CHEMISTRY
AN ASIAN JOURNAL

DOI: 10.1002/asia.200700231

Integrated Micro Flow Synthesis Based on Sequential Br–Li Exchange Reactions of *p*-, *m*-, and *o*-Dibromobenzenes

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Abstract: A micro flow system consisting of micromixers and microtube reactors provides an effective method for the introduction of two electrophiles onto *p*-, *m*-, and *o*-dibromobenzenes. The Br–Li exchange reaction of *p*-dibromobenzene with *n*BuLi can be conducted by using the micro flow system at 20 °C, although much lower temperatures (< −48 °C) are needed for a batch reaction. The resulting *p*-bromophenyllithium was allowed to react with an electrophile in the micro flow system at 20 °C. The *p*-substituted bromobenzene thus obtained was subjected to a second Br–Li exchange reaction followed by reaction with a second electrophile at 20 °C in one flow. A similar transformation can be carried out with *m*-dibromobenzene by using the micro flow system. However, the Br–Li exchange reaction of *o*-dibromobenzene followed by reaction with an electrophile should be conducted at −78 °C to avoid benzyne formation. The second Br–Li exchange reaction followed by reaction with an electrophile can be carried out at 0 °C. By using the present method, a variety of *p*-, *m*-, and *o*-disubstituted benzenes were synthesized in one flow at much higher temperatures than are required for conventional batch reactions.

Keywords: arenes · flow reactions · integrated micro flow synthesis · lithiation · microreactors

Introduction

The integration of chemical reactions has generated significant research interest, because the combination of plural reactions enables us to avoid the isolation of intermediate products.[1] Both tandem reactions,[2] in which the initial product undergoes further transformation under the applied reaction conditions, and one-pot reactions,[3] in which the initial product is used for subsequent transformation in the same reaction vessel by the addition of a second reagent, serve as powerful ways of synthesizing organic compounds. Very recently, one-flow reactions, in which the initial product is used for subsequent transformation by the addition of a second reagent in a continuous-flow system, have emerged as a new way of integrating chemical reactions.[4] Herein we report an example of the integration of chemical reactions by using a micro flow system in which the transformations can be conducted at much higher temperatures than those for macro batch systems by virtue of the advantages of micro flow systems.[5–8]

Generally, reactions that involve highly reactive and unstable intermediates with macro batch systems suffer from decomposition of the intermediates during accumulation. To avoid such decomposition, reactions are usually conducted at low temperatures. This problem can be solved by the use of a continuous-flow system, in which unstable intermediates are transferred to the next reactor and are subjected to a follow-up reaction immediately after generation. In micro flow systems in particular, the length of time that the solution remains inside the reactor, the residence time, can be greatly decreased by adjusting the length of the reactor and the flow rate. This feature of micro flow systems is extremely useful in controlling reactive species.[9] Unstable reactive species can be transferred to another location to be used in the next reaction before they decompose. Another important feature of flow systems is that sequential reactions can be conducted by simply connecting several micro flow reactors.

Fast heat transfer, which minimizes local variation in temperature, is also an important feature of micro flow systems.

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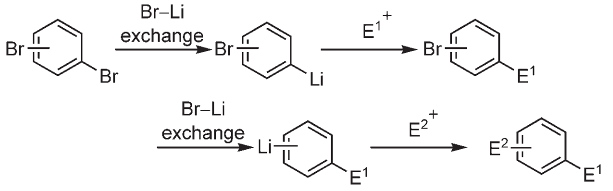
Fast and effective cooling through the reactor surface minimizes thermal decomposition of unstable intermediates due to hot spots generated by exothermic reactions. Importantly, macro flow systems suffer from heat-transfer problems because of their lower surface-to-volume ratios than those of micro systems.

We chose to study the sequential introduction of two electrophiles into dibromobenzenes based on the Br–Li exchange reaction,[10] because this type of transformation serves as one of the most straightforward methods for synthesizing disubsituted benzenes from dihalobenzenes (Scheme 1). We envisioned that the use of micro flow systems would enable us to conduct such transformations easily.



Scheme 1. Sequential introduction of two electrophiles into dibromobenzenes with the Br–Li exchange reaction.

Recently, we reported that the Br–Li exchange reaction of *o*-dibromobenzene can be conducted at −78 °C without benzyne formation by using a micro flow system, and that the sequential introduction of two electrophiles can be accomplished based on this reaction.[11] The successful preliminary results prompted us to perform a systematic study of the transformations of *p*-, *m*-, and *o*-dibromobenzenes. Herein we report the full details of our study of the sequential introduction of two electrophiles into *p*-, *m*-, and *o*-dibromobenzenes based on Br–Li exchange reactions by using micro flow systems.

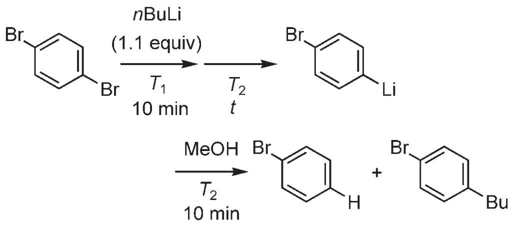
Abstract in Japanese:

マイクロミキサーとマイクロチューブリアクターから構成されるマイクロフローシステムを用いて *p*-, *m*-, *o*-ジブロモベンゼンに対して二つの異なる親電子剤の逐次導入を行った。*p*-, *m*-ジブロモベンゼンのハロゲン-リチウム交換反応は、バッチ型反応器で行う場合には−48 °C 以下の低温条件が必要であるが、マイクロフローシステムを用いた場合には 20 °C で行えることが分かった。また、o-ジブロモベンゼンのハロゲン-リチウム交換反応は、バッチ型反応器で行った場合には−78 °C で *o*-ブロモフェニルリチウムのベンザインへの分解反応が起こり、効率的に親電子剤の導入反応を行うことができなかったが、マイクロフローシステムを用いることにより、それが可能となった。さらに、このマイクロフローシステムを用いたハロゲン-リチウム交換反応を集積化することにより、*p*-, *m*-, *o*-二置換ベンゼン類の合成がバッチ型反応器に比べてより高い温度で効率的に行えることを明らかにした。

Results and Discussion

Sequential Introduction of Two Electrophiles into *p*-Dibromobenzene

First, we focused on the Br–Li exchange reaction of *p*-dibromobenzene to generate *p*-bromophenyllithium, which is the first and key step of the desired transformation. Before micro flow systems were used, the reaction with a conventional macro batch reactor was examined (Scheme 2). Such reactions are usually carried out at −78 °C in laboratory synthesis, although this temperature is not convenient for industrial synthesis.[12] Therefore, we examined the effect of temperature on the batch reaction.



Scheme 2. Br–Li exchange reaction of *p*-dibromobenzene with *n*BuLi followed by reaction with MeOH with the macro batch system.

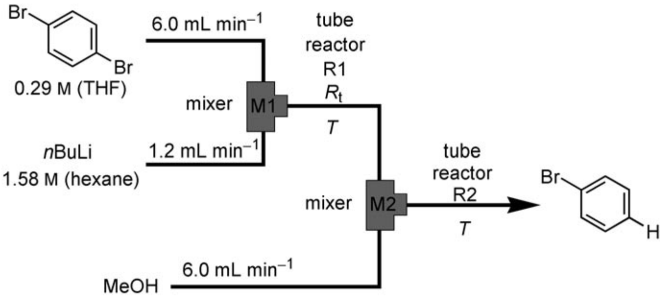
A solution of *n*BuLi in hexane was added dropwise (1 min) to a solution of *p*-dibromobenzene in THF in a 50-mL round-bottomed flask at temperature T_1 to generate *p*-bromophenyllithium. After the mixture was stirred for 10 min at T_1, the temperature was changed to T_2. The solution was kept there for time *t*, after which MeOH was added. After the mixture was stirred for 10 min at T_2, the solution was analyzed by gas chromatography (GC) to determine the yield of bromobenzene. It can be seen from Table 1 that the Br–Li exchange reaction should be carried out below −48 °C ($T_1 \leq -48$ °C), although the *p*-bromophenyllithium thus obtained can survive at 0 °C (T_2) for 5 min. *p*-Bromophenyllithium decomposes significantly at this temperature within 60 min. The major side product was *p*-bromobutylbenzene, which seems to be from the reaction of *p*-bromophenyllithium with 1-bromobutane produced by the Br–Li exchange reaction.

Table 1. Br–Li exchange reaction of *p*-dibromobenzene with *n*BuLi followed by reaction with MeOH with the macro batch system.

T_1 [°C]	T_2 [°C]	*t* [min]	Yield [%][a]	
			Bromobenzene	*p*-Bromobutylbenzene
−78	−78	5	82	0
−78	0	5	69	8
−78	0	60	11	41
−48	−48	5	71	0
−48	−48	60	70	3
−48	0	5	64	6
−48	0	60	10	38
0	0	5	14	6
0	0	60	5	6

[a] Determinated by GC.

To avoid such a side reaction, we next employed a micro flow system consisting of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2) (Scheme 3 and Figure 1). A solution of *p*-dibromobenzene (0.29 M) in THF (flow rate: 6 mL min^{-1}, 1.74 mmol min^{-1}) and a solution of *n*BuLi (1.58 M) in hexane (flow rate: 1.2 mL min^{-1}, 1.9 mmol min^{-1}) were introduced into M1 ($\phi = 250\ \mu m$) by using the technique of syringe pumping.[13] The mixture was passed through R1 ($\phi = 500$ or $1000\ \mu m$, length $= L$, residence time $= R_t$)[14] into M2 ($\phi = 500\ \mu m$), into which methanol (neat, flow rate: 6 mL min^{-1}) was also introduced. The resulting mixture was passed through R2 ($\phi = 1000\ \mu m$, $L = 50$ cm, $R_t = 1.79$ s). The temperature of the system was controlled by adjusting the bath temperature. The Br–Li exchange reaction and the quenching with MeOH were conducted at the same temperature. The residence time was adjusted by changing the length of the microtube reactor R1 at a fixed flow rate. After steady state was reached, an aliquot of the product solution was taken over 15 s. The amount of bromobenzene was determined by GC.



Scheme 3. Micro and macro flow system for the Br–Li exchange reaction of *p*-dibromobenzene followed by the reaction with MeOH.

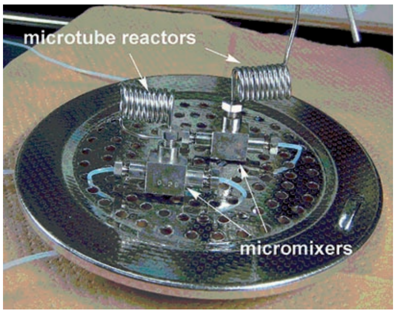


Figure 1. The micro flow system consisting of two micromixers and two microtube reactors.

The results obtained with varying temperature (T) and residence time (R_t) in R1 are summarized in Figure 2.[15,16] Interestingly, bromobenzene was obtained in good yields above −48 °C. The reaction can be conducted even at 20 °C, thus demonstrating a significant advantage of micro flow systems. Extremely fast heat transfer of the micro flow system seems to be responsible for preventing the side reaction.[17] In other words, the Br–Li exchange reaction can inherently be conducted at 20 °C, although the reaction in macro batch systems suffers from insufficient heat removal, which makes over-cooling necessary. At −40 to −78 °C, the yield increased with temperature. Presumably, the Br–Li exchange reaction is slow in this temperature range, and an increase in temperature causes an increase in the reaction rate. In this temperature range, the yield also increased with the residence time.

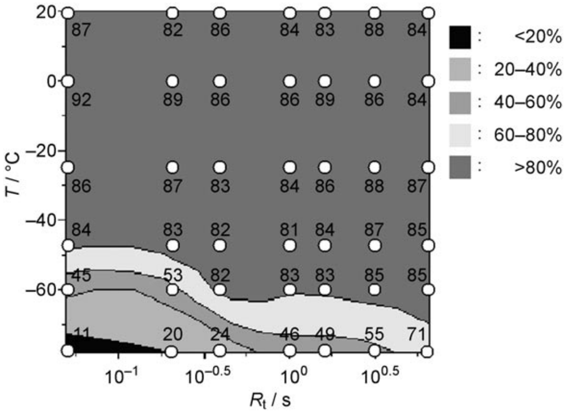


Figure 2. Effects of temperature and residence time on the yield of bromobenzene in the Br–Li exchange reaction of *p*-dibromobenzene with *n*BuLi with the micro flow system.

The importance of the micro system is well-supported by the flow control experiments with a macro flow system consisting of two T-shaped mixers (M1 and M2, $\phi = 2.3$ mm) and two macrotube reactors (R1: $\phi = 1.78$ or 2.58 mm, length $= L$, residence time $= R_t$; R2: $\phi = 1.78$ mm, $L = 15.9$ cm, $R_t = 3.27$ sec) (Scheme 3). As summarized in Table 2, the use of the macro flow systems resulted in much lower yields of bromobenzene. For example, in the case of $R_t = 1$ s, the reaction with a macro flow system (R1: $\phi = 1.78$ mm, 20 °C) gave the desired product in low yield (31 %), whereas the use of a micro flow system (R1: $\phi = 1000\ \mu m$, 20 °C) resulted in a much higher yield (84 %; Figure 2). Presumably, thermal decomposition of *p*-bromophenyllithium took place because of less-efficient heat transfer due to the low surface-to-volume ratio of the macro systems relative to the micro systems. Furthermore, the use of

Table 2. Br–Li exchange reaction of *p*-dibromobenzene with *n*BuLi followed by reaction with MeOH with the macro flow system at 20 °C.

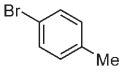
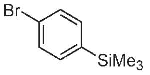
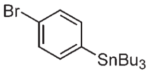
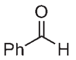
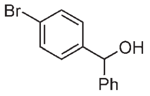
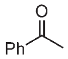
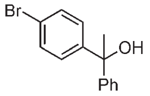
Macrotube reactor R1			Conv. [%][a]	Yield [%][a]
ϕ [mm]	L [cm]	R_t [s]		
1.78	4.8	1.0	64	31
	7.9	1.6	55	27
	15.9	3.3	72	30
	31.7	6.6	73	26
2.58	4.8	2.1	80	34
	7.5	3.3	54	18
	15.1	6.6	43	21

[a] Determinated by GC.

a macro flow system led to low reproducibility at flow rates similar to those of the micro flow case probably because of the instability of the flow. Therefore, conversion did not vary with residence time systematically. These results indicate that micro, not macro, flow systems are essential for conducting the present reaction at 20 °C.

The reactions of *p*-bromophenyllithium with various electrophiles were examined by using the micro flow system at 20 °C. Iodomethane, chlorotrimethylsilane, chlorotributylstannane, benzaldehyde, and acetophenone were effective. The reactions gave the corresponding *p*-substituted bromobenzene derivatives at 20 °C in good yields (Table 3).

Table 3. Br–Li exchange reaction of *p*-dibromobenzene with *n*BuLi followed by reaction with electrophiles with the micro flow system.

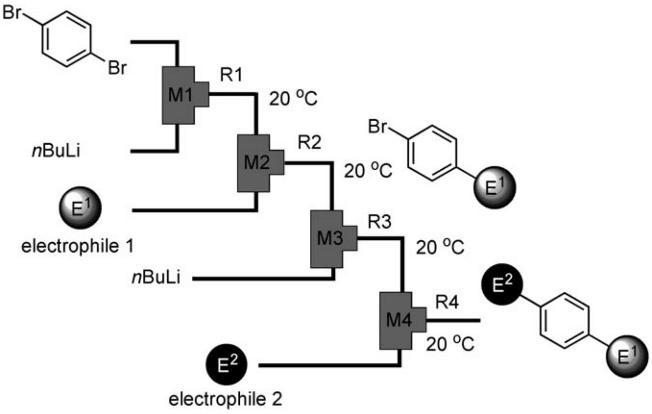
Electrophile	Product	Yield [%][a]
MeI		87
Me_3SiCl		85
Bu_3SnCl		86
		73
		87

[a] Determinated by GC.

With the successful Br–Li exchange reaction of *p*-dibromobenzene followed by the reaction with an electrophile by using the micro flow system in hand, we next examined the sequential introduction of two electrophiles into *p*-dibromobenzene with the micro flow system. This type of transformation has already been achieved by using a conventional macro batch system in a one-pot manner.[10] However, low reaction temperatures such as −78 °C are critical to avoid undesired side reactions. The requirement of such low temperatures causes severe limitations for industrial application.

A micro flow system consisting of four T-shaped micromixers (M1, M2, M3, and M4) and four microtube reactors (R1, R2, R3, and R4) (Scheme 4) was used. In this case, T-shaped micromixer M1 with an inside diameter of 500 instead of 250 μm was used to suppress the pressure increase due to the increase in the number of micromixers and microtube reactors in the system.

A solution of *p*-dibromobenzene (0.29 M) in THF (flow rate: 6 mL min^{-1}, 1.74 mmol min^{-1}) and a solution of *n*BuLi (1.58 M) in hexane (flow rate: 1.2 mL min^{-1}, 1.90 mmol min^{-1}) were introduced into M1 ($\phi=500$ μm) by syringe pumping. The mixture was passed through R1 ($\phi=1000$ μm, $L=6$ cm, $R_t=0.39$ s), and the resulting solution containing *p*-bromophenyllithium was introduced into M2 ($\phi=500$ μm), where a solution of the first electrophile (0.69 M) in THF (flow rate: 3 mL min^{-1}, 2.07 mmol min^{-1}) was also placed. The mixture was passed through R2 ($\phi=1000$ μm, $L=50$ or 200 cm, $R_t=2.31$ or 9.24 s), and the resulting solution containing the *p*-substituted bromobenzene was introduced into M3 ($\phi=500$ μm), where a solution of *n*BuLi (1.58 M) in hexane (flow rate: 1.8 mL min^{-1}, 2.84 mmol min^{-1}) was also placed. The mixture was passed through R3 ($\phi=1000$ μm, $L=12.5$ cm, $R_t=0.49$ s), and the resulting solution containing the second aryllithium intermediate was introduced into M4 ($\phi=500$ μm), where a solution of the second electrophile (1.72 M) in THF (flow rate: 3 mL min^{-1}, 5.16 mmol min^{-1}) was also placed. The mixture was passed through R4 ($\phi=1000$ μm, $L=50$ cm, $R_t=1.57$ s). All the reactions were conducted at 20 °C.



Scheme 4. Micro flow system for the sequential introduction of two electrophiles into *p*-dibromobenzene.

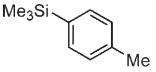
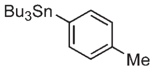
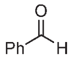
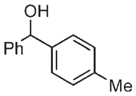
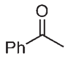
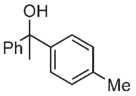
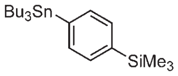
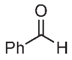
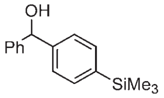
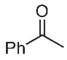
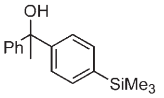
As summarized in Table 4, the sequential introduction of two electrophiles was achieved successfully with various combinations of electrophiles without isolation of the *p*-substituted bromobenzene intermediates. This integrated micro flow synthesis serves as a powerful and straightforward method for synthesizing various *p*-disubstituted benzenes from *p*-dibromobenzene and two electrophiles.

Sequential Introduction of Two Electrophiles into *m*-Dibromobenzene

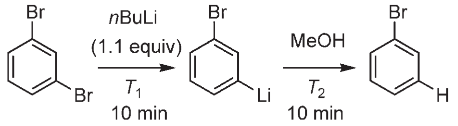
Next, we examined the sequential introduction of two electrophiles into *m*-dibromobenzene. The first step of this sequence is the Br–Li exchange reaction of *m*-dibromobenzene with *n*BuLi. The effect of temperature for the macro batch reaction was studied (Scheme 5), and the results are summarized in Table 5. Bromobenzene was obtained in good yields at $T_1 \leq -48$ °C. At higher temperatures, the yield decreased significantly. The effect of T_2 did not seem to be significant. These observations indicate that the Br–Li exchange reaction is more sensitive to temperature than the reaction of the *m*-bromophenyllithium thus generated with an electrophile.

The micro flow reactions were conducted with a system consisting of two T-shaped micromixers (M1 and M2) and

Table 4. Sequential introduction of two electrophiles onto *p*-dibromobenzene with the micro flow system.

Electrophile 1	Electrophile 2	Product	Yield [%][a]
MeI	Me_3SiCl		81
MeI	Bu_3SnCl		88
MeI			77
MeI			79
Me_3SiCl	Bu_3SnCl		79
Me_3SiCl			35
Me_3SiCl			79

[a] Determinated by GC.



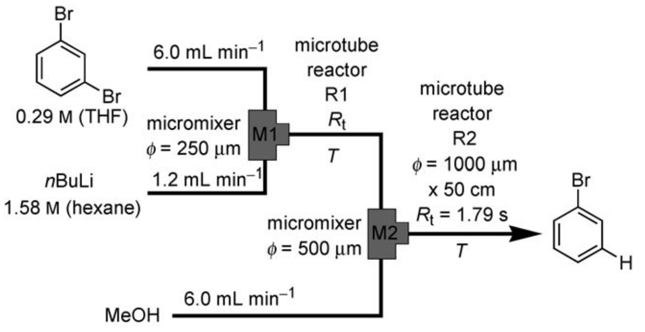
Scheme 5. Br–Li exchange reaction of *m*-dibromobenzene with *n*BuLi followed by the reaction with MeOH with the macro batch system.

Table 5. Br–Li exchange reaction of *m*-dibromobenzene with *n*BuLi followed by reaction with MeOH with a macro batch system.

T_1 [°C]	T_2 [°C]	Yield [%][a]
−78	−78	84
−78	0	75
−48	−48	79
−48	0	66
0	0	14

[a] Determinated by GC.

two microtube reactors (R1 and R2) (Scheme 6). A solution of *m*-dibromobenzene (0.29 M) in THF (flow rate: 6 mL min^{-1}, 1.74 mmol min^{-1}) and a solution of *n*BuLi (1.58 M) in hexane (flow rate: 1.2 mL min^{-1}, 1.9 mmol min^{-1}) were introduced into M1 (ϕ = 250 µm) by syringe pumping. The mixture was passed through R1 (ϕ = 500 or 1000 µm, length = L, residence time = R_t) into M2 (ϕ = 500 µm), into which methanol (neat, flow rate: 6 mL min^{-1}) was also introduced. The mixture was passed through R2 (ϕ = 1000 µm, L = 50 cm, R_t = 1.79 s). The Br–Li exchange reaction and the quenching with MeOH were conducted at the same temperature. The residence time was adjusted by changing the length of the microtube reactor R1 at a fixed flow rate. After steady state was reached, an aliquot of the product solution was taken over 15 s and analyzed. The amount of bromobenzene was determined by GC.



Scheme 6. Micro flow system for the Br–Li exchange reaction of *m*-dibromobenzene followed by the reaction with MeOH.

The results obtained with varying temperature (T) and residence time (R_t) in R1 are summarized in Figure 3. Interestingly, the results are very similar to those for *p*-bromobenzene: Bromobenzene was obtained in good yields above −48 °C, the reaction can be conducted at 20 °C, and the yield increased with temperature and residence time from −40 to −78 °C. Therefore, it is reasonable to consider that both *m*- and *p*-bromophenyllithium have similar thermal stability.

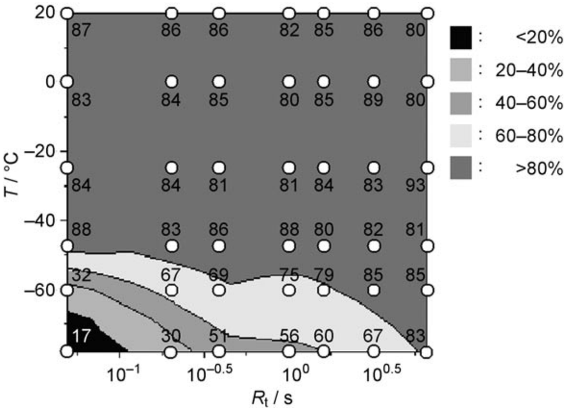
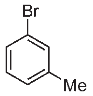
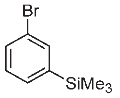
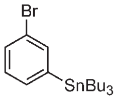
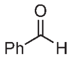
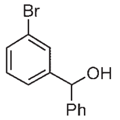
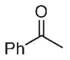
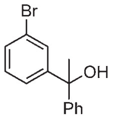


Figure 3. Effects of temperature and residence time on the yield of bromobenzene in the Br–Li exchange reaction of *m*-dibromobenzene with *n*BuLi with the micro flow system.

The reactions of *m*-bromophenyllithium with various electrophiles were examined in the micro flow system. Iodomethane, chlorotrimethylsilane, chlorotributylstannane, benzaldehyde, and acetophenone as well as methanol were effective, and the reactions gave the corresponding *m*-substituted bromobenzene derivatives in good yields at 20 °C (Table 6).

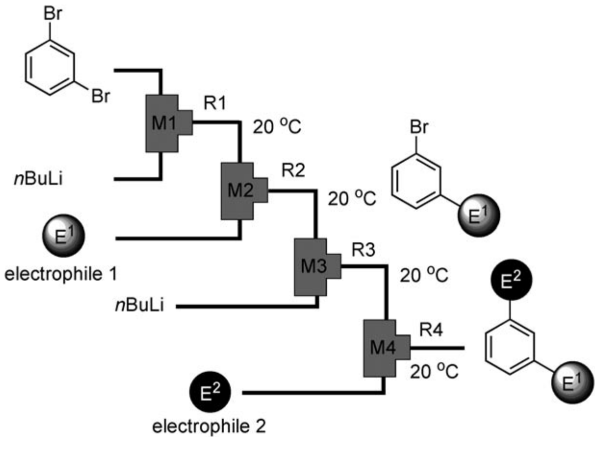
With the successful Br–Li exchange reaction of *m*-dibromobenzene followed by the reaction with an electrophile in

Table 6. Br–Li exchange reaction of *m*-dibromobenzene with *n*BuLi followed by reaction with electrophiles with the micro flow system.

Electrophile	Product	Yield [%][a]
MeI		81
Me_3SiCl		93
Bu_3SnCl		94
		86
		90

[a] Determinated by GC.

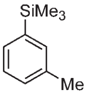
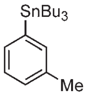
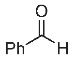
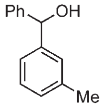
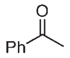
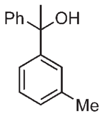
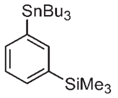
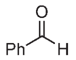
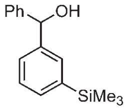
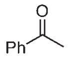
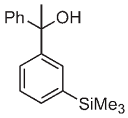
the micro flow system in hand, we next examined the sequential introduction of two electrophiles into *m*-dibromobenzene by using a micro flow system consisting of four T-shaped micromixers (M1, M2, M3, and M4) and four microtube reactors (R1, R2, R3, and R4) (Scheme 7).



Scheme 7. Micro flow system for the sequential introduction of two electrophiles into *m*-dibromobenzene.

A solution of *m*-dibromobenzene (0.29 M) in THF (flow rate: 6 mL min^{-1}, 1.74 mmol min^{-1}) and a solution of *n*BuLi (1.58 M) in hexane (flow rate: 1.2 mL min^{-1}, 1.90 mmol min^{-1}) were introduced into M1 ($\phi = 500$ μm) by syringe pumping. The mixture was passed through R1 ($\phi = 1000$ μm, $L = 6$ cm, $R_t = 0.39$ s). The solution containing *m*-bromophenyllithium was then mixed with the first electrophile (0.69 M) in THF (flow rate: 3 mL min^{-1}, 2.07 mmol min^{-1}) in M2 ($\phi = 500$ μm). The mixture was passed through R2 ($\phi = 1000$ μm, $L = 50$ cm, $R_t = 2.31$ s), and the resulting solution containing the *m*-substituted bromobenzene was introduced into M3 ($\phi = 500$ μm), where *n*BuLi (1.58 M) in hexane was also placed (flow rate: 1.8 mL min^{-1}, 2.84 mmol min^{-1}). The second Br–Li exchange reaction took place in R3 ($\phi = 1000$ μm, $L = 12.5$ cm, $R_t = 0.49$ s). The resulting solution was introduced into M4 ($\phi = 500$ μm), where it was mixed with the second electropile (1.72 M) in THF (flow rate: 3 mL min^{-1}, 5.16 mmol min^{-1}). The resulting solution was passed through R4 ($\phi = 1000$ μm, $L = 50$ cm, $R_t = 1.57$ s). As summarized in Table 7, the sequential introduction of two electrophiles on the benzene ring was successfully achieved with various electrophiles, thus indicating that this micro flow synthesis serves as a powerful and straightforward method for the synthesis of various *m*-disubstituted benzenes from *m*-dibromobenzene and two electrophiles.

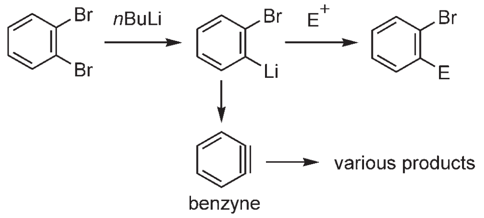
Table 7. Sequential introduction of two electrophiles onto *m*-dibromobenzene with the micro flow system.

Electrophile 1	Electrophile 2	Product	Yield [%][a]
MeI	Me_3SiCl		84
MeI	Bu_3SnCl		93
MeI			73
MeI			86
Me_3SiCl	Bu_3SnCl		67
Me_3SiCl			88
Me_3SiCl			82

[a] Determinated by GC.

Sequential Introduction of Two Electrophiles into *o*-Dibromobenzene

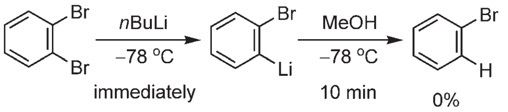
Finally, we examined the sequential introduction of two electrophiles into *o*-dibromobenzene based on the Br–Li exchange reaction in micro flow systems (Scheme 8).



Scheme 8. Generation and reaction of *o*-bromophenyllithium by the Br–Li exchange reaction of *o*-dibromobenzene.

It is well-known that the Br–Li exchange reaction of *o*-dibromobenzene[18,19] is problematic in macro batch systems because of benzyne formation even at −78 °C. Therefore, this reaction should be conducted at or below −110 °C. We envisioned that the short residence time and efficient heat transfer of micro flow systems should solve the problem.

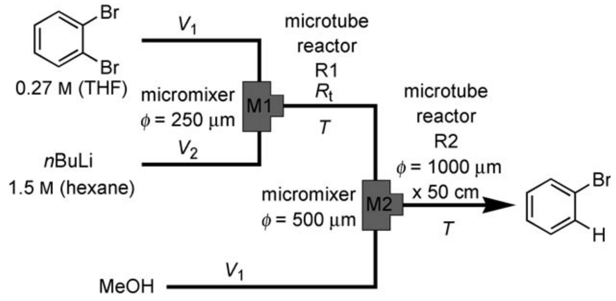
Before the micro flow systems were used, the reaction was examined with a conventional macro batch reactor at −78 °C (Scheme 9). *n*BuLi was added dropwise to a solution



Scheme 9. Br–Li exchange reaction of *o*-dibromobenzene with *n*BuLi followed by the reaction with MeOH with the macro batch system.

of *o*-dibromobenzene at a regular pace over 1 min. As soon as that was completed, methanol was added to quench the reaction. However, bromobenzene, the expected product, was not obtained at all. Because most of the starting material was consumed, the Br–Li exchange reaction of *o*-dibromobenzene seemed to be completed immediately. Therefore, benzyne formation took place before quenching with methanol even at −78 °C.

Thus, we examined the reaction with a micro flow system consisting of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2) (Scheme 10). A solution of *o*-dibromobenzene (0.27 M) in THF (flow rate: V_1 = 6 mL min^{-1}, 1.62 mmol min^{-1}) and a solution of *n*BuLi (1.5 M) in hexane (flow rate: V_2 = 1.2 mL min^{-1}, 1.8 mmol min^{-1}) were introduced into M1 (ϕ = 250 μm) by syringe pumping. The mixture was passed through R1 (ϕ = 500 μm, length = L, residence time = R_t), and the resulting solution containing *o*-bromophenyllithium was introduced into M2 (ϕ = 500 μm), where methanol was also placed (neat, flow rate: V_1 = 6 mL min^{-1}). The mixture was passed through R2 (ϕ = 1000 μm, L = 50 cm, R_t = 1.79 s). An aliquot of the outlet solution was collected, and the yield of bromobenzene was determined by GC.



Scheme 10. Micro flow system for the Br–Li exchange reaction of *o*-dibromobenzene followed by the reaction with MeOH.

The reactions were carried out by varying the residence time and temperature in the microtube reactor R1. As shown in Figure 4, the yield was very low at temperatures higher than −60 °C, presumably because of the decomposition of the *o*-bromophenyllithium intermediate to benzyne. At lower temperatures, the yield increased with a decrease in temperature because of slower benzyne formation. Further decrease in temperature, however, resulted in a decrease in yield, because the Br–Li exchange reaction could not be completed at such low temperatures. The effect of the residence time is interesting, as shown in Figure 5. At −70 °C, the yield increased with residence time and became a maximum at R_t = 0.8 s. This phenomenon can be explained in terms of the progress of Br–Li exchange with residence time. Further increase in residence time caused a decrease in yield, presumably because of benzyne formation. These results show that *o*-bromophenyllithium is much less stable than *p*- and *m*-bromophenyllithium. Extremely fast elimina-

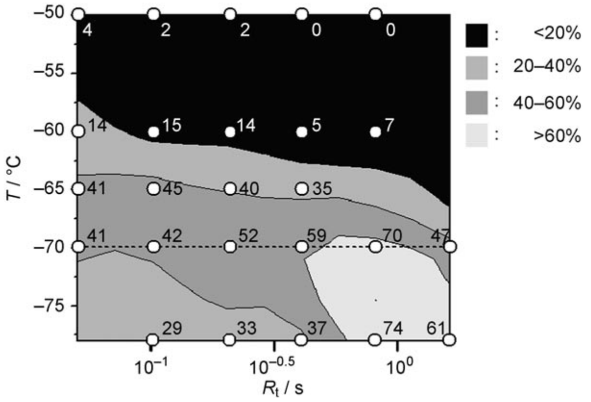


Figure 4. Effects of temperature and residence time on the yield of bromobenzene in the Br–Li exchange reaction of *o*-dibromobenzene with *n*BuLi with the micro flow system.

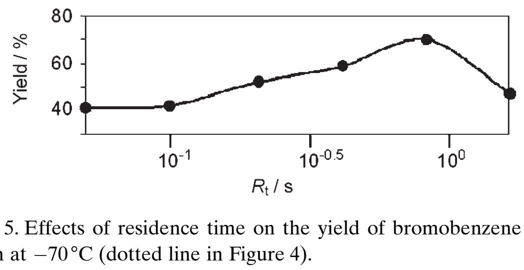


Figure 5. Effects of residence time on the yield of bromobenzene: cross-section at −70 °C (dotted line in Figure 4).

tion of LiBr to form benzyne seems to be responsible for the instability. Importantly, the present temperature–residence-time profile is quite effective for unveiling the features of the Br–Li exchange reaction and the stability of the organolithium intermediate thus formed. Therefore, micro flow systems serve as a powerful tool for mechanistic studies on reactions that involve highly unstable intermediates.

The flow rate is also a very important factor in carrying out the present reaction with the micro flow system shown in Scheme 10 (−78 °C, $R_t = 0.82$ s). With flow rates of more than 3 mL min^{-1}, the best result (67–74 % yield) was obtained as shown in Table 8. A decrease in flow rate, however, caused a significant decrease in yield. It is well-known that the mixing efficiency strongly depends on the flow rate.[20] Mixing efficiency or speed usually decreases with a decrease in flow rate. Therefore, the results indicate that fast mixing is also essential for conducting the present transformation. Furthermore, the use of a teflon microtube (ϕ = 500 μm) as R1 ($R_t = 0.82$ s) instead of a stainless-steel microtube gave a similar result (70 %), which indicates that the material from which R1 is made is not important under the conditions.

Table 8. Effect of flow rate.

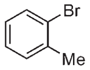
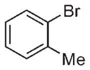
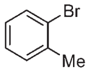
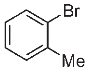
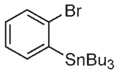
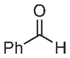
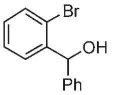
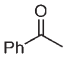
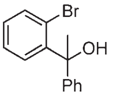
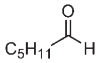
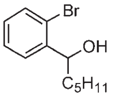
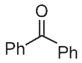
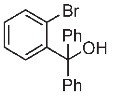
V_1 [mL min<-M>1]	V_2 [mL min<-M>1]	Yield [%][a]
1.5	0.3	31
3.0	0.6	70
6.0	1.2	74
6.0[b]	1.2	70
12.0	2.4	72

[a] Determinated by GC. [b] The teflon microtube reactor R1 was used.

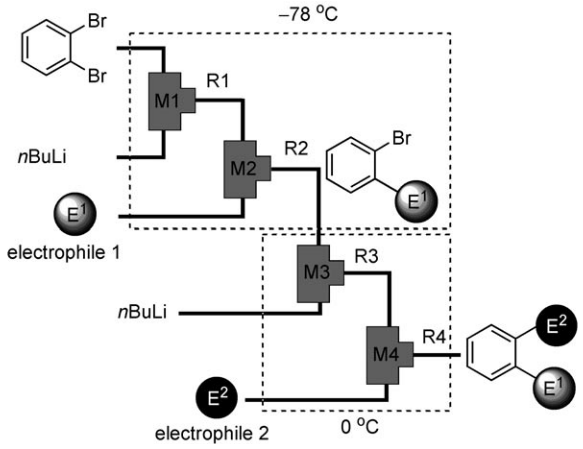
The reactions of *o*-bromophenyllithium with various electrophiles were examined in the micro flow system at −78 °C. Iodomethane was not effective as an electrophile, presumably because benzyne formation is faster in this case. However, the use of methyl triflate resulted in the formation of *o*-bromotoluene in good yield; the reaction with methyl triflate is probably faster than benzyne formation under the conditions. Similarly, trimethylsilyl triflate served as a good electrophile, whereas chlorotrimethylsilane was not effective. Chlorodimethylsilane was effective probably because it is less sterically demanding than chlorotrimethylsilane. Chlorotributylstannane, benzaldehyde, and acetophenone were also effective, and the reactions gave the corresponding *o*-substituted bromobenzenes in good yields (Table 9).

With the successful generation and reactions of the *o*-bromophenyllithium intermediate in hand, we next examined the sequential introduction of two electrophiles into *o*-dibromobenzene by using a micro flow system consisting of four micromixers (M1, M2, M3, and M4) and four microtube reactors (R1, R2, R3, and R4) (Scheme 11).

Table 9. Br–Li exchange reaction of *o*-dibromobenzene with *n*BuLi followed by reaction with electrophiles with the micro flow system.

Electrophile	Product	Yield [%][a]
MeOTf		79
MeI		5
Me_3SiOTf		69
Me_3SiCl		5
Bu_3SnCl		81
Me_2HSiCl		68
		75
		81
		42
		24

[a] Determined by GC. Tf = trifluoromethanesulfonyl.

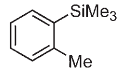
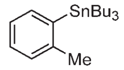
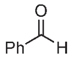
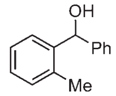
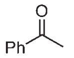
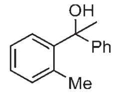
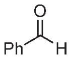
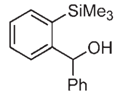
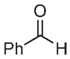
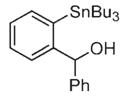
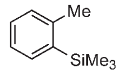


Scheme 11. Micro flow system for the sequential introduction of two electrophiles into *o*-dibromobenzene.

The reaction temperature for microtube reactors R1 and R2 was −78 °C, whereas that for R3 and R4 was 0 °C, because the second aryllithium intermediate is expected to be much more stable than *o*-bromophenyllithium. Thus, a solution of *o*-dibromobenzene (0.27 M) in THF (flow rate: 6 mL min^{-1}, 1.62 mmol min^{-1}) and a solution of *n*BuLi (1.5 M) in *n*-hexane (flow rate: 1.2 mL min^{-1}, 1.8 mmol min^{-1}) were introduced into M1 (ϕ = 250 μm) by syringe pumping. The mixture was passed through R1 (ϕ = 500 μm, L = 50 cm,

$R_t = 0.82$ s), and the resulting solution containing *o*-bromophenyllithium was mixed with the first electrophile (0.65 M) in THF or Et_2O (flow rate: 3 mL min^{-1}, 1.95 mmol min^{-1}) in M2 ($\phi = 500$ µm). The mixture was passed through R2 ($\phi = 1000$ µm, $L = 150$ cm, $R_t = 6.93$ s), and the resulting solution containing *o*-substituted bromobenzene was introduced into M3 ($\phi = 500$ µm), where *n*BuLi (1.5 M) in hexane (flow rate: 1.8 mL min^{-1}, 2.7 mmol min^{-1}) was also placed. The mixture was passed through R3 ($\phi = 1000$ µm, $L = 12.5$ cm, $R_t = 0.49$ s) into M4 ($\phi = 500$ µm), into which the second electrophile (1.62 M) in THF (flow rate: 3 mL min^{-1}, 4.86 mmol min^{-1}) was introduced. The mixture was passed through R4 ($\phi = 1000$ µm, $L = 50$ cm, $R_t = 1.57$ s), and the outlet solution was collected. As shown in Table 10, the sequential introduction of two groups onto the benzene ring was successfully achieved with various electrophiles.

Table 10. Sequential introduction of two electrophiles onto *o*-dibromobenzene with the micro flow system.

Electrophile 1	Electrophile 2	Product	Yield [%][a]
MeOTf	Me_3SiCl		67
MeOTf	Bu_3SnCl		62
MeOTf			61
MeOTf			53
	Me_3SiCl		74
	Bu_3SnCl		58
Me_3SiOTf	MeI		68

[a] Determined by GC.

Conclusions

Sequential introduction of two electrophiles into *p*-, *m*-, and *o*-dibromobenzenes based on Br–Li exchange reactions has been accomplished by using a micro flow system consisting of four micromixers and four microtube reactors at much higher temperatures than those for conventional macro batch systems by virtue of the control of residence time and temperature. The method serves as a straightforward and powerful access to disubstituted benzene derivatives. The results obtained in this study speak well for the potential of micro flow systems for the integration of chemical reactions that involve highly reactive intermediates. It is hoped that the micro flow system can be expanded to increase productivity,[12] and that the present method will be utilized in the industrial production of fine chemicals.

Experimental Section

General

GC analysis was performed on a Shimadzu GC-2014 gas chromatograph equipped with a flame ionization detector and a fused-silica capillary column (CBP1, 0.25 mm × 25 m, initial oven temperature 50 °C, rate of temperature increase 10 °C min^{-1}). ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian MERCURYplus-400 (^1H: 400 MHz; ^{13}C: 100 MHz) spectrometer with Me_4Si or $CHCl_3$ as a standard unless otherwise noted. EI and chemical ionization (CI) mass spectra were recorded on a JMS-SX102A spectrometer. FAB mass spectra were recorded on a JMX-HX110A spectrometer. Gel-permeation chromatography was carried out with a Japan Analytical Industry LC-9201 instrument. THF and Et_2O used as solvents for the reaction were purchased from Kanto Chemical Co., Inc. and used without further purification. Dehydrated MeOH, benzaldehyde, and acetophenone used for the reaction were purchased from Wako Pure Chemical Ind. Ltd. 1,2-, 1,3-, and 1,4-dibromobenzene, chlorotrimethylsilane, chlorotributylstannane, methyl trifluoromethanesulfonate, and chlorodimethylsilane used as solvents for the reaction were purchased from Aldrich Ltd. *n*BuLi used for the reaction was purchased from Kanto Chemical Co., Inc. Iodomethane, trimethylsilyl trifluoromethanesulfonate, and 1-hexanal used for the reaction were purchased from Nakarai. All materials were obtained from commercial suppliers and used without further purification.

The T-shaped micromixers were constructed and purchased from Sanko Seiki Co., Inc. The micromixers with stainless-steel bodies have inside diameters of 250 and 500 µm.

The micro flow system consists of micromixers and microtube reactors, which were connected with stainless joint fittings (GL Sciences, 1/16OUW). All solutions were prepared and taken up by gas-tight syringes purchased from GSE under argon atmosphere. The gas-tight syringes were then set in a Harvard Model 11 syringe pump. Introduction of solutions into the mixers was performed by syringe pumps. The whole micro flow system except the syringe pumps was placed in a cooling bath to control the temperature.

Syntheses

Representative procedure for sequential Br–Li exchange reactions of *p*-dibromobenzene: A microsystem A micro flow system consisting of four T-shaped micromixers (M1, M2, M3, and M4) and four microtube reactors (R1, R2, R3, and R4) was used. The whole microsystem was placed in a water bath (20 °C). A solution of *p*-dibromobenzene (0.289 M) in THF (flow rate: 6 mL min^{-1}, 1.72 mmol min^{-1}) and a solution of *n*BuLi (1.58 m) in *n*-hexane (flow rate: 1.2 mL min^{-1}, 1.90 mmol min^{-1}) were introduced into M1 ($\phi = 500$ µm) by syringe pumping. The resulting solution was passed through R1 ($\phi = 500$ µm, $L = 6$ cm, $R_t = 0.39$ s) and was mixed with iodomethane (0.689 m) in THF (flow rate: 3 mL min^{-1}, 2.07 mmol min^{-1}) in M2 ($\phi = 500$ µm). The resulting solution was passed through R2 ($\phi = 1000$ µm, $L = 50$ cm, $R_t = 2.31$ s) into M3 ($\phi = 500$ µm), where the solution was mixed with *n*BuLi (1.58 M) in *n*-hexane (flow rate: 1.8 mL min^{-1}, 2.84 mmol min^{-1}). The resulting solution was passed through R3 ($\phi = 1000$ µm, $L = 12.5$ cm, $R_t = 0.49$ s) into M4 ($\phi = 500$ µm), where it was mixed with chlorotrimethylsilane (1.72 M) in THF (flow rate: 3 mL min^{-1}, 5.16 mmol min^{-1}). The resulting solution was passed through R4 ($\phi = 1000$ µm, $L = 50$ cm, $R_t = 1.57$ s). After steady state was reached, an aliquot of the product solution was removed (15 s) and stirred for 1 h. Methanol was added, and the mixture was analyzed by GC, which indicated that *p*-(trimethylsilyl)toluene ($t_R = 12.9$ min) was formed in 81 % yield.

Representative procedure for sequential Br–Li exchange reactions of *m*-dibromobenzene: A microsystem A micro flow system consisting of four T-shaped micromixers (M1, M2, M3, and M4) and four microtube reactors (R1, R2, R3, and R4) was used. The whole microsystem was placed in a water bath (20 °C). A solution of *m*-dibromobenzene (0.293 M) in THF (flow rate: 6 mL min^{-1}, 1.76 mmol min^{-1}) and a solution of *n*BuLi (1.64 m) in *n*-hexane (flow rate: 1.2 mL min^{-1}, 1.97 mmol min^{-1}) were introduced into M1 ($\phi = 500$ μm) by syringe pumping. The resulting solution was passed through R1 ($\phi = 1000$ μm, $L = 6.0$ cm, $R_t = 0.39$ s) and mixed with iodomethane (0.687 M) in THF (flow rate: 3 mL min^{-1}, 2.06 mmol min^{-1}) in M2 ($\phi = 500$ μm). The resulting solution was passed through R2 ($\phi = 1000$ μm, $L = 200$ cm, $R_t = 9.24$ s) into M3 ($\phi = 500$ μm), where it was mixed with *n*BuLi (1.64 M) in *n*-hexane (flow rate: 1.8 mL min^{-}1, 2.95 mmol min^{-1}). The resulting solution was passed through R3 ($\phi = 1000$ μm, $L = 12.5$ cm, $R_t = 0.49$ s) into M4 ($\phi = 500$ μm), where it was mixed with chlorotrimethylsilane (1.75 M) in THF (flow rate: 3 mL min^{-1}, 5.25 mmol min^{-1}). The resulting solution was passed through R4 ($\phi = 1000$ μm, $L = 50$ cm, $R_t = 1.57$ s). After steady state was reached, an aliquot of the solution was removed (15 s), and H_2O was added to the aliquot. The mixture was analyzed by GC, which indicated that *m*-(trimethylsilyl)toluene ($t_R = 12.7$ min) was formed in 84 % yield.

Representative procedure for sequential Br–Li exchange reactions of *o*-dibromobenzene: A microsystem A micro flow system consisting of four T-shaped micromixers (M1, M2, M3, and M4) and four microtube reactors (R1, R2, R3, and R4) was used. The first half of the microsystem (M1, M2, R1, and a part of R2) was placed in a cooling bath (dry ice/acetone, −78 °C). The latter half (M3, M4, R3, R4, and the other part of R2) was placed in an ice bath (0 °C). A solution of *o*-dibromobenzene (0.27 M) in THF (flow rate: 6 mL min^{-1}, 1.62 mmol min^{-1}) and a solution of *n*BuLi (1.5 m) in *n*-hexane (flow rate: 1.2 mL min^{-1}, 1.8 mmol min^{-1}) were introduced into M1 ($\phi = 250$ μm) by syringe pumping. The resulting solution was passed through R1 ($\phi = 500$ μm, $L = 50$ cm, $R_t = 0.82$ s) into M2 ($\phi = 500$ μm), where it was mixed with methyl trifluoromethanesulfonate (0.65 M) in Et_2O (flow rate: 3 mL min^{-1}, 1.95 mmol min^{-1}). The resulting solution was passed through R2 ($\phi = 1000$ μm, $L = 150$ cm, $R_t = 6.93$ s) into M3 ($\phi = 500$ μm), where it was mixed with *n*BuLi (1.50 m) in *n*-hexane (flow rate: 1.8 mL min^{-1}, 2.7 mmol min^{-1}). The resulting solution was passed through R3 ($\phi = 1000$ μm, $L = 12.5$ cm, $R_t = 0.49$ s) into M4 ($\phi = 500$ μm), where it was mixed with chlorotrimethylsilane (1.62 M) in THF (flow rate: 3 mL min^{-1}, 4.86 mmol min^{-1}). The resulting solution was passed through R4 ($\phi = 1000$ μm, $L = 50$ cm, $R_t = 1.57$ s). After steady state was reached, an aliquot of the solution was removed (15 s) and stirred for 1 h (0 °C). The crude solution was then analyzed by GC, which indicated that *o*-(trimethylsilyl)toluene ($t_R = 13.5$ min) was formed in 67 % yield.

Acknowledgements

This work was partially supported by a Grant-in-Aid for Scientific Research and NEDO projects.

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[15] Figures 2–4 was produced by Origin 7.5J (scientific graphing and analysis software of OriginLab).

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Received: July 26, 2007