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# Selective Monolithiation of Dibromobiaryls Using Microflow Systems

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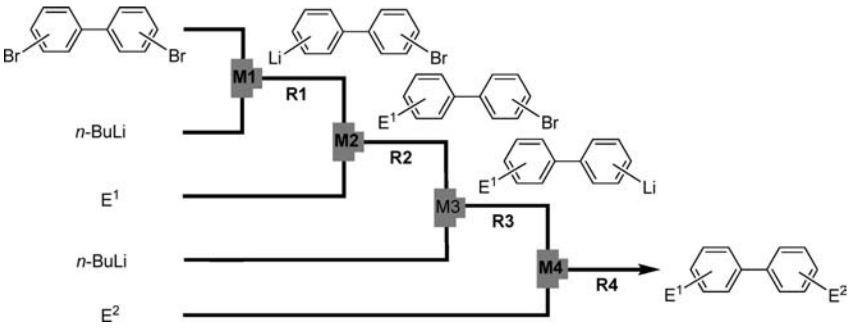
## ABSTRACT



**Selective monolithiation of dibromobiaryls, such as 2,2′-dibromobiphenyl, 4,4′-dibromobiphenyl, 2,7-dibromo-9,9-dioctylfluorene, 2,2′-dibromo-1,1′-binaphthyl, and 5,5′-dibromo-2,2′-bithiophene, with 1 equiv of *n*-butyllithium followed by the reaction with electrophiles was achieved using a microflow system by virtue of fast micromixing and precise temperature control. Sequential introduction of two different electrophiles based on this method was also achieved using a microflow system composed of four micromixers and four microtube reactors.**

Organolithium reagents serve as powerful tools in organic synthesis, and preparations of organolithium compounds based on a halogen−lithium exchange reaction have been widely utilized in organic synthesis.[1] Among them, selective monolithiation of dihalobiaryls attracts significant research interest.[2] The resulting monolithiated compounds serve as useful synthetic intermediates because the remaining halogen atom can be utilized for further transformations. However, halogen−lithium exchange reactions of dihalobiaryls usually give a mixture of mono- and dilithiated compounds, even if 1 equiv of butyllithium is used. To solve this problem, we envisaged that the use of a microflow system[3,4] would be effective.

Recent investigations revealed that selectivity of fast competitive consecutive reactions could be significantly improved using microflow systems.[5] If a reaction is faster

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[1] (a) Gilman, H.; Gorsich, R. D. *J. Am. Chem. Soc.* **1956**, *78*, 2217. (b) Chen, L. S.; Chen, G. J. *J. Organomet. Chem.* **1980**, *193*, 283. (c) Prabhu, U. D. G.; Eapen, K. C.; Tamborski, C. *J. Org. Chem.* **1984**, *49*, 2792. (d) Leroux, F.; Schlosser, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4272. See also: (e) Luliński, S.; Serwatowski, J. *J. Org. Chem.* **2003**, *68*, 5384.

[2] (a) Beak, P.; Liu, C. *Tetrahedron Lett.* **1994**, *20*, 5999. (b) Dolman, S. J.; Gosselin, F.; O'Shea, P. D.; Davies, I. W. *Tetrahedron* **2006**, *62*, 5092. (c) Klis, T.; Servatowski, J. *Tetrahedron Lett.* **2007**, *48*, 1169.

[3] Reviews. For example: (a) Fletcher, P. D. I.; Haswell, S. J.; Pombo-Villar, E.; Warrington, B. H.; Watts, P.; Wong, S. Y. F.; Zhang, X. *Tetrahedron* **2002**, *58*, 4735. (b) Jähnisch, K.; Hessel, V.; Löwe, H.; Baerns, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 406. (c) Doku, G. N.; Verboom, W.; Reinhoudt, D. N.; van den Berg, A. *Tetrahedron* **2005**, *61*, 2733. (d) Yoshida, J. *Chem. Commun.* **2005**, 4509.

[4] Some recent examples: (a) Fukuyama, T.; Shinmen, M.; Nishitani, S.; Sato, M.; Ryu, I. *Org. Lett.* **2002**, *4*, 1691. (b) Kobayashi, J.; Mori, Y.; Okamoto, K.; Akiyama, R.; Ueno, M.; Kitamori, T.; Kobayashi, S. *Science* **2004**, *304*, 1305. (c) Wu, T.; Mei, Y.; Cabrai, J. T.; Xu, C.; Beers, K. L. *J. Am. Chem. Soc.* **2004**, *126*, 9880. (d) Ducry, L.; Roberge, D. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 7972. (e) Iwasaki, T.; Yoshida, J. *Macromolecules* **2005**, *38*, 1159. (f) He, P.; Watts, P.; Marken, F.; Haswell, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 4146. (g) Uozumi, Y.; Yamada, Y.; Beppu, T.; Fukuyama, N.; Ueno, M.; Kitamori, T. *J. Am. Chem. Soc.* **2006**, *128*, 15994. (h) Tanaka, K.; Motomatsu, S.; Koyama, K.; Tanaka, S.; Fukase, K. *Org. Lett.* **2007**, *9*, 299.

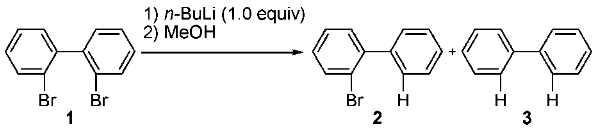
10.1021/ol8015572 CCC: $40.75

than mixing, the reaction takes place before the homogeneity of the solution is achieved. This often happens in macro batch reactors such as flasks. In such cases, arguments based on kinetics do not work, and product selectivity is determined by the manner of mixing (disguised chemical selectivity).[6] To obtain a predictable selectivity close to a kinetically based one, extremely fast mixing is necessary, and micromixing based on short diffusion paths proved quite effective for this purpose. Fast heat transfer by virtue of high surface-to-volume ratios in microspaces makes precise temperature control possible in highly exothermic reactions. It is also important to note that short residence time[7] in microflow systems is quite effective in controlling extremely fast reactions involving highly unstable intermediates such as organolithium compounds.[8,9]

With such information in hand, we set out to investigate halogen−lithium exchange reactions of dibromobiaryls, and we report herein that selective monolithiation can be achieved by extremely fast 1:1 micromixing of dibromobiaryls and *n*-butyllithium using microflow systems.

It is known that Br−Li exchange reaction of 2,2′-dibromobiphenyl (**1**) gives a significant amount of dilithiated product in a conventional macro batch system (Scheme 1).[10]

**Scheme 1.** Lithiation of 2,2′-Dibromobiphenyl with *n*-BuLi Using a Conventional Macro Batch System



To confirm this, we re-examined the Br−Li exchange reaction of **1** with 1 equiv of *n*-BuLi in a flask (20 mL round-bottom glass flask with a magnetic stirrer). The resulting organolithium compounds were allowed to react with methanol, and the yields of 2-bromobiphenyl (**2**, product derived from monolithiation) and biphenyl (**3**, product derived from dilithiation) were analyzed by GC. As shown in Table 1, **2** was obtained with high selectivity at −78 °C, but the yield was not very high. The selectivity decreased with an increase in temperature, and a significant amount of **3** was obtained at higher temperatures.

**Table 1.** Lithiation of 2,2′-Dibromobiphenyl Using a Conventional Macro Batch System

| temperature (°C) | reaction time (min) | **1** conversion (%) | **2** yield (%) | **3** yield (%) |
|---|---|---|---|---|
| −78 | 60 | 94[a] | 76 | 4 |
| −48 | 10 | 86[a] | 69 | 4 |
| −27 | 10 | 81[a] | 48 | 18 |
| 0 | 10 | 75[a] | 36 | 25 |
| 24 | 10 | 66[a] | 14 | 34 |

[a] 2-Bromo-2′-butylbiphenyl was produced as a byproduct (see the Supporting Information).

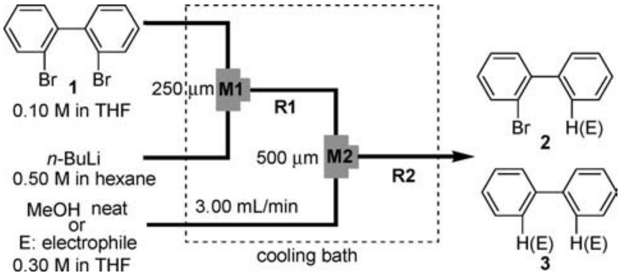


**Figure 1.** Microflow system for lithiation of 2,2′-dibromobiphenyl.

In the next step, we examined the reaction using a microflow system composed of two T-shaped micromixers (**M1** and **M2**) and two microtube reactors (**R1** and **R2**) shown in Figure 1.

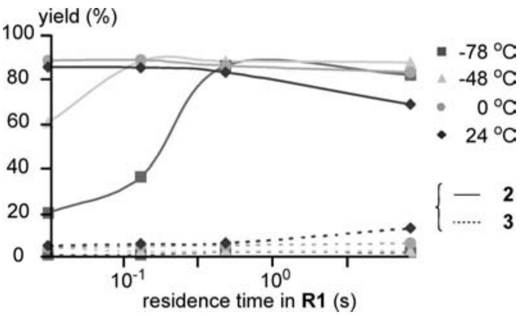


**Figure 2.** Effect of temperature and residence time in lithiation of 2,2′-dibromobiphenyl using microflow systems. Flow rate of a solution of **1**: 6.00 mL/min. Flow rate of *n*-BuLi/hexane: 1.20 mL/min. Flow rate of methanol: 3.00 mL/min.

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(5) (a) Suga, S.; Nagaki, A.; Yoshida, J. *Chem. Commun.* **2003**, 354. (b) Nagaki, A.; Togai, M.; Suga, S.; Aoki, N.; Mae, K.; Yoshida, J. *J. Am. Chem. Soc.* **2005**, *127*, 11666. (c) Suga, S.; Nagaki, A.; Tsutsui, Y.; Yoshida, J. *Org. Lett.* **2003**, *5*, 945. (d) Suga, S.; Tsutsui, Y.; Nagaki, A.; Yoshida, J. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1206. (e) Yoshida, J.; Nagaki, A.; Iwasaki, T.; Suga, S. *Chem. Eng. Technol.* **2005**, *28*, 259.

(6) (a) Rys, P. *Acc. Chem. Res.* **1976**, *9*, 345. (b) Rys, P. *Angew. Chem., Int. Ed.* **1977**, *12*, 807.

(7) (a) Kawaguchi, T.; Miyata, H.; Ataka, K.; Mae, K.; Yoshida, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 2413. (b) Nagaki, A.; Kawamura, K.; Suga, S.; Ando, T.; Sawamoto, M.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 14702. (c) Iwasaki, T.; Nagaki, A.; Yoshida, J. *Chem. Commun.* **2007**, 1263.

(8) (a) Usutani, H.; Tomida, Y.; Nagaki, A.; Okamoto, H.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2007**, *129*, 3047. (b) Nagaki, A.; Tomida, Y.; Usutani, H.; Kim, H.; Takabayashi, N.; Nokami, T.; Okamoto, H.; Yoshida, J. *Chem. Asian J.* **2007**, *2*, 1513.

(9) Halogen−lithium exchange reactions of simple aromatic halides in microflow systems: (a) Schwalbe, T.; Autze, V.; Hohmann, M.; Stirner, W. *Org. Process Res. Dev.* **2004**, *8*, 440. (b) Zhang, X.; Stefanick, S.; Villani, F. J. *Org. Process Res. Dev.* **2004**, *8*, 455. (c) Ushiogi, Y.; Hase, T.; Iinuma, Y.; Takata, A.; Yoshida, J. *Chem. Commun.* **2007**, 2947.

(10) For the lithiation of 2,2′-dibromobiphenyl: (a) Leroux, F.; Nicod, N.; Bonnafoux, L.; Quissac, B.; Colobert, F. *Lett. Org. Chem.* **2006**, *3*, 165. (b) Morrison, D. J.; Trefz, T. K.; Piers, W. E.; McDonald, R.; Parvez, M. *J. Org. Chem.* **2005**, *70*, 5309.

The results obtained with varying temperature (−78 ~ 24 °C) and residence time in **R1** (0.057 ~ 13 s) are shown in Figure 2. Residence time was controlled by changing the inner diameter ($\phi$) and the length ($L$) of **R1** with the fixed flow rate. It was surprising to find that high yields and high selectivities were obtained even at 0 and 24 °C.

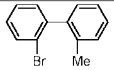
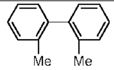
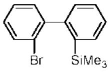
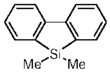
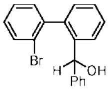
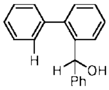
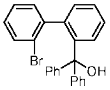
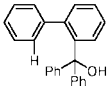
**Table 2.** Effect of Flow Rate and Inner Diameter of **M1** at 0 °C[a]

| flow rate of a solution of **1** (0.10 M) (mL/min) | flow rate of *n*-BuLi/hexane (0.50 M) (mL/min) | inner diameter of **M1** ($\mu$m) | **1** convn (%) | **2** yield (%) | **3** yield (%) |
|---|---|---|---|---|---|
| 6.00 | 1.20 | 250 | 97 | 88 | 3 |
| 3.00 | 0.60 | 250 | 90 | 80 | 7 |
| 1.50 | 0.30 | 250 | 76 | 57 | 15 |
| 0.600 | 0.120 | 250 | 69 | 41 | 19 |
| 6.00 | 1.20 | 500 | 93 | 77 | 7 |
| 6.00 | 1.20 | 800 | 79 | 62 | 9 |

[a] **R1**: $\phi = 500\ \mu$m, $L = 3.5$ cm, flow rate of methanol, 3.00 mL/min.

As shown in Table 2, the selectivity increases with a decrease in the diameter of **M1**, presumably because faster mixing can be achieved by a mixer of smaller diameter. The selectivity also increased with an increase in the flow rate. It is known that the mixing rate increases with an increase in the flow rate for other types of micromixers.[11] These observations indicate that extremely fast 1:1 mixing in the microflow system is responsible for selective monolithiation at much higher temperatures than those required for macro batch processes.

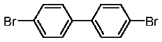
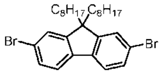
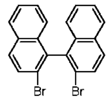
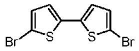
**Table 3.** Lithiation of 2,2′-Dibromobiphenyl Followed by the Reaction with an Electrophile Using the Microflow System[a]

| electrophile | monosubstituted product | yield (%) | disubstituted product | yield (%) |
|---|---|---|---|---|
| MeI[b] |  | 89 |  | trace |
| $Me_3SiCl$[b] |  | 80 |  | 3 |
| PhCHO |  | 90 |  | trace |
| $Ph_2CO$ |  | 93 |  | 2 |

[a] Flow rate of a solution of **1**: 6.00 mL/min. Flow rate of *n*-BuLi/hexane: 1.20 mL/min. **R1**: $\phi = 500\ \mu$m, $L = 3.5$ cm. [b] **R2**: $\phi = 1000\ \mu$m, $L = 200$ cm. Flow rate of a solution of an electrophile: 4.00 mL/min. The conversions were higher than 95% in all cases.

Under the optimized reaction conditions (reaction temperature, 0 °C; residence time, 0.057 s), reactions of the monolithiated intermediate with other electrophiles (0.30 M in THF) were examined (Table 3). The reaction with iodomethane gave 2-bromo-2′-methylbiphenyl in high yield with high selectivity. Chlorotrimethylsilane, benzaldehyde, and benzophenone were also effective as electrophiles, and the corresponding products were obtained in high yields and high selectivity.

**Table 4.** Selective Monolithiation of Dibromobiaryls Followed by Reactions with Electrophiles

| dibromobiaryl | reaction system[a] | temperature (°C) | electrophile | yield (%)[b] |
|---|---|---|---|---|
|  | macro batch[c] | -78 | MeOH | 87 (5) |
| | macro batch[d] | 0 | MeOH | 47 (6)[e] |
| | microflow | 0 | MeOH | 88 (4) |
| | microflow[f] | 0 | MeI | 85 (4) |
| | microflow | 0 | PhCHO | 83 (6) |
| | microflow | 0 | $Ph_2CO$ | 84 (5) |
|  | macro batch[c] | -78 | MeOH | 89 (6) |
| | macro batch[d] | 0 | MeOH | 54 (5)[g] |
| | microflow | 0 | MeOH | 95 (4) |
| | microflow[f] | 0 | MeI | 93 (3) |
| | microflow | 0 | PhCHO | 90 (2) |
|  | macro batch[c] | -78 | MeOH | 90 (10) |
| | macro batch[d] | 0 | MeOH | 86 (13) |
| | microflow | 0 | MeOH | 97 (1) |
| | microflow[f] | 0 | MeI | 85 (trace) |
| | microflow | 0 | PhCHO | 82 (trace) |
|  | macro batch[c] | -78 | MeOH | 43 (29) |
| | macro batch[d] | 0 | MeOH | 73 (13) |
| | microflow[h] | 0 | MeOH | 87 (5) |
| | microflow[h] | 0 | MeOTf | 81 (6) |
| | microflow[h] | 0 | PhCHO | 85 (3) |

[a] Microflow reactions were carried out under the following conditions unless otherwise stated. **R1**: $\phi = 500\ \mu$m, $L = 3.5$ cm. **R2**: $\phi = 1000\ \mu$m, $L = 50$ cm, flow rate of a solution of a dibromobiaryl, 6.00 mL/min; flow rate of *n*-BuLi/hexane, 1.20 mL/min; flow rate of a solution of an electrophile, 3.00 mL/min. [b] Yields of monosubstituted products. Yields of disubstituted products are shown in parenthesis. [c] Reaction time: 60 min. [d] Reaction time: 10 min. [e] 4-Bromo-4′-butylbiphenyl was produced as a byproduct (13% yield). [f] **R2**: $\phi = 1000\ \mu$m, $L = 200$ cm, flow rate of a solution of an electrophile, 4.00 mL/min. [g] 2-Bromo-7-butyl-9,9-dioctylfluorene was produced as a byproduct (31% yield). [h] **R1**: $\phi = 1000\ \mu$m, $L = 200$ cm.

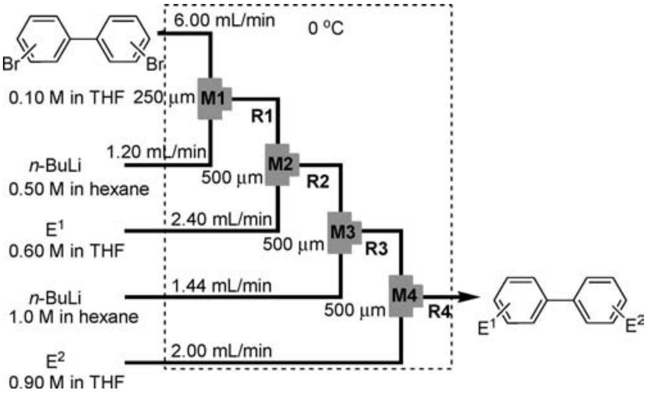
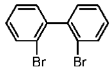
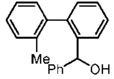
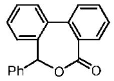
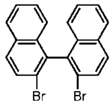
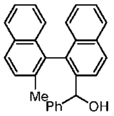
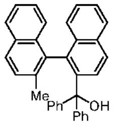


**Figure 3.** Microflow system for sequential introduction of two electrophiles. **R1**: $\phi = 500\ \mu$m, $L = 3.5$ cm (residence time: 0.057 s). **R2**: $\phi = 1000\ \mu$m, $L = 200$ cm (residence time: 9.8 s). **R3**: $\phi = 1000\ \mu$m, $L = 200$ cm (residence time: 8.5 s). **R4**: $\phi = 1000\ \mu$m, $L = 50$ cm (residence time: 1.8 s).

**Table 5.** Sequential Introduction of Two Electrophiles[a]

| dibromobiaryl | $E^1$ | $E^2$ | yield (%)[b] |
|---|---|---|---|
|  | MeI | PhCHO | <br>70 |
|  | PhCHO | MeOCOCl | <br>75 [c] |
|  | MeI | PhCHO | <br>71 |
|  | MeI | $Ph_2CO$ | <br>78 |

[a] Reactions were conducted using the microflow system shown in Figure 3 unless otherwise stated. [b] Small amounts of several byproducts were observed by $^1$H NMR, but they were not fully characterized. [c] **R2**: $\phi$ = 1000 $\mu$m, $L$ = 50 cm, benzaldehyde (0.30 M), methyl chlorocarbonate (0.30 M).

We next examined the reactions of other dibromobiaryls such as 4,4′-dibromobiphenyl, 2,7-dibromo-9,9-dioctylfluorene, 2,2′-dibromo-1,1′-binaphthyl,[12] and 5,5′-dibromo-2,2′-bithiophene using the microflow system. As summarized in Table 4, monolithiation was achieved with high selectivity even at 0 °C. Such high selectivity is difficult to obtain with macro batch reactors at similar temperatures. In addition, the resulting organolithium intermediate reacted with various electrophiles to give the corresponding products in high yields with high selectivity.

With successful monolithiation of dibromobiaryls followed by the reaction with an electrophile in hand, sequential introduction of two electrophiles ($E^1$ and $E^2$) into dibromobiaryls was examined using an integrated microflow system composed of four T-shaped micromixers (**M1**, **M2**, **M3**, and **M4**) and four microtube reactors (**R1**, **R2**, **R3**, and **R4**) shown in Figure 3. The results are summarized in Table 5. It is interesting to note that the use of an aldehyde ($E^1$) and methyl chlorocarbonate ($E^2$) as electrophiles led to effective formation of a seven-membered ring lactone.

In conclusion, we have developed an efficient method for selective monolithiation of dibromobiaryls at 0 °C by virtue of fast mixing in microflow systems. Electrophiles are introduced on one of the aromatic rings with high selectivity. Sequential introduction of two electrophiles by repeating the transformation has also been achieved using the integrated microflow systems. The method adds a new dimension in the selective lithiation of polyhalobiaryls.

**Acknowledgment.** This work was partially supported by the Grant-in-Aid for Scientific Research and the NEDO project.

**Supporting Information Available:** Experimental procedures and spectroscopic data of compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Ehrfeld, W.; Golbig, K.; Hessel, V.; Löwe, H.; Richter, T. *Ind. Eng. Chem. Res.* **1999**, *38*, 1075.

(12) Hoshi, T.; Hayakawa, T.; Suzuki, T.; Hagiwara, H. *J. Org. Chem.* **2005**, *70*, 9085.