Nucleophilic Ring-opening of Three-membered Heterocycles Based on Consideration of Basicity of Nucleophiles

(求核剤の塩基性の考察に基づくヘテロ３員環の求核的開環)

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Preface

This is the thesis for a doctorate of the University of Tokyo, which summarizes the results of about six years' research work.

List of Abbreviations

Bn	Benzyl
Boc	*t*-butoxycarbonyl
Bus	*tert*-butylsulfonyl
CD	circular dichroism
DCC	Dicyclohexylcarbodiimide
DMAP	4-dimethylaminopyridine
LG	Leaving group
Ms	Methanesulfonyl
Ns	*p*-nitrophenylsulfonyl
PG	Protecting group
ORD	optical rotatory dispersion
SES	2-(trimethylsilyl)-ethylsulfonyl
TBAF	Tetrabutylammonium fluoride
TBS	*t*-butyldimethylsilyl
Tf	Trifluoromethanesulfonyl
TMS	Trimethylsilyl
Tr	triphenylmethyl
Ts	*p*-tosyl
XRD	X-ray diffraction

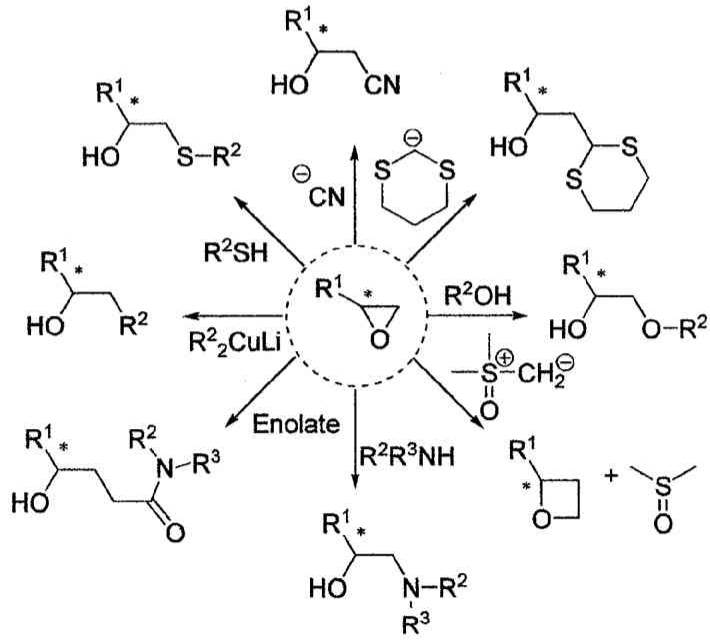
Chapter 1
General Introduction

1.1. Three-membered Ring: Epoxides and Azirdines

Epoxides and aziridnes are both three-membered rings containing an oxygen atom and nitrogen atom, respectively (Figure 1.1.1).

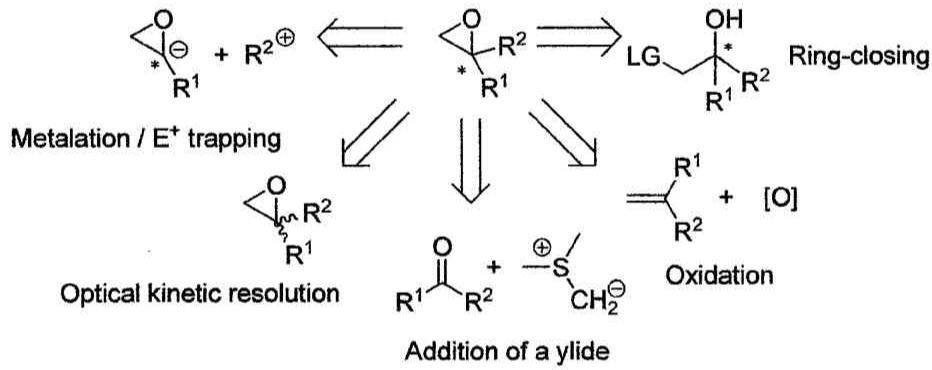
Figure 1.1.1 Epoxide and aziridine.

Epoxides are an important class of functional groups that are widely employed in organic synthesis. Particularly, epoxides are used as key intermediates in natural product syntheses mainly because optically pure epoxides can be converted into chiral alcohols via a ring-opening reaction by various kinds of nuclephiles as described (Scheme 1.1.1).[1-5] The accumulated efforts can be regarded as unambiguous proof of the importance.



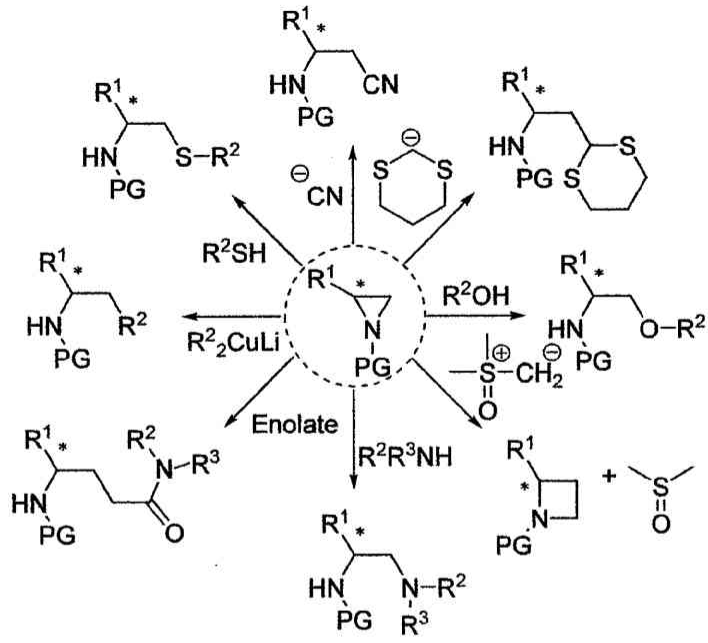
Scheme 1.1.1 Ring-opening reaction of epoxides by various kinds of nucleophile

Thus, intensive efforts have been also made by countless groups to develop synthetic methods of chiral epoxides such as a ring-closure of chiral *β*-halo-alcohols, the asymmetric oxidation of olefins, the addition of ylides to aldehydes, optical kinetic resolution of racemic epoxides, the electrophile trapping of lithiated chiral epoxides, and so forth (Scheme 1.1.2).[5-15] Especially, the Sharpless asymmetric epoxidation of allyl alcohols and the Jacobsen kinetic resolution of terminal mono-substituted epoxides with water should be noted because of their prominent usefulness.



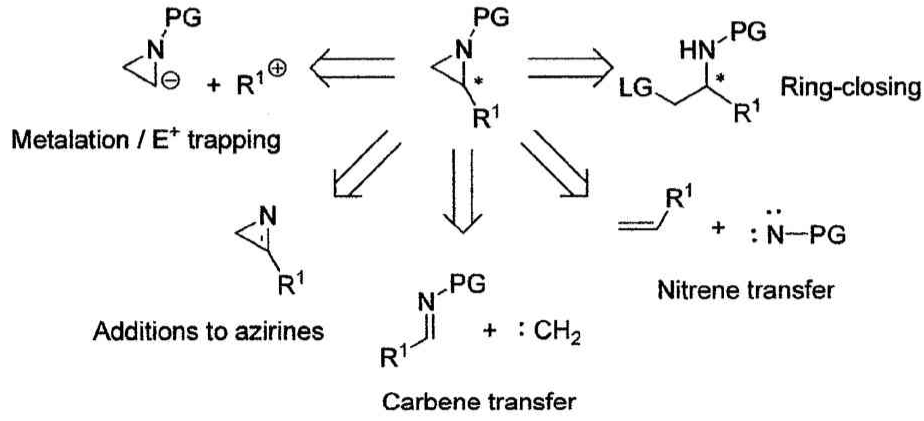
Scheme 1.1.2 Synthetic procedures for chiral epoxides

On the other hand, azirdines are the nitrogen analogues of epoxides and exhibit similar reactivity patterns as electrophilic reagents in spite of less amount of reports than those of epoxides (Scheme 1.1.3).[2,3,16-18] Apart from epoxides, aziridines can possess additional functional groups on their nitrogen atoms. Thus, protecting groups for an amine have been often introduced to the nitrogen atom such as sulfonyl and Boc. These groups can work not only as protective groups for an amine but also activators for the ring-opening reaction of aziridines. Particularly, aziridines bearing a sulfonyl group are convenient for active ring-opening reactions and easy preparation. Nevertheless, harsh conditions for deprotection have been regarded as an obstacle (*vide infra*). They undergo highly regio- and stereo-selective transformations and, therefore, are useful building blocks of organic synthesis to amine-containing natural products.



Scheme 1.1.3 Ring-opening reaction of aziridines by various kinds of nucleophiles.

This is why synthetic procedures of chiral aziridines have been developed strikingly such as the ring-closure of chiral *β*-halo-amines, asymmetric nitrene transfers to olefins, asymmetric carbene transfers to imines, the addition of Grignard reagents to azirines, the electrophile trapping of lithiated chiral aziridines, and so forth (Scheme 1.1.4).[19-23] Especially, the ring-closure of a chiral *β*-halo-amine derived from an amino acid is an efficient synthetic procedure for the easy availability of the starting material and no need of optical separation.

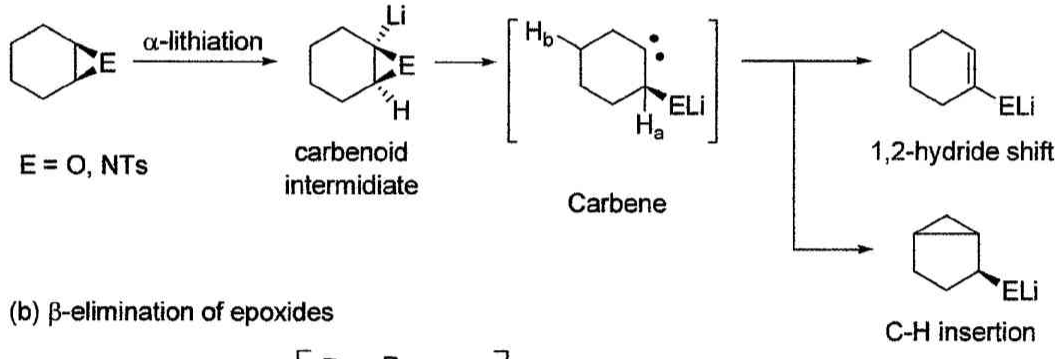


Scheme 1.1.4 Synthetic procedures for chiral aziridines.

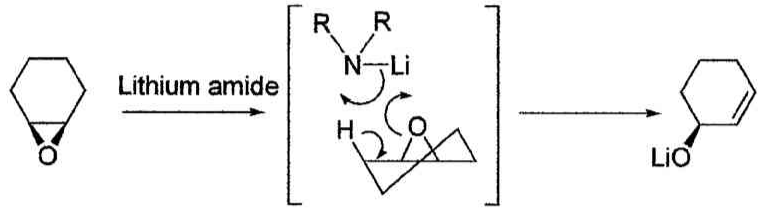
1.2. Obstacles to Ring-opening Reaction of Epoxides and Aziridines

In spite of intensive efforts by countless groups, the ring-opening reactions of epoxides and aziridines have often encountered many side reactions by strong bases derived from nucleophiles.[13,24-26] First of all, it has been well known that lithiations by the α-deprotonation of epoxides lead to carbenoid intermediates which can undergo various C-H insertions and 1,2-hydride shifts as well as cyclopropanations (Scheme 1.2.1a). On the other hand, the reaction of a lithium amide with an epoxide bearing an available β-hydrogen often results in a β-elimination giving an allylic alcohol (Scheme 1.2.1b). Furthermore, when epoxides and aziridines possess a highly electron-withdrawing group (ester, phenyl, perfluoro-alkyl groups), undesirable side reactions rather than smooth ring-opening reactions can easily occur, because the electron-withdrawing group stabilizes their α-anion originating from a deprotonation (Scheme 1.2.1c).

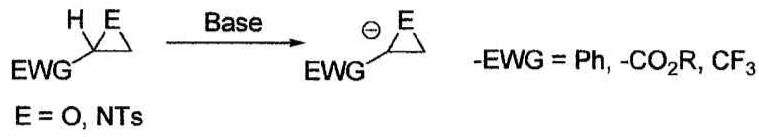
(a) α-deprotonation of epoxides



(b) β-elimination of epoxides

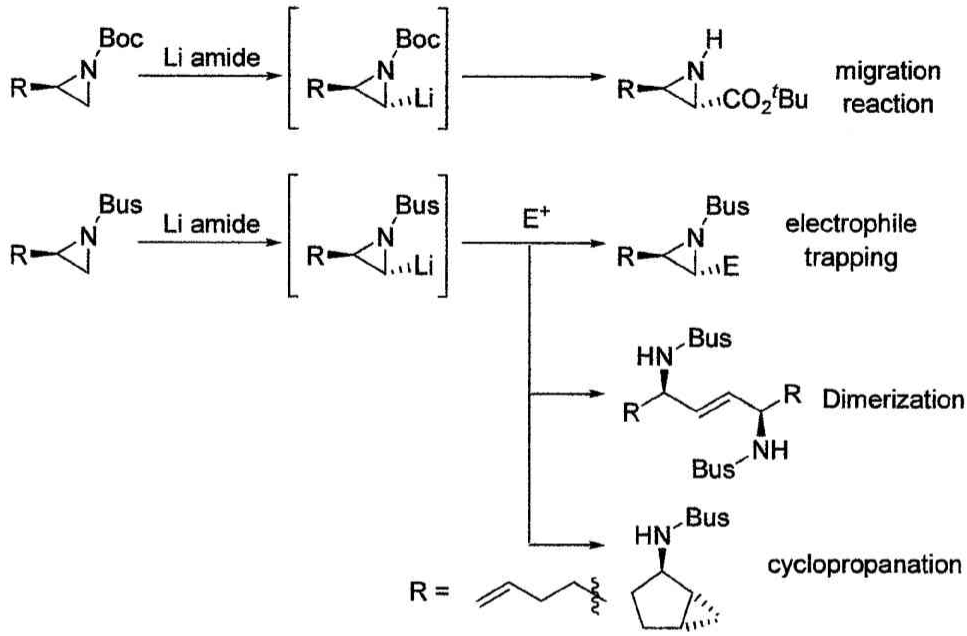


(c) α-deprotonation neighboring electron-withdrawing groups



Scheme 1.2.1 Various side reaction of epoxides and aziridines derived from basicity.

In the case of the aziridines, deprotonation of α–proton on the nitrogen atoms leads to further side reactions: migration, dimerization and cyclopropanation (Scheme 1.2.2).[24]



Scheme 1.2.2 Various side reaction of aziridines derived from basicity.

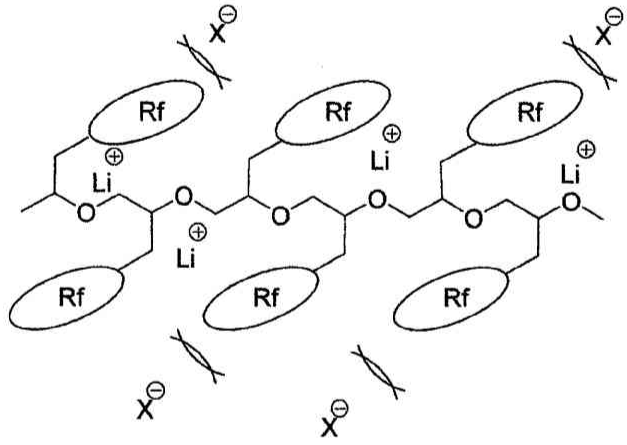
Hence, it is important to control nucleophilicity in order to achieve an exclusive ring-opening reaction by suppressing a deprotonation. Nevertheless, the enhancement of nucleophilicity often results in intensification of basicity to cause a deprotonation. Deep consideration on nucleophilicity should be a key to overcome this obstacle. In this thesis, the author demonstrates ring-opening reactions of epoxides bearing a perfluoro-alkyl groups and aziridines possessing a protective group, based on consideration on nucleophilicity and basicity.

1.3. Objective and Outline of This Thesis

1.3.1. Polymerization of fluorine-rich epoxides

In this thesis, the author achieved the smooth ring-opening reactions of epoxides and aziridines, based on consideration on the basicity of nuclephiles.

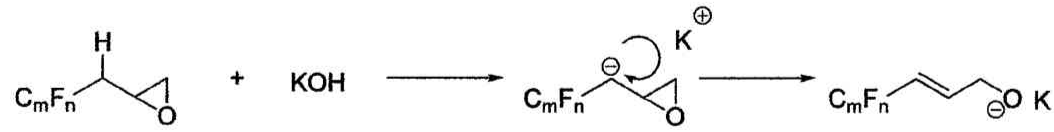
Fluorine-rich polyethers can be applied to the good lithium conductor for following reason. Highly condensed perfluoro alkyl groups will be expected to efficiently separate counter anion of lithium salt (Scheme 1.3.1.1). Thus, separated lithium cation will easily approach ether chains to be conducted efficiently.



Scheme 1.3.1.1 Fluorine-rich polyether as a lithium conductor.

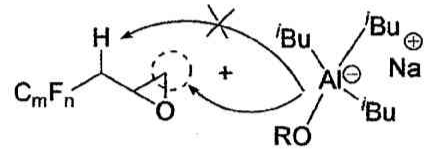
The author developed ring-opening polymerization of epoxides bearing a perfluoroalkyl groups without any possible side reactions, such as the deprotonation of α-proton to the perfluoro-alkyl group. The possible obstacles to the efficient polymerization of them are as follows. At first, fluorine-rich solvents are often used to handle perfluoroalkyl-containing compounds because of good affinity for them.[27] However, fluorine-rich solvents tend to possess much less solubility in general organic solvents or water. Thus, catalysts used in general organic solvents can not be applied to fluorous environment. Special modifications such as the introduction of perfluoroalkyl group into catalysts or ligands are often needed for good solubility in fluorous solvents. Nevertheless, the introduction of perfluoroalkyl groups is often redundant pathway. Furthermore, pricy reagents should be used for the modification. Thus, a proper catalyst which solves in fluorous solvents is essential. Secondly, as mentioned above, the stabilizing effect of the α-anion to a perfluoro-alkyl group often promotes a deprotonation as a side reaction.[13] A previous report indicated the deprotonation of the

β-hydrogen and the successive generation of an allyl alcohol (Scheme 1.3.1.2). Thus, well-controlled nucleophilicity will be essential to open fluorine epoxides.



Scheme 1.3.1.2 Deprotonation of epoxides bearing perfluoro-alkyl groups to allyl alcohol.

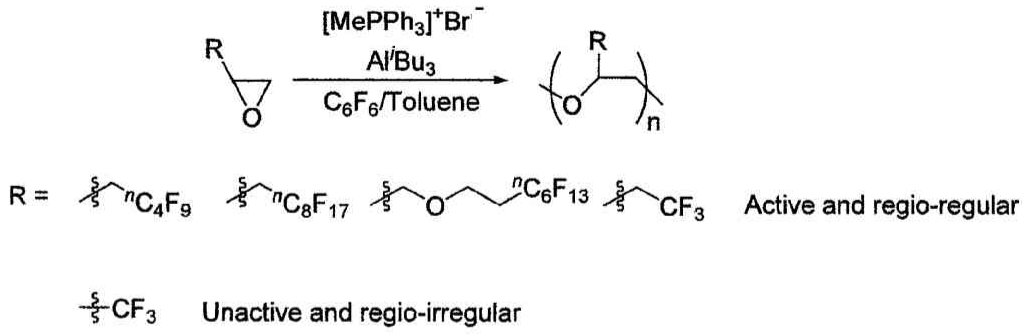
To solve these obstacles, the author applied Deffieux's system ($Al^iBu_3/^iPrONa$) to the polymerization of fluorine-rich compounds.[28] This catalyst system is suitable for the efficient polymerization of fluorine-rich epoxides for following reasons. Firstly, the catalyst of this system consists of Al^iBu_3 and $NaAl(OR)^iBu_3$ which are apolar and possess good solubility even in *cyclo*-hexane. Since fluorous solvents are as apolar as hydrocarbon solvents, Deffieux's system should be favorable for fluorous solvents. Secondly, Deffieux's system showed enough activity for the polymerization of propyleneoxide. Hence, epoxides bearing a perfluoro-alkyl group is also expected to polymerize actively. Thirdly, this system includes a large amount of the Lewis acid (Al^iBu_3). Consequently, the chain-end alkoxide of polymers can be masked by the Lewis acid, which would prevent the chain end alkoxide from working as a strong base to cause a deprotonation (Scheme 1.3.1.3). In addition, the methylene carbon was successively attacked to yield regio-regular atactic polymers.



Scheme 1.3.1.3 Prevention of deprotonation from epoxides bearing perfluoro-alkyl groups

The system can be applied to various epoxides bearing a perfluoro-alkyl group (Scheme 1.3.1.4). A regio-regular polymerization was seen. Atactic polymers were obtained from racemic epoxides. Isotactic polymers were obtained from enantiopure epoxides. Exceptionally, 3,3,3-trifluoropropylene-oxide was polymerized to yield a regio-irregular polymer much less

actively.



Scheme 1.3.1.4 Polymerization of fluorine-rich epoxides.

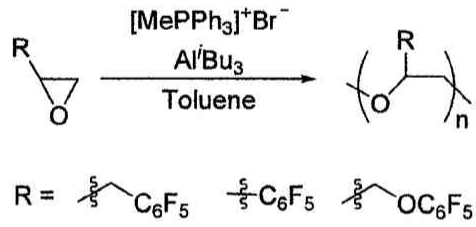
1.3.2. Polymerization of fluorine-rich epoxides: Scope and Polymer Structure

As a result of the author's research, the author demonstrated that $Al^{i}Bu_3$/$MePPh_3Br$ system is a good system for the polymerization of fluorine-rich epoxides. The polymerization system is extremely attractive because of high activity, wide scope of various fluorinated monomers and complete regiocontrol without any side reactions. Complete regioselectivity enabled the author to obtain isotactic polymers by using optically pure epoxides.

However, following problem is left. Detailed structures of obtained polymers were unexplored. Optically active isotactic polymers have often possessed some special conformations such as helical structures in both solution states and solid states (See Chapter 3). From this viewpoint, fluoroaryl epoxides were also investigated as a monomer to synthesize additional isotactic polymers.

Consequently, epoxides bearing a fluoroaryl group were polymerized regio-regularly. Structures of the polymers obtained were clearly assigned by ^{13}C NMR spectra. As well as epoxides bearing a perfluoro-alkyl group, atactic polymers were obtained from racemic epoxides. Isotactic polymers were obtained from enantiopure epoxides. Epoxides containing one methylene unit as a spacer in each side-chain were able to be applied to regioregular polymerization in our system. The side-chain methylene was regarded as a buffer of both

perfluoro-alkyl and perfluoro-aryl groups to alleviate their influence of electron-withdrawing effect. In addition, the structural difference between isotactic poly-fluorinated polymers and the corresponding hydrogen-substituted polymers was investigated. In the case of an isotactic polymer with pentafluorophenyl ethers, its structure was a identified as a chaotically ordered zigzag structure, while isotactic polymer with phenyl ether was completely well-ordered zigzag strucuture. The structual difference reflected on difference of solubility in organic solvents.

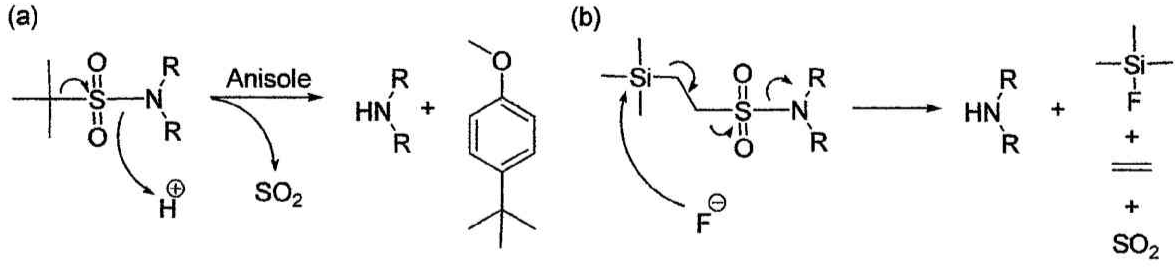


Scheme 1.3.2.3 Polymerization of fluorine-rich epoxides.

1.3.3. Ring-opening Reaction of Bus- or SES-bearing Aziridines by Lithiated Dithianes.

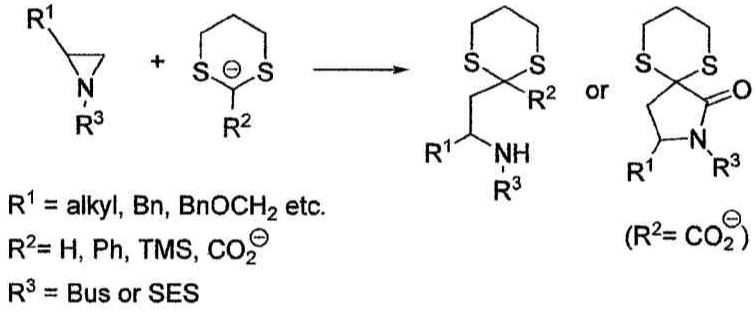
Secondly, the author developed a new ring-opening reaction of *N*-Bus(*tert*-butylsulfonyl)- and SES(2-trimethylsilyl-ethylsulfonyl)-aziridines by lithiated dithianes. The ring-opening reaction of aziridines by litiated dithianes is attractive for the syntheses of β-amino carbonyl compounds. However, the substrates for the ring-opening reaction using lithiated dithianes were limited to *N*-Ts(tosyl)-aziridines. Although *N*-Ts-aziridines are commonly employed because of their easy preparation and well-refined synthetic procedures, a major drawback is the difficulty in its deprotection (Na/Naphtalenide/DME).[29] Thus, the author focused on other sulfonyl groups which can be more easily removed than Ts. Bus-amides were deprotected by TfOH and a cation scavenger (Anisole) as shown in scheme 1.3.2.1a.[30] In contrast, SES-amides were deprotected by fluoride (TBAF or CsF) as shown in scheme 1.3.2.1b.[31] Especially, SES-bearing aziridines are attractive substrates because of mild conditions for

deprotection.



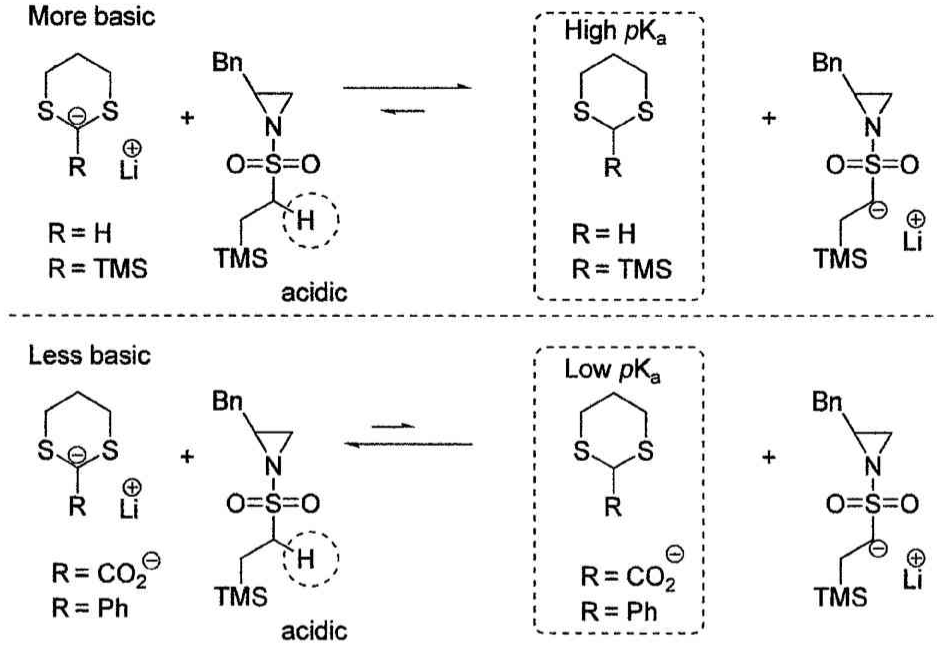
Scheme 1.3.3.1 Deprotection mechanism of Bus- and SES-amide.

As a result of the author's research, the author found that Bus- and SES-activated aziridines underwent an efficient ring-opening reaction by various lithiated dithianes to yield various *β*-amino carbonyl equivalents, *γ*-lactam (Scheme 1.3.3.2).



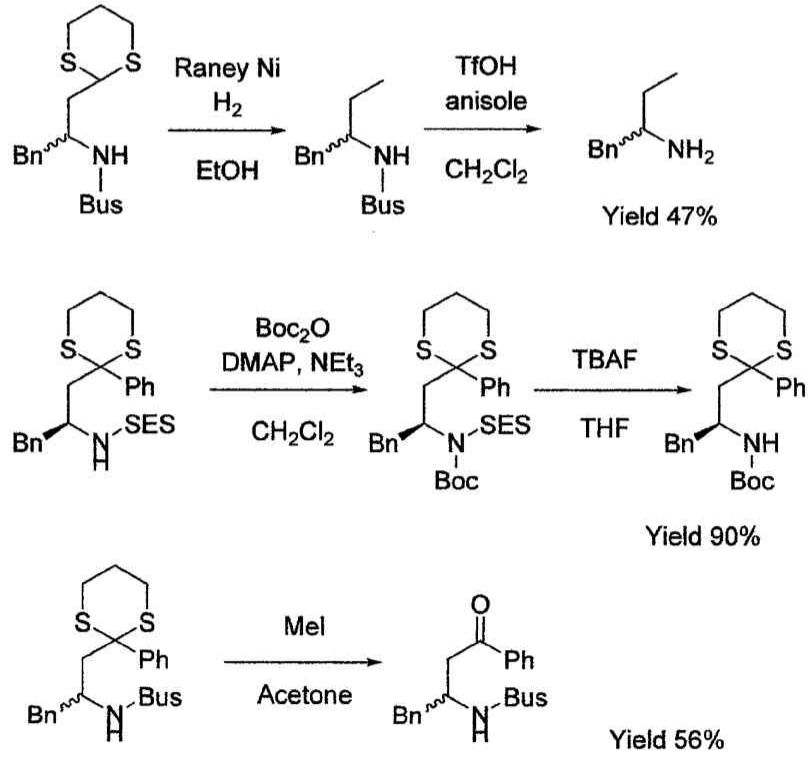
Scheme 1.3.3.2 Ring-opening reaction of Bus- and SES-aziridines using lithiated dithianes

In the case of SES, substrate scope was limited due to acidity of the α–proton to the sulfonyl group. SES-bearing aziridines can be opened by lithiated dithianes stabilized by an electron-withdrawing group such as Ph and CO_2^-. Because the pK_a values of these dithianes are lower than that of the α–proton to the sulfonyl group, the deprotonation of the α–proton to the sulfonyl group could be inhibited (Scheme 1.3.3.3). In contrast, simple lithiated dithiane and TMS-bearing lithiated dithiane deprotonated the α–proton to sulfonyl group to lead to a complex mixture.



Scheme 1.3.3.3 Equilibrium between lithiated dithaine and α–sulfonyl proton

Furthermore, Bus and SES-possessing dithaines obtained were deprotected. to demonstrate the synthetic usefulness (Scheme 1.3.3.4).



Scheme 1.3.3.4 Deprotection of Bus, SES and dithiane moieties.

1.4. References

(1) Movassagh, B.; Soleiman-Beigi, M. *Synthetic Communications* **2007**, *37*, 3239 - 3244.

(2) Pineschi, M. *Eur. J. Org. Chem.* **2006**, *2006*, 4979-4988.

(3) Smith, A. B., III; Adams, C. M. *Acc. Chem. Res.* **2004**, *37*, 365-377.

(4) Kwon, D. W.; Kim, Y. H.; Lee, K. *J. Org. Chem.* **2002**, *67*, 9488-9491.

(5) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421-431.

(6) Wong, O. A.; Shi, Y. *Chem. Rev.* **2008**, *108*, 3958-3987.

(7) Ikariya, T.; Blacker, A. J. *Acc. Chem. Res.* **2007**, *40*, 1300-1308.

(8) Xia, Q. H.; Ge, H. Q.; Ye, C. P.; Liu, Z. M.; Su, K. X. *Chem. Rev.* **2005**, *105*, 1603-1662.

(9) McGarrigle, E. M.; Gilheany, D. G. *Chem. Rev.* **2005**, *105*, 1563-1602.

(10) Yang, D. *Acc. Res. Chem.* **2004**, *37*, 497-505.

(11) Shi, Y. *Chem. Rev.* **2004**, *37*, 488-496.

(12) Aggarwal, V. K.; Winn, C. L. *Acc. Chem. Res.* **2004**, *37*, 611-620.

(13) Hodgson, D. M. *Enantioselective Synthesis by Lithiation Adjacent to Oxygen and Subseqent Rearrangement* In *Organolithiums in Enantioselective Synthesis*; Hodgson, D. M., Tomooka , K., Gras, E., Eds.; Springer: Oxford, 2003; Vol. 5, p 234-250.

(14) Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2024-2032.

(15) Li, A. H.; Dai, L. X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341-2372.

(16) Malik, S.; Nadir, U. K. *Synlett* **2008**, 108-110.

(17) Olsen, C. A.; Franzyk, H.; Jaroszewski, J. W. *Eur. J. Org. Chem.* **2007**, *2007*, 1717-1724.

(18) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701-2743.

(19) Hodgson, D. M.; Humphreys, P. G.; Ward, J. G. *Org. Lett.* **2005**, *7*, 1153-1156.

(20) Muller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905-2920.

(21) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247-258.

(22) Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693-1715.

(23) Tanner, D. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599-619.

(24) Hodgson, D. M.; Humphreys, P. G.; Miles, S. M.; Brierley, C. A. J.; Ward, J. G. *J. Org. Chem.* **2007**, *72*, 10009-10021.

(25) Muller, P.; Nury, P. *Helv. Chim. Acta* **2001**, *84*, 662-677.

(26) Yamauchi, Y.; Kawate, T.; Katagiri, T.; Uneyama, K. *Tetrahedron* **2003**, *59*, 9839-9847.

(27) Hiyama, T. *Organofluorine Compounds*; Springer: Berlin, 2000.

(28) Billouard, C.; Carlotti, S.; Desbois, P.; Deffieux, A. *Macromolecules* **2004**, *37*, 4038-4043.

(29) Howson, W.; Osborn, H. M. I.; Sweeney, J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2439-2445.

(30) Sun, P.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1997**, *62*, 8604-8608.

(31) Ribiere, P.; Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2006**, *106*, 2249-2269.

Chapter 2

Regio-controlled Ring-opening Polymerization of Epoxides Bearing Perfluoro-alkyl Groups

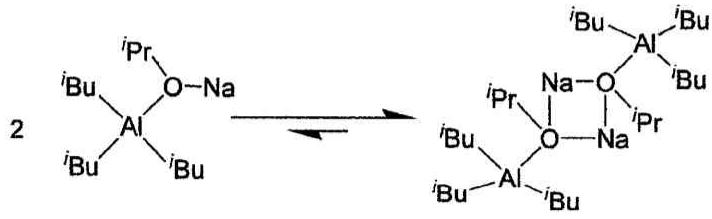
2.1. Introduction

Organofluorine compounds have demonstrated countless unique properties.[1,2] Thus, synthetic procedures of them have been widely studied. From material viewpoint, organofluorine polymers also have exhibited many useful qualities which non-fluorine polymers can not demonstrate such as small refractive index and low viscocity.[2] Since properties of the polymers depend much on molecular weight, molecular weight distribution, and structure of the main chain, their precise control is a challenging theme. Intensive efforts have been devoted to controlled polymerization of fluorinated olefins in coordination polymerization,[3-5] ring-opening metathesis polymerization,[6] atom-transfer radical polymerization,[7] and anionic polymerization.[8,9] However, in spite of recent rapid development of precision polymerization of epoxides and their derivatives,[10-17] no examples have been reported for controlled polymers from fluorinated epoxides. Only one report appeared on the regioregular polyether formation from 3,3,3-trifluoropropylene oxide.[18,19] Generally, standard synthetic strategies of non-fluorinated compounds cannot be directly applied to the reaction of organofluorine compounds because of their unusual properties. For example, highly fluorine-substituted molecules or fragments display low affinity with general organic or aqueous solvents. Furthermore, α-proton of perfluoroalkyl groups often show acidity due to the electron-withdrawing effect and thus basic initiator may get protonated. Hence, development of a new catalyst/initiator system is essential to obtain polymers starting from fluorine-rich epoxides. In this chapter, the author reports the polymerization system of highly fluorinated epoxides to give regioregular polyethers without any possible side reaction.

Isotatic polyethers were also synthesized by using enantiopure epoxides. The structures of the polymers were characterized by ^{13}C NMR spectroscopy and MALDI-TOF mass spectrometry.

2.2. Ring-Opening Polymerization of Epoxides Bearing Perfluoro-alkyl Groups

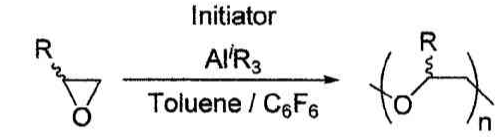
First, the author referred the catalyst/initiator system previously employed for the ring-opening polymerization of propylene oxide.[11-13,16,17] Among the examples with efficient production of regioregular polyethers, the author examined the system by Deffieux using ^{i}PrONa as an initiator and Al^{i}Bu$_3$ as a catalyst.[12] When fluorinated epoxide **1** was subjected to the conventional reaction condition, that is treatment of **1** with ^{i}PrONa/Al^{i}Bu$_3$ in cyclohexane, a trace amount of oligomer precipitated before full consumption of epoxide **1** (Table 2.2.1, run 1). Since the polymer of **1** is insoluble in general organic solvents, the use of fluorous solvents seems to be indispensable for the polymerization of **1**. Accordingly, epoxide **1** was next treated with ^{i}PrONa/Al^{i}Bu$_3$ in a fluorous solvent C_6F_6 to result in no polymerization (Table 2.2.1, run 2). It should be noted that even propylene oxide gave no product in C_6F_6. Given that Li[R$_3$AlCl] (R = alkyl) was reported to form a dimeric aggregate which consists of Li-Cl-Li-Cl four-membered ring,[20] aggregation of ^{i}PrONa/Al^{i}Bu$_3$ described in Scheme 1 or its related structure might be responsible for the catalyst deactivation in C_6F_6. The other two possible processes anticipated for the deactivation were (1) deprotonation from **1** by ^{i}PrONa to form an allyl alcohol[21] and (2) nucleophilic substitution of ^{i}PrONa on C_6F_6 to yield ^{i}PrOC_6F_5.[22] However, none of them were detected.



Scheme 2.2.1 Assumed aggregation structures of ^{i}PrONa/Al^{i}Bu$_3$.

Thus, as an initiator, the author next examined the use of organic salts which contain non-coordinating cations such as ammonium and phosphonium. These non-coordinating cations were expected to prevent themselves from aggregation.[13,23] No activity was seen by using $[^nBu_4N]^+Cl^-$ (run 3) but the use of $[Ph_3P{=}N{=}PPh_3]^+Cl^-$ ($[PPN]^+Cl^-$) as an initiator gave polymeric material as a viscous oil in 29% yield (run 4). A phosphonium salt $[MePPh_3]^+Cl^-$ also brought polymerization (run 5). Initiator with bromide $[MePPh_3]^+Br^-$ was proven to have much higher activity giving the polymer in 95% yield (run 6). Br^- can initiate polymerization much more fastly than Cl^-, because Al and Cl belong to the same principal quantum number and form stronger bond than the bond between Al and Br. The use of $AlEt_3$ as a catalyst resulted in no polymerization (run 7). In the absence of either Lewis acid catalyst or initiator, no polymerization occurred (runs 8 and 9).

Table 2.2.1 Optimization of Ring-Opening Polymerization of Epoxide **1**.[a]



R = **1** : $-CH_2-O-CH_2-CH_2-{}^nC_4F_9$

run	initiator	AlR_3	T (°C)	t (h)	yield (%)	M_n (g/mol)	M_w/M_n -	T_g (°C)
1[b]	^{i}PrONa	^{i}Bu	r.t.	6	3.8	-	-	-
2	^{i}PrONa	^{i}Bu	r.t.	12	0	-	-	-
3	$[^nBu_4N]^+Cl^-$	^{i}Bu	r.t.	12	0	-	-	-
4	$[PPN]^+Cl^-$	^{i}Bu	0	2	29	17000	1.8	–31
5	$[MePPh_3]^+Cl^-$	^{i}Bu	0	2	33	11000	1.9	–32
6	$[MePPh_3]^+Br^-$	^{i}Bu	0	1	95	14000	2.1	–31
7	$[MePPh_3]^+Br^-$	Et	r.t.	12	0	-	-	-
8	$[MePPh_3]^+Br^-$	-	r.t.	12	0	-	-	-
9	-	^{i}Bu	r.t.	12	0	-	-	-

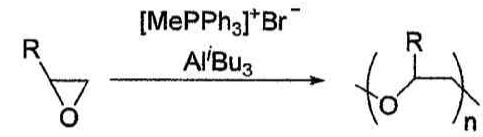
[a]Epoxide **1** (2.80 mmol), C_6F_6 (2.00 mL), initiator (0.0250 mmol), AlR_3 (0.250 mmol).

[b]Cyclohexane was used as a solvent instead of C_6F_6.

2.3. Ring-opening Polymerization of Epoxides with Various Perfluoro-alkyl Groups

The scope and generality of this reaction were further explored under the reaction condition (Run 6, Table 2.2.1.), and the results are summarized (Table 2.3.1). A polymer was efficiently produced from enantiopure **(*R*)-1** (run 1) in a similar manner to ***rac*-1**. Epoxide ***rac*-2** bearing a longer perfluoroalkyl chain was also polymerized (run 2), but full characterization of the product was impossible because of its low solubility in any solvents including fluorous ones. Epoxide ***rac*-3**, having a perfluoroalkyl chain through an ether linkage, was polymerized to give a polyether as viscous oil (run 3). The product was highly soluble in most of organic solvents. The polymer of optically pure **(*R*)-3** was also successfully obtained (run 4). The reaction of epoxide ***rac*-4** which has a trifluoromethyl group directly attached to the epoxide ring resulted in low active polymerization (run 5). However, in the case of monomer ***rac*-5** whose methylene carbon unit is inserted between the epoxide-rings and the electron-withdrawing group, it resulted in high active polymerization (run 6).

Table 2.3.1 Ring-Opening Polymerization of Various Perfluorinated Epoxides[a]



R = **1** : $-CH_2-{}^nC_4F_9$ **4** : $-CH_2-CF_3$

2 : $-CH_2-{}^nC_8F_{17}$ **5** : $-CH_2-CF_3$

3: $-CH_2-O-CH_2-{}^nC_6F_{13}$

run	monomer	*T* (°C)	*t* (h)	yield (%)	M_n (g/mol)	M_w/M_n -	T_g (°C)
1	**(*R*)-1**	0	1	81	15000	1.7	–31
2[b]	***rac*-2**	0	1	<~60	-	-	-
3	***rac*-3**	0	1	96	28000	1.9	–47
4	**(*R*)-3**	0	1	99	31000	1.8	–48
5[c]	***rac*-4**	r.t.	40	45	2200	1.2	–47
6[c]	***rac*-5**	0	1	99	16000	1.7	–34

[a] Conditions are common to those in Table 2.2.1.
[b] Polymer obtained was not purified due to the low solubility.
[c] Measurement of M_n employed different method from others (See experimental section).

2.4. Structural Analyses of Polymers Obtained

The production of regioregular polymers from **1** and **3** was manifested by ^{13}C NMR spectra of the polymers obtained in C_6F_6. Polymers prepared from ***rac*-1** in runs 4-6 of Table 2.2.1 showed four peaks of the methylene carbon in the main chain reflecting the tacticity. For the polymer in run 6 of Table 2.2.1, the area ratio was 22:25:25:28 from lower magnetic field to higher magnetic field (Figure 2.4.1a). In contrast, ^{13}C NMR spectrum of the polymer made from **(*R*)-1** (Table 2.3.1, run 1) gave only one methylene carbon peak in the lowest magnetic field of the four peaks (Figure 2.4.1b). In general, regioregular ring-opening polymerization of propylene oxide proceeds through successive nucleophilic attacks on the less hindered methylene carbon than the methine carbon.[12] Accordingly, it is reasonable to assume that the methine carbon retains its configuration and that isotactic polyethers are obtained by using enatiopure epoxide. As a result, the methylene peak at the lowest field of the four should be regarded as *mm*-triad. By comparing the two charts, four peaks can be assigned as triad [*mm*, *mr* (or *rm*), *rm* (or *mr*), *rr* from lower magnetic field to higher, P_m = 0.47]. Incidentally, polymers from ***rac*-2** and ***rac*-5** also possessed regioregular and atactic structures, because their ^{13}C NMR spectra showed similar peaks with those of polymer from ***rac*-1** (See Experimental Section).

A polymer obtained from ***rac*-3** (Table 2.3.1, run 3) also had regioregular structure. The peak split at 74.2 and 74.3 ppm with area ratio of 1:1 was assigned to a methylene carbon although it is not clear whether it is the one in the main chain or in the side chain (Figure 2.4.1c). Polyether from **(*R*)-3** (Table 2.3.1, run 4) brought only one peak at 74.3 ppm (Figure 2.4.1d). Judging from above, the two peaks corresponds to diad (*m* and *r* from lower to

higher) and P_m = 0.5. In contrast to the polymers from **1** and **3**, the polymer obtained from **4** had regioirregular structure.[18,19]

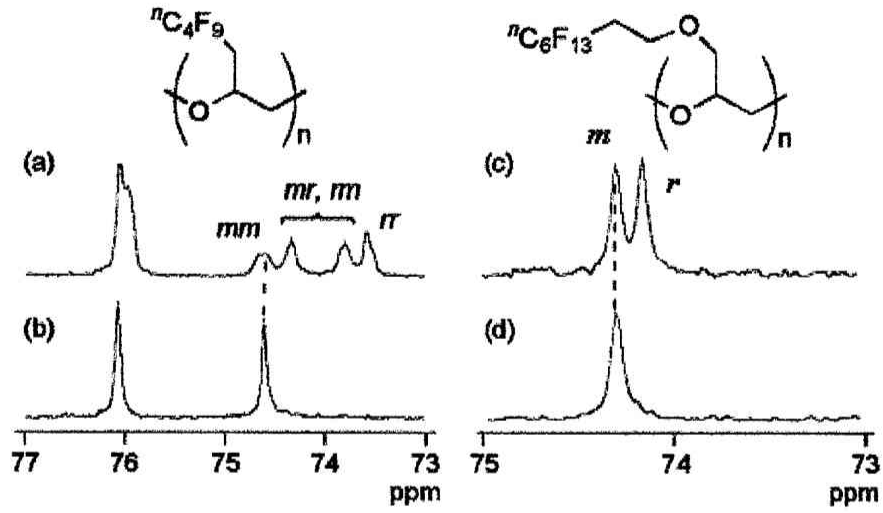
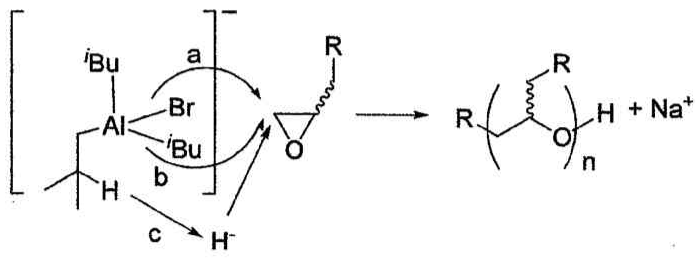


Figure 2.4.1 ^{13}C NMR spectra of polymers from

(a) ***rac*-1** (Table 2.2.1, run 6) (b) **(*R*)-1** (Table 2.3.1, run 1)

(c) ***rac*-3** (Table 2.3.1, run 3) (d) **(*R*)-3** (Table 2.3.1, run 4)

It was disclosed that not only bromide but also *iso*-butyl group and hydride attacked epoxides in the initiation step (Scheme 2.4.1a-c). Oligomers from **1** and **3** (monomer/initiator ratio of 11.2) and the oligomer from ***rac*-4** were analyzed by MALDI-TOF mass spectrometry. In each case, three series of polymers (a)-(c) were detected corresponding to bromide, isobutyl, and hydride end groups in accordance with the previous report that Al^iBu_3 could work as both hydride and isobutyl anion source in the ring-opening reaction of epoxides.[24,25]



(a) R = Br

81 + M × n + 1 + 23 = 105 + M × n

(b) R = ^{i}Bu

57 + M × n + 1 + 23 = 81 + M × n

(c) R = H

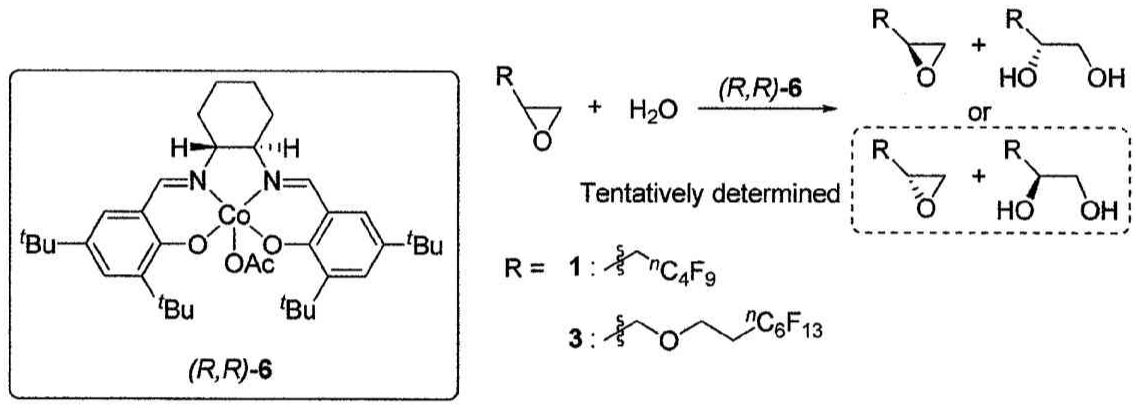
1 + M × n + 1 + 23 = 25 + M × n

Scheme 2.4.1 Initiation by (a) Br, (b) ^{i}Bu (c) H (M = molecular weight of monomer).

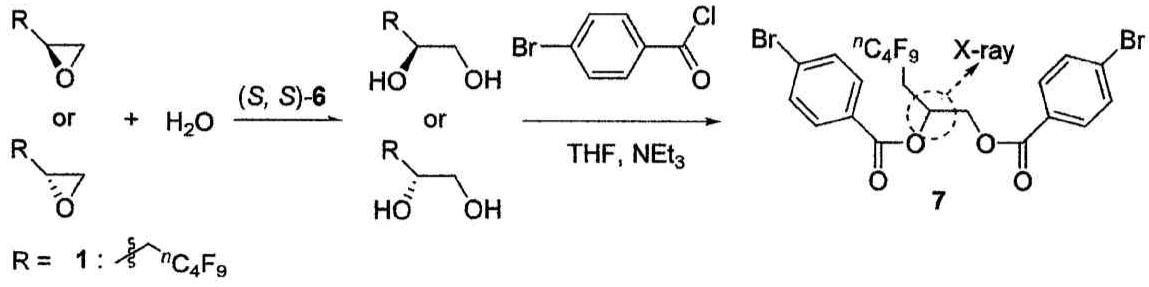
2.5. Determination of Absolute Configuration

Enatiopure epoxides **1** and **3** were obtained easily by using Jacobsen catalyst **(*R*,*R*)-6** (Scheme 2.5.1).[26] Based on previous insight of Jacobsen catalyst, their absolute configurations were determined empirically as **(*R*)-1** and **(*R*)-3**. In the case of enantiopure epoxide **1**, their absolute configurations are assigned unempirically by using Bijvoet method as follows (Scheme 2.5.2).[27] Enatiopure epoxide **1** was converted into diols by using **(*S*,*S*)-6** and H_2O. These diols were successively converted into ester **7** bearing Br and it was recrystalized for X-ray crystallographic analyses (Figure 2.5.1). Thus, enantiopure epoxide **1** was assigned as **(*R*)-1.** It coincided with empirical determinations. Thus, empirical determination of absolute configuration were applied to enantiopure epoxide **3** as **(*R*)-3**.

Scheme 2.5.1 Preparation of enantiopure epoxides.



Scheme 2.5.2 Conversion into ester possessing heavy atoms.



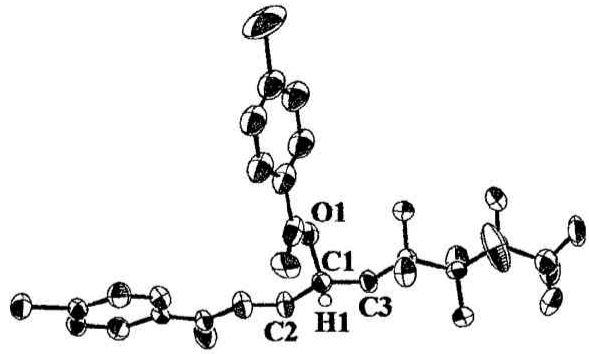


Figure 2.5.1 ORTEP drawing 7 (all hydrogen atoms except for H1 are omitted for clarity).

2.6. Conclusion

In conclusion, epoxides bearing perfluoro-alkyl groups were easily polymerizied under mild conditions. The obtained polymers had the exclusive regioregular structure. When optically pure epoxides were used, isotatic polymers were obtained. Initiating steps were elucidated unambiguously.

2.7. References

(1) Shimizu, M.; Hiyama, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 214-231.

(2) Hiyama, T. *Organofluorine Compounds*; Springer: Berlin, 2000.

(3) Fujita, T.; Nakano, K.; Yamashita, M.; Nozaki, K. *J. Am. Chem. Soc.* **2006**, *128*, 1968-1975.

(4) Nozaki, K.; Shibahara, F.; Elzner, S.; Hiyama, T. *Can. J. Chem.* **2001**, *79*, 593-597.

(5) Murtuza, S.; Harkins, S. B.; Sen, A. *Macromolecules* **1999**, *32*, 8697-8702.

(6) Feast, W. J.; Khosravi, E. *J. Fluorine Chem.* **1999**, *100*, 117-125.

(7) Matyjaszewski, K.; Xia, J. H. *Chem. Rev.* **2001**, *101*, 2921-2990.

(8) Narita, T. *Prog. Polym. Sci.* **1999**, *24*, 1095-1148.

(9) Ishizone, T.; Sugiyama, K.; Sakano, Y.; Mori, H.; Hirao, A.; Nakahama, S. *Polymer J.* **1999**, *31*, 983-988.

(10) Stewart, I. C.; Lee, C. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*,

17616-17617.

(11) Peretti, K. L.; Ajiro, H.; Cohen, C. T.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2005**, *127*, 11566-11567.

(12) Billouard, C.; Carlotti, S.; Desbois, P.; Deffieux, A. *Macromolecules* **2004**, *37*, 4038-4043.

(13) Braune, W.; Okuda, J. *Angew. Chem.-Int. Ed.* **2003**, *42*, 64-68.

(14) Nicol, E.; Bonnans-Plaisance, C.; Levesque, G. *Macromolecules* **1999**, *32*, 4485-4487.

(15) Brochu, S.; Ampleman, G. *Macromolecules* **1996**, *29*, 5539-5545.

(16) Aida, T.; Inoue, S. *Acc. Chem. Res.* **1996**, *29*, 39-48.

(17) Okamoto, Y.; Nakano, T. *Chem. Rev.* **1994**, *94*, 349-372.

(18) Umezawa, J.; Hagiwara, T.; Hamana, H.; Narita, T.; Furuhashi, K.; Nohira, H. *Polymer J.* **1994**, *26*, 715-721.

(19) Hagiwara, T.; Terasaki, Y.; Hamana, H.; Narita, T.; Umezawa, J.; Furuhashi, K. *Makromol. Chem., Rapid Commun.* **1992**, *13*, 363-370.

(20) Tian, X.; Frohlich, R.; Mitzel, N. W. *Dalton Trans.* **2005**, 380-384.

(21) Cirkva, V.; Ameduri, B.; Boutevin, B.; Paleta, O. *J. Fluorine Chem.* **1997**, *83*, 151-158.

(22) Brooke, G. M.; Young, A. C. *J. Fluorine. Chem.* **1976**, *8*, 223-241.

(23) Harlan, C. J.; Bott, S. G.; Barron, A. R. *J. Am. Chem. Soc.* **1995**, *117*, 6465-6474.

(24) Eisch, J. J.; Liu, Z. R.; Singh, M. *J. Org. Chem.* **1992**, *57*, 1618-1621.

(25) Boireau, G.; Abenhaim, D.; Henrybasch, E. *Tetrahedron* **1980**, *36*, 3061-3070.

(26) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307-1315.

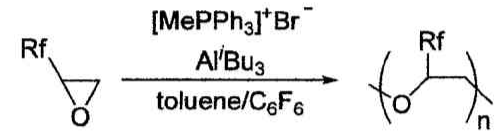
(27) Bijvoet, J. M.; Peerdeman, A. F.; van Bommel, A. J. *Nature* **1951**, *168*, 271-2.

Chapter 3
Ring-opening Polymerization of Fluorine-containing Epoxides: Scope and Polymer Structure.

3.1. Introduction

In chapter 2, the author reported novel initiator/catalyst system $[MePPh_3][Br]/Al^iBu_3$ in toluene/C_6F_6 for regioregular polymerization of perfluoro-alkyl-substituted epoxides **1-3** and **5** except for **4** by modification of Deffieux's system (^{i}PrONa/Al^{i}Bu$_3$ in ^{c}hexane).[1] The use of C_6F_6 and $MePPh_3^+Br^-$ as a co-solvent and an initiator was the key to the success (Scheme 3.1.1). It was essential to use C_6F_6 as a solvent because the product polymers were soluble only in fluorous solvents. For better activity of the initiator, $MePPh_3^+Br^-$ was chosen as an optimal initiator. The system regio-selectively polymerized much fluorine-richer epoxides than 3,3,3-trifluoropropylene oxide[2,3] and required no fluorous-containing ligands nor catalysts which have been used to enhance solubility of fluorine-rich compounds in fluorous solvents and super critical CO_2.[4-7] Additionally, this system enabled us to obtain optically active isotactic fluorine-containing polyethers by using enantiopure epoxides.

Scheme 3.1.1. Polymerization system for fluorine-rich epoxides.[8]



Rf = **1** : $-(CH_2)_2-{}^nC_4F_9$ **4** : $-(CH_2)_2-CF_3$

2 : $-(CH_2)_2-{}^nC_8F_{17}$ **5** : $-(CH_2)_2-CF_3$

3: $-(CH_2)_2-O-CH_2-{}^nC_6F_{13}$

However, following several problems and questions are left intact in Chapter 2. Firstly, epoxides bearing fluoroaryl groups were not examined as substrates. It will be interesting

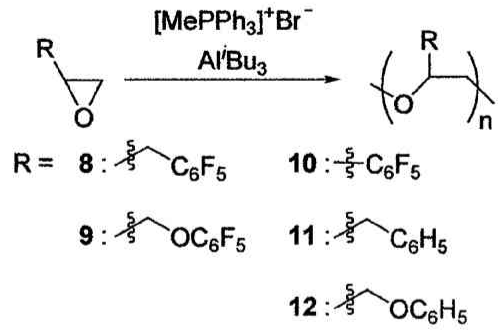
research object, because fluoroaryl groups have often demonstrated special structures (*vide infra*). Detailed structures of obtained polymers were unexplored. Optically active isotactic polymers often demonstrated special conformations such as helical structures in both solution states and solid states.[9-12] In addition, fluorinated (F) molecules have often showed different conformations from the corresponding hydrogen (H)-substituted molecules.[13-20] From these viewpoints, F-containing polyethers would be expected to possess different structures somehow from the corresponding H-substituted polyethers in both solution states and solid states. Many attempts to measure CD spectra or ORD spectra of optically active isotactic polyethers have been reported in solution states.[21-29] Hence, CD or ORD spectra of both F- and H-substituted optically active isotactic polyethers were measured in order to detect structural differences between F- and H-substituted polyether in solution states. On the other hand, there have been no reports for detailed information of fluorine-containing polyethers in solid states, while those of many fluorine-free polyepoxides have been reported.[30-38] Thus, XRD spectra of obtained isotatic polyethers were measured in order to detect structural difference between the two polymers in solid states.

In this chapter, the author reports the scope and generality of the method for tha polymerization of the fluorine-containing epoxides. Additionally, their corresponding non-fluorinated polyethers were also synthesized and characterized for detecting some structural differences from F-containing polyethers. Some of absolute configurations of synthesized enantiopure epoxides were determined by X-ray analyses non-empirically.

3.2. Syntheses of Monomers and Determinations of Absolute Configurations

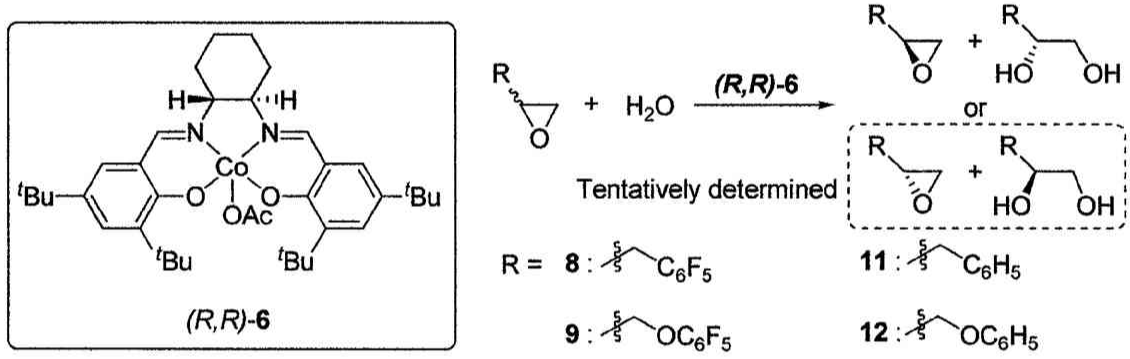
Monomers **8-12** bearing aryl groups were examined for polymerization in this chapter (Scheme 3.2.1).

Scheme 3.2.1 Polymerization for fluorine-containing epoxides **8-12**



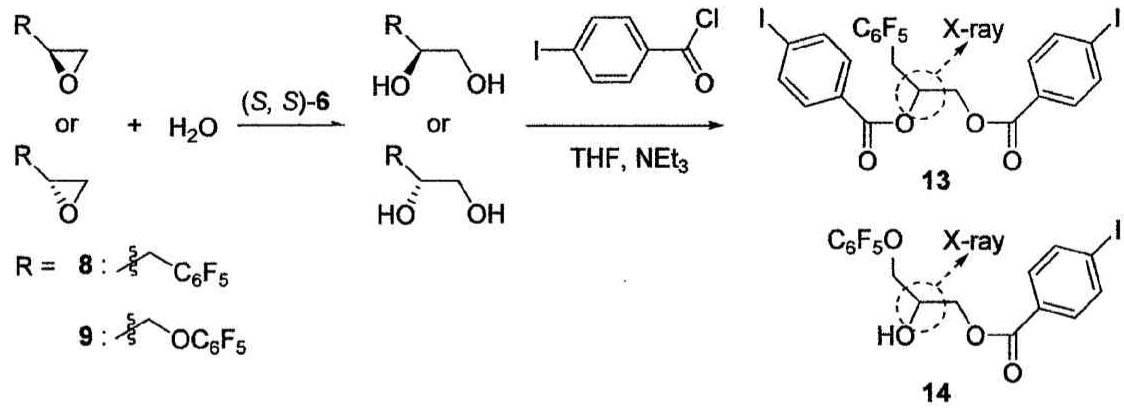
As previously described in Scheme 2.5.1, enatiopure epoxides **8-9** and **11-12** were obtained easily by using Jacobsen catalyst (***R,R***)-**6** (Scheme 3.2.2).[39]

Scheme 3.2.2 Preparation of enantiopure epoxides.



The absolute configurations of epoxides **11-12** synthesized from (***R,R***)-**6** were assigned previously as (***R***)-**11** and (***S***)-**12**.[39] Based on previous insight of Jacobsen catalyst, their absolute configurations were determined empirically as (***R***)-**8** and (***S***)-**9**. Their absolute configurations were also assigned unempirically by using Bijvoet method as follows (Scheme 3.2.3).[40] Enatiopure epoxides **8-9** were converted into diols by using (***S,S***)-**6** and H_2O. These diols were successively converted into esters **13-14** bearing iodine atoms and they were recrystalized for X-ray crystallographic analyses (Figure 3.2.1-2). Thus, enantiopure epoxides **8-9** were assigned as (***R***)-**8** and (***S***)-**9.** Both of them coincided with empirical determinations.

Scheme 3.2.3 Conversion into esters possessing iodine



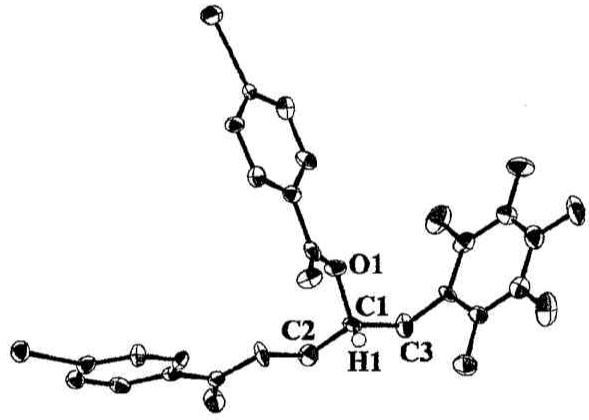


Figure 3.2.1 ORTEP drawing **13** (all hydrogen atoms except for H1 are omitted for clarity).

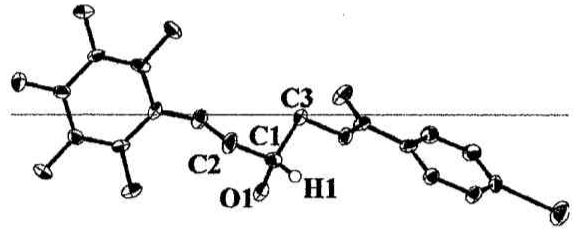


Figure 3.2.2 ORTEP drawing **14** (all hydrogen atoms except for H1 are omitted for clarity).

3.3. Polymerization of Epoxides.

Epoxides **8-10** (Scheme 3.2.1) were polymerized by previously described method in chapter 2[8] to scrutinize the scope and generality of the fluorine-containing epoxides. To detect structural differences between F-substituted optically active isotactic polyethers and the

corresponding H-substituted polyethers, polymers from **11-12** were also synthesized. The results are listed (Table 3.3.1).

Table 3.3.1 Polymerization of epoxides.[a]

Run	Monomer	Yield (%)	M_n (g/mol)	M_w/M_n	Tacticity *mm : mr + rm : rr*	Appearance	T_g and T_m (°C)
1	***rac*-8**	97	20000	1.2	Atactic[b]	liquid	T_g 12
2	**(*R*)-8**	97	21000	1.6	100 : 0: 0	liquid	T_g 10
3	***rac*-9**	88	24000	2.4	25 : 50 : 25	liquid	T_g -23
4	**(*S*)-9**	95	26000	1.6	100 : 0: 0	white solid	T_m 105
5	***rac*-10**	52	6000	1.3	-[c]	white solid	T_g 26 T_m 135
6	***rac*-11**	95	19000	1.7	25 : 50 : 25	liquid	T_g 1.9
7	**(*R*)-11**	98	21000	1.5	100 : 0 : 0	white solid	T_m 115[d]
8	***rac*-12**	98	24000	1.8	25 : 50 : 25	viscous solid	T_g 10
9	**(*S*)-12**	38	7900	1.4	100 : 0 : 0	white solid	T_m 175

[a] Epoxide (2.8 mmol), Solvent (toluene, 2.0 mL), $MePPh_3Br$ (0.025 mmol), Al^iBu_3 (0.25 mmol in 1 M toluene solution), 0 °C, 1 h

[b] Ratio could not be determined by ^{13}C NMR.

[c] Obtained polymer was regio-irregular and the ratio of head-to-tail : tail-to-tail : head-to-head could not be determined.

[d] The value was determined from the first heating scan, while the others were determined from the second scans.

Epoxides **8-9**, **11** and ***rac*-12** were polymerized efficiently to obtain polyethers (Table 3.3.1., runs 1-4 and 6-8). Due to the higher solubility of polymers, toluene could be employed as a solvent.

Polymerization of ***rac*-10** resulted in a lower yield (Table 3.3.1, run 5). Difference of activity between ***rac*-8** and ***rac*-10** may be due to the existence of the side chain methylene between C_6F_5 and ethylene oxide (Table 3.3.1, runs 1 and 5). The effect of side chain methylene on activity is discussed in the later section of this chapter.

Polymerization of **(*S*)-12** also resulted in a low yield because of the low solubility of the product obtained, isotactic poly(glycidyl phenyl ether) which precipitated before full consumption of substrate (Table 3.3.1, run 9). This assumption was supported by previously

reported isotactic poly(glycidyl phenyl ether).[41]

Polyethers from epoxides **8-9** and **11-12** clearly evidenced regio-regular polymerization (Table 3.3.1, runs 1-4 and 6-9) unlike regio-irregular polymerizations of epoxides **10** (Run 5 in Table 3.3.1). Polyethers from racemic epoxides disclosed atactic polymers (Table 3.3.1, runs 1, 3, 6 and 8), while polyethers from enantiopure epoxides gave isotactic polymers (Table 3.3.1, runs 2, 4, 7 and 9). Assignments of these structures by ^{13}C NMR will be discussed in the next section. Except for polymer from **(*S*)-12** (Table 3.3.1, run 9), all polyethers were soluble in general organic solvents (Table 3.3.1, runs 1-8). Polymer from **(*S*)-12** was well dissolved in hot *o*-$C_6H_4Cl_2$ (120 °C) and slightly soluble in hot DMSO (120 °C). It was notable that little difference of molecular weight determined by size exclusion chromatography (SEC) between F-substituted polyethers and the corresponding H-substituted polyethers (Table 3.3.1, runs 1 and 6, runs 2 and 7, runs 3 and 8) was seen, while molecular weight of each monomer varied. This phenomenon may be due to the small volume of fluorine-containing polymer compared with its weight. In spite of heavy atomic weight (F 19), van der Waals radius of fluorine atom was close on that of hydrogen atom,[42] which would result in displaying lower molecular weight through SEC than the absolute value.[43] Naturally, it can not be denied that degree of polymerization of fluorine-contining epoxides were lower than those of corresponding H-substituted epoxides

3.4. Polymer Characterization by ^{13}C NMR Spectra

Polymers obtained were characterized by ^{13}C NMR spectra (Figure 3.4.1). The productions of regio-regular **poly-*rac*-8** was also revealed by ^{13}C NMR spectrum of the obtained polymers in $CDCl_3$ (Figure 3.4.1a). **Poly-*rac*-8** showed seven broad peaks of the methylene in the main chain carbon reflecting the tacticity. In contrast, ^{13}C NMR spectrum of **poly-(*R*)-8** gave only one methylene carbon peak in the second lowest magnetic field of the

seven peaks (Figure 3.4.1b). Generally regioregular ring-opening polymerization of propylene oxide proceeds through successive nucleophilic attacks on the less hindered methylene carbon than the methine carbon.[1] Accordingly, it is reasonable to assume that the methine carbon retains its configuration and that isotactic polyether was obtained by using enatiopure epoxide. Seven peaks can not be assigned by comparing the two charts. However, given that only one sharp peak of **poly-(*R*)-8** reflected isotactic polymer, seven peaks probably indicated atactic polymer.

As above, a polymer from ***rac*-9** also had regioregular structure, while a polymer from **(*S*)-9** possessed isotactic sturucture (Figure 3.4.1c and d). In contrast, **poly-*rac*-10** had regioirregular structure, which was supported by the complex ^{13}C NMR peaks (Figure 3.4.1e). In the case of **poly-11** and **poly-12**, polymers from ***rac*-11** and ***rac*-12** also had regioregular structures (Figure 3.4.1f and 1h), while polymers from **(*R*)-11** and **(*S*)-12** were revealed to iso-specific structures (Figure 3.4.1g and 1i).

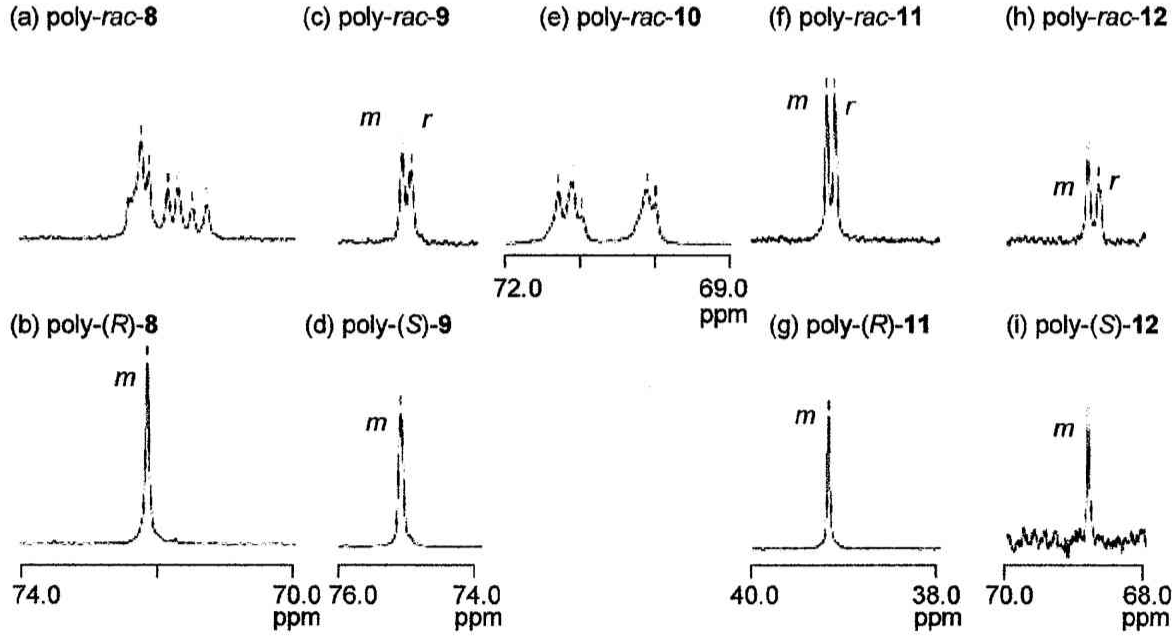
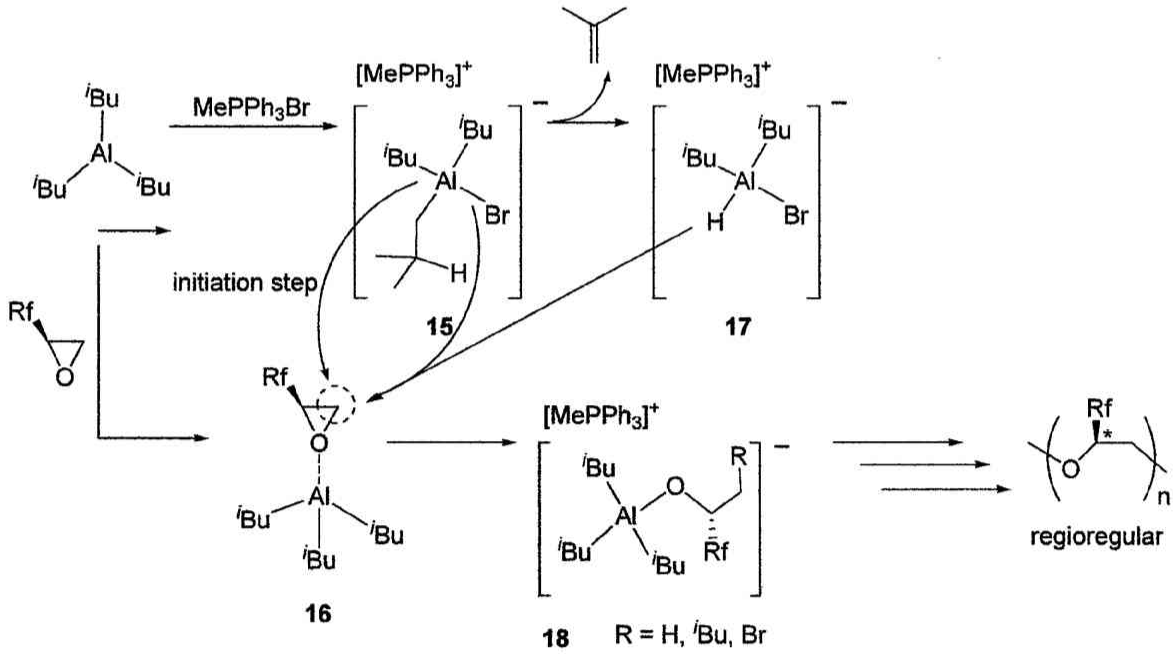


Figure 3.4.1 ^{13}C NMR spectra of polymers (a) **poly-*rac*-8** (b) **poly-(*R*)-8** (c) **poly-*rac*-9** (d) **poly-(*S*)-9** (e) **poly-*rac*-10** (f) **poly-*rac*-11** (g) **poly-(*R*)-11** (h) **poly-*rac*-12** (i) **poly-(*S*)-12**

3.5. Reaction Mechanism and Scope of Substrate.

A working mechanistic hypothesis was previously proposed (Scheme 3.5.1).[1,8] At first, aluminate complex **15** was formed from $MePPh_3Br$ and Al^iBu_3. On the other hand, an epoxide was activated by coordination on Al^iBu_3 (complex **16**) through an oxygen atom. This epoxide complexed Al^iBu_3 induced exclusive nucleophilic attack to methylene carbon by ^{i}Bu, Br or hydride derived from ate complex **17**, which reproduced new aluminate complex **18** and sequentially regio-selective ring-opening reaction of the epoxide. Repeated exclusive nucleophilic attacks on the methylene carbon yielded regio-regular polyethers. This hypothesis based on previous reports[1] is also supported by the fact that isotactic polyethers were obtained from enantiopure epoxides.[8]

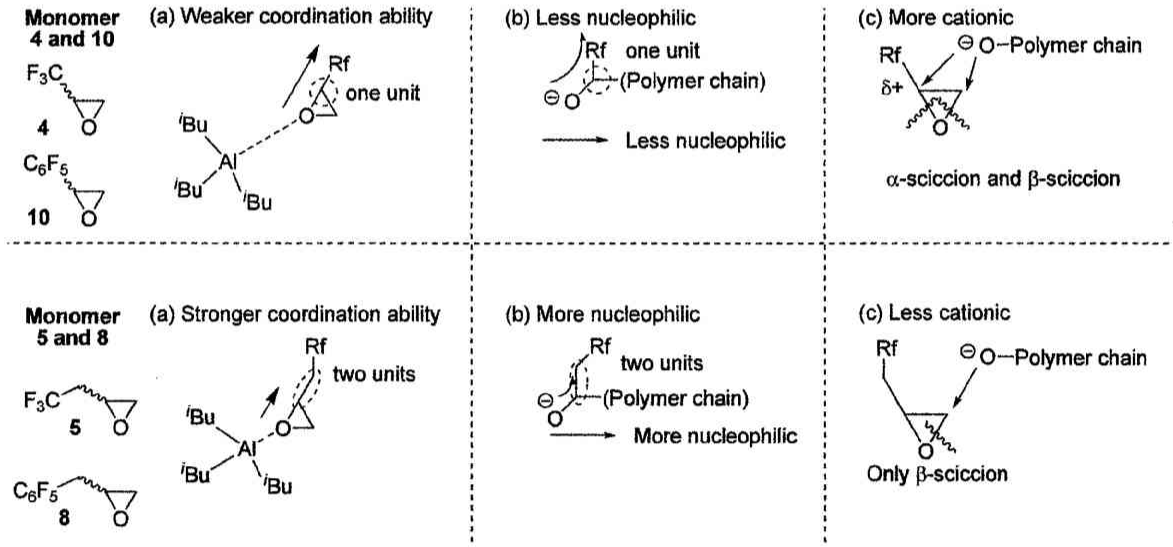
Scheme 3.5.1 Previously proposed mechanism of fluorine-containing epoxides.



Judging from this reaction mechanism, the lower activities and the regio-irregularities of **poly-*rac*-4** and **poly-*rac*-10** are reasonably explained as follows (Scheme 3.5.2). While methylene carbon units are inserted between the epoxide-rings and the electron-withdrawing groups (C_6F_5 and CF_3) in epoxides **5** and **8**, those in epoxides **4** and **10** are adjacent to

ethylene oxide directly. These neighboring electron-withdrowing groups decreased coordinating ability of the oxygen atom to $Al^{i}Bu_3$ and nucleophilicity of the chain-end alkoxide, which resulted in the decrease of polymerization activity (Scheme 3.5.2a and 3.5.2b). This hypothesis is probably supported by previous reports on the electronic effects of perfluoroalkyl groups in trialkylphosphines[44,45] that insertion of two or more methylene spacers between the phosphorous atom and the perfluoro-alkyl groups was essential as a buffer to insulate efficiently the electron-withdrawing effects on phosphorous atom. Similarly, such a insinulation of electron-withdrawing effect on polymerization activity was discussed in copolymerization of carbon monoxide and fluorine-containing olefin.[46,47]

Scheme 3.5.2 Elucidation of lower activities and regioirregularities of epoxides **4** and **10** (a) coordinating ability (b) nuclephilicity (c) cationic methine carbon



On the other hand, regio-irregularities of polymers from **4** and **10** would be due to the more cationic property of methine carbon of the epoxide ring as follows (Scheme 3.5.2c). Neighboring electron-withdrawing groups forced methine carbon to be more strongly cationic and induced nucleophilic attack of polymer chain ends to the methine carbon. As a result, both α–scission (cleavage between methine and oxygen) and β–scission (cleavage between methylene and oxygen) took place for **4** and **10** in spite of steric hinderence. In contrast, the

other epoxides **5** and **8** had methylene units to alleviate effects of the electron-withdrowing groups to induce exclusively nucleophilic attack on methylene carbon and cause only *β*–scission for steric hinderence. Normally regio-regular polyethers resulted from successive *β*–scission initiated by KOH and $Zn(OMe)_2$,[48] while regio-regular **poly-*rac*-4** was obtained by exclusive *α*–scission initiated by KOH and $(EtZnOEt)_6 \cdot Zn(OEt)_2$.[2,3] Based on this fact and the proposed mechanism above, it is reasonable to assume that epoxides ***rac*-4** and ***rac*-10** would polymerize through *α*–scisson by nature, and that Lewis acid Al^iBu_3 activated methylene carbons of ***rac*-4** and ***rac*-10** to cause both *α*–scission and *β*-scission.

3.6. ORD and CD Spectra of Optically Active Isotactic Polymers

To investigate the structural insights of isotactic polyethers (**poly-(*R*)-1**, **poly-(*R*)-3**, **poly-(*R*)-8**, **poly-(*S*)-9**, **poly-(*R*)-11**, **poly-(*S*)-12**) in solution state, ORD and CD spectroscopy were investigated. At first, **poly-(*R*)-1**, **poly-(*R*)-3**, their monomers **(*R*)-1** and **(*R*)-3** were studied (Figure 3.6.1a). Fluorous solvent AK-225® (CF_2ClCF_2CFHCl : $CF_3CF_2CFHCl_2$ = 11 : 9, v/v) was selected as a solvent because of good solubility of both polymers to detect plane curves of both polymers (Figure 3.6.1a). On the other hand, monomer **(*R*)-1** showed slightly detected peak top (peak $[\alpha]_{278}$ +8.59), while clearly distorted curve (peak $[\alpha]_{373}$ +7.24) was seen in ORD spectrum of monomer **(*R*)-3** (Figure 3.6.1a). Enantiopure propylene oxide showed both plane curve in benzene and distorted curve in chloroform, while enantiopure 1,2-diethoxypropane which was a model compound of repeating unit of optically active isotactic poly (propylene oxide) gave plane curve in these solvents.[28] This meant that there was no unambiguous information for helical structure of optically active isotactic poly (propylene oxide).[28] Hence, it is reasonable to assume that no data to support the helical structures of **poly-(*R*)-1** and **poly-(*R*)-3** were obtained from their ORD measurements.

Nextly, C_6F_5-substituted **poly-(*R*)-8**, **poly-(*S*)-9** and C_6H_5-substituted **poly-(*R*)-11** were evaluated by CD spectroscopy and UV spectroscopy in comparision with their monomers at the same concentration (Figure 3.6.1b-d). Unfortunately, although UV absorption of these polyethers ranged from 220 nm to 290 nm, these polyethers were insoluble in the solvents which are used for UV/CD measurements in the short wavelength region such as CH_3CN, $^cC_6H_{12}$, 1,4-dioxane and EtOH. Of good solvents (THF, $CHCl_3$, CH_2Cl_2 and toluene), THF was chosen for the most sufficient solubility and the smallest abosorption from 350 nm to 220 nm to detect CD spctroscopy of these three polymers. However, it should be noted that THF also has strong absorbance at short wavelength region. **Poly-(*S*)-12** was insoluble in any solvents at room temperature.

At first, CD spectra of **poly-(*R*)-8** showed slight positive Cotton effects, while monomer **(*R*)-8** exhibited negative Cotton effect (Figure 3.6.1b). Compared with circular dichroism values $\Delta\varepsilon$ of helical polymers,[9-12] that of **poly-(*R*)-8** disclosed much smaller $\Delta\varepsilon$.

Secondly, CD spectra of **poly-(*S*)-9** and its monomer **(*S*)-9** were obtained in THF solution (Figure 3.6.1c). Strong UV absorption derived from THF at low wavelength region forced us to measure CD spectra of monomer **(*S*)-9** and **poly-(*S*)-9** at low concentration because the measurement device has the limitation for absorbance to obtain unclear CD spectra. However, it seemed that CD spectrum of **poly-(*S*)-9** showed plane curve. Incidentally, it should be noted that plane curve of polyether CD spectrum indicated helical structure in the previous literature in spite of the lack of evidence.[23]

Lastly, monomer **(*R*)-11** gave vibrational curve, while **poly-(*R*)-11** showed more moderately oscillating curve (Figure 3.6.1d). Since optically active 1-phenyl-2-propanol which can be regarded as a model compounds of repeating unit of **poly-(*R*)-11** also showed vibrational curve,[49] moderate oscillating curves of **poly-(*R*)-11** would derive from unit structure of **poly-(*R*)-11**.

Conclusively, different curves between polymers and their monomers may result from structural differences of polymers and epoxides, but essentially no information was given for helical structures of the polymers in solution states through CD and ORD spectra.

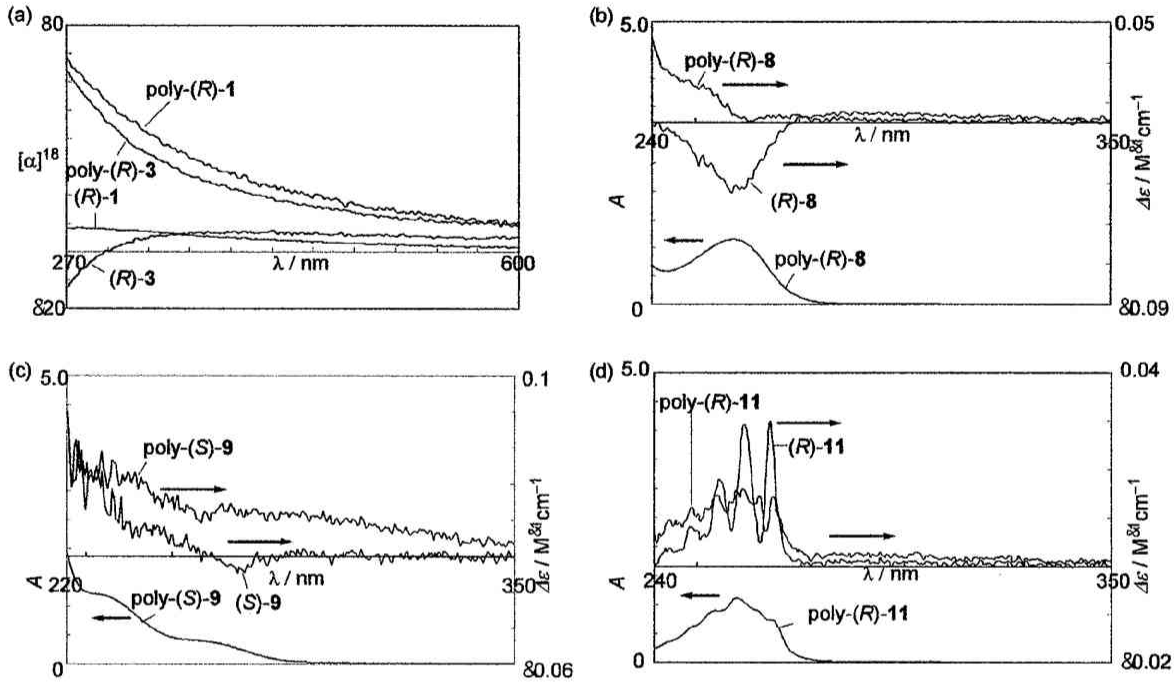


Figure 3.6.1 ORD or CD spectra of optically active isotactic polymers and their monomers. All concentration values of polymers were disclosed as concentration values of monomer-unit (a) ORD spectra of **poly-(*R*)-1** (c 1.06, AK-225®, 18 °C), **poly-(*R*)-3** (c 1.06, AK-225®, 18 °C), **(*R*)-1** (c 5.26, AK-225®, 18 °C) and **(*R*)-3** (c 1.06, AK-225®, 18 °C) (b) CD spectra of **poly-(*R*)-8**, **(*R*)-8** and UV/vis spectrum of **poly-(*R*)-8** (3.21×10^{-3} mol/L, THF, 25 °C) (c) CD spectra of **poly-(*S*)-9**, **(*S*)-9** and UV/vis spectrum of **poly-(*S*)-9** (1.27×10^{-3} mol/L, THF, 25 °C) (d) CD spectra of **poly-(*R*)-11**, **(*R*)-11** and UV/vis spectrum of **poly-(*R*)-11** (5.96×10^{-3} mol/L, THF, 25 °C)

3.7. Investigation on Bulk Structures of Isotactic Polyethers

To scrutinize difference between isotactic polyethers (**poly-(*R*)-1**, **poly-(*R*)-3**, **poly-(*R*)-8**,

poly-(*S*)-9, poly-(*R*)-11, poly-(*S*)-12) and atactic polyethers in the bulk state, T_g values of each isotactic polyether were compared with those of each atactic polyether. For aliphatic **poly-(*R*)-1, poly-(*R*)-3**, their T_g values were almost the same as those of corresponding atactic polyethers, which indicated no significant differences of bulk state between isotactic polyethers and atactic polyethers.[26] In addition, for aromatic polyether **poly-(*R*)-8**, its T_g value was almost same value as that of atactic polyether (Table 3.3.1, runs 1-2). In contrast, for **poly-(*S*)-9**, **poly-(*R*)-11** and **poly-(*S*)-12**, there were significant differences of T_g values and appearance from their atactic polyethers (Table 3.3.1, runs 3-4 and 6-9).

Powder XRD measurement was next examined for **poly-(*S*)-9**, **poly-(*R*)-11** and **poly-(*S*)-12** (Figure 3.7.1). Their d values and 2θ values were listed (Table 3.7.1). Since these three polymers were neither single crystal nor liquid crystal which did not have any isotropy, each polymer chain was chaoticaly dispersed in the solid and detected peaks would reflect on intramolecular regular structures.

While polyethers and their derivative possessing bulky side (^{i}Pr and ^{t}Bu) chain disclosed helical conformations in the bulk state,[30,31,34] polyethers and their derivative possessing unbulky side chain (Me, CH_2Cl) showed zig-zag conformations in the bulk state.[35-38] Since side chains of three polymers ($CH_2C_6F_5$, $CH_2OC_6F_5$, $CH_2OC_6H_5$) had one methylene unit to alleviate steric effects of aromatic rings, **poly-(*S*)-9**, **poly-(*R*)-11** and **poly-(*S*)-12** would be assumed to possess zig-zag conformations.

The presumption was confirmed by molecular modeling of MM2 calculations. Optimized structures of three polymers are shown (Figures 3.7.2a-c). In table 3.7.1, detected XRD peaks and unit distances of oxygen atoms from MM2 calculation roughly coincided. It supported that **poly-(*S*)-9**, **poly-(*R*)-11** and **poly-(*S*)-12** had zig-zag conformations. Incidentally, it should be noted that XRD spectra could also refelct on repeated length of lattice formed by intermolecular π-π stacking of aromatic rings.[50,51] Both unit distances of oxygen atoms and

intermolecular π-π stacking of aromatic rings would support existence of zig-zag conformations of **poly-(*S*)-9**, **poly-(*R*)-11** and **poly-(*S*)-12**.

It can be implied by MM2 calculations that **poly-(*S*)-9** possessed zig-zag structure with chaotical order, while **poly-(*S*)-12** gave completely well-ordered zig-zag structure. Presumed stuructures can be supported by the fact that **poly-(*S*)-9** is soluble in general oraganic solvents, while **poly-(*S*)-12** can solve in only hot (120 °C) DMSO and 1,2-$C_6H_4Cl_2$. It would be due to difference of F atom and H atom.

Table 3.7.1 Selected d values (Å) and angles (°) for polymers (a) **poly-(*S*)-9** (b) **poly-(*R*)-11** (c) **poly-(*S*)-12**

Polymer	2θ (°)	d (Å)	Selected atoms	d (Å) (MM2)
(*S*)-9	11.4	7.76		
	14.7	6.02		
	17.0	5.21		
	21.4	4.14		
	24.2	3.67	O1–O2	3.60
	25.9	3.44		
(*R*)-11	7.48	11.8		
	17.9	4.96		
	21.8	4.07	O1–O2	3.60
(*S*)-12	10.8	8.20		
	14.1	6.26		
	16.3	5.43		
	19.2	4.60		
	22.7	3.91	O1–O2	3.61
	26.6	3.35		

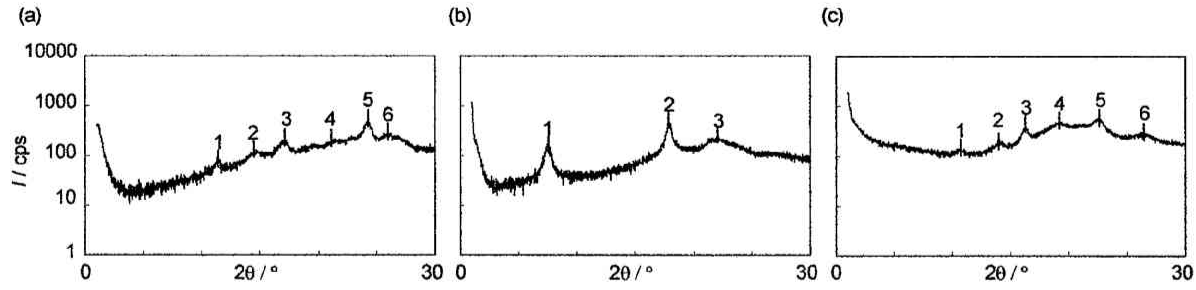
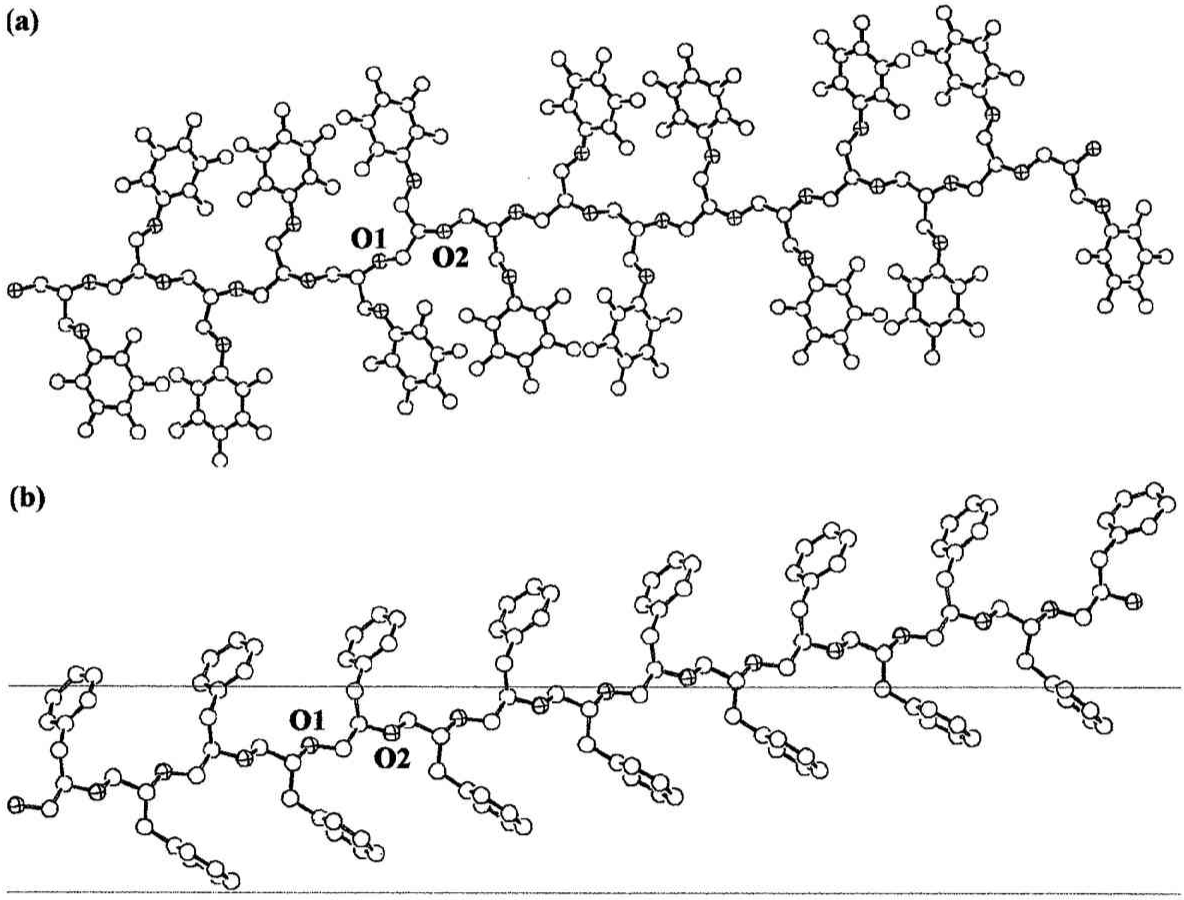


Figure 3.7.1 Powder XRD spectra (a) **poly-(*S*)-8** (b) **poly-(*R*)-11** (c) **poly-(*S*)-12**.



(c)

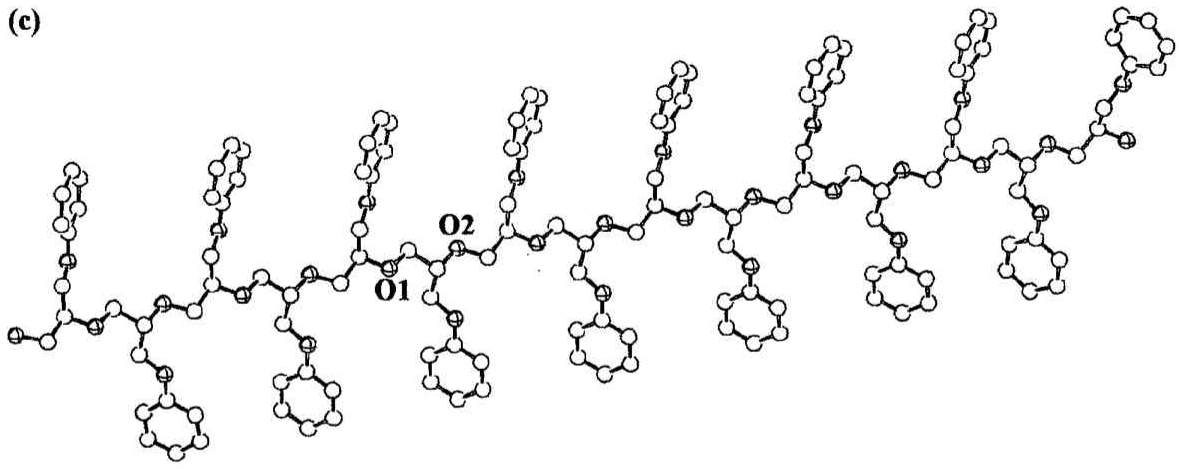


Figure 3.7.2 ORTEP drawing of assumed polymers by MM2 molecular modeling (H atoms were omitted and O atoms were depicted as foot balls) (a) **poly-(*S*)-9** (b) **poly-(*R*)-11** (c) **poly-(*S*)-12**

3.8. Conclusion

The substrate scope and generality of the present system was investigated and it was proved that fluoroaryl-substituted epoxides and the corresponding H-substituted epoxides were polymerized easily. Additionally, optically active isotactic polyethers were obtained by using enantiopure epoxides. Structures of the obtained polymers were clearly assigned by ^{13}C NMR spectra. Side chain methylene was regarded as a buffer of perfluoro-functions for alleviating their influence of electron-withdrawing effect to polymerize regio-regularly. Structures of obtained optically active isotactic polymers were investigated in both solution state and bulk state. None of them showed any proof for helical structures in solution state by CD and ORD spectra. On the other hand, zig-zag conformations were suggested in solid state of isotactic polyethers with aromatic side chains through XRD measurement supported by MM2 molecular modeling. In the case of **poly-(*S*)-9**, its structure was identified as a chaotically ordered zig-zag structure, while **poly-(*S*)-12** was completely well-oreded zig-zag strucuture.

3.9. References

(1) Billouard, C.; Carlotti, S.; Desbois, P.; Deffieux, A. *Macromolecules* **2004**, *37*, 4038-4043.

(2) Umezawa, J.; Hagiwara, T.; Hamana, H.; Narita, T.; Furuhashi, K.; Nohira, H. *Polymer J.* **1994**, *26*, 715-721.

(3) Hagiwara, T.; Terasaki, Y.; Hamana, H.; Narita, T.; Umezawa, J.; Furuhashi, K. *Makromol. Chem., Rapid Commun.* **1992**, *13*, 363-370.

(4) Blaser, H. U.; Studer, M. *Green Chem.* **2003**, *5*, 112-117.

(5) Yoshida, J.; Itami, K. *Chem. Rev.* **2002**, *102*, 3693-3716.

(6) Kendall, J. L.; Canelas, D. A.; Young, J. L.; DeSimone, J. M. *Chem. Rev.* **1999**, *99*, 543-563.

(7) Horvath, I. T. *Acc. Chem. Res.* **1998**, *31*, 641-650.

(8) Sakakibara, K.; Nakano, K.; Nozaki, K. *Chem. Commun.* **2006**, 3334-3336.

(9) Yashima, E.; Maeda, K.; Nishimura, T. *Chem. Eur. J.* **2004**, *10*, 43-51.

(10) Nakano, T.; Okamoto, Y. *Chem. Rev.* **2001**, *101*, 4013-4038.

(11) Fujiki, M. *Macromol. Rapid Commun.* **2001**, *22*, 539-563.

(12) Cornelissen, J.; Rowan, A. E.; Nolte, R. J. M.; Sommerdijk, N. *Chem. Rev.* **2001**, *101*, 4039-4070.

(13) Percec, V.; Rudick, J. G.; Peterca, M.; Staley, S. R.; Wagner, M.; Obata, M.; Mitchell, C. M.; Cho, W. D.; Balagurusamy, V. S. K.; Lowe, J. N.; Glodde, M.; Weichold, O.; Chung, K. J.; Ghionni, N.; Magonov, S. N.; Heiney, P. A. *Chem. Eur. J.* **2006**, *12*, 5731-5746.

(14) Monde, K.; Miura, N.; Hashimoto, M.; Taniguchi, T.; Inabe, T. *J. Am. Chem. Soc.* **2006**, *128*, 6000-6001.

(15) Gorske, B. C.; Blackwell, H. E. *J. Am. Chem. Soc.* **2006**, *128*, 14378-14387.

(16) Reichenbacher, K.; Suss, H. I.; Hulliger, J. *Chem. Soc. Rev.* **2005**, *34*, 22-30.

(17) Saxena, A.; Fujiki, M.; Naito, M.; Okoshi, K.; Kwak, G. *Macromolecules* **2004**, *37*, 5873-5879.

(18) Kim, S. Y.; Saxena, A.; Kwak, G.; Fujiki, M.; Kawakami, Y. *Chem. Commun.* **2004**, 538-539.

(19) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem. Int. Ed.* **2003**, *42*, 1210-1250.

(20) Desiraju, G. R. *Acc. Chem. Res.* **2002**, *35*, 565-573.

(21) Janssen, H. M.; Peeters, E.; vanZundert, M. F.; vanGenderen, M. H. P.; Meijer, E. W. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 122-125.

(22) Janssen, H. M.; Peeters, E.; van Zundert, M. F.; van Genderen, M. H. P.; Meijer, E. W. *Macromolecules* **1997**, *30*, 8113-8128.

(23) Janssen, H. M.; Meijer, E. W. *Macromolecules* **1997**, *30*, 8129-8138.

(24) Haouet, A.; Sepulchre, M.; Spassky, N. *Eur. Polym. J.* **1983**, *19*, 1089-1098.

(25) Hirano, T.; Sato, A.; Tsuruta, T.; Johnson, W. C. *J. Polym. Sci., Polym. Phys. Ed.* **1979**, *17*, 1601-1609.

(26) Araki, T.; Nagata, K.; Tsukube, H. *J. Polym. Sci., Polym. Chem. Ed.* **1979**, *17*, 731-746.

(27) Spassky, N.; Pourdjavadi, A.; Sigwalt, P. *Eur. Polym. J.* **1977**, *13*, 467-477.

(28) Tsunetsugu, T.; Furukawa, J.; Fueno, T. *J. Polym. Sci. A-1* **1971**, *9*, 3529-&.

(29) Tsunetsugu, T.; Fueno, T.; Furukawa, J. *J. Polym. Sci. A-1* **1971**, *9*, 3541-3546.

(30) Matsubayashi, H.; Chatani, Y.; Tadokoro, H.; Dumas, P.; Spassky, N.; Sigwalt, P. *Macromolecules* **1977**, *10*, 996-1002.

(31) Takahashi, Y.; Tadokoro, H.; Hirano, T.; Sato, A.; Tsuruta, T. *J. Polym. Sci., Polym. Phys. Ed.* **1975**, *13*, 285-294.

(32) Takahashi, Y.; Tadokoro, H. *Macromolecules* **1973**, *6*, 672-675.

(33) Takahashi, Y.; Sumita, I.; Tadokoro, H. *J. Polym. Sci., Polym. Phys. Ed.* **1973**, *11*, 2113-2122.

(34) Sakakihara, H.; Takahash, Y.; Tadokoro, H.; Oguni, N.; Tani, H. *Macromolecules* **1973**, *6*, 205-212.

(35) Perego, G.; Cesari, M. *Makromol. Chem.* **1970**, *133*, 133-138.

(36) Sakakihara, H.; Takahash, Y.; Tadokoro, H.; Sigwalt, P.; Spassky, N. *Macromolecules* **1969**,

2, 515-520.

(37) Cesari, M.; Perego, G.; Marconi, W. *Makromol. Chem.* **1966**, *94*, 194-204.

(38) Stanley, E.; Litt, M. *J. Polym. Sci.* **1960**, *43*, 453-458.

(39) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307-1315.

(40) Bijvoet, J. M.; Peerdeman, A. F.; van Bommel, A. J. *Nature* **1951**, *168*, 271-2.

(41) Noshay, A.; Price, C. C. *J. Polym. Sci.* **1959**, *34*, 165-70.

(42) Hiyama, T. *Organofluorine Compounds*; Springer: Berlin, 2000.

(43) Isemura, T.; Kakita, R.; Kawahara, K. *J. Chromatography A* **2004**, *1026*, 109-116.

(44) Jiao, H. J.; Le Stang, S.; Soos, T.; Meier, R.; Kowski, K.; Rademacher, P.; Jafarpour, L.; Hamard, J. B.; Nolan, S. P.; Gladysz, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 1516-1523.

(45) Horvath, I. T.; Kiss, G.; Cook, R. A.; Bond, J. E.; Stevens, P. A.; Rabai, J.; Mozeleski, E. J. *J. Am. Chem. Soc.* **1998**, *120*, 3133-3143.

(46) Fujita, T.; Nakano, K.; Yamashita, M.; Nozaki, K. *J. Am. Chem. Soc.* **2006**, *128*, 1968-1975.

(47) Nozaki, K.; Shibahara, F.; Elzner, S.; Hiyama, T. *Can. J. Chem.* **2001**, *79*, 593-597.

(48) Inoue, S.; Tsukuma, I.; Kawaguchi, M.; Tsuruta, T. *Makromol. Chem.* **1967**, *103*, 151-163.

(49) Smith, H. E.; Neergaard, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 7694-7701.

(50) Bruckner, S.; De Rosa, C.; Corradini, P.; Porzio, W.; Musco, A. *Macromolecules* **1996**, *29*, 1535-1539.

(51) De Rosa, C. *Macromolecules* **1997**, *30*, 5494-5500.

Chapter 4

Ring-opening Reaction of Bus- and SES-protected Aziridines Using Lithiated Dithianes

4.1. Introduction

Optically active *β*-amino carbonyl compounds are common intermediates for various kinds of biologically active compounds such as alkaloid syntheses. One of the common synthetic approaches to this type of compound is the asymmetric Mannich reaction.[1-3] As an alternative method, nucleophilic ring opening of *N*-*p*-toluenesufonyl (=Ts) aziridine using lithiated dithianes has been reported.[4-12]

The latter methodology is advantageous for several reasons: (1) Because the carbonyl group is masked in the product, undesirable side reactions such as self-aldol condensation are suppressed. (2) In using alkyl imine in Mannich reaction, self-Mannich reaction can be occurred. (3) The amino group in the product is protected by a *p*-tosyl group. (4) The reaction is not reversible; therefore, the products are obtained in high yields. (5) Enantiomerically pure aziridines[13-17] are easily available and the configuration is maintained throughout the reaction. However, the substrates for the ring-opening reaction using lithiated dithianes were limited to *N*-tosylaziridines. Although *N*-tosylaziridines are commonly employed because of their easy preparation, a major drawback is the difficulty in their deprotection.[9] Other sulfonyl-protecting groups such as *tert*-butylsulfonyl (Bus),[18-21] 2-trimethyl-silylethylsulfonyl (SES),[22,23] and *p*-nitrophenylsulfonyl (Ns),[24,25] are known to undergo deprotection under much milder reaction conditions (Figure 4.1.1).

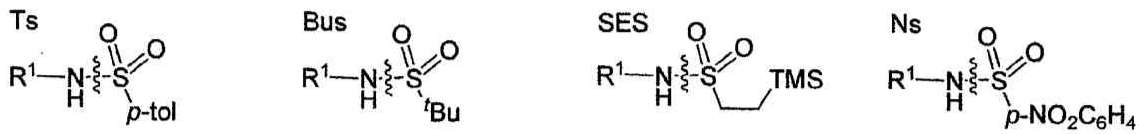


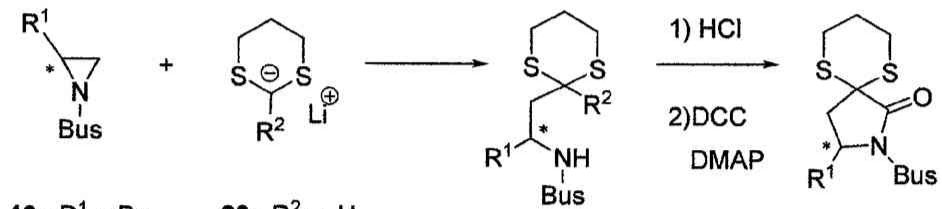
Figure 4.1.1 Possible sulfonyl protecting groups for aziridines.

In this chapter, the author describes the scope and limitation of *N*-sulfonylaziridines employable as electrophiles in the reaction with lithiated dithianes. Depending on the kinds of dithianes, *β*-amino carbonyl equivalents, a *γ*-lactam and 1,5-amino-alcohols were obtained in good yields with a Bus- and SES-protecting group on the nitrogen. Deprotection of Bus-, SES- and dithiane moiety is also described.

4.2. Ring-opening Reaction of Bus-activated Aziridine by Using Lithiated Dithianes

Bus-activated aziridines **19** and various dithiane anions **20–23** genrated from dithiane and BuLi were chosen as substrates (Table 4.2.1). Aziridine ***rac*-19** was allowed to react with lithiated 1,3-dithiane **20** to yield ***rac*-24** (Table 4.2.1, run 1). Enantiopure aziridine **(*S*)-19** was converted to **(*S*)-24** by **20** without any racemization (Table 4.2.1, run 2). Lithiated carboxyl-1,3-dithiane **21** opened ***rac*-19** in the presence of TMEDA (Table 4.2.1, run 3). The crude product could not be purified because of its high polarity. After neutralization by HCl/MeOH, the crude material was treated with DCC/DMAP and *γ*-lactam **25** was isolated. Ring opening of enantiopure aziridine **(*S*)-19** by **21** yielded **(*S*)-25** without racemization (Table 4.2.1, run 4). Aziridine ***rac*-19** yielded ***rac*-26** and ***rac*-27** by the reactions with lithiated dithianes **22** and **23** (Table 4.2.1, runs 5-6).

Table 4.2.1 Ring-opening reaction of Bus-activated aziridine **19** using lithiated dithianes



19 : R^1 = Bn

20 : R^2 = H
21 : R^2 = $CO_2^{\ominus}$
22 : R^2 = TMS
23 : R^2 = Ph

24 : R^1 = Bn, R^2 = H
26 : R^1 = Bn, R^2 = TMS
27 : R^1 = Bn, R^2 = Ph

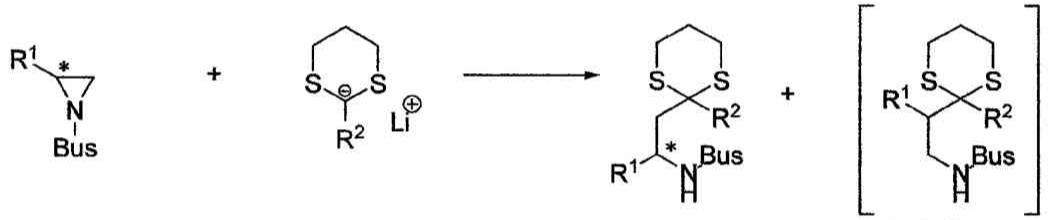
25 : R^1 = Bn

run	Aziridine	Dithiane	Product	Yield (%)
1[a]	***rac*-19**	**20** H	***rac*-24**	90
2[a]	**(*S*)-19**	**20** H	**(*S*)-24**	91
3[b]	***rac*-19**	**21** CO_2^-	***rac*-25**	76
4[b]	**(*S*)-19**	**21** CO_2^-	**(*S*)-25**	78
5[c]	***rac*-19**	**22** TMS	***rac*-26**	90
6[a]	***rac*-19**	**23** Ph	***rac*-27**	92

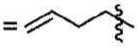
[a] Experimental procedure A [b] Experimental procedure B [c] Experimental procedure C

The author next examined the scope of Bus-activated aziridines **28-32** containing various substituents (Table 4.2.2, runs 1–5). All of them easily provided the ring-opening products **33-37**, while ring-opening product was not obtained from ***rac*-32** and **20** (Table 4.2.2, run 6). Only complex mixture was detected.

Table 4.2.2 Ring-opening reaction of various Bus-activated aziridines



regio-isomer
37' : $R^1 = R^2 = Ph$

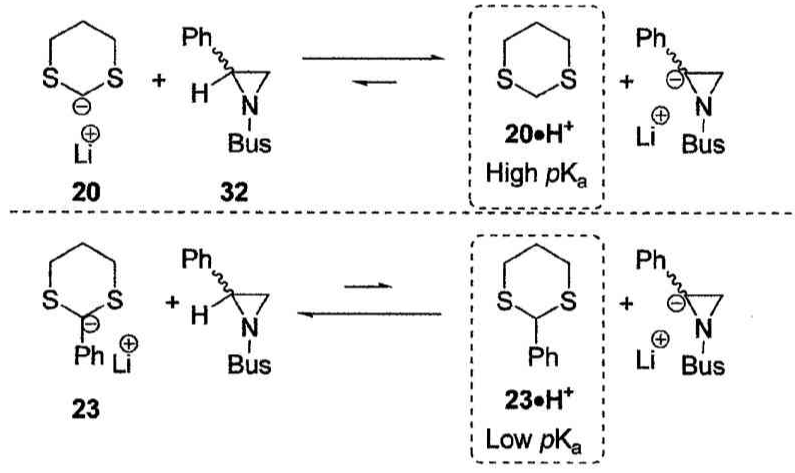
28 : R^1 =  **20** : R^2 = H
29 : $R^1 = {}^nC_{10}H_{21}$ **23** : R^2 = Ph
30 : $R^1 = BnOCH_2$
31 : $R^1 = TrOCH_2$
32 : R^1 = Ph

33 : R^1 =  R^2 = Ph
34 : $R^1 = {}^nC_{10}H_{21}$ R^2 = Ph
35 : $R^1 = BnOCH_2$ R^2 = Ph
36 : $R^1 = TrOCH_2$ R^2 = Ph
37 : R^1 = Ph R^2 = Ph

run	Aziridine	Dithiane	Product	Yield (%)
1[a]	***rac*-28**	**23**	***rac*-33**	83
2[a]	***rac*-29**	**23**	***rac*-34**	94
3[a]	***rac*-30**	**23**	***rac*-35**	90
4[a]	**(*R*)-31**	**23**	**(*R*)-36**	85
5[a]	***rac*-32**	**23**	***rac*-37**	95[b]
6[a]	***rac*-32**	**20**	-[c]	-[c]

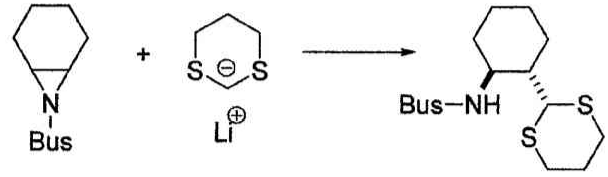
[a] Experimental procedure A [b] Regio-isomer was detected. [c] Complex mixture was detected.

The product ***rac*-37** was obtained as a mixture with its regio-isomer **37'** (~ 3 : 1) (Table 4.2.2). It should be noted that ring-opening product was not obtained from ***rac*-32** and lithiated dithiane **20**.[9] Only a complex mixture was given. Considering big difference in pK_a values between dithiane **20•H$^+$** (pK_a 39) and **23•H$^+$** (pK_a 30.7),[26] anion of dithiane **20** would cause deprotonation of aziridine ***rac*-14** to give complex mixture, while lithiated dithiane **23** triggered smooth ring-opening due to low pK_a value (Scheme 4.2.1). The order of pK_a can roughly be estimated to rationalize our hypothesis: **23•H$^+$** (pK_a 30.7) < α-proton to N atom and Ph group < **20•H$^+$** (pK_a 39).



Scheme 4.2.1 Ring-opening reaction of Bus-activated Ph-aziridine

Furthermore, di-substituted ***meso*-38** yielded the corresponding trans-substituted product ***rac*-39** (Scheme 4.2.2). Although several examples of ring opening using dithiane have been reported for 2,3-di-substituted oxiranes,[27-30] this is the first example of a ring-opening reaction of di-substituted aziridine using dithiane.



***meso*-38** **20** ***rac*-39** (91%)

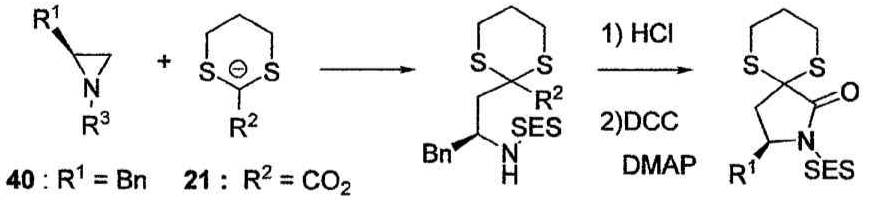
Experimental procedure D

Scheme 4.2.2 Ring-opening reaction of 2,3-di-substituted-aziridine.

4.3. Ring-opening Reaction of SES- and Ns-activated Aziridine

SES- and Ns-activated aziridines **40** and **41** were reacted with lithiated dithianes (Table 4.3.1, runs 1-5). Treatment of azridine **(*S*)-40** resulted in quantitative recovery of dithiane, and a complex mixture derived from aziridine was obtained (Table 4.3.1, run 1). **(*S*)-40** was treated with **21** to yield **(*S*)-42** via cyclization (Table 4.3.1, run 2). In contrast, reaction of **(*S*)-40** with **22** resulted in quantitative recovery of dithiane and a complex mixture derived from aziridine (Table 4.3.1, run 3). Lithiated dithiane **23** smoothly opened aziridine **(*S*)-40** to **(*S*)-43** (Table 4.3.1, run 4). The following may be an explanation for the quantitative recovery of dithiane and the complex mixture derived from aziridine (Table 4.3.1, runs 1 and 3). In the case of lithiated dithianes **20** and **22**, equilibrium between an α-carbanion on the sulfonyl group of SES and the anion of dithiane would lie to the right because of the higher pK_a of dithianes **20•H$^+$** and **22•H$^+$** (Scheme 4.3.1). Deprotonated aziridines would lead to a complex mixture and recovery of protonated dithiane. In contrast, lithiated dithanes **21** and **23** would retain the carbanion character to open the aziridines because of the lower pK_a of dithianes **21•H$^+$** and **23•H$^+$** (Scheme 4.3.1). The order of pK_a can roughly be estimated to rationalize our hypothesis: **21•H$^+$**, **23•H$^+$** (pK_a 30.7) < α-proton neighboring SES sulfonyl group < **20•H$^+$** (pK_a 39), **22•H$^+$**.[26,31] Given that 2-CO_2Me-1,3-dithiane (pK_a 20.9) and $MeSO_2Me$ (pK_a 31.1) have similar pK$_a$ values of dithiane **21** and α-proton neighboring SES sulfonyl group, our roughly estimated order of pK_a would be supported. Finally, Ns-aziridine **(*S*)-41** provided an insoluble complex mixture due to competing deprotection (Table 4.3.1, run 5).[32]

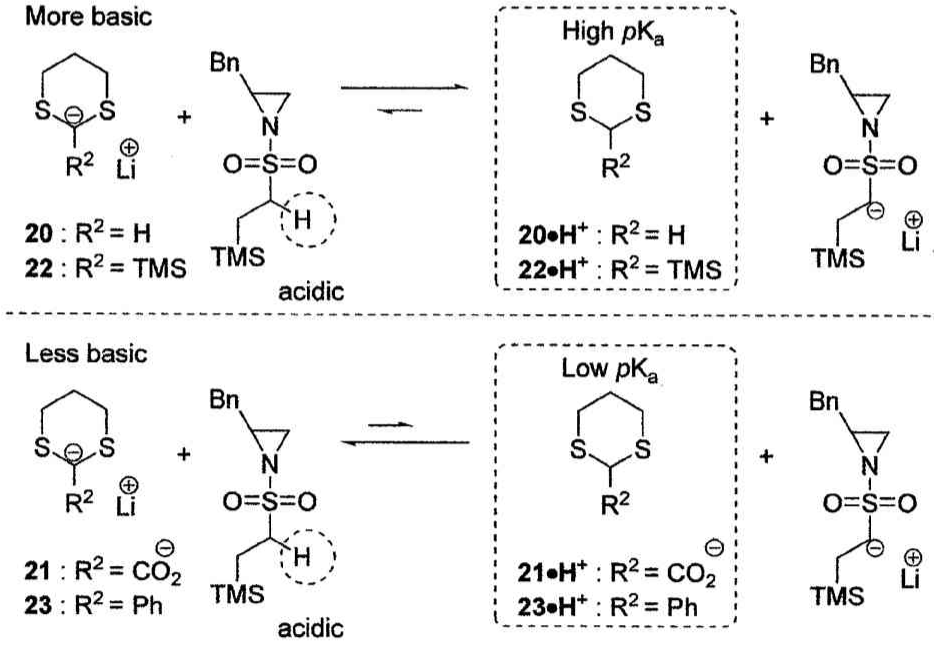
Table 4.3.1 Ring-opening reaction of SES- and Ns-activated aziridines



40 : R^1 = Bn R^3 = SES
41 : R^1 = Bn R^3 = Ns
21 : $R^2 = CO_2$
23 : R^2 = Ph
43 : R^1 = Bn, R^2 = Ph
42 : R^1 = Bn

run	Aziridine	Dithiane	Product	Yield (%)
1[a]	(*S*)-40	20	-	-[d]
2[b]	(*S*)-40	21	(*S*)-42	45
3[c]	(*S*)-40	22	-	-[d]
4[a]	(*S*)-40	23	(*S*)-43	86
5[a]	(*S*)-41	23	-	-[e]

[a] Experimental procedure A [b] Experimental procedure B [c] Experimental procedure C
[d] Recovery of dithiane and a complex mixture from aziridine were detected.
[e] A complex mixture was given.

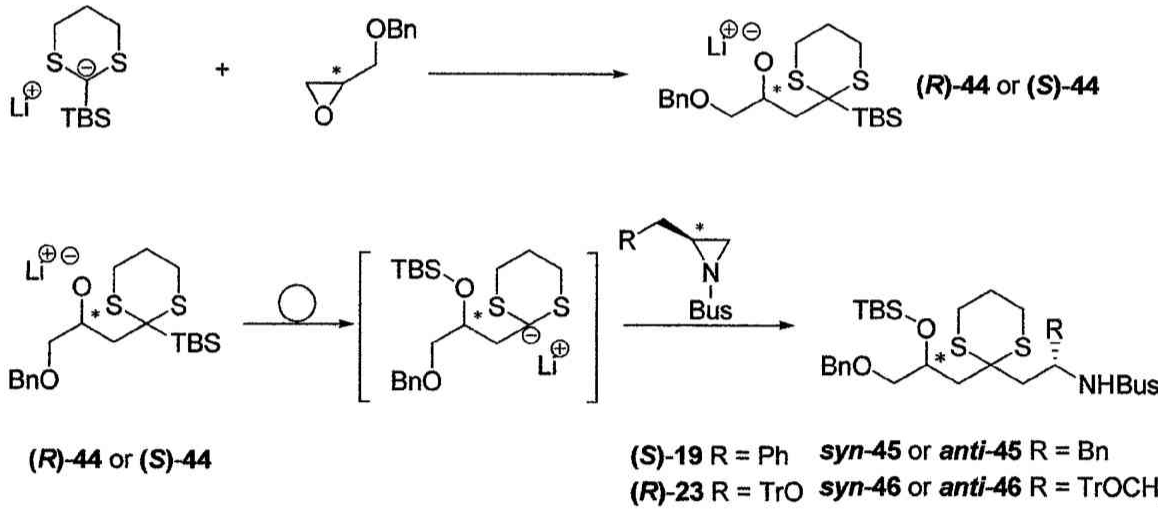


Scheme 4.3.1 Equilibrium between lithiated dithaine and α–sulfonyl proton

4.4. Ring-opening Reaction of Bus-activated Aziridine via Brook Rearrangement

The author has further extended the ring opening of Bus-activated aziridines to the syntheses of 1,5-amino alcohols (Table 4.4.1, runs 1–4). Chiral 1,5-amino alcohols are important intermediates for poly-substituted piperidines syntheses.[4] Lithiated carbinol **44** which was synthesized from epoxide and lithiated TBS-dithiane induced the 1,4-Brook rearrangement in the presence of HMPA, yielding 1,5-amino alcohols via the ring-opening reaction of Bus-activated aziridines.[4] As well as Ts-activated aziridine,[4] 1,5-amino alcohol ***syn*-45** can be obtained from aziridine **(*S*)-19** and lithiated dithiane **(*R*)-44** (Table 4.4.1, run 1). ***Anti*-45** can be exclusively obtained using the opposite enantiomer of **44** (Table 4.4.1, run 2). In addition, ***syn*-** and ***anti*-46** were obtained by using aziridine **(*R*)-31** and both enantiomers of lithiated dithiane **44** (Table 4.4.1, runs 3 and 4).

Table 4.4.1 Syntheses of 1,5-amino alcohols



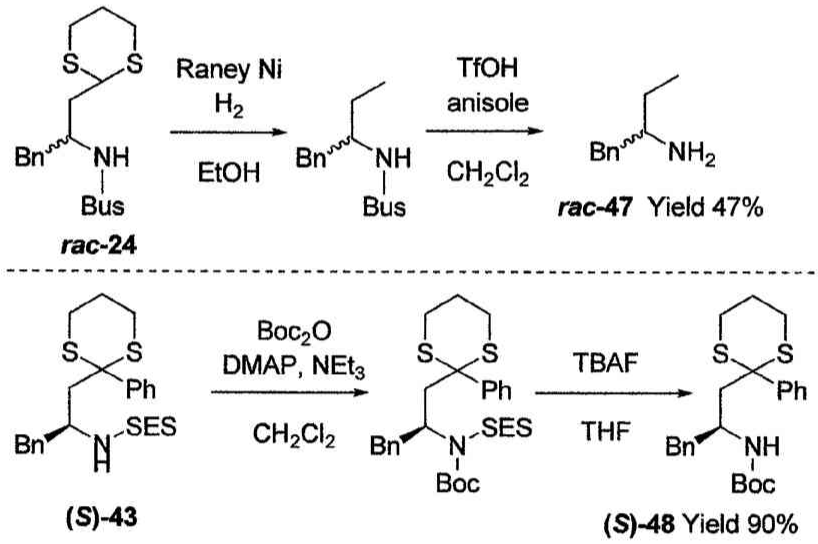
run	Aziridine	Dithiane	Product	Yield (%)
1[a]	**(*S*)-19**	**(*R*)-44**	***syn*-45**	69
2[a]	**(*S*)-19**	**(*S*)-44**	***anti*-45**	61
3[a]	**(*R*)-31**	**(*R*)-44**	***syn*-46**	58
4[a]	**(*R*)-31**	**(*S*)-44**	***anti*-46**	78

[a] Experimental procedure E

4.5. Deprotection of Bus, SES and Dithiane-ring

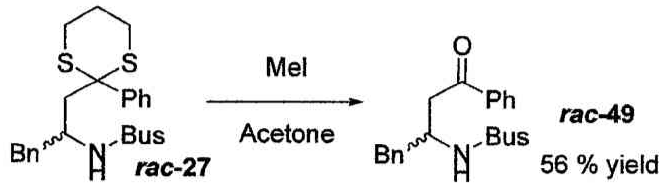
Finally, Bus and SES of dithianes obtained were removed to demonstrate the synthetic usefulness (Scheme 4.5.1). First of all, Bus-bearing dithiane ***rac*-47** was chosen as a substrate. Unfortunately, use of the normal condition (TfOH/anisole[21]) or use of the Ts-removing condition (Na/naphtalenide/DME[9]) led to the decomposition of the dithiane moiety. Thus, after dithiane moiety was removed by Raney Ni, the deprotected compound ***rac*-24** was obatined by using TfOH and anisole (Scheme 4.5.1). Nextly, SES-posessing dithiane **(*S*)-43** was efficiently deprotected via Boc-introduction to yield **(*S*)-48**. It was well known that *N*-acyl-SES was much more easily deprotected than monoproteced SES-amine.[23]

Scheme 4.5.1 Deprotection of Bus and SES.



Furthermore, dithiane-ring of the ring-opening product ***rac*-27** was also deprotected to convert into carbonyl compound ***rac*-49** by MeI/acetone (Scheme 4.5.2).

Scheme 4.5.2 Deprotection of dithiane-ring



4.6. Conclusion

The author reported that Bus- and SES-activated aziridines undergo an efficient ring-opening reaction with various lithiated dithiane anions to yield various *β*-amino carbonyl equivalents, *γ*-lactam and *syn*- and *anti*-1,5-amino-alcohols. Scope of substrates was elucidated by pK_a values. Deprotection of Bus, SES and dithiane ring is also conducted to demonstrate the synthetic usefulness.

4.7. Referneces

(1) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541-2569.

(2) Yus, M.; Najera, C.; Foubelo, F. *Tetrahedron* **2003**, *59*, 6147-6212.

(3) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069-1094.

(4) Smith, A. B., III; Kim, D. S. *J. Org. Chem.* **2006**, *71*, 2547-2557.

(5) Reich, H. J.; Sanders, A. W.; Fiedler, A. T.; Bevan, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 13386-13387.

(6) Mao, H.; Joly, G. J.; Peeters, K.; Hoornaert, G. J.; Compernolle, F. *Tetrahedron* **2001**, *57*, 6955-6967.

(7) Harms, G.; Schaumann, E.; Adiwidjaja, G. *Synthesis* **2001**, 577-580.

(8) Joly, G. J.; Peeters, K.; Mao, H.; Brossette, T.; Hoornaert, G. J.; Compernolle, F. *Tetrahedron Lett.* **2000**, *41*, 2223-2226.

(9) Howson, W.; Osborn, H. M. I.; Sweeney, J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2439-2445.

(10) Osborn, H. M. I.; Sweeney, J. B.; Howson, B. *Synlett* **1993**, 675-676.

(11) Bates, G. S.; Ramaswamy, S. *Can. J. Chem.* **1980**, *58*, 716-722.

(12) Bates, G. S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 161-163.

(13) Kim, S. K.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2004**, *43*, 3952-3954.

(14) Muller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905-2920.

(15) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247-258.

(16) Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693-1715.

(17) Tanner, D. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599-619.

(18) Schomaker, J. M.; Bhattacharjee, S.; Yan, J.; Borhan, B. *J. Am. Chem. Soc.* **2007**, *129*, 1996-2003.

(19) Hodgson, D. M.; Miles, S. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 935-938.

(20) Gontcharov, A. V.; Liu, H.; Sharpless, K. B. *Org. Lett.* **1999**, *1*, 783-786.

(21) Sun, P.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1997**, *62*, 8604-8608.

(22) Trost, B. M.; Zhang, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 3759-3761.

(23) Ribiere, P.; Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2006**, *106*, 2249-2269.

(24) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353-359.

(25) Alonso, D. A.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 9455-9461.

(26) Bordwell, F. G.; Drucker, G. E.; Andersen, N. H.; Denniston, A. D. *J. Am. Chem. Soc.* **1986**, *108*, 7310-7313.

(27) Ide, M.; Nakata, M. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2491-2499.

(28) Rubiralta, M.; Diez, A.; Reig, I.; Castells, J.; Bettiol, J. L.; Grierson, D. S.; Husson, H. P. *Heterocycles* **1990**, *31*, 173-186.

(29) Bennasar, M. L.; Torrens, A.; Rubiralta, M.; Bosch, J.; Grierson, D. S.; Husson, H. P. *Heterocycles* **1989**, *29*, 745-760.

(30) Amrein, W.; Schaffner, K. *Helv. Chim. Acta.* **1975**, *58*, 380-397.

(31) Bordwell, F. G.; Harrelson, J. A.; Zhang, X. *J. Org. Chem.* **1991**, *56*, 4448-4450.

(32) Maligres, P. E.; See, M. M.; Askin, D.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 5253-5256.

Chapter 5
General Conclusion

Ring-opening Polymerization of Fluorine-containing Epoxides

In Chapter 2 and Chapter 3, ring-opening polymerization of epoxides bearing various fluorine-containing groups was achieved. These polymers obtained would be potentially attractive materials. Isotactic polymers and atactic polymers were obtained by using optically pure monomers and racemic monomers. Furthermore, the structural information of isotactic polymers was obtained. However, following two subjects were remaining.

First, regio-regular polymerization of **4** and **10** is not achieved. Methylene spacer between epoxide-ring and the fluorine-containing groups was essential as a buffer to insulate efficiently the electron-withdrawing effects on methine atom for regio-regularity. Thus, regio-regular polymerization of following two epoxides **4** and **10** is remaining subject.

In addition, further precison polymerization of epoxides bearing various fluorine-containing groups such as iso-specific polymerization and syndio-specific polymerization is also challenging subject. Especially, syndio-specific polymerization is so attractive theme that even syndio-specific polymerization of propylene oxide has not been reported so far.

The author hopes that these two subjects will be solved in the future via the refined catalyst system.

Ring-opening Reaction of Aziridines Using Lithiated Dithianes

The author reported that Bus- and SES-activated aziridines undergo an efficient ring-opening reaction with various lithiated dithiane anions to yield various β-amino carbonyl equivalents, γ-lactam and syn- and anti-1,5-amino-alcohols. Scope of substrates was elucidated by pK_a values. Deprotection of Bus, SES and dithiane ring is also conducted to demonstrate the synthetic usefulness. However, following two issues are not solved.

First, Ns-activated aziridines are not be opened by lithiated dithianes. Considering that Ns-protected amine can be easily deprotected, ring-opening reaction of Ns-aziridine without side reactions should be achieved.

Second, further development of protecting groups for amine is essential. I propose new protecting group for amine via sulfonyl group: Trs-SO_2-. This protecting group for amine is a combination of Bus- and Bn-SO_2- to be easily deprotected and possess high stability.

Experimental Section

General Procedure

All manipulations involving air-sensitive and/or moisture-sensitive compounds were carried out using the standard Schlenk technique under argon purified by passing through a hot column packed with BASF catalyst R3-11. Gas chromatography analyses were performed on a SHIMADZU GC-2010 equipped with Chrompack CHIRASIL-DEX CB column, and helium was used as the carrier gas. Enantiopurity was also confirmed by chiral HPLC. HPLC analyses were carried out using a JASCO LC-2000Plus system equipped with a DAICEL CHIRALPAK IA or IB column (4.6 mm×250 mm). Differential scanning calorimetry (DSC) measurements were performed on a Mettler DSC 30. Heating rates were 5 °C/min. The reported T_g values were determined from the second heating scan. Optical rotations were measured on JASCO DIP-360 spectrometer using a 10-cm cell. The recycling preparative GPC was performed with a JAI LC-928 chromatograph equipped with JAI GEL-1H and -2H columns (chloroform as an eluent). X-ray crystallographic analyses were recorded on a Rigaku Mercury CCD diffractometer. Circular dichroism (CD) spectra were recorded on a Jasco J-700 spectropolarimeter fitted with a Jasco PTC-423 L temperature controller in 1-cm rectangular quartz cells. Optical rotatory dispersion (ORD) spectra were recorded on a Jasco J-820 spectropolarimeter fitted with a Jasco PTC-423 L temperature controller in 1-cm rectangular quartz cells. High resolution mass spectra were recorded by the FAB method using a JEOL JMS-700 mass spectrometer. All cif files for esters **7, 13** and **14** were checked by check-CIF (http://checkcif.iucr.org/). CCDC-634989–634991 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Spectra of newly synthesized compounds were listed in the literature except for ***rac*-49**.[1-3]

Chapter 2

All NMR spectra of obtained polymer except for **poly-*rac*-4** was recorded in hexafluorobenzene (C_6F_6) on JEOL JNM-ECP500 (^{1}H: 500 MHz; ^{13}C: 125 MHz; ^{19}F: 471 MHz) spectrometer. Exceptionally **poly-*rac*-4** was recorded in acetone-d_6. Chemical shifts are reported in ppm from following internal standards: tetramethylsilane (0 ppm) for ^{1}H and ^{13}C, C_6F_6 (−162 ppm) for ^{19}F. Gel permeation chromatography (GPC) analyses were carried out using two columns (Polymer Laboratories Ltd. gel mixed-C). The GPC columns were eluted with ASAHICLEAN® (CF_2ClCF_2CFHCl : $(CF_3)_2CHOH$ = 99 : 1, v/v) at 37 °C at 1 mL/min. Detailed information and condition were described in the previous report.[4] Exceptionally, in measuring **poly-*rac*-4** and **poly-*rac*-5** GPC analysis was carried out using Gel permeation chromatography (GPC) analyses which were carried out using two columns (Shodex KF-804L) and THF as an eluent at 40 °C at 1 mL/min. All solvents and fluorinated epoxides used for reactions were distilled under argon after drying over an appropriate drying reagent. Most of the reagents were purchased from Aldrich Chemical Co., Tokyo Kasei Kogyo Co., LTD., Kanto Kagaku Co., Ltd., or Daikin Industries, LTD., and were used without further purification unless otherwise specified. ^{i}PrONa was prepared according to literature method.[5]

Preparation of enantiopure epoxides through kinetic resolution of racemic epoxides.

Enantiopure epoxides were prepared from slightly modified literature method for kinetic Resolution by using (*R*,*R*)-Co-salen complex (Figure E1).[6]

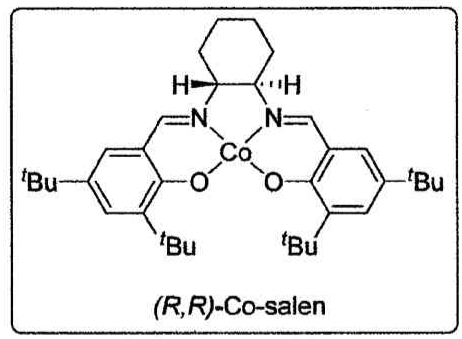


Figure E1 Jacobsen catalyst

Preparation of (*R*)-1 (*R*)-3-(nonafluorobutyl)-1,2-epoxypropane

A 100 mL flask equipped with a magnetic stirring bar was charged with Co–salen complex (604 mg, 1.00 mmol). The catalyst was dissolved in toluene (12.0 mL) and treated with acetic acid (2.00 mL, 34.9 mmol). The solution was allowed to stir at room temperature open to air for 45 min over which time the color changed from orange-red to a dark brown. The solution was concentrated *in vacuo* to leave a crude dark brown solid. The resulting catalyst residue was dissolved in ***rac*-1** (±)-3-(nonafluorobutyl)-1,2-epoxypropane (16.3 mL, 91.0 mmol) at room temperature. The reaction flask was cooled to 0 °C, and H_2O (0.864 mL, 48.0 mmol) was added in one portion. The biphasic reaction mixture was stirred at 0 °C for 7 h when **(*R*)-1** was exclusively seen. The termination of **(*S*)-1** consumption was confirmed by chiral GC analysis (30 °C, CHIRASIL-DEX CB, isothermal, t_R (*R*) = 11 min, t_R (*S*) = 12 min). The mixture was added to 3Å molecular sieve to remove water. After removal of the molecular sieves, unreacted epoxide in the mixture was transferred to a 20 mL Schlenk tube, which was cooled with liquid nitrogen, under reduced pressure. The trapped crude epoxide was left at −27 °C for 3 h and the supernatant epoxide was transferred into another 20 mL Schlenk tube through syringe rapidly under Ar, leaving unidentified solid byproducts. Obtained epoxide (1.24 g, 4.5 mmol, 4.94% yield) was preserved under Ar at −27 °C. Absolute configuration was determined by X-ray analyses (Experimental section of the chapter 3).

$[\alpha]^{18}_D$ = +3.6 (c 5.3 in AK-225®)

Preparation of (*R*)-3 (*R*)-3-[2-(tridecafluorohexyl)ethoxy]-1,2-epoxypropane.

A 100 mL flask equipped with a magnetic stirring bar was charged with Co–salen complex (670 mg, 1.11 mmol). The catalyst was dissolved in toluene (30.0 mL) and treated with acetic acid (10.0 mL, 175 mmol). The solution was allowed to stir at room temperature open to air for 45 min over which time the color changed from orange-red to a dark brown as above. The solution was concentrated *in vacuo* to leave a crude dark brown solid. The resulting catalyst residue was dissolved in ***rac*-3** (±)-3-[2-(tridecafluorohexyl)ethoxy]-1,2-epoxypropane (30.0 mL, 112 mmol) and THF (15.0 mL) at room temperature. The reaction flask was cooled to 0 °C, and H_2O (1.10 mL, 61.0 mmol) was added in one portion. The biphasic reaction mixture was stirred for 12 h under 0 °C and another 3 h under room temperature when **(*R*)-3** was exclusively seen as above. The termination of **(*S*)-3** was confirmed by chiral GC analysis (100 °C, CHIRASIL-DEX CB, isothermal, t_R (*R*) = 8.3 min, t_R (*S*) = 8.6 min). The mixture was purified by silica-gel column chromatography (hexane : AcOEt = 5 : 1, v/v). The resulting liquid was distilled (6 mmHg, 120 °C), and the obtained epoxide (5.70 g, 14 mmol, 12.1% yield) was preserved in a Schlenk tube under Ar at −27 °C. Absolute configuration was determined by X-ray analyses (*vide infra*).

$[\alpha]^{16}_{D} = +3.6$ (c 2.0 in AK-225®)

Synthetic procedure for diester 7

A 20 mL schlenk flask equipped with a magnetic stirring bar was charged with (*S,S*)-Co-salen complex (16.9 mg, 0.0280 mmol). The catalyst was dissolved in toluene (1.00 mL) and treated with acetic acid (0.200 mL, 210 mg, 3.50 mmol). The solution was allowed to stir at room temperature open to air for 1 h over which time the color changed from orange-red to dark brown as above. The solution was concentrated *in vacuo* to leave crude dark brown solid. The resulting catalyst residue was dissolved in **(*R*)-1** (386 mg, 1.40 mmol)

and THF (0.500 mL) and H_2O (0.0500 mL, 2.78 mmol) was added in one portion. The reaction mixture was stirred for overnight at room temperature. The resulting mixture was dried off to obtain crude diol. This diol was used without further purification. Subsequently, THF (2.00 mL), NEt_3 (729 mg, 7.20 mmol) and 4-bromobenzoyl chloride (615 mg, 2.80 mmol) were added into the crude diol. The reaction mixture was stirred at room for 2 d. After addition of H_2O, the mixture was dried off. Resulting material was dissolved into Et_2O (30.0 mL) and the resulting suspension was filtered through Celite® to remove organic salts $HCl{\cdot}NEt_3$. Purification by the recycling preparative GPC removed the catalyst residue to some extent. Obtained material was completely purified by recrystalization in hexane to yield diester **7** (0.515 mmol, 340 mg, 36.8% yield). Crystal for X-ray analysis was obtained in EtOH/pentane (–27 °C).

Polymerization Conditions.

A 20 mL Schlenk flask equipped with a magnetic stirring bar was charged with an initiator (0.0250 mmol), C_6F_6 (2.00 mL), and an epoxide (2.80 mmol) under Ar at room temperature. The mixture was cooled to 0 °C and trialkylaluminium (0.250 mmol, 0.250 mL of 1M toluene solution) was added in dropwise. After stirring at described temperature for desired period, the reaction was stopped by adding methanol/water (5.00 mL, MeOH : H_2O = 4 : 1, v/v) and the mixture was dried off under reduced pressure. Fluorous solvent AK-225® (15.0 mL) was added to this mixture and the resulting suspension was filtered through Celite®. The filtrate was dried off to give polymer.

References

(1) Sakakibara, K.; Nozaki, K. *Org. Biomol. Chem.* **2009**, *7*, 502-507.

(2) Sakakibara, K.; Nakano, K.; Nozaki, K. *Macromolecules* **2007**, *40*, 6136-6142.

(3) Sakakibara, K.; Nakano, K.; Nozaki, K. *Chem. Commun.* **2006**, 3334-3336.

(4) Isemura, T.; Kakita, R.; Kawahara, K. *J. Chromatography A* **2004**, *1026*, 109-116.

(5) Billouard, C.; Carlotti, S.; Desbois, P.; Deffieux, A. *Macromolecules* **2004**, *37*, 4038-4043.

(6) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307-1315.

NMR data of polymers

Atactic **poly-*rac*-1** (Table 2.2.1, runs 4-6)

^{1}H NMR: (C_6F_6) δ 2.50 to 2.90 (br, 2H), 3.89 to 4.48 (br, 3H); ^{13}C NMR: (C_6F_6) δ 36.2, 73.6, 73.8, 74.3, 74.6, 76.1, 109-124; ^{19}F NMR: (C_6F_6) δ −79.5 (br), −109 to −112 (m), −122 (br), −124 (br).

Isotactic **poly-(*R*)-1** (Table 2.3.1, run 1)

^{1}H NMR (C_6F_6): δ 2.45 to 2.90 (br, 2H), 3.80 to 4.47 (br, 3H); ^{13}C NMR (C_6F_6): δ 36.2, 74.6, 76.1, 109 to 124; ^{19}F NMR: (C_6F_6) δ−79.5 (br), −110 (q, J = 346 Hz), −122 (br), −124 (br).

Atactic **poly-*rac*-2** (Table 2.3.1, run 2)

^{1}H NMR (C_6F_6): δ 2.50 to 2.90 (br, 2H), 3.89 to 4.48 (br, 3H); ^{13}C NMR (C_6F_6): δ 36.3, 73.7, 73.8, 74.5, 74.8, 76.1, 109 to 124; ^{19}F NMR (C_6F_6) δ−79.2 (br), −109 to −112 (m), −118 (br), −119 (br), −120 (br), −121 (br), −124 (br).

Atactic **poly-*rac*-3** (Table 2.3.1, run 3)

^{1}H NMR: (C_6F_6) δ 2.51 to 2.78 (br, 2H), 3.69 to 4.17 (br, 7H); ^{13}C NMR (C_6F_6): δ 34.2, 65.9, 72.8, 74.2, 74.3, 82.0, 111 to 123; ^{19}F NMR: (C_6F_6) δ−79.2 (br), −111 (br), −119 (br), −120

(br), −121 (br), −124 (br).

Isotactic **poly-(*R*)-3** (Table 2.3.1, run 4)

^{1}H NMR (C_6F_6): δ 2.43 to 2.83 (br, 2H), 3.60 to 4.20 (br, 7H); ^{13}C NMR: (C_6F_6) δ 34.2, 65.9, 72.8, 74.3, 82.0, 111 to 123; ^{19}F NMR (C_6F_6): δ−79.2 (br), −111 (br), −119 (br), −120 (br), −121 (br), −124 (br).

Regioirregular **poly-*rac*-4** (Table 2.3.1, run 5)

^{1}H NMR (Acetone-d_6): δ 2.82 (br), 2.85 (br), 3.96 to 4.22 (m, 2H), 4.27 to 4.38 (br, 1H); ^{13}C NMR (Acetone-d_6): δ 70.6 to 72.1, 78.1 to 79.2, 120.7 to 128.3; ^{19}F NMR (C_6F_6): δ −75.0 to −75.5 (br)

Atactic **poly-*rac*-5** (Table 2.3.1, run 6)

^{1}H NMR ($CDCl_3$): δ 2.31 (m, 2H), 3.39 to 3.56 (m, 1H), 3.57 to 3.77 (m, 2H); ^{13}C NMR (C_6F_6): δ 40.96, 75.65, 75.83, 76.09, 76.23, 79.00, 131.19; ^{19}F NMR ($CDCl_3$): δ −64.82 to −65.22 (m, 3F).

Optical rotation of polymers.

poly-(*R*)-1: $[\alpha]^{18}_D$ = +13 (c 1.1 in AK-225®), **poly-(*R*)-3** $[\alpha]^{16}_D$ = +7.4 (c 2.0 in AK-225®).

MALDI-TOF Mass Measurement.

Low molecular-weight oligomers from **1** and **3** (monomer / initiator = 11.2) were prepared as above. Each of the obtained oligomers from **1** and **3** and the polymer from **4** was used for MALDI-TOF mass spectroscopy. MALDI-TOF mass spectrometric measurements were

performed on an Applied Biosystems Voyager-DE STR spectrometer equipped with a 337-nm nitrogen laser (pulse width, 3 ns), along with a delayed extraction capability. An accelerating voltage of 20 kV was used, and all mass spectra were recorded in the linear mode. In general, mass spectra from 10000 laser shots were accumulated to produce a final spectrum. Insulin (bovine pancreas 28.3; MW = 5733.50) (Nacalai) were used as an internal standard to calibrate the mass scale. Samples for analysis were prepared by mixing oligomers (1.7 wt % in C_6F_6), a matrix (1,8-dihydroxy-9(10H)-anthracenone, 5.0 wt % in THF), and a cationizing agent (CF_3CO_2Na) in the weight ratio 1/40/1. Then, 1.0 μL portions of the mixture were placed onto gold-coated plate and dried under ambient conditions.

Chapter 3

All NMR spectra of obtained polymers were recorded in hexafluorobenzene (C_6F_6), chloroholm-*d* ($CDCl_3$), DMSO-d_6 (CH_3SOCH_3) on JEOL JNM-ECP500 (^1H: 500 MHz; ^{13}C: 125 MHz; ^{19}F: 471 MHz) spectrometer. Chemical shifts are reported in ppm from following internal standards: tetramethylsilane (0 ppm) for ^1H and ^{13}C, $CF_3C_6H_5$ (–64.0 ppm) for ^{19}F. Gel permeation chromatography (GPC) analyses for polymer molecular weight were carried out using two columns (Shodex KF-804L) and tetrahydrofuran as an eluent at 40 °C at 1 mL/min calibrated by polystyrene standard (Table 3.3.1, runs 1-8). Exceptionally, the molecular weight and the molecular weight distribution of the polymer sample (Table 3.3.1, run 9) was determined at 120 °C by high temperature gel permeation chromatography (HT-GPC) on a HLC-8121GPC/HT apparatus (Tosoh Corporation) and 1,2-dichlorobenzene was employed as an eluent at a flow rate of 1.0 mL/min calibrated by polystyrene standard. Racemic fluorinated epoxides ***rac*-8-10** and optically active epoxides **(*R*)-8** and **(*S*)-9** were prepared according to following methods. **(*R*)-11**, **(*S*)-12**, **Poly-(*R*)-1** and **poly-(*R*)-3** were prepared according to the literature method.[1,2]

Syntheses of epoxides

Preparation of *rac*-3-(pentafluorophenyl)-1,2-epoxypropane *rac*-8

A 500 mL flask equipped with a magnetic stirring bar was charged with allylpentafluorobenzene (25.0 g, 120 mmol). The olefin was dissolved in CH_2Cl_2 (250 mL) and treated with MCPBA (>65.0 % purity, 50.0 g, >188 mmol). The solution was allowed to stir at room temperature for 22 h. The full consumption of the olefin was checked by ^{19}F NMR spectrum. After confirming termination of the substrate, the resulting suspension was filtered through Celite® to remove white solid. The filtrate was dried off and hexane (100 mL)

was added into the resulting solution. As a reductant, sodium thiosulfate pentahydrate $Na_2SO_3 \cdot 5H_2O$ (20.0 g, 80.6 mmol) was added into the filtrate and vigorously stirred for 30 min. The resulting suspension was filtered through Celite® again and the filtrate was dried off to give slightly yellow liquid. Resulting liquid was distilled (80.0 °C, 8.00 mmHg) to obtain colorless epoxide (18.7 g, 83.4 mmol, 69.5 % yield).

Preparation of *rac*-glycidyl-pentafluorophenyl-ether *rac*-9

A 500 mL flask equipped with a magnetic stirring bar was charged with pentafluorophenol (10.0 g, 54.3 mmol). The pentafluorophenol was dissolved in epichlorohydrin (70.9 g, 766 mmol) with K_2CO_3 (14.0 g, 101 mmol). The suspension was allowed to stir at 90 °C for 14 h. The full consumption of pentafluorophenol was checked by ^{19}F NMR spectrum. After confirming full consumption of the substrate, the resulting suspension was filtered through Celite® to remove inorganic salts. The filtrate was dried off to give slightly green liquid. The liquid was roughly purified by silica-gel column chromatography (hexane : ethylacetate = 5 : 1, v/v) to give crude epoxide. Then, hexane 2.00 mL was added into crude product to be left under –27 °C for over 1 h. Frreezed epoxide was washed by cooled hexane (–27 °C) rapidly. This manipulation was repeated three times. Obtained material was distilled (90 °C, 3.0 mmHg) to give colorless epoxide (7.93g, 33.0 mmol, 60.8% yield).

Preparation of *rac*-pentafluorostyreneoxide *rac*-10

A 500 mL flask equipped with a magnetic stirring bar was charged with pentafluorostyrene (25.0 g, 129 mmol). The olefin was dissolved in CH_2Cl_2 (300 mL) and treated with MCPBA (>65.0 % purity, 48.0 g, 180 mmol). The suspension was allowed to stir at room temperature for 3 days and reflux for 1 day. The full consumption of the olefin was checked with ^{19}F NMR spectrum. After confirmation of completely consuming substrate, the reaction flask was

cooled down at 0 °C. Reductant sodium thiosulfate pentahydrate (Na_2SO_3, 20.0 g, 80.0 mmol) was added into the reaction flask and vigorously stirred for 1 h. Hexane (500 mL) was added into the resulting suspension and filtered through Celite®. The filtrate was dried off and hexane (100 mL) was added into the resting suspension. The resulting suspension was filtered through Celite® again and the filtrate was dried off to give slightly yellow liquid. This liquid was distilled (80.0 °C, 13.0 mmHg) to obtain colorless epoxide (14.0 g, 66.6 mmol, 51.6 % yield).

Synthetic procedure of fluorinated enantiopure epoxides (*R*)-8 and (*S*)-9

Enantiopure epoxides **(*R*)-8** and **(*S*)-9** were prepared from slightly modified literature method for kinetic resolution by using Jacobsen catalyst (*R,R*)-Co-salen comple (Figure E1), as described in the Chapter 2.

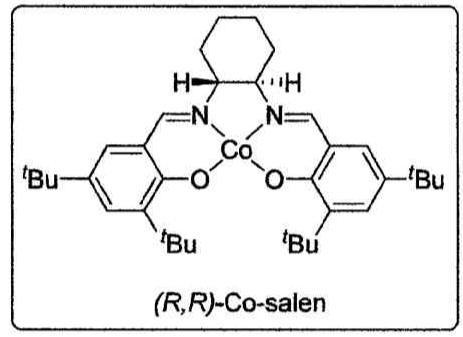


Figure E1 Jacobsen catalyst

Preparation of (*R*)-3-(pentafluorophenyl)-1,2-epoxypropane (*R*)-8

A 100 mL flask equipped with a magnetic stirring bar was charged with (*R,R*)-Co-salen complex (862 mg, 1.43mmol). The catalyst was dissolved in toluene (12.0 mL) and treated with acetic acid (1.00 mL, 1.05 g, 17.5 mmol). The solution was allowed to stir at room temperature open to air for 1 h over which time the color changed from orange-red to dark brown. The solution was concentrated in vacuo to leave crude dark brown solid. The resulting

catalyst residue was dissolved in ***rac*-8** (16.0 g, 71.4 mmol) and THF (20.0 mL) at room temperature. The reaction flask was cooled to 0 °C and H_2O (0.771 mL, 42.8 mmol) was added in one portion. The reaction mixture was stirred for 12 h under room temperature. The termination of **(*S*)-8** was confirmed by chiral GC analysis (80 °C, CHIRASIL-DEX CB, isothermal, t_R (*S*) = 21.8 min, t_R (*R*) = 22.4 min). The mixture was purified by silica-gel column chromatography (hexane : ethylacetate = 25 : 1, v/v) to completely remove diol. The resulting brown liquid was distilled to completely remove catalyst residue (80.0 °C, 8.00 mmHg) and give colorless epoxide (3.57 g, 15.9 mmol, 22.3 % yield) was preserved in a Schlenk tube under Ar at −27 °C. $[\alpha]^{20}_D = -0.676$ (c 7.65 in $CHCl_3$)

Preparation of (*S*)-glycidyl-pentafluorophenyl-ether (*S*)-9

A 100 mL flask equipped with a magnetic stirring bar was charged with (*R,R*)-Co-salen complex (317 mg, 0.525 mmol). The catalyst was dissolved in toluene (1.00 mL) and treated with acetic acid (0.200 mL, 210 mg, 3.50 mmol). The solution was allowed to stir at room temperature open to air for 1 h over which time the color changed from orange-red to a dark brown as above. The solution was concentrated in vacuo to leave a crude dark brown solid. The resulting catalyst residue was dissolved in ***rac*-9** (12.6 g, 52.5 mmol) and THF (16.0 mL) at room temperature. The reaction flask was cooled to 0 °C, and H_2O (0.504 mL, 28.0 mmol) was added in one portion. The reaction mixture was stirred for 5 h at 0 °C. The termination of **(*R*)-9** was confirmed by chiral GC analysis (60 °C, CHIRASIL-DEX CB, isothermal, t_R (*S*) = 105 min, t_R (*R*) = 107 min). The mixture was purified by silica-gel column chromatography (hexane : ethylacetate = 5 : 1, v/v) to remove resulting diol. Obtained brown liquid was distilled to completely remove catalyst residue (90 °C, 3 mmHg) and the obtained epoxide (5.67 g, 23.6 mmol, 45.0% yield) was preserved in a Schlenk tube under Ar at −27 °C. $[\alpha]^{20}_D$ = +1.08 (c 7.65 in $CHCl_3$)

Synthetic procedure for diester 13

A 20 mL schlenk flask equipped with a magnetic stirring bar was charged with (*S,S*)-Co-salen complex (Figure E2, 30.2 mg, 0.0500 mmol). The catalyst was dissolved in toluene (0.500 mL) and treated with acetic acid (0.100 mL, 105 mg, 1.75 mmol). The solution was allowed to stir at room temperature open to air for 45 min over which time the color changed from orange-red to a dark brown as above. The solution was concentrated *in vacuo* to leave crude dark brown solid. The resulting catalyst residue was dissolved in **(*R*)-8** (153 mg, 0.683 mmol) and THF (0.500 mL) to add H_2O (0.100 mL, 5.56 mmol) was added in one portion. The reaction mixture was stirred overnight at room temperature. The resulting mixture was dried off to obtain crude diol. This diol was used without further purification. Subsequently, THF (3.00 mL), NEt_3 (1.09 g, 10.8 mmol) and 4-iodobenzoyl chloride (584 mg, 2.19 mmol) were added into the crude diol. The reaction mixture was stirred at 60 °C for 18 h. After addition of H_2O, the mixture was dried off. The crude material was purified by silca gel column chromatography (hexane : ethylacetate : tetramethylethlenediamine = 5 : 1 : 0.08, v/v) and using the recycling preparative GPC. Obtained material was completely purified by reprecipitation in hexane and CH_2Cl_2 to yield diester **13** (0.303 mmol, 213 mg, 44.4 % yield). Crystal for X-ray analysis was obtained in EtOH/$CHCl_3$ (90 °C to room temperature).

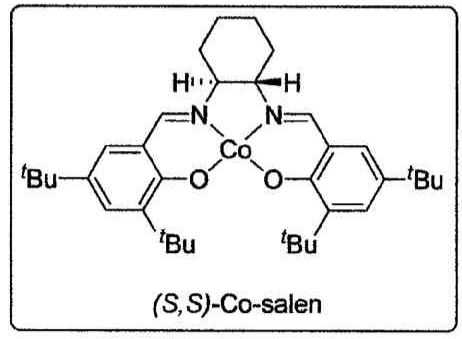


Figure E2 Jacobsen catalyst.

Synthetic procedure for monoester 14

A 20 mL schlenk flask equipped with a magnetic stirring bar was charged with (*S,S*)-Co salen complex (50.0 mg, 0.0828 mmol). The catalyst was dissolved in toluene (0.500 mL) and treated with acetic acid (0.100 mL, 1.75 mmol). The solution was allowed to stir at room temperature open to air for 45 min over which time the color changed from orange-red to dark brown as above. The solution was concentrated *in vacuo* to leave crude dark brown solid. The resulting catalyst residue was dissolved in **(*S*)-9** (918 mg, 3.82 mmol) and THF (1.20 mL) to add H_2O (0.500 mL, 27.8 mmol) was added in one portion. The reaction mixture was stirred for 3 h at room temperature. The resulting mixture was dried off to obtain crude diol. This diol was used without further purification. The crude diol was dissolve into THF (15.0 mL) and NEt_3 (2.19 g, 21.6 mmol). Solution of 4-bromobenzoyl chloride (640 mg, 2.40 mmol) in THF (3.00 mL) was added at dropwise into solution of the diol for 15 min at room temperature. The reaction mixture was stirred at room temperature for overnight. After addition of H_2O, the mixture was dried off. The crude material was purified by silca gel column chromatography (hexane : ethylacetate : tetramethylethlenediamine = 5 : 1 : 0.08, v/v) to remove extra diol. Obtained material was completely purified by reprecipitation in hexane and CH_2Cl_2 to yield monoester **14** (1.22 mmol, 597 mg, 51.0 % yield). Crystal for X-ray analysis was obtained in pentane/CH_2Cl_2 (room temperature to –27 °C).

Representative polymerization procedure of epoxides

A 20 mL Schlenk flask equipped with a magnetic stirring bar was charged with $MePPh_3Br$ as an initiator (0.0250 mmol), solvent (2.00 mL), and an epoxide (2.80 mmol) under Ar at room temperature. The mixture was cooled to 0 °C and trialkylaluminium (0.250 mmol, 0.25 mL of 1M toluene solution) was added in dropwise.

Typical isolation procedure for obtaining polymers.

After stirring at described temperature for desired period, the reaction was stopped by adding methanol/water (~5 mL, MeOH : H_2O = 4 : 1, v/v) and the mixture was dried off under reduced pressure. Then, dichloromethane (3×30.0 mL) was added to this mixture and the resulting suspension was filtered through Celite® to remove aluminium residue. The filtrate was dried off to give crude polymer. Obtained crude polymer was dissolved into CH_2Cl_2 (20.0 mL). Successively, hexane (100 mL) was added into this solution. The mixture was evaporated until the amount of solvent was ca. 20 mL. The supernatant was removed to exclude small amount of oligomers (M_n < 1500) and initiator residue. Obatined material was dried off to isolate polymer.

Other isolation procedures for obtaining polymers.

Run 5 in Table 3.3.1.

After stirring at described temperature for desired period, the reaction was stopped by adding methanol/water (ca. 5mL, MeOH : H_2O = 4 : 1, v/v) and the mixture was dried off under reduced pressure. Then, hot toluene (50.0 mL, 90 °C) was added to this mixture until solid polymer was completely dissolved. To remove aluminium residue, the resulting suspension was filtered through Celite®. Additional dichloromethane (150 mL) was added to the suspention to be filtered through Celite®. The filtrate was dried off to give white solid polymer. Obtained crude polymer was dissolved into CH_2Cl_2 (100 mL). Successively, hexane (100 mL) was added into this solution. The mixture was evaporated until the amount of solvents was ca. 30 mL. The mixture was filtered to remove small amount of oligomer (M_n < 1500) and initiator. Collected solid material was dried off to isolate polymer.

Run 10 in Table 3.3.1.

At first, dichloromethane (10.0 mL) was added to this mixture and the resulting supernatant was removed. Additional dichloromethane (10.0 mL) was added into this mixture again and the resulting supernatant was removed again to obtain white powder. The collected powder was dried off to obtain polymer.

NMR data of polymers

Atactic poly[3-(pentafluorophenyl)-1,2-epoxypropane] (Table 3.3.1, run 1, **poly-*rac*-8**). ^{1}H NMR ($CDCl_3$) δ 2.77 (br, 2H), 3.15-3.55 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 24.95, 25.02, 25.14, 25.31, 71.24, 71.44, 71.66, 71.81, 72.09, 72.20, 72.38, 78.44, 78.66, 111.93, 137.51, 140.02, 145.57; ^{19}F NMR ($CDCl_3$) δ −144.09 (br, 2F), −158.23 (br, 1F), −164.41 (br, 2F).

Isotactic poly[3-(pentafluorophenyl)-1,2-epoxypropane] (Table 3.3.1, run 2, **poly-(*R*)-8**). ^{1}H NMR ($CDCl_3$): δ 2.78 (m, 2H), 3.35 (m, 1H), 3.41-3.57 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 25.29, 72.18, 78.40, 111.76, 137.50, 140.01, 145.53; ^{19}F NMR ($CDCl_3$): δ −144.09 to −144.24 (m, 2F), −158.23 (m, 1F), −164.40 (m, 2F).

Atactic poly(glycidyl-pentafluorophenyl-ether) (Table 3.3.1, run 3, **poly-*rac*-9**). ^{1}H NMR ($CDCl_3$): δ 3.77 (br, 3H), 4.15 (br, 1H), 4.28 (br, 1H); ^{13}C NMR ($CDCl_3$): δ 68.95, 69.09, 74.99, 75.11, 78.59, 133.80, 137.53, 138.10, 141.68; ^{19}F NMR ($CDCl_3$): δ −158.28 to −158.71 (m, 2F), −164.34 to −165.04 (m, 3F).

Isotactic poly(glycidyl-pentafluorophenyl-ether) (Table 3.3.1, run 4, **poly-(*S*)-9**). ^{1}H NMR ($CDCl_3$): δ 3.77 (br, 3H), 4.09 to 4.19 (m, 1H), 4.22 to 4.32 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 69.16, 75.13, 78.62, 133.81, 137.56, 138.09, 141.74; ^{19}F NMR ($CDCl_3$): δ −156.70 to −156.89 (m, 2F), −162.79 (m, 1F), −163.09 (m, 2F).

Regioirregular poly(pentafluorostyreneoxide) (Table 3.3.1, run 5, **poly-*rac*-10**). ^{1}H NMR ($CDCl_3$): δ 3.32 to 3.96 (m, 2H), 4.70 to 4.93 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 69.80 to 70.40, 70.83 to 71.59, 72.41 to 73.79, 111.52, 137.61, 141.38, 145.49; ^{19}F NMR ($CDCl_3$): δ −143.11 to −144.46 (m, 2F), −153.9 to −154.71 (m, 1F), −161.93 to −163.51 (m, 2F).

Atactic poly[3-(phenyl)-1,2-epoxypropane] (Table 3.3.1, run 6, **poly-*rac*-11**). ^{1}H NMR ($CDCl_3$): δ 2.60 (br, 1H), 2.70 (br, 1H), 3.10 to 3.55 (m, 3H), 7.02 to 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 38.21, 38.39, 70.93, 71.05, 71.39, 71.49, 80.59, 80.67, 126.13, 128.21, 129.65, 138.89.

Isotactic poly[3-(phenyl)-1,2-epoxypropane] (Table 3.3.1, run 7, **poly-(*R*)-11**). ^{1}H NMR ($CDCl_3$): δ 2.60 (dd, J = 7.1, 11.3 Hz, 1H), 2.69 (dd, J = 4.9, 13.7 Hz, 1H), 3.20 (dd, J = 4.9, 9.8 Hz, 1H), 3.28 to 3.45 (m, 2H), 7.00 to 7.28 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 38.37, 71.44, 80.67, 126.13, 128.23, 129.61, 138.89.

Atactic poly(glycidyl-phenyl-ether) (Table 3.3.1, run 8, **poly-*rac*-12**). ^{1}H NMR (DMSO-d_6, 120 °C): δ 3.61 to 3.81 (m, 3H), 3.91 to 4.07 (m, 2H), 6.83 (m, 3H), 7.16 (m, 2H); ^{13}C NMR (DMSO-d_6, 120 °C): δ 67.71, 67.75, 68.71, 68.85, 77.28, 77.37, 77.45, 114.30, 120.05, 128.60, 158.16.

Isotactic poly(glycidyl-phenyl-ether) (Table 3.3.1, run 9, **poly-(*S*)-12**). ^{1}H NMR (DMSO-d_6, 120 °C): δ 3.63 to 3.78 (m, 3H), 3.88 to 4.06 (m, 2H), 6.83 (br, 3H), 7.15 (br, 2H); ^{13}C NMR (DMSO-d_6, 120 °C): δ 67.73, 68.85, 77.44, 114.32, 120.08, 128.64, 158.17.

Optical rotations of polymers

Poly-(*R*)-8 $[\alpha]^{22}_{D} = +5.69$ (c 1.54 in $CHCl_3$)

Poly-(*S*)-9 $[\alpha]^{21}_{D} = +3.01$ (c 0.308 in THF)

Poly-(*R*)-11 $[\alpha]^{22}_{D} = +5.45$ (c 0.400 in $CHCl_3$)

Molecular modeling of poly-(*S*)-9, poly-(*R*)-11 and poly-(*S*)-12

Starting polymer models were constructed by using Gauss View® 3.09[3] based on X-ray analyses results of polyethers whose conformations were zigzag. Calculations for minimized energies of starting models were conducted by using MM2 software implemented in Chem3D® Ultra 8.0.3 on the PC running under Windows® XP.

References

(1) Sakakibara, K.; Nakano, K.; Nozaki, K. *Chem. Commun.* **2006,** 3334-3336.

(2) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002,** *124,* 1307-1315.

(3) GaussView, Version 3.09, Dennington II, Roy; Keith, Todd; Millam, John; Eppinnett, Ken; Hovell, W. Lee; and Gilliland, Ray; Semichem, Inc., Shawnee Mission, KS, 2003.

Chapter 4

All NMR spectra were recorded in $CDCl_3$ using a 500 MHz spectrometer (^1H 500 MHz; ^{13}C 125 MHz). Chemical shifts are reported in ppm relative to the residual protiated solvent peak (7.26 ppm for $CHCl_3$) for ^1H and $CDCl_3$ (77.16 ppm) for ^{13}C. Otherwise, TMS (0.00 ppm) was used as an internal standard for ^1H. Data are presented below: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiplet resonances, br = broad), coupling constant in hertz (Hz), and signal area integration in natural numbers. Literature methods were used for known compounds ^{t}BuSO$_2$NH$_2$, 2-CO$_2$H-1,3-dithiane,[1] (*R*)- and (*S*)-carbinol dithiane (precursor of lithiated dithiane **44**),[2] (*R*)-(2,3-epoxypropyl)-benzene,[3] SESNHBoc[4] and most of aziridines.[5-8] Other aziridines ***rac*-30** and **(*S*)-40** were synthesized as follows. Spectra of newly synthesized compounds were listed in the literature except for ***rac*-49**.[9]

Synthetic procedure for aziridine *rac*-30

***rac*-1-(*Tert*-Butylsulfonyl)-2-(Benzyloxymethyl)-aziridine**

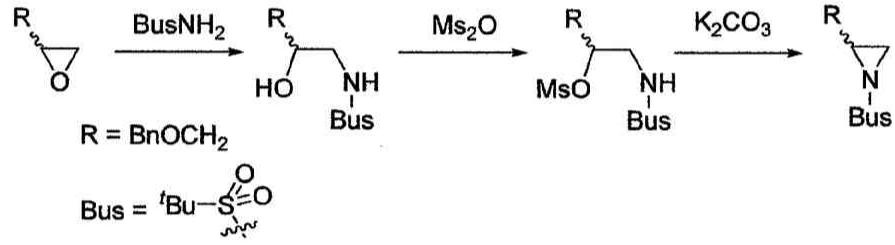
Aziridine ***rac*-30** was synthesized via the literature method with a slight modification (Scheme E1).[5] BnNEt$_3^+$Cl$^-$ (91.2 mg, 0.400 mmol) was added to a stirred suspension of Benzyl glycidyl ether (657 mg, 4.00 mmol), ^{t}BuSO$_2$NH$_2$ (823 mg, 6.00 mmol) and K_2CO_3 (55.3 mg, 0.400 mmol) in 1,4-dioxane (1.80 ml). The suspension was heated at 90 °C for 48 h, then cooled, and subsequently, the solvent was removed by rotary evaporation. Purification of the residue by column chromatography (hexane/Et$_2$O = 1:2, v/v) yielded β-hydroxysulfonamide, which was used directly in the next step.

The *β*-Hydroxysulfonamide obtained was dissolved in CH_2Cl_2 (20.0 mL) and pyridine (0.650 mL, 8.00 mmol). DMAP (49.0 mg, 0.400 mmol) and Ms$_2$O (1.04 g, 6.00 mmol)

were added to the resulting solution to stir for 2 h. Saturated aqueous K_2CO_3 solution was added to the suspension until bubbles were not longer produced, and then reduced pressure was applied. The material obtained was dissolved in CH_2Cl_2, dried over $MgSO_4$, filtered and the solvent was removed by rotary evaporation. The crude material was used directly in the next step.

The crude mesylate was dissolved in THF (30.0 mL) and H_2O (15.0 mL), and K_2CO_3 (2.20 g, 16.0 mmol) was added. Following stirring at 70 °C for 17 h, the reaction mixture was cooled and the solvents were removed under reduced pressure. Purification of the residue by column chromatography (hexane/AcOEt = 5:1, v/v) yielded a brown liquid. Complete purification was achieved by the recycling preparative SEC to obtain a colourless liquid (650 mg, 2.50 mmol, 63% yield)..

Scheme E1 Synthetic procedure for aziridine ***rac*-30**



Synthetic procedure for aziridine (*S*)-40

(2*S*)-2-Benzyl-1-[2-(trimethylsilyl)ethanesulfonyl]-aziridine

Aziridine **(*S*)-40** was synthesized via the literature method with a slight modification (Scheme E2).[10] A 20 mL Schlenk flask equipped with a magnetic stirring bar was charged with (*S*,*S*)-Co-salen complex (202 mg, 0.334 mmol). The catalyst was dissolved in toluene

(1.00 mL) and treated with acetic acid (0.200 mL, 210 mg, 3.50 mmol). The solution was stirred at room temperature open to air for 30 min; over this time the colour changed from orange-red to dark brown. The solution was concentrated *in vacuo* to yield a crude dark brown solid. The resulting catalyst residue was dissolved in (*R*)-(2,3-epoxypropyl)benzene (2.24 g, 16.7 mmol) and THF (1.00 mL). BocNHSES was added to the mixture. The reaction mixture was stirred overnight at room temperature. The resulting mixture was dried to obtain the crude material. This material was filtered by flash column chromatography (hexane/AcOEt = 1:1, v/v) to obtain a pale brown white solid.

This residue was dissolved in CH_2Cl_2 (14.0 mL) and cooled to 0 °C. TFA (14.0 mL) was added dropwise, and the reaction mixture was allowed to warm to room temperature with stirring. After 1.5 h, the solution was cooled to 0 °C and diluted with Et_2O (350 mL) and saturated aqueous $NaHCO_3$ (150 mL). The organic layer was washed with brine twice, dried over Na_2SO_4, filtered and concentrated.

The *β*-Hydroxysulfonamide obtained was dissolved in CH_2Cl_2 (120 mL) and pyridine (2.82 mL, 35.0 mmol); DMAP (208 mg, 1.70 mmol) and Ms_2O (4.36 g, 25.0 mmol) were added, and the resultant suspension was stirred for 2 h. Saturated aqueous K_2CO_3 solution was added to the suspension until bubbles were no longer produced, and put under reduced pressure. The obtained material was dissolved in CH_2Cl_2, dried over $MgSO_4$, filtered and the solvent was removed by rotary evaporation. The crude material was used directly in the next step.

The crude mesylate was dissolved in THF and H_2O (80.0 mL, 9.00 mL), and K_2CO_3 (20.0 g, 145 mmol) was added. Following stirring at 85 °C for 6 h, the reaction was cooled and the solvents were removed under reduced atmosphere. Purification of the residue by column chromatography (hexane/AcOEt = 5:1, v/v) yielded a colourless liquid (2.80 g, 9.40 mmol, 56% yield). Spectral data coincided with the previous data.[10]

Typical procedure A

A solution of dithiane 1,3-dithiane or 2-Ph-1,3-dithiane (0.550 mmol, 1.10 equiv) in THF (3.00 mL) was cooled to −78 °C and treated with a ~1.6 M hexane solution of ^{n}BuLi (0.550 mmol, 1.10 equiv) dropwise via syringe. After 2 h, a solution of the selected aziridine (0.500 mmol) in THF (2.00 mL) was added dropwise to the reaction mixture at −78 °C via syringe. The resultant solution was warmed to 0 °C and stirred for 3 h, and then poured into excess HCl in MeOH and concentrated *in vacuo*. Flash chromatography on silica gel, using AcOEt/hexane as eluant, provided the ring-opening product.

Typical procedure B

A solution of 2-CO_2H-1,3-dithiane (90.4 mg, 0.550 mmol, 1.10 equiv) in THF (3.50 mL) was cooled to 0 °C and treated with a ~1.6 M hexane solution of ^{n}BuLi (1.10 mmol, 2.20 equiv) dropwise via syringe. After 10 min, a solution of assigned aziridine (0.500 mmol) in THF (2.00 mL) and TMEDA (0.195 mL, 1.30 mmol, 2.60 equiv) was added dropwise to the reaction mixture at 0 °C via syringe. The resultant solution was warmed to 65 °C and stirred for 13 h. The resultant mixture was poured into excess HCl in MeOH and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (~50 mL), filtered and concentrated *in vacuo*. The resulting oil was dissolved in CH_2Cl_2 (5.00 mL), DMAP (7.33 mg, 0.0600 mmol) and DCC (124 mg, 0.600 mmol). The suspension was stirred for 1 h at room temperature. Flash chromatography on silica gel, using AcOEt/hexane as eluant, provided the γ-lactam.

Typical procedure C

A solution of 2-Me_3Si-1,3-dithiane (106 mg, 0.550 mmol, 1.10 equiv) in Et_2O (3.00 mL) was cooled to −78 °C and treated with a ~1.5 M pentane solution of ^{t}BuLi (0.550 mmol,

1.10 equiv) dropwise via syringe. The resulting solution was warmed to −45 °C over 1 h and then cooled to −78 °C. A solution of assigned aziridne (0.500 mmol) in Et_2O (2.00 mL) was added dropwise to the reaction mixture at −78 °C via syringe. The resultant solution was warmed to −20 °C over 15 min, and stirred for an additional 3 h at 0 °C. The isolation procedure was the same as described in typical procedure A.

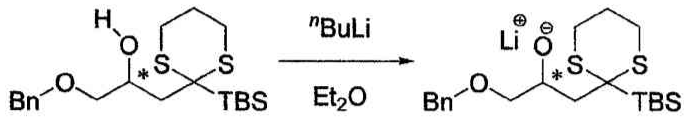
Typical procedure D

The molar ratio was the same as described in typical procedure A. The resultant solution was warmed to 30 °C and stirred for 12 h. The isolation procedure was the same as described in typical procedure A.

Typical procedure E

A solution of carbinol (250 mg, 0.627 mmol, 1.25 equiv) in Et_2O (4.00 mL) was cooled to 0 °C and treated with a ~1.6 M hexane solution of ^{n}BuLi (0.627 mmol, 1.25 equiv) dropwise via syringe (Scheme E3). The resulting solution was cooled to −78 °C. A solution of assigned aziridne (0.500 mmol) and HMPA (0.41 mmol, 0.820 equiv) in Et_2O (2.00 mL) was added dropwise to the reaction mixture at −78 °C via syringe. The resultant solution was warmed to 0 °C, and stirred for an additional 3 h at 0 °C. The resultant mixture was poured into aqueus NH_4Cl and concentrated *in vacuo*. Flash chromatography on silica gel, using AcOEt/hexane as eluant, yielded the ring-opening product.

Scheme E3 Preparation of lithiated dithiane **44**



(*R*) or (*S*)-Carbinol Lithiated dithiane **44**

Deprotection procedure

Deprotection of *rac*-18 to *rac*-47 2-Amino-1-phenylbutane

A suspension of Raney Ni in water (from TCI, ~3 mL)was added to a solution of dithiane ***rac*-24** (260 mg, 0.696 mmol) in EtOH (15.0 mL). The mixture was stirred under H_2 (1 atm) for 1 h at 80 °C. The resulting mixture was diluted with CH_2Cl_2 (~50 mL) and H_2O (~100 mL). The aquaios layer was extracted with CH_2Cl_2 (~50 mL×2) twice, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by using the recycling preparative GPC. The dithiane-removed material obtained (~60 mg, 0.223 mmol, 32.0 % yield) was used directly in the next step.

Next, *tert*-butylsulfamide moiety was deprotected by using the condition developed by Weinreb.[11] The crude product was purified by flash chromatography (AcOEt/MeOH/NEt_3 = 9:1:0.05, v/v, ref 0.2) to afford the amine ***rac*-47** (16.8 mg, 0.113 mmol, 2 steps 16.2 % yield). Spectral data coincided with the previous data.[12]

Deprotection of (*S*)-43 to (*S*)-48

(*S*)-1-(2-Phenyl-1,3-dithian-2-yl)-2-[*tert*-Butoxy-carbonyl]-3-phenyl-propane

A 80 mL Schlenk flask equipped with a magnetic stirring bar was charged with **(*S*)-43** (1.30g, 2.15 mmol) and DMAP (26.3 mg, 0.263 mmol). They were dissolved in CH_2Cl_2 (10.0 mL) and NEt_3 (435 mg, 4.30 mmol). Boc_2O (1.10 g, 5.00 mmol) was dropped in one portion into the resultant solution. The reaction mixture was stirred for 2 h at room temperature and overnight at 40 °C. The solution was concentrated *in vacuo* and the residue was treated with EtOAc and excess 1M HCl. The EtOAc was washed with brine twice, dreid ($NaSO_4$) and concentrated to leave viscuos solid. The material obtained was used without further purification.

The crude material in THF 20 mL was treated with TBAF in 1M THF solution (10 mL). Following stirring at room temperature for 2 h, the solvents were removed under reduced

pressure. Purification of the residue by column chromatography (hexane/AcOEt = 5:1, v/v) yielded a colorless liquid **(*S*)-48** (1.01 g, 2.35 mmol, 90% yield).

Deprotection of *rac*-27 to *rac*-49

3-(*tert*-butylsulfonamide)-1,4-diphenylbutane-1-one

To a solution of ***rac*-27** (180 mg, 0.400 mmol) in acetone (3.50 mL) was added MeI (0.800mL, 12.8 mmol) and the solution heated under reflux for 1 h. A few drops of H2O were then added to it and the solution heated under reflux for 16 h. Solvents were removed under reduced pressure. Cosumption of ***rac*-27** was confirmed by TLC. Purification of the residue by column chromatography (hexane/AcOEt) yielded a colorless liquid ***rac*-49** (80.0 mg, 0.222 mmol, 56 % yield). The characteristics of ***rac*-49** were as follows: white solid; mp 88–89 °C; R_f = 0.15 (hexane/EtOAc = 5:1, v/v); ^{1}H NMR ($CDCl_3$): δ 1.24 (s, 9H), 3.07 (d, J = 7.1 Hz, 2H), 3.28 (ddd, J = 4.9, 17.7, 36.3 Hz, 2H), 4.06 (m, 1H), 4.78 (d, J = 10.3 Hz, 3H), 7.14 to 7.38 (m, 5H), 7.46 (t, J = 7.7 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.89 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 24.06, 41.46, 42.72, 54.26, 60.04, 126.96, 128.16, 128.76, 128.80, 129.70, 133.67, 136.79, 138.02, 199.14; IR (KBr disc): 1001, 1022, 1067, 1126, 1215, 1304, 1366, 1448, 1684, 2872, 2932, 2976, 3028 cm^{-1}. Calcd. for $C_{20}H_{25}NO_3S$: C, 66.82; H, 7.01; N, 3.90. Found: C, 66.66; H, 7.13; N, 3.63.

References

(1) Juaristi, E.; Tapia, J.; Mendez, R. *Tetrahedron* **1986**, *42*, 1253-1264.

(2) Smith, A. B., III; Boldi, A. M. *J. Am. Chem. Soc.* **1997**, *119*, 6925-6926.

(3) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307-1315.

(4) Neustadt, B. R. *Tetrahedron Lett.* **1994**, *35*, 379-380.

(5) Hodgson, D. M.; Humphreys, P. G.; Miles, S. M.; Brierley, C. A. J.; Ward, J. G. *J. Org. Chem.* **2007**, *72*, 10009-10021.

(6) Hodgson, D. M.; Fleming, M. J.; Stanway, S. J. *Org. Lett.* **2005**, *7*, 3295-3298.

(7) Gontcharov, A. V.; Liu, H.; Sharpless, K. B. *Org. Lett.* **1999**, *1*, 783-786.

(8) Alonso, D. A.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 9455-9461.

(9) Sakakibara, K.; Nozaki, K. *Org. Biomol. Chem.* **2009**, *7*, 502-507.

(10) Kim, S. K.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2004**, *43*, 3952-3954.

(11) Sun, P.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1997**, *62*, 8604-8608.

(12) Haak, E.; Siebeneicher, H.; Doye, S. *Org. Lett.* **2000**, *2*, 1935-1937.

List of Publications

Original Papers

[1] An Efficient Pd(II)-Based Catalyst System for Carboxylation of Aromatic C-H bond by Addition of a Phosphenium Salt

Ken Sakakibara, Makoto Yamashita, Kyoko Nozaki *Tetrahedron Letters* **2005**, *46*, 959-962.

[2] Regio-Contorlled Ring-Opening Polymerization of Perfluoroalkyl-Substituted Epoxides

Ken Sakakibara, Koji Nakano, Kyoko Nozaki *Chemical Communications* **2006**, 3334-3336.

[3] Regioregular Polymerization of Fluorine-Containing Epoxides

Ken Sakakibara, Koji Nakano, Kyoko Nozaki *Macromolecules* **2007**, *40*, 6136-6142.

[4] Ring-opening reaction of Bus- and SES-protected aziridines using lithiated dithianes

Ken Sakakibara, Kyoko Nozaki *Organic & Biomolecular Chemistry* **2009**, *7*, 502-507.

[5] Sulfide-Bearing Phosphine Ligands: Their Pd Complexes and Application to Co-polymerizations of Olefins and CO

K. Sakakibara, K. Nozaki *Bulletin of the Chemical Society of Japan* **2009**, *82*, 1006-1008.

[6] Rhodium Catalysts Bearing Mixed Thioether-Phosphine Ligands for Carbonylation of Methanol

K. Sakakibara, K. Nozaki *Bulletin of the Chemical Society of Japan* **2009**, *82*, 1009-1011.

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Ken Sakakibara