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Linker-Oriented Design of Binaphthol Derivatives for Optical Resolution Using Lipase-Catalyzed Reaction

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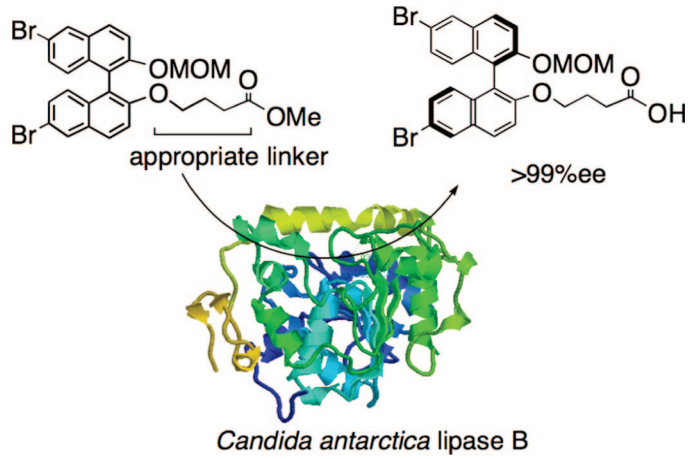

Candida antarctica lipase B (CAL-B) is one the most frequently used enzymes in organic synthesis for the preparation of optically active alcohols. However, it has not been used for the optical resolution of (±)-2,2′-binaphthol. We established an efficient linker-oriented design of 2,2′-binaphthol derivatives that is appropriate for optical resolution using CAL-B-catalyzed hydrolysis reaction. Methyl 4-(1-(6-bromo-2-methoxymethoxynaphthalen-1-yl)-6-bromonaphthalen-2-yloxy)butanoate was hydrolyzed by CAL-B to afford a corresponding acid with excellent enantioselectivity ($E > 200$). Two types of optically active binaphthol derivatives, 1-(2-hydroxy-6-(naphthalen-1-yl)naphthalen-1-yl)-6-(naphthalen-1-yl)naphthalen-2-ol and 6-butyl-1-(6-butyl-2-hydroxynaphthalen-1-yl)naphthalen-2-ol, were prepared by this chemo-enzymatic reaction protocol and were used as chiral templates for symmetric reactions.

Introduction

Axially chiral 2,2′-binaphthol is well respected as a milestone compound for modern asymmetric synthesis,[1,2] and numerous asymmetric reactions have been developed using chiral 2,2′-binaphthol derivatives as chiral templates.[1–5] However, tedious classical optical resolution of racemic binaphthol is employed for industrial scale syntheses,[6] although several methodologies have been developed for preparing optically active binaphthol compounds by many groups. [7–9] Therefore, development of an

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efficient practical method for chiral 2,2′-binaphthol derivatives has been awaited.

The enzymatic reactions are now well recognized as an easy and dependable means of providing enantiomerically pure products,[10] and optical resolution of (±)-**1** was demonstrated by enantiospecific hydrolyses using microorganisms.[11] Esterases are the most frequently used enzymes for asymmetric organic syntheses because of their acceptance of a broad range of substrates, stability, and availability. The first successful optical resolution of (±)-2,2′-binaphthol (**1**) by the esterase-catalyzed reaction was reported by Miyano and co-workers using porcine pancreatic lipase (PPL).[12] Kazlauskas next reported an efficient example of enantioselctive hydrolysis of dipentanoate of **1** using cholesterol esterase (EC 3.1.1.3).[13] Oda and co-workers further demonstrated enzymatic resolution of binaphthol **1** using *Pseudomonas aeruginosa* lipase (LPL-A or LIP, Toyobo).[14] After these works, two types of indirect methods were also developed by Lin[15] and Hauser,[16] respectively. However, development of a more efficient biocatalyst reaction protocol using commercially available enzymes for preparing chiral binaphthol has remained a challenging topic in organic synthesis.

We were especially interested in the poor reactivity of lipases for 2,2′-binaphthol derivatives and recognized that three types of typical commercially available lipase, *C. antarctica* lipase B (CAL-B: Novozym435 and Chirazyme L-2), lipase PS from *Burkholderia cepacia*, and *Candida rugosa* lipase, in fact, showed no reactivity for 2,2′-binaphthol (**1**) or binaphthyl

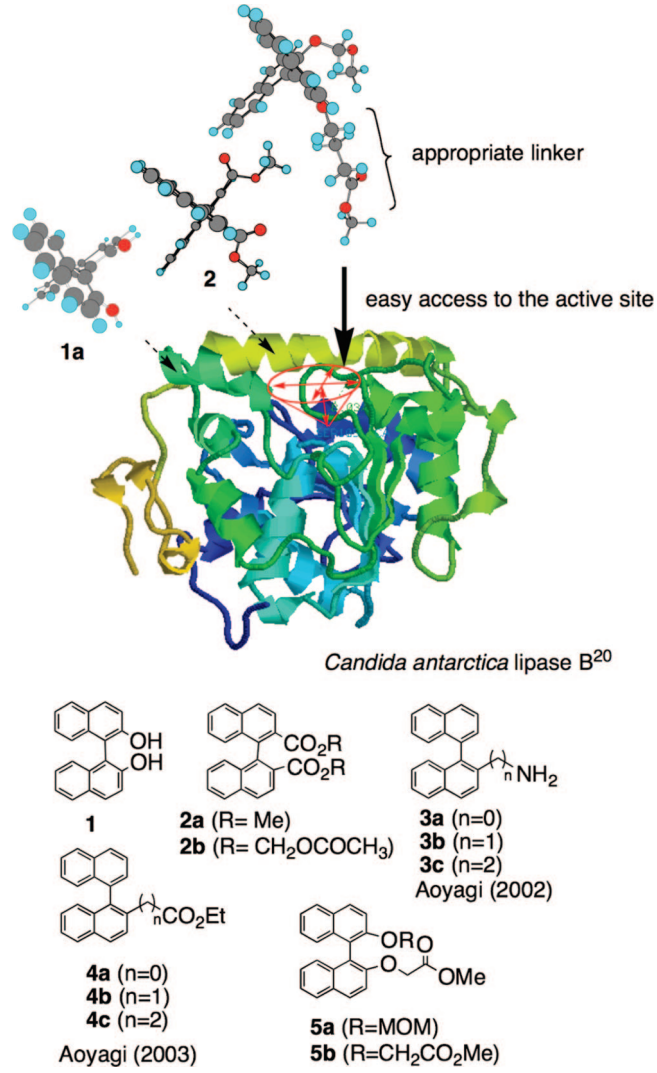

FIGURE 1. Working hypothesis of linker-oriented design of binaphthol derivatives applicable to CAL-B-catalyzed reaction. The 3D structure of CAL-B was produced by RasMol using X-ray structure data reported by Jones et al.[20]

carboxylic methyl ester (±)-**2a**. Sih[17a] and Achiwa[17b] independently reported the successful protocol for designing 4-aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylates as substrate for the enzymatic hydrolysis reaction: modification of the carbonyl group as acyloxymethyl ester made possible smooth hydrolysis by the *Pseudomonas* lipase with high enantioselectivity, while lipases showed poor reactivity vs a simple methyl ester.[17] However, we found that both CAL-B and lipase PS were inactive to binaphthyl diester **2b** (Figure 1).[17a]

Recently, Aoyagi and co-workers reported interesting results for the lipase-catalyzed reaction using binaphthol derivatives as substrates;[18] *P. aeruginosa* lipase-catalyzed acylation proceeded smoothly when (±)-**3c** ($n = 2$) was subjected to the reaction, while the lipase showed no reactivity for **3a** ($n = 0$) or **3b** ($n = 1$).[19] In addition, the same authors reported that compound **4c** ($n = 2$) was converted to the corresponding amide

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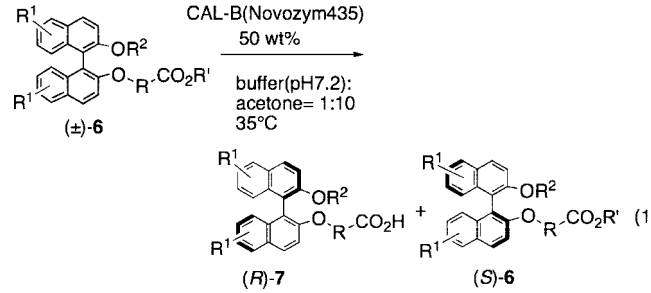
with acceptable enantioselectivity by the reaction with 3-aminopropanenitrile using CAL-B, while no reaction took place for biaryl compounds **4a** ($n = 0$) and **4b** ($n = 1$) (Figure 1).[19] These results clearly suggested that the chain length between the binaphthyl ring with the reaction point of the carboxyl group critically influenced reactivity of the lipase. We were fascinated by these interesting phenomena of lipase reactivity to the binaphthol derivatives and decided to investigate the designs of binaphthol derivatives that are appropriate for CAL-B-catalyzed transformation. We expected that useful information about the origin of enantioselectivity of the lipase might be obtained through this study.

It is reported that there exists a crevice in CAL-B and that the substrate is taken into the enzyme through this crevice. According to the results of X-ray crystallographic analysis (Figure 1), the area of the crevice was estimated to be 10 × 25 Å and the distance between the entryway from the active site of the enzyme (Ser 105) to be 8 Å.[20]

Although the size of the crevice seemed to be large enough for entry of the binaphthyl compounds **1** and **2**, no reaction took place when these compounds were treated with CAL-B. It is therefore anticipated that there is a certain narrow area within the crevice which might prevent hydroxyl groups on the binaphthyl rings from accessing the active site of the enzyme because the two naphthyl rings are twisted and act as a very bulky molecule. Ema proposed that the enantioselectivity of the lipase-catalyzed reaction might be determined mainly by the kinetic preference due to the conformational requirements and repulsive interaction in the transition state.[21] Kazlauskas and co-workers reported an efficient design of primary alcohols that are appropriate for the lipase-catalyzed reaction by tuning of acyl chain length.[22] Based on these results, we hypothesized that a binaphthol-substituted carboxylic acid methyl ester that has an appropriate linker group between the 2-hydroxyl group of binaphthol and the terminal methoxycarbonyl group might become a good substrate for lipase-catalyzed enantiospecific hydrolysis reaction. We tested the reaction of binaphthyl-substituted glycolic acid derivatives **5a** and **5b** and confirmed that no reaction took place for these compounds. Therefore, it was anticipated that at least two or three of the methylene groups might be required as a linker between the naphthyl ring and terminal carboxyl group for the enzymatic hydrolysis. In this paper we wish to report our successful design of binaphthol derivatives that are appropriate for efficient optical resolution by commercial CAL-B-catalyzed reaction.

Results and Discussion

1. Design of Binaphthol Derivatives for CAL-B-Catalyzed Reaction. We expected that CAL-B-catalyzed optical resolution of binaphthol derivatives might be possible using appropriately modified binaphthol (±)-**6**. Typically, the reaction was carried out as follows: to a mixture of substrate ester (±)-**6** in a mixed solvent of a buffer (0.1 M potassium phosphate buffer pH 7.2) and acetone (1:10) was added lipase (50 wt % vs substrate), and the resulting mixture was stirred at 35 °C (eq 1). The reaction was monitored by silica gel thin-layer chromatography (TLC), and lipase was removed by filtration through a glass sintered filter and washed with ethyl acetate. The combined organic layers were dried and evaporated, and the acid produced and remaining ester were purified by silica gel thin-layer chromatography (TLC). The results are summarized in Table 1.



As anticipated, the alkyl chain length of the linker group was very important for the reaction. We found that binaphthyl-substituted butanoic acid methyl ester (±)-**6a** was hydrolyzed smoothly by the lipase, but poor enantioselectivity was recorded (entry 1).

On the other hand, the desired enantioselective hydrolysis reaction was accomplished when methoxymethyl-protected 2,2′-binaphthol derivative (±)-**6b** was used as substrate for the CAL-B-catalyzed reaction; the desired acid (*R*)-(+)-**7b** was obtained in 66% yield with 75% ee and unreacted ester (*S*)-**6b** was obtained in 34% yield with 92% ee (entry 2).

The *E* value[23] was estimated as 21; although this value seems to be modest, this is an amazing selectivity because there is a great distance between the hydrolysis point and the chiral point of **6b**. To confirm the absolute configuration of the lipase-catalyzed reaction, (+)-**7b** (75% ee) was converted to 2,2′-binaphthol (**1**) by the reaction with boron tribromide (BBr_3) in dichloromethane (CH_2Cl_2) with 80% yield. Since the resulting 2,2′-binaphthol (**1**) showed a positive sign of optical rotation ($[\alpha]^{22}_D$ +27 (*c* 1.0, THF); lit.[14] $[\alpha]^{22}_D$ +31 (*R*)), the absolute configuration of (+)-**7b** produced was determined to be the (*R*)-form.

Design of the protecting group of the hydroxyl group on the binaphthyl ring was also important; no reaction for compound (±)-**6c** (entry 3) or (±)-**6d** (entry 4) was obtained, although these have the same alkylcarboxylic acid moiety to be hydrolyzed. It was thus established that protection of the 2′-hydroxy group on the binaphthyl ring as methoxymethyl (MOM) ether was essential for realization of the enantioselective reaction; the methoxymethyl (MOM) group of the hydroxyl group of BINOL seemed to play a very important role in the enantiomer discrimination step of the enzymatic reaction.

Flexibility of the linker portion was also a very important factor for the lipase-catalyzed reaction because lipase could not hydrolyze (±)-**6e** (entry 5). On the other hand, the hydrolysis reaction of octanoic ester derivative (±)-**6f** proceeded rapidly but with no enantioselectivity (entry 6). Since the chain length of (±)-**6f** is very long compared to the distance between the active site and entryway of the enzyme, these results might suggest that the origin of the enantioselectivity of the present

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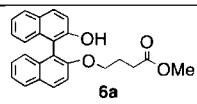
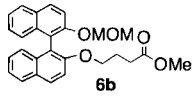
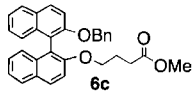
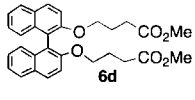
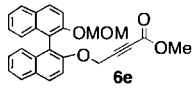
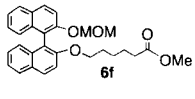
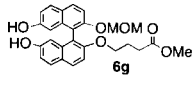
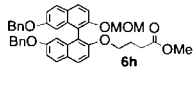
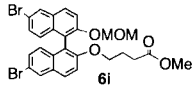
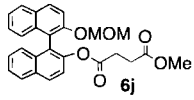
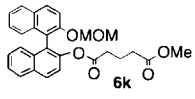
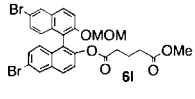
TABLE 1. Results of CAL-B-Catalyzed Hydrolysis of Binaphthol Derivatives (±)-6

Entry	Substrate	Time (h)	(*R*)-acid **7**		(*S*)-ester **6**		conv.[b]	E value[c]
			Yield (%)	% ee [a]	Yield (%)	% ee [a]		
1	 **6a**	24	58	9	31	11	0.55	1
2	 **6b**	20	66	75	34	92	0.55	21
3	 **6c**	72	0	--	97	0	0	--
4	 **6d**	72	0	--	98	0	0	--
5	 **6e**	72	0	--	95	0	0	--
6	 **6f**	4	48	0	58	0	0	1
7	 **6g**	72	40	92	48	90	0.52	74
8	 **6h**	72	0	--	95	0	0	--
9	 **6i**	64	35	>99	48	83	0.46	>200
10	 **6j**	72	0	--	95	0	0	--
11	 **6k**	12	29	85	66	33	0.28	17
12	 **6l**	66	32	91	62	60	0.41	40

[a] Determined by HPLC analysis (Chiralcel AD, hexane/2-propanol/TFA = 9:1:0.01). [b] $E = \ln[1 - c(1 + ee_p)]/\ln[1 - c(1 - ee_p)]$, where $c = ee_S/(ee_P + ee_S)$. [c] c = conv. See ref 23.

enzymatic reaction is basically caused by interaction of the axially chiral binaphyl group with the entryway of the lipase protein as we initially hypothesized.

We next discovered that the functional group existing on the B-ring of the naphthyl group significantly affected the reactivity of the lipase.[24] Introduction of the hydroxy group at the 7,7′-position of binaphthyl was effective to increase enantioselectivity

(24) (a) Taniguchi, T.; Fukuba, T.; Hayase, S.; Itoh, T. Abstract. *85th CSJ Annual Meeting*, Kanagawa, Japan, 2005, 2F2−29. Taniguchi, T.; Kawatsura, M.; Hayase, S.; Itoh, T. Abstract. Pacifichem, Hawaii, 2005.

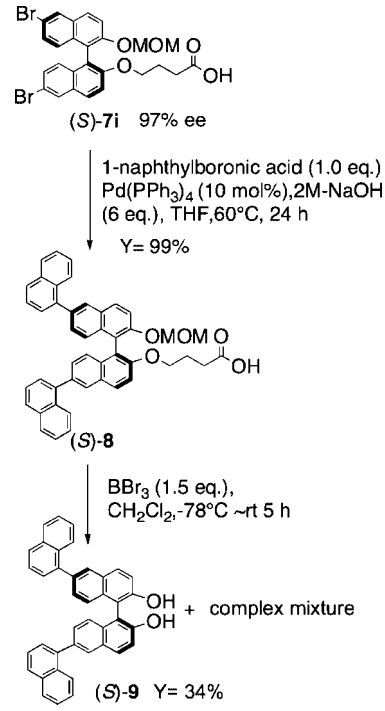
of the enzymatic reaction; a highly enantioselective reaction (*E* value 74) was accomplished for compound **6g** (entry 7). However, no reaction took place for benzyl-protected compound **6h** (Entry 8). We finally found that 6,6′-dibromobinaphthyl derivative **6i** was the best substrate for CAL-B catalyzed reaction (entry 9);[24] optically pure acid (*R*)-**7i** was obtained in 35% yield with over 99% ee, and the *E* value reached over 200. These results are very interesting in that such an excellent enantioselective hydrolysis was accomplished for the hydrolysis of the methoxycarbonyl group apart from the chiral binaphthyl moiety. Since a reduced reaction rate was obtained for **6i** compared to that of **6b**, we are assuming that presence of the appropriate functional group at the 6- and 7-positions of the naphthyl ring might play an important role in the arrangement of the compound to fit the active site correctly or may contribute to enhance the difference in transition-state energy over the course of the hydrolysis reaction between two enantiomers. It was thus found that 4-binaphthyloxybutanoates were suitable substrates for CAL-B-catalyzed reaction, and compounds **6j**, **6k**, and **6l** were next prepared and tested as substrates for this reaction. However, no reaction took place when methyl succinate (±)-**6j** was used as substrate (entry 10), although it was estimated that the distance between the reaction point and the binaphthyl ring was almost the same as that of (±)-**6b** (7.29 Å estimated by the PM3 calculation). Fortunately, good results were obtained when methyl glutarate derivatives, (±)-**6k** and (±)-**6l**, were subjected to the reaction; the *E* value reached 40 for the reaction of **6l** (entry 12) and 17 for the reaction of **6k** (entry 11). Since the present reaction is a kinetic resolution of racemic compounds, it is easy to obtain both enantiomers with optically pure form by stopping the reaction at an appropriate conversion. Because CAL-B is an economical and a commercially available enzyme, we thus established a practical method to prepare optically active 2,2′-binaphthol derivatives.

It is recognized that lipases are generally inactive to bulky substrates at room temperature. Recently, Sakai and Ema provided a surprisingly simple solution to this problem: they demonstrated that several bulky alcohols were acylated by a lipase under high temperature conditions (60−80 °C) while maintaining good enantioselectivity.[21b,25] It was, therefore, expected that high-temperature lipase-catalyzed reaction might be applicable to bulky binaphthol derivatives; this idea was realized by Aoyagi and co-workers recently: 1-(2-hydroxynaphthalen-1-yl)naphthlen-2-yl butyrate was converted to (*R*)-2,2′-binaphthol by CAL-B-catalyzed alcoholysis reaction at 80 °C, and no reaction took place if the reaction was carried out at 30 °C.[26]

On the other hand, we have established that lipase can hydrolyze binaphthol derivatives that connected with an appropriate linker even at 35 °C. Although our chemical modification protocol of binaphthol may be less convenient than the high-temperature method, it obviously provides another solution of enzymatic reactions for bulky compounds.

Since compound **7i** has two bromide groups at the 6,6′-point, various types of binaphthol derivatives could be converted from this compound. Synthesis of 6- and 6′-aryl-substituted binaphthol

SCHEME 1. Synthesis of Binaphthol Derivative (*S*)-9



(*S*)-**9** was next demonstrated using Suzuki−Miyaura coupling protocol (Scheme 1).[27]

Binaphthyl (*S*)-**7i** (97% ee) which was derived from (*S*)-**6i** was reacted with 1-naphthylboronic acid in the presence of 10 mol % of tetrakistriphenylphosphinepalladium ($Pd(PPh_3)_4$) in a mixed solvent of 2 M NaOH aqueous solution and THF at 60 °C for 24 h to give the corresponding coupling product (*S*)-**8** in 99% yield. This was treated with boron tribromide (BBr_3) in CH_2Cl_2 at 78 °C and allowed to warm to room temperature (rt) for 5 h. However, unfortunately, we encountered the unexpected problem that removal of the linker moiety of (*S*)-**8** was difficult and deprotection of the MOM group took place easily under the conditions used, so that desired (*S*)-**9**[28] was obtained in low yield with an unidentified complex mixture (Scheme 1).

On the other hand, we did succeed in removing the linker moiety more conveniently through hydrolysis of (*R*)-**7l** under basic conditions, and (*R*)-**10**[29] was obtained in 99% yield. (*R*)-**10** was then converted to di-MOM ether (*R*)-**11**, which was next converted to (*R*)-**12** using Pd-catalyzed alkylation by the reaction with butylmagnesium bromide (Scheme 2).[30] We next prepared (*R*)-**9** again using (*R*)-**11** following the Suzuki−Miyaura coupling reaction: Pd-catalyzed coupling reaction of (*R*)-**11** with 1-naphthylboronic acid proceeded very smoothly to give (*R*)-**13**, and subsequent deprotection of the MOM group gave (*R*)-**9**[30] in 77% yield (two steps). X-ray crystallographic analysis of (*R*)-**12** was successful, and the ORTEP view is shown in Figure 2.[31] (*S*)-**9** and (*S*)-**12** were also prepared following the same route from (*S*)-**6l**.

(25) (a) Ema, T.; Kageyama, M.; Korenaga, T.; Sakai, T. *Tetrahedron: Asymmetry* **2003**, *14*, 3943–3947. (b) Sakai, T.; Matsuda, A.; Tanaka, Y.; Korenaga, T.; Ema, T. *Tetrahedron: Asymmetry* **2004**, *15*, 1929–1932. (c) Ema, T.; Doi, T.; Sakai, T. *Chem. Lett.* **2008**, *37*, 90–91.

(26) Aoyagi, N.; Ogawa, N.; Izumi, T. *Tetrahedron Lett.* **2006**, *47*, 4797–4801.

(27) (a) Hoshino, Y.; Miyaura, N.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3008–3010. For a recent review, see: (b) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.

(28) Chen, R.-F.; Qian, C.-T.; Johannes, G. V.; Sun, P. P.; Wang, L.-M. *Chin. J. Chem.* **2001**, *19*, 1225–1231.

(29) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180–8186.

(30) Brunkan, N. M.; Gague, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 6217–6225.

(31) The crystallographic data of (*R*)-**12** is available as a CIF file (Supporting Information).

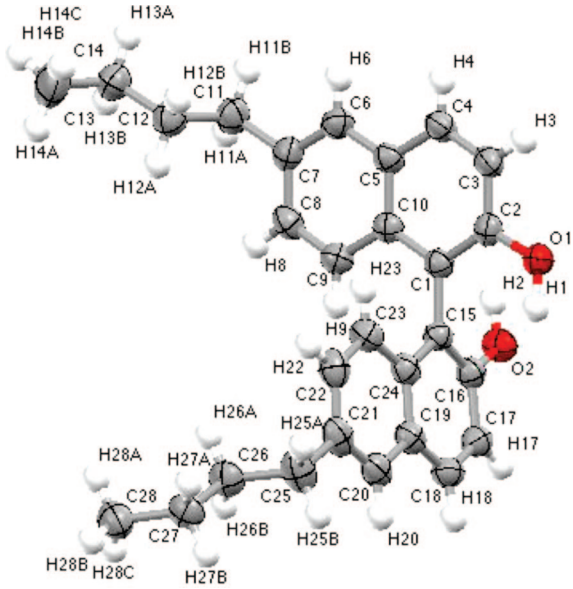


FIGURE 2. ORTEP view of (*R*)-**12**. $C_{28}H_{30}O_2$, formula weight = 398.54, monoclinic, space group *P*21(#4), a = 10.195(6) Å, b = 8.387(5) Å, c = 13.540(9) Å, b =108.076(17)°, V= 1100.6(11)^3, Z = 2, d_{calc} = 1.203 g cm^{-3}, R(Rw) = 0.0500 for 11705 diffraction data with $I > 2.00\sigma(I)$ and 281 valuable.

SCHEME 2. Synthesis of Two Types of Binaphthol Derivatives, (*R*)-9 and (*R*)-12

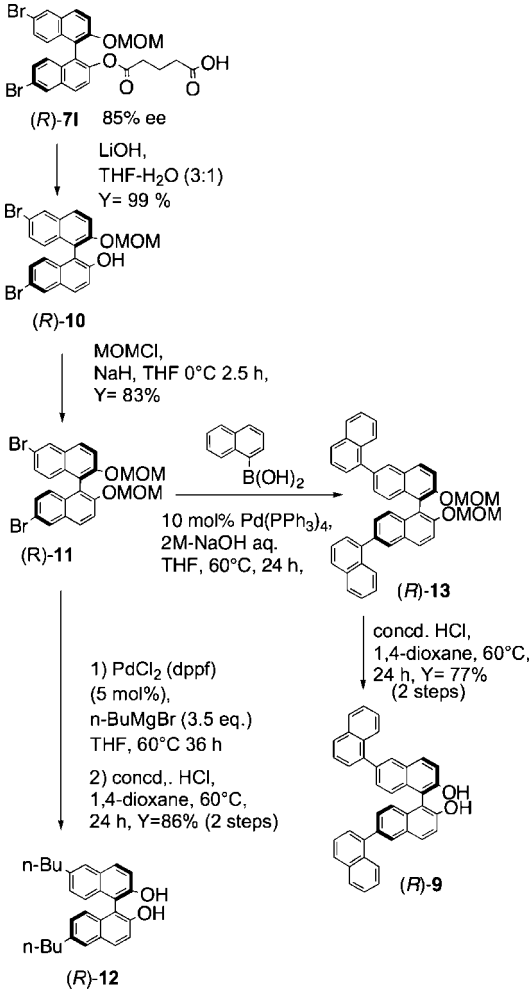
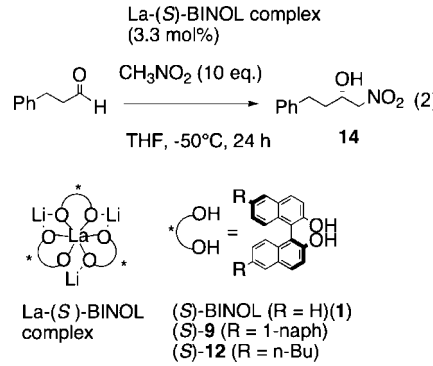


TABLE 2. Results of La-BINOL-Catalyzed Asymmetric Henry Reaction

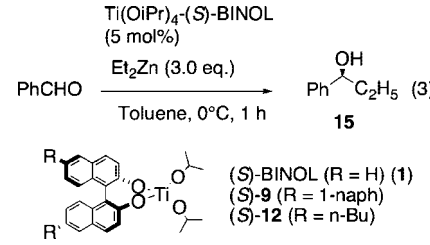
entry	catalyst	yield of **14** (%)	% ee[a]
1	(S)-BINOL (**1**)	63	74
2	(*S*)-**9**	70	79
3	(*S*)-**12**	81	73

[a] Determined by HPLC analysis (Chiralcel AD, hexane/2-propanol = 9:1, 35 °C).

2. Application of BINOL Derivatives As Templates for Asymmetric Reactions. We then investigated the applicability of BINOL derivatives **9** and **12** as chiral ligands for the asymmetric Henry reaction of 3-phenylpropionaldehyde catalyzed La−BINOL complex that was developed by Shibasaki (eq 2).[32]



We anticipated that La complexes prepared from (*S*)-**12** might be easily dissolved in a conventional organic solvent such as THF and thus contribute to increase the efficiency of the catalyst system. As expected, La complex made by (*S*)-**12** was easily dissolved in THF and chemical yield of the product nitro alcohol **14** was indeed improved to 81% (entry 3) from 63% (entry 1), which was obtained for the La complex made from (*S*)-BINOL ((*S*)-**1**) while maintaining the enantioselectivity (Table 2). On the other hand, a slightly enhanced enantioselectivity was recorded when the La complex made from (*S*)-**9** was used as catalyst (entry 2).



We next tested asymmetric diethyl zinc reaction with benzylaldehyde in the presence of Ti−BINOL complex developed by Mori and Nakai (eq 3).[33] In the reaction, it was again anticipated that solubility of the Ti complex toward the solvent system might affect the efficiency of the reaction. As expected, improved chemical yield of product **15** was obtained when the Ti complex made from (*S*)-**12** was used as catalyst (Table 3, entry 3), although no difference in the enatioselectivity was recorded. In this reaction, both chemical yield and enantiose-

(32) (a) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418–4420. (b) Sasai, H.; Tokunaga, T.; Watanabe, S.; Suzuki, T.; Itoh, N.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 7388–7389.

(33) Mori, M.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6233–6236.

TABLE 3. Results of Ti-BINOL-Mediated Asymmetric Addition of Benzaldehyde with Diethylzinc

entry	catalyst source	yield of **15** (%)	% ee[a]
1	(*S*)-BINOL (**1**)	79	84
2	(*S*)-**9**	76	72
3	(*S*)-**12**	85	82

[a] Determined by HPLC analysis (Chiralcel OD-H, hexane/2-propanol = 100:1, 35 °C).

lectivity were slightly reduced when the Ti complex made from (*S*)-**9** was used as catalyst to the reaction (entry 2).

Conclusion

In summary, we established a linker-oriented design of binaphthol derivatives that made it possible to modify binaphthol applicable for kinetic resolution of commercially available *C. antarctica* lipase B; methyl 4-(1-(2-(methoxymethoxy)-6-bromonaphthalen-1-yl)-6-bromonaphthalen-2-yloxy)butanoate (**6i**) and 6-bromo-1-(6-bromo-2-(methoxymethyloxy)naphthalen-1-yl)naphthalen-2-yl glutaric acid methyl ester (**6l**) were thus prepared as appropriate substrates for CAL-B-catalyzed reaction. CAL-B-catalyzed hydrolysis of (±)-**6i** or **6l** was very successful, and the corresponding acid (*R*)-**7i** or (*R*)-**7l** was obtained with excellent enantioselectivity. It is amazing that such an excellent enantioselective hydrolysis was accomplished by the hydrolysis of the methoxy carbonyl group of compounds **6i** or **6l**, both of which are apart from the chiral binaphthyl moiety. Since both compounds **7i** and **7l** have two bromide groups at 6,6′-points on the binaphthyl rings, it is possible to convert them to various types of binaphthol derivatives. Two types of 2,2′-binaphthol derivatives, **9** and **12**, were thus prepared and used as chiral templates for symmetric reactions. We believe that the present results provide not only a solution for preparation of chiral binaphthol derivatives using an enzymatic reaction but also provide a hint to the consideration of the origin of the enantiomer recognition of the lipase-catalyzed reaction.

Experimental Section

Using CAL-B-catalyzed hydrolysis, optical resolution of (±)-**6g**, (±)-**6i**, (±)-**6k**, and (±)-**6l** was accomplished. However, no reaction took place when (±)-**6c**, **6d**, **6e**, **6h**, or **6j** was subjected to the CAL-B-catalyzed reaction. For the syntheses of substrates **6a**−**l** for the enzymatic reaction, see the Supporting Information.

CAL-B-Catalyzed Enantioselective Hydrolysis of (±)-6b. To a solution of (±)-**6b** (50 mg, 0.12 mmol) in acetone (1 mL) and 0.1 mL of 0.1 M potassium phosphate buffer (pH7.2) was added CAL-B (Novozym435: 25 mg, 50 wt %). After being stirred at 35 °C for 48 h, the reaction mixture was filtered though a glass sintered filter with a Celite pad to remove the lipase. The filtrate was dried ($MgSO_4$), evaporated, and purified by silica gel thin-layer chromatography (TLC) (hexane/ethyl acetate/methanol = 10:10:1) to give (*R*)-**7b** (26 mg, 0.060 mmol, 66%) and (*S*)-**6b** (19.5 mg, 0.040 mmol, 34%). It was possible to reduce the amount of CAL-B while maintaining high enantioselectivity, but it took a longer reaction time (4 days) to reach ca. 50% conversion when 10 wt % of CAL-B was used. From a practical standpoint, we decided to test the reactions using 50 wt % of enzyme vs substrate.

(*R*)-**7b**: 75% ee (Chiralpak AD, hexane/2-propanol/trifluoroacetic acid (TFA) = 9:1:0.01, 35 °C); t_R = 10.2 min for (*R*)-isomer, 8.1 min for (*S*)-isomer; $[\alpha]^{28}_D$ +17.0 (*c* 1.0, $CHCl_3$); R_f 0.4 (hexane/ethyl acetate = 3:1) ; IR (KBr) 3010 (OH), 2936, 1705 (CO), 1622, 1593, 1506, 1355, 1240, 1015, 920, 810, 752 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.65−1.79 (2H, m), 1.82−1.95 (2H, m), 3.06 (3H, s), 3.12 (3H, s), 3.92−4.08 (2H, m), 4.93 (1H, d, *J* = 6.7 Hz), 5.08 (1H, d, *J*= 6.7 Hz), 7.05−7.28 (6H, m), 7.35 (1H, d, *J* = 9.1 Hz), 7.50 (1H, d, *J* = 9.1 Hz), 7.80 (2H, q, *J* = 5.5 Hz), 7.88 (2H, dd, 1.9 Hz, *J* = 8.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.2 (3C), 29.6 (2C), 55.7 (Me-MOM), 68.3 (4C), 95.0 (CH_2-MOM), 115.8, 117.1, 120.6, 121.2, 123.7, 124.0, 125.3, 125.4, 126.2, 126.3, 127.8, 127.9, 129.3, 129.4, 129.8, 133.9, 134.0, 152.5, 154.0, 179.3 (1C). Anal. Calcd for $C_{26}H_{24}O_5$: C, 74.98; H,5.81. Found: C, 74.69; H, 5.85.

(*S*)-**6b**: 92% ee (Chiralpak AD, hexane/2-propanol = 9:1, 35 °C); t_R = 5.9 min for (*S*)-isomer, 6.9 min for (*R*)-isomer; $[\alpha]^{28}_D$ −42.6 (*c* 1.0, $CHCl_3$) .

(*R*)-(+)-**7b** (75% ee) was treated with BBr_3 in dichloromethane at −78 °C to give (*R*)-(+)-2,2′-binaphthol (**1**): $[\alpha]^{22}_D$ +26 (*c* 1.0, THF) (lit.[14] $[\alpha]^{22}_D$ +31 (*c* 1.0, THF)) for 98% ee of (*R*)-**1a**. (*S*)-(−)-**6b** (92% ee) was converted to (*S*)-(−)-**1a** by the same procedure: $[\alpha]^{22}_D$ −32 (*c* 1.0, THF) (lit.[12] −35 (*c* 1.18, THF)), 100% ee .

(±)-**6b**: bp 198−200 °C, 3.0 mmHg (Kugelrohr); R_f 0.38 (hexane/ethyl acetate = 3/1); IR (KBr) 2902, 2825, 1732 (CO), 1622, 1591, 1433, 1015, 810 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.59−1.72 (2H, m), 1.74−1.88 (2H, m), 3.06 (3H, s), 3.46 (3H, s), 3.85−4.00 (2H, m), 4.88 (1H, d, *J* = 6.7 Hz), 5.02 (1H, d, *J*= 6.7 Hz) 7.05−7.28 (6H, m), 7.35 (1H, d, *J* = 9.1 Hz), 7.50 (1H, d, *J* = 9.1 Hz), 7.80 (2H, q, *J* = 5.5 Hz), 7.88 (2H, dd, 1.9 Hz, *J* = 8.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.7 (3C), 29.8 (2C), 51.59 (OMe), 55.9 (Me-MOM), 68.6 (4C), 95.3 (CH_2-MOM), 115.9, 117.4, 120.7, 121.4, 123.9, 124.1, 125.6, 126.3, 126.4, 128.0, 129.4, 129.4, 129.5, 130.0, 134.1, 134.2, 152.7, 154.2, 173.8 (1C). Anal. Calcd for $C_{27}H_{26}O_5$: C, 75.33; H,6.09. Found: C, 75.16; H, 6.14.

Optical Resolution of (±)-6g. (*R*)-**7g**: 92% ee (Chiralpak AD, hexane/2-propanol/TFA = 4:1:0.01, 35 °C), t_R = 18.7 min for (*R*)-isomer, 12.8 min for (*S*)-isomer; $[\alpha]^{25}_D$ +27.8 (*c* 1.0, MeOH); mp 215 °C (recrystallized from CH_2Cl_2); R_f 0.11 (hexane/ethyl acetate/MeOH = 20:20:1); IR (KBr) 3320, 2941, 1701 (CO), 1624, 1238, 1217, 1029, 966, 830 cm^{-1}; ^1H NMR (500 MHz, δ, methanol-d_4) δ 1.54−1.67 (2H, m), 1.80−1.92 (2H, m), 3.04 (3H, s), 3.84−3.96 (2H, m), 4.77 (b), 4.89 (1H, d, *J* = 6.4 Hz), 5.08 (1H, d, *J*= 6.4 Hz), 6.31 (1H, d, *J* = 2.3 Hz), 6.33 (1H, d, *J* = 2.8 Hz), 6.78 (1H, dd, *J* = 2.8 Hz, 9.0 Hz), 6.80 (1H, dd, *J* = 2.3 Hz, 9.0 Hz), 7.16 (1H, d, *J* = 9.1 Hz), 7.25 (1H, d, *J* = 8.7 Hz), 7.61 (1H, d, *J* = 6.4 Hz), 7.63 (1H, d, *J* = 6.4 Hz), 7.71 (1H, d, *J* = 7.3 Hz), 7.73 (1H, d, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, acetone-d_6) δ 25.1 (3C), 29.5 (2C), 55.2 (Me-MOM), 68.3 (4C), 95.0 (CH_2-MOM), 106.9, 107.1, 112.8, 114.3, 116.4, 116.7, 119.2, 120.1, 124.9, 125.3, 129.0, 129.3, 129.9, 130.0, 136.1, 136.2, 153.5, 155.1, 156.0, 156.1, 174.0(1C). Anal. Calcd for $C_{24}H_{26}O_7$: C, 69.63; H, 5.39. Found: C, 69.25; H, 4.94. (*S*)-**6g**: 90%ee (Chiralpak AD, hexane/2-propanol = 4:1, 35 °C), t_R = 16.7 min for (*R*)-isomer, 10.5 min for (*S*)-isomer; $[\alpha]^{25}_D$ −31.0 (*c* 1.0, MeOH).

(±)-**6g**: mp 145 °C (recrystallized from CH_2Cl_2); R_f 0.49 (hexane/ethyl acetate/methanol = 20/20/1); IR (KBr) 3377, 1709 (CO), 1624, 1510, 1439, 1217, 1146, 1030, 966, 829 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.72 (2H, qu, *J* = 6.0 Hz), 1.85−1.97 (2H, m), 3.10 (3H, s), 3.52 (3H, s), 3.92−4.02 (2H, m), 4.89 (1H, d, *J* = 6.9 Hz), 5.04 (1H, d, *J*= 6.9 Hz), 5.04 (1H, s), 5.26 (1H, brs), 6.40 (1H, d, *J* = 2.3 Hz), 6.41 (1H, d, *J* = 2.2 Hz), 6.91 (1H, dd, *J* = 2.3 Hz, 8.8 Hz), 6.94 (1H, dd, *J* = 2.3 Hz, 8.8 Hz), 7.20 (1H, d, *J* = 9.1 Hz), 7.32 (1H, d, *J*= 9.1 Hz), 7.72 (1H, d, *J* = 5.1 Hz), 7.74 (1H, d, *J* = 5.1 Hz), 7.80 (1H, s), 7.82 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.2 (3C), 29.5 (2C), 51.6 (OMe), 55.5 (Me-MOM), 68.0 (4C), 94.7 (CH_2-MOM), 107.0, 107.2, 112.8, 114.4, 115.8, 116.1, 118.7, 119.9, 124.6, 125.2, 129.0, 129.7, 135.1, 135.2, 152.7, 154.3, 174.5(1C). Anal. Calcd for $C_{27}H_{26}O_7$: C, 70.12; H, 5.67. Found: C, 70.06; H, 5.50.

Optical Resolution of (±)-6i. Since the enantioselectivity of the CAL-B-catalyzed reaction of (±)-**6i** was extremely high, we conducted the a multigram scale reaction for this compound as follows: To the solution of (±)-**6i** (2.95 g, 5.01 mmol) in acetone

(50 mL) and pH 7.2 buffer (5.0 mL) was added CAL-B (Novozym435: 1.45 g, 50 wt %). After being stirred at 35 °C for 64 h, the reaction mixture was filtered though a glass sintered filter with a Celite pad to remove the lipase. The filtrate was evaporated under vacuum, and then the residue was diluted with ether and washed with brine. The ether layer was dried ($MgSO_4$), evaporated, and chromatographed on a silica gel flash column (hexane/acetone = 5/1 and hexane/acetone = 2/1) to give (*R*)-**7i** (1.00 g, 1.75 mmol, 35%) and (*S*)-**6i** (1.42 g, 2.40 mmol, 48%). Since the reaction is a kinetic resolution, we succeeded in obtaining optically pure (*S*)-**6i** in 44% yield when (±)-**6i** was treated with lipase for 72 h.

(*R*)-**7i**: >99% ee (Chiralpak AD, hexane/2-propanol/TFA = 9:1:0.01, 35 °C), t_R = 13.5 min for (*R*)-isomer, 14.3 min for (*S*)-isomer; $[\alpha]^{24}_D$ +20.4 (*c* 1.0, $CHCl_3$): mp 156 °C (ether); R_f 0.3 (hexane/ethyl acetate/MeOH = 20:20:1); IR (KBr) 3433, 2920, 1705(CO), 1583, 1490, 1238, 1020, 875, 810 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.66−1.83 (2H, m), 1.87−2.00 (2H, m), 3.12 (3H, s), 3.93−4.06 (2H, m), 4.95 (1H, d, *J* = 6.9 Hz), 5.09 (1H, d, *J* = 6.9 Hz), 6.93 (1H, d, 9.1 Hz), 7.00 (1H, d, *J* = 9.2 Hz), 7.25−7.30 (2H, m), 7.41 (1H, d, *J* = 9.1 Hz), 7.56 (1H, d, *J* = 9.2 Hz), 7.84 (2H, t, *J* = 9.2 Hz), 8.00 (1H, s), 8.01 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.2 (3C), 29.5 (2C), 55.9 (Me-MOM), 68.2 (4C), 94.9 (CH_2-MOM), 116.4, 117.7, 118.0, 120.0, 120.7, 127.0, 128.7, 128.8, 129.7, 129.7, 129.9, 130.4, 130.8, 132.3, 132.4, 152.8, 154.3, 178.8 (1C). Anal. Calcd for $C_{26}H_{22}Br_2O_5$: C, 54.38; H, 3.86. Found: C, 54.37; H, 3.85.

(*S*)-**6i**: 83% ee (Chiralpak AD, hexane/2-propanol = 9:1, 35 °C), t_R = 10.6 min for (*R*)-isomer, 9.1 min for (*S*)-isomer; $[\alpha]^{23}_D$ −11.6 (*c* 1.0, $CHCl_3$); $[\alpha]^{23}_D$ −24.6 (*c* 1.0, $CHCl_3$) for >99% ee of (*S*)-**6i**.

(±)-**6i**: mp 107 °C (recrystallized from ether); R_f 0.33 (hexane/ethyl acetate = 3/1); IR (KBr) 3500, 2900, 1751 (CO), 1701 (CO), 1136, 1086, 1015, 802, 750 cm^{-1}; ^1H NMR (500 MHz, δ, $CDCl_3$) δ 1.67−1.79 (2H, m), 1.81−1.96 (2H, m), 3.15 (3H, s), 3.56 (3H, s), 3.93−4.07 (2H, m), 4.93 (aH, d, *J* = 6.9 Hz), 5.08 (1H, d, *J*= 6.9 Hz), 6.93 (1H, d, *J* = 9.1 Hz), 7.00 (1H, d, *J* = 9.1 Hz), 7.28 (2H, dt, *J*=1.8 Hz, 8.8 Hz), 7.42 (1H, d, *J* = 9.2 Hz), 7.58 (1H, d, *J* = 9.2 Hz), 7.86 (2H, dd, *J* = 6.9 Hz, 9.2 Hz), 8.02 (2H, dd, *J* = 2.3 Hz, 5.0 Hz) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.4 (3C), 29.5 (2C), 51.5 (OMe), 55.9 (Me-MOM), 68.2 (4C), 94.9 (CH_2-MOM), 116.3, 117.5, 117.9, 118.0, 119.9, 120.7, 127.0, 128.6, 128.7, 129.6, 129.7, 129.8, 130.7, 130.8, 132.3, 132.4, 152.8, 154.3, 173.4 (1C). Anal. Calcd for $C_{27}H_{24}Br_2O_5$: C, 55.12; H, 4.11. Found: C, 55.04; H, 3.72.

Optical Resolution of (±)-7k. (*R*)-**7k**: 85% ee (Chiralpak AD, hexane/2-propanol/TFA = 9/1/0.01, 35 °C), t_R = 23.2 min for (*R*)-isomer, 10.1 min for (*S*)-isomer; $[\alpha]^{24}_D$ −34 (*c* 1.0, $CHCl_3$); R_f 0.27 (hexane/ethyl acetate/MeOH = 20:20:1); IR (KBr) 3500 (broad), 2900, 1751 (CO), 1701 (CO), 1136, 1086, 1015, 802, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.35−1.48 (2H, m), 1.77−1.91 (2H, m), 2.08−2.18 (2H. m), 3.16 (3H, s), 4.98 (1H, d, *J*= 6.9 Hz), 5.06 (1H, d, *J* = 6.9 Hz), 7.14 (1H, d, *J* = 8.7 Hz), 7.22−7.46 (6H, m), 7.56 (1H, d, *J* = 9.2 Hz), 7.83 (1H, d, *J* = 8.3 Hz), 7.92 (1H, s), 7.94 (1H, d, *J* = 2.7 Hz), 7.99 (1H, d, *J* = 9.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3 (3C), 32.1 (4C), 32.9 (2C), 55.8 (Me-MOM), 94.9 (CH_2-MOM), 116.6, 119.2, 121.8, 124.2, 125.2, 125.4, 125.6, 126.2, 126.5, 126.6, 1278, 128.1, 129.1, 129.6, 130.0, 131.7, 133.5, 133.6, 146.6, 152.6, 170.9 (1C), 178.7 (5C). Anal. Calcd for $C_{27}H_{24}O_6$: C, 72.96; H, 5.44. Found: C, 72.74; H, 5.63.

(*S*)-**6k**: 33% ee (Chiralpak AD, hexane/2-propanol = 9:1, 35 °C), t_R = 18.0 min for (*R*)-isomer, 11.7 min for (*S*)-isomer; $[\alpha]^{23}_D$ −12 (*c* 1.0, $CHCl_3$) .

(±)-**6k**: R_f 0.40 (hexane/ethyl acetate = 2/1); IR (KBr) 2950, 1734 (CO), 1593, 1508, 1434, 1146, 1015, 814, 754 cm^{-1}; ^1H NMR (500 MHz, δ, $CDCl_3$) δ 1.36−1.50 (2H, m), 1.77−1.89 (2H, m), 2.05−2.17 (2H, m), 3.17 (3H, s), 3.60 (3H, s), 4.99 (1H, d, *J*= 6.9 Hz), 5.83 (1H, d, *J* = 6.9 Hz), 7.13 (1H, d, *J* = 8.3 Hz), 7.22−7.47 (7H, m), 7.56 (1H, d, *J* = 9.2 Hz), 7.85 (1H, d, *J* = 8.3 Hz), 7.93 (1H, s), 7.95 (1H, s), 7.99 (1H, d, *J* = 8.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.6 (3C), 32.2 (4C), 33.0 (2C), 51.4 (OMe), 55.8 (Me-MOM), 94.9 (CH_2-MOM), 116.5, 119.2, 121.8, 124.1, 125.1, 125.4, 125.5, 126.1, 126.4, 126.5, 127.7, 128.0, 129.0, 129.5, 129.9, 131.7, 133.5, 133.6, 146.6, 152.6, 170.9(5C), 173.0(1C). Anal. Calcd for $C_{28}H_{26}O_6$: C, 73.35; H, 5.72. Found: C, 73.70; H, 5.65.

Optical Resolution of (±)-7l. (*R*)-**7l**: 92% ee (Chiralpak AD, hexane/2-propanol/TFA = 4:1:0.01, 35 °C), t_R = 18.7 min for (*R*)-isomer, 12.7 min for (*S*)-isomer; $[\alpha]^{25}_D$ +28 (*c* 1.0, MeOH); R_f 0.2 (hexane/ethyl acetate/MeOH = 20:20:1); IR (KBr) 2950, 1757 (CO), 1709 (CO), 1585, 1492, 1201, 1024, 878, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.40−1.53 (2H, m), 1.87−1.99 (2H, m), 2.15 (2H, t, 7.3 Hz), 3.19 (3H, s), 5.00 (1H, d, *J*= 6.9 Hz), 5.08 (1H, d, *J* = 6.9 Hz), 6.97 (1H, d, *J* = 8.7 Hz), 7.10 (1H, d, *J* = 9.2 Hz), 7.31 (1H, dd, *J* = 2.3 Hz, 9.0 Hz), 7.37 (1H, dd, *J* = 1.8 Hz, 9.2 Hz), 7.44 (1H, d, *J* = 9.1 Hz), 7.58 (1H, d, *J* = 9.2 Hz), 7.86 (1H, d, *J* = 9.1 Hz), 7.91 (1H, d, *J* = 9.2 Hz), 8.01 (1H, d, *J* = 2.3 Hz), 8.11 (1H, d, *J* = 1.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3 (3C), 32.2 (4C), 32.8 (2C), 56.0 (Me-MOM), 94.8 (CH_2-MOM), 117.4, 118.2, 118.6, 119.8, 123.0, 125.0, 127.0, 127.7, 128.4, 129.4, 129.8, 129.9, 130.0, 130.1, 130.5, 131.9, 132.0, 132.8, 146.9, 152.9, 170.7 (5C), 178.3 (1C). Anal. Calcd for $C_{27}H_{22}Br_2O_6$: C, 53.84; H, 3.68. Found: C, 53.94; H, 3.68.

(*S*)-**6l**: 90% ee (Chiralpak AD, hexane/2-propanol=4/1, 35 °C), t_R =16.7 min for (*R*)-isomer, 10.5 min for (*S*)-isomer; $[\alpha]^{25}_D$ −31 (*c* 1.0, MeOH).

(±)-**6l**: mp 106 °C (recrystallized from ether); R_f 0.48 (hexane/ethyl acetate = 2/1); IR (KBr) 2950, 1757 (CO), 1736 (CO), 1585, 1493, 1200, 1022, 943, 812 cm^{-1}; ^1H NMR (500 MHz, δ, $CDCl_3$) δ 1.36−1.54 (2H, m), 1.79−1.90 (2H, m), 2.08−2.18 (2H, m), 3.19 (3H, s), 3.62 (3H, s), 5.00 (1H, d, *J*= 6.9 Hz), 5.08 (1H, d, *J* = 6.9 Hz), 6.96 (1H, d, *J* = 9.1 Hz), 7.09 (1H, d, *J* = 8.7 Hz), 7.31 (1H, dd, *J* = 1.9 Hz, 8.9 Hz), 7.36 (1H, dd, *J* = 1.9 Hz, 8.9 Hz), 7.44 (1H, d, *J* = 8.7 Hz), 7.59 (1H, d, *J* = 9.2 Hz), 7.86 (1H, d, *J* = 9.2 Hz), 7.91 (1H, d, *J* = 8.7 Hz), 8.01 (1H, d, *J* = 2.3 Hz), 8.11 (1H, d, *J* = 1.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.6 (3C), 32.2 (4C), 32.9 (2C), 51.5 (OMe), 56.0 (Me-MOM), 94.8 (CH_2-MOM), 117.4, 118.2, 119.8, 123.1, 125.0, 127.0, 127.7, 128.4, 129.3, 129.8, 129.9, 130.0, 130.1, 130.5, 131.9, 132.0, 132.8, 147.0, 152.9, 170.8 (5C), 172.9 (1C). Anal. Calcd for $C_{28}H_{24}Br_2O_6$: C, 54.57; H, 3.93. Found: C, 54.68; H, 3.93.

Preparation of (*S*)-1-(2-Hydroxy-6-(naphthalen-1-yl)naphthalen-1-yl)-6-(naphthalen-1-yl)naphthalen-2-ol (9)[28] by the Suzuki−Miyaura Coupling Reaction[27] (Scheme 1). A mixture of (*S*)-**7i** (574 mg, 1.0 mmol, 97% ee), 1-naphthylboronic acid (378 mg, 2.2 mmol), $Pd(PPh_3)_4$ (116 mg, 0.10 mmol), 2 M NaOH aq (3.3 mL), and THF (15 mL) was heated at 60 °C for 24 h with stirring. After being cooled to rt, 2 M HCl was added to the reaction mixture, and then the organic layer was extracted with ethyl acetate, dried ($MgSO_4$), and evaporated. Silica gel flash column chromatography using hexane/acetone (3:1) gave (*S*)-**8** (666 mg, 0.99 mmol, 99%). This compound was then converted to (*S*)-**9**.[28] To the solution of (*S*)-**8** (134 mg, 0.20 mmol) in CH_2Cl_2 (2.0 mL) was added BBr_3 (1.0 mL) at −78 °C, and then the mixture was warmed to rt for 3 h with stirring. The reaction was quenched by addition of 2 M HCl and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and evaporated to give a brown solid. This was purified by silica gel TLC using hexane/ethyl acetate (2:1) to give (*S*)-**9** (40 mg, 0.074 mmol, 34%). However, a large amount of unidentified byproduct was formed.

(*S*)-**9**: $[\alpha]^{25}_D$ +173.2 (*c* 1.0, $CHCl_3$), <99% ee after recrystallization, lit.[28] $[\alpha]^{20}_{589}$ +357 ($CHCl_3$) for (*S*): mp 140 °C (recrystallized from cyclohexane/$CHCl_3$); R_f 0.22 (hexane/ethyl acetate = 3:1) ; IR (KBr) 3414 (broad s), 3013, 1697, 1597, 1477, 1352, 1020, 930, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.15 (2H, brs), 7.30−7.99 (22H, m); ^{13}C NMR (125 MHz, acetone-d_6) δ 115.1, 120.0, 125.4, 126.3, 126.6, 126.9, 128.0, 128.3, 129.2, 129.5, 129.7, 129.9, 130.8, 132.5, 134.6, 134.9, 136.0, 141.0, 154.9. Anal. Calcd for $C_{40}H_{26}O_2$: C, 89.19, H, 4.87. Found: C, 89.24, H, 4.79.

(*S*)-4-(1-(2-(Methoxymethoxy)-6-(naphthalen-1-yl)naphthalen-1-yl)-6-(naphthalen-1-yl)naphthalen-2-yloxy)butanoic Acid (8): $[\alpha]^{25}_D$ −24 (*c* 1.0, $CHCl_3$), 97% ee; mp 132 °C (recrystallized from $CHCl_3$); R_f 0.3 (hexane/ethyl acetate/methanol = 20:20:1); IR (KBr) 3433, 2920, 1705 (CO), 1576, 1479, 1240, 1020, 777, 754 cm^{-1}; ^1H NMR (500 MHz, δ, $CDCl_3$) δ 1.76−1.87 (2H, m), 1.97−2.05 (2H, m), 3.24 (3H, s), 4.03−4.17 (2H, m), 5.06 (1H, d, *J* = 6.9 Hz), 5.18(1H, d, *J* = 6.9 Hz), 7.33−8.04 (22H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.3 (3C), 29.7 (2C), 55.9 (Me-MOM), 68.3 (4C), 95.2 (CH_2-MOM), 115.9, 117.6, 120.5, 121.2, 125.2, 125.3, 125.4, 125.7, 126.0, 126.1, 126.2, 127.2, 127.2, 127.5, 128.2, 128.3, 128.8, 128.9, 129.0, 129.4, 129.6, 129.7, 129.9, 131.7, 133.2, 133.2, 133.7, 133.8, 136.2, 136.4, 140.2, 152.8, 154.2, 179.1(1C). Anal. Calcd for $C_{46}H_{36}O_5$: C, 82.61, H, 5.43. Found: C, 82.64, H, 5.36.

Preparation of (*R*)-9 and (*R*)-12 starting from (*R*)-7l. (*R*)-6-Bromo-1-(6-bromo-2-(methoxymethoxy)naphthalen-1-yl)naphthalen-2-ol (10) (Scheme 2). To the solution of (*R*)-**7l**(4.33 g, 7.02 mmol, 85% ee) in a mixed solvent (9.0 mL of water and 26 mL of THF) was added $LiOH\cdot H_2O$ (1.18 g, 28.1 mmol) at 0 °C, and then the mixture was allowed to warm to rt with stirring for 40 h. The reaction was quenched by addition of 2 M HCl at 0 °C and then extracted with ethyl acetate, and the organic layer was washed with brine. The combined organic layers were dried ($MgSO_4$), evaporated, and chromatographed on silica gel flash column (hexane/ethyl acetate = 5:1) and gave (*R*)-**10** (3.39 g, 6.94 mmol, 99%) as a colorless oil: $[\alpha]^{23}_D$ −86 (*c* 1.0, $CHCl_3$); 85% ee, Chiralcel AD (hexane/2-propanol = 4:1) t_R = 6.2 min for (*S*)-isomer, 8.1 min for (*R*)-isomer; ^1H NMR (500 MHz, $CDCl_3$) δ 3.16 (3H, s), 5.03 (1H, b), 4.98 (1H, d, *J*= 6.9 Hz), 5.08 (1H, d, *J*= 6.9 Hz), 6.89 (1H, d, *J* = 8.7 Hz), 7.00 (1H, d, *J* = 8.7 Hz), 7.24−7.35 (3H, m), 7.59 (1H, d, *J* = 8.7 Hz), 7.79 (1H, d, *J* = 6.9 Hz), 7.90 (1H, d, *J* = 9.0 Hz), 8.00 (1H, d, *J* = 2.3 Hz), 8.04 (1H, d, *J* = 1.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.2, 56.2, 94.8, 114.8, 117.2, 117.9, 118.7, 118.8, 126.4, 126.7, 129.1, 129.8, 130.0, 130.1, 130.2, 131.1, 132.2, 132.3, 151.6, 153.8.

(*R*)-6-Bromo-1-(6-bromo-2-(methoxymethoxy)naphthalen-1-yl)-2-(methoxymethoxy)naphthalene (11).[29] To the suspension of NaH (224 mg, 9.34 mmol) in THF (10 mL) was added a THF (8.0 mL) solution of (*R*)-**10** (2.28 g, 4.67 mmol, 85% ee) at 0 °C, the mixture was stirred at 0 °C for 2 h, and then MOMCl (1.12 mg, 13.9 mmol) was added to this mixture at 0 °C and allowed to warm to rt with stirring for 3 h. The reaction was quenched by saturated NH_4Cl aqueous solution and acidified with 2 M HC, and filtered though a glass filter. The filtrate was extracted with ether and the combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Silica gel flash column chromatography (hexane/ethyl acetate = 10:1) and subsequent recrystallization from ether gave (*R*)-**11** (2.06 g, 3.87 mmol, 83%) as a colorless plate: $[\alpha]^{23}_D$ +20.2 (*c* 1.0, $CHCl_3$), >99% ee after recrystallization from ether (lit.[29] $[\alpha]_D$ +23.1 (*c* 1.0, THF); mp 147 °C (ether); R_f 0.53 (hexane/ethyl acetate = 3:1) ; ^1H NMR (500 MHz, $CDCl_3$) δ 3.16 (6H, s), 5.03 (4H, dd, *J* = 6.9 Hz, 53.2 Hz), 6.98 (2H, d, *J* = 9.2 Hz), 7.29 (2H, dd, *J* = 1.8 Hz, 9.2 Hz), 7.59 (2H, d, *J* = 9.1 Hz), 7.86 (2H, d, *J* = 9.1 Hz), 8.03 (2H, d, *J* = 1.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.9, 95.0, 118.0, 118.0, 120.7, 127.1, 128.7, 129.7, 129.9, 130.8, 133.4, 152.9. Anal. Calcd for $C_{24}H_{20}Br_2O_4$: C, 54.16; H, 3.79. Found: C, 53.87; H, 3.72. We prepared (*S*)-**11** through the same route starting from (*S*)-**7l** (78% ee). Although the starting material (*S*)-**7l** was not an optically pure form, it was successful to enhance the optical purity of (*S*)-**11** (99% ee) by recrystallization from ether.

(*R*)-6-Butyl-1-(6-butyl-2-hydroxynaphthalen-1-yl)naphthalen-2-ol (12).[30] To a mixture of (*R*)-**11** (532 mg, 1.0 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (41 mg, 0.05 mmol), and THF (5.0 mL) was added a THF solution of *n*-BuMgBr (1.0 M THF solution, 3.5 mL, 3.5 mmol) at 0 °C, and the mixture was stirred at 60 °C for 24 h. After being cooled to rt, the reaction was quenched by addition of saturated NH_4Cl aqueous solution and was extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and evaporated to dryness. Silica gel flash column chromatography using hexane/ethyl acetate (30:1) gave the corresponding coupling product (421 mg, 0.87 mmol, 87%) as a colorless oil: $[\alpha]^{25}_D$ +19 (*c* 1.0, $CHCl_3$) . This compound was treated with concd. HCl (0.40 mL) in dioxane (2.0 mL) and the mixture was stirred at 60 °C for 24 h. After being cooled to rt, the reaction mixture was poured into water, and was extracted with ether. The combined organic layers were dried and purified by silica gel flash column chromatography (hexane/ethyl acetate = 10:1) and recrystallization from hexane to give optically pure (*R*)-**12** (344 mg, 0.86 mmol) as a colorless needle: $[\alpha]^{28}_D$ −68.6 (*c* 1.0, $CHCl_3$), >99% ee; R_f 0.43 (hexane/ethyl acetate = 3:1); IR (KBr) 3440, 2860, 1600, 1510, 1460, 1360, 1310, 1240, 1260, 1220, 1160, 950, 880, 830, 680 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.94 (6H, t, *J* = 7.3 Hz), 1.38 (4H, sext, *J* = 7.3 Hz), 1.65 (4H, qu, *J* = 7.8 Hz), 2.72 (4H, t, *J* = 7.8 Hz), 4.97 (2H, brs), 7.09 (2H, d, *J* = 8.8 Hz), 7.16 (2H, dd, *J* = 1.8 Hz, 8.8 Hz), 7.34 (2H, d, *J*= 9.1 Hz), 7.66 (2H, s), 7.090 (2H, d, *J*= 9.1 Hz) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 22.4, 33.5, 35.4, 55.7, 110.9, 117.6, 124.2, 126.8, 129.0, 129.6, 130.7, 131.7, 138.5, 152.0.

We also prepared (*S*)-**12** ($[\alpha]^{25}_D$ +69.4 (*c* 1.0, $CHCl_3$), >99% ee) from (*S*)-**7l** through the same route. X-ray crystallographic analysis of (*R*)-**12** was successfully carried out. Crystal and refinement data for (*R*)-**12**: $C_{28}H_{30}O_2$, formula weight = 398.54, monoclinic, space group *P*21(#4), *a* = 10.195(6) Å, *b* = 8.387(5) Å, *c* = 13.540(9) Å, *b* = 108.076(17)°, *V* = 1100.6(11)^3, *Z* = 2, d_{calc} = 1.203 g cm^{-3}, *R*(Rw) = 0.0500 for 11705 diffraction data with $I > 2.00\sigma(I)$ and 281 valuable.

(*R*)-6-(Naphthalen-1-yl)-1-(6-(naphthalen-1-yl)-2-hydroxynaphthalen-1-yl)naphthalen-2-ol (9)[28] (Scheme 2). A mixture of (*R*)-**11**[29] (532 mg, 1.0 mmol), 1-naphthylboronic acid (344 mg, 2.0 mmol), $Pd(PPh_3)_4$ (116 mg, 0.10 mmol), 2 M NaOH (3.0 mL, 6.0 mmol), and THF (10 mL) was heated under reflux conditions for 24 h. After being cooled to rt, the reaction mixture was quenched by the addition of water and then extracted with ethyl acetate. The combined organic layers were washed with brine and dried ($MgSO_4$), and the solvent was removed by evaporation. The residue was purified by silica gel flash column chromatography (hexane/ethyl acetate = 10:1) to give di-MOM ether (*R*)-**13** (570 mg, 0.91 mmol, 91%) as a white solid. This di-MOM ether was then treated with 0.55 mL of concd HCl in 1,4-dioxane (3.0 mL) at 60 °C for 16 h to give (*R*)-**9** (400 mg, 0.74 mmol) in 94% yield: mp 300 °C (recrystallized from hexane and ethyl acetate): R_f 0.22 (hexane/ethyl acetate = 3:1) ; IR (KBr) 3520, 3410, 3010, 1700, 1600, 1480, 1460, 1350, 1130, 1020, 960, 930, 890, 870, 760, 690, 670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.15 (2H, brs), 7.30−7.99 (22H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 115.1, 120.0, 125.4, 126.3, 126.6, 126.9, 128.0, 128.3, 129.2, 129.5, 129.7, 129.9, 130.8, 132.5, 134.6, 134.9, 136.0, 141.0, 154.9; $[\alpha]^{26}_D$ −173.10 (*c* 1.0, $CHCl_3$), >99% ee (lit. [26] $[\alpha]^{20}_{589}$ +357 (*c* 0.89, $CHCl_3$) (*S*)).

Di-MOM-ether of (*R*)-**13**: mp 197 °C (recrystallized from ether); $[\alpha]^{26}_D$ −43.2 (*c* 1.0, $CHCl_3$), >99% ee; R_f 0.49 (hexane/ethyl acetate = 3:1); IR (KBr) 2900, 2780, 1580, 1470, 1330, 1230, 1190, 1140, 1070, 1010, 950, 920, 890, 770, 420 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.27 (6H, s), 5.010 (1H, d, *J* = 6.9 Hz), 5.18 (1H, d, *J* = 6.9 Hz), 7.38−7.56 (12H, m), 7.68 (2H, d, *J* = 9.1 Hz), 7.87 (2H, d, *J* = 7.8 Hz), 7.92 (2H, d, *J* = 8.2 Hz), 7.98 (2H, d, *J* = 8.2 Hz), 8.02 (2H, s), 8.03 (2H, d, *J* = 8.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.9, 95.3, 117.6, 121.2, 125.7, 126.0, 126.1, 127.2, 127.6, 128.3, 128.8, 129.0, 129.6, 129.9, 131.7, 133.2, 133.8, 136.5, 140.1, 152.9. Anal. Calcd for $C_{44}H_{34}O_4$: C, 84.32; H, 5.47. Found: C, 84.11; H, 5.47.

Asymmetric Henry Reaction Catalyzed by La−BINOL Complex.[32] Synthesis of (*S*)-1-Nitro-4-phenylbutan-2-ol (14).[32] La−BINOL complex was prepared following the method reported by Shibasaki et al:[32] (*S*)-BINOL derivatives (0.15 mmol) were dried under a vacuum at 60 °C for 2 h prior to the La complex. To a solution of dried BINOL derivatives in THF (1.35 mL) was added a 0.2 M THF solution of La(O-*i*-Pr)$_3$ (0.25 mL, 0.05 mmol) at 0 °C, the mixture was stirred for 30 min at rt, and then to this mixture

was added 0.1 mL of *n*-BuLi (1.52 M in hexane, 0.15 mmol) at 0 °C. After being stirred at rt for 12 h, 0.05 mL of 1.0 M THF solution of H_2O (0.05 mmol) was added at rt to give a THF solution of La−BINOL complex (0.03 M). This solution was immediately used for the reaction.

A 0.03 M THF solution of La−BINOL complex (0.67 mL, 0.02 mmol) was diluted with 2.0 mL of THF, and then the solution was cooled to −50 °C and stirred for 30 min at the same temperature. To the mixture was added nitromethane (366 mg, 6.0 mmol), the mixture was stirred for 30 min at −50 °C, and then 3-phenylprorionaldehyde (80.6 mg, 0.6 mmol) was added to the mixture. After being stirred for 24 h at −50 °C, the reaction was quenched by addition of 2 M HCl and extracted with ethyl acetate. The combined organic layer was dried ($MgSO_4$), filtered, evaporated, chromatographed on silica gel TLC, using hexane/ethyl acetate =3:1, and gave (*S*)-1-nitro-4-phenylbutan-2-ol (**14**):[32b] ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.76−1.91(2H, m), 2.60 (1H, d, J= 5.1 Hz), 2.72−2.89 (2H, m), 4.47−4.34 (1H, m), 4.36−4.44 (2H, m), 7.32−7.55 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.2, 35.1, 67.8, 80.5, 126.2, 128.3, 128.5, 140. 6; enantiomeric excess of **14** was determined by HPLC analysis (Chiralpak AD, hexane/2-propanol = 9:1, 35 °C), t_R = 11.0 min for (*R*)-isomer, 12.8 min for (*S*)-isomer.

Asymmetric Ethylation Catalyzed by Ti−BINOL Complex.[33] **Synthesis of (*S*)-1-Phenylpropan-1-ol (15).**[33] A mixture of (*S*)-BINOL derivatives (0.05 mmol) and Ti(O-*i*-Pr)$_4$ (0.6 mmol) in toluene (1.5 mL) was stirred at rt for 30 min. To this solution was added 1.5 mL of a hexane solution of diethylzinc (1.5 mmol) at −78 °C, the mixture was stirred for 30 min, and then benzaldehyde (0.5 mmol) was added to this mixture at the same temperature. The resulting mixture was allowed to warm to 0 °C and stirred for 1 h at rt, and the reaction was quenched by addition of saturated NH_4Cl aqueous solution at 0 °C. The resulting mixture was next filtered through a glass filter with a Celite pad to remove the solid formed. The filtrate was dried ($MgSO_4$), evaporated, and purified by silica gel TLC (hexane/ethyl acetate = 3:1) to give (*S*)-**15**: ^{1}H NMR (400 MHz, δ, $CDCl_3$) δ 0.92 (3H, t, J = 7.4 Hz), 1.70−1.88 (2H, m), 2.20 (1H, brs), 4.60 (1H, t, J = 7.0H z), 7.33−7.37 (5H, m). Enantiomeric excess of (*S*)-**14** was determined by HPLC analysis (Chiralcel OD-H, hexane/2-propanol = 100:1, 35 °C): t_R = 18.6 min for (*R*)-isomer, 21.6 min for (*S*)-isomer.

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Supporting Information Available: Experimental procedure for the syntheses of compounds **6a**−**l**. Enzymatic resolution of (±)-**6g**, **6k**, and **6l**. ^{1}H and ^{13}C NMR spectra for **6a**−**l**, **7g**−**l**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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