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Kinetic resolution of 1,1′-binaphthylamines via lipase-catalyzed amidation

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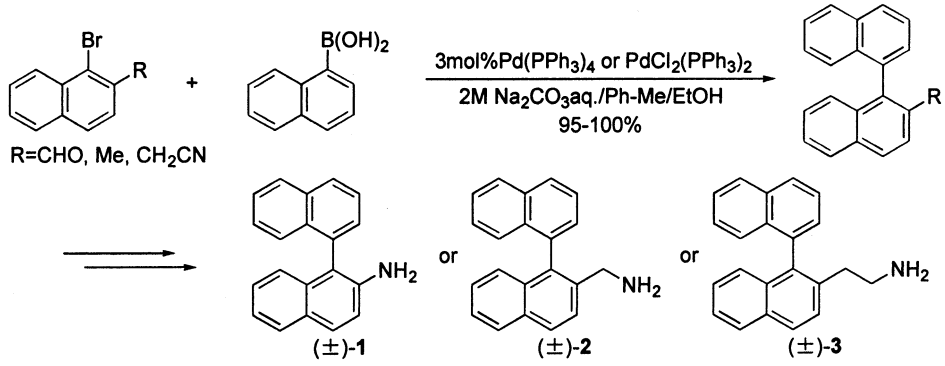
Abstract—Lipase-catalyzed amidation of 2-(2-aminoethyl)-1,1′-binaphthyl (±)-**3** gave optically active 2-[2-(acylamino)ethyl]-1,1′-binaphthyls (*R*)-**6a**–**c** with high enantiomeric excess.

Lipases in organic solvents have been widely used for the synthesis of many chiral compounds.[1] Lipase-catalyzed amidation of racemic amines or esters can be used to obtain chiral compounds.[2] Moreover, lipase-catalyzed resolution should be an easier procedure than the usual chemical resolution which needs a stoichiometric amount of a covalently-bonded chiral auxiliary.[3]

Optically active 1,1′-binaphthylamine derivatives are very useful for chiral ligands of various asymmetric reactions.[4] However, enzymatic kinetic resolution of 1,1′-binaphthylamine derivatives has been scarcely reported. We now report that LIP-300 (*Pseudomonas aeruginosa*, immobilized on Hyflo Super-Cel) and LPL-311 (*P. aeruginosa*) on Toyonite 200-M[5] are a particularly effective lipase for optical resolution of (±)-**3**.

The synthesis of (±)-**1**–**3**[6] succeeded with high yields by using the Suzuki cross-coupling reaction (Scheme 1).[7] The enzymatic resolution of (±)-**1**–**3** was undertaken against 10 commercially available lipase[8] preparations under acylating conditions (Scheme 2).

As a typical experiment, the lipase (40 mg) and an acylating agent (0.0672 mmol) were added to a solution of (±)-**3** (20 mg, 0.0672 mmol) in isopropyl ether (2 mL). The resulting mixture was stirred at 30°C and the reaction course was monitored by HPLC analysis. The reaction was stopped by filtering off the lipase, and the lipase portion was washed with 2 mL of isopropyl ether. The filtrate was added to 6 mL of 4N sulfuric acid and stirred for 10 min, to generate the salt. Standard work-up afforded (*R*)-**6a**–**c** from the organic layer, and yielded (*S*)-**3** from the salt and aqueous layer. The enantiomeric excess (% e.e.) values were determined by HPLC (Daicel, Chiralcel OD column, hexane/2-



Scheme 1. Racemic synthesis of (±)-**1**–**3**.

Keywords: binaphthyl; Suzuki cross-coupling; enzymes; amidation.

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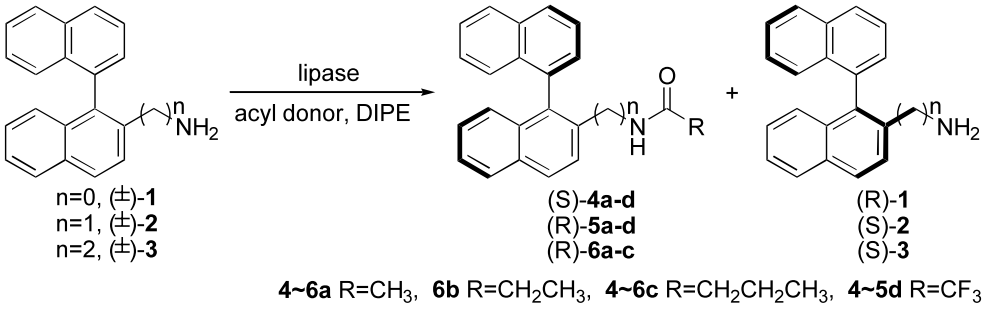


Scheme 2. Lipase-catalyzed amidation of (±)-**1**–**3**.

propanol = 9/1). The *E* values were calculated according to the literature.[10] Absolute configuration of the products was determined from the circular dichroism spectra.

As shown in Table 1, LIP was found to catalyze selectively the acylation of (*R*)-**6c**[9] (99% e.e.) in 40% yield (entry 16). The enantioselectivity of the lipase catalyzed reaction increases with the bulkiness of the acyl donor (entries 12–14). It is expected that the binding of the acyl donor to the enzyme should have a large effect on the enantioselectivity of binaphthylamines (Scheme 3). A similar effect is reported on the LIP-catalyzed amidation.[13]

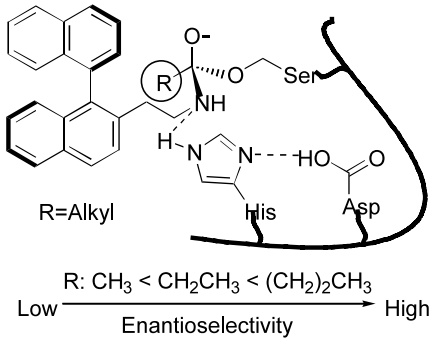
For the amidation reaction with 2,2,2-trifluoroethyl butyrate (TFEOBu) as the acyl donor, the theoretical enantiomeric excess is 38% in 73% yield. Interestingly, LPL on Toyonite 200-M was found to selectively acylate (*R*)-**6c** (88% e.e.) in 73% yield (Table 1, entry 17). A similar effect is seen when the acyl donor is TFEOBu (Table 1, entry 18). It is conceivable that the asymmetric induction is due to relative orientations of the substrates when bound to the lipase. In contrast, under the same reaction conditions other lipases such as CAL (*Candida antarctica*), CCL, OF, MY (*Candida cylindrasea*), PPL (*Porcine pancreas*), PS (*Pseudomonas cepacia*), AK (*Pseudomonas fluorescene*) and AY (*Candida rugosa*) were less enantioselective than LIP and immobilized LPL.

As substrates for LIP, (±)-**2** was less reactive and enantioselective relative to (±)-**3**. However, (±)-**2** was converted to (*R*)-**5c** in 94% optical purity when TFEOBu was used as the acylating agent (Table 1, entry 10). TFEOBu is a highly reactive acyl donor for

Table 1. Amidation of racemic-**1**–**3** by *Pseudomonas aeruginosa* lipase (LIP) catalyst

Entry	Amine	Acyl donor	Time (h)	Amide		Amine		E[d]
				Yield (%)[a]	e.e. (%)[b]	Yield (%)[a]	e.e. (%)[b,c]	
1	**1**	$MeCO_2Ph$	120	No reaction				–
2	**1**	$MeCO_2Me$	120	No reaction				–
3	**1**	$MeCO_2CH{=}CH_2$	120	No reaction				–
4	**1**	CF_3CO_2Et	120	No reaction				–
5	**1**	$PrCO_2CH_2CF_3$	120	No reaction				–
6	**2**	$MeCO_2Ph$	0.75	50	3.1	41	1.0	1.1
7	**2**	$MeCO_2Me$	120	Trace	–	89	–	–
8	**2**	$MeCO_2CH{=}CH_2$	0.33	18	9.0	74	4.3	1.1
9	**2**	CF_3CO_2Et	5	43	5.0	53	2.0	1.2
10	**2**	$PrCO_2CH_2CF_3$	12	27	94	63	29	45
11	**3**	$MeCO_2Ph$	0.33	35	42	52	11	3.0
12	**3**	$MeCO_2CH{=}CH_2$	0.16	44	67	48	22	8.5
13	**3**	$EtCO_2CH{=}CH_2$	0.16	38	86	50	23	22
14	**3**	$PrCO_2CH{=}CH_2$	0.16	28	99	68	25	291
15	**3**	$PrCO_2CH{=}CH_2$[e]	0.16	37	93	52	55	48
16	**3**	$PrCO_2Et$	12	40	99	51	67	473
17[f]	**3**	$PrCO_2CH_2CF_3$	0.50	73	88	25	77	–
18[f,g]	**3**	$PrCO_2CH_2CF_3$	12	99	28	0	–	–

[a] Isolated yield.
[b] Determined by HPLC using Chiralcel OD (254 nm, 0.5 mL/min, *n*-hexane/IPA = 9/1).
[c] Acetylation of amine for determination.
[d] $E = \ln[1-c(1+\text{e.e.(p)})]/\ln[1-c(1-\text{e.e.(p)})]$; see Ref. 10.
[e] Solvent of DIPE/TEa = 9/1.
[f] The lipase used was immobilized lPL on Toyonite 200-M; see Ref. 11.
[g] 3 equiv. of $PrCO_2CH_2CF_3$, 40°C; see Ref. 12.



Scheme 3. Acyl group effect on LIP-catalyzed amidation.

amine acylation reactions,[14] and 2,2,2-trifluoroethyl esters are highly selective acyl donors in acylation of amines catalyzed by LIP, LPL and CCL.[13,15] Amine (±)-**1** was not a substrate under any of the reaction conditions. The lack of reactivity could be due to the steric hindrance caused by the bulky binaphthyl ring. The reaction of aromatic amines does not proceed, except under severe conditions.[16]

In conclusion, the lipase-catalyzed amidation of binaphthylamines is sensitive to the length of the alkyl chain between the binaphthyl ring and amino group. An efficient synthesis of enantiopure 2-[2-(butyryl-amino)ethyl]-1,1′-binaphthyl (*R*)-**6c** was accomplished through a combination of the Suzuki cross-coupling reaction and the lipase-catalyzed kinetic resolution of 2-(2-aminoethyl)-1,1′-binaphthyl (±)-**3**. LIP and immobilized LPL are excellent catalysts for the kinetic resolution of (±)-**3**. The present synthesis is advantageous in terms of the simple operation and high yields of the lipase-catalyzed amidation. Work is under way to synthesize chiral ligands using (*R*)-**3** as a substrate.

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5. Toyonite 200-M (Toyo Denka Kogyo Co., Ltd).
6. (±)-**1**: mp 199–201°C; IR ν_{max} (KBr)/cm^{-1} 3471, 3380, 1617 ($ArNH_2$); ^{1}H NMR ($CDCl_3$) δ 3.58 (2H, s, NH_2), 7.02 (1H, d, J=7.2 Hz, ArH), 7.10–7.51 (7H, m, ArH), 7.65 (1H, t, J=7.6 Hz, ArH), 7.80 (1H, d, J=9.0 Hz, ArH), 7.97 (1H, d, J=7.0 Hz, ArH); FABMS (m/z) 270 (M+H)$^+$.
(±)-**2**: IR ν_{max} (neat)/cm^{-1} 3370 (NH_2); ^{1}H NMR ($CDCl_3$) δ 1.44 (2H, br, NH_2), 3.57 (2H, s, CH_2), 7.15–8.00 (13H, m, ArH); FABMS (m/z) 284 (M+H)$^+$.
(±)-**3**: IR ν_{max} (neat)/cm^{-1} 3360, 3290 (NH_2); ^{1}H NMR ($CDCl_3$) δ 1.28 (2H, br, NH_2), 2.42–2.70 (2H, m, CH_2), 2.78 (2H, t, J=7.8 Hz, CH_2), 7.08–8.00 (13H, m, ArH); MS (m/z) 297 (M^+).
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8. LIP and LPL (Toyobo Co., Ltd); CAL (Novo Nordisk Co., Ltd); CCL and PPL (Sigma Chemical Co., Ltd); PS, AK and AY (Amano Pharmaceutical Co., Ltd); OF and MY (Meito Sangyo Co., Ltd).
9. (*R*)-**6c**: IR ν_{max} (neat)/cm^{-1} 3300, 1650, 1550 (CONH); ^{1}H NMR ($CDCl_3$) δ 0.84 (3H, t, J=7.4 Hz, CH_3), 1.51 (2H, q, J=7.8 Hz, CH_2), 1.91 (2H, t, J=7.5 Hz, CH_2), 2.62 (2H, sex., J=7.6 Hz, CH_2), 3.35 (2H, q, J=6.0 Hz, CH_2), 5.15 (1H, br, NH), 7.10–7.66 (9H, m, ArH), 7.88–8.00 (4H, m, ArH); FAB MS (m/z) 368 (M+H)$^+$.
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11. LPL (10 mg) was dissolved in 0.1 M potassium phosphate buffer (pH 7.0, 2 mL) at 0°C. Toyonite 200-M (100 mg) and 0.1 M potassium phosphate buffer (pH 7.0, 3 mL) were added to the enzyme solution. The mixture was shaken (150 rpm) at room temperature for 16 h, the solvent was removed in vacuo. The residue was washed with H_2O (10 mL), hexane (10 mL), and then dried in desiccator for 5 h, giving immobilized LPL (110 mg).
12. (*R*)-**6c**. 2,2,2-Trifluoroethyl butyrate (17.2 mg, 0.101 mmol) was added to a suspension of Toyonite 200-M LPL (20 mg) in isopropyl ether (1 mL). The mixture was vigorously stirred for 20 min at 40°C. (±)-**3** (10 mg, 0.0336 mmol) in isopropyl ether (1 mL) was added in 10 min to the reaction mixture and it was stirred for 11.5 h at 40°C. After work-up, column chromatography (SiO_2; chloroform/methanol=1/0–20/1) gave 12.4 mg of (*R*)-**6c** (99%, 28% e.e.).
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