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# Carbolithiation of Conjugated Enynes with Aryllithiums in Microflow System and Applications to Synthesis of Allenylsilanes

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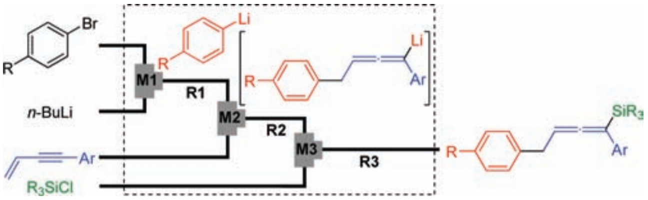
## ABSTRACT



**Carbolithiation of conjugated enynes with aryllithiums generated by Br−Li exchange reaction followed by reaction of the allenyllithium compounds with chlorosilanes was carried out in a microflow system to obtain various allenylsilanes in good yields.**

Organolithium compounds are important intermediates in organic synthesis.[1] Various methods for generation of organolithium intermediates have been developed so far. Among them, carbolithiation of unsaturated compounds such as alkenes,[2] alkynes,[3] and enynes[4] serves as an attractive method because carbon−carbon bond formation leads to the formation of a second organolithium intermediate, which can be utilized for subsequent reactions with various electrophiles. Commercially available *n*-BuLi, *sec*-BuLi, and *tert*-BuLi are often used as starting organolithium compounds.[5] The use of aryllithiums as starting organolithium compounds seems to be more attractive from a viewpoint of organic synthesis. However, only a few examples of carbolithiation using aryllithiums have been reported in the literature because the additions of aryllithiums to unsaturated compounds such as enynes are difficult.[6] This is presumably because of the following reason. At low temperatures, addition of aryllithiums to a carbon−carbon unsaturated bond is rather slow. At higher temperatures, the addition takes place at a reasonable rate, but the resulting organolithium compound

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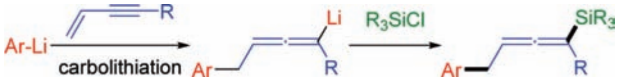
reacts with a butyl halide, which is generated in the halogen−lithium exchange reaction. This side reaction competes the follow-up reaction with an electrophile.[7] Therefore, it is very difficult to choose an appropriate reaction condition.

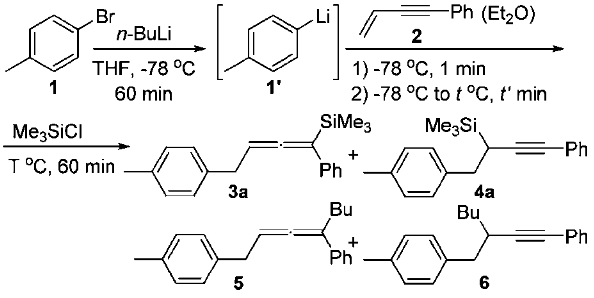
Microflow systems[8,9] have received significant research interest. Recently, we have reported that aryllithiums can be generated by halogen−lithium exchange reaction of bromoarenes at 0 and 20 °C by using a microflow system,[10] whereas much lower temperatures such as −78 °C are required for a conventional macrobatch reaction. The generated aryllithiums can be reacted with an electrophile avoiding the side reaction with a butyl halide. Precise control of the residence time (milliseconds to seconds) is responsible for the success of the reaction.[11] Therefore, we envisioned that the use of a microflow system is also effective for carbolithiation with aryllithiums followed by reaction with an electrophile. The concept works. In this paper, we report carbolithiation of enynes with aryllithiums using an integrated microflow system and their application to the synthesis of allenylsilanes (Scheme 1).

**Scheme 1.** Synthesis of Allenylsilane via Carbolithiation of Conjugated Enynes with Aryllithium



Before using a microflow system, the reaction in a conventional macrobatch reactor was examined (Scheme 2).

**Scheme 2.** Carbolithiation of 4-Phenyl-but-1-en-3-yne (**2**) with 4-Methylphenyllithium (**1′**) Generated by Br−Li Exchange Reaction of 4-Bromotoluene (**1**) in a Conventional Macrobatch Reactor



The carbolithiation of 4-phenyl-but-1-en-3-yne (**2**) using 4-methylphenyllithium (**1′**) generated by Br−Li exchange reaction of 4-bromotoluene (**1**) followed by the reaction with chlorotrimethylsilane was carried out with varying temperatures (*t*) and reaction times (*t′*). The results are summarized in Table 1.

**Table 1.** Carbolithiation of 4-Phenyl-but-1-en-3-yne (**2**) with 4-Methylphenyllithium (**1′**) Followed by the Reaction with Chlorotrimethylsilane in a Macrobatch System[a]

| entry | equiv of **1** | *t* (°C) | *t′* (min) | convn of **2**(%) | yield (%) | |
|---|---|---|---|---|---|---|
| | | | | | **3a** + **4a** (**3/4**) | **5** + **6** |
| 1 | 1.0 | −78 | 60 | 2 | 0 | 0 |
| 2 | 3.0 | −78 | 60 | 17 | 0 | 0 |
| 3 | 1.0 | −48 | 10 | 15 | 4 (85/15) | 0 |
| 4 | 1.0 | −48 | 60 | 66 | 11 (92/8) | 2 |
| 5 | 3.0 | −48 | 60 | 96 | 15 (90/10) | 11 |
| 6 | 1.0 | −28 | 10 | 74 | 26 (91/9) | 4 |
| 7 | 1.0 | −28 | 60 | 100 | 7 (91/9) | 19 |
| 8 | 3.0 | −28 | 10 | 95 | 33 (89/11) | 10 |
| 9 | 1.0 | 0 | 10 | 98 | 21 (91/9) | 26 |
| 10 | 1.0 | 25 | 10 | 100 | 9 (89/11) | 40 |

[a] A solution of *n*-BuLi in hexane was added dropwise (1 min) to a solution of *p*-bromotoluene (**1**) in THF in a 20 mL round-bottomed flask at −78 °C to generate 4-methylphenyllithium (**1′**). After the mixture was stirred for 60 min, a solution of 4-phenyl-but-1-en-3-yne (**2**) in $Et_2O$ was added dropwise (1 min) to the reaction mixture, and the reaction temperature was changed to *t*/°C. After the mixture was stirred for *t′* min, a solution of chlorotrimethylsilane in THF was added dropwise (1 min) to the reaction solution. The mixture was stirred for 60 min at *t*/°C and was analyzed by gas chromatography (GC) to determine the yield and conversion.

At −78 °C, the carbolithiation reaction was slow, and a significant amount of **2** remained unchanged even after 60 min. At −48 °C, most of **2** was consumed after 60 min, but the yields of desired 4-(4-methylphenyl)-1-trimethylsilyl-1-

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(7) The formation of a butyl halide can be avoided by use of *t*-BuLi for halogen−lithium exchange reactions. However, the use of highly reactive *t*-BuLi is not suitable for large scale synthesis. It should be noted that continuous microflow reactions can be applied to industrial production. See: Wakami, H.; Yoshida, J. *Org. Process Res. Dev.* **2005**, *9*, 787.

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(9) Some recent examples: (a) Nagaki, A.; Togai, M.; Suga, S.; Aoki, N.; Mae, K.; Yoshida, J. *J. Am. Chem. Soc.* **2005**, *127*, 11666. (b) Kawaguchi, T.; Miyata, H.; Ataka, K.; Mae, K.; Yoshida, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 2413. (c) He, P.; Watts, P.; Marken, F.; Haswell, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 4146. (d) Uozumi, Y.; Yamada, Y.; Beppu, T.; Fukuyama, N.; Ueno, M.; Kitamori, T. *J. Am. Chem. Soc.* **2006**, *128*, 15994. (e) Tanaka, K.; Motomatsu, S.; Koyama, K.; Tanaka, S.; Fukase, K. *Org. Lett.* **2007**, *9*, 299. (f) Sahoo, H. R.; Kralj, J. G.; Jensen, K. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 5704. (g) Hornung, C. H.; Mackley, M. R.; Baxendale, I. R.; Ley, S. V. *Org. Process Res. Dev.* **2007**, *11*, 399. (h) Fukuyama, T.; Kobayashi, M.; Rahman, M. T.; Kamata, N.; Ryu, I. *Org. Lett.* **2008**, *10*, 533.

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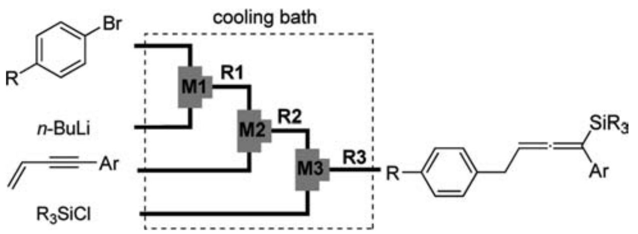


**Figure 1.** Integrated microflow system for carbolithiation of a conjugated enyne with an aryllithium followed by the reaction with a chlorosilane. T-shaped micromixer: **M1** ($\phi = 250\ \mu$m), **M2** ($\phi = 500\ \mu$m), **M3** ($\phi = 500\ \mu$m). Microtube reactor: **R1** ($\phi = 1000\ \mu$m, $L = 50$ cm (residence time in **R1**: 7.9 s)), **R2** ($\phi = 1000\ \mu$m), **R3** ($\phi = 1000\ \mu$m, $L = 50$ cm (residence time in **R3**: 2.0 s)). Flow rate of a solution of bromoarene (1.2 M in THF (3.0 equiv)):[12] 1.50 mL/min. Flow rate of a solution of *n*-BuLi (1.2 M in hexane): 1.50 mL/min. Flow rate of a solution of 4-aryl-but-1-en-3-yne (0.10 M in $Et_2O$): 6.00 mL/min. Flow rate of a solution of chlorosilane (0.80 M in THF): 3.00 mL/min.

phenyl-but-1,2-diene (**3a**) and 4-(4-methylphenyl)-3-trimethylsilyl-1-phenyl-but-1-yne (**4a**) were low. The major side products were 1-butyl-4-(4-methylphenyl)-1-phenyl-but-1,2-diene (**5**) and 3-butyl-4-(4-methylphenyl)-1-phenyl-but-1-yne (**6**), which seem to be produced by the reaction of the lithium intermediate with butyl bromide produced in the Br−Li exchange reaction. At higher temperatures such as −28, 0, and 25 °C, the yields of **3a** and **4a** were still low, and significant amounts of **5** and **6** were obtained.

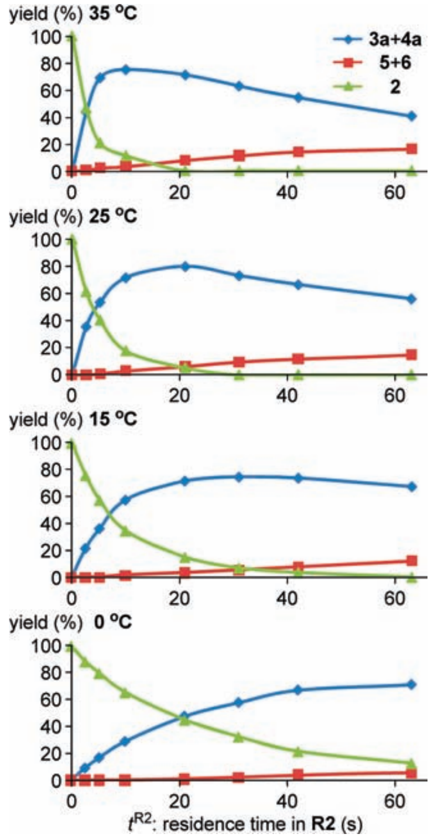
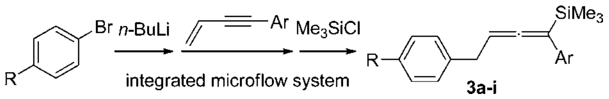
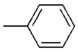
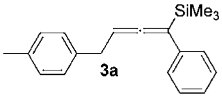
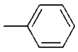
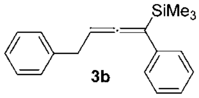
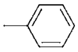
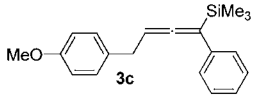
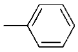
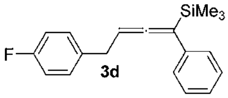
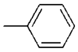
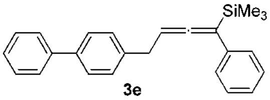
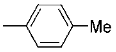
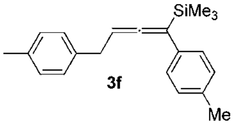
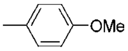
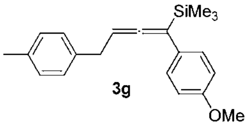
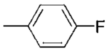
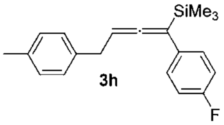
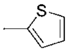
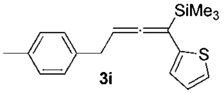


**Figure 2.** Effects of temperature and residence time in **R2** in the integrated microflow system.

**Table 2.** Carbolithiation of 4-Aryl-but-1-en-3-yne and 4-Heteroaryl-but-1-en-3-yne using Various Aryllithiums Followed by the Reaction with Chlorotrimethylsilane in the Integrated Microflow System[a]



| entry | R | Ar | product | yield (%) (**3**/**4**)[b] |
|---|---|---|---|---|
| 1[c] | -Me |  |  **3a** | 80 (91/9) |
| 2[c] | -H |  |  **3b** | 75 (91/9) |
| 3[c] | -OMe |  |  **3c** | 78 (90/10) |
| 4[d] | -F |  |  **3d** | 47 (91/9) |
| 5[c] | -Ph |  |  **3e** | 73 (90/10) |
| 6[c] | -Me |  |  **3f** | 82 (83/17) |
| 7[d] | -Me |  |  **3g** | 81 (80/20) |
| 8[c] | -Me |  |  **3h** | 80 (94/6) |
| 9[c] | -Me |  |  **3i** | 62 (98/2) |

[a] Bromoarene (3.0 equiv) in THF (1.2 M), *n*-BuLi (3.0 equiv) in hexane (1.2 M), 4-aryl-but-1-en-3-yne or 4-heteroaryl-but-1-en-3-yne in $Et_2O$ (0.10 M), and chlorotrimethylsilane (4.0 equiv) in THF (0.80 M) were allowed to react using the integrated microflow system at 25 °C. [b] Determined by GC. [c] Residence time in **R2**, 21 s. [d] Residence time in **R2**, 42 s.

Next, we examined the reactions using an integrated microflow system consisting of three T-shaped micromixers (**M1**, **M2**, and **M3**) and three microtube reactors (**R1**, **R2**, and **R3**) (Figure 1). The reactions were carried out with varying temperatures ($t$) and residence times ($t^{R2}$) in **R2**. The results are summarized in Figure 2.

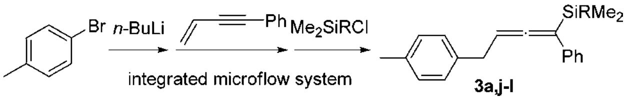
As profiled in Figure 2, the conversion and the yields significantly depend on both temperature and residence time. At 0 °C, the carbolithiation did not complete within the residence time of 60 s. At higher temperatures, the enyne (**2**) was consumed within 60 s, but the reaction with butyl bromide also took place in some extent to give **5** and **6** before adding chlorotrimethylsilane. The desired **3a** and **4a** were obtained in high yields at 25 °C by choosing an appropriate residence time in **R2** (21 s).[13] It is important to note that the Br−Li exchange reaction could be also carried out at the same temperature using the microflow system. The use of a macrobatch reactor requires much lower temperatures such as −78 °C for this purpose. Therefore, the use of the intergrated microflow system is the key to the success of the present transformation.

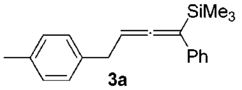
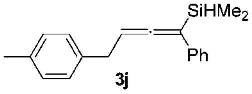
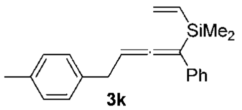
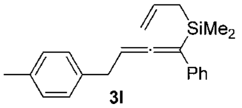
Next, reactions of **2** with various aryllithium compounds generated by Br−Li exchange reaction were examined by using the integrated microflow systems. As shown in Table 2, reactions with phenyllithium having an electron-donating and an electron-withdrawing group were successfully achieved to obtain the corresponding allenylsilanes in good yields. Various 4-aryl-but-1-en-3-ynes and 4-heteroaryl-but-1-en-3-yne can be also used for the present reaction, and the corresponding allenylsilanes were obtained in good yields without being influenced by the nature of substituents on the benzene ring.

Next, reactions with other chlorosilanes such as chlorodimethylsilane, chlorodimethyl(vinyl)silane, and allylchlorodimethylsilane were examined, and the corresponding allenylsilanes were obtained in high yields (Table 3).

Allenylsilanes have attracted a great deal of attention as intermediates in synthetic chemistry.[14,15] Although allenylsilanes are often prepared by organocuprate substitution of $\gamma$-acetoxyalkynylsilanes, the present transformation serves as a straightforward and powerful method for this purpose.

**Table 3.** Carbolithiation of 4-Phenyl-but-1-en-3-yne (**2**) followed by the Reaction with Various Chlorosilanes[a]



| entry | clorosilane | product | yield (%) (**3**/**4**) |
|---|---|---|---|
| 1 | $Me_3SiCl$ |  **3a** | 80[b] (91/9) |
| 2 | $Me_2SiHCl$ |  **3j** | 83[c] (75/25) |
| 3 |  |  **3k** | 84[c] (80/20) |
| 4 |  |  **3l** | 81[d] (91/9) |

[a] Bromotoluene (**1**) (3.0 equiv) in THF (1.2 M), *n*-BuLi (3.0 equiv) in hexane (1.2 M), 4-phenyl-but-1-en-3-yne (**2**) in $Et_2O$ (0.10 M), and a chlorolsilane (4.0 equiv) in THF (0.80 M) were allowed to react using the integrated microflow system at 25 °C and residence time in **R2** (21 s). [b] Determined by GC. [c] Isolated yield. [d] Determined by NMR.

In conclusion, we have developed carbolithiation of conjugated enynes with aryllithiums generated by Br−Li exchange reactions followed by reactions with chlorosilanes using an integrated microflow system. Precise residence time control is responsible for the success of the transformation. The method adds a new possibility in carbolithiation chemistry, and further studies on its applications are currently in progress.

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

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(12) The use of 3 equiv of bromoarene gave the best results. The yields of the desired products decreased with a decrease in the amount of bromoarene. For example, when 1 equiv of 4-bromotoluene was used ($t^{R2}$: 21 s), the desired **3a** and **4a** were obtained in 65% yield (**3**/**4** = 91/9), and the conversion of 4-phenyl-but-1-en-3-yne (**2**) was 83%.

(13) In all cases, the ratio of **3a** and **4a** was ca 90:10. See the Supporting Information for details.

(14) Review for reactions of allenylsilanes: Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293.

(15) (a) Danheiser, R. L.; Carini, D. J. *J. Org. Chem.* **1980**, *45*, 3925. (b) Danheiser, R. L.; Carini, D. J.; Kwasigroch, C. A. *J. Org. Chem.* **1986**, *51*, 3870. (c) Danheiser, R. L.; Fink, D. M. *Tetrahedron Lett.* **1985**, *26*, 2513. (d) Buckle, M. J. C.; Fleming, I. *Tetrahedron Lett.* **1993**, *34*, 2383.