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Lipase-catalyzed Kinetic Resolution of Phenylcyclohexanone Oxime Esters

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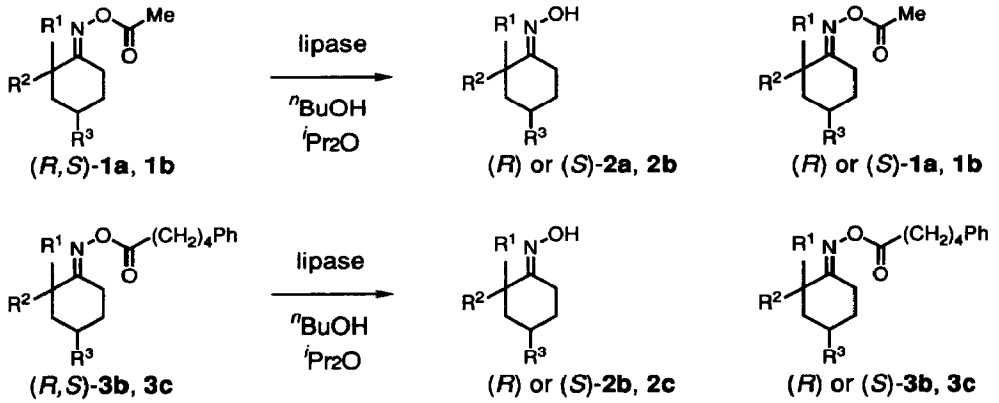
Abstract: Formation of optically active α or γ-phenylcyclohexanone oximes (**2a** and **2b, c**) and their esters (**1a** and **3b, c**) by lipase mediated transesterification of the corresponding racemic esters is described. Furthermore, 2(*S*)-phenyl and 2,2-dimethyl-4(*R*)-phenylcyclohexanones (**4** 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.