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Effect of the alkyl chain length of 1,1′-binaphthyl esters in lipase-catalyzed amidation

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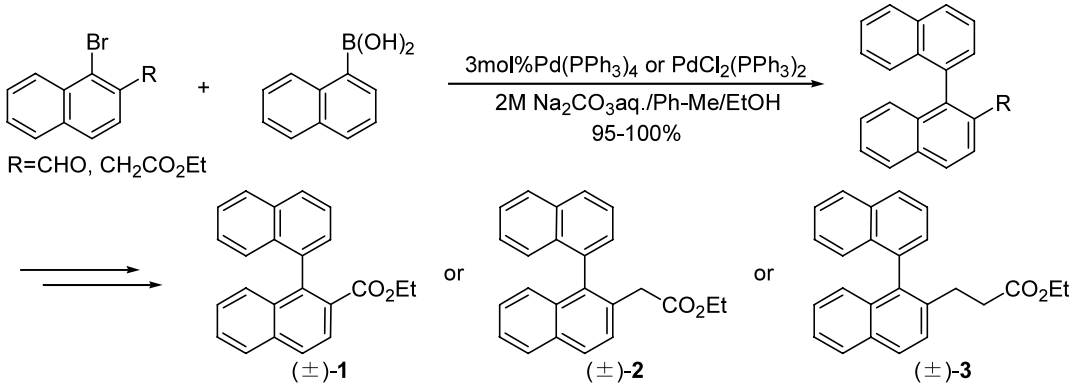
Abstract—Lipase-catalyzed amidation of 2-[2-(ethoxycarbonyl)ethyl]-1,1′-binaphthyl [(±)-**3**] yielded optically active (*S*)-**3** and 2-[2-(2-cyanoethylaminocarbonyl)ethyl]-1,1′-binaphthyl [(*R*)-**6a**] with high enantiomeric excess. For these lipase-catalyzed amidations, the optimal alkyl chain length between the binaphthyl ring and the ester group was determined to be an ethylene spacer.

Lipases in organic solvents have been employed as catalysts in the synthesis of extensive optically active compounds.[1] Furthermore, it has been shown that lipase-catalyzed amidation of racemic esters or amines can afford chiral compounds.[2] Lipase-catalyzed resolution offers the advantage of an easier procedure as compared to typical chemical resolutions that require a stoichiometric amount of a covalently-bonded chiral auxiliary.[3]

Recently, chiral biaryl derivatives have received much attentions in the context of chiral ligands,[4] pharmaceutical products,[5] natural products,[6] and liquid crystals,[7] that include the biaryl unit. Although lipase-catalyzed esterification and hydrolysis of biaryls have been reported for the synthesis of chiral biaryl alcohols,[8] little is known about the enzymatic aminolysis resolution of biaryl derivatives.

We have previously reported on the efficient resolution of 2-(2-aminoethyl)-1,1′-binaphthyl using lipase-catalyzed amidation.[9] Our studies have revealed that the resolution was sensitive to the length of the alkyl chain between the binaphthyl ring and the amino group, in which an ethylene group as the alkyl chain offered greater reactivity and higher enantioselectivity. Consequently, we became interested in exploring the applicability of this reaction by using binaphthyl ester derivatives and comparing the effects of the alkyl chain



Scheme 1. Synthesis of racemic esters (±)-**1**∼**3**.

Keywords: binaphthyl; Suzuki cross-coupling; lipase; amidation; aminolysis.
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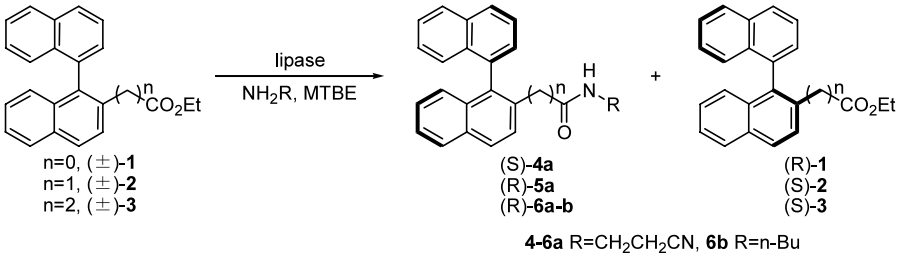
lengths between the binaphthyl ring and, in this case, the ester group. Herein, we present the results of these studies.

Racemic mixtures of esters (±)-**1**∼**3**[10] were obtained in high yields using the Suzuki cross-coupling reaction (Scheme 1).[11] The enzymatic resolution of (±)-**1**∼**3** were carried out under aminolysis conditions, using thirteen commercially available lipase preparations (Scheme 2).[12]

In a typical experiment, lipase (40 mg) and an amino agent (0.202 mmol) were added to a solution of (±)-binaphthyl ester (22∼24 mg, 0.0672 mmol) and naphthalene (1.0 mg, standard substance) in *tert*-butyl methyl ether (2 mL) (MTBE). The resulting mixture was shaken (150 cycles/min) at 30°C, during which the course of the reaction was monitored using HPLC (GL Sciences, Inertsil ODS-2 column, acetonitrile/water = 8:2). Upon completion, the reaction was stopped by removal of the lipase by filtration. The lipase portion was washed with MTBE (10 mL). The combined filtrate and washes were evaporated at 30°C, and the resulting crude residue was purified by column chromatography (silica gel, ethyl acetate) to yield the chiral ester and amide. Enantiomeric excess (ee) values were determined using HPLC (Daicel, Chiralcel OD column, hexane/2-propanol = 9:1). *E* values were calculated according to the literature.[13] Absolute configurations of the products were determined using their circular dichroism spectra (dihedral angles of the binaphthyl backbones were calculated by WinMOPAC.).[14]

As shown in Table 1, aminolysis of (±)-**3** catalyzed by NOVOZYM 435 and CHIRAZYME L-2 (*Candida antarctica*) proceeded to approximately 50% conversion after 8 h (entries 4 and 7, respectively).[15] Passing over this conversing of aminolysis reaction, leave chiral ester (*S*)-**3** was obtained with high enantiomeric excess using NOVOZYM 435 (98% ee, 25% yield; entry 5) and CHIRAZYME L-2 (99% ee, 21% yield; entry 8). Interestingly, our results show that 3-aminopropionitrile, rather than typical agents such as *n*-butylamine, is more efficient as the amine agent for these lipase-catalyzed amidations (entries 3–8). Accordingly, we have previously reported on the high yielding enzymatic amidation of methyl laurate with 3-aminopropionitrile.[16] As an explanation, it is reasonable to suggest the enhanced interactions between 3-aminopropionitrile and the biomolecule as caused by hydrogen bonding according to dipole moment of cyano group.

It has been reported that LIP lipase can serve effectively for the acylate optical resolution of binaphthyl derivatives, such as binaphthol[8a] and 2-(2-aminoethyl)-1,1′-binaphthyl (Table 2, entry 4); however, binaphthyl ester (±)-**3** was not a substrate under these LIP-catalyzed conditions. It can be suggested that the acyl-enzyme complex in the active site of LIP is able to incorporate the binaphthyl derivatives, whereas the



Scheme 2. Lipase-catalyzed amidation of ester (±)-**1**∼**3**.

Table 1. Amidation of racemic-**1**–**3** using lipase catalyst

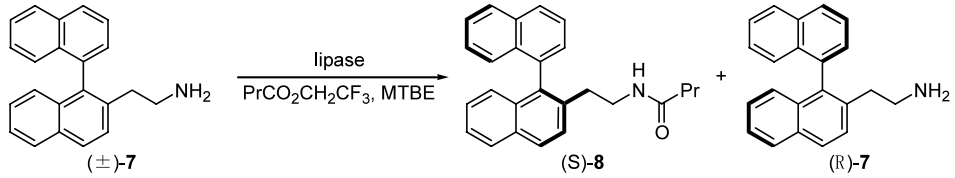
Entry	Ester	Lipase	Amino agent	Time (h)	(*R*)-Amide		(*S*)-Ester		*E* value[d]
					Yield/%[b]	e.e./%[c]	Yield/%[b]	e.e./%[c]	
1[a]	**1**	CHIRAZYME L-2	$NCCH_2CH_2NH_2$	120	No reaction				–
2[a]	**2**	CHIRAZYME L-2	$NCCH_2CH_2NH_2$	120	No reaction				–
3[a]	**3**	CHIRAZYME L-2	*n*-$BuNH_2$	120	No reaction				–
4	**3**	NOVOZYM 435	$NCCH_2CH_2NH_2$	8	42	83	55	43	16
5	**3**	NOVOZYM 435	$NCCH_2CH_2NH_2$	48	72	49	25	98	12
6	**3**	NOVOZYM 525L[e]	$NCCH_2CH_2NH_2$	360	3	73	97	8	5
7	**3**	CHIRAZYME L-2	$NCCH_2CH_2NH_2$	8	48	84	50	44	18
8	**3**	CHIRAZYME L-2	$NCCH_2CH_2NH_2$	54	75	46	21	99	13

[a] Another 12 commercially available lipases (Ref. 12) were not reacted.
[b] Determined by internal standard method of HPLC using ODS-2 (254 nm, 0.8 mL/min, $CH_3CN/H_2O = 8/2$).
[c] Determined by HPLC 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. 13.
[e] Adsorbed on Celite; see Ref. 17.

Table 2. Amidation of racemic-**7** by lipase catalyst[a]

Entry	Amine	Lipase	Acyl donor	Time (h)	(*S*)-Amide		(*R*)-Amide		*E* value[e]
					Yield/%[b]	e.e./%[c]	Yield/%[b]	e.e./%[c,d]	
1	**7**	–	$PrCO_2CH_2CF_3$	24	No reaction				–
2	**7**	NOVOZYM 435	$PrCO_2CH_2CF_3$	0.5	41	18	55	20	1.6
3	**7**	CHIRAZYME L-2	$PrCO_2CH_2CF_3$	0.5	57	18	40	24	1.8
4	**7**	LIP	$PrCO_2CH_2CH_3$	12	40	99[f]	51	67[f]	473

[a] (±)-**7** (20 mg, 0.0672 mmol), acyl donor (0.0672 mmol), lipase (40 mg), MTBE (2 mL), 30°C.
[b] Isolated yield. Reaction was followed by HPLC using RP-18e (254 nm, 1.5 mL/min, CH_3CN/0.1% TFA water = 1/1).
[c] Determined by HPLC using Chiralcel OD (254 nm, 0.5 mL/min, *n*-hexane/IPA = 9/1).
[d] Acetylation of amine for determination.
[e] $E = \ln[1-c(1+ee_p)]/\ln[1-c(1-ee_p)]$; See Ref. 13.
[f] Configurations were (*R*)-amide and (*S*)-amine.



Scheme 3. Lipase-catalyzed amidation of amine (±)-**7**.

binaphthyl esters are not able to form the acyl-enzyme (binaphthoyl-enzyme) complex on LIP. Nine other commercially available lipases[12] were not reacted in the same manners in Table 1.

Analogously to the lipase-catalyzed amidation of 1,1′-binaphthylamines[9], ester (±)-**1** was not an effective substrate under these lipase-catalyzed conditions (Table 1, entry 1). Similarly, (±)-**2** was also not effective as a substrate (Table 1, entry 2). The alkyl chain effect of 1,1′-binaphthyl esters markedly appeared that of 1,1′-binaphthylamines, because the corresponding binaphthylamine with (±)-**2** was found to low reactivity and selectivity on lipase-catalyzed amidation.[9]

In order to compare the reactivities of the starting functional group, lipase-catalyzed amidation was carried out using (±)-**7**, which has an amino group, as illustrated in Scheme 3. Although the aminolysis reactions catalyzed by NOVOZYM 435 and CHIRAZYME L-2 proceeded to about 50% conversion within 0.5 h (Table 2, entries 2 and 3, respectively), the opposite enantioselectivity of the axially binaphthyl ring was exhibited by *Candida antarctica* lipase. In this case, the acyl-enzyme complex in the active site of the enzyme recognized amine (*S*)-**7**, whereas the serine residue in the active site of the enzyme recognized ester (*R*)-**3**. Again, focused on the ethylene spacer of the binapthyl moiety was shown to play an important role in the lipase-catalyzed amidation for both binaphthyl esters and amines.

In conclusion, as previously reported for the lipase-catalyzed amidation of 1,1′-binaphthylamines, the lipase-catalyzed amidation of binaphthyl esters is sensitive to the length of the alkyl chain between the binaphthyl ring and the ester group. The efficient chiral synthesis of 2-[2-(ethoxycarbonyl)ethyl]-1,1′-binaphthyl (*S*)-**3** was accomplished through a combination of the Suzuki cross-coupling reaction and the lipase-catalyzed kinetic resolution of (±)-**3**. However, although LIP was an successful catalyst in the aminolysis resolution of aminobinaphthyl (±)-**7**, ester (±)-**3** was not effective as a substrate under similar LIP-catalyzed conditions. In our studies, only NOVOZYM 435 and CHIRAZYME L-2 served as effective catalysts for the kinetic resolution of (±)-**3**. 3-Aminopropionitrile was found to be highly reactive to the lipase-catalyzed amidation of binaphthyl ester. The present synthetic methodology offers the following two advantages: (1) simplicity of operation, and (2) high yields of the lipase-catalyzed amidation without the use of toxic resolving agents. Currently, the applicability of this method is extended to the lipase-catalyzed resolution of binaphthyl alcohols and 2,2′-disubstituted-1,1′-binaphthyls.

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10. (±)-**1**: IR ν_{max} (KBr)/cm^{-1} 1700 (CO_2R); ^{1}H NMR ($CDCl_3$) δ 0.54 (3H, t, $J=7.2$ Hz, CH_3), 3.81 (2H, q, $J=7.2$ Hz, CH_2), 7.23–8.10 (13H, m, ArH); FABMS (m/z) 327 (M+H)$^+$.
(±)-**2**: IR ν_{max} (KBr)/cm^{-1} 1730 (CO_2R); ^{1}H NMR ($CDCl_3$) δ 1.03 (3H, t, $J=7.1$ Hz, CH_3), 3.41 (2H, s, CH_2), 3.91 (2H, q, $J=7.3$ Hz, CH_2), 7.17–7.97 (13H, m, ArH); MS (m/z) 340 (M$^+$).
(±)-**3**: mp 85–89; IR ν_{max} (KBr)/cm^{-1} 1730 (CO_2R); ^{1}H NMR ($CDCl_3$) δ 1.13 (3H, t, $J=7.2$ Hz, CH_3), 2.40 (2H, t, $J=8.0$ Hz, CH_2), 2.60–2.90 (2H, m, CH_2), 3.99 (2H, q, $J=7.2$ Hz, CH_2), 7.10–7.99 (13H, m, ArH); FABMS (m/z) 355 (M+H)$^+$.
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15. (*R*)-**6a**: IR ν_{max} (neat)/cm^{-1} 3290, 1650, 1540 (CONH), 2250 (CN); ^{1}H NMR ($CDCl_3$) δ 2.23 (2H, t, $J=7.6$ Hz, CH_2), 2.42 (2H, t, $J=6.2$ Hz, CH_2), 2.60–2.88 (2H, m, CH_2), 3.26 (2H, q, $J=6.2$ Hz, CH_2), 5.49 (1H, br, NH), 7.08–7.65 (9H, m, ArH), 7.86–8.00 (4H, m, ArH); FABMS (m/z) 379 (M+H)$^+$.
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17. Liquid lipase (15 g) and sucrose (9.0 g) were dissolved in 20 mM Tris–HCl buffer (360 mL, pH 7.8) at 0°C. Celite (51 g) was added to the enzyme solution. The mixture was vigorously stirred at 30°C for 1 h, the solvent was removed in vacuo. The residue was dried at room temperature, giving immobilized lipase.