	6.0	0.38		100	80	89	45
1000	12.5	0.79		100	77	94	42
1000	100	6.3		100	43	100	14
250	3.5	0.014	-58	64	56	86	61
250	6.0	0.028		- ^c	- ^c	89	72
500	3.5	0.055		100	88	87	62
1000	3.5	0.22		100	82	90	62
1000	6.0	0.38		100	77	90	55
1000	12.5	0.79		100	78	92	49
1000	100	6.3		100	62	100	33
250	3.5	0.014	-78	51	33	52	33
250	6.0	0.028		- ^c	- ^c	51	33
500	3.5	0.055		60	43	58	33
1000	3.5	0.22		67	52	66	41
1000	6.0	0.38		85	56	76	49
1000	12.5	0.79		89	64	85	46
1000	100	6.3		96	58	81	34

^a Ethyl *o*-bromobenzoate (**1c**) was used as a substrate. ^b Methyl *o*-bromobenzoate (**1d**) was used as a substrate. ^c The reaction was not conducted.

The Br-Li Exchange Reaction of *o*-Bromobenzoates Followed by Reaction with Electrophiles Using Microflow Systems. A flow microreactor system consisting of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2) was used. A solution of an alkyl *o*-bromobenzoate (0.10 M) in THF (flow rate: 6.0 mL min⁻¹) and a solution of *s*-BuLi (0.42 M) in hexane/cyclohexane (19/31 v/v) (flow rate: 1.5 mL min⁻¹) were introduced to M1 (ϕ = 250 μ m) by syringe pumps. The resulting solution was passed through R1 and was mixed with a solution of electrophile (0.60 M) in THF (Et₂O in case of methyl triflate and trimethylsilyl triflate; flow rate: 3.0 mL min⁻¹) in M2 (ϕ = 250 μ m). The resulting solution was passed through R2 (ϕ = 1000 μ m, L = 50 cm). After a steady state was reached, the product solution was collected for 30 s while being quenched with H₂O (1 M HCl aqueous solution when benzaldehyde was used as an electrophile). The reaction mixture was analyzed by GC.

The reactions were carried out under the following conditions: for **1a**, T = 0 °C and t^R = 0.01 s; **1b**, T = -28 °C and t^R = 0.01 s; **1c**, T = -48 °C and t^R = 0.06 s; **1d**, T = -48 °C and t^R = 0.02 s.

***tert*-Butyl *o*-methylbenzoate.** 88% yield (GC t^R 16.1 min) from **1a** and iodomethane. The spectral data were identical to those reported in the literature.¹⁶

***tert*-Butyl *o*-trimethylsilylbenzoate.** 96% yield (GC t^R 18.6 min) from **1a** and chlorotrimethylsilane. After extraction, the crude product was purified by flash chromatography (hexane/ethyl acetate = 100 : 1): ¹H NMR (400 MHz, CDCl₃) δ 0.33 (s, 9H), 1.60 (s, 9H), 7.38 (ddd, J = 7.2, 7.2, 1.6 Hz, 1H), 7.46 (ddd, J = 7.2, 7.2, 1.6 Hz, 1H), 7.66 (dd, J = 7.2, 1.6 Hz, 1H), 7.88-7.92 ppm (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 0.55, 28.3, 80.8, 128.4, 129.4, 130.6, 135.1, 137.7, 142.0, 167.3 ppm; HRMS (EI) m/z calcd for C₁₄H₂₁O₂Si (M⁺-H): 249.1311, found: 249.1299.

3-Phenylphthalide. 82% yield (GC t^R 23.7 min) from **1a** and benzaldehyde. The spectral data were identical to those reported in the literature.¹⁷

Isopropyl *o*-methylbenzoate. 62% yield (GC t^R 16.0 min) from **1b** and iodomethane. 82% yield from **1b** and methyl triflate. The spectral data were identical to those reported in the literature.¹⁸

Isopropyl *o*-trimethylsilylbenzoate. 93% yield (GC t_R 18.2 min) from **1b** and chlorotrimethylsilane. After extraction, the crude product was purified by flash chromatography (hexane/ethyl acetate = 20 : 1): 1H NMR (400 MHz, $CDCl_3$) δ 0.33 (s, 9H), 1.38 (d, J = 6.4 Hz, 6H), 5.22 (hept, J = 6.2 Hz, 1H), 7.40 (ddd, J = 7.4, 7.4, 1.6 Hz, 1H), 7.47 (ddd, J = 7.6, 7.2, 1.2 Hz, 1H), 7.67 (dd, J = 6.8, 1.2 Hz, 1H), 7.95-7.99 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.48, 22.1, 68.4, 128.5, 129.5, 131.0, 135.2, 136.2, 142.3, 167.5 ppm; HRMS (EI) m/z calcd for $C_{13}H_{21}O_2Si$ (MH^+): 237.1311, found: 237.1299.

3-Phenylphthalide. 77% yield from **1b** and benzaldehyde.

Ethyl *o*-methylbenzoate. 12% yield (GC t_R 15.5 min) from **1c** and iodomethane. 61% yield from **1c** and methyl triflate. The spectral data were identical to those reported in the literature.¹⁸

Ethyl *o*-trimethylsilylbenzoate. 61% yield (GC t_R 17.8 min) from **1c** and chlorotrimethylsilane. 79% yield from **1c** and trimethylsilyl triflate. After extraction, the crude product was purified by flash chromatography (hexane/ethyl acetate = 20 : 1): 1H NMR (400 MHz, $CDCl_3$) δ 0.36 (s, 9H), 1.42 (t, J = 7.0 Hz, 3H), 4.39 (q, J = 7.1 Hz, 2H), 7.42 (m, 1H), 7.50 (m, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.99-8.02 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.45, 14.5, 61.0, 128.6, 129.7, 131.1, 135.2, 135.8, 142.2, 168.0 ppm; HRMS (EI) m/z calcd for $C_{12}H_{17}O_2Si$ ($M^+ - H$): 221.0998, found: 221.0997.

3-Phenylphthalide. 70% yield from **1c** and benzaldehyde.

Methyl *o*-methylbenzoate. 65% yield (GC t_R 14.1 min) from **1d** and methyl triflate. The spectral data were identical to those reported in the literature.¹⁹

Methyl *o*-trimethylsilylbenzoate. 82% yield (GC t_R 17.4 min) from **1d** and trimethylsilyl triflate. The spectral data were identical to those reported in the literature.²⁰

3-Phenylphthalide. 85% yield from **1d** and benzaldehyde.

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Chapter 2

Generation and Reactions of *m*- and *p*- Alkoxycarbonyl-Substituted Aryllithiums Based on I-Li Exchange Using Flow Microreactor System

Abstract

A flow microreactor system consisting of micromixers and microtube reactors provides an effective tool for the generation and reactions of aryllithiums bearing an alkoxycarbonyl group at *para*- and *meta*-positions. Alkyl *p*- and *m*-lithiobenzoates were generated by the I-Li exchange reaction with PhLi, because the Br-Li exchange reaction were unsuccessful. Subsequent reactions of the resulting aryllithiums with electrophiles gave the desired products in good yields.

Introduction

In general, it is well known that the generation of aryllithium compounds bearing an electrophilic functional group at the *para*- and *meta*-position is more difficult than those at the *ortho*-position. It has been reported that *ortho*-, *meta*-, and *para-tert*-butoxycarbonyl-substituted aryllithiums could be generated by halogen-lithium exchange reactions in conventional batch macro reactors only at -100 °C in spite of the presence of a highly sterically demanding *tert*-butyl group.¹ Generation and reactions of aryllithium compounds bearing an isopropoxycarbonyl group at the *ortho*-position could also be achieved though the yield was moderate. Presumably, the carbonyl group facilitates the halogen-lithium exchange reaction as a directing group. However, a similar transformation of aryllithiums bearing an isopropoxycarbonyl group at the *meta*- and *para*-position has been known to be impossible because of the lack of the directing effect.¹

In the *ortho* case, the coordination of the carbonyl oxygen atom in a neighboring position to lithium seems to accelerate the rate of the halogen-lithium exchange reaction, which may be much faster than the nucleophilic attack on the carbonyl group. In the *meta* and *para* cases, however, such coordination is impossible, and therefore the rate of halogen-lithium exchange and that of the nucleophilic attack seem to be closer, giving rise to lower selectivity. Furthermore, generation and reactions of aryllithium compounds bearing less sterically demanding alkoxycarbonyl groups, such as ethoxycarbonyl and methoxycarbonyl, have also been known to be impossible.

Results and Discussions

Generation and reactions of alkyl *p*-lithiobenzoates by Br-Li exchange

First, we examined Br-Li exchange reactions of alkyl *p*-bromobenzoates **1** to generate the corresponding alkyl *p*-lithiobenzoates **2**. It is well known that the Br-Li exchange reaction of alkyl bromobenzoates followed by a reaction with an electrophile, can be performed in a conventional batch macro reactor only when *tert*-butyl bromobenzoates are used at very low temperatures, such as -100 °C.¹ The use of esters bearing less sterically demanding alkoxycarbonyl groups, such as isopropoxycarbonyl, ethoxycarbonyl, and methoxycarbonyl groups, is known to be unsuccessful as mentioned above. To confirm this, we reexamined the Br-Li exchange reactions of alkyl

p-bromobenzoates **1** using a conventional batch macro reactor (Table 1).

Table 1. The Br-Li exchange reaction of alkyl *p*-bromobenzoates **1** followed by reaction with alcohols in a conventional batch reactor.

<i>p</i> -Bromobenzoates 1	Conversion of 1 (%)	Yield of 3 (%) ^a
R = <i>tert</i> -butyl: 1a	98	35 (49) ^b
R = isopropyl: 1b	74	trace (7) ^b
R = ethyl: 1c	82	0
R = methyl: 1d	42	0

^a Determined by GC. ^b The reaction time for Br-Li exchange reaction was 1 min.

The reaction of **1a** (R = *t*-Bu) at -78 °C gave the desired product **3a** in 35% yield (Table 1). A low yield of **3a** seems to be attributed to partial decomposition of **2a** at this temperature. According to the literature,¹ the reaction should be carried out at -100 °C, because significant amounts of byproducts were produced when the reaction was conducted at -78 °C. In the case of **1b** (R = *i*-Pr), only a trace amount of **3b** was obtained. Although the reaction time for the Br-Li exchange reaction was reduced to 1 min to prevent the decomposition of generated aryllithium compounds bearing alkoxy carbonyl group, significant increase of yields was not observed. Moreover, in the cases of **1c** (R = Et) and **1d** (R = Me), the desired products were not obtained at all. In case of **1d**, the conversion was quite low (42%) though the 1.1 equiv. of *s*-BuLi was used, presumably because the organolithium reagent was partially consumed for the nucleophilic attack to the sterically small methoxycarbonyl group.

Next, the reaction was conducted in a flow microreactor system consisting of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2) as shown in Figure 1. The reaction temperature was controlled by adjusting the temperature of a cooling bath (*T*). The residence time in R1 (*t*^R) was adjusted by changing the length and diameter of R1 with a fixed flow rate. The results are summarized in Figure 2 in which the yield of **3** is plotted against the *T* and *t*^R as a contour map with a scattered overlay.

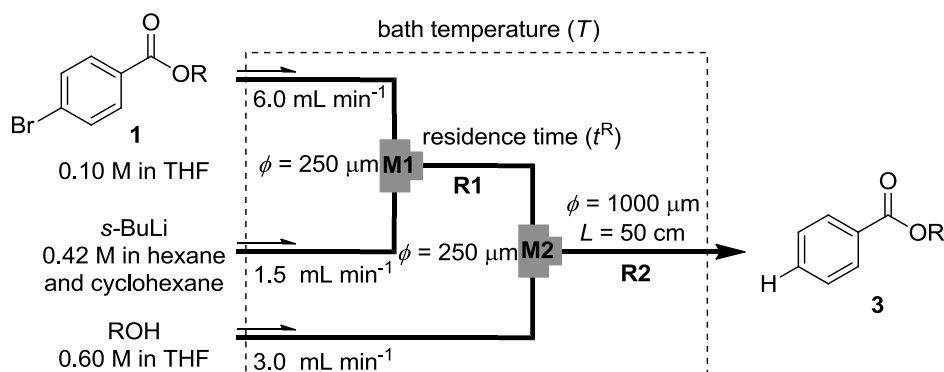


Figure 1. A microreactor system for the Br-Li exchange reaction of alkyl *p*-bromobenzoates **1** followed by reaction with alcohols.

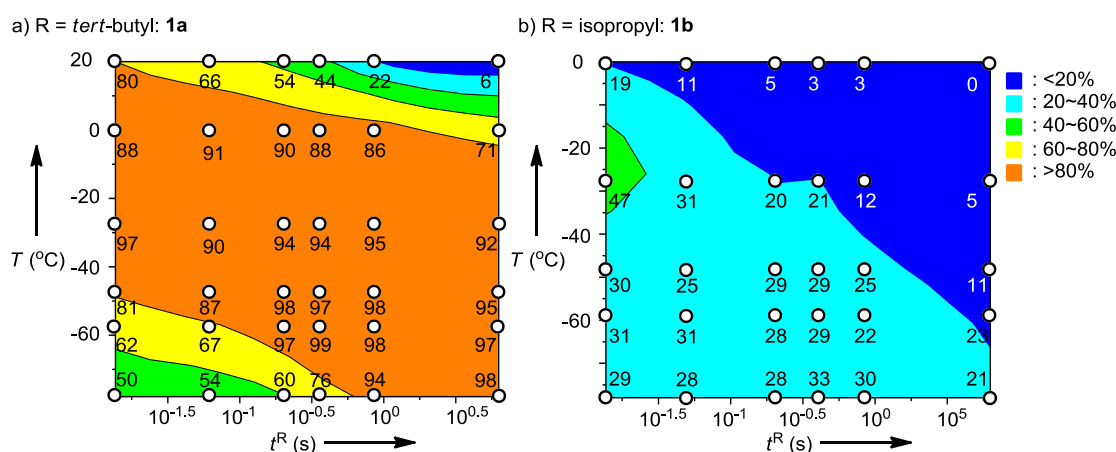


Figure 2. Effects of temperature and residence time on the yield in the Br-Li exchange reaction of a) *tert*-butyl *p*-bromobenzoates (**1a**) and b) isopropyl *p*-bromobenzoates (**1b**) with *s*-BuLi in the flow microreactor system.

In the case of **1a** ($R = t\text{-Bu}$), the desired product **3a** was obtained in high yields (> 80%) over a wide range of temperatures and residence times, which demonstrated that the flow microreactor system is more efficient for the generation and reactions of *tert*-butyl *p*-lithiobenzoate under milder conditions than conventional batch macro reactors. At low temperatures and short residence times the yields were low, presumably because of incomplete Br-Li exchange reactions. Low yields were also observed in the high-temperature long-residence-time region, probably because of the decomposition of aryllithium intermediates **2a**. In the case of **1b** ($R = i\text{-Pr}$), the yields were much lower throughout all regions (> 47%), though it was better than results using batch reactor. This is presumably because the isopropyl group is less sterically demanding than the *tert*-butyl group. Therefore, it was difficult to generate aryllithium compounds bearing

an isopropoxycarbonyl group without decomposition even in a flow microreactor system. This means that it must be also difficult to generate less hindered alkoxycarbonyl-substituted aryllithium compounds in a similar manner.

Generation and reactions of alkyl *p*-lithiobenzoates by I-Li exchange

We decided to conduct the I-Li exchange reaction of alkyl *p*-iodobenzoates **4** because I-Li exchange reactions are generally much faster than the corresponding Br-Li exchange reactions.² Before using a flow microreactor system, the reaction in a conventional batch reactor was examined. It is noteworthy that PhLi, which is less nucleophilic than *s*-BuLi, could be used for I-Li exchange reactions.

Table 2. The I-Li exchange reaction of alkyl *p*-iodobenzoates **1** followed by reaction with alcohols in a conventional batch macro reactor.

<i>p</i> -Iodobenzoates 4	Conversion of 4 (%)	Yield of 3 (%) ^a
R= <i>tert</i> -butyl: 4a	100	81 (99) ^b
R=isopropyl: 4b	100	7 (24) ^b
R=ethyl: 4c	100	trace
R=methyl: 4d	67	trace

^a Determined by GC. ^b The reaction time for I-Li exchange reaction was 1 min.

The reactions of *tert*-butyl *p*-iodobenzoate (**4a**) proceeded at -78 °C to give **3** (81%), after treatment with *tert*-butyl alcohol (Table 2). These results indicate that iodobenzoates are more effective than bromobenzoates as precursors of aryllithium compounds. In the case of isopropyl *p*-iodobenzoate (**4b**), the yield of the desired product was very low. When the reaction time for the I-Li exchange reaction was reduced to 1 min, yield was slightly increased, because the decomposition was partially prevented. However, in the case of ethyl and methyl *p*-iodobenzoates (**4c** and **4d**), the desired products were obtained in trace amounts.

Next, we examined the reactions in a flow microreactor system consisting of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2) as shown in Figure 3.

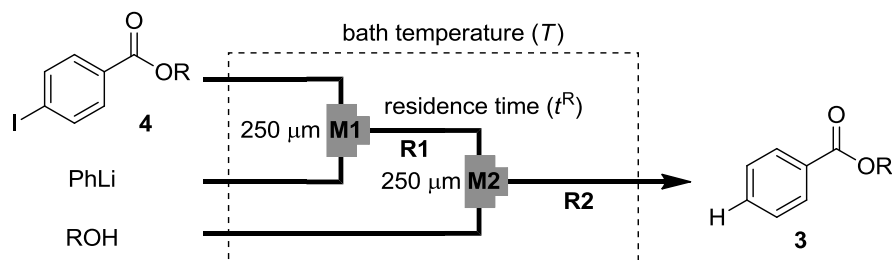


Figure 3. A microreactor system for the I-Li exchange reaction of alkyl *p*-iodobenzoates **4** followed by reaction with alcohols.

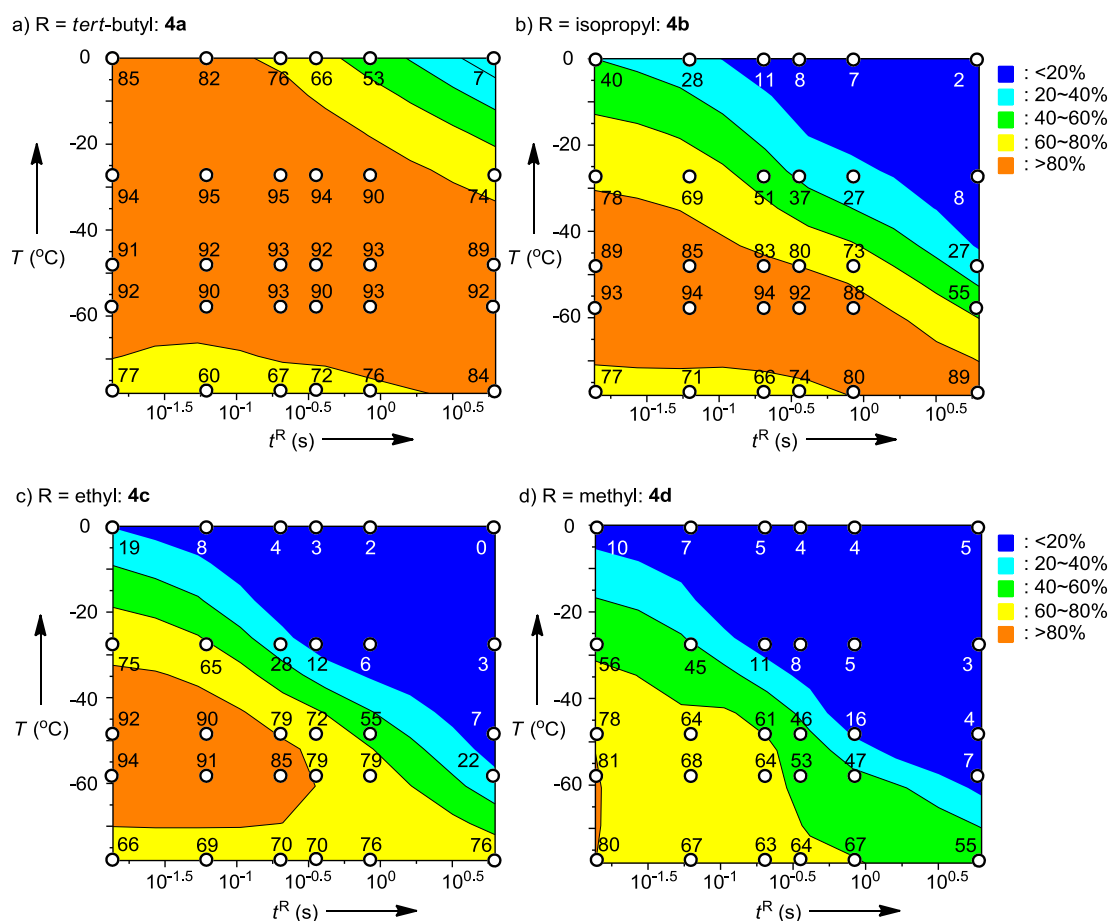


Figure 4. Effects of temperature and residence time on the yield in the Br-Li exchange reaction of a) *tert*-butyl *p*-iodobenzoates (**4a**), b) isopropyl *p*-iodobenzoates (**4b**), c) ethyl *p*-iodobenzoates (**4c**) and d) methyl *p*-iodobenzoates (**4d**) with PhLi in the flow microreactor system.

The residence time in R1 was adjusted by changing the length and diameter of R1 with a fixed flow rate. The results obtained with varying T ($-78 \sim 0$ °C) and t^R (0.01 ~ 6.3 s) are shown in Figure 4.

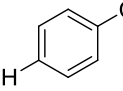
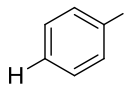
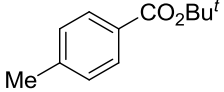
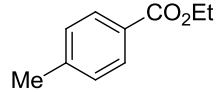
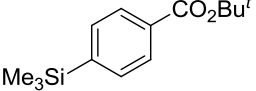
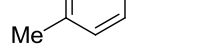
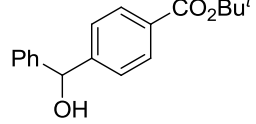
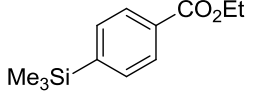
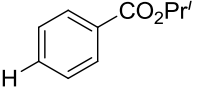
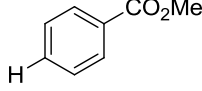
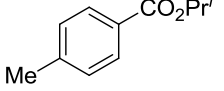
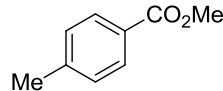
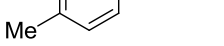
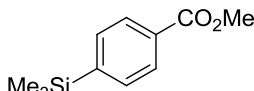
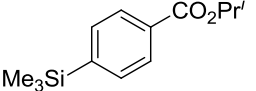
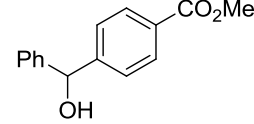
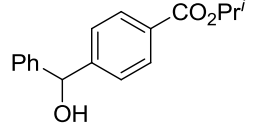
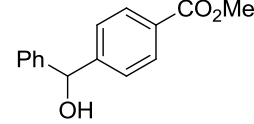
In the case of **4a** ($R = t\text{-Bu}$), the corresponding product **3a** was obtained in high yields ($> 80\%$) for a wide range of temperatures and residence times. The reaction can be conducted even at 0 °C, which demonstrates a significant advantage of flow microreactor systems. This means that the present reaction can be inherently conducted at 0 °C, although the reaction in conventional batch macro reactors requires over-cooling because of insufficient heat removal. The yields were low at low temperatures and short residence times, because of incomplete I-Li exchange reaction. Low yields were also observed in the high-temperature/long-residence-time region, probably because of the decomposition of aryllithium intermediates **2a**. In the case of **4b** ($R = i\text{-Pr}$), a similar reaction profile was observed, although the high-yield region became smaller. The reaction of **4c** also exhibited a similar profile. The ridge shifted to a lower temperature and shorter residence time region, because of faster decomposition of organolithium compounds **2c**. More astounding is the observation that methyl benzoates (**3d**) can be obtained in good yields ($> 80\%$) from **4d**, although the high-yield region was very small presumably because steric hindrance of the methoxycarbonyl group is small.

These results clearly show that the stability of the aryllithium compounds decreases in the order of **2a** > **2b** > **2c** > **2d**. The present temperature-residence time profile is quite effective at unveiling the features of the I-Li exchange reaction and stability of the resulting aryllithium intermediate. In addition, it is important to note that the I-Li exchange reaction followed by reaction with an electrophile can be successfully carried out without significant decomposition of the aryllithium intermediate **2** by optimizing temperature and residence time even in case of methyl ester.

Under the optimized conditions, the reactions of **2a-d** with other electrophiles, such as iodomethane, methyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, and benzaldehyde, were examined. As shown in Table 3, the reactions took place successfully and the corresponding products were obtained in good yields. For the generation of *p*-*tert*-butoxycarbonyl-substituted aryllithium compound, arylbromide **1a** can be used as a precursor and desired product was also obtained in good yields. It is interesting that iodomethane can be used as an electrophile for the reactions of **4a**, whereas methyl triflate should be used for the reactions of **4b-d**. The reaction of the aryllithium with iodomethane is slow, and therefore only the more sterically demanding *tert*-butoxycarbonyl groups can survive until the reaction is complete. However, methyl

triflate is more reactive, and therefore can trap less stable aryllithium compounds before they decompose.

Table 3. The optimized I-Li exchange reaction of alkyl *p*-iodobenzoates **4** followed by reaction with electrophiles.^a

Ester	Electrophile	Product	Yield (%) ^b	Ester	Electrophile	Product	Yield (%) ^b
R= <i>t</i> -Bu : 4a	<i>t</i> -BuOH		85 (88) ^c	R=Et : 4c	EtOH		84
	MeI		74 (81) ^c		MeI		25
	Me ₃ SiCl		87 (87) ^c		MeOTf		77
	PhCHO		67 ^d		MeI		67
R= <i>i</i> -Pr : 4b	<i>i</i> -PrOH		89	R=Me : 4d	MeOH		80
	MeI		38		MeOTf		81
	MeOTf		82		Me ₃ SiCl		81
	Me ₃ SiCl		74		PhCHO		80
R= <i>i</i> -Pr : 4b	PhCHO		79	R=Me : 4d	PhCHO		80

^a For **4a**, *T* = 0 °C; **4b**, *T* = -48 °C; **4c**, *T* = -58 °C; **4d**, *T* = -78 °C; *t*^R was 0.01 s in all cases.

^b Determined by GC. ^c *tert*-butyl *p*-bromobenzene (**1a**) and *s*-BuLi were used. ^d Isolated yield.

Generation and reactions of alkyl *m*-lithiobenzoates by Br-Li exchange

Next, we examined the Br-Li exchange reactions of alkyl *m*-bromobenzoates **5**. Reactions in a conventional batch macro reactor were carried out and the results are summarized in Table 4. Reactions of **5a** (R = *t*-Bu) at -78 °C gave the desired product in 40% yield, presumably because of partial decomposition of **6a**. The use of **5b** (R = *i*-Pr) caused a significant decrease in the yield of the product (**3b**). Moreover, in the case of **5c** (R = Et) and **5d** (R = Me), the yields of the desired products were negligibly low.

Table 4. The Br-Li exchange reaction of alkyl *m*-bromobenzoates **5** followed by the reaction with alcohols in a batch reactor

<i>m</i> -Bromobenzoates 5	Conversion of 5 (%)	Yield of 3 (%) ^a
R = <i>tert</i> -butyl: 5a	96	40
R = isopropyl: 5b	80	5
R = ethyl: 5c	73	trace
R = methyl: 5d	56	0

^a Determined by GC

Next, the reactions were conducted in the flow microreactor. The results are summarized in Figure 5, in which the yield of **3** is plotted against the temperature and t^R as a contour map with scattered overlay. In the case of **5a** (R = *t*-Bu), the desired product was obtained in high yields over a wide range of residence times and temperatures. In the case of **5b** (R = *i*-Pr), the yields were much lower. This is presumably because the isopropyl group is less sterically demanding than the *tert*-butyl group. Therefore, it was difficult to generate *m*-isopropoxycarbonyl-substituted aryllithium compounds by Br-Li exchange reaction without decomposition even in a flow microreactor system as the case of *para*-substituted one.

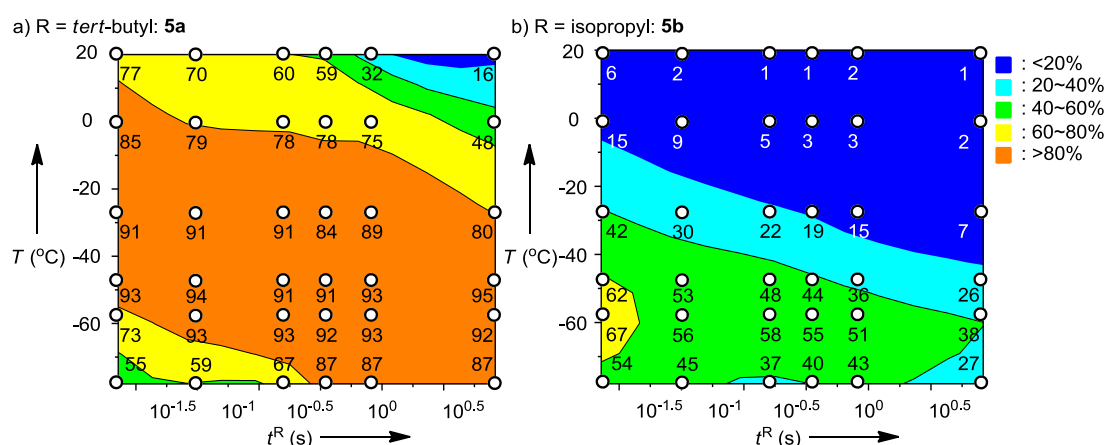


Figure 5. Effects of temperature and residence time on the yield in the Br-Li exchange reaction of a) *tert*-butyl *m*-bromobenzoates (**5a**) and b) isopropyl *m*-bromobenzoates (**5b**) with *s*-BuLi in the flow microreactor system.

Generation and reactions of alkyl *m*-lithiobenzoates by I-Li exchange

Next, we examined the I-Li exchange reaction of alkyl *m*-iodobenzoates **7** to generate the corresponding *m*-alkoxycarbonyl-substituted aryllithiums **6**. Before using a flow microreactor system, the reaction in a batch macro reactor was examined and the results are summarized in Table 5.

The reaction of **7a** proceeded at -78 °C to give **3a** in 78% yield. These results indicate that iodobenzoates are more effective than bromobenzoates as precursors of aryllithium compounds. However, in the case of **7b**, the yield of the desired product was very low. In case of ethyl or methyl iodobenzoates (**7c** and **7d**), the desired products were obtained only in trace amounts.

Table 5. The I-Li exchange reaction of alkyl *m*-iodobenzoates **7** followed by the reaction with alcohols in a batch macro reactor

<i>m</i> -Iodobenzoates 7	Conversion of 7 (%)	Yield of 3 (%) ^a
R = <i>tert</i> -butyl: 7a	100	78
R = isopropyl: 7b	100	12
R = ethyl: 7c	98	trace
R = methyl: 7d	54	trace

^a Determined by GC

Next, we examined the reactions in a flow microreactor system. As shown in Figure 6, in the case of **7a** (R = *t*-Bu), the corresponding product **3a** was obtained in high yields (>80%) for a wide range of temperatures and residence times. In the case of **7b** (R = *i*-Pr), a similar reaction profile was observed, although the high-yield region became smaller. The reaction of **7c** also exhibited a similar profile, though the ridge shifted to a lower temperature and shorter residence time region because of faster decomposition of organolithium compounds **6c**. Methyl benzoates (**3d**) can be obtained in good yields (> 80%) from **7d**, although the high-yield region was very small.

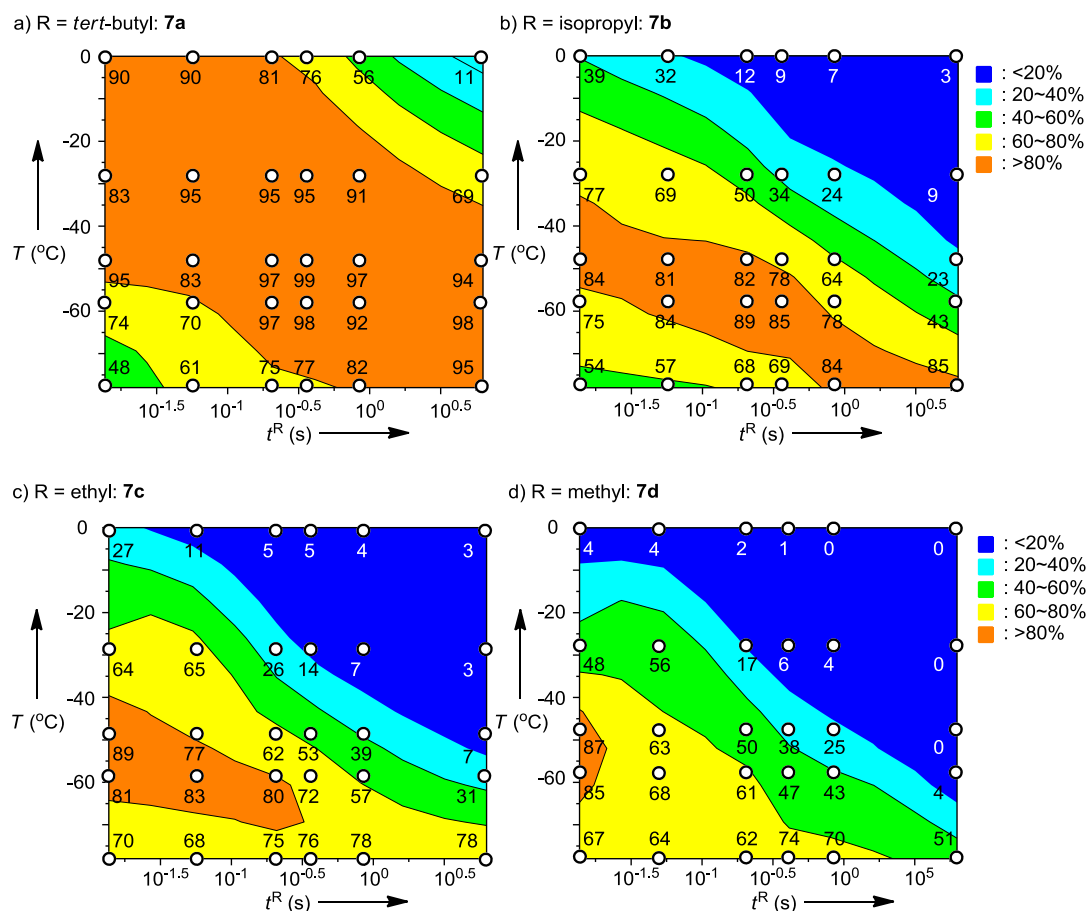


Figure 6. Effects of temperature and residence time on the yield in the Br-Li exchange reaction of a) *tert*-butyl *m*-iodobenzoates (**7a**), b) isopropyl *m*-iodobenzoates (**7b**), c) ethyl *m*-iodobenzoates (**7c**) and d) methyl *m*-iodobenzoates (**7d**) with PhLi in the flow microreactor system.

These results clearly show that the stability of the aryllithium compounds decreases in the order of **6a** ($R = t\text{-Bu}$) > **6b** ($R = i\text{-Pr}$) > **6c** ($R = \text{Et}$) > **6d** ($R = \text{Me}$). It is also noteworthy that the comparison between Figures 4 and 2 revealed that *m*-lithiobenzoates and *p*-lithiobenzoates have similar stability.

Under the optimized conditions, the reactions of **6a-d** with other electrophiles were examined. As shown in Table 6, the reactions took place successfully and the corresponding products were obtained in good yields.

Table 6. The optimized I-Li exchange reaction of alkyl *m*-iodobenzoates **7** followed by reaction with electrophiles.^a

Ester	Electrophile	Product	Yield (%) ^b	Ester	Electrophile	Product	Yield (%) ^b
R= <i>t</i> -Bu : 7a	<i>t</i> -BuOH		90	R=Et : 7c	EtOH		81
	MeI		78		MeI		21
	Me ₃ SiCl		94		MeOTf		78
	PhCHO		90		Me ₃ SiOTf		74
R= <i>i</i> -Pr : 7b	<i>i</i> -PrOH		84	R=Me : 7d	PhCHO		72 ^c
	MeI		34		MeOH		85
	MeOTf		75		MeOTf		79
	Me ₃ SiCl		78		Me ₃ SiOTf		87
	PhCHO		67		PhCHO		81 ^c

^a For **7a**, *T* = 0 °C; **7b**, *T* = -48 °C; **7c**, *T* = -58 °C; **7d**, *T* = -78 °C; *t*^R was 0.01 s in all cases.^b Determined by GC. ^c Isolated yield.

Conclusion

Generation of *m*- and *p*-alkoxycarbonyl-substituted aryllithium compounds followed by reaction with electrophiles has been accomplished by using a flow microreactor system consisting of micromixers and microtube reactors by virtue of precise residence time control and temperature control. Sterically less-demanding ethoxycarbonyl and methoxycarbonyl groups can survive by choosing appropriate conditions. The present method enables not only the generation of a variety of *tert*-butoxycarbonyl-substituted aryllithiums at much higher temperatures than those required for conventional macrobatch reactors but also the generation of less stable isopropoxycarbonyl-, ethoxycarbonyl-, and methoxycarbonyl-substituted aryllithiums, which are practically impossible to achieve by using conventional batch macro reactors. Therefore, the present method serves as a straightforward and powerful method for introducing substituents into the benzene ring of alkyl benzoates without protecting the alkoxycarbonyl group. The observations illustrated here open a new possibility of organic synthesis via unstable functionalized organolithiums.

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; initial oven temperature, 50 °C; rate of temperature increase, 10 °C min⁻¹). ¹H and ¹³C NMR spectra were recorded on Varian MERCURY plus-400 (¹H 400 MHz, ¹³C 100 MHz) spectrometer with Me₄Si or CDCl₃ as a standard in CDCl₃ unless otherwise noted. EI mass spectra were recorded on JMS-SX102A spectrometer. THF and Et₂O 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. All materials were obtained from commercial supplier and used without purification unless otherwise noted. *tert*-Butyl *p*-bromobenzoate (**1a**), isopropyl *p*-bromobenzoate (**1b**), *tert*-butyl *m*-bromobenzoate (**5a**), isopropyl *m*-bromobenzoate (**5b**) were prepared according to the literature.³ *tert*-Butyl *p*-iodobenzoate (**4a**), isopropyl *p*-iodobenzoate (**4b**), *tert*-butyl *m*-iodobenzoate (**7a**), isopropyl *m*-iodobenzoate (**7b**) were prepared according to the literature.⁴ The flow microreactor system was identical with that which was used in chapter 1.

The Br-Li Exchange Reaction of Alkyl Bromobenzoates Followed by Reaction with Alcohols Using a Batch Reactor. A solution of *s*-BuLi (0.42 M, 0.75 mL) in hexane/cyclohexane (19/31 v/v) was added dropwise to a solution of an alkyl bromobenzoate (0.10 M, 3.0 mL) in THF in a 20 mL round bottom glass flask for 1 min at -78 °C. The mixture was stirred for 10 min, and a solution of the corresponding alcohol (0.60 M, 1.5 mL) in THF was added. After stirring for 10 min, a cooling bath was removed. The mixture was analyzed by GC.

The Br-Li Exchange Reaction of Alkyl Bromobenzoates Followed by Reaction with Alcohols Using Flow Microreactor Systems. A flow microreactor system consisting of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2) was used. A solution of an alkyl *p*- or *m*-bromobenzoate (0.10 M) in THF (flow rate: 6.0 mL min⁻¹) and a solution of *s*-BuLi (0.42 M) in hexane/cyclohexane (19/31 v/v; flow rate: 1.5 mL min⁻¹) were introduced to M1 ($\phi = 250\ \mu\text{m}$) by syringe pumps. The resulting solution was passed through R1 and was mixed with a solution of alcohol (0.60 M) in THF (flow rate: 3.0 mL min⁻¹) in M2 ($\phi = 250\ \mu\text{m}$). The resulting solution was passed through R2 ($\phi = 1000\ \mu\text{m}$, $L = 50\ \text{cm}$). After a steady state was reached, the product solution was collected for 30 s while being quenched with sat. NH₄Cl aq. solution. The reaction mixture was analyzed by GC. The results are summarized in Table 7 and 8.

Table 7. The Br-Li exchange reaction of *tert*-butyl *p*-bromobenzoate (**1a**) and isopropyl *p*-bromobenzoate (**1b**) followed by reaction with alcohols in flow microreactor systems

ϕ in R1 (μm)	L in R1 (cm)	t^{R} (s)	T ($^{\circ}\text{C}$)	Conv. ^a (%)	Yield ^a (%)	Conv. ^b (%)	Yield ^b (%)
250	3.5	0.014	0	100	88	82	19
500	3.5	0.055		100	91	87	11
1000	3.5	0.22		100	90	88	5
1000	6.0	0.38		100	88	88	3
1000	12.5	0.79		100	86	93	3
1000	100	6.3		100	71	97	0
250	3.5	0.014	-28	100	97	78	47
500	3.5	0.055		100	90	84	31
1000	3.5	0.22		100	94	89	20
1000	6.0	0.38		100	94	94	21
1000	12.5	0.79		100	95	92	12
1000	100	6.3		100	92	95	5
250	3.5	0.014	-48	92	81	57	30
500	3.5	0.055		96	87	59	25
1000	3.5	0.22		100	98	62	29
1000	6.0	0.38		100	97	87	29
1000	12.5	0.79		100	98	84	25
1000	100	6.3		100	95	93	11
250	3.5	0.014	-58	69	62	51	31
500	3.5	0.055		76	67	73	31
1000	3.5	0.22		100	97	81	28
1000	6.0	0.38		100	99	88	29
1000	12.5	0.79		100	98	94	22
1000	100	6.3		100	97	91	23
250	3.5	0.014	-78	59	50	45	29
500	3.5	0.055		65	54	54	28
1000	3.5	0.22		67	60	59	28
1000	6.0	0.38		81	76	56	33
1000	12.5	0.79		100	94	64	30
1000	100	6.3		100	98	94	21

^a *tert*-Butyl *p*-bromobenzoate (**1a**) was used as a substrate. ^b Isopropyl *p*-bromobenzoate (**1b**) was used as a substrate.

Table 8. The Br-Li exchange reaction of *tert*-butyl *m*-bromobenzoate (**5a**) and isopropyl *m*-bromobenzoate (**5b**) followed by reaction with alcohols in flow microreactor systems

ϕ in R1 (μm)	L in R1 (cm)	t^{R} (s)	T ($^{\circ}\text{C}$)	Conv. ^a (%)	Yield ^a (%)	Conv. ^b (%)	Yield ^b (%)
250	3.5	0.014	0	97	85	84	15
500	3.5	0.055		98	79	97	9
1000	3.5	0.22		99	78	90	5
1000	6.0	0.38		99	78	90	3
1000	12.5	0.79		99	75	92	3
1000	100	6.3		99	48	91	2
250	3.5	0.014	-28	99	91	91	42
500	3.5	0.055		99	91	93	30
1000	3.5	0.22		99	91	95	22
1000	6.0	0.38		98	84	97	19
1000	12.5	0.79		99	89	98	15
1000	100	6.3		99	80	99	7
250	3.5	0.014	-48	97	93	93	62
500	3.5	0.055		99	94	94	53
1000	3.5	0.22		99	91	98	48
1000	6.0	0.38		99	91	99	44
1000	12.5	0.79		99	93	99	36
1000	100	6.3		99	95	99	26
250	3.5	0.014	-58	83	73	91	67
500	3.5	0.055		85	93	85	56
1000	3.5	0.22		98	93	97	58
1000	6.0	0.38		98	92	98	55
1000	12.5	0.79		99	93	99	51
1000	100	6.3		99	92	99	38
250	3.5	0.014	-78	61	55	65	54
500	3.5	0.055		69	59	63	45
1000	3.5	0.22		77	67	65	37
1000	6.0	0.38		98	87	70	40
1000	12.5	0.79		98	87	78	43
1000	100	6.3		95	87	85	27

^a *tert*-Butyl *m*-bromobenzoate (**5a**) was used as a substrate. ^b Isopropyl *m*-bromobenzoate (**5b**) was used as a substrate.

The I-Li Exchange Reaction of Alkyl Iodobenzoates Followed by Reaction with Alcohols Using a Batch Reactor. A solution of PhLi (0.42 M, 0.75 mL) in Et₂O/cyclohexane (72/28 v/v) was added dropwise to a solution of an alkyl iodobenzoate (0.10 M, 3.0 mL) in THF in a 20 mL round bottom glass flask for 1 min at -78 °C. The mixture was stirred for 10 min, and a solution of the corresponding alcohol (0.60 M, 1.5 mL) in THF was added. After stirring for 10 min, a cooling bath was removed. The mixture was analyzed by GC.

The I-Li Exchange Reaction of Alkyl Iodobenzoates Followed by Reaction with Alcohols Using Flow Microreactor Systems. A flow microreactor system consisting of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2) was used. A solution of an alkyl *p*- or *m*-iodobenzoate (0.10 M) in THF (flow rate: 6.0 mL min⁻¹) and a solution of PhLi (0.42 M) in Et₂O/cyclohexane (28/72 v/v; flow rate: 1.5 mL min⁻¹) were introduced to M1 (ϕ = 250 μ m) by syringe pumps. The resulting solution was passed through R1 and was mixed with a solution of alcohol (0.60 M) in THF (flow rate: 3.0 mL min⁻¹) in M2 (ϕ = 250 μ m). The resulting solution was passed through R2 (ϕ = 1000 μ m, L = 50 cm). After a steady state was reached, the product solution was collected for 30 s while being quenched with sat. NH₄Cl aqueous solution. The reaction mixture was analyzed by GC. The results are summarized in Table 9, 10, 11 and 12.

Table 9. The I-Li exchange reaction of *tert*-butyl *p*-iodobenzoate (**4a**) and isopropyl *p*-iodobenzoate (**4b**) followed by reaction with alcohols in flow microreactor systems

ϕ in R1 (μm)	L in R1 (cm)	t^{R} (s)	T ($^{\circ}\text{C}$)	Conv. ^a (%)	Yield ^a (%)	Conv. ^b (%)	Yield ^b (%)
250	3.5	0.014	0	96	85	95	40
500	3.5	0.055		93	82	93	28
1000	3.5	0.22		97	76	97	11
1000	6.0	0.38		97	66	97	8
1000	12.5	0.79		97	53	89	7
1000	100	6.3		98	7	100	2
250	3.5	0.014	-28	96	94	92	78
500	3.5	0.055		97	95	94	69
1000	3.5	0.22		97	95	96	51
1000	6.0	0.38		97	94	97	37
1000	12.5	0.79		97	90	100	27
1000	100	6.3		98	74	100	8
250	3.5	0.014	-48	93	91	92	89
500	3.5	0.055		94	92	90	85
1000	3.5	0.22		94	93	91	83
1000	6.0	0.38		95	92	93	80
1000	12.5	0.79		94	93	96	73
1000	100	6.3		96	89	100	27
250	3.5	0.014	-58	93	92	93	93
500	3.5	0.055		91	90	96	94
1000	3.5	0.22		94	93	97	94
1000	6.0	0.38		92	90	97	92
1000	12.5	0.79		95	93	97	88
1000	100	6.3		95	92	98	55
250	3.5	0.014	-78	81	77	79	77
500	3.5	0.055		84	60	73	71
1000	3.5	0.22		69	67	69	66
1000	6.0	0.38		65	72	77	74
1000	12.5	0.79		86	76	84	80
1000	100	6.3		84	84	95	89

^a *tert*-Butyl *p*-iodobenzoate (**4a**) was used as a substrate. ^b Isopropyl *p*-iodobenzoate (**4b**) was used as a substrate.

Table 10. The I-Li exchange reaction of ethyl *p*-iodobenzoate (**4c**) and methyl *p*-iodobenzoate (**4d**) followed by reaction with alcohols in flow microreactor systems

ϕ in R1 (μm)	L in R1 (cm)	t^{R} (s)	T ($^{\circ}\text{C}$)	Conv. ^a (%)	Yield ^a (%)	Conv. ^b (%)	Yield ^b (%)
250	3.5	0.014	0	98	19	89	10
500	3.5	0.055		100	8	93	7
1000	3.5	0.22		97	4	100	5
1000	6.0	0.38		100	3	95	4
1000	12.5	0.79		100	2	100	4
1000	100	6.3		100	0	88	5
250	3.5	0.014	-28	98	75	97	56
500	3.5	0.055		100	65	100	45
1000	3.5	0.22		100	28	100	11
1000	6.0	0.38		100	12	100	8
1000	12.5	0.79		100	6	100	5
1000	100	6.3		100	3	100	3
250	3.5	0.014	-48	98	92	95	78
500	3.5	0.055		98	90	94	64
1000	3.5	0.22		100	79	100	61
1000	6.0	0.38		100	72	100	46
1000	12.5	0.79		100	55	100	16
1000	100	6.3		100	7	100	4
250	3.5	0.014	-58	97	94	91	81
500	3.5	0.055		97	91	79	68
1000	3.5	0.22		96	85	92	64
1000	6.0	0.38		96	79	90	53
1000	12.5	0.79		100	79	100	47
1000	100	6.3		100	22	100	7
250	3.5	0.014	-78	69	66	84	80
500	3.5	0.055		71	69	72	67
1000	3.5	0.22		74	70	70	63
1000	6.0	0.38		73	70	71	64
1000	12.5	0.79		82	76	87	67
1000	100	6.3		96	76	93	55

^a Ethyl *p*-iodobenzoate (**4c**) was used as a substrate. ^b Methyl *p*-iodobenzoate (**4d**) was used as a substrate.

Table 11. The I-Li exchange reaction of *tert*-butyl *m*-iodobenzoate (**7a**) and isopropyl *m*-iodobenzoate (**7b**) followed by reaction with alcohols in flow microreactor systems

ϕ in R1 (μm)	L in R1 (cm)	t^{R} (s)	T ($^{\circ}\text{C}$)	Conv. ^a (%)	Yield ^a (%)	Conv. ^b (%)	Yield ^b (%)
250	3.5	0.014	0	95	90	95	39
500	3.5	0.055		96	90	97	22
1000	3.5	0.22		100	81	100	12
1000	6.0	0.38		100	76	100	9
1000	12.5	0.79		100	56	100	7
1000	100	6.3		100	11	100	3
250	3.5	0.014	-28	85	83	93	77
500	3.5	0.055		97	95	97	69
1000	3.5	0.22		100	95	100	50
1000	6.0	0.38		100	95	100	34
1000	12.5	0.79		100	91	100	24
1000	100	6.3		100	69	100	9
250	3.5	0.014	-48	95	95	87	84
500	3.5	0.055		84	83	90	81
1000	3.5	0.22		100	97	98	82
1000	6.0	0.38		100	99	98	78
1000	12.5	0.79		100	97	100	64
1000	100	6.3		100	94	100	23
250	3.5	0.014	-58	76	74	79	75
500	3.5	0.055		71	70	87	84
1000	3.5	0.22		100	97	95	89
1000	6.0	0.38		100	98	95	85
1000	12.5	0.79		100	92	96	78
1000	100	6.3		100	98	100	43
250	3.5	0.014	-78	65	63	55	54
500	3.5	0.055		64	61	58	57
1000	3.5	0.22		76	75	69	68
1000	6.0	0.38		80	77	71	69
1000	12.5	0.79		84	82	84	84
1000	100	6.3		95	95	94	85

^a *tert*-Butyl *m*-iodobenzoate (**7a**) was used as a substrate. ^b Isopropyl *m*-iodobenzoate (**7a**) was used as a substrate.

Table 12. The I-Li exchange reaction of ethyl *m*-iodobenzoate (**7c**) and methyl *m*-iodobenzoate (**7d**) followed by reaction with alcohols in flow microreactor systems

ϕ in R1 (μm)	L in R1 (cm)	t^{R} (s)	T ($^{\circ}\text{C}$)	Conv. ^a (%)	Yield ^a (%)	Conv. ^b (%)	Yield ^b (%)
250	3.5	0.014	0	97	27	99	5
500	3.5	0.055		98	11	97	4
1000	3.5	0.22		95	5	100	2
1000	6.0	0.38		97	5	100	1
1000	12.5	0.79		97	4	80	0
1000	100	6.3		97	3	100	0
250	3.5	0.014	-28	96	64	100	48
500	3.5	0.055		99	65	99	53
1000	3.5	0.22		99	26	100	17
1000	6.0	0.38		98	14	100	6
1000	12.5	0.79		98	7	100	4
1000	100	6.3		97	3	100	0
250	3.5	0.014	-48	94	89	97	87
500	3.5	0.055		96	77	97	63
1000	3.5	0.22		94	62	99	50
1000	6.0	0.38		97	53	99	38
1000	12.5	0.79		99	39	99	25
1000	100	6.3		99	7	100	5
250	3.5	0.014	-58	86	81	93	85
500	3.5	0.055		90	81	100	68
1000	3.5	0.22		96	80	96	61
1000	6.0	0.38		97	72	99	47
1000	12.5	0.79		99	57	99	43
1000	100	6.3		99	31	100	13
250	3.5	0.014	-78	72	70	83	67
500	3.5	0.055		69	68	81	64
1000	3.5	0.22		72	75	79	62
1000	6.0	0.38		81	76	88	74
1000	12.5	0.79		84	78	84	70
1000	100	6.3		99	78	100	51

^a Ethyl *m*-iodobenzoate (**7c**) was used as a substrate. ^b Methyl *m*-iodobenzoate (**7d**) was used as a substrate.

The Br-Li Exchange Reaction of Iodobenzoates Followed by Reaction with Electrophiles Using Microflow Systems. A flow microreactor system consisting of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2) was used. A solution of an alkyl *p*- or *m*-iodobenzoate (0.10 M) in THF (flow rate: 6.0 mL min⁻¹) and a solution of PhLi (0.42 M) in Et₂O/cyclohexane (28/72 v/v; flow rate: 1.5 mL min⁻¹) were introduced to M1 (ϕ = 250 μ m) by syringe pumps. The resulting solution was passed through R1 (ϕ = 250 μ m, L = 3.5 cm, t^R = 0.014 s) and was mixed with a solution of electrophile (0.60 M) in THF (Et₂O in case of methyl triflate and trimethylsilyl triflate; flow rate: 3.0 mL min⁻¹) in M2 (ϕ = 250 μ m). The resulting solution was passed through R2 (ϕ = 1000 μ m, L = 50 cm). After a steady state was reached, the product solution was collected for 30 s while being quenched with sat. NH₄Cl aqueous solution. The reaction mixture was analyzed by GC.

The reactions were carried out at 0 °C for **4a** and **7a**; -48 °C for **4b** and **7b**; -58 °C for **4c**, **7c** and **7d**.; -78 °C for **4d**.

***tert*-Butyl *p*-methylbenzoate.** 74% yield (GC ^tR 17.2 min) from **4a** and iodomethane. The spectral data were identical to those reported in the literature.⁵

***tert*-Butyl *p*-trimethylsilylbenzoate.** 87% yield (GC ^tR 20.4 min) from **4a** and chlorotrimethylsilane. The spectral data were identical to those reported in the literature.⁶

***tert*-Butyl *p*-(hydroxy(phenyl)methyl)benzoate.** 67% isolated yield from **4a** and benzaldehyde. After extraction, the crude product was purified by chromatography (hexane/ethyl acetate=3/1): The spectral data were identical to those reported in the literature.⁷

Isopropyl *p*-methylbenzoate. 38% yield (GC ^tR 16.7 min) from **4b** and iodomethane. 82% yield from **4b** and methyl triflate. The spectral data were identical to those reported in the literature.⁸

Isopropyl *p*-trimethylsilylbenzoate. 74% yield (GC ^tR 19.9 min) from **4b** and chlorotrimethylsilane. After extraction, the crude product was purified by chromatography (hexane/ethyl acetate=30/1): ¹H NMR (400 MHz, CDCl₃) δ 0.27 (s, 9H), 1.37 (d, J = 6.4 Hz, 6H), 5.25 (sept, J = 6.4 Hz, 1H), 7.58 (d, J = 7.6 Hz, 2H), 7.99 ppm (d, J = 7.2 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ -1.38, 21.9, 68.1, 128.4, 131.0,

133.1, 146.4, 166.2 ppm; HRMS (EI) m/z calcd for $C_{13}H_{20}O_2Si$ (M^+): 236.1233, found: 236.1236.

Isopropyl *p*-(hydroxy(phenyl)methyl)benzoate. 79% yield (GC t_R 27.6 min) from **4b** and benzaldehyde. After extraction, the crude product was purified by chromatography (hexane/ethyl acetate = 3:1): 1H NMR (400 MHz, $CDCl_3$) δ 1.35 (d, J = 6.4 Hz, 6H), 2.25 (d, J = 3.6 Hz, 1H), 5.24 (sept, J = 6.2 Hz, 1H), 5.89 (d, J = 3.6 Hz, 1H), 7.28-7.38 (m, 5H), 7.47 (d, J = 8.0 Hz, 2H), 8.01 ppm (d, J = 8.8 Hz 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 68.2, 75.2, 126.0, 126.3, 127.3, 128.2, 129.2, 129.3, 143.2, 148.8, 165.9 ppm; HRMS (EI) m/z calcd for $C_{17}H_{18}O_3$ (M^+): 270.1256, found: 270.1253.

Ethyl *p*-methylbenzoate. 25% yield (GC t_R 16.2 min) from **4c** and iodomethane. 77% from **4c** and methyl triflate.

Ethyl *p*-trimethylsilylbenzoate. 67% yield (GC t_R 19.6 min) from **4c** and chlorotrimethylsilane. 88% yield from **4c** and trimethylsilyl triflate. The spectral data were identical to those reported in the literature.⁹

Ethyl *p*-(hydroxy(phenyl)methyl)benzoate. 81% yield (GC t_R 27.4 min) from **4c** and benzaldehyde. The spectral data were identical to those reported in the literature.¹⁰

Methyl *p*-methylbenzoate. 81% yield (GC t_R 14.8 min) from **4d** and methyl triflate.

Methyl *p*-trimethylsilylbenzoate. 81% yield (GC t_R 18.4 min) from **4d** and trimethylsilyl triflate. The spectral data were identical to those reported in the literature.⁶

Methyl *p*-(hydroxy(phenyl)methyl)benzoate. 80% yield (GC t_R 26.2 min) from **4d** and benzaldehyde. The spectral data were identical to those reported in the literature.¹¹

***tert*-Butyl *m*-methylbenzoate.** 78% yield (GC t_R 17.1 min) from **7a** and iodomethane. After extraction, the crude product was purified by chromatography (hexane/ethyl acetate = 20:1): 1H NMR (400 MHz, $CDCl_3$) δ 1.59 (s, 9H), 2.39 (s, 3H), 7.26-7.38 (m, 2H), 7.77-7.83 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 28.2, 80.8, 126.5, 128.0, 129.9, 131.9, 133.1, 137.9, 165.9 ppm; HRMS (EI) m/z calcd for $C_{12}H_{16}O_2$ (M^+): 192.1150, found: 192.1149.

***tert*-Butyl *m*-trimethylsilylbenzoate.** 94% yield (GC t_R 19.7 min) from **7a** and chlorotrimethylsilane. After extraction, the crude product was purified by chromatography (hexane/ethyl acetate = 50:1): ^1H NMR (400 MHz, CDCl_3) δ 0.28 (s, 9H), 1.59 (s, 9H), 7.39 (td, $J = 7.6, 0.5$ Hz, 1H), 7.66 (dt, $J = 7.2, 1.3$ Hz, 1H), 7.92-7.97 (m, 1H), 8.13-8.16 ppm (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ -1.25, 28.2, 80.8, 127.5, 129.7, 131.1, 134.2, 137.3, 140.7, 166.1 ppm; HRMS (EI) m/z calcd for $\text{C}_{14}\text{H}_{22}\text{O}_2\text{Si}$ (M^+): 250.1389, found: 250.1394.

***tert*-Butyl *m*-(hydroxy(phenyl)methyl)benzoate.** 90% yield (GC t_R 26.9 min) from **7a** and benzaldehyde. After extraction, the crude product was purified by chromatography (hexane/ethyl acetate = 3:1): ^1H NMR (400 MHz, CDCl_3) δ 1.58 (s, 9H), 2.31 (s, 1H), 5.89 (s, 1H), 7.24-7.42 (m, 6H), 7.51-7.58 (m, 1H), 7.89 (d, $J = 7.6$ Hz, 1H), 8.00-8.04 ppm (m, 1H); ^{13}C NMR (100 MHz, CDCl_3 , Some of the ^{13}C NMR signals were the same places.) δ 28.1, 75.9, 81.1, 126.5, 127.4, 127.7, 128.3, 128.6, 130.5, 132.1, 143.4, 144.0, 165.6 ppm; HRMS (EI) m/z calcd for $\text{C}_{18}\text{H}_{20}\text{O}_3$ (M^+): 284.1412, found: 284.1412.

Isopropyl *m*-methylbenzoate. 34% yield (GC t_R 16.5 min) from **7b** and iodomethane. 75% yield from **7b** and methyl triflate. After extraction, the crude product was purified by chromatography (hexane/ethyl acetate = 20:1): ^1H NMR (400 MHz, CDCl_3) δ 1.37 (d, $J = 6.4$ Hz, 6H), 2.40 (s, 3H), 5.25 (sept, $J = 6.2$ Hz, 1H), 7.27-7.39 (m, 2H), 7.80-7.87 ppm (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.4, 22.1, 68.2, 126.5, 128.0, 129.8, 130.6, 133.3, 137.8, 166.0 ppm; HRMS (EI) m/z calcd for $\text{C}_{11}\text{H}_{14}\text{O}_2$ (M^+): 178.0994, found: 178.0996.

Isopropyl *m*-trimethylsilylbenzoate. 78% yield (GC t_R 19.3 min) from **7b** and chlorotrimethylsilane. After extraction, the crude product was purified by chromatography (hexane/ethyl acetate = 50:1): ^1H NMR (400 MHz, CDCl_3) δ 0.29 (s, 9H), 1.37 (d, $J = 6.8$ Hz, 6H), 5.26 (sept, $J = 6.2$ Hz, 1H), 7.41 (t, $J = 7.6$ Hz, 1H), 7.68-7.72 (m, 1H), 7.98-8.04 (m, 1H), 8.16-8.20 ppm (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ -1.25, 21.9, 68.2, 127.6, 129.8, 130.1, 134.2, 137.6, 140.8, 166.4 ppm; HRMS (EI) m/z calcd for $\text{C}_{13}\text{H}_{20}\text{O}_2\text{Si}$ (M^+): 236.1233, found: 236.1237.

Isopropyl *m*-(hydroxy(phenyl)methyl)benzoate. 67% yield (GC t_R 26.6 min) from **7b** and benzaldehyde. After extraction, the crude product was purified by chromatography (hexane/ethyl acetate = 3:1): ^1H NMR (400 MHz, CDCl_3) δ 1.36 (d, $J = 6.0$ Hz, 6H),

2.26 (d, $J = 3.6$ Hz, 1H), 5.24 (sept, $J = 6.3$ Hz, 1H), 5.91 (d, $J = 3.2$ Hz, 1H), 7.24-7.46 (m, 6H), 7.54-7.58 (m, 1H), 7.84 (dt, $J = 8.0, 1.6$ Hz, 1H), 8.07-8.13 ppm (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.7, 68.4, 75.4, 126.4, 127.4, 127.4, 128.2, 128.3, 128.3, 130.6, 130.7, 143.4, 144.2, 166.0 ppm; HRMS (EI) m/z calcd for $\text{C}_{17}\text{H}_{18}\text{O}_3$ (M^+): 270.1256, found: 270.1260.

Ethyl *m*-methylbenzoate. 21% yield (GC t_R 16.0 min) from **7c** and iodomethane. 78% yield from **7c** and methyl triflate.

Ethyl *m*-trimethylsilylbenzoate. 74% yield (GC t_R 19.1 min) from **7c** and trimethylsilyl triflate. The spectral data were identical to those reported in the literature.⁹

Ethyl *m*-(hydroxy(phenyl)methyl)benzoate. 72% isolated yield from **7b** and benzaldehyde. After extraction, the crude product was purified by chromatography (hexane/ethyl acetate = 3:1): ^1H NMR (400 MHz, CDCl_3) δ 1.37 (t, $J = 7.0$ Hz, 3H), 2.63 (s, 1H), 4.34 (q, $J = 7.2$ Hz, 2H), 5.85 (s, 1H), 7.23-7.29 (m, 1H), 7.29-7.41 (m, 5H), 7.55 (d, $J = 7.6$ Hz, 1H), 7.92 (dt, $J = 7.6, 1.2$ Hz, 1H), 8.07 ppm (t, $J = 1.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.3, 61.0, 75.8, 126.5, 127.5, 127.8, 128.5, 128.6, 128.6, 130.6, 130.8, 143.4, 144.1, 166.5 ppm; HRMS (EI) m/z calcd for $\text{C}_{16}\text{H}_{16}\text{O}_3$ (M^+): 256.1099, found: 256.1100.

Methyl *m*-methylbenzoate. 79% yield (GC t_R 14.8 min) from **7d** and methyl trifluoromethanesulfonate.

Methyl *m*-trimethylsilylbenzoate: 87% yield (GC t_R 18.1 min) from **7d** and trimethylsilyl triflate. The spectral data were identical to those reported in the literature.¹²

Methyl *m*-(hydroxy(phenyl)methyl)benzoate: 81% isolated yield from **7d** and benzaldehyde. After extraction, the crude product was purified by chromatography (hexane/ethyl acetate = 3:1): ^1H NMR (400 MHz, CDCl_3) δ 2.42 (d, $J = 3.2$ Hz, 1H), 3.89 (s, 3H), 5.88 (d, $J = 3.2$ Hz, 1H), 7.24-7.43 (m, 6H), 7.55-7.61 (m, 1H), 7.93 (dt, $J = 7.6, 1.4$ Hz, 1H), 8.07-8.11 ppm (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 52.1, 75.9, 126.5, 127.5, 127.8, 128.6, 128.6, 128.7, 130.3, 130.9, 143.4, 144.2, 167.0 ppm; HRMS (EI) m/z calcd for $\text{C}_{15}\text{H}_{14}\text{O}_3$ (M^+): 242.0943, found: 242.0941.

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Chapter 3

Flow Microreactor Synthesis via Cyano-Substituted Aryllithiums: Multistep Transformations

Abstract

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

Introduction

Organometallic compounds bearing a cyano group is very important because the activating effect of the cyano group such as the *ortho*-directing effect and its transformation into various other functional groups are advantageous from a synthetic point of view.¹ To generate the cyano-substituted organometallic compounds such as arylmetallics, halogen–metal exchange reactions involving halogen–Mg,² halogen–Cu³ and halogen–Zn⁴ have been extensively investigated, as they allow conventional access to functionalized arylmetallics; such reactions are often essential in the use of aryl iodides. Because of the high reactivity of halogen–Li exchange reactions, their application in the generation of functionalized aryllithiums enables the use of aryl bromide.

The remarkable pioneer work of Parham et al. has shown that various aryl- or heteroaryllithium compounds bearing a cyano group can be prepared by a Br–Li exchange reaction.⁵ However, it has been reported that the Br–Li exchange reaction of bromobenzonitrile and *n*-BuLi requires extremely low temperature such as -100 °C to obtain satisfactory yields. The work of Zajak *et al.*⁶ has shown that two major pathways could occur at the initial stage of the Br–Li exchange reaction of bromobenzonitriles at relatively high temperatures. One is the nucleophilic addition of generated lithiobenzonitrile to a cyano group of substrate (bromobenzonitrile), and the other is deprotonation of substrate with lithiobenzonitrile. It is revealed that the reaction could be conducted at a little bit higher temperatures (*c.a.* -70 °C) if the reverse addition (addition of bromobenzonitrile to *n*-BuLi) was employed.

Results and Discussions

This study focused on Br–Li exchange reactions of bromobenzonitriles. Lithiation of bromobenzonitriles followed by reaction with electrophiles in a conventional batch macro reactor requires very low temperatures, in the range of -70 to -100 °C, to avoid unwanted reactions at the cyano group as mentioned above.⁵ To confirm this we examined the Br–Li exchange reactions of the bromobenzonitriles such as *o*-bromobenzonitrile (**1a**), *m*-bromobenzonitrile (**1b**) and *p*-bromobenzonitrile (**1c**) using a conventional batch macro reactor and the results are shown in Table 1. The Br–Li exchange reaction with **1a** followed by protonation at -78 °C gave benzonitrile (**3**) in high yield. The reactions of *m*- and *p*-bromobenzonitrile (**1b** and **1c**) were not as

effective as that of **1a** (61% and 68%, respectively). At 0 °C, however, the reactions of **1** afforded **3** in very poor yields (Table 1). These results are in agreement with the results reported in the literature.

Table 1. Br-Li exchange reaction of bromobenzonitrile **1** in conventional batch reactor.

Bromobenzonitrile 1	T (°C)	Conversion of 1 (%)	Yield of 3 (%) ^a
<i>ortho</i> :-: 1a	-78	97	86
	0	100	3
<i>meta</i> :-: 1b	-78	90	61
	0	94	6
<i>para</i> :-: 1c	-78	90	68
	0	99	8

^a Determined by GC.

We then examined the Br-Li exchange reaction of *o*-, *m*- and *p*-bromobenzonitriles and sequential reactions with methanol using flow microreactor consisting of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2) as shown in Figure 1. The reactions were carried out with varying residence times (t^R) in R1, and varying reaction temperature (T) in the flow microreactor system.

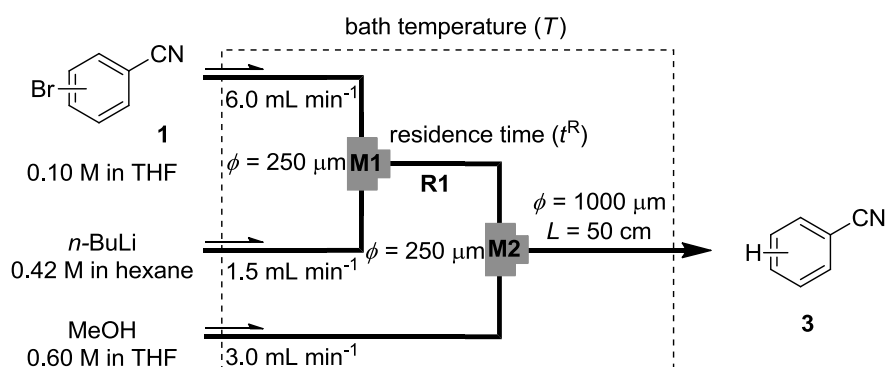


Figure 1. A microreactor system for the Br-Li exchange reaction of benzonitriles **1** followed by reaction with MeOH.

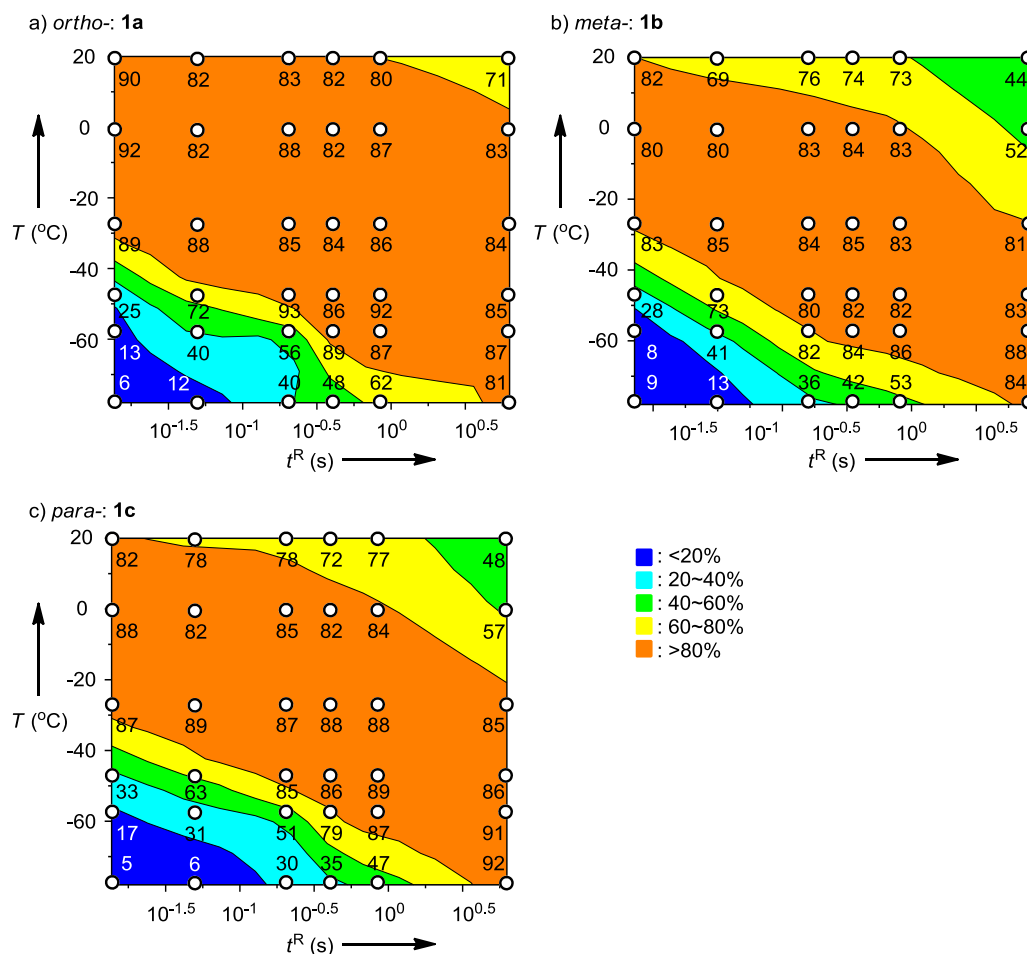
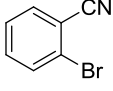
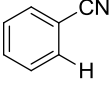
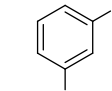
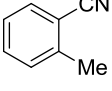
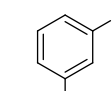
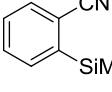
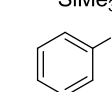
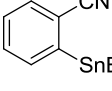
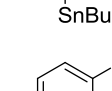
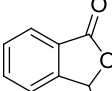
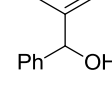
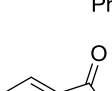
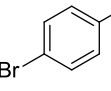
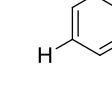
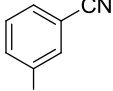
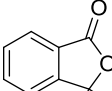
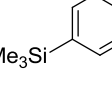
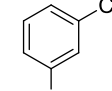
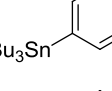
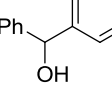


Figure 2. Effect of the temperature and the residence time on the yield of **3** in the Br-Li exchange reaction of a) *o*-bromobenzonitrile (**1a**), b) *m*-bromobenzonitrile (**1b**), c) *p*-bromobenzonitrile (**1c**) in flow microreactor systems.

As shown in Figure 2, the yield depended on both the temperature and the residence time. With a short residence time the reaction of **1a**, **1b** and **1c** gave **3** in high yields even at 20 $^{\circ}\text{C}$ (**1a**: 90%, **1b**: 82%, **1c**: 82%). An increase in the residence time caused a decrease in the yield probably because the nucleophilic attack on the cyano group. Figure 2 also shows that the stabilities of *m*-lithiobenzonitrile (**2b**) and *p*-lithiobenzonitrile (**2c**) are similar. In contrast, the stability of *o*-lithiobenzonitrile (**2a**) is higher than that of **2b** and **2c** because of the *ortho*-directing effect of the cyano group.

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

Table 2. The Br-Li exchange reaction of bromobenzonitrile **1** followed by reaction with an electrophile under the optimized conditions.^a

Nitrile	Electrophile	Product	Yield (%) ^b	Nitrile	Electrophile	Product	Yield (%) ^b
 1a	MeOH		90	 1b	MeI		81
	MeI		93		Me ₃ SiCl		96
	Me ₃ SiCl		90		Bu ₃ SnCl		95
	Bu ₃ SnCl		85		PhCHO		81
	PhCHO		92		MeOH		88
	<i>n</i> -HexCHO		81 ^c	 1c	MeI		90
 1b	PhCHO		94 ^c		Me ₃ SiCl		85
	MeOH		80		Bu ₃ SnCl		93
					PhCHO		87

^a For **1a**, T = 20 °C; for **1b** and **1c**, T = 0 °C; in all case t^R = 0.01 s.^b Determined by GC. ^c Isolated yield.

The integration of chemical reactions is of significant research interest because combining reactions avoids the isolation of intermediate products. The easy modulation of flow microreactor systems is advantageous for the integration of chemical reactions. To demonstrate the utility of the present flow microreactor method, sequential reactions were conducted using an integrated flow microreactor system. As shown in Table 2, the reaction of carbonyl compounds with **2a** gave lactone derivatives (cyclization products) after cyclization of the nitrile group with alkoxy lithium followed by hydrolysis. We

hypothesized that sequential protecting reactions of alkoxy lithium compounds generated by reaction of carbonyl compounds with **2a** could be achieved by the addition of an electrophile. The integrated flow microreactor system consisted of three T-shaped micromixers (M1, M2 and M3) and three microtube reactors (R1, R2 and R3) shown in Figure 3 was used.

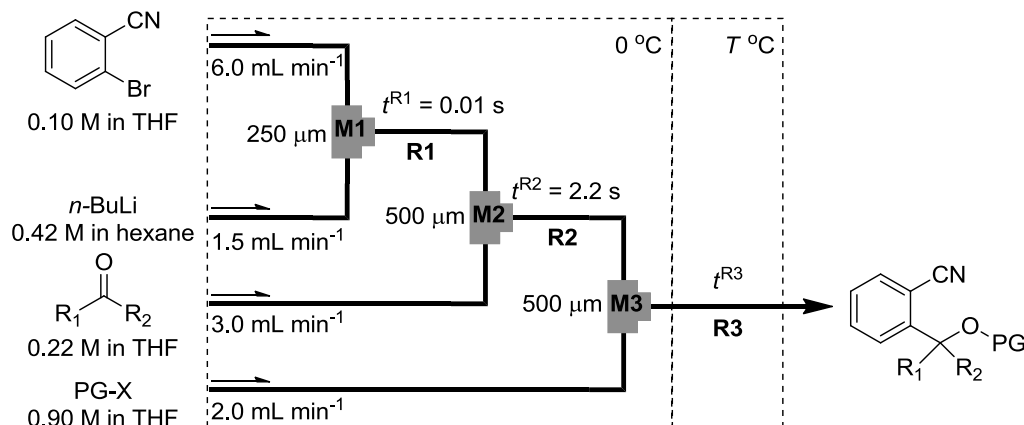
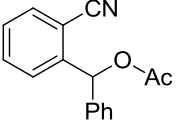
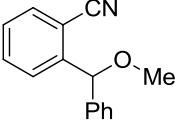
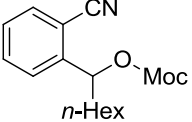
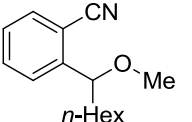
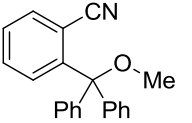


Figure 3. A flow microreactor system for the generation of *o*-lithiobenzonitriles and reaction with carbonyl compounds followed by the protection.

Table 3. Generation of *o*-lithiobenzonitriles and reaction with carbonyl compounds followed by the protection.

RCOR'	PG-X	<i>T</i> (°C)	<i>t</i> ^{R3} (s)	Product	Yield (%) ^a
PhCHO	AcCl	0	1.9		97
	Me ₂ SO ₄ ^b	50	97		83
<i>n</i> -HexCHO	MeO ₂ CCl	0	1.9		75
	Me ₂ SO ₄ ^b	50	97		51
Ph ₂ CO	Me ₂ SO ₄ ^b	50	97		66

^a Isolated yield. ^b 3 eq of HMPA was added to a solution of Me₂SO₄ as an additive.

The sequential transformations were successfully achieved to give the corresponding products in good yields as shown in Table 3. In case of the reactions with acetyl chloride and methyl chlorocarbonate, the reactions were fast even at 0 °C and the desired products were obtained in high yields within 2 s of residence time in R3. In case of methylation using dimethyl sulfate, the reaction was relatively slow. Although higher temperature (50 °C), longer residence time (97 s) and an additive (HMPA) were necessary for the full conversion, the desired compounds were also obtained in good yields.

Conclusions

We have developed an effective method for the generation and reactions of cyano-substituted aryllithium using a flow microreactor system based on a short residence time, fast mixing, and efficient temperature control. In addition, sequential transformations were achieved using an integrated flow microreactor system; the generation and reactions of *o*-lithiobenzonitrile followed by trapping reactions with electrophiles. The method provides a new dimension in functionalized organolithium chemistry.

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; initial oven temperature, 50 °C; rate of temperature increase, 10 °C min⁻¹). ¹H and ¹³C NMR spectra were recorded on Varian MERCURY plus-400 (¹H 400 MHz, ¹³C 100 MHz) spectrometer with Me₄Si or CDCl₃ as a standard in CDCl₃ unless otherwise noted. EI mass spectra were recorded on JMS-SX102A spectrometer. THF and Et₂O 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. All materials were obtained from commercial supplier and used without purification unless otherwise noted. The flow microreactor system was identical with that which was used in chapter 1.

The Br-Li Exchange Reaction of Bromobenzonitriles Followed by Reaction with MeOH Using a Batch Reactor. A solution of *n*-BuLi (0.42 M, 0.75 mL) in hexane was added dropwise to a solution of a bromobenzonitrile (0.10 M, 3.0 mL) in THF in a 20 mL round bottom glass flask for 1 min at -78 °C. The mixture was stirred for 10 min, and a solution of the MeOH (0.60 M, 1.5 mL) in THF was added. After stirring for 10 min, a cooling bath was removed. The mixture was analyzed by GC.

The Br-Li Exchange Reaction of Bromobenzonitriles Followed by Reaction with MeOH Using Flow Microreactor Systems. A flow microreactor system consisting of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2) was used. A solution of a bromobenzonitrile (0.10 M) in THF (flow rate: 6.0 mL min⁻¹) and a solution of *n*-BuLi (0.42 M) in hexane (flow rate: 1.5 mL min⁻¹) were introduced to M1 ($\phi = 250\ \mu\text{m}$) by syringe pumps. The resulting solution was passed through R1 and was mixed with a solution of MeOH (0.60 M) in THF (flow rate: 3.0 mL min⁻¹) in M2 ($\phi = 500\ \mu\text{m}$). The resulting solution was passed through R2 ($\phi = 1000\ \mu\text{m}$, $L = 50\ \text{cm}$). After a steady state was reached, the product solution was collected for 30 s while being quenched with H₂O. The reaction mixture was analyzed by GC. The results are summarized in Table 4.

Table 4. The Br-Li exchange reaction of bromobenzonitrile **1** followed by reaction with MeOH in flow microreactor systems.

ϕ of R1 (μm)	L of R1 (cm)	t^{R} (s)	T ($^{\circ}\text{C}$)	Conv. ^a (%)	Yield ^a (%)	Conv. ^b (%)	Yield ^b (%)	Conv. ^c (%)	Yield ^c (%)
250	3.5	0.014	20	100	90	100	80	100	82
500	3.5	0.055		100	82	100	75	100	78
1000	3.5	0.22		100	83	100	76	100	78
1000	6.0	0.38		100	82	100	74	100	72
1000	12.5	0.79		100	80	100	73	100	77
1000	100	6.3		100	71	100	44	100	41
250	3.5	0.014	0	100	91	100	80	100	88
500	3.5	0.055		100	87	100	80	100	82
1000	3.5	0.22		100	86	100	83	100	85
1000	6.0	0.38		100	87	100	84	100	82
1000	12.5	0.79		100	87	100	83	100	84
1000	100	6.3		100	83	100	52	100	48
250	3.5	0.014	-28	100	89	100	83	100	87
500	3.5	0.055		100	88	100	85	100	89
1000	3.5	0.22		100	85	100	84	100	87
1000	6.0	0.38		100	84	100	85	100	88
1000	12.5	0.79		100	86	100	83	100	88
1000	100	6.3		100	84	100	81	100	85
250	3.5	0.014	-48	26	25	47	28	50	33
500	3.5	0.055		74	72	93	73	84	63
1000	3.5	0.22		94	93	100	80	100	85
1000	6.0	0.38		100	86	100	82	100	86
1000	12.5	0.79		100	92	100	82	100	89
1000	100	6.3		100	85	100	83	100	86
250	3.5	0.014	-58	13	13	17	8	34	17
500	3.5	0.055		43	40	67	41	54	37
1000	3.5	0.22		60	56	98	82	68	51
1000	6.0	0.38		100	89	100	84	95	79
1000	12.5	0.79		100	87	100	86	100	87
1000	100	6.3		100	87	100	88	100	91
250	3.5	0.014	-78	6	6	7	3	7	2
500	3.5	0.055		12	12	26	19	38	27
1000	3.5	0.22		49	40	44	36	45	30
1000	6.0	0.38		56	48	51	42	50	41
1000	12.5	0.79		74	62	76	67	73	61
1000	100	6.3		100	81	100	84	100	92

^a *o*-Bromobenzonitrile (**1a**) was used as a substrate. ^b *m*-Bromobenzonitrile (**1b**) was used as a substrate. ^c *p*-Bromobenzonitrile (**1c**) was used as a substrate.

The Br-Li Exchange Reaction of Bromobenzonitriles Followed by Reaction with Electrophiles Using Microflow Systems. A flow microreactor system consisting of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2) was used. A solution of a bromobenzonitrile (0.10 M) in THF (flow rate: 6.0 mL min⁻¹) and a solution of *n*-BuLi (0.42 M) in hexane (flow rate: 1.5 mL min⁻¹) were introduced to M1 (ϕ = 250 μ m) by syringe pumps. The resulting solution was passed through R1 (ϕ = 250 μ m, L = 3.5 cm, t^R = 0.014 s) and was mixed with a solution of electrophile (0.60 M) in THF (flow rate: 3.0 mL min⁻¹) in M2 (ϕ = 500 μ m). The resulting solution was passed through R2 (ϕ = 1000 μ m, L = 50 cm). After a steady state was reached, the product solution was collected for 30 s while being quenched with H₂O (or 1 M HCl aqueous solution when carbonyl compound was used as an electrophile). The reaction mixture was analyzed by GC. The reactions were carried out at 20 °C when **1a** was used as a substrate, or 0 °C for **1b** and **1c**.

2-Trimethylsilylbenzonitrile. 90% yield (GC t^R 15.8 min) from **1a** and chlorotrimethylsilane. The spectral data were identical to those reported in the literature.⁶

2-Tributylstannylbenzonitrile. 85% yield (GC t^R 26.7 min) from **1a** and chlorotributylstannane. The spectral data were identical to those reported in the literature.⁷

2-Methylbenzonitrile. 93% yield (GC t^R 11.8 min) from **1a** and methyl iodide.

3-Phenylphthalide. 98% yield (GC t^R 24.2 min) from **1a** and benzaldehyde. The spectral data were identical to those reported in the literature.⁸

3-Hexylphthalide. 81% isolated yield from **1a** and *n*-heptanal. After extraction, the crude product was purified by silica gel chromatography (hexane/ethyl acetate = 5:1) to afford 52.9 mg of product. The spectral data were identical to those reported in the literature.⁸

3,3-Diphenyl-1(3*H*)-isobenzofuranone. 94% isolated yield from **1a** and benzophenone. After extraction, the crude product was purified by silica gel chromatography (hexane/ethyl acetate = 3:1) to afford 81.3 mg of the product. The spectral data were identical to those reported in the literature.⁹

3-Trimethylsilylbenzonitrile. 96% yield (GC t_R 16.3 min) from **1b** and chlorotrimethylsilane. After extraction, the crude product was purified by silica gel chromatography (hexane/ethyl acetate = 50:1): 1H NMR (400 MHz, $CDCl_3$) δ 0.28 (s, 9H), 7.41-7.46 (m, 1H), 7.59-7.64 (m, 1H), 7.69-7.74 (m, 1H), 7.75-7.79 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -1.8, 111.7, 118.8, 128.0, 131.8, 136.5, 137.1, 142.1 ppm; HRMS (EI) m/z calcd for $C_{10}H_{13}NSi$: 175.0817, found: 175.0817.

3-Tributylstannylbenzonitrile. 95% yield (GC t_R 27.8 min) from **1b** and chlorotributylstannane. After extraction, the crude product was purified by silica gel chromatography (hexane/ethyl acetate = 20:1): 1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 7.4 Hz, 9H), 0.98-1.18 (m, 6H), 1.32 (sext, J = 7.3 Hz, 6H), 1.40-1.62 (m, 6H), 7.34-7.42 (m, 1H), 7.53-7.78 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.5, 13.4, 27.1, 28.8, 112.0, 119.1, 127.9, 131.2, 139.4, 140.3, 143.9 ppm; HRMS (EI) m/z calcd for $C_{19}H_{31}NSn$: 393.1478, found: 393.1479.

3-Methylbenzonitrile. 81% yield (GC t_R 12.2 min) from **1b** and methyl iodide.

3-(Hydroxyphenylmethyl)-benzonitrile. 81% yield (GC t_R 24.6 min) from **1b** and benzaldehyde. The spectral data were identical to those reported in the literature.¹⁰

4-Trimethylsilylbenzonitrile. 85% yield (GC t_R 16.4 min) from **1c** and chlorotrimethylsilane. The spectral data were identical to those reported in the literature.¹¹

4-Tributylstannylbenzonitrile. 93% yield (GC t_R 28.3 min) from **1c** and chlorotributylstannane. The spectral data were identical to those reported in the literature.¹²

4-Methylbenzonitrile. 90% yield (GC t_R 12.5 min) from **1c** and methyl iodide.

4-(Hydroxyphenylmethyl)-benzonitrile. 93% yield (GC t_R 24.7 min) from **1c** and benzaldehyde. The spectral data were identical to those reported in the literature.¹³

The Br-Li Exchange Reaction of *o*-Bromobenzonitrile and Reactions with Carbonyl Compounds Followed by Protection. A flow microreactor system consisting of three T-shaped micromixers (M1, M2 and M3) and three microtube reactors (R1, R2 and R3) was used. A solution of *o*-bromobenzonitrile (0.10 M) in THF (flow rate: 6.0 mL min⁻¹) and a solution of *n*-BuLi (0.42 M) in hexane (flow rate: 1.5 mL min⁻¹) were introduced to M1 (ϕ = 250 μ m) by syringe pumps. The resulting solution was passed through R1 (ϕ = 250 μ m, L = 3.5 cm, t^R = 0.014 s) and was mixed with a solution of carbonyl compound (0.22 M) in THF (flow rate: 3.0 mL min⁻¹) in M2 (ϕ = 500 μ m). The resulting solution was passed through R2 (ϕ = 1000 μ m, L = 50 cm) and was mixed a solution of electrophile (0.90 M) in THF (flow rate: 2.0 mL min⁻¹) in M3 (ϕ = 500 μ m). The resulting solution was passed through R3. After a steady state was reached, the product solution was collected for 30 s while being quenched with H₂O. The microtube reactor R3 (ϕ = 1000 μ m, L = 50 cm) was used for the reaction with acetyl chloride or methyl chlorocarbonate as an electrophile. For the reaction with dimethyl sulfate (with 3 eq of HMPA), longer microtube reactor R3 (ϕ = 1000 μ m, L = 2560 cm (50 cm at 0 °C, 10 cm at ambient temperature, and 2500 cm at 50 °C)) was used for the full conversion.

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

2-(Methoxy(phenyl)methyl)benzonitrile. 93% isolated yield from benzaldehyde and dimethyl sulfate. After extraction, the crude product was purified by silica gel chromatography (hexane/ethyl acetate = 10:1) to afford 62.7 mg of the product: ¹H NMR (400 MHz, CDCl₃) δ 3.43 (s, 3H), 5.64 (s, 1H), 7.26-7.39 (m 4H), 7.42-7.46 (m, 2H), 7.55-7.65 ppm (m, 3H); ¹³C NMR (100MHz, CDCl₃) δ 57.3, 82.6, 111.3, 117.7, 126.9, 127.0, 127.9, 128.1, 128.6, 132.8, 133.1, 139.8, 146.0 ppm; HRMS (EI) m/z calcd for C₁₅H₁₃NO: 223.0997, found: 223.1002.

1-(2-Cyanophenyl)heptyl ethyl carbonate. 75% isolated yield from *n*-heptanal and methyl chlorocarbonate. After extraction, the crude product was purified by silica gel

chromatography (hexane/ethyl acetate = 5:1) to afford 62.1 mg of the product: ^1H NMR (400 MHz, CDCl_3) δ 0.87 (t, J = 6.8 Hz, 3H), 1.20-1.38 (m, 7H), 1.38-1.50 (m, 1H), 1.79-1.90 (m, 1H), 1.93-2.05 (m, 1H), 3.76 (s, 3H), 5.84-5.90 (m, 1H), 7.40 (td, J = 7.8, 1.2 Hz, 1H), 7.50-7.55 (m, 1H), 7.57-7.63 (m, 1H), 7.63-7.67 ppm (m, 1H); ^{13}C NMR (100MHz, CDCl_3) δ 13.9, 22.4, 25.1, 28.7, 31.5, 36.1, 54.9, 77.6, 110.9, 117.0, 126.3, 128.3, 132.8, 133.1, 144.3, 154.9 ppm; HRMS (EI) m/z calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_3$: 275.1521, found: 275.1524.

2-(1-Methoxyheptyl)benzonitrile. 51% isolated yield from *n*-heptanal and dimethyl sulfate. After extraction, the crude product was purified by silica gel chromatography (hexane/ethyl acetate = 10:1) to afford 35.4 mg of the product: ^1H NMR (400 MHz, CDCl_3) δ 0.86 (t, J = 6.8 Hz, 3H), 1.20-1.38 (m, 7H), 1.38-1.50 (m, 1H), 1.62-1.73 (m, 1H), 1.73-1.85 (m, 1H), 4.52-4.58 (m, 1H), 7.37 (td, J = 7.5, 1.6 Hz, 1H), 7.52-7.58 (m, 1H), 7.58-7.68 ppm (m, 2H); ^{13}C NMR (100MHz, CDCl_3) δ 14.0, 22.5, 25.5, 29.0, 31.7, 37.8, 57.1, 81.4, 111.4, 117.4, 126.6, 127.8, 132.7, 133.1, 146.9 ppm; HRMS (FAB) m/z calcd for $\text{C}_{15}\text{H}_{22}\text{NO}$: 232.1701, found: 232.1697.

2-(Methoxydiphenylmethyl)benzonitrile: 66% isolated yield from benzophenone and dimethyl sulfate. After extraction, the crude product was purified by silica gel chromatography (hexane/ethyl acetate = 10:1) to afford 59.6 mg of the product: ^1H NMR (400 MHz, CDCl_3) δ 3.10 (s, 3H), 7.28-7.39 (m, 7H), 7.45-7.51 (m, 5H), 7.63-7.67 ppm (m, 2H); ^{13}C NMR (100MHz, CDCl_3) δ 52.2, 87.0, 111.7, 118.8, 127.2, 127.7, 128.0, 129.1, 129.3, 131.8, 135.5, 141.1, 148.9 ppm; HRMS (EI) m/z calcd for $\text{C}_{21}\text{H}_{17}\text{NO}$: 299.1310, found: 299.1313.

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Chapter 4

Flow Microreactor Synthesis via Nitro-Substituted

Aryllithiums:

Switch between Kinetic and Thermodynamic Control

Abstract

We developed a flow microreactor method for the generation and reactions of aryllithiums bearing a nitro group. The flow microreactor method enabled the selective use of either the kinetically or the thermodynamically preferred intermediate. This transformation via a nitro-substituted aryllithium reagent would serve as an alternative straightforward route for the synthesis of Macbecin I.

Introduction

The synthetic importance of nitro compounds has ensured longstanding studies of their utilization in organic synthesis.¹ The activating effect of the nitro group is exploited in carrying out many organic reactions and its facile transformation into various functional groups has broadened the utility of nitro compounds in the synthesis of complex molecules.² Such advantages can boost the usefulness of organometallic compounds bearing a nitro group.³

However, use of nitro compounds in organic synthesis has been very limited, presumably because of their incompatibility with various nucleophilic and electrophilic reagents.⁴ In fact, a nitro group reacts with organometallic compounds such as organolithium reagents and Grignard reagents very quickly.⁵ For example, in case of Bartoli's indole synthesis, the nitro group reacts with vinylmagnesium bromide at -40 °C even in the presence of bromine atom.^{5a} Moreover, the reaction of arylmagnesium compounds and the nitroarenes serves as an effective route for the preparative synthesis of diarylamines.⁶

For these reasons, only scarce examples of the transformation via nitro-substituted arylmagnesium and aryllithium compounds have been reported. The generation of aryllithium and arylmagnesium compounds bearing a nitro group at the *ortho*-position can be conducted at low temperatures (generally -100 °C for Li and -40 °C for Mg).⁷ For these type of transformations, the *ortho* relationship between the carbon-metal bond and the nitro group is known to be essential for a selective halogen-metal exchange reaction.⁸ Actually, all attempts for the generation of *m*- or *p*-nitro substituted aryllithium and arylmagnesium compounds and their reactions with electrophiles failed. For example, the addition of PhMgCl to *m*- or *p*-iodonitrobenzene did not lead to any exchange product, but instead led only to reduction of the nitro group.⁸ Therefore, there is no general method to prepare all three isomers (*ortho*, *meta* and *para*) of lithiated or magnesiated nitroarenes.

Results and Discussions

At first, we examined the halogen-lithium exchange reactions of *p*-nitro-substituted halobenzenes with various commercial available organolithiums such as *s*-BuLi, *n*-BuLi, MeLi and PhLi using a conventional batch macro reactor.

Table 1. The I-Li exchange reaction of *p*-halonitrobenzenes **1** followed by reaction with MeOH in a conventional batch macro reactor.

X	RLi	Conversion of 1 (%)	Yield of 3 (%) ^a	
Br	<i>s</i> -BuLi	51	0	
	<i>n</i> -BuLi	63	0	
	MeLi	47	0	
	PhLi	44	0	
I	<i>s</i> -BuLi	36	11	
	<i>n</i> -BuLi	55	22	
	MeLi	77	23	
	PhLi	83	39	

^a Determined by GC.

The exchange reaction of *p*-bromonitrobenzene at -78 °C, followed by quenching with an alcohol, did not give the desired product **3** at all. This result can be attributed to the selective nucleophilic attack to the nitro group (reduction) by an added organolithium reagent as reported in the literature. When PhLi was used for this reaction, large amount of phenol (> 50%) was detected as a by-product. The use of *p*-iodonitrobenzene as the starting material, however, resulted in a formation of desired product though the yield was very low. In addition, we found that PhLi is quite effective for selective halogen-lithium exchange of halonitrobenzenes, presumably because of the low nucleophilicity of PhLi to the nitro group, whereas the use of *s*-BuLi, *n*-BuLi and MeLi gave rise to lower conversions of the starting material and lower yields of the product.

Next, the reaction was conducted in a flow microreactor system consisting of T-shaped micromixers (M1 and M2) and microtube reactors (R1 and R2) as shown in Figure 1. *o*-Iodonitrobenzene (**1a**), *m*-iodonitrobenzene (**1b**) and *p*-iodonitrobenzene (**1c**) were used and the reactions were conducted with varying temperatures (*T*) and the residence time (*t*^R) in R1.

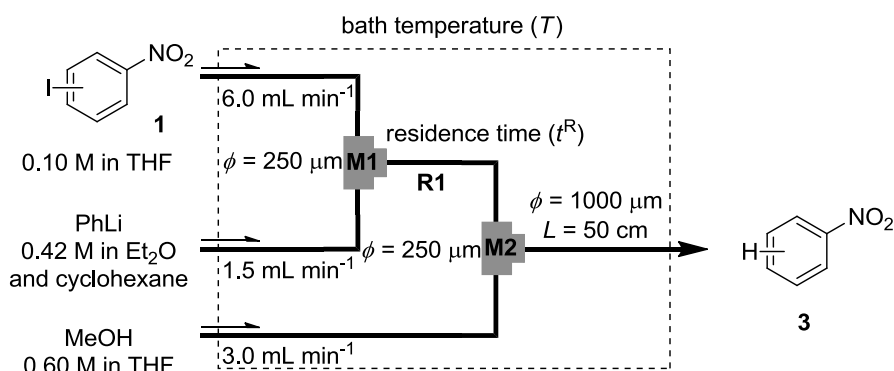


Figure 1. A microreactor system for the I-Li exchange reaction of iodonitrobenzenes **1** followed by reaction with MeOH.

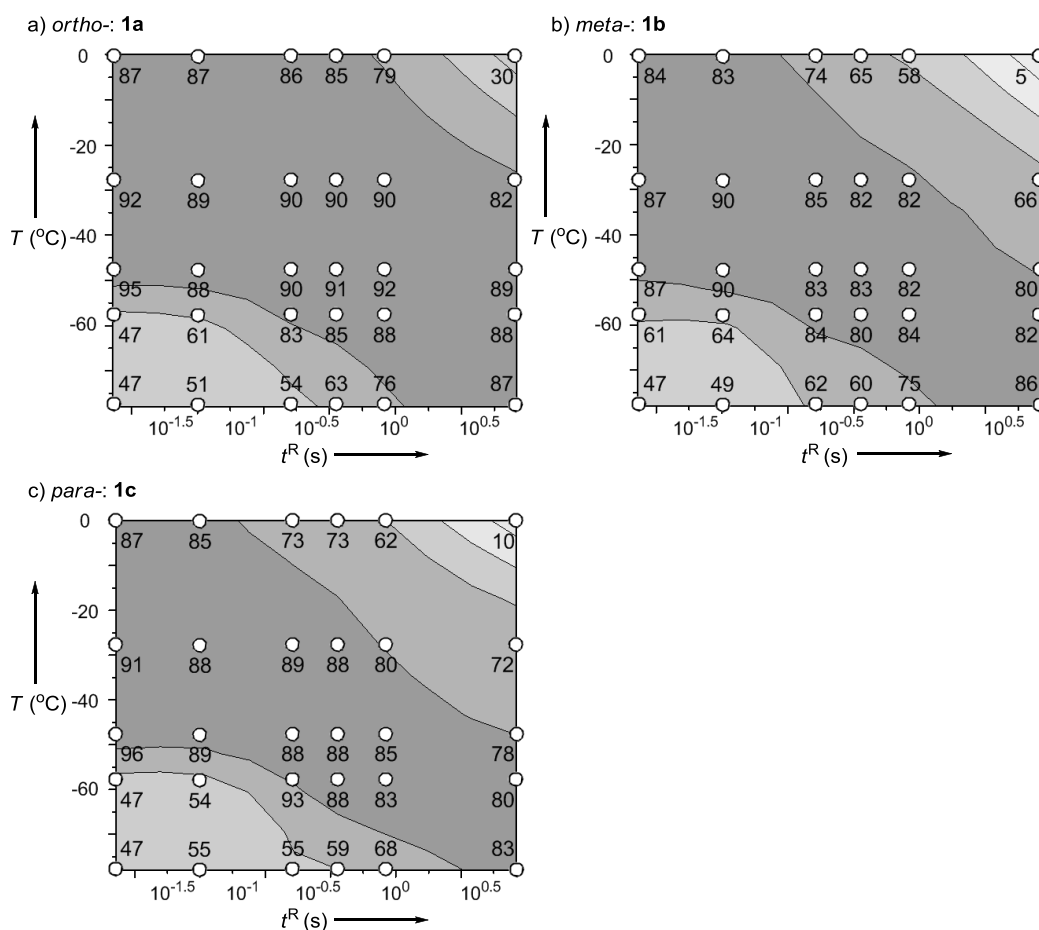


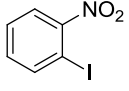
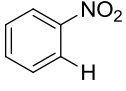
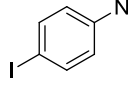
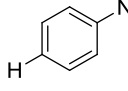
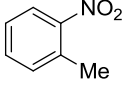
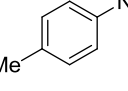
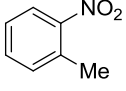
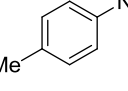
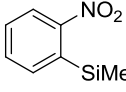
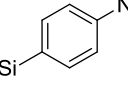
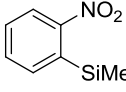
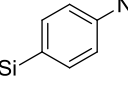
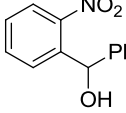
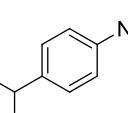
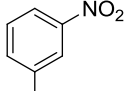
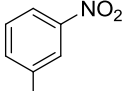
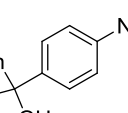
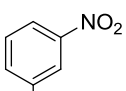
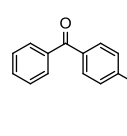
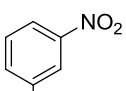
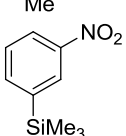
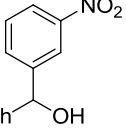
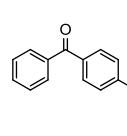
Figure 2. Effects of the reaction temperature and residence time on the yield of nitrobenzene (**3**) in the I-Li exchange reaction of a) *o*-iodonitrobenzene (**1a**), b) *m*-iodonitrobenzene (**1b**), and c) *p*-iodonitrobenzene (**1c**) with PhLi in the flow microreactor system.

Figure 2 summarizes the results obtained with varying the temperature and residence time. Irrespective of the substitution pattern, the products were obtained in high yields even at 0 °C by choosing an appropriate residence time. This result demonstrates a significant advantage of a flow microreactor system over a conventional batch macro system, which requires much lower temperatures (yield of **3**: 70% from **1a**, 43% from **1b**, 39% from **1c** at -78 °C). The yield obtained with the flow microreactor system decreased with an increase in t^R , presumably because of decomposition of the nitrophenyllithiums. These results show that shorter residence time is required at higher temperatures to get the products in good yields. The higher stability of *o*-nitrophenyllithium (**2a**) than those of *m*- and *p*-nitrophenyllithiums (**2b** and **2c**), respectively is also noteworthy. This is presumably because of the chelation effect. Slightly better yields were observed when the reactions were conducted at -28 °C.

Under the optimized conditions, reactions with various electrophiles were conducted using flow microreactor systems (Table 2). In case of the reactions with iodomethane, the longer reaction time was necessary for the full conversion. For example, if the residence time in R2 was relatively short (2.2 s) in the reaction of *p*-nitro-substituted aryllithium (**2c**) and iodomethane at -28 °C, the desired product was obtained in lower yield (31%) and a large amount of nitrobenzene (31%) derived from unreacted nitro-substituted aryllithium was detected (Table 4 of Experimental Section). It seems that strong electron-withdrawing ability of nitro group make the reactivity of aryllithiums low. When the residence time in R2 was increased to 4.5 s, the generated aryllithium compounds seems to be almost consumed (2% of nitrobenzene was detected) and the yield of the desired product was enhanced, however, it is still low (45%), presumably because of a partial decomposition of generated aryllithium species. Moreover, in case of *o*-nitro-substituted aryllithium (**2a**), the reaction with iodomethane was slower than **2c**, (6% of desired product and 72% of nitrobenzene at the same condition; $T = -28$ °C, $t^R = 4.5$ s), because of *o*-chelation effect as well as electron-withdrawing ability of nitro group. This problem can be solved by using more reactive electrophiles.

The reactions with methyl triflate, trimethylsilyl triflate, benzaldehyde and benzophenone were successfully achieved and the products were obtained in high yields. Moreover, functionalized ketones such as 4-nitrobenzophenone and 4-(dimethylamino)-benzophenone could be used in this reaction, and desired carbinol compounds were successfully obtained in high yields.

Table 2. The I-Li exchange reaction of iodonitrobenzenes **1** followed by reaction with electrophiles.^a

Nitro	Electrophile	Product	Yield (%) ^b	Nitro	Electrophile	Product	Yield (%) ^b
 1a	MeOH		87	 1c	MeOH		91
	MeI		36		MeI		46 (31) ^c
	MeOTf		82		MeOTf		82
	Me ₃ SiCl		62		Me ₃ SiCl		70
	Me ₃ SiOTf		88		Me ₃ SiOTf		80
	PhCHO		93		PhCHO		86
 1b	MeOH		87		Ph ₂ CO		95 ^{c,d}
	MeI		44				86 ^{c,d}
	MeOTf		86				88 ^{c,d}
	Me ₃ SiCl		85				
	PhCHO		93				

^a t^R in R1 = 0.01 s, t^R in R2 = 9.0 s, $T = 0\text{ }^\circ\text{C}$ for **1a**; $T = -28\text{ }^\circ\text{C}$ for **1b** and **1c**.^b Determined by GC. ^c t^R in R2 = 2.2 s. ^d Isolated yield.

This type of reaction via nitro-substituted aryllithium species using flow microreactor system could be applied to the target-oriented synthesis. In the synthesis of Macbecin I, Micalizio *et. al* used compound **4**, which was converted to compound **7** in 5 steps including protection/deprotection process.⁹ In their synthesis, compound **4** was reduced to the amine which was protected as diallylamine (Figure 3). Then, the aryllithium bearing a protected amino group was generated by Br-Li exchange and was reacted with an aldehyde. The resulting alcohol was methylated, and the deprotection of the amino group gave compound **7**.

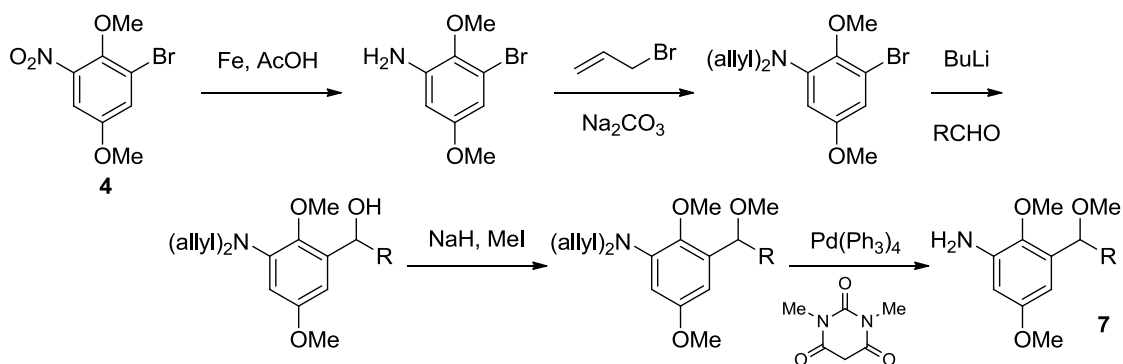


Figure 3. Synthesis of compound **7** as an intermediate for Macbecin I.^{9,10}

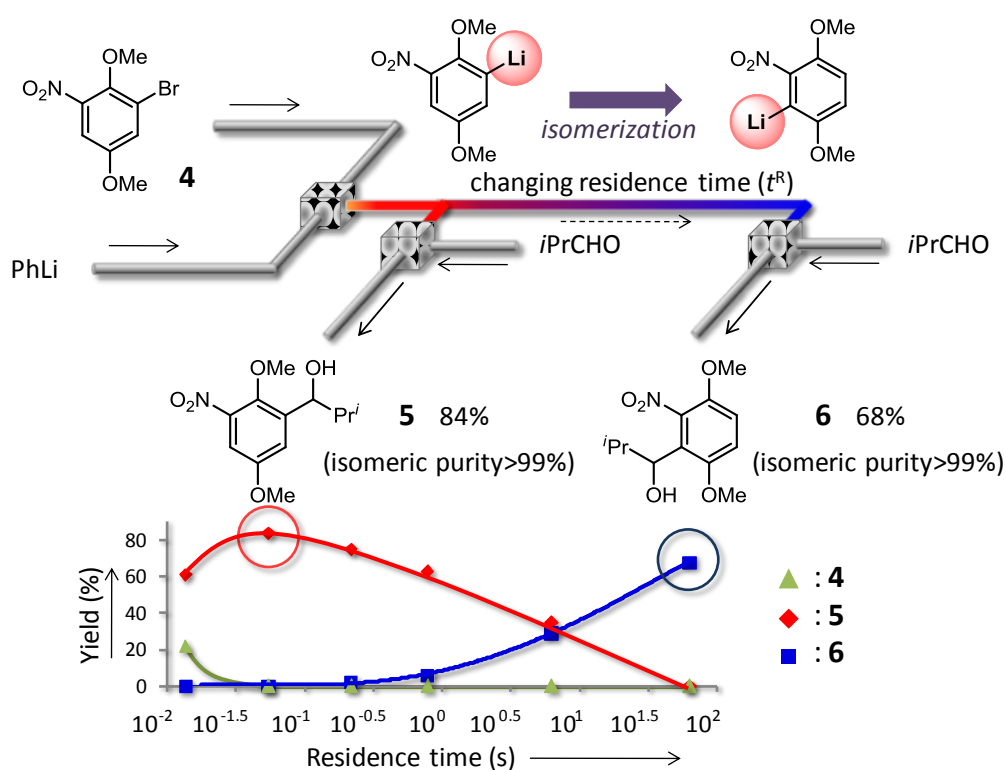


Figure 4. Switch between kinetic and thermodynamic control by changing the residence time.

As shown in Figure 4, the organolithium reaction of unprotected **4** demonstrates the potential of the flow microreactor method. The treatment with PhLi ($t^R = 0.06$ s at -48 °C) followed by the reaction with an aldehyde gave product **5** in 82% yield. It is also noteworthy that an increase in t^R resulted in the formation of a significant amount of isomeric product **6**, which was derived from isomerization of the aryllithium.¹¹ With t^R equal to 63 s, product **6** was obtained exclusively, indicating that the isomerization was complete in this period. The present result demonstrates that the flow microreactor

method is quite effective for the selective use of either the kinetically preferred organolithiums or the thermodynamically preferred organolithiums by controlling the residence time.

Next, we conducted the sequential methylation of generated lithium alkoxide in one flow. By simple optimizing the reaction conditions including flow rate, temperature and equivalence of reagents, the desired product was obtained in 73% yield as shown in Figure 5.

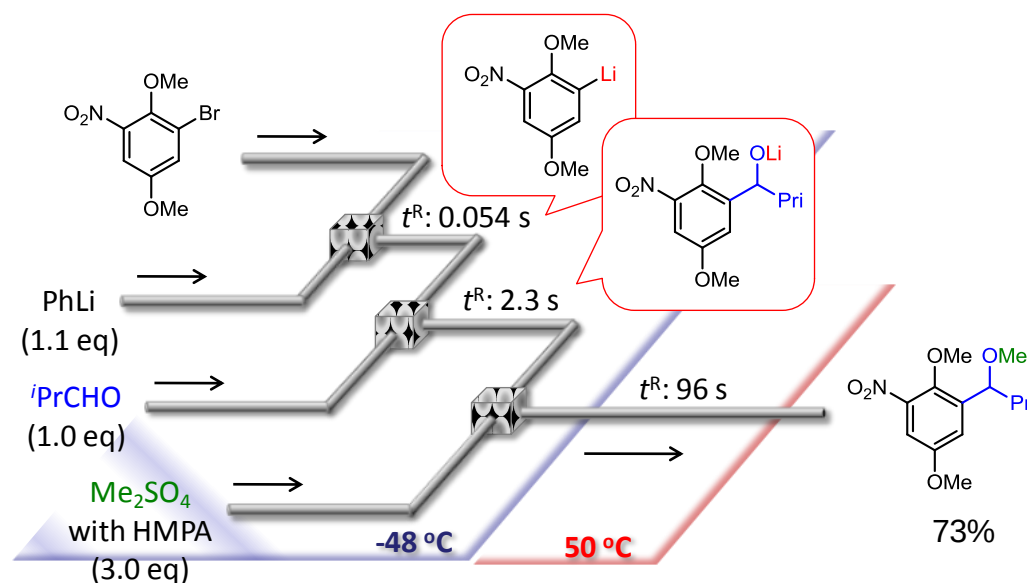


Figure 5. One-flow synthesis involving Br-Li exchange, reaction with an aldehyde and subsequent O-methylation.

The present transformation using a nitro-substituted aryllithium would serve as an alternative straightforward route for the synthesis of Macbecn I. After the flow reaction, simple reduction of the nitro group should give the desired compound **7** avoiding the protection–deprotection processes.¹²

Conclusion

We have developed the flow microreactor method for the generation and reaction of *o*-, *m*- and *p*-nitrophenyllithiums, which are known to be very difficult or impossible to generate and use in a conventional macrobatch method. Furthermore, the selective use of either kinetically preferred organolithiums or thermodynamically preferred organolithiums by changing the residence time demonstrates the power of the flow microreactor method in organic synthesis.

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. ^1H and ^{13}C NMR spectra were recorded on Varian MERCURYplus-400 (^1H 400 MHz, ^{13}C 100 MHz) spectrometer with CDCl_3 . EI and CI mass spectra were recorded on JMS-SX102A spectrometer. Gel permeation chromatography (GPC) was carried out on Japan Analytical Industry LC-9201. Unless otherwise noted, all materials were obtained from commercial supplier and used without further purification. 1-Bromo-2,5-dimethoxy-3-nitrobenzene (**4**) was prepared according to the literature.¹³ The flow microreactor system was identical with that which was used in chapter 1.

The Halogen-Lithium Exchange Reaction of Halonitrobenzenes Followed by Reaction with Methanol in a Batch Reactor. A solution of organolithium reagent (0.42 M, 0.75 mL) was added dropwise to a solution of halonitrobenzene (0.10 M in THF, 3.0 mL) for 1.0 min at $-78\text{ }^\circ\text{C}$. The mixture was stirred for 10 min, and a solution of methanol (0.60 M in THF, 1.5 mL) was added. After stirring for 10 min, a cooling bath was removed. The reaction mixture was analyzed by GC.

The I-Li Exchange Reaction of Iodonitrobenzenes Followed by Reaction with Methanol. A Flow microreactor system consisting of two T-shaped micromixers (M1 and M2), two microtube reactors (R1 and R2) was used. A solution of iodonitrobenzene (0.10 M in THF, flow rate: 6.0 mL min^{-1}) and a solution of PhLi (0.42 M in Et_2O and cyclohexane (72/28 v/v), flow rate: 1.5 mL min^{-1}) were introduced to M1 ($\phi = 250\text{ }\mu\text{m}$) by syringe pumps. The resulting solution was passed through R1 and was mixed with a solution of methanol (0.60 M in THF, flow rate: 3.0 mL min^{-1}) in M2 ($\phi = 250\text{ }\mu\text{m}$). The resulting solution was passed through R2 ($\phi = 1000\text{ }\mu\text{m}$, $L = 50\text{ cm}$). After a steady state was reached, the product solution was collected for 30 s while being quenched with H_2O . The reaction mixture was analyzed by GC. The results are summarized in Table 3.

Table 3. The I-Li exchange reaction of iodonitrobenzene **1** followed by reaction with methanol in flow microreactor systems.

ϕ in R1 (μm)	L in R1 (cm)	t^{R} (s)	T ($^{\circ}\text{C}$)	Conv. ^a (%)	Yield ^a (%)	Conv. ^b (%)	Yield ^b (%)	Conv. ^c (%)	Yield ^c (%)
250	3.5	0.014	0	97	87	100	84	97	87
500	3.5	0.055		99	87	100	83	100	85
1000	3.5	0.22		98	86	100	74	100	73
1000	6.0	0.38		98	85	100	75	100	73
1000	12.5	0.79		98	79	100	58	100	62
1000	100	6.3		100	30	96	5	96	10
250	3.5	0.014	-28	100	92	100	87	100	91
500	3.5	0.055		100	89	100	90	100	88
1000	3.5	0.22		100	90	100	85	100	89
1000	6.0	0.38		100	90	100	82	100	88
1000	12.5	0.79		100	92	100	82	100	80
1000	100	6.3		100	89	100	66	100	72
250	3.5	0.014	-48	100	95	97	87	100	96
500	3.5	0.055		100	88	100	90	100	89
1000	3.5	0.22		100	90	100	83	100	88
1000	6.0	0.38		100	91	100	83	100	88
1000	12.5	0.79		100	92	100	82	100	85
1000	100	6.3		100	89	100	80	97	78
250	3.5	0.014	-58	65	47	61	61	62	51
500	3.5	0.055		68	61	64	64	69	54
1000	3.5	0.22		97	83	100	84	100	93
1000	6.0	0.38		100	85	100	80	100	88
1000	12.5	0.79		100	88	100	84	100	83
1000	100	6.3		100	88	100	82	100	80
250	3.5	0.014	-78	68	47	52	47	65	47
500	3.5	0.055		72	51	59	49	68	55
1000	3.5	0.22		76	54	79	62	77	55
1000	6.0	0.38		82	63	79	60	74	59
1000	12.5	0.79		85	76	90	75	80	68
1000	100	6.3		96	87	100	86	100	83

^a *o*-Iodonitrobenzene (**1a**) was used as a substrate. ^b *m*-Iodonitrobenzene (**1b**) was used as a substrate. ^c *p*-Iodonitrobenzene (**1c**) was used as a substrate.

The I-Li Exchange Reaction of Iodonitrobenzenes Followed by Reaction with Electrophiles. A Flow microreactor system consisting of two T-shaped micromixers (M1 and M2), two microtube reactors (R1 and R2) was used. A solution of iodonitrobenzene (0.10 M in THF, flow rate: 6.0 mL min⁻¹) and a solution of PhLi (0.42 M in Et₂O and cyclohexane (72/28 v/v), flow rate: 1.5 mL min⁻¹) were introduced to M1 (ϕ = 250 μ m) by syringe pumps. The resulting solution was passed through R1 and was mixed with a solution of electrophile (0.60 M in THF or Et₂O for methyl triflate and trimethylsilyl triflate, flow rate: 3.0 mL min⁻¹) in M2 (ϕ = 250 μ m). The resulting solution was passed through R2 (ϕ = 1000 μ m, L = 400 cm). After a steady state was reached, the product solution was collected for 30 s while being quenched with H₂O. The reaction mixture was analyzed by GC. The organic phase was separated and the aqueous phase was extracted with ethyl acetate. After the combined organic phase was dried over Na₂SO₄, and solvent was removed, the reaction mixture was analyzed by ¹H and ¹³C NMR.

2-Methyl-1-nitrobenzene. 36% yield from **1a** and iodomethane. 82% yield from **1a** and methyl triflate.

2-Trimethylsilyl-1-nitrobenzene. 62% yield from **1a** and chlorotrimethylsilane. 88% yield from **1a** and trimethylsilyl triflate. The spectral data were identical to those reported in the literature.¹⁴

(2-Nitrophenyl)(phenyl)methanol. 93% yield from **1a** and benzaldehyde. The spectral data were identical to those reported in the literature.¹⁵

3-Methyl-1-nitrobenzene. 44% yield from **1b** and iodomethane. 86% yield from **1b** and methyl triflate.

3-Trimethylsilyl-1-nitrobenzene. 85% yield from **1b** and chlorotrimethylsilane. The spectral data were identical to those reported in the literature.¹⁴

(3-Nitrophenyl)(phenyl)methanol. 93% yield from **1b** and benzaldehyde. The spectral data were identical to those reported in the literature.¹⁵

4-Methyl-1-nitrobenzene. 46% yield from **1c** and iodomethane. 82% yield from **1c** and methyl trifluoromethanesulfonate.

4-Trimethylsilyl-1-nitrobenzene. 70% yield from **1c** and chlorotrimethylsilane. 80% yield from **1c** and trimethylsilyl triflate. The spectral data were identical to those reported in the literature.¹⁶

(4-Nitrophenyl)(phenyl)methanol. 86% yield from **1c** and benzaldehyde. The spectral data were identical to those reported in the literature.¹⁴

(4-Nitrophenyl)diphenylmethanol. 95% isolated yield from **1c** and benzophenone. After extraction, the crude product was purified by chromatography (hexane/ethyl acetate = 5:1). The spectral data were identical to those reported in the literature.¹⁷

Bis(4-nitrophenyl)(phenyl)methanol. 86% isolated yield from **1c** and 4-nitrobenzophenone. After extraction, the crude product was purified by chromatography (hexane/ethyl acetate = 5:1): ¹H NMR (400 MHz, CDCl₃) δ 2.93 (s, 1H), 7.16-7.22 (m, 2H), 7.36-7.42 (m, 3H), 7.54 (dt, *J* = 9.2, 2.4 Hz, 4H), 8.21 ppm (dt, *J* = 9.2, 2.4 Hz, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 81.4, 123.4, 127.6, 128.6, 128.6, 128.8, 144.5, 147.2, 152.3 ppm; HRMS (APCI) calcd. for C₁₉H₁₄ClN₂O₅⁻ [M+Cl]⁻: 385.0587; found: 385.0586.

(4-(Dimethylamino)phenyl)(4-nitrophenyl)(phenyl)methanol. 88% isolated yield from **1c** and 4-(dimethylamino)benzophenone. After extraction, the crude product was purified by chromatography (hexane/ethyl acetate = 5:1): ¹H NMR (400 MHz, CDCl₃) δ 2.74 (s, 1H), 2.96 (s, 1H), 6.66 (dt, *J* = 9.2, 2.4 Hz, 2H), 7.04 (dt, *J* = 8.8, 2.4 Hz, 2H), 7.25-7.37 (m, 5H), 7.56 (dt, *J* = 9.2, 2.4 Hz, 2H), 8.15 ppm (dt, *J* = 8.8, 2.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 40.6, 81.8, 112.0, 123.2, 127.8, 128.0, 128.4, 128.9, 129.1, 133.6, 146.4, 147.0, 150.2, 154.8 ppm; HRMS (APCI) calcd. for C₂₁H₂₀ClN₂O₃⁻ [M+Cl]⁻: 383.1162; found: 383.1157.

Table 4. The I-Li exchange reaction of iodonitrobenzene **1** followed by reaction with iodomethane in flow microreactor systems.^a

substrate	<i>T</i> (°C)	ϕ in R2 (μm)	<i>L</i> in R2 (cm)	<i>t</i> ^R in R2 (s)	GC Yield	
					MePhNO ₂ (%)	PhNO ₂ (%)
1a	0	1000	200	4.5	29	30
	0	1000	400	9.0	36	25
	-28	1000	200	4.5	6	72
	-48	1000	200	4.5	2	86
1b	-28	1000	50	2.2	28	34
	-28	1000	200	4.5	42	4
	-28	1000	400	9.0	44	3
1c	-28	1000	50	2.2	31	31
	-28	1000	200	4.5	45	2
	-28	1000	400	9.0	46	1

^a *t*^R in R1 = 0.01 s

The I-Li Exchange Reaction of 1-Bromo-2,5-dimethoxy-3-nitrobenzene (4) Followed by Reaction with Isobutyraldehyde in Flow Microreactor Systems. A flow microreactor system consisting of two T-shaped micromixers (M1 and M2), two microtube reactors (R1 and R2) was used. A solution of 1-bromo-2,5-dimethoxy-3-nitrobenzene (**3**, 0.10 M in THF, flow rate: 6.0 mL min⁻¹) and a solution of PhLi (0.42 M in Et₂O and cyclohexane (72/28 v/v), flow rate: 1.5 mL min⁻¹) were introduced to M1 (ϕ = 250 μm) by syringe pumps. The resulting solution was passed through R1 and was mixed with a solution of isobutyraldehyde (0.22 M in THF, flow rate: 3.0 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. NH₄Cl aqueous solution. The reaction mixture was analyzed by GC. The results are summarized in Table 5.

1-(2,5-Dimethoxy-3-nitrophenyl)-2-methylpropan-1-ol (5). 84% yield (residence time in R1: 0.06 s). After extraction, the crude product was purified by flash chromatography (hexane/ethyl acetate = 3:1). Then, **4** was isolated with GPC: ¹H NMR (400 MHz, CDCl₃) δ 0.87 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.4 Hz, 3H), 1.91-2.04 (m, 2H), 3.85 (d, *J* = 2.4 Hz, 6H), 4.74 (d, *J* = 6.8 Hz, 1H), 7.23 (d, *J* = 3.2 Hz, 1H), 7.26 ppm (d, *J* = 3.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 17.4, 19.3, 34.5, 55.9, 62.8, 73.3, 108.5, 118.8, 141.0, 143.4, 144.5, 155.1 ppm; HRMS (EI) *m/z* calcd for C₁₂H₁₇NO₅ (M⁺): 255.1107, found: 255.1111.

1-(3,6-Dimethoxy-2-nitrophenyl)-2-methylpropan-1-ol (6). 68% yield (residence time in R1: 63 s). After extraction, the crude product was purified by chromatography (hexane/ethyl acetate = 3:1): ^1H NMR (400 MHz, CDCl_3) δ 0.72 (d, J = 6.8 Hz, 3H), 1.06 (d, J = 6.4 Hz, 3H), 2.17-2.31 (m, 1H), 3.15 (d, J = 10.0 Hz, 1H), 3.81 (s, 3H), 3.85 (s, 1H), 4.14 (t, 1H), 6.90 (d, J = 8.8 Hz, 1H), 6.96 ppm (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 19.2, 19.3, 33.6, 56.0, 56.6, 75.7, 111.5, 112.6, 124.2, 141.3, 144.2, 150.7 ppm; HRMS (EI) m/z calcd for $\text{C}_{12}\text{H}_{17}\text{NO}_5$ (M^+): 255.1107, found: 255.1111.

Table 5. The I-Li exchange reaction of 1-bromo-2,5-dimethoxy-3-nitrobenzene (**4**) followed by reaction with isobutyraldehyde in flow microreactor systems.

ϕ in R1 (μm)	L in R1 (cm)	t^{R} (s)	Conv. (%)	GC yield (%)	
				5	6
250	3.5	0.014	78	61	0
500	3.5	0.055	100	84	0
1000	3.5	0.22	100	75	2
1000	12.5	0.76	100	63	6
1000	100	6.3	100	35	29
1000	1000	63	100	0	68

The I-Li Exchange Reaction of 1-Bromo-2,5-dimethoxy-3-nitrobenzene (4) and Reaction with Isobutyraldehyde Followed by Methylation in a Flow Microreactor System. A flow microreactor system consisting of three T-shaped micromixers (M1, M2 and M3), three microtube reactors (R1, R2 and R3) was used. A solution of 1-bromo-2,5-dimethoxy-3-nitrobenzene (**3**, 0.10 M in THF, flow rate: 6.0 mL min^{-1}) and a solution of PhLi (0.42 M in Et_2O and cyclohexane (72/28 v/v; flow rate: 1.6 mL min^{-1}) were introduced to M1 ($\phi = 250 \mu\text{m}$) by syringe pumps. The resulting solution was passed through R1 and was mixed with a solution of isobutyraldehyde (0.22 M in THF, flow rate: 2.8 mL min^{-1}) in M2 ($\phi = 250 \mu\text{m}$). The resulting solution was passed through R2 ($\phi = 1000 \mu\text{m}$, $L = 50 \text{ cm}$) and was mixed a solution of dimethyl sulfate (0.90 M) containing HMPA (0.90 M) in THF (flow rate: 2.0 mL min^{-1}) in M3 ($\phi = 500 \mu\text{m}$). The resulting solution was passed through R3 ($\phi = 1000 \mu\text{m}$, $L = 2560 \text{ cm}$ (50 cm at 0°C , 10 cm at ambient temperature, and 2500 cm at 50°C)). After a steady state was reached, the product solution was collected for 30 s while being quenched with sat. NH_4Cl aq. solution. The reaction mixture was analyzed by GC.

2,5-Dimethoxy-1-(1-methoxy-2-methylpropyl)-3-nitrobenzene. 73% GC yield: ^1H NMR (400 MHz, CDCl_3) δ 0.83 (d, $J = 6.8$ Hz, 3H), 0.98 (d, $J = 6.4$ Hz, 3H), 1.89 (sext, $J = 6.8$ Hz, 1H), 3.24 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 4.25 (d, $J = 6.4$ Hz, 1H), 7.16 (d, $J = 2.8$ Hz, 1H), 7.29 ppm ($J = 3.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 18.0 and 19.0, 34.5, 55.9, 57.3, 62.7, 82.3, 108.9, 118.4, 139.2, 143.6, 145.6, 155.2 ppm; HRMS (APCI) calcd. for $\text{C}_{13}\text{H}_{20}\text{NO}_5^+ [\text{M}+\text{H}]^+$: 270.1328; found: 270.1336.

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Chapter 5

A Flow Microreactor Synthesis via Organolithium

Intermediates Bearing Ketone Carbonyl Groups:

A New Approach to Protecting-Group-Free Synthesis

Abstract

Protecting-group-free synthesis has received significant recent research interest in the context of ideal synthesis and green sustainable chemistry. In general, organolithium species react with ketones very rapidly, and therefore ketone carbonyl groups should be protected before an organolithium reaction, if they are not involved in the desired transformation. If organolithium chemistry could be free from such a limitation, its power would be greatly enhanced. Here we show that a flow microreactor enables such protecting-group-free organolithium reactions by greatly reducing the residence time (0.003 s or less). Aryllithium species bearing ketone carbonyl groups are generated by iodine-lithium exchange reactions of the corresponding aryl iodides with mesityllithium and are reacted with various electrophiles using a flow microreactor system. The present method has been successfully applied to the formal synthesis of Pauciflorol F.

Introduction

Although organolithium species serve as powerful reagents in organic synthesis, they are not compatible with electrophilic functional groups such as ketone carbonyl groups. In fact, organolithium species react with ketones very rapidly. In some cases, organolithium species can be generated in the presence of ketones and quenched *in situ* by the ketone carbonyl group.¹ However, if a ketone carbonyl group is not involved in the desired transformation, it should be protected before an organolithium reaction, although ketone carbonyl groups survive in reactions of some less reactive organometallics.² Therefore, if organolithium reactions can be conducted without protecting the ketone carbonyl groups, the power of organolithium chemistry will be greatly enhanced.

Results and Discussions

We began our investigation by conducting the I–Li exchange reaction of *o*- and *p*-acyliodobenzenes followed by trapping with methanol using the flow microreactor system, as shown in Figure 1.

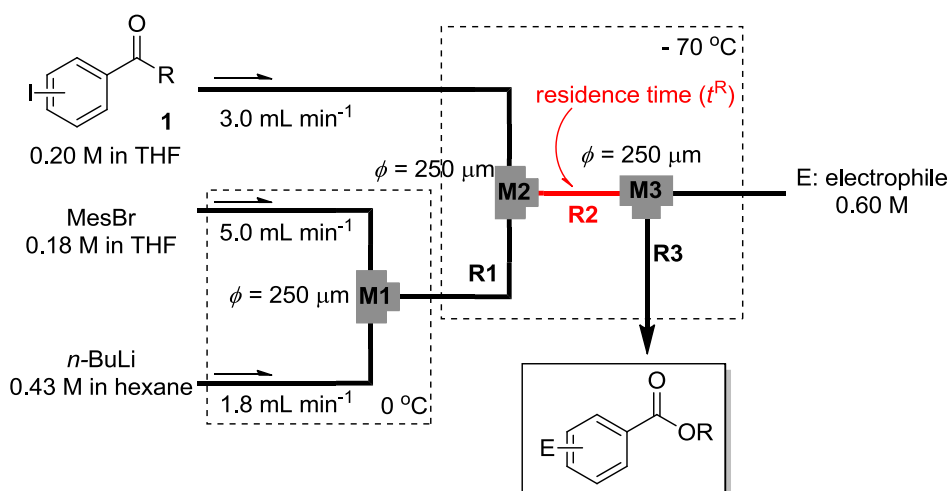


Figure 1. A microreactor system for the I–Li exchange reaction of iodoarenes bearing ketone carbonyl group followed by reaction with alcohols.

Mesityllithium was first generated by a Br-Li exchange reaction of 2-bromo-1,3,5-trimethylbenzene (mesityl bromide) and *n*-BuLi at 0 °C, because preliminary studies showed that mesityllithium was the most effective compound for this purpose. The I-Li exchange reaction of an acyliodobenzene using the resulting mesityllithium was conducted at -70 °C. The short-lived acylphenyllithium species thus produced was trapped with methanol as an electrophile at -70 °C (Figure 1a).

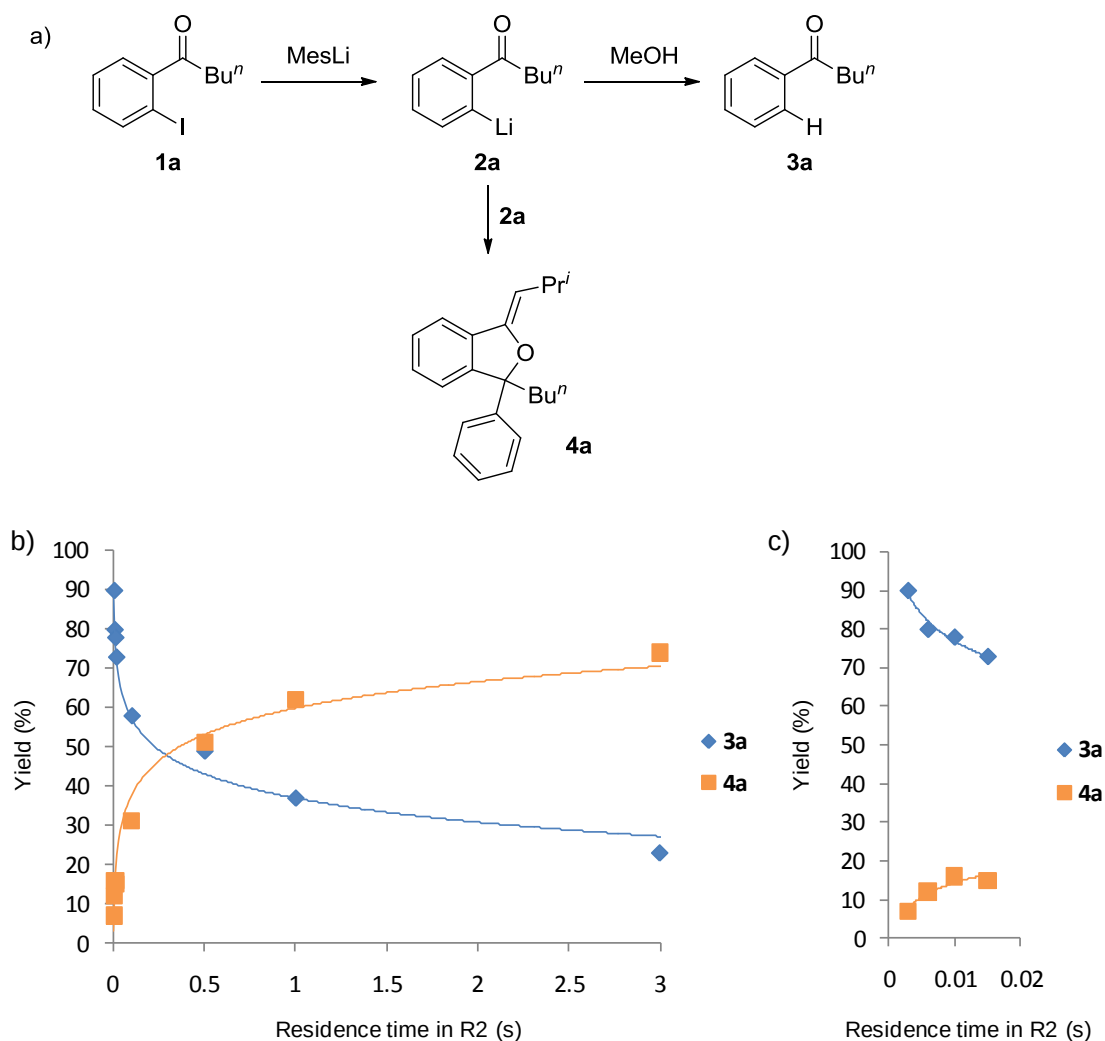


Figure 2. Effect of residence time on the yield in the I-Li exchange reaction of *o*-pentanoyliodobenzene (**1a**) followed by reaction with MeOH in the flow microreactor systems.

We focused on the generation of *o*-pentanoyl-substituted phenyllithium (**2a**) generated from *o*-pentanoyliodobenzene (**1a**). Methanol was used as a quenching electrophile (Fig. 2a). The reactions were carried out with variation in the residence

time in R2, and the yield of the protonated product **3a** was determined by gas chromatography (GC). The yield of **3a** increased with a decrease in the residence time (Figure 2b). However, acceptable yields were not obtained even at the minimum limit of the residence time of our current system (0.01 s), although this residence time was successful for the generation of alkoxycarbonyl-³, nitro-⁴ and cyano-substituted⁵ aryllithiums. Aryllithium **2a** bearing a ketone carbonyl group decomposed very rapidly, the major by-product being dimeric compound **4**.

To avoid the decomposition of **2a**, we developed a new integrated device in which two T-shaped micromixers and one microreactor are combined (Figure 3). Although the Reynolds number is $\sim 10^2$, extremely fast mixing takes place at the T-shaped mixers, presumably because of engulfment flow.⁸ Using this device, the residence time could be reduced to 0.003 s, giving rise to a dramatic increase in the yield of product **3a** (Figure 2c). The result clearly indicates that a ketone carbonyl group could survive a residence time of a few milliseconds.

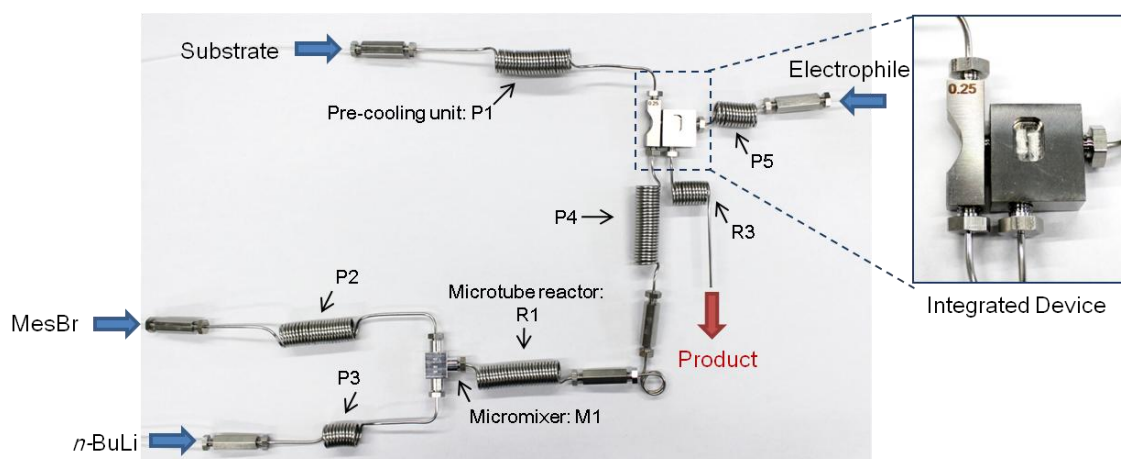


Figure 3. A picture of the system including the integrated device in which R2, M2 and M3 are combined.

Next, we conducted the I-Li exchange reaction of four iodoarenes bearing different ketone carbonyl groups (Figure 4). Aryllithium intermediates were generated from *o*-propanoyliodobenzene (**1b**), *o*-acetyliodobenzene (**1c**), *p*-pentanoyliodobenzene (**1d**) and *p*-acetyliodobenzene (**1e**). As shown in Figure 3, an increase in the residence time led to the decrease in the yield of the desired protonated product (**3**). In general, *o*-substituent gave the better result than *p*-substituent, presumably because of the coordination of the ketone carbonyl group to lithium. By reducing the residence time to 3 ms using an integrated device, the protonated products were obtained in good yields.

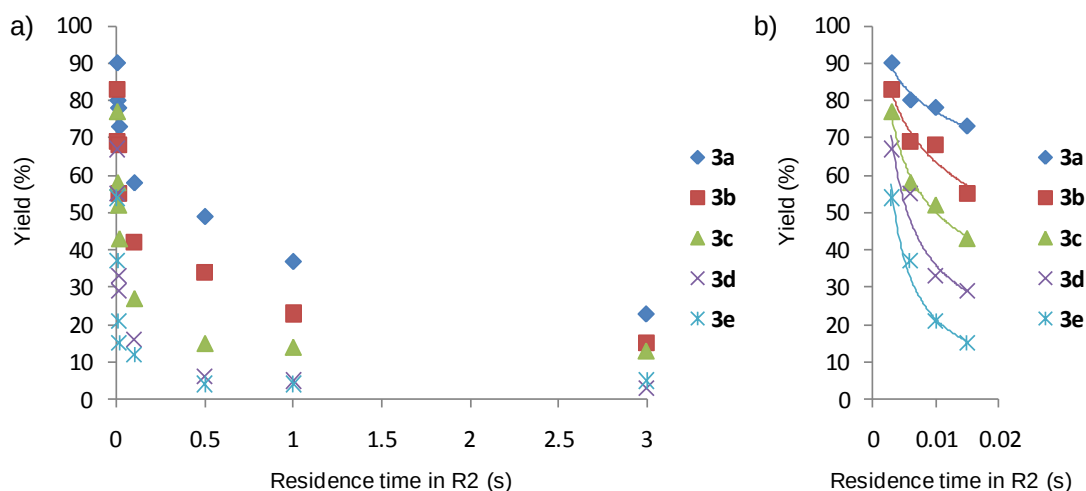
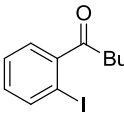
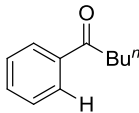
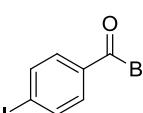
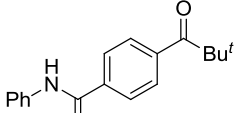
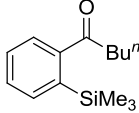
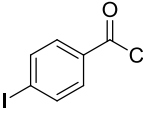
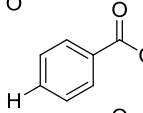
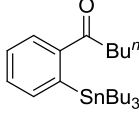
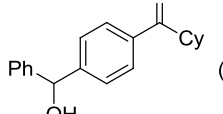
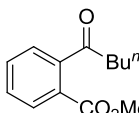
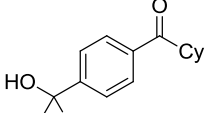
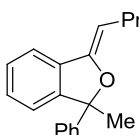
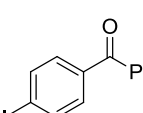
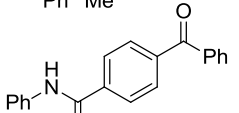
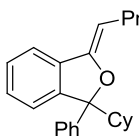
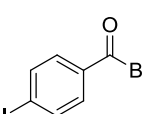
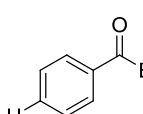
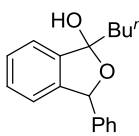
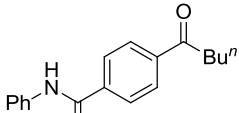
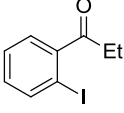
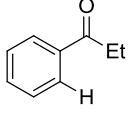
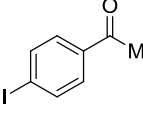
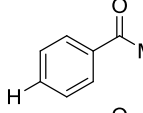
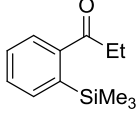
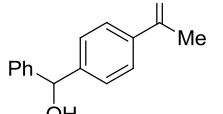
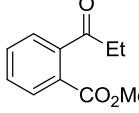
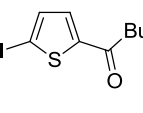
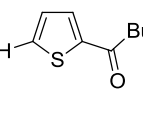
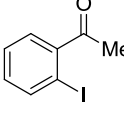
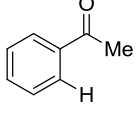
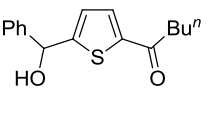
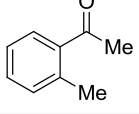
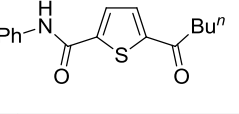


Figure 4. Effect of residence time on the yield in the I-Li exchange reaction of **1** followed by reaction with MeOH in the flow microreactor systems.

At a residence time of 0.003 s, generation of various *o*-acyl-substituted aryllithium species followed by reactions with various electrophiles including Me₃SiOTf, Bu₃SnCl and ClCO₂Me were successfully conducted, and the corresponding products bearing unchanged ketone carbonyl groups were obtained in good yields and in good productivity (0.25-0.54 mmol/min; Table 1). It is interesting that some ketones could be used as electrophiles, although they should be more reactive than the carbonyl group of the acylphenyllithium species.

The generation and reaction of *p*-acyl-substituted phenyllithiums led to slightly lower yields of the products compared with the corresponding *o*-acyl-substituted phenyllithiums, presumably because of the lack of coordination of the carbonyl group to lithium. In particular, in the case of *p*-acetylphenyllithium (**2e**) generated from *p*-acetyliodobenzene (**1e**), the protonated product **3e** was obtained only in moderate yield (54%). This problem could be solved by further reducing the residence time in R2, which was achieved by increasing the flow rate using high-pressure syringe pumps. As shown in Figure 5, the yield of **3e** increased with a decrease in the residence time, and an acceptable yield (76%) was obtained at a residence time of 0.0015 s. This residence time also allowed efficient reaction with PhCHO to produce the corresponding product in 78% yield. Heteroaromatic iodides such as 1-(5-iodothiophen-2-yl)pentan-1-one could also be lithiated and the resulting organolithium compounds were effectively trapped with electrophiles without affecting the ketone carbonyl group.

Table 1. The optimized I-Li exchange reaction of acyl-substituted iodobenzenes **1** followed by reaction with an electrophile.^a

Substrate	Electrophile	Product	Yield (%) ^a	Substrate	Electrophile	Product	Yield (%) ^a
	MeOH		90 (91) ^b		PhNCO		87
	Me ₃ SiOTf		86 (91) ^b		MeOH		78 ^b
	Bu ₃ SnCl		86		PhCHO		73 (75) ^b
	MeO ₂ CCl		68 (70) ^b		PhCOMe		76
	PhCOMe		81		PhNCO		71
	PhCOCy		81		MeOH		67 ^b
	PhCHO		60		PhNCO		51
	MeOH		83		MeOH		54 (76) ^c
	Me ₃ SiOTf		81 (84) ^b		PhCHO		78 ^c
	MeO ₂ CCl		65 (69) ^b		MeOH		74
	MeOH		77 ^b		PhCHO		77
	MeOTf		42 ^b		PhNCO		59

^a Isolated yield. ^b Determined by GC. ^c Residence time=0.00015 s

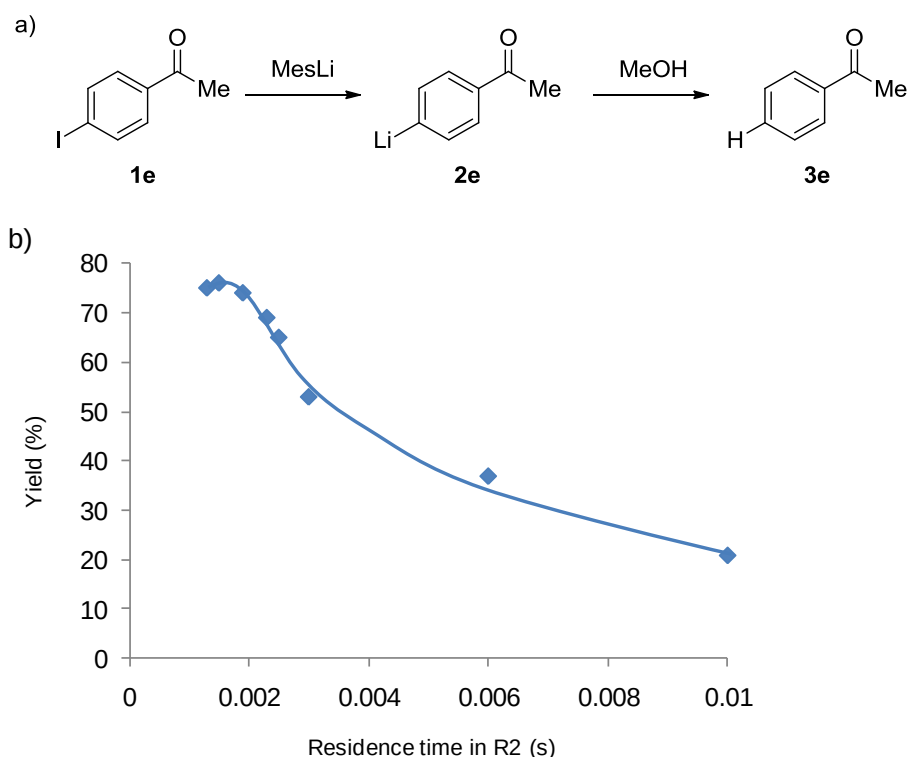


Figure 5. The effect of residence time in R2 for the reaction of *p*-acyliodobenzene **1e**.

a) Reaction of **1e** with MesLi followed by reaction with MeOH. b) Dependence of the yield **3e** on the residence time in R2 (< 0.01 s).

Using the present method, Pauciflorol F⁶, a natural product isolated from stem bark, which has recently been synthesized by Snyder's group⁷ and Sarpong's group⁸, was synthesized. The starting material **5** was prepared from commercially available 3,5-dimethoxyphenylmagnesium chloride in two steps (67% yield; Figure 6). The iodine-lithium exchange reaction of **5** followed by reaction with 3,5-dimethoxybenzaldehyde was conducted using a flow microreactor system consisting of the integrated device (residence time in R2: 0.003 s) to produce **6** (ref. 49) in 81% isolated yield. Presumably, dehydration took place upon acidic work-up. Treatment of **6** with HCl/*i*-PrOH in the presence of O₂ in a batch macro reactor gave **7** in 75% yield, which can be converted to Pauciflorol F by one-pot hydrogenation and epimerization (87%)⁸ followed by deprotection (86%).⁷

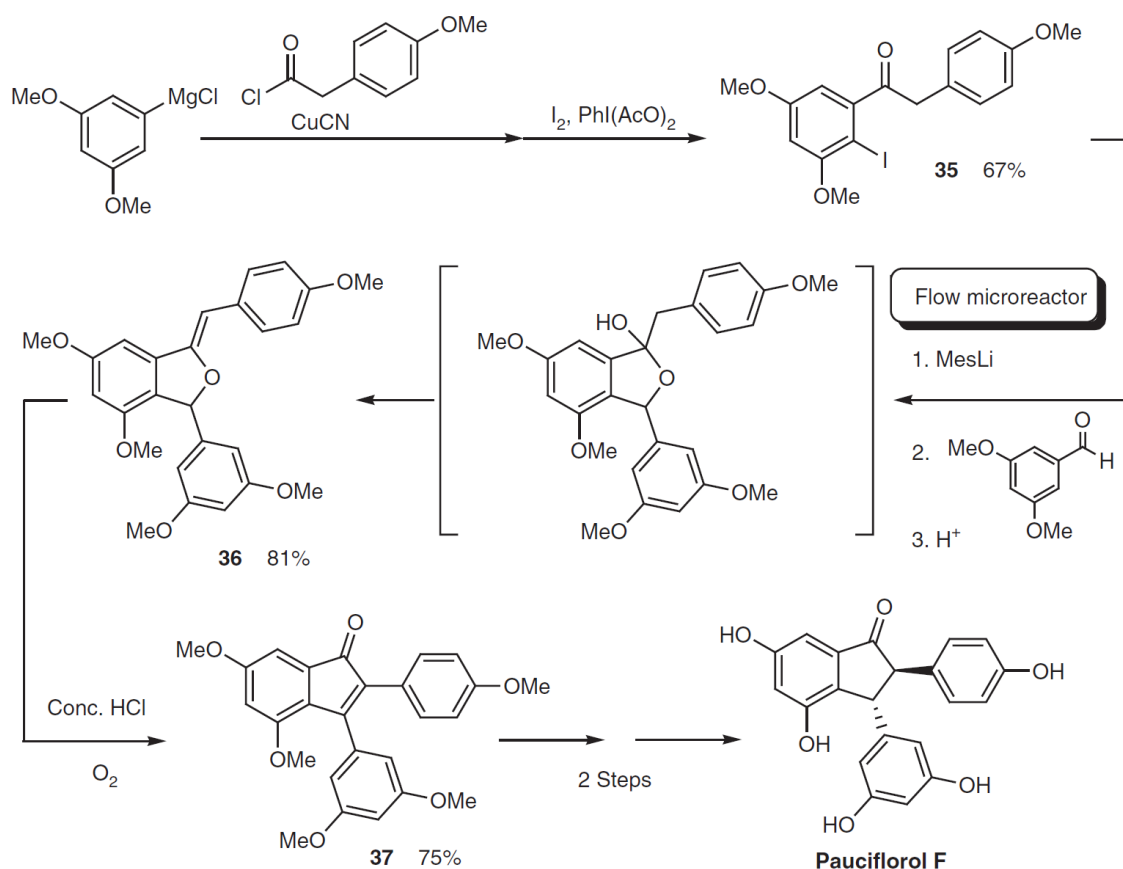


Figure 6. Formal total synthesis of Pauciflorol F.

The formal synthesis of Pauciflorol F achieved in this study (Figure 6) demonstrates the potential of the present flow microreactor approach. Although the synthesis by Snyder's group based on a biomimetic strategy and the synthesis by Sarpong's group based on a Larock annulations strategy are elegant and concise, our synthesis is comparable from the viewpoints of atom economy and step economy. Because the productivity of the present method is relatively high (1.06 g for 5 min operation), it is hoped that the flow microreactor method will provide a green and sustainable way of producing useful compounds such as Pauciflorol F in the pharmaceutical and fine chemicals industries in the future.

Conclusion

The present approach based on control of the residence time in a flow microreactor serves as a powerful method for protecting-group-free synthesis using organolithium reagents, which is complementary to other approaches using less reactive and more chemoselective reagents. Although the flow microreactor approach is still in its infancy, it is clearly capable, powerful and useful from both scientific and practical viewpoints.

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). ^1H and ^{13}C NMR spectra were recorded on Varian MERCURYplus-400 (^1H 400 MHz, ^{13}C 100 MHz) spectrometer with Me_4Si or CDCl_3 as a standard in CDCl_3 unless otherwise noted. EI and CI mass spectra were recorded on a JEOL JMS-SX102A spectrometer. ESI mass spectra were recorded on a JEOL JMS-T100CS spectrometer. THF and Et_2O were purchased from Kanto Chemical Co., Inc. as a dry solvent and used without further purification. Hexane was purchased from Wako, distilled before use, and stored over molecular sieves 4A. $n\text{-BuLi}$ was purchased from Kanto Chemical Co., Inc.. Commercial available starting materials were purchased from commercial sources and used without further purification.

Stainless steel (SUS304) T-shaped micromixer with inner diameter of 250 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 (Figure 7a). The micromixer and microtube reactors were connected with stainless steel fittings (GL Sciences, 1/16 OUW). Stainless steel (SUS316) integrated device (inner diameter of M2, M3 and R2: 250 μm , length of R2: 10 mm) was manufactured by YMC Co., Ltd. (Figure 7b and 7c). The flow microreactor system was dipped in a cooling bath to control the temperature. Solutions were introduced to the flow microreactor system using syringe pumps, Harvard Apparatus PHD 2200, equipped with gastight syringes purchased from SGE, (basically) or using syringe pumps, Harvard Apparatus PHD 4400 equipped with stainless steel syringes (#70-2255) purchased from Harvard Apparatus PHD for control the residence time to less of 3 ms.

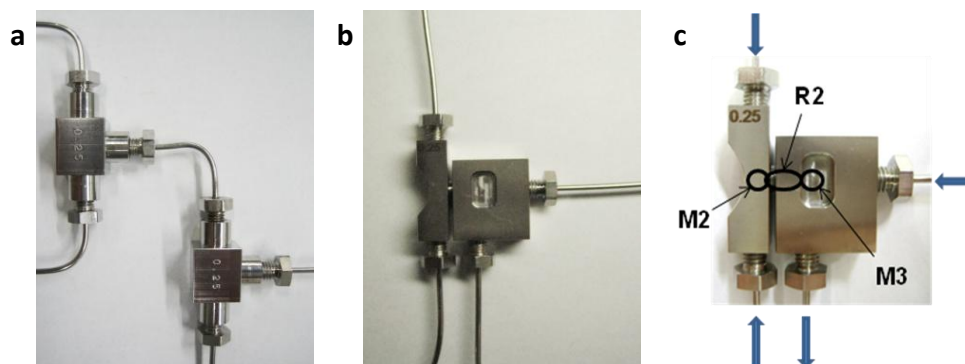


Figure 7. a) Conventional flow microreactor system, b) and c) Integrated device

1. Synthesis of Acyl-Substituted Iodobenzenes

1-(2-iodophenyl)-1-pentanone (1a).⁹ *n*-Butyllithium (2.64 M in THF, 69 mL, 182.2 mmol) was added dropwise to a solution of 2-aminobenzonitrile (10.452 g, 88.5 mmol) in THF (80 mL) at 0 °C for 23 min (3 mL min⁻¹). After stirred for 1 h at this temperature, the reaction was quenched by slow addition of 1 M HCl solution (300 mL). The organic layer was separated and the remaining aqueous layer was extracted with ethyl acetate (300 mL × 3). The combined organic layers were dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography (hexane/ethyl acetate = 20:1) to give 1-(2-aminophenyl)-1-pentanone (8.752 g, 56%) as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 7.75 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.25 (td, *J* = 7.6, 1.2 Hz, 1H), 6.70–6.58 (m, 2H), 6.26 (br s, 2H), 2.93 (t, *J* = 7.6 Hz, 2H), 1.70 (quint, *J* = 7.5 Hz, 2H), 1.41 (sext, *J* = 7.5 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). *p*-TsOH·H₂O (11.990 g, 63.0 mmol) was added to a solution of 1-(2-aminophenyl)-1-pentanone (3.480 g, 19.6 mmol) in CH₃CN (80 mL). The resulting suspension of amine salt was cooled to 0 °C and a solution of NaNO₂ (2.713 g, 39.3 mmol) and KI (8.190 g, 49.3 mmol) in H₂O (12 mL) was added very slowly (0.1 mL/min to 0.5 mL/min) for 80 min, causing a vigorous emission of nitrogen. Then, the cooling bath was removed and allowed to stir for 1 h (30 min at ambient temperature and 30 min at 40 °C). The reaction was quenched by addition of H₂O (100 mL), sat. NaHCO₃ solution (25 mL) and sat. Na₂S₂O₃ solution (25 mL). The organic layer was separated and the remaining aqueous layer was extracted with Et₂O (100 mL × 3). The combined organic layers were dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography (hexane/ethyl acetate = 20:1) to give the title product (5.055 g, 89%) as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 7.76 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.42–7.32 (m, 2H), 7.11 (td, *J* = 7.5, 1.8 Hz, 1H), 2.89 (t, *J* = 7.4 Hz, 2H), 1.71 (quint, *J* = 7.6 Hz, 2H), 1.41 (sext, *J* = 7.4 Hz,

2H), 0.94 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (400 MHz, CDCl_3): δ 204.8, 144.6, 140.2, 131.2, 127.8, 127.4, 90.7, 41.6, 25.9, 22.1, 13.7; HRMS (APCI) calcd. for $\text{C}_{11}\text{H}_{14}\text{IO}^+$ $[\text{M}+\text{H}]^+$: 289.0084; found: 289.0089.

1-(2-Iodophenyl)-1-propanone (1b). Ethylmagnesium chloride (2.0 M in THF, 159 mL, 318.0 mmol) was added dropwise to a solution of 2-aminobenzonitrile (12.530 g, 106.1 mmol) in THF (40 mL) at 0°C for 30 min. After stirred for 30 min at this temperature, the cooling bath was removed and allowed to stir at ambient temperature for 11.5 h. The reaction was quenched at 0°C by slow addition of 1 M HCl solution. Then, a solution was made basic (pH 8) by the addition of sat. NaHCO_3 solution. The organic layer was separated and the remaining aqueous layer was extracted with Et_2O (300 mL $\times$ 3). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (hexane/ethyl acetate = 10:1) to give 1-(2-aminophenyl)-1-propanone (9.481 g, 60%) as a yellow solid: ^1H NMR (400 MHz, CDCl_3) δ 7.75 (dd, $J = 8.2, 1.4$ Hz, 1H), 7.29–7.22 (m, 1H), 6.68–6.61 (m, 2H), 6.26 (br s, 1H), 2.98 (q, $J = 7.2$ Hz, 2H), 1.21 (t, $J = 7.2$ Hz, 3H). The transformation from 1-(2-aminophenyl)-1-propanone to title product was carried out as described above. The crude product was purified by column chromatography (hexane/ethyl acetate = 15:1) to give the title product (20 mmol scale, 77%) as a yellow oil: ^1H NMR (400 MHz, CDCl_3) δ 7.91 (d, $J = 8.0$ Hz, 1H), 7.44–7.32 (m, 2H), 7.12 (td, $J = 7.6, 1.6$ Hz, 1H), 2.91 (q, $J = 7.3$ Hz, 2H), 1.23 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (400 MHz, CDCl_3): δ 205.2, 144.6, 140.1, 131.2, 127.8, 127.3, 90.6, 35.1, 7.9; HRMS (APCI) calcd. for $\text{C}_9\text{H}_{10}\text{IO}^+$ $[\text{M}+\text{H}]^+$: 260.9771; found: 260.9776.

1-(4-Iodophenyl)-2,2-dimethyl-1-propanone. *n*-Butyllithium (1.57 M in THF, 48 mL, 75.4 mmol) was added dropwise to a solution of *p*-diiodobenzene (25.074 g, 76.0 mmol) in THF (250 mL) at -78°C for 16 min (3 mL min^{-1}). After stirred for 10 min at this temperature, trimethylacetaldehyde (6.822 g, 79.2 mmol) was added dropwise for 2 min. After stirred for 20 min, MeOH (6 mL) was added. Then, the cooling bath was removed and allowed to ambient temperature. The solution was quenched by addition of sat. NH_4Cl solution (100 mL). The organic layer was separated and the remaining aqueous layer was extracted with ethyl acetate (150 mL $\times$ 3). The combined organic layers were dried over Na_2SO_4 and concentrated to afford 1-(4-iodophenyl)-2,2-dimethylpropan-1-ol (22.017 g, quant) as a yellow solid which was carried forward without additional purification: ^1H NMR (400 MHz, CDCl_3) δ 7.64 (dd, $J = 6.8, 2.0$ Hz, 2H), 7.06 (dd, $J = 6.6, 1.4$ Hz, 2H), 4.34 (d, $J = 2.8$ Hz, 1H), 1.83 (d, $J = 2.8$ Hz, 1H),

0.90 (s, 9H). A solution of DMSO (14.2 mL, 200 mmol) in CH_2Cl_2 was added to a solution of oxalyl chloride in CH_2Cl_2 (0.67 M, 150 mL, 100 mmol) at $-55\text{ }^\circ\text{C}$ for 10 min. After stirred for 5 min, a solution of 4-iodophenyl-*t*-butylmethanol (22.017 g) in CH_2Cl_2 (30 mL) was added dropwise for 10 min. After stirred 20 min at this temperature, the mixture was quenched by triethylamine (40 mL). Then, the cooling bath was removed and allowed to ambient temperature. After addition of H_2O (200 mL), the organic layer was separated and the remaining aqueous layer was extracted with ethyl acetate (200 mL $\times$ 3). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by distillation and flash column chromatography (hexane/ethyl acetate = 50:1) to give the title product (15.80 g, 72% in two steps) as a white solid: ^1H NMR (400 MHz, CDCl_3) δ 7.76 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 1.33 (s, 9H); ^{13}C NMR (400 MHz, CDCl_3) δ 208.1, 137.6, 137.2, 129.5, 97.9, 44.1, 27.9; HRMS (EI) m/z calcd. for $\text{C}_{11}\text{H}_{13}\text{IO}$: 288.0011; found: 288.0007.

Cyclohexyl(4-iodophenyl)methanone. *n*-Butyllithium (1.57 M in THF, 20 mL, 31.4 mmol) was added dropwise to a solution of *p*-diiodobenzene (9.901 g, 30.0 mmol) in THF (100 mL) at $-78\text{ }^\circ\text{C}$ for 10 min (2 mL/min). After stirred for 10 min at this temperature, a solution of CuCN (2.970 g, 33.2 mmol) and LiCl (2.801 g, 66.1 mmol) in THF (35 mL) was added dropwise for 10 min. After stirred for 10 min, cyclohexanecarbonyl chloride (5.823 g, 39.7 mmol) was added. The reaction mixture was slowly warmed to reach ambient temperature, and then was quenched by sat. NH_4Cl solution (50 mL). The organic layer was separated and the remaining aqueous layer was extracted with Et_2O (200 mL $\times$ 3). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (hexane/ethyl acetate = 20:1) to give the title product (6.581 g, 70%) as a white solid: ^1H NMR (400 MHz, CDCl_3) δ 7.82 (dt, J = 8.6 Hz, 2.0 Hz, 2H), 7.65 (dt, J = 8.4 Hz, 2.0 Hz, 2H), 3.18 (tt, J = 11.2, 3.0 Hz, 1H), 1.92–1.80 (m, 4H), 1.78–1.69 (m, 1H), 1.55–1.18 (m, 5H); ^{13}C NMR (400 MHz, CDCl_3) δ 203.1, 137.9, 135.5, 129.7, 100.5, 45.5, 29.3, 25.9, 25.8; HRMS (EI) m/z calcd. for $\text{C}_{13}\text{H}_{15}\text{IO}$: 314.0168; found: 314.0169.

4-Iodobenzophenone. The synthesis from commercially available 4-aminobenzophenone was carried out as described above. The crude product was purified by column chromatography (hexane/ethyl acetate = 30:1) to give the title product (127 mmol scale) as a white solid: ^1H NMR (400 MHz, CDCl_3) δ 7.85 (dt, J = 8.4 Hz, 2.0 Hz, 2H), 7.79–7.75 (m, 2H), 7.60 (tt, J = 7.4, 2.9 Hz, 1H), 7.55–7.46 (m,

4H); ^{13}C NMR (400 MHz, CDCl_3) δ 195.8, 137.5, 137.0, 136.8, 132.6, 131.4, 129.9, 128.4, 100.1; HRMS (EI) m/z calcd. for $\text{C}_{13}\text{H}_9\text{IO}$: 307.9698; found: 307.9697.

1-(4-Iodophenyl)-1-pentanone (1d). The synthesis from *p*-diiodobenzene and pentanoyl chloride was carried out as described above. The crude product was purified by column chromatography (hexane/ethyl acetate = 20:1) to give the title product (76 mmol scale, 77%) as a white solid: ^1H NMR (400 MHz, CDCl_3) δ 7.82 (dt, J = 8.8 Hz, 2.0 Hz, 2H), 7.67 (dt, J = 8.4 Hz, 2.2 Hz, 2H), 2.92 (t, J = 7.4 Hz, 2H), 1.71 (quint, J = 7.6 Hz, 2H), 1.40 (sext, J = 7.4 Hz, 2H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, CDCl_3) δ 199.7, 137.8, 136.3, 129.5, 100.7, 38.2, 26.3, 22.4, 13.9; HRMS (EI) m/z calcd. for $\text{C}_{11}\text{H}_{13}\text{IO}$: 288.0011; found: 288.0016.

1-(4-Iodophenyl)-1-propanone. The synthesis *p*-diiodobenzene and propanoyl chloride was carried out as described above. The crude product was purified by column chromatography (hexane/ethyl acetate = 20:1) to give the title product (76 mmol scale, 56%) as a white solid: ^1H NMR (400 MHz, CDCl_3) δ 7.81 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 2.96 (q, J = 7.3 Hz, 2H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, CDCl_3): δ 200.0, 137.8, 136.1, 129.4, 100.7, 31.7, 8.1; HRMS (EI) m/z calcd. for $\text{C}_9\text{H}_9\text{IO}$: 259.9698; found: 259.9698.

1-(5-Iodothiophen-2-yl)pentan-1-one. The synthesis from 2,5-diiodothiophene and pentanoyl chloride was carried out as described above. The crude product was purified by column chromatography (hexane/ethyl acetate = 20:1) to give the title product (30 mmol scale, 53%) as a slightly yellow solid: ^1H NMR (400 MHz, CDCl_3) δ 7.32 (d, J = 4.0 Hz, 1H), 7.29 (d, J = 4.0 Hz, 1H), 2.82 (t, J = 7.6 Hz, 2H), 1.71 (quint, J = 7.5 Hz, 2H), 1.39 (sext, J = 7.4 Hz, 2H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR (400 MHz, CDCl_3): δ 192.0, 150.2, 138.0, 132.4, 84.8, 38.7, 26.7, 22.4, 13.8; HRMS (APCI) calcd. for $\text{C}_9\text{H}_{12}\text{IOS}^+ [\text{M}+\text{H}]^+$: 294.9648; found: 294.9640.

2. Generation and Reactions of Acyl-Substituted Aryllithium Species with MeOH (General Procedure). A flow microreactor system consisting of three T-shaped micromixers (M1, M2 and M3), three microtube reactors (R1, R2 and R3) was used. A solution of 2-bromomesitylene (0.18 M in THF, 5.0 mL min⁻¹) and a solution of *n*-BuLi (0.43 M in hexane, 1.8 mL min⁻¹) were introduced to M2 ($\phi = 250\ \mu\text{m}$) by syringe pumps. The resulting solution was passed through R1 ($\phi = 1000\ \mu\text{m}$, $L = 210\ \text{cm}$ (100 cm at 0 °C, 10 cm at ambient temperature and 100 cm at -70 °C)) and was mixed with a solution of acyliodobenzene (0.20 M in THF, 3 mL min⁻¹) in M2 ($\phi = 250\ \mu\text{m}$). The resulting solution was passed through R2 (various size) and was mixed with a solution of MeOH (0.60 M in THF, 2.0 mL min⁻¹) in M3 ($\phi = 250\ \mu\text{m}$). The resulting solution was passed through R3 ($\phi = 1000\ \mu\text{m}$, $L = 50\ \text{cm}$). After a steady state was reached, the product solution was collected for 30 s while being quenched with sat. NH₄Cl solution. The reaction mixture was analyzed by GC. The results are summarized in Table 2 and Table 3.

Table 2. The I-Li exchange reaction of acyliodobenzene **1** and reaction with MeOH.^a

Substrate	ϕ of R2 (μm)	L of R2 (μm)	t^{R} in R2 (s)	GC yield of 3 (%)
<i>o</i> -COBu 1a	250	1.0 ^b	0.003	90
	250	2.0 ^b	0.006	80
	250	3.3	0.010	78
	250	5.0	0.015	73
	500	8.3	0.100	58
	1000	10.4	0.500	49
	1000	20.8	1.000	37
	1000	62.4	3.000	23
<i>o</i> -COEt 1b	250	1.0 ^b	0.003	83
	250	2.0 ^b	0.006	69
	250	3.3	0.010	68
	250	5.0	0.015	55
	500	8.3	0.100	42
	1000	10.4	0.500	34
	1000	20.8	1.000	23
	1000	62.4	3.000	15
<i>o</i> -COMe 1c	250	1.0 ^b	0.003	77
	250	2.0 ^b	0.006	58
	250	3.3	0.010	52
	250	5.0	0.015	43
	500	8.3	0.100	27
	1000	10.4	0.500	15
	1000	20.8	1.000	14
	1000	62.4	3.000	13
<i>p</i> -COBu 1d	250	1.0 ^b	0.003	67
	250	2.0 ^b	0.006	55
	250	3.3	0.010	33
	250	5.0	0.015	29
	500	8.3	0.100	16
	1000	10.4	0.500	6
	1000	20.8	1.000	5
	1000	62.4	3.000	3
<i>p</i> -COMe 1e	250	1.0 ^b	0.003	54
	250	2.0 ^b	0.006	37
	250	3.3	0.010	21
	250	5.0	0.015	15
	500	8.3	0.100	12
	1000	10.4	0.500	4
	1000	20.8	1.000	4
	1000	62.4	3.000	5

^a In all cases, conversion > 90%. ^b The integrated microreactor was used to control residence time very shortly.

Table 3. The I-Li exchange reaction of **1a** and reaction with MeOH.^a

ϕ of R2 (μm)	L of R2 (μm)	t^R in R2 (s)	GC yield of product 3a (%)	GC yield of byproduct 4 (%)
250	1.0 ^a	0.003	90	7
250	2.0 ^a	0.006	80	12
250	3.3	0.010	78	16
250	5.0	0.015	73	15
500	8.3	0.100	58	31
1000	10.4	0.500	49	51
1000	20.8	1.000	37	62
1000	62.4	3.000	23	74

^a The integrated microreactor was used to control residence time very shortly.

Valerophenone (3a). Colorless oil; 90% yield; the spectral data were identical to those of commercially available compound.

1-Butyl-3-butyldiene-1-phenyl-1,3-dihydroisobenzofuran (4). To characterize byproduct **4** the reaction was carried out using longer **R2** (ϕ = 1000 μm , L = 62.4 cm), which led to the formation of **4** as a major product. The product solution was collected for 180 s while being quenched with 1 M HCl solution (50 mL). The organic layer was separated and the remaining aqueous layer was extracted with Et₂O (50 mL $\times$ 3). The combined organic layers were dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography (hexane) to give the title product (98.2 mg, 71%) as a colorless oil; Slightly unstable in air; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.57–7.50 (m, 2H), 7.50–7.45 (m, 2H), 7.36–7.18 (m, 5H), 5.06 (t, J = 7.4 Hz, 1H), 2.37–2.13 (m, 4H), 1.49 (sext, J = 7.0 Hz, 2H), 1.30–0.99 (m, 4H), 0.96 (t, J = 7.2 Hz, 3H), 0.76 (t, J = 7.0 Hz, 3H); ¹³C NMR (400 MHz, DMSO-*d*₆): δ 153.5, 145.2, 144.4, 132.6, 128.3, 128.2, 127.9, 126.9, 124.3, 121.8, 119.4, 94.8, 91.2, 39.8, 26.8, 25.5, 22.6, 22.1, 13.7, 13.7; HRMS (ESI) calcd. for C₂₂H₂₇O⁺ [M+H]⁺: 307.2056; found: 307.2057.

3. Reactions with various electrophiles. A flow microreactor system consisting of three T-shaped micromixers (M1, M2 and M3), three microtube reactors (R1, R2 and R3) was used. A solution of 2-bromomesitylene (0.18 M in THF, 5.0 mL min⁻¹) and a solution of *n*-BuLi (0.43 M in hexane, 1.8 mL min⁻¹) were introduced to M2 (ϕ = 250 μm) by syringe pumps. The resulting solution was passed through R1 (ϕ = 1000 μm ,

$L = 210$ cm (100 cm at 0 °C, 10 cm at ambient temperature and 100 cm at -70 °C)) and was mixed with a solution of acyliodobenzene (0.20 M in THF, 3.0 mL min⁻¹) in M2 ($\phi = 250$ μ m). The resulting solution was passed through R2 (various size) and was mixed with a solution of electrophile (0.60 M in THF or Et₂O for methyl triflate or trimethylsilyl triflate, 2 mL min⁻¹) in M3 ($\phi = 250$ μ m). The resulting solution was passed through R3 ($\phi = 1000$ μ m, $L = 50$ cm). After a steady state was reached, the product solution was collected for 30 s while being quenched with 15 mL of sat. NH₄Cl solution (or 1M HCl solution to form dehydrated compound). After Et₂O (20 mL) was added, the organic layer was separated and the remaining aqueous layer was extracted with Et₂O (25 mL $\times$ 3). The combined organic layers were dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography. *Only in case of 1-butyl-3-phenyl-1,3-dihydroisobenzofuran-1-ol, the crude product was purified by recrystallization, because the compound was seemed to be unstable in acidic condition.*

Methyl 2-pentanoylbenzoate. Colorless oil; 68% yield; ¹H NMR (400 MHz, CDCl₃) δ 7.89 (ddd, $J = 7.6, 1.4, 0.4$ Hz, 1H), 7.56 (td, $J = 7.5, 1.3$ Hz, 1H), 7.49 (td, $J = 7.7, 1.5$ Hz, 1H), 7.35 (ddd, $J = 7.7, 1.3, 0.7$ Hz, 1H), 3.89 (s, 3H), 2.80 (t, $J = 7.6$ Hz, 2H), 1.71 (quint, 7.5 Hz, 2H), 1.40 (sext, $J = 7.4$ Hz, 2H), 0.94 (t, $J = 7.2$ Hz, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 205.5, 167.0, 143.0, 131.9, 129.6, 129.4, 128.3, 126.1, 52.2, 42.2, 25.9, 22.0, 13.7; HRMS (EI) m/z calcd. for C₁₃H₁₆O₃: 220.1099; found: 220.1133.

1-(2-(Trimethylsilyl)phenyl)pentan-1-one. White solid; 86% yield; ¹H NMR (400 MHz, CDCl₃) δ 7.87 (d, $J = 7.6$ Hz, 1H), 7.74 (d, $J = 7.6$ Hz, 1H), 7.54–7.41 (m, 2H), 2.97 (t, $J = 7.4$ Hz, 2H), 1.72 (quint, 7.6 Hz, 2H), 1.42 (sext, $J = 7.5$ Hz, 2H), 0.96 (t, $J = 7.4$ Hz, 3H), 0.29 (s, 1H); ¹³C NMR (400 MHz, CDCl₃) δ 203.1, 142.9, 141.9, 136.0, 131.2, 128.7, 128.7, 39.1, 26.7, 22.5, 13.9, 0.38; HRMS (ESI) calcd. for C₁₄H₂₂OSiNa⁺ [M+Na]⁺: 257.1332; found: 257.1332.

1-(2-(Tributylstannyl)phenyl)pentan-1-one. Colorless oil; 86% yield; ¹H NMR (400 MHz, CDCl₃) δ 7.99 (d, $J = 6.8$ Hz, 1H), 7.77–7.63 (m, 1H), 7.54–7.46 (m, 1H), 7.44–7.37 (m, 1H), 3.00 (t, $J = 7.4$ Hz, 2H), 1.71 (quint, 7.5 Hz, 2H), 1.54–1.34 (m, 8H), 1.29 (sext, $J = 7.3$ Hz, 6H), 1.11–0.89 (m, 9H), 0.85 (t, $J = 7.4$ Hz, 9H); ¹³C NMR (400 MHz, CDCl₃) δ 202.1, 146.0, 141.6, 137.5, 131.8, 129.4, 127.9, 38.1, 29.3, 27.5, 27.1, 22.5, 13.9, 13.7, 11.0; HRMS (APCI) calcd. for C₂₃H₃₉OSn⁻ [M-H]⁻: 451.2028; found: 451.2009.

3-Butylidene-1-methyl-1-phenyl-1,3-dihydroisobenzofuran. Colorless oil; Slightly unstable in air; 81% yield; ^1H NMR (400 MHz, DMSO- d_6) δ 7.57–7.40 (m, 4H), 7.37–7.22 (m, 5H), 5.09 (t, J = 7.4 Hz, 1H), 2.34–2.17 (m, 2H), 1.48 (sext, J = 7.4 Hz, 2H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (400 MHz, DMSO- d_6) δ 153.0, 146.4, 144.8, 132.1, 128.4, 128.3, 128.0, 127.2, 124.3, 121.7, 119.5, 95.1, 88.8, 27.5, 26.8, 22.6, 13.7; HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{21}\text{O}^+$ $[\text{M}+\text{H}]^+$: 265.1587; found: 265.1588.

3-Butylidene-1-cyclohexyl-1-phenyl-1,3-dihydroisobenzofuran. Colorless oil; Slightly unstable in air; 81% yield; ^1H NMR (400 MHz, DMSO- d_6) δ 7.61–7.53 (m, 3H), 7.49–7.43 (m, 1H), 7.37–7.17 (m, 5H), 5.03 (t, J = 7.6 Hz, 1H), 2.44–2.26 (m, 3H), 1.69–1.45 (m, 5H), 1.43–1.31 (m, 1H), 1.22–0.90 (m, 5H); ^{13}C NMR (400 MHz, DMSO- d_6) δ 153.8, 144.5, 143.8, 132.8, 128.3, 128.2, 127.8, 126.7, 124.3, 121.9, 119.3, 94.4, 93.5, 45.7, 26.8 and 26.8, 26.1, 25.8 and 26.8, 25.5, 22.6, 13.8; HRMS (APCI) calcd. for $\text{C}_{24}\text{H}_{29}\text{O}^+$ $[\text{M}+\text{H}]^+$: 333.2213; found: 333.2216.

1-Butyl-3-phenyl-1,3-dihydroisobenzofuran-1-ol. White solid; 60% yield; ^1H NMR (400 MHz, DMSO- d_6) δ 7.51 (d, J = 7.2 Hz, 2H), 7.38–7.24 (m, 6H), 6.98 (d, J = 7.2 Hz, 1H), 6.63 (s, 1H), 5.99 (s, 1H), 2.05–1.89 (m, 2H), 1.42–1.18 (m, 3H), 1.12–0.95 (m, 1H), 0.82 (t, J = 7.4 Hz, 3H); ^{13}C NMR (400 MHz, DMSO- d_6) δ 142.7, 142.6, 141.2, 128.5, 128.0, 127.6, 127.4, 126.8, 122.2, 121.7, 109.0, 83.1, 40.5, 25.8, 22.2, 13.9; HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{19}\text{O}_2^-$ $[\text{M}-\text{H}]^-$: 267.1391; found: 267.1382.

Propiophenone. 83% GC yield (GC t_R 13.9 min).

1-(2-(Trimethylsilyl)phenyl)propa-1-one. Colorless oil; 81% yield; ^1H NMR (400 MHz, CDCl_3) δ 7.85 (dd, J = 7.6, 0.8 Hz, 1H), 7.73 (ddd, J = 7.2, 1.4, 0.5 Hz, 1H), 7.50 (td, J = 7.3, 1.5 Hz, 1H), 7.44 (td, J = 7.6, 1.6 Hz, 1H), 3.00 (q, J = 7.3 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, CDCl_3) δ 203.6, 142.9, 141.7, 135.9, 131.2, 128.7, 128.5, 32.6, 8.5, 0.32; HRMS (APCI) calcd. for $\text{C}_{12}\text{H}_{17}\text{OSi}^-$ $[\text{M}-\text{H}]^-$: 205.1054; found: 205.1043.

Methyl 2-propionylbenzoate. Colorless oil; 65% yield; ^1H NMR (400 MHz, CDCl_3) δ 7.90 (dd, J = 8.2, 1.4 Hz, 1H), 7.57 (td, J = 7.5, 1.3 Hz, 1H), 7.49 (td, J = 7.6, 1.2 Hz, 1H), 7.34 (dd, J = 7.4, 1.4 Hz, 1H), 3.89 (s, 3H), 2.81 (q, J = 7.2 Hz, 2H), 1.23 (t, J = 7.4 Hz, 3H); ^{13}C NMR (400 MHz, CDCl_3) δ 206.5, 167.1, 143.4, 122.2, 129.9, 129.6, 128.2, 126.1, 52.5, 36.1, 8.1; HRMS (ESI) calcd. for $\text{C}_{11}\text{H}_{12}\text{O}_3\text{Na}^+$ $[\text{M}+\text{Na}]^+$: 215.0679;

found: 215.0679.

Acetophenone. 77% GC yield (GC t_R 11.9 min).

2'-Methylacetophenone. 42% GC yield (GC t_R 13.4 min).

N-Phenyl-4-pivaloylbenzamide. White solid; 84% yield; ^1H NMR (400 MHz, CDCl_3) δ 7.90 (dt, J = 8.8, 2.0 Hz, 2H), 7.83 (br s, 1H), 7.74 (dt, J = 8.8, 2.0 Hz, 2H), 7.65 (d, J = 7.6 Hz, 2H), 7.39 (tt, J = 8.0, 2.0 Hz, 2H), 7.18 (tt, J = 7.4, 1.2 Hz, 1H), 1.36 (s, 9H); ^{13}C NMR (400 MHz, CDCl_3) δ 209.4, 165.2, 141.5, 137.8, 136.6, 129.0, 127.7, 126.9, 124.7, 120.4, 44.3, 27.7; HRMS (APCI) calcd for $\text{C}_{18}\text{H}_{20}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$: 282.1489; found: 282.1492.

Cyclohexyl phenyl ketone. 78% GC yield (GC t_R 20.6 min).

Cyclohexyl(4-(hydroxy(phenyl)methyl)phenyl)methanone. White solid; 73% yield; ^1H NMR (400 MHz, CDCl_3) δ 7.91 (dt, J = 8.4, 2.0 Hz, 2H), 7.51–7.46 (m, 2H), 7.39–7.25 (m, 5H), 5.88 (s, 1H), 3.23 (tt, J = 11.2, 3.2 Hz, 1H), 1.93–1.78 (m, 4H), 1.78–1.19 (m, 7H); ^{13}C NMR (400 MHz, CDCl_3) δ 203.7, 148.7, 143.3, 135.1, 128.5, 128.4, 127.7, 126.5, 126.4, 75.6, 45.5, 29.3, 25.8, 25.7; HRMS (APCI) calcd. for $\text{C}_{20}\text{H}_{23}\text{O}_2^+$ $[\text{M}+\text{H}]^+$: 295.1693 found: 295.1693.

Cyclohexyl(4-(1-hydroxy-1-phenylethyl)phenyl)methanone. White solid; 76% yield; ^1H NMR (400 MHz, CDCl_3) δ 7.87 (dt, J = 8.8, 2.0 Hz, 2H), 7.50 (dt, J = 8.8, 2.0 Hz, 2H), 7.44–7.38 (m, 2H), 7.35–7.28 (m, 2H), 7.25 (tt, J = 7.2, 1.7 Hz, 1H), 3.22 (tt, J = 11.2, 3.2 Hz, 1H), 2.51 (br s, 1H), 1.96 (s, 3H), 1.91–1.77 (m, 4H), 1.77–1.65 (m, 1H), 1.53–1.19 (m, 5H); ^{13}C NMR (400 MHz, CDCl_3) δ 203.6, 152.8, 147.2, 134.7, 128.3, 128.2, 127.2, 125.9, 125.8, 76.0, 45.6, 30.5, 29.3, 25.9, 25.8; HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{24}\text{O}_2\text{Na}^+$ $[\text{M}+\text{Na}]^+$: 331.1669; found: 331.1670.

4-Benzoyl-N-phenylbenzamide. White solid; 70% yield; ^1H NMR (400 MHz, CDCl_3) δ 7.98 (d, J = 8.0 Hz, 2H), 7.93 (br s, 1H), 7.89 (d, J = 8.0 Hz, 2H), 7.84–7.79 (m, 2H), 7.67 (d, J = 7.6 Hz, 2H), 7.62 (dt, J = 7.2, 1.6 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.40 (t, J = 7.8 Hz), 7.19 (tt, J = 7.4, 1.6 Hz, 1H); ^{13}C NMR (400 MHz, CDCl_3) δ 196.1, 165.1, 140.1, 138.2, 137.7, 136.8, 133.0, 130.1, 130.0, 129.0, 128.4, 127.1, 124.8, 120.4; HRMS (APCI) calcd. for $\text{C}_{20}\text{H}_{16}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$: 302.1176; found: 302.1172.

Valerophenone. 67% GC yield (GC t_R 17.1 min); the spectral data were identical to those of commercially available compound.

4-Pentanoyl-*N*-phenylbenzamide. White solid; 51% yield; ^1H NMR (400 MHz, CDCl_3) δ 8.07 (dt, $J = 8.4, 1.6$ Hz, 2H), 7.96 (dt, $J = 8.4, 1.6$ Hz, 2H), 7.81 (br s, 1H), 7.65 (d, $J = 8.0$ Hz, 2H), 7.40 (t, $J = 7.8$ Hz, 2H), 7.19 (tt, $J = 7.4, 1.2$ Hz, 1H), 3.01 (t, $J = 7.4$ Hz, 2H), 1.75 (quint, $J = 7.5$ Hz, 2H), 1.43 (sext, $J = 7.4$ Hz, 2H), 0.97 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (400 MHz, CDCl_3) δ 199.9, 164.8, 139.5, 138.6, 137.6, 129.2, 128.5, 127.3, 124.9, 120.3, 38.7, 26.3, 22.4, 13.9; HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{20}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$: 282.1489; found: 282.1490.

Acetophenone. 54% GC yield (GC t_R 11.9 min); the spectral data were identical to those of commercially available compound.

1-(Thiophen-2-yl)pentan-1-one. Slightly yellow oil; 74% yield; ^1H NMR (400 MHz, CDCl_3) δ 7.71 (dd, $J = 3.8, 1.4$ Hz, 1H), 7.62 (dd, $J = 4.8, 1.2$ Hz, 1H), 7.13 (dd, $J = 5.2, 3.6$ Hz, 1H), 2.90 (t, $J = 7.4$ Hz, 2H), 1.74 (quint, $J = 7.5$ Hz, 2H), 1.41 (sext, $J = 7.5$ Hz, 2H), 0.95 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (400 MHz, CDCl_3) δ 193.5, 144.5, 133.3, 131.6, 128.0, 39.1, 26.9, 22.4, 13.9; HRMS (ESI) calcd. for $\text{C}_9\text{H}_{13}\text{OS}^+$ $[\text{M}+\text{H}]^+$: 169.0682; found: 169.0674.

1-(5-(Hydroxy(phenyl)methyl)thiophen-2-yl)pentan-1-one. Colorless oil; 77% yield; ^1H NMR (400 MHz, CDCl_3) δ 7.55 (d, $J = 4.0$ Hz, 1H), 7.46–7.30 (m, 5H), 6.91 (dd, $J = 3.8, 0.5$ Hz, 1H), 6.03 (d, $J = 4.0$ Hz, 1H), 2.83 (t, $J = 7.4$ Hz, 2H), 2.47 (d, $J = 4.0$ Hz, 1H), 1.70 (quint, $J = 7.5$ Hz, 2H), 1.39 (sext, $J = 7.4$ Hz, 2H), 0.93 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (400 MHz, CDCl_3) δ 193.8, 156.9, 143.2, 142.4, 131.7, 128.7, 128.3, 126.3, 125.2, 72.6, 38.8, 26.9, 22.4, 13.8; HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{18}\text{O}_2\text{SNa}^+$ $[\text{M}+\text{Na}]^+$: 297.0920; found: 297.0921.

5-Pentanoyl-*N*-phenylthiophene-2-carboxamide. White solid; 59% yield (purified by recrystallization from $\text{MeOH}/\text{CH}_2\text{Cl}_2$ mixture); ^1H NMR (400 MHz, CDCl_3) δ 7.71–7.57 (m, 4H), 7.66 (br s, 1H), 7.42–7.34 (m, 2H), 7.22–7.15 (m, 1H), 2.93 (t, $J = 7.6$ Hz, 2H), 1.75 (quint, $J = 7.6$ Hz, 2H), 1.42 (sext, $J = 7.4$ Hz, 2H), 0.96 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (400 MHz, $\text{DMSO}-d_6$) δ 193.7, 159.1, 146.7, 146.1, 138.2, 132.9, 129.6, 128.7, 124.1, 120.4, 37.9, 26.0, 21.7, 13.7; HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{17}\text{NO}_2\text{SNa}^+$ $[\text{M}+\text{Na}]^+$: 310.0872; found: 310.0875.

4. The Reactions Using High-Pressure Syringe Pumps. Solutions were introduced to the flow microreactor system using syringe pumps, Harvard Apparatus PHD 4400, equipped with stainless steel syringes purchased from Harvard Apparatus (#70-2255). A flow microreactor system consisting of T-shaped micromixer (M), integrated micro device (I), two microtube reactors (R1 and R2) was used. A solution of mesitylbromide (0.18 M in THF, 5X mL min⁻¹) and a solution of *n*-BuLi (0.43 M in hexane, 1.8X mL min⁻¹) were introduced to M (ϕ = 250 μ m) by syringe pumps. The resulting solution was passed through R1 (ϕ = 1000 μ m, L = 210 cm (100 cm at 0 °C, 10 cm at ambient temperature and 100 cm at -70 °C)) and was subsequently mixed with a solution of *p*-iodoacetophenone **1e** (0.18 M in THF, 5X mL min⁻¹) and a solution of MeOH (0.6 M in THF, 2X mL min⁻¹) in I (ϕ = 250 μ m, L = 10 cm). The resulting solution was passed through R3 (ϕ = 1000 μ m, L = 50 cm). After a steady state was reached, the product solution was collected for 30 s while being quenched with sat. NH₄Cl solution. The reaction mixture was analyzed by GC. The results are summarized in Table 4.

Table 4. The I-Li exchange reaction of *p*-iodoacetophenone (**1e**) using high-pressure syringe pumps.

X	Total flow rate (mL min ⁻¹)	Residence time (s)	Yield (%)
1.0	11.8	3.0	53
1.2	14.2	2.5	65
1.3	15.3	2.3	69
1.6	18.9	1.9	74
2.0	23.6	1.5	76
2.3	27.1	1.3	75

When benzaldehyde was used as electrophile instead of MeOH, desired product was formed in 78% isolated yield.

1-(4-(Hydroxy(phenyl)methyl)phenyl)ethanone. Colorless oil; 78% isolated yield; the spectral data were identical to those of reported in the literature.¹⁰

5. Formal Total Synthesis of Pauciflorol F

1-(3,5-Dimethoxyphenyl)-2-(4-methoxyphenyl)ethanone. 1 M CuCN·2LiCl THF solution (44 mL, 44.0 mmol) was added dropwise to a solution of 3,5-dimethoxyphenylmagnesium chloride (0.5 M in THF, 80 mL, 40.0 mmol) at -25 °C for 10 min. After stirred for 40 min at -20 °C, 4-methoxyphenylacetyl chloride (9.793 g, 53.0 mmol) was added dropwise for 5 min. After a solution was slowly warmed to -10 °C during 1 h, the reaction was quenched by slow addition of sat. NH₄Cl solution (120 mL). The organic layer was separated and the remaining aqueous layer was extracted with Et₂O (150 mL × 3). The combined organic layers were dried over Na₂SO₄ and concentrated. The crude product was purified by flash column chromatography (CHCl₃) and washed with cold hexane to obtain the title compound: slight red solid; 91% (10.390 g); ¹H NMR (400 MHz, CDCl₃) δ 7.18 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 2.0 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.63 (t, *J* = 2.2 Hz, 1H), 4.18 (s, 2H), 3.82 Hz (s, 6H), 3.79 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 197.4, 160.7, 158.4, 138.4, 130.3, 126.4, 114.0, 106.3, 105.1, 55.4, 55.0, 44.6; HRMS (APCI) calcd. for C₁₇H₁₉O₄⁺ [M+H]⁺: 287.1278; found: 287.1280.

1-(2-Iodo-3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)ethanone (5). Iodobenzene diacetate (242.0 mg, 0.75 mmol) was added to a solution of 1-(3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)ethanone (146.8 mg, 0.51 mmol) and iodine (70.9 mg, 0.28 mmol) in CH₂Cl₂ (4 mL) at 0 °C. After stirred for 0 °C for 10 h, a solution was slowly warmed to ambient temperature. After stirred for 14 h, the reaction was quenched by addition of half-saturated Na₂S₂O₃ solution (10 mL). The organic layer was separated and the remaining aqueous layer was extracted with CH₂Cl₂ (25 mL × 3). The combined organic layers were dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography (hexane/ethyl acetate = 4:1) to obtain the title compound: white solid; 74% (156.2 mg); ¹H NMR (400 MHz, CDCl₃) δ 7.19 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.43 (d, *J* = 2.8 Hz, 1H), 6.28 (d, *J* = 2.8 Hz, 1H), 4.13 (s, 2H), 3.89 (s, 3H), 3.80 (s, 3H), 3.75 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 203.7, 161.1, 158.8, 158.6, 147.9, 130.8, 125.2, 113.9, 104.1, 99.5, 71.8, 56.5, 55.6, 55.2, 48.4; HRMS (APCI) calcd. for C₁₇H₁₈IO₄⁺ [M+H]⁺: 413.0244; found: 413.0238.

3-(3,5-Dimethoxyphenyl)-4,6-dimethoxy-1-(4-methoxybenzylidene)-1,3-dihydroisobenzofuran (6). A flow microreactor system consisting of T-shaped micromixer (M), integrated micro device (I), two microtube reactors (R1 and R2) was used. A solution of

mesitylbromide (0.18 M in THF, 5.0 mL min⁻¹) and a solution of *n*-BuLi (0.43 M in hexane, 1.8 mL min⁻¹) were introduced to M (ϕ = 250 μ m) by syringe pumps. The resulting solution was passed through R1 (ϕ = 1000 μ m, *L* = 210 cm (100 cm at 0 °C, 10 cm at ambient temperature and 100 cm at -70 °C)) and was subsequently mixed with a solution of acyliodobenzene **5** (0.18 M in THF, 5.0 mL min⁻¹) and a solution of 3,5-dimethoxybenzaldehyde (0.60 M in THF, 2.0 mL min⁻¹) in I (ϕ = 250 μ m, *L* = 10 cm). The resulting solution was passed through R2 (ϕ = 1000 μ m, *L* = 50 cm). After a steady state was reached, the product solution was collected for 5 min while being quenched with H₂O (20 mL). After 1M HCl solution (80 mL) was added, the organic layer was separated and the remaining aqueous layer was extracted with Et₂O (100 mL $\times$ 3). The combined organic layers were dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography (hexane/ethyl acetate = 2:1) to obtain the title compound: white solid; Slightly unstable in air; 81% yield (1.058 g); ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.59 (dt, *J* = 9.2, 2.4 Hz, 2H), 6.93 (d, *J* = 1.6 Hz, 1H), 6.89 (dt, *J* = 9.2, 2.4 Hz, 2H), 6.53 (s, 1H), 6.52 (d, *J* = 2.0 Hz, 1H), 6.45 (t, *J* = 2.4 Hz, 1H), 6.41 (d, *J* = 2.4 Hz, 2H), 6.12 (s, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 3.69 (s, 3H), 3.69 (s, 6H); ¹³C NMR (400 MHz, DMSO-*d*₆) δ 162.0, 160.3, 157.1, 154.8, 153.5, 142.1, 136.8, 128.8, 128.6, 121.6, 113.8, 104.9, 99.7, 99.4, 95.9, 95.1, 85.3, 55.6, 55.5, 55.0, 54.9; HRMS (APCI) calcd. for C₂₆H₂₇O₆⁺ [M+H]⁺: 435.1802; found: 435.1795.

3-(3,4-Dimethoxyphenyl)-4,6-dimethoxy-2-(4-methoxyphenyl)-1H-inden-1-one (**7**).

The conc. HCl aqueous solution (4 mL) was added dropwise for 30 min to a solution of **6** (44.0 mg, 0.101 mmol) in *i*-PrOH (20 mL) at 25 °C. After stirred for 12 h, the reaction was quenched by slow addition of sat. NaHCO₃ aqueous solution (60 mL) and water (40 mL) at 0 °C. The organic layers were extracted with ethyl acetate (40 mL $\times$ 3) and washed with brine (40 mL). The combined organic layers were dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography (hexane/ethyl acetate = 3:1) to obtain the title compound: red solid; 75% (32.7 mg); ¹H NMR (400 MHz, CDCl₃) δ 7.12 (dt, *J* = 9.2, 2.6 Hz, 2H), 6.86 (d, *J* = 2.0 Hz, 1H), 6.75 (dt, *J* = 8.8, 2.6 Hz, 2H), 6.49 (d, *J* = 2.4 Hz, 2H), 6.43 (t, *J* = 2.2 Hz, 2H), 3.86 (s, 3H), 3.76 (s, 3H), 3.70 (s, 6H), 3.61 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 196.6, 162.5, 160.2, 158.7, 156.6, 154.7, 137.0, 134.1, 131.0, 130.6, 123.6, 122.7, 113.4, 106.5, 104.1, 102.7, 101.0, 55.9, 55.7, 55.3, 55.1; HRMS (ESI) calcd. for C₂₆H₂₄NaO₆⁺ [M+Na]⁺: 455.1465; found: 455.1451.

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