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One-pot lipase-catalyzed synthesis of enantiopure secondary alcohols from carbonyl compounds: a new protocol for lipase-mediated resolution†

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Abstract—Reduction of acetophenones with sodium borohydride in the presence of neutral alumina in hexane followed by enantioselective acylation catalyzed by *Pseudomonas cepacia* lipase has been achieved in one-pot. Further, immobilized lipase offered a high degree of selectivity with spontaneity.

1. Introduction

Enantiomerically pure secondary alcohols are important synthetic intermediates and are also useful chiral auxiliaries for both synthetic and analytical applications.[1] Many synthetic methods for their preparation have been reported in the literature based on enantioselective reduction of the corresponding ketones[2,3] and enantioselective enzymatic hydrolysis of the corresponding esters.[4] Some of the methods are unsuitable for practical applicability because of numerous drawbacks including tedious workup, expensive chiral auxiliaries and large reaction volumes.[5,6] The recent studies on the use of enzymes in low polarity organic solvents initially discovered by Klibanov[6] has allowed the extension of these reactions for the enzymatic resolution by esterification and transesterification.[7–10] Resolution based on enzymatic transesterification overcomes some of the important practical problems associated with the enzymatic hydrolysis, such as low solubility of many organic compounds in water, the recovery of the enzyme for recycling and the need for pH adjustment during the reaction process.[11]

A recent study[12] on the alumina-assisted reduction of carbonyl compounds with sodium borohydride in an aprotic solvent such as hexane and our interest in biotransformations[13,14] prompted us to explore the transesterification employing the lipase in the same pot for the enantioselective preparation of secondary alcohols. Herein, we report for the first time the use of lipases for the transesterification in the presence of borohydride. Lipases in nature catalyze the hydrolysis of triacylglycerides, and interestingly they also catalyze related reactions such as esterification or transesterification in non-natural reaction conditions like anhydrous organic media.[15] Moreover, there are instances where the thermostability of the enzyme increases in organic media.[16] However, the reaction rates are generally reduced mainly due to altered partitioning of the reactant between the solvent and the active site. In this investigation, the in situ acylation of a wide range of secondary alcohols has been carried out after the reduction of the corresponding carbonyl compounds by sodium borohydride employing moist alumina in hexane.

2. Results and discussion

A number of lipases have been examined for this one-pot transesterification process for a representative substrate (acetophenone). The results in Table 1 indicate that there is no conversion employing porcine pancreatic lipase (PPL) and *Candida cylindracea* lipase (CCL) under these conditions. The other lipases viz. PS 'Amano', wheat germ, horse liver acetone powder (HLAP) have given good conversion in 3–6 days. How-

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Table 1. In situ reduction of acetophenone and transesterification using different lipases[a]

Lipases	Time (h)	Conversion (%)[b]	E.e. (%)[c]
PS 'Amano'	60	53	96
PS-C 'Amano'II	1.5	50	>99
HLAP	48	60	23
Wheat germ	144	33	20
PPL	96	–[d]	–
CCL	96	–[d]	–

[a] One equivalent of lipase (w/w).
[b] Determined by HPLC.
[c] All (*R*)-acetates were obtained.
[d] No significant conversion was observed.

ever, of all the lipases screened, lipase PS-C 'Amano' II (*Pseudomonas cepacia* lipase, immobilized on ceramic) catalyses this transesterification process in an extremely efficient manner.

The effect of temperature by employing lipase PS-C 'Amano' II has also been studied and it was observed that the amount of lipase used and the temperature has considerable effect on the transesterification process. Five sets of reactions, **A** to **E** were carried out with various amounts of lipase and at different temperatures (Table 2). The set **B** combination gave the best results and hence a number of substrates have been studied under these reaction conditions (Table 3). It was observed that about half the quantity of the lipase (0.25 equiv. w/w) could be employed when it was performed at 40°C without much difference in conversion and selectivity (set **C**).

Neutral alumina acts as a support, providing a surface for binding the substrate which assists in the formation of the enzyme–substrate complex and hence enhances the reaction rate. Alumina was activated and moistened to perform the reduction with sodium borohydride in hexane. A detailed kinetic study has been carried out for 1-phenylethanol and the effect of alumina in lipase-mediated transesterification has also been examined (Fig. 1). It is interesting to note that alumina enhances the transesterification process, which proceeds up to 50% conversion within 5–6 h. Moreover, the alumina prevents further transesterification and the reaction becomes almost steady after 50% conversion. In contrast the reaction without alumina proceeds slowly and goes beyond 50% leading to the observed poor selectivity. Thus, alumina acts as a controlling factor in association with the lipase for the transesterification process, which leads to high degrees of enantioselectivity for both acetate and alcohol.

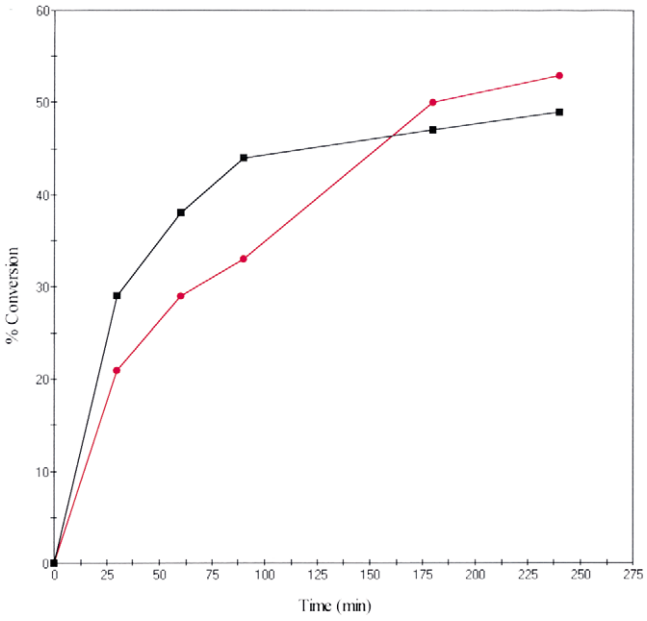


Figure 1. Transesterification (without Al_2O_3 –●– (red)) of phenylethanol catalyzed by Amano PS-C II lipase and its comparison to the one-pot process (with Al_3O_3 –■– (black)).

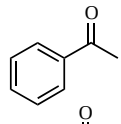
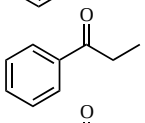
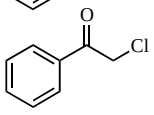
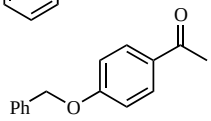
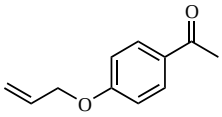
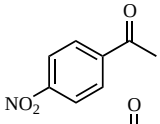
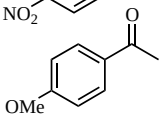
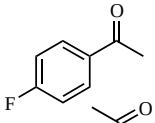
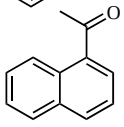
Therefore, a number of enantiopure secondary alcohols have been prepared from the corresponding carbonyl compounds employing lipase PS-C 'Amano' II. It is interesting to note that the transesterification process by lipase PS-C 'Amano' II (0.5 equiv. w/w) takes place in 4–12 h at room temperature with high enantioselectivity for most of the substrates examined (Table 3). One-pot lipase-catalyzed resolution of secondary alcohols, **a**, **b**, **c**, **g**, and **i** have been compared to their previously reported lipase-mediated transesterification.[1,17] For instance, compound **2a** and **3a** have been resolved in >99% e.e. at room temperature in 4 h, whereas literature reports[1] for these compounds exhibit relatively poorer enantioselectivities and longer reaction times (92 and 99% e.e. in 2 days), respectively. Similarly for substrates **b** and **g** the reported procedures[17a] have given lower selectivity even after 2–3 days of reaction time. On the other hand, the present method provides >99% selectivity for compounds **2c** and **3c** in about 10 h. Furthermore, this one-pot transesterification process

Table 2. The effect of temperature and amount of lipase on one-pot transesterification[a]

Set	A	B	C	D	E
PS-C 'Amano'II (mg)	60	30	15	15	30
Temp. (°C)	25	25	25	40	40
Time (h)	1.5	4	6.0	6.0	3.0
Conversion (%)[b]	50	50	42	50	47

[a] 0.5 mmol of acetophenone was reduced according to the general procedure for in situ transesterification.
[b] Determined by HPLC.

Table 3. Lipase[a]-mediated resolution of secondary alcohols in one-pot reduction of their corresponding carbonyl compounds

Entry	Substrate (1)	Time (h)[b]	Conversion *c* (%)[c]	2			3			E[c]
				Yield (%)[d]	E.e. (%)[e]	Configuration[f]	Yield (%)[d]	E.e. (%)[e]	Configuration[f]	
a		4	50	50	>99	*S*	48	>99	*R*	1057
b		4	50	43	>99	*S*	49	>99	*R*	1057
c		10	50	48	>99	*R*	44	>99	*S*	1057
d		4	49	40	>99	*S*	42	98	*R*	356
e		6	50	38	>99	*S*	45	>99	*R*	1057
f		6	50	45	>99	*S*	49	>99	*R*	1057
g		8	—[g]	46	—[g]	*S*	44	98	*R*	—[g]
h		10	—[g]	41	—[g]	*S*	43	—[g]	*R*	—[g]
i		12	41	38	70	*S*	42	>99	*R*	412

[a] Lipase PS-C, (0.5 equiv w/w), isopropenyl acetate, (6 equiv), rt.

[b] Time taken for transesterification.

[c] Conversion *c* calculated from ee_2 and ee_3; E values calculated from *c* and ee_p (ee_3), see ref 20.

[d] Isolated yields after column chromatography.

[e] Determined by chiral HPLC[19].

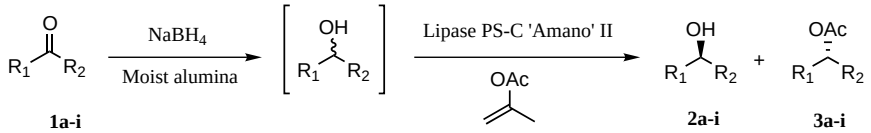
[f] The absolute configuration assigned by sign of rotation.

[g] Not determined.

has been carried out on a 5 gram scale (substrate **a**) and interestingly the results depict the consistency with the milligram level reactions, thus, exhibiting the potential of this methodology for large-scale preparations (Scheme 1).

3. Conclusion

A new efficient enzymatic pathway has been developed for the synthesis of enantiopure alcohols. The method is not only cost effective but also offers reduced reac-



Scheme 1.

tion times compared to previous methods. We have described for the first time that lipase catalyzes a transesterification process in one-pot for the secondary alcohols after the reduction of the corresponding carbonyl compounds with alumina-assisted sodium borohydride. The faster reaction rates with high selectivity in organic media like hexane and environmentally acceptable reaction conditions provides a practical and mild in situ biocatalytic resolution process for secondary alcohols starting from their carbonyl precursors.

4. Experimental

4.1. General

Unless specified, all solvents and reagents were reagent grade and used without purification. Moist neutral alumina was prepared according to the procedure of Yakabe et al.[12] Melting points have been recorded on an electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on KBr pellet and are reported in wavenumbers (cm^{-1}). ^1H NMR spectra were recorded as solutions in $CDCl_3$ and chemical shifts are reported in parts per million (PPM, δ) on a 200 MHz instrument. Coupling constants are reported in hertz (Hz). Spectral patterns are designated as s, singlet; d, doublet; tr, triplet; br, broad; m, multiplet. Low resolution mass spectra were recorded on VG 7070H Micromass mass spectrometer at 200°C, 70 eV with a trap current of 200 μA and 4 KV acceleration voltage. Analytical TLC of all reactions was performed on Merck prepared plates (silica gel 60 F-254 on glass). Column chromatography was performed using Acme silica gel (60–120 mesh, unless otherwise mentioned). Percentage yields are given for compounds. HPLC analysis was performed on an instrument that consisted of a Shimadzu LC-6A system controller, SPD-6A fixed wavelength UV monitor as detector, FCV-100B fraction collector and chromatopac C-R4A data processor as a recording integrator.

4.2. General procedure for one-pot synthesis of enantiomerically pure alcohols and acetates (A)

To a solution of the ketone (1 mmol) in hexane (10 mL) previously prepared[12] moist alumina (1.0 g) and $NaBH_4$ (2 mmol) were added. The resulting reaction mixture was stirred at 40°C for 3 h and monitored for completion of the reduction by TLC. At the end of the reaction Lipase 'Amano' PS-C II (0.5 equiv. w/w) and isopropenyl acetate (0.65 mL) were added. The mixture was stirred at room temperature for 4–12 h until the reaction reached 50% conversion, as indicated by HPLC.[18] The reaction was filtered through Celite, diluted with EtOAc and washed with water. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give an oily residue, which was purified by silica gel column chromatography to obtain enantiomerically pure acetate and alcohol. Products, thus obtained were analyzed by chiral HPLC and compared with corresponding racemic products.[19]

4.3. (1*S*)-1-Phenylethan-1-ol, 2a[1]

Prepared according to the general procedure **A** starting from substrate **a**, yield = 50%; >99% e.e.;[19a] $[\alpha]_D^{25}$ −66.5 (*c* 1.4, $CHCl_3$); IR (KBr) 3444 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.5 (3H, d, J = 6.89 Hz), 4.8 (1H, q, J = 6.89 Hz), 7.2–7.4 (5H, m); EIMS (*m*/*z*): 122 (M+), 107 (M^+−17); anal. calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.25; H, 8.12%.

4.4. (1*R*)-1-Phenylethyl acetate, 3a[1]

Prepared according to the general procedure **A** starting from substrate **a**, yield = 48%; >99% e.e.;[19c] $[\alpha]_D^{25}$ +86.7 (*c* 1.5, $CHCl_3$); IR (KBr) 1732 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.5 (3H, d, J = 6.76 Hz), 2.1 (3H, s), 5.9 (1H, q, J = 6.76 Hz), 7.2–7.4 (5H, m); EIMS (*m*/*z*): 164 (M^+), 122 (M^+−42); anal. calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.00; H, 7.20%.

4.5. (1*S*)-1-Phenylpropan-1-ol, 2b[17a]

Prepared according to the general procedure **A** starting from substrate **b**, yield = 43%; >99% e.e.;[19b] $[\alpha]_D^{25}$ −45.6 (*c* 1.3, $CHCl_3$); IR (KBr) 3369 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.9 (3H, t, J = 9.2 Hz), 1.7–1.9 (2H, m), 4.6 (1H, t, J = 6.88 Hz), 7.2–7.4 (5H, m); EIMS (*m*/*z*): 136 (M^+).

4.6. (1*R*)-1-Phenylpropyl acetate, 3b[17a]

Prepared according to the general procedure **A** starting from substrate **b**, yield = 49%; >99% e.e.;[19b] $[\alpha]_D^{25}$ +104.7 (*c* 1.7, $CHCl_3$); IR (KBr) 1737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.9 (3H, t, J = 4.28 Hz), 1.7–1.9 (2H, m), 2.1 (3H, s), 5.6 (1H, t, J = 3.21 Hz), 7.2–7.4 (5H, m); EIMS (*m*/*z*): 178 (M^+), 136 (M^{+-}42).

4.7. (1*R*)-2-Chloro-1-phenylethan-1-ol, 2c[17b]

Prepared according to the general procedure **A** starting from substrate **c**, yield = 48%; >99% e.e.;[19c] $[\alpha]_D^{25}$ −56.2 (*c* 1.1, $CHCl_3$); IR (KBr) 3499 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.6 (1H, d, J = 6.89 Hz), 3.5–3.9 (2H, m), 5.9 (1H, m), 7.3–7.5 (5H, m).

4.8. (1*S*)-2-Chloro-1-phenylethyl acetate, 3c[17b]

Prepared according to the general procedure **A** starting from substrate **c**, yield = 44%; >99% e.e.;[19c] $[\alpha]_D^{25}$ +76.6 (*c* 1.1, $CHCl_3$). IR (KBr); 1747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.2 (3H, s), 3.7–3.9 (2H, m), 5.9 (1H, m), 7.3–7.4 (5H, m); EIMS (*m*/*z*): 162 (M^+−36), 120 (M^+−78).

4.9. (1*S*)-1-(4-Benzyloxyphenyl)ethan-1-ol, 2d

Prepared according to the general procedure **A** starting from substrate **d**, yield = 40%; mp 64–65°C; >99% e.e.;[19c] $[\alpha]_D^{25}$ −31.8 (*c* 1.2, $CHCl_3$); IR (KBr) 3373 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.5 (3H, d, J = 6.89 Hz), 4.8 (1H, q, J = 6.89 Hz), 5.1 (2H, s), 6.9 (2H, d, J = 9.19 Hz), 7.2–7.5 (6H, m); EIMS (*m*/*z*): 228 (M^+);

anal. calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.47; H, 6.95%.

4.10. (1*R*)-1-(4-Benzyloxyphenyl)ethyl acetate, 3d

Prepared according to the general procedure **A** starting from substrate **d**, yield = 42%; mp 50–51°C; 98% e.e.;[19c] $[\alpha]_D^{25}$ +89.8 (*c* 1.4, $CHCl_3$); IR (KBr) 1732 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.5 (3H, d, J = 6.89 Hz), 2.1 (3H, s), 5.1 (1H, q, J = 6.89 Hz), 5.1 (2H, s) 6.9 (2H d, J = 9.19 Hz), 7.3 (2H, d, J = 9.19 Hz) 7.4–7.5 (5H, m); EIMS (*m*/*z*): 270 (M^+); anal. calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: $C_{17}H_{18}O_3$: C, 75.20; H, 6.23%.

4.11. (1*S*)-1-(4-Allyloxyphenyl)ethan-1-ol, 2e

Prepared according to the general procedure **A** starting from substrate **e**, yield = 38%; >99% e.e.;[19b] $[\alpha]_D^{25}$ −35.4 (*c* 0.7, $CHCl_3$); IR (KBr) 3417 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.4 (3H, d, J = 5.71 Hz), 4.5 (3H, d, J = 5.71 Hz), 4.8 (1H, q, J = 5.72 Hz), 5.2 (1H, dd, J = 2.85, 11.42 Hz), 5.4 (1H, d, J = 17.14 Hz), 6.0 (1H, m), 6.8 (2H, d, J = 8.57 Hz), 7.2 (2H, d, J = 8.57); EIMS (*m*/*z*): 178 (M^+), 163 (M^+−15); anal. calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.25; H, 7.88%.

4.12. (1*R*)-1-(4-Allyloxyphenyl)ethyl acetate, 3e

Prepared according to the general procedure **A** starting from substrate **e**, yield = 45%; >99% e.e.;[19a] $[\alpha]_D^{25}$ +116.5 (*c* 1.2, $CHCl_3$); IR (KBr) 1734 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.5 (3H, d, J = 6.89 Hz), 2.0 (3H, s), 4.5 (2H, m, J = 5.74 Hz), 5.3 (1H, d, J = 10.34 Hz), 5.4 (1H, d, J = 17.47 Hz), 5.7–5.9 (1H, q, J = 6.89 Hz), 5.9–6.2 (1H, m), 6.8 (2H, d, J = 8.27 Hz), 7.3 (2H, d, J = 8.27); EIMS (*m*/*z*): 220 (M^+); anal. calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.42; H, 7.14%.

4.13. (1*S*)-1-(4-Nitrophenyl)ethan-1-ol, 2f

Prepared according to the general procedure **A** starting from substrate **f**, yield = 45%; >99% e.e.;[19b] $[\alpha]_D^{25}$ −32.7 (*c* 1.0, $CHCl_3$); IR (KBr) 3411 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.5 (3H, d, J = 7.56 Hz), 5.9 (1H, q, J = 7.56 Hz), 7.5 (2H, d, J = 8.10 Hz), 8.2 (2H, d, J = 8.10 Hz); anal. calcd for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.15; H, 5.32; N, 8.15%.

4.14. (1*R*)-1-(4-Nitrophenyl)ethyl acetate, 3f

Prepared according to the general procedure **A** starting from substrate **f**, yield = 49%; >99% e.e.;[19b] $[\alpha]_D^{25}$ +99.2 (*c* 1.4, $CHCl_3$); IR (KBr) 1734 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.5 (3H, d, J = 7.59 Hz), 2.0 (3H, s), 5.9 (1H, q, J = 7.59 Hz), 7.5 (2H, d, J = 8.86) 8.2 (2H, d, J = 8.86 Hz); EIMS (*m*/*z*): 167 (M^+−42); anal. calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 30.59; N, 5.30. Found: C, 57.15; H, 30.38; N, 5.23%.

4.15. (1*S*)-1-(4-Methoxyphenyl)ethan-1-ol, 2g[17a]

Prepared according to the general procedure **A** starting from substrate **g**, yield = 46%; >99% e.e.;[19c] $[\alpha]_D^{25}$ −59.0 (*c* 1.0, $CHCl_3$); IR (KBr) 3523 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.5 (3H, d, J = 6.86 Hz), 1.8 (3H, s), 4.8 (1H, q, J = 6.86 Hz), 6.8 (2H, d, J = 9.15), 7.3 (2H, d, J = 9.15 Hz); FABMS: 152 (M^+).

4.16. (1*R*)-1-(4-Methoxyphenyl)ethyl acetate, 3g[17a]

Prepared according to the general procedure **A** starting from substrate **g**, yield = 44%; 98% e.e.;[19c] $[\alpha]_D^{25}$ +134 (*c* 1.4, $CHCl_3$); IR (KBr) 1739 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.6 (3H, d, J = 7.64 Hz), 2.1 (3H, s), 3.8 (3H, s), 5.8 (1H, q, J = 7.64 Hz), 6.8 (2H, d, J = 8.91 Hz) 7.2–7.4 (2H, d, J = 8.91 Hz); EIMS (*m*/*z*): 194 (M^+).

4.17. (1*S*)-1-(4-Fluorophenyl)ethan-1-ol, 2h

Prepared according to the general procedure **A** starting from substrate **h**, yield = 41%; $[\alpha]_D^{25}$ −35.6 (*c* 0.5, $CHCl_3$); IR (KBr) 3457 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.4 (3H, d, J = 6.89 Hz), 1.9 (1H, s), 4.8 (1H, q, J = 6.89 Hz), 7.0 (2H, t, J = 8.04 Hz), 7.2–7.4 (2H, dd, J = 8.04, 2.29 Hz); EIMS (*m*/*z*): 140 (M^+), 125 (M^+−15); anal. calcd for C_8H_9FO: C, 68.56; H, 6.47. Found: C, 68.35; H, 6.12%.

4.18. (1*R*)-1-(4-Fluorophenyl)ethyl acetate, 3h

Prepared according to the general procedure **A** starting from substrate **h**, yield = 43%; $[\alpha]_D^{25}$ −94.2 (*c* 1.1, $CHCl_3$); IR (KBr) 1732 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.5 (3H, d, J = 6.41 Hz), 2.0 (3H, s), 5.8 (1H, q, J = 6.41 Hz), 7.0 (2H, t, J = 8.97 Hz), 7.2–7.4 (2H, dd, J = 8.97, 2.56 Hz); anal. calcd for $C_{10}H_{11}FO_2$: C, 65.92; H, 6.09. Found: C, 65.68; H, 5.95%.

4.19. (1*S*)-1-(1-Napthyl)ethan-1-ol, 2i[17c]

Prepared according to the general procedure **A** starting from substrate **i**, yield = 38%; 70% e.e.;[19c] $[\alpha]_D^{25}$ −44.6 (*c* 1.4, $CHCl_3$); IR (KBr) 3369 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.7 (3H, d, J = 7.36 Hz), 5.7 (1H, q, J = 7.36 Hz), 7.5 (3H, m), 7.7 (1H, d, J = 7.89 Hz) 7.9 (1H, d, J = 7.89 Hz), 8.2 (1H, d, J = 7.89 Hz); EIMS (*m*/*z*): 172 (M^+), 157 (M^+−15).

4.20. (1*R*)-1-(1-Napthyl)ethyl acetate, 3i[17c]

Prepared according to the general procedure **A** starting from substrate **i**, yield = 42%; >99% e.e.;[19c] $[\alpha]_D^{25}$ +52.7 (*c* 1.1, $CHCl_3$); IR (KBr) 1739 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.7 (3H, d, J = 7.22 Hz), 2.1 (3H, s), 6.6 (1H, q, J = 7.22 Hz), 7.4–7.6 (5H, m), 7.2–7.9 (2H, m), 8.1 (1H, d, J = 7.3 Hz); EIMS (*m*/*z*): 214 (M^+), 172 (M^+–42).

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References

1. Laumen, K.; Breitgoff, D.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1988**, 1459.
2. Matsuda, T.; Harada, T.; Nakajima, N.; Nakamuna, K. *Tetrahedron Lett.* **2000**, *41*, 4135.
3. Ohtsuka, Y.; Ikeno, T.; Yamada, T. *Tetrahedron: Asymmetry* **2000**, *11*, 3671.
4. Zhou, H.; Lu, S.; Xie, R.; Chan, A. S. C.; Yang, T. K. *Tetrahedron Lett.* **2001**, *42*, 1107.
5. Jones, J. B. *Tetrahedron* **1986**, *42*, 3551.
6. Zaks, A.; Klibanov, A. M. *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 3192.
7. Tramper, J.; Vander Plas, H. C.; Linko, P. *Biocatalysis in Organic Synthesis*; Elsevier: New York, 1985.
8. Drauz, K.; Waldman, H. *Enzyme Catalysis in Organic Synthesis*: *A Comprehensive Handbook*; VCH: New York, 1995.
9. Koskinen, A. M. P.; Klibanov, A. M. *Enzymatic Reactions in Organic Media*; Blackie: New York, 1996.
10. Kita, Y.; Takabe, Y.; Murata, K.; Naka, T.; Akai, S. *J. Org. Chem.* **2000**, *65*, 83.
11. Pozo, M.; Gotor, V. *Tetrahedron* **1993**, *49*, 4321.
12. Yakabe, S.; Hiano, M.; Morimoto, T. *Can. J. Chem.* **1998**, *76*, 1916.
13. Kamal, A.; Ramana, K. V.; Rao, M. V. *J. Org. Chem.* **2001**, *65*, 997.
14. Kamal, A.; Khanna, G. B. R. *Tetrahedron: Asymmetry* **2001**, *12*, 405.
15. Wilson, W. K.; Baca, S. B.; Barber, Y. J.; Scallen, T. J.; Morrow, C. J. *J. Org. Chem.* **1983**, *48*, 3960.
16. Zaks, A.; Klibanov, A. M. *Science* **1984**, *224*, 1249.
17. (a) Janseen, A. J. M.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1991**, *47*, 7645; (b) Hiratake, J.; Inagaki, M.; Nishioka, T.; Oda, J. *J. Org. Chem.* **1988**, *53*, 6130; (c) Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 2374.
18. Estimated by HPLC on silica column (Supelcosil LC-Si, 5×4.6 mm, 5 μm) employing EtOAc:hexane (90:10) as mobile phase, 1.0 mL/min and monitored at 254 nm wavelength.
19. (a) Determined by chiral HPLC (Chiracel, OJ-H column, Daicel) employing hexane/isopropanol = 90/10 (v/v) as mobile phase, 0.5 mL/min flow and monitored at 254 nm wavelength; (b) Determined by chiral HPLC (Chiracel, OJ-H column, Daicel) employing hexane/isopropanol = 95/5 (v/v) as mobile phase, 0.5 mL/min flow and monitored at 254 nm wavelength; (c) Determined by chiral HPLC (Chiracel OD column, Daicel) employing hexane/isopropanol = 85/15 (v/v) as mobile phase, 0.7 mL/min flow and monitored at 254 nm wavelength.
20. Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.