## A Catalytic and Mechanistic Investigation of Optically Active Helical Poly[3-(9-alkylfluoren-9-yl)propylene oxide]s in the Enantioselective Addition of Ethylmagnesium Bromide to Aldehydes

Anlin Zhang, Nianfa Yang,\* Liwen Yang,\* and Dan Peng

Key Laboratory of Environmentally Friendly Chemistry and Applications of Ministry of Education, College of Chemistry, Xiangtan University, Hunan 411105, P. R. China

(E-mail: nfyang@mail.sdu.edu.cn)

Optically active helical poly[(S)-3-(9-alkylfluoren-9-yl)propylene oxide]s (poly-(S)-AFPOs) without additional stereogenicunits were used to induce the enantioselective addition ofethylmagnesium bromide to aldehydes, giving up to 53% ee ofthe products. It is the helically chiral environment rather than thepoint chirality that governs the enantioselective inducementof the addition reaction. Poly-(S)-AFPOs could be recoveredsimply, post-treated conveniently and used repeatedly.

The helical conformation is inherently chiral, and right- and left-handed helices are exactly mirror images of each other; therefore, they cannot be superimposed.<sup>1</sup> Accordingly, if one of the helices could be selectively synthesized, induced, or constructed for molecules, supramolecules, oligomers, or polymers, they should be optically active without any additional configurationally chiral components. Inspired by sophisticated biological helices that are of key importance for their elaborate functions in living systems involving molecular recognition<sup>2</sup> and catalytic activity,<sup>3</sup> chemists have challenged to develop artificial helical polymers, supramolecules, and oligomers with a controlled handedness, not only to mimic biological helices and functions but also for their potential applications in materials science, such as ferroelectric liquid crystals and nonlinear optical materials, sensing specific molecules, the separation of enantiomers, and asymmetric catalysis.<sup>4</sup> So far, some helical polymers have been applied to a variety of asymmetric catalytic reactions. Such as palladium-catalyzed allylic substitution reaction,<sup>5</sup> asymmetric hydrogenation reaction,<sup>6</sup> asymmetric hydrogen-transfer reaction,7 epoxidation of chalcone derivatives,8 asymmetric hydrosilylation of styrene,9 allylation reaction of benzaldehyde with allyltrichlorosilane,<sup>10</sup> the asymmetric Henry reaction,<sup>11</sup> and asymmetric aldol reaction.<sup>12</sup> These static and dynamic helical polymeric catalysts showed enantioselectivity mainly based on their helical chirality, thus producing optically active products with a modest enantiomeric excess.

Our previous research work has shown that helical poly[3-(9-alkylfluoren-9-yl)propylene oxide]s (poly-AFPOs)<sup>13</sup> had the following advantages and characteristic: a) mild synthetic conditions and high isolated yields; b) a highly stable helical structure, even in solution, with no racemization or denaturation; c) modifiable side chains onto which catalytically active sites can be introduced without affecting the helical structure; d) additional stereogenic units and multiactive coordination sites such as N, P, and S are not included. Most nonracemic helical polymers are unable to fulfill all of these requirements. Recently, our group used poly-AFPOs as chiral ligands in the addition of methyllithium to aldehydes, giving the products in moderate to good yields and with high enantioselectivities up to 88% ee. We hold that it is the helically chiral environment rather than the point chirality that govern the enantioselective inducement of the addition reaction.<sup>14</sup> Moreover, to our knowledge, there is no report about polymer-catalyzed asymmetric addition reaction of ethylmagnesium bromide with aldehyde. Given this, the present study takes the lead in research on helical polyethers as chiral ligands in the asymmetric reaction of ethylmagnesium bromide with aldehydes.

We investigated the ability of poly[(S)-3-(9-alkylfluoren-9yl)propylene oxide]s 4 to promote asymmetric addition of ethylmagnesium bromide to aldehydes. Under the optimal conditions, treatment of benzaldehyde with EtMgBr in the presence of 4a, 4b, 4c, and 4d respectively, afforded (R)-1phenyl-1-propanol in 57-75% yields and 17-28% ee (Table 1, Entries 1-4). The enantioselectivity of 4a was slightly higher than that of 4b, 4c, and 4d. Then a series of sec-alcohols with 30%-52% ee and 52%-78% yield were obtained in the asymmetric addition of ethylmagnesium bromide to aldehydes (Table 1, Entries 5–14). In the presence of a catalytic amount of 4a (50 mol%), the addition of EtMgBr to the representative aromatic aldehydes proceeded in moderate yields and with enantioselectivities in the range of 30-42% ee (Table 1, Entries 5-12). However, in the case of sterically bulky aldehydes such as 9-anthraldehyde and 1,1,1-triphenylpropanal, it gave two significant amounts of addition products with up to 52% ee (Table 1, Entries 13 and 14). That is to say, the addition of EtMgBr to sterically bulky aldehydes afforded the products in generally higher enantioselectivity than that observed with ordinary aldehydes.

**4a** could be recovered simply by pouring the reaction mixture into methanol at the end of the reaction and separating the precipitated polymer via filtration. The recovered **4a** could be reused for many times to induce the asymmetric addition of EtMgBr to aldehyde without losing its enantioselective inducement ability. Table 2 shows the enantioselective inducing ability of the recovered **4a** for the asymmetric addition of EtMgBr to 9-anthraldehyde. After **4a** was reused six times, the ee of the addition product did not change obviously.

A plausible explanation for the stereochemical outcome of the reaction inspired by our previous research<sup>13,14</sup> can be based on model transition states **I–III** depicted at Scheme 1. **I** is the virtual steric structure of **4a** simulated by "Chem 3D Ultra 8.0" software, in which the black dot is oxygen atom. We speculate that, when the solution of **4a** is mixed with EtMgBr, the oxygenrounding hole should hold metal cation (Mg<sup>2+</sup>). In other words, the metal cation (Mg<sup>2+</sup>) is embedded in the hole of one-handed helical column of the polymer, leaving the negative alkyl ion Table 1. The enantioselective reaction of ethylmagnesium bromide with aldehydes in the presence of poly-(S)-AFPOs  $4^{a}$ 



4a: R=CH<sub>2</sub>CH<sub>3</sub>; 4b: R=H; 4c: R=CH<sub>3</sub>; 4d: R=CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>

OH

$R^{1}$ -CHO + EtMgBr $\frac{ZnCl_{2}, \text{ ligand 4}}{THF, Ti(O-i-Pr)_{4}} R^{1}$						
Entry	Ligand	$\mathbb{R}^1$	Yield <sup>b</sup> /%	ee <sup>c</sup> /%		
1	<b>4</b> a	Ph	75	28 (R)		
2	4b	Ph	58	17 ( <i>R</i> )		
3	<b>4</b> c	Ph	57	19 ( <i>R</i> )		
4	<b>4d</b>	Ph	60	21 (R)		
5	<b>4</b> a	2-furyl	52	36 (R)		
6	<b>4</b> a	2-naphthyl	65	32 (R)		
7	<b>4</b> a	1-naphthyl	58	33 (R)		
8	<b>4</b> a	$4-MeO-C_6H_4$	78	33 (R)		
9	<b>4</b> a	3-MeO-C <sub>6</sub> H <sub>4</sub>	62	40 (R)		
10	<b>4</b> a	$4-Me-C_6H_4$	65	39 (R)		
11	<b>4</b> a	2-pyridyl	55	42 (R)		
12	<b>4</b> a	2-phenylvinyl	62	30 (R)		
13	<b>4</b> a	9-anthryl	78	52 (R)		
14	4a	Ph <sub>3</sub> CCH <sub>2</sub>	70	52 (R)		

<sup>a</sup>R<sup>1</sup>CHO: 1 mmol; solvent: THF; reaction time: 24 h; temperature:  $-15 \,^{\circ}\text{C}$ ;  $n(\text{R}^{1}\text{CHO}):n(\text{ligand 4}):n(\text{Ti}(\text{O}-i-\text{Pr})_{4}):$  $n(EtMgBr):n(ZnCl_2) = 1:0.5:1.5:2:1$ . <sup>b</sup>Isolated yield. <sup>c</sup>The ee were determined by HPLC (Chiralcel OD-H), the absolute configuration assigned by comparison to literature values.

Table 2. The recycling and the reuse of 4a in enantioselective addition of EtMgBr to 9-anthraldehyde<sup>a</sup>

CHO + $EtMgBr$ $\frac{4a,Ti(O-i-Pr)_4}{ZnCl_2, THF}$						
Recycling time	Yield/% <sup>b</sup>	ee/% <sup>c</sup>	Config.d			
1	70	53	R			
2	80	53	R			
3	75	50	R			
4	76	48	R			
5	78	52	R			
6	77	50	R			

<sup>a</sup>9-Anthraldehyde: 1 mmol; solvent: THF; reaction time: 24 h; reaction temperature:  $-15 \,^{\circ}\text{C}$ ; n(9-anthraldehyde):n(4a):  $n(EtMgBr):n(ZnCl_2):n(Ti(O-i-Pr)_4) = 1:0.5:2:1:1.5.$  <sup>b</sup>Isolated yields. <sup>c</sup>Determined by HPLC (Chiralcel OD-H). <sup>d</sup>Absolute configuration assigned by comparison with the sign of specific rotation of a known compound and the known elution order from a Chiralcel OD-H column.



Scheme 1. The possible stereochemical models for the alkylation of aldehydes in the present of 4a.



Figure 1. The monomer 4e of poly-(S)-EFPO and two poly-(S)-EFPOs 4f and 4g with differences in average polymerization degree.

(Et<sup>-</sup>) outside the one-handed helical column (II); the alkyl anion (Et<sup>-</sup>) abuts tightly against the helical polymer and acquires a chiral environment. When these negative ethyl ions react with electrophile aldehydes (III), the reaction must be enantioselective, i.e., it is this helically chiral environment that results in the enantioselective inducement of the reaction. It is worth mentioning that although titanium(IV) isopropoxide has a positive effect on the asymmetric addition of aldehydes with EtMgBr, titanium cation may not be held by the oxygenrounding hole (I) because of large diameter.<sup>14</sup>

In order to conclude the correlation between the helical conformation and the enantioselectivity. (S)-1-Ethoxy-3-(9ethylfluoren-9-yl)propan-2-ol (4e), the model compound of monomeric unit of poly[(S)-3-(9-ethylfluoren-9-yl)propylene oxide] (poly-(S)-EFPO) 4a, the poly-(S)-EFPO( $M_n = 500$ ) 4f without a helical conformation, and the helical poly-(S)-EFPO( $M_n = 3700$ ) 4g with relatively high molecular weight (Figure 1), were synthesized. The CD spectrum properties of 4f and 4g are entirely different in their specific rotation properties. The Cotton effect of 4f, whose monomers have a positive Cotton effect, is positive, and is opposite to that of 4a. The Cotton effect of 4g is negative, and is the same as that of 4a. These properties support intensively that 4g keeps prevailing helical conformation in solution but 4f does not (see Supporting Information for details).15

4e, 4f, and 4g were used to replace 4a to induce the addition of EtMgBr to 9-anthraldehyde. The experimental results showed that 4e gave only 4.5% ee, and 4f gave only 5.8% ee under the same reaction conditions. These products had S configurations, opposite to those of the products obtained by using 4a ( $M_n =$ 2500). We speculate that the enantioselectivity of 4e and 4f without helical conformation results from the hydroxy at the edge of their main-chains. These ee values were so small that it could be ignored, indicating that the enantioselectivity of the addition reaction results from the chirality of the helical conformation of the polymer rather than the chirality of the asymmetric carbon. It was also observed that a slightly higher ee of the product (55%) was obtained by using 4g than by using 4a under same reaction conditions, though the molecular weight of 4g was much bigger than that of 4a.

In summary, we have proposed several kinds of one-handed helical polyether ligands applicable to enantioselective additions of ethylmagnesium bromide to aldehydes. We have shown that the reaction of EtMgBr with aldehydes in the presence of **4a** proceed with moderate yield and moderate ee up to 53%. **4a** could be recovered simply, operated simply, post-treated conveniently and used repeatedly. The investigation confirmed that the enantioselectivity resulted from the chirality of the helical conformation of the polymer rather than the chirality of the asymmetric carbon.

We thank the National Science Foundation of China (No. 21172186) for financial support of this work.

## **References and Notes**

- E. Yashima, K. Maeda, H. Iida, Y. Furusho, K. Nagai, *Chem. Rev.* 2009, *109*, 6102.
- 2 a) Y. Okamoto, E. Yashima, Angew. Chem., Int. Ed. 1998, 37, 1020. b) T. Nakano, J. Chromatogr., A 2001, 906, 205. c)
   C. Yamamoto, Y. Okamoto, Bull. Chem. Soc. Jpn. 2004, 77,

227. d) Y. Okamoto, T. Ikai, *Chem. Soc. Rev.* 2008, *37*, 2593.
e) Y. Okamoto, *J. Polym. Sci., Part A: Polym. Chem.* 2009, *47*, 1731.

- 3 a) Y. Okamoto, T. Nakano, *Chem. Rev.* 1994, 94, 349. b) T. Nakano, Y. Okamoto, *Chem. Rev.* 2001, 101, 4013.
- 4 E. A. C. Davie, S. M. Mennen, Y. Xu, S. J. Miller, *Chem. Rev.* 2007, 107, 5759.
- 5 M. Reggelin, M. Schultz, M. Holbach, *Angew. Chem., Int. Ed.* **2002**, *41*, 1614.
- 6 M. Reggelin, S. Doerr, M. Klussmann, M. Schultz, M. Holbach, *Proc. Natl. Acad. Sci. U.S.A.* 2004, 101, 5461.
- 7 F. Sanda, H. Araki, T. Masuda, Chem. Lett. 2005, 34, 1642.
- 8 K. Maeda, K. Tanaka, K. Morino, E. Yashima, *Macro-molecules* 2007, 40, 6783.
- 9 T. Yamamoto, M. Suginome, Angew. Chem. 2009, 121, 547.
- 10 C. A. Müller, T. Hoffart, M. Holbach, M. Reggelin, *Macromolecules* 2005, 38, 5375.
- 11 Z. Tang, H. Iida, H.-Y. Hu, E. Yashima, ACS Macro Lett. 2012, 1, 261.
- 12 D. Zhang, C. Ren, W. Yang, J. Deng, *Macromol. Rapid* Commun. 2012, 33, 652.
- 13 Y. Sun, N. Yang, J. Liu, J. Cao, H. Gong, *Polymer* 2010, 51, 5712.
- 14 C. Huang, N. Yang, A. Zhang, L. Yang, *Polymer* **2012**, *53*, 3514.
- 15 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.