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A tandem and fully enzymatic procedure for the green resolution of chiral alcohols: acylation and deacylation in non-aqueous media

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ABSTRACT

A green and fully enzymatic procedure for the resolution of chiral alcohols through lipase/esterase-catalyzed acylation and subsequent lipase-catalyzed aminolysis using anhydrous ammonia was demonstrated. Both enantiomers can be obtained in high ee values (up to >99%) under ambient reaction conditions. The solvent and acyl donors can be recycled, and the enzyme can be reused for up to five times.

1. Introduction

Enantiopure secondary alcohols are very important as they are pivotal compounds in organic synthesis,[1] as well as the pharmaceutical, agrochemical, and fine chemical industries.[2] There are numerous routes for the preparation of chiral secondary alcohols and of them, the enzyme-catalyzed kinetic resolution of secondary alcohols remains a standard procedure and is still the most practical[3] for obtaining both enantiomers compared with dynamic kinetic resolution or oxidative kinetic resolution methods.[4] The major disadvantage of the oxidative kinetic resolution is the inherent 50% upper limit for theoretical conversion while the other isomer is transformed into a ketone and discarded. Nevertheless, the subsequent green deacylation step is less developed. Conventional deacylation methods require a strong base or acid which are not compatible with sensitive groups. Therefore, most of the (chemical) deacylation procedures only afford enantiomers without sensitive groups. Furthermore, they give rise to an undesirable salt waste stream. Other methods for deacylation include hydrolases promoted by hydrolysis in an aqueous media. Nevertheless, the gradually increasing pH value of an aqueous solution might deactivate the hydrolases. Moreover, the hydrolases are much difficult to recycle from an aqueous solution as they easily dissolved in water. Recently, enzymatic ammonolysis/aminolysis reactions have been used for the preparation of chiral synthons in high enantiomeric excess. The mild reaction conditions and the high enantioselectivities often obtained make these biocatalytic processes very useful. There have been several reviews published showing the application of enzymes in aminolysis/ammonolysis reactions for the resolution of esters or amines;[5] the initial purpose of such a reaction was to obtain enantiopure nitrogen-containing organic compounds.[5a,6]

To date, the combination of aminolysis/ammonolysis with acylation for the preparation of chiral alcohols has been less well studied but is thought to afford an alternative for the green resolution of chiral alcohols to obtain both enantiomers in high enantiomeric excess under mild reaction conditions.

Herein, we report a new, and fully enzymatic procedure for green resolution of chiral alcohols, which enables us to obtain both enantiomers in high enantiomeric excess (ee up to >99%). In this procedure, free ammonia is applied as a deacylation reagent in an organic solvent at ambient temperature (Scheme 1). No strong base, acid or aqueous media were required with properties of producing an undesired salt waste stream and being unable to recycle the enzymes. The acyl donors and organic solvent can be recycled and the immobilized biocatalyst can be reused for up to five times with no major loss in activity or enantioselectivity.

The approach consists of two main steps (Scheme 1): (a) racemic alcohols are subjected to enzymatic kinetic resolution with vinyl acetate (as the acyl donor and solvent, which is better than using organic solvent since changing the concentration of the acyl donor may reduce the reaction rate, especially when it was recycled). The reactions were not stopped until the enzyme-accepted enantiomers were fully converted to the corresponding esters, which resulted in substrate conversion of more than 50% (Fig. 1). Such a strategy ensured that the unchanged enantiomers remained in high enantiomeric excess; (b) acylated alcohols from the former step are then subjected to deacylation by enzymatic aminolysis in an organic solvent. After these two steps, both enantiomers are obtained in high enantiomeric excess.

In this method, CALB and *Escherichia coli* BioH (a lipase and an esterase, one with excellent enantioselectivity and the other with good to excellent enantioselectivity, respectively) were selected as biocatalysts in the acylation step due to their excellent

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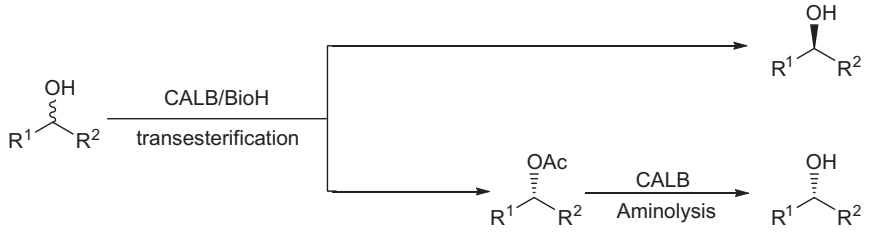


Scheme 1. General scheme of tandem and fully enzymatic procedure for the green resolution of a chiral alcohol.

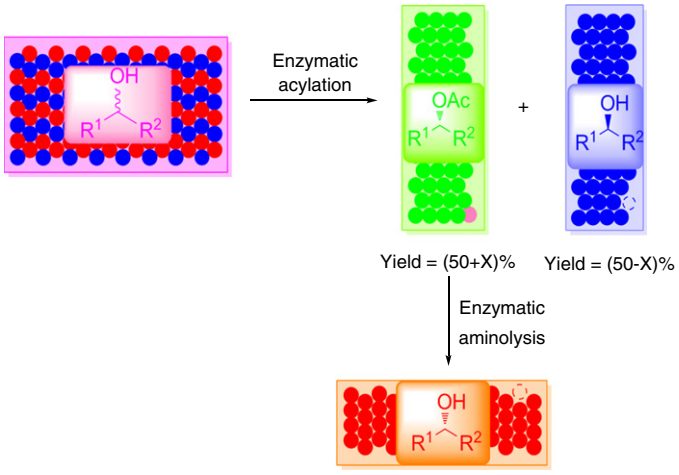


Figure 1. Principle of tandem and green resolution of chiral alcohols ([●], the enzyme-accepted enantiomer, marked in red; [●], the unchanged enantiomer, in blue; [●], ester derived from enzyme-accept enantiomer, in green; [●], ester from unchanged enantiomer, in pink, here, X >0).

performance for the kinetic resolution of alcohols,[7] and their ready tolerance of non-natural reactants and reaction conditions. For the purpose of recycling the acyl donors easily while keeping in mind the principles of green chemistry,[8] the acyl donors which had previously been employed in the literature, were compared and vinyl acetate was chosen for its low boiling point, since it could be easily separated from the products by distillation under vacuum.

2. Results and discussion

2.1. Enzymatic kinetic resolution of secondary alcohols

In our initial studies, (*R*,*S*)-1-phenylethanol was employed as the model substrate to evaluate suitable conditions for acylation. Various conditions, such as the ratio of solvents to vinyl acetate, temperatures and reaction times, were investigated. The results are summarized in Table 1. For consideration of easy recycling and re-utilization of acyl donors, the conditions under which the largest *E*-value was obtained and (*R*)-1-phenylethanols almost fully converted to the corresponding acetate were chosen as the optimized conditions for acylation (Table 1, entries 3 and 4).[9] The unchanged (*S*)-1-phenylethanol was generated in conversions of >49% and 47% for CALB and *E. coli* BioH with ee values of 99% and 98%, respectively. It was determined that the optimized conditions were: vinyl acetate as acyl donor and solvent; temperature: for CALB, 30 °C, reaction time, 25 h and for *E. coli* BioH, 35 °C, 30 h, the *E* values were >978 and 91 for CALB and *E. coli* BioH, respectively. Increasing the reaction temperature or time led to low ee values of the acylated alcohols and low yields of (*S*)-1-phenylethanol.

To achieve an ideal resolution (Conversion of (*R*,*S*)-1-phenylethanol was (50 + *X*)%, here, '*X*%' was described as

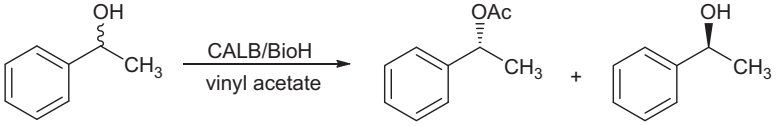
$$X\% = \frac{c_o(S) - c_e(S)}{c_o(S) + c_e(R)} \times 100\%$$

X >0, Fig. 2), reactions should be ceased when the (*R*)-1-phenylethanols were fully transformed. It should be noted that the value of '*X*' was determined by the enantioselectivity, the activity of the biocatalyst and the reaction time.

2.2. Enzymatic deacylation of esters

After evaluating the suitable acylation conditions, we carried out deacylation reactions employing (*R*,*S*)-1-phenylethyl acetate as a model substrate to evaluate suitable deacylation reaction connditions. In this step, (*R*,*S*)-1-phenylethyl acetate was enzymatically aminolyzed for deacylation to obtain pure (*R*)-1-phenylethanol. Reaction conditions such as enzymes, organic solvents, temperatures and reaction times were investigated and the results are summarized in Table 2. As can be seen, CALB performed much

Table 1
Evaluation of the reaction conditions using CALB and *E. coli* BioH for the acylation of (*R*,*S*)-1-phenylethanol[a]



Entry	Solvent	Ratio[b]	Time (h)		*T* (°C)	Conversion[c]		*E*[d]
			C	B		C	B	C/B
1	—	—	16	22	20	41	42	413/70
2	—	—	22	25	30	49	49	>978/53
3	—	—	25	28	30	>50	>51	>978/53
4	—	—	24	30	35	50	>52	920/91

[a] Reactions were performed on a 1 mmol scale: immobilized enzyme: 10 mg, (*R*,*S*)-1-phenylethanol, 1 mmol; solvent and vinyl acetate, 5 mL; 'C' and 'B' represent 'CALB' and '*E. coli* BioH', respectively.
[b] Here, the ratio was vinyl acetate: solvent.
[c] Conversions of (*R*,*S*)-1-phenylethanol were determined by GC-analysis with a chiral column.
[d] *E* values were calculated by the formula: $E = \ln[1 - c \times (1 + ee_p)]/\ln[1 - c \times (1 - ee_p)]$, $c = ee_s/ee_p + ee_s$.

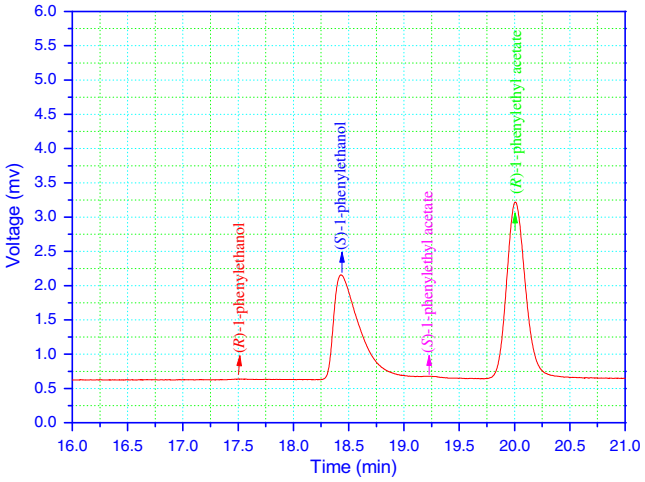


Figure 2. Chromatogram of the nearly-ideal resolution of (*R*,*S*)-1-phenylethanol.

Table 3
Effects of reused times of biocatalysts on conversions and ee values for resolution of (*R*,*S*)-1-phenylethanol[a]

Entry	Reused times	Conversion[b] (%)		*E*[c]	
		BioH	CALB	BioH	CALB
1	0	52	>50	116	>1000
2	1	47	49	105	789
3	2	44	45	97	510
4	3	42	43	78	451
5	4	37	41	43	413
6	5	30	38	26	372
7	6	21	32	14	317

[a] All reactions were carried out under the optimized conditions mentioned in the main text; conversions and ee values were determined by GC-analysis equipped a chiral column (Cyclodex-B, 30 m × 0.32 mm × 0.25 μm, Agilent Technologies). Here, 'B/C' in parentheless represents '*E. coli* BioH/CALB'.
[b] Conversions of (*R*,*S*)-1-phenylethanol were recorded at 25 h for CALB, and 30 h for *E. coli* BioH.
[c] *E* values were calculated by the same formula mentioned in the footnote of Table 1.

better than *E. coli* BioH, and was thus chosen as the suitable deacylation biocatalyst for further studies. With CALB as the biocatalyst, (*R*)-1-phenylethanol was formed in ee values of up to >99% when ethyl ether, *n*-hexane or isopropyl ether was used as the solvent.

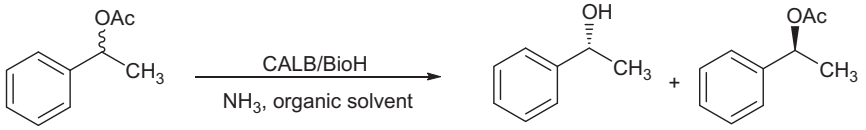
Nevertheless, when considering a more efficient, greener and safer procedure, ethyl ether and *n*-hexane were excluded due to their easy volatilization and low ammonia absorption, respectively. Isopropyl ether was the optimum solvent for deacylation, and the best reaction temperature was determined to be 35 °C. The only by-product (acetamide) formed was during the precipitation from the heterogeneous solution, which could be removed by simple filtration.

Both (*R*)- and (*S*)-1-phenylethanol were obtained in high enantiomeric excess under ambient reaction conditions through this procedure. The CALB participated deacylation using free ammonia as the deacylation reagent provides a useful tool for the deacylation of chiral 1-phenylethanol. CALB showed a high activity and enantioselectivity when deacylating (*R*)-1-phenylethyl acetate, with almost all of the (*R*)-1-phenylethyl acetate being successfully transformed to (*R*)-1-phenylethanol in high enantiomeric excess, while (*S*)-1-phenylethyl acetate remained unchanged with an ee value of no less than 98%. Finally, a theoretical yield (50%) of the (*R*)-configured enantiomer could be achieved and almost all of the (*S*)-configured enantiomers [the (*S*)-configured alcohol and the ester, both of which were in high enantiomeric excess) could be made full use of.

2.3. Biocatalyst and organic solvent recovery

After the reaction had taken place, the immobilized enzyme, and the organic solvent (isopropyl ether) were recycled and reused in order to evaluate the relationship between reused times, ee values and conversions in resolution of (*R*,*S*)-1-phenylethanol in both the acylation and deacylation procedures under the optimized conditions described. The results are summarized in Table 3. As shown in the acylation, with increasing reused times, the conversions of substrates applying both CALB and *E. coli* BioH changed to 28 h; when the enzyme was reused for 6 times, the conversion changed to less than 40% with *E* values decreased to 26 and 372 for BioH and CALB, respectively; this was considered unsuitable for further reaction as when (*R*)-1-phenylethanol was fully acylated, the

Table 2
Investigation of reaction parameters for the deacylation employing (*R*,*S*)-1-phenylethyl acetate as the model substrate[a]



Entry	Solvent	*T* (°C)	Time (h)	ee$_p$[b] (%)		Conversion[c] (%)		*E*
				C	B	C	B	C/B
1	*n*-Hexane	20	10	>99	>99	42	3	>431/>205
2	*n*-Hexane	25	10	>99	>99	47	5	>584/>209
3	*n*-Hexane	30	8	>99	99	45	6	>510/211
4	*n*-Hexane	35	5	>99	99	45	3	>500/205
5	Ethyl ether	20	6	>99	>99	37	2	>363/>203
6	Ethyl ether	25	6	>99	>99	43	5	>451/>209
7	Ethyl ether	30	6	>99	99	46	7	>543/214
8	*iso*-Propyl ether	25	8	>99	99	44	3	>482/205
9	*iso*-Propyl ether	35	8	>99	99	49	8	>789/216
10	DMF	25	6	98	97	41	1	202/66
11	*iso*-Octane	35	6	>99	99	45	5	>510/201

[a] Reaction conditions: immobilized CALB or *E. coli* BioH, 10 mg; organic solvent, 10 mL; (*R*,*S*)-1-phenylethyl acetate, 1 mmol; 'C' and 'B' represent 'CALB' and '*E. coli* BioH', respectively.
[b] Unless otherwise stated, ee values were determined by GC-analysis with a chiral column mentioned in Table 1.
[c] Conversions were determined by GC-analysis.

Table 4
Effects of recycled times of organic solvent (isopropyl ether) on conversions for deacylating (*R*)-1-phenylethyl acetate[a]

Entry	Reuse times	Conversion (%)	ee (%)
1	0	>99	>99
2	1	>99	>99
3	2	>99	>99
4	3	>99	>99
5	4	>99	>99
6	5	>99	>99
7	10	>99	>99
...	...	>99	>99

[a] Reaction conditions: immobilized CALB, 10 mg; isopropyl ether, 10 mL; (*R*)-1-phenylethyl acetate, 1 mmol; Temperature, 35 °C; Conversions and ee values were determined by GC-analysis equipped with a chiral column (Cyclodex-B, 30 m × 0.32 mm × 0.25 μm, Agilent Technologies).

reaction time increased to more than double its original reaction time. This is mainly due to the incomplete recycling of the immobilized enzymes as part of the enzyme powder dropped off carriers. In the deacylation, a longer reaction time was required with reused times. However, the enantiomeric excess of the desired product remained basically the same. No obvious adverse impact on the yield or enantiomeric purity was observed. In both steps of the acylation and deacylation, the enzyme could be reused for up to five times (Table 3) with no major loss of its activity or enantioselectivity, and the organic solvent and acyl donor could be repeatedly recycled (Table 4).

3. Conclusion

Under the optimized conditions, a range of aromatic alcohols were tested and the results are summarized in Table 5. Due to the different properties of the substrates employed in the kinetic resolutions, the reaction time for the acylation varied for each substrate. As has been elucidated in our previous work,[7] *E. coli* BioH accepted only benzylic substrates, while others remained unchanged (Table 5, entry 9).

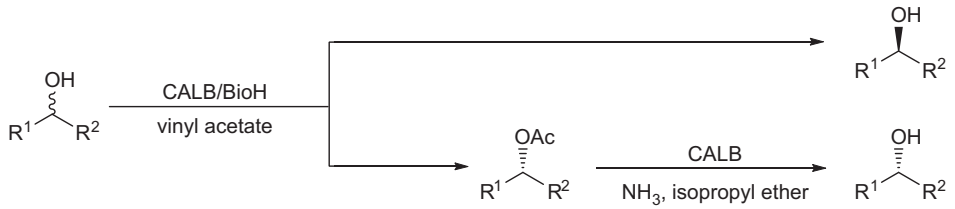
Compared with previously applied chemicals or hydroxylases in aqueous media,[10] this procedure can afford both enantiomers in high ee values. As shown in Table 5, when *E. coli* BioH was employed for the resolution of (*R*,*S*)-1-phenylethanol, (*R*)-1-phenylethyl acetate was formed in a low ee value (84%), although (*S*)-1-phenylethanol was afforded in ⩾98% ee (Table 5, entry 1). However, after deacylation, the corresponding (*R*)-1-phenylethanol was obtained in 99% ee. The enantiomeric excess of the (*R*)-configured enantiomer increased to its upper limit [from 84% of (*R*)-1-phenylethyl acetate to >99% of (*R*)-1-phenylethanol]. The enzymatic amminolysis is a re-selectively catalyzed process. Using this approach, a variety of racemic substrates were efficiently resolved, with no other waste being generated and no racemization being observed. This methodology could be extended to other enzymes and substrates.

In conclusion, we have demonstrated a green and fully enzymatic method for the resolution of chiral alcohols to obtain both enantiomers in up to theoretical yields (50%) or high ee values (up to >99%). This procedure has the following advantages: (a) no strong base, acid, aqueous media and elevated temperatures are required; (b) no waste salt stream is generated and thus is considered as being environmentally benign; (c) this procedure is compatible with sensitive groups; (d) the biocatalyst can be recycled and reused for up to five times, and the acyl donors and organic solvent can be repeatedly recycled. This approach is a useful tool for the green and efficient resolution of chiral alcohols, and could have potential applications in industry.

4. Experimental

^{1}H Nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker AV400 instrument operating at the frequency of 400 MHz for ^{1}H NMR. All chemical shifts (δ) are quoted in parts per million (ppm) and reported relative to an internal tetramethylsilane (TMS, $\delta = 0.00$) standard. Conversions and ee values were determined by GC- or HPLC-analysis. Gas chromatography was performed with a Fuli 9790 instrument equipped with a

Table 5
Results of tandem and fully enzymatic resolution of chiral alcohols[a]



Entry	R^1	R^2	Time A [b](h)		Time[c] D (h)	Conversion (%)		ee$_R$[d] (%, BioH)		ee$_R$[e] (%, CALB)		ee$_S$[f] (%)	
			B	C		B	C	b	a	b	a	B	C
1	C_6H_5	CH_3	30	25	7	52	>50	84	>99	99	>99	98	>99
2	4-$CH_3C_6H_4$	CH_3	32	28	8	51	>50	92	>99	99	>99	99	>99
3	4-ClC_6H_4	CH_3	28	26	7	52	>50	92	>99	99	>99	98	>99
4	4-$NO_2C_6H_4$	CH_3	25	22	6	51	51	95	>99	99	>99	99	>99
5	3-$NO_2C_6H_4$	CH_3	27	24	7	>50	>50	97	>99	99	>99	98	>99
6	4-$CH_3OC_6H_4$	CH_3	35	30	11	51	51	96	>99	99	>99	98	>99
7	4-$C_2H_5OC_6H_4$	CH_3	36	32	12	51	51	96	>99	99	>99	98	>99
8[g]	4-$C_6H_5C_6H_4$	CH_3	34	26	9	>50	>50	99	>99	>99	>99	>99	>99
9	C_6H_5	C_2H_5	—	28	13	0	>50	—	—	99	>99	0	99

[a] Reactions were carried out on 1 mmol scale, immobilized enzyme: 10 mg, vinyl acetate: 5 mL in the acylation step, temperature for *E. coli* BioH, 35 °C and for CALB, 30 °C; In the deacylation step, reactions were conducted on a 10 mL scale, ester, 0.5 mmol; immobilized CALB, 5 mg; *iso*-propyl ether, 10 mL; temperature, 35 °C; Except otherwise stated, ee values and conversions (conv) were determined by GC-analysis with a chiral column; 'B' and 'C' represent CALB and *E. coli* BioH, respectively.
[b,c] Here, 'A' and 'D' represent 'acylation' and 'deacylation', respectively.
[d,e] Ee values after deacylation of esters from *E. coli* BioH or CALB catalysed acylation, respectively.
[f] Ee values of the (*S*)-alcohols generated from the reactions catalyzed by *E. coli* BioH (B) or CALB (C).
[g] HPLC-analysis was performed with an Agilent 1100 instrument equipped with a Chiralpak AD-H column (150 × 4.6 mm, Daicel Chemical Industries, Ltd) at a wavelength of 254 nm.

Cyclodex-B (30 m × 0.32 mm × 0.25 μm, Agilent Technologies). HPLC analysis was performed with an Agilent 1100 instrument equipped with a Chiralpak AD-H column (150 × 4.6 mm, Daicel Chemical Industries, Ltd) at the wavelength of 254 nm.

4.1. Synthesis of secondary alcohols

All racemic alcohols except for the (*R*,*S*)-1-phenylethanol were prepared using the following procedure: a mixture of ketone (5 mmol) and sodium borohydride (10 mmol) in anhydrous methanol (50 mL) was stirred at room temperature for 30 min. Next, saturated $NaHCO_3$ (50 mL) and CH_2Cl_2 (100 mL) were introduced, and the mixture was stirred at room temperature for another 10 min. The organic layer was removed, and the aqueous layer was extracted twice with 25 mL CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to give the corresponding crude alcohols. The crude alcohols were then chromatographed to afford pure products. The ^{1}H NMR spectra of these products were in good agreement with the literature.

4.2. Preparation of (*R*)-phenylethyl acetate

At first, (*R*,*S*)-1-phenylethanol (0.04 mol, 4.89 g) was dissolved in vinyl acetate (20 ml) and transferred to a two necked flask (50 ml) equipped with a condenser, a thermometer (−50–50 °C), and then 0.01 g of immobilized lipase (*Novozym 435*) was added. The reaction was kept at 35–40 °C and stirred for 48 h. When the reaction was stopped, the reaction mixture was filtered and concentrated. The residues were then poured into ice-water, and stirred for 0.5 h. The pH of the solution was kept at 8.0 with sodium bicarbonate. After extracting three times with 20 ml of ethyl acetate, the combined organic layers were dried over anhydrous magnesium sulfate ($MgSO_4$) and concentrated. The residues were purified to obtain pure (*R*)-1-phenylethyl acetate (ee = 99.5%) by chromatography.

4.3. Immobilization of esterase *E. Coli* BioH

The esterase powder (25,000 U/g), produced from shaking the flask fermentation of the recombinant strain Escherichia coli BL21 carrying $pET^{-30a(+)}$, was used for enzymatic reaction after lyophilization with no further purification. Macroporous adsorptive resins were obtained from Xuzhou Liangchen Co., Ltd (Jiangsu, China). One milliliter of Macroporous adsorptive resin was added to 5 ml of 50 mM Tris–HCl buffer esterase solution (4 mg/ml) at pH 8. The mixture was stirred at 4 °C and 180 rpm for 12 h. The resin was then removed from the enzyme solution and washed exhaustively with the corresponding buffer solution. Next, the resin was collected by filtration followed by 12 h lyophilization. The amount of enzyme immobilized on the resins was calculated based on the difference of the protein contents in the buffer before and after adsorption.

4.4. General procedure for the green resolution of chiral alcohols

A 25 ml round-bottom flask was charged with 1 mmol racemic secondary alcohol, 5 mL vinyl acetate. Then 10 mg of immobilized enzyme was added in the previous mixture. When this was completed, the resulting mixture was stirred at ambient temperature for a certain time. Conversions and ee values were determined by GC analysis or HPLC analysis. When the reaction was complete, the solution was filtered through a pad of cotton; the solvent and the unreacted vinyl acetate were removed in vacuum. The resulting residues were purified by chromatography on silica gel with petroleum ether–ethyl acetate (1:10–1:5) to afford the corresponding pure (*R*)-configured esters. A 25 ml round-bottom flask was charged with the (*R*)-ester of 0.5 mmol, 10 mL isopropyl ether and immobilized CALB (*Novozym 435*) recycled from the former round or new addition, sealed and anhydrous ammonia was added to the solution. The resulting mixture was stirred at 35 °C for a certain time. Samples were taken at 1 h intervals, each time 20 μl of solution were used for analyzing. When the reaction was complete, the solution was filtered through a pad of cotton and the solvent was removed in vacuo. The resulting residues were purified by chromatography on silica gel with petroleum ether–ethyl acetate (1:1–1:5) to afford the corresponding (*R*)-alcohols; the ee values of the desired products are summarized in Table 5.

4.4.1. (*S*)-1-Phenylethanol and (*R*)-1-phenylethanol ($R^1 = C_6H_5$, $R^2 = CH_3$)

^{1}H NMR ($CDCl_3$) δ 1.49 (3H, d, J = 6.0 Hz), 1.66 (1H, s), 4.90 (1H, q, J = 6.8 Hz), 7.19–7.39 (5H, m). Ee values and conversion were determined by GC analysis. GC-analysis conditions: oven temperature, 108 °C, injector temperature, 230 °C, detector temperature, 230 °C. Retention time: (*S*)-1-phenylethanol, 16.98 min; (*R*)-1-phenylethanol, 16.27 min.

4.4.2. (*S*)-1-(*p*-Tolyl)ethanol and (*R*)-1-(*p*-tolyl)ethanol ($R^1 = 4\text{-}CH_3C_6H_4$, $R^2 = CH_3$)

^{1}H NMR ($CDCl_3$) δ 1.47 (3H, d, J = 6.8 Hz), 2.35 (3H, s), 4.08 (1H, t, J = 6.0 Hz), 7.11–7.27 (4H, m). Ee values and conversion were determined by GC analysis. GC-analysis conditions: oven temperature, 108 °C, injector temperature, 230 °C, detector temperature, 230 °C. Retention time: (*S*)-1-(*p*-tolyl)ethanol, 28.23 min; (*R*)-1-(*p*-tolyl)ethanol, 29.43 min.

4.4.3. (*S*)-1-(4-Chlorophenyl)ethanol and (*R*)-1-(4-chlorophenyl)ethanol ($R^1 = 4\text{-}ClC_6H_4$, $R^2 = CH_3$)

^{1}H NMR ($CDCl_3$) δ 1.46 (3H, d, J = 7.2 Hz), 4.10 (1H, d, J = 6.0 Hz), 4.87 (1H, q, J = 6.0 Hz), 7.25–7.33 (4H, m). Ee values and conversion were determined by GC analysis. GC-analysis conditions: oven temperature, 112 °C, injector temperature, 230 °C, detector temperature, 230 °C. Retention time: (*S*)-1-(4-chlorophenyl)ethanol, 37.85 min; (*R*)-1-(4-chlorophenyl)ethanol, 38.65.

4.4.4. (*S*)-1-(4-Nitrophenyl)ethanol and (*R*)-1-(4-nitrophenyl)-ethanol ($R^1 = 4\text{-}NO_2C_6H_4$, $R^2 = CH_3$)

^{1}H NMR ($CDCl_3$) δ 1.50 (3H, d, J = 6.8 Hz), 4.09 (1H, d, J = 6.0 Hz), 5.00 (1H, t, J = 8.0 Hz), 7.23–8.24 (4H, m). Ee values and conversion were determined by GC analysis. GC-analysis conditions: oven temperature, 170 °C, injector temperature, 260 °C, detector temperature, 230 °C. Retention time: (*S*)-1-(4-nitrophenyl)ethanol, 35.85 min; (*R*)-1-(4-nitrophenyl)ethanol, 41.23 min.

4.4.5. (*S*)-1-(3-Nitrophenyl)ethanol and (*R*)-1-(3-nitrophenyl)-ethanol ($R^1 = 3\text{-}NO_2C_6H_4$, $R^2 = CH_3$)

^{1}H NMR ($CDCl_3$) δ 1.51 (3H, d, J = 6.0 Hz), 1.81 (1H, t, J = 6.8 Hz), 5.00–5.02 (1H, m), 7.25 (1H, s), 7.51 (1H, s), 7.70 (1H, s), 8.11 (1H, s), 8.25 (1H, s). Ee values and conversion were determined by GC analysis. GC-analysis conditions: oven temperature, 170 °C, injector temperature, 260 °C, detector temperature, 230 °C. Retention time: (*S*)-1-(3-nitrophenyl)ethanol, 27.95 min; (*R*)-1-(3-nitrophenyl)ethanol, 29.68 min.

4.4.6. (*S*)-1-(4-Methoxyphenyl)ethanol and (*R*)-1-(4-methoxyphenyl)ethanol ($R^1 = 4\text{-}CH_3OC_6H_4$, $R^2 = CH_3$)

^{1}H NMR ($CDCl_3$) δ 1.44 (3H, d, J = 6.8 Hz), 1.87 (1H, d, J = 7.2 Hz), 3.78 (1H, s), 4.48 (1H, s), 4.83 (1H, m), 6.86–7.30 (4H, m). Ee values and conversion were determined by GC analysis. GC-analysis conditions: oven temperature, 138 °C, injector temperature, 230 °C, detector temperature, 230 °C. Retention time: (*S*)-1-(4-methoxy-

phenyl)ethanol, 22.99 min; (*R*)-1-(4-methoxyphenyl)ethanol, 28.08 min.

4.4.7. (*S*)-1-(4-Ethoxyphenyl)ethanol and (*R*)-1-(4-ethoxyphenyl)ethanol (R^1 = 4- $C_2H_5OC_6H_4$, R^2 = CH_3)

^{1}H NMR ($CDCl_3$) δ 1.34 (3H, t, J = 6.0 Hz), 1.39 (3H, d, J = 6.8 Hz), 1.69 (1H, s), 4.13 (2H, q, J = 7.0 Hz), 4.18 (1H, m), 6.85 (1H, s), 6.87 (1H, s), 7.15 (1H, s), 7.17 (1H, s). Ee values and conversion were determined by GC analysis. GC-analysis conditions: oven temperature, 148 °C, injector temperature, 230 °C, detector temperature, 230 °C. Retention time: (*S*)-1-(4-ethoxyphenyl)ethanol, 15.72 min; (*R*)-1-(4-ethoxyphenyl)ethanol, 14.14 min.

4.4.8. (*S*)-1-([1,1′-Biphenyl]-4-yl)ethanol and (*R*)-1-([1,1′-biphenyl]-4-yl)ethanol (R^1 = 4-$C_6H_5C_6H_4$, R^2 = CH_3)

^{1}H NMR ($CDCl_3$) δ 1.34 (3H, t, J = 6.0 Hz), 1.39 (3H, d, J = 6.8 Hz), 1.69 (1H, s), 4.13 (2H, q, J = 7.0 Hz), 4.18 (1H, m), 6.85 (1H, s), 6.87 (1H, s), 7.15 (1H, s), 7.17 (1H, s). Ee values were determined by HPLC analysis. Retention time (*n*-hexane–IPA = 9:1, column temperature, 35 °C, 1 ml/min); (*S*)-1-([1,1′-biphenyl]-4-yl) ethanol, 13.69 min; (*R*)-1-([1,1′-biphenyl]-4-yl)ethanol, 15.15 min.

4.4.9. (*S*)-1-Phenylpropan-1-ol and (*R*)-1-phenylpropan-1-ol (R^1 = C_6H_5, R^2 = C_2H_5)

^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 6.0 Hz), 1.69–1.86 (2H, m), 1.76 (1H, t, J = 6.0 Hz), 7.27 (1H, t, J = 6.8 Hz), 7.25–7.37 (5H, m). Ee values and conversion were determined by GC analysis. GC-analysis conditions: oven temperature, 120 °C, injector temperature, 230 °C, detector temperature, 230 °C. Retention time: (*S*)-1-(4-ethoxyphenyl)ethanol, 17.20 min; (*R*)-1-(4-ethoxyphenyl)ethanol, 16.84 min.

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