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Facile synthesis of chiral 2-formyl-1,1′-binaphthyl via lipase-catalyzed acylation and hydrolysis of 1,1′-binaphthyl oximes

Naoto Aoyagi,* Tomoyuki Ohwada and Taeko Izumi

Department of Chemistry and Chemical Engineering, Graduate School of Science and Engineering, Yamagata University, Jyonan, Yonezawa, Yamagata 992-8510, Japan

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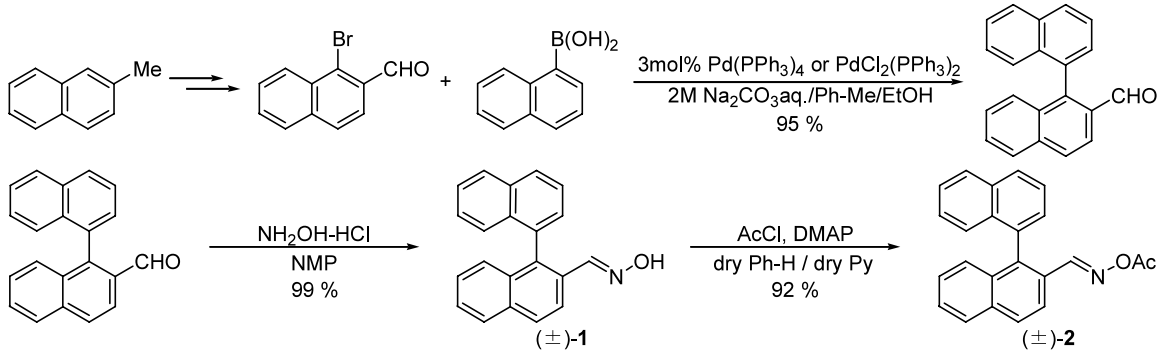
Abstract—Lipase-catalyzed acylation of 2-hydroxyiminomethyl-1,1′-binaphthyl [(±)-**1**] and hydrolysis of 2-acetoxyiminomethyl-1,1′-binaphthyl [(±)-**2**] yielded optically active oximes **1** and **2** with high enantiomeric excess. Successful synthesis of the optically active aldehyde **4** from chiral *O*-acetyl oxime **2** occurred without a decrease of enantiomeric excess.

Lipases in organic solvents have been employed as catalysts in the synthesis of extensive optically active compounds.[1] Typical substrates used for lipase-catalyzed resolutions include alcohol, amine, carboxylic acid and ester. Recently, it was reported that oxime derivatives were resolved by lipase-catalyzed acylation and hydrolysis.[2] However, little is known about the lipase-catalyzed resolution of oxime derivatives of axial biaryl compounds.

Recently, chiral biaryl derivatives have received much attention in the context of chiral ligands,[3] pharmaceutical products,[4] natural products,[5] and liquid crystals.[6] Although lipase-catalyzed esterification and hydrolysis of biaryls has been reported for the synthesis of chiral biaryl alcohols,[7] enzymatic kinetic resolutions of biaryl aldehydes proved to be extremely challenging. For example, kinetic resolution of racemic 2-formyl-1,1′-binaphthyls by baker's yeast reduction yielded chiral 2-hydroxymethyl-1,1′-binaphthyls, leaving chiral aldehydes with low enantioselectivities.[8] Chiral binaphthyl aldehydes are generally synthesized by oxidation of chiral binaphthyl alcohols.[7c,9] However, it is well known that these alcohols were previously reduced from binaphthyl esters, after which chiral alcohols must be oxidized by a large excess of manganese(IV) oxide,[7c]



Scheme 1. Synthesis of racemic oximes (±)-**1**∼**2**.

Keywords: binaphthyl; Suzuki cross-coupling; oxime; lipase; acylation; hydrolysis.
* Corresponding author. Tel.: +81-238-26-3126; fax: +81-238-26-3413; e-mail: tp455@dip.yz.yamagata-u.ac.jp

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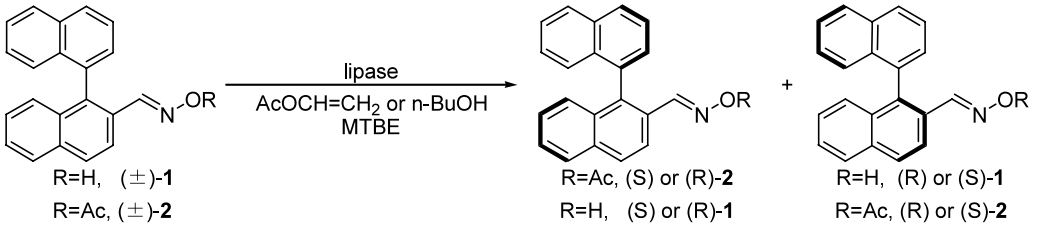


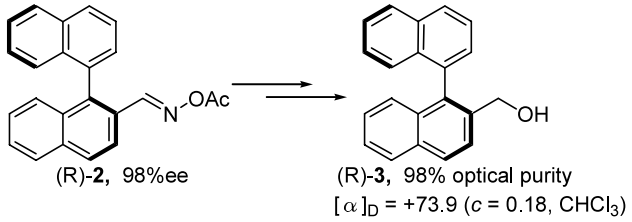
Scheme 2. Lipase-catalyzed resolution of oxime (±)-**1**∼**2**.

toxic Jones reagent,[9] or expensive Fetizon reagent[10] in order to yield chiral aldehydes. Therefore, a novel, facile synthesis of chiral biaryl aldehydes was developed.

An efficient resolution of 1,1′-binaphthyl amine and 1,1′-binaphthyl ester using lipase-catalyzed amidations was previously reported.[11] Consequently, the applicability of these reactions using binaphthyl oxime derivatives and synthesis of the chiral 2-formyl-1,1′-binaphthyl from 1,1′-binaphthyl oximes became an area of research interest.

Racemic mixtures of oximes (±)-**1**∼**2**[12] were obtained in high yields using the Suzuki cross-coupling reaction (Scheme 1).[13] The enzymatic resolution of (±)-**1**∼**2** was conducted under esterification and hydrolysis conditions, using 13 commercially available lipase preparations (Scheme 2).[14]

In a typical experiment, lipase (40 mg) and vinyl acetate (0.202 mmol) [or *n*-butanol (0.0672 mmol)] were added to a solution of oxime (±)-**1** (20 mg, 0.0672 mmol) [or *O*-acetyl oxime (±)-**2** (23 mg, 0.0672 mmol)] and 2′-acetonaphthone (1.0 mg, standard substance) in *tert*-butyl methyl ether (4 mL) (MTBE). The resulting mixture was shaken (150 cycles/min) at 30°C, during which the course of the reaction was monitored by a high performance liquid chromatograph (HPLC) equipped with a UV detector (GL Sciences, Column: Inertsil ODS-2, Mobile phase: acetonitrile/water = 8:2, Flow rate: 0.8 mL/min, Wavelength-UV: 254 nm). Upon completion, the reaction was stopped by filtering to remove the lipase enzyme. The lipase portion was washed with MTBE (10 mL). The combined filtrate and wash were evaporated at 30°C, and the resulting crude residue was purified by silica gel column chromatography (Mobile phase: chloroform) to yield the chiral *O*-acetyl oxime **2** and oxime **1**. Enantiomeric excess (ee) values were determined using HPLC (Daicel, Column: Chiralcel OD, Mobile phase: hexane/2-propanol = 100:1, Flow rate: 0.4 mL/min (0–50 min)—1.4 mL/min (50–80 min), Wavelength-UV: 254 nm). *E* Values were calculated according to the literature.[15] Absolute configurations of the products were determined using their circular dichromism spectra (dihedral angles of the binaphthyl backbones were calculated by WinMOPAC.).[16] These determinations were confirmed by converting chiral *O*-acetyl oxime **2** to (*R*)-(+)-2-hydroxymethyl-1,1′-binaphthyl **3** by the established mechanism (Scheme 3).[9]



Scheme 3. Synthesis of known configuration (*R*)-**3**.

As shown in Table 1, *Pseudomonas* species lipases (LIP, AH and PS)[14] were found to give the most effective selectivity for esterification (entries 1∼3). Although the esterification reactions catalyzed by *Candida antarctica* lipases (NOVOZYM 435 and CHIRAZYME L-2) proceeded at a high reaction rate, the enantioselectivities were relatively low, the highest being 31% ee (entries 4 and 5). Selectivity for the opposite enantiomer of the axial binaphthyl ring was shown by *C. antarctica* lipase against *Pseudomonas* lipase-catalyzed esterification (entries 1∼5).

As with the lipase-catalyzed esterification of (±)-**1**, *Pseudomonas* species lipases (LIP, AH and PS) were found to yield the most effective selectivity for hydrolysis (Table 2, entries 1, 3, 5). Passing over this conversing of hydrolysis reaction, leave chiral oxime ester (*R*)-**2** was obtained with high enantiomeric excess using LIP (99% ee, 36% yield; entry 2) and AH (98% ee, 41% yield; entry 4). In general, hydrolysis reactions of (±)-**2** were much more reactive than esterification reactions of (±)-**1**.

The hydrolysis of the *O*-acetyl oxime (*R*)-**2** to the aldehyde (*R*)-**4** was then investigated. We found that synthesis of the chiral aldehyde (*R*)-**4** from (*R*)-**2** with acetic acid and 8N hydrochloric acid in acetone at ambient temperature (99% yield) was successful without a decrease of enantiomeric excess (Scheme 4).

In conclusion, the efficient chiral synthesis of 2-formyl-1,1′-binaphthyl (*R*)-**4** was accomplished using a combination of the Suzuki cross-coupling reaction and the lipase-catalyzed kinetic resolution of (±)-**2**. *Pseudomonas* species lipases (LIP, AH and PS) served as effective catalysts for the kinetic resolution of (±)-**1** and (±)-**2**. The present synthetic methodology offers the following two advantages: (1) simplicity of operation, and (2) high yields of the lipase-catalyzed resolution without the use of toxic resolving agents. Currently, the applicability of this method is being extended to the lipase-catalyzed resolution of 2,2′-diformyl-1,1′-biaryls.

Table 1. Acylation of racemic-**1** a using lipase catalyst

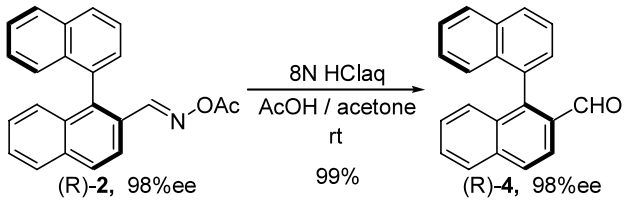
Entry	Lipase[a,b]	Time (h)	Acetyloxime **2**			Oxime **1**			*E* value[e]
			Yield (%)[c]	E.e. (%)[d]	Config.	Yield (%)[c]	E.e. (%)[d]	Config.	
1	LIP	24	45	73	*S*	38	84	*R*	17
2	AH	24	32	84	*S*	68	39	*R*	17
3	PS	24	10	63	*S*	87	7	*R*	5
4	NOVOZYM 435	24	38	29	*R*	47	31	*S*	2
5	CHIRAZYME L-2	24	35	23	*R*	40	31	*S*	2
6	AK	24	10	Racemate		80	Racemate	–	–

[a] Another seven commercially lipases (Ref. 14) were not reacted.
[b] NOVOZYM 525L and *Thermomyces lanuginosus* lipases adsorbed on Celite; see Ref. 17.
[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, 0.4 mL/min (0–50 min)–1.4 mL/min (50–80 min), *n*-hexane/IPA = 100:1).
[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. 15.

Table 2. Hydrolysis of racemic-**2** by lipase catalyst

Entry	Lipase	Time (h)	Oxime **1**			Acetyloxime **2**			*E* value[c]
			Yield (%)[a]	E.e. (%)[b]	Config.	Yield (%)[a]	E.e. (%)[b]	Config.	
1	LIP	1	57	76	*S*	42	98	*R*	33
2	LIP	2	64	63	*S*	36	>99	*R*	>22
3	AH	1	47	78	*S*	52	62	*R*	15
4	AH	2	59	68	*S*	41	98	*R*	23
5	PS	7	55	44	*S*	45	48	*R*	4
6	PS	15	75	24	*S*	22	94	*R*	5
7	NOVOZYM 435	0.1	42	38	*R*	57	37	*S*	3
8	NOVOZYM 525L[d]	24	Not detected		–	Recovery		–	–
9	CHIRAZYME L-2	0.1	45	36	*R*	55	29	*S*	3
10	*Thermomyces lanuginosus*[d]	24	Not detected		–	Recovery		–	–
11	PPL	24	Not detected		–	Recovery		–	–
12	CCL	15	48	11	*S*	51	<1	*R*	<1
13	AK	8	53	Racemate	–	42	Racemate	–	–
14	AY	15	51	24	*S*	48	5	*R*	1
15	OF	4	53	Racemate	–	46	Racemate	–	–
16	MY	15	50	6	*S*	50	8	*R*	1

[a] Determined by internal standard method of HPLC using ODS-2 (254 nm, 0.8 mL/min, $CH_3CN/H_2O = 8/2$).
[b] Determined by HPLC using Chiralcel OD (254 nm, 0.4 mL/min (0–50 min)—1.4 mL/min (50–80 min), *n*-hexane/IPA = 100/1).
[c] $E = \ln[(ee_p(1-ee_s))(ee_p+ee_s)^{-1}]/\ln[ee_p(1+ee_s))(ee_p+ee_s)^{-1}]$; see Ref. 15.
[d] These lipases adsorbed on Celite; see Ref. 17.



Scheme 4. Synthesis of chiral aldehyde (*R*)-**4**.

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12. (±)-**1**: mp 155–157°C; IR ν_{max} (KBr)/cm^{-1} 3300 (OH); ^{1}H NMR ($CDCl_3$) δ 7.20 (2H, d, J=7.5 Hz, ArH), 7.25–7.51 (6H, m, ArH), 7.62 (1H, t, J=7.5 Hz, ArH), 7.76 (1H, s, OH), 7.91–8.02 (4H, m, ArH), 8.13 (1H, d, J=9.0 Hz, CH); MS (m/z) 297 (M^+).
(±)-**2**: mp 175–176°C; IR ν_{max} (KBr)/cm^{-1} 1780, 1190 (CO_2R); ^{1}H NMR ($CDCl_3$) δ 2.09 (3H, s, CH_3), 7.17–7.33 (4H, m, ArH), 7.43 (1H, d, J=7.0 Hz, ArH), 7.52 (2H, q, J=7.0 Hz, ArH), 7.52 (2H, q, J=7.0 Hz, ArH), 7.64 (1H, t, J=7.5 Hz, ArH), 7.94 (1H, d, J=8.0 Hz, ArH), 7.97–7.99 (3H, m, ArH), 8.03 (1H, d, J=8.5 Hz, ArH), 8.32 (1H, d, J=9.0 Hz, CH); FABMS (m/z) 340 $(M+H)^+$.
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14. LIP from *Pseudomonas aeruginosa* (Toyobo Co., Ltd.); *Thermomyces lanuginosus* (Novo Nordisk Co., Ltd.); NOVOZYM 435, NOVOZYM 525L and CHIRAZYME L-2 from *Candida antarctica* (Novo Nordisk Co., Ltd.); PPL from *Porcine pancreas* (Sigma Chemical Co., Ltd.); CCL from *Candida cylindrasea* (Sigma Chemical Co., Ltd.); PS and AH from *Pseudomonas cepacia* (Amano Pharmaceutical Co., Ltd.); AK from *Pseudomonas fluorescene* (Amano Pharmaceutical Co., Ltd.); AY from *Candida rugosa* (Amano Pharmaceutical Co., Ltd.); OF and MY from *Candida cylindrasea* (Meito Sangyo Co., Ltd.).
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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, yielding immobilized lipase.