DOI: 10.1002/chem.201000815

Generation and Reactions of Oxiranyllithiums by Use of a Flow Microreactor System

Aiichiro Nagaki, Eiji Takizawa, and Jun-ichi Yoshida*[a]

Dedicated to Professor Saverio Florio on the occasion of his 70th birthday

Abstract: A flow microreactor system consisting of micromixers and microtubes provides an effective reactor for the generation and reactions of aryloxiranyllithiums without decomposition by virtue of short residence time and efficient temperature control. The deprotonation of styrene oxides with *s*BuLi can be conducted by using the flow microreactor system at −78 or −68 °C (whereas much lower temperatures (< −100 °C) are needed for the same reactions conducted under macrobatch conditions). The resulting α-aryloxiranyllithiums were allowed to react with electrophiles in the flow microreactor system at the same temperature. The sequential introduction of various electrophiles onto 2,3-diphenyloxiranes was also achieved by using an integrated flow microreactor, which serves as a powerful system for the stereoselective synthesis of tetrasubstituted epoxides.

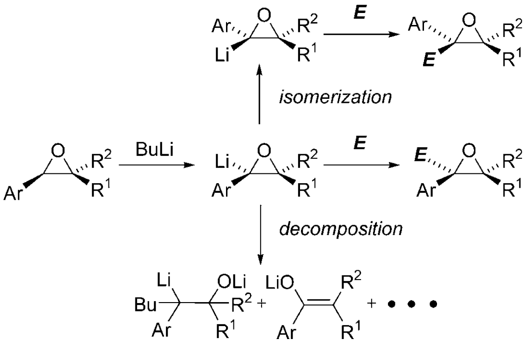
Keywords: epoxidation • microreactors • organolithium compounds • stereoselectivity • synthetic methods

Introduction

Epoxides, three-membered cyclic compounds containing an oxygen atom in the ring, serve as versatile intermediates and building blocks in organic synthesis.[1] Various methods, such as oxidation of olefins, reactions of sulfur ylides with carbonyl compounds, and reactions of α-halo enolates with carbonyl compounds, have been developed for making epoxides.

The oxiranyl anion methodology, which is based on the generation of oxiranyllithiums by deprotonation of functionalized epoxides followed by trapping with an electrophile, also serves as a powerful method for making epoxides, and extensive studies have been carried out in this field, especially by Florio and co-workers.[2] However, the generation and reactions of oxiranyllithiums generally need to be carried out at very low temperatures, because oxiranyllithiums exhibit carbene-like reactivity, and readily undergo decomposition reactions, such as C−H insertion, 1,2-hydride shift, β-C−H insertion, and reductive alkylation (see Scheme 1).[3] Oxiranyllithiums also undergo stereochemical isomerization, although the ease of this process strongly depends on the nature of the carbon substituents.[4] If such issues could be resolved, the utility of the oxiranyl anion methodology would be dramatically enhanced.

Recently, flow microreactors have received significant research interest, both from academia and industry, because they are expected to make a revolutionary change in chemical synthesis and production.[5–6] For example, highly exothermic reactions can be conducted in a controlled way by



Scheme 1. Generation and reactions of α-aryloxiranyllithiums by deprotonation of epoxides (**E**: electrophile).

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[a] Dr. A. Nagaki, E. Takizawa, Prof. Dr. J.-i. Yoshida
Department of Synthetic and Biological Chemistry
Graduate School of Engineering, Kyoto University Nishikyo-ku
Kyoto, 615-8510 (Japan)
Fax: (+81) 75-383-2727
E-mail: yoshida@sbchem.kyoto-u.ac.jp

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201000815.

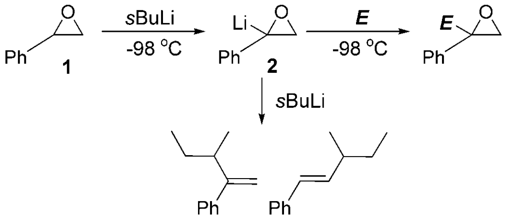
taking advantage of the efficient heat transfer of flow microreactors.[7]

Flow microreactors are also advantageous for reactions that involve unstable intermediates. The length of time that the solution remains inside the reactor (the residence time, t^R) can be greatly reduced by adjusting the length of the microchannels and the flow speed. Unstable reactive species can be transferred to another location to be used in the next reaction before they decompose. Therefore, many chemical conversions that are impossible in macroreactors may be possible in flow microreactors.[8–9]

The above features of flow microreactors are beneficial for oxiranyl anion methodology. In a preliminary communication, we reported that α-aryloxiranyllithiums could be easily generated and used for reactions with electrophiles in a controlled way by using flow microreactors.[10] Herein, we wish to report the full details of this study.

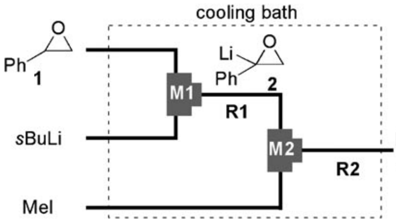
Results and Discussion

Generation and reactions of α-aryloxiranyllithiums: It has been reported that α-phenyloxiranyllithium (**2**; see Scheme 2) could be generated from styrene oxide (**1**) by using *t*BuLi or *s*BuLi in the presence of tetramethylethylenediamine (TMEDA) at −98 °C in a conventional batch reactor.[11] In contrast, the use of *s*BuLi in the absence of TMEDA caused decomposition of **2** even at −98 °C to give a mixture of (*E*)-3-methyl-1-phenyl-1-pentene and 3-methyl-2-phenyl-1-pentene (Scheme 2). The formation of these undesired products did indicate, however, that **2** was produced as a short-lived intermediate even in the absence of TMEDA.



Scheme 2. Deprotonation of styrene oxide (**1**) with *s*BuLi followed by reaction with an electrophile in a conventional macrobatch reactor (**E**: electrophile).

Thus, we examined the reaction without TMEDA in a flow microreactor system that consisted of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2), as shown in Scheme 3. A solution of styrene oxide (**1**) and a solution of *s*BuLi were introduced to M1 by syringe pump. The mixture was passed through R1, and the resulting solution of oxiranyllithium **2** was introduced to M2, where a solution of iodomethane was introduced. The resulting mixture was passed through R2 ($t^R = 2.00$ s) to obtain the desired product **3**. Deprotonation and quenching with iodomethane were conducted at the same temperature (*T*), which was controlled by adjusting the bath temperature. t^R in R1 was controlled by changing the length of R1 with a fixed flow rate. The results obtained with various t^R and *T* are summarized in Figure 1. The desired product **2** was obtained in good yield if we chose an appropriate temperature–residence time region, as shown in Figure 1 a (flow rate of a solution of *s*BuLi: 1.92 mL min^{-1} (2.4 equiv)), which indicates that **2** could be used for a subsequent reaction before it decomposed. Note also that the reaction can be carried out in the absence of TMEDA at higher temperatures than those required for batch reactions.



Scheme 3. A flow microreactor system for deprotonation of styrene oxide (**1**) with *s*BuLi followed by reaction with an electrophile. T-shaped micromixer: M1 and M2, microtube reactor: R1 and R2.

Next, we examined the effect of the amount of *s*BuLi by changing the flow rate of a solution of *s*BuLi (Figure 1 b and c); flow rates: 1.60 mL min^{-1} (2.0 equiv) and 1.20 mL min^{-1} (1.5 equiv)). The yield depended significantly not only on *T* and t^R, but also on the amount of *s*BuLi. As the amount of *s*BuLi decreased, the yield dropped. The use of 2.4 equivalents of *s*BuLi produced the best yields because it gave the fastest deprotonation among the conditions examined.

Next, the reactions with various electrophiles were examined under two sets of conditions; A ($T = -78$ °C, $t^R = 23.8$ s) and B ($T = -68$ °C, $t^R = 5.95$ s). As shown in Table 1, reactions with iodomethane, chlorotrimethylsilane, chlorodimethylsilane, benzyl bromide, allyl bromide, benzaldehyde, acetophenone, benzophenone, acetone, cyclopentanone, and cyclohexanone could be successfully performed on a preparative scale to give the corresponding α-substituted styrene oxide derivatives in good yields. Note that an increase in collection time leads to the generation of a large quantitiy of compounds.[12]

To gain insight into the reaction mechanism, the effects of phenyl ring substituents were examined. In Figure 2, the amount of starting material (4-chlorostyrene oxide (**4**), styrene oxide (**1**), and 4-methylstyrene oxide (**6**)) and the yields of the products obtained by the reaction of the resulting oxiranyllithium with iodomethane (**5**, **3**, and **7**, respectively) at −78 °C are plotted against t^R. The rate of deprotonation increased on introduction of an electron-withdrawing group (Cl) on the phenyl ring, whereas it decreased on introduction of an electron-donating group (Me). At this temperature no appreciable decomposition of the oxiranyllithium intermediates took place because the yields of the products did not decrease with an increase in t^R.

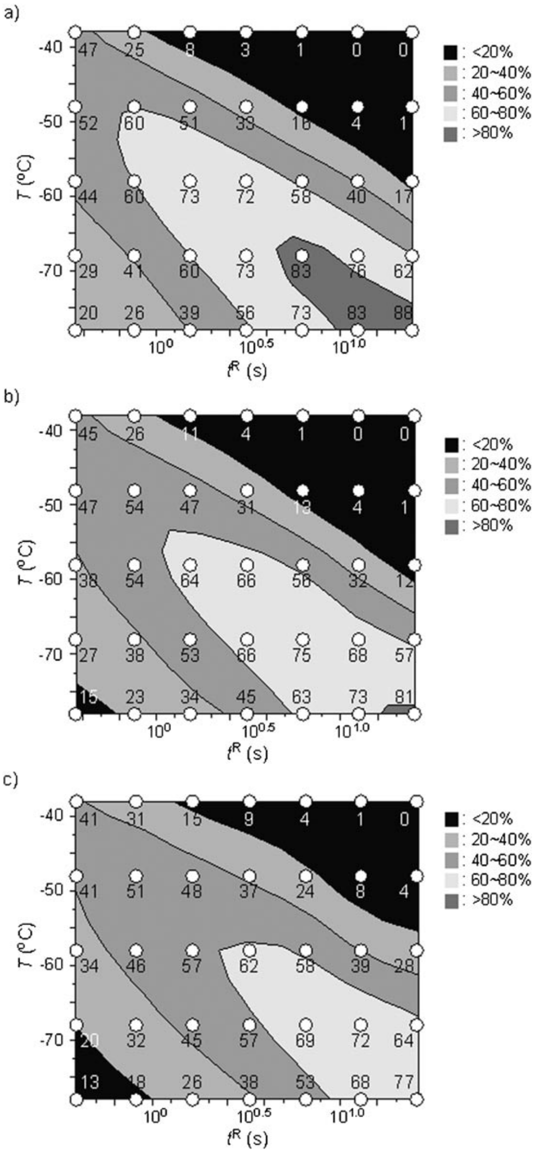
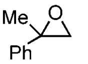
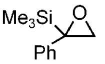
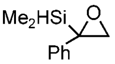
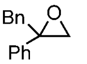
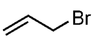
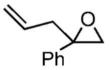
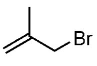
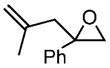
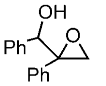
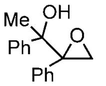
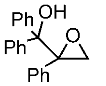
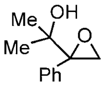
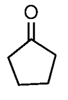
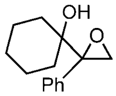
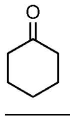
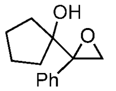


Figure 1. Effects of reaction temperature (T) and residence time (t^R) on the yield of **3** under the following conditions; a) *s*BuLi (2.4 equiv), b) *s*BuLi (2.0 equiv), and c) *s*BuLi (1.5 equiv).

However, at −68 °C, decomposition of the oxiranyllithium intermediate did take place at an appreciable rate, as shown in Figure 3. Interestingly, the decomposition rate increased on introduction of an electron-donating group (Me) on the phenyl ring, whereas it decreased on introduction of an electron-withdrawing group (Cl).

The reactions of the styrene oxides bearing various substituents on the phenyl group followed by the reactions with various electrophiles were examined at −78 °C (t^R = 23.8 s). The results are summarized in Table 2. 2-(2-Naphthyl)ethylene oxide and 2-(1,1′-biphenyl-4-yl)ethylene oxide were also used as substrates; the corresponding substituted epoxides were obtained on a preparative scale in good yields.

Table 1. Reactions of **2** with electrophiles.[a]

Electrophile	Conditions[b]	Product	Yield [%]	Productivity [g h^{-1}]
MeI	A		88[c]	4.2
	B		83[c]	4.0
Me_3SiCl	A		72[c]	5.0
	B		73[c]	5.1
Me_2SiHCl	A		50[c]	3.2
	B		49[c]	3.1
BnBr	A		54[c]	4.1
	B		51[c]	3.9
	A		45[c]	2.6
	A		38[d]	2.4
PhCHO	A		84[d] (67:33)[e]	6.8
	B		80[d] (63:37)[e]	6.5
$PhCOCH_3$	A		70[d] (82:18)[e]	6.1
	B		67[d] (82:18)[e]	5.8
Ph_2CO	A		82[d]	9.0
CH_3COCH_3	A		50[d]	3.2
	A		61[d]	4.5
	A		58[d]	4.5

[a] Solutions of styrene oxide (**1**) (0.10 M in THF), *s*BuLi (0.75 M in hexane), and electrophiles (0.45 M in THF) were allowed to react in the flow microreactor system. [b] Reaction conditions A: T = −78 °C, t^R = 23.8 s, B: T = −68 °C, t^R = 5.95 s. [c] Determined by GC. [d] Isolated yield. [e] Diastereomeric ratio as determined by ^{1}H NMR spectroscopy.

Generation and reactions of β-substituted-α-aryloxiranyllithiums: A point of further interest was the configurational stability of the oxiranyllithiums.[13] Thus, we examined the generation and reactions of β-substituted-α-aryloxiranyllithiums. (2*S**,3*R**)-2-Methyl-3-phenyloxirane (***c*-8**), (2*S**,3*S**)-2-methyl-3-phenyloxirane (***t*-8**), (2*R**,3*S**)-2,3-diphenyloxirane (***c*-10**), and (2*S**,3*S**)-2,3-diphenyloxirane (***t*-10**) were selected as precursors for the generation of β-substituted-α-aryloxiranyllithiums (Scheme 4).

Before using the flow microreactor system, we examined the reactions in a conventional flask. A solution of *s*BuLi (0.75 M in hexane) was added dropwise (1 min) to a solution of β-substituted styrene oxides (0.10 M in THF) in a 30 mL round-bottomed flask. After stirring for *t* min (*t* = 60 min at −78 °C, 5 min at −48 °C, or 1 min at 0 °C), a solution of iodomethane (0.45 M in hexane/cyclohexane (31:69 v/v)) was

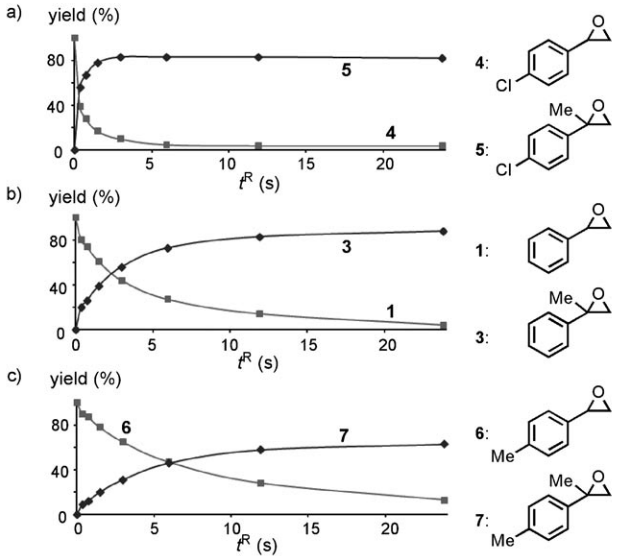


Figure 2. Plots of the amount of the starting material (a) 4-chlorostyrene oxide (**4**), b) styrene oxide (**1**), and c) 4-methylstyrene oxide (**6**)) and the yield of the corresponding products (**5**, **3**, and **7**) against residence time (t^R) for deprotonation with *s*BuLi followed by reaction with iodomethane at −78 °C in the flow microreactor system.

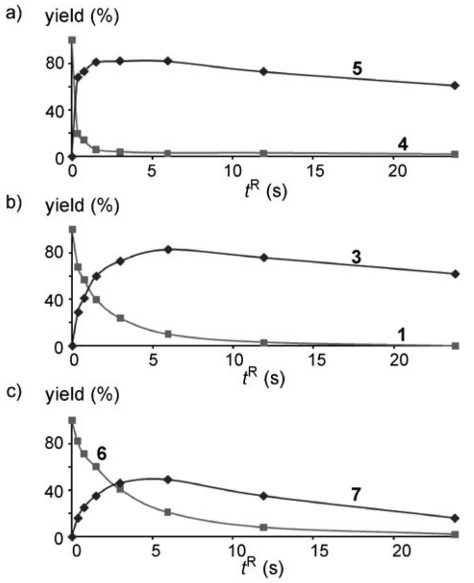
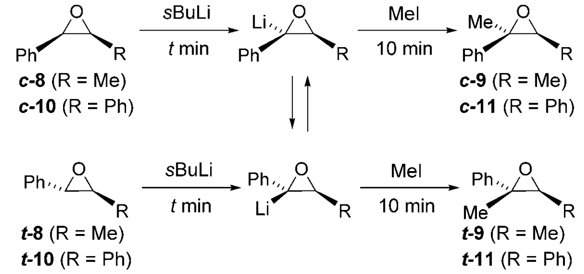


Figure 3. Plots of the amount of the starting material (a) 4-chlorostyrene oxide (**4**), b) styrene oxide (**1**), and c) 4-methylstyrene oxide (**6**)) and the yield of the corresponding products (**5**, **3**, and **7**) against residence time (t^R) for deprotonation with *s*BuLi followed by reaction with iodomethane at −68 °C in the flow microreactor system.

added. The mixture was stirred for 10 min, and the resulting solution was quenched with H_2O. The results are summarized in Table 3.

The reaction of **_c_-8** at −78 °C resulted in the formation of (2*R**,3*S**)-2,3-dimethyl-2-phenyloxirane (**_c_-9**) in 87 % yield. The amount of the isomerized product (2*S**,3*S**)-2,3-dimethyl-2-phenyloxirane (**_t_-9**) was negligibly small. The increase in temperature resulted in a decrease in yield because the oxiranyllithium intermediate decomposed. The reaction of **_t_-8** gave **_t_-9** in 35 % yield. The amount of isomerized product **_c_-9** was negligibly small. A similar tendency was observed for **_c_-10** and **_t_-10**. (2*R**,3*S**)-2-Methyl-2,3-diphenyloxirane (**_c_-11**) and (2*S**,3*S**)-2-methyl-2,3-diphenyloxirane (**_t_-11**) were obtained as major products, although isomerization was observed for **_c_-10** to some extent at −48 °C.



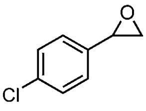
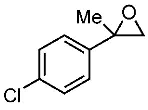
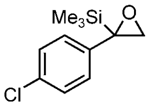
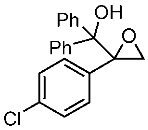
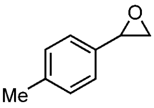
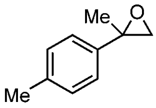
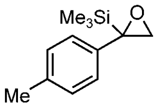
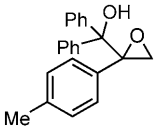
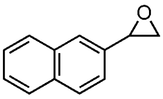
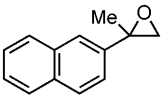
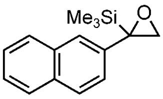
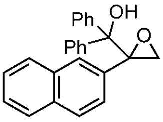
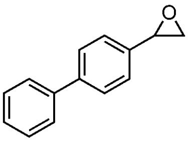
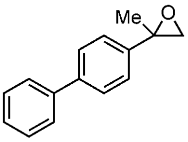
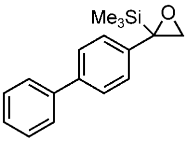
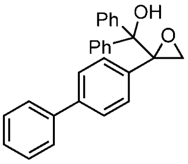
Scheme 4. Generation of β-substituted-α-aryloxiranyllithiums followed by reaction with iodomethane by using a conventional macrobatch reactor.

In the next step, we examined the reactions by using the flow microreactor system. As profiled in Figure 4 a, compound **_c_-9** was obtained from **_c_-8** in high yields for a wide range of reaction temperatures and residence times. Note that the reaction can be conducted at much higher temperatures (−28 to −48 °C) than those required for the batch reaction (−78 °C) because the residence time is reduced. In contrast, compound **_t_-9** was obtained from **_t_-8** in high yields in only a very small region of the temperature–residence time map as shown in Figure 4 b. Presumably the deprotonation of **_t_-8** is slow because of the steric effect of the methyl group. As shown in Figure 4 c, the reaction profile of **_c_-10** is very similar to that of **_c_-8**, although isomerization did take place to some extent, which is consistent with the results of the batch reactions. The reaction profile of **_t_-10** is very similar to that of **_t_-8** (Figure 4 d). Presumably, the steric effect plays an important role. In addition, the *ortho*-methylated epoxide on the phenyl ring was obtained as a byproduct (see the Supporting Information for details).[14]

Based on the conditions optimized by using the results shown in Figure 4, the reactions of β-substituted α-phenyloxiranyllithiums with other electrophiles were examined. As summarized in Table 4, the corresponding products were obtained in high yields with high stereoselectivities and no isomerization.

Generation and reactions of β,β-disubstituted-α-aryloxiranyllithiums: Next, the generation and reactions of trisubstituted oxiranyllithiums were examined. (2R*,3S*)-2-Methyl-2,3-diphenyloxirane (**_c_-11**) and (2S*,3S*)-2-methyl-2,3-diphenyloxirane (**_t_-11**) were chosen as as precursors for the generation of β,β-disubstituted α-aryloxiranyllithiums, and iodomethane was used as an electrophile (Scheme 5). The isomerization of the intermediate was of interest from the viewpoint of the configurational stability of trisubstituted oxiranyllithiums.

Table 2. Reactions of α-aryloxiranyllithiums with electrophiles.[a]

Epoxide	Electrophile	Product	Yield [%]	Productivity [$g\,h^{-1}$]
 **4**	MeI	 **5**	82[b]	5.0
	Me_3SiCl		73[c]	6.0
	Ph_2CO		82[c]	9.9
 **6**	MeI	 **7**	63[b]	3.4
	Me_3SiCl		68[c]	5.1
	Ph_2CO		59[c]	6.8
	MeI		92[b]	6.1
	Me_3SiCl		92[c]	8.1
	Ph_2CO		85[c]	10.8
	MeI		84[b]	6.4
	Me_3SiCl		72[c]	7.0
	Ph_2CO		82[c]	11.1

[a] A solution of styrene oxides (0.10 M in THF), a solution of *s*BuLi (0.75 M in hexane) and a solution of electrophiles (0.45 M in THF) were allowed to react in the flow microreactor system. [b] Determined by GC. [c] Isolated yield.

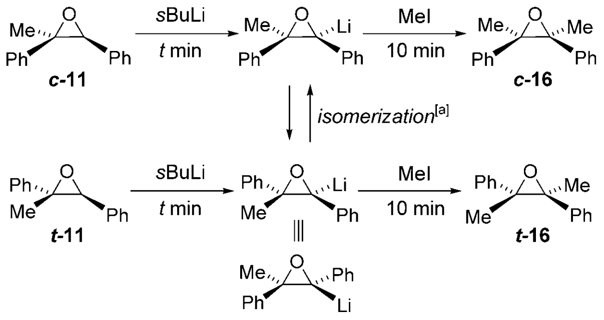
The macrobatch reactions were examined before the flow microreactor system was used. A solution of *s*BuLi (0.75 M in hexane) was added dropwise (1 min) to a solution of a β,β-disubstituted styrene oxide (0.10 M in THF) in a 30 mL round-bottomed flask. After stirring for *t* min (*t* = 60 min at −78 °C, 5 min at −48 °C, or 1 min at 0 °C), a solution of iodomethane (0.45 M in hexane/cyclohexane (31:69 v/v)) was added. After stirring for 10 min at the same temperature, the solution was quenched with H_2O. As shown in Table 5, (2*R**,3*S**)-2,3-dimethyl-2,3-diphenyloxirane (***c*-16**) and (2*S**,3*S**)-2,3-dimethyl-2,3-diphenyloxirane (***t*-16**) were obtained with high selectivity at −78 °C. However, a further increase in reaction temperature caused a decrease in the diastereomeric ratio and yield.

The reactions were carried out with the flow microreactor system at various temperatures. It can be seen from Figure 5 that the oxiranyllithium species was generated very quickly from ***c*-11** at 24 °C, because the amount of ***c*-16**, increased rapidly with an increase in t^R. Decomposition also took place, although it is much slower than in the case of styrene oxide (see the Supporting Information for details). Note also that the oxiranyllithium intermediate isomerized at this temperature to give ***t*-16**. By decreasing the temperature, both the isomerization and decomposition were decelerated. At −28 °C, no appreciable decomposition took place, and isomerization took place only slowly, while at −48 °C not even isomerization took place appreciably. The reaction of ***t*-11** took place similarly, although deprotonation was slower than in the case of ***c*-11**, as shown in Figure 6.

Table 3. Deprotonation of β-substituted styrene oxides with *s*BuLi followed by reaction with iodomethane by using a conventional macrobatch reactor.[a]

β-Substituted styrene oxide	*T* [°C]	*t* [min]	Conversion [%]	Yield [%]	*c*/*t* ratio
***c*-8**	−78	60	100	87	***c*-9**/***t*-9** > 99:1
	−48	5	100	43	> 99:1
	0	1	100	0	–
***t*-8**	−78	60	100	35	< 1:99
	−48	5	100	0	–
	0	1	100	0	–
***c*-10**[b]	−78	60	99	87	***c*-11**/***t*-11** 99:1
	−48	5	95	43	90:10
	0	1	100	0	–
***t*-10**	−78	60	93	52	< 1:99
	−48	5	96	54	< 1:99
	0	1	100	1	–

[a] A solution of *s*BuLi (0.75 M) in hexane/cyclohexane (31:69 v/v) was added dropwise to a solution of β-substituted styrene oxides (0.10 M) in THF at −78 or −48 or 0 °C. After stirring for *t* min, a solution of iodomethane (0.45 M) in THF was added as an electrophile. After stirring for 10 min at the same temperature, the yield and diastereomeric ratio of methylated products were determined by GC. [b] *s*BuLi (0.38 M), iodomethane (0.23 M).



Scheme 5. Generation of β,β-disubstituted-α-aryloxiranyllithiums followed by reaction with iodomethane. [a] Although the isomerization takes place on the lithiated carbon center, the structural formula in which the isomerization takes place on the other carbon in the three-membered ring is shown for easy comparison with Scheme 4.

By using the optimized reaction conditions, deprotonation of ***c*-11** and ***t*-11** followed by reactions with other electrophiles could be achieved with the flow microreactor system. As shown in Table 6, the corresponding tetrasubstituted epoxides were obtained in high yields with high stereoselectivity. These results indicate that the isomerization of the oxiranyllithium intermediates can be avoided by choosing appropriate reaction temperatures and residence times.

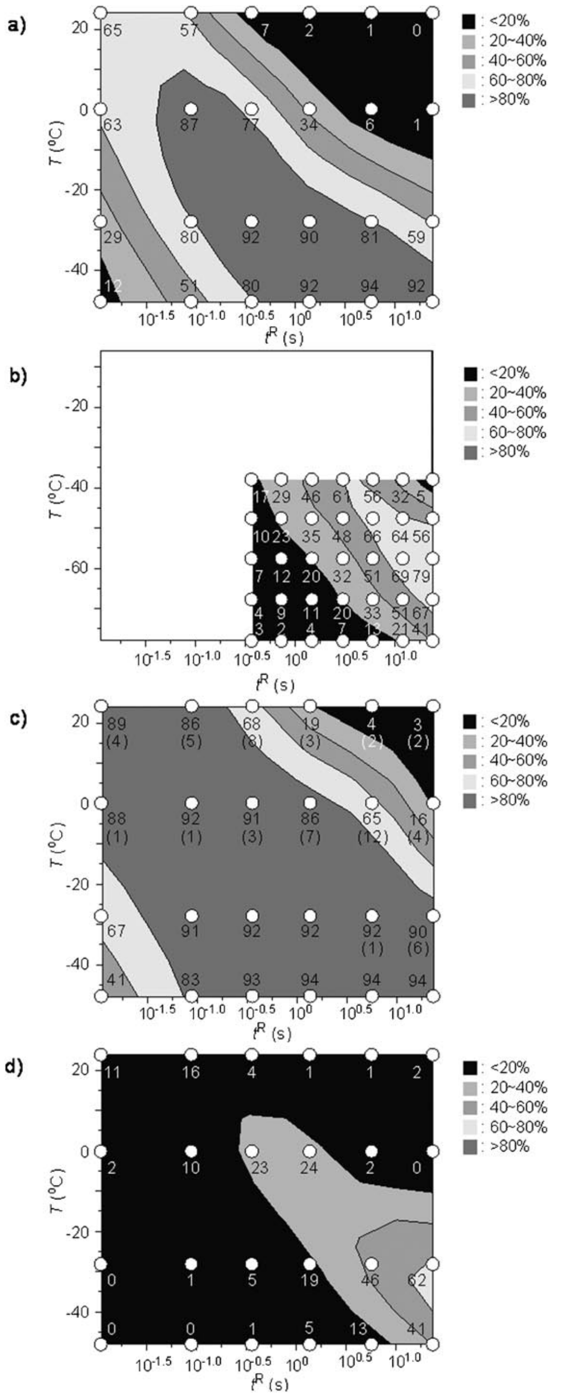
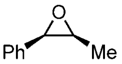
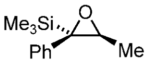
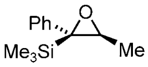
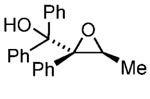
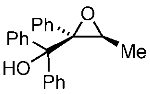
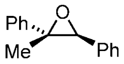
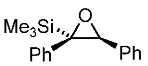
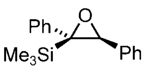
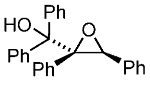
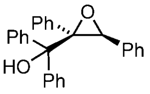


Figure 4. Effects of reaction temperature (*T*) and residence time (t^R) on the yield of methylated products in the deprotonation of β-substituted styrene oxides: a) (2*S**,3*R**)-2-methyl-3-phenyloxirane (***c*-8**), b) (2*S**,3*S**)-2-methyl-3-phenyloxirane (***t*-8**), c) (2*R**,3*S**)-2,3-diphenyloxirane (***c*-10**), and d) (2*S**,3*S**)-2,3-diphenyloxirane (***t*-10**). The yields in parentheses are those of the isomerized product.

Integrated oxiranyl anion methodology: stereoselective synthesis of tetrasubstituted epoxides by sequential introduction of two electrophiles: As an extension of the present method, we examined the stereoselective synthesis of tetrasubstituted epoxides by repeating the sequence of deprotonation followed by reaction with an electrophile (Scheme 6). By choosing appropriate reaction temperatures and residence times with the integrated flow microreactor system, which consists of four micromixers (M1, M2, M3, M4) and four microtube reactors (R1, R2, R3, R4) (Scheme 7), two electrophiles could be introduced to disubsituted epoxides such as

Table 4. Reactions of β-substituted-α-aryloxiranyllithiums with electrophiles.[a]

β-Substituted styrene oxide	Electrophile	Yield [%] (*c*-/*t*- ratio)	Productivity [$\mathrm{g\,h^{-1}}$]
 ***c*-8**	MeI	 ***c*-9**  ***t*-9** 92 (>99:1)[b]	5.0
 ***t*-8**	MeI	***c*-9** ***t*-9** 79 (<1:99)[b]	4.2
***c*-8**	Me_3SiCl	 ***c*-12**  ***t*-12** 85[c] (>99:1)[d]	6.3
***t*-8**	Me_3SiCl	***c*-12** ***t*-12** 75[c] (<1:99)[d]	5.6
***c*-8**	Ph_2CO	 ***c*-13**  ***t*-13** 91[c] (>99:1)[d]	10.7
***t*-8**	Ph_2CO	***c*-13** ***t*-13** 65[c] (<1:99)[d]	7.4
 ***c*-10**	MeI	 ***c*-11**  ***t*-11** 92 (>99:1)[b]	7.0
 ***t*-10**	MeI	***c*-11** ***t*-11** 62 (<1:99)[b]	4.7
***c*-10**	Me_3SiCl	 ***c*-14**  ***t*-14** 94[c] (>99:1)[d]	9.1
***t*-10**	Me_3SiCl	***c*-14** ***t*-14** 48[c] (<1:99)[d]	4.6
***c*-10**[e]	Ph_2CO	 ***c*-15**  ***t*-15** 96[c] (>99:1)[d]	13.1
***t*-10**	Ph_2CO	***c*-15** ***t*-15** 56[c] (<1:99)[d]	7.7

[a] A solution of β-substituted styrene oxides (0.10 M in THF), *s*BuLi (0.75 M in hexane) and electrophiles (0.45 M in THF) were allowed to react in the flow microreactor system. ***c*-8**: $T=-28\,°C$, $t^R=0.365$ s, ***t*-8**: $T=-58\,°C$, $t^R=23.8$ s, ***c*-10**: $T=-28\,°C$, $t^R=0.365$ s, ***t*-10**: $T=-28\,°C$, $t^R=23.8$ s. [b] Determined by GC. [c] Isolated yield. [d] Diastereomeric ratio was determined by ^{1}H NMR spectroscopy. [e] *s*BuLi (0.38 M), electrophiles (0.23 M).

(2*R**,3*S**)-2,3-diphenyloxirane (***c*-10**) and (2*S**,3*S**)-2,3-diphenyloxirane (***t*-10**) without decomposition and isomerization of the oxiranlylithium intermediate, as shown in Table 7.

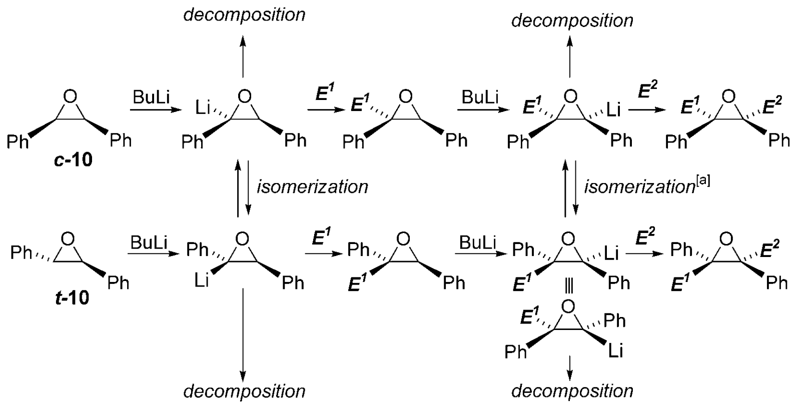
Conclusion

We have developed an efficient method for the generation and reactions of α-aryloxiranyllithiums without decomposition or isomerization by virtue of the short residence times and efficient temperature control in flow microreactor systems. In addition, we obtained deeper insights into the chemical and configurational stabilities of oxiranyllithiums by using the flow microreactor system. The use of flow microreactor systems serves as a powerful method for introducing substitutents to epoxides. Moreover, repeating the sequence of deprotonation and electrophilic reaction with the integrated flow microreactor system serves as a powerful method for the stereoselective synthesis of tetrasubstituted epoxides.

Experimental Section

General: Stainless steel (SUS304) T-shaped micromixers with inner diameters of 250 μm and 500 μm were manufactured by Sanko Seiki. Stainless steel (SUS316) microtube reactors with inner diameter of 250, 500, and 1000 μm were purchased from GL Sciences. The micromixers and the microtube reactors were connected with stainless steel fittings (GL Sciences, 1/16 OUW). The flow microreactor system was submerged in a cooling bath to control the temperature. Solutions were introduced to the flow microreactor system by using syringe pumps, Harvard Model 11, equipped with gastight syringes purchased from SGE.

Typical procedure for deprotonation of an epoxide followed by reaction with an electrophile with a flow microreactor system: A flow microreactor system was used, which consisted of two T-shaped micromixers (M1 ($\phi=250$ μm) and M2 ($\phi=500$ μm)), two microtube reactors (R1 and R2 ($\phi=1000$ μm, $L=50$ cm)), and three tube-precooling units (P1 (inner diameter $\phi=1000$ μm, length $L=100$ cm), P2 ($\phi=1000$ μm, $L=50$ cm), and P3 ($\phi=1000$ μm, $L=100$ cm)). A solution of epoxides (0.100 M) in THF (flow rate: 6.00 $\mathrm{mL\,min^{-1}}$) and a solution of *s*BuLi (0.750 M) in *n*-hexane/cyclohexane (31:69 v/v) (flow rate: 1.92 $\mathrm{mL\,min^{-1}}$) were introduced to M1 by syringe pump. The resulting solution was passed through R1, and was mixed with a solution of an electrophile (0.450 M) in THF (flow rate: 3.84 $\mathrm{mL\,min^{-1}}$) in M2 before



Scheme 6. Sequential deprotonation of $(2R^*,3S^*)$-2,3-diphenyloxirane (***c*-10**) or $(2S^*,3S^*)$-2,3-diphenyloxirane (***t*-10**) followed by reactions with different electrophiles. [a] Isomerization takes place on the lithiated carbon center, the structural formula in which the isomerization takes place on the other carbon in the three-membered ring.

being passed through R2. After a steady state was reached, the product solution was collected for 60 s while being quenched with H_2O. NH_4Cl (saturated aqueous; 5 mL) and brine (20 mL) were added, and the organic layer was analyzed by gas chromatography (GC).

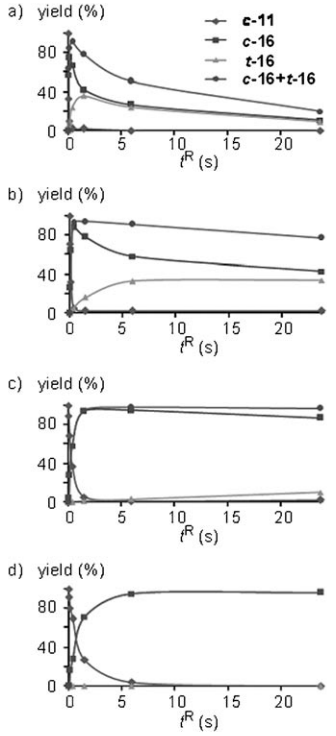


Figure 5. Reactions of $(2R^*,3S^*)$-2-methyl-2,3-diphenyloxirane (***c*-11**) with *s*BuLi followed by reaction with iodomethane to give $(2R^*,3S^*)$-2,3-dimethyl-2,3-diphenyloxirane (***c*-16**) and $(2S^*,3S^*)$-2,3-dimethyl-2,3-diphenyloxirane (***t*-16**). Dependence on the residence time (t^R) at various reaction temperatures (T): a) $T = 24\,°C$, b) $T = 0\,°C$, c) $T = -28\,°C$, d) $T = -48\,°C$.

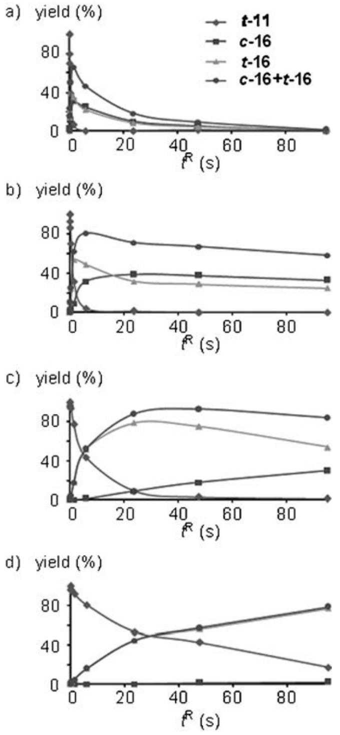
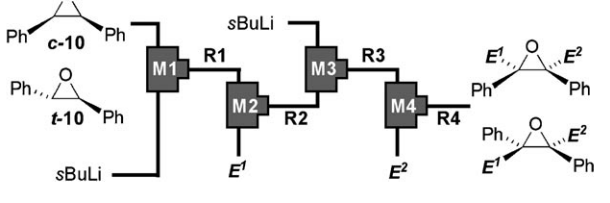


Figure 6. Reactions of $(2S^*,3S^*)$-2-methyl-2,3-diphenyloxirane (***t*-11**) with *s*BuLi followed by reaction with iodomethane to give $(2S^*,3S^*)$-2,3-dimethyl-2,3-diphenyloxirane (***t*-16**) and $(2R^*,3S^*)$-2,3-dimethyl-2,3-diphenyloxirane (***c*-16**). Dependence on the residence time (t^R) at various reaction temperatures (T): a) $T = 24\,°C$, b) $T = 0\,°C$, c) $T = -28\,°C$, d) $T = -48\,°C$.



Scheme 7. An integrated flow microreactor system for the synthesis of tetrasubstituted epoxides by sequential introduction of two electrophiles ($\mathbf{E}^1$, $\mathbf{E}^2$).

Typical procedure for synthesis of tetrasubstituted epoxides with an integrated flow microreactor system: A flow microreactor system was used, which consisted of four T-shaped micromixers (M1, M2, M3, and M4), four microtube reactors (R1, R2, R3, and R4) and five microtube-precooling units (P1 ($\phi = 1000$ µm, $L = 50$ cm), P2 ($\phi = 1000$ µm, $L = 25$ cm), P3 ($\phi = 1000$ µm, $L = 50$ cm), P4 ($\phi = 1000$ µm, $L = 50$ cm), and P5 ($\phi = 1000$ µm, $L = 100$ cm)). The whole flow microreactor system was submerged in a cooling bath (−28 °C). A solution of $(2S^*,3S^*)$-2,3-diphenyloxirane (*t*-10) (0.100 M) in THF (flow rate = 3.00 mL min^{-1}) and a solution of *s*BuLi (0.750 M) in hexane/cyclohexane (31:69 v/v) (flow rate: 0.960 mL min^{-1}) were introduced to M1 ($\phi = 250$ µm). The resulting solution was passed through R1 ($\phi = 1000$ µm, $L = 200$ cm) and was mixed with a solution of the first electrophile (0.450 M) in THF (flow rate: 1.92 mL min^{-1}) in M2 ($\phi = 500$ µm). The solution was then passed through R2 ($\phi = 1000$ µm, $L = 100$ cm) and was introduced to

Table 5. Deprotonation of β,β-disubstituted styrene oxide by using a conventional macrobatch reactor.[a]

β,β-Disubstituted styrene oxide	T [°C]	t [min]	Conversion [%]	Yield [%]	***c*-16/*t*-16** ratio
***c*-11**	−78	60	99	95	99:1
	−48	5	98	89	86:14
	0	1	99	41	57:43
***t*-11**	−78	60	97	92	<1:99
	−48	5	99	90	15:85
	0	1	100	39	57:43

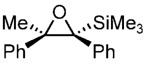
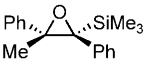
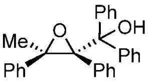
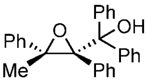
[a] A solution of *s*BuLi in hexane was added dropwise to a solution of β,β-disubstituted styrene oxides in THF. After stirring for *t* min, iodomethane was added as an electrophile. After stirring for 10 min at the same temperature, the yield and diasteromeric ratio of methylated products were determined by GC.

M3 ($\phi = 250$ μm), where it was mixed with a solution of *s*BuLi (0.750 M) in hexane/cyclohexane (31:69 v/v) (flow rate = 1.92 mL min^{-1}). The resulting solution was passed through R3 ($\phi = 1000$ μm, $L = 400$ cm) and was introduced to M4 ($\phi = 500$ μm) where it was mixed with a solution of the second electrophile (0.450 M) in THF (flow rate = 3.84 mL min^{-1}). The resulting solution was passed through R4 ($\phi = 1000$ μm, $L = 50$ cm). After a steady state was reached, the product solution was collected for 60 s while being quenched with H_2O. NH_4Cl (saturated aqueous; 5 mL) and brine (20 mL) were added and the organic layer was analyzed by GC, or isolated by flash chromatography on silica gel.

Acknowledgements

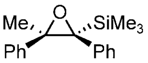
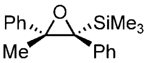
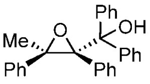
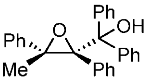
This work was partially supported by the Grant-in-Aid for Scientific Research.

Table 7. Synthesis of tetrasubstituted epoxides by sequential introduction of two electrophiles.[a]

Styrene oxide	Electrophile	Yield [%] (***c*-/*t*-** ratio)	Productivity [g h^{-1}]
 ***c*-10**	**E**^{1}: MeI **E**^{2}: MeI	 ***c*-16**  ***t*-16** 91 (>99:1)[b]	3.7
 ***t*-10**	**E**^{1}: MeI **E**^{2}: MeI	59 (7:93)[b]	2.4
***c*-10**	**E**^{1}: MeI **E**^{2}: Me_3SiCl	 ***c*-17**  ***t*-17** 94 (>99:1)[b]	4.8
***t*-10**	**E**^{1}: MeI **E**^{2}: Me_3SiCl	51 (10:90)[b]	2.6
***c*-10**	**E**^{1}: MeI **E**^{2}: Ph_2CO	 ***c*-18**  ***t*-18** 84[c] (>99:1)[d]	6.0
***t*-10**	**E**^{1}: MeI **E**^{2}: Ph_2CO	43[c] (13:87)[d]	3.0

[a] ***c*-10**: The first sequence was carried out at −28 °C, whereas the second sequence was carried out at −48 °C. ***t*-10**: Both sequences were carried out at −28 °C. [b] Determined by GC. [c] Isolated yield. [d] Diastereomeric ratio was determined by ^{1}H NMR spectroscopy.

Table 6. Reactions of β,β-disubstituted-α-aryloxiranyllithiums with electrophiles.[a]

β,β-Disubstituted styrene oxide	Electrophile	Yield [%] (*c*/*t* ratio)	Productivity [g h^{-1}]
 ***c*-11**	MeI	 ***c*-16**  ***t*-16** 96[b] (>99:1)[e]	7.8
 ***t*-11**	MeI	88[c] (11:89)[e] 81[d] (2:98)[e]	7.1 3.3
***c*-11**	Me_3SiCl	 ***c*-17**  ***t*-17** 97[b] (>99:1)[e]	9.9
***t*-11**	Me_3SiCl	83[c] (12:88)[e] 79[d] (4:96)[e]	8.4 4.0
***c*-11**	Ph_2CO	 ***c*-18**  ***t*-18** 92[b,f] (>99:1)[g]	13.0
***t*-11**	Ph_2CO	81[c,f] (13:87)[g] 72[d,f] (4:96)[g]	11.4 5.1

[a] A solution of β,β-disubstituted styrene oxides in THF (0.10 M), *s*BuLi in hexane (0.75 M) and electrophiles in THF (0.45 M) were allowed to react in the flow microreactor system. [b] −48 °C, $t^R = 23.8$ s. [c] −28 °C, $t^R = 23.8$ s. [d] −48 °C, $t^R = 95.2$ s. [e] Determined by GC. [f] Isolated yield. [g] Diastereomeric ratio was determined by ^{1}H NMR spectroscopy.

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Received: April 1, 2010