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Selected Paper

Easy Separation of Optically Active Secondary Alcohols by Enzymatic Hydrolysis of Soluble Polymer-Supported Carbonates

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The enzyme-mediated enantioselective hydrolysis of middle molecular weight poly(ethylene glycol) (PEG)-supported carbonates is disclosed. The representative water-soluble substrate was prepared by the immobilization of (±)-1-phenylethanol onto a monomethoxy PEG (MPEG, av. M_w 5000) or PEG (av. M_w 4600) through a carbonate linker. Porcine pancreas lipase (PPL) enantioselectively catalyzed the hydrolysis of the polymer-supported substrate in a mixed solvent (hexane/buffer = 9/1) at 0 °C to afford the corresponding optically active compounds. In this system, the separation of the remaining (*S*)-substrate and the resulting (*R*)-alcohol was achieved by a simple procedure without any laborious column chromatography. The substrate was easily hydrolyzed with NaOH in MeOH–H_2O to give the (*S*)-alcohol. This procedure was also applicable to the preparation of other optically active secondary alcohols. As expected, an introduction of a hydrophobic spacer between the MPEG moiety and the carbonate linker affected both the reactivity and enantioselectivity. An *o*-substitution produced a lower conversion than those of the reaction of the *m*- and *p*-substituted substrates. While the substrate with a *p*-phenylethyl spacer gave the best *E* value (>200) with low conversion, the reaction of the substrate with a *p*-phenylmethyl spacer smoothly proceeded with high enantioselectivity (*E* value = 151).

Optically active secondary alcohols are versatile intermediates in organic syntheses. The kinetic resolution of racemic alcohols and esters using hydrolytic enzymes is one of the practical methods for the preparation of optically active compounds, and a significant number of examples have been reported.[1] During the reaction, the enantiomers, the remaining substrate, and the resulting product, should be separated, however the tedious and wasteful separation step by column chromatography is still a big problem for an easy operation and a sustainable product. Although several easy separation process studies have been published,[2–5] facile and efficient procedures are still desired.

On the other hand, solid-phase chemistry using insoluble polymers (polystyrene, silica gel, etc.) has been developed, especially in the field of combinatorial chemistry. Although enzymatic transformation on a polymer support is also an attractive method for the easy isolation of the products, there have been relatively few reports on polymer-supported reactions by enzymes.[6–12] Recently, poly(ethylene glycol) (PEG) has been recognized as an inexpensive and convenient soluble polymer,[13–16] and the synthetic approach using a soluble polymer is termed liquid-phase chemistry. We noticed that a PEG-supported strategy could be suitable for an enzymatic transformation and potentially useful for the easy isolation of the products, and we have already succeeded in the kinetic resolution of a low-molecular weight monomethoxy PEG (MPEG, av. M_w 550 and 750)-supported substrate with a carbonate linker using a hydrolytic enzyme (porcine pancreas lipase (PPL), lipase Type II from Sigma).[17] The broad solubility of PEG facilitated the analysis of the PEG-supported substrates, and the easy separation of the products by an extraction procedure was achieved. However, for the isolation of the MPEG-supported compounds through all processes of the substrate syntheses, the column chromatography steps were still needed because the compounds were liquids. We now disclose the enzyme-mediated kinetic resolution of higher-molecular weight MPEG (av. M_w 5000) and PEG (av. M_w 4600)-supported carbonates, which are solids and easier to handle.[18] We also report the introduction of an appropriate hydrophobic spacer between the PEG moiety and the carbonate linker, and the structure of the linker affects both the reactivity and enantioselectivity.

Results and Discussion

We selected the carbonate (±)-**1** as the basic substrate without a spacer (Scheme 1). The carbonate is a typical linker used in organic synthesis on a polymer support, and (±)-**1** was easily prepared by the coupling of a racemic imidazolide (±)-**2** derived from 1-phenylethanol ((±)-**3**) with $MPEG_{5000}$-OH (**4**). We are also interested in the affect of a hydrophobic spacer between the MPEG moiety and the carbonate linker. The substrates (±)-**5a**–**5e**, which contain the *ortho*-, *meta*-, and *para*-substituted spacers on the benzene ring, were also synthesized in 3 steps from the mesylate **6** and the corresponding esters **7a**–**7e**. By making use of $MPEG_{5000}$-OH, which has been utilized in many studies, as the basic matrix, it allows us to isolate and purify the intermediates **8** and **9** and the substrates (±)-**1** and -**5** by a simple precipitation procedure from diethyl ether.[14] In a similar manner, the substrate (±)-**10** supported by PEG_{4600}-OH (**11**) was prepared from an imida-

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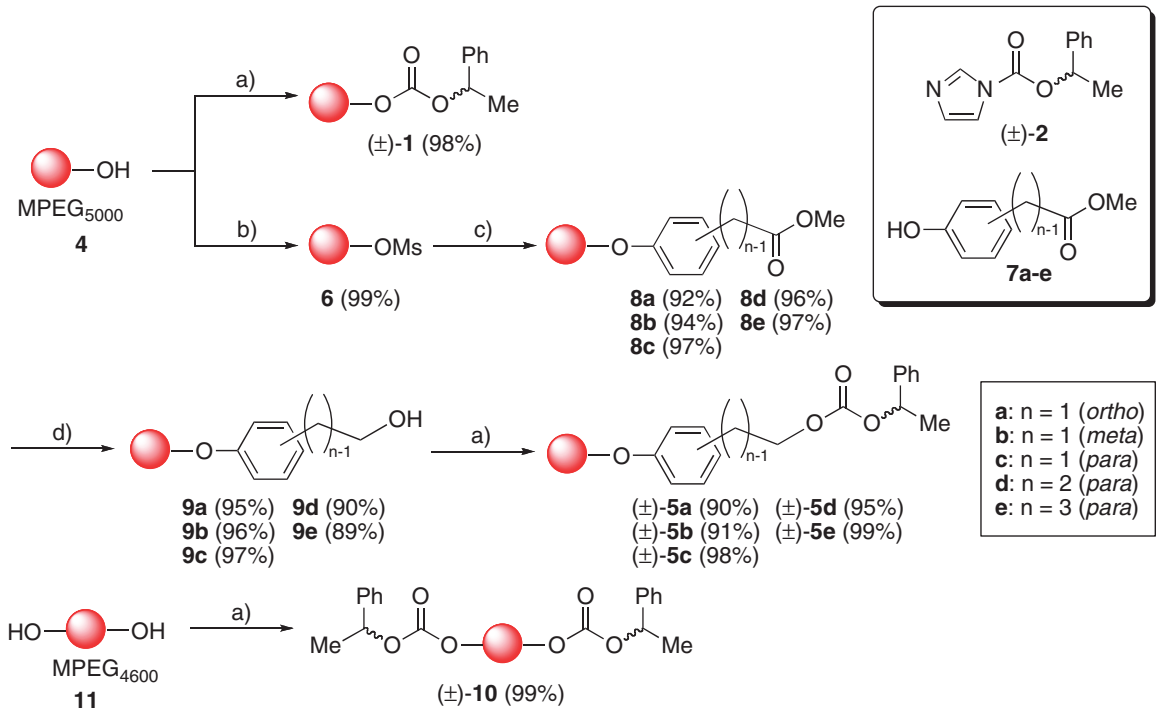
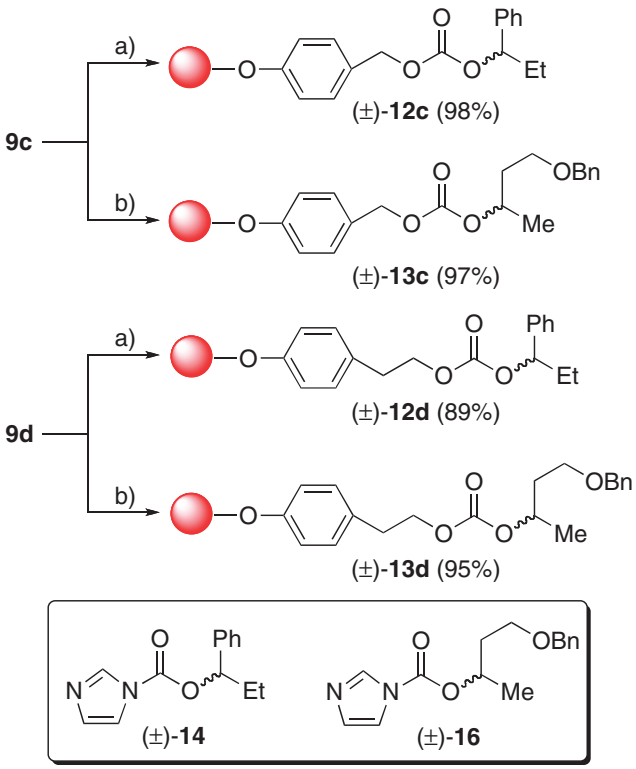


Scheme 1. a) (±)-**2**, DMAP/DMF, 100 °C (**1** and **5**) or 120 °C (**10**); b) MsCl, Et_3N/CH_2Cl_2, rt; c) **7a**–**7e**, Cs_2CO_3/DMF, 70 °C; and d) DIBAL/CH_2Cl_2, 0 °C.

zolide (±)-**2**. On the other hand, the substrates (±)-**12** and -**13** were also constructed by the coupling of an imidazolide (±)-**14** from (±)-1-phenyl-1-propanol (**15**) or (±)-**16** from (±)-4-benzyloxy-2-butanol (**17**) with **9c** and **9d** (Scheme 2). The yields of the PEG-supported compounds were based on the weights of the starting materials. The purities were determined by ^{1}H NMR analysis, and the terminal methyl group and/or the PEG-methylenes were used as the reference. Moreover, the productions of the PEG-supported substrates were also confirmed by ESI-TOFMS. For example, Figure 1a shows a part of the mass spectrum obtained for $MPEG_{5000}$-OH (**4**). Because the spectrum shows the characteristic PEG series of ions with m/z 22 spacing, the most abundant ion is estimated to be 2352 Da and the molecular mass of **4** is determined to be ca. 4658 Da ($[CH_3O(CH_2CH_2O)_{105}H\cdot 2Na]^{2+}$; $z = +2$). On the other hand, the mass spectrum series of the compound (±)-**5c** is shifted to a higher m/z range (Figure 1b). The estimated m/z of **5c** is then 2479 Da as the most abundant ion, and the molecular mass is evaluated at ca. 4912 Da. This result is fairly consistent with the calculated mass (4909 Da) from $CH_3O(CH_2CH_2O)_{105}C_{16}H_{15}O_3$.

The PPL-catalyzed reactions of (±)-**1** were examined under various reaction conditions, and the results are shown in Table 1. In a typical experiment, 125 mg of (±)-**1** (sub. concn. 5 mM) and 10 mg of PPL were added to a medium (5 mL) in a test tube, and the mixture was stirred for 24 h at a constant temperature. At first, the reaction was carried out in 0.1 M phosphate buffer (pH 6.5) at 30 °C (Entry 1).[17] Although the hydrolysis of (±)-**1** proceeded, both the reactivity and enantioselectivity were moderate (conv. = 0.27, E value = 12).[19] In general, lipases works at an interface between organic phase and water. In our case, the reaction was examined in a homogeneous system, which was not suitable for PPL. Moreover, the procedure had few advantages for easy preparation versus using low molecular-weight $MPEG_{550}$-supported substrates because the unreacted **1** should be extracted from the mixture by EtOAc. We then tried to examine the reaction in a



Scheme 2. a) (±)-**14**, DMAP/DMF, 100 °C (**12c**) or 120 °C (**12d**) and b) (±)-**16**, DMAP/DMF, 130 °C.

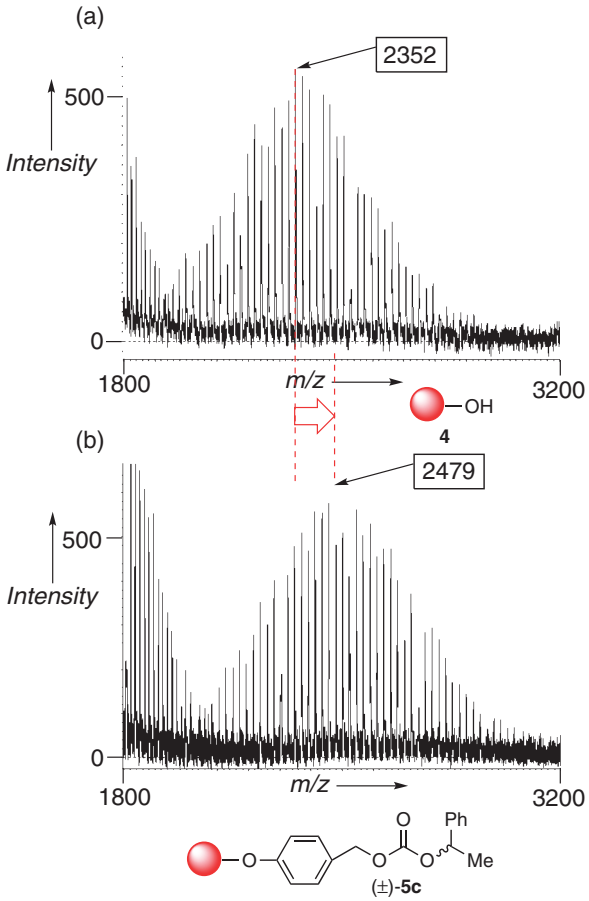
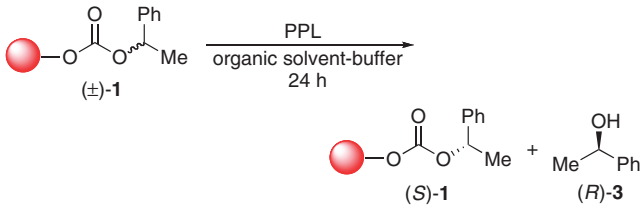


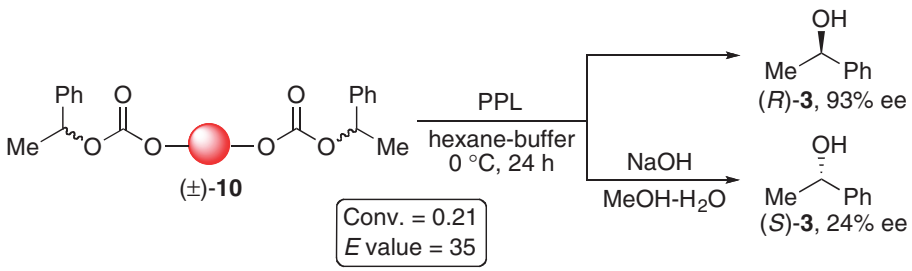
Figure 1. The ESI-TOFMS spectra of $MPEG_{5000}$-supported compounds: (a) the original $MPEG_{5000}$-OH (**4**) and (b) the $MPEG_{5000}$-supported carbonate with a spacer (±)-**5c**.

Table 1. Enantioselective Hydrolysis of $MPEG_{5000}$-Supported Carbonates (±)-**1** without a Spacer[a)]



Entry	Organic solvent (ratio of media)[b)]	Temp /°C	Ee of **1**/%[c)]	Ee of **3**/%[d)]	Conv.[e)]	*E* value[f)]
1	— (0/10)	30	29	80	0.27	12
2	hexane (1/9)	30	18	73	0.20	8
3	hexane (3/7)	30	28	79	0.26	11
4	hexane (5/5)	30	28	78	0.26	11
5	hexane (7/3)	30	30	82	0.27	14
6	hexane (9/1)	30	88	65	0.58	13
7	hexane (40/1)	30	83	61	0.58	10
8	toluene (9/1)	30	15	78	0.16	9
9	*i*-Pr_2O (9/1)	30	18	78	0.19	10
10	Et_2O (9/1)	30	4	36	0.10	2
11	hexane (9/1)	20	50	88	0.36	26
12	hexane (9/1)	10	41	93	0.31	41
13	hexane (9/1)	0	18	96	0.16	58

a) The reaction was performed using 5 mM of the substrates with PPL in a medium (organic solvent–0.1 M phosphate buffer (pH 6.5)) for 24 h. b) A ratio in parentheses reveals the volume of organic solvent against the volume of buffer. c) Determined by GLC analysis after hydrolysis of the unreacted substrates. d) Determined by GLC analysis. e) Calculated by ee(**1**)/[ee(**1**) + ee(**3**)]. f) Calculated by $\ln[(1 - \text{conv.})(1 - \text{ee}(\mathbf{1}))]/\ln[(1 - \text{conv.})(1 + \text{ee}(\mathbf{1}))]$.

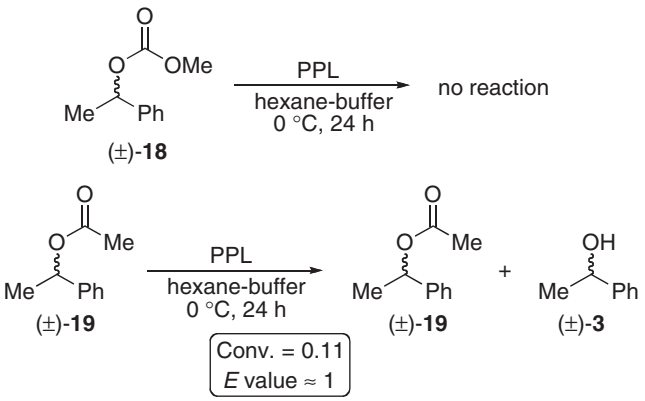


Scheme 3.

two-phase system, and we selected hexane as an additional hydrophobic organic solvent (Entries 2–7). While the reaction in a solvent containing 10% hexane proceeded in the lowest conversion with the lowest *E* value, increasing the ratio of hexane improved both the reactivity and enantioselectivity. In particular, the conversion and *E* value were up to 0.58 and 13, respectively, in the case of a mixed solvent containing 90% hexane (Entry 6). Interestingly, the reaction also smoothly proceeded in hexane with a small amount of water (hexane/water = 40/1; Entry 7), but the *E* value (=10) was smaller than that in the case of Entry 6. Unfortunately, changing the organic solvent to toluene, *i*-Pr_2O, and Et_2O (Entries 8–10) decreased both the reactivity and enantioselectivity. For kinetically controlled reactions, lowering the temperature could improve the enantioselectivity in many cases.[20] We then investigated the temperature effect of the reaction (Entries 11–13), and it was found that the reaction at a lower temperature proceeded with a higher enantioselectivity. For the reaction at 0 °C (Entry 13), the *E* value was up to 58 and (*R*)-**3** with a 96% ee was obtained, although the conversion apparently decreased to 0.16. This reaction was applicable to the reaction of the PEG_{4600}-supported substrate (±)-**10**, and the conversion and *E* value were 0.21 and 35, respectively (Scheme 3). In this case, two molecules of optically active **3** could be released from one molecule of the racemic substrate **10**. On the other hand, for the reaction of the methyl carbonate (±)-**18** under the same conditions (Scheme 4), the reaction scarcely proceeded. In the same way, the acetate (±)-**19** was slowly hydrolyzed

(conv. = 0.11) without any enantioselectivity. These results indicate that the hydrophilic $MPEG_{5000}$ matrix could significantly change the physical properties of the alcohol **3** and that the substrate would favorably fit the enzyme active site.

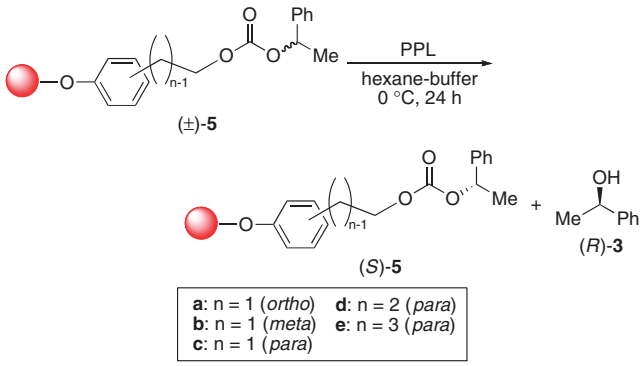
During the reaction, we also achieved an easier separation procedure of the products due to the use of the $MPEG_{5000}$-OH (**4**) as the basic matrix and the two-phase reaction system. The separation process in the case of (±)-**1** is illustrated in Scheme 5. First, the resulting alcohol (*R*)-**3** was already extracted in the hexane layer, and was isolated after evaporation. Second, CH_2Cl_2 was added to the aqueous layer, and dried over anhydrous Na_2SO_4. After evaporation, the residue was poured into Et_2O to precipitate the mixture of the (*S*)-carbonate and **4** as a white solid, which was collected by simple filtration. Third, chemical hydrolysis with NaOH in MeOH–H_2O gave the optically active (*S*)-**3**. In all cases, we succeeded in developing a facile work-up procedure to separate the enantiomers.



Scheme 4.

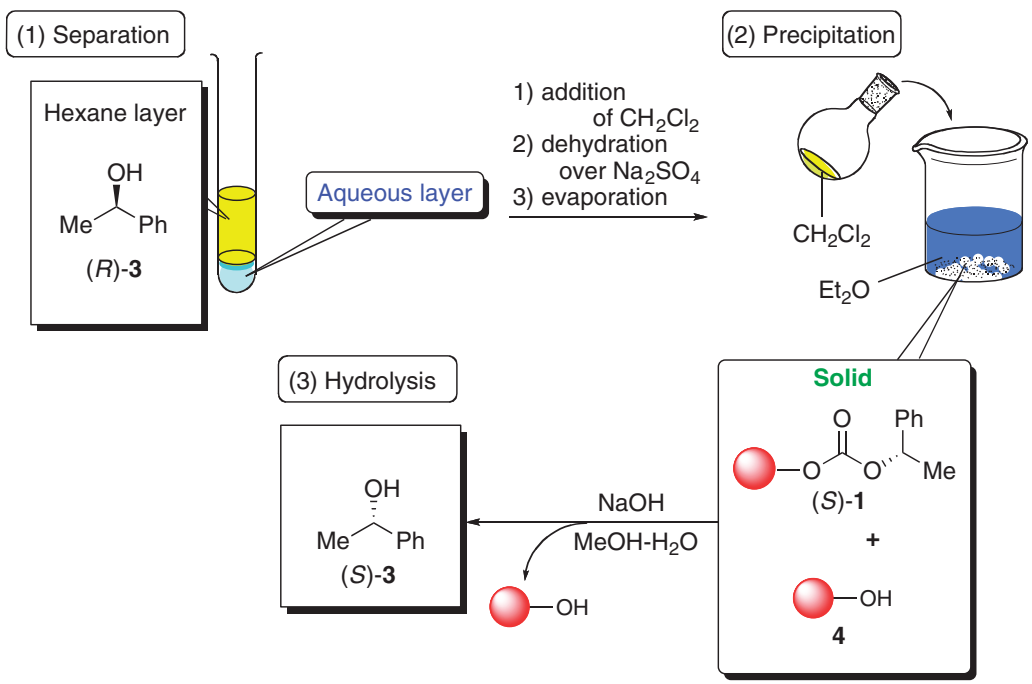
In order to improve the conversion of the reaction, we next considered that a suitable spacer could increase the affinity to the active site of the enzyme, which had many hydrophobic amino residues inside the binding pocket. The results using the substrates with a spacer are shown in Table 2. Beyond our expectation, the introduction of the spacer and the substitution pattern on the benzene ring of the spacer drastically increased

Table 2. Enantioselective Hydrolysis of $MPEG_{5000}$-Supported Carbonates (±)-**5** with a Spacer[a)]



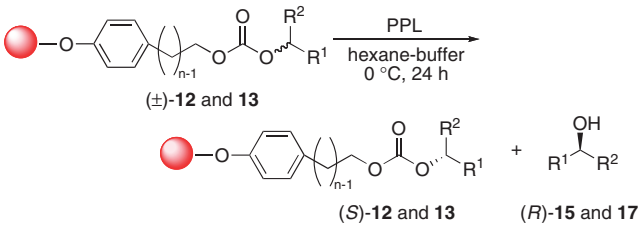
Entry	Substrate	Ee of **5**/%[b)]	Ee of **3**/%[c)]	Conv.	*E* value
1	**5a**	46	95	0.33	61
2	**5b**	82	94	0.47	83
3	**5c**	76	97	0.44	151
4	**5d**	31	99	0.24	>200
5	**5e**	42	96	0.30	74

a) The reaction was performed using 5 mM of the substrates with PPL in a mixed medium (hexane/0.1 M phosphate buffer (pH 6.5) = 9/1) for 24 h at 0 °C. b) Determined by GC analysis after hydrolysis of the unreacted substrates. c) Determined by GC analysis.



Scheme 5.

Table 3. Enantioselective Hydrolysis of $MPEG_{5000}$-Supported Carbonates (±)-**12** and -**13**[a)]



12c: n = 1, R^1 = Et, R^2 = Ph
13c: n = 1, R^1 = Me, R^2 = -CH_2CH_2OBn
12d: n = 2, R^1 = Et, R^2 = Ph
13d: n = 2, R^1 = Me, R^2 = -CH_2CH_2OBn

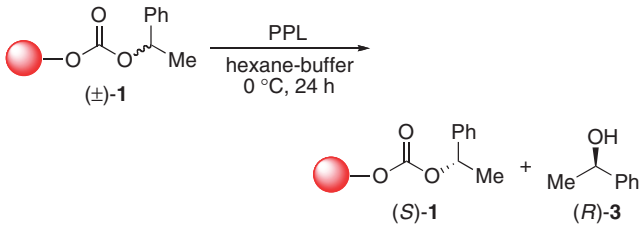
15: R^1 = Et, R^2 = Ph
17: R^1 = Me, R^2 = -CH_2CH_2OBn

Entry	Substrate	Ee of substrate/%[b)]	Ee of product/%[c)]	Conv.	*E* value
1	**12c**	86	94	0.48	90
2	**13c**	68	81	0.46	19
3	**12d**	49	93	0.35	45
4	**13d**	7	91	0.07	23

a) The reaction was performed using 5 mM of the substrate with PPL in a mixed medium (hexane/0.1 M phosphate buffer (pH 6.5) = 9/1) for 24 h at 0 °C. b) Determined by GC analysis after hydrolysis of the unreacted substrates. c) Determined by GC analysis.

not only the conversion, but also the enantioselectivity. When using the phenylmethyl spacers (±)-**5a**, -**5b**, and -**5c** ($n = 1$; *ortho*-, *meta*-, and *para*-substitutions, respectively), the conversions were up to 0.33, 0.47, and 0.44, respectively (Entries 1–3). In addition, the reactions also proceeded with higher enantioselectivities. In particular, the carbonate (±)-**5c** with a *para*-substitution was hydrolyzed with an excellent enantioselectivity and the *E* value was up to 151. The carbon number in the spacer also affected the *E* value, and the phenylpropyl spacers (±)-**5e** ($n = 3$) gave almost the same result (conv. = 0.30, *E* value = 74) as the case of (±)-**5a** (Entry 5). In these cases, we assumed that the substrates would more favorably fit the enzyme active site than the original substrate (±)-**1**. On the other hand, the phenylethyl spacer (±)-**5d** ($n = 2$) proceeded with the highest enantioselectivity (*E* value > 200) to afford the almost optically pure (*R*)-**3**, although the conversion was not apparently improved over that of the substrate (±)-**1** (Entry 4). This result suggests that the introduction of the phenylethyl spacer could drastically decrease the reactivity of (*S*)-enantiomer of **5d**, thus this phenomenon could lead to the lower conversion and higher enantioselectivity. A 48-h reaction was also performed using 3.6 g of the substrate (±)-**5d** in a recovery flask. In this case, we finally obtained (*R*)-**3** (98% ee, $[\alpha]_D^{18} = +32.8$ (*c* 0.96, MeOH); lit.[21] $[\alpha]_D^{20} = +45$ (*c* 5.15, MeOH)) in 12% and (*S*)-**3** (58% ee, $[\alpha]_D^{25} = -21.0$ (*c* 1.06, MeOH)) in 46% isolated yields (conv. = 0.37, *E* value = 179). The concept of this reaction was applicable to the preparation of the other optically active alcohols (Table 3). The reactions of the substrates (±)-**12** and -**13** also enantioselectively proceeded to afford the corresponding optically active compounds **15** and **17**. Comparing the reactions using **12c** and **13c** bearing a phenylmethyl spacer, the reactions of **12d** and **13d** bearing a phenylethyl spacer slowly proceeded, and the results were not inconsistent with the cases of **3** described above.

Table 4. Hydrolysis of $MPEG_{5000}$-Supported Carbonates (±)-**1**[a)]



Entry	Enzyme	Ee of **1**/%	Ee of **3**/%	Conv.	*E* value
1	α-Chymotrypsin[b)]	ca. 0	—	trace	—
2	Cholesterol esterase[c)]	93	48	0.66	9
3	Purified PPL[d)]	1	96	0.01	49

a) The reaction was performed using 5 mM of (±)-**1** with the enzyme in a mixed medium (hexane/0.1 M phosphate buffer (pH 6.5) = 9/1) for 24 h at 0 °C. b) Using 5 mg (30000 U mg^{-1}). c) Using 1 mg (54 U mg^{-1}). d) Using 2.5 mg (20100 U mg^{-1}).

Although commercially available PPL (Type II, Sigma) works well in this enzymatic reaction, the crude enzyme contains a number of hydrolases besides the true PPL. The existence of the several active enzymes might affect the reactivity and enantioselectivity. In our previous paper, we found that the hydrolysis of $MPEG_{550}$-supported carbonate in buffer could be catalyzed by not the true PPL, but another unknown enzyme.[17b] In order to evaluate the accuracy of the results for $MPEG_{5000}$-supported substrates under the two phase system, we then investigated the reaction using commercially available purified PPL (lipase Type VI-S, Sigma) and two kinds of major contaminant hydrolases, α-chymotrypsin (Type-II, Sigma) and cholesterol esterase (Sigma), and the results are shown in Table 4. While α-chymotrypsin did not show the hydrolytic activity (Entry 1), cholesterol esterase showed a very low *E* value (Entry 2). It is noteworthy that the purified PPL catalyzed the hydrolysis of (±)-**1** with a high enantioselectivity, although the conversion was very low (Entry 3). These results suggest that the enantioselectivity in this reaction could be due to the true PPL, and the reaction using crude PPL proceeds with a lower enantioselectivity because of a contamination of cholesterol esterase. Further detailed investigations are now in progress.

Conclusion

In summary, we have demonstrated the enzyme-mediated kinetic resolution of soluble polymer ($MPEG_{5000}$ and PEG_{4600})-supported carbonates to afford optically active secondary alcohols **3**, **15**, and **17**. Moreover, we have disclosed that the reactivity and enantioselectivity can be controlled using a suitable hydrophobic spacer between the MPEG moiety and the carbonate linker. In our method, the separation and isolation of the reaction products were achieved by a simple precipitation technique without using time- and solvent-consuming column chromatography. The method was also applicable to gram-scale experiments. Moreover, the use of the PEG matrix changed the

physical properties of the substrates, and that lead to improved reactivity. We anticipate that the concept of the enzymatic reaction using PEG-supported substrates can provide a useful protocol in not only organic chemistry, but also medicinal chemistry for the development of PEG-supported pro-drugs, which gradually release native drugs by enzymatic hydrolysis.

Experimental

General Procedure and Instruments. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on a JEOL α-500 with tetramethylsilane as the internal standard. ESI-TOF mass spectra were measured in MeOH–H_2O solution including AcONa with a JEOL JMS-T100. IR spectra were recorded on a Shimadzu Prestige-21 FT-IR Spectrometer. All enzymatic reactions were performed in a SANYO incubator MIR-253. Analytical TLC was performed on Kieselgel 60 F_{254} Art. 5715 (E. Merck). Preparative TLC was performed on Kieselgel 60 F_{254} Art. 5744 (E. Merck). The optical rotations were measured with a Jasco DIP-1000 polarimeter. HPLC data were obtained on a Shimadzu LC-10AD_{vp}, SPD-10A_{vp}, and sic 480II date station (System Instruments Inc.). GLC data were obtained on GL Sciences GC 353B and sic 480 II. $MPEG_{5000}$-OH (**4**) was purchased from Fluka, PEG_{4600}-OH (**11**) from Aldrich. All other chemicals were also obtained from commercial sources. The synthetic procedure of imidazolides (±)-**2**, -**14**, and -**16** have already been reported.[17]

Preparation of $MPEG_{5000}$-Supported Carbonate Coupled with 1-Phenylethanol (3) without a Spacer ((±)-1). Under an argon atmosphere, imidazolide (±)-**2** (131 mg, 0.605 mmol) and DMAP (73.8 mg, 0.604 mmol) were added to a solution of **4** (1.01 g, 0.201 mmol) in DMF (13 mL), and the solution was stirred for 12 h at 100 °C. After evaporation in vacuo, the residue was precipitated into Et_2O to afford the compound (±)-**1** as a white solid in 98% yield (1.02 g; purity, ca. >99%); IR (KBr): 2887, 1744, 1636, 1466, 1342, 1281, 1113, 964, 843 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.59 (d, $J = 6.5$ Hz, 3H), 3.38 (s, 3H), 3.45–3.85 (m, PEG-methylenes), 4.23 (td, $J_1 = 4.5$ Hz, $J_2 = 12.0$ Hz, 1H), 4.28 (td, $J_1 = 5.0$ Hz, $J_2 = 12.0$ Hz, 1H), 5.72 (q, $J = 6.5$ Hz, 1H), 7.23–7.39 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.2, 58.8, 66.7, 68.7, 70.4 (PEG), 70.6, 71.7, 76.3, 125.9, 127.9, 128.3, 140.8, 154.3; ESI-TOF MS m/z 2426 Da (2424 Da calcd for $[CH_3O(CH_2CH_2O)_{105}C_9H_9O_2 \cdot 2Na]^{2+}$).

Preparation of $MPEG_{5000}$-Supported Carbonate with an *ortho*-Phenylmethyl Spacer ((±)-5a). Under an argon atmosphere, methanesulfonyl chloride (0.35 mL, 4.51 mmol) and triethylamine (1.50 mL, 10.8 mmol) were added to a solution of **4** (3.00 g, 0.60 mmol) in CH_2Cl_2 (13 mL), and the solution was stirred overnight at room temperature. After evaporation in vacuo, the residue was poured into Et_2O to precipitate a white solid. After the solid was washed with 2-propanol, evaporation and precipitation gave the mesylate **6** as a white solid in 99% yield (3.03 g; purity, ca. >99%); IR (KBr): 2886, 1636, 1466, 1360, 1342, 1281, 1242, 1113, 962, 843 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.09 (s, 3H), 3.38 (s, 3H), 3.46–3.82 (m, PEG-methylenes), 4.39 (t, $J = 4.5$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 37.6, 58.9, 68.9, 69.2, 70.4 (PEG), 70.5, 70.6, 71.8.

Under an argon atmosphere, methyl salicylate (**7a**, 60.5 mg, 0.398 mmol) and cesium carbonate (193 mg, 0.589 mmol) were added to a solution of **6** (1.004 g, 0.1977 mmol) in DMF (6.5 mL), and the solution was stirred overnight at 70 °C. The mixture was filtrated through a celite pad, and the filtrate was evaporated in vacuo. After the residue was dissolved in CH_2Cl_2, the solution was washed with 2 M HCl, and dried over Na_2SO_4. After evaporation, the residue was poured into Et_2O to precipitate the compound **8a** as a white solid in 92% yield (935 mg; purity, ca. >99%); IR (KBr): 2886, 1734, 1466, 1342, 1281, 1242, 1113, 962, 843 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.38 (s, 3H), 3.47–3.81 (m, PEG-methylenes), 3.88 (s, 3H), 3.91 (t, $J = 5.0$ Hz, 2H), 4.20 (t, $J = 5.0$ Hz, 2H), 6.97–7.01 (m, 2H), 7.45 (ddd, $J_1 = 1.5$ Hz, $J_2 = 9.0$ Hz, $J_3 = 9.0$ Hz, 1H), 7.78 (dd, $J_1 = 1.5$ Hz, $J_2 = 8.0$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 51.8, 58.9, 68.8, 69.4, 70.4 (PEG), 70.5, 70.9, 71.8, 113.6, 120.4, 120.5, 131.5, 133.3, 158.2, 166.6.

Under an argon atmosphere, DIBAL-H (0.627 mL, 1.0 M solution in toluene) was added to a solution of **8a** (805 mg, 0.157 mmol) in CH_2Cl_2 (5.6 mL) at 0 °C, and the solution was warmed to room temperature. After stirring overnight, the reaction was quenched with water, and the suspension was filtrated through a celite pad. After evaporation, the residue was precipitate into Et_2O to afford the compound **9a** as a white solid in 95% yield (756 mg; purity, ca. >99%); IR (KBr): 3460, 2887, 1649, 1466, 1360, 1342, 1281, 1242, 1115, 964, 843 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.25 (t, $J = 6.5$ Hz, 1H), 3.38 (s, 3H), 3.45–3.82 (m, PEG-methylenes), 3.86 (t, $J = 4.5$ Hz, 2H), 4.21 (t, $J = 4.5$ Hz, 2H), 4.66 (d, $J = 7.0$ Hz, 2H), 6.89 (d, $J = 8.0$ Hz, 1H), 6.95 (dt, $J_1 = 1.0$ Hz, $J_2 = 7.5$ Hz, 1H), 7.23–7.28 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 58.9, 61.8, 67.7, 69.4, 70.4 (PEG), 70.5, 71.7, 112.0, 121.0, 128.6, 128.8, 130.2, 156.7.

Under an argon atmosphere, (±)-**2** (84.9 mg, 0.393 mmol) and DMAP (46.2 mg, 0.378 mmol) were added to a solution of **9a** (641 mg, 0.126 mmol) in DMF (8.4 mL), and the solution was stirred for 12 h at 100 °C. After the solution was evaporated in vacuo, the residue was precipitate into Et_2O to afford the compound (±)-**5a** as a white solid in 90% yield (593 mg; purity, ca. >99%); IR (KBr): 2882, 1746, 1651, 1466, 1360, 1342, 1279, 1242, 1113, 964, 843 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.59 (d, $J = 6.5$ Hz, 3H), 3.38 (s, 3H), 3.45–3.87 (m, PEG-methylenes), 4.13 (t, $J = 5.0$ Hz, 2H), 5.19 (d, $J = 12.5$ Hz, 1H), 5.22 (d, $J = 12.5$ Hz, 1H), 5.74 (q, $J = 6.5$ Hz, 1H), 6.87 (d, $J = 8.0$ Hz, 1H), 6.93 (dt, $J_1 = 1.0$ Hz, $J_2 = 7.5$ Hz, 1H), 7.23–7.40 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.3, 58.9, 64.9, 67.8, 69.5, 70.4 (PEG), 70.6, 70.8, 71.8, 76.2, 111.5, 120.5, 123.8, 125.9, 128.0, 128.4, 129.5, 129.6, 141.0, 154.5, 156.5; ESI-TOF MS m/z 2479 Da (2477 Da calcd for $[CH_3O(CH_2CH_2O)_{105}C_{16}H_{15}O_3 \cdot 2Na]^{2+}$).

Other substrates were synthesized by the same procedure.

Compound (±)-5b: Yield 91% (purity, ca. >99%) from **9b**; IR (KBr): 2887, 1746, 1651, 1466, 1342, 1279, 1242, 1115, 964, 843 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.59 (d, $J = 6.5$ Hz, 3H), 3.38 (s, 3H), 3.45–3.82 (m, PEG-methylenes), 3.85 (t, $J = 5.0$ Hz, 2H), 4.11 (t, $J = 5.0$ Hz, 2H), 5.06 (d, $J = 12.0$ Hz, 1H), 5.11 (d, $J = 12.0$ Hz, 1H), 5.73 (q, $J = 6.5$ Hz, 1H), 6.87 (dd, $J_1 = 2.0$ Hz, $J_2 = 8.0$ Hz, 1H), 6.91 (s, 1H), 6.93 (d, $J = 7.5$ Hz, 1H), 7.25 (t, $J = 8.0$ Hz, 1H), 7.28–7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.2, 58.9, 67.2, 69.2, 70.4 (PEG), 70.6, 70.7, 70.8, 71.8, 76.4, 114.1, 114.6, 120.4, 125.9, 128.0, 128.4, 129.4, 136.5, 140.8, 154.3, 158.7; ESI-TOF MS m/z 2479 Da (2477 Da calcd for $[CH_3O(CH_2CH_2O)_{105}C_{16}H_{15}O_3 \cdot 2Na]^{2+}$).

Compound (±)-5c: Yield 98% (purity, ca. 94%) from **9c**; IR (KBr): 2886, 1742, 1651, 1466, 1342, 1279, 1242, 1115, 964, 843 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.58 (d, $J = 6.5$ Hz, 3H), 3.38 (s, 3H), 3.45–3.82 (m, PEG-methylenes), 3.85 (t, $J = 5.0$ Hz, 2H), 4.12 (t, $J = 5.0$ Hz, 2H), 5.03 (d, $J = 12.0$ Hz, 1H), 5.08 (d, $J = 12.0$ Hz, 1H), 5.72 (q, $J = 6.5$ Hz, 1H), 6.88 (d, $J = 9.0$ Hz, 2H), 7.18–7.40 (m, 5H), 7.28 (d, $J = 9.0$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.2, 58.9, 67.3, 69.3, 69.5, 70.4 (PEG),

70.65, 70.70, 71.8, 76.3, 114.5, 125.9, 127.4, 128.0, 128.4, 130.1, 140.9, 154.4, 158.9; ESI-TOF MS m/z 2479 Da (2477 Da calcd for $[CH_3O(CH_2CH_2O)_{105}C_{16}H_{15}O_3 \cdot 2Na]^{2+}$).

Compound (±)-5d: Yield 95% (purity, ca. 99%) from **9d**; IR (KBr): 2886, 1744, 1638, 1468, 1342, 1281, 1242, 1111, 962, 843 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.58 (d, $J = 6.5$ Hz, 3H), 2.89 (t, $J = 7.0$ Hz, 2H), 3.38 (s, 3H), 3.45–3.82 (m, PEG-methylenes), 3.84 (t, $J = 5.0$ Hz, 2H), 4.10 (t, $J = 5.0$ Hz, 2H), 4.26 (dt, $J_1 = 2.5$ Hz, $J_2 = 7.0$ Hz, 2H), 5.70 (q, $J = 6.5$ Hz, 1H), 6.83 (d, $J = 8.5$ Hz, 2H), 7.10 (d, $J = 8.5$ Hz, 2H), 7.28–7.40 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.2, 34.1, 58.9, 67.3, 68.3, 69.6, 70.4 (PEG), 70.6, 70.7, 71.8, 76.2, 114.5, 125.9, 128.0, 128.4, 129.2, 129.7, 140.9, 154.3, 157.4; ESI-TOF MS m/z 2486 Da (2484 Da calcd for $[CH_3O(CH_2CH_2O)_{105}C_{17}H_{17}O_3 \cdot 2Na]^{2+}$).

Compound (±)-5e: Yield 99% (purity, ca. 96%) from **9e**; IR (KBr): 2884, 1742, 1638, 1512, 1466, 1344, 1281, 1252, 1113, 953, 843 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.59 (d, $J = 6.5$ Hz, 3H), 1.89–1.98 (m, 2H), 2.61 (t, $J = 7.5$ Hz, 2H), 3.37 (s, 3H), 3.45–3.81 (m, PEG-methylenes), 3.83 (t, $J = 5.0$ Hz, 2H), 4.086 (dt, $J_1 = 6.5$ Hz, $J_2 = 10.5$ Hz, 1H), 4.088 (t, $J = 5.0$ Hz, 2H), 4.12 (dt, $J_1 = 6.5$ Hz, $J_2 = 10.5$ Hz, 1H), 5.72 (q, $J = 6.5$ Hz, 1H), 6.81 (d, $J = 8.5$ Hz, 2H), 7.04 (d, $J = 8.5$ Hz, 2H), 7.18–7.42 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.2, 30.2, 30.8, 58.9, 67.0, 67.2, 69.6, 70.4 (PEG), 70.58, 70.62, 71.7, 76.1, 114.4, 125.8, 127.9, 128.4, 129.1, 133.0, 140.9, 154.4, 156.9; ESI-TOF MS m/z 2493 Da (2491 Da calcd for $[CH_3O(CH_2CH_2O)_{105}C_{18}H_{19}O_3 \cdot 2Na]^{2+}$).

Compound (±)-12c: Yield 98% (purity, ca. 97%) from **9c**; IR (KBr): 2884, 1744, 1645, 1466, 1342, 1281, 1242, 1113, 962, 843 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.89 (t, $J = 7.5$ Hz, 3H), 1.77–2.03 (m, 2H), 3.37 (s, 3H), 3.44–3.87 (m, PEG-methylenes), 4.11 (t, $J = 5.0$ Hz, 2H), 5.02 (d, $J = 12.0$ Hz, 1H), 5.06 (d, $J = 12.0$ Hz, 1H), 5.49 (t, $J = 6.5$ Hz, 1H), 6.87 (d, $J = 9.0$ Hz, 2H), 7.25 (d, $J = 9.0$ Hz, 2H), 7.26–7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 9.8, 29.3, 59.0, 67.3, 69.3, 69.6, 70.5 (PEG), 70.67, 70.72, 71.8, 81.5, 114.5, 126.4, 127.4, 128.0, 128.3, 130.1, 139.8, 154.6, 158.9; ESI-TOF MS m/z 2486 Da (2484 Da calcd for $[CH_3O(CH_2CH_2O)_{105}C_{17}H_{17}O_3 \cdot 2Na]^{2+}$).

Compound (±)-12d: Yield 89% (purity, ca. 61%) from **9d**; IR (KBr): 2886, 1748, 1638, 1466, 1342, 1281, 1242, 1115, 964, 843 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.90 (t, $J = 7.5$ Hz, 3H), 1.77–1.89 (m, 1H), 1.91–2.03 (m, 1H), 2.88 (t, $J = 7.0$ Hz, 2H), 3.37 (s, 3H), 3.44–3.88 (m, PEG-methylenes), 4.11 (t, $J = 5.0$ Hz, 2H), 4.25 (dt, $J_1 = 4.5$ Hz, $J_2 = 7.5$ Hz, 2H), 5.47 (t, $J = 6.5$ Hz, 1H), 6.82 (d, $J = 9.0$ Hz, 2H), 7.07 (d, $J = 9.0$ Hz, 2H), 7.21–7.36 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 9.8, 29.2, 34.1, 58.9, 67.2, 68.3, 69.6, 70.4 (PEG), 70.6, 70.7, 71.8, 81.3, 126.3, 127.9, 128.3, 129.2, 129.7, 139.8, 154.5, 160.9; ESI-TOF MS m/z 2493 Da (2491 Da calcd for $[CH_3O(CH_2CH_2O)_{105}C_{18}H_{19}O_3 \cdot 2Na]^{2+}$).

Compound (±)-13c: Yield 97% (purity, ca. 69%) from **9c**; IR (KBr): 2886, 1734, 1647, 1466, 1342, 1281, 1242, 1115, 964, 843 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.31 (d, $J = 6.0$ Hz, 3H), 3.38 (s, 3H), 3.42–3.93 (m, PEG-methylenes), 4.12 (t, $J = 5.0$ Hz, 2H), 4.46 (s, 2H), 4.98 (td, $J_1 = 1.5$ Hz, $J_2 = 6.5$ Hz, 1H), 5.05 (d, $J = 12.0$ Hz, 1H), 5.06 (d, $J = 12.0$ Hz, 1H), 6.89 (d, $J = 9.0$ Hz, 2H), 7.22–7.37 (m, 5H), 7.30 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.0, 35.8, 58.9, 66.2, 67.3, 69.0, 69.5, 70.4 (PEG), 70.6, 70.7, 71.8, 72.7, 72.9, 114.4, 114.5, 127.4, 127.5, 128.2, 130.1, 138.1, 154.5, 158.9; ESI-TOF MS m/z 2508 Da (2506 Da calcd for $[CH_3O(CH_2CH_2O)_{105}C_{19}H_{21}O_4 \cdot 2Na]^{2+}$).

Compound (±)-13d: Yield 95% (purity, ca. 89%) from **9d**; IR (KBr): 2886, 1738, 1645, 1468, 1342, 1281, 1242, 1111, 962, 843 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.29 (d, $J = 6.5$ Hz, 3H), 1.78–2.01 (m, 2H), 2.89 (t, $J = 7.5$ Hz, 2H), 3.37 (s, 3H), 3.44–3.80 (m, PEG-methylenes), 3.82 (t, $J = 5.0$ Hz, 2H), 4.09 (t, $J = 5.0$ Hz, 2H), 4.26 (dt, $J_1 = 2.0$ Hz, $J_2 = 7.0$ Hz, 2H), 4.47 (s, 2H), 4.88–4.97 (m, 1H), 6.84 (d, $J = 9.0$ Hz, 2H), 7.10 (d, $J = 8.5$ Hz, 2H), 7.22–7.36 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.0, 34.1, 35.8, 58.9, 66.2, 67.2, 68.1, 69.6, 70.4 (PEG), 70.6, 70.7, 71.8, 72.6, 72.9, 114.5, 127.4, 127.5, 128.2, 129.3, 129.7, 138.1, 154.5, 157.4; ESI-TOF MS m/z 2515 Da (2514 Da calcd for $[CH_3O(CH_2CH_2O)_{105}C_{20}H_{23}O_4 \cdot 2Na]^{2+}$).

PEG_{4600}-Supported Substrate Coupled with 1-Phenylethanol ((±)-10): Yield 99% (purity, ca. 89%) from **11**; IR (KBr): 2884, 1744, 1647, 1466, 1342, 1281, 1242, 1115, 964, 843 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.59 (d, $J = 6.5$ Hz, 6H), 3.45–3.82 (m, PEG-methylenes), 4.24 (td, $J_1 = 4.5$ Hz, $J_2 = 12.0$ Hz, 2H), 4.27 (td, $J_1 = 5.0$ Hz, $J_2 = 11.5$ Hz, 2H), 5.72 (q, $J = 6.5$ Hz, 2H), 7.17–7.45 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.2, 66.7, 68.8, 70.4 (PEG), 70.5, 70.6, 76.4, 125.9, 128.0, 128.4, 140.8, 154.4; ESI-TOF MS m/z 2449 Da (2447 Da calcd for $[(CH_2CH_2O)_{103}C_{18}H_{18}O_5 \cdot 2Na]^{2+}$).

Typical Experimental Procedure for Enantioselective Hydrolysis of PEG-Supported Substrates. To a test tube containing 125 mg of (±)-**1** (sub. concn., 5 mM) was added 4.5 mL of hexane and 0.5 mL of 0.1 M phosphate buffer (pH 6.5). To the mixture was added 10 mg of lipase from porcine pancreas (PPL; Type II, Sigma) (187 U mg^{-1}, using olive oil at pH 7.7), and the solution was stirred for 24 h at 0 °C. After the organic layer was separated and evaporated in vacuo, the ee of the resulting (*R*)-alcohol **3** (96% ee) in the residue was determined by GC analysis. On the other hand, the aqueous layer was diluted with CH_2Cl_2, and dried over Na_2SO_4. After evaporation, the residue was hydrolyzed with 2 M NaOH aq. (1.0 mL) in MeOH (4.0 mL). The products were extracted with hexane (×3), and the organic layer was dried over Na_2SO_4. After evaporation, the ee of the corresponding (*S*)-**3** (18% ee) was determined by GC analysis.

Other reactions were carried out by the same procedure.

Typical Preparative Scale Reaction of PEG-Supported Substrates. To a recovery flask containing 3.6 g of (±)-**5d** (sub. concn., 5 mM) was added 130.5 mL of hexane and 14.5 mL of 0.1 M phosphate buffer. To the mixture was added 290 mg of PPL, and the solution was stirred for 48 h at 0 °C. After the organic layer was separated and evaporated in vacuo, the residue was purified by preparative TLC (hexane/AcOEt = 2/1) to give (*R*)-**3** (9.6 mg, 12%, 98% ee, $[\alpha]_D^{18} = +32.8$ (*c* 0.96, MeOH)). On the other hand, the aqueous layer was diluted with CH_2Cl_2, and dried over Na_2SO_4. After the solution was evaporated in vacuo, the residue was precipitate into Et_2O to afford the compound (*S*)-**5d** as a white solid. To a solution of the solid in MeOH (120 mL) was added 2 M NaOH aq. (30 mL), and the solution was stirred for 1 h at rt. The products were extracted with ether (×3), and the organic layer was washed with brine and dried over Na_2SO_4. After evaporation, the residue was purified by column chromatography (hexane/EtOAc = 2/1) on silica gel to give the corresponding (*S*)-**3** (37.9 mg, 46%, 58% ee, $[\alpha]_D^{25} = -21.0$ (*c* 1.06, MeOH)).

Several data of alcohols are as follows.

1-Phenylethanol (3): The spectral data were in full agreement with that of a commercial source. GLC conditions: column, CP-Cyclodextrin-B-236-M19 (Chrompack), 0.25 mm × 50 m; injection, 160 °C; detection, 160 °C; oven, 140 °C; carrier gas, He; head pressure, 2.4 kg cm^{-2}; retention time, 8.9 (*R*) and 9.2 (*S*) min.

1-Phenyl-1-propanol (15): The spectral data were in full agreement with that of a commercial source. (*S*)-**15**, $[\alpha]_D^{30} = -38.3$ (c 1.02, $CHCl_3$) (86% ee); (*R*)-**15**, $[\alpha]_D^{30} = +41.4$ (*c* 1.20, $CHCl_3$)

(94% ee); lit.[22] (*S*)-form, $[\alpha]_D^{20} = -47.0$ (*c* 1.00, $CHCl_3$). GLC conditions: column, CP-Cyclodextrin-B-236-M19 (Chrompack), 0.25 mm × 50 m; injection, 140 °C; detection, 140 °C; oven, 120 °C; carrier gas, He; head pressure, 2.4 kg cm^{-2}; retention time, 22.6 (*R*) and 23.4 (*S*) min.

4-Benzyloxy-2-butanol (17): The spectral data were in full agreement with those reported.[17b] (*R*)-**17**, $[\alpha]_D^{29} = -14.9$ (*c* 1.08, MeOH) (97% ee); (*S*)-**17**, $[\alpha]_D^{29} = +2.1$ (*c* 1.05, MeOH) (13% ee)); lit.[17b] (*S*)-form, $[\alpha]_D^{27} = +19.0$ (*c* 0.95, MeOH). HPLC conditions: column, CHIRALCEL OD-H (Daicel Chemical Industries, Ltd.); eluent, hexane/2-propanol = 90/10; flow rate, 0.5 mL min^{-1}; 254 nm; temperature, 25 °C; retention time, 13 (*S*) and 14 (*R*) min.

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