Kinetic Resolution of Racemic 2-Substituted 3-Cyclopenten-1-ols by Lipase-Catalyzed Transesterifications: A Rational Strategy To Improve Enantioselectivity

Tadashi Ema,* Soichi Maeno, Yusuke Takaya, Takashi Sakai, and Masanori Utaka*

Department of Applied Chemistry, Faculty of Engineering, Okayama University, Tsushima, Okayama 700, Japan

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The effect of the acyl group of acylating agents on the enantioselectivity in the *Pseudomonas cepacia* lipase-catalyzed acylations of racemic alcohols has been studied. 2-[(*N*,*N*-Dimethylcarbamoyl)-methyl]-3-cyclopenten-1-ol (**1**) and 2-[2-(*tert*-butyldimethylsilyloxy)ethyl]-3-cyclopenten-1-ol (**4**) were resolved with a variety of enantioselectivities. In the case of alcohol **1**, the enantiomeric ratio (the *E* value) was increased by changing the acylating agent from vinyl acetate ($E = 30$) to vinyl butyrate ($E = 156$) and dropped substantially with longer acyl donors. With vinyl chloroacetate, the reaction rate was fast and the enantioselectivity was high ($E = 89$), whereas the resolution with vinyl trifluoroacetate resulted in a very poor enantioselectivity ($E = 4$). The bulky acylating agent, vinyl pivalate, gave a moderate enantioselectivity ($E = 15$). In the case of alcohol **4**, the enantioselectivities were excellent ($E > 142$) except vinyl pivalate ($E = 12$). It is indicated that the acyl group transiently attached at the active site of the lipase acts as a stereochemical controller. The solvent effect is also described briefly. A clear correlation was observed between the *E* values and the log *P* values of the organic solvents; the smaller the log *P* value of the solvent, the higher the *E* value.

Introduction

The kinetic resolution of racemic alcohols and amines catalyzed by hydrolases such as lipases and serine proteases has received considerable attention in recent years[1] and has been utilized in the chemoenzymatic syntheses of optically active natural products and pharmaceuticals. The hydrolases have been reported to exert a broad range of enantioselectivity. Hence, various methods of artificially improving the enantioselectivity in the hydrolase-catalyzed asymmetric reactions have been so far explored,[2−11] and they can be classified mainly into two groups according to the types of perturbations on an enzyme: the noncovalent and covalent bond-based strategies.

The choice of organic solvent (the solvent engineering),[1h,2] the effect of additives,[3] the imprinting method,[4] and others[5] belong to the former (noncovalent bond-based) strategy. Among them, the solvent engineering has become one of the most important methods, since Klibanov *et al*. have demonstrated that organic solvents have a marked effect on the enantioselectivity of enzymatic reactions.[2] The kinetic resolution with (immobilized) enzymes in a variety of organic solvents allows one to optimize the reaction conditions easily.[2,6] However, satisfactory improvement in the enantioselectivity is not necessarily attained by changing the solvent. Hence, other rational strategies to alter the thermodynamic stability of the enzyme−substrate complex and/or the transition state also need to be pursued.

The site-directed or residue-selective chemical modification methods[7] and the covalent immobilization[8] belong to the latter (covalent bond-based) strategy. The site-directed mutagenesis[9] can also be included in this category as a special case. A well-defined chemical structural change can be brought about in an enzyme by the site-directed chemical or mutagenetic modifications. Another covalent bond-based strategy is the *active-site-directed transient chemical modification* of an enzyme, which will be discussed in detail in this paper.

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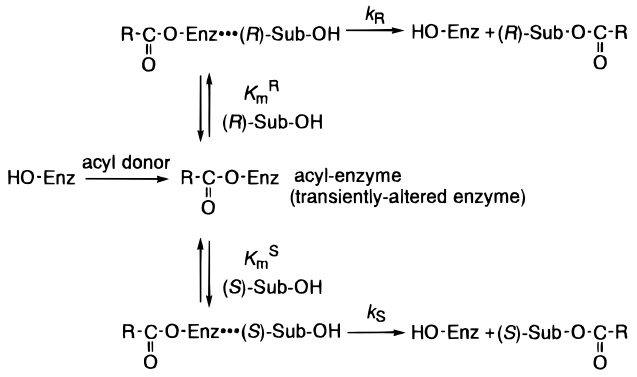
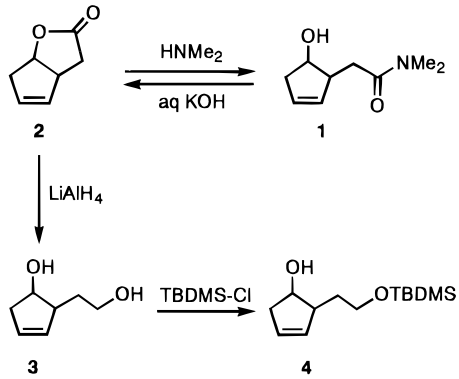
Scheme 1



Scheme 2



The fact that the hydrolase-catalyzed reactions proceed through the covalent intermediates such as the acyl-enzyme and the tetrahedral intermediates provides a clue to modulate the enantioselectivity. By changing the acyl group of acylating agents, a hydrolytic enzyme is transformed into a variety of acyl-enzyme intermediates in an organic solvent. Sih *et al.* have proposed that various acyl-enzyme intermediates thus produced *in situ*, whose active site structures differ from one another, can in principle exert various chiral discrimination abilities in the course of the enantioselective acylation of racemic alcohols.[1b] A simplified scheme is shown in Scheme 1, where R represents a variety of substituents (*vide infra*). Thus, *the acyl group directly incorporated into the active site of the hydrolase can act as a stereochemical controller*. Because the serine residue at the active site of the hydrolases can be easily acylated by using various kinds of acylating agents in organic solvents, the *transiently-altered* enzyme (the acyl-enzyme intermediate) optimal for an asymmetric acylation can be easily searched. There have been reported only several systematic studies to examine this concept,[1b,10,11] though this is an easier method to modify an enzyme (transiently *in situ*) compared with other covalent bond-based strategies. Much about the potential of this method evidently remains to be investigated. A combination of this methodology with the solvent engineering will help us realize a highly enantioselective kinetic resolutions of a wide range of racemic alcohols.

Lipases (EC 3.1.1.3) have recently been attracting great interest because of their (1) broad substrate specificity, (2) good enantioselectivity, and (3) thermostability in organic solvents. Recently we have reported the lipase-catalyzed resolutions of 2-[(*N*,*N*-dimethylcarbamoyl)methyl]-3-cyclopenten-1-ol (**1**).[12,13] In this paper, we report in detail the effect of the acyl group of acylating agents on the enantioselectivity in the lipase-catalyzed kinetic resolutions of racemic alcohols. Among various types of acyl donors, enol esters were used, because they are considered to be the most suitable for our investigation because of their high reactivity and irreversibility.[10,14]

Results and Discussion

Synthesis of Racemic Alcohols. (1*S*,5*R*)-2-Oxabicyclo[3.3.0]oct-6-en-3-one ((1*S*,5*R*)-**2**) is a well-known chiral building block for prostaglandins,[15] and the development of its efficient asymmetric synthetic method has been an important subject.[15b−f] For examination of the aforementioned strategy, it was necessary to convert the lactone **2** to an alcohol derivative. After several attempts, we found that the aminolysis of **2** with aq dimethylamine in THF gave alcohol **1** that is convertible back to **2** (Scheme 2).[12] We also examined another related alcohol derived from **2**, 2-[2-(*tert*-butyldimethylsilyloxy)ethyl]-3-cyclopenten-1-ol (**4**). Enantiomers (1*R*,5*S*)-**2** and (1*R*,2*S*)-**4** are chiral building blocks for natural products such as pseudomonic acids.[16]

Preparative Kinetic Resolutions. Effect of Acyl Donor on Enantioselectivity. We examined several vinyl esters in the kinetic resolutions of **1** using *Pseudomonas cepacia* lipase (Amano lipase PS) in diisopropyl ether (Scheme 3). The reactions were monitored by TLC and stopped by filtration at an appropriate conversion. Alcohol **1** and esters **5a**−**k** were separated by column chromatography, and their optical purities were determined by capillary gas chromatography after they were lactonized by saponification (Scheme 2). The enantioselectivities were compared on the basis of the enantiomeric ratios (*E* values) calculated according to the literature[17] and are shown in Table 1.

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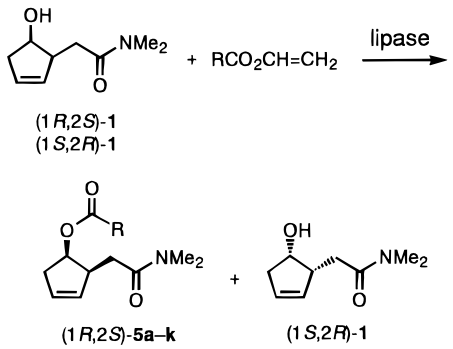
Scheme 3



Scheme 4

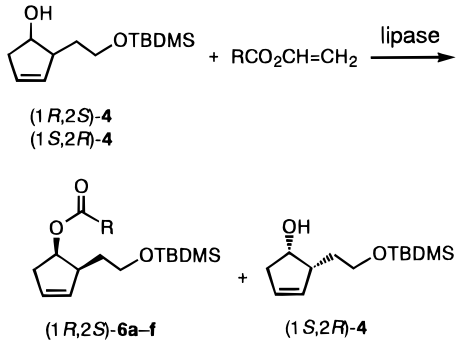


Table 1. Enantioselective Lipase-Catalyzed Acylation of Alcohol 1 with Various Acylating Agents ($RCO_2CH{=}CH_2$)[a]

			% yield[c] (% ee[d])		
vinyl ester (R)	time (h)	c (%)[b]	(1*R*,2*S*)-**5**	(1*S*,2*R*)-**1**	*E* value[e]
CH_3	3	50	**5a** 47 (84)	46 (83)	30
C_2H_5	3	42	**5b** 41 (95)	48 (69)	81
n-C_3H_7	3	45	**5c** 42 (97)	51 (78)	156
n-C_5H_{11}	3	51	**5d** 43 (70)	47 (72)	12
n-C_7H_{15}	2	55	**5e** 51 (70)	40 (86)	15
n-C_9H_{19}	1.5	49	**5f** 44 (89)	42 (84)	45
$ClCH_2$	0.5	51	**5g** 48 (92)	43 (95)	89
CF_3	0.75	20	**5h** 18 (52)	43 (13)	4
t-C_4H_9	48	24	**5i** 19 (84)	10[f] (27)	15
C_6H_5	48	14	**5j** 19 (89)	53[f] (15)	20
$CH_3CH{=}CH$	48	7	**5k** 12 (92)	16[f] (7)	26

[a] Conditions: lipase PS (400 mg), **1** (1.2 mmol), vinyl ester (2.4 mmol), dry (*i*-Pr)$_2$O (10 mL), 30 °C. [b] Conversion calculated from $c = 100 \times$ ee(**1**)/(ee(**1**) + ee(**5**)) according to ref 17. [c] Isolated yield. [d] Determined by capillary GC with Chrompack CP-cyclodextrin-β-2,3,6-M-19, after **1** and **5** were lactonized. [e] Calculated from $E = \ln\{1 - c(1 + \text{ee}(\mathbf{5}))\}/\ln\{1 - c(1 - \text{ee}(\mathbf{5}))\}$ according to ref 17. [f] Large amounts of lactone **2** were obtained due to the prolonged reaction time.

Table 2. Enantioselective Lipase-Catalyzed Acylation of Alcohol 4 with Various Acylating Agents ($RCO_2CH{=}CH_2$)[a]

			% yield[c] (% ee[d])		
vinyl ester (R)	time (h)	c (%)[b]	(1*R*,2*S*)-**6**	(1*S*,2*R*)-**4**	*E* value[e]
CH_3	2.5	44	**6a** 44 (>99)	52 (77)	>466
n-C_3H_7	6	47	**6b** 46 (98)	53 (87)	283
n-C_9H_{19}	9	40	**6c** 40 (>99)	58 (67)	>402
$ClCH_2$	1	50	**6d** 46 (>99)	50 (>99)	>1057
t-C_4H_9	48	–	**6e** 40 (–[f])	59 (52)	12[g]
C_6H_5	144	43	**6f** 40 (97)	55 (72)	142

[a] Conditions: lipase PS (200 mg), **4** (0.41 mmol), vinyl ester (0.82 mmol), dry (*i*-Pr)$_2$O (10 mL), 30 °C. [b] Conversion calculated from $c = 100 \times$ ee(**4**)/(ee(**4**) + ee(**6**)) according to ref 17. [c] Isolated yield. [d] Determined by ^{1}H NMR spectra, after **4** and **6** were converted to the MTPA ester. [e] Calculated from $E = \ln\{1 - c(1 + \text{ee}(\mathbf{6}))\}/\ln\{1 - c(1 - \text{ee}(\mathbf{6}))\}$ according to ref 17. [f] Not determined due to the tolerance of the pivalic ester for saponification. [g] Calculated from $E = \ln\{(1 - c)(1 - \text{ee}(\mathbf{4}))\}/\ln\{(1 - c)(1 + \text{ee}(\mathbf{4}))\}$ by using the % yield and % ee of the alcohol **4** recovered.

The racemic alcohol (±)-**1** was found to be resolved into the enantiomers with a variety of optical purities. It is interesting to note that a slight elongation of the alkyl chain of the vinyl esters caused dramatic changes in the enantioselectivity. The enantioselectivity was successfully improved by changing the acylating agent from vinyl acetate ($E = 30$) to vinyl butyrate ($E = 156$) and dropped substantially with longer acyl donors. The reaction time became shorter as the acyl donor was longer, because the rate of the acylation with longer vinyl ester was faster.[13] This trend can be ascribed to the inherently high affinity of the lipase toward the long-chain acyl group (natural substrates of lipases are triacyl glycerides of long-chain fatty acids) and indicates that the lipase in dry organic solvent retains its native molecular recognition property to some degree. We further investigated other types of vinyl esters (Table 1). With vinyl chloroacetate, the reaction rate was found to be fast and the enantioselectivity was excellent, which can be ascribed, respectively, to the electronegativity and to the size of the chlorine atom (*vide infra*). This trend is different from the results reported by Miyazawa *et al.* that the use of vinyl chloroacetate caused the inversion of the stereoselectivity.[10f] On the contrary, the resolution with vinyl trifluoroacetate resulted in a very poor enantioselectivity. This is partly because nonenzymatic reactions occurred dominantly.[18] The transesterification with the bulky acylating agent, vinyl pivalate, did proceed, although the reaction rate was very slow. This result presents a striking contrast to the fact that tertiary alcohols usually show no reactivity in the lipase-catalyzed (trans)esterifications. The enantioselectivity was moderate in this particular case, but the steric effect of the pivaloyl group may be effective for other substrates not examined. The reactions using vinyl benzoate and vinyl crotonate were very slow, probably because of the low reactivity of the conjugated esters, and the prolonged reaction time led to the spontaneous lactonization of **1**. It is interesting to note that the resolution using vinyl crotonate resulted in a drop in the *E* value as compared with that using vinyl butyrate, although both of them have the C4 chain lengths in the acyl moieties.

Next, we examined alcohol **4** in the lipase-mediated kinetic resolutions (Scheme 4). The enantioselectivities were excellent when linear acyl donors with various alkyl chain lengths were used (Table 2). The side chain (CH_2-CH_2OTBDMS) of **4** appears to be recognized by the lipase more strictly than that ($CH_2CON(CH_3)_2$) of alcohol **1**, and so the magnitudes of the perturbations caused by various alkyl chains of the linear vinyl esters against **4** are difficult to evaluate. On the other hand, vinyl pivalate altered the *E* value markedly. Severe steric repulsion seems to operate between the tertiary butyl group of vinyl pivalate and the TBDMS group of **4** in the course of the lipase-catalyzed transesterification, which can also be indirectly suggested by the fact that the pivalic ester **6e** obtained by the lipase-catalyzed reaction using vinyl pivalate could not be hydrolyzed at all by aq KOH in refluxing EtOH overnight. The transesterification with

(18) The acylation with vinyl trifluoroacetate in the absence of the lipase did proceed, and small amounts of trifluoroacetic acid generated *in situ* seemed to induce the lactonization of **1** during the reaction; isolated yield of **2** 27% (13% ee for (1*S*,5*R*)-form).

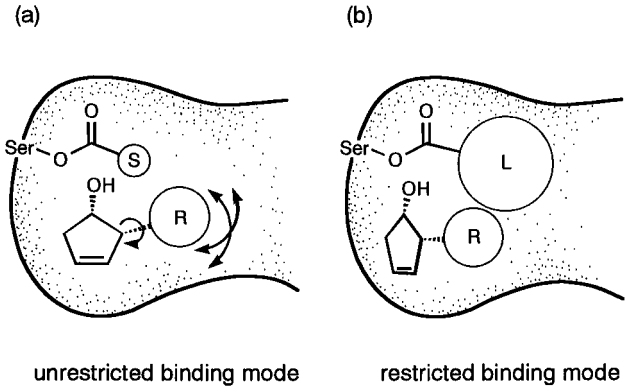


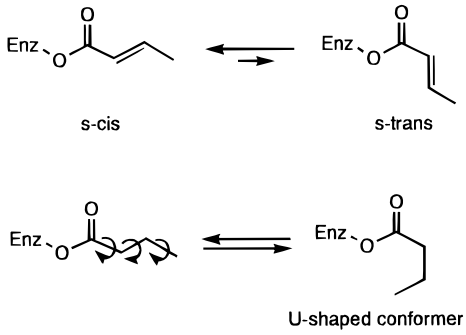
Figure 1. Schematic representations of the complex of the acyl-lipase intermediate with the substrate. A differential degree of additional spatial constraint (steric bias) imposed by the acyl moiety against the fast- and slow-reacting enantiomers in the Michaelis complex and/or in the subsequent transition state will influence the enantioselectivity. (a) The binding site of the lipase is not crowded, and the substrate can freely rotate, adopting a favorable conformation. (b) Both the orientation and conformation of the substrate are restricted by the spatial constraint caused by the large acyl group.

vinyl chloroacetate showed both the highest reactivity and the highest enantioselectivity ($E > 1057$) and resulted in a perfect resolution.

Thus, various acyl groups were adopted because of the high enzymatic activity of the lipase in diisopropyl ether; the total turnover number (TTN)[1e] is calculated to be *ca.* 5000 when the reaction was stopped at 50% conversion.[19] A wide variety of the enantioselectivities shown in Tables 1 and 2 demonstrates that the present strategy has a good potential to alter the enantioselectivity and indicates that the acyl group directly incorporated into the active site of the lipase acts as a stereochemical controller.[20]

Stereochemical Role of the Acyl Moiety in the Enantiomer-Differentiating Step. The enantioselectivity in the lipase-catalyzed transesterification results from the diastereomeric interaction in the acyl-lipase–substrate complex and/or in the following transition state (Scheme 1).[22] It is evident from the above results that not only the chiral binding site of the lipase itself but also the acyl moiety covalently linked to the active site of the lipase play an important role in the enantioselective acylation of **1** and **4**. Figure 1 shows schematic representations of the complex between the slow-reacting enantiomer of **1** (or **4**) and the acyl-lipase intermediate, where direct (attractive or repulsive[23]) interactions are assumed to occur between the acyl substituent of the intermediate and the substrate. A larger acyl moiety makes the binding cavity more crowded than a smaller acyl moiety does. A differential degree of such additional spatial constraint against the fast- and slow-reacting enantiomers in the Michaelis complex and/or in the subsequent transition state will influence the enantioselectivity.[24]

Scheme 5



Indeed, the results in Tables 1 and 2 indicate that such steric bias with respect to each enantiomer of **1** (or **4**) operates when the acyl donor was changed. For example, the steric hindrance of vinyl pivalate retarded the reaction of the fast-reacting enantiomer more than that of the slow-reacting enantiomer, leading to the dropped *E* values compared with those obtained by using vinyl acetate. This effect seems important especially for **4**, which is considered to experience severer spatial constraint than **1**, judging from the long reaction time and the large decrease in the *E* value. On the other hand, in the case of vinyl chloroacetate, the acylation of the fast-reacting enantiomer of **1** (or **4**) was accelerated by the electronegative chlorine atom, whereas the acylation of the slow-reacting enantiomer was suppressed by the increased steric hindrance in comparison with vinyl acetate, resulting in excellent enantioselectivities. Hence, we propose that the bulky and moderately activated vinyl esters such as vinyl chloroacetate may be good candidates to exert high enantioselectivities for a wide range of racemic alcohols. The fact that the reaction using vinyl crotonate resulted in a lower enantioselectivity than that using vinyl butyrate having the same chain length (C4) in the acyl moiety (Table 1) may suggest that the conformation of the acyl moiety in the acyl-lipase is important. As for the crotonate moiety, only two conformers (s-cis and s-trans) are possible, and the s-cis (less hindered) conformation may predominate in the acyl-lipase intermediate as shown in Scheme 5. On the other hand, the butyrate moiety can take many conformations, among which the U-shaped (more hindered) conformation could retard the acylation of the slow-reacting enantiomer of **1** more efficiently than the crotonate (s-cis) moiety (Scheme 5).

Solvent Effect. To investigate the usefulness of a combination of the present methodology with the solvent engineering,[10g] we examined various organic solvents for the lipase-catalyzed resolution of **1** using vinyl butyrate. As a result, we obtained higher *E* values in hydrophilic

(19) Lipase PS powder contains 1% (w/w) lipase in Celite, whose molecular weight is ca. 33000 (private communication with Dr. Y. Hirose). A kinetic measurement indicated that in the absence of the lipase the reaction rate was too slow to determine, and that the apparent rate-acceleration by the lipase catalysis in diisopropyl ether was at least $\gg 10^5$.

(20) Although the enantioselectivity was dramatically altered by changing the acyl donor, the stereochemical preference obeyed Kazlauskas's rule,[21] indicating that the stereochemistry is governed primarily by the size and shape of the binding pocket of the lipase.

(21) Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656.

(22) Fersht, A. *Enzyme Structure and Mechanism*, 2nd ed.; Freeman: New York, 1985; Chapters 3 and 13.

(23) It should be noted here that the present strategy is quite different from the enzymatic hydrolysis of racemic esters in water, where ester derivatives of a racemic alcohol with various acyl groups are examined; e.g. Ehrler, J.; Seebach, D. *Liebigs Ann. Chem.* **1990**, 379. By changing the solvent from water to organic solvents, attractive interactions such as hydrophobic interaction change to another types of interactions such as steric repulsion. Such transition of the intermolecular force will change the thermodynamic stability of the intermediates, and hence can potentially lead to a drastically altered enantioselectivity as compared with the reaction in water.

(24) This tactics was also found to be effective for the kinetic resolution of other types of racemic alcohols such as linear aliphatic alcohol.

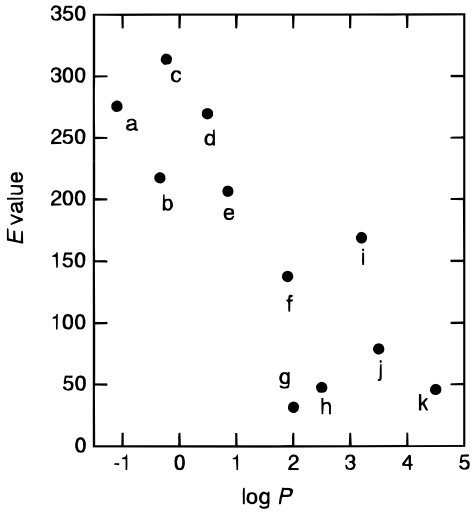


Figure 2. The correlation between the enantioselectivities (*E* values) in the *Pseudomonas cepacia* lipase-catalyzed acylations of the alcohol **1** and the log *P* values of the solvents. Conditions: lipase PS (400 mg), **1** (1.2 mmol), vinyl butyrate (2.4 mmol), dry organic solvent (10 mL), 30 °C. The log *P* values were taken from ref 25. Solvents (reaction time, conversion): (a) 1,4-dioxane (23 h, 47%), (b) acetonitrile (12 h, 43%), (c) acetone (9 h, 32%), (d) THF (7 h, 24%), (e) ether (6 h, 50%), (f) diisopropyl ether (5 h, 42%), (g) benzene (7 h, 25%), (h) toluene (7 h, 30%), (i) cyclohexane (2 h, 35%), (j) hexane (2 h, 33%), (k) isooctane (2 h, 49%). The log *P* value of isooctane was taken from that of octane.

solvents, and significantly, a clear correlation was observed between the *E* values and the log *P* values[25] of the solvents as shown in Figure 2; the smaller the log *P* value of the solvent, the higher the *E* value. Clear correlations between the *E* values and the log *P* values have been so far reported.[2,6] On the other hand, no correlation between the dielectric constants of the solvents and the *E* values was observed (not shown). The reaction rate was slow in hydrophilic solvents (log $P <$ 0.5).

Klibanov *et al.* have reported that the enantioselectivities in hydrolase-catalyzed reactions in various organic solvents correlate well with the solvent hydrophobicity[2a,d,e] (log *P*), or with the solvent polarity[2c] (the dielectric constant and the dipole moment). They have suggested that the former physicochemical parameter is related to the driving force of the binding, and the latter parameters are related to the steric constraint that stems from the rigidity of the enzyme. Applying their explanation to the present study, the rigidity of the lipase is not important for the enantioselectivity, whereas tight binding of the substrate in the hydrophobic pocket of the lipase occurs in hydrophilic solvents, leading to high enantioselectivity. Because hydrophilic solvents destabilize the lipase and lower its activity to some degree by disordering or stripping off the "essential water" from the lipase,[1b,25b] the organic solvents with moderate hydrophobicity such as ether and diisopropyl ether, where both the enantioselectivity of the reaction and the activity of the lipase are high, are optimal in this case.

Conclusions

Development of the strategies for effectively improving the enantioselectivity of the lipase-catalyzed kinetic resolution of racemic alcohols is an important subject. This paper presents that the effect of the acyl group of acylating agents on the enantioselectivity in the lipase-catalyzed acylations of racemic alcohols is large. By using this method, the versatile chiral building blocks, **1**, **2**, and **4**, have been successfully resolved into their enantiomers with high optical purities. The results strongly indicates that the acyl group transiently attached at the active center of the lipase participates in the alteration of the enantioselectivity as a stereochemical controller. The efficient conditions for the kinetic resolution of a racemic alcohol can be easily searched simply by changing the acyl group of the vinyl ester. The present method has been combined with the solvent engineering to effectively optimize the reaction conditions. It can also be potentially used even in the solvent-free system and in the supercritical carbon dioxide,[26] both of which are very important from the environmental as well as the economical viewpoints and may also be effective for controlling the regioselectivity in the acylation of polyols such as sugars.[27] The results in this paper will provide us with useful hints to develop new acylating agents in the future.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra measured in $CDCl_3$ at 200 and 50 MHz, respectively, are reported. Column chromatography was carried out using Nacalai silica gel 60 (70−230 mesh) or Fuji Silysia BW-127 ZH (100−270 mesh), and thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254}. Mass spectra were measured by Dr. S. Nakajima (Okayama University). Lactone **2** and diol **3** were prepared according to the literature.[15a] Lipase PS provided by Amano Pharmaceutical Co. was used without further purification. The dry organic solvents used in the lipase-catalyzed kinetic resolutions were prepared as follows. Hexane, cyclohexane, isooctane, toluene, ether, diisopropyl ether, THF, and 1,4-dioxane were distilled from sodium. Benzene was distilled from CaH_2, and acetone was dried over 4 Å molecular sieves. Anhydrous acetonitrile purchased from Wako Pure Chemical Industries was used without further purification.

(±)-2-[(*N*,*N*-Dimethylcarbamoyl)methyl]-3-cyclopenten-1-ol (1). To a solution of lactone **2** (2.00 g, 16.1 mmol) in THF (40 mL) was added slowly aq 50% dimethylamine solution (80 mL) at room temperature, and the reaction mixture was stirred for 4 h. The solution was cooled in an ice bath and adjusted to pH 7 by adding concd HCl slowly. The resulting solution was extracted with ethyl acetate (50 mL × 8), dried over $MgSO_4$, and then concentrated. The crude product was purified by column chromatography on silica gel (hexane/EtOAc (2:1)−(0:1)) to give alcohol **1** (1.80 g, 59%) as a colorless viscous oil. The product **1** was used without distillation to prevent lactonization and can be stored in a refrigerator at least for a week without lactonization: ^{1}H NMR δ 2.32−2.73 (m, 4H), 3.01 (m, 1H), 2.96 (s, 3H), 3.06 (s, 3H), 4.52−4.63 (m, 1H), 5.47−5.77 (m, 2H); ^{13}C NMR δ 31.7, 35.6, 37.7, 40.5, 46.5, 72.0, 129.3, 131.8, 173.7; IR (neat) 3406, 1626 cm^{-1}. For (1*S*,2*R*)-**1**: 95% ee after the lipase-catalyzed kinetic resolution; $[\alpha]^{27}_D = -24.2$ (*c* 1.12, $CHCl_3$).

(±)-2-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-3-cyclopenten-1-ol (4). To a solution of diol **3** (1.00 g, 7.8 mmol) and imidazole (1.29 g, 19.0 mmol) in dry THF (20 mL) was slowly added dropwise a solution of *t*-$BuMe_2SiCl$ (1.14 g, 7.6 mmol) in dry THF (10 mL) in an ice bath. The reaction mixture was stirred in an ice bath for 1 h and then stirred at room temperature for 19 h. After the reaction was quenched with H_2O (2 mL), the resulting solution was extracted with ethyl

(25) The parameter *P* represents the partition coefficient of a solvent between 1-octanol and water. (a) Leo, A.; Hansch, C.; Elkins, D. *Chem. Rev.* **1971**, *71*, 525. (b) Laane, C.; Boeren, S.; Vos, K.; Veeger, C. *Biotechnol. Bioeng.* **1987**, *30*, 81.

(26) Nakamura, K. *Trends Biotechnol.* **1990**, *8*, 288.

(27) Panza, L.; Brasca, S.; Riva, S.; Russo, G. *Tetrahedron: Asymmetry* **1993**, *4*, 931.

acetate, dried over $MgSO_4$, and then concentrated. The residue was purified by column chromatography on silica gel (hexane/EtOAc (10:1)) to give alcohol **4** (1.25 g, 66%) as a colorless viscous oil: ^{1}H NMR δ 0.09 (s, 6H), 0.91 (s, 9H), 1.69−2.02 (m, 2H), 2.29−2.45 (m, 1H), 2.56−2.77 (m, 2H), 3.55 (br s, 1H), 3.65 (dt, J = 9.8, 3.0 Hz, 1H), 3.77−3.90 (m, 1H), 4.44 (t, J = 6.1 Hz, 1H), 5.45−5.78 (m, 2H); ^{13}C NMR δ −5.6, 18.2, 25.8, 30.4, 41.6, 50.6, 63.2, 71.6, 128.4, 132.9; IR (neat) 3435 cm^{-1}. For (1*S*,2*R*)-**4**: >98% ee after the lipase-catalyzed kinetic resolution; $[\alpha]^{23}_D$ = −48.9 (*c* 1.10, $CHCl_3$).

General Procedure for the Preparative Kinetic Resolutions. A heterogeneous solution of lipase PS (400 mg), **1** (200 mg, 1.18 mmol), and vinyl ester (2.36 mmol) in dry organic solvent (10 mL) were 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 stopped by filtration at an appropriate conversion (typically 40−50%). Alcohol **1** and esters **5a**−**k** were separated by column chromatography (SiO_2, hexane/EtOAc (2:1)−(0:1)). The reaction conditions for **4** were similar to those for **1**: lipase PS (200 mg), **4** (100 mg, 0.41 mmol), vinyl ester (0.82 mmol), dry diisopropyl ether (10 mL).

Determination of the Optical Purity and the Absolute Configuration. A solution of the optically active alcohol **1** (or esters **5a**−**k**) (0.15 mmol) in 1 N aq KOH (3 mL)/MeOH (0.2 mL) was stirred at room temperature overnight and then adjusted to pH 7 by adding 10% HCl. The resulting solution was extracted with ethyl acetate (1 mL × 3), dried over $MgSO_4$, and concentrated to give lactone **2** (89−100%). The optical purity of **2** was determined by capillary gas chromatography fitted with Chrompack CP-cyclodextrin-β-2,3,6-M-19 column (injection temperature, 250 °C; column temperature, 120 °C; carrier gas, He). The optical purities of **4** and **6a**−**f** except **6e** were determined by conversion to the corresponding MTPA ester.[28] The signals of an allyl proton (2.32−2.47 ppm) were integrated. Both of the absolute configurations of alcohols **1** and **4** obtained in the lipase-catalyzed resolutions were determined to be (1*S*,2*R*) by comparison with the signs of the reported optical rotations after the optically active alcohols **1** and **4** were converted to lactone **2** with >99% ee ($[\alpha]^{26}_D$ = −109 (*c* 1.34, MeOH), lit.[15b] $[\alpha]^{25}_D$ = −106 (*c* 1.00, MeOH) for (1*S*,5*R*)-**2**) and diol **3** with >99% ee ($[\alpha]^{26}_D$ = −62 (*c* 1.02, MeOH), lit.[15b] $[\alpha]^{25}_D$ = −74 (*c* 1.00, MeOH) for (1*S*,2*R*)-**3**), respectively.

(1*R*,2*S*)-2-[(*N*,*N*-Dimethylcarbamoyl)methyl]-3-cyclopenten-1-yl Acetate (5a). Colorless oil; 84% ee; $[\alpha]^{25}_D$ = +48.9 (*c* 1.57, $CHCl_3$); ^{1}H NMR δ 2.01 (s, 3H), 2.28−2.40 (m, 2H), 2.56 (dd, J = 15.8, 7.0 Hz, 1H), 2.65−2.82 (m, 1H), 2.95 (s, 3H), 3.01 (s, 3H), 3.30−3.44 (m, 1H), 5.45 (dt, J = 6.5, 3.1 Hz, 1H), 5.73 (s, 2H); ^{13}C NMR δ 21.1, 31.9, 35.4, 37.2, 39.2, 44.3, 75.0, 128.1, 133.0, 170.5, 171.6; IR (neat) 1734, 1644 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{17}O_3N$ 211.1208, found 211.1193. Anal. Calcd for $C_{11}H_{17}O_3N$: C, 62.56; H, 8.06; N, 6.64. Found: C, 62.75; H, 8.33; N, 6.70.

(1*R*,2*S*)-2-[(*N*,*N*-Dimethylcarbamoyl)methyl]-3-cyclopenten-1-yl Propanoate (5b). Colorless oil; 95% ee; $[\alpha]^{25}_D$ = +36.2 (*c* 1.20, $CHCl_3$); ^{1}H NMR δ 1.11 (t, J = 7.6 Hz, 3H), 2.26 (t, J = 7.6 Hz, 2H), 2.27−2.39 (m, 2H), 2.55 (dd, J = 15.8, 7.0 Hz, 1H), 2.68−2.82 (m, 1H), 2.94 (s, 3H), 3.00 (s, 3H), 3.28−3.46 (m, 1H), 5.47 (dt, J = 7.0, 3.1 Hz, 1H), 5.73 (s, 2H); ^{13}C NMR δ 9.1, 27.7, 31.9, 35.3, 37.1, 39.3, 44.3, 74.7, 128.1, 132.9, 171.6, 173.8; IR (neat) 1733, 1652 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{19}O_3N$ 225.1365, found 225.1370.

(1*R*,2*S*)-2-[(*N*,*N*-Dimethylcarbamoyl)methyl]-3-cyclopenten-1-yl Butanoate (5c). Colorless oil; 97% ee; $[\alpha]^{26}_D$ = +29.6 (*c* 1.24, $CHCl_3$); ^{1}H NMR δ 0.93 (t, J = 7.4 Hz, 3H), 1.53−1.72 (m, 2H), 2.23 (t, J = 7.4 Hz, 2H), 2.31−2.40 (m, 2H), 2.55 (dd, J = 15.8, 7.0 Hz, 1H), 2.68−2.83 (m, 1H), 2.94 (s, 3H), 3.00 (s, 3H), 3.27−3.45 (m, 1H), 5.47 (dt, J = 6.5, 2.9 Hz, 1H), 5.73 (s, 2H); ^{13}C NMR δ 13.6, 18.4, 32.0, 35.3, 36.3, 37.1, 39.4, 44.3, 74.7, 128.1, 132.9, 171.6, 173.0; IR (neat) 1731, 1651 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{21}O_3N$ 239.1521, found 239.1531. Anal. Calcd for $C_{13}H_{21}O_3N$: C, 65.25; H, 8.84; N, 5.85. Found: C, 64.81; H, 8.69; N, 5.79.

(1*R*,2*S*)-2-[(*N*,*N*-Dimethylcarbamoyl)methyl]-3-cyclopenten-1-yl Hexanoate (5d). Colorless oil; 70% ee; $[\alpha]^{26}_D$ = +26.1 (*c* 1.24, $CHCl_3$); ^{1}H NMR δ 0.88 (t, J = 6.7 Hz, 3H), 1.20−1.40 (m, 4H), 1.59 (quintet, J = 7.3 Hz, 2H), 2.24 (t, J = 7.9 Hz, 2H), 2.30−2.40 (m, 2H), 2.55 (dd, J = 15.8, 7.0 Hz, 1H), 2.68−2.83 (m, 1H), 2.94 (s, 3H), 3.00 (s, 3H), 3.28−3.44 (m, 1H), 5.45 (dt, J = 6.5, 3.0 Hz, 1H), 5.73 (s, 2H); ^{13}C NMR δ 13.9, 22.3, 24.7, 31.3, 32.0, 34.5, 35.4, 37.2, 39.4, 44.4, 74.8, 128.2, 133.0, 171.7, 173.3; IR (neat) 1732, 1651 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{25}O_3N$ 267.1834, found 267.1809.

(1*R*,2*S*)-2-[(*N*,*N*-Dimethylcarbamoyl)methyl]-3-cyclopenten-1-yl Octanoate (5e). Colorless oil; 70% ee; $[\alpha]^{25}_D$ = +29.7 (*c* 1.18, $CHCl_3$); ^{1}H NMR δ 0.87 (t, J = 6.7 Hz, 3H), 1.19−1.40 (m, 8H), 1.50−1.70 (m, 2H), 2.25 (t, J = 7.9 Hz, 2H), 2.30−2.40 (m, 2H), 2.54 (dd, J = 15.8, 6.9 Hz, 1H), 2.67−2.82 (m, 1H), 2.95 (s, 3H), 3.01 (s, 3H), 3.28−3.44 (m, 1H), 5.44 (dt, J = 7.6, 2.7 Hz, 1H), 5.73 (s, 2H); ^{13}C NMR δ 14.0, 22.5, 25.0, 28.9, 29.1, 31.6, 32.0, 34.5, 35.4, 37.2, 39.4, 44.4, 74.8, 128.1, 133.0, 171.6, 173.2; IR (neat) 1733, 1653 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{29}O_3N$ 295.2147, found 295.2169.

(1*R*,2*S*)-2-[(*N*,*N*-Dimethylcarbamoyl)methyl]-3-cyclopenten-1-yl Decanoate (5f). Colorless oil; 89% ee; $[\alpha]^{28}_D$ = +23.6 (*c* 1.21, $CHCl_3$); ^{1}H NMR δ 0.87 (t, J = 6.9 Hz, 3H), 1.18−1.40 (m, 12H), 1.50−1.70 (m, 2H), 2.25 (t, J = 7.8 Hz, 2H), 2.27−2.39 (m, 2H), 2.55 (dd, J = 15.8, 7.0 Hz, 1H), 2.68−2.83 (m, 1H), 2.95 (s, 3H), 3.00 (s, 3H), 3.29−3.44 (m, 1H), 5.47 (dt, J = 6.2, 2.8 Hz, 1H), 5.73 (s, 2H); ^{13}C NMR δ 14.1, 22.6, 25.0, 29.1, 29.2, 29.3, 29.4, 31.8, 32.0, 34.5, 35.4, 37.2, 39.4, 44.4, 74.8, 128.1, 133.0, 171.7, 173.3; IR (neat) 1733, 1653 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{33}O_3N$ 323.2460, found 323.2450.

(1*R*,2*S*)-2-[(*N*,*N*-Dimethylcarbamoyl)methyl]-3-cyclopenten-1-yl Chloroacetate (5g). Colorless oil; 92% ee; $[\alpha]^{26}_D$ = +26.4 (*c* 1.24, $CHCl_3$); ^{1}H NMR δ 2.31−2.47 (m, 2H), 2.60 (dd, J = 16.1, 7.7 Hz, 1H), 2.72−2.87 (m, 1H), 2.95 (s, 3H), 3.00 (s, 3H), 3.34−3.50 (m, 1H), 4.00 (s, 2H), 5.57 (dt, J = 6.9, 2.6 Hz, 1H), 5.73 (s, 2H); ^{13}C NMR δ 32.1, 35.6, 37.4, 39.4, 41.2, 44.7, 128.1, 133.0, 166.8, 171.7; IR (neat) 1752, 1643 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{16}O_3NCl$ 245.0819, found 245.0826.

(1*R*,2*S*)-2-[(*N*,*N*-Dimethylcarbamoyl)methyl]-3-cyclopenten-1-yl Trifluoroacetate (5h). The trifluoroacetate ester was relatively unstable and was gradually changed to lactone **2**. ^{1}H NMR δ 2.37−2.85 (m, 4H), 2.93 (s, 3H), 2.98 (s, 3H), 3.44−3.60 (m, 1H), 5.66−5.82 (m, 3H).

(1*R*,2*S*)-2-[(*N*,*N*-Dimethylcarbamoyl)methyl]-3-cyclopenten-1-yl Pivalate (5i). Mp 54−55 °C; 84% ee; $[\alpha]^{24}_D$ = +33.0 (*c* 1.03, $CHCl_3$); ^{1}H NMR δ 1.16 (s, 9H), 2.22−2.42 (m, 2H), 2.56 (dd, J = 16.0, 6.9 Hz, 1H), 2.70−2.83 (m, 1H), 2.94 (s, 3H), 2.99 (s, 3H), 3.30−3.44 (m, 1H), 5.43 (dt, J = 6.4, 2.8 Hz, 1H), 5.72 (s, 2H); ^{13}C NMR δ 27.0, 32.3, 35.3, 37.1, 38.8, 39.6, 44.4, 74.6, 128.1, 132.9, 171.6, 177.8; IR (KBr) 1717, 1637 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{23}O_3N$ 253.1678, found 253.1665.

(1*R*,2*S*)-2-[(*N*,*N*-Dimethylcarbamoyl)methyl]-3-cyclopenten-1-yl Benzoate (5j). Colorless oil; 89% ee; $[\alpha]^{19}_D$ = +52.1 (*c* 1.31, $CHCl_3$); ^{1}H NMR δ 2.37−2.53 (m, 2H), 2.68 (dd, J = 15.9, 7.0 Hz, 1H), 2.81−3.00 (m, 1H), 2.85 (s, 3H), 2.94 (s, 3H), 3.44−3.58 (m, 1H), 5.72 (dt, J = 6.1, 2.8 Hz, 1H), 5.79 (s, 2H), 7.37−8.04 (m, 5H); ^{13}C NMR δ 32.2, 35.3, 37.2, 39.3, 44.7, 75.6, 128.2, 128.3, 129.4, 130.5, 132.8, 133.0, 166.0, 171.5; IR (neat) 1716, 1647 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{19}O_3N$ 273.1365, found 273.1370.

(1*R*,2*S*)-2-[(*N*,*N*-Dimethylcarbamoyl)methyl]-3-cyclopenten-1-yl Crotonate (5k). Colorless oil; 92% ee; $[\alpha]^{24}_D$ = +30.5 (*c* 1.02, $CHCl_3$); ^{1}H NMR δ 1.84−1.93 (m, 3H), 2.28−2.44 (m, 2H), 2.56 (dd, J = 14.1, 6.6 Hz, 1H), 2.69−2.84 (m, 1H), 2.94 (s, 3H), 3.00 (s, 3H), 3.30−3.45 (m, 1H), 5.51 (dt, J = 6.5, 3.1 Hz, 1H), 5.75 (s, 2H), 5.77−5.84 (m, 1H), 6.85−7.04 (m, 1H); ^{13}C NMR δ 17.9, 31.9, 35.4, 37.2, 39.1, 44.5, 74.7, 122.6, 128.1, 132.9, 144.6, 165.9, 171.7; IR (neat) 1716, 1652 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{19}O_3N$ 237.1365, found 237.1325.

(1*R*,2*S*)-2-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-3-cyclopenten-1-yl Acetate (6a). Colorless oil; >99% ee; $[\alpha]^{20}_D$ = +24.3 (*c* 1.36, $CHCl_3$); ^{1}H NMR δ 0.05 (s, 6H), 0.89 (s, 9H), 1.50−1.83 (m, 2H), 2.04 (s, 3H), 2.28−2.40 (m, 1H), 2.60−2.79 (m, 1H), 2.85−2.97 (m, 1H), 3.67 (t, J = 6.7 Hz, 2H), 5.39 (dt, J = 6.3, 3.0 Hz, 1H), 5.73 (s, 2H); ^{13}C NMR δ −5.3, 18.3, 21.2, 26.0, 31.4, 39.3, 44.7, 61.9, 75.3, 127.6, 133.2, 170.9; IR (neat) 1736 cm^{-1}.

(28) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(1*R*,2*S*)-2-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-3-cyclopenten-1-yl Butanoate (6b). Colorless oil; 98% ee; $[\alpha]^{20}_D$ = +16.5 (*c* 1.08, $CHCl_3$); ^{1}H NMR δ 0.04 (s, 6H), 0.89 (s, 9H), 0.93 (t, *J* = 7.4 Hz, 3H), 1.50−1.83 (m, 4H), 2.26 (t, *J* = 7.3 Hz, 2H), 2.27−2.39 (m, 1H), 2.60−2.76 (m, 1H), 2.86−2.98 (m, 1H), 3.66 (t, *J* = 6.6 Hz, 2H), 5.40 (dt, *J* = 6.4, 2.8 Hz, 1H), 5.72 (s, 2H); ^{13}C NMR δ −5.3, 13.7, 18.3, 18.5, 25.9, 31.4, 36.4, 39.4, 44.7, 61.9, 75.0, 127.6, 133.2, 173.5; IR (neat) 1735 cm^{-1}.

(1*R*,2*S*)-2-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-3-cyclopenten-1-yl Decanoate (6c). Colorless oil; >99% ee; $[\alpha]^{24}_D$ = +4.49 (*c* 1.38, $CHCl_3$); ^{1}H NMR δ 0.04 (s, 6H), 0.87 (t, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 1.20−1.34 (m, 12H), 1.48−1.81 (m, 4H), 2.27 (t, *J* = 7.7 Hz, 2H), 2.33−2.38 (m,1H), 2.62−2.76 (m, 1H), 2.84−2.98 (m, 1H), 3.66 (t, *J* = 6.6 Hz, 2H), 5.39 (dt, *J* = 6.4, 2.8 Hz, 1H), 5.72 (s, 2H); ^{13}C NMR δ −5.3, 14.1, 18.3, 22.7, 25.0, 25.9, 29.2, 29.3, 29.4, 31.4, 31.8, 34.6, 39.4, 44.7, 61.9, 75.0, 127.6, 133.2, 173.7; IR (neat) 1735 cm^{-1}.

(1*R*,2*S*)-2-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-3-cyclopenten-1-yl Chloroacetate (6d). Colorless oil; >99% ee; $[\alpha]^{20}_D$ = +12.0 (*c* 1.15, $CHCl_3$); ^{1}H NMR δ 0.05 (s, 6H), 0.89 (s, 9H), 1.54−1.84 (m, 2H), 2.33−2.46 (m, 1H), 2.66−2.80 (m, 1H), 2.92−3.04 (m, 1H), 3.68 (t, *J* = 6.5 Hz, 2H), 4.03 (s, 2H), 5.48 (dt, *J* = 6.2, 2.8 Hz, 1H), 5.74 (s, 2H); ^{13}C NMR δ −5.3, 18.3, 25.9, 31.1, 39.3, 41.0, 44.9, 61.7, 127.4, 133.0, 167.1; IR (neat) 1757 cm^{-1}.

(1*R*,2*S*)-2-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-3-cyclopenten-1-yl Pivalate (6e). Colorless oil; % ee not determined; $[\alpha]^{22}_D$ = +10.1 (*c* 1.78, $CHCl_3$); ^{1}H NMR δ 0.04 (s, 6H), 0.88 (s, 9H), 1.18 (s, 9H), 1.48−1.84 (m, 2H), 2.20−2.33 (m, 1H), 2.62−2.77 (m, 1H), 2.86−3.02 (m, 1H), 3.66 (t, *J* = 6.5 Hz, 2H), 5.35 (dt, *J* = 6.5, 2.8 Hz, 1H), 5.71 (s, 2H); ^{13}C NMR δ −5.3, 18.3, 25.9, 27.1, 31.4, 38.9, 39.5, 44.8, 61.8, 74.8, 127.5, 133.1, 178.2; IR (neat) 1728 cm^{-1}.

(1*R*,2*S*)-2-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-3-cyclopenten-1-yl Benzoate (6f). Colorless oil; 97% ee; $[\alpha]^{22}_D$ = +17.3 (*c* 1.15, $CHCl_3$); ^{1}H NMR δ 0.01 (s, 6H), 0.87 (s, 9H), 1.62−1.97 (m, 2H), 2.41−2.55 (m, 1H), 2.75−2.88 (m, 1H), 2.99−3.11 (m, 1H), 3.70 (t, *J* = 6.5 Hz, 2H), 5.63 (dt, *J* = 6.4, 2.9 Hz, 1H), 5.74−5.83 (m, 2H), 7.38−8.06 (m, 5H); ^{13}C NMR δ −5.3, 18.3, 25.9, 31.6, 39.5, 45.1, 61.9, 75.9, 127.7, 128.3, 129.6, 130.6, 132.8, 133.2, 166.3; IR (neat) 1719 cm^{-1}.

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Supporting Information Available: ^{1}H NMR spectra for compounds **1**−**6** and detailed data for the solvent effect in Figure 2 (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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