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Asymmetric polymerization of *N*-substituted maleimides with organolithium – bisoxazolines complex

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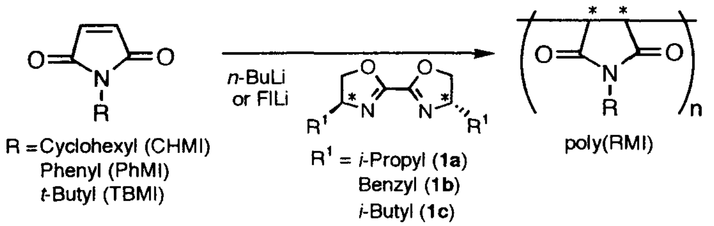
Summary

Asymmetric anionic polymerizations of achiral *N*-substituted maleimide (RMI) (*N*-cyclohexyl (CHMI), *N*-phenyl (PhMI), *N*-*tert*-butyl (TBMI)) by *n*-butyllithium (*n*-BuLi) or fluorenyllithium (FlLi) complexes of chiral bisoxazoline derivatives in toluene gave optically active polymers ($[\alpha]^{25}_{435}$ – 2.9° to – 8.2°). The polymers prerared with initiator of *n*-BuLi – 2,2'-bis(4,4'-isopropyl-1,3-oxazoline) showed negative specific rotations (poly(RMI), $[\alpha]^{25}_{435}$ – 5.8° to – 8.2°) which were greater than those ($[\alpha]^{25}_{435}$ – 2.9° to – 5.9°) with other chiral 2,2'-bis(4,4'-alkyl-1,3-oxazoline) (alkyl group = *iso*-butyl and benzyl).

Introduction

In recent years there has been very interesting research on the syntheses of optically active polymers (1). Asymmetric polymerization can be classified into *asymmetric synthesis polymerization* (2), *helix sense selective polymerization* (3) and *enantiomer selective polymerization* (4).

There have been many reports on asymmetric synthesis polymerizations and copolymerizations of *N*-substituted maleimide (RMI) which is a 1,2-disubstituted cyclic olefin type monomer. The authors reported that chirality is induced to polymer main chains of optically active RMI bearing chiral substituent by the side chain chromophors (5). On the other hand, polymerizations of achiral monomers initiated by optically active compounds are efficient methods to prepare optically active polymers by catalytic amount of chiral species. In previous studies, anionic homopolymerizations of achiral RMI were carried out with complexes of *n*-butyllithium (*n*-BuLi) with (–)-sparteine (Sp) to obtain optically active polymers (6). The obtained poly(RMI) can contain stereogenic centers,



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(*S*, *S*) or (*R*, *R*) in the polymer main chain. The chirality of the poly(RMI) may be ascribed to the excessive chiral centers of (*S*, *S*) or (*R*, *R*). However, the influence of chiral ligands on asymmetric synthesis polymerizations of achiral RMI is not found yet. Because no example has been known of polymerization of RMI using ligands except for Sp derivatives and 2,3-dimethoxy-1,4-bis(dimethylamino)butane (DDB) (6). The authors attempted to clarify the structure and the chiroptical properties of the poly(RMI) initiated by other chiral ligands. The authors report here that homopolymerizations of achiral RMI are performed with organolithium / chiral 4,4'-disubstituted bisoxazolines in toluene, and that the obtained polymers have specific rotation. Chiral bisoxazolines have recently been employed as ligands in wide variety of metal-catalyzed asymmetric reactions (7). The advantages of the bisoxazolines are capable of designing to oxazoline ring bearing different 4-positional substituents by various amino alcohols.

Experimental

RMI Monomers. RMI were prepared from maleic anhydride and the corresponding primary amine by the usual methods (8). Melting points and boiling points of RMI are as follows: CHMI mp 89°C, PhMI mp 90-91°C, TBMI bp 55°C/2 mmHg.

Reagents and Solvents. Commercially available *n*-BuLi in a hexane solution was used without further purification. Dimethylmaleic anhydride was obtained from Aldrich Chemical Co. Cyclohexylamine and diisopropylamine were distilled before use. Solvents; toluene (Tol), and methanol were purified by the usual methods. Bisoxazolines were synthesized by the published procedure (9). 2,2'-Bis[(4*S*)-(1-methylethyl)]-1,3-oxazoline (**1a**) $[\alpha]_D = -159.8°$ (c 1.0 gdl^{-1}, $CHCl_3$), 2,2'-Bis[(4*S*)-benzyl]-1,3-oxazoline (**1b**) $[\alpha]_D = -43.8°$ (c 1.0 gdl^{-1}, EtOH), 2,2'-Bis[(4*S*)-(2-methylpropyl)]-1,3-oxazoline (**1c**) $[\alpha]_D = -68.5°$ (c 1.0 gdl^{-1}, $CHCl_3$)

Polymerization. Anionic homopolymerizations of RMI were carried out in toluene under dry nitrogen. Chiral 4,4'-disubstituted bis(oxazolines) and *n*-BuLi were mixed at 0°C just before use. An initiator solution was added to the monomer solution cooled to 0°C. The reaction was terminated by the addition of a few drops of methanol. The polymer was precipitated in a large amount of methanol containing a small amount of hydrochloric acid, separated by filtration, and purified by re-precipitation from chloroform-methanol or THF-methanol system three times.

Measurements . Gel permeation chromatography (GPC) measurement of the polymer was done with HSG-10, 15, 20, 40H column (Shimadzu), and the molecular weight was calibrated with standard polystyrene. Hg-line or D-line specific rotations were measured with a Jasco DIP-140 (Japan Spectroscopic Co.) at 25 °C (quartz cell length: 10 cm; 1.0 g dl^{-1} in THF or $CHCl_3$). Circular dichroism (CD) spectra were obtained at 25 °C using a Jasco J-20C (Japan Spectroscopic Co.), equipped with a xenon source and a computing data processor (quartz cell length: 0.1 and 0.2 mm; *ca* 0.5 – 1.0 g dl^{-1} in THF) Ultraviolet (UV) spectra were obtained with a Shimadzu UV 2200 spectrophotometer (quartz cell length: 1 mm; *ca* 0.5 – 1.0 g dl^{-1} in THF) ^1H and ^{13}C NMR spectra of the polymers were measured in chloroform-*d* at room temperature in the presence of tetramethylsilane (TMS) as an internal standard using a JEOL EX-270 (^1H, 270

MHz, ^{13}C, 68.7 MHz) spectrometer.

Model Compound of poly(CHMI): 3,4-Dimethyl-*N*-cyclohexylsuccinimide (10)

3,4-Dimethyl-*N*-cyclohexylmaleimide: Dimethylmaleic anhydride (2.27 g, 18.0 mmol) was dissolved in 40 ml of $CHCl_3$. This solution was stirred magnetically while freshly distilled cyclohexylamine (2.00 ml, 18.0 mmol) was added dropwise, after which it was stirred at 50 °C for 24 h. The mixture was concentrated under reduced pressure to leave the residue, which was purified by chromatography (silica gel, hexane/EtOAc = 4/1, v/v). 3,4-Dimethyl-*N*-cyclohexylmaleimide was recrystallized from cyclohexane to yield 2.82 g (13.6 mmol, 76 %).

colorless prisms, mp 65.5 - 66.5 °C, ^1H NMR ($CDCl_3$) δ 1.12 - 1.39 (2H, m, cyclohexyl H-4), 1.60 - 1.68 (2H, m, cyclohexyl CH_2), 1.79 - 1.84 (2H, m, cyclohexyl CH_2), 1.93 (6H, s, Me), 1.95 - 2.07 (2H, m, cyclohexyl CH_2), 3.87 (1H, m, cyclohexyl H-1)

***cis*-3,4-Dimethyl-*N*-cyclohexylsuccinimide:** A suspension of 10 % Pd-C (0.100 g) and 3,4-Dimethyl-*N*-cyclohexylmaleimide (0.83 g, 4.00 mmol) in EtOH (20 ml) was stirred at rt under 1 atm of H_2 for 12 h. The catalyst was filtered off through Celite pad, and the Celite was washed with EtOH. The filtrate was concentrated to afford an oil, which was purified by chromatography (silica gel, hexane/EtOAc = 4/1, v/v) to give *cis*-3,4-dimethyl-*N*-cyclohexylsuccinimide 0.83 g (3.90 mmol, 99 %).

colorless oil, ^1H NMR ($CDCl_3$) δ 1.13 - 1.37 (2H, m, cyclohexyl H-4), 1.54 - 1.65 (2H, m, cyclohexyl CH_2), 1.69 - 1.84 (2H, m, cyclohexyl CH_2), 2.13 (2H, m, cyclohexyl CH_2), 2.85 (2H, m, H-3, 4), 3.93 (1H, m, cyclohexyl H-1); ^{13}C NMR ($CDCl_3$) δ 11.20 (Me), 24.73 (cyclohexyl C-4), 25.50 (cyclohexyl C-3, 5), 28.47 (cyclohexyl C-2,6), 37.70 (C-3, 4), 50.95 (cyclohexyl C-1), 180.11 (C-2, 5)

***trans*-3,4-Dimethyl-*N*-cyclohexylsuccinimide**: *cis*-3,4-Dimethyl-*N*-cyclohexylsuccinimide (0.21 g, 1.00 mmol) was dissolved in DMSO-d_6 (0.5 ml) in an NMR tube. A drop of diisopropylamine was added to the solution, and the tube was pleaced in a 60 °C water bath. Continued epimerization (monitored periodically with ^{13}C NMR) for 48 days gave *cis*:*trans* ratio 33:67, as judged from ^{13}C NMR peak intensities. The reaction mixture was concentrated under reduced pressure to leave the residue, which was purified and separated on silica gel (hexane/EtOAc = 9/1, v/v) to afford pure *trans*-3,4-dimethyl-*N*-cyclohexylsuccinimide 0.11 g (0.55 mmol, 55 %) and recovered starting material (*cis* derivative) 0.06 g (0.27 mmol, 27 %).

colorless oil, ^1H NMR ($CDCl_3$) δ 1.21 - 1.35 (2H, m, cyclohexyl H-4), 1.55 - 1.67 (2H, m, cyclohexyl CH_2), 1.79 - 1.89 (2H, m, cyclohexyl CH_2), 2.09 - 2.19 (2H, m, cyclohexyl CH_2), 2.31 (2H, m, H-3, 4), 3.93 (1H, m, cyclohexyl H-1); ^{13}C NMR ($CDCl_3$) δ 15.04 (Me), 24.94 (cyclohexyl C-4), 25.75 (cyclohexyl C-3, 5), 28.57, 28.9 (cyclohexyl C-2, 6), 42.70 (C-3, 4), 51.38 (cyclohexyl C-1), 179.46 (C-2, 5)

Results and discussion

Table shows the results of the homopolymerization of RMI with the 2,2'-bis(4,4'-alkyl-1,3-oxazoline) – organolithium complexes in toluene at 0°C. In every case, an optically active polymer was obtained. The ^1H NMR of the polymer showed no peaks based on 4,4'-disubstituted bis(oxazolines). The specific rotations of polymers were influenced by *N*-substituent of maleimide. For the polymerization using chiral oxazoline

1a, all RMI polymers showed negative specific rotations. The specific rotation ($[\alpha]_{435}^{25}$ −8.2°; run 3) of poly(TBMI) was greater than those of poly(CHMI) ($[\alpha]_{435}^{25}$ −7.4°; run 1) and poly(PhMI) ($[\alpha]_{435}^{25}$ −5.8°; run 2). The specific rotation of polymers obtained increased in proportion to bulkiness of *N*-substituent (*tert*-butyl > cyclohexyl > phenyl).

The relationship between the specific rotation of polymers and the substituent at 4-position in oxazoline was described below. When the polymerization of PhMI was carried out with three bisoxazoline ligands **1a-c** - *n*-BuLi complexes, the specific rotations of the polymers obtained were influenced by 4-positional substituent of oxazoline. Using **1a** and **1c**, the specific rotation of polymers were larger, compared with the polymer obtained by use of **1b**. The result suggests that much greater bulkiness of 4-positional substituent induced chirality to the polymer main chain. In addition, polymers initiated by FlLi were similar to those for the polymers initiated by *n*-BuLi.

Table Anionic Polymerization of RMI with Bis(oxazoline) 1 – Organolithium Complexes

run	RMI (mol/l)	initiator [a]	Time (h)	Yield (%)	M_n [b] x 10^{-3}	M_w/M_n	$[\alpha]_{435}^{25}$ [c] (deg.)
1	CHMI (0.28)	^{n}BuLi-**1a**	24	69	4.84	1.74	−7.4
2	PhMI (0.28)	^{n}BuLi-**1a**	24	62	3.46	1.24	−5.8
3	TBMI (0.64)	^{n}BuLi-**1a**	24	36	12.74	2.69	−8.2
4	CHMI (0.14)	^{n}BuLi-**1b**	19	55	4.64	1.60	−4.5
5	PhMI (0.28)	^{n}BuLi-**1b**	24	61	3.65	1.24	−2.9
6	PhMI (0.28)	^{n}BuLi-**1c**	24	32	3.60	1.12	−5.9
7	CHMI (0.28)	FlLi-**1a**	20	96	6.61	2.57	−5.9
8	PhMI (0.28)	FlLi-**1a**	20	69	3.86	1.39	−5.7

a) 10 mol%, [RLi]/[Ligand] = 1.0/1.2, b) By GPC
c) c = 1.0 gdl^{-1}, l = 10 cm, THF (run 1, 3, 4, 6, 7, 8), $CHCl_3$ (run 2, 5)

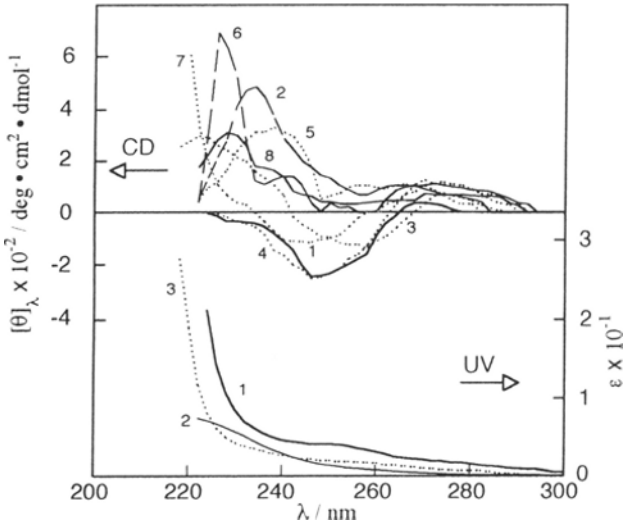


Figure 1 CD and UV spectra for poly(RMI): (1) run 1, (2) run 2, (3) run 3, (4) run 4, (5) run 5, (6) run 6, (7) run 7, (8) run 8

Figure 1 shows the typical UV and CD spectra of the polymers. Characteristic CD peaks due to electronic transitions based on carbonyl and phenyl groups were observed at the range from 290 nm to 220 nm. These results suggest that the optical rotations of poly(RMI) were ascribed to main chain chirality induced by chiral 2,2'-bis(4,4'-alkyl-1,3-oxazoline) – lithium complexes.

Figure 2 shows ^{13}C NMR spectra of the polymers obtained with chiral oxazoline **1a** - *n*-BuLi (a) and *n*-BuLi only (b). The signals based on the polymer main-chain appeared at about 40 ppm and 43 ppm in their ^{13}C NMR spectra. The higher magnetic field peak

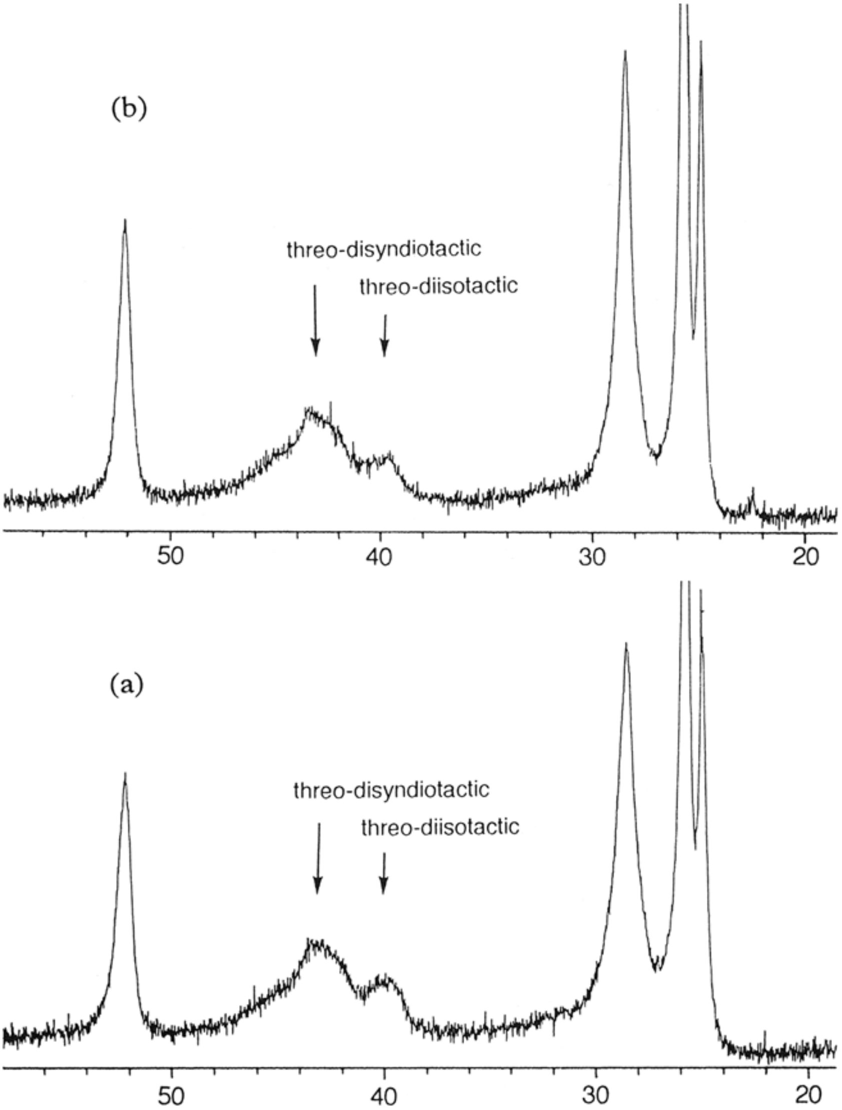


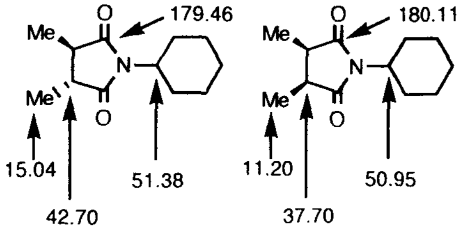
Figure 2 ^{13}C NMR spectra for poly(CHMI) obtained with (a) *n*-BuLi – **1a**, (b) *n*-BuLi in toluene

for the polymer (lower magnetic field : higher magnetic field = 73 : 27) was larger compared with that initiated by *n*-BuLi only (80 : 20).

The anionic polymerization of RMI proceeds via stereoregularity of *cis* and *trans* addition. The chirality of polymer obtained from RMI such as C_2 symmetrical monomer was attributed to the asymmetric center of the main chain. Cubbon reported that the formation of poly(RMI) containing *cis* configuration of the main chain is difficult because of steric hindrance (11). In order to establish stereochemistry for poly(CHMI), model compounds of poly(CHMI), *i. e.*, *cis-* and *trans*-3,4-dimethyl-*N*-cyclohexylsuccinimide, were synthesized from dimethylmaleic anhydride and cyclohexylamine (10). Reaction of dimethylmaleic anhydride and cyclohexylamine in $CHCl_3$ at 50 °C and subsequent *in situ* cyclization of the resulting *N*-cyclohexylmaleamic acid gave 3,4-dimethyl-*N*-cyclohexylmaleimide. The maleimide derivative was reduced by catalytic hydrogenation to *cis*-3,4-dimethyl-*N*-cyclohexyl-succinimide (*cis*-**2**). The *trans* derivative (*trans*-**2**) was synthesized by equilibrium epimerization of *cis*-**2** with diisopropylamine in DMSO-d_6 at 60 °C. The *cis:trans* ratio of the reaction mixture was judged by ^{13}C NMR peak heights to afford a 33:67 mixture of diastereomer. The diastereomers were readily separated by column chromatography on silica gel.

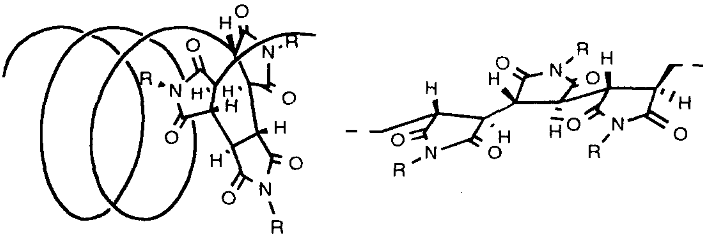
The assignment of the model compounds and their ^{13}C NMR chemical shifts in $CDCl_3$ are shown in Figure 3. A particularly remarkable observation was the chemical shift difference between the carbons at positions 3 and 4 corresponding to the main chain of poly(RMI). The signal for methine carbons of *trans* compound appeared at 42.70 ppm and shifted to lower magnetic field than that for *cis* compound (37.70 ppm). The peaks assigned to the poly(CHMI) main-chain exhibited *only* at about 40 ppm and 43 ppm, no peaks at about 37 ppm. This suggests that the polymerization of RMI proceeded *trans* addition only. When the polymerizations of RMI proceed via *trans* addition, the structure of the resulting polymer has two configurations, that is, threo-diisotactic and threo-disyndiotactic structures (Figure 4). The threo-disyndiotactic polymer cannot have optical activity because the configuration of main chain is an equivalent mixture of chiral centers (*R*, *R*) and (*S*, *S*). The main-chain signals of the polymer prepared with radical polymerizations exhibited only one single peak at about 43 ppm which was assigned to main-chain of threo-disyndiotactic structures. The peak at the higher magnetic field for the polymer initiated by the **1a** - *n*-BuLi complex or *n*-BuLi only was assigned to threo-diisotactic structures. Using bisoxazoline derivatives in the polymerization of RMI, the proportion of threo-diisotactic structure increased. However, it seems that the obtained poly(RMI) does not consist of complete helix structures because the $[\alpha]^{25}_{435}$ for the polymer was too small. Thus, the optical rotations of poly(RMI) are practically attributable to excessive chiral center of (*R*, *R*) or (*S*, *S*) on the main chain (Figure 5). The results suggest that the optical rotations of poly(RMI) were ascribed to main chain chirality induced by chiral 2,2'-bis(4,4'-alkyl-1,3-oxazoline) – organolithium complexes. Poly(CHMI) initiated by Sp - *n*-BuLi complex showed high specific rotations ($[\alpha]_D$ – 39.5°, $[\alpha]^{25}_{435}$ – 74.9°) (6). But polymers obtained with bisoxazoline as chiral ligands showed low specific rotations ($[\alpha]^{25}_{435}$ – 2.9° to – 8.2°). The authors assumed that the Sp - lithium complex forming a six-membered chelate was more rigid than bisoxazoline complexes forming five-membered chelates (Figure 6). Since Sp was capable of building better asymmetric field at growth-end of polymers, the obtained polymers showed high specific rotation.

In conclusion, the anionic polymerizations using bisoxazolines - organolithium complexes produced optically active poly(RMI). The main-chain structures of the polymers obtained were mixtures of threo-diisotactic and threo-disyndiotactic structures. The polymers obtained with bisoxazoline ligands included more threo-diisotactic structure.



trans-2 *cis*-2

Figure 3 Model compound of poly(CHMI):
^{13}C NMR chemical shifts ($CDCl_3$, ppm from TMS)



threo-diisotactic threo-disyndiotactic

Figure 4 Poly(RMI) structures

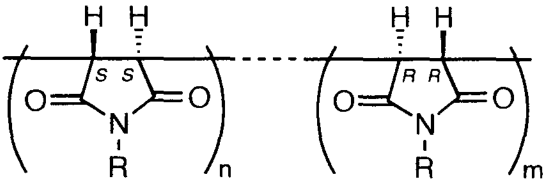
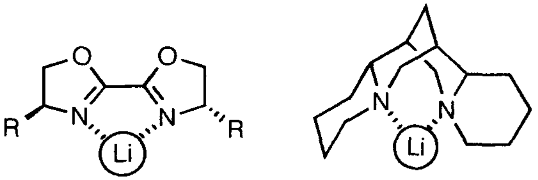


Figure 5 Optically active poly(RMI)



Bisoxazoline - Li (–)-Sparteine - Li

Figure 6 Chiral ligands - Lithium complexes

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