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Effects of reaction temperature and acyl group for lipase-catalyzed chiral binaphthol synthesis

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Abstract—*Candida antarctica* lipase-catalyzed hydrolysis of *O*-butyryl-BINOL [(±)-**3**] or *O*-butyryl-6,6′-dibromo-BINOL [(±)-**5**] yielded optically active BINOL [(*R*)-**1**] or 6,6′-dibromo-BINOL [(*R*)-**4**] with high enantiomeric excess at 80 °C. Reaction temperature and acyl group of substrate had a great influence on the reactivity and enantioselectivity, respectively, of lipase-catalyzed hydrolysis for chiral binaphthol synthesis.

Chiral 2,2′-dihydroxy-1,1′-binaphthyl (BINOL) derivatives have been widely used as chiral ligands of catalysts for asymmetric synthesis.[1] Illustration of recent asymmetric reactions using BINOL ligands are alkynylation of aldehydes,[2] hydrogenation of olefines and allylic alkylation,[3] cyanation of aldehydes,[4] Mannich-type reactions,[5] Diels–Alder reactions,[6] Michael and epoxidation reactions,[7] aldol reactions,[8] and addition of diethyl zinc to benzaldehyde.[9] Additionally, chiral BINOL derivatives have received much attentions in the context of chiral resolving agent,[10] chiral host compounds,[11] liquid crystals,[12] and chiral polymers,[13] that include the biaryl unit.

A wide range of oxidative coupling methods for the preparation of chiral BINOL derivatives have been developed in the presence of chiral transition metal catalyst, for example, diamine-copper(I),[14] schiff-copper(I),[15] amino ester-oxovanadium(IV)[16] and salen-ruthenium complexes.[17] Recently, palladium-catalyzed kinetic resolution of 1,1′-biaryls by alcoholysis of their vinyl ethers has been reported.[18] However, synthesis of BINOL vinyl ethers need hard condition or expensive reagent. For another approach to chiral BINOL derivatives, chemical[19] and enzymatic[20] resolution of racemic mixtures have been reported. Although lipases have been widely employed as catalysts in the synthesis of extensive optically active compounds in comparison with other enzymes, BINOL derivatives can be resolved only by lipase from *Pseudomonas* species.[20a,b] It can be seen that reactivity of BINOL in the presence of lipase catalyst is affected by steric hindrance of bulky binaphthyl ring. Our previous work demonstrated that lipase-catalyzed amidation of 1,1′-binaphthyl amines or esters was also ineffective in the case of amino or ester groups directly bonded to the aromatic ring, whereas the enzymatic resolution was successful when the amino or ester group was located on the alkyl side chain.[21]

Candida antarctica lipase B (CALB) can induce high enantioselectivity on a broad range of substrates,[22] including secondary alcohols[23] and other compounds. CALB is an interesting lipase with potential application in a number of industrial processes such as the synthesis of triglycerides,[24] esterification of terpenic alcohols,[25] etc. In addition, immobilized CALB is thermostable and can be used at 60–80 °C for long periods of time without loss of activity.[26] Consequently, the applicability of immobilized CALB-catalyzed resolutions using BINOL derivatives at high temperature became an area of research interest.

Racemic mixtures of 2-acetoxy-2′-hydroxy-1,1′-binaphthyl (±)-**2** and 2-butyroxy-2′-hydroxy-1,1′-binaphthyl (±)-**3** were synthesized by known procedures.[20b,27] 6,6′-Dibromo-2-butyroxy-2′-hydroxy-1,1′-binaphthyl (±)-**5** was obtained from BINOL via two steps (Scheme 1).[28] At first, we chose cyclopentyl methyl ether (CPME) as a solvent of lipase-catalyzed hydrolysis, because the

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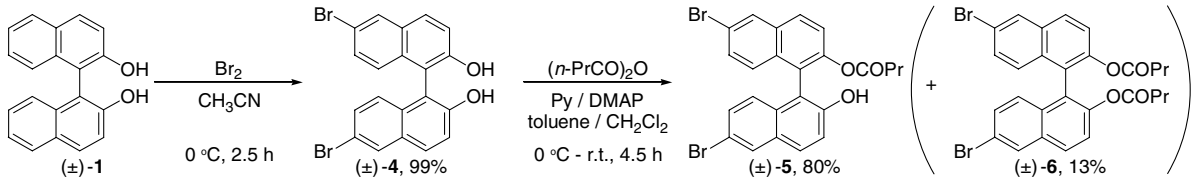


Scheme 1. Synthesis of substrate (±)-**5**.

chemical properties of CPME is similar to methyl *tert*-butyl ether (MTBE) and diisopropyl ether (DIPE) which are very useful for solvent of enzymatic resolutions. In addition, CPME has high boiling point (106 °C) and can be used at high temperature in lipase-catalyzed hydrolysis. As shown in Table 1, CALB-catalyzed hydrolysis of (±)-**2** was initially attempted at 30 °C.[29,30] However, (±)-**2** was not a substrate of choice at 30 °C condition (entry 1). In the case of 60 °C condition, hydrolysis of (±)-**2** proceeded to 35% yield after 96 h (entry 2), with poor selectivity (28% ee). The reaction rate at 80 °C was more rapid than 60 °C condition (entry 3). When the reaction temperature was increased, the reaction rate evidently increased as shown in Figure 1. However, enantioselectivity of (±)-**2** was not satisfactory (Fig. 2).

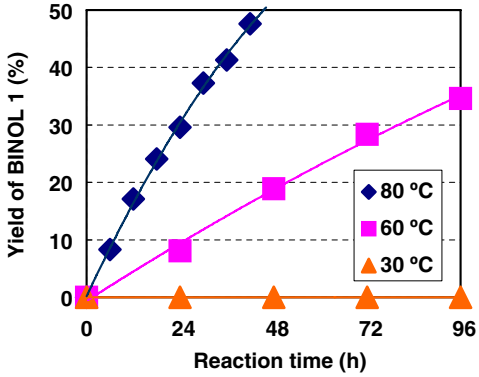
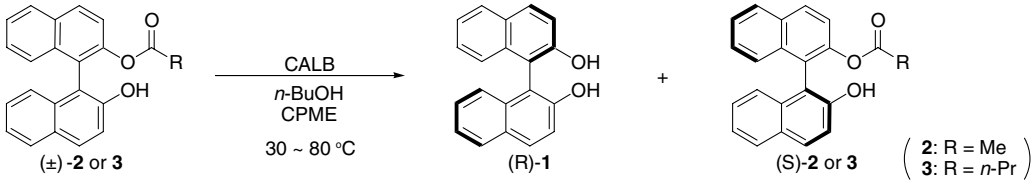


Figure 1. Time conversion for CALB-catalyzed hydrolysis of (±)-**2** at various temperatures.

Next, (±)-**3** was used as substrate of enzymatic hydrolysis with the view of high enantioselective resolution. Similar to the lipase-catalyzed hydrolysis of (±)-**2**, ester (±)-**3** was not a substrate under 30 °C condition (Table 1, entry 4). In the case of 60 °C condition, hydrolysis of (±)-**3** proceeded at a low reaction rate, although this reaction gave high enantioselectivity (entry 5). CALB-catalyzed hydrolysis of (±)-**3** at 80 °C proceeded to 43% yield after 72 h (entry 6), with high enantioselectivity (91% ee). As shown in Figure 3, temperature effect for hydrolysis of (±)-**3** was shown more evidently than hydrolysis of (±)-**2**. In addition, enantioselectivity with (±)-**3** was higher than that with (±)-**2** (Fig. 4). It could be seen that enantioselectivity of monoacylated BINOL in the presence of CALB catalyst was affected by alkyl size of the substituted acyl group.

We optimized the solvents for the reaction at 80 °C condition. As shown in Table 2, toluene resulted in the excellent yields (entries 7, 8), with higher enantioselectivities than hydrolysis using CPME. Hydrolysis conversions using other solvents were very low (entries 1–6), although these reactions afforded high enantioselectivities, with the exception of using *N*,*N*-dimethylformamide (DMF). The scale-up reaction in toluene was carried out at 100 °C in order to obtain the isolated

Table 1. Effects of temperature and acyl group for CALB-catalyzed hydrolysis of (±)-**2** and **3**[a]



Entry	Substrate	Temperature (°C)	Time (h)	Diol (*R*)-**1**[c]		Monoester (*S*)-**2** or **3**[c]		*E* value[d]
				Yield (%)[b]	ee (%)[c]	Yield (%)[b]	ee (%)[c]	
1	(±)-**2**	30	96	Not detected		Recovery		—
2	(±)-**2**	60	96	35	28	65	14	2
3	(±)-**2**	80	48	52	23	48	24	2
4	(±)-**3**	30	96	Not detected		Recovery		—
5	(±)-**3**	60	96	12	99	88	16	233
6	(±)-**3**	80	72	43	91	57	65	42

[a] Reaction conditions: 0.0672 mmol of substrate, 0.672 mmol of *n*-butanol, 40 mg of CALB, 2 mL of CPME, 2.0 mg of acetophenone (standard substance).
[b] Determined by internal standard method of HPLC using Chiralcel OG (254 nm, 0.5 mL/min, *n*-hexane/IPA = 15:1).
[c] Configuration and enantioselectivity were determined by HPLC analysis using Chiralcel OG (254 nm, 0.5 mL/min, *n*-hexane/IPA = 15:1).
[d] $E = \ln[(ee_p(1 - ee_s))(ee_p + ee_s)^{-1}] / \ln[(ee_p(1 + ee_s))(ee_p + ee_s)^{-1}]$; see Ref. 31.

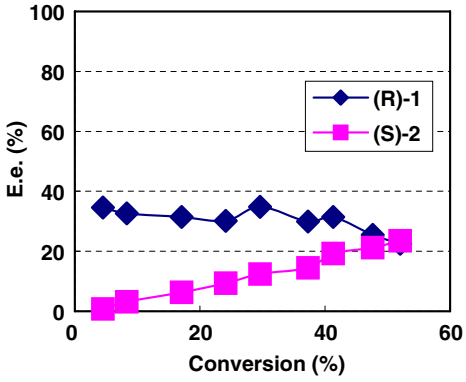


Figure 2. Conversion versus ee plots for CALB-catalyzed hydrolysis of (±)-**2** at 80 °C.

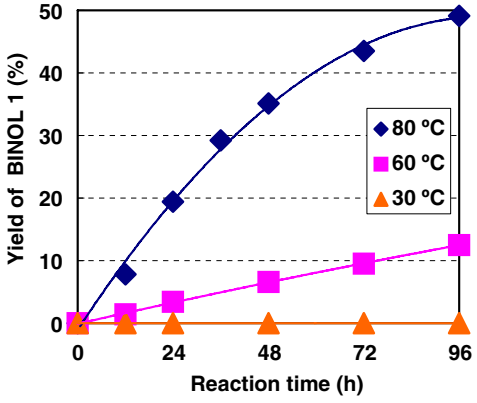


Figure 3. Time conversion for CALB-catalyzed hydrolysis of (±)-**3** at various temperatures.

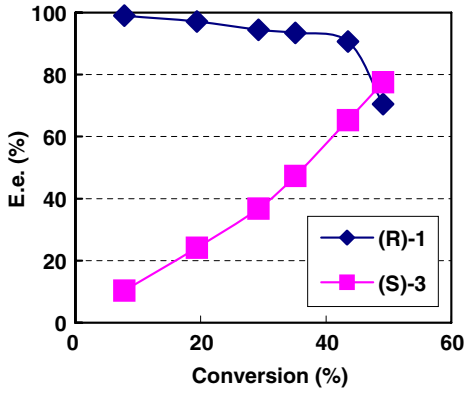
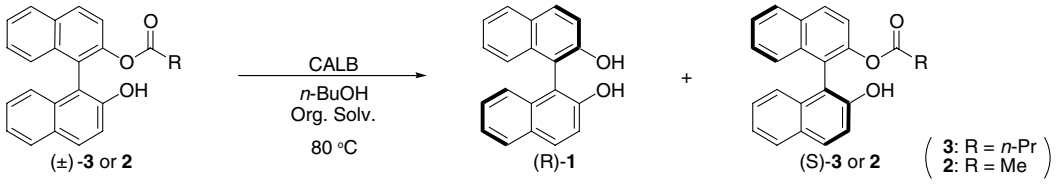


Figure 4. Conversion versus ee plots for CALB-catalyzed hydrolysis of (±)-**3** at 80 °C.

chiral BINOLs and to decrease the amount of CALB.[32] This reaction temperature could permit high isolated yield [(*R*)-**1**, 51%; (*S*)-**3**, 48%] with high enantioselectivity [(*R*)-**1**, 92% ee; (*S*)-**3**, 93% ee] even at half amount of CALB in comparison with 80 °C condition.

Finally, in order to compare the reactivity of (±)-**3**, lipase-catalyzed hydrolysis was carried out using 6,6′-dibromo substituted (±)-**5**.[33] The hydrolysis of (±)-**5** gave (*R*)-**4** with moderate enantioselectivity (68% ee), although this reaction took place more rapidly than (±)-**3** (Table 3, entry 1). To explore the effect of alcoholysis agent, we examined reaction of (±)-**5** using alcohol other than the *n*-butanol. Although 2-chloroethanol was the best alcoholysis agent in terms of enantioselectivity

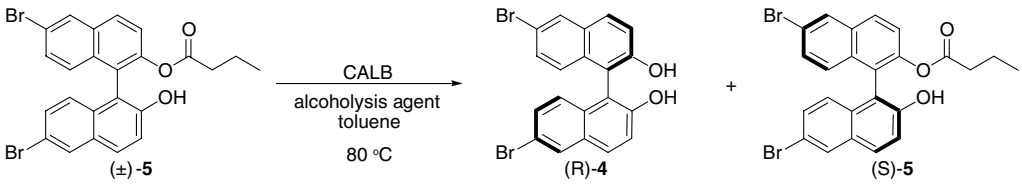
Table 2. Effect of solvents for CALB-catalyzed hydrolysis of (±)-**3** and **2** at 80 °C[a]



Entry	Substrate	Solvent[b]	Time (h)	Diol (*R*)-**1**[d]		Monoester (*S*)-**3** or **2**[d]		*E* value[e]
				Yield (%)[c]	ee (%)[d]	Yield (%)[c]	ee (%)[d]	
1	(±)-**3**	Dioxane	72	7	99	93	7	213
2	(±)-**3**	CH_3CN	72	5	99	95	4	207
3	(±)-**3**	MEK	72	6	99	94	7	213
4	(±)-**3**	DMF	72	7	4	93	1	1
5	(±)-**3**	1,2-DCE	72	7	99	93	7	213
6	(±)-**3**	*n*-BuOH	72	5	99	95	3	205
7	(±)-**3**	Toluene	72	51	93	49	92	91
8	(±)-**2**	Toluene	36	53	48	47	47	4
cf.	(±)-**3**	CPME	72	43	91	57	65	42
	(±)-**2**	CPME	48	52	23	48	24	2

[a] Reaction conditions: 0.0672 mmol of substrate, 0.672 mmol of *n*-butanol, 40 mg of CALB, 2 mL of solv., 2.0 mg of acetophenone (standard substance).
[b] MEK: methylethylketone, DMF: *N*,*N*-dimethylformamide, 1,2-DCE: 1,2-dichloroethane.
[c] Determined by internal standard method of HPLC analysis using Chiralcel OG (254 nm, 0.5 mL/min, *n*-hexane/IPA = 15:1).
[d] Configuration and enantioselectivity were determined by HPLC analysis using Chiralcel OG (254 nm, 0.5 mL/min, *n*-hexane/IPA = 15:1).
[e] $E = \ln[(ee_p(1 - ee_s))(ee_p + ee_s)^{-1}] / \ln[(ee_p(1 + ee_s))(ee_p + ee_s)^{-1}]$; see Ref. 31.

Table 3. Effect of alcoholysis agent for CALB-catalyzed hydrolysis of (±)-**5** at 80 °C[a]



Entry	Substrate	Alcohol	Time (h)	Diol (*R*)-**4**[c]		Monoester (*S*)-**5**[c]		*E* value[d]
				Yield (%)[b]	ee (%)[c]	Yield (%)[b]	ee (%)[c]	
1	(±)-**5**	*n*-BuOH	48	48	68	52	63	10
2	(±)-**5**	*n*-BuOH	72	61	62	39	97	17
3	(±)-**5**	$PhCH_2OH$	48	54	79	46	94	30
4	(±)-**5**	$ClCH_2CH_2OH$	178	34	92	66	47	38
cf.	(±)-**3**	*n*-BuOH	72	51	93	49	92	91

[a] Reaction conditions: 0.0672 mmol of substrate, 0.672 mmol of alcohol, 40 mg of CALB, 2 mL of toluene, 2.0 mg of acetophenone (standard substance).
[b] Determined by internal standard method of HPLC analysis using Chiralcel OD (254 nm, 0.5 mL/min, *n*-hexane/IPA = 9:1).
[c] Configuration and enantioselectivity were determined by HPLC analysis using Chiralcel OD (254 nm, 0.5 mL/min, *n*-hexane/IPA = 9:1).
[d] $E = \ln[(ee_p(1 - ee_s))(ee_p + ee_s)^{-1}] / \ln[(ee_p(1 + ee_s))(ee_p + ee_s)^{-1}]$; see Ref. 31.

((*R*)-**4**, 92% ee), rate of alcoholysis reaction was slower than *n*-butanol condition (entry 4).

In conclusion, we have found that the CALB-catalyzed hydrolysis reactions at high temperature (80 °C) of monoacylated binaphthols are able to give chiral BINOLs. It is proved that these reactions are influenced by the reaction temperature and configuration of the substituted acyl group. The hydrolysis of butyryl group containing (±)-**3** in toluene at 80 °C was the optimum condition. Hydrolysis of 6,6′-dibromo substituted (±)-**5** gave high enantioselectivity by the use of 2-chloroethanol as alcoholysis agent. Currently, this method is applied to the CALB-catalyzed resolution of amino and ester substituted 1,1′-binaphthyls.

References and notes

1. (a) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857–897; (b) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155–3211.
2. Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13760–13761.
3. Reetz, M. T.; Bondarev, O. G.; Gais, H. J.; Bolm, C. *Tetrahedron Lett.* **2005**, *46*, 5643–5646.
4. Qin, Y. C.; Liu, L.; Pu, L. *Org. Lett.* **2005**, *7*, 2381–2383.
5. Ihori, Y.; Yamashita, Y.; Ishitani, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2005**, *127*, 15528–15535.
6. Kano, T.; Konishi, T.; Konishi, S.; Maruoka, K. *Tetrahedron Lett.* **2006**, *47*, 873–875.
7. Kumaraswamy, G.; Jena, N.; Sastry, M. N. V.; Rao, G. V.; Ankamma, K. *J. Mol. Catal. A: Chem.* **2005**, *230*, 59–67.
8. Villano, R.; Acocella, M. R.; De Rosa, M.; Soriente, A.; Scettri, A. *Tetrahedron: Asymmetry* **2004**, *15*, 2421–2424.
9. Gadenne, B.; Hesemann, P.; Moreau, J. J. E. *Tetrahedron: Asymmetry* **2005**, *16*, 2001–2006.
10. (a) Kang, C. Q.; Cheng, Y. Q.; Guo, H. Q.; Qiu, X. P.; Gao, L. X. *Tetrahedron: Asymmetry* **2005**, *16*, 2141–2147; (b) Deng, J. G.; Chi, Y. X.; Fu, F. M.; Cui, X.; Yu, K. B.; Zhu, J.; Jiang, Y. Z. *Tetrahedron: Asymmetry* **2000**, *11*, 1729–1732.
11. Mazaleyrat, J. P.; Wright, K.; Azzini, M. V.; Gaucher, A.; Wakselman, M. *Tetrahedron Lett.* **2003**, *44*, 1741–1745.
12. (a) Piao, G.; Akagi, K.; Shirakawa, H.; Kyotani, M. *Curr. Appl. Phys.* **2001**, *1*, 121–123; (b) Akagi, K.; Piao, G.; Kaneko, S.; Higuchi, I.; Shirakawa, H.; Kyotani, M. *Synth. Met.* **1999**, *102*, 1406–1409.
13. Cheng, Y. X.; Chen, L. W.; Song, J. F.; Zou, X. W.; Liu, T. D. *Polym. J.* **2005**, *37*, 355–362.
14. Nakajima, M.; Miyoshi, I.; Kanayama, K.; Hashimoto, S.; Noji, M.; Koga, K. *J. Org. Chem.* **1999**, *64*, 2264–2271.
15. Gao, J.; Reibenspies, J. H.; Martell, A. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 6008–6012.
16. Barhate, N. B.; Chen, C. T. *Org. Lett.* **2002**, *4*, 2529–2532.
17. Irie, R.; Masutani, K.; Katsuki, T. *Synlett* **2000**, 1433–1436.
18. Aoyama, H.; Tokunaga, M.; Kiyosu, J.; Iwasawa, T.; Obora, Y.; Tsuji, Y. *J. Am. Chem. Soc.* **2005**, *127*, 10474–10475.
19. (a) Li, Z.; Liang, X.; Wu, F.; Wan, B. *Tetrahedron: Asymmetry* **2004**, *15*, 665–669; (b) Schanz, H. J.; Linseis, M. A.; Gilheany, D. G. *Tetrahedron: Asymmetry* **2003**, *14*, 2763–2769; (c) Periasamy, M.; Venkatraman, L.; Sivakumar, S.; Sampathkumar, N.; Ramanathan, C. R. *J. Org. Chem.* **1999**, *64*, 7643–7645.
20. (a) Hernandez, M. J.; Johnson, D. V.; Holland, H. L.; McNulty, J.; Capretta, A. *Tetrahedron: Asymmetry* **2003**, *14*, 289–291; (b) Inagaki, M.; Hiratake, J.; Nishioka, T.; Oda, J. *Agric. Biol. Chem.* **1989**, *53*, 1879–1884; (c) Kazlauskas, R. *J. Am. Chem. Soc.* **1989**, *111*, 4953–4959.
21. (a) Aoyagi, N.; Izumi, T. *Tetrahedron Lett.* **2002**, *43*, 5529–5531; (b) Aoyagi, N.; Kawauchi, S.; Izumi, T. *Tetrahedron Lett.* **2003**, *44*, 5609–5612.
22. Anderson, E. M.; Karin, M.; Kirk, O. *Biocatal. Biotransform.* **1998**, *16*, 181–204.
23. Uppenberg, J.; Ohrner, N.; Norin, M.; Hult, K.; Kleywegt, G. J.; Patkar, S.; Waagen, V.; Anthonsen, T.; Jones, T. A. *Biochemistry* **1995**, *34*, 16838–16851.
24. Akoh, C. C. *Biotechnol. Lett.* **1993**, *15*, 949–954.
25. Claon, P. A.; Akoh, C. C. *Enzyme Microb. Technol.* **1994**, *16*, 835–838.
26. Orsat, B.; Wirz, B.; Bischos, F. *Chimia* **1999**, *53*, 579–584.
27. Compound (±)-**2**: colorless crystal; mp 125–127 °C; IR ν_{max} (KBr)/cm^{-1} 3460 (OH), 1740, 1230 (OAc); ^1H

NMR (500 MHz, $CDCl_3$) δ 1.86 (3H, s, CH_3), 5.22 (1H, s, OH), 7.03 (1H, d, $J = 8.5$ Hz, ArH), 7.23–7.26 (2H, ArH), 7.31–7.35 (3H, ArH), 7.40 (1H, d, $J = 8.5$ Hz, ArH), 7.50 (1H, t, $J = 7.5$ Hz, ArH), 7.85 (1H, d, $J = 8.0$ Hz, ArH), 7.91 (1H, d, $J = 8.5$ Hz, ArH), 7.97 (1H, d, $J = 8.5$ Hz, ArH), 8.07 (1H, d, $J = 9.0$ Hz, ArH); FABMS (*m*/*z*) 329 $(M+H)^+$.

Compound (±)-**3**: colorless crystal; mp 136–137 °C; IRν_{max} (KBr)/cm^{-1} 3410 (OH), 1730, 1170 (OCOPr); ^1H NMR (500 MHz, $CDCl_3$) δ 0.57 (3H, t, $J = 7.5$ Hz, CH_3), 1.21 (2H, sex, $J = 7.5$ Hz, CH_2), 2.04–2.17 (2H, m, CH_2), 5.21 (1H, s, OH), 7.04 (1H, d, $J = 9.0$ Hz, ArH), 7.23–7.27 (1H, m, ArH), 7.31–7.36 (4H, ArH), 7.39 (1H, d, $J = 9.0$ Hz, ArH), 7.51 (1H, t, $J = 7.5$ Hz, ArH), 7.84 (1H, d, $J = 8.0$ Hz, ArH), 7.90 (1H, d, $J = 9.0$ Hz, ArH), 7.97 (1H, d, $J = 8.5$ Hz, ArH), 8.07 (1H, d, $J = 9.0$ Hz, ArH); FABMS (*m*/*z*) 357 $(M+H)^+$.

28. Compound (±)-**4**: colorless solid; mp 202–204 °C; IRν_{max} (KBr)/cm^{-1} 3480, 3420 (OH); ^1H NMR (500 MHz, $CDCl_3$) δ 5.00 (2H, s, OH), 6.96 (2H, d, $J = 9.0$ Hz, ArH), 7.37 (2H, dd, $J = 9.0$, 2.0 Hz, ArH), 7.40 (2H, d, $J = 9.0$ Hz, ArH), 7.90 (2H, d, $J = 9.0$ Hz, ArH), 8.05 (2H, ds, $J = 2.0$ Hz, ArH); MS (*m*/*z*) 442, 444, 446 (M^+).

Compound (±)-**5**: colorless crystal; mp 159–160 °C; IRν_{max} (KBr)/cm^{-1} 3420 (OH), 1730, 1180 (OCOPr); ^1H NMR (500 MHz, $CDCl_3$) δ 0.60 (3H, t, $J = 7.5$ Hz, CH_3), 1.24 (2H, sex, $J = 7.5$ Hz, CH_2), 2.06–2.19 (2H, m, CH_2), 5.19 (1H, s, OH), 6.86 (1H, d, $J = 9.0$ Hz, ArH), 7.08 (1H, d, $J = 9.0$ Hz, ArH), 7.31 (1H, dd, $J = 9.0$, 2.0 Hz, ArH), 7.33 (1H, d, $J = 9.0$ Hz, ArH), 7.40 (1H, d, $J = 9.0$ Hz, ArH), 7.41 (1H, dd, $J = 9.0$, 2.0 Hz, ArH), 7.81 (1H, d, $J = 9.0$ Hz, ArH), 7.98 (1H, d, $J = 9.0$ Hz, ArH), 8.00 (1H, ds, $J = 2.0$ Hz, ArH), 8.14 (1H, ds, $J = 2.0$ Hz, ArH); MS (*m*/*z*) 512, 514, 516 (M^+).

Compound (±)-**6**: pale yellow syrup; IRν_{max} (KBr)/cm^{-1} 1760, 1180 (OCOPr); ^1H NMR (500 MHz, $CDCl_3$) δ 0.59 (6H, t, $J = 7.5$ Hz, CH_3), 1.19–1.29 (4H, m, CH_2), 2.06–2.10 (4H, m, CH_2), 7.04 (2H, d, $J = 9.0$ Hz, ArH), 7.36 (2H, dd, $J = 9.0$, 2.0 Hz, ArH), 7.42 (2H, d, $J = 9.0$ Hz, ArH), 7.90 (2H, d, $J = 9.0$ Hz, ArH), 8.09 (2H, ds, $J = 2.0$ Hz, ArH); MS (*m*/*z*) 584, 586 (M^+).

29. The immobilized *Candida antarctica* lipase B (CALB) was provided by Novo Nordisk Co., Ltd. as CHIRAZYME L-2 (5 KU/g).
30. *General procedure*: CALB (40 mg) and *n*-butanol (0.672 mmol) were added to a solution of *O*-acyl binaphthol (±)-**2** or (±)-**3** (0.0672 mmol) and acetophenone (2.0 mg, standard substance) in solvent (2 mL) and the resulting mixture was stirred at 30–80 °C. The reaction conversion and enantiomeric excess were determined using HPLC (column, Daicel Chiralcel OG; mobile phase, hexane/2-propanol = 15:1; flow rate, 0.5 mL/min; UV detection at 254 nm). E values were calculated according to literature (see Ref. 31). Absolute configurations of the products were determined using HPLC (OG column) data of commercially available (*R*) and (*S*) BINOL.
31. Chen, C. S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299.
32. *Large scale procedure*: CALB (900 mg) and *n*-butanol (2.24 g, 30.2 mmol) was added to a solution of (±)-**3** (1.08 g, 3.02 mmol) in toluene (90 mL) and the resulting mixture was stirred at 100 °C. The reaction was monitored periodically using HPLC. Upon completion (96 h), the reaction was terminated by removing the lipase via filtration. The lipase portion was washed with toluene (50 mL). The filtrate and wash were combined, evaporated, and the resulting crude residue was purified using silica gel column chromatography with chloroform/methanol (100:1) as the eluent to yield the (*S*)-**3** {48%, 93% ee, $[\alpha]_D^{20}$ −43.4 (*c* 1.0, THF)} and (*R*)-**1** {51%, 92% ee, $[\alpha]_D^{20}$ +32.6 (*c* 1.0, THF)}.
33. *Procedure of (R)-**4** and (S)-**5***: CALB (40 mg) and alcohol (0.672 mmol) were added to a solution of (±)-**5** (0.0672 mmol) and acetophenone (2.0 mg, standard substance) in toluene (2 mL) and the resulting mixture was stirred at 80 °C. The reaction conversion and enantiomeric excess were determined using HPLC (column, Daicel Chiralcel OD; mobile phase, hexane/2-propanol = 9:1; flow rate, 0.5 mL/min; UV detection at 254 nm). *E* values were calculated according to literature (see Ref. 31). Absolute configurations of the products were determined using HPLC (OD column) data of (*R*)-**4** which was derived from commercially available (*R*)-BINOL.