Lipase AK-Mediated Synthesis of Both Antipodes of 2-Phenyl- and 2-(1-Naphthyl)cyclohexanols in Enantiomerically Pure Form

Yi-Hsuan She, Chen-Fan Wu, Kak-Shan Shia, Jen-Dar Wu, Rama Krishna Peddinti, Hsing-Jang Liu*

Department of Chemistry, National Tsing Hua University, Hsinchu, Taiwan 300, P. R. of China
E-mail: hjliu@mx.nthu.edu.tw

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Abstract: Both (*R*,*S*)- and (*S*,*R*)-enantiomers of 2-phenylcyclohexanol and 2-(1-naphthyl)cyclohexanol were prepared in enantiomerically pure form and in excellent chemical yields by lipase AK (*Pseudomonas fluorescens*)-catalyzed kinetic acetylation of racemic alcohols with vinyl acetate in *t*-butyl methyl ether at 35 °C. The enantioselectivity of this biocatalytic transformation was found to be independent of reaction time.

Key words: lipase AK, kinetic acetylation, pure enantiomers, 2-phenylcyclohexanol, 2-(1-naphthyl)cyclohexanol

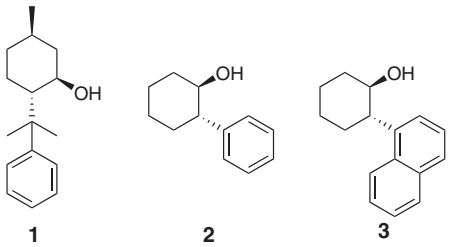

Figure 1 Cyclohexyl-based chiral auxiliaries

Due to their versatility and the high levels of stereocontrol achieved, cyclohexyl-based chiral auxiliaries[1] such as Corey's (–)-8-phenylmenthol (**1**)[2] and Whitesell's (–)-2-phenylcyclohexanol (**2**)[3] (Figure 1), have a unique place in the construction of a large variety of chiral target molecules. The asymmetric induction achieved is a consequence of selective facial shielding of the functional group to be transformed by the aryl moiety of the auxiliary[1] and the occurrence of interactions[4,5] between them. The prominence of enantiomerically pure **2** as effective inducers of chirality has prompted the development of both non-enzymatic as well as enzymatic routes towards both antipodes.[1] Several non-enzymatic synthetic routes via asymmetric hydroboration,[6] epoxidation,[7] and dihydroxylation[8] of 1-phenylcyclohexene and non-enzymatic kinetic resolutions[9,10] have been reported for the preparation of optically active alcohol **2**. Among the various enzymes[11,12] employed for the kinetic resolution of **2**, lipases *Pseudomonas* sp,[11c,12b] PS30,[12a] *Candida rugosa*[11a] were found to yield best results. Nevertheless, carefully controlled reaction conditions, in particular the reaction time, are necessary to obtain both enantiomers in optimum chemical and optical yields. 2-(1-Naphthyl)cyclohexanol (**3**, Figure 1) is another promising chiral auxiliary as it bears a bulkier aryl moiety. Recently, non-enzymatic[10] and enzymatic[11b,13] methods were reported for the kinetic resolution of **3**. Herein, we report a highly efficient kinetic acetylation of **2** and **3** using lipase AK (*Pseudomonas fluorescens*) that allows for convenient access to optically pure antipodes of these compounds.

The racemic *trans*-alcohols (±)-**2**[11d] and (±)-**3**[13] were prepared via a copper-catalyzed ring opening of epoxycyclohexane with phenylmagnesium bromide and 1-naphthylmagnesium bromide, respectively. The transesterification of (±)-**2** was performed using a lipase with vinyl acetate as acetyl donor in *t*-butyl methyl ether (Scheme 1). Lipases *Rhizopus oryzae* (lipase N, Amano), *Rhizomucor miehei* (lipase MAP-10, Amano), *Candida rugosa* (lipases MY and OF-360, Sangyo), and *Pseudomonas fluorescens* (lipase AK, Amano) were tested under the present acetyl transfer reaction. The progress of the reaction was monitored by TLC analysis and the enantioselectivity of the alcohol was judged by HPLC analysis using a chiral column. No reaction was observed with lipase N after a reaction time of 50 hours, while lipase MAP-10 could not differentiate the enantiomers satisfactorily. However, lipases OF-360 and AK provided encouraging results when the reactions were carried out at 35 °C. Thus, lipases OF-360 and AK produced acetate (–)-**4** in >99% ee and alcohol (+)-**2** in 44% and 79% ee, respectively, in a reaction time of 50 hours (Table 1). After considerable experimentation, it was found that lipase AK catalyzes the reaction to afford both antipodes in optically pure form and in quantitative yield in five days when the amount of the lipase used was increased. The transesterification is highly selective and formation of (+)-**4** was not observed even after the reaction time was extended to 10 days. The catalytic activity of the recovered enzyme was tested and its activity was found to be the same as it had been prior to the initial transesterification. When lipase PS30 was used for this transformation, we were able to reproduce the results reported by Carpenter et al.[12a] However, when the reaction time for the transesterification of (±)-**2** using PS30 was extended, the (1*S*,2*R*)-**2** formed reacted further, albeit slowly, resulting in the formation of both enantiomers in lower optical purities (Table 1, entries 6 and 7).

We have also separated the enantiomers (±)-2-(1-naphthyl)cyclohexanol (**3**) by kinetic resolution using several lipases. Again, lipase AK was found to yield optimum re-

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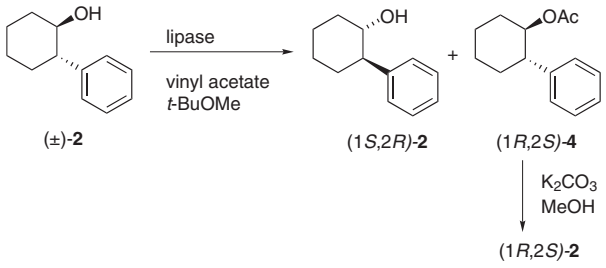
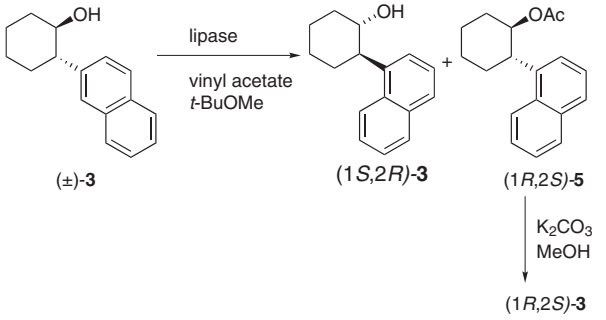


Scheme 1



Scheme 2

sults. The transesterification catalyzed by this lipase proceeded efficiently, and in 10 days both enantiomers were obtained in optically pure form and in virtually quantitative yield (Scheme 2 and Table 2). As in the previous case, lipase AK is very specific to the (1*R*,2*S*)-enantiomer and the (1*S*,2*R*)-enantiomer was not esterified under these conditions even after 20 days.

The above experimental results clearly reveal that lipase AK is a superior enzyme to those previously reported for kinetic acetylation of 2-phenyl- (**2**) and 2-(1-naphthyl)cyclohexanols (**3**). By the use of this enzyme, each of the enantiomeric pairs was cleanly resolved, and each enantiomer was obtained in optically pure form. The complete enantioselectivity observed using lipase AK was shown to be totally independent of the reaction time. Consequently, the tedious monitoring of the reaction becomes unnecessary. An added advantage is the low cost of lipase AK, which is considerably less expensive than the commonly used lipase PS 30. The low cost, reaction time independency, and reusability of lipase AK make it a viable asset for large-scale preparations of pure enantiomers of **2** and **3**, which have found extensive use (the former in particular) as chiral auxiliaries for asymmetric synthesis.

The spectral properties (IR, ^{1}H NMR, ^{13}C NMR, and MS) of the compounds were found to be in good agreement with those reported.[11b,13] FTIR spectra were recorded on a Nicolet Magna 750 instrument. ^{1}H and ^{13}C NMR spectra were measured using a Varian Inova 300 instrument with chemical shifts reported in δ (ppm) downfield from TMS (δ = 0.00) using the residual solvent signal of $CDCl_3$ (^{1}H NMR: δ = 7.26, singlet; ^{13}C NMR: δ = 77.0, triplet) as an internal standard. HRMS were recorded using a Kratos MS-50 mass spectrometer (electron impact). Analytical TLC was performed using Merck 60 F_{254} precoated silica gel plates (0.25 mm thickness). Flash chromatography was performed using silica gel (Kieselgel 60, 230–400 mesh, Merck). Determination of ee was done by HPLC (Waters 2410) using chiral column ChiraCel OD, and specific rotation was measured on a Jasco P-1020 polarimeter.

Optically Pure (+)- and (–)-2-Phenylcyclohexanol

A suspension of (±)-**2** (1.76 g, 10 mmol), vinyl acetate (9.3 mL, 100 mmol), and lipase AK on Celite (3.52 g, Amano) in *t*-BuOMe (30

Table 1 Lipase-Mediated Kinetic Resolution of (±)-**2**[a]

Entry	Enzyme[b]	Reaction Time	(1*S*,2*R*)-**2**		(1*R*,2*S*)-**4**	
			Yield (%)[c]	ee (%)[d]	Yield (%)[c]	ee (%)[e]
1	OF	50 h	69	44	29	99
2	AK	50 h	50	79	42	99
3	AK	5 d	49.5	>99	49.5	>99
4	AK	10 d	49.5	>99	49.5	>99
5[f]	AK	5 d	49.5	>99	49.5	>99
6	PS	3 d	49	85	40	97
7	PS	5 d	40	81	47	79

[a] All reactions were carried out in *t*-BuOMe (0.333 M concentration) with 10 equiv of vinyl acetate at 35 °C. For entries 1, 2, 6, and 7, (±)-**2**/enzyme = 0.85 mmol/80 mg; for entries 3–5, (±)-**2**/enzyme = 10 mmol/3.52 g.
[b] OF: lipase OF-360, AK: lipase AK, PS: lipase PS 30.
[c] All yields are for the isolated compound. For entries 1, 2, 6, and 7, various amounts of the enantiomer were detected in the isolated material.
[d] Determination of ee was done by HPLC analysis using chiral column ChiralCel OD (*i*-PrOH–hexane, 1:99; flow rate: 2 mL/min, t_R 14.51 min for (+)-**2**; t_R 3.94 min for (–)-**4**; UV: λ = 254 nm).
[e] Determination of ee was by HPLC analysis of the corresponding alcohol using chiral column ChiralCel OD (*i*-PrOH–hexane, 1:99; flow rate: 2 mL/min; t_r 15.87 min for (–)-**2**, λ = 254 nm).
[f] Recovered enzyme was used.

Table 2 Lipase-Mediated Kinetic Resolution of (±)-**3**[a]

Entry	Enzyme[b]	Reaction Time	(1*S*,2*R*)-**3**		(1*R*,2*S*)-**5**	
			Yield (%)[c]	ee (%)[d]	Yield (%)[c]	ee (%)[e]
1	OF	14 d	90	<50	9	99
2[f]	AK	7 d	66	<50	29	>98
3	AK	10 d	49.5	>99	49.5	>99
4	AK	20 d	49.5	>99	49.5	>99
5[g]	AK	10 d	49.5	>99	49.5	>99

[a] All reactions were carried out in *t*-BuOMe (0.285 M concentration) with 10 equiv of vinyl acetate at 35 °C unless otherwise mentioned. For entries 1 and 2, (±)-**3**/enzyme = 0.22 mmol/44 mg; for entries 3–5, (±)-**3**/enzyme = 10 mmol/4.52 g.
[b] OF: lipase OF-360, AK: lipase AK.
[c] All yields are for the isolated compound. For entries 1 and 2, various amounts of the enantiomer were detected in the isolated material.
[d] ee was determined by HPLC analysis using a chiral column ChiralCel OD (*i*-PrOH–hexane, 1: 99; flow rate: 2 mL/min; t_R 23.01 min for (+)-**3**; 7.66 min for (+)-**5**, λ = 254 nm).
[e] ee was determined by the HPLC analysis of the corresponding alcohol using a chiral column, ChiralCel OD (*i*-PrOH–hexane, 1:99; flow rate: 2 mL/min; t_R 28.42 min for (–)-**3**, λ = 254 nm).
[f] Reaction was carried out at r.t.
[g] Recovered enzyme was used.

mL) was stirred at 35 °C for 5 d. To determine the completion of the reaction, aliquots were taken and purified by flash chromatography on silica gel (EtOAc–hexanes, 5:95), and the optical purity was determined by HPLC using chiral column chiralcel OD (*i*-PrOH–hexane, 1:99; flow rate: 2 mL/min). After completion of the reaction, the mixture was cooled to r.t., filtered through a sintered-glass funnel, and rinsed with EtOAc (100 mL). The combined organic layers were dried over anhyd $MgSO_4$, concentrated in vacuo and chromatographed on silica gel (EtOAc–hexane, 5:95 to 10:90) to furnish (+)-**2** (0.87 g) as white crystals and (–)-**4** (1.08 g) as a pale yellow oil.

(+)-2
Mp 63.5–64.5 °C (Lit.[14] 64–65 °C); $[\alpha]_D^{25}$ +56.9 (*c* 1.0, EtOH) {Lit.[14] $[\alpha]_D^{23}$ +55.0 (*c* 0.10, MeOH)}.

(–)-4
$[\alpha]_D^{25}$ –6.5 (*c* 0.32, EtOH) [Lit.[15] $[\alpha]_D$ –6.2].

The optically active ester (–)-**4** was chemically hydrolyzed. To a solution of (–)-**4** (0.99 g, 4.5 mmol) in MeOH (10 mL), was added K_2CO_3 (1.86 g, 13.5 mmol). After stirring at r.t. for 10 h, the reaction mixture was concentrated in vacuo, and the residue was partitioned between EtOAc (50 mL) and H_2O (20 mL). The organic layer was washed with brine (20 mL), dried over anhyd $MgSO_4$, the EtOAc evaporated under reduced pressure and the residue was chromatographed on silica gel (EtOAc–hexanes, 10:90) to afford pure (–)-**2** (0.78 g).

Mp 64–65 °C (Lit.[11b] 64–65 °C); $[\alpha]_D^{25}$ –56.8 (*c* 1.0, EtOH) {Lit.[11b] $[\alpha]_D^{23}$ –58.6 (*c* 1.19, MeOH)}.

The spectral properties (IR, ^{1}H NMR, ^{13}C NMR and MS) of the above compounds were found to be in good agreement with those reported.[11b,16]

Optically Pure (+)- and (–)-2-(1-Naphthyl)cyclohexanol
A suspension of (±)-**3** (2.26 g, 10 mmol), vinyl acetate (9.3 mL, 100 mmol), and lipase AK on Celite (4.52 g, Amano) in *t*-BuOMe (35 mL) was stirred at 35 °C for 10 d. The reaction was worked up as mentioned above. Chromatography of the crude product on silica gel (EtOAc–hexanes, 5:95 to 10:90) furnished (+)-**3** (1.12 g) as white crystals and (+)-**5** (1.33 g) as a pale yellow oil.

(+)-3
Mp 99.5–100.5 °C (Lit.[13] 100–101 °C); $[\alpha]_D^{25}$ +72.2 (*c* 1.0, EtOH) {Lit.[13] $[\alpha]_D^{26}$ +78.8 (*c* 1.0, $CHCl_3$)}.

(+)-5
$[\alpha]_D^{25}$ +34.9 (*c* 1.0, EtOH) {Lit.[13] $[\alpha]_D^{26}$ +36.2 (*c* 1.05, $CHCl_3$)}.

Hydrolysis of (+)-**5** (1.33 g, 4.9 mmol) using the same method described in the preceding experiment gave pure (–)-**3** (1.11 g).

(–)-3
Mp 99.5–100.5 °C (Lit.[13] 100–100.5 °C); $[\alpha]_D^{25}$ –71.9 (*c* 1.1, EtOH) {Lit.[13] $[\alpha]_D^{26}$ –72.6 (*c* 1.0, $CHCl_3$)}.

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