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Oxiranyl Anion Methodology Using Microflow Systems

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Epoxides serve as versatile intermediates and building blocks in organic synthesis, and various methods such as epoxidation of olefins and reactions of carbonyl compounds with sulfur ylides have been developed for making epoxides.[1] Oxiranyl anion methodology, which is based on the generation of oxiranyllithiums by deprotonation of epoxides followed by trapping with an electrophile, has also led to extensive synthetic studies on functionalized epoxides.[2] There are two important aspects in this methodology: the chemical and configurational stabilities of oxiranyllithiums (Figure 1).[3] It is well-known that oxiranyllithiums exhibit carbene-like reactivity and undergo various decomposition reactions such as C−H insertion, 1,2-hydride shift, β−C-H insertion, and the reductive alkylation.[2] Oxiranyllithiums also undergo isomerization, although ease of this process strongly depends on the nature of the substituent on the carbon.[4] Deeper insights into these two aspects are essential for further development of this useful methodology. In this paper, we report our studies on chemical and configurational stabilities of oxiranyllithiums and the applications to preparative scale synthesis of substituted epoxides by taking advantage of microflow systems.

Though the stopped-flow method has been utilized for many years to facilitate mechanistic studies of fast organic reactions involving unstable intermediates,[5] alternative methods have been strongly needed for further progress of this important field. We envisaged that microflow systems[6,7] could serve as a powerful tool for mechanistic studies on extremely fast reactions, because residence times can be varied in the range of milliseconds to seconds by adjusting the length of a microchannel and flow speed.[8] Therefore, the time-dependent concentration of chemical species can be easily determined by the analysis of a product solution after quenching (quench flow).[9] In addition, it is important to note that we can perform the reaction in a preparative scale using the same microflow system.

We chose to use 1,2-epoxyethylphenyllithium **2** for the study of chemical stability of oxiranyllithiums. In a macrobatch system, **2** is usually generated by deprotonation of styrene oxide **1** with *tert*-BuLi or *sec*-BuLi in the presence of TMEDA at low temperature such as −95 °C.[10] At higher temperatures decomposition takes place to give various byproducts. In fact, deprotonation of **1** with 2.4 equiv of *sec*-BuLi in the absence of TMEDA (1 min) followed by reaction with MeI (2.9 equiv) at −78 °C in a macrobatch reactor gave the desired product only in 34% yield.

Thus, a microflow system consisting of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2) (Figure 2) was used. Mixing of styrene oxide **1** with *sec*-BuLi in the absence of TMEDA in M1 leads to generation of 1,2-epoxyethylphenyllithium **2** in R1. In M2, **2** was trapped with MeI to give product **3**. The reactions were carried with varying the residence time (t^R) in R1 at various temperatures, and the results are summarized in Figure 3 (see also the Supporting Information).

At −48 °C, the amount of **3** increases with t^R very rapidly at the expense of **1**, indicating that deprotonation is very fast. However,

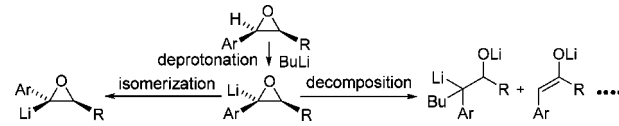

Figure 1. Chemical and configurational stabilities of oxiranyllithium species.

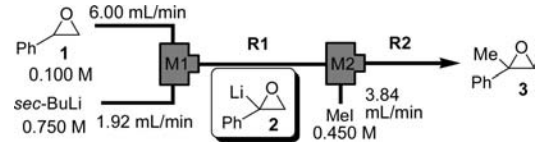

Figure 2. Microflow system for generation and reaction of oxiranyllthiums.

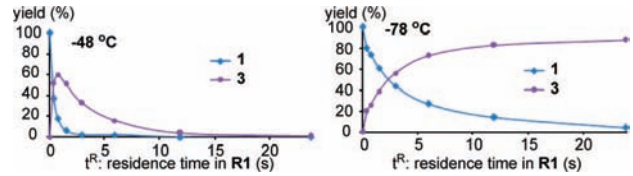

Figure 3. Reaction of **1** with *sec*-BuLi followed by trapping with MeI to give **3**.

Table 1. Deprotonation of **1** Followed by Reactions with Electrophiles Using a Microflow System[a]

electrophile	MeI	Me_3SiCl	PhCHO	$PhCOCH_3$	PhCOPh
product	**3**	**4**	**5**	**6**	**7**
% yield	88	72	84[b]	70[c]	82
productivity g/h	4.2	5.0	6.8	6.1	9.0

[a] Temperature, −78 °C; t^R, 23.8 s. [b] Diastereomer ratio 67:33 (^{1}H NMR). [c] Diastereomer ratio 82:18 (^{1}H NMR).

in the region of $t^R > 1$ s, **3** was consumed very rapidly. Presumably, the decomposition of **2** takes place very rapidly at this temperature.[11] By lowering the temperature, the decomposition could be slowed down, although the deprotonation was also slowed down. It is interesting to note that at −78 °C the amount of **3** did not decrease appreciably with an increase in the residence time until most of **1** was consumed. This means that **2** can be used for the subsequent reaction before it decomposes within such a range of time (<25 s) at this temperature. In fact, reactions with various electrophiles were successfully carried out in a preparative scale to obtain the corresponding products (**3**, **4**, **5**, **6**, **7**) as shown in Table 1.

We next examined the configurational stability of oxyranyllithium species.[12] (2*R**,3*S**)-2-Methyl-2,3-diphenyloxirane (***c*-8**) was chosen

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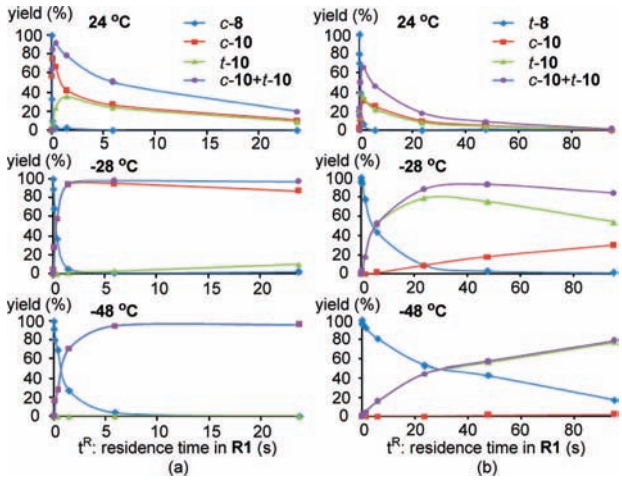
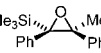
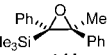
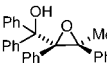
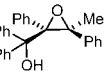


Figure 4. Reactions of ***c*-8** (a) and ***t*-8** (b) with *sec*-BuLi followed by reaction with MeI to give ***c*-10** and ***t*-10**.

Table 2. Deprotonation of **8** Followed by Reactions with Electrophiles Using a Microflow System

epoxide	oxyranyllithium	electrophile	yield (%) (c/t ratio)	productivity g/h
 ***c*-8**[a]	 ***c*-9**	MeI	 ***c*-10**  ***t*-10** 96 (> 99 : 1)[c]	7.8
 ***t*-8**[b]	 ***t*-9**	MeI	82 (2 : 98)[c]	3.3[e]
***c*-8**[a]	***c*-9**	Me_3SiCl	 ***c*-11**  ***t*-11** 97 (> 99 : 1)[c]	9.9
***t*-8**[b]	***t*-9**	Me_3SiCl	79 (4 : 96)[c]	4.0[e]
***c*-8**[a]	***c*-9**	PhCOPh	 ***c*-12**  ***t*-12** 92 (> 99 : 1)[d]	13
***t*-8**[b]	***t*-9**	PhCOPh	72 (4 : 96)[d]	5.1[e]

[a] Temperature, −48 °C; t^R, 23.8 s. [b] Temperature, −48 °C; t^R, 95.2 s. [c] Determined by GC. [d] Determined by ^{1}H NMR. [e] All flow rates were a half of the standard ones.

as a precursor, and the reactions were carried using a similar microflow system shown in Figure 2 with varying t^R in R1 at various temperatures. It can be seen from Figure 4a that the oxyranyllithium species (***c*-9**) was generated very quickly from ***c*-8** at 24 °C, because the amount of ***c*-10**, the product of the reaction of ***c*-9** with MeI, increased rapidly with t^R. Decomposition of ***c*-9** also took place simultaneously to give 4-methyl-2,3-diphenyl-2-hexene and 1,2-diphenylpropan-1-one, though it is much slower than that of **2** (see the Supporting Information for details). It is also noteworthy that ***c*-9** isomerized to ***t*-9**, which gave ***t*-10**. By decreasing the temperature, both the isomerization and decomposition were decelerated. At −28 °C, the decomposition did not take place appreciably, and only the isomerization took place slowly. At −48 °C even the isomerization did not take place appreciably. The reaction of ***t*-8** took place similarly, although the deprotonation was slower as shown in Figure 4b.

Based on the thus-obtained information, the reactions with other electrophile were successfully carried out in a preparative scale at −48 °C, and the corresponding tetrasubstituted epoxides (**11**, **12**) were obtained in high yields with high stereoselectivity as shown in Table 2. The reaction with ***t*-8** could also be carried out similarly. However, in this case much longer reaction time was required because of slow deprotonation of ***t*-8**.

In conclusion, we could obtain deeper insight into the chemical and configurational stabilities of oxyranyllithiums using the microflow system. The present method opens a new aspect in mechanistic studies of fast organic reactions involving an unstable intermediate. On the basis of the thus-obtained information, deprotonation of epoxides followed by trapping with various electrophiles were successfully carried out in a preparative manner without decomposition and isomerization of the oxyranyllithiums. The method adds a new dimension in oxiranyl anion methodology for stereoselective synthesis of epoxides.

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

References

(1) Aggarwal, V. K.; Badine, D. M.; Moorthie, V. A. *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, Germany, 2006.
(2) (a) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303. (b) Hodgson, D. M.; Bray, C. D.; Humphreys, P. G. *Synlett* **2006**, *1*, 1. (c) For a special issue on oxiranyl anions, see *Tetrahedron Symposia-in-print:* Florio, S. *Tetrahedron* **2003**, *59*, 9693–9864. (d) Boche, G.; Lohrenz, J. C. W. *Chem. Rev.* **2001**, *101*, 697. (e) Capriati, V.; Florio, S.; Luisi, R. *Chem. Rev.* **2008**, *108*, 1918.
(3) (a) Capriati, V.; Florio, S.; Luisi, R. *Synlett* **2005**, *9*, 1359. (b) Hodgson, D. M.; Gras, E. *Synthesis* **2002**, *12*, 1625. (c) Doris, E.; Dechoux, L.; Mioskowski, C. *Tetrahedron Lett.* **1994**, *21*, 4175. (d) Morgan, K. M.; O'Connor, M. J.; Humphrey, J. L.; Buschman, K. E. *J. Org. Chem.* **2001**, *66*, 1600.
(4) (a) Molander, G. A.; Mautner, K. *J. Org. Chem.* **1989**, *54*, 4042. (b) Taniguch, M.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1991**, *32*, 2783. (c) Santiago, B.; Lopez, C.; Soderquist, J. A. *Tetrahedron Lett.* **1991**, *32*, 3457. (d) Abbotto, A.; Capriati, V.; Degennaro, L.; Florio, S.; Luisi, R.; Pierrot, M.; Salomone, A. *J. Org. Chem.* **2001**, *66*, 3049. (e) Luisi, R.; Capriati, V.; Carlucci, C.; Degennaro, L.; Florio, S. *Tetrahedron* **2003**, *59*, 9707.
(5) Gomez-Hens, A.; Perez-Bendito, D. *Anal. Chim. Acta* **1991**, *242*, 147.
(6) Reviews for microreactor:(a) Jähnisch, K.; Hessel, V.; Löwe, H.; Baerns, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 406. (b) Doku, G. N.; Verboom, W.; Reinhoudt, D. N.; van den Berg, A. *Tetrahedron* **2005**, *61*, 2733. (c) Watts, P.; Haswell, S. J. *Chem. Soc. Rev.* **2005**, *34*, 235. (d) Geyer, K.; Codee, J. D. C.; Seeberger, P. H. *Chem. Eur. J.* **2006**, *12*, 8434. (e) deMello, A. J. *Nature* **2006**, *442*, 394. (f) Song, H.; Chen, D. L.; Ismagilov, R. F. *Angew. Chem., Int. Ed.* **2006**, *45*, 7336. (g) Kobayashi, J.; Mori, Y.; Kobayashi, S. *Chem. Asian J.* **2006**, *1*, 22. (h) Mason, B. P.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. *Chem. Rev.* **2007**, *107*, 2301. (i) Ahmed-Omer, B.; Brandtand, J. C.; Wirth, T. *Org. Biomol. Chem.* **2007**, *5*, 733. (j) Fukuyama, T.; Rahman, M. T.; Sato, M.; Ryu, I. *Synlett* **2008**, 151. (k) Yoshida, J.; Nagaki, A.; Yamada, T. *Chem.—Eur. J.* **2008**, *14*, 7450.
(7) Some recent examples:(a) Nagaki, A.; Togai, M.; Suga, S.; Aoki, N.; Mae, K.; Yoshida, J. *J. Am. Chem. Soc.* **2005**, *127*, 11666. (b) He, P.; Watts, P.; Marken, F.; Haswell, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 4146. (c) Uozumi, Y.; Yamada, Y.; Beppu, T.; Fukuyama, N.; Ueno, M.; Kitamori, T. *J. Am. Chem. Soc.* **2006**, *128*, 15994. (d) Tanaka, K.; Motomatsu, S.; Koyama, K.; Tanaka, S.; Fukase, K. *Org. Lett.* **2007**, *9*, 299. (e) Sahoo, H. R.; Kralj, J. G.; Jensen, K. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 5704. (f) Hornung, C. H.; Mackley, M. R.; Baxendale, I. R.; Ley, S. V. *Org. Process Res. Dev* **2007**, *11*, 399. (g) Fukuyama, T.; Kobayashi, M.; Rahman, M. T.; Kamata, N.; Ryu, I. *Org. Lett.* **2008**, *10*, 533.
(8) (a) Kawaguchi, T.; Miyata, H.; Ataka, K.; Mae, K.; Yoshida, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 2413. (b) Usutani, H.; Tomida, Y.; Nagaki, A.; Okamoto, H.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2007**, *129*, 3046. (c) Nagaki, A.; Kim, H.; Yoshida, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7822.
(9) For example:(a) Barman, T. E.; Bellamy, S. R. W.; Gutfreund, H.; Halford, S. E.; Lionne, C. *Cell. Mol. Life Sci.* **2006**, *63*, 2571. (b) Bula, W. P.; Verboom, W.; Reinhoudt, D. N.; Gardeniers, J. G. E. *Lab Chip* **2007**, *7*, 1717.
(10) (a) Eisch, J. J.; Galle, E. J. *J. Organomet. Chem.* **1976**, *121*, C-10. (b) Eisch, J. J.; Galle, E. J. *J. Org. Chem.* **1990**, *55*, 4835. (c) Capriati, V.; Florio, S.; Luisi, R.; Salomone, A. *Org. Lett.* **2002**, *4*, 2445.
(11) (*E*)-3-Methyl-1-phenyl-1-pentene and 3-methyl-2-phenyl-1-pentene were produced as by-products. When 1.5 equiv of *sec*-BuLi was used, the yields of the alkenes were almost the same, though the yield of **3** and conversion of **1** were lower (see the Supporting Information for details).
(12) (a) Capriati, V.; Degennaro, L.; Favia, R.; Florio, S.; Luisi, A. *Org. Lett.* **2002**, *4*, 1551. (b) Florio, S.; Aggarwal, V.; Salomone, A. *Org. Lett.* **2004**, *6*, 4191. (c) Capriati, V.; Florio, S.; Luisi, R.; Nuzzo, I. *J. Org. Chem.* **2004**, *69*, 3330.

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