JOC Article

Liquid-Phase Synthesis of Chiral Tartrate Ligand Library for Enantioselective Sharpless Epoxidation of Allylic Alcohols

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This paper reports a successful development of a group of efficient soluble polymer-supported chiral tartrate ligands by liquid-phase synthesis for Sharpless epoxidation of a variety of allylic alcohols through ligand diversity. The influence of substituent in chiral tartrate ligands on the enantioselectivities of the reaction was disclosed. Moderate chemical yields and good enantiomeric excesses were obtained by using soluble polymer-supported tartrate ester in the epoxidation of allylic alcohols with Ti(O-*i*-Pr)$_4$/*tert*-butyl hydroperoxide.

Introduction

It has been demonstrated that asymmetric catalysis is an extremely useful protocol in modern organic synthesis.[1] Finding highly efficient and enantioselective asymmetric catalysts for asymmetric reactions is one of the important goals in the research of chemical synthesis.[2] To achieve efficient catalysis for asymmetric reactions, use of chiral ligands to make the perfect match between chiral ligands and metallic ions is a key point. The introduction of new approaches to accelerate identification and optimization of such ligands has received particular attention. Very recently, combinatorial asymmetric catalysis is now taking in asymmetric catalysis to speed up the development of this challenging research area.[3] Particularly, the synthesis of ligand libraries on solid supports and the screening of the members of ligand libraries in the target reaction have been a powerful tool for the rapid development of finally soluble ligands for enantioselective catalysis.[4]

In general, this strategy requires that the results obtained with the immobilized ligands should correctly display the same trends in stereoselection as the corresponding soluble catalyst systems.[4k] However, the heterogeneous nature of this strategy might result in relatively low reactivity and selectivity. As a result, the immobilized ligands might not correctly show the same trends in stereoselection as the corresponding soluble catalyst systems. Therefore, development of liquid-phase synthesis using soluble polymers could provide an excellent opportunity to overcome the shortcomings of the solid-phase approach to combinatorial library production.[5] This has the advantages of liquid-phase reaction and easy separation/purification of the products in solid-phase synthesis. Generally, soluble polymer-supported ligands show the same enantioselection as the corresponding free ligands.[6] Moreover, the soluble polymer-bound species allow the use of routine analytical methods (NMR, TLC, or IR) to monitor the reaction process and to determine the structures of products attached to the polymer support directly. Poly(ethylene glycol) (PEG) is one type of polymer that is soluble in many solvents, such

(1) For comprehensive reviews on asymmetric catalysis, see: (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*, Wiley-Interscience: New York, 1993. (b) *Advances in Catalytic Processes: Asymmetric Chemical Transformations*; Doyle, M., Ed.; JAI: Greenwich, CT, 1995; Vol.1. (c) *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N., Pfaltz, A., Yamamoto, H. Eds.; Springer: Berlin, 1999; Vol. I−III. (d) *Catalytic Asymmetric Synthesis*, 2nd ed., Ojima, I., Ed.; Wiley-VCH: New York, 2000.

(2) Noyori, R. *Adv. Synth. Catal.* **2001**, *343*, 1.

(3) For recent reviews on combinatorial approach to the screening of chiral catalysts, see: (a) Borman, S. *Chem. Eng. News* **1996**, *74*, 4(45), 37. (b) Gennari, C.; Nestler, H. P.; Piarulli, U.; Salom, B. *Liebigs Ann./Recueil* **1997**, 637. (c) Shimizu, K. D.; Snapper, M. L.; Hoveyda, A. H. *Chem. Eur. J.* **1998**, *4*, 1885. (d) Hoveyda, A. H. *Chem. Biol.* **1998**, *5*, R187. (e) Francis, M. B.; Jamison, T. F.; Jacobsen, E. N. *Curr. Opin. Chem. Biol.* **1998**, *2*, 422. (f) Kagan, H. B. *J. Organomet. Chem.* **1998**, *567*, 3. (g) Jandeleit, B.; Schaefer, D. J.; Powers, T. S.; Turner, H. W.; Weinberg, W. H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2494. (h) Whiting, A. *Chem. Br.* **1999**, *35* (3), 31. (i) Reetz, M. T.; Jaeger, K.-E. *Chem. Eur. J.* **2000**, *6*, 407. (j) Gilbertson, S. R. In *Progress in Inorganic Chemistry*; Carlin, K., Ed.; Wiley: New York, 2001; Vol. 50. (k) Dahmen, S.; Bräse, S. *Synthesis* **2001**, 1431. (l) Reetz, M. T. *Angew. Chem., Int. Ed.* **2001**, *40*, 284. (m) Reetz, M. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1335. (n) Gennari, C.; Piarulli, U. *Chem. Rev.* **2003**, *103*, 3071.

(4) For representative examples, see: (a) Liu, G.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 7712. (b) Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1668. (c) Shimizu, K. D.; Cole, B. M.; Krueger, C. A.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1704. (d) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (e) Vidal-Ferran, A.; Bampos, N.; Moyano, A.; Pericas, M. A.; Riera, A.; Sanders, J. K. M. *J. Org. Chem.* **1998**, *63*, 6309. (f) Matsuo, J.; Odashima, K.; Kobayashi, S. *Org. Lett.* **1999**, *1*, 345. (g) Francis, M. B.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 937. (h) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279. (i) Brouwer, A. J.; van der Linden, H. J.; Liskamp, R. M. J. *J. Org. Chem.* **2000**, *65*, 1750. (j) Gilbertson, S. R.; Collibee, S. E.; Agrakov, A. *J. Am. Chem. Soc.* **2000**, *122*, 6522. (k) Huttenloch, O.; Laxman, E.; Waldmann, H. *Chem. Eur. J.* **2002**, *8*, 4767. (l) Pelotier, B.; Anson, M. S.; Campbell, I. B.; Macdonald, S. J. F.; Priem, G.; Jackson, R. F. W. *Synlett* **2002**, 1055.

(5) (a) Han, H.; Wolfe, M. M.; Brenner, S.; Janda, K. D. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 6419. (b) Janda, K. D.; Han, H. *Methods Enzymol.* **1996**, *267*, 234. (c) Yeh, C.; Sun, C. *Tetrahedron Lett.* **1999**, *40*, 7247. (d) Shang, Y.; Wang, Y. *Tetrahedron Lett.* **2002**, *43*, 2247. (e) Shang, Y.; Wang, Y. *Synthesis* **2002**, 1663. (f) Guo, H.; Ding, K. *Tetrahedron Lett.* **2003**, *44*, 7103.

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as CH_2Cl_2, $CHCl_3$, THF, CH_3OH, and H_2O, at room temperature and can be precipitated from a solution by addition of diethyl ether, hexane, or *tert*-butyl methyl ether. Therefore, PEG can be considered as an ideal support for liquid-phase synthesis of a ligand library in terms of its controllable solubility in different solvents.

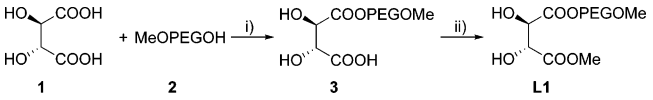
The Sharpless epoxidation of allylic alcohols is one of the most important transformations of organic synthesis.[7] Although some heterogeneous Sharpless-type epoxidation catalysts have been published,[8] there are few reports of the immobilization of the Sharpless Ti−tartrate ester-based asymmetric alkene epoxidation catalyst by use of soluble polymer. The linear poly(tartrate ester) system developed by Sherrington and co-workers[9] showed only moderate selectivities. The observed enantioselectivity for the epoxidation was up to 79% ee (enantiomer excess). Compared with 98% ee obtained by the solution-phase reaction with L-(+)-dimethyl tartrate, the catalytic system needs to be reworked.

Recently we have reported the synthesis of a group of soluble polymer-supported tartrate esters and their use with titanium tetraisopropoxide [Ti(O-*i*-Pr)$_4$] and *tert*-butyl hydroperoxide (TBHP) as the oxidant in epoxidation of (*E*)-2-hexen-1-ol in high chemical yield and good ee.[10] To find more efficient catalysts, here we describe in full detail the combinatorial synthesis of a library of soluble polymer-bound tartrate ligands and its evaluation in the Sharpless epoxidation of allylic alcohols.

Results and Discussion

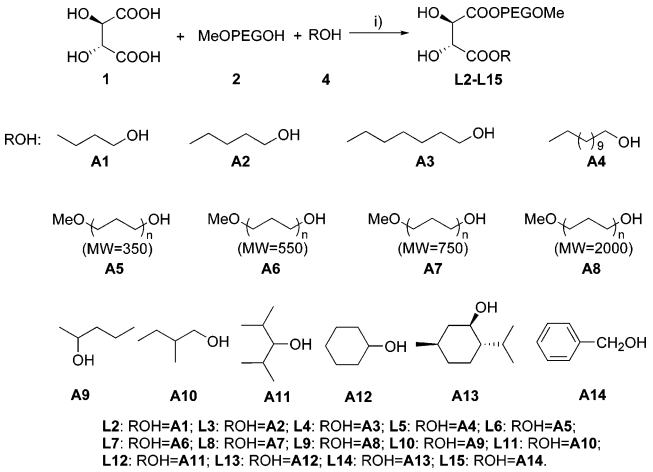
Synthesis of the Ligand Library. Tartrate ester **L1** was synthesized from L-(+)-tartaric acid by two steps (Scheme 1). First, poly(ethylene glycol) monomethyl ether (MeOPEGOH, MW = 2000) and excess L-(+)-tartaric acid reacted in the presence of *p*-toluenesulfonic acid to give **3**, and then **3** and diazomethane reacted at room temperature to afford **L1**. Tartrate ester **L2**−**L15** were synthesized from L-(+)-tartaric acid, poly(ethylene glycol) monomethyl ether (MeOPEGOH, MW = 2000), and alcohols (ROH, **A1**−**A14**) with molar ratios of MeOPEGOH/ROH = 1:4.25 and acid/(MeOPEGOH + ROH) = 1:2.10 as described by Yamamoto and co-workers[11] (Scheme 2). After reaction, the solvent toluene was removed by distillation under reduced pressure at the end of the reaction, and then the resulting solid was dissolved in a small amount of CH_2Cl_2. Diethyl ether was added to the resulting solution to precipitate tartrate ester under ice−salt cooling, and tartrate esters were obtained by filtration. All 15 kinds of MeOPEG-supported tartrate ligands shown in Schemes 1 and 2 were characterized by ^{1}H NMR and IR. In Scheme 2, MeOPEGOH (compound **2**, MW = 2000) is equal to **A8**. On the basis of ^{1}H NMR, the purity of **L12** was only 70%. This is mainly attributed to the steric hindrance of alcohol **A11**. When **L12** was synthesized from L-(+)-tartaric acid, MeOPEGOH (MW = 2000, **A8**), and **A11** by Scheme 2, **L9** was inevitably produced. In the ^{1}H NMR spectra, the signals (-CH_2OOC-C*H*(OH)- and C*H*(OH)-COOCH_2-) at 4.0−5.0 were the characteristic peaks of all ligands.

SCHEME 1[a]



[a] (i) *p*-Toluenesulfonic acid (5 mass %), toluene, ca. 115 °C, 45 h; (ii) CH_2N_2, CH_2Cl_2, rt.

SCHEME 2[a]



L2: ROH=**A1**; **L3**: ROH=**A2**; **L4**: ROH=**A3**; **L5**: ROH=**A4**; **L6**: ROH=**A5**; **L7**: ROH=**A6**; **L8**: ROH=**A7**; **L9**: ROH=**A8**; **L10**: ROH=**A9**; **L11**: ROH=**A10**; **L12**: ROH=**A11**; **L13**: ROH=**A12**; **L14**: ROH=**A13**; **L15**: ROH=**A14**.

[a] (i) *p*-Toluenesulfonic acid (5 mass %), toluene, ca. 115 °C, 45 h.

Asymmetric Catalysis of Sharpless Epoxidation of (*E*)-2-Hexen-1-ol with L1/Ti Complex and L9/Ti Complex. We initiated this work by focusing our effort on the investigation of the influence of titanium complex of MeOPEG-supported ligand **L1** on the asymmetric induction for Sharpless epoxidation of (*E*)-2-hexen-1-ol. It was observed that (*E*)-2-hexen-1-ol underwent Sharpless epoxidation with *tert*-butyl hydroperoxide (TBHP) at −20 °C in the presence of 5 mol % **L1**−Ti(IV) complex

(6) For recent reviews on soluble polymer-supported ligands, see: (a) Harwig, C. W.; Gravert, D. J.; Janda, K. D. *Chemtracts* **1999**, *12*, 1. (b) Wentworth, J.; Janda, K. D. *Chem. Commun.* **1999**, 1917. (c) Bergbreiter, D. E. *Med. Res. Rev.* **1999**, *19*, 439. (d) Dickerson, T. J.; Reed, N. N.; Janda, K. D. *Chem. Rev.* **2002**, *102*, 3325. (e) Bergbreiter, D. E. *Chem. Rev.* **2002**, *102*, 3345. For representative examples, see: (f) Bolm C.; Gerlach A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 741. (g) Han H.; Janda, K. D. *Tetrahedron Lett.* **1997**, *38*, 1527. (h) Kuang, Y.; Zhang, S.; Wei, L. *Tetrahedron Lett.* **2001**, *42*, 5925. (i) Han, H.; Janda, K. D. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1731. (j) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Pitillo, M. *J. Org. Chem.* **2001**, *66*, 3160. (k) Glos, M.; Reiser, O. *Org. Lett.* **2000**, *2*, 2045. (l) Benaglia, M.; Celentano, G.; Cozzi, F. *Adv. Synth. Catal.* **2001**, *343*, 171. (m) Doyle, M. P.; Eismont, M. Y. *J. Org. Chem.* **1992**, *57*, 6103. (n) Felder, M.; Giffels, G.; Wandrey, C. *Tetrahedron: Asymmetry* **1997**, *8*, 1975.

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(8) (a) Farrall, M. J.; Alexis, M.; Trecarten, M. *Nouv. J. Chim.* **1983**, *7*, 449 (b) Karjalainen, J. K.; Hormi, O. E. O.; Sherrington, D. C. *Tetrahedron: Asymmetry* **1998**, *9*, 1563. (c) Karjalainen, J. K.; Hormi, O. E. O.; Sherrington, D. C. *Tetrahedron: Asymmetry* **1998**, *9*, 2019. (d) Karjalainen, J. K.; Hormi, O. E. O.; Sherrington, D. C. *Tetrahedron: Asymmetry* **1998**, *9*, 3895.

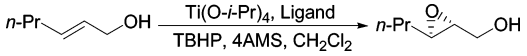
(9) Canali, L.; Karjalainen, J. K.; Sherrington, D. C.; Hormi, O. *Chem. Commun.* **1997**, 123.

(10) Guo, H. C.; Shi, X. Y.; Qiao, Z.; Hou, S. C.; Wang, M. *Chem. Commun.* **2002**, 118.

(11) Ikeda, N.; Arai, I.; Yamamoto, H. *J. Am. Chem. Soc.* **1986**, *108*, 483.

(12) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

TABLE 1. Asymmetric Catalysis of Sharpless Epoxidation of (*E*)-2-hexen-1-ol with L1/Ti Complex and L9/Ti Complex



entry	ligand	substrate:Ti:tartrate	temp (°C)	time[a] (h)	epoxide yield[b] (%)	isolated yield[c] (%)	ee[d] (%)
1	**L1**	100:5:6	−20	8	75	57	90
2	**L9**	100:5:6	−20	8	72	55	60
3	**L9**	100:5:10	−20	8	82	60	93
4	**L9**	100:10:12	−20	8	70	45	20
5	**L9**	100:20:24	−20	8	80	61	4

[a] From addition of substrates. [b] By GC analyses. [c] After workup and Kugelrohr distillation. [d] The enantiomeric excesses were determined by GC on a chiral capillary column, and the absolute configurations were determined as (−)-(2*S*,3*S*)-trans from the optical rotations by literature.

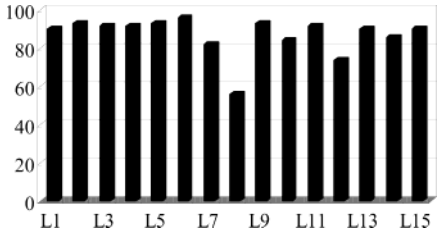


FIGURE 1. Ligand optimization by variation of subtituent in MeOPEG-supported tartrate ligand.

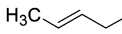
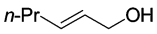
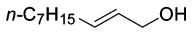
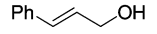
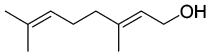
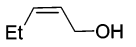
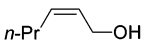
prepared by in situ mixing of **L1** and Ti(O-*i*-Pr)$_4$. The reaction afforded the epoxide product in 90% ee (Table 1, entry 1). For ligand **L9**, up to 93% ee was obtained when the Sharpless epoxidation of (*E*)-2-hexen-1-ol was carried out with a molar ratio of substrate/Ti(O-*i*-Pr)$_4$/ligand =100:5:10 (entry 3). (−)-(2*S*, 3*S*)-*trans*-Epoxide was obtained from **L1** or **L9**, and this is consistent with the results by the classical Sharpless epoxidation[12] using dialkyl tartrate from L-(+)-tartaric acid. But this result was different from that reported in our initial research.[10] In initial research, we may have mistaken the optical rotation of the product and the literature data. Because it was relatively difficult to prepare **L1** and the loading of chiral species of the MeOPEG-supported ligand **L9** was low, it is necessary to screen the ligand library and find more efficient ligands. In the following screening of chiral MeOPEG-supported ligands, the reactions were carried out in CH_2Cl_2 at −20 °C with a molar ratio of substrate/Ti(O-*i*-Pr)$_4$/ligand = 100:5:10 as a standard condition.

Substituent Effect of MeOPEG-Supported Ligands on the Enantioselectivity of the Sharpless Epoxidation: Screening of Highly Efficient Chiral Ligands. To achieve an efficient catalyst for asymmetric reaction, a key issue is to tune the catalyst to make the perfect match among chiral ligand, metallic ion, additive, substrate, and so on. With the lead results mentioned above, we switched our effort to improve the enantioselectivity of the reaction through ligand diversity by altering the substituents attached to the tartrate moiety. Accordingly, a library with 15 kinds of MeOPEG-supported tartrate esters (Scheme 1, 2) was then screened. As shown in Figure 1, **L1**−**L6**, **L9**, **L11**, **L13**, and **L15** were found to be nearly equally effective for the Ti-catalyzed Sharpless epoxidation reaction, whereby 90.0−96.0% enantiomeric excesses of the product could be achieved. For ligands **L1**−**L6** that were synthesized from the straight-chain alcohols, the chain length of the R substituent has almost no influence on enantioselectivity. **L6** with the longest chain of the six ligands gave up to 96% ee, but when the length of the R substituent continued to increase, the enantioselectivity dropped. For ligands **L7** and **L8**, 82% and 56% ee of epoxides were obtained, respectively. When **L9**, in which the R substituent (MeOPEG-, ROH = **A8**, MW = 2000) was equal to the support (MeOPEGOH, MW = 2000), was used, enantiomeric excesses of the product increased to 90% again. The steric effects have little influence on the enantioselectivity of the Sharpless epoxidation. Besides **L12**, **L10**, **L11**, **L13**, and **L14**, with relatively bulky R substituents, in the Ti-catalyzed Sharpless epoxidation reaction could give 84−92% ee. **L15** with an aromatic R substituent (benzyl group) could give 90% ee. The electronic properties of the R group appear to have little influence on the enantioselectivity in the Sharpless epoxidation.

Screening of Highly Efficient Chiral Catalysts for the Sharpless Epoxidatin Reaction. The screening of chiral ligands led us to understand the influence of the R substituent in MeOPEG-supported ligands on the enantioselectivity. Although **L6**/Ti complex catalyzed the epoxidation of (*E*)-2-hexen-1-ol to give the best enantioselectivity (96% ee) of all catalysts, to combine the advantages of easy preparation, high loading of chiral species, and good enantioselectivity, we chose the ligand **L4** to construct the Ti catalyst. With the catalyst in hand, the adaptability between catalyst and substrates was then screened in a parallel manner. A series of experiments with different substrate:Ti:ligand ratios were performed. The enantioselectivities varied a lot with different substrate:Ti:ligand ratios. As shown in Table 2, the optimized catalyst was applicable for the promotion of the Sharpless epoxidation of a variety of allylic alcohols, including trans-disubstituted, cis-disubstituted, and trans-trisubstituted derivatives, to give the corresponding epoxide products in moderate to high yields and enantioselectivities. When (*E*)-2-decen-1-ol was used as substrate, up to >99% ee of the corresponding product was obtained. Although the enantiomeric excesses are in general a little lower than those achieved for the corresponding low molecular weight species, and in some cases, they are compared to the corresponding low molecular weght template, they are still significantly better than those previously reported for insoluble polymer-supported systems.

Recovery and Recycling of MeOPEG-Supported Tartrate. Using (*E*)-2-hexen-1-ol as the epoxidation substrate, the ligand **L4** was recycled three times, and only moderate ee was obtained. The ees of the first,

TABLE 2. Parallel Screening of Matched Substrate/Catalyst Pair for L4-Ti(IV) Catalyzed the Sharpless Epoxidation Reaction of Allylic Alcohols

Entry	Substrates	MS	Substrate:Ti : Ligand	Temp. °C	Time h[a]	Yield %[b]	Ee %[d]
1		3Å	100:5:7.5	-20	8	45	65
2		3Å	100:10:15	-20	8	65	68
3		4Å	100:5:6	-20	8	78	67
4		4Å	100:5:7.5	-20	8	77	93
5		4Å	100: 5:10	-20	8	84	92
6		4Å	100: 5:7.5	-20	8	45[c]	>99
7		4Å	100: 5:10	-20	8	69[c]	97
8		4Å	100:5:7.5	-20	8	40[c]	90
9		4Å	100: 5:10	-20	8	40[c]	91
10		4Å	100: 5:7.5	-20	8	53	82
11		4Å	100: 5:10	-20	8	56	85
12		4Å	100: 5:7.5	-20	24	50	53
13		4Å	100:10:14	-20	24	53	52
14		4Å	100:15:30	-20	24	50	68
15		4Å	100:20:30	-20	24	47	80
16		4Å	100: 5:7.5	-20	24	70	30
17		4Å	100: 5:10	-20	24	68	63
18		4Å	100:15:30	-20	24	65	63
19		4Å	100:20:30	-20	24	73	79

[a] From addition of substrates. [b] By GC analyses unless other stated. [c] Isolated yield after workup and recrystallization. [d] The enantiomeric excesses were determined by GC on a chiral capillary column or by ^{1}H NMR analyses, and the absolute configurations were determined as (−)-(2*S*, 3*S*)-trans for *trans*-allylic alcohols and (−)-(2*S*, 3*R*)-cis for *cis*-allylic alcohols from the optical rotations by literature.

TABLE 3. Recovery and Recycling of MeOPEG-Supported Tartrate L4

entry	recycled times	substrate:Ti:ligand	time[a] (h)	yield[b] (%)	ee[c] (%)
1	0	100:5:10	8	80	92
2	first	100:5:10	8	66	85
3	second	100:5:10	8	62	77
4	third	100:5:10	8	67	66

[a] From addition of substrates. [b] By GC analyses. [c] The enantiomeric excesses were determined by GC on chiral capillary column, and the absolute configurations were determined as (−)-(2*S*, 3*S*)-trans from the optical rotations by literature.

second, and third recycle were 85%, 77%, and 66%, respectively (Table 3). Obviously, the enantioselectivity of the catalyst in the recycled experiments could not maintain an invariable value. ^{1}H NMR spectroscopic analysis showed that the ^{1}H NMR spectra of the recovered tartrate and the tartrate before the reaction have some differences. Although the shift value of characteristic peaks of the recovered tartrate is nearly the same as before the reaction, the ratio of the number of hydrogens in high field to that in low field varied much in contrast to the tartrate before the reaction. This maybe is mainly because of partial degrading of ligand under the oxidation conditions in the reaction process. The recycle results were not satisfactory, but the recovery of ligand by simple precipitation and filtration supports the isolation of products. The complex workup required in the Sharpless procedure is considerably simplified, and emulsions are avoided.

Experimental Section

Preparation of L1 (Scheme 1). To a 500 mL three-necked flask equipped with a magnetic stirrer, a thermometer, and a Dean−Stark trap were added 3 g of L-(+)-tartaric acid, 5 g of MeOPEGOH (MW 2000), 0.50 g of *p*-toluenesulfonic acid monohydrate, and 300 mL of toluene. The resulting mixture was refluxed at about 115 °C for 45 h with removal of water, and then the residual solvent was removed at reduced pressure. The resulting solid was dissolved in a small amount of CH_2Cl_2. Diethyl ether was added to the resulting solution to precipitate tartrate ester under ice−salt cooling, and **3** was obtained by filtration. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.40(d, J = 1.9 Hz, 1H), 4.32 (d, J = 2.6 Hz, 1H), 4.10−4.25 (m, 2H), 3.27−3.74 [m, poly(ethylene glycol) peaks], 3.24 (s, 3H).

Dried **3** (5 g) was dissolved in 50 mL of CH_2Cl_2 and the solution was cooled to 0 °C. With moderate stirring, the diethyl ether solution of diazomethane was slowly added into the CH_2Cl_2 solution of **3**. After the reaction was completed, the solvent was removed at reduced pressure to give a white solid. The white solid was dried under high vacuum to give **L1**: white powder, 4.92 g, 98% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.42 (s, 1H), 4.33 (d, J = 2.4 Hz, 1 H), 4.17−4.21 (m, 2H), 3.26−3.76 [m, poly(ethylene glycol) peaks and -$COOCH_3$], 3.24 (s, 3H). IR (KBr, cm^{-1}) 3400, 2960, 1740, 1460, 1350, 1280, 1110, 950, 840.

Preparation of L2−L15 (Scheme 2). To a 500 mL three-necked flask equipped with a magnetic stirrer, a thermometer, and a Dean−Stark trap were added 2.40 g (0.016 mol) of L-(+)-tartaric acid, 0.0272 mol of ROH, 12.8 g (0.0064 mol) of

MeOPEGOH (MW 2000), 0.60 g of *p*-toluenesulfonic acid monohydrate, and 150 mL of toluene. The resulting mixture was refluxed for 45 h at about 115 °C with removal of water and then the residual solvent was removed at reduced pressure. The resulting solid was dissolved in a small amount of CH_2Cl_2. Diethyl ether was added to the resulting solution to precipitate tartrate ester under ice−salt cooling, and tartrate esters were obtained by filtration. The ligands were dried under high vacuum.

L2, white powder, 13.26 g, 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.59 (dd, J = 1.8 and 6.0 Hz, 2H), 4.39−4.42 (m, 2H), 4.22−4.27 (m, 2H), 3.41−3.89 [m, poly(ethylene glycol) peaks], 3.38 (s, 3H), 1.62−1.70 (m, 2H), 1.36−1.44 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H). IR (KBr, cm^{-1}) 3400, 2880, 2150, 1960, 1750, 1630, 1575, 1465, 1360, 1340, 1275, 1245, 1110, 1060, 960, 840.

L3, white powder, 13.65 g, 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.58 (dd, J = 1.7 and 6.2 Hz, 2H), 4.39−4.42 (m, 2H), 4.24 (t, J = 6.6 Hz, 2H), 3.39−3.89 [m, poly(ethylene glycol) peaks], 3.38 (s, 3H), 3.23 (br s, 2H), 1.67−1.71 (m, 2H), 1.33−1.37 (m, 4H), 0.91 (t, J = 6.9 Hz, 3H). IR (KBr, cm^{-1}) 3400, 2880, 2150, 1960, 1745, 1625, 1575, 1465, 1360, 1340, 1280, 1245, 1145, 1110, 1060, 960, 840.

L4, white powder, 13.32 g, 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.58 (dd, J = 1.8 and 6.2 Hz, 2H), 4.39−4.43 (m, 2H), 4.23 (t, J = 6.7 Hz, 2H), 3.39−3.90 [m, poly(ethylene glycol) peaks], 3.38 (s, 3H), 1.64−1.71 (m, 2H), 1.29−1.34 (m, 8H), 0.89 (t, J = 6.9 Hz, 3H). IR (KBr, cm^{-1}) 3400, 2880, 2150, 1950, 1745, 1625, 1580, 1465, 1360, 1340, 1275, 1145, 1110, 1060, 960, 840.

L5, white powder, 13.98 g, 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.58 (dd, J = 1.8 and 5.9 Hz, 2H), 4.37−4.41 (m, 2H), 4.22 (t, J = 6.7 Hz, 2H), 3.39−3.89 [m, poly(ethylene glycol) peaks], 3.38 (s, 3H), 1.65−1.70 (m, 2H), 1.26−1.32 (br m, 18H), 0.88 (t, J = 6.9 Hz, 3H). IR (KBr, cm^{-1}) 3400, 2860, 2150, 1960, 1750, 1630, 1580, 1465, 1420, 1360, 1340, 1280, 1245, 1145, 1110, 1060, 960, 840.

L6, white powder, 14.10 g, 89% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.63 (s, 2H), 4.37−4.41 (m, 4H), 3.39−3.88 [m, poly(ethylene glycol) peaks], 3.38 (s, 6H). IR (KBr, cm^{-1}) 3400, 2870, 2160, 1960, 1750, 1630, 1580, 1465, 1360, 1340, 1280, 1245, 1110, 1060, 960, 840.

L7, white powder, 16.40 g, 96% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.63 (s, 2H), 4.38−4.40 (m, 4H), 3.41−3.90 [m, poly(ethylene glycol) peaks], 3.38 (s, 6H). IR (KBr, cm^{-1}) 3400, 2880, 2150, 1970, 1750, 1650, 1460, 1360, 1340, 1280, 1245, 1110, 1060, 960, 840.

L8, white powder, 16.95 g, 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.63 (s, 2H), 4.38−4.40 (m, 4H), 3.56−3.88 [m, poly(ethylene glycol) peaks], 3.38 (s, 6H). IR (KBr, cm^{-1}) 3400, 2880, 2150, 1960, 1750, 1630, 1580, 1465, 1360, 1340, 1280, 1245, 1110, 1060, 960, 840.

L9, white powder, 25.01 g, 95% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.41 (d, J = 1.7 Hz, 2H), 4.14−4.25 (m, 4H), 3.23−3.76 [m, poly(ethylene glycol) peaks]. IR (KBr, cm^{-1}) 3400, 2880, 1745, 1638, 1465, 1340, 1280, 1245, 1110, 960, 840.

L10, white powder, 12.95 g, 92% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.05−5.07 (m, 1H), 4.56 (d, J = 13.1 Hz, 2H), 4.39−4.43 (m, 2H), 3.38−3.90 [m, poly(ethylene glycol) peaks], 1.26−1.63 (m, 7H), 0.89−0.95 (m, 3H). IR (KBr, cm^{-1}) 3380, 2870, 2150, 1960, 1745, 1630, 1580, 1465, 1360, 1340, 1275, 1245, 1105, 1060, 960, 840.

L11, white powder, 13.51 g, 96% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.57 (d, J = 4.2 Hz, 2H), 4.39−4.42 (m, 2H), 4.25−4.30 (m, 2H), 3.39−3.89 [m, poly(ethylene glycol) peaks], 3.38 (s, 3H), 1.65−1.76 (m, 1H), 1.54−1.61 (m, 2H), 0.92−0.95 (m, 6H). IR (KBr, cm^{-1}) 3400, 2880, 2160, 1960, 1750, 1630, 1580, 1465, 1420, 1360, 1340, 1280, 1145, 1110, 1060, 960, 840.

L12, white powder, 12.86 g, 70% purity, 87% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.70−4.74 (br m, 2H), 4.59−4.64 (br m, 2H), 4.39−4.44 (br m, 4H), 3.38−3.90 [m, poly(ethylene glycol) peaks], 1.93−1.96 (br m, 2H), 0.88−0.94 (br m, 12H). IR (KBr, cm^{-1}) 3350, 2880, 2150, 1960, 1750, 1630, 1580, 1465, 1360, 1340, 1280, 1245, 1110, 1060, 960, 840.

L13, white powder, 13.45 g, 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.88−4.94 (m, 1H), 4.57 (dd, J = 1.6 and 14.0 Hz, 2H), 4.41 (t, J = 4.7 Hz, 2H), 3.38−3.90 [m, poly(ethylene glycol) peaks], 3.32 (br s, 2H), 1.87 (br s, 2H), 1.72 (br s, 2H), 1.27−1.56 (m, 6H). IR (KBr, cm^{-1}) 3380, 2870, 2160, 1960, 1745, 1630, 1580, 1465, 1360, 1340, 1280, 1245, 1145, 1110, 1060, 960, 840.

L14, white powder, 13.65 g, 94% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.77−4.83 (m, 1H), 4.54−4.63 (m, 2H), 4.39−4.42 (m, 2H), 3.38−3.90 [m, poly(ethylene glycol) peaks], 2.05 (br d, J = 11.4 Hz, 1H), 1.91−1.94 (br m, 1H), 1.70 (br d, J = 11.7 Hz, 2H), 1.41−1.49 (br m, 2H), 1.01−1.09 (m, 2H), 0.88−0.93 (m, 6H), 0.75 (d, J = 6.9 Hz, 3H). IR (KBr, cm^{-1}) 3300, 2960, 1960, 1745, 1465, 1360, 1340, 1280, 1245, 1105, 1060, 960, 840.

L15, white powder, 13.17 g, 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.37 (m, 5H), 5.26 (t, J = 14.8 Hz, 2H), 4.63 (s, 2H), 4.34−4.40 (m, 2H), 3.38−3.89 [m, poly(ethylene glycol) peaks]. IR (KBr, cm^{-1}) 3400, 2880, 2150, 1960, 1750, 1630, 1575, 1465, 1360, 1340, 1280, 1245, 1110, 1060, 960, 840.

Epoxidation of Allylic Alcohols: (2*S*, 3*S*-*trans*)-3-Propyloxiranemethanol (E1). The epoxidation was carried out as described in the general procedure (see Supporting Information), in this case with 75 mL of dried CH_2Cl_2, 3 g of 4 Å MS, 5.58 g of **L4** (2.5 mmol, 10% mol), 0.38 mL of Ti(O-*i*-Pr)$_4$ (0.355 g, 1.25 mmol, 5% mol), and 8.44 mL of TBHP solution (50 mmol, 5.922 M) in isooctane. The mixture was stirred for 1 h at −20 °C and 2.5 g (25 mmol, 96% purity) of (*E*)-2-hexen-1-ol dissolved in 25 mL of CH_2Cl_2 was added in 15 min. The mixture was stirred for an additional 8 h at −20 to −15 °C. Workup A (see Supporting Information) was then performed to give the crude product as a colorless oil. Purification by distillation under reduced pressure (2 mmHg, 49−52 °C) afforded 1.74 g of a colorless oil: 60% yield, 92% ee (after acetylation, determined by GC with 2,6-di-*O*-benzyl-3-*O*-heptanonyl-β-cyclodextrin as chiral stationary phase). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.89−3.94 (m, 1H), 3.58−3.64 (m, 1H), 2.91−2.99 (m, 2H), 2.31 (br s, 1H), 1.43−1.60 (m, 4H), 0.97 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.5, 58.3, 55.5, 33.0, 18.7, 13.3, 13.2. IR (film, cm^{-1}) 3380, 2950, 2850, 1460, 1380, 1220, 1100, 1070, 1045, 1010, 945, 900, 850, 810, 770, 750, 710.

(2*S*,3*S*-*trans*)-3-Heptyloxiranemethanol (E2). A 250 mL flask was charged with 3 g of 4 Å MS and 30 mL of dried CH_2Cl_2 and cooled to 0 °C. **L4** (1.0 g, 0.47 mmol, 7.5% mol) and 0.1 mL of Ti(O-*i*-Pr)$_4$ (0.091 g, 0.32 mmol, 5% mol) were added sequentially with stirring, and the mixture was cooled to −20 °C. TBHP solution (2.16 mL, 12.80 mmol, 5.922 M) in isooctane was added dropwise through the addition funnel in about 5 min. The resulting mixture was stirred at −20 °C for 1 h. (*E*)-2-Decen-1-ol (1.00 g, 6.4 mmol) was added dropwise. The mixture was stirred at −20 °C for an additional 8 h. Workup B was then performed to give the crude product as a pale yellow viscous liquid. The crude product was purified by recrystallization from petroleum ether (60−90 °C) to give 0.49 g of a colorless crystal. 45% yield, >99% ee (by ^{1}H NMR analysis of Mosher ester); mp 49−51 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (br d, J = 12.5 Hz, 1H), 3.63 (br d, J = 12.5 Hz, 1H), 2.91−2.98 (m, 2H), 1.28−1.67 (m, 13H), 0.88 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.7, 58.6, 56.0, 31.6, 31.4, 29.2, 29.0, 25.8, 22.4, 13.9. IR (KBr, cm^{-1}) 3250, 3120, 2920, 2900, 2840, 1480, 1455, 1425, 1405, 1375, 1340, 1320, 1300, 1250, 1085, 1060, 1035, 1005, 975, 950, 905, 870, 820, 760, 715, 585.

(2*S*,3*S*-*trans*)-3-Phenyloxiranemethanol (E3). The epoxidation was carried out as described in the general procedure, in this case with 350 mL of dried CH_2Cl_2, 6.24 g of **L4** (2.8 mmol, 7.5% mol), 3 g of activated 4 Å MS, 0.56 mL of Ti(O-*i*-Pr)$_4$ (0.530 g, 1.9 mmol, 5% mol), and 12.60 mL of TBHP solution (74.6 mmol, 5.922 M) in isooctane. The mixture was stirred at −20 °C for 1 h. The substrate, 5.0 g of freshly

distilled (*E*)-3-phenyl-2-propenol (37.3 mmol) in 10 mL of dried CH_2Cl_2, was added dropwise. The resulting mixture was stirred at −20 °C for an additional 8 h. Workup B was performed to afford a yellow viscous oil. The crude product was purified by recrystallization from petroleum ether (60−90 °C)/diethyl ether (9/1) mixed solvent to give 2.24 g of pale yellow crystals: 40% yield, 90% ee (by ^{1}H NMR analysis of Mosher ester); mp 51−53 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26−7.39 (m, 5H), 4.03−4.10 (m, 1H), 3.94 (d, J = 2.1 Hz, 1H), 3.77−3.85 (m, 1H), 3.22−3.25 (m, 1H), 1.83−1.87 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.4, 128.2, 128.0, 125.5, 62.4, 61.1, 55.4. IR (KBr, cm^{-1}) 3400, 2850, 1495, 1460, 1430, 1400, 1370, 1310, 1285, 1250, 1230, 1200, 1070, 985, 930, 860, 765, 740, 700, 640.

(2*S*,3*S*-*trans*)-3-Methyl-3-(4-methyl-3-pentenyl)oxiranemethanol (E4). The epoxidation was carried out as described in the general procedure, in this case with 25 mL of dried CH_2Cl_2, 1 g of powdered activated 4 Å MS, 0.48 mL of Ti(O-*i*-Pr)$_4$ (0.455 g, 1.6 mmol, 5% mol), 5.35 g of **L4** (2.40 mmol, 7.5% mol), and 8.19 mL of TBHP solution (48.5 mmol, 5.922 M) in isooctane. The mixture was stirred at −20 °C for 1 h, and then 5.0 g of freshly distilled (*E*)-3,7-dimethyl-2,6-octadien-1-ol (32.5 mmol) in 10 mL of dried CH_2Cl_2 was added. The resulting mixture was stirred at −20 °C for an additional 8 h. Workup B was performed to afford a colorless oil. The crude product was purified by distillation under reduced pressure (0.3 mmHg, 72−74 °C) to give 2.38 g of a colorless oil: 41% yield, 83% ee [by ^{1}H NMR shift analysis of the derived acetates with Eu(hfc)$_3$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06−5.11 (m, 1H), 3.80−3.85 (m, 1H), 3.64−3.70 (m, 1H), 2.96−3.00 (m, 1H), 2.04−2.12 (m, 3H), 1.42−1.73 (m, 8H), 1.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.4, 123.5, 63.4, 61.6, 61.5, 38.7, 25.9, 23.9, 17.9, 17.0. IR (film, cm^{-1}) 3400, 2950, 2900, 1450, 1380, 1250, 1080, 1035, 960.

(2*S*,3*S*-*trans*)-3-Methyloxiranemethanol (E5). The epoxidation was carried out as described in the general procedure, in this case with 50 mL of dried CH_2Cl_2, 3 g of powdered activated 3Å MS, 4.18 g of **L4** (1.875 mmol, 7.5% mol), 1.80 g of (*E*)-2-buten-1-ol (25 mmol), and 0.38 mL of Ti(O-*i*-Pr)$_4$ (0.355 g, 1.25 mmol, 5% mol). The mixture was stirred at −20 °C for 1.5 h, and then 8.34 mL of TBHP solution (50 mmol, 5.995 M) in isooctane was added dropwise. The resulting mixture was stirred at −20 °C for an additional 8 h. Workup B was performed to afford the crude product as a colorless liquid. The crude product was purified by distillation under reduced pressure (4 mmHg, 59−61 °C) to give 0.66 g of a colorless liquid: 30% yield, 65% ee (after acetylation, determined by GC with 2,6-di-*O*-benzyl-3-*O*-heptanonyl-β-cyclodextrin as chiral stationary phase). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87−3.94 (m, 1H), 3.57−3.65 (m, 1H), 3.01−3.07 (m, 1H), 2.88−2.92 (m, 1H), 2.35 (br t, J = 5.6 Hz, 1H), 1.34 (d, J = 5.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.3, 59.3, 51.8, 16.6. IR (film, cm^{-1}) 3380, 2950, 2900, 1480, 1445, 1380, 1100, 1040, 990, 865, 815, 720.

(2*S*,3*R*-*cis*)-3-Ethyloxiranemethanol (E6). The epoxidation was carried out as described in the general procedure, in this case with 60 mL of dried CH_2Cl_2, 3 g of 4 Å MS, 0.77 mL of Ti(O-*i*-Pr)$_4$ (0.728 g, 2.56 mmol, 20% mol), 8.56 g of **L4** (3.84 mmol, 30% mol), and 4.27 mL of TBHP solution (25.6 mmol, 5.995 M) in isooctane. The mixture was stirred at −20 °C for 1.5 h, and then 1.1 g of (*Z*)-2-penten-1-ol (12.8 mmol) in 10 mL of CH_2Cl_2 was added dropwise. The resulting mixture was stirred at −20 °C for an additional 24 h. Workup B was performed to afford the crude product as a colorless oil. The crude product was purified by distillation under reduced pressure (6 mmHg, 58−60 °C) to give 0.51 g of a colorless liquid: 39% yield, 80% ee (by ^{1}H NMR analysis of Mosher ester, or after acetylation, determined by GC with 2,3-di-*O*-benzyl-6-*O*-octanoyl-β-cyclodextrin as chiral stationary phase). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (br d, J = 12.1 Hz, 1H), 3.57−3.64 (m, 1H), 3.09−3.14 (m, 1H), 2.92−2.98 (m, 1H), 2.51 (br s, 1H), 1.45−1.58 (m, 2H), 0.99 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.0, 58.7, 57.4, 21.5, 10.9. IR (film, cm^{-1}) 3380, 2950, 2870, 1460, 1380, 1305, 1270, 1150, 1040, 950, 895, 815, 800, 725.

(2*S*,3*R*-*cis*)-3-Propyloxiranemethanol (E7). The epoxidation was carried out as described in the general procedure, in this case with 37.5 mL of dried CH_2Cl_2, 3 g of 4 Å MS, 8.37 g of **L4** (3.75 mmol, 30% mol), 0.75 mL of Ti(O-*i*-Pr)$_4$ (0.71 g, 2.5 mmol, 20% mol), and 4.17 mL of TBHP solution (25 mmol, 5.995 M) in isooctane. The mixture was stirred at −20 °C for 1.5 h, and then 1.25 g (12.5 mmol) of (*Z*)-2-hexen-1-ol in 10 mL of dried CH_2Cl_2 was added dropwise. The resulting mixture was stirred at −20 to −15 °C for an additional 24 h. Workup B was performed to afford the crude product as a colorless oil. The crude product was purified by distillation under reduced pressure (6 mmHg, 83−84 °C) to give 0.58 g of a colorless liquid: 40% yield, 79% ee (by ^{1}H NMR analysis of Mosher ester). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (br d, J = 9.7 Hz, 1H), 3.63−3.70 (m, 1H), 3.14−3.19 (m, 1H), 3.02−3.07 (m, 1H), 2.58 (br s, 1H), 1.45−1.59 (m, 4H), 0.95−1.01 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.1, 57.4, 57.2, 30.1, 20.1, 14.1. IR (film, cm^{-1}) 3380, 2950, 2850, 1460, 1380, 1260, 1145, 1105, 1045, 915, 860, 825, 765.

Recovery of Ligands. After the epoxidation reaction was completed, the CH_2Cl_2 was removed by distillation under reduced pressure at 25 °C, and then diethyl ether was added to the resulting mixture to precipitate the tartrate at −10 to −20 °C under vigorous stirring conditions. The mixture was filtered under reduced pressure to obtain a white solid with slight yellow color, which was tartrate ligand. The solid obtained was redissolved in 100 mL of CH_2Cl_2 and stirred for 10 min. The resulting mixture was filtered under reduced pressure. Nearly all CH_2Cl_2 in the filtrate was removed under reduced pressure. Diethyl ether was added to the resulting solution to precipitate the tartrate at −10 to −20 °C under vigorous stirring conditions, and the mixture was filtered under reduced pressure to give a white solid with slight yellow color. The solid was dried under high vacuum to afford the pale yellow powder and the recovery of ligand was >98%. The dried recovered ligand was reused in the Sharpless epoxidation of allylic alcohols.

Conclusion

In conclusion, a group of highly efficient chiral titanium catalysts for Sharpless epoxidation reaction of allylic alcohols have been discovered through ligand diversity. The influences of substituent in chiral tartrate ligands on the enantioselectivities of the epoxidation reactions were disclosed as well. The approach taken in this work is a privileged example to demonstrate how one can generate a large number of modular ligands by liquid-phase synthesis. To the best of our knowledge, this is the first example of constructing a chiral ligand library by liquid-phase synthesis. We hope that our work in this article will stimulate further work on the use of liquid-phase synthesis in combinatorial asymmetric catalysis and the design of new catalytic asymmetric reaction systems through ligand diversity.

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Supporting Information Available: Experimental procedures for the epoxidation reactions of allylic alcohols and the analyses of the epoxide products as well as ^{1}H NMR of all ligands and ^{1}H NMR and ^{13}C NMR of all epoxide products. This material is available free of charge via the Internet at http://pubs.acs.org.

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