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Different recognitions of (*E*)- and (*Z*)-1,1′-binaphthyl ketoximes using lipase-catalyzed reactions

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Abstract—Lipase-catalyzed hydrolysis of (*E*)-2-[α-(acetoxyimino)benzyl]-1,1′-binaphthyl [(±)-**1a**] and (*Z*)-2-[α-(acetoxyimino)benzyl]-1,1′-binaphthyl [(±)-**1b**] yielded optically active (*E*)-2-[α-(hydroxyimino)benzyl]-1,1′-binaphthyl [(*S*)-**2a**] and (*Z*)-2-[α-(hydroxyimino)benzyl]-1,1′-binaphthyl [(*R*)-**2b**], respectively, with high enantiomeric excess. Selectivity for the opposite enantiomer of the axial binaphthyl skeleton was shown by (*Z*)-isomer **1b** against (*E*)-isomer **1a**.

Lipases in organic solvents have been employed as stereoselective catalysts in the synthesis of optically active compounds,[1] using substrates such as alcohols, amines, carboxylic acids, and esters. Although it has recently been reported that oxime derivatives can be resolved by lipase-catalyzed acylation and hydrolysis,[2] little is known about the lipase-catalyzed resolution of oxime derivatives, such as the (*E*)- and (*Z*)-isomers.

We have recently reported on the efficient resolutions of 1,1′-binaphthyl amine, ester, and oxime using lipase-catalyzed reactions.[3–5] Because the binaphthyl oxime was not of the ketoxime type, but rather of the aldehyde oxime type, the compound existed mostly as the (*E*)-isomer. Consequently, the study of reactions involving the (*E*)- and (*Z*)-isomer of binaphthyl ketoximes (e.g., phenyl group containing ketoximes) developed into an area of research interest.

The synthetic methodology of ketoximes **1a**, **1b**, **2a**, and **2b** are shown in Scheme 1.[6] 2-Formyl-1,1′-binaphthyl **3** was treated with phenyl lithium[7] to afford tertiary alcohol **4**, which was oxidized[8] to give ketone **5**. Condensation[9] of ketone **5** yielded a mixture of (*E*)- and (*Z*)-oximes (**2a** and **2b**, respectively), which were separated using silica gel column chromatography with chloroform as the eluent. Oximes **2a** and **2b** were esterified[10] to afford esters **1a** and **1b**, respectively.

As a note, the acetylations of ketoximes (±)-**2a** and (±)-**2b** were initially attempted via enzymatic esterification in an organic solvent. However, ketoximes (±)-**2a** and (±)-**2b** were not effective as substrates for any of the six commercially available lipase preparations under the conditions for lipase catalysis (Scheme 2).[11] Because the aldehyde oxime of 1,1′-binaphthyl was effective as a substrate for lipase-catalyzed esterification,[5] the phenyl group at the iminomethyl position presumably causes steric hindrance at the active site of the lipase.

The successful approach involved the enzymatic resolution of (±)-**1a** and (±)-**1b** under hydrolysis condition, using the six commercially available lipase preparations (Schemes 3 and 4).[11]

In a typical experiment, lipase (40 mg) and *n*-butanol (0.0672 mmol) were added to a solution of *O*-acetyl ketoxime (±)-**1a** or (±)-**1b** (28 mg, 0.0672 mmol) and 2′-acetonaphthone (1.0 mg, standard substance) in *tert*-butyl methyl ether (6 mL) (MTBE) and the resulting mixture was shaken (150 c/min) at 30 °C. The reaction was monitored periodically using HPLC (column, GL Sciences Inertsil ODS-2; mobile phase, acetonitrile/water = 8:2; flow rate, 0.8 mL/min; UV detection at 254 nm). Upon completion, the reaction was terminated by removing the lipase via filtration. The lipase portion was washed with MTBE (15 mL). The filtrate and wash were combined, evaporated at 30 °C, and the resulting

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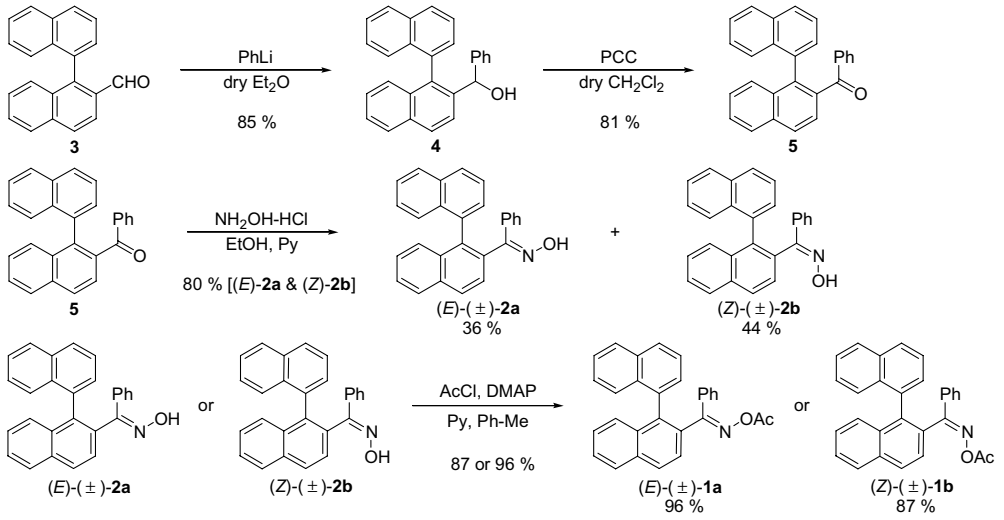
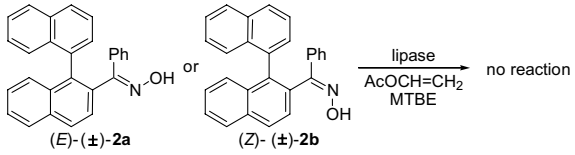
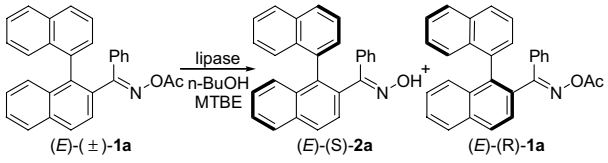


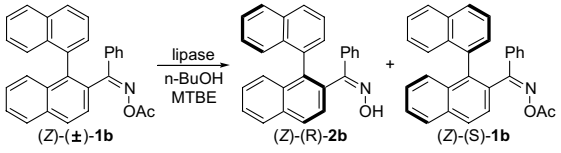
Scheme 1. Synthesis of racemic ketoximes (±)-**1a**–**2b**.



Scheme 2. Lipase-catalyzed esterification of (±)-**2a**–**b**.



Scheme 3. Lipase-catalyzed hydrolysis of (±)-**1a**.



Scheme 4. Lipase-catalyzed hydrolysis of (±)-**1b**.

crude residue was purified using silica gel column chromatography with chloroform as the eluent to yield the corresponding chiral *O*-acetyl ketoxime **1a**–**b** and ketoxime **2a**–**b**. Enantiomeric excess (ee) values were determined using chiral HPLC [column, Daicel Chiralcel OG (or OD); mobile phase, hexane/2-propanol = 50:1 (or 20:1); flow rate, 0.5 mL/min; UV detection at 254 nm]. *E* values were calculated according to literature.[12] Absolute configurations of the products were determined using their circular dichroism spectra (dihedral angles of the binaphthyl backbones were calculated using WinMOPAC).[13]

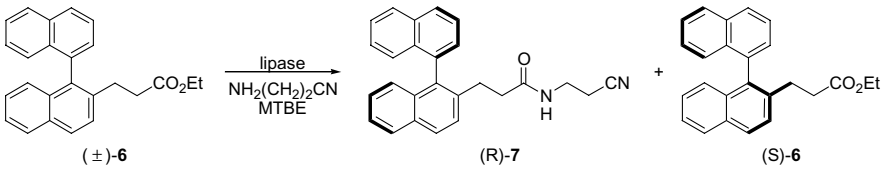
As shown in Table 1, hydrolysis of (±)-**1a** catalyzed by NOVOZYM 435 (8200 PLU/g) and CHIRAZYME L-2 (5 KU/g) (*Candida antarctica*) proceeded to approximately 50% conversion after 4 h (entries 1 and 2, respectively), with relatively high enantioselectivity (82–90% ee). In contrast, although the hydrolysis reaction catalyzed by LIP (0.59 KU/g) (*Pseudomonas aeruginosa*) lipase exhibited the highest enantioselectivity (99% ee), its conversion was low (9%) (entry 3).

Similarly as the lipase-catalyzed hydrolysis of (±)-**1a**, *Candida antarctica* lipases, NOVOZYM 435 and

Table 1. Hydrolysis of (*E*)-**1a** and (*Z*)-**1b** by lipase catalyst

Entry	Substrate	Lipase[a]	Time (h)	Ketoxime **2a**–**b**			*O*-Acetyl ketoxime **1a**–**b**			*E* value[e]
				Yield (%)[b]	Ee (%)[c,d]	Config.	Yield (%)[b]	Ee (%)[c]	Config.	
1	(*E*)-**1a**	NOVOZYM 435	4	41	82[d]	*S*	56	90	*R*	31
2	(*E*)-**1a**	CHIRAZYME L-2	4	43	85[d]	*S*	56	90	*R*	31
3	(*E*)-**1a**	LIP	287	9	99[d]	*S*	85	11	*R*	222
4	(*Z*)-**1b**	NOVOZYM 435	264	41	88[c]	*R*	59	48	*S*	25
5	(*Z*)-**1a**	CHIRAZYME L-2	264	48	87[c]	*R*	50	50	*S*	24
6	(*Z*)-**1b**	LIP	96	Not detected		—	Recovery		—	—

[a] Another three commercially lipases (Ref. 11) 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 OG (254 nm, 0.5 mL/min, *n*-hexane/IPA = 50:1).
[d] Determined by HPLC using Chiralcel OD (254 nm, 0.5 mL/min, *n*-hexane/IPA = 20:1).
[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. 12.



Scheme 5. Lipase-catalyzed aminolysis of ester (±)-**6** for the comparison purposes.

Table 2. Aminolysis of (±)-**6** by lipase catalyst[a]

Entry	Substrate	Lipase[b]	Time (h)	Amide			Ester			*E* value[e]
				Yield (%)[c]	Ee (%)[d]	Config.	Yield (%)[c]	Ee (%)[d]	Config.	
1	**6**	NOVOZYM 435	8	42	83	*R*	59	48	*S*	16
2	**6**	CHIRAZYME L-2	8	48	84	*R*	50	50	*S*	18
3	**6**	LIP	96	Not detected		—	Recovery		—	—

[a] (±)-**6** (24 mg, 0.0672 mmol), amino agent (0.202 mmol), lipase (40 mg), MTBE (2 mL), 30 °C.
[b] Another three commercially lipases (Ref. 11) were not reacted.
[c] Determined by internal standard method of HPLC using ODS-2 (254 nm, 0.8 mL/min, $CH_3CN/H_2O = 8:2$).
[d] Determined by HPLC using Chiralcel OD (254 nm, 0.5 mL/min, *n*-hexane/IPA = 9:1).
[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. 12.

CHIRAZYME L-2 exhibited the highest selectivity in the hydrolysis of (±)-**1b** (Table 1, entries 4 and 5). However, these lipases hydrolyzed (±)-**1b** slowly, with rates as much as 66 times slower than the hydrolysis of (±)-**1a**. Interestingly, selectivity for the opposite enantiomer of the axial binaphthyl skeleton was shown by (*Z*)-isomer **1b** against (*E*)-isomer **1a** (Table 1, entries 1–5). Our results clearly demonstrate that the lipase-catalyzed resolutions of binaphthyl ketoximes are affected by the structural differences between the (*E*)- and (*Z*)-isomers of the ketoxime.

In order to compare the reactivities of the starting functional group, lipase-catalyzed aminolysis was carried out using (±)-**6**, which has an ethylene spacer between the binaphthyl ring and the ester group, as illustrated in Scheme 5.[4] Our results show that the recognition of the axial binaphthyl skeleton in the aminolysis reaction was identical to that in the hydrolysis of (*E*)-(±)-**1a**, probably because of the similarity of the side chains of **1a** and **6** (Table 2, entries 1–2). Again, the side chain of the binaphthyl moiety was shown to play an important role in the lipase-catalyzed resolution of binaphthyl derivatives.

In conclusion, the lipase-catalyzed hydrolysis reactions of *O*-acetyl binaphthyl ketoximes are influenced by the length and configuration of the side chain between the binaphthyl ring and the carbonyloxy group. This is similar to the results of a previous report for the lipase-catalyzed aminolysis of 1,1′-binaphthyl esters. A mixture of (*E*),(*Z*)-binaphthyl ketoxime having phenyl group was readily separated using silica gel column chromatography with chloroform as the eluent. Although *Candida antarctica* lipases were successful as catalysts in the hydrolysis resolution of ketoximes (±)-**1a** and (±)-**1b**, ketoximes (±)-**2a**, and (±)-**2b** were not effective as substrates under esterification conditions. Selectivity for the opposite enantiomer of the axial binaphthyl skeleton was shown by (*Z*)-isomer **1b** against (*E*)-isomer **1a**. The present synthetic methodology offers two advantages: (1) simplicity of operation, and (2) high yields of the lipase-catalyzed resolution without the use of toxic resolving agents.

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6. (*E*)-(±)-**1a**: pale yellow oil; IR ν_{max} (neat)/cm^{-1} 1768, 1199 (CO_2R); ^1H NMR ($CDCl_3$): δ 1.94 (3H, s, CH_3), 6.60–7.55 (13H, m, ArH), 7.72 (2H, t, $J = 7.6$ Hz, ArH), 7.91 (1H, d, $J = 8.6$ Hz, ArH), 7.97 (1H, d, $J = 8.2$ Hz, ArH), 8.05 (1H, d, $J = 8.4$ Hz, ArH); FABMS (*m*/*z*) 416 $(M+H)^+$.
(*Z*)-(±)-**1b**: pale yellow crystal; mp 182–184 °C; IR ν_{max} (KBr)/cm^{-1} 1768, 1193 (CO_2R); ^1H NMR (DMSO-d_6): δ 1.18, 2.12 (3H, ds, CH_3), 6.93–7.99 (16H, m, ArH), 8.16 (1H, d, $J = 8.4$ Hz, ArH), 8.25 (1H, d, $J = 8.6$ Hz, ArH); FABMS (*m*/*z*) 416 $(M+H)^+$.
(*E*)-(±)-**2a**: colorless crystal; mp 189–190 °C; IR ν_{max} (KBr)/cm^{-1} 3200 (OH); ^1H NMR (DMSO-d_6): δ 6.74 (2H, d, $J = 8.0$ Hz, ArH), 6.85–6.91 (4H, m, ArH), 7.00 (1H, d,

$J = 8.0$ Hz, ArH), 7.06 (1H, d, $J = 7.0$ Hz, ArH), 7.14 (1H, t, $J = 7.5$ Hz, ArH), 7.30 (1H, t, $J = 8.0$ Hz, ArH), 7.35–7.39 (2H, m, ArH), 7.53 (1H, t, $J = 7.5$ Hz, ArH), 7.74 (1H, d, $J = 8.5$ Hz, ArH), 7.84 (2H, d, $J = 8.0$ Hz, ArH), 8.07 (1H, d, $J = 8.0$ Hz, ArH), 8.13 (1H, d, $J = 8.0$ Hz, ArH), 11.12 (1H, s, C=NOH); MS (m/z) 373 (M^+).
(*Z*)-(±)-**2b**: colorless crystal; mp 221–222 °C; IR ν_{max} (KBr)/cm^{-1} 3200 (OH); ^{1}H NMR (DMSO-d_6): δ 6.89–7.86 (15H, m, ArH), 8.09 (1H, d, $J = 8.5$ Hz, ArH), 8.16 (1H, d, $J = 8.5$ Hz, ArH), 8.32 (1H, s, ArH), 10.93, 11.43 (1H, ds, C=NOH); MS (m/z) 373 (M^+).

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