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Mechanism-based enzymatic method for reliable determination of absolute configuration of chiral 1-substituted ethanols: combination with NMR method

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Abstract—It has been demonstrated that lipase is useful not only for kinetic resolution but also for the rapid determination of absolute configurations. We have previously proposed a mechanism represented by transition-state models to rationalize the enantioselectivity in the lipase- and subtilisin-catalyzed kinetic resolutions of secondary alcohols. The mechanism indicates that the enzyme-catalyzed reactions can be used as a tool for determining the absolute stereochemistry of secondary alcohols. In order to increase reliability, the enzymatic method was combined with Mosher's method using MTPA, to give a protocol which is named *the double-confirmation method*. The absolute configurations of six 1-substituted ethanols were determined consistently by this new procedure. The enzymatic method is quick, easy, economical, and reliable. An interesting similarity in conformation between the transition-state models and MTPA esters is also described.

1. Introduction

There are a large number of secondary alcohols whose absolute configuration remains to be established. Although several methods for determining the absolute configuration of chiral molecules, such as X-ray crystallographic methods,[1a] CD methods,[1] and NMR methods,[2,3] have been developed, determining an absolute configuration is still a laborious task. Rapid determination of the absolute configuration of chiral compounds, particularly simple ones, is desirable because, in most cases, determining an absolute configuration is not the primary aim of research work. The development of a time-saving and economical method for this purpose is therefore needed.

Lipases and subtilisins are the widely used biocatalysts for the kinetic resolution of a wide range of secondary alcohols.[4] The mechanism by which these enzymes simultaneously achieve high enantioselectivity and broad substrate specificity has been elucidated,[5–8] and the theoretical basis for using the enzymes as tools for determining the absolute configuration of secondary alcohols has already been established as described below. The aim of this paper is to propose and examine an enzymatic method, a mechanism-based catalytic method for determination of absolute configurations using a lipase. The enzymatic method is characterized by the use of a racemic mixture, in contrast to spectroscopic methods using an enantiomerically pure or enriched sample.[1–3] The enzymatic method is therefore useful and efficient when a racemic mixture is available. While an empirical rule,[9] known for a decade, itself has allowed only *tentative* assignment of absolute configurations, the mechanism-based procedures and criteria that are formulated in this paper enable us to determine absolute configurations reliably. Herein, we report the determination of the absolute configurations of six 1-substituted ethanols by means of the enzymatic technique and Mosher's method using MTPA[2] and we compare the two protocols.

2. Results and discussion

2.1. Proposal of enzymatic method

As shown in Fig. 1, *the enantiopreferences of lipases and subtilisins for secondary alcohols originate from the spatial arrangement of a minimal set of the amino acid residues*.[5–8] This is because the local conformational requirements and repulsive interactions in the transition

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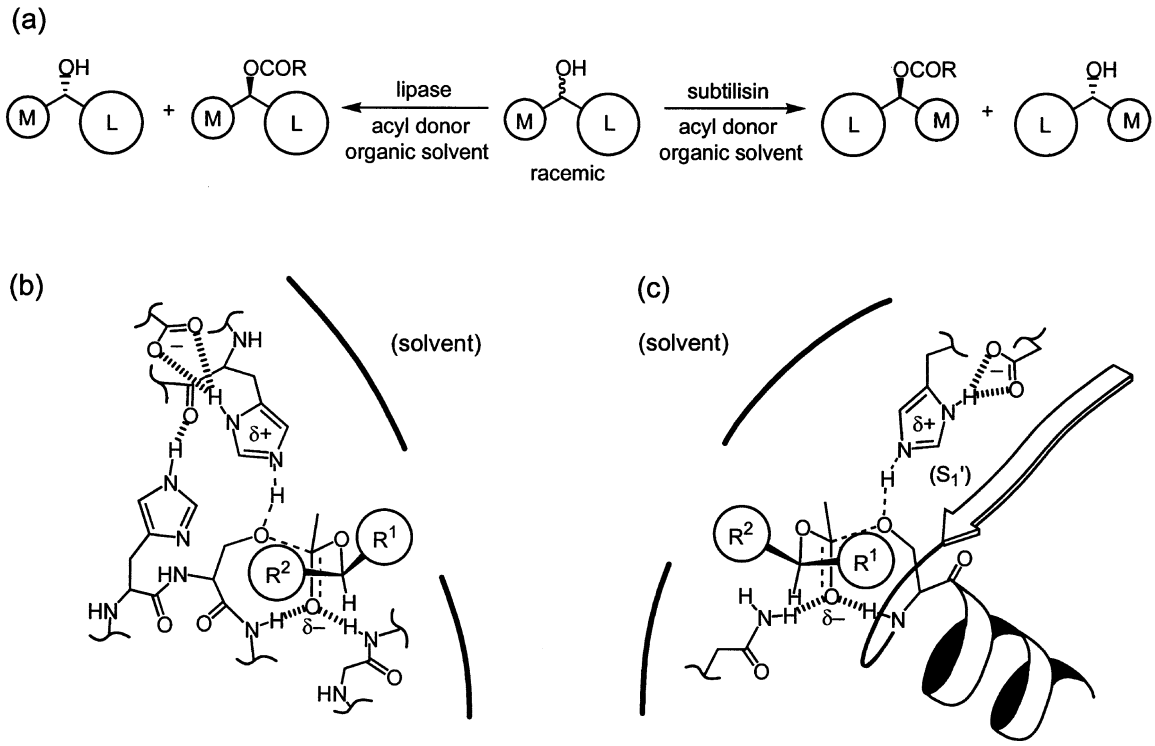


Figure 1. (a) Empirical rules for the lipase- and subtilisin-catalyzed kinetic resolutions of secondary alcohols. L and M represent the larger and smaller substituents, respectively. Typically, (*R*)- and (*S*)-enantiomers react faster in the lipase- and subtilisin-catalyzed kinetic resolutions, respectively. (b) (c) Transition-state models for the (b) lipase- and (c) subtilisin-catalyzed kinetic resolutions of secondary alcohols. In both models, (i) the C–O bond of a substrate has the *gauche* conformation with respect to the breaking C···O bond, which is due to the stereoelectronic effect, and (ii) the H atom attached to the asymmetric C atom of the substrate is *syn*-oriented toward the carbonyl O atom of the acetyl group. When such a locally favorable conformation is taken, the faster-reacting enantiomer can direct the larger substituent (R^1 in (b) and R^2 in (c)) toward the external solvent without severe steric hindrance, whereas the slower-reacting enantiomer directs the larger substituent (R^2 in (b) and R^1 in (c)) toward the protein wall, causing a severe steric repulsion. Even if any other conformation is taken, the slower-reacting enantiomer necessarily becomes less stable than the antipodal enantiomer. For details, see Ref. 5.

state are the predominant factors, and because binding interactions between the enzyme pockets and the substituents of the substrate, which would narrow substrate specificity, are the minor factors. In this sense, these enzymes are 'chemical reagent-like'.[10] The transition-state models have been derived on the basis of MO calculations and molecular modeling[5] and have been supported by the kinetic[5,7] and thermodynamic[8] studies. The local conformation shown in the transition-state models has been supported by using an extremely large secondary alcohol, 5-[4-(1-hydroxyethyl)phenyl]-10,15,20-triphenylporphyrin.[6] In general, the transition-state models can be used to rationalize the following experimental observations: (i) the simultaneous achievement of high enantioselectivity and broad substrate specificity, (ii) the opposite enantiopreferences of lipases and subtilisins toward secondary alcohols, (iii) low activity for secondary alcohols having bulky substituents on both sides, and (iv) little or no activity for tertiary alcohols.[5–8]

Because binding interactions, which are fortuitous and unpredictable, are ruled out, and because the well-defined mechanism is available, the hydrolases can be in principle used as a tool for determining the absolute configuration of secondary alcohols. The enzyme-catalyzed kinetic resolution affords the enantiomerically enriched alcohol and ester whose absolute configurations can be predicted by the mechanism. One can predict non-empirically which enantiomer will react faster or slower; Figs. 1b and c show that the faster-reacting enantiomer can direct the larger substituent (R^1 in (b) and R^2 in (c)) towards the external environment, avoiding severe steric hindrance, whereas the slower-reacting enantiomer tends to direct the larger substituent (R^2 in (b) and R^1 in (c)) toward the protein wall, causing steric repulsion and/or substantial strain.

2.2. Demonstration

Because there is a clear tendency for subtilisin Carlsberg to show much lower enantioselectivity compared to lipases,[7] a lipase (lipase PS, Amano Pharmaceutical Co.) was employed for our purpose. An organic solvent, diisopropyl ether, was used because hydrophobic interactions, which might have an opposite effect on the intrinsic enantiopreference of the enzyme, are unlikely to occur in non-aqueous media.[11] We began the investigation with the simplest alcohols, 1-substituted ethanols, because the difference in bulkiness between

the two substituents is obvious,[12] and also, because the smaller substituent (a methyl group) of the (*R*)-enantiomers is unlikely to disturb the protein wall considerably.[5] For the same reason, for example, the configuration of cyclic secondary alcohols such as monosubstituted cyclopentanols and cyclohexanols can also be safely judged. Alcohols **1a**–**f** were selected in this study.

Scheme 1 outlines the procedures consisting of one or two steps. We propose *the double-confirmation method* using both enzymatic (step 1) and MTPA (step 2) methods in addition to *the rapid method* (only step 1). Detailed experimental procedures are described in Section 4. The lipase-catalyzed kinetic resolutions were performed with vinyl acetate in dry diisopropyl ether at 30°C (Scheme 1). The enantiomeric excess values (% e.e.) were determined by means of chiral HPLC or chiral GC, and the *E* values were calculated according to the literature.[13] The absolute configurations were predicted by the transition-state model (Fig. 1b) and were determined by the lipase-catalyzed kinetic resolutions. The optically active alcohols obtained in the lipase-catalyzed kinetic resolutions were then converted to the corresponding MTPA (α-methoxy-α-(trifluoromethyl)phenylacetic acid) esters using (*S*)-MTPA-Cl (the acyl chloride of (*R*)-MTPA) (Scheme 1). Absolute configuration determination by the MTPA method was then performed according to the literature.[2] The results are summarized in Table 1. The relationship between the absolute configuration and the sign of the specific rotation is shown in Section 4.

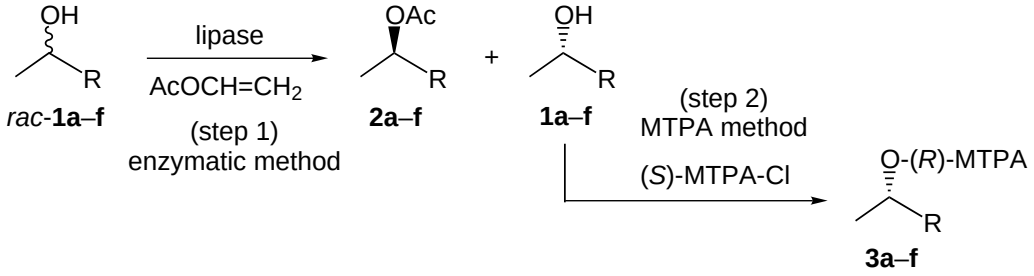
The absolute configurations of the optically active alcohols **1a**–**f** obtained in the lipase-catalyzed kinetic resolutions were consistently determined to be (*S*) by the two methods. The *E* value can be used as a reliability index for the enzymatic method, and they are high in all cases. An *E* value of >20 is enough for reliable assignment. In the NMR method, the doublet signals of the methyl group of the alkoxy moiety were used for the configurational assignments. The positive sign of the $\Delta\delta$ values indicates that the product is enriched in the (*S*)-enantiomer, and the magnitude of the $\Delta\delta$ values can be used as another reliability index. In all cases, signal separation was good when 500 MHz ^{1}H NMR was used. The absolute configurations of alcohols **1a**,[14] **1b**,[15] and **1f**[6] have been determined elsewhere by other methods, and the present results agree with the previous assignments. The absolute configurations of alcohols **1c**–**e** were newly determined in this study. The reaction of **1d** was very sluggish probably due to steric repulsion with some part of the enzyme. Despite the slow reaction, the assignment is reliable, judging from the high reliability index ($E=29$) and the result based on the MTPA method. Although the enzymatic activity for the very bulky alcohol **1f** was also poor, the *E* value is very high.[6] The absolute configuration of **1f** has previously been established by tedious chemical interconversion, and the prediction based on the transition-state model has been demonstrated to be correct.[6] In this study, the MTPA method also afforded the correct assignment for **1f**.

There are a large number of secondary alcohols whose absolute configuration remains to be established, especially unnatural alcohols having an aromatic ring(s). For example, introduction of substituents to the benzene ring of 1-phenylethanol easily gives a compound, such as **1c**–**e**, whose absolute configuration has not been established. Because a large number of chiral secondary alcohols of natural and nonnatural types are nowadays commercially available and/or can be easily prepared on a laboratory scale, a time-saving and economical method for determining absolute configurations is required. The present method is very useful and practical because lipase is used for both kinetic resolution and absolute configuration determination.

Other empirical or mechanism-based methods using an enantioselective or diastereoselective reaction have been reported;[16] however, none of them is widely used to determine absolute configurations, and spectroscopic methods are currently preferred.[1–3] The enzymatic method we have reported in this paper is promising for the following reasons: (i) lipases are commercially available at low prices, are easy to handle, and find widespread use as a reagent for preparing optically active compounds; (ii) the mechanistic origin of the enantioselectivity is disclosed; (iii) the reliability index (*E* value) is defined, and reliability is high ($E>20$) in many cases; (iv) the method can be combined effectively with the widely used, mechanism-based method (MTPA method).

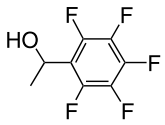
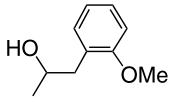
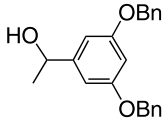
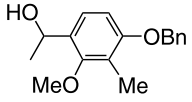
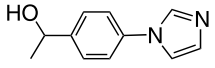
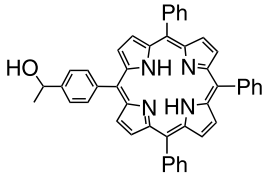
2.3. Comparison between enzymatic method and MTPA method

The MTPA method and the enzymatic method differ in principle. The former utilizes NMR spectroscopy: the enantiomers (diastereomers) are detected by the differential chemical shift mainly caused by the ring-current effect of the phenyl group in the acyl (MTPA) moiety. The latter, on the other hand, utilizes the difference in



Scheme 1. The double-confirmation method (step 1 followed by step 2) and the rapid method (only step 1).

Table 1. Determination of absolute configurations of 1-substituted ethanols by enzymatic method and MTPA method

Alcohol		Enzymatic method[a]		MTPA method	
		Config. of **1**[b]	*E* value[c]	Config. of **1**[d]	$\Delta\delta$[e]
	**1a**	(*S*)	>386	(*S*)	+0.053
	**1b**	(*S*)	62	(*S*)	+0.034
	**1c**	(*S*)	>203	(*S*)	+0.063
	**1d**	(*S*)	29	(*S*)	+0.051
	**1e**	(*S*)	>458	(*S*)	+0.054
	**1f**	(*S*)	>298[f]	(*S*)	+0.053

[a] *Reagents and conditions*: **1** (0.82 mmol), lipase PS (270 mg), vinyl acetate (1.64 mmol), dry *i*-Pr_2O (5 mL), 30°C.
[b] Absolute configuration of alcohol **1** obtained in the lipase-catalyzed kinetic resolution, as predicted by the transition-state model. The relationship between the absolute configuration and the sign of the specific rotation is shown in Section 4.
[c] Calculated from $E=\ln[1-c(1+\text{e.e.}(\mathbf{2}))]/\ln[1-c(1-\text{e.e.}(\mathbf{2}))]$, where $c=\text{e.e.}(\mathbf{1})/(\text{e.e.}(\mathbf{1})+\text{e.e.}(\mathbf{2}))$ according to Ref. 13.
[d] Absolute configuration of alcohol **1** obtained in the lipase-catalyzed kinetic resolution, as determined by the MTPA method.
[e] Chemical shift difference between the diastereomeric (*R*)-MTPA derivatives **3** shown in ppm. The doublet signals of the methyl group of the alkoxy moiety were used for assignment. $\Delta\delta=\delta$ (major diastereomer)$-\delta$ (minor diastereomer). The positive sign of the $\Delta\delta$ value indicates that the (*S*)-enantiomer is enriched.
[f] Data taken from Ref. 6.

reaction rate: the enantiomers are discriminated by the differential activation energy caused primarily by the conformational requirements and repulsive interactions in the transition state. Interestingly, despite the difference in principle, there is a similarity in conformation between MTPA esters and the transition-state models. The conformation proposed for MTPA esters is shown in Fig. 2.[2,3] The hydrogen attached to the alkoxy carbon is proposed to be synperiplanar to the carbonyl oxygen (Fig. 2). *It should be noted that this conformational requirement is retained not only in the ground state* (Fig. 2) *but also in the transition state* (Figs. 1b and c) *to play an essential role in both methods.*

In the MTPA method, absolute configurations are estimated from the sign of the chemical-shift difference ($\Delta\delta$) between diastereomers, assuming the proposed conformation and the ring-current effect of the phenyl group of the MTPA moiety (Fig. 2). In some cases, however, multiple signals with small chemical-shift differences appear, making the assignment difficult. The small chemical-shift difference arises partly from rapid rotation of the phenyl group of the MTPA moiety and of the bond between the carbonyl C atom and the asymmetric C atom of the MTPA moiety.[17] The enzymatic method, on the other hand, is based on the more straightforward procedure: kinetic resolution affords the enantiomerically enriched alcohol and ester whose absolute configurations are predicted by the transition-state model. The protein wall to feel a steric pressure is spatially fixed well, leading to high *E* values (adequate reliability) (Table 1). Furthermore, the enzymatic method uses a catalytic amount of enzyme in contrast

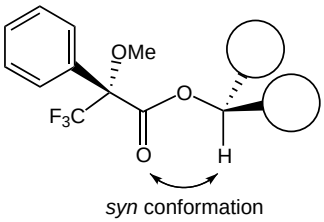


Figure 2. The conformation proposed for MTPA esters. The H atom attached to the alkoxy C atom is *syn*-oriented toward the carbonyl O atom. A similar conformation is taken in the transition state (see Fig. 1).

to the MTPA method using at least one equivalent of MTPA-Cl: the enzyme makes approximately 5000 turnovers at 50% conversion under the reaction conditions except for **1f**.[6b,18]

Despite the drawbacks described above, the MTPA method is a well-established and useful method. Because an enantiomerically enriched alcohol is always necessary for the MTPA method, the sequential procedure, involving lipase-catalyzed kinetic resolution followed by the MTPA method, is efficient and practical when a racemic alcohol is available.

3. Conclusion

We have stressed the theoretical background of the enzymatic method to show its validity and reliability as a methodology. The enzymatic method, called the rapid method, is an easy, rapid, economical and reliable method, at least for 1-substituted ethanols. This method will be applicable to other simple secondary alcohols whose substituents flanking the stereocenter have significantly different bulkiness. Although the enzymatic method is reliable enough alone, its reliability can be further enhanced by the double-confirmation method, which will be important particularly for secondary alcohols other than 1-substituted ethanols. Instead of the NMR method, other methods can also be used in the double-confirmation method.[19] There is a similarity in conformation between the transition-state models and MTPA esters, and this common requirement of conformation plays an important role in both enzymatic and MTPA methods. Further work is in progress to develop a more general technique for absolute configuration determination that is applicable to secondary alcohols possessing bulky substituents on both sides of the stereocenter.

4. Experimental

4.1. General

NMR spectra were recorded on Varian VXR-500, Varian VXR-200S, or Varian Gemini-200 spectrometers. IR spectra were recorded on a Shimadzu FTIR-8900 spectrophotometer. Optical rotations were measured on a Horiba SEPA-300 polarimeter. Elemental analyses were performed on a Yanaco MT-6 CHN coder. GC was performed on a Shimadzu GC-14B. HPLC was performed on a Shimadzu LC-9A fitted with a SPD-6A UV detector or a Hitachi L-7100 fitted with a L-7400 UV detector. Column chromatography was carried out using Fuji Silysia BW-127 ZH (100–270 mesh). Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F_{254}. Lipase PS (1% (w/w) powder) purchased from Amano Pharmaceutical Co. was used without further purification. The enantiomeric purities of **1b–e** were determined by HPLC using Chiralpak AD (**1b–d**) and Chiralcel OJ (**1e**) columns (Daicel Chemical Industries), and that of **1a** was determined by capillary gas chromatography using a CP-cyclodextrin-β-2,3,6-M-19 column (Chrompack, ϕ 0.25 mm×25 m). Commercially available (*R*)-MTPA was converted to the corresponding (*S*)-MTPA-Cl according to the literature.[20]

4.2. General procedure for preparation of racemic alcohols

Alcohols **1c–e** were prepared from the corresponding ketones commercially available. To a solution of ketone (4.0 mmol) in EtOH (10 mL) were added a few drops of saturated aqueous $NaHCO_3$ and then $NaBH_4$ (2.0 mmol). The mixture was stirred at room temperature overnight and then acidified with 10% HCl to pH 3. After EtOH was removed under reduced pressure, water (0.5 mL) was added. The product was extracted with EtOAc (4×2 mL) and dried over $MgSO_4$. After the solvent was removed, the product was purified by silica gel column chromatography (**1c**) or by recrystallization from ether–hexane (**1d**) or from EtOAc (**1e**).

4.2.1. (±)-1-(3,5-Dibenzyloxyphenyl)ethanol, 1c. Yield 70%; white crystals; mp 68–70°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.47 (d, J=6.5 Hz, 3H), 4.83 (q, J=6.5 Hz, 1H), 5.04 (s, 4H), 6.54 (t, J=2.2 Hz, 1H), 6.64 (d, J=2.2 Hz, 2H), 7.29–7.45 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.1, 70.1, 70.4, 100.9, 104.4, 127.5, 128.0, 128.6, 136.8, 148.5, 160.0; IR (KBr): 3296, 1593, 1163, 1034 cm^{-1}. Anal. calcd for $C_{22}H_{22}O_3$: C, 79.02; H, 6.63. Found: C, 78.63; H, 6.60%.

4.2.2. (±)-1-(4-Benzyloxy-2-methoxy-3-methylphenyl)-ethanol, 1d. Yield 81%; white crystals; mp 79–80°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.51 (d, J=6.3 Hz, 3H), 2.23 (s, 3H), 3.79 (s, 3H), 5.08 (s, 2H), 5.15 (q, J=6.3 Hz, 1H), 6.72 (d, J=8.4 Hz, 1H), 7.20 (d, J=8.4 Hz, 1H), 7.31–7.45 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 9.4, 23.6, 61.2, 65.1, 70.1, 107.6, 120.0, 123.4, 127.1, 127.8, 128.5, 130.8, 137.3, 156.6, 157.3; IR (KBr): 3323, 1605, 1271, 1111 cm^{-1}. Anal. calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.81; H, 7.36%.

4.2.3. (±)-1-(4-(Imidazol-1-yl)phenyl)ethanol, 1e. Yield 76%; pale yellow crystals; mp 83–86°C; ^{1}H NMR (500 MHz, CD_3OD): δ 1.47 (d, J=6.5 Hz, 3H), 4.89 (q, J=6.5 Hz, 1H), 7.18 (br s, 1H), 7.50–7.57 (m, 5H), 8.12 (br s, 1H); ^{13}C NMR (50 MHz, CD_3OD): δ 25.7, 70.1, 119.8, 122.2, 128.1, 130.1, 136.9, 137.3, 147.5; IR (KBr): 3408, 3103, 1526, 1258 cm^{-1}. Anal. calcd for

$C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 69.77; H, 6.47; N, 14.68%.

4.3. General procedure for determination of absolute configurations

The typical experimental procedures for the rapid method and the double-confirmation method are as follows. The latter is recommended to raise reliability, but the former is much more time- and cost-effective.

4.3.1. Rapid method (step 1). A heterogeneous solution of lipase PS (270 mg), alcohol (0.82 mmol), and vinyl ester (1.64 mmol) in dry *i*-Pr_2O (5 mL) was stirred at 450 rpm in a test tube with a rubber septum in a thermostat at 30°C. The progress of the reaction was monitored by TLC, and the reaction was stopped by filtration at an appropriate conversion (typically 30–50%). After the solvent was removed under reduced pressure, alcohol and ester were separated by silica gel column chromatography. The ester was converted to the corresponding alcohol, and the enantiomeric excesses were then determined by chiral HPLC or chiral GC. The *E* value was calculated according to the literature.[13] The absolute configurations were determined by the transition-state model.

4.3.2. Double-confirmation method (step 2). Subsequently, the optically active alcohol obtained in the lipase-catalyzed kinetic resolution was converted to the MTPA derivative as follows. A solution of the alcohol (0.05 mmol), (*S*)-MTPA-Cl (0.15 mmol, acyl chloride of (*R*)-MTPA), 4-(dimethylamino)pyridine (0.03 mmol), and dry pyridine (1.2 mmol) in dry toluene (0.5 mL) was stirred at room temperature overnight. The reaction was stopped by adding water (1 mL). The product was extracted with EtOAc (5×1 mL), washed with 10% HCl (0.5 mL), and then washed with saturated aqueous $NaHCO_3$ (0.5 mL). The mixture was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The product was purified by silica gel column chromatography. 500 MHz ^{1}H NMR spectrum was measured, and the doublet signals of the methyl group of the alkoxy moiety were used for absolute configuration determination according to the literature.[2]

4.3.3. Kinetic resolution of 1-(pentafluorophenyl)ethanol, 1a. Reaction time 3 days. (*S*)-**1a**: 45% yield; 64% e.e.; $[\alpha]_D^{18}=-4.2$ (*c* 0.45, *n*-pentane), lit.[14] $[\alpha]_D^{28}=-7.1$ (*c* 1.0, *n*-pentane) for (*S*)-**1a** with >94% e.e.; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.65 (d, $J=6.8$ Hz, 3H), 5.26 (q, $J=6.8$ Hz, 1H); GC: CP-cyclodextrin, Inj. 250°C, Col. 100°C, Det. 220°C, (*R*) 15 min, (*S*) 18 min. (*R*)-**2a**: 29% yield; >99% e.e.; $[\alpha]_D^{16}=+43$ (*c* 0.82, *n*-pentane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.65 (d, $J=6.8$ Hz, 3H), 2.07 (s, 3H), 6.09 (q, $J=6.8$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.6, 20.8, 63.3, 170.1; IR (neat): 1747, 1521, 1236 cm^{-1}.

4.3.4. Kinetic resolution of 1-(2-methoxyphenyl)-2-propanol, 1b. Reaction time 25 h. (*S*)-**1b**: 55% yield; 63% e.e.; $[\alpha]_D^{21}=+23.6$ (*c* 1.00, CH_2Cl_2), lit.[15] $[\alpha]_D^{25}=+30.6$ (*c* 1.08, CH_2Cl_2) for (*S*)-**1b** with 85% e.e.; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.23 (d, $J=6.2$ Hz, 3H), 2.65–2.90 (m, 2H), 3.83 (s, 3H), 4.00–4.12 (m, 1H), 6.86–6.95 (m, 2H), 7.13–7.27 (m, 2H); HPLC: Chiralpak AD, hexane/*i*-PrOH = 9:1, flow rate 0.5 mL/min, detection 254 nm, (*S*) 14 min, (*R*) 16 min. (*R*)-**2b**: 18% yield; 94% e.e.; $[\alpha]_D^{25}=-20$ (*c* 0.50, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.21 (d, $J=6.4$ Hz, 3H), 1.96 (s, 3H), 2.85 (d, $J=7.0$ Hz, 2H), 3.82 (s, 3H), 5.16 (sext., $J=6.4$ Hz, 1H), 6.82–6.90 (m, 2H), 7.09–7.27 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.7, 21.3, 36.6, 55.2, 70.5, 110.2, 120.2, 126.0, 127.8, 131.1, 157.7, 170.6; IR (neat): 1736, 1244 cm^{-1}.

4.3.5. Kinetic resolution of 1-(3,5-dibenzyloxyphenyl)ethanol, 1c. Reaction time 8 h. (*S*)-**1c**: 54% yield; 68% e.e.; $[\alpha]_D^{26}=-12.4$ (*c* 1.00, $CHCl_3$); HPLC: Chiralpak AD, hexane/*i*-PrOH = 9:1, flow rate 0.5 mL/min, detection 280 nm, (*R*) 51 min, (*S*) 58 min. (*R*)-**2c**: 40% yield; >98% e.e.; $[\alpha]_D^{28}=+73.9$ (*c* 1.01, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.50 (d, $J=6.5$ Hz, 3H), 2.06 (s, 3H), 5.03 (s, 4H), 5.80 (q, $J=6.5$ Hz, 1H), 6.55 (t, $J=2.2$ Hz, 1H), 6.60 (d, $J=2.2$ Hz, 2H), 7.35–7.41 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.3, 22.2, 70.1, 72.1, 101.1, 105.3, 127.6, 128.0, 128.6, 136.7, 144.2, 160.0, 170.3; IR (neat): 1736, 1597, 1240 cm^{-1}.

4.3.6. Kinetic resolution of 1-(4-benzyloxy-2-methoxy-3-methylphenyl)ethanol, 1d. Reaction time 7 days. (*S*)-**1d**: 69% yield; 43% e.e.; $[\alpha]_D^{22}=-11.1$ (*c* 1.00, $CHCl_3$); HPLC: Chiralpak AD, hexane/*i*-PrOH = 9:1, flow rate 0.5 mL/min, detection 254 nm, (*S*) 22 min, (*R*) 24 min. (*R*)-**2d**: 30% yield; 90% e.e.; $[\alpha]_D^{22}=+56.7$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.50 (d, $J=6.5$ Hz, 3H), 2.06 (s, 3H), 2.22 (s, 3H), 3.79 (s, 3H), 5.07 (s, 2H), 6.17 (q, $J=6.5$ Hz, 1H), 6.72 (d, $J=8.5$ Hz, 1H), 7.17 (d, $J=8.5$ Hz, 1H), 7.33–7.44 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 9.4, 21.4, 21.9, 61.0, 67.6, 70.1, 107.6, 120.1, 123.9, 127.1, 127.5, 127.8, 128.5, 137.3, 156.3, 157.6, 170.3; IR (neat): 1736, 1600, 1240 cm^{-1}.

4.3.7. Kinetic resolution of 1-(4-(imidazol-1-yl)-phenyl)ethanol, 1e. Despite the poor solubility of **1e** in *i*-Pr_2O, the reaction proceeded. Reaction time 2 days. (*S*)-**1e**: 51% yield; >98% e.e.; $[\alpha]_D^{17}=-33$ (*c* 0.48, MeOH); HPLC: Chiralcel OJ, hexane/*i*-PrOH = 7:1 (0.1% diethylamine), flow rate 0.7 mL/min, detection 254 nm, (*S*) 50 min, (*R*) 58 min. (*R*)-**2e**: 47% yield; >98% e.e.; $[\alpha]_D^{14}=+108$ (*c* 0.66, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.56 (d, $J=6.5$ Hz, 3H), 2.09 (s, 3H), 5.90 (q, $J=6.5$ Hz, 1H), 7.22 (t, $J=1.0$ Hz, 1H), 7.28 (t, $J=1.5$ Hz, 1H), 7.37–7.48 (m, 4H), 7.89 (t, $J=1.0$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.2, 22.2, 71.5, 118.3, 121.6, 127.6, 130.0, 135.4, 136.7, 141.3, 170.2; IR (neat): 1732, 1525, 1244 cm^{-1}.

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