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Empirical method for predicting enantioselectivity in catalytic reactions: demonstration with lipase and oxazaborolidine

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ABSTRACT

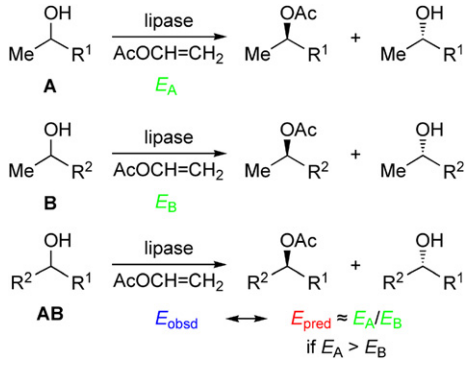
We derived a novel equation capable of predicting the degree of enantioselectivity in a catalytic reaction without any knowledge of the reaction mechanism and/or the transition-state structure, and tested the validity of this equation by changing substrates systematically in the lipase or oxazaborolidine-catalyzed reactions. A good correlation was observed between the predicted and observed *E* values, and the stereochemistry of the products could be predicted correctly in most cases (28 out of 30).

1. Introduction

In general, predicting the degree of enantioselectivity in a catalytic reaction without any knowledge of a reaction mechanism and/or a transition-state structure is almost impossible. Even if the mechanism of enantioselectivity of the catalytic reaction is clear, the quantitative prediction of enantioselectivity is still difficult because the magnitudes of the steric and/or electronic effects that the chiral catalyst experiences in the transition state are hard to predict. Although it is well-known that the essence of chemical reactions lies in the transition state, only a limited number of methods are available for investigating the transition state, which has a lifetime of femto-second order: kinetic constants, the Eyring plot giving the activation enthalpy and entropy, Hammett's substituent constants, isotope effects, spectroscopic detection of reaction intermediates, estimation based on a series of derivatives of catalyst and substrate, and theoretical calculations.[1] Although the E_s value, defined by Taft, is a useful measure of the magnitude of the steric effect,[2] the E_s values cannot address this issue because different catalysts have different steric effects on the same substituent and because the electronic property and solvent can also affect the transition state. Here we report an empirical method for predicting the degree of enantioselectivity without any knowledge of a reaction mechanism and/or a transition-state structure.

2. Results and discussion

During our mechanistic study on the lipase-catalyzed kinetic resolution,[3] we noticed that the *E* value[4] (E_{AB}) for substrate **AB** having two substituents R^1 and R^2 can be predicted by using the *E* values (E_A and E_B) experimentally determined for two reference substrates **A** and **B** having substituent R^1 and R^2, respectively, as shown in Scheme 1.



Scheme 1. Empirical prediction of the *E* value for the lipase-catalyzed kinetic resolution of alcohols.

The equation for the prediction is quite simple:

$$E_{AB} \approx E_A/E_B \quad (1)$$

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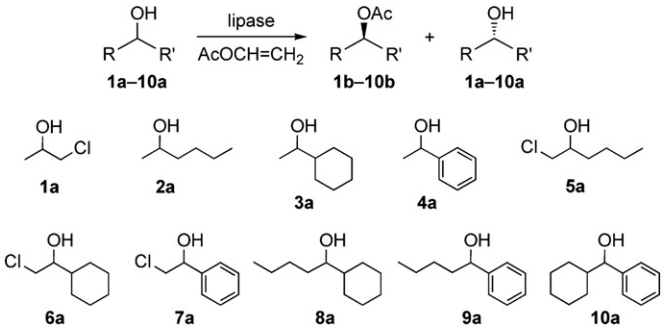
As shown in Experimental section and Supplementary data, this equation can be applied to various reactions where the approximation of additivity and substitution is fulfilled. Eq. 1 means that information needed to predict the degree of enantioselectivity for **AB** is included in the E_A and E_B values involving the steric and electronic effects that a chiral catalyst experiences in the transition state. In this method, the steric effect is not separated from the electronic effect, but both of them are involved in the substituent effect. To test the validity of our hypothesis Eq. 1, we examined two types of enantioselective reactions: (i) the lipase-catalyzed kinetic resolution of secondary alcohols and (ii) the oxazaborolidine-catalyzed reduction of ketones.

We initially carried out the lipase-catalyzed kinetic resolution of alcohols **1a**–**10a** (Scheme 2).[5] The lipase-catalyzed reactions were conducted with vinyl acetate in dry *i*-Pr_2O or Et_2O at 30 °C, and the *E* values were calculated according to the literature.[4b] Based on the results obtained with reference substrates **1a**–**4a**, the *E* values for **5a**–**10a**, which possess two substituents out of the chloromethyl, *n*-butyl, cyclohexyl, and phenyl groups, were predicted. The results are summarized in Table 1. The correlation between the predicted and observed *E* values is plotted in Figure 1a.



Scheme 2. Alcohols used for the lipase-catalyzed kinetic resolution.

Although the *E* values could not be predicted precisely, the enantiopreferences (*R*/*S*) were predicted successfully in most cases (19 out of 20; see Table 1); only the kinetic resolution of **5a** mediated by lipase PS-C II in *i*-Pr_2O did not give a correct enantiopreference. A tendency can be seen that the *E* values predicted by using an *E* value of >200, such as that for **4a**, deviate considerably from the observed *E* values (Table 1), which is partly because a high *E* value exceeding 200 is less reliable. Nevertheless, Figure 1a clearly indicates that the data are scattered around a line inclined 45°. This means that the predicted *E* values are qualitatively in good agreement with the observed *E* values and that the equation, $E_{AB} \approx E_A/E_B$, is valid as the first approximation. In other words, the approximation of additivity and substitution is valid to some extent. (The good correlation in Fig. 1a does not justify the use of the *E* values greater than 200 and the *E* values less than 200 should be used for a reliable prediction.)

It should be noted that the enantiopreference for **10a**, having the cyclohexyl and phenyl substituents of similar sizes, could be predicted correctly in all cases. Because of the similar bulkiness of the two substituents, it would be impossible to unambiguously predict, which enantiomer reacts faster a priori. The lipases did discriminate both the difference and order of the bulkiness of the two substituents correctly.

Lipase PS-C II exhibited very low enantioselectivities for **5a** in *i*-Pr_2O (E=1.53, *R*-preference) and Et_2O (E=1.18, *S*-preference), and low *E* values were predicted (E=1.29, 2.14, *S*-preference). This enzyme experiences or 'feels' a similar degree of steric hindrance against the chloromethyl and *n*-butyl groups, leading to a wrong prediction under condition 1 (Table 1). Changing the enzyme was found to be more effective for improving reliability than changing the solvent; both the predicted and observed *E* values were enhanced by using lipase LIP or Chirazyme L-2 (see conditions 3 and 4 in Table 1).

We next examined the oxazaborolidine-catalyzed reduction of ketones **11a**–**25a**.[6,7] The outline of the method is shown in Scheme 3. The asymmetric reduction was conducted with (*S*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine and $H_3B{\cdot}SMe_2$ in dry THF at 30 °C and the E_{obsd} value was calculated from E_{obsd}=(100+%ee)/(100−%ee). Based on the results obtained with reference ketones **11a**–**15a**, the *E* values for **16a**–**25a**, which possess two substituents out of the benzyl, *n*-butyl, 2-phenylethyl, cyclohexyl, and phenyl groups, were predicted, which were then converted to the %ee values. The results are summarized in Figure 2. The correlation between the predicted and observed *E* values is plotted in Figure 1b. (Note that although compounds **12b**, **14b**, **15b**, **21b**, **22b**, and **25b** (Fig. 2) are identical to **2a**, **3a**, **4a**, **8a**, **9a**, and **10a** (Scheme 2), respectively, different compound numbers are used intentionally to avoid confusion. The characterization of them is also described separately in Experimental section.)

The sense of enantioselectivity (*R*/*S*) could be predicted correctly in most cases (9 out of 10; see Fig. 2), and a good correlation can be seen in Figure 1b. The *E* values for the reference ketones decreased

Table 1
Empirical prediction of the *E* value and enantiopreference for the lipase-catalyzed kinetic resolution of secondary alcohols

Alcohol	Condition 1[a]				Condition 2[b]				Condition 3[c]				Condition 4[d]			
	E_{obsd}[e]	*R*/*S*[f]	E_{pred}[g]	*R*/*S*[h]	E_{obsd}	*R*/*S*	E_{pred}	*R*/*S*	E_{obsd}	*R*/*S*	E_{pred}	*R*/*S*	E_{obsd}	*R*/*S*	E_{pred}	*R*/*S*
1a	12.0	*R*	—	—	10.6	*R*	—	—	4.70	*R*	—	—	117	*R*	—	—
2a	15.5	*R*	—	—	22.7	*R*	—	—	52.7	*R*	—	—	1976	*R*	—	—
3a	164	*R*	—	—	279	*R*	—	—	334	*R*	—	—	>6961	*R*	—	—
4a	2321	*R*	—	—	2397	*R*	—	—	1102	*R*	—	—	8493	*R*	—	—
5a	1.53	*R*	1.29	*S*	1.18	*S*	2.14	*S*	11.5	*S*	11.2	*S*	13.6	*S*	16.9	*S*
6a	47.5	*S*	13.7	*S*	63.5	*S*	26.3	*S*	462	*S*	71.1	*S*	237	*S*	>59	*S*
7a	783	*S*	193	*S*	706	*S*	226	*S*	2453	*S*	234	*S*	74.5	*S*	72.6	*S*
8a	1.89	*R*	10.6	*R*	3.91	*R*	12.3	*R*	14.6	*R*	6.34	*R*	—[i]	—	—	—
9a	37.5	*R*	150	*R*	53.1	*R*	106	*R*	43.7	*R*	20.9	*R*	—[i]	—	—	—
10a	47.6	*R*	14.2	*R*	54.2	*R*	8.59	*R*	28.2	*R*	3.30	*R*	—[i]	—	—	—

[a] Conditions: lipase, alcohol (0.82 mmol), vinyl acetate (1.63 mmol), dry solvent (5 mL), 30 °C. Lipase PS-C II (180 mg), *i*-Pr_2O.
[b] Conditions: lipase, alcohol (0.82 mmol), vinyl acetate (1.63 mmol), dry solvent (5 mL), 30 °C. Lipase PS-C II (180 mg), Et_2O.
[c] Conditions: lipase, alcohol (0.82 mmol), vinyl acetate (1.63 mmol), dry solvent (5 mL), 30 °C. Lipase LIP (80 mg), *i*-Pr_2O.
[d] Conditions: lipase, alcohol (0.82 mmol), vinyl acetate (1.63 mmol), dry solvent (5 mL), 30 °C. Chirazyme L-2 (120 mg), *i*-Pr_2O.
[e] Observed *E* value. E=ln[1−c(1+ee(**b**))]/ln[1−c(1−ee(**b**))], where c=ee(**a**)/(ee(**a**)+ee(**b**)).
[f] Observed absolute configuration of the ester.
[g] Predicted *E* value. For the method of prediction, see Scheme 1 and text.
[h] Predicted absolute configuration of the ester.
[i] No reaction.

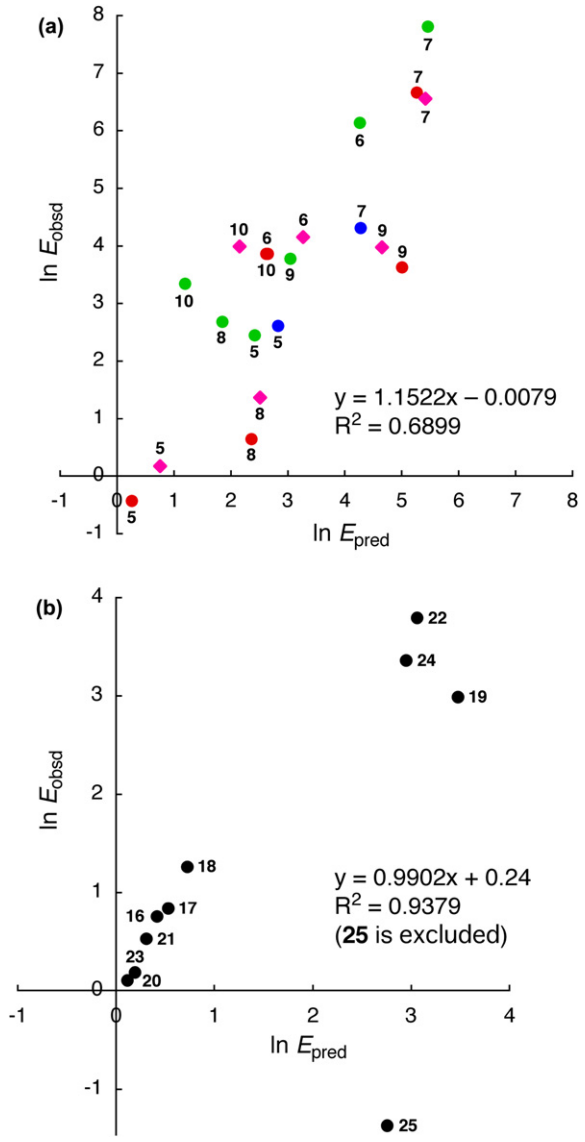
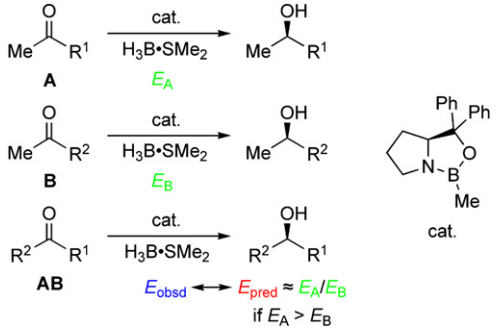


Figure 1. Correlation plots for the ln E_{obsd} and ln E_{pred} values. When the sense of the observed enantioselectivity was opposite to that of the predicted one, the sign of the ln E_{obsd} value was set to negative. Note that multiplying ln E by $-RT$ gives the differential free energy of activation, $\Delta\Delta G^{\ddagger}$. (a) Lipase-catalyzed kinetic resolution of alcohols. The data obtained under conditions 1, 2, 3, and 4 in Table 1 are plotted by red circle, pink diamond, green circle, and blue circle, respectively. (b) Oxazaborolidine-catalyzed reduction of ketones. The data in Figure 2 are plotted.



Scheme 3. Empirical prediction of the E value for the oxazaborolidine-catalyzed reduction of ketones.

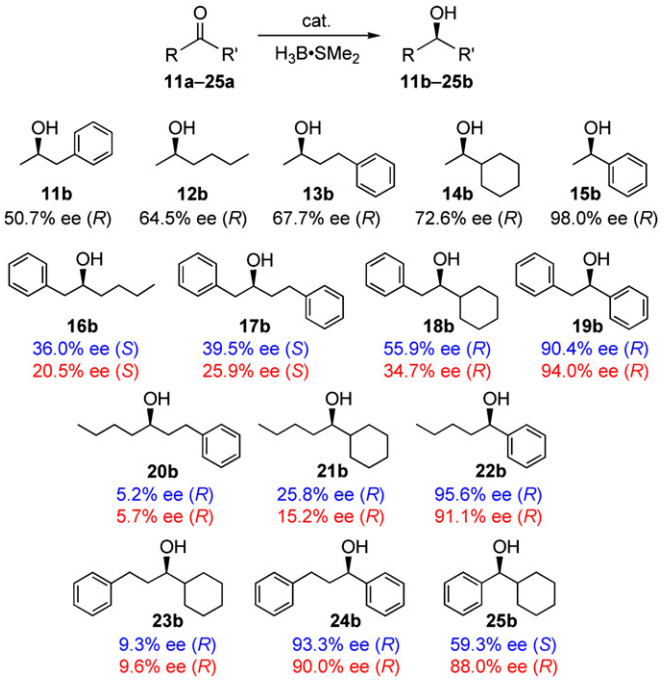


Figure 2. The optically active alcohols **11b**–**25b** obtained by the oxazaborolidine-catalyzed reduction of the corresponding ketones **11a**–**25a** are shown. The observed and predicted % ee values of **16b**–**25b** are shown in blue and red, respectively. The E_{obsd} value was calculated from E_{obsd}=(100+%ee)/(100−%ee), while the E_{pred} value was calculated as shown in Scheme 3. The E_{pred} value was then converted to the predicted %ee value according to the equation, $\%ee_{pred}=100\times(E_{pred}-1)/(E_{pred}+1)$. Conditions: (*S*)-α,α-diphenyl-2-pyrrolidinemethanol (0.22 mmol), trimethylboroxine (0.14 mmol), $H_3B{\cdot}9{\cdot}SMe_2$ (0.6 mmol), ketone (1.0 mmol, slow addition via a syringe pump over 2 h), dry THF (3 mL), 30 °C.

in the following order: **15a**>**14a**>**13a**>**12a**>**11a**. This order reflects the magnitude of steric hindrance that the catalyst feels. The excellence of the present method can be seen from the fact that the absolute configuration of **16b** could be predicted correctly, where the *n*-butyl group is recognized to be bulkier than the benzyl group, which would be impossible to predict a priori. On the other hand, in the reduction of **25a**, the predicted sense of enantioselectivity was found to be wrong (Figs. 1b and 2). This type of deviation can help us gain an insight into the reaction mechanism. For example, we can suppose that the two bulky substituents (phenyl and cyclohexyl) connected to the carbonyl group interfere with each other to rotate and strain the two substituents and that the ground-state and transition-state structures should be very crowded and different from those of reference substrates **14a** and **15a**, which may disrupt the approximation of additivity and/or substitution.

3. Conclusion

In summary, we derived an equation, $E_{AB}\approx E_A/E_B$, capable of predicting the degree of enantioselectivity without any knowledge of a reaction mechanism and/or a transition-state structure, and tested the validity of this equation by changing the structure of substrates systematically in the enzymatic and nonenzymatic reactions. As a result, the degree of enantioselectivity and the stereochemistry of the product could be predicted correctly in most cases (28 out of 30). The same analysis was also applied to the reported data on the enantioselective hydrosilylation of ketones to give a good correlation as shown in Supplementary data. Such a quantitative relationship as characterized by Eq. 1 has been unknown. This type of analysis can afford a hint to gain an insight into the event occurring in the transition state of an enantioselective reaction.

4. Experimental

4.1. Derivation of Eq. 1 based on thermodynamics

Eq. 1 can be derived as described below, assuming the two approximations shown in Figure 3.

The differential free energy of activation for **AB** can be expressed by

$$\Delta\Delta G^{\ddagger}_{AB} = \Delta G^{\ddagger}_{RAB} - \Delta G^{\ddagger}_{SAB}$$

When additivity is assumed for both substituents (R^1 and R^2), the free energy of activation can be divided as follows (approximation of additivity):

$$\Delta\Delta G^{\ddagger}_{AB} \approx \left(\Delta G^{\ddagger}_{RAB(R^1)} + \Delta G^{\ddagger}_{RAB(R^2)}\right) - \left(\Delta G^{\ddagger}_{SAB(R^1)} + \Delta G^{\ddagger}_{SAB(R^2)}\right)$$

$$= \left(\Delta G^{\ddagger}_{RAB(R^1)} - \Delta G^{\ddagger}_{SAB(R^1)}\right) - \left(\Delta G^{\ddagger}_{SAB(R^2)} - \Delta G^{\ddagger}_{RAB(R^2)}\right)$$

If the effects of R^1 in **RAB** and **SAB** are equal to those of R^1 in **RA** and **SA**, respectively, and if the effects of R^2 in **RAB** and **SAB** are equal to those of R^2 in **SB** and **RB**, respectively (approximation of substitution), then

$$\Delta\Delta G^{\ddagger}_{AB} \approx \left(\Delta G^{\ddagger}_{RA} - \Delta G^{\ddagger}_{SA}\right) - \left(\Delta G^{\ddagger}_{RB} - \Delta G^{\ddagger}_{SB}\right)$$

(The effect of the methyl group in **A** and **B** is cancelled out and eliminated.)

$$= \Delta\Delta G^{\ddagger}_{A} - \Delta\Delta G^{\ddagger}_{B}$$

$$= -RT\ln E_A + RT\ln E_B = -RT\ln E_A/E_B$$

(For the formula of $\Delta\Delta G^{\ddagger} = -RT \ln E$, see Refs. 5a,b.)

On the other hand, the differential free energy of activation for **AB** is given by

$$\Delta\Delta G^{\ddagger}_{AB} = -RT\ln E_{AB}$$

Therefore,

$$E_{AB} \approx E_A/E_B (\text{if } E_A > E_B) \quad (2)$$

To meet the above conditions, all the reactions must be conducted under the same conditions. Although the above derivation is done for kinetic resolution, the same derivation can also be applied to asymmetric synthesis if the approximation of additivity and substitution is fulfilled.

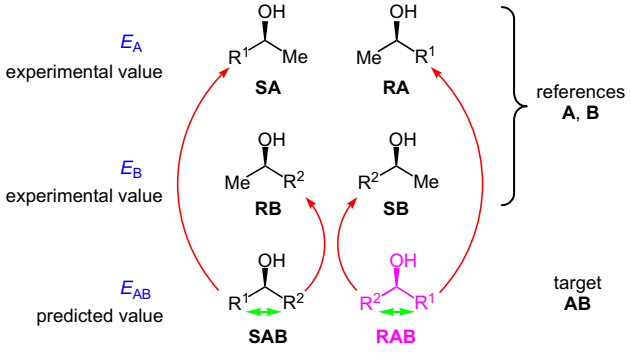


Figure 3. Two approximations for the derivation of Eq. 1. The (*R*)-enantiomers (**RA** and **RB**) are assumed to be the faster-reacting enantiomers in the derivation. The *R*/*S* descriptor for **AB** is arbitrary (It depends on the priority of R^1 and R^2 in the IUPAC nomenclature). When E_A is greater than E_B, **RAB** is predicted to be the faster-reacting enantiomer, and the magnitude of E_{AB} is predicted by E_A/E_B. Red arrow: approximation of substitution; green arrow: approximation of additivity.

4.2. Lipase-catalyzed kinetic resolution

4.2.1. Materials and methods. Lipase PS-C II (*Burkholderia cepacia* lipase) purchased from Amano Enzyme Inc., lipase LIP (*Pseudomonas aeruginosa* lipase) purchased from Toyobo Co., and Chirazyme L-2 (*Candida antarctica* lipase B) provided by Boehringer Mannheim GmbH were used. Alcohols **1a**, **7a**, and **10a** were prepared by the reduction of the corresponding ketones commercially available, as shown below. Alcohols **5a** and **6a** were prepared by the reduction of the corresponding ketones synthesized as shown below. Alcohols **2a**, **3a**, **4a**, **8a**, and **9a** were purchased. All the alcohols were purified by distillation or column chromatography before use in the lipase-catalyzed reactions. Acetates **1b**,[8] **2b**,[9] **3b**,[10] **4b**,[11] **5b**,[12] **7b**,[13] **8b**,[14] **9b**,[15] and **10b**[16] were characterized according to the literature.

*4.2.2. Synthesis of α-chloro ketones **5c** and **6c**.* α-Chloro ketones **5c** and **6c** were prepared from ethyl pentanoate and methyl cyclohexylacetate, respectively, which are commercially available, according to the literature.[17] A mixture of Mg (2.71 g, 111 mmol) and I_2 (one piece) in dry Et_2O (10 mL) was stirred under N_2 at room temperature for several minutes, and a small amount of *tert*-butyl chloride (0.8 mL, 7.4 mmol) was added. After the reaction had been initiated, a solution of *tert*-butyl chloride (7.4 mL, 68 mmol) in dry Et_2O (30 mL) was added dropwise to the suspended solution over 1 h in a water bath. After the mixture had been stirred for a few hours, the mixture was added dropwise to a mixture of ester (15.0 mmol), sodium chloroacetate (3.50 g, 30.0 mmol), and Et_3N (2.5 mL, 18 mmol) in dry Et_2O (15 mL) under N_2 over 1 h in an ice bath. After the mixture had been stirred at room temperature overnight, the reaction was stopped by adding 10% HCl in an ice bath. After brine (3 mL) had been added, the product was extracted with Et_2O (10 mL×2), and the solution was neutralized with saturated aqueous $NaHCO_3$ (3 mL×5). The mixture was dried over $MgSO_4$, filtered, and concentrated. The product was purified by silica gel column chromatography.

*4.2.2.1. 1-Chloro-2-hexanone (**5c**)*[18]. 44% yield; colorless oil; ^{1}H NMR (200 MHz) δ 0.91 (t, J=7.2 Hz, 3H), 1.34 (sext, J=7.4 Hz, 2H), 1.61 (quint, J=7.0 Hz, 2H), 2.59 (t, J=7.2 Hz, 2H), 4.07 (s, 2H); ^{13}C NMR (50 MHz) δ 13.7, 22.2, 25.7, 39.4, 48.2, 202.6; IR (neat) 2959, 2936, 2874, 1732, 1466, 1404, 1381 cm^{-1}.

*4.2.2.2. Chloromethyl cyclohexyl ketone (**6c**)*[19]. The product was used in the next reaction without purification.

*4.2.3. Typical procedure for the preparation of racemic alcohols (**1a**, **5a–7a**, **10a**).* To a solution of ketone (20 mmol) in EtOH (30 mL) was added $NaBH_4$ (0.38 g, 10 mmol) in an ice bath. The mixture was stirred at room temperature for a few hours and then acidified with 3% HCl. After the solvent had been removed under reduced pressure, brine (3 mL) was added. The product was extracted with Et_2O (5 mL×3), and the solution was neutralized with saturated aqueous $NaHCO_3$ (3 mL). The mixture was dried over $MgSO_4$, filtered, and concentrated. Alcohol **1a** was purified by distillation (60–61 °C/55 mmHg). Alcohols **5a–7a** were purified by silica gel column chromatography and distillation (**5a**: 71–72 °C/12 mmHg, **6a**: 75–77 °C/4 mm Hg, **7a**: 85 °C/3 mm Hg). Alcohol **10a** was purified by silica gel column chromatography.

*4.2.3.1. (±)-1-Chloro-2-propanol (**1a**)*[8]. 50% yield; colorless oil; ^{1}H NMR (200 MHz) δ 1.27 (d, J=6.4 Hz, 3H), 2.19 (d, J=4.6 Hz, 1H), 3.45 (dd, J=7.0, 11.0 Hz, 1H), 3.60 (dd, J=3.6, 11.0 Hz, 1H), 3.94–4.10

(m, 1H); ^{13}C NMR (50 MHz) δ 20.2, 51.4, 67.6; IR (neat) 3369, 2978, 2957, 1456, 1429, 1375 cm^{-1}.

*4.2.3.2. (±)-1-Chloro-2-hexanol (**5a**)*[18]. 86% yield; colorless oil; ^{1}H NMR (200 MHz) δ 0.91 (t, J=7.0 Hz, 3H), 1.24–1.62 (m, 6H), 2.14 (d, J=4.8 Hz, 1H), 3.48 (dd, J=7.3, 11.1 Hz, 1H), 3.65 (dd, J=3.3, 11.1 Hz, 1H), 3.74–3.89 (m, 1H); ^{13}C NMR (50 MHz) δ 13.9, 22.6, 27.7, 33.9, 50.5, 71.4; IR (neat) 3381, 2957, 2934, 2862, 1468, 1433, 1379 cm^{-1}.

*4.2.3.3. (±)-2-Chloro-1-cyclohexylethanol (**6a**)*[20]. 41% yield; colorless oil; ^{1}H NMR (200 MHz) δ 0.93–1.98 (m, 11H), 2.10 (d, J=4.6 Hz, 1H), 3.47–3.76 (m, 3H); ^{13}C NMR (50 MHz) δ 25.9, 26.0, 26.3, 28.3, 29.0, 41.3, 49.2, 75.6; IR (neat) 3391, 2926, 2853, 1450, 1435 cm^{-1}.

*4.2.3.4. (±)-2-Chloro-1-phenylethanol (**7a**)*[21]. 60% yield; colorless oil; ^{1}H NMR (200 MHz) δ 2.65 (d, J=3.0 Hz, 1H), 3.65 (dd, J=8.5, 11.3 Hz, 1H), 3.76 (dd, J=3.7, 11.3 Hz, 1H), 4.87–4.95 (m, 1H), 7.28–7.41 (m, 5H); ^{13}C NMR (50 MHz) δ 50.8, 74.0, 125.9, 128.3, 128.5, 139.8; IR (neat) 3391, 3063, 3031, 2955, 1495, 1454, 1427 cm^{-1}.

*4.2.3.5. (±)-Cyclohexylphenylmethanol (**10a**)*[22]. 93% yield; white solid; mp 49 °C (lit.[22] 46–48 °C); ^{1}H NMR (200 MHz) δ 0.84–1.48 (m, 6H), 1.54–1.86 (m, 5H), 1.96–2.02 (m, 1H), 4.37 (d, J=7.2 Hz, 1H), 7.24–7.42 (m, 5H); ^{13}C NMR (50 MHz) δ 26.0, 26.1, 26.4, 28.8, 29.3, 44.9, 79.3, 126.5, 127.3, 128.1, 143.5; IR (KBr) 3408, 3086, 3061, 3032, 2915, 2846, 1493, 1442, 1323 cm^{-1}.

4.2.4. General procedure for lipase-catalyzed kinetic resolutions. After a mixture of lipase (180 mg for lipase PS-C II, 80 mg for lipase LIP, or 120 mg for Chirazyme L-2) and alcohol (0.82 mmol) in dry *i*-Pr_2O (5 mL) or dry Et_2O (5 mL) had been stirred in a test tube with a rubber septum in a thermostat at 30 °C for 30 min, vinyl acetate (150 μL, 1.63 mmol) was added to start the reaction. The progress of the reaction for **4a**, **7a**, **9a**, and **10a** was monitored by TLC, and that for **1a**–**3a**, **5a**, **6a**, and **8a** was monitored by GC. For sluggish reactions, vinyl acetate (150 μL, 1.63 mmol) was added every two days. The reaction was stopped by filtration at an appropriate conversion. After the solvent had been removed under reduced pressure, alcohol and ester were separated by silica gel column chromatography. In Chirazyme L-2-catalyzed resolution of **6a** and **7a**, after removal of the lipase powder, unknown white precipitate probably originating from supporting material was formed, which was removed by centrifugation (3000 rpm, 5 min) before column chromatography. In the case of **1** and **2**, which are very volatile, the chromatographic fractions containing the products were found by GC, and the solvent was not removed completely because of volatility. In the case of **4a** and **7a**, the enantiomeric purities of both alcohol and acetate were determined by chiral GC with a CP-cyclodextrin-β-2,3,6-M-19 column (Varian, φ 0.25 mm×25 m). In the case of **1a**–**3a**, **5a**, and **6a**, the alcohol was converted to the corresponding acetate to determine the enantiomeric purities by means of chiral GC. In the case of **8a**–**10a**, the ester was converted to the corresponding alcohol to determine the enantiomeric purity. That of **8a** was then determined by chiral GC, and those of **9a** and **10a** were determined by HPLC using Chiralcel OB-H and Chiralpak AS-H columns (Daicel Chemical Industries), respectively. The absolute configurations of optically active **2b**, **3a**–**5a**, and **7a**–**10a** were determined by comparing the sign of their specific rotations with that of the reported specific rotations. The absolute configurations of optically active **1a** and **6a** were determined after conversion to the corresponding MTPA esters.

*4.2.4.1. Kinetic resolution of 1-chloro-2-propanol (**1a**).* GC for monitoring the reaction: PEG-20 M (3 m), Inj. 250 °C, Col. 100 °C, Det. 220 °C, **1b** 6.2 min, **1a** 6.7 min. Reaction time 7 min. (*S*)-**1a**: 43.2% ee. (*R*)-**1b**: 75.0% ee; GC: CP-cyclodextrin-β-2,3,6-M-19, Inj. 250 °C, Col. 70 °C, Det. 220 °C, (*S*) 11.5 min, (*R*) 12.3 min.

*4.2.4.2. Kinetic resolution of 2-hexanol (**2a**).* GC for monitoring the reaction: PEG-20 M (3 m), Inj. 250 °C, Col. 100 °C, Det. 220 °C, **2b** 3.9 min, **2a** 4.6 min. Reaction time 6 min. (*S*)-**2a**: 88.4% ee. (*R*)-**2b**: 16% yield; colorless oil; 99.7% ee; $[\alpha]^{27}_D$=−6.8 (*c* 0.82, $CHCl_3$); lit.[9] $[\alpha]^{20}_D$=+4.8 (*c* 1, $CHCl_3$) for (*S*)-**2b** with 99% ee; ^{1}H NMR (200 MHz) δ 0.89 (t, J=6.6 Hz, 3H), 1.20 (d, J=6.2 Hz, 3H), 1.20–1.40 (m, 4H), 1.40–1.64 (m, 2H), 2.03 (s, 3H), 4.89 (sext, J=6.2 Hz, 1H); ^{13}C NMR (50 MHz) δ 14.0, 20.0, 21.4, 22.6, 27.6, 35.6, 71.1, 170.7; IR (neat) 2959, 2936, 2862, 1740, 1456, 1371, 1244 cm^{-1}; GC: CP-cyclodextrin-β-2,3,6-M-19, Inj. 250 °C, Col. 80 °C, Det. 220 °C, (*S*) 7.7 min, (*R*) 8.7 min.

*4.2.4.3. Kinetic resolution of 1-cyclohexylethanol (**3a**).* GC for monitoring the reaction: PEG-20 M (3 m), Inj. 250 °C, Col. 120 °C, Det. 220 °C, **3b** 8.1 min, **3a** 9.5 min. Reaction time 20 min. (*S*)-**3a**: 52% yield; colorless oil; 81.0% ee; $[\alpha]^{29}_D$=+2.90 (*c* 1.00, $CHCl_3$); lit.[23] $[\alpha]_D$=−3.3 (*c* 0.4, $CHCl_3$) for (*R*)-**3a** with 80% ee; ^{1}H NMR (200 MHz) δ 0.90–1.39 (m, 10H), 1.62–1.93 (m, 5H), 3.55 (quint, J=6.2 Hz, 1H). (*R*)-**3b**: 43% yield; Colorless oil; 97.0% ee; $[\alpha]^{29}_D$=+7.45 (*c* 1.02, $CHCl_3$); ^{1}H NMR (200 MHz) δ 0.90–1.55 (m, 9H), 1.55–1.85 (m, 5H), 2.03 (s, 3H), 4.72 (quint, J=6.3 Hz, 1H); ^{13}C NMR (50 MHz) δ 17.1, 21.4, 26.0, 26.1, 26.4, 28.5, 42.6, 74.6, 170.7; IR (neat) 2980, 2928, 2855, 1736, 1450, 1371, 1248 cm^{-1}; GC: CP-cyclodextrin-β-2,3,6-M-19, Inj. 250 °C, Col. 100 °C, Det. 220 °C, (*S*) 21.0 min, (*R*) 23.4 min.

*4.2.4.4. Kinetic resolution of 1-phenylethanol (**4a**).* Reaction time 1.5 h. (*S*)-**4a**: 43% yield; colorless oil; 97.0% ee; $[\alpha]^{26}_D$=−55.1 (*c* 1.02, $CHCl_3$); lit.[24] $[\alpha]^{23}_D$=−43.7 (*c* 0.90, $CHCl_3$) for (*S*)-**4a** with 69% ee; ^{1}H NMR (200 MHz) δ 1.51 (d, J=6.4 Hz, 3H), 1.81 (br s, 1H), 4.85–4.94 (m, 1H), 7.26–7.42 (m, 5H); GC: CP-cyclodextrin-β-2,3,6-M-19, Inj. 250 °C, Col. 100 °C, Det. 220 °C, (*R*) 24.6 min, (*S*) 26.1 min. (*R*)-**4b**: 41% yield; colorless oil; 99.9% ee; $[\alpha]^{25}_D$=+112 (*c* 1.00, $CHCl_3$); ^{1}H NMR (200 MHz) δ 1.54 (d, J=6.6 Hz, 3H), 2.07 (s, 3H), 5.88 (q, J=6.6 Hz, 1H), 7.26–7.40 (m, 5H); ^{13}C NMR (50 MHz) δ 21.4, 22.2, 72.3, 126.0, 127.8, 128.4, 141.6, 170.2; IR (neat) 3065, 3033, 2982, 2934, 1732, 1495, 1456, 1371, 1240 cm^{-1}; GC: CP-cyclodextrin-β-2,3,6-M-19, Inj. 250 °C, Col. 100 °C, Det. 220 °C, (*S*) 21.6 min, (*R*) 23.6 min.

*4.2.4.5. Kinetic resolution of 1-chloro-2-hexanol (**5a**).* GC for monitoring the reaction: PEG-20 M (3 m), Inj. 250 °C, Col. 120 °C, Det. 220 °C, **5b** 8.7 min, **5a** 10.4 min. Reaction time 35 min. (*R*)-**5a**: 44% yield; 4.2% ee; $[\alpha]^{13}_D$=−0.19 (*c* 1.03, $CHCl_3$); lit.[25] $[\alpha]_D$=−1.1 (*c* 2.0, $CHCl_3$) for (*R*)-**5a** with 80% ee. (*S*)-**5b**: 24% yield; colorless oil; 6.7% ee; $[\alpha]^{13}_D$=−1.33 (*c* 1.05, $CHCl_3$); ^{1}H NMR (200 MHz) δ 0.90 (t, J=6.6 Hz, 3H), 1.23–1.46 (m, 4H), 1.60–1.74 (m, 2H), 2.09 (s, 3H), 3.55 (dd, J=5.4, 11.7 Hz, 1H), 3.64 (dd, J=4.6, 11.7 Hz, 1H), 4.96–5.10 (m, 1H); ^{13}C NMR (50 MHz) δ 13.9, 21.0, 22.4, 27.2, 31.2, 45.7, 72.8, 170.4; IR (neat) 2959, 2934, 2862, 1747, 1468, 1435, 1373, 1236 cm^{-1}; GC: CP-cyclodextrin-β-2,3,6-M-19, Inj. 250 °C, Col. 80 °C, Det. 220 °C, (*R*) 39.2 min, (*S*) 44.5 min.

*4.2.4.6. Kinetic resolution of 2-chloro-1-cyclohexylethanol (**6a**).* GC for monitoring the reaction: PEG-20 M (3 m), Inj. 300 °C, Col. 145 °C, Det. 220 °C, **6b** 15.7 min, **6a** 17.2 min. Reaction time 1.5 h. (*R*)-**6a**: 44% yield; 62.7% ee; $[\alpha]^{30}_D$=−6.70 (*c* 1.00, $CHCl_3$). (*S*)-**6b**: 38% yield; colorless oil; 92.3% ee; $[\alpha]^{30}_D$=−0.50 (*c* 1.01, $CHCl_3$); ^{1}H NMR (200 MHz) δ 0.90–1.40 (m, 6H), 1.62–1.84 (m, 5H), 2.10 (s, 3H), 3.60 (dd, J=5.7, 11.9 Hz, 1H), 3.69 (dd, J=4.1, 11.9 Hz, 1H), 4.83–4.93 (m, 1H); ^{13}C NMR (50 MHz) δ 20.9, 25.7, 25.8, 26.1, 28.1, 28.7, 38.8, 44.3, 76.4, 170.5; IR (neat) 2929, 2854, 1734, 1451, 1371, 1228 cm^{-1}; Anal. Calcd for $C_{10}H_{17}O_2Cl$: C, 58.68; H, 8.37. Found: C,

58.59; H, 8.17. GC: CP-cyclodextrin-β-2,3,6-M-19, Inj. 300 °C, Col. 120 °C, Det. 220 °C, (*R*) 33.5 min, (*S*) 35.4 min.

*4.2.4.7. Kinetic resolution of 2-chloro-1-phenylethanol (**7a**).* Reaction time 2.5 h. (*R*)-**7a**: 50% yield; 86.6% ee; $[\alpha]^{14}_{D}=-50.4$ (*c* 1.01, $CHCl_3$); lit.[21] $[\alpha]^{25}_{D}=-56.2$ (*c* 1.1, $CHCl_3$) for (*R*)-**7a** with >99% ee; GC: CP-cyclodextrin-β-2,3,6-M-19, Inj. 250 °C, Col. 120 °C, Det. 220 °C, (*S*) 47.6 min, (*R*) 50.3 min. (*S*)-**7b**: 43% yield; colorless oil; 99.2% ee; $[\alpha]^{14}_{D}=+82.8$ (*c* 1.01, $CHCl_3$); ^{1}H NMR (200 MHz) δ 2.15 (s, 3H), 3.72 (dd, *J*=4.8, 11.5 Hz, 1H), 3.80 (dd, *J*=7.8, 11.5 Hz, 1H), 5.96 (dd, *J*=4.8, 7.8 Hz, 1H), 7.30–7.43 (m, 5H); ^{13}C NMR (50 MHz) δ 21.0, 46.5, 75.0, 126.5, 128.6, 128.7, 137.0, 169.8; IR (neat) 3065, 3034, 2961, 1747, 1495, 1456, 1429, 1373, 1229 cm^{-1}; GC: CP-cyclodextrin-β-2,3,6-M-19, Inj. 250 °C, Col. 130 °C, Det. 220 °C, (*R*) 25.8 min, (*S*) 26.8 min.

*4.2.4.8. Kinetic resolution of 1-cyclohexyl-1-pentanol (**8a**).* GC for monitoring the reaction: PEG-20 M (3 m), Inj. 300 °C, Col. 145 °C, Det. 220 °C, **8b** 10.5 min, **8a** 12.9 min. Reaction time 17 h. (*S*)-**8a**: 56% yield; colorless oil; 15.0% ee; $[\alpha]^{26}_{D}=-2.87$ (*c* 1.01, MeOH); lit.[26] $[\alpha]_{D}=-10.2$ (*c* 1.0, MeOH) for (*S*)-**8a** with 62% ee; ^{1}H NMR (200 MHz) δ 0.91 (t, *J*=6.7 Hz, 3H), 1.02–1.90 (m, 18H), 3.30–3.42 (m, 1H); GC: CP-cyclodextrin-β-2,3,6-M-19, Inj. 300 °C, Col. 105 °C, Det. 220 °C, (*S*) 62.3 min, (*R*) 64.5 min. (*R*)-**8b**: 37% yield; colorless oil; 24.6% ee; $[\alpha]^{26}_{D}=+6.73$ (*c* 1.04, MeOH); ^{1}H NMR (200 MHz) δ 0.88 (t, *J*=6.8 Hz, 3H), 0.91–1.81 (m, 17H), 2.05 (s, 3H), 4.73 (q, *J*=6.6 Hz, 1H); ^{13}C NMR (50 MHz) δ 14.0, 21.1, 22.6, 26.1, 26.4, 27.6, 28.1, 29.0, 30.8, 41.2, 77.9, 170.8; IR (neat) 2929, 2855, 1732, 1450, 1370, 1243 cm^{-1}.

*4.2.4.9. Kinetic resolution of 1-phenyl-1-pentanol (**9a**).* Reaction time 34 h. (*S*)-**9a**: 53% yield; colorless oil; 75.7% ee; $[\alpha]^{23}_{D}=-33.3$ (*c* 1.03, $CHCl_3$); lit.[24] $[\alpha]^{24}_{D}=-39.3$ (*c* 0.57, $CHCl_3$) for (*S*)-**9a** with 92% ee; ^{1}H NMR (200 MHz) δ 0.89 (t, *J*=6.8 Hz, 3H), 1.20–1.52 (m, 4H), 1.65–1.90 (m, 3H), 4.67 (t, *J*=6.6 Hz, 1H), 7.28–7.40 (m, 5H); HPLC: Chiralcel OB-H, hexane/*i*-PrOH=20:1, flow rate 0.5 mL/min, detection 254 nm, (*S*) 15.5 min, (*R*) 18.1 min. (*R*)-**9b**: 45% yield; colorless oil; 90.1% ee; $[\alpha]^{23}_{D}=+76.7$ (*c* 1.01, $CHCl_3$); ^{1}H NMR (200 MHz) δ 0.87 (t, *J*=6.7 Hz, 3H), 1.14–1.42 (m, 4H), 1.66–2.00 (m, 2H), 2.07 (s, 3H), 5.72 (t, *J*=7.0 Hz, 1H), 7.26–7.40 (m, 5H); ^{13}C NMR (50 MHz) δ 13.9, 21.3, 22.4, 27.6, 36.0, 76.1, 126.4, 127.7, 128.3, 140.7, 170.2; IR (neat) 3065, 3034, 2957, 2934, 2862, 1736, 1495, 1456, 1371, 1240 cm^{-1}.

*4.2.4.10. Kinetic resolution of cyclohexylphenylmethanol (**10a**).* Reaction time 91 h. (*S*)-**10a**: 55% yield; 59.4% ee; $[\alpha]^{31}_{D}=-22.5$ (*c* 1.00, Et_2O); lit.[27] $[\alpha]^{25}_{D}=-36.0$ (*c* 2.25, Et_2O) for (*S*)-**10a** with 80% ee; HPLC: Chiralpak AS-H, hexane/*i*-PrOH=20:1, flow rate 0.5 mL/min, detection 254 nm, (*R*) 13.9 min, (*S*) 15.6 min. (*R*)-**10b**: 37% yield; colorless oil; 92.6% ee; $[\alpha]^{32}_{D}=+58.4$ (*c* 1.01, Et_2O); ^{1}H NMR (200 MHz) δ 0.82–1.46 (m, 6H), 1.58–1.93 (m, 5H), 2.06 (s, 3H), 5.48 (d, *J*=8.0 Hz, 1H), 7.25–7.38 (m, 5H); ^{13}C NMR (50 MHz) δ 21.2, 25.8, 26.3, 29.0, 42.9, 80.2, 127.1, 127.6, 128.1, 139.6, 170.3; IR (neat) 3031, 2928, 2852, 1729, 1370, 1237 cm^{-1}.

4.2.5. Typical procedure for the acetylation of alcohol. To a mixture of alcohol (0.15 mmol) and DMAP (22 mg, 0.18 mmol) in dry Et_2O (1 mL) was added acetic anhydride (60 μL, 0.63 mmol) under N_2. The mixture was stirred at room temperature for a few hours and then acidified with 3% HCl. The product was extracted with Et_2O (1 mL×3), and the solution was neutralized with saturated aqueous $NaHCO_3$ (1 mL). The mixture was dried over Na_2SO_4, filtered, and concentrated. The product was purified by silica gel column chromatography.

4.2.6. Typical procedure for the hydrolysis of acetate. To a solution of acetate (0.20 mmol) in EtOH (1 mL) was added 1.0 M aqueous NaOH (1 mL). The mixture was stirred at room temperature overnight and then acidified with 3% HCl. After the solvent had been removed under reduced pressure, the product was extracted with Et_2O (1 mL×3), and the solution was neutralized with saturated aqueous $NaHCO_3$ (1 mL). The mixture was dried over Na_2SO_4, filtered, and concentrated. The product was purified by silica gel column chromatography.

*4.2.7. Typical procedure for the synthesis of MTPA ester of alcohols **1a** and **6a**.* To a mixture of alcohol (0.05 mmol), DMAP (7.6 mg, 0.062 mmol), and pyridine (0.1 mL, 1.2 mmol) in dry toluene (0.5 mL) was added (*S*)-MTPA-Cl (28 μL, 0.15 mmol, acyl chloride of (*R*)-MTPA) under N_2. After the mixture had been stirred at room temperature overnight, water (1 mL) was added. The product was extracted with EtOAc (1 mL×4). The mixture was washed with 10% HCl, and then neutralized with saturated aqueous $NaHCO_3$ (1 mL). The mixture was dried over Na_2SO_4, filtered, and concentrated. The product was purified by silica gel column chromatography.

4.3. Oxazaborolidine-catalyzed reduction

4.3.1. Materials and methods. Ketones **11a** and **21a** were prepared by the Swern oxidation of the corresponding alcohols commercially available. Ketones **17a**,[28] **18a**,[28] **20a**,[29] and **23a**[30] were prepared by the Grignard reaction according to the literature, followed by the Swern oxidation. Ketones **12a**–**16a**, **19a**, **22a**, **24a**, and **25a** were purchased. All the liquid ketones were purified by distillation before use in the oxazaborolidine-catalyzed reactions. All alcohols and ketones **11a**,[31] **17a**,[32] **18a**,[33] **20a**,[34] **21a**,[35] and **23a**[30] were characterized according to the literature.

4.3.2. Typical procedure for the Swern oxidation of alcohols. DMSO (0.84 mL, 12 mmol) was added dropwise to a stirred solution of oxalyl chloride (0.6 mL, 7.0 mmol) in dry CH_2Cl_2 (60 mL) at −78 °C under N_2. After 5 min, alcohol (5.9 mmol) was added to the reaction mixture, and stirring was continued for 30 min. Et_3N (3.2 mL, 23 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature. After 30 min, water was added to the reaction mixture. The solution was acidified (pH 3) and the product was extracted with CH_2Cl_2 three times. The combined organic layers were washed with brine and dried over $MgSO_4$. The product was purified by silica gel column chromatography.

*4.3.2.1. Phenylacetone (**11a**)[31].* 77% yield; colorless oil; ^{1}H NMR (300 MHz) δ 2.16 (s, 3H), 3.70 (s, 2H), 7.19–7.23 (m, 2H), 7.25–7.37 (m, 3H).

*4.3.2.2. 1,4-Diphenyl-2-butanone (**17a**)[32].* 55% yield; white solid; mp 44–46 °C; ^{1}H NMR (500 MHz) δ 2.77 (t, *J*=7.8 Hz, 2H), 2.87 (t, *J*=7.8 Hz, 2H), 3.67 (s, 2H), 7.12–7.20 (m, 5H), 7.24–7.33 (m, 5H).

*4.3.2.3. Benzyl cyclohexyl ketone (**18a**)[33].* 44% yield; colorless oil; ^{1}H NMR (500 MHz) δ 1.17–1.40 (m, 5H), 1.64–1.84 (m, 5H), 2.46 (tt, *J*=3.5, 11.5 Hz, 1H), 3.73 (s, 2H), 7.17–7.33 (m, 5H).

*4.3.2.4. 1-Phenyl-3-heptanone (**20a**)[34].* 62% yield; colorless oil; ^{1}H NMR (200 MHz) δ 0.88 (t, *J*=7.2 Hz, 3H), 1.28 (sext, *J*=7.2 Hz, 2H), 1.53 (quint, *J*=7.2 Hz, 2H), 2.38 (t, *J*=7.2 Hz, 2H), 2.68–2.76 (m, 2H), 2.86–2.94 (m, 2H), 7.16–7.32 (m, 5H).

*4.3.2.5. n-Butyl cyclohexyl ketone (**21a**)[35].* 88% yield; colorless oil; ^{1}H NMR (200 MHz) δ 0.89 (t, *J*=7.1 Hz, 3H), 1.20–1.84 (m, 14H), 2.31–2.33 (m, 1H), 2.42 (t, *J*=7.3 Hz, 2H).

*4.3.2.6. 1-Cyclohexyl-3-phenyl-1-propanone (**23a**)*[30]. 91% yield; colorless oil; ^{1}H NMR (500 MHz) δ 1.15–1.36 (m, 5H), 1.64–1.82 (m, 5H), 2.28–2.34 (m, 1H), 2.75 (t, J=7.6 Hz, 2H), 2.88 (t, J=7.6 Hz, 2H), 7.17–7.20 (m, 3H), 7.26–7.29 (m, 2H).

4.3.3. General procedure for the asymmetric reduction of ketones. A 20 mL Schlenk tube was charged with (*S*)-α,α-diphenyl-2-pyrrolidinemethanol (55.5 mg, 0.22 mmol) and dry toluene (2 mL) under Ar. The suspended solution was heated at 50 °C to afford a colorless solution, which was cooled to room temperature. To the solution was added trimethylboroxine (20 μL, 0.14 mmol). After the solution had been stirred at room temperature for 2 h, the solution was concentrated to 1 mL by distillation. To the reaction mixture was added dry toluene (1 mL), and then the solution was concentrated to 1 mL again. After this cycle had been repeated three times, the remaining toluene was removed in vacuo to give (*S*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine as a colorless solid: ^{1}H NMR (500 MHz) δ 0.42 (s, 3H), 0.82–0.90 (m, 1H), 1.61–1.67 (m, 1H), 1.77–1.84 (m, 2H), 3.05–3.10 (m, 1H), 3.36–3.41 (m, 1H), 4.39 (dd, J=6.0, 9.5 Hz, 1H), 7.22–7.39 (m, 8H), 7.57 (d, J=7.5 Hz, 2H).[7a] To a solution of oxazaborolidine in dry THF (2 mL) was added $H_3B\cdot SMe_2$ (57 μL, 0.6 mmol), and the solution was stirred at 30 °C for 15 min. A solution of ketone (1.0 mmol) in dry THF (1 mL) was added via a syringe pump over 2 h, and then the reaction mixture was stirred at 30 °C for 12–13 h. To the mixture was added MeOH (1.5 mL), and then the solvent was removed under reduced pressure. The product was purified by silica gel column chromatography. In the case of **12b** and **14b**, the alcohol was converted to the corresponding acetate to determine the enantiomeric purity. Enantiomeric excesses of **12b** (acetate form), **13b**, **14b** (acetate form), **15b**, and **21b** were determined by chiral GC, and those of **11b**, **16b**–**20b**, and **22b**–**25b** were determined by chiral HPLC. The absolute configurations of optically active **11b**–**15b**, **19b**, and **21b**–**25b** were determined by comparing the sign of their specific rotations with that of the reported values. The absolute configurations of optically active **16b**–**18b**, and **20b** were determined by retention times of HPLC as reported previously.

*4.3.3.1. Reduction of phenylacetone (**11a**).* Reaction time 12.5 h. (*R*)-**11b**: 76% yield; colorless oil; 50.7% ee; $[\alpha]^{28}_D$=−20.7 (*c* 1.08, $CHCl_3$); lit.[36] $[\alpha]^{27}_D$=+41.8 (*c* 2.15, $CHCl_3$) for (*S*)-**11b** with >95% ee; ^{1}H NMR (500 MHz) δ 1.25 (d, J=6.1 Hz, 3H), 1.51 (br s, 1H), 2.70 (dd, J=8.0, 13.5 Hz, 1H), 2.80 (dd, J=5.0, 13.5 Hz, 1H), 4.03 (sext, J=6.1 Hz, 1H), 7.20–7.26 (m, 3H), 7.31–7.33 (m, 2H); ^{13}C NMR (150 MHz) δ 22.6, 45.7, 68.8, 126.5, 128.6, 129.4, 138.6; IR (neat) 3364, 3063, 3024, 2970, 2932, 1605, 1497, 1450, 1373, 1312, 1196, 1111, 1080, 1065, 941, 841, 741, 702 cm^{-1}; HPLC: Chiralcel AD-H, hexane/*i*-PrOH=20:1, flow rate 0.3 mL/min, detection 254 nm, (*S*) 26.2 min, (*R*) 27.9 min.

*4.3.3.2. Reduction of 2-hexanone (**12a**).* Reaction time 13 h. (*R*)-**12b**: 77% yield; colorless oil; 64.5% ee; $[\alpha]^{20}_D$=−12.4 (*c* 1.09, $CHCl_3$); lit.[37] $[\alpha]^{25}_D$=+10.39 ($CHCl_3$) for (*S*)-**12b** with 96% ee; ^{1}H NMR (500 MHz) δ 0.91 (t, J=7.0 Hz, 3H), 1.19 (d, J=6.1 Hz, 3H), 1.18–1.46 (m, 7H), 3.79 (sext, J=6.1 Hz, 1H); ^{13}C NMR (125 MHz) δ 13.9, 22.6, 23.3, 27.9, 38.9, 67.9; IR (neat) 3348, 2963, 2932, 2862, 1458, 1373, 1327, 1146, 1111, 1053, 1018, 941, 841 cm^{-1}; *the corresponding acetate*: ^{1}H NMR (200 MHz) δ 0.89 (t, J=6.6 Hz, 3H), 1.20 (d, J=6.2 Hz, 3H), 1.20–1.40 (m, 4H), 1.40–1.64 (m, 2H), 2.03 (s, 3H), 4.89 (sext, J=6.2 Hz, 1H); GC: CP-cyclodextrin-β-2,3,6-M-19, Inj. 250 °C, Col. 85 °C, Det. 220 °C, (*S*) 6.36 min, (*R*) 7.16 min.

*4.3.3.3. Reduction of benzylacetone (**13a**).* Reaction time 12.5 h. (*R*)-**13b**: 46% yield; white solid; mp 49 °C; 67.7% ee; $[\alpha]^{25}_D$=−12.6 (*c* 0.532, $CHCl_3$); lit.[38] $[\alpha]^{15}_D$=−1.19 (*c* 1.13, $CHCl_3$) for (*R*)-**13b** with 6% ee; ^{1}H NMR (600 MHz) δ 1.24 (d, J=6.0 Hz, 3H), 1.34 (br s, 1H), 1.73–1.83 (m, 2H), 2.65–2.70 (m, 1H), 2.74–2.79 (m, 1H), 3.83 (sext, J=6.0 Hz, 1H), 7.18–7.21 (m, 3H), 7.28–7.30 (m, 2H); ^{13}C NMR (150 MHz) δ 23.6, 32.1, 40.8, 67.4, 125.8, 128.3, 142.0; IR (KBr) 3364, 3024, 2963, 2924, 2862, 1605, 1497, 1458, 1373, 1312, 1180, 1126, 1057, 957, 856, 748, 702 cm^{-1}; GC: CP-cyclodextrin-β-2,3,6-M-19, Inj. 300 °C, Col. 110 °C, Det. 220 °C, (*S*) 37.9 min, (*R*) 38.8 min.

*4.3.3.4. Reduction of cyclohexyl methyl ketone (**14a**).* Reaction time 13 h. (*R*)-**14b**: 36% yield; colorless oil; 72.6% ee; $[\alpha]^{26}_D$=−2.91 (*c* 0.515, $CHCl_3$); lit.[23] $[\alpha]_D$=−3.3 (*c* 0.4, $CHCl_3$) for (*R*)-**14b** with 80% ee; ^{1}H NMR (500 MHz) δ 0.93–1.05 (m, 2H), 1.16 (d, J=6.5 Hz, 3H), 1.17–1.31 (m, 5H), 1.65–1.84 (m, 5H), 3.54 (quint, J=6.5 Hz, 1H); ^{13}C NMR (125 MHz) δ 20.2, 26.1, 26.2, 26.4, 28.3, 28.6, 45.0, 72.0; IR (neat) 3364, 2970, 2924, 2851, 2669, 1447, 1373, 1312, 1265, 1188, 1126, 1088, 1061, 1042, 999, 937, 891, 833, 733 cm^{-1}; *the corresponding acetate*: ^{1}H NMR (500 MHz) δ 0.87–1.76 (m, 11H), 1.16 (d, J=6.5 Hz, 3H), 2.03 (s, 3H), 4.72 (quint, J=6.5 Hz, 1H); GC: CP-cyclodextrin-β-2,3,6-M-19, Inj. 250 °C, Col. 100 °C, Det. 220 °C, (*S*) 18.2 min, (*R*) 20.3 min.

*4.3.3.5. Reduction of acetophenone (**15a**).* Reaction time 13 h. (*R*)-**15b**: 58% yield; colorless oil; 98.0% ee; $[\alpha]^{26}_D$=+75.1 (*c* 1.05, $CHCl_3$); lit.[24] $[\alpha]^{23}_D$=−43.7 (*c* 0.90, $CHCl_3$) for (*S*)-**15b** with 69% ee; ^{1}H NMR (500 MHz) δ 1.51 (d, J=6.5 Hz, 3H), 1.80 (br s, 1H), 4.91 (q, J=6.5 Hz, 1H), 7.26–7.40 (m, 5H); ^{13}C NMR (125 MHz) δ 25.1, 70.4, 125.4, 127.4, 128.5, 145.8; IR (neat) 3364, 3086, 3063, 3021, 2970, 2924, 2878, 1952, 1882, 1805, 1605, 1489, 1450, 1366, 1304, 1204, 1080, 1011, 895, 764, 702 cm^{-1}; GC: CP-cyclodextrin-β-2,3,6-M-19, Inj. 250 °C, Col. 97 °C, Det. 220 °C, (*R*) 24.9 min, (*S*) 29.2 min.

*4.3.3.6. Reduction of 1-phenyl-2-hexanone (**16a**).* Reaction time 13 h. (*S*)-**16b**: 43% yield; colorless oil; 36.0% ee; $[\alpha]^{28}_D$=+6.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz) δ 0.92 (t, J=6.8 Hz, 3H), 1.30–1.57 (m, 7H), 2.65 (dd, J=8.3, 13.8 Hz, 1H), 2.84 (dd, J=4.3, 13.8 Hz, 1H), 3.81–3.85 (m, 1H), 7.21–7.26 (m, 3H), 7.30–7.33 (m, 2H); ^{13}C NMR (125 MHz) δ 14.0, 22.7, 27.9, 36.5, 44.0, 72.7, 126.4, 128.5, 129.4, 138.7; IR (neat) 3395, 3063, 3028, 2932, 2858, 1601, 1497, 1454, 1126, 1080, 1030, 745, 698 cm^{-1}; HPLC: Chiralcel OD-H, hexane/*i*-PrOH=99.5:0.5, flow rate 1.0 mL/min, detection 254 nm, (*S*) 12.2 min, (*R*) 15.8 min.[28]

*4.3.3.7. Reduction of 1,4-diphenyl-2-butanone (**17a**).* Reaction time 13 h. (*S*)-**17b**: 26% yield; white solid; mp 38–40 °C (lit.[28] 43–44 °C); 39.5% ee; $[\alpha]^{29}_D$=−8.3 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz) δ 1.51 (d, J=4.0 Hz, 1H), 1.82–1.89 (m, 2H), 2.67–2.75 (m, 2H), 2.83–2.88 (m, 2H), 3.83–3.87 (m, 1H), 7.17–7.33 (m, 10H); ^{13}C NMR (125 MHz) δ 32.1, 38.4, 44.1, 71.9, 125.8, 126.5, 128.37, 128.43, 128.6, 129.4, 138.3, 142.0; IR (KBr) 3302, 3063, 3025, 2928, 1601, 1497, 1454, 1084, 1030, 926, 856, 748, 698 cm^{-1}; HPLC: Chiralcel OD-H, hexane/*i*-PrOH=95:5, flow rate 1.0 mL/min, detection 254 nm, (*S*) 10.8 min, (*R*) 15.5 min.[28]

*4.3.3.8. Reduction of benzyl cyclohexyl ketone (**18a**).* Reaction time 13 h. (*R*)-**18b**: 61% yield; white solid; mp 58–60 °C (lit.[28] 55–57 °C); 55.9% ee; $[\alpha]^{28}_D$=+21.8 (*c* 0.73, $CHCl_3$); ^{1}H NMR (500 MHz) δ 1.06–1.31 (m, 5H), 1.40–1.46 (m, 2H), 1.68–1.93 (m, 5H), 2.60 (dd, J=9.4, 13.5 Hz, 1H), 2.89 (dd, J=3.5, 13.5 Hz, 1H), 3.57–3.60 (m, 1H), 7.22–7.33 (m, 5H); ^{13}C NMR (125 MHz) δ 26.1, 26.3, 26.5, 27.9, 29.3, 40.7, 43.1, 76.8, 126.2, 128.4, 129.3, 139.2; IR (KBr) 3317, 3028, 2928, 2889, 2855, 1493, 1447, 1404, 1339, 1292, 1188, 1084, 1061, 1034, 1003, 748, 698 cm^{-1}; HPLC: Chiralcel OD-H, hexane/*i*-PrOH=99.6:0.4, flow rate 1.0 mL/min, detection 254 nm, (*R*) 16.7 min, (*S*) 23.5 min.[28]

*4.3.3.9. Reduction of benzyl phenyl ketone (**19a**).* Reaction time 12.5 h. (*R*)-**19b**: 22% yield; white solid; mp 67–68 °C (lit.[28] 64–66 °C); 90.4% ee; $[\alpha]^{32}_D$=−51.6 (*c* 0.940, EtOH); lit.[39] $[\alpha]^{25}_D$=+54.8 (*c* 3.52, EtOH) for (*S*)-**19b** with 98% ee; ^{1}H NMR (500 MHz) δ 1.56 (br s, 1H), 2.99 (dd, J=8.5, 13.8 Hz, 1H), 3.05 (dd, J=5.0, 13.8 Hz, 1H), 4.91

(dd, J=5.0, 8.5 Hz, 1H), 7.20–7.36 (m, 10H); ^{13}C NMR (125 MHz) δ 46.0, 75.3, 125.9, 126.6, 127.6, 128.4, 128.5, 129.5, 138.0, 143.8; IR (KBr) 3333, 3024, 2916, 2862, 1497, 1454, 1072, 1022, 760, 745, 698 cm^{-1}; HPLC: Chiralcel OD-H, hexane/*i*-PrOH=9:1, flow rate 0.5 mL/min, detection 254 nm, (*R*) 17.0 min, (*S*) 19.4 min.

*4.3.3.10. Reduction of 1-phenyl-3-heptanone (**20a**).* Reaction time 13 h. (*R*)-**20b**: 68% yield; colorless oil; 5.2% ee; $[\alpha]^{34}_{D}=-1.53$ (*c* 1.05, $CHCl_3$); lit.[40] $[\alpha]^{25}_{D}=-11.6$ (*c* 3.9, $CHCl_3$) for (*R*)-**20b** with 97% ee; ^{1}H NMR (500 MHz) δ 0.91 (t, J=7.0 Hz, 3H), 1.26–1.52 (m, 6H), 1.54 (br s, 1H), 1.70–1.84 (m, 2H), 2.65–2.71 (m, 1H), 2.77–2.83 (m, 1H), 3.61–3.66 (m, 1H), 7.17–7.21 (m, 3H), 7.27–7.30 (m, 2H); ^{13}C NMR (125 MHz) δ 14.0, 22.7, 27.8, 32.0, 37.3, 39.1, 71.4, 125.7, 128.35, 128.37, 142.2; IR (neat) 3364, 3063, 3028, 2932, 2858, 1940, 1605, 1558, 1497, 1454, 1126, 1042, 999, 934, 903, 748, 698 cm^{-1}; HPLC: Chiralcel OD-H, hexane/*i*-PrOH=20:1, flow rate 0.5 mL/min, detection 254 nm, (*R*) 15.7 min, (*S*) 21.4 min.[40]

*4.3.3.11. Reduction of n-butyl cyclohexyl ketone (**21a**).* Reaction time 13 h. (*R*)-**21b**: 97% yield; colorless oil; 25.8% ee; $[\alpha]^{32}_{D}=+5.83$ (*c* 1.06, MeOH); lit.[26] $[\alpha]_{D}=-10.2$ (*c* 1.0, MeOH) for (*S*)-**21b** with 62% ee; ^{1}H NMR (500 MHz) δ 0.91 (t, J=7.0 Hz, 3H), 0.96–1.81 (m, 18H), 3.33–3.37 (m, 1H); ^{13}C NMR (125 MHz) δ 14.0, 22.8, 26.2, 26.4, 26.6, 27.7, 28.1, 29.3, 33.8, 43.6, 76.2; IR (neat) 3364, 2924, 2855, 1450, 895 cm^{-1}; GC: CP-cyclodextrin-β-2,3,6-M-19, Inj. 300 °C, Col. 105 °C, Det. 220 °C, (*S*) 59.1 min, (*R*) 60.9 min.

*4.3.3.12. Reduction of valerophenone (**22a**).* Reaction time 12.5 h. (*R*)-**22b**: 53% yield; colorless oil; 95.6% ee; $[\alpha]^{31}_{D}=+39.2$ (*c* 0.536, $CHCl_3$); lit.[24] $[\alpha]^{24}_{D}=-39.3$ (*c* 0.57, $CHCl_3$) for (*S*)-**22b** with 92% ee; ^{1}H NMR (500 MHz) δ 0.81 (t, J=7.3 Hz, 3H), 1.15–1.35 (m, 4H), 1.60–1.67 (m, 1H), 1.69–1.76 (m, 2H), 4.58 (t, J=6.8 Hz, 1H), 7.17–7.29 (m, 5H); ^{13}C NMR (125 MHz) δ 14.0, 22.6, 28.0, 38.8, 74.7, 125.9, 127.5, 128.4, 144.9; IR (neat) 3364, 3063, 3032, 2932, 2862, 1944, 1882, 1805, 1605, 1458, 1335, 1204, 1111, 1034, 910, 756, 702 cm^{-1}; HPLC: Chiralcel OB-H, hexane/*i*-PrOH=20:1, flow rate 0.3 mL/min, detection 254 nm, (*S*) 23.8 min, (*R*) 27.3 min.

*4.3.3.13. Reduction of 1-cyclohexyl-3-phenyl-1-propanone (**23a**).* Reaction time 13 h. (*R*)-**23b**: 34% yield; white solid; mp 75–77 °C (lit.[41] 96 °C, The discrepancy in the melting point may be due to the difference in the enantiomeric purity.); 9.3% ee; $[\alpha]^{32}_{D}=+5.89$ (*c* 1.04, $CHCl_3$); lit.[41] $[\alpha]^{20}_{D}=+28.7$ (*c* 0.91, $CHCl_3$) for (*R*)-**23b** with >95% ee; ^{1}H NMR (500 MHz) δ 0.98–1.28 (m, 5H), 1.31–1.38 (m, 2H), 1.65–1.83 (m, 7H), 2.62–2.68 (m, 1H), 2.81–2.87 (m, 1H), 3.39 (q, J=4.2 Hz, 1H), 7.17–7.22 (m, 3H), 7.27–7.30 (m, 2H); ^{13}C NMR (125 MHz) δ 26.2, 26.3, 26.5, 27.8, 29.1, 32.3, 35.9, 43.8, 75.6, 125.7, 128.3, 128.4, 142.4; IR (KBr) 3206, 3024, 2912, 2851, 1605, 1497, 1454, 1346, 1319, 1265, 1088, 1061, 1030, 961, 918, 891, 745, 694 cm^{-1}; HPLC: Chiralcel AD-H, hexane/*i*-PrOH=9:1, flow rate 0.5 mL/min, detection 254 nm, (*S*) 12.1 min, (*R*) 13.1 min.

*4.3.3.14. Reduction of 1,3-diphenyl-1-propanone (**24a**).* Reaction time 13 h. (*R*)-**24b**: 52% yield; white solid; mp 50 °C; 93.3% ee; $[\alpha]^{26}_{D}=+27.3$ (*c* 0.506, $CHCl_3$); lit.[38] $[\alpha]^{20}_{D}=+13.4$ (*c* 0.22, $CHCl_3$) for (*R*)-**24b** with 47% ee; ^{1}H NMR (600 MHz) δ 1.83 (br s, 1H), 2.01–2.07 (m, 1H), 2.11–2.17 (m, 1H), 2.65–2.70 (m, 1H), 2.73–2.78 (m, 1H), 4.70 (t, J=6.6 Hz, 1H), 7.17–7.36 (m, 10H); ^{13}C NMR (150 MHz) δ 32.0, 40.4, 73.8, 125.8, 125.9, 127.5, 128.3, 128.38, 128.43, 141.7, 144.5; IR (KBr) 3271, 3086, 3063, 3024, 2939, 2924, 2878, 2862, 1952, 1882, 1605, 1489, 1450, 1350, 1312, 1281, 1211, 1150, 1065, 1018, 1003, 934, 764, 733, 694 cm^{-1}; HPLC: Chiralcel OD-H, hexane/*i*-PrOH=95:5, flow rate 0.5 mL/min, detection 254 nm, (*S*) 16.1 min, (*R*) 18.2 min.

*4.3.3.15. Reduction of cyclohexyl phenyl ketone (**25a**).* Reaction time 13 h. (*S*)-**25b**: 74% yield; white solid; mp 62–65 °C (lit.[27] 66 °C); 59.3% ee; $[\alpha]^{29}_{D}=-16.4$ (*c* 1.04, Et_2O); lit.[27] $[\alpha]^{25}_{D}=-36.0$ (*c* 2.25, Et_2O) for (*S*)-**25b** with 80% ee; ^{1}H NMR (500 MHz) δ 0.90–1.27 (m, 5H), 1.36–1.40 (m, 1H), 1.58–1.68 (m, 3H), 1.75–1.80 (m, 2H), 1.97–2.00 (m, 1H), 4.37 (dd, J=3.3, 7.3 Hz, 1H), 7.25–7.35 (m, 5H); ^{13}C NMR (150 MHz) δ 25.96, 26.0, 26.4, 28.8, 29.2, 44.9, 79.3, 126.6, 127.4, 128.1, 143.6; IR (KBr) 3348, 2970, 2924, 2855, 1450, 1373, 1312, 1265, 1188, 1126, 1096, 1065, 1042, 941, 887 cm^{-1}; HPLC: Chiralcel OD-H, hexane/*i*-PrOH=9:1, flow rate 0.3 mL/min, detection 254 nm, (*S*) 18.2 min, (*R*) 20.3 min.

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Supplementary data

Detailed explanation of Eq. 1, detailed data for the lipase-catalyzed kinetic resolution, and a correlation plot for the hydrosilylation of ketones reported by other researchers.[42] The supplementary data associated with this article can be found in the on-line version at doi:10.1016/j.tet.2009.09.058.

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