

Generation and Reactions of *o*-Bromophenyllithium without Benzyne Formation Using a Microreactor

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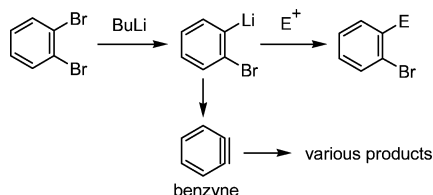
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Chemical synthesis in microreactors has received significant research interests both from academia and industry.^{1,2} Among characteristic features of microreactors, residence time control in the microchannel is especially important.³ The length of time that the solution remains inside the reactor, that is, residence time, can be greatly reduced by reducing the microchannel length and increasing the flow speed. On the basis of residence time control, a highly unstable intermediate can be transferred to another location where the follow-up reaction is conducted. Fast heat transfer, which minimizes local deviation of temperature, is another important feature of microsystems. In this paper, we wish to demonstrate that these features are extremely useful in analyzing and controlling reactions involving highly unstable organometallic intermediates.

We chose to study lithiation of *o*-dibromobenzene because *o*-bromophenyllithium thus generated is well-known to undergo rapid elimination to form benzyne, which gives various undesired products, even at $-78\text{ }^{\circ}\text{C}$.^{4,5} Therefore, in the case of a macroscale batch reactor, the Br–Li exchange reaction should be carried out at $-100\text{ }^{\circ}\text{C}$ or below, and an electrophile should be added at the same temperature. We began with optimizing the conditions of the

Scheme 1



Br–Li exchange reaction⁶ using the microsystem involving T-shaped micromixers⁷ shown in Figure 1. *o*-Bromophenyllithium was trapped by the reaction with methanol and the yield of bromobenzene was determined.

The reactions were carried with varying the residence time⁸ and temperature⁹ in the microtube reactor **R1**. As profiled in Figure 2a, the yield was very low at temperatures higher than $-60\text{ }^{\circ}\text{C}$, presumably because of the decomposition of *o*-bromo-phenyllithium intermediate to benzyne. At lower temperatures, the yield increased with the decrease of the temperature because of slower benzyne formation. Further decrease of temperature, however, resulted in the decrease of the yield, because Br–Li exchange reaction did not complete at lower temperatures. The effect of the residence time is interesting as shown in Figure 2b. At $-70\text{ }^{\circ}\text{C}$, the yield increased with the residence time and became the maximum at residence time of 0.8 s. This phenomenon can be explained in terms of the progress of Br–Li exchange with the residence time. Further increase of the residence time caused decrease of the yield, presumably because of the benzyne formation. It is important to note that the present temperature–residence-time profile is quite effective

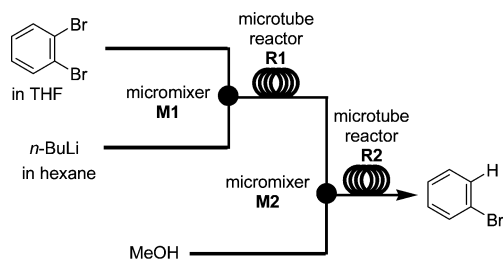


Figure 1. Microsystem for Br–Li exchange reaction.

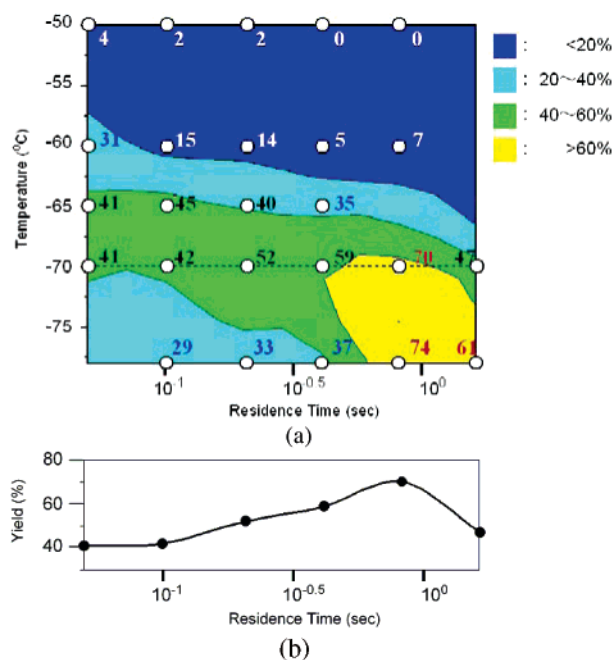




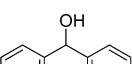


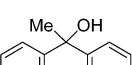


Figure 2. Effects of temperature and residence time on the yield of bromobenzene. (a) Counter plot with scatter overlay of the yields (%); (b) crossover at $-70\text{ }^{\circ}\text{C}$.

to unveil the features of the Br–Li exchange reaction together with the stability of *o*-bromophenyllithium, although the efficiency of the mixing may also affect the residence time. Therefore, microflow systems serve as a powerful tool for mechanistic studies on reactions involving highly unstable intermediates.

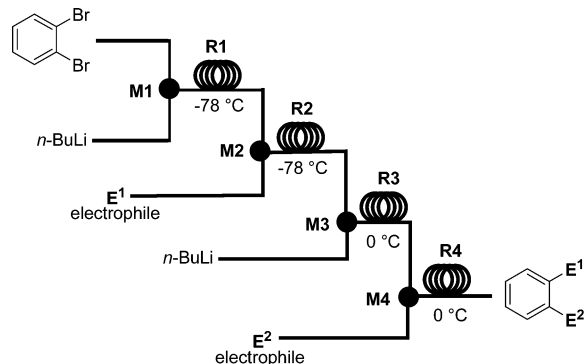
Using the optimized conditions ($-78\text{ }^{\circ}\text{C}$, 0.8 s), the reactions with various electrophiles were examined. Methyl triflate, chlorodimethylsilane, trimethylsilyl triflate, chlorotributyl-stannane, aldehydes, and ketones were effective to give the corresponding substituted bromobenzene derivatives (Table 1).

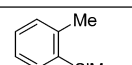
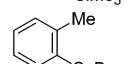

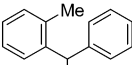

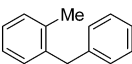

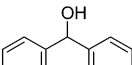
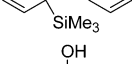
With successful generation and reactions of *o*-bromophenyllithium intermediate in hand, we next examined the sequential use of two bromine atoms in *o*-dibromobenzene with Br–Li exchange

Table 1. Reactions of *o*-Bromophenyllithium with Electrophiles

electrophile	product	% yield	electrophile	product	% yield
MeOTf		79 ^a			75 ^a
HMe ₂ SiCl		68 ^a			81 ^a
Me ₃ SiOTf		69 ^a			
Bu ₃ SnCl		81 ^b			

^a Determined by GC. ^b Isolated yield.

**Figure 3.** Sequential reactions of *o*-dibromobenzene.**Table 2.** Sequential Reactions of *o*-Dibromobenzene with Two Electrophiles Using the Microflowsystem

electrophile (E ¹)	electrophile (E ²)	product	% yield
MeOTf	Me ₃ SiCl		67 ^a
	Bu ₃ SnCl		62 ^a
			61 ^a
			53 ^a
	Me ₃ SiCl		74 ^a
	Bu ₃ SnCl		58 ^b

^a Determined by GC. ^b Isolated yield

reactions followed by the reaction with electrophiles using the microsystem consisting of four micromixers and four microtube reactors shown in Figure 3. The reaction temperature for microtube reactors **R1** and **R2** was $-78\text{ }^{\circ}\text{C}$, whereas that for **R3** and **R4** was $0\text{ }^{\circ}\text{C}$, because the second aryllithium intermediate should be much more stable than *o*-bromophenyllithium. As shown in Table 2, the sequential introduction of two groups on the benzene ring was

successfully achieved with various electrophiles. The method adds a new dimension in organolithium chemistry.

In conclusion, we have revealed that microflow systems serve as a powerful tool for mechanistic studies on reactions involving highly unstable intermediates such as *o*-bromophenyllithium, which is known to decompose to benzyne very quickly even at $-78\text{ }^{\circ}\text{C}$. It is also noteworthy that an efficient way of controlling the generation and reactions of highly reactive intermediates can be accomplished by virtue of precise residence time control and temperature control inherent in microsystems. Various applications based on the present principle are now in progress in our laboratory.

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Supporting Information Available: Experimental procedures, spectroscopic data of compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- Although it is difficult to determine the mixing time for the T-shape mixers, it seems to be much less than 0.8 sec at the present flow rate, because most of the starting material (*o*-dibromobenzene) was consumed within this residence time.
- Residence time was controlled by changing the length of **R1** with the fixed flow rate.
- Microtube reactors made by stainless steel are quite effective for rapid heat transfer. Thermal decomposition of a radical initiator revealed that the temperature inside the microtube reactor is practically the same as the bath temperature even if highly exothermic radical polymerization takes place in the microtube reactor. See, Iwasaki, T.; Yoshida, J. *Macromolecules* **2005**, *38*, 1159.

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