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One-pot synthesis and resolution of chiral allylic alcohols

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Abstract—Substituted α,β-unsaturated ketones were selectively reduced to the corresponding allylic alcohols under mild reaction conditions. The allylic alcohols thus obtained were kinetically resolved by lipase catalyzed transesterification in the same pot to afford chiral allylic alcohols in excellent enantioselectivity. Various lipases were screened for this one-pot transesterification of allylic alcohols. Effects of different solvent have also been studied under these conditions. *Pseudomonas cepacia* lipase immobilized on ceramic particles (PS-C) and on diatomaceous earth (PS-D) catalyzes this transesterification in diisopropyl ether in a highly efficient manner.

1. Introduction

Chiral allylic alcohols represent an important structural motif and have attracted synthetic chemists for their wide range of applications.[1] They are useful chiral synthons in sigmatropic reactions[2a] as well as for the synthesis of natural products viz. octalactin A, (−)- and (+)-*cis*-α-irone.[2b,c] They have been used as chiral precursors for the synthesis of (*S*)- and (*R*)-verapamil,[3] a calcium channel blocker used for the treatment of classical angina pectoris and superventricular tachycardia. Allylic alcohols are synthesized in enantiomerically pure form from prochiral ketones by microbial reduction, and chemically by stereoselective reduction or hydrogenation processes.[4] Among the methods currently available for the synthesis of enantiopure allylic alcohols, two of the most practical are the dynamic kinetic resolution of racemic allylic alcohols,[5a] asymmetric epoxidation[5b] and enzymatic acylation[6] in organic solvents and in ionic liquids.[6d] These methods have some limitations which make them unsuitable for the practical synthesis of chiral allylic alcohols. Whole cell reductions of α,β-unsaturated ketones are less applicable because of low yields and poor enantioselectivities and needs the complementary approaches of metal catalyzed asymmetric hydrogenation.[4a] Whereas chemical hydrogenation methods afford poor chemoselectivity in reducing α,β-unsaturated ketone and give saturated alcohols, saturated ketones and β-hydroxy ketones as side products.[6b] Moreover, these methods need high pressure, longer reaction time and expensive metal catalysts. In lipase catalyzed transesterification of (*RS*)-*trans*-4-phenyl-3-butene-2-ol **2** using dimethylmalonate as the acyl donor the enantiomeric excess did not exceed 93% for the unsaturated alcohol and the condition applied such as reaction under reduced pressure and use of $KHCO_3$ limit its application at a large scale.[2a] In continuation of our earlier work on the one-pot synthesis and lipase catalyzed resolution of enantiopure secondary alcohols[7a] and their applications for the synthesis of biologically important intermediates[7b] and chiral γ- and δ-lactones,[7c] herein we report stereoselective syntheses of chiral allylic alcohols using one-pot reduction and lipase resolution protocols.

2. Result and discussion

In the selective reduction of carbonyls considerable progress has been made in the development of reducing agents derived from $NaBH_4$.[8] We report $NaBH_4$/activated alumina[9] mediated selective reduction of carbonyl group of α,β-unsaturated ketone quantitatively under mild conditions. The racemic alcohol thus obtained was subjected to lipase catalyzed transesterification in the same pot. Both the enantiomers of the chiral allylic alcohol were obtained in good enantioselectivity by using this one-pot lipase resolution process.

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2.1. Lipase screening

The efficiency of different commercially available lipases to catalyze the transesterification of the racemic allylic alcohol **2a** after the one-pot reduction of the corresponding α,β-unsaturated ketone **1a** was investigated. *trans*-4-(3-Phenoxyphenyl)-3-butene-2-one was chosen as a model substrate for lipase screening because of good separation of the enantiomers of allylic alcohol **2a** and acylated product **3a** in an OD column. Substrate **1a** was treated with $NaBH_4$ and activated alumina in diisopropyl ether at 40°C. The reduction was complete in 3 h, lipase from various sources and isopropenyl acetate were then added. The transesterification was monitored on chiral HPLC.[11b] The results of the one-pot reduction and lipase-catalyzed transesterifications of **1a** are summarized in Table 1. *Pseudomonas cepacia* lipase immobilized on ceramic particles (PS-C) and on diatomaceous earth (PS-D) displayed high enantioselectivity for **2a** with equal enantiomeric ratios[12] $E=278$. *Pseudomonas fluorescens* lipase (Amano AK-20) and *P. fluorescens* lipase immobilized in Sol-Gel-AK on sintered glass offered acetate **3a** with high enantioselectivity (98 to >99%) at longer reaction time. There was no significant conversion in this one-pot transesterification with *Candida antarctica* lipase immobilized on glass beads, *Candida rugosa*, and *Candida cylindracea* lipase.

2.2. Solvent effect

The effect of solvent on substrate specificity, enantiomeric or enantiotopic selectivity and rate of reaction and rate of lipase-catalyzed kinetic resolution is well documented in the literature.[10] One-pot reduction of α,β-unsaturated ketone, **1a** and further acetylation of racemic alcohol, **2a** with isopropenyl acetate at 40°C in presence of immobilized *P. cepacia* lipase 'Amano' PS-C were performed in various organic solvents.

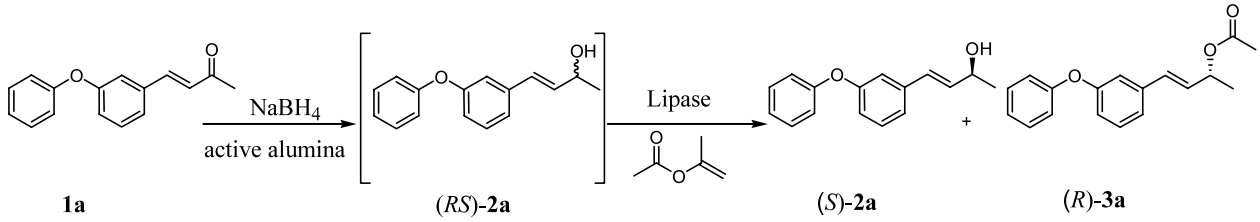


Table 1. One-pot reduction of α,β-unsaturated ketone, **1a** to (*RS*)-**2a** and resolution of (*RS*)-**2a** by lipase catalyzed transesterification[a]

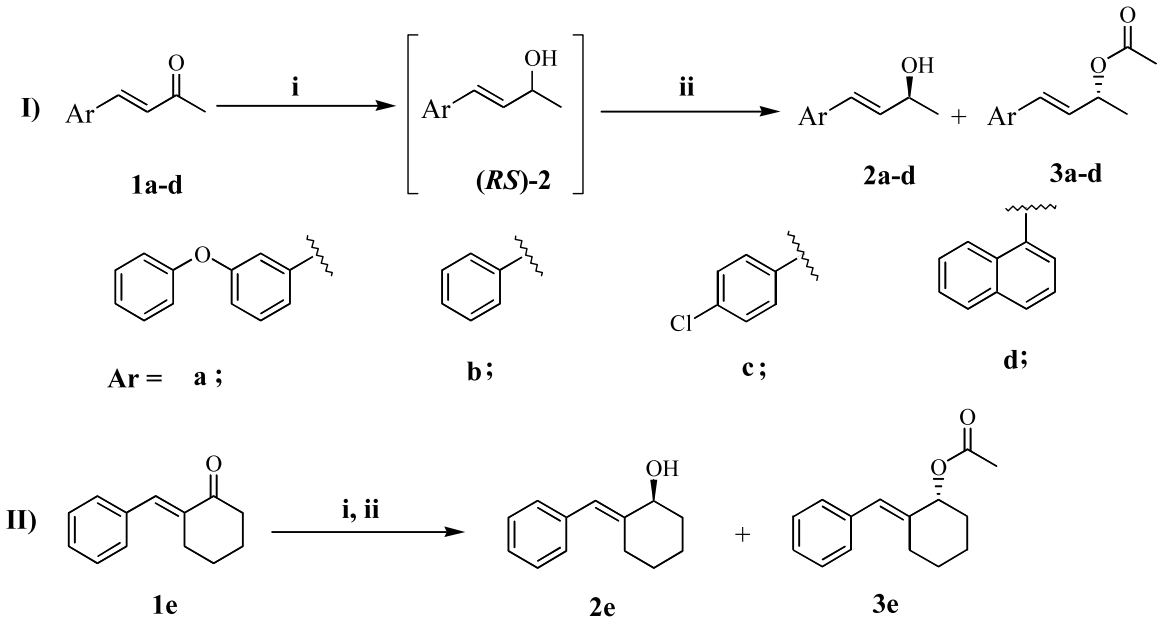
Lipase	Time[b] (h)	(*S*)-**2a** e.e.[c] (%)	(*R*)-**3a** e.e.[c] (%)	(%) Conversion[d]	E[d]
P. fluorescens (Amano AK-20)	36	94	98	49	356
P. cepacia (Amano PS)	72	46	97	32	103
P. cepacia (Amano PS-C)	12	>99	97	50	278
P. cepacia (Amano PS-D)	16	>99	97	50	278
P. fluorescens (Fluka)	96	93	>99	48	645
M. miehei (Fluka)	96	15	>99	13	230

[a] Conditions: 0.25 mmol of **1**, 2.5 mL of diisopropyl ether, 0.25 g activated alumina, 2 eq. $NaBH_4$; after 3 h lipase 1 equiv. w/w, 1.5 mmol isopropenyl acetate at 40°C.
[b] Time taken for transesterification.
[c] Determined by chiral HPLC.[11b]
[d] Conversion $c=\text{e.e.}_2/\text{e.e.}_2+\text{e.e.}_3$, enantiomeric ratio $E=\{\ln[1-c(1+\text{e.e.}_3)]/\{\ln[1-c(1-\text{e.e.}_3)]\}$.[12]

Table 2. Effect of solvent on one-pot reduction and transesterification of **1a** using immobilized *P. cepacia* lipase 'Amano' PS-C[a]

Solvent	log P	Time[b] (h)	(*S*)-**2a** e.e.[c] (%)	(*R*)-**3a** e.e.[c] (%)	(%) Conversion[d]	E[d]
Diisopropyl ether	1.9	12	>99	97	50	278
n-Hexane	3.5	15	97	82	54	40
Toluene	2.5	15	99	98	50	458
Ethyl acetate	–	15	>99	98	50	458
THF	0.49	72	>99	88	53	85
Acetonitrile	−0.33	72	97	49	66	10
1,4-Dioxane	−1.1	72	14	92	13	27

[a] Conditions: 0.25 mmol of **1**, 2.5 mL of solvent, 0.25 g activated alumina, 2 eq. $NaBH_4$; after 3 h lipase Amano PS-C (1 equiv. w/w), 1.5 mmol isopropenyl acetate at 40°C.
[b] Time taken for transesterification.
[c] Determined by chiral HPLC.[11b]
[d] Conversion $c=\text{e.e.}_2/\text{e.e.}_2+\text{e.e.}_3$, enantiomeric ratio $E=\{\ln[1-c(1+\text{e.e.}_3)]/\{\ln[1-c(1-\text{e.e.}_3)]\}$.[12]



Scheme 1. *Reagents and conditions*: (i) $NaBH_4$, activated alumina, diisopropyl ether; (ii) Lipase PS-C 'Amano' II, isopropenyl acetate.

The results summarized in Table 2 show that lipase PS-C affords higher activity for the one-pot transesterification in solvent of low polarity as indicated by their Log *P* (the logarithm of the partition coefficient of a given solvent between 1-octanol and water). Diisopropyl ether, *n*-hexane, toluene, (log $P = 1.9–3.5$) and ethyl acetate catalyze this transesterification with high enantioselectivity (>99% e.e.) for **2a** at faster reaction rates (12–15 h). On the other hand solvents such as acetonitrile, and dioxane (log $P = -1.1$ and 0.49) provide poor enantioselectivity at longer reaction times. The one-pot transesterification of allylic alcohols in THF solvent afforded >99% e.e. for **2a**.

Table 3. Synthesis of chiral allylic alcohol by lipase mediated one-pot reduction resolution process[a]

Substrate	Time[b] (h)	(*S*)-2		(*R*)-3		(%) Conversion[d]	E[d]
		E.e.[c](%)	Yield[e]	E.e.[c](%)	Yield[e]		
PhO, **1a**	12	>99	46	97	49	50	278
1b	9	96	42	98	45	49	357
Cl, **1c**	12	>99	40	78	52	56	44
1d	12	98	44	91	47	52	105
1e	9	92	43	>99	42	48	645

[a] Conditions: 1 mmol of **1**, 10 ml of diiso-propyl ether, 1 g activated alumina, 2 mmol $NaBH_4$; after 3 hours lipase "Amano" PS-C (1 eq. w/w), 6 mmol isopropenyl acetate at 40 °C.

[b] Time taken for transesterication.

[c] See experimental for individual HPLC analysis data.

[d] See Table 1.

[e] Isolated yield from column chromatography.

2.3. Synthesis of chiral allylic alcohol

Various chiral allylic alcohols have been synthesized in high enantiopurity based on this one-pot reduction followed by resolution protocol. *P. cepacia* lipase immobilized on ceramic particles (PS-C) is the lipase of choice employing diisopropyl ether as solvent. Five α,β-unsaturated ketones have been studied, and are selectively reduced to a corresponding racemic allylic alcohols in a quantitative manner in 3 h using $NaBH_4$ and active neutral alumina in diisopropyl ether. The racemic allylic alcohol thus obtained is kinetically resolved by lipase 'Amano' PS-C catalyzed transesterification at 40°C in the same pot (Scheme 1).

Both the unsaturated chiral allylic alcohols and acetates are obtained in high enantiomeric purity in a short reaction time (9–12 h), see Table 3. It is interesting to note that unsaturated allylic alcohols, **2a**, **2c** and **2d**, are obtained in 98 to >99% enantiomeric excess. Moreover, the acetates **3a**, **3b** and **3e** are obtained in 97 to >99% enantiomeric excess. The importance of this one-pot reduction–resolution protocol for the synthesis of chiral allylic alcohol has been ascertained by comparison of the enantiopurity of alcohol **2a**–**e** and acetate **3a**–**e** with earlier reports. Lindner et al.[6b] have synthesized chiral allylic alcohols by using two consecutive approaches, asymmetric hydrogenation of α,β-unsaturated ketone by ruthenium metal complex and lipase catalyzed kinetic resolution of the hydrogenated product. In this method unsaturated acetate **3b** has been prepared by asymmetric reduction of ketone **1b** to chiral alcohol **2b** which was further resolved to obtain chiral unsaturated acetate **3b** in 91–92% e.e. by employing 'Amano' PS-D lipase. In another attempt allylic alcohol **2b** and acetate **3b** were obtained in 95% e.e. in 12 h by lipase Amano AK-20 catalyzed kinetic resolution employing vinyl acetate in hexane. Whereas the present method provides 92% enantiomeric excess for **2b** and 98% for **3b** in a short time (5 h). From the practical point of view, this one-pot reduction-transesterification process has been carried out on a 2 gram scale for the substrate **1a**, and interestingly the results obtained are consistent with those observed on the milligram scale reaction of this substrate. This shows the potential of the present method for the large scale preparation of chiral allylic alcohols in high enantiopurity.

3. Conclusion

A new efficient enzymatic pathway has been developed for the synthesis of both (*R*) and (*S*) enantiopure allylic alcohols from the corresponding α,β-unsaturated ketone. The carbonyl functionality of α,β-unsaturated ketones has been reduced selectively in a quantitative manner to the corresponding alcohols under mild reaction conditions. We have described for the first time, the reduction of α,β-unsaturated ketones with alumina-assisted sodium borohydride followed by the lipase-catalyzed in situ transesterification of the racemic allylic alcohol in one-pot. The enhanced reaction rates in the presence of alumina with high regio- and enantioselectivity in organic media such as diisopropyl ether provides a practical in situ synthesis and biocatalytic resolution process for allylic alcohols from their carbonyl precursors.

4. Experimental

4.1. Material and methods

Enzymatic reactions were carried out on 'Lab-line environ-shaker' at 150 rpm. Infrared spectra of neat sample are reported in wave numbers (cm^{-1}). ^1H NMR was 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). 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. HPLC analysis was performed on an instrument that consisted of a Shimadzu LC-10AT system controller, SPD-10A fixed wavelength UV monitor as detector. Specific rotation were recorded on SEPA-300 Horiba high sensitive polarimeter, fixed with sodium lamp of wavelength 589 nm.

4.2. Chemicals and enzymes

Sodium borohydride, neutral alumina and solvents were obtained commercially and used without purification. Activated neutral alumina was prepared by homogeneous addition of 1.1 mL water to 10 g of neutral alumina (preheated in oven at 200°C).[7a] Lipase from *P. cepacia* (PS), *P. fluorescens* (AK), *P. cepacia* immobilized on ceramic particles (PS-C), *P. cepacia* immobilized on diatomaceous earth (PS-D), were purchased from Amano (Nagoya, Japan). *P. fluorescens* lipase immobilized in Sol-Gel-AK on sintered glass, *C. antarctica*, Lipozyme, immobilized from *Mucor miehei* were purchased from Fluka. *Candida rugosa* lipase type VII, *C. cylindracea* lipase type VII were purchased from Sigma.

4.3. Synthesis of the substrates

α,β-Unsaturated ketones **1a**–**e** were prepared by well known aldol condensation of the corresponding ketones, purified by column chromatography and were fully characterized by ^1H NMR, IR, and E.I. mass spectroscopy. Racemic unsaturated allylic alcohol **2a**–**e** were prepared by reduction of corresponding α,β-unsaturated ketone **1a**–**e** by $NaBH_4$ and activated alumina and the corresponding racemic acetates were prepared from racemic allylic alcohol **2a**–**e** by a well known acetylation procedure using acetic anhydride, triethyl amine and DMAP in dry DCM.

4.4. General procedure for one-pot synthesis of enantiopure allylic alcohol 2a–e and acetate 3a–e

To a solution of the α,β-unsaturated ketone (1 mmol) in diisopropyl ether (10 mL) was added activated alumina (1.0 g) and $NaBH_4$ (2 mmol). The suspension was

shaken at 150 rpm at 40°C in a conical flask for 3–4 h and monitored by TLC for the complete reduction to racemic alcohol. Then lipase 'Amano' PS-C (1 equiv. w/w) and isopropenyl acetate (1.1 mL) were added to the reaction mixture. The reaction was monitored on chiral HPLC analysis until it reaches 50% conversion (9–12 h, as indicated in Table 3). The reaction was filtered through a pad of Celite and thoroughly washed with ethyl acetate. The combined filtrate was washed with water, followed by brine. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure and purified by silica gel column chromatography. The enantiopure products **2** and **3**, were analyzed by chiral HPLC[11,13,14] and compared with corresponding racemic products.

4.4.1. (*S*)-(*E*)-4-(3-Phenoxyphenyl)-3-buten 2-ol 2a. Yield: 46%; >99% e.e.[11a] ($t_R = 36.75$ min); $[\alpha]_D^{25}$ −10.4 (*c* 2, $CHCl_3$); IR (neat): 3400 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.2–1.6 (3H, d, $J = 6.69$ Hz), 4.5 (1H, q, $J = 6.69$ Hz), 6.2 (1H, dd, $J = 16.68$, 6.69 Hz), 6.5 (1H, d, $J = 16.68$ Hz), 6.8–7.6 (9H, m); EIMS (*m*/*z*): 240 (M^+), 197 (M^+–43). Anal. calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.60; H, 6.50%.

4.4.2. (*R*)-(*E*)-2-Acetoxy-4-(3-phenoxyphenyl)-3-butene 3a. Yield: 49%; 97% e.e.[11a] ($t_R = 12.42$ min); $[\alpha]_D^{25}$ +91.7 (*c* 1.6, $CHCl_3$); IR (neat): 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.4 (3H, d, $J = 6.69$ Hz), 2.1 (3H, s), 5.5 (1H, q, $J = 6.69$ Hz), 6.2 (1H, dd, $J = 16.68$, 6.69 Hz), 6.5 (1H, d, $J = 16.68$ Hz), 6.8–7.4 (9H, m); EIMS (*m*/*z*): 282 (M^+), 240 (M^+–42), 197 (M^+–85). Anal. calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.40; H, 6.15%.

4.4.3. (*S*)-(*E*)-4-Phenyl-3-butene-2-ol 2b[5a]. Yield: 42%; 96% e.e.[11b] ($t_R = 15.76$ min); $[\alpha]_D^{25}$ −29.6 (*c* 2.0, $CHCl_3$) [lit. $[\alpha]_D^{25}$ −29.2 (*c* 2.0, $CHCl_3$), e.e. 95%];[6c] IR (neat): 3450, cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.4 (3H, d, $J = 6.69$ Hz), 4.4 (1H, q, $J = 6.69$ Hz), 6.2 (1H, dd, $J = 16.68$, 6.69 Hz), 6.5 (1H, d, $J = 16.68$ Hz), 7.2–7.4 (5H, m); EIMS (*m*/*z*): 148 (M^+), 105 (M^+–43). Anal. calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.60; H, 7.85%.

4.4.4. (*R*)–(*E*)-2-Acetoxy-4-phenyl-3-butene 3b. Yield: 45%; 98% e.e.[13] ($t_R = 13.59$ min); $[\alpha]_D^{25}$ +138 (*c* 1.1, $CHCl_3$); IR (neat): 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.4 (3H, d, $J = 6.69$ Hz), 2.1 (3H, s), 5.5 (1H, q, $J = 6.69$ Hz), 6.0–6.2 (1H, dd, $J = 16.68$, 6.69 Hz), 6.6 (1H, d, $J = 16.68$ Hz), 7.2–7.4 (5H, m); EIMS (*m*/*z*): 190 (M^+), 148 (M^+–42). Anal. calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.6; H, 7.05%.

4.4.5. (*S*)-(*E*)-4-Chlorophenyl-3-butene-2-ol 2c. Yield: 40%; >99% e.e.[13] ($t_R = 8.97$ min); $[\alpha]_D^{25}$ −18.8 (*c* 1.3, $CHCl_3$); IR (neat): 3450 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.4 (3H, d, $J = 6.68$ Hz), 4.4 (1H, q, $J = 6.68$ Hz), 6.2 (1H, dd, $J = 15.60$, 5.94 Hz), 6.5 (1H, d, $J = 15.60$ Hz), 7.2–7.4 (4H, m); EIMS (*m*/*z*): 182 (M^+). Anal. calcd for $C_{10}H_{11}ClO$: C, 65.76; H, 6.07; Cl, 19.41 Found: C, 65.56; H, 6.0; Cl, 19.01%.

4.4.6. (*R*)-(*E*)-2-Acetoxy-4-chlorophenyl-3-butene 3c[5a]. Yield: 52%; 78% e.e.[13]($t_R = 12.84$ min); $[\alpha]_D^{25}$ +103 (*c* 2.0 $CHCl_3$); IR (neat): 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.4 (3H, d, $J = 6.68$ Hz), 2.0 (3H, s), 5.4 (1H, q, $J = 6.68$ Hz), 6.0–6.2 (1H, dd, $J = 15.60$, 5.94 Hz), 6.4–6.6 (1H, d, $J = 15.60$ Hz), 7.2–7.4 (5H, m); EIMS (*m*/*z*): 224 (M^+), 182 (M^+–42). Anal. calcd for $C_{12}H_{13}ClO_2$: C, 64.15; H, 5.83; Cl, 15.78. Found: C, 64.03; H, 5.62; Cl, 15.21%.

4.4.7. (*S*)-(*E*)-4-(1-Naphthyl)-3-butene-2-ol 2d. Yield: 44%; 98% e.e.[11b] ($t_R = 15.63$ min); $[\alpha]_D^{25}$ −10.4 (*c* 2.0, $CHCl_3$); IR (neat): 3480 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.4 (3H, d, $J = 6.68$ Hz), 4.6 (1H, q, $J = 6.68$ Hz), 6.2 (1H, dd, $J = 15.60$, 6.68 Hz), 7.2–7.6 (5H, m), 7.8 (2H, m), 8.1 (1H, m); EIMS (*m*/*z*): 198 (M^+), 155 (M^+–43). Anal. calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.64; H, 7.0%.

4.4.8. (*R*)-(*E*)-2-Acetoxy-4-(1-naphthyl)-3-butene 3d[5a]. Yield: 47%; 91% e.e.[14] ($t_R = 16.13$ min); $[\alpha]_D^{25}$ +63.3 (*c* 1.4, $CHCl_3$); IR (neat): 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.5 (3H, d, $J = 6.67$ Hz), 2.1 (3H, s), 5.6 (1H, q, $J = 6.68$ Hz), 6.2 (1H, dd, $J = 15.60$, 6.68 Hz), 7.2–7.6 (5H, m), 7.8 (2H, m), 8.1 (1H, m); EIMS (*m*/*z*): 240 (M^+), 198 (M^+–42). Anal. calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 7.12. Found: C, 79.8; H, 7.04%.

4.4.9. (*S*)-2-[1-Phenyl-(*E*)-methylidene]-1-cyclohexanol 2e. Yield: 43%; 92% e.e.[11b] ($t_R = 10.91$ min); $[\alpha]_D^{25}$ −12.9 (*c* 1.0, $CHCl_3$); IR (neat): 3400 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.4–1.8 (6H, m), 2.0 (1H, m), 2.6 (1H, m), 4.2 (1H, m), 6.5 (1H, s), 7.1–7.4 (5H, m); EIMS (*m*/*z*): 184 (M^+–4). Anal. calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.64; H, 8.12%.

4.4.10. (*R*)-2-[1-Phenyl-(*E*)-methylidene]-1-cyclohexyl acetate 3e. Yield: 42%; >99% e.e.[13] ($t_R = 8.37$ min); $[\alpha]_D^{25}$ +36.0 (*c* 0.8, $CHCl_3$); IR (neat): 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 1.2–1.8 (6H, m), 2.0 (3H, s), 2.2–2.6 (2H, m), 5.4 (1H, m), 6.5 (1H, s), 7.1–7.4 (5H, m); EIMS (*m*/*z*): 230 (M^+), 188 (M^+–42). Anal. calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.02; H, 7.46%.

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