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Lipase-catalyzed Kinetic Resolution of Phenylcyclohexanone Oxime Esters

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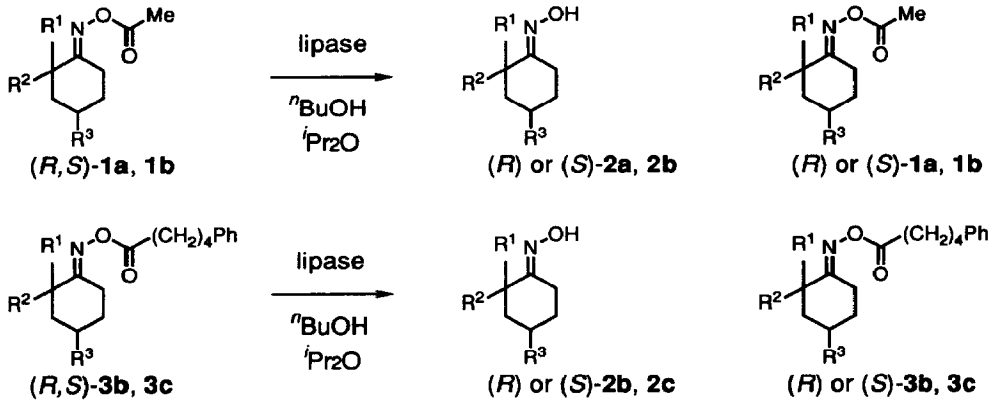
Abstract: Formation of optically active α or γ-phenylcyclohexanone oximes (**2a** and **2b, c**) and their esters (**1a** and **3b, c**) by lipase mediated transesterification of the corresponding racemic esters is described. Furthermore, 2(*S*)-phenyl and 2,2-dimethyl-4(*R*)-phenylcyclohexanones (**4** and **5**) were prepared without any racemization by treatment with dimethyldioxirane in acetone or sodium hydrogen sulfite in refluxing aqueous ethanol.

Lipase-catalyzed resolution of racemic alcohols or esters is well known as one of the most useful methods for the preparation of enantiomerically pure compounds.[1] During our investigation[2] concerning the kinetic resolution of acetates of tetrahydroisoquinolinols, it has recently been reported that hydrolysis of acetates of certain phenolic (*R, S*)-1-arylalkyltetrahydroisoquinolines[3] or (*R, S*)-aporphines[4] with lipases in organic solvents takes place kinetically to give (*R*) or (*S*)-phenols and (*S*) or (*R*)-acetates in fair to good enantiomeric excess. In spite of such an extensive investigation of enzymatic resolution of esters, the formation of optically active oximes from the racemic oxime esters[5] has been reported only once[6] on an aldoxime. Kinetic resolution of oxime esters focused our attention on an efficient preparation of optically active oximes, since they are versatile intermediates in organic synthesis. We describe here kinetic resolutions of phenylcyclohexanone oxime esters by the use of lipase and the preparation of optically active phenylcyclohexanones.

In order to examine how the asymmetric recognition with lipase can be effected by the distance between the ester group and the stereogenic centre, (*R, S*)-phenylcyclohexanone oxime esters (**1** and **3**) having stereogenic carbon centres at the α or γ positions to the oxime group were chosen as substrates (Scheme 1).

At first, transesterification of racemic (E)-2-phenylcyclohexanone oxime acetate (**1a**) with ^{n}BuOH in ^{i}Pr2O by the use of various commercially available lipases (Amano A-6 from *Aspergillus niger*; Amano AY-30 from *Candida cylindracea*; No L-1754 from *Candida cylindracea*; MY-30 from *Candida cylindracea*; OF-360 from *Candida cylindracea*; Amano GC-20 from *Geotrichum candidum*; Amano M-10 from *Mucol japonicus*; L-3126 from *Porcine pancreas*; Pancreatin F from *Porcine pancreas*; Amano P from *Pseudomonas fluorescens*; PS from *Pseudomonas fluorescens*; Amano F-AP-15 from *Rhizopus japonicas*; Newlase F from *Rhizopus niveus*; L-3001 from *Wheat Germ*; PL from *Alcaligenes*) was examined. The enantiomeric excess (e.e.) of the oxime and remaining oxime ester, which were isolated from the reaction mixture by silica gel column chromatography, was determined by HPLC on a chiral phase. Among the lipases used, lipase F-AP-15 showed (E)-2(*S*)-phenylcyclohexanone oxime (**2a**) to be obtained in 66% e.e. (28% chemical yield).

The similar procedure was applied to (*R, S*)-4-phenylcyclohexanone oxime esters **1b**, **3b**, **c** to investigate the possibility of remote asymmetric recognition with lipase. The results are shown in Table 1. (*R, S*)-4-Phenylcyclohexanone oxime acetate (**1b**) showed only poor enantioselectivity against all lipases mentioned above, although transesterification proceeded smoothly (84% chemical yield). However, when the 5-phenylvaleryl[3, 7] instead of the acetyl groups in the ester moiety of **1b** was used, the enantioselectivity increased. Interestingly, in the reaction of **3b** with lipase PL, the e.e. of recovered oxime ester dramatically was raised to 93% (33% chemical yield). In the present reaction, (+)-4-phenylcyclohexanone oxime (**2b**) was found to racemize easily due to E-Z isomerization of the oxime.[8] Furthermore, this methodology can also be applied to the unracemizable 2, 2-disubstituted 4-phenylcyclohexanone oxime. As expected, transesterification of (*R, S*)-(E)-2,2-dimethyl-4-phenylcyclohexanone oxime 5-phenylvalerate (**3c**) with lipase L-3126 afforded 90% e.e. (31% chemical yield) of recovered oxime ester **3c**.



a: $R^1 = R^3 = H$, $R^2 = Ph$; **b**: $R^1 = R^2 = H$, $R^3 = Ph$; **c**: $R^1 = R^2 = Me$, $R^3 = Ph$

Scheme 1

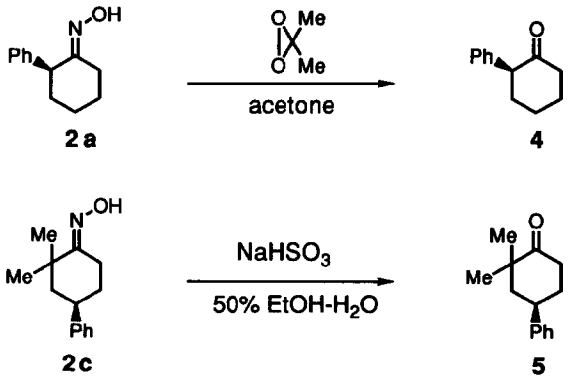
Table 1 Transesterification of (*R, S*)-phenylcyclohexanone oxime esters (**1** and **3**) catalyzed by lipases[a]

Run	(*R,S*)-Oxime ester	Lipase[b]	Reaction time (h)	E.e %[c] (yield)[d] Ester	Oxime	Config. of oxime
1	**1a**	F-AP-15	54	**1a** 25 (71)	**2a** 66 (28)	*S*
2	**3b**	PL	0.5	**3b** 93 (33)	**2b** 46 (65)	-[e]
3	**3c**	L-3126	23	**3c** 90 (31)	**2c** 41 (67)	*R*

[a] All reactions were carried out with ^{n}BuOH in ^{i}Pr2O at room temperature. [b] F-AP-15 from *Rhizopus javanicus*, (Amano Pharmaceutical Co., Ltd.); PL from *Alcaligenes*, (Meito Sangyo Co., Ltd.); L-3126 from *porcine pancreas*, (Sigma Chemical Co., Ltd.). [c] Determined by HPLC using a chiral column (see Experimental). [d] Values in parenthesis showed isolated yield (%) of each product. [e] Not determined.

In the present reaction, it was proved that asymmetric recognition took place effectively not only at the α-position to the oxime group but also at the γ-position. It is also noteworthy that lipase-catalyzed kinetic resolution afforded optically active oxime ester (Run 2 in Table 1), although racemization of the oxime easily occurred.

Preparation of optically active phenylcyclohexanones was accomplished by employing oximes thus obtained (Scheme 2). Namely, treatment of 2-phenylcyclohexanone oxime (**2a**) with dimethyldioxirane[9] in acetone at room temperature for 24 h gave optically active 2(*S*)-phenylcyclohexanone (**4**)[10] in 58% yield. On the other hand,[11] the reaction of **2c** with sodium hydrogen sulfite[12] in 50% ethanol-water under reflux for 30 min smoothly proceeded to afford optically active 2,2-dimethyl-4(*R*)-phenylcyclohexanone (**5**) in 83% yield. The absolute configuration of **5** was determined by circular dichroism measurement.[13]



Scheme 2

The present method provides an efficient approach to the asymmetric synthesis of oxime esters, which should be useful as synthons for the synthesis of various optically active compounds. Further investigation on application of this methodology is currently under way.

Experimental

Analysis

All melting points were measured on a Yanagimoto (hot plate) melting point apparatus and are uncorrected. IR spectra were performed with a Hitachi 260-10 spectrometer and ^{1}H NMR spectra were recorded with a JEOL JMX-FX100 (100 MHz) or a JEOL GSX-500 (500 MHz) spectrometer in $CDCl_3$ solution using tetramethylsilane as an internal standard, unless otherwise noted. Mass spectra were measured on a Hitachi M-80 or a JEOL JMS D-300 spectrometer. Specific rotation was measured on a JASCO DIP-360 digital polarimeter. Circular dichroism was measured on a JASCO J-720 spectropolarimeter. The e.e. of the oximes and recovered oxime esters was determined by HPLC analysis (hexane - ^{i}PrOH = 9 : 1) using chiralcel OB, OC or OD (DAICEL).

Preparation of the Racemic Oximes

Racemic oximes were prepared from corresponding ketones in usual way. The E configuration of oxime was determined on the basis of ^{1}H NMR (500 MHz) spectrum, in which a peak due to C_{6eq}-H appears in down field.[14]

(*R, S*)-(E)-2-Phenylcyclohexanone Oxime (2a): m.p. 183 °C (^{i}Pr$_2$O); ^{1}H NMR (500 MHz) δ 1.55-1.65 (2H, m), 1.79-1.87 (2H, m), 1.99-2.11 (2H, m), 2.15-2.20 (1H, m), 2.94 (1H, dt, *J* 5, 14 Hz, C_{6eq}-H), 3.48 (1H, dd, *J* 5, 14 Hz), 7.20-7.25 (3H, m), 7.32 (2H, m), 7.49 (1H, bs, NOH); IR (KBr) 3250, 2950, 2875, 1670, 1500, 1450 cm^{-1}; MS *m/z* 189 (M^+). Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.18; H, 7.72; N, 7.28.

(*R, S*)-4-Phenylcyclohexanone Oxime (2b): m.p. 113-114 °C (ligroin), (lit.[15] 112-113 °C); ^{1}H NMR (100 MHz) δ 1.40-3.00 (8H, m), 3.44 (1H, dt, *J* 4, 14 Hz, C_{6eq}-H), 7.00-7.40 (5H, m), 8.60 (1H, bs, NOH); IR ($CHCl_3$) 3250, 2930, 2860, 1660, 1600, 1490, 1440, 1100 cm^{-1}; MS *m/z* 189 (M^+).

(*R, S*)-(E)-2,2-Dimethyl-4-phenylcyclohexanone Oxime (2c): m.p. 109-111 °C (Et_2O); ^{1}H NMR (500 MHz) δ 1.21 (3H, s), 1.28 (3H, s), 1.56-1.64 (1H, m), 1.70 (1H, t, *J* 13 Hz), 1.78 (1H, ddd, *J* 2, 3, 13 Hz), 2.01-2.09 (2H, m), 3.03 (1H, tt, *J* 3, 13 Hz), 3.48 (1H, ddd, *J* 2, 3, 13 Hz, C_{6eq}-H), 7.00-7.40 (5H, m); IR ($CHCl_3$) 3250, 2960, 2920, 1600, 1490, 1450, 1130 cm^{-1}; MS *m/z* 217 (M^+). Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.51; H, 8.77; N, 6.39.

Preparation of the Racemic Oxime Esters

Racemic oxime acetates **1a, b** were prepared from corresponding oximes **2a, b** in usual manner. Racemic oxime valerates **3b, c** were prepared by the reaction of the corresponding oximes **2b, c** with 5-phenylvaleric acid in CH_2Cl_2 in the presence of dicyclohexylcarbodiimide.

(*R, S*)-(E)-2-Phenylcyclohexanone Oxime Acetate (1a): m.p. 47-49 °C (hexane); ^{1}H NMR (500 MHz) δ 1.62-1.71 (2H, m), 1.73-1.83 (2H, m), 2.00-2.06 (1H, m), 2.15 (3H, s), 2.24-2.29 (1H, m), 2.41-2.70 (1H, m), 2.82 (1H, dt, *J* 4.5, 14 Hz), 3.89 (1H, t, *J* 5 Hz), 7.22-7.35 (5H, m); IR (KBr) 2940, 2920, 2855, 1755, 1635, 1600, 1225, 1190 cm^{-1}; MS *m/z* 231 (M^+). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.92; H, 7.10; N, 6.03.

(*R, S*)-4-Phenylcyclohexanone Oxime Acetate (1b): m.p. 97-98 °C (Et_2O); ^{1}H NMR (100 MHz) δ 1.48-3.00 (8H, m), 2.16 (3H, s), 3.38 (1H, dt, J 4.0, 14 Hz), 7.00-7.40 (5H, m); IR ($CHCl_3$) 3020, 2950, 2895, 1765, 1635, 1600, 1510, 1460, 1190 cm^{-1}; MS *m/z* 231 (M^+). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.89; H, 7.47; N, 6.04.

(*R, S*)-4-Phenylcyclohexanone Oxime 5-Phenylvalerate (3b): Oil; ^{1}H NMR (100 MHz) δ 1.48-3.00 (16H, m), 3.32 (1H, dt, *J* 4.0, 14 Hz), 7.00-7.40 (10H, m); IR (neat) 2930, 2850, 1760, 1640, 1600, 1500, 1460, 1120 cm^{-1}; MS *m/z* 349 (M^+). HRMS *m/z* calcd for $C_{23}H_{27}NO_2$ (M^+): 349.2040. Found: 349.2044.

(*R, S*)-(E)-2.2-Dimethyl-4-phenylcyclohexanone Oxime 5-Phenylvalerate (3c): Oil; ^{1}H NMR (500 MHz) δ 1.30 (3H, s), 1.32 (3H, s), 1.61 (1H, dt, *J* 4, 13 Hz), 1.68-1.79 (5H, m), 1.82 (1H, ddd, *J* 3, 4, 13 Hz), 2.03-2.08 (1H, m), 2.15 (1H, ddd, *J* 3, 4, 15 Hz), 2.47 (2H, t, *J* 7 Hz), 2.65 (2H, t, *J* 7 Hz) 3.02 (1H, tt, *J* 4, 13 Hz) 3.30 (1H, ddd, *J* 3, 4, 13 Hz) 7.14-7.33 (10H, m); IR (neat) 2940, 2860, 1760, 1630, 1600, 1500, 1460, 1130 cm^{-1}; MS *m/z* 377 (M^+). HRMS *m/z* calcd for $C_{25}H_{31}NO_2$ (M^+): 377.2352. Found: 377.2347.

General Procedure for Lipase-catalyzed Kinetic Resolution of Oxime Esters (1a,b and 3b,c)

To a solution of racemic oxime ester (1.8 mmol) in $^{i}Pr_2O$ (20 ml) containing $^{n}BuOH$ (0.84 ml) was added lipase (630 mg). The suspension was stirred vigorously at room temperature. After the reaction time described in Table 1, the reaction mixture was filtered to remove the lipase. The filtrate was diluted with ether and washed with saturated aq. $NaHCO_3$. The organic layer was washed with saturated aq. NaCl, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (silica gel, see below) to give oximes (**2a,b,c**) and recovered oxime esters (**1a, b** and **3b, c**). ^1H NMR and mass spectra were identical with those for racemates.

(E)-2(*R*)-Phenylcyclohexanone Oxime Acetate (1a): 25% e.e. (71% chemical yield); HPLC [flow rate 1 ml / min; chiralcel OB; Rt (min) 22 for (*R*)-**1a**, 17 for (*S*)-**1a**], after flash column chromatography ($CHCl_3$) followed by bulb-to-bulb distillation. Oil; $[\alpha]_D^{22}$ +51 (*c* 1.03, PhH).

(E)-2(*S*)-Phenylcyclohexanone Oxime (2a): 66% e.e. (28% chemical yield); HPLC [flow rate 0.3 ml / min; chiralcel OC; Rt (min) 26 for (*R*)-**2a**, 29 for (*S*)-**2a**], after flash column chromatography ($CHCl_3$). Solid mass (after crystallization from $^{i}Pr_2O$); $[\alpha]_D^{23}$ -43 (*c* 1.08, PhH), 57% e.e. by HPLC.

4-Phenylcyclohexanone Oxime 5-Phenylvalerate (3b): 93% e.e. (33% chemical yield); HPLC [flow rate 1 ml / min; chiralcel OC; Rt (min) 29 and 41], after flash column chromatography ($CHCl_3$). Oil; $[\alpha]_D^{23}$ -43 (*c* 1.06, cyclohexane).

4-Phenylcyclohexanone Oxime (2b): 46% e.e. (65% chemical yield); HPLC [flow rate 0.3 ml / min; chiralcel OC; Rt (min) 27 and 31], after flash column chromatography ($CHCl_3$). Solid mass (after crystallization from hexane); $[\alpha]_D^{26}$ +32 (*c* 1.03, EtOH), 40% e.e. by HPLC.

(E)-2,2-Dimethyl-4(*S*)-phenylcyclohexanone Oxime 5-Phenylvalerate (3c): 90% e.e. (31% chemical yield); HPLC [flow rate 0.5 ml / min; chiralcel OD; Rt (min) 29 for (*R*)-**3c**, 38 for (*S*)-**3c**], after column chromatography (CH_2Cl_2). Oil; $[\alpha]_D^{23}$ -77 (*c* 1.06, cyclohexane).

(E)-2,2-Dimethyl-4(*R*)-phenylcyclohexanone Oxime (2c): Obtained in 41% e.e. as solid mass (67% chemical yield); HPLC [flow rate 0.5 ml / min; chiralcel OD; Rt (min) 13 for (*R*)-**2c**, 15 for (*S*)-**2c**], after column chromatography (CH_2Cl_2). Oil (from the filtrate after crystallization from hexane); $[\alpha]_D^{23}$ +120 (*c* 1.16, EtOH), 91% e.e. by HPLC.

Preparation of 2(*S*)-Phenylcyclohexanone (4) and 2,2-Dimethyl-4(*R*)-phenylcyclohexanone (5)

4: To a stirred acetone solution (8 ml) of dimethyldioxirane[9] was added an acetone (1.5 ml) solution of optically active oxime **2a** (61.7 mg, 0.33 mmol; 64% e.e.). The mixture was stirred for 24 h at room temperature. After evaporation of the solvent, the resulting crude product was purified by column chromatography (silica gel, hexane - EtOAc = 4 : 1) followed by bulb-to-bulb distillation to give optically active ketone **4** (33.3 mg, 58%; 64% e.e.). The e.e. was determined by HPLC [flow rate 0.5 ml / min; chiralcel OC; Rt (min) 40 for (*R*)-**4**, 35 for (*S*)-**4**]. Oil; ^1H NMR[16] (60 MHz) δ 1.40-2.70 (8H, m), 3.30-3.80 (1H, m), 6.90-7.50 (5H, m); IR ($CHCl_3$) 1750, 1500, 1455 cm^{-1}; MS *m/z* 174 (M^+); $[\alpha]_D^{22}$ -72.6 (*c* 1.51, PhH) [lit.[10], $[\alpha]_D^{24}$ -113.5 (*c* 0.60, PhH) for (*S*)-**4**].

5: To a stirred solution of optically active oxime **2c** (59.0 mg, 0.27 mmol; 91% e.e.) in 50% aq. EtOH (7 ml) was added $NaHSO_3$[12] (170 mg, 1.60 mmol). The mixture was heated under reflux for 30 min. After evaporation of the solvent, the residue was dissolved in ether. To this solution was added 0.5N HCl at 0 °C. The organic layer was separated, and washed with saturated aq. NaCl. After drying (Na_2SO_4) and evaporation of the solvent, the resulting crude product was purified by flash column chromatography (silica gel, hexane - Et_2O = 6 : 1) followed by bulb-to-bulb distillation (120 °C at 2 mmHg) to give optically active ketone **5** (45.2 mg, 83%; 91% e.e.). The e.e. was determined by HPLC [flow rate 0.2 ml / min; chiralcel OD; Rt (min) 25 for (*R*)-**5**, 28 for (*S*)-**5**]. Oil; ^{1}H NMR (100 MHz) δ 1.08 (3H, s), 1.28 (3H, s), 1.40-3.00 (6H, m), 3.00-3.40 (1H, m), 7.00-7.40 (5H, m); IR (neat) 1720 cm^{-1}; MS *m/z* 202 (M^+). HRMS *m/z* calcd for $C_{14}H_{18}O$ (M^+): 202.1356. Found: 202.1356; $[\alpha]_D^{24}$ +98 (*c* 1.60, EtOH), $[\theta]_{295}$ +5097 (*c* 0.013, MeOH).

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