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Alkylolithiums Bearing Electrophilic Functional Groups: A Flash Chemistry Approach

Aiichiro Nagaki,* Hiroki Yamashita, Katsuyuki Hirose, Yuta Tsuchihashi, and Jun-ichi Yoshida*

Abstract: Flash chemistry based on flow microreactor systems allowed alkylolithiums bearing electrophilic functional groups to be successfully generated and used for subsequent reactions. The series of reactions with high reactivity was achieved by extremely accurate control over residence time in a controlled and selective manner.

Having high reactivity, organolithium compounds have been one of the most commonly used reactants in organic synthesis.^[1] Especially, alkylolithiums have been used as lithiating reagents and initiators of anionic polymerization extensively due to their superior reactivity.^[2] However, in general, the synthetic use of alkylolithium is limited to commercially available and stable alkylolithiums such as simple alkyl, benzylic, and allylic lithiums.^[3,4] In fact, alkylolithiums are not compatible with electrophilic functionality. Therefore, it was believed impossible to prepare alkylolithiums bearing such functional groups in conventional batch chemistry. Also, even in flow microreactor chemistry^[7,8,9] alkylolithiums bearing electrophilic functionalities still have remained extremely challenging, although aryllithiums bearing electrophilic functionalities have been enjoying synthetic applications.^[6] In fact, alkylolithiums are more reactive than aryllithiums and react with electrophilic functional groups much faster. In this paper, a novel approach for the generation and application with various electrophiles, of alkylolithiums bearing electrophilic functional groups will be presented.

We first examined the generation of alkylolithiums bearing an epoxy group. The epoxy group serves as versatile building blocks in organic synthesis.^[10] However, such alkylolithiums would decompose very quickly via intra- or intermolecular nucleophilic attack on the epoxy ring. In order to suppress the decomposition and identify the optimal reaction condition, a number of flow microreactor systems with different residence times in **R1** and reaction temperatures were examined (Figure 1). A residence time was varied by modifying the distance in **R1** while the flow rate remained unchanged.

Figure 2 shows the relationship between the residence time and temperature, and the yield. The numbers below the dots indicate the yields from target reactions: the lithiation of 2-(3-bromopropyl) oxirane; and trapping reaction with tributylstannyl chloride. The residence time of 6.9 ms and reaction temperature of $-60\text{ }^{\circ}\text{C}$ were found to be the optimal condition, resulting in the highest yield of 79%. The yield was inversely proportional to the residence time in **R1**: the longer the residence time in **R1**, the lower the yield. The identical tendency was observed between the yield and the reaction temperature: the higher the temperature, the lower the yield. The alkylolithium intermediate bearing an epoxy

group decomposes almost completely with the residence time of 10 s at $0\text{ }^{\circ}\text{C}$.

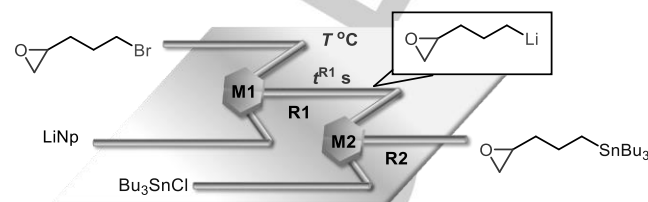


Figure 1. A flow microreactor system for reductive lithiation of 2-(3-bromopropyl)oxirane followed by reaction with tributylstannyl chloride. Micromixers: **M1** and **M2**, microtube reactors: **R1** and **R2**.

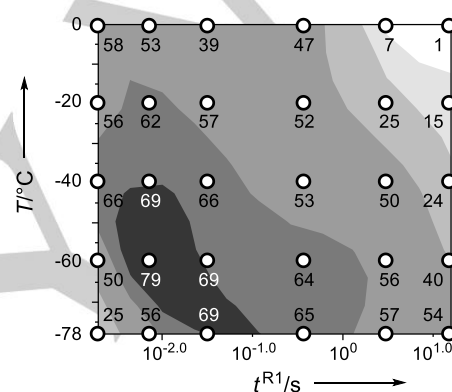


Figure 2. Temperature (T) - residence time (t^{R1}) map for the lithiation of 2-(3-bromopropyl)oxirane followed by reaction with tributylstannyl chloride in the flow microreactor system.

Likewise, the flow microreactor system was used for the generation of various primary alkylolithiums bearing an epoxy group with different carbon chain lengths, which were then reacted with various electrophiles such as tributylstannyl chloride, and phenylisocyanate. The results are summarized in Table 1.

Table 1. Generation of primary alkylolithiums bearing an epoxide group followed by reaction with electrophiles.

	t^{R1} [ms]	T [$^{\circ}\text{C}$]	electrophile	product	yield [a] [%]
	6.9	-60	Bu_3SnCl		79
	6.9	-60	PhNCO		67 ^[b]
	6.9	-60	Bu_3SnCl		83
	6.9	-60	PhNCO		78 ^[b]
	6.9	-60	Bu_3SnCl		78

^a Unless otherwise stated the yields were determined by GC using an internal standard. ^b Isolated yield.

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Next, we examined generation of primary alkylolithiums bearing a cyano group, which has higher electrophilicity than an epoxide

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group. It is critical to set the reaction time extremely short by employing high-resolution control of the residence time.^[11] For this purpose, For this purpose, a built-in type system in which **M1** (inner diameter: 250 μm), **R1** (inner diameter: 250 μm , length: 1.0 cm) and **M2** (inner diameter: 250 μm) was newly constructed to achieve a shorter residence time of $t^{R1} = 3.4$ ms (Figure 3 (a)). This built-in device was used for highly unstable compounds while a conventional modular device was employed for reactions with more stable reactants, which required longer residence times, like over 6.9 ms (Figure 3 (b)). The short residence time of 3.4 ms enabled the generation and reaction with benzaldehyde, of alkyllithiums bearing a cyano group in a good yield while a reactive cyano group was unaffected (Figure 4, Table 2).

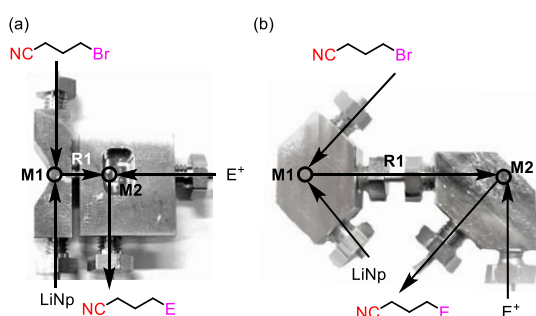


Figure 3. Flow microreactor systems. (a) Built-in type system, (b) modular type system.

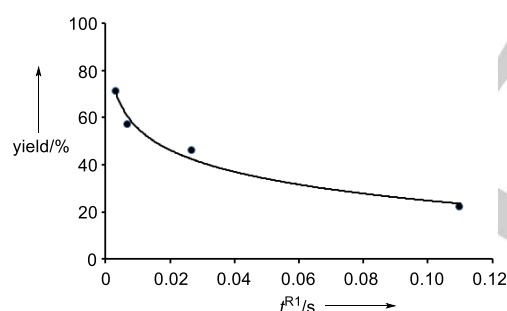


Figure 4. Plots of the yield of 5-hydroxy-5-phenylpentanenitrile against the residence time (t^{R1}) for lithiation of 4-bromobutanenitrile with LiNp followed by reaction with benzaldehyde at -80 $^{\circ}\text{C}$ in the flow microreactor system.

Table 2. Generation and reactions of highly functional alkyllithiums bearing an electrophilic functional group.

	t^{R1} [ms]	T [$^{\circ}\text{C}$]	electrophile	product	yield ^[a] [%]
	3.4	-80	PhCHO		71 ^[b]
	3.4	-80	MeOTf		52
	3.4	-80	PhCHO		72 ^[b]
	3.4	-90	PhCHO		50 ^[b]
	2.0	-78	PhMe ₂ SiCl		80

^a Unless otherwise stated the yields were determined by GC using an internal standard. ^b Isolated yield.

Moreover, an alkyllithium bearing an alkoxy carbonyl was also generated and then used for further reaction with electrophiles while the alkoxy carbonyl group remained unchanged (Table 2). It is noteworthy that an alkyllithium bearing a carbonyloxy group at the α position was also generated and reacted with an electrophile with the residence time of 2.0 ms (Table 2, See the Supporting Information for details). It is worth mentioning that these transformations are virtually impossible with conventional macro batch reactors.

Secondary and tertiary alkyllithiums are more reactive and unstable than primary alkyllithiums. In fact, commercially available *sec*-BuLi and *tert*-BuLi readily react with THF (tetrahydrofuran) that is often used as a solvent in organolithium reactions.^[12] Therefore, even at a temperature as low as -78 $^{\circ}\text{C}$, it is not possible to treat such alkyllithiums as a THF stock solution. In addition, tertiary alkyllithiums have high flammability. The flow microreactor method solves abovementioned problems found in secondary and tertiary alkyllithiums. First, lithiation of adamantyl bromide was performed with LiNp, and the product was reacted with electrophiles. Although the set of reactions mostly resulted in the desired products in good yields, it did not work for adamantyl chloride because the reaction is too slow. Therefore, LiDTBB^[13] was used instead of LiNp for lithiation of adamantyl chloride. LiDTBB proved to be more efficient lithiating reagent, which indicated the use of LiDTBB is quite effective to generate secondary and tertiary alkyllithiums from alkyl chlorides.

High usability of the present method was demonstrated by the last example: successful generation of a secondary alkyllithium bearing two epoxy groups followed by reaction with tributylstannyl chloride with the residence time of 2.8 ms.

Table 3. Generation and reactions of secondary and tertiary alkyllithiums

	lithiating reagent	t^{R1} [s]	T [$^{\circ}\text{C}$]	electrophile	product	yield ^[a] [%]
	LiNp	7.9		PhCHO		76
	LiNp	6.3		PhNCO		78
	LiNp	6.3		PhCOCH ₃		72
	LiNp	6.3		PhCOCH ₃		0
	LiDTBB	6.3		PhCOCH ₃		64
	LiDTBB	15.7		PhCHO		64
	LiDTBB	15.7		PhCHO		57
	LiDTBB	6.3		PhCHO		97
	LiDTBB	6.3		PhCHO		65 ^[b]
	LiNp	0.0028		Bu ₃ SnCl		79

^a Unless otherwise stated the yields were determined by GC using an internal standard. ^b Isolated yield.

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In conclusion, flash chemistry based on flow microreactor systems allowed alkyllithiums bearing electrophilic functional groups to be successfully generated and used for subsequent reactions. The series of reactions with high reactivity was achieved by extremely accurate control over residence time in a controlled and selective manner. The present findings open a new world of organolithium chemistry.

Acknowledgements

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[1] a) P. Knochel, *Handbook of Functionalized Organometallics*, Wiley-VCH, Weinheim, **2005**; b) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4414.

[2] W. F. Bailey, J. D. Brubaker, K. P. Jordan, *J. Organomet. Chem.* **2003**, *681*, 210.

[3] a) K. Zielger, H. Colonius, *Annalene* **1930**, *479*, 135; b) J. Barluenga, J. Florez, M. Yus, *J. Chem. Soc., Chem. Commun.* **1972**, 752.

[4] a) P. K. Freeman, L. L. Hutchinson, *J. Org. Chem.* **1980**, *45*, 1924; b) J. Barluenga, J. Florez, M. Yus, *J. Chem. Soc., Chem. Commun.* **1972**, 752; c) G. Cecilia, F. H. Fernando, Y. Miguel, *Tetrahedron* **1998**, *54*, 1853-1866; d) T. Cohen, T. Kreethadumrongdat, X. Liu, V. Kulkarni, *J. Am. Chem. Soc.* **2001**, *123*, 3478-3483.

[5] a) J. Yoshida, *Chem. Commun.* **2005**, 4509; b) J. Yoshida, A. Nagaki, T. Yamada, *Chem. Eur. J.* **2008**, *14*, 7450; c) P. J. Nieuwland, K. Koch, N. van Harskamp, R. Wehrens, J. C. M. van Hest, F. P. J. T. Rutjes, *Chem. Asian J.* **2010**, *5*, 799; d) J. Yoshida, Y. Takahashi, A. Nagaki, *Chem. Commun.* **2013**, *49*, 9896.

[6] Some examples of generation and reactions of short-lived organolithiums in flow: a) H. Usutani, Y. Tomida, A. Nagaki, H. Okamoto, T. Nokami, J. Yoshida, *J. Am. Chem. Soc.* **2007**, *129*, 3046; b) A. Nagaki, E. Takizawa, J. Yoshida, *J. Am. Chem. Soc.* **2009**, *131*, 1654; c) A. Nagaki, A. Kenmoku, Y. Moriwaki, A. Hayashi, J. Yoshida, *Angew. Chem., Int. Ed.* **2010**, *49*, 7543; d) Y. Tomida, A. Nagaki, J. Yoshida, *J. Am. Chem. Soc.* **2011**, *133*, 3744; e) H. Kim, A. Nagaki, J. Yoshida, *Nat. Commun.* **2011**, *2*, 264; f) A. Nagaki, C. Matsuo, S. Kim, K. Saito, A. Miyazaki, J. Yoshida, *Angew. Chem., Int. Ed.* **2012**, *51*,

3245.

[7] Books on flow microreactor synthesis: a) W. Ehrfeld, V. Hessel, H. Löwe, *Microreactors*, Wiley-VCH, Weinheim, **2000**; b) V. Hessel, S. Hardt, H. Löwe, *Chemical Micro Process Engineering*, Wiley-VCH, Weinheim, **2004**; c) J. Yoshida, *Flash Chemistry. Fast Organic Synthesis in Microsystems*, Wiley-Blackwell, Oxford, **2008**; d) *Micro Process Engineering*; (Eds.: V. Hessel, A. Renken, J. C. Schouten, J. Yoshida), Wiley-Blackwell, Oxford, **2009**; e) *Microreactors in Organic Chemistry and Catalysis*, 2nd ed. (Ed.: T. Wirth), Wiley, Hoboken, **2013**; f) *Microreactors in Preparative Chemistry*; (Ed.: W. Reschetilowski), Wiley-VCH, Weinheim, **2013**; g) F. Darvas, V. Hessel, G. Dorman, *Flow Chemistry*, DeGruyter: Berlin, **2014**; h) J. Yoshida, *Basics of Flow Microreactor Synthesis*, Springer, Tokyo, **2015**; i) *Organometallic Flow Chemistry*; (Ed.: T. Noël), Springer, **2016**.

[8] Reviews on flow microreactor synthesis: a) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107*, 2300; b) B. Ahmed-Omer, J. C. Brandt, T. Wirth, *Org. Biomol. Chem.* **2007**, *5*, 733; c) P. Watts, C. Wiles, *Chem. Commun.* **2007**, 443; d) T. Fukuyama, M. T. Rahman, M. Sato, I. Ryu, *Synlett* **2008**, 151; e) R. L. Hartman, K. F. Jensen, *Lab Chip* **2009**, *9*, 2495; f) J. P. McMullen, K. F. Jensen, *Annu. Rev. Anal. Chem.* **2010**, *3*, 19; g) J. Yoshida, H. Kim, A. Nagaki, *ChemSusChem* **2011**, *4*, 331; h) C. Wiles, P. Watts, *Green Chem.* **2012**, *14*, 38; i) A. Kirschning, L. Kupracz, J. Hartwig, *Chem. Lett.* **2012**, *41*, 562; j) D. T. McQuade, P. H. Seeberger, *J. Org. Chem.* **2013**, *78*, 6384; k) K. S. Elvira, X. C. i Solvas, R. C. R. Wootton, A. J. deMello, *Nat. Chem.* **2013**, *5*, 905; l) J. C. Pastre, D. L. Browne, S. V. Ley, *Chem. Soc. Rev.* **2013**, *42*, 8849; m) I. R. Baxendale, *J. Chem. Technol. Biotechnol.* **2013**, *88*, 519; n) T. Fukuyama, T. Totoki, I. Ryu, *Green Chem.* **2014**, *16*, 2042; o) H. P. L. Gemoets, Y. Su, M. Shang, V. Hessel, R. Luque, T. Noël, *Chem. Soc. Rev.* **2016**, *45*, 83; p) D. Cambié, C. Bottecchia, N. J. W. Straathof, V. Hessel, T. Noël, *Chem. Rev.* **2016**, *116*, 10276; q) M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796.

[9] Some selected recent examples: a) Fuse, S.; Mifune, Y.; Takahashi, T. *Angew. Chem. Int. Ed.* **2014**, *53*, 851; b) He, Z.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2014**, *53*, 3353; c) Nagaki, A.; Takahashi, Y.; Yoshida, J. *Chem. Eur. J.* **2014**, *20*, 7931; d) Chen, M.; Ichikawa, S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2015**, *54*, 263; e) Fuse, S.; Mifune, Y.; Nakamura, H.; Tanaka, H. *Nat. Commun.* **2016**, *7*, 13491; f) Nagaki, A.; Takahashi, Y.; Yoshida, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 5327; g) Seo, H.; Katcher, M. H.; Jamison, T. F. *Nat. Chem.* **2017**, *9*, 453.

[10] a) M. Caron, K. B. Sharpless, *J. Org. Chem.* **1985**, *50*, 1557; b) R. J. Grütter, *Reactions of cyclic ethers*, pp.373-443, *The Chemistry of the ether Linkage*, (Ed.: S. Patai), Wiley, **1967**.

[11] a) A. Nagaki, Y. Tsuchihashi, S. Haraki, J. Yoshida, *Org. Biomol. Chem.* **2015**, *13*, 7140-7145; b) A. Nagaki, Y. Takahashi, A. Henseler, C. Matsuo, J. Yoshida, *Chem. Lett.* **2015**, *44*, 214-216.

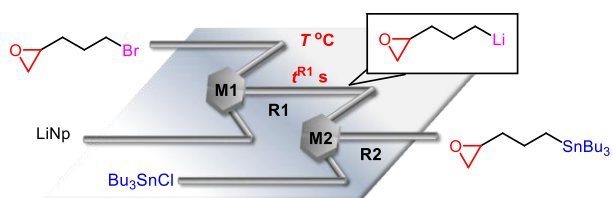
[12] a) A. Maercker *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 972; b) A. Maercker, W. Theysohn, *Liebigs Ann. Chem.* **1971**, *746*: 70; c) J. Corset, M. Castellà-Ventura, F. Froment, T. Strzalko, L. Wartski. *J. Raman Spectrosc.* **2002**, *33*, 652-668.

[13] P. K. Freeman, L. L. Llutchinson, *Tetrahedron Lett.* **1976**, *22*, 1849-1852.

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